Emergence of a Signal from Background Noise in the "Memory of Water" Experiments: How to Explain It?

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After more than 20 years, the case of the "memory of water" still has not been resolved satisfactorily. After the affair with the journal *Nature*, Benveniste extended his results on high dilutions to an "electromagnetic biology" and then to a "digital biology," where electromagnetic signals supposed to be emitted from biologically active solutions were said to be stored on magnetic memories. Although the results obtained by Benveniste and coworkers were obvious, the difficulties in reproducibility by other teams created doubt of the reality of the alleged phenomenon. In a first step, we analyzed a set of experiments obtained by Benveniste's team in the 1990s. We quantified the relationship between "expected" effects (ie, labels of the tested samples) and apparatus outcomes, and we defined the experimental conditions to observe significant correlations. We concluded that the results of these experiments were related to experimenter-dependent correlations, which did not support the initial "memory of water" hypothesis. The fact that a signal emerged from background noise, however, remained puzzling. Therefore, in a second step, we described Benveniste's experiments according to the relational interpretation of quantum physics of C. Rovelli. In this interpretation, the state of a system is observer-dependent and the collapse of the wave function appears only in the states relative to a given observer. This interpretation allowed us to elaborate a model describing Benveniste's experiments in which the emergence of a signal from background noise was described by the entanglement of the experimenter with the observed system. In conclusion, the pursuit of the experimental "proof" to support the "memory of water" hypothesis has prevented other interpretations. Although our hypothesis does not definitely dismiss the possibility of "memory of water," the experimenter-dependent entanglement could be an attractive alternative interpretation of Benveniste's experiments.

Key words: Memory of water, high dilutions, digital biology, scientific controversy, experimenter effect

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> "My own conviction is that it remains to be shown that there is a phenomenon to be explained"
>
> John Maddox (1988)[1]

INTRODUCTION

In June 1988, an article published in the prominent journal *Nature* was the start of a scientific controversy that remains unresolved today.[2] The experiments described by this article suggested that serially diluted solutions of antibodies, shaken between each dilution, retained their specific biological activity to stimulate white blood cells called basophils. For any reader, it was a shock to realize that less than one active molecule was present in the highly diluted solutions. If true, these results were a ground-breaking discovery. But how to explain them if no active molecule from the initial solution was present? Were "ghosts" of molecules produced by the dilution process, or did the molecules "imprint" a template in water?

The article was accompanied with an unusual editorial reservation, which warned the reader of accepting these odd results. Another unusual circumstance was that the publication of the manuscript had been made on the condition that *Nature*'s team could perform an inquiry into the laboratory of Jacques Benveniste, the lead author of the article. Performing the inquiry after—and not before—the publication was nevertheless a surprising method.

This publication was the result of a long battle of Benveniste with the editorial team of *Nature*, more particularly with the Editor John Maddox, who feared that the proponents of homeopathy would find scientific support with the paper once it was published. Indeed, although the word homeopathy was not present in the manuscript, high dilutions are one of the principles of this disputed alternative medicine, and it was clear that the experiments had been performed in the context of industrial contracts with homeopathy firms.

However, this manuscript could not be easily discarded by the editorial board of *Nature* because Benveniste was a reputed senior director of INSERM, the French medical research organization. He was one of the discoverers in the 1970s of the platelet-activating factor, which belongs to a new class of inflammatory mediators. In other words, Benveniste was not an isolated eccentric scientist but a member of the scientific establishment. Moreover, Benveniste was a tenacious man and during the two years of negotiations with *Nature*, he answered all the demands—which were perhaps also designed to postpone the final decision—and particularly the request for the reproduction of the results by other laboratories.

One month after the publication of the article, the five-day inquiry began in the laboratory of Benveniste at Clamart, in the suburbs of Paris. To compose the team of investigators, Maddox, himself a former theoretical physicist, did not recruit specific

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experts but the pseudoscience debunker and stage magician James Randi and the fraud investigator Walter Stewart. Indeed, Maddox, as he reported later, suspected that someone in the entourage of Benveniste was cheating. During the first three days, the investigators examined the laboratory notebooks and observed one scientist performing high-dilutions experiments. Rapidly, the suspicion of cheating was abandoned; nevertheless, the results of the ongoing experiments, including one blind experiment, were in favor of an effect of high dilutions. From this moment, the investigators involved themselves in the experiments, not only in the blinding of the highly diluted samples, but also in the pipetting of the cell suspensions for their allocation to the two members of Benveniste's team who counted the stained basophils under a microscope. The experiments performed during these last two days with the assistance of the investigators failed. All the experiments of the inquiry week have been described in details.[3]

The report published in *Nature* in the next weeks concluded that Benveniste's team did not reproduce the initial results and that the alleged results were mainly the result of an observer's bias and unawareness of statistical laws.[4] In summary, the authors of the report concluded that the disputed results were the consequence of self-delusion. All the experiments performed for years by Benveniste's team were not taken into account or were dismissed as statistically flawed. During the weeks that followed the investigation, the debate raged in the correspondence pages of *Nature* and other leading journals. Although most scientists remained skeptical about the claims of Benveniste, the role of *Nature* and its Editor was criticized. This debate was popularized in mainstream press as the "memory of water" affair.

In the next years after publication, attempts to reproduce the results of the *Nature*'s article produced negative,[5] ambiguous,[6] and positive[7-9] reports. This scientific saga is now considered as a classic example of scientific controversy and is often described as a conflict between "pseudo sciences" and mainstream science. The different opinions have been polarized in two irreconcilable camps, and no certainty has emerged. The only conclusion that can be held for certain is that Benveniste's work illustrates the difficulty in exploring the fringes of science. Although the article of 1988 has never been retracted, the role played by *Nature* has probably hampered the efforts of some scientists who wished to explore this controversial issue.

Today, for many scientists, the affair of the "memory of water" is only an example of poor-quality science, and most of them think that the *Nature*'s report marked the end of Benveniste's research on high dilutions. Actually, after the episode of 1988, Benveniste abandoned the criticized basophil model for other biological models that he hoped to be more easily convincing. Several biological models were thus explored during the next years and the most impressive results were obtained successively with the isolated heart model and the in vitro coagulation model. However, after all these years, the failure to convince other scientists of the existence of a new research area is now obvious. Even if conservative forces do exist in science as in other human activities, Benveniste himself admitted that the reproducibility of the experiments was a real concern. The thesis developed here argues that the effects observed by Benveniste and coworkers and supposed to be related to "memory of water" were in fact related to a phenomenon that occurred unbeknown to them. We will see that the obstacles encountered by Benveniste's team were not trivial and paradoxically could be a key to understanding these puzzling results.

In this text, we first focus on the results obtained with the isolated heart model. These results were obtained by Benveniste's team from 1990 to 1999. Less famous than the results on basophils, these findings were nevertheless published as abstracts and posters at international congresses. Moreover, Benveniste's team set up many "public demonstrations" aimed to convince other scientists of the reality of the "memory of water." Most of these demonstrations were carefully designed with a written protocol, and after completion, the participants received a detailed report with the experimental raw data. Therefore, considerable data were available that could be reanalyzed. These experiments–and the whole story of the "memory of water"–have been described in detail.[3] In a second step, a formal description of these results based upon the principles of the relational interpretation of quantum physics will be proposed.

BRIEF DESCRIPTION OF THE BIOLOGICAL MODEL (THE LANGENDORFF APPARATUS)

The Langendorff apparatus allows maintaining a live rat or guinea pig heart while different parameters (beat frequency, coronary flow, muscular tension) are recorded before and after injection of pharmacological agents in the perfusion circuitry. As reported in the section *The successive devices used to "inform water"*, coronary flow was the most noticeable parameter because it responded to "informed water" with large changes. In the Langendorff system, the perfusion liquid is forced to pass through the coronary arteries before flowing outside the heart. Therefore, any change in the diameter of the coronary arteries modifies the flow rate. In the apparatus set up by Benveniste and coworkers, the liquid that flowed out from the heart was recovered into a series of tubes (one tube per minute), and the volume of liquid was measured in each tube. Each run (test of one sample) was performed in approximately 30 minutes. For each test, the profile of the changes in coronary flow with time could be drawn and the maximal coronary flow change was calculated as a percentage of basal flow. An empirical limit of 10% of the maximal coronary flow change allowed the separation of "active" samples ($>10\%$) from "inactive" samples and background noise (both $<10\%$).

THE SUCCESSIVE DEVICES USED TO "INFORM" WATER

In the early experiments with the Langendorff system, J. Benveniste and coworkers observed some changes in the cardiac physiological parameters after injection of highly diluted pharmacological agents (eg, histamine) into the perfusion liquid.[10] In fact, the most impressive effects were obtained in the coronary flow. The effects observed in the other parameters, such as cardiac frequency, were more erratic. Therefore, Benveniste's team focused its attention on the changes in coronary flow, and this parameter became the main criterion for detecting the effects of "informed" water. The major advantage of the Langendorff

model over the basophil model was the possibility to demonstrate the biological effect to a public in real time. Indeed, the 20% to 30% change from the baseline flow was directly visible in the series of tubes that collected the physiological solution from coronary circulation. However, the criticism of possible contamination of samples containing high dilutions by active molecules remained.

In 1992, Benveniste claimed that he was able to "transfer" to naive water, through a low-frequency amplifier, the biological activity of a biologically active solution placed in an electric coil. This "electromagnetic transfer" could be applied to naive water contained in a sealed vial. Therefore, explaining the observed effects by contamination was less relevant.

A further step was achieved in 1996 when Benveniste used a personal computer with a sound card to "record" and to store as a digital file the "activity" of the biological sample placed in the electric coil. The "replay" to a naive water sample, which was put inside an electric coil wired at the output of the sound card, could then be performed. Positive results similar to those observed with high dilutions were obtained. If reproducible, these experiments offered huge possibilities in the area of diagnosis, therapeutics, and fundamental biology. Benveniste then coined the expression "digital biology." The next successful step was accomplished by placing the electric coil (which diffused the electromagnetic "information") directly around the column of physiological liquid that perfused the isolated heart. Therefore, no intermediary water sample was necessary, and the experiment could be piloted directly from the computer. The electromagnetic field of the electric coil was the unique link between the electronic device and the biological system. The contamination argument, which had been frequently proposed to explain these results, was thus definitively discarded.

However, despite these successive improvements, a problem persistently plagued the demonstrations aimed to provide "proof" of the reality of the "memory of water." This odd phenomenon is described in the context of a "public demonstration" in the next section.

AN EXAMPLE OF "PUBLIC DEMONSTRATION"

As a representative "public demonstration," an experiment performed in September 1997, is described in detail; other similar examples have been described elsewhere.[3] For this experiment designed as a "proof of concept" to demonstrate the validity of "digital biology," Benveniste and coworkers performed the recording step in a foreign laboratory and tested the coded computer files in their laboratory. Two types of samples were "recorded": water alone for negative controls and a solution of calcium ionophore for positive controls. Calcium ionophore is a compound that activates cells by causing calcium to permeate the cell membrane.

In the foreign laboratory, J. Benveniste first recorded two computer files (in .WAV sound file format) named "File water initial" and "File iono initial" from tubes containing water or a solution of calcium ionophore placed successively in the electric coil. Then, the members of the foreign laboratory themselves recorded three files named "File water 1" through "File water 3," followed by three files named "File iono 1" through "File iono 3." Finally, Benveniste recorded two files named "File water final" and "File iono final."

The four files recorded by Benveniste were kept "open"; the six files recorded by the guest laboratory members were copied randomly into 10 files (some of the initial six files were thus copied into more than one file) and then coded blind from 1 to 10. Then, Benveniste's team moved back to their laboratory for the second step. The recorded files were then "played" to naive water and the resulting "imprinted" water was perfused to isolated hearts. It is important to note that each file to be tested was coded again (including the four "open-label" files) by a member of Benveniste's laboratory and then given to the experimenter assigned to the tests. When all the experiments had been performed, the results were sent to the scientists of the foreign laboratory, who compared the effects observed on the apparatus with the initial records that had been given a code-name. The results are shown in Table 1.

We see in Table 1 that the differences between the samples that appeared to be "active" or "inactive" were clear-cut. However, after code breaking, the "guessing game," although based on coherent experimental results, was not better than random. Furthermore, some computer files, which had been simply duplicated, gave contradictory results (see, for example, "File iono #1"). Note also that six files were found to be "active" in this experiment, whereas only five "active" files were included in the set of 10 files. In other public experiments where the number of "active" samples had been fixed by the protocol and was public, the correct number was obtained.[3] In other words, the experimental results revealed only information that was available and not hidden by the coding. It is important to insist again that in this experiment described in Table 1, all runs were performed blind for the experimenter.

Such disappointing results were the rule for public demonstrations.[3] Faced with these results, J. Benveniste did not conclude that these experiments "falsified" (in the Popperian sense) the "memory of water" hypothesis, but he considered that the experimental conditions needed improvements to produce more convincing results. He successively suggested several possible causes that could disturb the results, such as electromagnetic pollution, quality of water, "remnant" memory in the apparatus, and the jump of "activity" between tubes. How explain, however, why the results with open-label samples, which were managed in parallel with the blinded samples, were as "expected" and were not affected by the supposed *ad-hoc* disturbances? Nevertheless, the determination of Benveniste to continue these experiments was understandable: indeed, the experimental system provided coherent outcomes, passed blind in-house tests, and produced results that supported the initial hypothesis.

DISTRIBUTION OF THE SIZES OF THE BIOLOGICAL EFFECTS ATTRIBUTED TO "INFORMED WATER"

Obviously, the causal relationship between biological effects (changes in coronary flow greater or $<10\%$) and their supposed causes (samples of "specifically informed water") was disturbed in some circumstances. As a first approach in the reanalysis of these results, the abstracts of congress communications on the Langendorff model written by Benveniste's team were collec-

Table 1. Example of a "Public Demonstration" with Participating Outside Observer Performed by Benveniste and Coworkers in September 1997

Tested Files[a]	Size of Biological Effect (%) (in Increasing Order) Mean ± SD	Unblinding of Blinded Files	Expected Biological Effect
Blind files with participating outside observer			
File 4	4.3 ± 0.2 (n = 4)	File "water," 1	Yes
File 2	4.7 ± 1.6 (n = 7)	File "water," 3	Yes
File 7	5.0 ± 2.4 (n = 5)	File "iono," 1	No
File 8	5.1 ± 4.0 (n = 4)	File "iono," 1	No
File 1	16.2 ± 9.1 (n = 11)	File "water," 2	No
File 3	17.1 ± 10.8 (n = 5)	File "iono," 3	Yes
File 10	20.3 ± 15.8 (n = 6)	File "iono," 2	Yes
File 5	21.3 ± 11.3 (n = 4)	File "water," 1	No
File 6	22.9 ± 10.3 (n = 4)	File "water," 3	No
File 9	26.9 ± 16.2 (n = 6)	File "iono," 1	Yes
In-house blind files			
File "water" (initial)	3.1 ± 0.3 (n = 5)	—	Yes
File "water" (final)	2.3 ± 1.2 (n = 6)	—	Yes
File "iono" (initial)	24.0 ± 4.5 (n = 5)	—	Yes
File "iono" (final)	25.2 ± 15.0 (n = 7)	—	Yes
Positive control			
Iono 1 μmol/L	36.7 ± 18.5 (n = 8)	—	Yes

[a]The participating outside observer produced 10 blind files and four open-label files; the four open-label files were nevertheless in-house blinded before measurements (see text for details). After completion of the measurements, the results were sent to the participating outside observer, who compared the two series (labels of files and size of biological effects). The biological effect observed was the maximal change in coronary flow (expressed in percentages) using a Langendorff apparatus. Despite the coherence of the results for each file, blind files were associated randomly with "effect" (size of biological effect >10%) and "no effect" (size of biological effect <10%). In contrast, expected results were constantly obtained with the in-house blinded files. "Iono 1 μmol/L" was a positive control of calcium ionophore at "classical" concentration and was the last sample tested on a heart preparation. The number within parentheses in the second column is the number of experiments performed for a given sample (on different heart preparations).

ted.[10-20] Then, all results were extracted, and they were classified regardless of the methods supposed to have "informed" the water samples and regardless of the biological molecules supposed to have left an "imprint" in water. It appeared that the distribution of the biological effects for samples reported to be active was unimodal (modal class with 20%-30% of the maximal change in coronary flow). This distribution is described in Figure 1.

The unimodal distribution was confirmed by examining other experiments performed by Benveniste's team but not communicated at congresses. Particularly, large-scale demonstrations confirmed this notion of a unimodal distribution for alleged "active" samples (data not shown). For example, homeopathic granules ("acetylcholine" or controls) were dissolved in water and the solution applied to the Langendorff system after proper dilution in physiological liquid. Again, a maximal change in coronary flow of approximately 20% to 30% was measured for "active" samples.

Such uniformity in results was rather astonishing. Indeed, the processes used to "inform" water were very different. What is common among high dilutions, direct "electromagnetic transfer" from a biological sample, "electromagnetic transfer" from a stored file, and transfer of the "biological activity" of homeopathic granules to water? Moreover, a variety of electronic devices have been used, particularly electric coils with various technical characteristics.

Thus, the dynamic range of the "measure apparatus" used to evidence "informed water" appeared to be extremely large for the "input" but was nevertheless associated with a monotonous response for the "output." In other words, the effect size appeared to be binary ("it works" or "it does not work") and not continuous. What seemed to be important for the outcome was the fact that it was the sample that was labeled as "inactive" or "active" and not the specific physical process used to supposedly "inform" the water.

CORRELATIONS OF PARALLEL MEASURES ON TWO LANGENDORFF DEVICES

Without making any assumption on causal relationships, we pursued this analysis by studying which events were observed together. For this purpose, a set of experiments performed with the Langendorff model between 1992 and 1996 was analyzed. Indeed, two parallel Langendorff apparatus (here named A and B) were used during this period in Benveniste's laboratory. This double apparatus was used to confirm the results of measurements, particularly for the public demonstrations (note that such double apparatus is seldom used in "normal" research).

These duplicate measures gave us the opportunity to analyze the correlations between the measures obtained with apparatus A and B. All the measures performed in duplicate during large-scale experiments, essentially public demonstrations, were col-

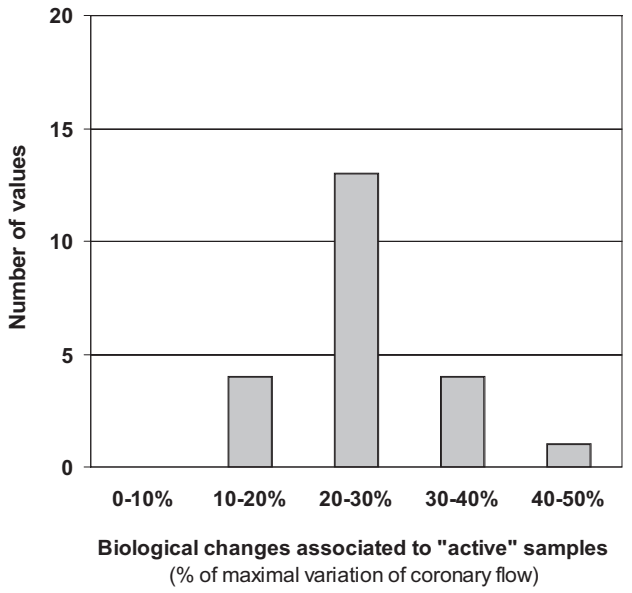

Figure 1. Distribution of the size of the biological effects in different experimental conditions (Langendorff system). Eleven communications to congresses written by Benveniste's team were analyzed.[10-20] Mean values of active samples (maximal change in coronary flow expressed as percentages of basal value) were extracted, and their distribution was studied. Inactive controls (not represented in this figure) were all in the range of 0% to 10%. Although the processes used to "imprint" water were very different, the Langendorff system appeared to be able to detect them, thus exhibiting a surprisingly large dynamic range for input and a narrow range for output.

lected (these experiments have been described in detail[3]). All the results (574 pairs of measures) were pooled regardless of the process used to "inform" water (ie, high dilutions, direct electromagnetic transfer, transfer of "biological activity" previously recorded in computer files) or according to the biological molecules involved (ie, acetylcholine, ionophore, ovalbumin).

Figure 2A indicates that the measures of the biological parameter (ie, maximal changes in coronary flow) obtained with apparatus A and B were correlated. After log transformation (Figure 2B), we observe a more regular dispersion of the experimental points. Indeed, the variable is a flow, which has the mathematical form $K\ \pi R^2$; after log transformation, the mathematical expression is linearized to $K'\ \pi R$ (K and K′ are constants). The change in R, the coronary artery radius, is the real random variable, which is indirectly measured by flow measurements.

In Figure 3A and 3B, the distributions of the measure values are represented when the first value was <10% (Figure 3A) or >10% (Figure 3B). We observe that when the value measured on apparatus A is >10%, the probability to obtain a value >10% on apparatus B is high (this is symmetrical for measures <10%). This is another way to evaluate the degree of correlation for the results obtained with the two devices. These samples were not blinded between the first measure with A and the second measure with B.

The distributions of the measures in Figure 3A and 3B confirm the existence of two "states" of the biological model, each with its own modal value ("inactive" and "active" states). The very large dynamic range of the "measurement device" and the monotonous profile of "active" samples observed above are confirmed here with a modal value of 20% to 30%.

Mixing results from a variety of experimental settings (with various devices for water "information" and "transmission" of different molecules) could be criticized. However, one could argue that despite the combination of results obtained in heterogeneous experimental conditions, the robustness of the uni-

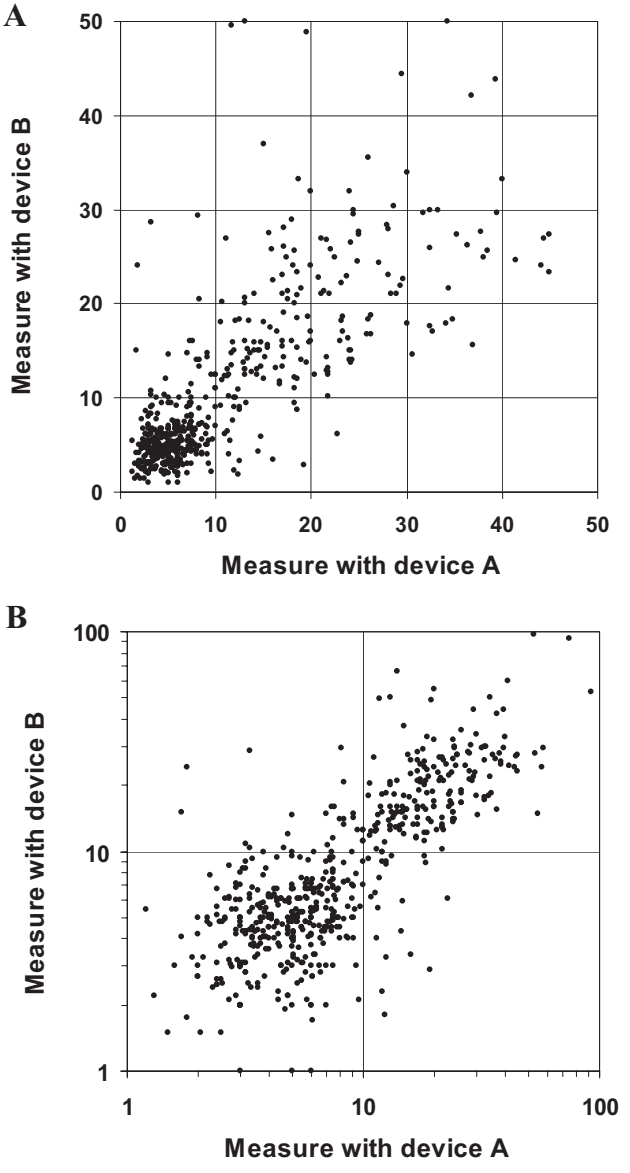

Figure 2. Correlations of measurements performed in parallel with the two Langendorff apparatus. A systematic analysis of large-scale experiments from 1992 to 1996 (including mainly "public demonstrations") produced 574 pairs of measures. These duplicate measures are plotted in *A* (scales limited to 50% for clarity). The log transform of the values from *A* are plotted in *B*.

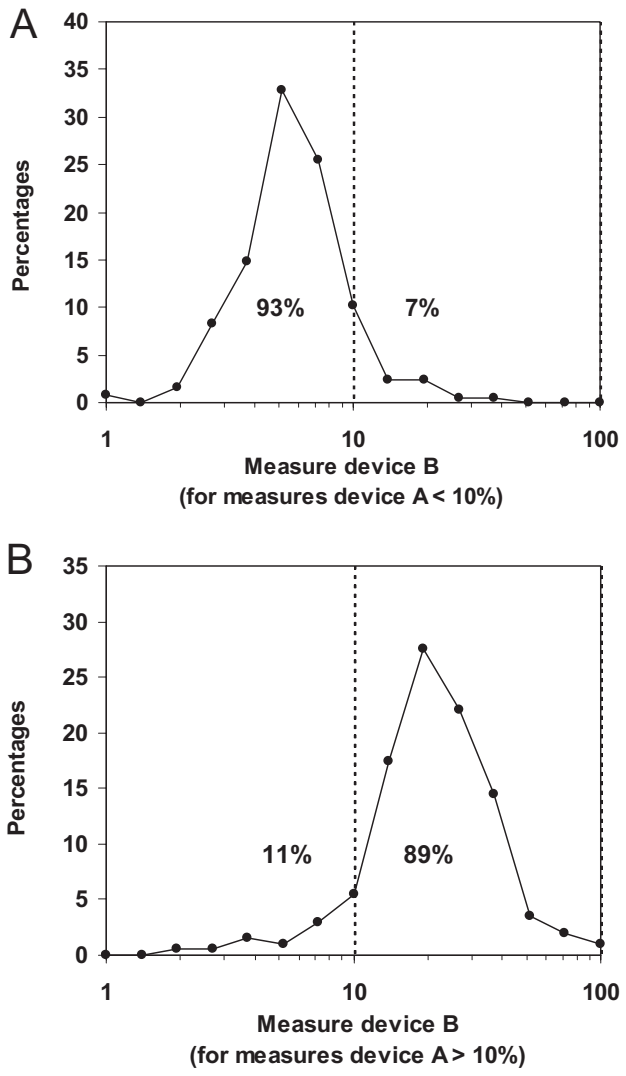

Figure 3. Concordance of outcomes between identical apparatus A and B for paired measurements. The distributions of the measures on the two parallel Langendorff apparatus when the first measure was <10% (*A*) or >10% (*B*) are described; samples were not blinded between A and B measurements (same experimental points as in Figure 2). The percentages on the figures indicate the proportions of results below or above the 10% limit (n = 372 and n = 202 paired measurements for *A* and *B*, respectively).

modal distribution of the size of the effects of the "active" samples is in favor of a unique alternative explanation.

It is important to note that log transformation was not used by Benveniste and coworkers. Therefore, the symmetrical aspect (Gaussian) of the two populations of effects ("inactive" and "active"), which is evidenced in Figure 3A and 3B only after log transformation, is an indirect evidence of the relevance of the reported results. It is also important to note that the aim of the public demonstrations performed by Benveniste was not to prove a correlation between apparatus A and B but to verify the fit of the results with the initial samples supposed to be "inactive" or "active." Therefore, these correlated duplicate measures did not draw any particular attention and have not been highlighted by Benveniste. Nevertheless, I think these results are particularly important because they indicate that coherence was present in these puzzling experiments despite apparent discordances. The aim of the following analyses is to understand when correlations persist and when they are broken.

IN WHICH EXPERIMENTAL CONDITIONS DID CORRELATIONS VANISH?

Experimental Situations with Correlations

We have seen in the last section that the values of the measures with the two parallel devices A and B were correlated. Thus, when the value on apparatus A was >10%, the probability to obtain a value >10% on apparatus B was high (this was symmetrical for measures <10%; Figure 3A and 3B; situation 1 in Table 2).

In Table 2, other experimental situations are described. Thus, in situation 2, an in-house coding was performed between the first and the second measurements (both measurements were performed with the same apparatus). In these in-house blind conditions, correlations were also obtained (in this case, we do not worry about the initial "label" of the sample, ie, samples supposed to be active or controls). Again we observe that the results of the measurements (>10% or <10%) were concordant despite the blinding. In situation 3, open-label samples supposed to be "inactive" and "active" were prepared. Measurements were performed after in-house blinding and correlations were also observed. Therefore, in these first three situations with open-label experiments or in-house blind experiments, the statistical difference in effects between "inactive" and "active" samples is very significant.

Experimental Situation without Correlation

The crucial issue is depicted by the experiments of situation 4 with coding of the samples by a participating outside observer (an experimental situation comparable to the public demonstration described above). When all measurements had been performed by the experimenter on the Langendorff apparatus, the results were sent by Benveniste's team to the participating outside observer, who held the code of the samples and who compared the two series (biological effects and labels of the corresponding samples). In this situation, the biological effects (<10% and >10%) were distributed at random according to the initial label ("inactive" or "active" samples; Table 2). In summary, correlations were evidenced either in open-label experiments or in-house blind experiments; in sharp contrast, in blind experiments involving a participating outside observer, the correlations vanished.

WHAT HAS BEEN MODIFIED IN THE EXPERIMENTAL PROTOCOL TO ADAPT IT TO BLIND PUBLIC DEMONSTRATIONS?

All bench scientists know that tiny modifications in an experimental protocol could have unexpected negative consequences on outcomes. Therefore, we have to wonder what has been

Table 2. Reappraisal of Benveniste's experiments with the Langendorff Apparatus: Concordant and Discordant Outcomes in Different Experimental Conditions

	Number of Experimental Points	% of Experimental Points with Size of the Biological Effects <10%	% of Experimental Points with Size of the Biological Effects >10%	*P*-Value[a]
Open-label experiments				
Situation 1: apparatus A vs. apparatus B[b]				
Value <10% after measurement with apparatus A	n = 372	**93%** (apparatus B)	7% (apparatus B)	$< 1 \times 10^{-83}$
Value >10% after measurement with apparatus A	n = 202	11% (apparatus B)	**89%** (apparatus B)	
In-house blind experiments				
Situation 2: first vs. second measurements of the same sample				
Value <10% after first measurement	n = 50	**96%** (second measurement)	4% (second measurement)	$< 1 \times 10^{-13}$
Value >10% after first measurement	n = 28	7% (second measurement)	**93%** (second measurement)	
Situation 3: "Inactive" vs. "active" samples				
"Inactive" samples	n = 68	**88%**	12%	$< 1 \times 10^{-13}$
"Active" samples	n = 58	19%	**81%**	
Blind experiments with participating outside observer				
Situation 4: "Inactive" vs. "active" samples				
"Inactive" samples	n = 54	57%	43%	0.25
"Active" samples	n = 54	44%	56%	

Percentages of concordant outcomes that are statistically significant are indicated in bold type.

[a]Chi-square test.

[b]See also Figure 3 for situation 1.

modified between in-house and public experiments. The public demonstrations set up by Benveniste's team were generally performed in two steps. In a first step, negative and positive samples were produced (high dilutions, samples of "informed water" or digital files) and were blinded with a code by an observer not belonging to Benveniste's team (whom we call a "participating outside observer"). Some negative and positive samples were kept open. In a second step, Benveniste's team tested all blind and open-label samples. When all measurements were completed, the results were sent (by fax or e-mail) to the participating outside observer who checked the experimental outcomes and the labels of the corresponding initial samples.

Therefore, a noteworthy modification to the initial protocol was the checking of the two series after completion of experimental data. We can now describe two experimental situations that gave quite different results. In the first case, there was no blinding or in-house blinding, and the expected correlations were observed. In the second case, a participating outside observer checked the two series after completion of the measures, and the experiment was a "failure" (no significant correlations were observed). Once more, it is important to emphasize that usually samples kept open-labeled by the participating outside observer were nevertheless in-house blinded (see the section *An Example of "Public Demonstration"*).

Because the outcomes of the trials seem to strongly depend on the people who performed the experiments and checked the results, these experiments appear to be experimenter-dependent. A similar unusual conclusion was already reported for these experiments by a multidisciplinary team that was mandated to assess the "digital biology" of Benveniste, as explained in the next section.

THE END OF THE "MEMORY OF WATER" HYPOTHESIS?

Laboratories able and willing to reproduce the experiments with the Langendorff system were rare when Benveniste proposed to replicate them. Therefore, Benveniste developed a new biological model based upon the coagulation of plasma. An automated robot analyzer was then set up to perform the coagulation experiments with a limited intervention by the experimenter. The different steps of the experiments were automatically performed: random choice of computer files, "irradiation" of water samples, distribution of samples and biological reagents in wells, and quantification of coagulation (by optical density reading). In its last version, the coagulation model was purely biochemical, with coagulation of fibrinogen by thrombin in the presence of inhibitory "digital heparin." The previous results of "digital biology" and high dilutions were confirmed using this model, either manually or with the automated analyzer.

The story of "digital biology" reached its highest point in 2001 when a multidisciplinary team of scientists attempted to repli-

cate Benveniste's experiments on coagulation experiments by using the automatic robot analyzer at the request of the United States Defense Advanced Research Projects Agency. As reported in an article describing the results of these experiments, some effects that supported the concept of "digital biology" were observed.[21] However, the experts in the multidisciplinary team did not conclude that the effects of "digital biology" were real because they noticed that these effects could not be observed independently of the experimenter in Benveniste's team assigned to this experimentation. Interestingly, the authors concluded that unknown "experimenter factors" could explain these odd results but that a theoretical framework was necessary before trying to apprehend them; they added: "Without such a framework, continued research on this approach to digital biology would be at worst an endless pursuit without likely conclusion, or at best premature."[21]

Indeed, if the presence of some people is necessary to observe a biological effect, are we still talking about water properties?[22] Taken together, all these results suggest strongly that the "memory" in the "memory of water" experiments was not located in water. However, a puzzling question remains: how did a signal nevertheless emerge from background noise? To answer this issue, we propose to describe these experiments by using concepts from relational quantum physics.

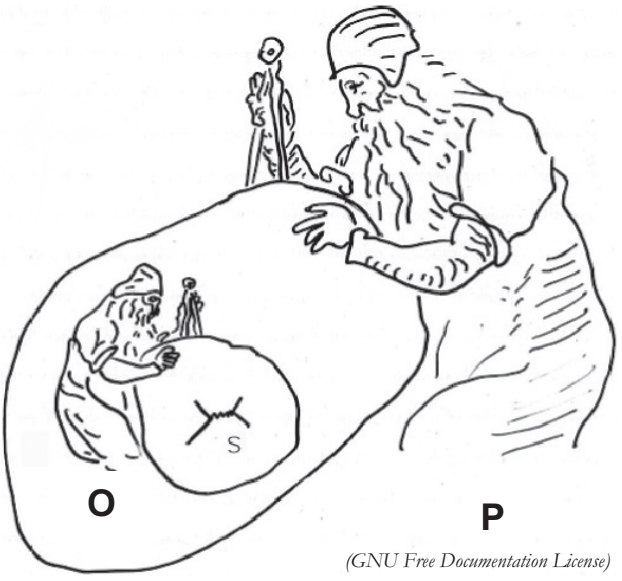

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Figure 4. The observer observed in the relational interpretation of quantum mechanics. The observer O measures system S and P observes O. What information does P have on O? (see text).

RELATIONAL QUANTUM PHYSICS

Description of the Relational Interpretation

In quantum physics, the evolution of a system is described by the Schrödinger equation; it is called the evolution of the wave function. This evolution is determinist, but this determinism is not for events, as in classical physics, but for the probabilities of these events. As a consequence, we cannot predict the outcomes of individual measurements but only their probabilities.

The "measurement problem" has its roots in the discrepancy between the linear superposition of the different states (as described by the Schrödinger's equation) and the actual measurements, which always find the physical system in a definite state (and not in a superposed state). Moreover, there is no indication in the quantum formalism of a boundary between the microscopic and the macroscopic world: the observers and their measurement apparatus are themselves described by a determinist wave function and for them also no precise results can be predicted for measurements, only probabilities. The purpose of the different interpretations of quantum physics is to establish a correspondence between quantum and classical reality.

The relational interpretation of quantum physics arose from a reflection on the measurement problem.[23,24] To explicitly address the measurement problem, Rovelli[23] supposes an observer (named O) who makes a measurement of a parameter of a quantum system S, which has two possible outcomes, namely " $\downarrow$ " and " $\uparrow$."

In quantum physics, all the knowledge on a physical object can be summarized by a "state vector" written as $|\psi\rangle$, and the state of the system S is described by the following state vector: $|\psi\rangle = \alpha|\downarrow\rangle + \beta|\uparrow\rangle$. This means that, after a measurement, the probability to observe the result " $\downarrow$ " is α^2 and the probability to observe the result " $\uparrow$ " is β^2 (with $\alpha^2 + \beta^2 = 1$; α and β are complex numbers).

In relational quantum mechanics (RQM), the state vector is the information that a given observer possesses on a quantum object. Therefore, a quantum description of the reality should be always in reference to an observer, and there is no metaobserver of the reality. In addition, there is no distinction between microscopic and macroscopic worlds in RQM; all physical events are quantum events and there is no "wave function collapse" (ie, the wave function remains in a superposed state and the wave function collapse appears only in the states relative to a given observer).

After a measurement, O observes either " $\downarrow$ " or " $\uparrow$," with the respective probabilities α^2 and β^2. If we suppose that the outcome of the measurement by O is " $\uparrow$," then the evolution of the system between t_1 and t_2 is:

$$|\psi\rangle = \alpha|\downarrow\rangle + \beta|\uparrow\rangle \rightarrow |\uparrow\rangle$$

We now suppose an observer P, who describes the system formed by S and O, and its evolution (Figure 4). We suppose that P has complete information on the initial state of this system but does not make an observation of it during its evolution. If the initial state vector of O is $|init\rangle$, then the evolution of the system S–O between t_1 and t_2 is described by P as:

$$(\alpha|\downarrow\rangle + \beta|\uparrow\rangle) \otimes |init\rangle \rightarrow \alpha|\downarrow\rangle \otimes |O_\downarrow\rangle + \beta|\uparrow\rangle \otimes |O_\uparrow\rangle$$

where $|O_\downarrow\rangle$ and $|O_\uparrow\rangle$ are the state vectors of O who has observed " $\downarrow$ " or " $\uparrow$ ", respectively. Therefore, the wave function describing the system S–O evolves into a superposition of two states: the observer has obtained the result " $\downarrow$ " in one state and the result is " $\uparrow$ " in the other state.

We conclude that, at the time t_2, O and P make different accounts of the same events. For P, the system is in a superposed

state after measurement; for O, a unique value has been obtained. Thus, we have at our disposal two correct descriptions, but they differ according to the observer considered. If, at a time t_3 after t_2, P interacts *physically* with S–O, then the state vector of S–O "collapses" and only one "branch" is observed by P. In each "branch," P observes that the state of S and the state of O are correlated. The state of P himself becomes correlated with one possible state of S–O. The states of S, O and P are correlated and S, O and P are said to be entangled. This is what Rovelli names the "main observation" on which the rest of the relational interpretation relies: "In quantum mechanics different observers may give different accounts of the same sequence of events."

EPR Experiment and Relational Interpretation

The relational interpretation provides an interesting solution to the EPR "paradox" by dissolving it.[25] The EPR paradox considers two quantum objects in the following superposed state: $|\psi\rangle = \alpha|\downarrow\rangle_1 |\uparrow\rangle_2 + \beta|\uparrow\rangle_1 |\downarrow\rangle_2$. The measurements on the two objects are correlated (the two quantum objects are entangled).

According to the orthodox interpretation of Copenhagen, as soon as a result has been obtained after the first measurement (for example " ↑ "), then the value of the second object is immediately fixed (" ↓ " in this case). Therefore, the price to pay for this interpretation is to suppose superluminal transfer of information (nevertheless, this superluminal transfer cannot carry useful information because the pairs of measures " $\downarrow_1 \uparrow_2$ " or " $\uparrow_1 \downarrow_2$ " are obtained at random). Moreover, we have to admit a "nonlocal" description of the world: a measurement at one place in the universe could have immediate consequences at another place, even if there is an astronomical distance between them.

According to the Everett's interpretation (as popularized by De Witt), after measurement, the two possible pairs of results (" $\downarrow_1 \uparrow_2$ " and " $\uparrow_1 \downarrow_2$ ") are both observed (there is no wave function collapse) but in two different universes. The locality is preserved in this interpretation, but the price to pay is the proliferation of universes.

In the context of relational quantum physics, Rovelli and Smerlak[25] pointed out that, in a system of two entangled quantum objects, an observer never makes both measurements simultaneously. Indeed, the observer makes a measurement of the first object and one "branch" of the superposed state of the first object is selected at random. Then, the observer uses classical means (at a speed below light velocity) to measure the second quantum object *which remains superposed* (for an observer P) even after the first measurement. The "branch" of the superposed state of the second object is selected by taking into account the past of the observer, that is, the result he or she has obtained after the first measurement. Therefore, there is no superluminal transfer of information and the principle of locality is preserved for each observer. The price to pay for this interpretation is a weakening of realism. The interpretation of Rovelli could be of some help in our present issue with the notion of experimenter-dependent outcome and with the absence of a distinction between microscopic and macroscopic worlds.

DESCRIPTION OF BENVENISTE'S EXPERIMENTS USING THE RELATIONAL INTERPRETATION OF ROVELLI

Definitions

The purpose of the experiments to be described was to correlate sample labels with apparatus outcomes. We summarize the sample labels as "inactive" and "active" (abbreviated as *IN* and *AC*, respectively); the outcomes of the apparatus are "background noise" and "signal" (symbolized as " ↓ " and " ↑ ," respectively).

We describe a minimal experiment where the effect of a unique "sample" is observed. It should be clear that, according to the previous analyses, we consider all samples physically indistinguishable. The only difference is between "labels," namely, the "properties" that samples are supposed to possess.

The experimenter A (Alice) observes, in a first step, sample labels and apparatus and, in a second step, she assesses the concordance of the paired observations (label *IN* with outcome " ↓ "; label *AC* with outcome " ↑ "). If the statistical analysis of repeated experiments indicates that the pairs are significantly correlated, the experiment is considered a "success." If there are too many discordant pairs (defined as label *IN* with outcome " ↑ " or label *AC* with outcome " ↓ "), the experiment is a "failure."

We consider the point of view of an observer P as defined previously, who describes Alice observing sample labels and apparatus outcomes. This observer P has a complete knowledge of the initial conditions of the system (Alice) and describes its evolution, but he does not interact with it.

Open-Label Experiments

The evolution of the state vector of Alice when she observes the label is:

$$|\psi_{A\,init}\rangle \rightarrow |\psi_A\rangle = \alpha|A_{IN}\rangle + \beta|A_{AC}\rangle \quad \text{with } \alpha^2 + \beta^2 = 1$$

The evolution of the state vector of Alice when she observes the apparatus outcome is:

$$|\psi_{A\,init}\rangle \rightarrow |\psi_A\rangle = a|A_{\downarrow}\rangle + b|A_{\uparrow}\rangle \quad \text{with } a^2 + b^2 = 1$$

For an observer P, the state vector of A after completion of the experiment (ie, observation of both label and outcome) is:

$$|\psi_A\rangle = (|A_{IN}\rangle + |A_{AC}\rangle) \otimes (|A_{\downarrow}\rangle + |A_{\uparrow}\rangle) \qquad (1)$$

N.B. For clarity, the coefficients associated with the vectors are not indicated in this equation and in the following equations. For the moment we admit that the signal (" ↑ ") is observed by Alice with a probability that is not negligible (we will detail in the section *Emergence of a Signal from Background Noise* how the signal could have emerged from the background). We have seen that open-label experiments were considered as successes (Table 2). In this experimental situation, statistically significant correlations between *IN* and " ↓ ," on one hand, and *AC* and " ↑ ," on the other hand, are observed. Therefore, the state vector of A after an open-label experiment can be described as follows:

$$|\psi_A\rangle = |A_{IN}\rangle|A_{\downarrow}\rangle + |A_{AC}\rangle|A_{\uparrow}\rangle \qquad (2)$$

In the description of the evolution of the system from Equation 1 to Equation 2, it is as if the discordant pairs $|A_{IN}\rangle|A_{\uparrow}\rangle$ and

$|A_{AC}\rangle|A_{\downarrow}\rangle$ were "filtered." If we suppose that all samples tested in these experiments are physically undistinguishable (only their labels are different: *AC* and *IN*) and that trivial causal relationships have been discarded, there is no reason to observe different outcomes with the different samples. Yet, significant correlations have been observed.

Therefore, the question is what or who decides for concordant paired observations? If there is nothing in the history of the universe that could explain the "decision," then the choice should be considered as free. As a consequence, we make the assumption that concordant paired observations result from an act of free will. This free will is exerted by Alice on her own state as formalized by the evolution of the state vector $|\psi_A\rangle$. Alice's free will is based upon her *a priori* knowledge about the results of experiments. Some comments on free will in the context of quantum physics are added in the section *Free Will and Quantum Physics*.

In-House Blind Experiments

In Equation 2, the order of the two observations (labels and outcomes) has no consequence, eg, $|A_{AC}\rangle|A_{\uparrow}\rangle$ is equivalent to $|A_{\uparrow}\rangle|A_{AC}\rangle$. This formalism simply means that *AC* and " ↑ ," on one hand, and *IN* and " ↓ ," on the other hand, are observed together by Alice, regardless of the order of the observations. This indicates that the two experimental situations: (1) Alice observes the label before the outcome (*open-label experiment*) or (2) Alice observes the outcome before the label (*in-house blind experiment*), are formally identical. This description fits precisely to Benveniste's experiments where both situations led to significant correlations (Table 2).

Emergence of a Signal from Background Noise

Using the same formalism, we describe now the emergence of a signal from background noise. Indeed, if Alice does not exert her free will, there is no "filter," and her state vector is equal to the Equation 1 after development:

$$|\psi_A\rangle = \underbrace{|A_{IN}\rangle|A_{\downarrow}\rangle + |A_{AC}\rangle|A_{\downarrow}\rangle}_{\text{High probability}} + \underbrace{|A_{IN}\rangle|A_{\uparrow}\rangle + |A_{AC}\rangle|A_{\uparrow}\rangle}_{\text{Low probability}}$$

In the absence of a "filter," we have seen that the probability of Alice observing a signal is low; background noise is most probably observed. We have to remember that the numbers of "inactive" and "active" labels have been defined by the experimental protocol. If we suppose that there are as many "inactive" as "active" labels, then the most probable states of Alice after completion of the experiment are $|A_{IN}\rangle|A_{\downarrow}\rangle$ with a 50% probability and $|A_{AC}\rangle|A_{\downarrow}\rangle$ with a 50% probability (we consider that the probability of the states $|A_{IN}\rangle|A_{\uparrow}\rangle$ and $|A_{AC}\rangle|A_{\uparrow}\rangle$ are negligible but not equal to zero).

If Alice exerts her free will, "discordant pairs" are filtered and the distribution of the probabilities between the different states of Alice is changed because the state vector of Alice has evolved to: $|\psi_A\rangle = |A_{IN}\rangle|A_{\downarrow}\rangle + |A_{AC}\rangle|A_{\uparrow}\rangle$ (Equation 2). We see easily that the probability associated with $|A_{IN}\rangle|A_{\downarrow}\rangle$ is again 50% (half of labels are *IN*); the probability associated with $|A_{AC}\rangle|A_{\uparrow}\rangle$, which was negligible before filtration, is now increased to 50% (half of labels are *AC*). In other words, a signal has been forced to emerge from the background as a result of branch selection.

The result of this process is like a magnifying glass, which enlarges some parts of the reality perceived by the observer. Nevertheless, this "reality" can be shared with other observers. If an observer E (Eve) interacts physically with Alice after completion of the experiment, the state vector that describes Alice and Eve is:

$$|\psi_{AE}\rangle = |A_{IN}\rangle|A_{\downarrow}\rangle|E_{IN}\rangle|E_{\downarrow}\rangle + |A_{AC}\rangle|A_{\uparrow}\rangle|E_{AC}\rangle|E_{\uparrow}\rangle$$

In both branches of the state vector, Eve agrees with Alice–after several experiments–that there is (1) an emergence of a signal from the background and (2) a statistically significant correlation between labels and outcomes: samples supposed to be active are associated with a signal, and samples supposed to be inactive are associated with background noise.

It is important to note that we are not presently supporting remote effects by free will. Indeed, remote effects suppose a classical causal relationship involving forces or fields. In the present case, the emergence of a signal is the consequence of entangled states. In this sense, the relationship between labels and outcomes could be considered as acausal.

In the context of Benveniste's experiments, we propose that the different and successive experimenters acquired skill by manipulating the biological systems and measurement devices (for example by using "classical" stimuli). We can see this ability to filter random outcomes as an extension of associative learning from the classical world to the quantum world. This could explain why some experimenters (such as Alice) were more competent to obtain the "expected" correlations.

Experiments with Participating Outside Observer

Let us consider now the case with a participating outside observer B (Bob). Bob is introduced into the experimental design to blind and control the results of Alice; he does not interact with Alice during her measurements. The experimental process is therefore modified. Thus, after completion of the measurements, Alice sends the results she obtained (ie, which samples are associated with signal) to Bob, who compares them with the labels he blinded. As a consequence, the assessment of correlations by Bob is a chief difference for this modified experimental design. We have seen that this experimental design with a participating outside observer was not successful because no significant correlations between labels and outcomes were observed. The state vector of Alice and Bob in this experimental situation can be described as:

$$|\psi_{AB}\rangle = \left(|B_{IN}\rangle + |B_{AC}\rangle\right) \otimes \left(|A_{\downarrow}\rangle + |A_{\uparrow}\rangle\right) \quad (3)$$

$$= |B_{IN}\rangle|A_{\downarrow}\rangle + |B_{IN}\rangle|A_{\uparrow}\rangle + |B_{AC}\rangle|A_{\downarrow}\rangle + |B_{AC}\rangle|A_{\uparrow}\rangle \quad (4)$$

In this experimental situation, a signal emerges nevertheless from background, but we have to wonder why no significant correlations are observed. Indeed, it could be argued that Bob is nothing else than a quantum object and that there should be no obstacle for Alice's free will to filter the state vector of Equation 4 to get $|\psi_{AB}\rangle = |B_{IN}\rangle|A_{\downarrow}\rangle + |B_{AC}\rangle|A_{\uparrow}\rangle$.

However, this reasoning cannot be held. The main argument relies on intersubjective agreement, which is guaranteed by

quantum physics. Indeed, after completion of the measurements, Bob assesses the correlations between labels and biological outcomes independently of Alice. Bob observes a significant proportion of discordant pairs (Bob is supposed to be unable to filter them). Moreover, Bob cannot feel himself in a superposed state. Therefore, when Alice and Bob come together, these discordant pairs must be present in the state vector that describes the two observers. Indeed, it is impossible that significant correlations exist (according to Alice) and do not exist (according to Bob) simultaneously. Therefore, the only way to reach an intersubjective agreement is to suppose that the state vector $|\psi_{AB}\rangle = |B_{IN}\rangle|A_{\downarrow}\rangle + |B_{AC}\rangle|A_{\uparrow}\rangle$ is not possible and that only Equation 4 (which includes all possible pairs, both concordant and discordant ones) is the correct description of the intersubjective reality of Alice and Bob. In this shared reality, Bob and Alice agree that no significant correlations were observed in the series of experiments they performed.

FREE WILL AND QUANTUM PHYSICS

When two electrons interact (ie, they are next to each other), their spins (up or down) align in opposite directions like small magnets. Before the interaction, the state vector that describes the state of the system composed of the two electrons is:

$$|\psi_{e1e2}\rangle = |up\rangle_1|down\rangle_2 + |up\rangle_1|up\rangle_2 + |down\rangle_1|down\rangle_2 + |down\rangle_1|up\rangle_2$$

After the interaction, the state vector is $|\psi_{e1e2}\rangle = |up\rangle_1|down\rangle_2 + |down\rangle_1|up\rangle_2$. We see that some branches of the superposed state vector (branches with spins of the two electrons pointing in the same direction) have been "filtered."

In physics, there are conservation laws, and one of them requires that, after an interaction of two electrons, the sum of their spins must be zero (ie, they must have opposite spins). Whatever happens to these electrons–they can be separated at great distances–their total combined spin must remain zero. If one measures " $\downarrow$ " for the first electron of the entangled pair, then we can hold for sure that the measure of the second electron will be " $\uparrow$ ": the electrons are said to be entangled. Therefore, we can suggest that the notion of free will that we have introduced previously plays a role analogous to a conservation law (at least for a limited duration) by filtering some states and therefore entangling quantum objects.

The use of the notion of free will in a quantum description should not surprise. When an outcome is not determined by the past history of the universe, it can be considered as a consequence of free will. On this basis, Conway and Kochen[26] have demonstrated that if we have (some) free will, then quantum particles also have (some) free will. Free will, defined in this sense, together with the central role of the observer, is an essential element of the description of quantum events by quantum theory. Zeilinger insists on two freedoms in quantum experiments: first, the freedom of the experimenter when he chooses the setting of the measuring apparatus, and second, the freedom of the nature, which gives an answer; detection with a measuring apparatus can thus be considered as an "elementary act of creation."[27] These views will certainly be important to consider for a theory of free will and consciousness that remains to be written.

ANSWER TO THE MAIN OBJECTION

The usual criticism to our description of Benveniste's experiments using quantum formalism can be summarized by this comment: "How quantum superposition could be guaranteed at ambient temperature? Indeed, the environment of the experiment should lead to quick decoherence."

This comment would be quite pertinent within the framework of the Copenhagen interpretation of quantum physics, but in the context of RQM, this criticism is irrelevant. Therefore, we have to insist briefly on some particular issues in RQM.

In RQM, the only way to say that an event has occurred or has not occurred is to *index it*. If I measure that the spin of an electron is up, I cannot conclude that the spin of the electron *is* up. I can only say that the spin of this electron *as measured by me* is up. In other words, the actual outcome is real only with respect to the observer. Therefore, in contrast with classical physics, where there is a unique account of the reality by multiple observers, in RQM there are as many accounts as observers. The comparison of results between different observers is also a physical process and coherence is guaranteed by RQM; as suggested by Vecchi,[28] "reality" is the locus of intersubjective agreement. As a consequence of the multiple possible observers, there is *no wave function collapse*; more precisely, the wave function collapse appears only in the states relative to *a given observer* and decoherence in this context is the theory that explains how the actualization of the variable occurred for this observer. RQM allows describing not the physical world itself but rather the *general form of information* that one system can obtain about another. This description is expressed in the form of correlations (between entangled objects and observers); describing correlations in the physical world is precisely the exact definition of science.

This simple (and easily acceptable) restriction to our discourse on the physical world by indexing an event to an observer has a huge advantage: it allows overcoming some of the difficulties of other interpretations of quantum physics (Copenhagen, Everett, etc). As an example, the relativization of actuality to each observer allows reconciling quantum physics with locality.[25] As already said, one consequence of RQM is a weakening of realism.

It is important to insist that RQM should not be confused with the "relative state" interpretation of Everett where there is a multiplicity of realities; in RQM, a quantum event refers only to a pair of systems. These few comments can be completed by further readings on RQM, which is outside the scope of the present paper.[23-25]

CONCLUSIONS

In summary, our reappraisal of Benveniste's experiments has led to the conclusion that the results were experimenter-dependent. A model based on the relational interpretation of quantum physics describes the characteristics of these experiments: (1) experimenter-dependent emergence of a signal from background noise, (2) loss of correlations between the supposed

"causes" and the observed effects in some defined experimental conditions, and (3) difficulties for other independent teams to produce a signal and significant correlations. Therefore, although our hypothesis does not dismiss definitely the possibility of "memory of water," the experimenter-dependent entanglement could be an attractive alternative interpretation of Benveniste's experiments.

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