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"Memory of Water" Experiments Explained with No Role Assigned to Water: Pattern Expectation after Classical Conditioning of the Experimenter

Francis Beauvais [1,*]

[1] Scientific and Medical Writing, 91 Grande Rue, 92310 Sèvres, France
* Correspondence: beauvais@netcourrier.com; Tel.: +33 6 68 36 58 36

ABSTRACT

Introduction. The "memory of water" experiments suggested the existence of molecular-like effects without molecules. Although no convincing evidence of modifications of water – specific of biologically-active molecules – has been reported, consistent changes of biological systems were nevertheless recorded. We propose an alternate explanation based on classical conditioning of the experimenter.
Methods. Using a probabilistic modelling, we describe not only the biological system, but also the experimenter engaged in an elementary dose-response experiment. We assume that during conventional experiments involving genuine biologically-active molecules, the experimenter is involuntarily conditioned to expect a pattern, namely a relationship between the descriptions (or "labels") of experimental conditions and the corresponding biological system states.
Results. The modelling predicts that the conditioned observer could continue to record the learned pattern even in the absence of the initial cause, namely biologically-active molecules. The phenomenon is self-sustained since the observation of the expected pattern reinforces the initial conditioning. A necessary requirement is the use of a system submitted to random fluctuations with autocorrelated successive states (no forced return to the initial position). The relationship observed by the conditioned observer is however not causal and has a quantum-like structure. The modelling predicts also that blind experiments with an "outside" supervisor lead to a loss of correlations (*i.e.* system states randomly associated to "labels").
Conclusion. This psychophysical modelling allows explaining the results of "memory of water" experiments without referring to water or another local cause. It could be extended to other scientific fields in biology, medicine and psychology when an experimenter effect is suspected.

Keywords: *Experimenter effect; "Memory of water"; Quantum-like correlations; Classical conditioning.*

1. Introduction

The controversy over the "memory of water" that burst in 1988 continues to maintain in the shadow the whole story of Benveniste's experiments that extended over 20 years from 1984 to 2004 [1]. Admittedly these claims were anything but insignificant: the experiments presented in *Nature* suggested the existence of molecular-like effects without molecules [2]. The authors of this article stated that dilutions biologically-active molecules beyond the limit defined by Avogadro's number had nevertheless a biological effect.

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The violence of the controversy had most probably its roots in the "two centuries of observation and rationalization" that these results were supposed to reconsider [3]. Since the idea that a "structuration" of water could mimic the effects of biologically-active molecules was considered impossible, the inevitable conclusion was that the experiments were flawed. As a consequence, there was no place for an alternate theoretical framework that would consider these results, but without involving water and its alleged "memory". The fact that this work could give arguments to homeopathy, also highly controversial, was another reason for this strong opposition. It is out of the scope of this article to describe this controversy; details on the debate and disputed experiments can be found elsewhere [1, 4, 5].

According to the judgement of many scientists, there was nothing to explain in these experiments since there was no scientific fact, only poor science. Therefore, the report of *Nature*'s investigation in Benveniste's laboratory has been generally considered to put the last word to the public debate [6, 7]. My purpose in this introduction is not to fuel again this debate but simply to structure the arguments from both sides in order to explain why Benveniste failed to convince his peers. Indeed, after the basophil model described in 1988 in *Nature*'s article, other experimental models, mainly isolated rodent heart and plasma coagulation were developed by Benveniste's team. Experimental data accumulated seemingly in favour of a role of water for the storage of information on molecules in solution [8-14]. During this period, Benveniste made a step further by stating that molecular information could be "imprinted" in water through electromagnetic fields (1992) as in a "magnetic tape" [9] and even digitized (1995) [14]. At this occasion he coined the expression "digital biology" [14, 15].

In **Table 1**, arguments from Benveniste's experiments in favour or against "memory of water" are summarized. The arguments in favour of "memory of water" are mainly the observation of "activated" states of the biological systems associated to samples "imprinted" with different methods and the apparent specificity of the biological effects. The arguments against "memory of water" are mostly difficulties to make reproduce the results by other teams and the absence of a theoretical framework. There is also another reason – less known – that prevented Benveniste to go further in his quest of the perfect experiment that would be totally convincing. This reason was a stumbling block that was more particularly highlighted during public demonstrations where colleagues from other teams were invited to supervise proof-of-concept experiments. The role of these outside supervisors was to produce "inactive" and "active" samples (water samples with high dilutions or "imprinted" water; computer files for digital biology) and to mask them under a code number. After the outside supervisors had left, the coded samples were tested by Benveniste's team. When all measurements were finished, the results were sent to the supervisors who assessed the rate of success by comparing for each run the measured system state and the corresponding "label" (unbeknown of the experimenter who did the test). These proof-of-concept experiments systematically failed in the sense that "activated" states were always randomly distributed between samples with "inactive" and "active" labels [1, 16, 17]. In order to explain these troublesome failures, Benveniste proposed many *post hoc* explanations (*e.g.* water contaminations, interferences with external electromagnetic fields, "jumps of activity" from one sample to another, human errors for sample allocation, etc.) [1] Despite further improvements of devices and procedures to prevent these disturbances, the weirdness persisted. The important point however is that these possible external disturbances did not account for open-label samples and in blind experiments with an "inside" supervisor or an automatic device that were successful (more precise definitions of "inside" and "outside" supervisors will be given later).

In this article, I propose in the same time to take into consideration Benveniste's experiments and to abandon the "memory of water" hypothesis. A theoretical framework is constructed where these experiments are related to an experimenter effect which is the consequence of a previous classical conditioning of the experimenter. In this setting, all samples are nothing more than controls (or placebos) and the different procedures to "imprint" water samples are nothing more than rituals.

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The proposed modelling describes all features of Benveniste's experiments: emergence of an "activated state" of a biological system without local cause, correlations between "labels" and system states and mismatches of outcomes in blind experiments with an outside supervisor. No role is attributed to water or another local cause but the attention is now displaced toward the experimenter.

The proposed experimenter effect is original and could have consequences beyond the "memory of water" controversy. Therefore, considering Benveniste's experiments only as an example of specious science miss the point and prevents from seeing what these experiments could teach us. The price to pay for the proponents of "memory of water" is the abandon of the initial hypothesis (*i.e.* a molecular-like effect without molecules). For the opponents, the price to pay is to accept that these weird experiments – admittedly misinterpreted by its authors – had nevertheless a scientific interest.

Table 1. The arguments for and against molecular-like effects without molecules in Benveniste's experiments.

Arguments for	Arguments against
• Emergence of an "activated" state of biological models mimicking the effect of biologically-active molecules [a]	• Not compatible with current scientific knowledge on water (*e.g.* very short half-lives of chemical bonds between water molecules)
• Emergence of a relationship between experimental conditions and states of system	• Not compatible with current scientific knowledge on biochemical interactions (*e.g.* law of mass action)
• Specificity of the molecular-like effects [b]	• No theoretical framework
• Consistency of the results with different experimenters, biological systems and procedures	• Difficulties to make reproduce the results by other teams
• Successful tests in blind experiments with local/inside supervisor or automated devices. [c]	• Proximity with homeopathy
	• Loss of correlations in blind experiments with an outside supervisor. [c]

[a] In "memory of water" experiments, water samples are supposed to induce a biological activity although the biologically-active molecules have been removed via extensive serial dilutions ("high dilutions") or after water samples have been "imprinted" through electromagnetic fields using different devices ("electronic transmission" or "digital biology").

[b] Water samples supposed to have been "imprinted" kept the specificity exhibited by original molecules ("imprints" of biologically-inactive molecules were inactive even though their structure was close of biologically-active molecules).

[c] See definitions of "inside" or "outside" supervisors in text.

2. Classical conditioning during ordinary dose-response experiments

Classical conditioning (or Pavlovian conditioning) is a well-known associative learning process [18]. We will briefly describe classical conditioning with a classical example before making a parallel with an experimenter who handles an experimental system. Classical conditioning supposes first an "unconditioned stimulus" that produces an "unconditioned response" in an organism. In the classical example of Pavlov's dog, smelling or tasting food (unconditioned stimulus) induces salivation (unconditioned response). The purpose of the learning is to pair a "neutral stimulus" to the unconditioned stimulus. In this case, a bell (neutral stimulus) systematically rings just before

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food (unconditioned stimulus) is presented to the dog. Thus, the dog learns to associate the ring bell and the coming of food. During this learning process, the former neutral stimulus becomes a "conditioned stimulus". Indeed, salivation (conditioned response) is now induced when bell rings. To be complete, we must add that no food is expected (no salivation) by the dog when the bell does not ring. Thus, a relationship is established between the conditioned stimulus (ring *vs.* no ring) and the conditioned response (salivation *vs.* no salivation).

The purpose of most *in vitro* or physiology experiments is to study the effect of a biologically-active compound on a biological system. A dose-response is performed meaning that the effect of the compound is evaluated at different concentrations (0, x, $2x$, $3x$, etc.) For simplifying, we suppose that only one "active" condition vs. one "inactive" condition (or control) are assessed during the experiments. These experiments are sufficiently repeated to allow probability calculations. We suppose also that the biological system has only two states: "resting" state (not different from background noise) and "activated" state (different from background noise).

In such *in vitro* experiments, one usually forgets that the biological stimulus has not only a direct effect on the biological system under scrutiny but also an indirect effect on another "biological system", namely the experimenter. Even with automated systems there is always an experimenter that prepares the experiment, records the outcomes and interprets them. Therefore, it is easy to make a step further and to consider that during the repetitions of experiments, the experimenter unintentionally learns to combine the experimental conditions with the states of the biological system. Thus, the "inactive" condition (control) is associated to the "resting" state and the "active" condition (biologically-active molecules at pharmacological concentrations) is associated to the "activated" state.

After this classical conditioning process, the cognitive structures of the experimenter are changed. The "*labels*" of the experimental conditions are associated to the respective system states: "inactive" label is associated to "resting" state and "active" label is associated to "activated" state.

In the modelling that we will construct, we posit that all samples to be tested are identical and equivalent to controls (or placebos). They are all biologically-inactive in the sense that they do not induce a local causal biological effect. Even though the test samples are subjectively named "inactive" and "active" by the experimenter, it would be impossible to distinguish one test sample from another one on physical bases; only their identification with "labels" – *i.e.* their *meaning for the experimenter* – is different. "Labels" are nothing more than a short description for the experimenter about the expected effect. In **Figure 1**, the "labels" have the non-specific names *L1* or *L2* that does not presuppose to which experimental condition ("inactive" or "active") they are respectively associated by the experimenter.

It is important to underline that a relationship has a higher degree of abstraction than its components ("labels" and corresponding system states). A relationship is like a *pattern* (or a shape) that is thought in its wholeness, not as the simple sum of its individual components. In other words, after conditioning, the experimenter expects an "image" (a continuous entity), not "pixels" (discrete stuffs).

Since the primary purpose of this article is to propose an explanation of Benveniste's experiments, we must underscore that the members of Benveniste's laboratory were accustomed to perform "classical" experiments day to day. Therefore, classical conditioning can be easily assumed in this context.

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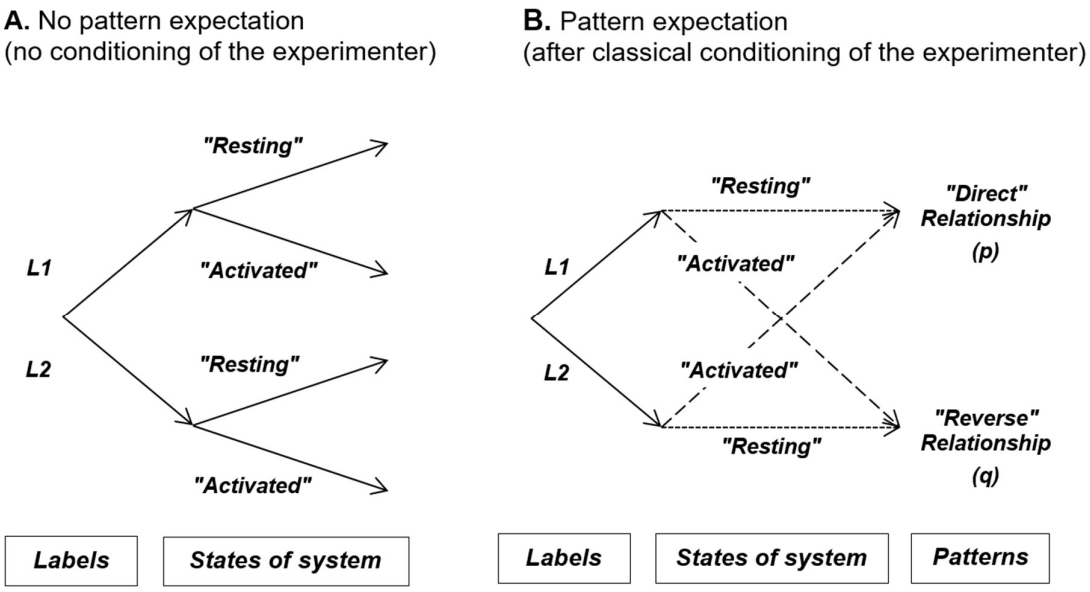

Figure 1. Expectation of patterns by the experimenter after classical conditioning. The two "labels" ("*L1*" *vs.* "*L2*") and the two possible system states ("resting" *vs.* "activated") define four couples of outcomes (**A**). The "labels" have the non-specific names *L1* or *L2* that does not presuppose to which experimental condition ("inactive" or "active") they are respectively associated by the experimenter. After classical conditioning (*i.e.* Pavlovian conditioning) with "conventional" experiments involving biologically-active molecules at pharmacological concentrations, the two possible relationships expected by the experimenter are named "direct" or "reverse" relationships with probabilities *p* and *q*, respectively (**B**). A relationship has a higher degree of abstraction than its components and is like a *pattern* that is thought in its wholeness, not as the simple sum of its individual components.

3. Consequences of the classical conditioning of the experimenter for future outcomes

In this section, we explore the probabilistic consequences of the classical conditioning of an experimenter named *O* who observes the experimental system *S* **(Figure 2**). The experimental scene is described from the point of view of an observer *O'*. This observer *O'* is outside the laboratory when the experiment is performed; she knows the experimental protocol and the initial conditions of *O* and *S*. *O'* knows that the experimenter *O* has been conditioned to observe a relationship between "labels" and system states. Although she knows that some samples are associated to an "inactive" label whereas the others are associated to an "active" label, she has no information on the on-going experiment. She calculates in a probabilistic modelling the evolution of the states of *O* and *S*.[1] These probability calculations allow *O'* to know on what to expect when she will enter the laboratory after the experiment is finished.

[1] This description of the experimental situation is reminiscent of "Wigner's friend" which is a Gedankenexperiment proposed in quantum physics by the physicist Eugene Wigner.

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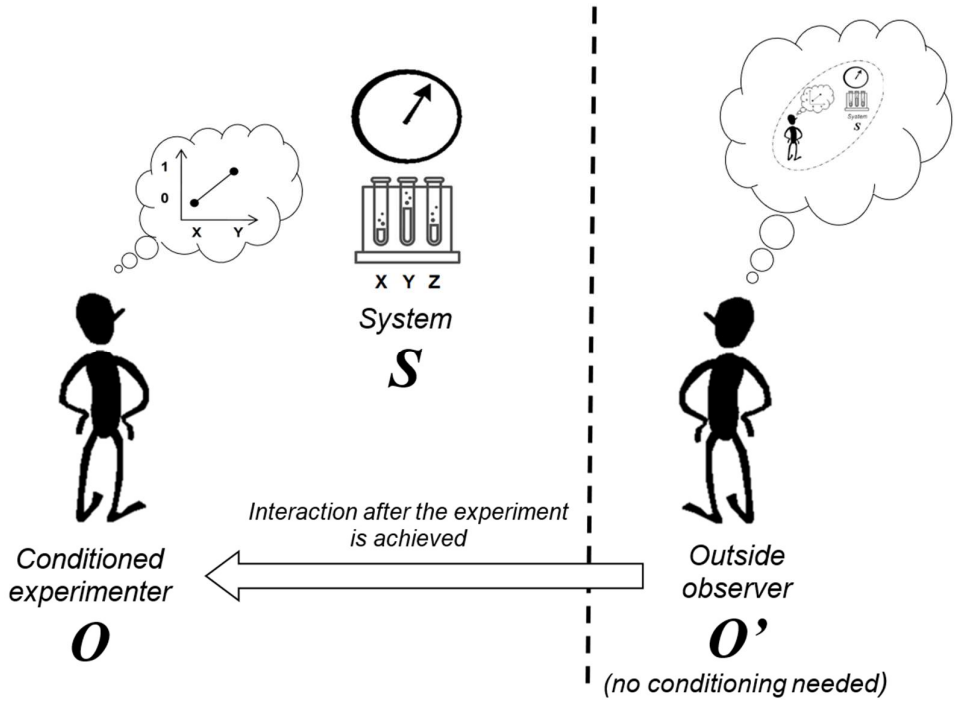

Figure 2. Description of the experimental situation from the point of view of an outside observer**.** An elementary dose-response experiment performed by an experimenter *O* is described from the outside point of view of an outside observer *O'* who is uninvolved in the on-going experimental process. The experimenter *O* has been conditioned to expect a pattern. This pattern is the relationship between the descriptions of experimental conditions *X, Y, Z* ("labels") and the corresponding system states. *O'* does not need to be conditioned. *O'* knows the initial conditions of *O* and *S* and she calculates the probabilistic evolution of their states. These calculations will allow *O'* to know on what to expect when she will enter the laboratory after the experiment is achieved.

The probabilistic consequences of the classical conditioning of the experimenter *O* who observes the system *S* are described in three sequential steps:

Step 1: O-S taken as a whole. The state of the system *S* ("resting" or "activated" state) at the end of the experiment is obviously a property of *S*. However, as previously said, *O* has been conditioned and *expects a pattern* (direct or reverse relationship). Each future outcome to be recorded by *O* is therefore the combination of an abstraction (pattern) and a physical variable (state of *S*). As a consequence, the future outcome to be recorded by *O* through his reading grid is neither an individual property of *O* nor an individual property of *S*, but is a property of *O* and *S taken as a whole.* It is important to underline that this future outcome is not the simple juxtaposition of a first sub-event that is a property of *O* and a second sub-event that is a property of *S*. Indeed, *O* and *S* constitute a new "entity" *O-S* that cannot be dissociated.

Step 2: The outcome does not preexist. Since the future outcome to be recorded by *O* is a property of *O-S* taken as a whole (not the single addition of properties of *O* and *S*), it means that this outcome (direct or reverse relationship) is *created* when *O* and *S* join together to form *O-S* (*i.e.* when *O* measures *S*). In other words, the outcome *does not preexist* to the measurement/observation of *S* by *O*. A probability can nevertheless be attributed to each potential future outcome (direct or reverse relationship) before the experiment begins.

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Step 3: Independence of the potential future outcomes and shared reality. We have now to translate into mathematical terms an event that does not preexist to its measurement.

We describe the experimental situation from the outside point of view of *O'* who is uninvolved in the on-going measurement process. A probabilistic space is constructed that describes all potential future outcomes to be recorded by the participants. In this probabilistic space, the future outcome A to be recorded by *O* and the future outcome B to be recorded by *O'* are *independent* events. Indeed, suppose that A and B are not independent events but are perfectly correlated. This means that there are constraints on the choice of the future outcome A. In other words, this choice is not free and cannot be the result of a creation process at the moment of the measurement/observation process. This absence of freedom of choice corresponds to a classical approach for which reality preexists to its observation and is not created at this moment.[2] As a consequence, if we want to describe the event A not preexisting to its measurement, it must be independent from the event B.

By definition, the two events A and B are independent if their joint probability is the product of their respective probabilities:

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

Note that if A is independent from B is equivalent to B is independent from A. The subset $A \cap B$ describes the "shared reality" experienced by *O* and *O' after* they interact. Note also that Eq. 1 applies if at least one future potential event does not preexist (*i.e.* if at least one of the two observers is conditioned to expect the pattern).

4. Probability of a direct relationship with a conditioned experimenter

We note the probability of a direct relationship as Prob (*direct*) = p and the probability of a reverse relationship as Prob (*reverse*) = q (with $p + q = 1$) (**Figure 1B**). From the outside point of view of *O'*, Eq. 1 is used both Prob (A) and Prob (B) are replaced with p. Thus, *before* *O* and *O'* interact, Prob (*direct*) = $p \times p = p^2$ and Prob (*reverse*) = $q \times q = q^2$ (**Figure 3**).

After the experiment is finished, *O'* enters the laboratory and *O* and *O'* agree on the record of each elementary outcome (association of a "label" with a system state). Therefore, some situations are not allowed (*e.g.* *O* observes a direct relationship whereas *O'* observes a reverse relationship) and they are discarded from the list of the possible outcomes (**Figure 3**). Since the total probability must remain equal to one, renormalization of probability calculation is necessary after discarding the not-allowed situations. For this purpose, the probability of each possible event is divided by the sum of the probabilities of all possible events:

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

We write now Eq. 2 in order to get only p as a variable by dividing both numerator and denominator by p^2 and by considering that $q = 1 - p$:

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

[2] For example, in classic physics, the mass of an object preexists to its measurement; in contrast, in quantum physics, the value of the spin of an electron according to a given direction does not preexist before its measurement by a macroscopic apparatus.

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This equation can be generalized from 2 to N observers by considering that all N observers agree on the outcome:

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

This generalized equation allows calculating the special case $N = 0$, which is the experimental situation in the absence of any observer:

$$p_0 = \frac{1}{1+\left(\frac{1}{p}-1\right)^{0}} = \frac{1}{1+1} = \frac{1}{2} \qquad \text{(Eq. 5)}$$

Starting from this situation without observers, we introduce again the observers O and O' in the modelling by using Eq. 3 and by replacing p with $p_0 = 1/2$. We obtain again Prob (*direct*) = 1/2.

At first sight, the introduction of an experimenter – conditioned or not – in the modelling has no advantage over the classical approach. Indeed, considering that the outcome preexists (classical approach) or does not preexist (present modelling) leads to the same result; direct and reverse relationship are evenly observed (only the resting state of S is observed). This is consistent with common sense: two control situations (or two placebos) are both associated to the "resting state", regardless the presence or not of an observer.

The advantage of the present modelling will appear in the next section after considering the fluctuations inherent to any measurement with a macroscopic system.

Probabilities of the future outcomes to be recorded by the observers O and O'

Before interaction of the observers		***Event A to be recorded by O***	
		Direct (p)	***Reverse (q)***
Event B to be recorded by O'	***Direct (p)***	p^2	pq
	Reverse (q)	pq	q^2

Observers' agreement on outcomes ("Reality" shared by the observers O and O')

After interaction of the observers*		***Event recorded by O and O'***	
		Direct (p)	***Reverse (q)***
Event recorded by O and O'	***Direct (p)***	p^2	pq *(not allowed)*
	Reverse (q)	pq *(not allowed)*	q^2

* Probabilities are given before renormalization (see text)

Figure 3. Expectations of the observers and shared reality. The independence of the future outcomes to be observed by the observers O and O' has some probabilistic consequences that are depicted in this figure. The upper panel describes the relationship expected by the observers O and O' before interaction in the probabilistic space described by an uninvolved super-observer. The two events A and B are independent because at least one of them does not pre-exist to the measurement process (see text). The lower panel describes the shared "reality" of O and O' after their interaction. Only situations that fit intersubjective agreement are allowed (in these situations, O and O' agree on their records for each couple of experimental condition and system states).

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5. Emergence of correlations between "labels" and system states

Any macroscopic system is associated with random fluctuations. We note $\pm \varepsilon_n$ (with $| \pm \varepsilon_n | << 1$) a small fluctuation of Prob (*direct*) at time t_n.

We have seen that before the observation of the system, Prob (*direct*) = $p_0 = 1/2$. At time t_1, after the first fluctuation ε_1, the new value of Prob (*direct*) is p_1 that is calculated by replacing p_0 with $p_0 \pm \varepsilon_1$ in Eq. 3.

For the next fluctuations, we are faced to two possibilities. Either the system comes back to its previous position or its new position is the starting point for the next state. We will consider these two possibilities separately by modifying Eq. 3 with random fluctuations.

In the first case where the system comes back to its initial position after each fluctuation, p_{n+1} is calculated with $p_n = p_0 = 1/2$:

$$\text{Prob}_{n+1}\,(direct) = p_{n+1} = \frac{1}{1+\left(\frac{1}{1/2 \pm \varepsilon_{n+1}} - 1\right)^2} \quad (\text{with } p_0 = 1/2)$$
$$= 1/2 \pm \varepsilon_{n+1} \qquad \text{(Eq. 6)}$$

In the second case, each state *n* is the starting point of the state *n+1*. A mathematical sequence is obtained where each p_n is used for the calculation of p_{n+1}:

$$\text{Prob}_{n+1}\,(direct) = p_{n+1} = \frac{1}{1+\left(\frac{1}{p_n \pm \varepsilon_{n+1}} - 1\right)^2} \quad (\text{with } p_0 = 1/2) \qquad \text{(Eq. 7)}$$

The distinction between return to initial position and new position as a starting point for the next state allows specifying systems that have different behaviours confronted to small random fluctuations. Thus, Eq. 6 can be simplified to $p_{n+1} = 1/2 \pm \varepsilon_{n+1}$ (with $p_0 = 1/2$). In this case, despite fluctuations, Prob (*direct*) remains centred on 1/2. As a consequence, no specific relationship is established between "labels" and system states. Such systems can be qualified as "rigid" because small fluctuations do not move the system state away from the initial position. For example, thermal agitation induces small vibrations of a coin, but the inertia is sufficiently high that an immobile coin has no chance to jump from head to tail (within a reasonable timeframe). Similarly, after tossing, the trajectory of the coin is not influenced by internal thermal agitation. These systems that are "set to zero" after each tiny fluctuation have no interest for the present issue. Nevertheless, they allow to underscore that any experimental system is not suitable in this modelling.

In the second case described by Eq. 7, random fluctuations may deviate the experimental system from its initial position (no forced return). Each new state is dependent on the previous one (autocorrelation). A classical example is a pollen grain on water surface. In this case, the grain is sufficiently small and with sufficiently degrees of freedom to move away from its initial position due to the agitation of water molecules. Biological systems are more complex but some of them have sufficiently degrees of freedom to move from a "resting" state to an "activated" state after a series of random fluctuations (*e.g.* coronary dilatation of isolated rodent heart in Benveniste's experiments). Biological system must be understood in an extended sense; thus, biochemical systems can also be suitable (*e.g. in vitro* coagulation with fibrinogen and thrombin in Benveniste's experiments).

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The mathematical sequence described by Eq. 7 is computed in **Figure 4**. After a series of tiny fluctuations, there is always a dramatic transition of Prob (*direct*) from 1/2 to 0 or 1, at random for each run. This transition reveals an instability of the initial value ($p_0 = 1/2$) due to the introduction of fluctuations in the renormalized equation of Prob (*direct*). In both cases, Prob (*direct*) tends to achieve stable positions equal to 0 or 1. As a consequence, a relationship (direct or reverse) emerges between "labels" and system states.

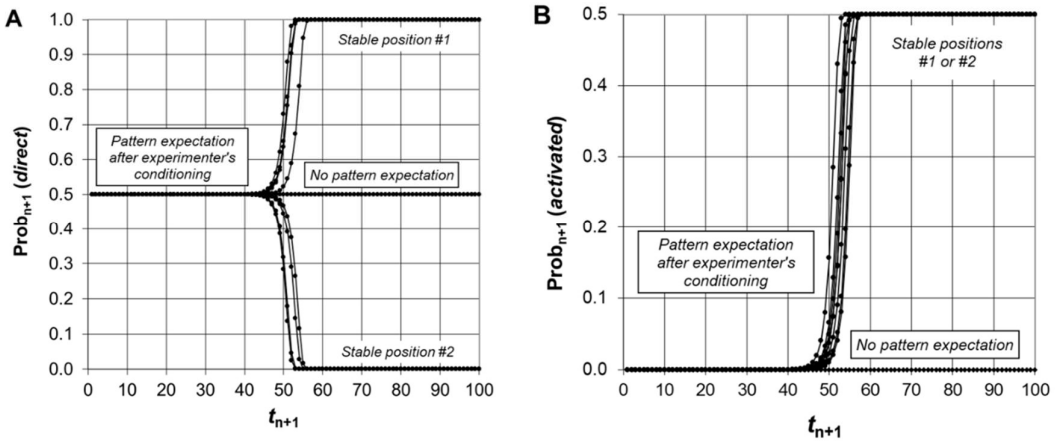

Figure 4. Computer calculation of the modelling. The mathematical sequence of Eq. 7 is calculated and eight computer calculations are showed. Each probability fluctuations ε_{n+1} during an elementary time (*t*) is randomly obtained in the interval from –0.5 to +0.5 × 10^{-15}. Panel A describes the probability to observe a direct relationship after the interaction of *O* and *O'*. There is a dramatic transition from 0.5 to 0 or 1 at random after a few fluctuations. The tiny random fluctuations reveal the instable characteristic of the mathematical sequence for Prob (*direct*). The consequence is the establishment of a relationship (direct *vs.* indirect) between "labels" (*L1 vs. L2*) and system states (resting state *vs.* activated state). This relationship is the consequence of the classical conditioning of the experimenter for pattern expectation (see text). The probability to observe an activated state increases from ε to 1/2; indeed, each test with "active" label is associated to an "activated" state (Panel B). In contrast, in the absence of conditioning, Prob (direct) is equal to $1/2 \pm \varepsilon_n$ and there is no emergence of an "activated state" for each test with "active" label (Panels A and B).

Before testing any experimental condition (samples with "inactive" or "active" labels), the experimental system is prepared in a "resting" state (control condition) that is associated to the inactive "label". In stable position #1, the "label" *L1* is the "inactive" label and therefore the "label" *L2* is the "active" label; conversely, in stable position #2, the "labels" *L1* and *L2* are the "active" and "inactive" labels, respectively.

Therefore, the mathematical sequence described in Eq. 7 allows explaining in the same time two major features of Benveniste's experiments, namely the emergence of an "activated" state from background noise and the significant correlations between "labels" and system states (**Figure 4)**. No hypothesis on the physical properties of samples or another local cause has been necessary.

Application to "memory of water" experiments. Perhaps the strongest argument in favour of a "memory" related to water was the emergence of an "activated" state. This was particularly striking in Benveniste's experiments with isolated rodent heart which allowed "live" demonstrations of the coronary flow variations. Moreover, from 1992 to 1996, the experiments with the isolated rodent heart were performed using two systems that worked in parallel [1]. These

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parallel experiments were used to confirm the measurement of each test sample, particularly in experiments designed as proof of concept. I reanalysed in a previous publication the duplicates outcomes from a series of experiments performed with this double system [16]. These results were pooled regardless of the method used to "inform" water. The high correlation of the duplicate measurements (changes of coronary flow) was a very strong argument indicating that these experiments had an internal consistency and deserved to be considered through a scientific approach.

There were however some features that should have drawn attention of Benveniste's team. Indeed, many devices, settings, protocols, procedures or molecules were used in Benveniste's experiments involving very different physical principles. Despite these diverse approaches, the response of the biological system was generally in the same range: for example 20–30% of coronary flow variation for the isolated heart for "active" conditions (the same remark applies to basophil degranulation or plasma coagulation) [16]. Yet, the physical mechanisms involved in the different methods of "water" imprinting were quite different (high dilutions, "electromagnetic transfer" of a molecule in a solution, "electromagnetic transfer" from a computer file, solubilization of homeopathic granules). The diluted or "electronically transmitted" molecules were also various from small pharmacological molecules to large proteins (*e.g.* acetylcholine, ionophore, ovalbumin). In other words, what seemed to be important was the *a priori* "inactive" vs. "active" status of the sample and not the physical process supposed to "inform" water. It was as if a unique "cause" was at work and that the different methods used to "imprint" water were only rituals, perhaps helping the experimenters to focus on their expectations.

At first sight, the apparent specificity of the active samples was also a strong argument in favour of "memory of water". Thus, it was reported that water "imprinted" with an antigen induced a biological change in isolated heart, only if the animals were immunized to the same antigen [1, 11, 12]. Similar arguments have been reported for high dilutions in basophil degranulation (*e.g.* active histamine *vs.* inactive histidine; active anti-IgE *vs.* inactive anti-IgG) [2]. In fact, this argument is not valid if one considers that specificity is always indirectly "demonstrated" through an intellectual construct. These comparisons were nothing more than comparisons of "active" *vs.* "inactive" labels.

6. Consequences of the modelling for blind experiments

In this section, we see how the modelling predicts the vanishing of the correlations between "labels" and system states in blind experiments with an outside supervisor.

We suppose that the observer *O'* plays the role of an outside supervisor. In this experimental situation, the role of *O'* is to provide *O* with experimental samples under a coded name (the "inactive" and "active" labels are masked). As previously said, *O'* does not interact with *O* and *S* when the experiments are ongoing and when all outcomes have been recorded by *O* their measurement values are sent to *O'*. The comparison of the two lists, namely "labels" (unknown to the experimenters during the experiments) and states of the system measured during the experiments are compared by the supervisor *O'* in order to assess the rate of success. In this setting, the experimenter continues to expect a pattern but, in the absence of information on "labels", the outcomes (direct or reverse relationships) are randomly distributed. Therefore, Prob (*direct*) = Prob (*reverse*); since Prob (*direct*) + Prob (*reverse*) = 1, then Prob (*direct*) = Prob (*reverse*) = 1/2, thus indicating that there is no significant relationship between "labels" and system states. It is important to underscore that the "activated" state is always observed but evenly distributed among "inactive" and "active" labels.

Blind experiments can also be performed with a local/inside supervisor or with automatic devices for the blind random choice of "labels". In this setting, the local supervisor or the automatic device

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is nothing more than a part of the system *S* and the outcome is a property of *O-S* taken as a whole as previously described for open-label experiments. Prob (*direct*) = 1 in this situation, thus indicating a significant relationship between "labels" and system states. Blind experiments with or without outside supervisors have therefore different consequences that cannot be described within a classical framework.

Application to "memory of water" experiments. The vanishing of the apparent relationship in proof-of-concept demonstrations with an outside supervisor was a stumbling block for Benveniste's experiments. It is important to underscore that despite the vanishing of correlations, activated states persisted – as described with this modelling – but they were randomly associated with "inactive" and "active" labels [1, 16]. As explained in the introduction, the spreading of "activated" states regardless "labels" was interpreted as the consequence of external disturbances. However, further improvements of experimental conditions and devices did not prevent this unwanted phenomenon [19, 20].

In 2013, I reanalysed in depth a series of experiments performed by Benveniste's team with "digital biology" methods for experiments using isolated rodent heart [17]. The main interest of this series of experiments was that both inside and outside supervisors operated on the same samples. For these experiments, a wealth of precautions had been taken and nevertheless the disturbing effect of an outside supervisor was clearly evidenced.

7. Quantum-like nature of correlations

Although only classical probabilities were used until now, a quantum-like structure appears in the modelling.
The four possible outcomes depicted in **Figure 1** obey to the law of total probability (the sum of their probabilities is equal to one):

$$\text{Prob}(L1) \times \text{Prob}(resting) + \text{Prob}(L1) \times \text{Prob}(activated) + \text{Prob}(L2) \times \text{Prob}(resting) + \text{Prob}(L2) \times \text{Prob}(activated) = 1 \quad \text{(Eq. 8)}$$

When the stable position #1 is achieved (**Figure 4**), it means that *L1* is defined by the experimenter as the "inactive" label associated to the "resting" state and *L2* is defined as the "active" label associated to the "activated" state: Prob (*L1*) = Prob (*resting*) and Prob (*L2*) = Prob (*activated*); conversely, in the stable position #2, Prob (*L1*) = Prob (*activated*) and Prob (*L2*) = Prob (*resting*). These equalities are replaced in Eq. 8 (the same equation is obtained in both cases):

$$[\text{Prob}(In)]^2 + [\text{Prob}(Ac)]^2 + 2 \times \text{Prob}(In) \times \text{Prob}(Ac) = 1 \quad \text{(Eq. 9)}$$

Eq. 9 is a remarkable identity that can be written as:

$$[\text{Prob}(In) + \text{Prob}(Ac)]^2 = 1 \quad \text{(Eq.10)}$$

These two latter equations are rewritten after defining the positive real numbers *a* and *b* as Prob (*In*) = a^2 (or *a.a*) and Prob (*Ac*) = b^2 (or *b.b*):

$$(a \cdot a + b \cdot b)^2 = (a \cdot a)^2 + (b \cdot b)^2 + 2 \times (a \cdot b)^2 = 1 \quad \text{(Eq. 11)}$$

For symmetry reasons, we add $(b \cdot a - a \cdot b)^2$, which is equal to zero, to the left-hand side of the equation; in addition, $(a \cdot b)^2 = (b \cdot a)^2$ in the right-hand side:

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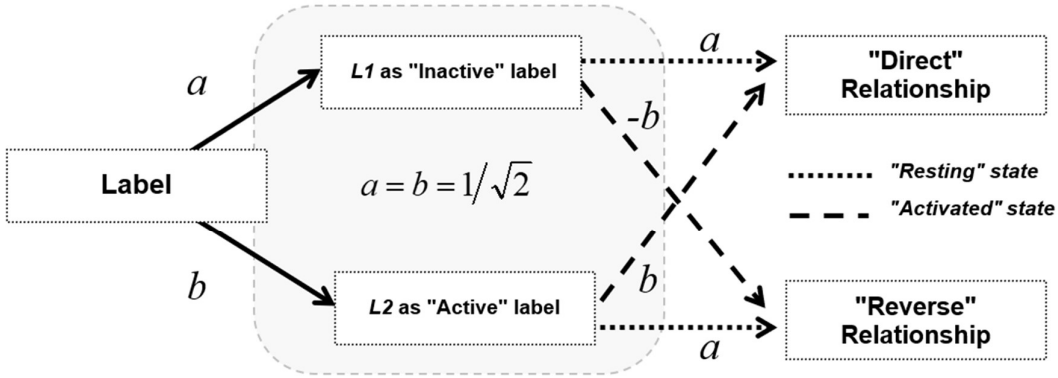
$$(a\cdot a + b\cdot b)^2 + (b\cdot a - a\cdot b)^2 = (a\cdot a)^2 + (b\cdot b)^2 + (b\cdot a)^2 + (a\cdot b)^2 = 1 \qquad \text{(Eq. 12)}$$

$$1 \quad + \quad 0 \quad = \quad 1/2 \quad + \quad 1/2 \quad = \quad 1 \qquad \text{(Eq. 13)}$$

As depicted in **Figure 5**, the left-hand side of Eq. 12 is the sum of Prob (*direct*) plus Prob (*reverse*) without an outside supervisor whereas the right-hand side is the sum of Prob (*direct*) plus Prob (*reverse*) with an outside supervisor. The real numbers *a* and *b* can be assimilated to probability amplitudes (their squaring gives probabilities). **Figure 5** and the associated calculations are for the stable state #1 (*L1* as inactive label); for the stable state #2 (*L2* as inactive label), the "inactive" and "active" labels and the cross-terms *b* and *-b* should be switched.



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

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

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

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

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

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

Figure 5. Quantum-like structure of the modelling. When a stable state is achieved, the logical structure of the modelling for experiments performed by conditioned experimenters is reminiscent of Young's two-slit experiment. Indeed, in Young's experiment, the interferences observed on the screen vanish if the path of photon is detected. Similarly, the significant relationship between "labels" and system vanishes – *i.e.* Prob (*direct*) decreases from 1 to 1/2 – if this relationship is assessed by an outside supervisor in a blind experiment (see text). In this case, the "activated" state is randomly associated to "inactive" and "active" labels.
Without an outside supervisor, the probability of measurement outcomes is calculated by adding the probability amplitudes and squaring the sum (quantum-like superposition). With an outside supervisor, the individual probability amplitudes are squared and then summed (classic mixture).
The figure and calculations are for stable state #1 (*L1* as inactive label); for stable state #2 (*L2* as inactive label), the labels "inactive" and "active" and the cross-terms *b* and *-b* should be switched.

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The mathematical structure described in Eq. 12 and in **Figure 5** reminds the single-photon self-interferences in Young's double-slit experiment (or in a Mach-Zehnder interferometer). In Young's experiment, the detection or not of the path of the photon is responsible of light duality that appears either as a particle or as a wave. In the present modelling, the supervision of the experiment by an outside supervisor is similar to path detection and classical probabilities apply: Prob (*direct*) = $a^2 \times a^2 + b^2 \times b^2 = 1$. In contrast, the absence of control by an outside supervisor is like an interference process. In this latter case, Prob (*direct*) is obtained by adding the probability amplitudes of the different paths and by squaring them: Prob (*direct*) = $(a \times a + b \times b)^2 = 1$.

Application to "memory of water" experiments. The disturbances related to an outside supervisor, which persisted despite improvement of devices and protocols, could be considered as the scientific fact that emerges from Benveniste's experiments. As explained above, this experimental situation was reminiscent of the two-slit Young experiment where detection of the particle path is crucial for the experimental outcomes. Therefore, in previous articles, I proposed a modelling of Benveniste's experiments based on some mathematical tools of quantum physics [21-23]. Apart this analogy, there was however no justification to use mathematical notions from quantum physics (*e.g.* states vectors), but it provided a possible theoretical framework for the experiments. Moreover, the use of mathematical notations unfamiliar to most biologists or physicians was also an inconvenience. In a further step, it appeared that the modelling could be built by using only classical probability even though the quantum logic was inconspicuously at work [19, 24]. The present article completes the modelling by proposing classical conditioning as the *primum movens* of Benveniste's experiments.

8. Experimenter's conditioning as a stepwise learning process

For simplicity, we considered in a first approach that the classical conditioning of the experimenter was 100% efficient. However, as every learning process, conditioning can be only partial. In this section, we will complete the modelling for experimental situations between non-conditioning and perfect conditioning. These considerations will also allow to deepen the understanding of the probabilistic consequences of the classical conditioning of the experimenter.

In a first step, we vary the degree of independence of the future outcomes A and B expected by *O* and *O'*, respectively. We generalize Eq. 1 by adding a parameter named *d*:

$$\text{Prob}\,(A \cap B) = \text{Prob}\,(A) \times \text{Prob}\,(B) + d \quad (\text{with } 0 \leq d \leq 1) \qquad \text{(Eq. 14)}$$

The future outcomes A and B are independent if $d = 0$; their degree of correlation increases when *d* increases (*d* can be understood as the abbreviation of "dependence"). In a second step, the generalization of Eq. 3 follows (**Figure 6**):

$$\text{Prob}\,(direct) = \frac{p^2 + d}{p^2 + q^2 + 2d} \quad (\text{with } 0 \leq d \leq pq) \qquad \text{(Eq. 15)}$$

If $d = 0$, Eq. 15 is equal to Eq. 2 and after introduction of probability fluctuations there is a dramatic shift from 1/2 toward 1 or 0 as previously shown with Eq. 7. In contrast, the future outcomes A and B are maximally correlated with $d = pq$ and we find again the classical situation:

$$\text{Prob}\,(direct) = \frac{p^2 + pq}{p^2 + q^2 + 2pq} = \frac{p \times (p+q)}{(p+q)^2} = \frac{p}{p+q} = p \qquad \text{(Eq.16)}$$

Probability fluctuations can be introduced in Eq. 16:

$$p_{n+1} = p_n \pm \varepsilon_{n+1} \quad (\text{with } p_0 = 1/2) \qquad \text{(Eq.17)}$$

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We easily see with Eq. 17 that there is no dramatic transition from $p_0 = 1/2$ toward 0 or 1 and therefore no emergence of the "activated" state of *S*; there are only tiny fluctuations of Prob (*direct*) around 1/2. From the outside uninvolved point of view of *O'*, it is as if there was only one future outcome (A and B are perfectly correlated) that pre-existed to its measurement. Therefore, varying the value of d from pq to 0 allows describing the progressive shift from non-conditioning (no pattern expectation) to perfect conditioning (pattern expectation) of the experimenter (**Figure 7**). Even with a small conditioning (value of d near 1/4), Prob (*direct*) > 1/2. In this case, provided that the statistical power is sufficient, significant correlations between "labels" and system states could be evidenced.

We can also calculate when the classical approach (preexistence of outcome to measurement) and the original approach of the present modelling (creation of outcome by measurement) are not discernible. This situation is achieved when $p = p^2 / (p^2 + q^2)$. We can easily calculate that the two members of the equation are equal in only three situations: $p = 0$, $p = 1$ and $p = 1/2$. We have seen that the situation with $p = 1/2$ is unstable and evolves towards either $p = 0$ or $p = 1$. For a causal relationship associated to $p = 0$ or $p = 1$ (*i.e.* a sure event), considering that the outcome preexists or not to its observation has no practical consequence and could be considered just as a matter of personal taste. For a quantum-like relationship associated to $p = 0$ or $p = 1$, the causality is only apparent as demonstrated in blind experiments with an outside supervisor.

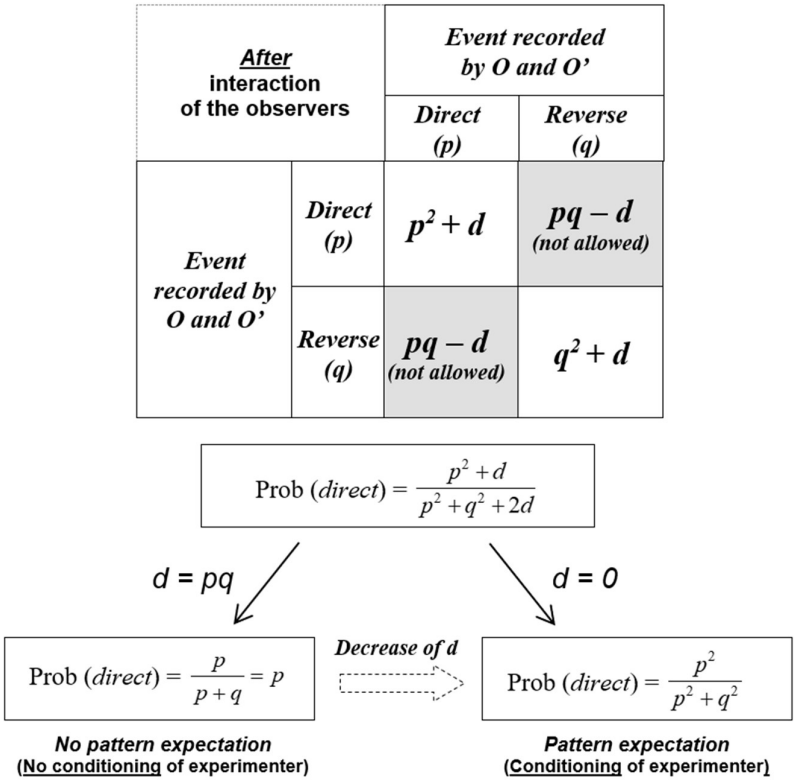

Figure 6. Shift from no conditioning to conditioning of the experimenter. The conditioning process is more or less achieved; this is mathematically translated by varying the degree of independence of the future events to be observed by *O* and *O'*. The change of the parameter d from pq to 0 is therefore an assessment of the experimenter's conditioning to expect a pattern (a relationship). When $d = pq$, the experimental outcome is a property of *S* alone (no conditioning) and, when $d = 0$, the experimental outcome is a property of *O-S* taken as whole (conditioning of experimenter).

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Application to "memory of water" experiments. The consequences of the degree of conditioning of the experimenter described in this section finds particular resonance in "memory of water" experiments through the reproducibility issue which was a major concern. Needless to insist on the difficulties to make reproduce the experiments by other teams but – even in Benveniste's laboratory – it was a common lore that some experimenters were more "gifted" than others [1, 25, 26]. Thus, in a series of blind experiments with basophils published in 1991 by Benveniste's team, a statistically significant difference in favour of a biological effect of high dilution was reported. However, this conclusion rested on the results from only one of the two experimenters who participated to the study [1, 27]. Interestingly, the experimenter who obtained significant results was the more experienced.

Another example is the robot analyser built by Benveniste's team in order to perform automatically experiments based on plasma coagulation. In these experiments that provided clear-cut results, the "molecular signature" of an anticoagulant drug recorded on the hard disk of a computer was supposed to be "transmitted" by an electromagnetic field to water samples and then added to plasma in order to inhibit the coagulation process [1]. This robot was precisely built to minimize a possible interference of the experimenter with the on-going experiment. Thus, "inactive" and "active" files were randomly chosen by the computer and were masked to the experimenter until the experiment was finished. The intervention of the experimenter was limited to the supply of consumables and the start button. In 2001, the robot analyser has been evaluated by a multidisciplinary team mandate on behalf of the United States Defense Advanced Research Projects Agency (DARPA). These experts concluded that they observed some effects supporting the concepts of "digital biology" when the scientist from Benveniste's team who was dedicated to this research was present. However, the experts were unable to reproduce these results after the team left [25]. Of interest, the experts suggested that an experimenter effect could be the cause of these curious results, but in the absence of a theoretical framework, they stated that they could not go further.

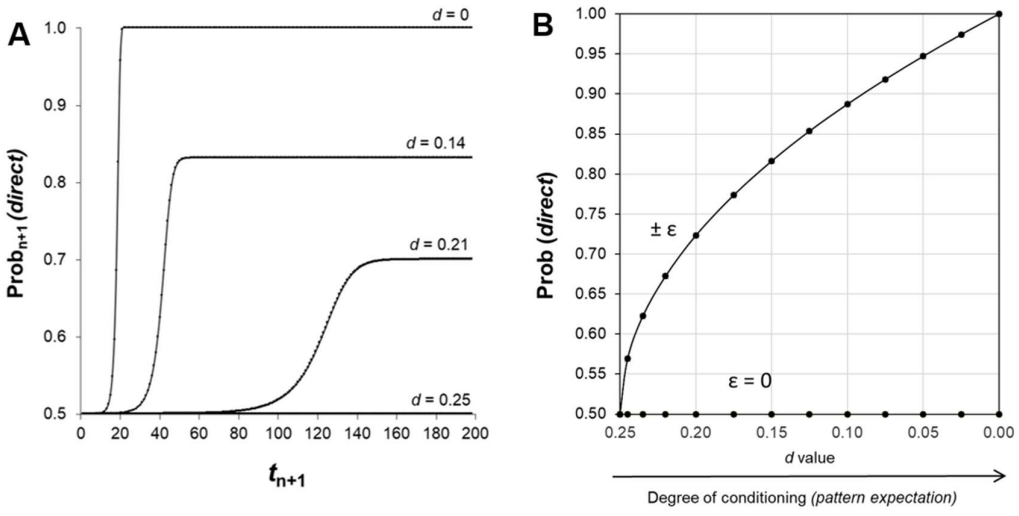

Figure 7. Experimenter's conditioning as a stepwise learning process. The probabilities of Prob (*direct*) achieved with different value of *d* from 1/4 to 0 are calculated in panel **A**. The maximal values achieved by Prob (*direct*) as a function of the value of *d* is depicted in panel **B**. In the absence of probability fluctuations ($\varepsilon = 0$) or if $d = p_0 q_0 = 1/4$, Prob (*direct*) = 1/2, thus meaning that there is no relationship between "labels" and system states. Only with probability fluctuations ($\pm \varepsilon$) and with values of $d \neq 0$, correlations between "labels" and system states emerge as a function of *d* value. For simplicity, only data corresponding for *L1* as "inactive" label are shown.

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9. Discussion

Modelling and Benveniste's experiments. The strong point of this modelling is that all features of Benveniste's experiments are described: 1) emergence of an "activated state" from the background noise of a biological system without local cause; 2) correlations between "labels" and system states; 3) mismatches of outcomes in blind experiments with an outside supervisor. It is important to insist that these characteristics emerge from the formalism and are not *ad hoc* hypotheses. The modelling rests on reasonable assumptions about the measurement process of a biological experiment aimed to establish an elementary dose-response. Classical conditioning is also a plausible hypothesis. Moreover, the conditioning is self-sustained since the observation of the expected pattern reinforces it. Indeed, the more significant correlations are recorded by the experimenter, the more these correlations have a chance to be recorded in the next experiments.

Quantum-like structure. The quantum-like structure of the formalism was not postulated as a prerequisite of the modelling and it emerges from classical probabilities. In this sense, we may say with humour that the modelling is the consequence of the unexpected meeting of Pavlov's dog with Schrödinger's cat.

The quantum-like structure of the modelling has its roots in an outcome that does not preexist to its observation. The outcome of the measurement of a quantum "object" also does not pre-exist *(e.g.* the spin value of an electron). The "quantum-like object" in the modelling is constituted by the "superposition" of the expected outcomes (direct relationship *and* reverse relationship). From the outside standpoint of *O',* after the experimenter *O* measures *S*, the "superposed" state is transferred to *O-S* taken as a whole. When *O'* measures *O-S,* there is a transition from the "superposed" state towards a stable state (direct relationship *or* reverse relationship). This transition plays a role comparable to the decoherence process during a quantum measurement.

The modelling is in line with interpretations of quantum physics where the outcome of any measurement is described relatively to an observer (*e.g.* relational interpretation of Rovelli or quantum Bayesianism [28, 29]). Thus, for an outside observer *O''* who remains uninvolved in the measurement process, *O-O'-S* taken as a whole is in a superposed state (even after *O'* has observed *O-S*) and *O, O'* and *S* are entangled. Thus, from the point of view of *O''*, the states of *O* and *O'* before interaction could be written as $(O_d + O_r) \times (O'_d + O'_r)$ (independent states of *O* and *O'*); after interaction, these states become $O'_dO_d + O'_rO_r$ (correlated or entangled states). Note that the correlations between "labels" and system states (direct and reverse relationships) are not due to a selection of "favourable" cases, but to the elimination of impossible configurations required by the intersubjective agreement.

Gestalt psychology and quantum structure. The modelling has some common points with Gestalt psychology [30]. This theory states that the human mind perceives objects as a whole or a form (Gestalt) and not as the simple sum of their constitutive parts. This whole has its own independent existence. Necker cube is an example of the perception of a two-dimension design as a three-dimension Gestalt (**Figure 8**). Of interest, this three-dimension configuration "exists" only for an observer. Therefore, the "cube" is not a property of the two-dimension sheet alone where a two-dimension picture has been drawn, but is a property of the sheet and the observer taken as a whole. The three-dimension "cube" does not preexist to its observation but is created at the very moment of its observation. The link between our modelling with quantum structure and Gestalt psychology is not fortuitous. Indeed, as pointed out by Amann, there is a relationship between quantum physics and Gestalt concepts: *"Similarly as with the Gestalt concept, the shape of a quantum object does not a priori exist but it depends on the interaction of this quantum object with the environment (for example: an observer or a measurement apparatus). Quantum mechanics and Gestalt perception are organized in a holistic way. Subentities do not necessarily exist in a distinct, individual sense"* [31].

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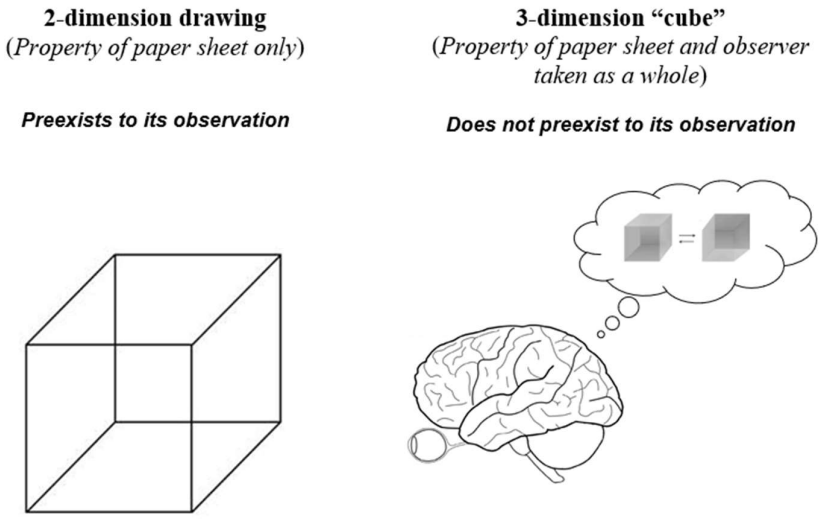

Figure 8. Necker cube as an example of pattern expectation after learning. Necker cube is a 2-dimension drawing that is perceived as a 3-dimension volume as a consequence of learning at an early age. Due to the ambiguous drawing, perception from top and bottom alternate (only one of the two patterns can be "seen" at one time) (**A**). The 2-dimension drawing is a property of the paper sheet alone, whereas the interaction of the observer with the 2-dimension drawing literally "creates" the 3-dimension cube that does not preexist to its observation. As Necker cube with top/bottom configurations, direct/reverse relationships are perceived as patterns after learning (through classical conditioning). Both three-dimensional Necker cube and relationships (between "labels" and system states) are constructs of observer's mind which consider them in their wholeness and not as the simple sum of their individual components (**B**). Mixtures of the two relationships are possible (half direct and half reverse relationships), but each relationship is always perceived or expected in its wholeness by the conditioned experimenter.

In previous studies, the mathematical formalism of quantum physics has been applied to some cognitive processes and quantum-like models of information processing have been developed. Thus, it has been shown that some cognitive processes related to decision-making, language, memory, judgment, reasoning or perception could not be described with classical probabilities, but required quantum mathematical tools [32]. Our modelling suggests that some cognitive processes (namely classical conditioning) with an underlying quantum structure may extent to external devices spatially separated from the observer.

Consequences of blinding. With this modelling, the consequences of "external" blinding that disturbed so much Benveniste's team are easily explained. It is important to underscore that the relationship between "labels" and system states in this setting is not a local causal relationship ("labels" and states are just coincident events). Indeed, if these correlations are forced into a causal relationship (for example, to send a message or to give an order), the correlations vanish and the outcomes become evenly distributed among labels. This is precisely what happened with Benveniste's proof-of-concept experiments with outside supervisors when the results seemed to become crazy. These apparent "jumps of activity" among test samples were not due to external disturbances but were intrinsic to the phenomenon at work.

Mathematically, the calculation of the probabilities without external supervisor is like a superposition in quantum physics: probability amplitudes are added and the sum is squared. In

contrast, with an outside supervisor, the calculation is like a mixture: the individual probability amplitudes are squared and then summed up.

Note that an outside supervisor is not immune of conditioning. In order to avoid conditioning, the outside supervisor should be systematically replaced for series of experiments.

Application of the modelling to other situations. The modelling constructed to describe Benveniste's experiments and more generally experiments related to "memory of water" could be extended to other experimental situations in medicine, biology or psychology where repetitions of experiments by the experimenters lead possibly to their conditioning. Alternative medicines such as homeopathy or placebo effect are examples where this modelling could be applied [33]. As depicted in this article, this structuration of observer's mind could interfere in the observations and measurements. In such a situation, the experimenters are trapped into a circular process: they describe what they contribute to construct and they construct what contributes to their description. Moreover, the observation of the expected pattern reinforces the experimenter's conditioning. Although many other classical explanations are possible, such processes could be also at work in the reproducibility crisis reported in experimental biology, medicine and psychology [34]. As we have seen, there is nevertheless a possibility to detect and to avoid these unintended interferences of the experimenters with the experimental system that they describe. Generalizing the use of an outside supervisor in blind experiments is a method to confirm that an observed relationship is really causal.

In conclusion, this psychophysical modelling allows explaining the results of "memory of water" experiments without referring to water or another local cause. It could be extended to other scientific fields in biology, medicine and psychology when an experimenter effect is suspected.

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