From "Water Memory" to Experimenter-System Coupling: A Contextual Probabilistic Model of Benveniste's Experiments

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ABSTRACT

Benveniste's experiments known in the lay press as the "water memory" phenomenon are generally considered to be a closed case. However, the amount of data generated by twenty years of well-conducted experiments prevents closing the file so simply. Indeed, if Benveniste failed to persuade his peers of the value of his experiments, it was mainly because of a stumbling block, namely the difficulty of convincingly proving the causal relationship between the supposed cause ("informed water") and the experimental outcomes in different biological models. To progress in the understanding of this phenomenon, we abandon the idea of any role of water in these experiments ("water memory" and its avatars). Here, we propose a probabilistic framework which, rather than focusing solely on the biological system, describes the experimental outcomes as emerging from a global configuration that includes the biological system and the experimenter, embedded in the informational context of the laboratory. The experimenter, conditioned by past "classical" experiments, is a key element of the model. Together, these results suggest that these experiments may reflect a context-dependent organization of probabilities, rather than a violation of standard biological or physical principles. Therefore, this model provides an alternative explanation to Benveniste's experiments where water plays no role and where the place of the experimenter is central. More broadly, this highlights how experimental outcomes can depend on the global structure of the experimental setting, opening new perspectives at the interface between biology, statistics and the theory of complex systems.

Keywords: *Water memory*; *High dilutions*; *Scientific controversy; Quantum-like model; Experimenter effect.*

1. Introduction

Serendipity has been defined as the act of making an unexpected discovery by chance [1]. The history of science is full of such chance discoveries as X-rays, radioactivity or penicillin. In this article, we will see why Benveniste's experiments, also known in the lay press as the "water memory" phenomenon, could be a new example of serendipity.

The purpose of this article is not to tell again the entire story with all the details of the scientific debate and controversies that can be found elsewhere. A complete and systematic account of this case has been published by the author in a freely available text, both in a French version [2] and in its English translation [3]. Other points of views can be found in several books or articles [4-12]. The present article is hoped to be an element to reach a constructive conclusion and, more importantly, to open new horizons.

It is important to remember that the experiments we are talking about were spread over almost 20 years (from 1983 to Benveniste's death in 2003). This saga is too often reduced to the famous controversy with the journal *Nature* in 1988 [13-15]. Moreover, before this controversy, Benveniste had a position in the scientific community that was far from marginal. His research unit was affiliated with INSERM, the French national medical research institution, and Benveniste himself was recognized internationally. The original idea to test extreme dilutions was not from Benveniste himself who, as a good Cartesian, was rather reluctant initially to test homeopathic medicines, but was nevertheless open to countercurrent ideas. Indeed, homeopathy is an alternative medicine which, to put it mildly, is based on ideas from another time and has never proven its efficacy. B. Poitevin who was a thesis student at that time was also involved in the practice of homeopathy and proposed to Benveniste collaborations with the homeopathy industry [3, 7]. Thus, the famous "Benveniste's experiments" were initially nothing more than research contracts with homeopathy firms aimed to evaluate some homeopathic medications. It is important to notice that Benveniste's team was not the first to test homeopathic medications. What was probably new was that a renowned laboratory from a public research institution managed such a research topic and that Benveniste did not hesitate to promote the high-dilution issue into the academic debate.

In the former experiments (years 1983–1991), high dilutions of various preparations were tested on human basophils which are cells involved in allergic disorders. Some of the diluted compounds were used in homeopathic practice, but others were not homeopathic medications (antibodies, for example). The hypothesis behind these first experiments performed in the 1980s was that a drug or a biologically-active compound could apparently continue to manifest some activity after being highly diluted. Obtaining a specific effect on a biological model with high dilutions was theoretically impossible given physicochemical laws. To get an idea, less than one molecule of antibody was theoretically present in the assay after about fifteen serial ten-fold dilutions of the initial sample. Therefore, the first positive results were received with surprise and skepticism in the laboratory, including Benveniste himself.

However, the basophil model needed fastidious and time-consuming counting under a microscope by trained experimenters and required a number of tricks to avoid pitfalls. In addition, the controversy with the journal *Nature* prompted Benveniste to consider other biological models. A physiological model already in use in the laboratory, namely the isolated rodent heart, appeared to be promising (years 1992–1998). Changes in the state of this biological model (coronary flow variations) could be followed live by observers and this new model was therefore more convincing and demonstrative than the basophil model. The results with high dilutions of various compounds were confirmed using the isolated rodent heart model [3].

After high dilutions, Benveniste developed from the year 1992 different devices based on electromagnetism and made of electric coils and electronic amplifiers which were supposed to "transfer the activity" of biologically-active molecules directly to water samples without the dilution process [3, 16-21]. The "transmission" experiments were also supposed to avoid contaminations that could be responsible for the observed effects. In a further refinement, Benveniste obtained in 1995 experimental data suggesting that the "activity" issued from a biologically-active solution could be captured and stored in a computer memory. The electric current that passed through a coil surrounding a biologically-active sample was supposed to be modulated by an electromagnetic emission from the sample and was digitized before being stored in a computer file. Then the "biological activity" recorded in the file could be diffused via an electric coil to a water sample initially devoid of any "information". In another variation of this device, the diffusion of the "biological activity" was done directly to the biological system via the electric coil without intermediate water sample. Benveniste coined at this occasion the term of "digital biology". These new developments and his new ideas about a future breakthrough in biology and medicine thanks to "digital biology" further isolated Benveniste from the scientific community and caused him to lose his early supports.

The isolated heart rodent model, however, appeared to be difficult to export into other laboratories because few teams had the experience to use it routinely. Benveniste then developed experiments based on plasma (or fibrinogen) coagulation that could be easily performed in most laboratories (years 1999–2001). This experimental model offered also the possibility of being completely automated. A robot that performed all steps of an experiment, including the random selection of experimental conditions and processing of biological samples, was thus developed. Again, the successful results obtained with this new device convinced Benveniste that he was on the right track. This robot attracted the attention of the US Defense Advanced Research Projects Agency (DARPA), which commissioned an expertise [22]. We will talk of the results of this expertise in the discussion section.

However, if these astonishing results were so obvious, why did Benveniste fail to convince his peers? The main reason was that he could not get rid of a strange phenomenon that literally poisoned his experiments, in particular when he tried to carry out proof-of-concept experiments involving other researchers he wanted to convince. In Section 3, we will see what this stumbling block was and why it systematically and constantly stopped Benveniste in his race to the "decisive experiment". But first, we need some conventions and definitions to describe these experiments.

2. Causal relationships in experimental biology

Suppose that we are interested in a parameter of a biological experimental system that we study in the laboratory in various experimental conditions. A change of this parameter during an experiment is noted Δ^+ while no change is noted Δ^0. Experimental conditions are either control condition (noted C) or test condition (noted T). If we notice that C is always associated to Δ^0 and that T is always associated to Δ^+, we conclude that a relationship exists between the experimental conditions (designated by the *labels* C and T) and the biological system states (Δ^0 and Δ^+ obtained after measurement).

By convention, we name "direct" the relationship that associates C with Δ^0 or T with Δ^+; the "reverse" relationship associates C with Δ^+ or T with Δ^0.

In experimental biology, the principle of locality, which states that a physical object is only influenced by its immediate environment, is always implicit. As a matter of fact, most biologists do not even imagine that other types of relationships could be involved or simply envisioned. In Benveniste's experiments, the principle of locality was also implicit since the supposed causes ("structured water" or electromagnetic fields) were thought to exert their effects locally. But are local cause-and-effect relationships the only ones possible? A clue is provided by the results of Benveniste's experiments themselves as we will see in the next section.

3. When the scientific interest is not where it was supposed to be

We must now explain in detail why the field of research based on "water memory" or "digital biology" was blocked in its development despite well-conducted experiments and seemingly convincing results. In short, the central problem was the difficulty of proving the causal nature of the relationship observed between experimental conditions and states of the biological system. Another reason, which is related to it as we shall see, was the difficulty of having these experiments replicated by independent teams.

First, we will explain why Benveniste was convinced, with sound arguments, that he had discovered "something". For this purpose, we will describe three experimental settings: open-label experiments, internal blinding and external blinding (**Figure 1**).

The experiments described below are summarized largely for the purposes of this article. If needed, additional details can be found elsewhere [2, 3].

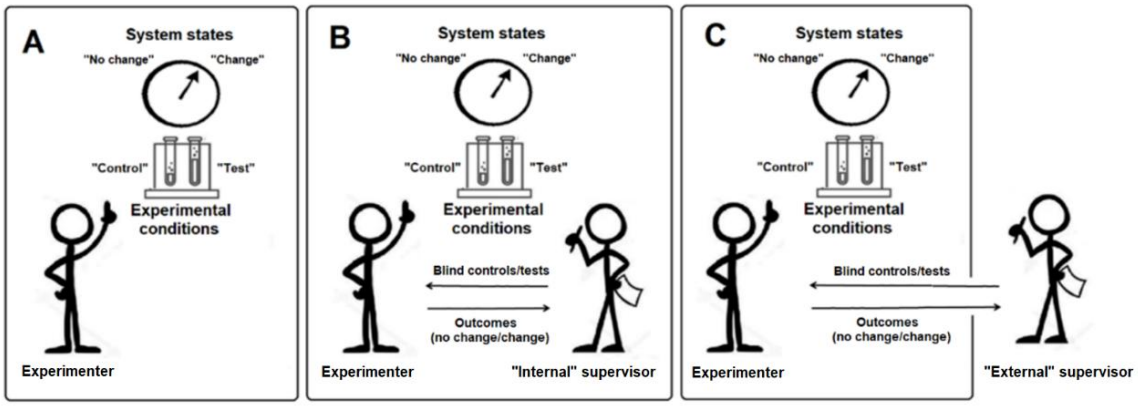

Figure 1. Configurations for (A) open-label, (B) "internally" blinded and (C) "externally" blinded experiments. The "internal" or "external" supervisor provides the experimenter with "control" and "test" samples whose labels have been masked (blind controls/tests). After the experiment is done, the experimenter returns to the supervisor the outcomes which have been obtained (change or no change of biological system state noted Δ^0 and Δ^+, respectively) for each control or test. The supervisor assesses the rate of "success" of the experiment (*i.e.* how many direct relationships have been obtained with the masked samples: "control" associated with "no change" or "test" associated with "change").

Open-label experiments. **Figure 2** reports results on two devices that were used in parallel in 1992–1996. There was no blinding between the two measurements; these duplicate experiments were done in order to confirm the outcomes. To analyze these results, we do not care of the nature of the samples tested (C or T, high dilutions, electronic transmission, etc.) We only consider the concordance of the outcomes obtained with the two devices. We observe a high correlation of these measurement (the most probable pairs of outcomes are Δ^0/Δ^0 and Δ^+/Δ^+). The important point is for the pairs Δ^+/Δ^+. Indeed, these correlated pairs are a strong argument in favor of Benveniste's theses. They indicate that there is "something" that occurs in these experiments. Whether one agrees or not with Benveniste's views on the interpretation of these experiments, the *source of correlations* needs to be explored. This is precisely the purpose of the present article.

Internal blinding. The data of **Table 1** indicate that these correlations persist after an internal blinding. Internal blinding means a blinding of labels of the samples to be tested (controls and tests) by a colleague who interacts with the experimenter in the laboratory (**Figure 1**). These data show that the pairs C/Δ^0 and T/Δ^+ are the most probable, thus strongly suggesting a direct relationship between labels and biological system states. Again, we understand why Benveniste defended his research with determination and why he could not resign himself to forgetting his results in a drawer as many suggested he should do [3].

External blinding. To share his experimental results and to convince his peers, Benveniste organized "public demonstrations" carried out in the presence of an audience of colleagues and observers who did not belong to the laboratory. These demonstrations were designed in order to give a "definitive" confirmation on the reality of these experiments and to establish their scientific interest. For this purpose, an experimental protocol was written and then a study report with all raw data was shared with participants [3]. During a typical session of demonstration, controls and tests were prepared (either high dilutions for the early demonstrations or computer files later) in another laboratory than Benveniste's laboratory. These samples were prepared under supervision of all participants. Then, the labels of the control and test samples were replaced by a code by

participants not belonging to Benveniste's laboratory. Some samples were also kept unblinded to check that everything was fine in non-blinded conditions. Then, Benveniste's team recovered all samples and tested them in its laboratory within the next days. After all measurements had been done, the outcomes (Δ^0 and Δ^+) corresponding to all blind samples were sent to the external supervisor who detained the code (**Figure 1**). This supervisor compared the two lists: list of labels (C vs. T) under a code name and list of outcomes (Δ^0 vs. Δ^+) and assessed whether outcomes were as expected (C associated to Δ^0 and T associated to Δ^+).

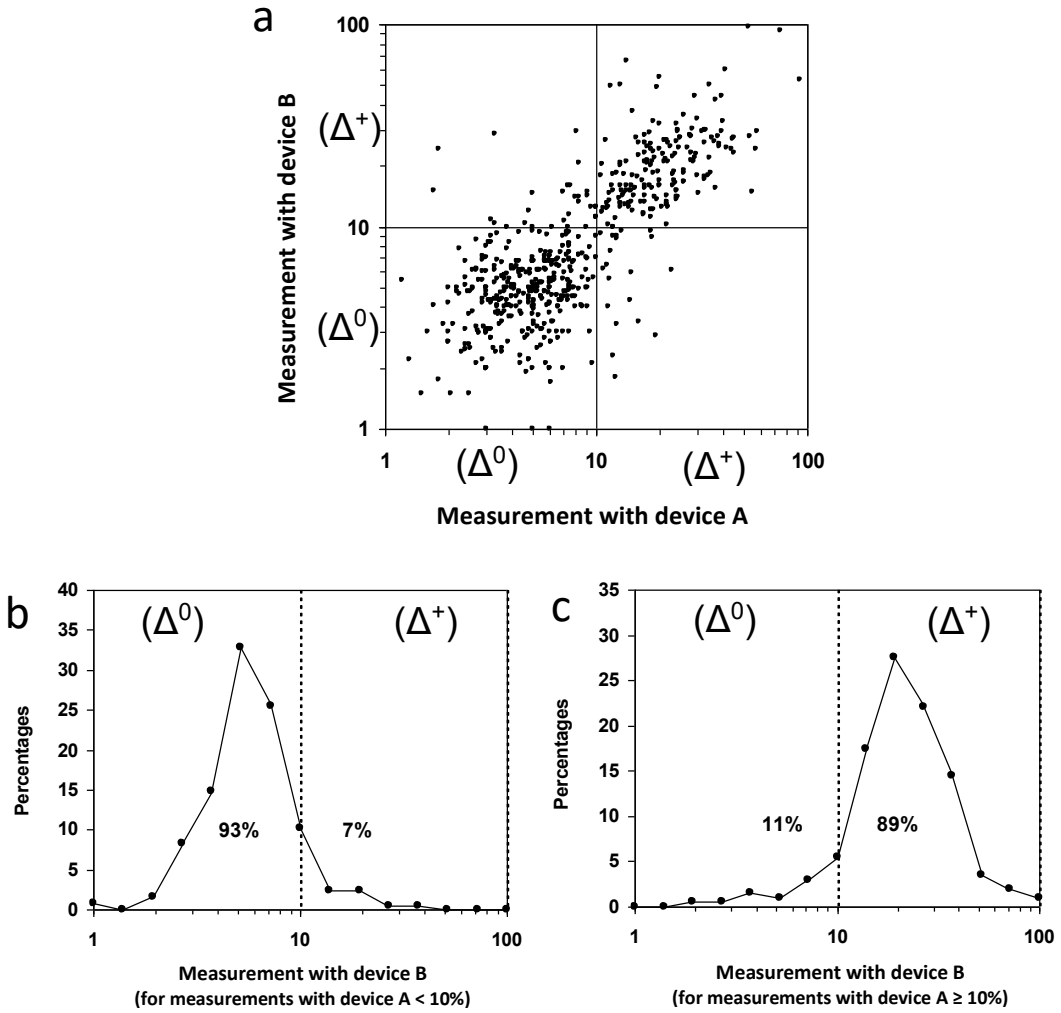

Figure 2. Open-label experiments made in duplicate on two experimental systems (dates: 1992–1996; experimental model: changes of coronary flow in isolated rodent heart; N=574 pairs of measurements) [23]. (a) In this figure we do not care about the label (control or test), only the concordance of the system biological states (Δ^0 or Δ^+) on the two devices matters. We also do not care of the method used by Benveniste's team to produce controls and tests (high dilutions, electronic transmission, digital biology, etc.) The data obtained in devices A and B appear to be highly correlated. (b) If the value measured on the device A is < 10% (no change; Δ^0), then the probability of a value < 10% on device B is 0.93. (c) If the value measured on the device A is ≥10% (change; Δ^+), then the probability of a value ≥ 10% on device B is 0.89. Note that scales are logarithmic.

Table 1. Experiments with internal blinding (dates: 1993–1997; experimental model: changes of coronary flow in isolated rodent heart) [23].

Experimental situations	N	System states after internal blinding	
		No change (Δ^0)	Change (Δ^+)
Interim blinding between 1st and 2nd measurement of the same sample			
No change (Δ^0) for 1st measurement	50	**96%** (2nd measurement)	4% (2nd measurement)
Change (Δ^+) for 1st measurement	28	7% (2nd measurement)	**93%** (2nd measurement)
Blind labels			
Label "Control"	68	**88%**	12%
Label "Test"	58	19%	**81%**

Table 2. "Digital biology" experiments with external blinding (dates: 1996-1997; experimental model: changes of coronary flow in isolated rodent heart) [3]. In these experiments (public demonstrations with external supervisor), system states are distributed at random in contrast with open-label or internal blinding experiments presented in Figure 2 and Table 1). Therefore, no relationship can be established between labels and system states. If a causal relationship existed, one would expect square labels to be superimposed on round labels of the same color. These "mismatches" were considered by Benveniste as experimental failures. In the present analysis, we consider that "successful" and "failed" experiments are the two faces of the same phenomenon. Note that the observation of changes of state (noted ●), whatever their place, requires an explanation. Indeed, according to current scientific knowledge, we would expect to observe *only no change of biological system state* (○-○-○-○-○-○-○, etc.) The scientific context and the experimental details of these experiments can be found in [3].

February 27, 1996	Labels (□ = C, ■ = T)	□-■-■-□-■-□-■-□-■-□-■-■-■-■-■-■-■-□
	States (○ = Δ^0, ● = Δ^+)	●-○-●-●-●-○-●-●-○-●-●-○-●-●-○-●-●-○
May 7, 1996	Labels (□ = C, ■ = T)	■-□-■-□-□-■-□-■-□-■
	States (○ = Δ^0, ● = Δ^+)	○-●-○-●-○-●-○-●-○-●
June 12, 1996* (two parts)	Labels (□ = C, ■ = T)	□-□-■-□-■-■-■-■ / ■-□-■-■-■-■-□-□
	States (○ = Δ^0, ● = Δ^+)	○-●-○-○-●-○-○-● / ●-○-○-●-○-○-●-○
September 30, 1996*	Labels (□ = C, ■ = T)	■-□-□-□-□-■-■-□-□
	States (○ = Δ^0, ● = Δ^+)	○-●-●-○-●-●-○-○-●
November 4, 1996	Labels (□ = C, ■ = T)	■-■-□-■-■-□-■-□-□-□
	States (○ = Δ^0, ● = Δ^+)	●-○-○-●-○-○-○-●-○-●
December 4, 1996*	Labels (□ = C, ■ = T)	□-■-■-□-□-■-□
	States (○ = Δ^0, ● = Δ^+)	●-○-○-○-●-○-●
September 27, 1997*	Labels (□ = C, ■ = T)	□-□-■-□-□-□-■-■-■-■
	States (○ = Δ^0, ● = Δ^+)	●-○-●-○-●-●-○-○-●-●

* The number of controls and tests to be evaluated was not known from the experimenter.

There was an internal blinding between the series of measurements for all these experiments (except November 4, 1996) to verify the consistency of the outcomes. Note that experiments done in 1996 were performed on two apparatus to confirm results as described in Figure 2.

A series of experiments with external blinding is presented in **Table 2**. It is easy to see that the relationship between labels and biological system states was lost in the experiments with external blinding. Indeed, in this table, square labels are not superimposed on round labels of the same color but distributed at random. There was still an "effect", *i.e.* the observation of changes of biological system state (Δ^+), but not at the place where they were supposed to be.

To explain these oddities, Benveniste put forward various hypotheses (human errors for label allocation, water contamination, electromagnetic pollution, "remnant activity" in the apparatus, spontaneous "jumps of activity" from one sample to another, etc.) These mismatches prompted a technological race in which Benveniste engaged to rule out these supposedly disturbing external events. In contrast, in the present analysis, we consider that "successes" with open-label/internal blinding experiments (A and B in **Figure 1**) and "failures" with external blinding experiments (C in **Figure 1**) are the two faces of the same phenomenon. Actually, we think that these disturbing events are the scientific fact of this story. One important point must again be stressed. If Benveniste's experiments were of no scientific interest, *no change at all* of the biological system state should be observed, whatever the experimental conditions.

In summary, there were experimental arguments in favor of Benveniste's statements: appearance of a "signal" (variation of a biological parameter) in various experimental biological systems, numerous consistent results (highly significant correlations) and success in blind experiments (with an "internal" supervisor).

The arguments against were as follows: numerous incompatibilities with well-established physics laws (high dilutions, "memory of water", "digital biology", etc.), difficulty in reproducing the experiments by other teams and failure of blind experiments with an "external" supervisor.

4. A probabilistic model of experimental configurations

4.1 Introduction

To consider all these aspects of Benveniste's experiments, *i.e.* both "successes" and "failures", we propose to abandon the idea of any role of water or electromagnetic waves. We consider that all various procedures for diluting solutions or electronic stuff aimed to "transfer biological activity" make no sense. We state that they have no more value than a ritual or meaningless gesticulations.

Consequently, we state that the "experimental conditions" (control or test) do not originate in the physical world, but are only "labels" whose meaning depends on the experimenter's cognitive states.

In addition, in the proposed framework, the relevant unit of analysis is not the biological system S alone, but the *coupled system* formed by the biological system S and the experimenter A, embedded in the informational context of the laboratory.

4.2 Configuration space and experimental variables

We consider a configuration space Ω whose elements ω represent complete experimental configurations. Each configuration includes:

(i) The state of the biological system S, described by two possible outcomes Δ^0 and Δ^+.

(ii) The experimental condition associated with the experimenter A, denoted C or T.

(iii) The degree of label information partitioned outside Ω (quantified by the parameter σ).

Under internal blinding, the label information is held by an internal supervisor B_{int}. Although not accessible by the experimenter, these variables remain part of Ω (**Figure 3**).

Under external blinding, the label information is held by an external agent (B_{ext}) outside Ω, introducing a structural partition. The parameter σ quantifies the degree of informational partition: $\sigma \approx 0$ when all variables are contained within Ω, and $\sigma \to 1$ when part of the information lies outside Ω.

Experimental observations are described as statistical properties of a probability distribution P defined over Ω (**Figure 3**).

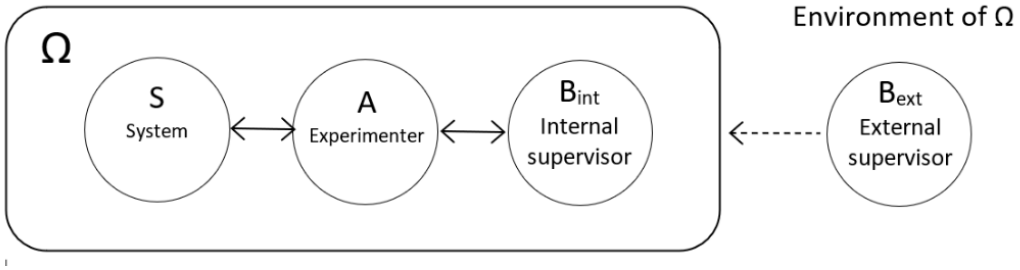

Figure 3. Conceptual structure of the experimental configuration space Ω. The configuration space Ω includes the biological system (S), the experimenter (A) and internal informational variables such as the internal supervisor (B_{int}). In open-label and internal blind conditions, all relevant informational variables are contained within Ω, even if not directly accessible to A. In contrast, under external blinding, the label information is held by an external agent (B_{ext}) outside Ω, introducing a structural partition.

4.3 Geometric representation of dichotomous variables

We consider two binary variables:

- The state of the biological system S: Δ^0 (no change) or Δ^+ (change)
- The experimental condition associated with A: C (control) or T (test).

Each binary distribution can be represented geometrically by taking the square roots of probabilities (**Figure 4**).

- For the biological system: $P(\Delta^0) = a^2$ and $P(\Delta^+) = b^2$, with $a^2 + b^2 = 1$; we define the system vector: $\vec{S} = (a, b)$.
- For the experimenter: $P(\mathrm{C}) = \cos^2\theta$ and $P(\mathrm{T}) = \sin^2\theta$; we define the experimenter vector: $\vec{A} = (\cos\theta, \sin\theta)$.

These two vectors lie on the unit circle and encode the marginal distributions of S and A. Their scalar product: $\vec{S}.\vec{A} = a.\cos\theta + b.\sin\theta$ measures the alignment between the two distributions. This representation is purely geometric. It does not imply any underlying wave or quantum structure, but provides a minimal way to capture statistical coupling between contributions without introducing additional parameters.

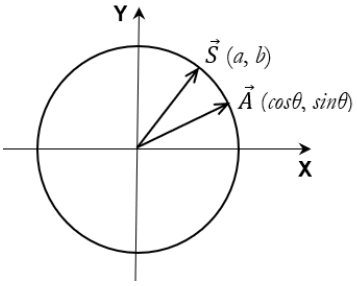

Figure 4. Vectorial representation of dichotomic probabilities on unit circle. $\vec{S}$ is the vector for the biological system which has two possible states: no change (Δ^0) and change (Δ^+) with respective probabilities a^2 and b^2 with $a^2 + b^2 = 1$; $\vec{A}$ is the vector for the experimenter which has two possible states: control (C) and test (T) with respective probabilities $\cos^2\theta$ and $\sin^2\theta$, with $\cos^2\theta + \sin^2\theta = 1$.

4.4 Combination of contributions and statistical coupling

We focus on the probability of a *direct relationship*, defined as: (C, Δ^0) or (T, Δ^+).

This joint event can be decomposed into two contributions:

- D1: (Δ^0, C) with probability $a^2.\cos^2\theta$
- D2: (Δ^+, T) with probability $b^2.\sin^2\theta$

We introduce the corresponding amplitudes (square roots of probabilities) of the two contributions:

$\pi_1 = a.\cos\theta$ and $\pi_2 = b.\sin\theta$

The total probability of the direct relationship depends on how these contributions combine within the probability distribution over Ω. Two regimes can be described:

The scalar product $\vec{S}.\vec{A} = a.\cos\theta + b.\sin\theta$, which measures the alignment between the vectors $\vec{S}$ and $\vec{A}$, is the sum of the amplitudes of the two contributions D1 and D2.

Therefore, the probability of a direct relationship is:

$P(direct) = (\vec{S}.\vec{A})^2 = (a.\cos\theta + b.\sin\theta)^2 = a^2.\cos^2\theta + b^2.\sin^2\theta + 2ab\cos\theta\sin\theta$

In the absence of statistical coupling between the contributions, the total probability reduces to the sum of the *independent terms*:

$P(direct) = a^2.\cos^2\theta + b^2.\sin^2\theta = \pi_1^2 + \pi_2^2$

To describe situations intermediate between the two regimes (perfect coupling and independent contributions), we introduce a parameter $\sigma \in [0, 1]$:

$P_\sigma(direct) = (a.\cos\theta + b.\sin\theta)^2 - \sigma.2ab\cos\theta\sin\theta = (\pi_1 + \pi_2)^2 - \sigma.2\pi_1\pi_2$

The parameter σ does not act on the biological system *S*, nor on the realization of configurations, but only on the statistical structure of the probability distribution over Ω. It controls the degree of coupling between *S* and *A*:

- When $\sigma = 0$, the cross-term is maximal and the probability becomes:
  $P_0(direct) = (\pi_1 + \pi_2)^2$
- When $\sigma = 1$, the cross-term vanishes and classical additivity of probabilities is recovered:
  $P_1(direct) = \pi_1^2 + \pi_2^2$

4.5 Conditioning dynamics of the experimenter

The previous construction becomes physically meaningful when a dynamical conditioning process is taken into account.

The conditioning evolves as the experimenter interacts with the biological system in *standard experiments*. By "standard", we mean an experiment with a local cause involving genuine physical causes (*e.g.*, molecules of a biologically-active compound added to the biological system).

We model this evolution as a gradual adjustment that increases the probability of observing a direct relationship. Formally, this can be described as a gradient ascent on $P_0(direct)$:

$$\theta_{n+1} = \theta_n + \eta.\partial P_0(direct)/\partial\theta$$

where $\eta > 0$ is a learning rate.

Using $P_0(direct) = (a.\cos\theta + b.\sin\theta)^2$, we obtain:

$\partial P_0(direct)/\partial\theta = 2(a.\cos\theta + b.\sin\theta)(b.\cos\theta - a.\sin\theta)$

The evolution converges toward the angle $\theta^* = \arctan(b/a)$ (**Figure 5**). At this point $\cos\theta^* = a$ and $\sin\theta^* = b$ so that the experimenter vector aligns with the biological system vector: $\vec{A} \rightarrow \vec{S}$ and $P_0\ (direct) \rightarrow 1$.

This limiting case corresponds to an idealized regime in which the statistical weights of the contributing configurations become maximally aligned within the probability distribution over Ω.

The conditioning process defines the formation of the aligned regime, independently of the value of σ (**Figure 6**).

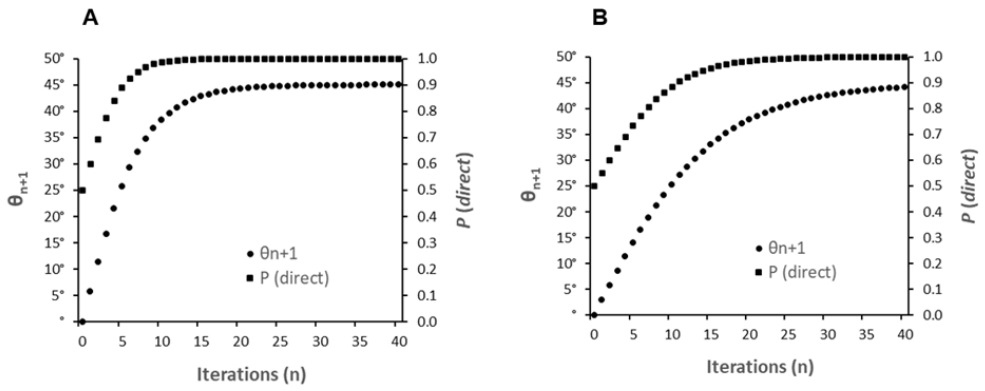

Figure 5. Evolution of θ and $P\,(direct)$ during the conditioning process. The parameters are $a = b = 1/\sqrt{2}$ and $\eta = 0.1$ in left panel and $\eta = 0.05$ in right panel. In both figures, θ increases steadily from 0 to $\theta^*=45°$ ($\pi/4$) and $P\,(direct)$ from 0.5 to 1. The plateau is reached more quickly when the learning rate η is higher.

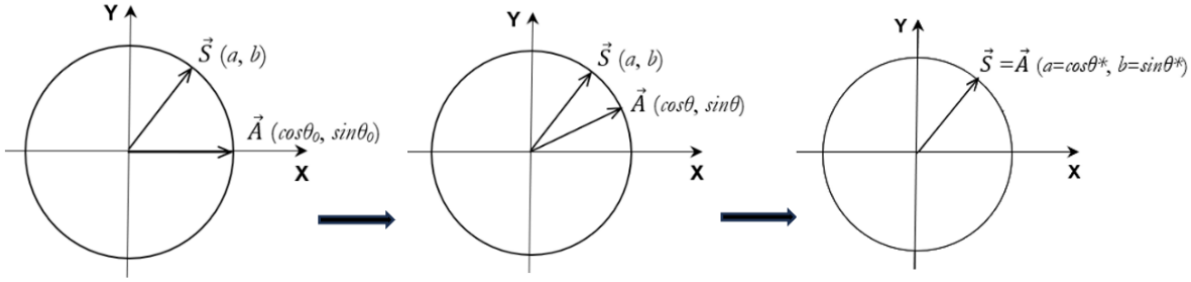

Figure 6. Alignment of the experimenter vector $\vec{A}$ with the biological system vector $\vec{S}$ through conditioning. The observation of experiments in which a real physical cause (a biologically active molecule at a known concentration) produces a measurable effect on the biological system. In these experiments, *A* repeatedly observes that state Δ^+ occurs generally when an active compound is added (condition T), and rarely when nothing is added (condition C).

4.6 Role of informational partition (parameter σ)

The parameter σ reflects how the informational structure of the experiment modifies the probability distribution over Ω. It does not describe a physical property of the biological system *S*, but a structural property of the experimental context.

- When $\sigma = 0$ (open-label or internal blind conditions), all relevant informational variables are contained within the same configuration space Ω, even if they are not directly accessible to the experimenter.
- When $\sigma = 1$, part of the information (the labels) is held by an external supervisor (B_{ext}) and is not accessible within Ω. In this case, σ suppresses the coupling between variables without modifying the underlying probability weights.

More generally, σ defines a continuous transition between these two regimes. The experimental protocol does not change the set of possible configurations Ω, but modifies how these configurations are weighted probabilistically. This provides a unified interpretation of the three experimental situations: open-label and internal blind experiments ($\sigma \approx 0$; strong correlations) and external blind experiments ($\sigma \approx 1$; loss of correlations) within a single probabilistic framework.

Table 3 applies the formula $P_\sigma(direct) = (\pi_1 + \pi_2)^2 - \sigma.2\pi_1\pi_2$ to Benveniste's three configurations.

Table 3. Summary of experimental configurations and their predicted *P* (*direct*) under the unified formula, at convergence ($\theta = \theta^*$, $\vec{A}$ aligned with $\vec{S}$).

Configuration	Supervisor	σ	$P_\sigma(direct)$	Observed pattern
Open-label	None	0	$(\pi_1 + \pi_2)^2 = 1$	Strong correlations
Internal blinding	B_{int}	0	$(\pi_1 + \pi_2)^2 = 1$	Correlations preserved
External blinding	B_{ext}	1	$\pi_1^2 + \pi_2^2 \approx 1/2$ [a]	Random associations

[a] If C and T have equal probability.

The consequences of the model are not fully intuitive and one could ask the following questions.

Why are correlations preserved under internal blinding?

Once the aligned regime is established, *i.e.* $P_0(direct) = (a.\cos\theta + b.\sin\theta)^2 = 1$, the corresponding probability structure is stable as long as all relevant informational variables remain within the same configuration space Ω. As a result, the statistical structure established through conditioning is preserved and strong correlations between biological system states and experimental conditions can still be observed. This persistence does not require any access to hidden information by the experimenter, but reflects the global organization of Ω.

How Δ^+ emerges from a low-probability background?

In baseline conditions, Δ^+ events are rare but exist and can be interpreted as *background fluctuations*.[1] However, when the alignment process described above takes place, the probability distribution over Ω is reorganized so that configurations associated with the direct relationship dominate. As a consequence, Δ^+ events, which initially had a low marginal probability, become statistically prominent within the aligned regime. This transition appears as an emergence from background noise, but is described here as a *redistribution of probabilities* driven by the global alignment of the biological system and the experimental context. Importantly, this increase in frequency is not tied to the experimenter's access to label information, but to the structure of the configuration space.

Why correlations disappear under external blinding?

When the label information is moved outside the configuration space (external blinding; $\sigma \rightarrow 1$), the probabilistic coupling between contributions is suppressed without modifying the underlying probability weights. In this regime, the joint distribution becomes effectively factorized, meaning that biological system states and experimental conditions behave as statistically independent variables and correlations between biological system states and experimental conditions disappear. However, this transition does not undo the prior reorganization of the probability distribution induced by conditioning. In this sense, σ does not control the emergence of the aligned regime, but only its observable relational structure. The marginal probability of Δ^+ remains elevated, even though its occurrence is no longer associated with the test labels. Thus, external blinding disrupts the relational structure of the distribution without restoring the baseline regime.

4.7 Complete model summary

The model is based on two key ingredients:

(i) A configuration space Ω that contains all relevant variables (system states, labels of experimental conditions, degree of information available on labels);

(ii) A dynamical conditioning process that drives the alignment of the system and the labels.

Together, these elements provide a unified framework in which:

(i) Strong correlations between system states and labels arise from alignment;

(ii) Their persistence under internal blinding follows from the inclusion of all variables within Ω;

(iii) Their disappearance under external blinding results from factorization;

(iv) The emergence of Δ^+ from background noise reflects a redistribution of probabilities within the aligned regime.

[1] All the systems used in Benveniste's experiments were biological systems and, as such, were subject to minute random fluctuations at rest. The transition from Δ^0 to Δ^+ was therefore a possible event in these systems as required by the model. This suggests that random systems that do not exhibit random fluctuations at rest such a die or a coin could not serve as substitutes for the biological system *S*.

5. Discussion

The present framework proposes a reinterpretation of Benveniste's experimental results based on the structure of the joint probability distribution describing the experimental configuration. Rather than invoking any physical transmission mechanism or anomalous property of water, the model assumes that the relevant unit of analysis is the global configuration space Ω, which includes the biological system, the experimenter and the informational context in which the experiment is embedded.

5.1 Operational definition of Ω and informational partition

A potential objection to the present framework concerns the apparent arbitrariness of the partition of the configuration space Ω into "internal" and "external" components. If such a partition were freely adjustable, the model could, in principle, be tuned post hoc to reproduce a wide range of observations, thereby weakening its explanatory value.

In the present approach, however, the partition of Ω is not a free modeling choice, but is operationally defined by the experimental protocol itself. More precisely, it is determined by the physical and informational localization of relevant variables, including the generation, storage, and accessibility of experimental labels, as well as the procedures governing randomization and data acquisition.

The distinction between open-label, internal blinding and external blinding corresponds to well-defined procedural configurations. In open-label and internally blinded experiments, all relevant informational variables remain within a single experimental environment, even if they are not directly accessible to the experimenter at the time of measurement. In contrast, external blinding introduces a physical and organizational separation, whereby key variables, such as the correspondence between labels and experimental conditions, are held by an independent system or agent outside the local experimental context. Within this framework, the parameter σ quantifies the degree of informational partition induced by these procedural differences. It should therefore be understood as an empirical property of the experimental configuration, rather than as an adjustable parameter introduced at the level of the model.

The case of fully automated experiments provides an important clarification. In these configurations, randomization, sample processing and measurement are carried out by a device without real-time human intervention. As a result, the notion of partition cannot be reduced to the cognitive state or expectations of the experimenter. Instead, it must be defined at the level of the entire experimental system, including the device, its programming and the localization of control variables. This supports the interpretation of Ω as a global configuration space encompassing both human and non-human components.

5.2 Absence of local causal influence

A central assumption of this approach is that no direct causal influence of the experimenter on the biological system is required to account for the observed correlations. In particular, no exchange of energy, signal, or information between the experimenter and the biological system is postulated. Instead, the correlations emerge from the statistical structure of the joint distribution defined over Ω. In this sense, the model departs from the standard local causal framework of experimental biology, while remaining fully compatible with established physical principles.

The key idea is that experimental outcomes reflect a selection of configurations within Ω whose statistical weights have been shaped by prior interactions between the experimenter and the system under standard experimental conditions. This conditioning process does not act on individual events, but on the organization of probabilities across the configuration space. This organization

should not be interpreted as an active influence of the experimenter, but as a statistical property of the joint configuration space Ω shaped by prior interactions.

5.3 Role of conditioning and alignment

The introduction of a dynamical conditioning process provides a mechanism by which the joint probability distribution becomes structured. Through repeated exposure to standard cause-and-effect relationships, the experimenter's effective probabilistic state becomes aligned with that of the biological system. In the model, this alignment corresponds to a configuration in which joint events consistent with a "direct" relationship, namely (C, Δ^0) and (T, Δ^+), become statistically dominant. Importantly, this alignment does not imply that the experimenter has access to hidden variables or that any information is transmitted during the experiment. Rather, it reflects a global organization of the probability distribution that persists even when the labels are no longer accessible to the experimenter, as in internally blinded conditions.

The expertise commissioned by DARPA in 2001 reported that an inhibition of coagulation by a digital signal was observed. However, they concluded that the alleged phenomenon of digital biology was not replicable [22]. Indeed, the report noted that the presence of Benveniste's experienced experimenter appeared to be necessary for the expected results to be observed, and that after the departure of Benveniste's team, no effect at all could be recorded by the robot analyzer. This observation, which the DARPA report described as evidence of unknown "experimenter factors", is precisely what the present model predicts. The DARPA outcome should be distinguished from external blinding in the strict sense. Under external blinding ($\sigma \to 1$), the conditioned experimenter remains present and the alignment of A with S is preserved, so that the marginal probability of Δ^+ may stay elevated even after correlations vanish (Section 5.4). In the DARPA scenario, by contrast, the conditioned experimenter is absent: with no aligned cognitive vector to draw the system out of baseline, Δ^+ events recover their unconditioned frequency. The "no effect at all" reported by DARPA is the expected consequence of removing the conditioning component itself.

5.4 Informational partition and loss of correlation

The parameter σ captures the effect of the experimental protocol on the structure of the probability distribution. It quantifies the degree to which relevant informational variables are partitioned outside the configuration space Ω. When all variables are included within Ω (open-label or internal blinding), the joint distribution retains its structured, coupled form and strong correlations are observed. In contrast, when part of the information (such as the labels) is held by an external agent, the distribution becomes effectively factorized. This corresponds to σ approaching unity and results in the disappearance of correlations between experimental conditions and system states. Crucially, this loss of correlation does not imply a return to a baseline state: the marginal distribution of system states may remain altered due to prior conditioning.

5.5 Emergence of biological responses (Δ^+) without local causes

Within this framework, the occurrence of Δ^+ events in the absence of identifiable local causes can be understood as a consequence of the redistribution of probabilities within the aligned regime. Events that would be rare under baseline conditions can become statistically prominent when the joint distribution is structured by conditioning. This does not correspond to the generation of new physical effects, but to a change in the relative frequencies of configurations within Ω.

5.6 Relation to experimental context and reproducibility

The model emphasizes the role of the experimental context as a determinant of statistical outcomes. Because the structure of the probability distribution depends on the inclusion or exclusion of informational variables, changes in protocol, such as the introduction of external

blinding, can qualitatively alter the observed correlations. This provides a unified interpretation of the coexistence of "successful" and "failed" experiments.

From this perspective, the difficulty in reproducing Benveniste's results across independent laboratories does not necessarily reflect the absence of an underlying phenomenon, but rather differences in the global configuration of the experimental context. In particular, the absence of conditioning or the introduction of informational partitions may prevent the emergence of structured correlations.

5.7 Scope and limitations of the model

The present framework is a probabilistic reinterpretation of a specific class of experimental observations and should not be understood as a mechanistic theory. It does not identify any physical interaction, signal, or molecular pathway responsible for the observed responses. Instead, it describes how correlations between experimental conditions and system states may arise from the structure of a global configuration space Ω, which includes the experimental context.

A central consequence of this choice is that the model remains agnostic at the microscopic level: it does not introduce new physical entities, but neither does it provide a causal mechanism in the conventional sense. Its explanatory power is therefore structural rather than dynamical, focusing on the organization of probabilities rather than on underlying processes.

An important empirical constraint on any interpretation of these experiments is provided by the automated coagulation system developed in the later stages of the work [22]. In this setup, experimental conditions (controls vs. tests) were selected randomly by the device itself and all steps of the protocol, including sample handling, measurement and data recording, were performed without real-time intervention by the experimenter. Under such conditions, conventional explanations based on direct experimenter bias, expectation effects, or behavioral influence during measurement become difficult to sustain.

More generally, the model faces a problem of underdetermination: different underlying mechanisms may produce similar statistical patterns. The model accounts qualitatively for the contrast between open-label, internally blinded and externally blinded conditions, but does not yet provide precise quantitative predictions for effect sizes, nor a fully specified dynamical law governing the evolution of the conditioning process. Nevertheless, the model offers a parsimonious way to integrate a set of otherwise inconsistent observations, including those obtained under automated conditions.

5.8 Constraints for possible underlying mechanisms

It should be noted that the mathematical structure of the model is not neutral. The expression:

$$P_\sigma(\textit{direct}) = (\pi_1 + \pi_2)^2 - \sigma.2\pi_1\pi_2$$

is formally identical to the two-path quantum interference formula:

$$P = |A_1 + A_2|^2 - \delta.2|A_1||A_2|$$

where δ is the degree of "which path" information. The parameter σ plays exactly the role of δ: when $\sigma = 0$, the contributions interfere (open double-slit); when $\sigma = 1$, they add classically (double-slit with path detector). This is not a superficial formal coincidence. It is a *structural constraint* on the type of mechanism sought: it must be the one that, in physics, generates interference terms and destroys them through information extraction.

In the double-slit experiment, when the information about "which path" is extracted, even without reading it, simply by making it *available in the environment*, the interference patterns disappear. It is not necessary for an observer to consult the information; it is sufficient that it be encoded in the

environment in a redundant and, in principle, accessible manner. This is precisely what σ describes in the model.

The mechanism would then be: the biological system-experimenter taken as a whole evolves in a state space formally analogous to a 2-dimensional Hilbert space and σ measures the degree of decoherence induced by the informational partition without any physical signal being necessary. However, this is not to claim that the experimenter's brain is in quantum superposition with the biological system. Indeed, thermal decoherence would make this impossible on the nanosecond timescale. The hypothesis is more precise: the formal quantum structure applies to the *space of macroscopic configurations*, not to microscopic degrees of freedom. This is what some physicists call a "quantum-like" theory, an amplitude formalism applied to classical variables for statistical reasons, not because the objects are literally in superposition. Such an approach has been proposed by some authors, such as Khrennikov [24] and Atmanspacher [25] in quantum-type models in biology and cognition.

In **Appendix A**, we propose a physical process to explain how the alignment forms.

In **Appendix B**, we provide a physical interpretation to explain how this alignment is observable or not according to the informational topology.

5.9 Conclusion

We have shown how simple geometric considerations (unit vectors, dot products and a gradient ascent) lead to a description of non-classical correlations involving the experimenter. This probabilistic model provides an alternative explanation to Benveniste's experiments in which water plays no role and the experimenter is central. All aspects of the experimental data are accounted for within a single framework: the record of physiological responses, the preservation of correlations under internal blind conditions and their systematic destruction under external blind conditions. The obstacle that prevented Benveniste from convincing his peers is not, in this model, a technical failure to be overcome, it is a predicted and necessary feature of the phenomenon itself. Because Benveniste persisted in his quest for the definitive experiment despite this obstacle, he transmitted a corpus of carefully conducted observations that, reanalyzed here, point toward the possible existence of non-classical correlations between an experimenter and a biological system. Although these correlations mimic classical relationships, they are not causal in the ordinary sense: causality is not absent, but it operates at the level of the experimental context taken as a whole (experimenter, apparatus and biological system) rather than at the level of any single agent acting on another.

Appendix A

How Experimenter-System Alignment Forms: A Learning-Based Mechanism

A.1 What physical process establishes the alignment state $\theta = \theta^*$?

The framework developed in the article leaves an important question open: what physical process establishes the alignment state $\theta = \theta^*$? The model postulates that alignment exists in a fully conditioned experimenter and describes its mathematical consequences, but does not explain how repeated exposure to standard pharmacological cause-and-effect relationships produces this alignment.

The present section addresses this question. We propose that the formation of alignment is driven by *predictive learning*, a well-characterized process in neuroscience, and that θ^* is not an arbitrary endpoint but the unique cognitive state at which the experimenter's internal representation of the experimental system has reached its optimal precision. We argue that this optimum follows from properties of learning that are well established in cognitive and systems neuroscience.

A.2 The physical mechanism: predictive learning through active inference

Phase 1. Calibration through standard pharmacology

The alignment process begins with what appears, from the outside, to be ordinary laboratory training: the experimenter repeatedly observes the effects of genuinely active compounds on the biological system ($T \rightarrow \Delta^+$) and the absence of effect with inactive controls ($C \rightarrow \Delta^\circ$). These are straightforward pharmacological observations, not different in principle from the training of any skilled experimenter.

At this stage, the experimenter's nervous system behaves as a standard Bayesian observer. Each observation updates the experimenter's internal estimates of $P(\Delta^+ | T)$ and $P(\Delta^\circ | C)$. Over many sessions, these estimates converge toward the true values b^2 and a^2, respectively. This is standard Bayesian learning, mathematically equivalent to maximum likelihood estimation in the limit of many observations and it drives the experimenter's internal model angle θ step by step toward θ^*.

Phase 2. Predictive coding and anticipatory neural states

A critical feature of the mammalian nervous system, documented across sensory, motor, and prefrontal cortices, is that it does not passively record inputs but *actively predicts* them. The framework of *predictive coding* proposes that the brain continuously generates top-down predictions of incoming sensory signals, and that only the *prediction error*, that is the discrepancy between prediction and reality, is propagated up the cortical hierarchy [26, 27]. Learning consists precisely in updating the predictions to reduce future errors.

In the context of Benveniste's experiments, this means that a conditioned experimenter entering the laboratory generates anticipatory neural activation patterns *before* touching the biological system:

$|A_C\rangle$: a neural pattern anticipating Δ°, activated when the experimenter A is about to process what may be a control sample.

$|A_T\rangle$: a neural pattern anticipating Δ^+, activated when the experimenter A is about to process what may be a test sample.

These anticipatory states are not merely mental representations: they are physical neural activation patterns with measurable correlates (*e.g.* preparatory potentials, autonomic pre-activation). As conditioning progresses, these patterns become more precisely calibrated to the actual biological responses. The prediction error decreases session by session as θ approaches θ^*.

Phase 3. Synaptic plasticity as the cellular substrate

The synaptic mechanism implementing this learning is synaptic plasticity, encapsulated in the principle attributed to Hebb [28]: *"Neurons that fire together, wire together."* More precisely, the modern formulation, *spike-timing-dependent plasticity* (STDP), states that synaptic connections between neurons are strengthened when pre-synaptic activation repeatedly and reliably precedes post-synaptic activation, and weakened in the reverse order. Applied to the conditioning scenario:

- The neural circuit encoding "test condition T" is repeatedly co-activated with the circuit encoding the perception of Δ^+. Their synaptic connection is progressively strengthened, so that activation of the "T" representation comes to reliably predict and pre-activate the "Δ^+" representation.
- Symmetrically, the "C" circuit becomes strongly connected to the "Δ^0" circuit.
- After sufficient conditioning, the anticipatory state $|A_T\rangle$ has become a faithful internal correlate of the Δ^+ response (a neural pattern that systematically pre-activates whenever a Δ^+ outcome is to be expected) and $|A_C\rangle$ a corresponding correlate of Δ^0.

This is the cellular implementation of the angle convergence $\theta \to \theta^*$: as the synaptic weights are adjusted by STDP, the cosines and sines parameterizing the experimenter's cognitive vector converge to the values (a, b) that characterize the biological system's response amplitudes. The gradient dynamics $\theta_{n+1} = \theta_n + \eta.\partial P_0(direct)/\partial\theta$, introduced in Section 4 as a mathematical description of the conditioning process, is the macroscopic expression of this underlying synaptic plasticity.

A.3 From alignment to cognitive path indistinguishability

The mechanism described in Section A.2 establishes how the angle θ converges to θ^*, but it does not yet explain *why* this convergence produces the *cognitive path indistinguishability* required for the interference term $2\pi_1\pi_2$ to be non-zero. The connection is made in four steps.

Step 1. The anticipatory state is oriented toward alignment, not toward a specific path

At $\theta = \theta^*$, the experimenter's anticipatory states $|A_C\rangle$ and $|A_T\rangle$ have been calibrated through repeated exposure to standard pharmacological experiments. These states are not aimed at predicting D_1 or D_2 individually: they are the two components of a single cognitive expectation, which is the expectation of *alignment* between system response and anticipation. Whether the realized configuration is $D_1 = (\Delta^0, C)$ or $D_2 = (\Delta^+, T)$, the experimenter's expectation is met in the same way: what was anticipated coincides with what is observed.

This leads to the central conceptual move of the framework. What the conditioned experimenter expects is not "either D_1 or D_2"; it is *alignment*, regardless of which path produces it. The two paths converge to the same expected outcome and, at the level of the anticipatory state, become functionally indistinguishable. This is what we call *cognitive path indistinguishability*.

Step 2. Indistinguishability is structural, not procedural

It is important to note that this indistinguishability is not the result of the experimenter being uncertain about which path will occur, nor of any procedural feature such as label masking. It is a *structural property of the conditioned cognitive system itself*: by virtue of how conditioning has shaped the anticipatory state, the two paths D_1 and D_2 are no longer distinct objects of expectation. They are two routes to the same anticipated outcome (alignment) and this is what makes them indistinguishable in the cognitive sense relevant to the model. The conditioning process, by

construction, builds a cognitive architecture for which D_1 and D_2 are not separately anticipated states but components of a *unified expectation*.[2]

Step 3. Classical probabilities versus amplitudes

When two contributions leading to the same outcome are indistinguishable in this sense, the appropriate probability calculus is not the classical disjunctive rule, which would add the probabilities of the two paths, $P_{\text{classical}}(\textit{direct}) = \pi_1^2 + \pi_2^2$, but the amplitude rule, which adds the path amplitudes and squares the sum afterwards:

$$P(\textit{direct}) = |\pi_1 + \pi_2|^2 = (\pi_1 + \pi_2)^2 = \pi_1^2 + \pi_2^2 + 2\pi_1\pi_2 \qquad \text{(Eq. A1)}$$

The difference between these two expressions, $2\pi_1\pi_2$, is the *interference term*. It is non-zero precisely under the regime of cognitive path indistinguishability established by conditioning. This is the mechanism by which the alignment $\theta \rightarrow \theta^*$ translates into the observable interference contribution at the level of the joint statistics of {label, system state}.

Step 4. Formal representation: from anticipatory state to realized joint configuration

The transition from the conditioned experimenter's anticipation to the realized outcome of an experiment can be described step by step in the bra-ket formalism, which we use here as a compact representation of macroscopic configuration amplitudes without implying that the experimenter or the biological system is in a microscopic quantum superposition.

Before a sample is processed, the conditioned experimenter is in an anticipatory state (with angle θ established by conditioning) that takes the form of a coherent superposition over the two pre-activated cognitive components while the system is in the rest state S_0:

$$|\Phi_A\rangle \otimes |S_0\rangle = (\cos\theta\ |A_C\rangle + \sin\theta\ |A_T\rangle) \otimes |S_0\rangle \qquad \text{(Eq. A2)}$$

The biological system at rest has its baseline distribution described by amplitudes (a_0, b_0) such that $a_0^2 = P_{\text{baseline}}(\Delta^0)$, $b_0^2 = P_{\text{baseline}}(\Delta^+)$, $a_0^2 + b_0^2 = 1$. Since the system is essentially in the state $|\Delta^0\rangle$, $a_0^2 \approx 1$ and $b_0^2 \approx 0$.

When the experimenter processes the sample, the anticipatory superposition of the experimenter and the state of the system *become coupled* due to the interference term of Eq. A1 related to *indistinguishability*. The resulting joint state of {system, experimenter} reads:

$$|\Phi\rangle = a.\cos\theta\ |\Delta^0\rangle \otimes |A_C\rangle + b.\sin\theta\ |\Delta^+\rangle \otimes |A_T\rangle \qquad \text{(Eq. A3)}$$

$$|\Phi\rangle = \pi_1\,|D_1\rangle + \pi_2\,|D_2\rangle$$

$|D_1\rangle \equiv |\Delta^0\rangle \otimes |A_C\rangle$ (system in Δ^0; experimenter *A* anticipating control)

$|D_2\rangle \equiv |\Delta^+\rangle \otimes |A_T\rangle$ (system in Δ^+; experimenter *A* anticipating test)

For $\theta = \theta^*$ (maximal conditioning), alignment is maximal and $(a.\cos\theta + b.\sin\theta)^2 = (\pi_1 + \pi_2)^2 = 1$.

The coupling between the experimenter's anticipatory superposition and the biological system can be understood as a propagation. This coupling shifts the system's distribution away from its resting baseline (a_0, b_0): in particular, the marginal probability of Δ^+ is no longer the baseline value $b_0^2 \approx 0$ but the coupled value b^2, which at alignment equals $\sin^2\theta^*$. The pre-activated anticipatory components $|A_C\rangle$ and $|A_T\rangle$ of the experimenter have, in effect, drawn the system out of its baseline into a distribution that mirrors the structure of the anticipation itself.

[2] These considerations are reminiscent of Gestalt theory. According to this theory, objects are perceived as a whole or as a form (Gestalt) by the mind and not as the sum of their parts; the whole has therefore its own independent existence [29, 30].

A.4 Scope and limitations

The mechanism proposed in this section is deliberately conservative. It invokes no exotic neuroscience: predictive coding, Bayesian updating and Hebbian plasticity are well-established results. The proposal is that these standard processes, applied to the specific experimental context of repeated pharmacological conditioning, naturally drive θ toward θ^*.

This mechanism makes θ^* a biological-system-specific property. This is an empirical prediction, but it also implies that the observed correlations cannot be attributed to generic experimenter skill or general expertise: they should be *specific* to the system on which the experimenter was conditioned and should decay when the experimenter shifts to a different biological model.

Within these limits, this mechanism explains why structured correlations exist in conditioned experimenters and grounds their existence in the progressive, iterative and ultimately optimal calibration of perception and prediction to the statistical structure of the system that the experimenter has spent much time studying.

The conditions under which the interference term remains observable in the joint statistics, depending on whether the label information remains within Ω or is partitioned to an external record, are the subject of Appendix B.

Appendix B
Cognitive Path Indistinguishability and Informational Decoherence

B.1 Aim

The aim of this appendix is to provide a physical interpretation of the parameter σ that complements the operational definition adopted in the main text. We do so by representing the conditioned experimenter and the biological system within a simple bra-ket formalism analogous to that of two-path interference experiments. The three experimental configurations of Section 3 (open-label, internal blind and external blind) appear as three distinct states of the joint configuration, distinguished by the presence or absence of an entanglement with an external informational record. The parameter σ then emerges naturally from this structure.

As in Appendix A, the bra-ket notation is used throughout as a compact representation of macroscopic configuration amplitudes, in the spirit of "quantum-like" models [24, 25]. It does not imply that the experimenter or the biological system is in a literal microscopic quantum superposition; the implications of this distinction are discussed in B.6.

B.2 The two cognitive paths

Two basis states represent the configurations that constitute a direct relationship in the conditioned regime:

$|D_1\rangle \equiv |\Delta^0\rangle \otimes |A_C\rangle$ (system in Δ^0; experimenter A anticipating control)

$|D_2\rangle \equiv |\Delta^+\rangle \otimes |A_T\rangle$ (system in Δ^+; experimenter A anticipating test)

These two states are orthogonal, $\langle D_1|D_2\rangle = 0$, since the system basis vectors are orthogonal and so are the anticipatory states.

In a fully conditioned experimenter, neither path is realized in isolation: both anticipatory components $|A_C\rangle$ and $|A_T\rangle$ are simultaneously active (Appendix A). The joint state of {system, experimenter} is therefore a coherent superposition over the two paths:

$$|\Phi\rangle = \pi_1|D_1\rangle + \pi_2|D_2\rangle \qquad \text{(Eq. B1)}$$

with the path amplitudes $\pi_1 = a.\cos\theta^*$ and $\pi_2 = b.\sin\theta^*$ defined in Section 4.4. The probability of a direct relationship is then given, following the standard amplitude rule, by the squared modulus of the coherent sum of path amplitudes:

$$P(direct) = |\pi_1 + \pi_2|^2 = (\pi_1 + \pi_2)^2 \qquad \text{(Eq. B2)}$$

This is the $\sigma = 0$ case of the unified expression of Section 4.4.

B.3 The three experimental configurations

The contrast between the three configurations of Section 3 becomes transparent once one specifies what, if anything, lies *outside* Ω.

Open-label and *internal blind*: no environmental record exists outside Ω. The joint state of {system, experimenter} is the pure superposition $|\Phi\rangle$ of Eq. B1.

External blind: an external supervisor B_{ext}, whose physical state lies outside Ω, holds a record correlated with the actual label assignment: $|R_1\rangle$ if path D_1 is realized, $|R_2\rangle$ if D_2 is realized, with $|R_1\rangle \perp |R_2\rangle$. The joint state of {system, experimenter, external record} is the *entangled* state:

$$|\Phi_{total}\rangle = \pi_1|D_1\rangle|R_1\rangle + \pi_2\,|D_2\rangle|R_2\rangle \qquad \text{(Eq. B3)}$$

The narrative consequences of these three configurations are developed in Section B.5.

B.4 From entanglement to loss of interference

The experimenter has no access to the external record located in the environment (outside Ω). Any prediction concerning the joint state of {system, experimenter} must therefore be obtained by *tracing out* the record, *i.e.* by eliminating its degrees of freedom while preserving the statistical consequences of its existence for Ω. The partial trace over R is defined, on an elementary tensor product of operators, by

$$\mathrm{Tr}_R\,[(|D_i\rangle\langle D_j|)\otimes(|R_k\rangle\langle R_l|)] = |D_i\rangle\langle D_j|\cdot\langle R_l|R_k\rangle$$

The rule is straightforward: the operator acting on Ω is left untouched, while the operator acting on R is replaced by its trace, the scalar $\langle R_l|R_k\rangle$. We apply this rule to the four terms that appear when $|\Phi_{total}\rangle\langle\Phi_{total}|$ is expanded by distributivity.

Expansion of $|\Phi total\rangle\langle\Phi total|$

Starting from Eq. B3 and forming the corresponding bra (with π_1 and π_2 real positive),

$$\langle\Phi_{total}| = \pi_1\langle D_1|\langle R_1| + \pi_2\langle D_2|\langle R_2|$$

the outer product $|\Phi_{total}\rangle\langle\Phi_{total}|$ develops into four contributions:

(i) $\pi_1^2|D_1\rangle|R_1\rangle\langle D_1|\langle R_1|$

(ii) $\pi_1\pi_2|D_1\rangle|R_1\rangle\langle D_2|\langle R_2|$

(iii) $\pi_1\pi_2|D_2\rangle|R_2\rangle\langle D_1|\langle R_1|$

(iv) $\pi_2^2\,|D_2\rangle|R_2\rangle\langle D_2|\langle R_2|$

Each term can be rewritten as a tensor product of operators acting respectively on Ω and on R:

Term	Operator on Ω	Operator on R	Coefficient
(i)	$\|D_1\rangle\langle D_1\|$	$\|R_1\rangle\langle R_1\|$	π_1^2
(ii)	$\|D_1\rangle\langle D_2\|$	$\|R_1\rangle\langle R_2\|$	$\pi_1\pi_2$
(iii)	$\|D_2\rangle\langle D_1\|$	$\|R_2\rangle\langle R_1\|$	$\pi_1\pi_2$
(iv)	$\|D_2\rangle\langle D_2\|$	$\|R_2\rangle\langle R_2\|$	π_2^2

Application of the partial trace

Using the partial-trace rule and the normalization of the records ($\langle R_1|R_1\rangle = \langle R_2|R_2\rangle = 1$), each term yields:

(i) $\rightarrow \pi_1^2|D_1\rangle\langle D_1|\cdot 1 = \pi_1^2|D_1\rangle\langle D_1|$

(ii) $\rightarrow \pi_1\pi_2|D_1\rangle\langle D_2|\cdot\langle R_2|R_1\rangle$

(iii) $\rightarrow \pi_1\pi_2|D_2\rangle\langle D_1|\cdot\langle R_1|R_2\rangle$

(iv) $\rightarrow \pi_2^2|D_2\rangle\langle D_2|\cdot 1 = \pi_2^2|D_2\rangle\langle D_2|$

Without loss of generality, the phases of the records may be chosen so that $\langle R_1|R_2\rangle$ is real and positive; then $\langle R_2|R_1\rangle = \langle R_1|R_2\rangle^* = \langle R_1|R_2\rangle$. Summing the four contributions yields the reduced density operator:

$$\rho = \mathrm{Tr_R}\,[|\Phi_{\mathrm{total}}\rangle\langle\Phi_{\mathrm{total}}|] =$$

$$\pi_1^2|D_1\rangle\langle D_1| + \pi_2^2|D_2\rangle\langle D_2| + \pi_1\pi_2\,\langle R_1|R_2\rangle(|D_1\rangle\langle D_2| + |D_2\rangle\langle D_1|) \quad \text{(Eq. B.4)}$$

Matrix representation

In the orthonormal basis $\{|D_1\rangle, |D_2\rangle\}$ of Ω, ρ admits a 2×2 matrix representation:

$$\rho = \begin{pmatrix} \pi_1^2 & \pi_1\pi_2\langle R_1|R_2\rangle \\ \pi_1\pi_2\langle R_1|R_2\rangle & \pi_2^2 \end{pmatrix}$$

The diagonal entries $\rho_{11} = \pi_1^2$ and $\rho_{22} = \pi_2^2$ are the probabilities of finding the joint system in configuration D_1 or D_2. They do not depend on $\langle R_1|R_2\rangle$: the mere existence of external records leaves the marginal probability of each path unchanged. The off-diagonal entries $\rho_{12} = \rho_{21} = \pi_1\pi_2\langle R_1|R_2\rangle$ encode the phase correlations between the two paths and are modulated by the overlap $\langle R_1|R_2\rangle$ of the external records.

Two limits make the role of $\langle R_1|R_2\rangle$ immediate:

If $\langle R_1|R_2\rangle = 1$, the records are indistinguishable: $\rho = \begin{pmatrix} \pi_1^2 & \pi_1\pi_2 \\ \pi_1\pi_2 & \pi_2^2 \end{pmatrix}$

This matrix has rank 1 (its determinant is $\pi_1^2\pi_2^2 - (\pi_1\pi_2)^2 = 0$). It is the density operator of a *pure state*, equivalent to $\pi_1|D_1\rangle + \pi_2|D_2\rangle$ up to normalization. The inter-path coherence is fully preserved.

If $\langle R_1|R_2\rangle = 0$, the records are orthogonal: $\rho = \begin{pmatrix} \pi_1^2 & 0 \\ 0 & \pi_2^2 \end{pmatrix}$

This is the density operator of a *classical statistical mixture*: D_1 with probability π_1^2 and D_2 with probability π_2^2. No coherence remains between the two paths.

Probability of a direct relationship

The probability of a direct relationship follows from ρ as the coherent combination of diagonal populations and off-diagonal coherences:

$$P(direct) = \rho_{11} + \rho_{22} + 2\mathrm{Re}(\rho_{12}) = \pi_1^2 + \pi_2^2 + 2\pi_1\pi_2\langle R_1|R_2\rangle \quad \text{(Eq. B.5)}$$

(Re denotes the real part; since $\langle R_1|R_2\rangle$ was chosen real, $\mathrm{Re}(\rho_{12}) = \rho_{12}$. Two cases recover the regimes of the unified formula of Section 4.4:

If $\langle R_1|R_2\rangle = 1$, Eq. B5 reduces to $\pi_1^2 + \pi_2^2 + 2\pi_1\pi_2 = (\pi_1 + \pi_2)^2$: full interference, $\sigma = 0$.

If $\langle R_1|R_2\rangle = 0$, Eq. B5 reduces to $\pi_1^2 + \pi_2^2$: no interference, $\sigma = 1$.

A central feature of this mechanism is its *non-locality*. The decoherence of the joint state ρ does not require any signal to be transmitted between the external record and the experimental system: the mere physical existence of distinguishable records is sufficient to suppress the interference. This is the same non-locality that operates in the two-slit experiment with a which-path detector, the loss of interference depends on the availability of which-path information in the environment, not on its consultation.

B.5 The continuous parameter σ

Setting $\langle R_1|R_2\rangle = 1 - \sigma$ with $\sigma \in [0, 1]$ in Eq. B5 yields exactly the unified expression of Section 4.4:

$$P_\sigma(direct) \;=\; \pi_1^2 + \pi_2^2 + 2\pi_1\pi_2(1-\sigma) \;=\; (\pi_1 + \pi_2)^2 - \sigma.2\pi_1\pi_2 \qquad \text{(Eq. B6)}$$

The parameter σ thus admits a precise physical interpretation: it measures the *orthogonality of the external records*, i.e., the extent to which the environment outside Ω physically encodes which-path

information. The three experimental configurations of Section 3 are the three regimes of this single parameter:

Open-label. In open-label experiments, the labels are known to the experimenter and to all participants throughout the measurement; they are not held by any agent outside the laboratory. No external record exists whose physical state correlates with the path actually realized. The joint state of {system, experimenter} is therefore described directly by the pure superposition

$$|\Phi\rangle = \pi_1|D_1\rangle + \pi_2|D_2\rangle$$

The off-diagonal coherences between $|D_1\rangle$ and $|D_2\rangle$ are intact, and the probability of a direct relationship is the squared modulus of the coherent sum of amplitudes:

$$P(\textit{direct}) = (\pi_1 + \pi_2)^2, \quad \sigma = 0$$

The statement is not that the experimenter is cognitively "uncertain" between the two paths, they may know perfectly well, sample by sample, which condition is being processed. What matters is that, at the level of the statistical ensemble described by π_1 and π_2, no environmental degree of freedom outside Ω carries which-path information.

Internal blind. In internal blinding, the experimenter is no longer informed of the labels at the moment of measurement: an internal supervisor B_{int} holds them. One might be tempted to introduce a state $|R\rangle$ for the supervisor and write an entangled state of the form $\pi_1|D_1\rangle|R_1\rangle + \pi_2|D_2\rangle|R_2\rangle$, as for external blinding. The crucial point of the framework is that this is not the appropriate description.

The supervisor's record exists only as a procedural arrangement within the laboratory: a code held in the supervisor's mind, a list in a notebook on a nearby desk, a sealed envelope in the same office. Physically, all of these belong to Ω, the configuration space defined by the experimental setting. They are not delocalized environmental degrees of freedom of the kind that produces decoherence; they are part of the same coherent informational structure as the experimenter and the system. There is, in this framework, no environmental degree of freedom to trace out: the supervisor, the experimenter, the system and their procedural records jointly occupy Ω.

The joint state of {system, experimenter} therefore remains the pure superposition $|\Phi\rangle$ and the probability of a direct relationship is again

$$P(\textit{direct}) = (\pi_1 + \pi_2)^2, \sigma = 0$$

The persistence of correlations under internal blinding is, in this framework, a direct consequence of the fact that no record outside Ω has been generated, even though the experimenter does not know the labels.

External blind. In external blinding, the labels are physically removed from Ω. The external supervisor B_{ext} is institutionally and physically separate from the laboratory: codes are generated elsewhere, sealed records are held in another building, the correspondence between code and condition is reconstituted only after the experimenter has returned all measurements. The record is now a genuine external degree of freedom and the joint state of {system, experimenter, external record} is the entangled state:

$$|\Phi_{\text{total}}\rangle = \pi_1|D_1\rangle|R_1\rangle + \pi_2\,|D_2\rangle|R_2\rangle \text{ with } \langle R_1|R_2\rangle = 0$$

To predict any observable that does not include the external record (the experimenter has no access to it), the appropriate description is the reduced density operator of {system, experimenter}, obtained by tracing out the record. The off-diagonal coherences are then suppressed by the orthogonality of $|R_1\rangle$ and $|R_2\rangle$, and ρ becomes the classical mixture:

$$\rho = \pi_1^2|D_1\rangle\langle D_1| + \pi_2^2\,|D_2\rangle\langle D_2|$$

The probability of a direct relationship is now the classical sum:

$$P(\textit{direct}) = \pi_1^2 + \pi_2^2, \quad \sigma = 1$$

The interference term has been destroyed, not by any signal exchanged between the external record and the laboratory, but by the simple fact that the record's physical state is correlated with the path realized. This non-locality is the central property of the mechanism: what suppresses the interference is the existence of distinguishable which-path information *in the environment*, not its retrieval by anyone.

The contrast between the three regimes therefore does not depend on what the experimenter knows, but on where the label record physically resides relative to Ω. This independence from conscious access is precisely what aligns the present framework with the two-slit phenomenology, in which the interference pattern is destroyed by the existence of which-path information in the environment, not by its consultation.

B.6 Scope and limitations

The bra-ket formalism employed in this appendix should not be taken to imply that the experimenter's brain is in genuine quantum superposition with the biological system. Thermal decoherence in biological tissue would suppress any such microscopic quantum coherence on timescales far shorter than the duration of an experimental measurement. The formalism is adopted here as a *quantum-like* representation [24], in which an amplitude-based probability calculus is applied to macroscopic configuration variables for structural reasons, namely, to capture the contrast between coherent ($\sigma = 0$) and decoherent ($\sigma = 1$) regimes that the experimental data require.

Whether this formal structure reflects an underlying mechanism that is itself quantum at some level, or whether it arises from a structurally analogous but distinct macroscopic process, remains an open question. What the framework offers is a precise mathematical articulation of the constraint identified in Section 5.8: any candidate physical mechanism for the observed correlations must be of a type that produces interference contributions and destroys them through the redundant encoding of which-path information in the environment, *without requiring any physical signal to be transmitted*. The formal identification $\langle R_1|R_2\rangle = 1 - \sigma$ is not a free parameter adjustment but a structural consequence of the two-path reading of the model.

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