MEANING AND PLACEBO EFFECT: A PROBABILISTIC EXPERIMENTER-CENTERED MODELING

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ABSTRACT

By definition, a placebo has no biological effect. Therefore, besides classical non-specific effects, the outcome associated to a placebo rests on its "meaning". Meaning is always for someone and understanding the effects attributed to placebo requires to describe the expectations and interpretations of the agents involved in the experiment.

We present a probabilistic modeling of the "placebo effect" that has its roots in the act of measuring and – in contrast with other hypotheses such as patient's expectation or conditioning – is centered on experimenters and not only on patients. Therefore, this modeling potentially applies to any biology experiment aimed to demonstrate a causal relationship. Its originality is the description of the experimental situation from the point of view of an uninvolved participant who does not interact with the experimenters and the biological system.

When probability fluctuations inherent to any measurement are taken into account, a counterintuitive result emerges: two placebos with different "meanings" can be associated with different "effects" after measurement of a biological system. In clinical trials, this "meaning effect" due to the experimenters could add to the drug effect and contribute to the "placebo effect".

This simple modeling suggests that the act of measuring is not always neutral and some correlations between apparent causes and observed outcomes may emerge, thus contributing to conclude for obvious – but false – causal relationship. These results could have consequences in the design and interpretation of experiments in life sciences, medicine and psychology.

Keywords: *Placebo effect; Experimenter effect; Expectancy effect; Randomized clinical trials.*

1. INTRODUCTION

As pointed out by some authors, speaking about "placebo effect" is paradoxical because – by definition – placebos have no pharmacological effect [1]. "Placebo effect" usually refers to the clinical outcome associated to the placebo group in a clinical trial. Classically, regression to the mean, natural evolution of the disease and other non-specific effects participate to the "placebo effect". Other effects related to patient expectation and patient conditioning are also considered as important components of the placebo effect [1-6]. Thus, Kaptchuk and Miller underscored that the participation of patients "in the therapeutic encounter, with its rituals, symbols, and interactions" was responsible for the improvement of their symptoms [7].

In order to clarify the definition of placebo effect, Ernst and Resch proposed to distinguish "true" and "perceived" placebo effect [8]. "Perceived" placebo effect is the outcome in placebo group and "true" placebo effect is the difference between the "perceived" effect and the outcome in an untreated group. However, "untreated" groups are rarely performed in clinical trials. Moreover, the inclusion of a patient in an "untreated" group is not neutral and the mere participation in a clinical trial can elicit a "placebo effect".

For Moerman and Jonas, the concept of "placebo effect" is confusing because too many components have been included in this concept. For these authors, mean regression and natural history are clearly not elements of the "placebo effect", which presumes a participation of the patient [1]. Therefore, Moerman proposed to define a "meaning response" as the physiological or psychological effects of meaning in the treatment of illness [9].

Any definition of placebo usually refers to patients. The present article takes an opposite – but complementary – view by attributing a role to the experimenters. We must insist that this role is not trivial and different from experimenters' effects that have been previously suggested by some authors. Indeed, it is well known that biases can be introduced by the experimenters, for example biases related to *a priori* expectations on the results of the experiment. Such experimenter effects have been largely described by Rosenthal [10] In clinical studies, the role of physician expectancies in the "placebo effect" has also been suggested [11].

In a clinical trial, the expectancies of the investigators are somewhat different to those of patients. A patient expects an improvement of his health independently of the outcome of the other patients included in the trial. On the contrary, the investigators seek *to establish a relationship* between medicines (placebo *vs.* verum) and patient outcomes (improved vs. not improved). If a statistically significant relationship can be established (i.e. patients

improve more frequently in verum group), then the trial is considered as a success by the investigators, independently of each individual outcome.

We hypothesized that, besides the classical components of the "placebo effect", the experimenters themselves play a non-trivial role. This hypothesis is supported by simple probabilistic considerations. For this purpose, the states of a biological system associated to two placebos are compared in a modeling. An experimental procedure with different types of blind designs is proposed to test this hypothesis.

2. METHODS

2.1 The uninvolved point of view

The originality of this modeling is the description of the experimental situation from an uninvolved point of view. For this purpose, we suppose a participant (named *P*) who *does not interact* with the experimenters/observers (named *O, O', O''*, etc) or with the system (named *S*) during the experiment. The participant *P* knows the initial conditions and his role is to calculate the probabilistic evolution of the system *S* and the team of interacting experimenters.

Therefore, two spaces are defined for the modeling: the first one is an abstract space where the probabilities of the outcomes are described by *P*; the second one is the locus of the "reality" experienced by *O* and *O'*.

2.2 Meaningful associations

The purpose of the modeling is to describe an elementary experiment aimed to establish a relationship between some experimental conditions and the corresponding states of a biological system. We define the simplest possible biological system with only two possible states. Before any test, biological systems are prepared in a "resting" state (noted "↓" in the modeling; also named background noise or control conditions). If after test, the state of the biological system is significantly different from the resting state, then the biological system is said in an "activated" state (noted "↑").

The two experimental conditions are two placebos that are labeled Pcb_0 and Pcb_1 in the modeling. These labels correspond to characteristics (e.g. names, color, size) that allow experimenters to distinguish one placebo from the other.

There are four possible combinations of labels and biological states (Figure 1A). These four combinations can be associated if the purpose is the description of a relationship between some experimental conditions and the possible outcomes of a biological system (Figure 1B):

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

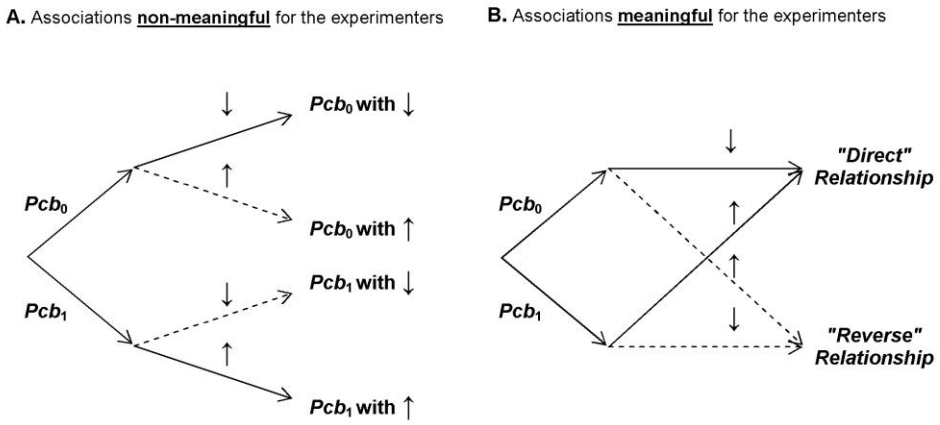

Figure 1. Description of an experiment with non-meaningful or meaningful associations. In panel A, "independent causes" designated by their labels (Pcb_0 and Pcb_1) and corresponding outcomes (states ↓ and ↑ of system S) are described as the simple sum of the elementary sub-events (Pcb_0 with ↓, Pcb_0 with ↑, etc). In contrast, in panel B, direct relationship is defined as the association of Pcb_0 with ↓ or Pcb_1 with ↑ and "reverse" relationship is defined as the association of Pcb_0 with ↑ or Pcb_1 with ↓. In panel B, the associations between labels and states of the biological system are meaningful for the observers.

The total probability of these two relationships is equal to one and is noted: Prob (*direct*) + Prob (*reverse*) = 1. Since placebos have no effect by definition, common sense suggests that the rates of "activated" states associated with Pcb_0 or Pcb_1 are comparable:

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

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

Pcb_0 and Pcb_1 play a symmetrical role and therefore for probabilistic calculations, Prob (Pcb_0) = Prob (Pcb_1). In Figure 1B, if there is no relationship between the two labels and the two system states – i.e. Prob ($\uparrow \mid Pcb_0$) = Prob ($\uparrow \mid Pcb_1$) – then the probability of a direct relationship is Prob (*direct*) = 1/2 and similarly Prob (*reverse*) = 1/2. The objective of the modeling is precisely to explore whether in some conditions Prob (*direct*) could be different from 1/2.

3. RESULTS

3.1 Probability of a direct relationship

The experimental situation, including both the system *S* and the experimenters *O* and *O*', is described from the point of view of the uninvolved participant *P*.

We assume that, before any 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*. Nevertheless, when the experimenters interact and compare their records, they agree on the observed event. This condition of independence will be justified in section "*From non-meaningful to meaningful associations: the role of the observers*".

The independence of the events *A* and *B before interaction* and the intersubjective agreement *after interaction* can be easily described mathematically. Indeed, two events *A* and *B* are independent if the joint probability of *A* and *B* equals the product of their probabilities:

$$\text{Prob}(A \cap B) = \text{Prob}(A) \times \text{Prob}(B) \qquad \text{(Eq. 2)}$$

According to the definitions of the previous section, we suppose a relationship such as Prob (*direct*) = p and Prob (*reverse*) = q (with $p + q = 1$).

Before *O* and *O*' interact, the best estimate of the probability to observe a direct relationship is p from the point of view of *O* and is also p from the point of view of *O*'. When the experimenters *O* and *O'* interact, they agree on the outcomes that they recorded (events of the set $A \cap B$). Therefore, from the point of view of *P*, Prob (*direct*) = $p \times p$ and similarly Prob (*reverse*) = $q \times q$ (Figure 2). Some situations such as *O* records a direct relationship whereas *O'* records a reverse relationship are however not allowed. Since the total probability of all possible events must be equal to one, a renormalization is necessary by dividing the probability of each event by the sum of all possible events (i.e. probability of direct relationship and probability of reverse relationship):

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

By dividing the numerator and the denominator by p^2 and by taking into account that $p + q = 1$, we obtain the same equation with only p as a variable:

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

We can easily generalize this equation to N experimenters:

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

A particular case is the absence of experimenters ($N = 0$):

$$\text{Prob}\,(direct) = \frac{1}{1+\left(\frac{1}{p}-1\right)^{0}} = \frac{1}{2} \qquad \text{(Eq. 6)}$$

At first sight, the calculation of Prob (*direct*) according to the modeling does not bring any advantage compared with the classical approach. Indeed, with the classical approach, the probability to observe a direct relationship is 1/2 since Pcb_0 and Pcb_1 play a symmetrical role ($p = q$ with $p + q = 1$). In the modeling, this probability is calculated by replacing p with 1/2 in Eq. 4 and 1/2 is also obtained as with the classical approach. These results are conform to common sense: two placebos have comparable "effects" that are not different from background noise. The interest of Eq. 4 will appear in the next sections after introducing probability fluctuations.

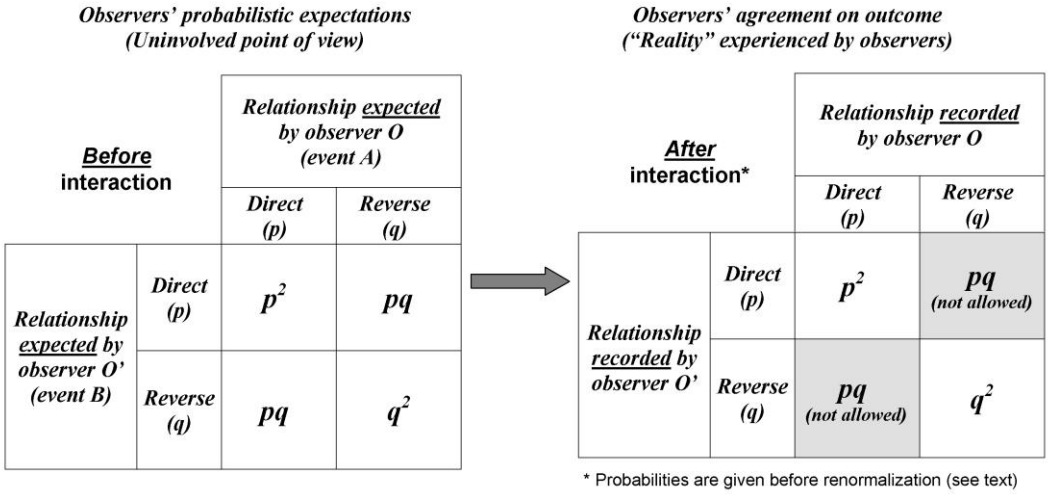

Figure 2. Probability of direct (p) or reverse (q) relationship expected and recorded by the experimenters O and O'. In the probabilistic space constructed by P (left panel), the observation of a direct relationship by O (event A) and the observation of a direct relationship by O' (event B) are independent events (see text). When the observers interact and compare their records, they agree on the observed event (right panel).

3.2 Introduction of probability fluctuations in the modeling

Any experimental system is submitted to fluctuations. Therefore the probability to observe a direct relationship is also submitted to fluctuations: they are noted ε_n in the modeling and are positive or negative real numbers with an absolute value that is very small compared to 1.

In the absence of any observer ($N = 0$), Prob (*direct*) = $p_0 = 1/2$. In the presence of the experimenters, after a first fluctuation ε_1, we calculate p_1 with Eq. 4 for $p_0 + \varepsilon_1$. For the calculation of p_2, we are faced with two situations. Either the system comes back to its initial state after each elementary fluctuation or each state n is the starting point for the state $n+1$. We generalize the calculation of each probability $n+1$ by modifying Eq. 4 for the first situation in Eq. 6 and for the second situation in Eq. 7.

In the first case, p_{n+1} is calculated with $p_n = p_0 = 1/2$:

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

In the second case, each p_n is reintroduced for the calculation of the corresponding p_{n+1} in a mathematical sequence:

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

The choice between Eq. 6 and Eq. 7 depends on the behavior of the experimental system in the presence of a series of small random fluctuations:

- In the first situation (Eq. 6), the structure of the experimental system is sufficiently "rigid" to come back to the initial position after each fluctuation. This is the case for random systems strongly deterministic such as coin toss, dice rolling or a beam splitter that randomly transmits or reflects a photon. With these systems, fluctuations (due to thermal agitation for example) have no significant influence on the mean probability of outcomes which remains set around the same value.
- The second situation (Eq. 7) is encountered with systems that may deviate significantly from their initial state after a series of random fluctuations. This is the case for experimental systems, such as biological systems, which are sufficiently "deformable". "Deformable" in this context means that the positions of the different components of the system can be affected by random fluctuations. If the mean position of the "resting" state is able to move toward the mean position of the "activated" state, then Eq. 7 can apply.

With Eq. 6, we easily calculate that $p_{n+1} = 1/2 + \varepsilon_{n+1}$. Therefore, Prob (*direct*) fluctuates around 1/2. The consequences of Eq. 7 for experimental situations that are the issue of the present article, namely biological systems, are described in the next section.

3.3 Two placebos with different labels associated to different "effects"

A series of computing simulations of Eq. 7 with 100 successive tiny fluctuations ε_n is presented in Figure 3A. For the calculations of the values of Prob (*direct*) after each probability fluctuation, the random ε_n values are very small (around 10^{-15}). After several dozens of steps around 1/2, Prob (*direct*) dramatically moves toward one of two stable positions: either stable position #1 corresponding to Prob (*direct*) = 0 or stable position #2 corresponding to Prob (*direct*) = 1.

These results indicate that an "activated" state of the biological system is systematically associated with the label Pcb_1 (for stable position #1) or an "activated" state is systematically associated with the label Pcb_0 (for stable position #2). The choice of one of the two stable positions depends on the series of random ε_n.

There are two important consequences after the achievement of a stable position: First, an "activated" state *emerges from random fluctuations* (Figure 3B) and, second, a *relationship is established* (direct or reverse) between labels and biological states (Figure 3A).

Therefore we have answered to the initial question: in some circumstances, it is possible to establish a relationship between simple labels of placebos (i.e. words) and the states of a biological system (resting or activated). This relationship is however direct in half of cases and reverse for the other half. Nevertheless, as previously said, biological systems are prepared in a "resting" state. When one seeks to establish a relationship by comparing the outcomes associated to two experimental conditions, one of them is considered as a "control" – for example Pcb_0 – and the other as a "test" (Pcb_1). As a consequence, the stable position #2 is not allowed in the modeling since Pcb_0 cannot be associated both to "resting" state after preparation of the system (before testing) and to an "activated" state with Pcb_0 labels (after testing). Since only the possible state #1 is possible, Prob (*direct*) = 1 in all cases. In other words, at the end of the experiment, the participant *P* calculates that *O* and *O'* have the guarantee to observe Pcb_0 always associated to "↓" and Pcb_1 always associated to "↑". These results suggest that labels and system states are engaged in a causal relationship. In a next section we will see that the causality of this relationship is only apparent.

3.4 From non-meaningful to meaningful associations: the role of the observers

We assumed that the two events *A* and *B* (future events expected by *O* and *O'*, respectively) were independent events. As previously said, the joint probability of two independent events *A* and *B* equals the product of their probabilities. We can easily write a generalized equation where the degree of independence varies according to a parameter *d*:

$$\text{Prob}\,(A \cap B) = \text{Prob}\,(A) \times \text{Prob}\,(B) + d \quad (\text{with } 0 \leq d \leq 1) \qquad \text{(Eq. 9)}$$

The independence of the two events *A* and *B* increases when the value of *d* decreases; when $d = 0$ is achieved, the two events are completely independent. In other words, the degree of correlation of the two events increases with the value of *d*.

Eq. 4 that allows calculating the probability of a direct relationship for *O* and *O'* is easily modified for events *A* and *B* more or less independent (see legend of Figure 4 for details on calculations):

$$\text{Prob}\,(direct) = \frac{p^2 + d}{p^2 + q^2 + 2d} \text{ (with } 0 \le d \le pq) \qquad \text{(Eq. 10)}$$

The shift from $d = pq$ to $d = 0$ is summarized in Figure 4. We calculate Eq. 10 with $d = 0$ or with $d = pq$. With $d = 0$ in Eq. 10, we obtain as expected Eq. 3:

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

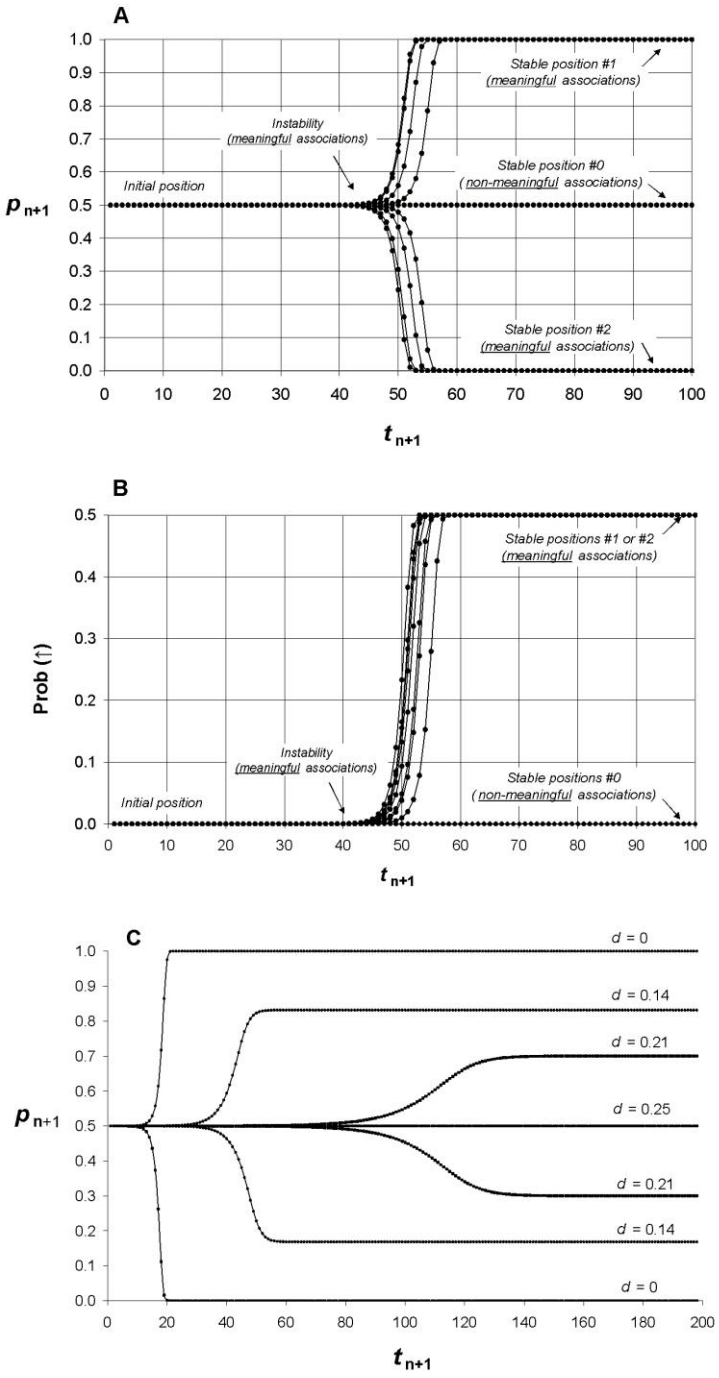

Figure 3. Emergence of a direct relationship from the point of view of an uninvolved participant. The successive values of the probability to record a direct relationship according to Eq. 7 are computed in panel A. Each

probability p_{n+1} of the sequence is calculated by using p_n and a probability fluctuation ε_{n+1} that is randomly obtained between –0.5 and +0.5 × 10^{-15}. This simulation shows that the initial state (probability of direct relationship equal to 1/2) is instable for meaningful associations. Indeed, after a few dozens of calculation steps, a dramatic transition always occurs toward one of two stable positions: either Prob (direct) = 1 or Prob (direct) = 0. This transition is also systematically observed with different values of probability fluctuations (data not shown). Panel B shows the emergence of an "activated" state" (↑) from background noise. In contrast, for non-meaningful associations, the probability of direct relationship remains close to 1/2 (A) and the probability to observe an "activated" state" (↑) is near zero (B). Eight computer simulations for meaningful associations and one simulation for non-meaningful associations are shown in A and B. Panel C shows the probability to observe a direct relationship with different values of d from d = 0 to d = pq. For panel C, probability fluctuation ε_{n+1} are randomly obtained between –0.5 and +0.5 × 10^{-5} for better display.

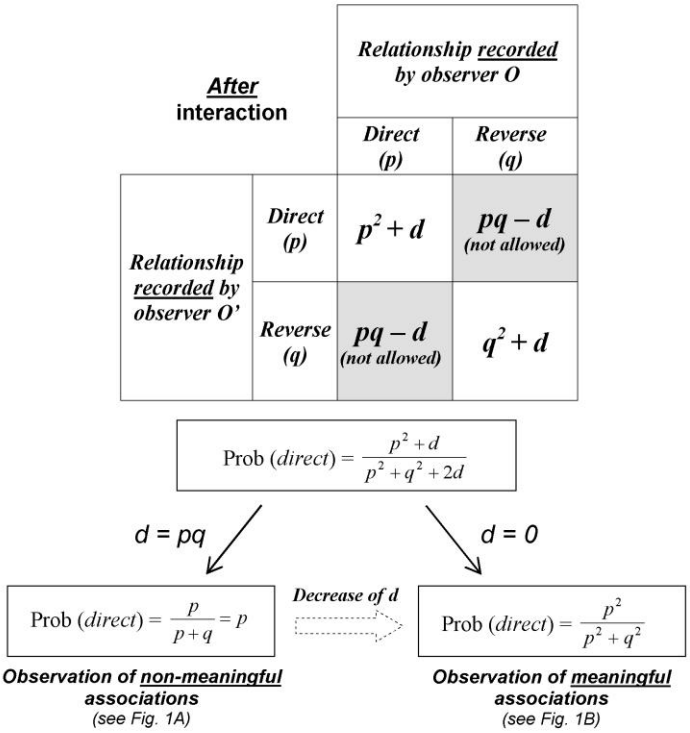

Figure 4. From non-meaningful to meaningful associations. This figure is a generalization of Figure 3 with an additional parameter d that decreases when the independence of the events A and B increases. According to Eq. 9, the joint probability of a direct relationship for O and O' is equal to $p^2 + d$ (before renormalization). Therefore, the probability of each grey area is equal to $p – (p^2 + d) = p × (1 – p) – d = pq – d$. The value of d can be interpreted as an assessment of the degree of meaning of the experiment for the interacting team of experimenters.

We have seen that with $d = 0$, the probability of a direct relationship tends toward 1 or 0 when fluctuations are taken into account (Figure 3A).

With $d = pq$ in Eq. 10:

$$\text{Prob}\,(direct) = \frac{p^2 + pq}{p^2 + q^2 + 2pq} = \frac{p \times (p+q)}{(p+q)^2} = \frac{p}{p+q} = p \qquad \text{(Eq.11)}$$

After introducing probability fluctuations in Eq. 11, we obtain a mathematical sequence:

$$p_{n+1} = p_n + \varepsilon_{n+1} \text{ (with } p_0 = 1/2) \qquad \text{(Eq.12)}$$

In this last case, the probability of a direct relationship fluctuates around 1/2 and there is no dramatic transition (Figure 3A); as well, the probability to observe an "activated" state (↑) remains near zero (Figure 3B). We easily see using Figure 1 that this situation with $d = pq$ corresponds to non-meaningful associations:

$$p = \text{Prob}\,(Pcb_0) \times \text{Prob}\,(\downarrow \mid Pcb_0) + \text{Prob}\,(Pcb_1) \times \text{Prob}\,(\uparrow \mid Pcb_1) \qquad \text{(Eq. 13)}$$

Therefore, varying *d* value from *pq* to 0 allows a shift from non-meaningful to meaningful associations, i.e. a shift from the simple addition of unconnected sub-events to a relationship considered as a whole (Figure 1 and Figure 3C). These considerations suggest that *d* could be interpreted as an evaluation of the *degree of meaning* of the experiment for the experimenters' team.

We understand now the rationale of the independence of the events *A* and *B*. If we consider the independence of the future events *A* and *B* jointly with intersubjective agreement, this implies that the event observed by *O* and *O'* (direct or reverse relationship) does not preexist to the experimenters' interaction in the probabilistic space constructed by *P*. In other words, the event is created by the experimenters' interaction. This is consistent with the fact that meaningful associations are abstract entities that subjectively connect experimental sub-events (Figure 1). These associations "exist" only when they are recognized as such by the experimenters, i.e. after a measurement/interaction. In contrast, non-meaningful associations are the simple addition of sub-events that preexist to the interaction. In this case, a classical approach is sufficient to describe the experimental situation.

3.5 Consequences of the modeling in blind experiments

Blind experiments are performed in order to avoid biases in particular those related to the experimenters. In blind experiments, the experimenters do not know which sample or drug is being tested until the experiment is achieved.

We consider first a blind experiment where Pcb_0 and Pcb_1 are evaluated under another label that is unrelated to the previous one and is therefore meaningless for the experimenters. The blinding is performed by a member of the interacting team of experimenters or by an automatic device; the assessment of the rate of direct relationship after completion of measurements is performed by a member of the team. From the point of view of an uninvolved participant *P*, the results for such an experiment are not different compared to an open-label experiment as described in Eq. 7 since the assessment of the outcome is performed locally by the interacting experimenters.

In blind randomized clinical trials, the experiment is generally under the supervision of a statistician who does not interact with the experimenters when the experiments are performed. After all measurements have been done, this remote supervisor assesses the rate of direct relationship by comparing two lists: the list of the states of the systems sent by the experimenters and the list of the corresponding labels that he kept secret and was unknown of the experimenters. In this experimental situation with a remote supervisor, the experimenters have no feedback on the result (direct or reverse relationship) and the supervisor is the first to assess the rate of direct relationship. From the point of view of a participant *P*, Prob (*direct*) = Prob (*reverse*) for *O* and *O'* since they have no information on labels. Since Prob (*direct*) + Prob (*reverse*) = 1, then Prob (*direct*) = 1/2.

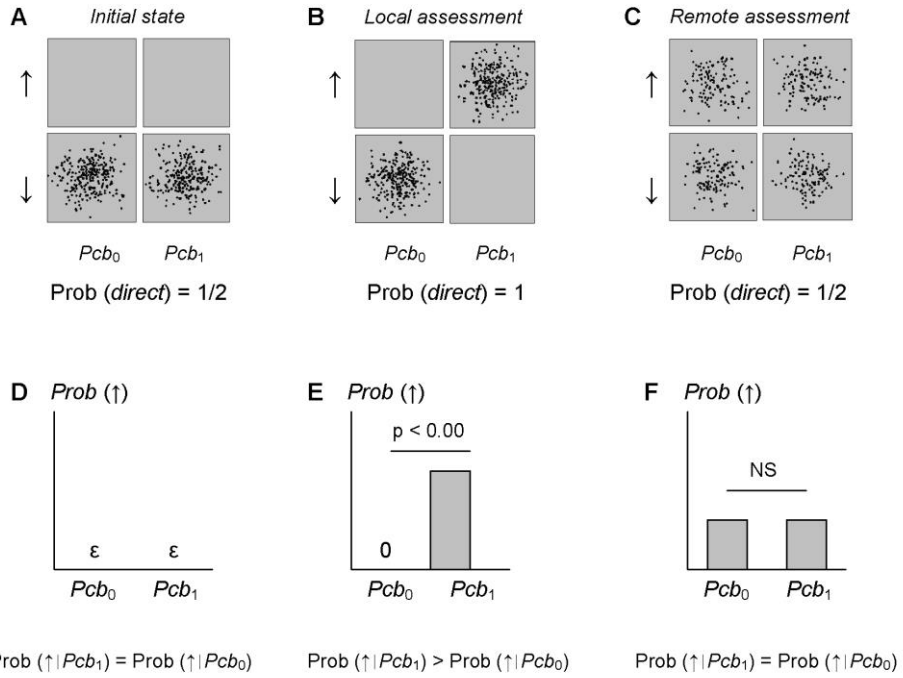

Figure 5. The relationship between labels and biological system is not a causal relationship. In the starting situation, only resting state of the biological system is associated with the label of each placebo (A and D). Correlations between labels and biological states emerge according to Eq. 7 if the assessment of the experiments is local (open-label experiment or local blinding) (B and E). These correlations disappear if the assessment of the experiment is done in a blind experiment with a remote supervisor (C and F). The crucial point is: who is the first to realize how the experiment is "successful" (rate of direct relationships)? If the interacting team of experimenters (local assessment) is first then there is a significant difference of the biological changes associated to Pcb_0 and Pcb_1. If the remote supervisor is first, there is no significant difference (NS) between the biological changes associated to Pcb_0 and Pcb_1. Note that in both situations, biological change ("↑") emerge from background noise. In the first situation (local assessment), the rate of biological change is associated only with Pcb_1 (see text) and, in the second situation, is evenly distributed among the two placebos (remote assessment). The difference of results in local vs. remote assessments indicates that the relationship between labels and biological states is not causal. NS, not significant.

We observe that the results of an experiment can be different according to the design: Prob (*direct*) = 1 for a local assessment (blind or open-label experiments) and Prob (*direct*) = 1/2 for a remote assessment.

Figure 5 summarizes these results. The results obtained with a remote assessment indicate that the relationship that emerges from the modeling is not causal. If it was the case, then the results with a remote assessment should not change compared with a blind local assessment. With a remote assessment, the relationship vanishes and the "activated" states of the system *S* are evenly distributed between Pcb_0 and Pcb_1.

In a double-blind clinical trial, if $d > 0$ in Eq. 10, the act of measuring by the interacting investigators could be responsible of changes in success rates in the study groups by adding to the classical "placebo effect" and to the specific drug effect (Figure 6). However, in contrast with the classical placebo effect, changes associated with meaningful associations are different after local vs. remote assessment. Local assessment means that investigators are involved both in measurements and in data analysis and assess both clinical (or biological) endpoints (e.g. arterial pressure, cholesterol concentration) and compare them with the study drug administered (placebo or verum). In contrast, in a remote experiment, the investigators have no feedback on the study drug administered before the statistician has established the success rate of each group of the trial.

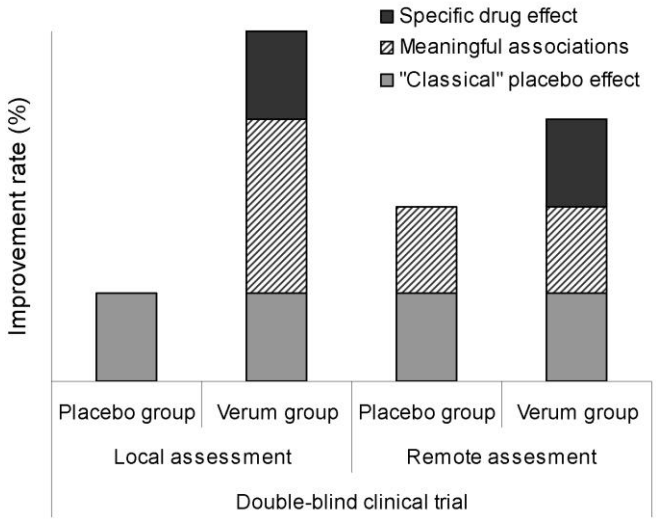

Figure 6. Application of the modeling to the setting of a double-blind clinical trial. In a double-blind clinical trial, the "classical" components of the placebo effect are evenly distributed in each study group (placebo and verum) whatever the design of the blind experiment. In contrast, the success rates (difference of improvement rates between verum and placebo groups) related to meaningful associations are different according to the design of the blind experiment (local vs. remote assessment of success rates) (see text).

4. DISCUSSION

This modeling introduces unusual considerations about the expectations of the experimenters and includes them in the description of the experiment. Indeed, "meaning" is always for someone and such subjective notions are usually not considered for predicting experimental outcomes. Nevertheless, in the modeling, meaning has concrete consequences as soon as it is shared among observers. Indeed, the observation of meaningful associations by different experimenters introduces instability in the probability space constructed by the uninvolved participant *P*. As a consequence, a dramatic transition of probability occurs and correlations emerge between supposed causes and observed effects.

This probabilistic modeling applies only to experimental systems that are not "rigid", but are sufficiently "deformable". Deformable must be understood as the capability of the system to move (in the absence of any obstacle) from a "resting" state toward an "activated" state thanks to random fluctuations. Note that the correlations between simple words and states of a biological system have nothing mysterious. Indeed, these correlations are not causal and the modeling itself shows that no message or order can be sent from a laboratory to another one by using these correlations.

Of interest, the probability transition cannot be described with a classical approach where probabilities are expressed relatively to the observed system. In the present modeling, probabilities are expressed relatively to each observer and the entire scene is described by an uninvolved participant. The absence of transition in the classical approach is related to the demonstration of Breuer that a complete self-measurement is impossible [12]. In other words, no apparatus (or observer) can distinguish all states of a system in which it is itself contained. Only a second apparatus (or observer) is able to measure both the system and the first apparatus [13].

In medicine, a drug has an effect as a chemical entity through a causal relationship, but has other possible consequences through its "label". In a clinical trial, it is difficult to attribute what is due to unspecific effects, placebo response and drug response. Indeed, these different components that participate to the final outcome are not necessarily additive [14]. However, the modeling predicts a counterintuitive behavior for meaningful correlations. Indeed, if the interacting experimenters are the first to have a feed-back on the conclusion of the experiment (local assessment) then meaningful correlations emerge. If a remote supervisor is the first (remote assessment), these correlations vanish and the "activated" states are randomly distributed among study groups. Such blind comparisons could be useful in trials of complementary and alternative medicines that are usually considered as consequences of "placebo effect".

Because the modeling potentially applies to any biological experiment, the question of meaningful associations goes beyond the issue of placebo stricto sensu. Indeed, “control” conditions used in experiments in biology or in psychology play the same role as placebos. For experimental scientists, it is important to be aware that unwanted correlations can emerge between the observers of an experiment and the observed system. Some years ago, some authors evidenced the high variability of behavioral experiments in rodents due to environment factors; an “experimenter effect” explained a large part of this variability [15]. There is also a current debate on reproducibility in sciences in general, more particularly in biological sciences and in psychology [16-19]. Trivial explanations are likely in most cases, but the role of meaningful associations merits being explored when poor reproducibility is reported. Meaningful associations could be responsible in some cases for the emergence of “causal” relationships for one scientist team, but not observed by other teams.

In conclusion, this simple modeling suggests that the act of measuring is not always neutral and some correlations between apparent causes and observed outcomes may possibly emerge, thus contributing to conclude for obvious, but false, causal relationship. These results could have consequences in the design and interpretation of experiments in life sciences, medicine and psychology.

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