ARE BIOLOGICAL SYSTEMS AND EXPERIMENTERS REALLY SEPARATED?

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ABSTRACT

Background. In experimental sciences, conception of an experiment and record of the outcomes must be strictly separated. Although many possible pitfalls have been described, particularly in biological sciences, one cannot exclude unknown loopholes.
Methods. A simple probabilistic modeling is constructed in order to describe experimenters testing the hypothesis of a relationship between some experimental conditions (supposed causes) and states of a biological system (observed effects). The modeling rests on two preliminary remarks. First, after assessment of a relationship, the outcome is not a property of the system alone, but is a property of the experimenters and the system taken as a whole. Second, as a consequence, the outcome does not preexist to measurement.
Results. A biological system with two possible states ("resting" and "activated") exposed to two control conditions distinguished only by their "labels" is modeled. A classical approach suggests that the two control conditions are both associated with the "resting" state (*i.e.* no relationship). Nevertheless, if the fluctuations of the system are considered, the hypothesis of a significant relationship between "labels" and system states is confirmed. In contrast, if the outcomes are not globally recognized as a relationship, but remains unconnected by the experimenters, no significant relationship emerges.
Conclusion. This probabilistic modeling suggests that, despite precautions, the strict separation of biological systems and experimenters is an ideal not necessarily achieved when the hypothesis of a relationship is tested. The consequences could be wrong conclusions about causal relationships. Specific blind procedures are proposed to prevent unwanted correlations involving the experimenters.

Keywords: *Probabilistic modeling; Experimenter effect; Experimental biases; Blind experiments; Quantum-like correlations; Quantum biology.*

1. INTRODUCTION

The modern concepts of experimental biology have been formalized in 1865 by the French physiologist Claude Bernard in his famous book "*Introduction to the Study of Experimental Medicine*" [1]. As in other experimental sciences, biologists seek to evidence the immediate causes of natural phenomena in living beings. There are however some well-known pitfalls and Claude Bernard was one of the first to warn against projection of scientist's preconceived ideas on the studied phenomena. He proposed to separate the experimenter who conceives the experiment and the observer – preferably naïve – who passively records the outcomes [1].

In experimental psychology, the Pygmalion effect described by Rosenthal is an example of correlations between the expectations of the teachers and the performances of the students [2]. This author reported also correlations between expected results and observed results in experimenters who tested rats for cognitive performances [2]. In order to avoid such biases, the double-blind method is now the rule for the evaluation of new drugs in clinical trials. However, blind procedures are rarely used for biology experiments performed on lab bench.

The absence of collusion between experimenters and observed systems is an essential condition in experimental sciences. In the absence of a strict separation, the risk is that experimenters describe what in fact they contribute to construct. Indeed, an objective and scientific description of natural phenomena becomes impossible in the absence of reliable "controls". Besides the classical pitfalls of experimental research, one cannot exclude unknown "backdoors" that remain to be discovered.

In the present article, we present a probabilistic modeling that suggests that correlations could be established between observers and experimental systems as a consequence of the measuring act itself. Biological systems appear to be more appropriate to evidence these correlations because they have a great number of degrees of freedom. The originality of the modeling is the description of the interactions of experimenters and observed system from an outsider point of view. Although this approach is purely theoretical, the simplicity of the modeling merits attention. Furthermore, different types of blind procedures are proposed to prevent the establishment of such correlations.

2. METHODS

2.1 Rationale for an uninvolved point of view

If we measure the length or the mass of an object, we easily accept that the measured value preexists to the measurement and exists independently of any observation. If after assessing the mass of an object we obtain a result equal to 1.26 kg, we consider that we have gained knowledge on a property of the object. The name "property" itself strongly suggests that the measured value is an intrinsic characteristic of the object. In other words, the measured values and the object's properties can be matched on a one-to-one basis. In this section, we will see that the assessment of a *relationship* between different variables of an experimental system cannot be considered as a property of the system alone.

We suppose an observed system *S* and an experimenter/observer named *O*. The purpose of the experiment is not to measure a single variable of *S*, but to evaluate a relationship between two variables which have been chosen by *O* (*e.g.* getting seven with two rolling dices). The outcome expectation by *O* could be compared to the setting of a measuring device before a measurement. The different possible states of *S* (*e.g.* the 36 possible outcomes with two rolling dices) are properties that obviously belong to *S*. However, after measurement of *S* by *O* for a *predefined relationship*, the outcome recorded by *O* (*e.g.* the observation – or not – of a total of seven with two rolling dices) is not a property of *S* alone, but is a property of *O* and *S taken as a whole* (**Figure 1**). Another observer, who does not know the specific game rules, has no answer for this specific question (just one of the 36 possible outcomes), thus demonstrating that the value recorded by *O* is not an obvious property of *S*.

Since *O* and *S* constitute a new "object" *O*-*S* that cannot be dissociated, one could suggest that a second experimenter would be able to measure it. But, for the same reasons, the consequence of the measurement (*i.e.* the interaction) of *O*-*S* by another experimenter *O*' for the same relationship is the creation of a new entity *O*'-*O*-*S* that cannot be dissociated (and so on for further observers).

Because the experimental situation cannot be described from an insider point of view – *i.e.* the perspective of an agent who interacts with *S* and/or *O* – it is described from an outsider point of view. For this purpose, one supposes an agent named *P* who is uninvolved in the measurement process and does not interact with the experimenters when the experiment is performed. This agent describes the experimental scene (including *O*, *O*' and *S*) in terms of probabilities of expected outcomes and interactions/measurements.

Two spaces are thus defined for the description of the experimental process. The first space is a probabilistic space that is constructed by *P*. This space allows *P* to know on what to expect if he decides to interact with *O*-*O*'-*S* after the experiment is finished. The second space corresponds to "reality" defined by the intersubjective agreement (*O* and *O*' always agree on their joint observations/measurements).

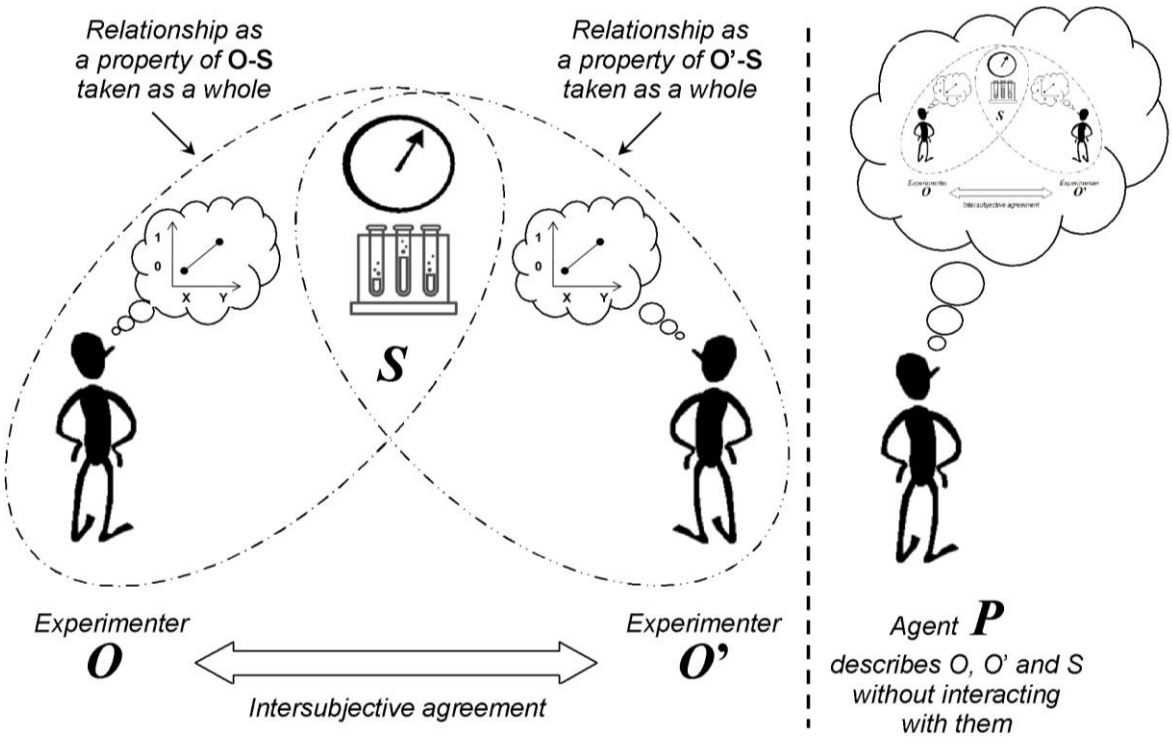


Figure 1. Experimental outcome as a property of system and observer taken as a whole when a relationship is assessed. After a measurement of the experimental system *S* by an experimenter *O* (or *O*') for a predefined relationship, the measured value is not a property of *S* alone, but is a property of *O*-*S* (or *O*'-*S*) taken as a whole. The experimenters agree on their observations (intersubjective agreement). The situation is described from the standpoint of an agent *P* who does not interact with *O*, *O*' and *S*. The agent *P* describes the experimental scene (including the experimenters and the observed system) in terms of probabilities of expected outcomes and interactions/measurements. Note that from the point of view of *P*, the order of the interactions of *O*, *O*' and *S* does not matter: *e.g. O* with *S,* then *O*' with *S* and finally *O*-*S* with *O*'-*S*; *O* with *S* and then *O*' with *O*-*S*.

2.2 Mathematical description of a result not preexisting to measurement

An important consequence of the previous section is that the result of a measurement for a relationship *does not preexist* to the measurement process. Indeed, if the result is a property of *O*-*S* taken as a whole and not an individual property of *S*, it means that the result is created when *O* and *S* join together to form *O*-*S*, *i.e.* when *O* measures *S*.

The second experimenter *O*' is introduced in the modeling in order to observe the measurement process of *S* by *O* (symmetrically, *O* observes the measurement process of *S* by *O*').

We now describe in mathematical terms an outcome that does not preexist but is created by the measurement process. We state that, *before the measurement*, the future event expected by *O* (event *A*) and the future event expected by *O*' (event *B*) are *independent* events in the probabilistic space constructed by *P*. Indeed, suppose that the events *A* and *B* are not independent but strictly correlated: if the event *B* is defined with certainty (*i.e.* Prob (*B*) = 0 or 1), then the event *A* is also defined with certainty before being measured. This means that, in this case, the result of the measurement of *S* by *O* preexists to this process.

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

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

The right side of the equation refers to the probabilistic space constructed by the uninvolved agent *P* and the left side refers to the "reality" shared by *O* and *O*'. "Reality" is thus defined as the events in the subset $A \cap B$ of the probabilistic space constructed by *P*. In other words, each "real" event is randomly obtained from the subset $A \cap B$ that corresponds to the interaction of *O* and *O*'. The events observed by *O* and *O*' in the subset $A \cap B$ are *coincident events* from the point of view of *P* and therefore *do not preexist* before the interaction of *O*-*S* and *O*'-*S* (they are properties of *O*-*O*'-*S* taken as a whole, not properties of *O*-*S* alone or *O*'-*S* alone).

Combining independence of expected outcomes and intersubjective agreement will be the basis for the construction of a modeling that describes outcomes not preexisting to their measurement.

Note that one implicitly considers in this section that "reality" is defined by measurements and interactions. This point will be specified in the discussion.

2.3. Definitions of "direct" and "reverse" relationships

In most experiments in medicine or biology, the experimenters seek to evaluate a relationship between a "cause" (independent variable) and an "effect" (dependent variable). Control samples in experimental biology (or placebos in clinical trials) allow assessing the effects of variables other than the independent variable, but not controlled by the experimenter.

We propose to describe an elementary experiment aimed at evaluating a relationship between some experimental situations and the corresponding states of a biological system. For simplicity, we suppose that the biological system has only two mutually exclusive states symbolized with "↓" (= resting state; not different from background noise) and "↑" (= "activated" state; significantly different from background noise). We suppose also that

the experimental system can be exposed to two experimental conditions that are both control conditions (or placebos). Their only difference is their "labels" noted Pcb_0 and Pcb_1. Note that labels must be understood in a broad sense; it could be names, colors, procedures or "rituals". A classical approach suggests that the two control conditions are always associated with "resting" state (*i.e.* no relationship). This can be translated in mathematical language:

$$\text{Prob}\,(\downarrow \mid Pcb_0) = \text{Prob}\,(\downarrow \mid Pcb_1) = 1 \qquad \text{(Eq. 2)}$$

with Prob ($x \mid y$) which is the conditional probability of x given y (or the probability of x under the condition y).

The experimenters combine the four possible combinations of labels and biological states into two groups that are *meaningful* for them because this association supposes the existence of a relationship (to be demonstrated by future experiments) (**Figure 2**). These two relationships are arbitrarily named "direct" and "reverse":

- "Direct" relationship is the association of Pcb_0 with "↓" and Pcb_1 with "↑";
- "Reverse" relationship is the association of Pcb_0 with "↑" and Pcb_1 with "↓".

The total probability of these two relationships is equal to one and is noted: Prob (*direct*) + Prob (*reverse*) = 1.

The labels Pcb_0 and Pcb_1 play a symmetrical role and consequently Prob (Pcb_0) = Prob (Pcb_1) in probabilistic calculations. Thus, in **Figure 2B**, according to Eq. 2 (no relationship between labels and system states), Prob (*direct*) = Prob (*reverse*) = 1/2. In the present modeling we will explore if, in some conditions, Prob (*direct*) could be different from 1/2.

Note that the definition of direct/reverse relationships is general and does not prejudge which relationship is assessed (*e.g.* getting seven with two rolling dices, a double six, etc).

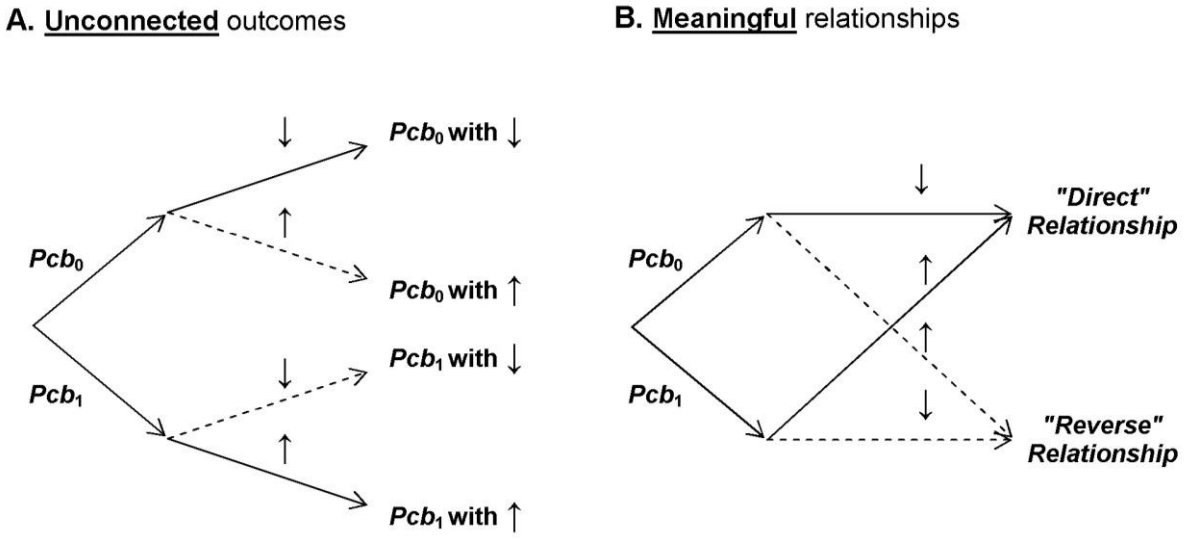


Figure 2. Unconnected outcomes *vs.* meaningful relationships. The two experimental conditions named Pcb_0 and Pcb_1 and the two system states (↓, "resting" state; ↑, "activated" state) are described either as unconnected outcomes or as relationships meaningful for the experimenters ("direct" or "reverse" relationships).

3. RESULTS

3.1 Probabilistic observer-centered modeling

For the modeling of an elementary experiment, we suppose a relationship between labels and states of the system according to the definitions of the previous section. The experimenters *O* and *O'* observe that Prob (*direct*) = p and Prob (*reverse*) = q (with $p + q = 1$).

Since the experimental situation is described from the point of view of the uninvolved agent *P*, Prob (*A*) = p and Prob (*B*) = p in Eq. 1. Therefore, *before* the experimenters interact, the probability of a direct relationship is Prob (*direct*) = $p \times p = p^2$ and similarly Prob (*reverse*) = $q \times q = q^2$ (**Figure 3**). *After* the experimenters interact, some situations such as *O* records a direct relationship whereas *O'* records a reverse relationship are prohibited by intersubjective agreement.

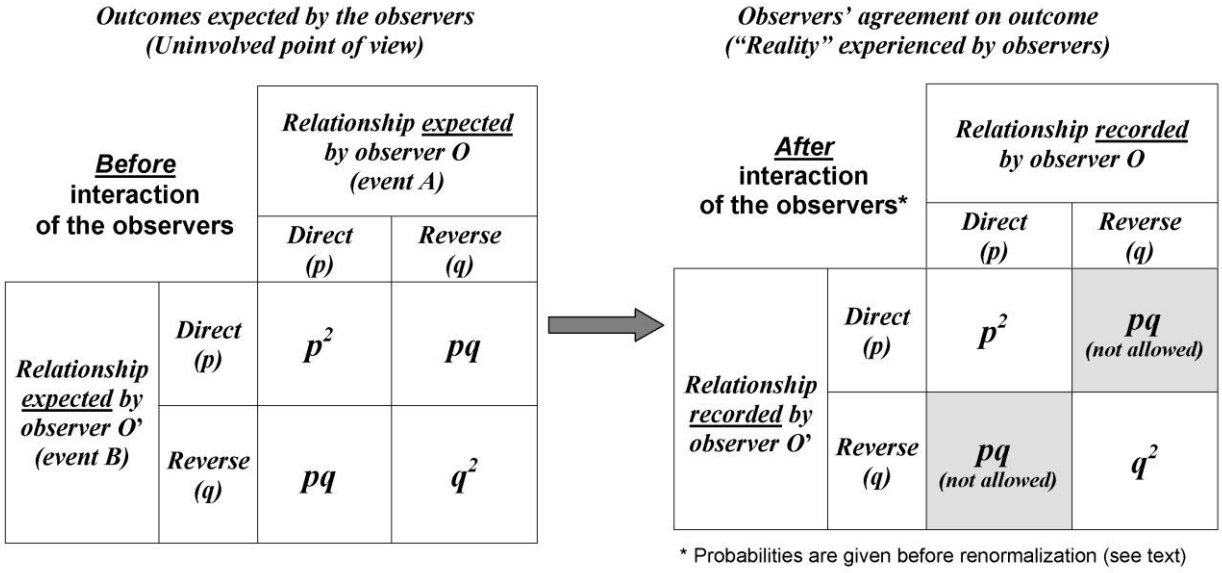


Figure 3. The two spaces of the modeling. The left panel describes the relationship expected by the observers *O* and *O'* in the probabilistic space described by the uninvolved agent *P*. These two events *A* and *B* are independent because the result obtained after the assessment of a relationship is a property of observer and system taken as a whole (*O*-*S* and *O'*-*S*). The right panel describes the "reality" experienced by *O* and *O'* defined by intersubjective agreement (*O* and *O'* agree on their records). Some situations are not possible (grey areas) and renormalization of probabilities is necessary (see text).

As a consequence, renormalization of probabilities is necessary since the total probability must be equal to one:

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

The numerator and the denominator are divided by p^2 in order to get an equation with only p as a variable (taking into account that $p + q = 1$):

$$\text{Prob}(direct) = \frac{1}{1+\left(\frac{1}{p}-1\right)^2} \qquad \text{(Eq. 4)}$$

This equation is easily generalized to N experimenters:

$$\text{Prob}(direct) = \frac{1}{1+\left(\frac{1}{p}-1\right)^N} \qquad \text{(Eq. 5)}$$

A particular case of Eq. 5 is the absence of experimenters ($N = 0$) that gives Prob (*direct*) = 1/2. After introduction of the experimenters in the modeling, the uninvolved agent P replaces p with 1/2 in Eq. 5 and he calculates that Prob (*direct*) = 1/2.

Remember that with the classical approach, which does not consider experimenters and their outcome expectations, Prob (*direct*) = 1/2. Therefore, the classical approach (the outcome preexists to measurement) and the modeling (the outcome does not preexist) lead to the same conclusion. This is consistent with common sense: two "placebos" (or two "controls) are associated with the same "effect" (not different from background noise).

At this stage, considering that the outcome preexists or not to the measurement process is a matter of personal taste since the same results are obtained in both cases. Nevertheless, in the next section, by taking into account random fluctuations in the modeling will differentiate these two approaches.

3.2 Probabilistic observer-centered modeling with fluctuations

Random fluctuations are inherent to any measurement or interaction. For the modeling, we note $\pm \varepsilon_n$ a random fluctuation of Prob (*direct*) at time t_n as a positive or negative real number (with $| \pm \varepsilon_n | << 1$).

Before the observation of the system ($N = 0$), Prob (*direct*) = p_0 = 1/2. At time t_1, the fluctuation of the probability is equal to ε_1. Therefore, p_1 is calculated for $p_0 \pm \varepsilon_1$ using Eq. 4.

Until now no specific conditions were imposed to the experimental system. But, for the calculation of p_2, there are two possibilities. In the first case, the system comes back to its previous position after each ε_n; in the second case, each state n is the starting point for the state $n+1$. Therefore we write Eq. 6 and Eq. 7 that generalize Eq. 4 according to these two situations, respectively.

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

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

For the second case, each state *n* is the starting point of the state *n+1*; therefore each p_n is reintroduced for the calculation of the corresponding p_{n+1} in a mathematical sequence:

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

Eq. 6 and Eq. 7 refer to experimental systems with different behaviors when submitted to small random fluctuations:

- In the first case (Eq. 6), the experimental system has a structure that is "rigid". When the system slightly moves apart from its initial position because of a fluctuation (due to thermal agitation for example), it quickly comes back (the system is repeatedly "set to zero"). In other words, the system "vibrates" around a fixed position and the *mean values* of outcomes are not affected by these tiny vibrations. As examples of such systems, one could cite roulette, coin toss, dice rolling or a beam splitter that randomly transmits or reflects a photon. Thus, if we put a glass on a table, the probability that it will move a few centimeters from it initial position under the sole action of molecular agitation in a reasonable time lapse can be considered equal to zero in practice.
- In the second case (Eq. 7), the experimental system may deviate from its initial state after a series of random fluctuations. Each new state of the system after an elementary fluctuation is dependent on the previous one (the successive states are autocorrelated). Thus, a pollen grain at the surface of water will deviate from its initial position to a distant position because the grain is sufficiently small to be submitted to the agitation of water molecules. Biological systems, although more complex, are also a good example of such systems. Some of them can deviate from an initial position ("resting" state) to another position ("activated" state) after a series of random fluctuations. Indeed, biological systems have a "deformable" structure thanks to the rather weak cohesion of their components; the structure of biological systems is intermediary between liquid state (maximal disorder; no structure) and solid state (minimal disorder; structure completely "rigid").

With Eq. 6, $p_{n+1} = 1/2 \pm \varepsilon_{n+1}$ (with $p_0 = 1/2$). This means that, with "rigid" systems, despite small fluctuations, Prob (*direct*) remains centered on 1/2 and no relationship is established between "labels" and system states.

The consequences of Eq. 7 that applies to "deformable" systems such as biological systems are described in the next section.

3.3 Establishment of meaningful relationships

As depicted in **Figure 4A**, the consideration of tiny probability fluctuations of a system described by Eq. 7 introduces *instability* for Prob (*direct*). Indeed, in these computer simulations, there is a systematic dramatic transition of Prob (*direct*) from 1/2 toward one of two stable positions. In the stable position #1 where Prob (*direct*) = 1, any relationship between labels and system states are "direct" whereas with stable position #2 where Prob (*direct*) = 0 any relationship is "reverse". The choice among stable position #1 or #2 is random. In both cases a relationship (direct or reverse) is established between labels and system states.

In fact, only one of the two stable positions is allowed in the probabilistic space constructed by *P*. Indeed, biological systems are always prepared in a resting state (↓) before test. In any experiment, one of the experimental situations is considered as a "control" condition. If we suppose that samples with label Pcb_0 are for "control" conditions and those with label Pcb_1 are for "test", then only the stable position #1 is allowed. Otherwise, in the stable position #2, Pcb_0 would be associated to "resting" state before test and to "activated" state after test.

3.4 Test of the modeling with blind experiments

When a resting state is achieved, this means that the events *A* and *B* are strictly correlated. For the experimenters *O* and *O*', it is as if there was a causal relationship between labels and system states. In this section, we show that the causal link is only apparent. In addition, we show that a specific blind design offers a possibility to test the modeling.

Blind experimenters are performed in order to avoid classical biases related to the experimenter. We suppose first a supervisor who is a member of the interacting team of experimenters (local supervision). His role is to transmit experimental samples under another name (not meaningful to the experimenters). Note that this task can be also performed by an automatic device. From the point of view of the uninvolved agent *P*, this local supervision is comparable to an open-label experiment (as described in the previous section). Indeed, the assessment of "success" (direct relationship) is performed in all cases locally by a member of the interacting team.

Blind experiments can be also performed with a centralized supervision as frequently done in clinical trials (generally with a statistician supervisor). In this case, the outcomes of the experiments are performed blind by the experimenters' team and the results are transmitted to the supervisor who does not assist to the experiments. This remote supervisor assesses the rate of "success" by comparing the list of labels (unknown to the experimenters) and the outcomes (states of the system). In this case, Prob (*direct*) = Prob (*reverse*) since the assessment of "success" (direct relationship) is not performed locally by a member of the interacting team. Consequently, Prob (*direct*) = 1/2 since Prob (*direct*) + Prob (*reverse*) = 1.

Therefore, blind experiments with different designs offer the possibility to test the modeling:

- With local assessment, Prob (*direct*) = 1 (significant relationship);
- With remote assessment, Prob (*direct*) = 1/2 (no significant relationship).

These results emphasize that the relationship between labels and system states is not causal. Indeed, if there were the case, local and remote assessments of the relationship in blind experiments should lead to the same conclusion.

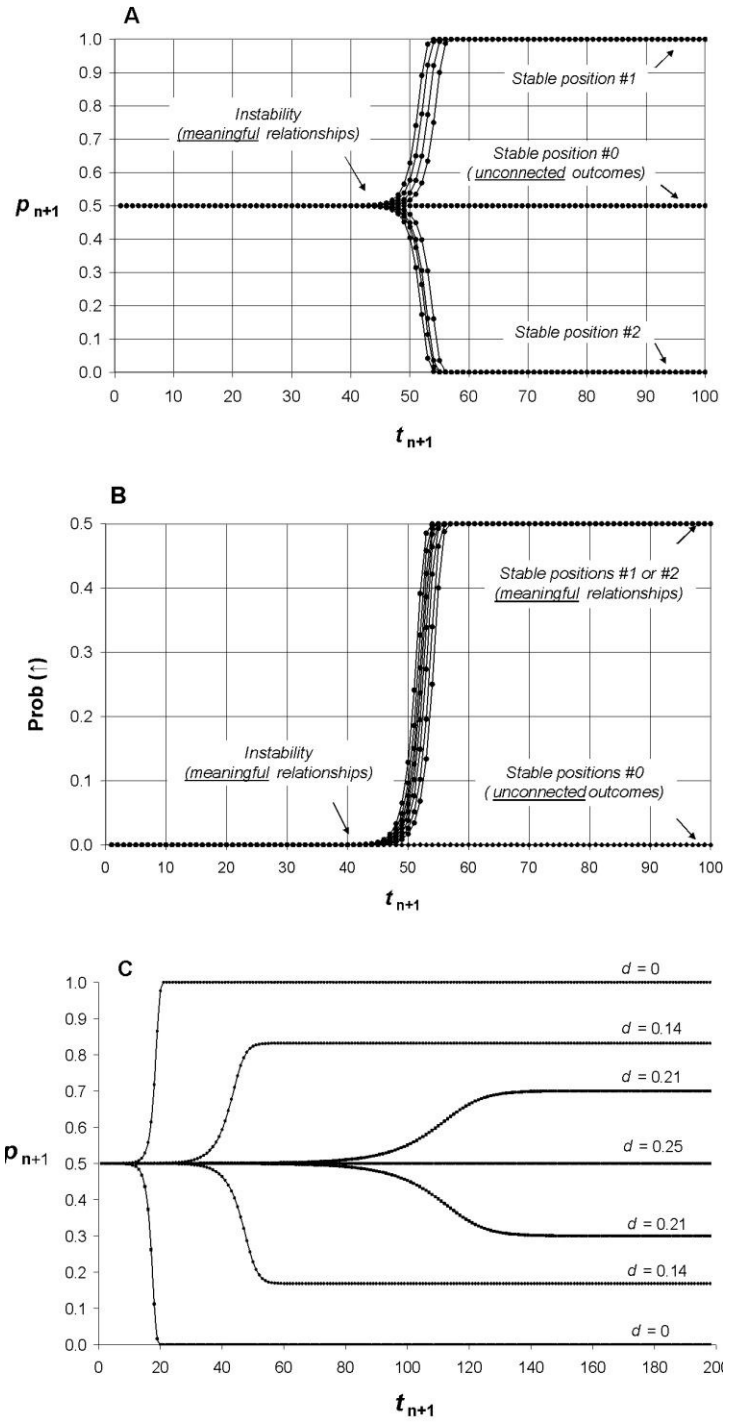


Figure 4. Emergence of relationships between "labels" and states of a deformable system (*e.g.* a biological system). Panel A describes the probability to observe a meaningful relationship after *O*-*S* and *O*'-*S* interact if the fluctuations of the system are taken into consideration (Eq. 7). There is a dramatic transition of the probability from 1/2 toward 1 or 0. If the results expected by the experimenters are the simple sum of unconnected events then no relationship emerges and Prob (*direct*) remains equal to 1/2. Panel B corresponds to the emergence of an "activated" state for meaningful relationships. Panel C is obtained by varying the independence of the events expected by *O* and *O*' (from $d = 0.25$ to $d = 0$) using Eq. 15 (see text). The mathematical sequences presented in panels A and B have been obtained after eight computer calculations. Each probability p_{n+1} of the sequence is calculated by using p_n and a probability fluctuations ε_{n+1} which is randomly obtained between –0.5 and $+0.5 \times 10^{-15}$. For panel C, the range of probability fluctuation was from –0.5 to $+0.5 \times 10^{-5}$ for a better display.

3.5 Quantum-like structure of the emerging relationships

The modeling uses only classic probability. Nevertheless, as explained in this section, the logic of the relationship between labels and system states is structured by an underlying quantum-like structure.

According to the law of total probability, the sum of the probabilities of the four outcomes described in **Figure 2** is equal to 1:

$$\text{Prob}(Pcb_0)\times\text{Prob}(\downarrow)+\text{Prob}(Pcb_0)\times\text{Prob}(\uparrow)+\text{Prob}(Pcb_1)\times\text{Prob}(\downarrow)+\text{Prob}(Pcb_1)\times\text{Prob}(\uparrow)=1 \quad \text{(Eq. 8)}$$

When the stable position #1 is achieved, Prob (Pcb_0) = Prob (↓) and Prob (Pcb_1) = Prob (↑); for stable position #2, Prob (Pcb_0) = Prob (↑) and Prob (Pcb_1) = Prob (↓). In both cases, by replacing these equalities in Eq. 8, we get the same equation:

$$\left[\text{Prob}\,(Pcb_0)\right]^2+\left[\text{Prob}\,(Pcb_1)\right]^2+2\times\text{Prob}\,(Pcb_0)\times\text{Prob}\,(Pcb_1)=1 \quad \text{(Eq. 9)}$$

We recognize a remarkable identity:

$$\left[\text{Prob}\,(Pcb_0)+\text{Prob}\,(Pcb_1)\right]^2=1 \quad \text{(Eq. 10)}$$

We introduce now the real numbers a and b that are defined as Prob (Pcb_0) = a^2 (or $a.a$) and Prob (Pcb_1) = b^2 (or $b.b$). These definitions are for the stable position #1 (note that for the stable position #2, b^2 must be taken equal to $-b\times-b$). Eq. 9 and Eq. 10 are rewritten with a and b:

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

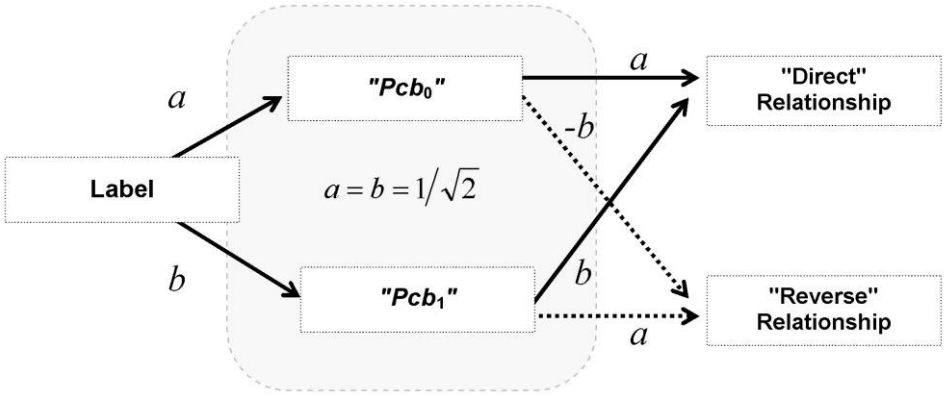
Since a and b are real numbers, $(b\cdot a-a\cdot b)^2$ is equal to zero and can be introduced for symmetry reasons in the equation; moreover $(a\cdot b)^2=(b\cdot a)^2$:

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

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

Eq. 12 is sketched in **Figure 5** for a better understanding**.** Thus, the left-hand side of Eq. 12 is the sum of Prob (*direct*) plus Prob (*reverse*) without a remote supervisor whereas the right-hand side is the sum of Prob (*direct*) plus Prob (*reverse*) with a remote supervisor. The terms a and b can be considered as probability amplitudes (their squaring give the corresponding probabilities).

We can recognize in Eq. 12 and **Figure 5** a mathematical structure that is analogous to single-photon self-interferences in Young's double-slit experiment. In this experiment, photons behave either as particles or waves according to path detection or not, respectively. Path detection is analogous to supervision by a remote supervisor and no path detection is analogous to the absence of supervision by a remote supervisor.



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

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

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

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

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

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

Figure 5. Quantum-like logic of the emerging relationship. The underlying logic of the relationship that emerges in the modeling is isomorphic to Young's two-slit experiment. In Young's two-slit experiment, the screen interferences disappear if the paths of photons are detected. In the modeling, the relationship between labels and system states is not better than random (*i.e.* equal to 1/2) if the relationship of labels with system states is assessed by a remote supervisor.

3.6 Shift from unconnected outcomes to meaningful relationships

In this section we will deepen the role of the experimenters by studying the progressive shift from a property that belongs only to the system *S* (classical approach) to a property that belongs to *O-S* taken as a whole (present modeling). For this purpose, we vary the degree of independence of outcome expectations. Eq. 1 is generalized by adding the parameter *d*:

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

When $d = 0$, the events *A* and *B* are independent and when *d* increases, their degree of correlation increases. Eq. 3 is easily generalized (**Figure 6**):

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

We have seen that $d = 0$ in Eq. 10 and introduction of probability fluctuation leads Prob (*direct*) to a dramatic shift from 1/2 toward 1 or 0.

In contrast, with $d = pq$, the degree of correlation of the two events *A* and *B* is maximal:

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

Probability fluctuations are then introduced in Eq. 16:

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

Consequently, if initially $d = p_0q_0 = 1/4$, there is no instability of Prob (*direct*) and Prob (*direct*) fluctuates slightly around 1/2; there is no dramatic transition toward 0 or 1 and no emergence of the "activated" state of *S* (**Figure 4A** and **Figure 4B**). It is as if the outcome *preexisted* to its measurement since the events *A* and *B* are perfectly correlated. When $d = pq$, we see with the help of **Figure 1** that *p* is equivalent to the sum of the probabilities of the sub-events considered individually:

$$p = \text{Prob}\,(Pcb_0) \times \text{Prob}\,(\downarrow \mid Pcb_0) + \text{Prob}\,(Pcb_1) \times \text{Prob}\,(\uparrow \mid Pcb_1) \qquad \text{(Eq. 18)}$$

Therefore, varying *d* value from *pq* to 0 allows a shift from unconnected outcomes to a relationship meaningful for the experimenters (**Figure 1** and **Figure 4C**).

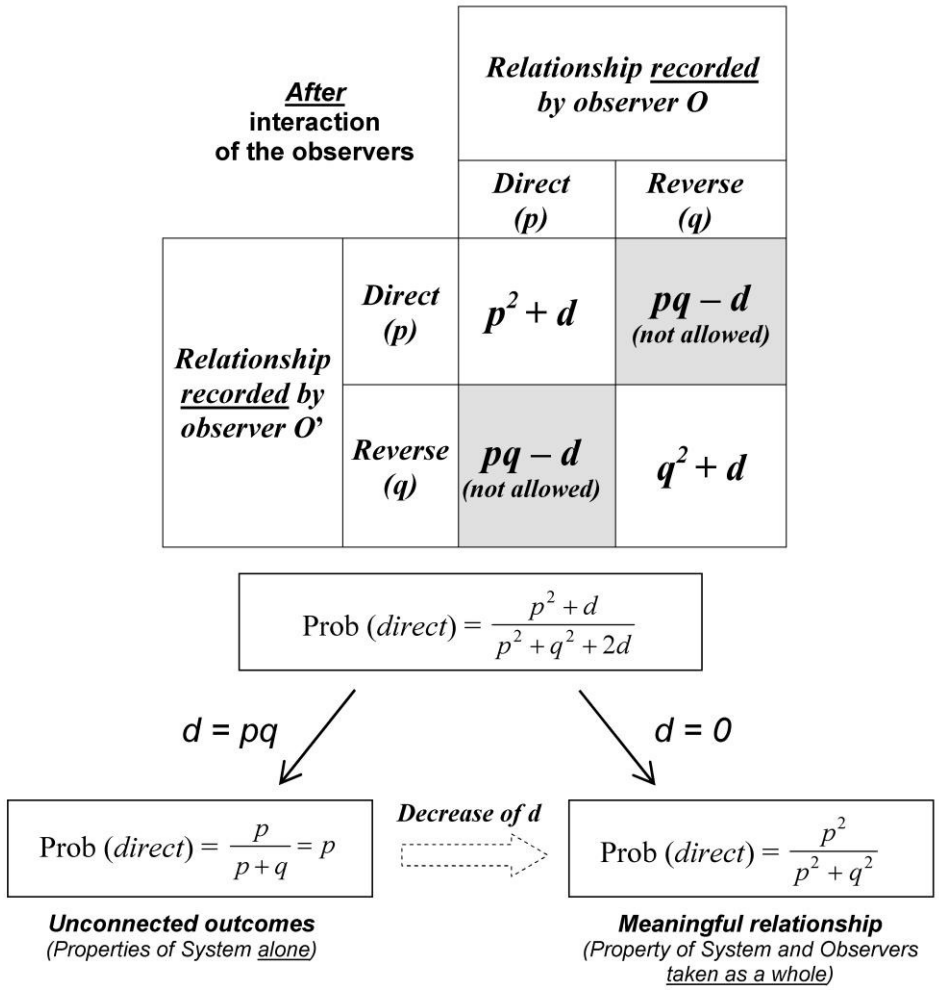


Figure 6. From perfect correlation to complete independence of observers' expectations. The modeling is generalized in order to consider in the same equation outcomes that are properties of *S* alone and outcomes that are properties of *O*-*S* and *O*'-*S* (taken as a whole). Thus, the variation of the parameter *d* from 0 to *pq* allows a progressive shift from unconnected outcomes to a meaningful relationship.

Note that in the absence of experimenters ($N = 0$ in Eq. 7), no relationship emerges; the situation is the same if the experimenters are physically present, but not paying attention to this specific experiment. As a consequence, the parameter d could be interpreted as the degree of *commitment in expecting a meaningful relationship* (the commitment of the experimenters is maximal when $d = 0$).

4. DISCUSSION

The question of the title ("*Are biological systems and experimenters really separated?*") has now some response elements. Indeed, this probabilistic modeling suggests that the conclusion of an experiment could depend on how the experimenters grasp the "reality", either expecting a global relationship or only unconnected outcomes (*i.e.* a "form" *vs.* separate dots).

The fact that a result about a relationship is a property of the observed system and the observer taken as a whole is the basis of the modeling. In **Figure 4A**, due to the instability introduced in the modeling, a significant relationship emerges from random probability fluctuations. During this process where the probability of a meaningful relationship changes from 1/2 (no relationship) to 1 (certainty of a relationship), the relationship gains its existence whereas its components loose their identity. If the experiment has been designed to ensure that the components keep their identity (*i.e.* with a remote supervisor), then the significant relationship vanishes and the emergent "activated" states are evenly distributed among the "labels".

Not surprisingly, the correlations that appear between labels and system states have a quantum-like structure. In quantum mechanics also outcomes do not preexist to their measurements and the underlying logic of the modeling is comparable to Young's two-slit experiment, an emblematic experiment of quantum physics. In Young's experiment, if the experimenter decides to observe the phenomenon in its wholeness, light interference patterns appear on the screen. In contrast, if the experimenter decides to break down the phenomenon into elementary sub-events which are individually identified (photons passing through path "1" or path "2"), then the system adopts a classical behavior without interferences.

These considerations remind concepts from Gestalt theory [3]. According to this theory, human mind perceives objects as a shape (Gestalt) that is independent of its parts. Amann has well described the structural similarities between Gestalt concepts and quantum mechanics:

> "*Similarly as with the Gestalt concept, the shape of a quantum object does* not *a priori exist but it depends on the interaction of this quantum object with the environment (for example: an observer or a measurement apparatus).*
>
> *Quantum mechanics and Gestalt perception are organized in a holistic way. Subentities do not necessarily exist in a distinct, individual sense.*
>
> *In quantum mechanics and Gestalt perception* objects have to be created *by elimination of holistic correlations with the 'rest of the world' "* [4].

Admittedly, these concepts are not intuitive and this is not surprising for notions related to quantum physics. A classical example in Gestalt theory, namely Necker cube, could be of some use to understand the complementarity of the whole and the parts that exists

both in quantum mechanics and in Gestalt psychology. In **Figure 8B**, we immediately see the 2D lines as a 3D cube in one of the two mutually exclusive configurations. This 3D cube is not a property of the paper sheet alone, but is a property of the paper sheet and the reader taken as a whole. Therefore, the 3D cube does not preexist to the observation of the paper sheet. We perceive a 3D cube because we are able to "connect" the separate 2D lines and associate them with the abstract idea of "cube". This faculty is not innate and we have learned to perceive perspective in 2D drawings. A 3D vision requires perceiving all element of the picture at the same time and not to look at each element one by one. Thus, if the reader looks one by one the lines of **Figure 8B,** for example by using a magnifying glass, she/he will loose the 3D vision of the cube.

The parallel with the modeling is immediate: learning and training could allow perceiving the different variables of an experimental system as a meaningful relationship. In other words, a relationship emerges from background for teams of interacting experimenters who have been trained to expect firstly a *continuum* (*i.e.* a meaning) from a data set which by its very nature is discontinuous. When "bench scientists" explore a new field, they generally assess unconnected outcomes because no hypothesis has been yet defined. In contrast, when they repeat experiments again and again, they know more and more the relationship to expect.

Another issue important to emphasize is the non-causal characteristics of the correlations between labels and system states, like for quantum (or quantum-like) correlations. Indeed, "labels" cannot be considered as the causes of the observed system states; "labels" and states are only associated. Thus, the observed correlations cannot serve to send a message or an order; otherwise the distribution of outcomes according to "causes" becomes scrambled. This is precisely what happens for the correlations between labels and states with a local supervisor that vanish with a remote supervisor.

A perspective from an uninvolved standpoint was adopted in the modeling. The reader must resist the temptation to put her/himself in the place of the experimenters. Indeed, as established by Breuer, a complete self-measurement is impossible [5, 6]. This author demonstrated that a measurement apparatus or an observer *O* cannot distinguish all the states of a system in which it/he is contained (*O*-*S* in the modeling). A second external apparatus/observer (*P* in the modeling) is necessary to describe all the states of the first apparatus/observer. The nature of the system, classical or quantum, does not matter.

An implicit assumption of the uninvolved standpoint coupled with the intersubjective agreement is that "reality" exists only through measurements or interactions. The chosen perspective is more epistemological than ontological and the price to pay is a weakness of realism; in other words, asking on an "absolute reality" of the world outside measurements is pointless. This position is close to the Copenhagen interpretation and other interpretations of quantum physics [7, 8]. According to these interpretations, the quantum formalism does not describe "reality" as "it is", but allows predicting the results of measurements performed by devices considered as classical objects (these classical measurement devices being nothing more than an extension of our sensory organs). What is guaranteed in an epistemic perspective is the *consistency of the correlations* between measurements, not the specific content of these measurements.

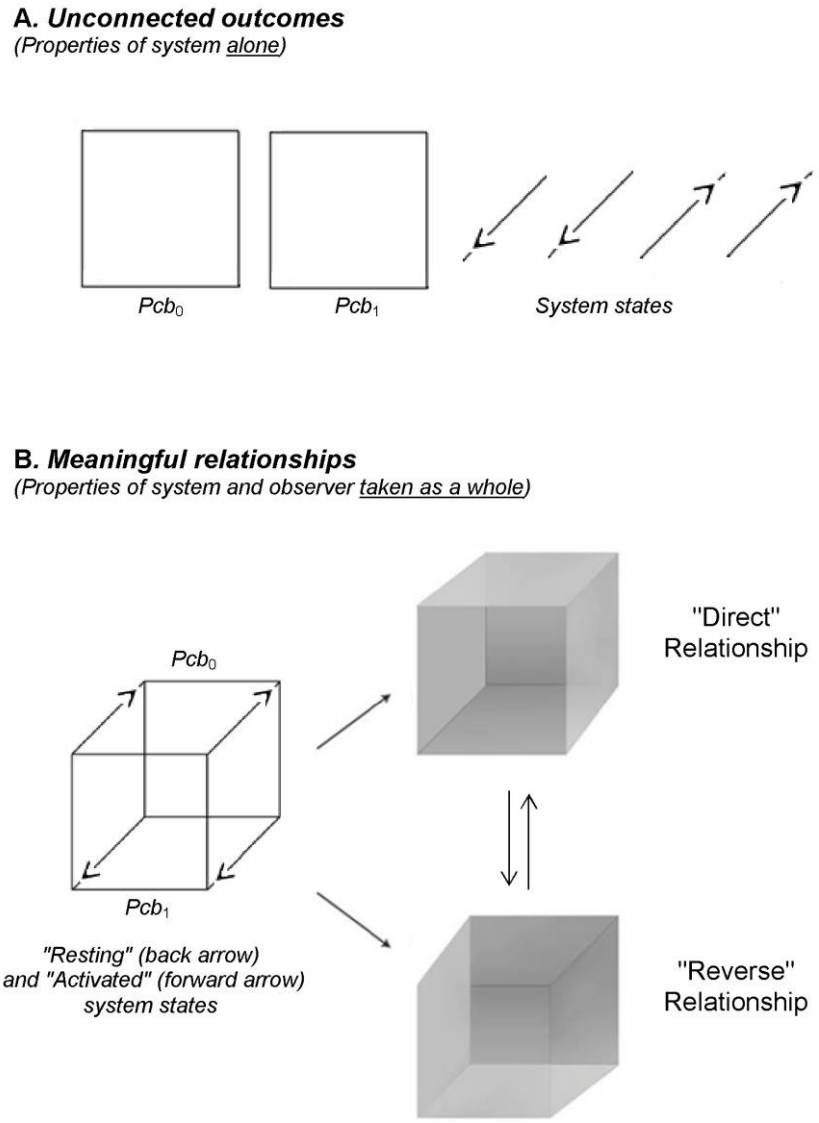


Figure 8. Isomorphism of Necker cube and present modeling. The 2D elements of the drawing are presented in A (properties of *S* alone). These 2D elements of Necker cube are perceived as one of the two possible 3D configurations in B when they are correctly connected (properties of *O-S* taken as a whole). In this analogy, the 2D drawing is equivalent to unconnected outcomes, whereas the 3D relationships are the equivalent of direct/reverse relationships. For direct relationship, backward arrows are associated with Pcb_0 and frontward arrow with Pcb_1; for reverse relationship, frontward arrows are associated with Pcb_0 and backward arrows with Pcb_1. Note that direct and reverse relationship are mutually exclusive forms (they cannot be perceived simultaneously).

Previous studies in experimental psychology have shown that cognitive processes such as decision making, memory, judgment, reasoning, language or perception could be described with mathematical quantum tools thus offering a generalized probability theory for these processes [9]. More general than the classical approach, the present modeling also offers the possibility of new interpretations for some questions debated in different areas of biology, medicine or psychology. As an example, proponents of alternative medicines such as homeopathy claim that there is a relationship between their medicines and the improvement of patient symptoms [10]. However, according to evidenced-based medicine, no causal relationship is evidenced in double-blind trials and opponents to

these alternative treatments consider they are nothing more than placebos [11, 12]. A new approach considering not only the "biological systems" (patients), but also the various "experimenters" and participants (physicians, patients, statisticians, etc) could be fruitful. Similarly, studies on placebo effect could also benefit from this original perspective if the "meaning" of the medicines – for both patients and physicians – is also considered [13, 14].

Another possible application of the present approach is the current debate about reproducibility in biology, medicine, oncology and psychology [15-18]. Of course, classical explanations are probably involved in most cases that are questioned in this "replication crisis" [19]. We have seen how the emergence of apparent causal relationships could vary according to experimenters' characteristics (*e.g.* experimenters' commitment, meaning of outcomes, training for a specific experiment). One cannot exclude such "mechanisms" when poor reproducibility between different teams is reported. As a hypothesis, one could suggest that training could be facilitated if the experimenters usually perform similar experiments based on a "true" causal relationship.

In conclusion, this probabilistic modeling suggests that the strict separation of biological systems and experimenters is an ideal not necessarily achieved despite precautions when the hypothesis of a relationship is tested. The consequences could be wrong conclusions about causal relationships. Specific blind procedures are proposed to prevent unwanted correlations involving the experimenters.

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REFERENCES

1. Bernard C. Introduction à l'étude de la médecine expérimentale. Paris, Garnier-Flammarion, 1966 [1865].
2. Rosenthal R, Fode KL. The effect of experimenter bias on the performance of the albino rat. Behav Sci. 1963;8:183-9.
3. Jakel F, Singh M, Wichmann FA, Herzog MH. An overview of quantitative approaches in Gestalt perception. Vision Res. 2016;126:3-8.
4. Amann A. The Gestalt problem in quantum theory: generation of molecular shape by the environment. Synthese. 1993;97:125-56.
5. Breuer T. The impossibility of accurate state self-measurements. Philos Sci. 1995;62:197-214.
6. Laudisa F, Rovelli C. "Relational Quantum Mechanics", The Stanford Encyclopedia of Philosophy (Summer 2013 Edition), Zalta EN (ed.). Available at http://plato.stanford.edu/archives/sum2013/entries/qm-relational/.
7. Rovelli C. Relational quantum mechanics. Int J Theor Phys 1996;35:1637-78.
8. Fuchs CA, Mermin ND, Schack R. An introduction to QBism with an application to the locality of quantum mechanics. Arxiv preprint. 2013:arXiv:1311.5253.
9. Busemeyer J, Bruza P. Quantum models of cognition and decision: Cambridge University Press; 2012.

10. Hahn RG. Homeopathy: meta-analyses of pooled clinical data. Forsch Komplementmed. 2013;20:376-81.
11. Shang A, Huwiler-Muntener K, Nartey L, Juni P, Dorig S, Sterne JA, et al. Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. Lancet. 2005;366:726-32.
12. Brien S, Lachance L, Prescott P, McDermott C, Lewith G. Homeopathy has clinical benefits in rheumatoid arthritis patients that are attributable to the consultation process but not the homeopathic remedy: a randomized controlled clinical trial. Rheumatology (Oxford). 2011;50:1070-82.
13. Moerman DE. Meaningful placebos--controlling the uncontrollable. N Engl J Med. 2011;365:171-2.
14. Beauvais F. Possible contribution of quantum-like correlations to the placebo effect: consequences on blind trials. Theor Biol Med Model. 2017;14:12.
15. Baker M. 1,500 scientists lift the lid on reproducibility. Nature. 2016;533:452-4.
16. Open Science Collaboration. Estimating the reproducibility of psychological science. Science. 2015;349:aac4716.
17. Begley CG, Ellis LM. Drug development: Raise standards for preclinical cancer research. Nature. 2012;483:531-3.
18. Prinz F, Schlange T, Asadullah K. Believe it or not: how much can we rely on published data on potential drug targets? Nat Rev Drug Discov. 2011;10:712.
19. Schooler JW. Metascience could rescue the 'replication crisis'. Nature News. 2014;515:9.