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The Population Dynamics of the Placebo Effect and Its Role in the Evolution of Medical Technology

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Abstract
The placebo effect, used today as the benchmark to evaluate treatment efficacy, plays a major functional role in traditional medical practices. To better understand its effect at the population level, I use a formal approach to examine the population dynamics of the placebo effect and show a reciprocal causal relationship between belief and efficacy: belief in the efficacy of treatments enhances their realized efficacy, which in turn increases people's confidence in their therapeutic power. A unique equilibrium for subjective belief and realized efficacy always exists. Its magnitude depends on how beliefs are constructed (relative weight on observed action vs. observed outcome). I further investigate how the placebo effect affects the maintenance of existing medical technologies and the invasion of new technologies by explicitly modeling a belief construction process. Analytical and simulation results show that although the placebo effect primarily suppresses the spread of new technologies, it may occasionally enhance the adoption of superior technological variants under specific parameter combinations.

Keywords Placebo effect · Technological evolution · Cultural evolution · Social learning

Introduction

The suggestive power of the human mind has long fascinated people across cultures and historical times (Kaptchuk, 1998). Under the influence of psychological suggestion, subjective experience often profoundly shapes our perception of reality. Such subjective experience can be self-induced (e.g., psychedelic substances) or by the active manipulation from others (e.g., hypnotism). Importantly, our inner experience can also be affected by perceived reality. This interesting reciprocal causal relationship is nicely illustrated by Sir Edward Tylor's example on dreams in his seminal work *Primitive Culture* (1871), in which he describes indigenous people's conception of dreams as a "vicious circle": one's beliefs about the world influences what he dreams, which in turns is used to confirm his beliefs.

Tylor's discussion on dreams primarily occurs in the context of animism, but his point of the reciprocal nature of belief and reality is relevant for many psycho-physio phenomena. The placebo effect, for instance, is a typical case of belief and reality reinforcing each other: certain treatments "work" because their efficacy is believed, and their efficacy is believed because they are perceived to "work". The term "placebo effect," which is frequently used in contemporary medical setting owes its modern meaning in the Eighteenth-century medical context (De Craen et al., 1999) and has become part of the gold standard for evaluating treatment efficacy (Misra, 2012). To date, much research has been devoted to understanding psychological, sociological, and cultural factors that contribute to its potency. At its core, the placebo effect relies on patients' expectation that certain therapeutic interventions will be effective. As such, anything that contributes to the belief in therapeutic efficacy will likely induce a placebo effect. For example, the optimism/enthusiasm (Shapiro, 1969), as well as the perceived authority (Kirmayer, 1994) of the physician, elaborate procedures and devices (De Craen et al., 2000; Kaptchuk et al., 2000), costliness of the intervention (Waber et al., 2008) have all been shown to enhance

"What he believes he therefore sees; and what he sees he therefore believes."

—Edward Tylor

Primitive Culture

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therapeutic efficacy through the placebo effect. In addition to the specific features of the physician and therapeutic practice themselves, observing other patients improve after taking a certain drug increases one's own recovery under the same drug treatment (Faasse & Petrie, 2016). Though not the prime focus of the current placebo research, this last point illustrates the possibility where reality (drugs observed working) shapes subjective belief (the drug is efficacious), which then enhances the realized therapeutic effect in a medical setting.

At the population level, the belief-efficacy feedback loop likely plays a non-negligible role in the maintenance of traditional healing practices. Such feedback loop may be due to personal experience: one may undergo some medical treatment and recovers, which increases her confidence in the efficacy of the treatment and makes her more likely to recover from illness the next time using the same treatment. It can also occur as a result of social learning: she can have confidence in some treatment because others have told her that the treatment had worked for them; she then tries the treatment and in the case of recovery, advertises the effectiveness of the treatment and such testimony may then further increase people's confidence in the treatment. In reality, the efficacy information of medical treatments and interventions primarily transmits through social learning because 1) individuals often lack first-hand experience of these treatments and their efficacy outcomes, and 2) even when they do have such personal experience, culturally-acquired efficacy information may override it, as occasional failures of medical treatments can be easily explained away (Evans-Pritchard, 1937; Smith & Dale Andrew Murray, 1920; Turnbull, 1965).

The large literature on cultural evolution has amply shown the importance of social learning of beliefs, values, and cultural practices (Boyd & Richerson, 1985; Henrich & McElreath, 2003). In traditional, small-scale societies, knowledge transmission is largely de-centralized (Lancy et al., 2010) and individuals most likely obtain the efficacy information of some medical treatment from observation and inference of others' actions and associated outcomes. Therefore, examining the population dynamics of the placebo effect offers important insights regarding the process in which these medical practices are transmitted and maintained. In this paper, I will first briefly describe illness and treatment in small scale societies as well as the role of the placebo effect, and then formally model the mutual reinforcement of belief and treatment efficacy as well as how the adoption of new medical practices may be affected in a cultural evolutionary framework.

Placebo Effect in the Context of Traditional Healing Practices

Theories of illness in most traditional societies are often supernatural, where people attribute causes of illness to soul loss, spirit aggression, sorcery, and witchcraft (Murdock, 1980). Even the more "natural" theories, such as the balance of humors or *qi* (Sigerist, 1951) usually lack a sound scientific basis. Given these theories, treatments such as ritualized sacrifice, offerings, or bloodletting are often intuitive responses to address the presumed causes. From our modern scientific perspective, these forms of traditional healing practices seem utterly ineffective. However, it should be kept in mind that this modern conception of effectiveness is defined in opposition to the placebo effect (Kaptchuk & Miller, 2015). In other words, medical treatment is only considered effective if it can be shown through randomized controlled trials (RCT) that it has a therapeutic effect on top of the placebo component. Therefore, many forms of traditional and alternative medicine are often dismissed as "just placebo." The implication here, however, is that patients do get better under such treatment compared to no treatment precisely due to the presence of the placebo effect, and the eventual therapeutic outcome depends on the degree to which the patient believes in the efficacy of the treatment.

But what makes people believe in these seemingly ineffective practices in the first place? Evolutionarily minded anthropologists tend to focus on the intuitive plausibility of treatments due to evolved psychological biases; for example, the prevalence of bloodletting has been attributed to some universal cognitive mechanisms that make "letting go of bad blood" appear an attractive cure (Miton et al., 2015, Tylor, 1871). Such cognitive biases certainly play a role; yet another important reason for people to believe in the efficacy of these treatments has to do with people trusting culturally transmitted information. Ethnographically, plenty of anecdotal evidence suggests that people believe in the efficacy of some treatment because they were told anecdotal stories in which these treatments yield positive results[1] (Harrell, 1983). My fieldwork in southwest China also shows that people frequently use observed positive outcomes from others ("it worked on my friend") to justify their own belief in the efficacy of some culturally transmitted medical treatment. In fact, some even acknowledge that they were initially skeptical of some medical treatment but became convinced after some closer relative or friend was successfully treated (Hong, 2016 unpublished).

Intuitive plausibility, trust in social information sources, and a range of other cultural factors such as

[1] On the other hand, people may become skeptical of the treatment if it doesn't yield positive results (Bianchi 1989).

positive physician–patient relationships likely collectively contribute to the placebo effect of medical treatments. In a recent comprehensive review, Hróbjartsson and Gøtzsche (2010) show that the placebo effect most prominently manifests itself in subjectively reported pain reduction, which is especially relevant in small scale societies as the feeling of pain is often a major indicator by which people tell whether the illness is getting better or worse. The magnitude of the placebo effect can be substantial; some recent estimates of its effect size in contemporary medical settings range from d = 0.28 to d = 0.64 (Hunsley & Westmacott, 2007; Wartolowska et al., 2016), and it is likely that culturally trusted medical practices such as acupuncture may have an even more significant placebo effect (Vickers et al., 2018). In some traditional societies, the effect of belief on realized therapeutic efficacy is well recognized; for example, the Karanga in Zimbabwe know that the effectiveness of some medical treatment depends on the patient's belief, and the curing procedure is specifically designed to induce the patient's confidence, such as having the patient's relatives testify their trust in the doctor and his treatment method (Aschwanden & Cooper, 1987).

Model

Here I take a modeling approach to examine the population-level dynamics of the placebo effect more rigorously. I discuss two models that share the same set of assumptions but aim to address different questions. The first model formalizes the verbal argument of the feedback relationship between subjective belief and efficacy; specifically, it aims to describe the temporal evolution of belief and efficacy. I am particularly interested in whether some equilibrium states will be obtained in the population, that is, whether the belief and efficacy of some medical technology will reach stable values and resist further change. The second model examines the situation where there are two technological variants (one existing, the other invading) that are susceptible to the placebo effect in a population, and individuals need to decide which variant to adopt. This dynamics is explicitly modeled in a general cultural evolutionary framework (Boyd & Richerson, 1985) where naive individuals acquire information regarding the efficacy of these technological variants from observing other individuals' actions (i.e., which technological variant did that person possess/perform?) as well as the outcomes of the technological variants (i.e., did this technological variant work for that person?). Special attention will be paid to the role of the placebo effect in the adoption of novel, potentially superior technological variants. Note that in contrast with classic models in the cultural evolution literature where individuals "copy" cultural variants from others, my model takes a more cognitive approach in the sense that various types of information are first translated into subjective belief in the efficacy of the technology (Hong & Henrich, 2021 forthcoming), which affects the realized efficacy (through placebo effect) and subsequent trait adoption decisions.

Modeling the Feedback Between Belief and Efficacy of Medical Technology

I assume that the outcome of some treatment practice is a binary variable and can either be positive or negative and define its efficacy as the proportion of time that the practice yields a positive outcome. The assumption that technological practices yield binary outcomes is based on the historical evidence that the outcome of many forms of medical treatments are recorded in a binary fashion, i.e., success or failure (Hong, unpublished). Additionally, given that testimony is often the primary transmission channel for efficacy information, such information is unlikely to be adequately quantified.

Each treatment practice has a "baseline efficacy" of E_b, which refers to the efficacy that is independent of the placebo effect (i.e., the effectiveness rate when the patient is utterly skeptical of the efficacy of the treatment), and the "realized efficacy" E_r is the numeric sum of the baseline efficacy and the additional efficacy due to the patient's confidence in the treatment. For a particular individual, the relationship between realized efficacy and baseline efficacy of some treatment T is defined as

$$E_r = \begin{cases} E_b + \beta \cdot p + \beta_1 \cdot E_b \cdot p & if E_b + \beta \cdot p + \beta_1 \cdot E_b \cdot p \leq 1 \\ 1 & if E_b + \beta \cdot p + \beta_1 \cdot E_b \cdot p > 1 \end{cases} \quad (1)$$

where p denotes the individual's subjective belief ($0 \leq p \leq 1$) of the T's efficacy, and the placebo effect is modeled as having two components: $\beta \cdot p$ represents the additive component of the placebo effect, and $\beta_1 \cdot E_b \cdot p$ represent the interactive component to account for potential drug-placebo interaction (Hammami et al., 2010). The difference between these two terms is that while in the first term β is the only multiplier that controls the extent to which belief contributes to realized efficacy, in the second term β_1's effect also depends on baseline efficacy E_b. In other words, the second term ($\beta_1 \cdot E_b \cdot p$)'s contribution to overall realized efficacy would be relatively small if baseline efficacy is low.

Because E_b and p are strictly non-negative, positive β and β_1 will increase realized efficacy of T. Equation (1) thus captures the intuition that the more one believes in the effectiveness of some treatment, the more likely the treatment yields a positive outcome for her. Note that because E_r maybe numerically larger than 1 if either E_b, β, β_1, or p is sufficiently large, E_r is set to be 1 when $E_b + \beta \cdot p + \beta_1 \cdot E_b \cdot p > 1$ to ensure

that it meaningfully represents the probability of treatment success (this condition applies to all subsequent analyses). Regarding the transmission of efficacy information, I consider two sources: observed action and observed outcome (payoff information of treatment variants) from other individuals. In other words, one may believe that some treatment T is effective because he observes other people practicing T or he observes (or is told by others) that T yields positive outcomes. Suppose the focal individual is trying to evaluate the efficacy of some technology to form a subjective belief. To do so, she samples n individuals from the population, all of whom have performed the technology exactly once, and constructs her belief p according to the following equation:

$$p = \frac{n \cdot w_a + T_{pos} \cdot w_o}{n \cdot w_a + n \cdot w_o} \tag{2}$$

where w_a denotes the weight attached to observed action, w_o denotes weight attached to observed outcome, and T_{pos} denotes the number of positive outcomes. From an epistemic perspective, the denominator $(n \cdot w_a + n \cdot w_o)$ can be viewed as the total amount of information available to the observer, and the numerator $(n \cdot w_a + T_{pos} \cdot w_o)$ represents the amount of information/evidence that is confirmatory regarding the efficacy of T. As such, their ratio $(\frac{n \cdot w_a + T_{pos} \cdot w_o}{n \cdot w_a + n \cdot w_o})$ is simply the proportion of evidence that is in favor of T being effective. The weight terms (w_a and {w_o} can be viewed as the individual's subjective evaluation of the importance of different kinds of information (i.e., action vs. outcome). For example, someone with small w_a and large w_o pays little attention to observed action (whether the treatment is being used) but takes observed outcome (whether the treatment works on other people) very seriously. In both models presented here these internal weightings are assumed to be fixed and given; in other words, all individuals in the population have the same w_a and w_o which remain constant. Elsewhere I have explicitly modeled the evolution of these epistemic weights and show that natural selection should favor w_a, though w_o is likely to be substantial as well in a domain-specific way (Hong, unpublished). To sum up, Eq. (2) represents the belief formation process where the focal individual takes both observed action and observed outcome into consideration. This particular way of constructing belief p is informed by two well-recognized transmission biases in the cultural evolution literature, frequency-dependent transmission (Henrich & Boyd, 1998) and payoff biased transmission (Vale et al., 2017). In this first model, although individuals are not picking amongst multiple cultural variants, they consider both the relative number of individuals possessing a cultural variant in a population and the payoff of cultural variants in forming a belief, which serves as the basis for variants adoption when multiple treatment variants are available in the second model.

Equation (2) essentially partitions the belief into two components whose relative importance are modulated by w_a and w_o. In the extreme case of $w_a = 0$, belief p is determined entirely by the proportion of positive outcomes among sampled individuals $p = \frac{T_{pos}}{n}$; on the other extreme end when $w_o = 0$, outcome information is completely ignored and therefore $p = 1$.

Since we are interested in the evolutionary dynamics of p at the population level, in particular potential equilibrium states, we now introduce a temporal dimension. For the sake of analytic convenience, I employ the typical assumptions in the theoretical biology of non-overlapping generations (Day & Bonduriansky, 2011). Suppose the subjective belief of the focal individual at time $t + 1$ is $p_{(t+1)}$, we have

$$p_{(t+1)} = \frac{n \cdot w_a + T_{pos(t)} \cdot w_o}{n \cdot w_a + n \cdot w_o} \tag{3}$$

where $T_{pos(t)}$ refers to the number of sampled individuals who have positive outcomes at time t. Using Eq. (1), we now construct the realized efficacy of T at time $t + 1$:

$$\begin{aligned} E_{r(t+1)} &= E_b + \beta p_{(t+1)} + \beta_1 E_b p_{(t+1)} \\ &= E_b + \beta \frac{nw_a + T_{pos(t)} w_o}{nw_a + nw_o} + \beta_1 E_b \frac{nw_a + T_{pos(t)} w_o}{nw_a + nw_o} \end{aligned} \tag{4}$$

To find the equilibrium state, set $E_{r(t+1)} = E_{r(t)}$, meaning that the realized efficacy no longer changes with time. Recall that the expected number of sampled individuals with a positive outcome is numerically equivalent to the product of realized efficacy at t and the total number of sampled individuals ($T_{pos(t)} = E_{r(t)} \cdot n$). We thus have

$$E_b + \beta \frac{n \cdot w_a + n \cdot E_{r(t)} \cdot w_o}{n \cdot w_a + n \cdot w_o} + \beta_1 E_b \frac{n \cdot w_a + n \cdot E_{r(t)} \cdot w_o}{n \cdot w_a + n \cdot w_o} = E_{r(t)} \tag{5}$$

Solving for the equilibrium value of $E_{r(t)}$ (denoted by E_r^*), we have

$$E_r^* = \frac{w_a \cdot (E_b + \beta + \beta_1 \cdot E_b) + w_o \cdot E_b}{w_a + w_o \cdot (1 - \beta - \beta_1 \cdot E_b)} \tag{6}$$

Equation (6) has some interesting properties. The number of sampled individuals n drops out, and the magnitude of the placebo effect (β, β_1) as well as baseline efficacy (E_b) both contribute to realized efficacy at equilibrium positively if the denominator $w_a + w_o \cdot (1 - \beta - \beta_1 \cdot E_b)$ is larger than zero. Reassuringly, the interaction term β_1 matters more when E_b is large. In the extreme case where $w_o = 0$ (agents ignore outcome information completely), $E_r^* = E_b + \beta + \beta_1 \cdot E_b$, which is simply substituting $p = 1$ into Eq. (2), as all individuals fully believe in the efficacy of the treatment.

Figure 1 provides a graphical illustration of the temporal evolution of belief (p) and realized efficacy (E_r). In both

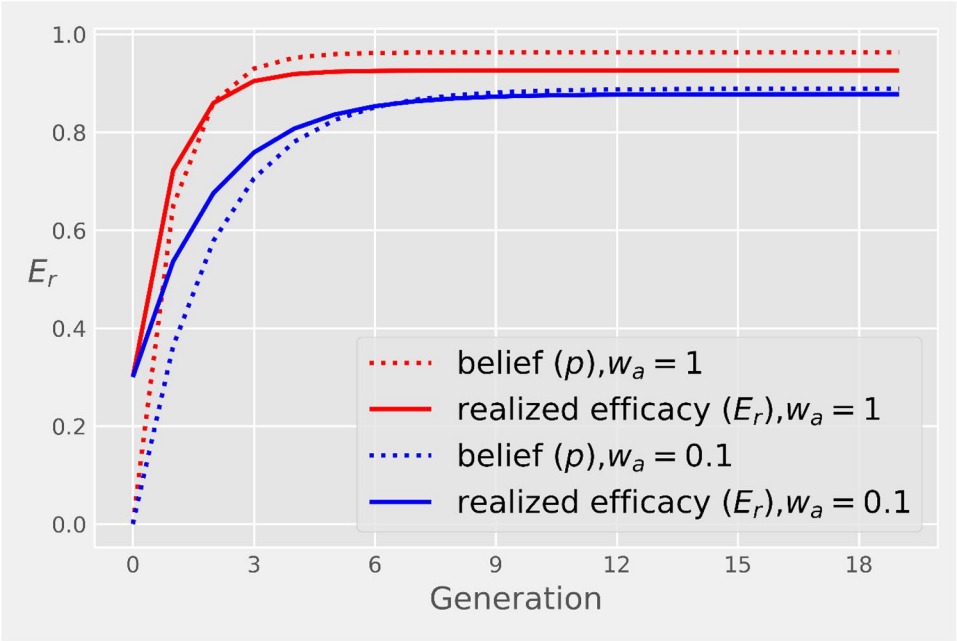

Fig. 1 Numerical illustration of the temporal evolution of belief and realized the efficacy of some technology under two-weight conditions ($w_a = 0.1$ and $w_a = 1$). w_a is fixed at 1. Other parameter values: $E_b = 0.3$, $\beta = \beta_1 = 0.5$

conditions, the initial beliefs are set to be 0, meaning that individuals are entirely skeptical of the technology (but adopt the treatment nonetheless as there is no other alternative), and the baseline efficacies are set at 0.3. Notice that both belief and realized efficacy quickly increase and reach equilibrium, especially when w_a is large. From an epistemic perspective, observed action provides unambiguous evidence for the efficacy of the treatment as all sampled individuals utilize the treatment (whereas observed outcome may be either positive or negative). Weighing more on action thus increases individuals' confidence and consequently realizes efficacy.

Figure 2 shows the realized efficacy at equilibrium under various parameter combinations. In the absence of any placebo effect ($\beta = \beta_1 = 0$, top left graph), realized efficacy is always the same as baseline efficacy regardless of w_a (note that the three w_a conditions completely overlap). This makes intuitive sense: when there is no placebo effect, realized efficacy does not depend on what people believe. When there is the placebo effect, however, realized efficacy is always larger than baseline efficacy as the placebo effect adds to the therapeutic effect of treatment. The more weight placed on observed action, the larger the difference, especially when baseline efficacy is low. The intuition here is that in order to benefit from the placebo effect, individuals need to first increase their belief in the efficacy of the treatment, and as already pointed out, weighing more on observed action to construct belief is a better way than weighing on the observed outcome, because most outcomes may turn out to be negative (especially when E_b is small) while everyone in the population performs the action.

Note that in Fig. 2, all E_r^* values that are larger than one are transformed into 1. As mentioned, although an equilibrium value of realized efficacy always exists in theory, Eq. (6) itself doesn't constrain E_r^* within 0 and 1. In reality, of course, E_r^* is a probability and is always bound within 0 and 1. This suggests that there is a ceiling effect of the placebo effect when E_b is sufficiently large: when the treatment already works 100% of the time, additional trust in the treatment does not affect realized efficacy.

Two conclusions may be drawn from the above model. First, the belief-efficacy feedback loop can significantly drive up both individuals' subjective belief in the efficacy of some treatment and its actual (realized) efficacy. Second, when realized efficacy is influenced by agents' subjective belief, a unique stable equilibrium always exists, and its value is determined by not only the parameters that directly control the magnitude of the placebo effect (β and β_1), but also how much individuals trust different sources of information (w_a and w_o). Both subjective belief and realized efficacy can be maintained at high levels when individuals weigh more on observed action in constructing their beliefs. The implication here is that the prevalent belief in the efficacy of some newly introduced treatment may quickly increase when it is the only game in town. When people are confident in the treatment, the realized efficacy may be substantially higher than baseline efficacy.

Modeling the Adoption of Different Treatment Variants and the Role of the Placebo Effect

In the second model, I use a combination of analytic modeling and agent-based simulation to examine the conditions under which a new treatment variant may be able to "invade" a population where there is already existing treatment. I

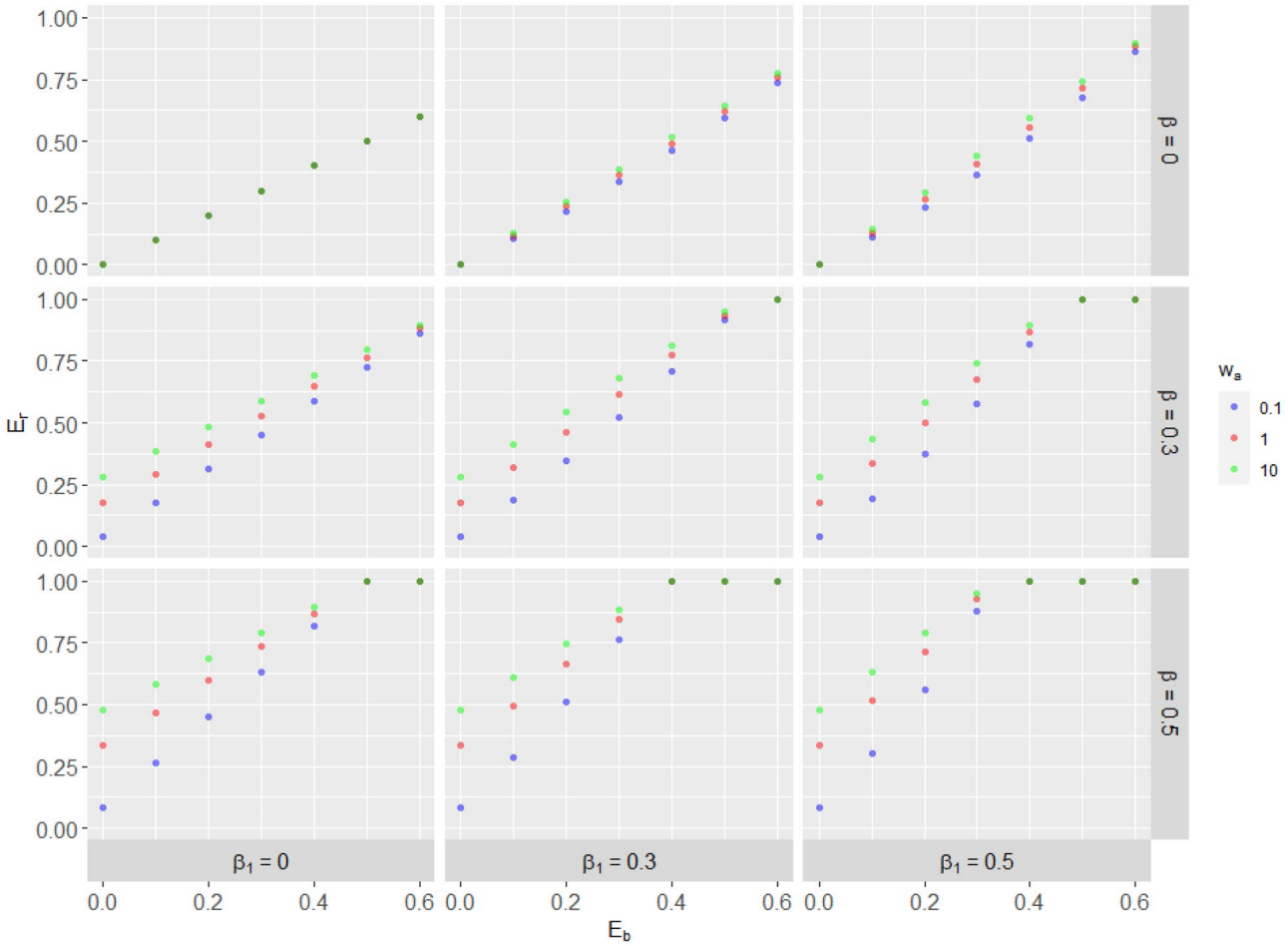

Fig. 2 Relationship between β, β_1, E_b, w_a and E_r at equilibrium. Weight for the observed outcome w_o is fixed at 1

assume that individuals evaluate the efficacy of both treatment variants through social learning, but they can only adopt one variant at a time. We are particularly interested in the role of the placebo effect: if the existing treatment dominates the population, how does the placebo effect influence the invasion of a new, potentially superior (higher baseline efficacy) treatment? One intuition may be that the placebo effect prevents new treatment variants from spreading because they do not enjoy its full benefit as the existing treatment does. Below we examine such intuition formally.

Agent Construction and Life Cycle

Each agent is represented as a list $[T, p]$ where T denotes the treatment variant that the agent possesses, and p denotes the agent's subjective belief about the efficacy ($0 < p < 1$) of the treatment variant that he possesses. Let T_1 be the existing treatment variant and T_2 be the invading treatment variant.

To set up the initial condition, we create a starting population of N agents (hereafter referred to as F1 agents), with most agents possessing treatment 1 (T_1) and the rest possessing treatment 2 (T_2). Assuming that the realized efficacy of T_1 has reached equilibrium in the population ($E^*_{r1} = \frac{w_a \cdot (E_{b1} + \beta + \beta_1 \cdot E_{b1}) + w_o \cdot E_{b1}}{w_a + w_o \cdot (1 - \beta - \beta_1 \cdot E_{b1})}$, Eq. (6)) before the invasion of T_2, where E_{b1} and E_{r1} represents the baseline efficacy of T_1 and realized the efficacy of T_1 respectively. Individuals' belief of T_1's efficacy is therefore $p_1 = \frac{w_a + w_o \cdot E^*_{r1}}{w_a + w_o}$. Agents with T_2, on the other hand, have belief of 0 regarding the efficacy of T_2, meaning that since it is the new treatment and these agents have no prior experience with it, they do not believe it will work at all. Therefore, the realized efficacy of treatment 2 (E_{r2}) initially is the same as baseline efficacy (E_{b2}).

The life cycle of the agents is as follows:

1) In the first generation, each F1 agent will "use" the treatment variant she possesses and generates either a "positive" or "negative" outcome probabilistically based on the treatment's realized efficacy.

2) A F2 generation is created with the same size N (no population growth). Each F2 agent will sample several F1 agents as their models. Note that these models could all have

T_1, all have T_2, or a mixture of the two treatments, along with the outcomes of the treatments. The focal F2 agent will then construct her belief regarding the efficacy of T_1 and T_2 using the following formula based on Eq. (2):

$$p_1 = \frac{n_1 \cdot w_a + T_{1pos} \cdot w_o}{(n_1 + n_2) \cdot w_a + n_1 \cdot w_o} \tag{7}$$

$$p_2 = \frac{n_2 \cdot w_a + T_{2pos} \cdot w_o}{(n_1 + n_2) \cdot w_a + n_2 \cdot w_o} \tag{8}$$

where n_1 and n_2 represent the number of models in the sample that have T_1 and T_2 respectively ($n_1 + n_2 = n$), T_{1pos} and T_{2pos} represent the number of positive outcomes of T_1 and T_2, and w_a and w_o represent the weights associated with observed action and observed outcomes.

3) The focal agent then decides regarding which treatment variant to adopt. If all models possess T_1 orT_2, then the focal F2 agent will adopt T_1 or T_2 with probability 1. If the models possess a mixture of T_1 andT_2, then she will adopt T_1 or T_2 with probability proportional to the relative magnitude of the agent's subjective belief p_1 andp_2, that is, she will adopt T_1 with probability$\frac{p_1}{p_1+p_2}$, and T_2 with probability $\frac{p_2}{p_1+p_2}$.

4) After all agents in F2 have adopted a treatment variant and constructed the corresponding belief, they become the parent generation and the cycle continues.

Analytic Result for the Probability of Adopting Technological Variants

We will first derive some analytic results based on the above setup. Let r denote the proportion of T_1 individuals in the parental generation at a given time; because each naive individual picks n models from the parental generation, the expected value of n_1 and n_2 (number of models with T_1 and T_2, respectively) is thus $r \cdot n$ and $(1 - r) \cdot n$, and the expected value of T_{1pos} and T_{2pos} (number of models with T_1/T_2 who have the positive outcome) is $r \cdot n \cdot E_{r1}$ and $(1 - r) \cdot n \cdot E_{r2}$. Let q denote the probability of picking T_1 when there is a mixture of models with T_1 and T_2. Substitute the above expressions into Eqs. (1) and (2), we have

$$q = \frac{p_1}{p_1 + p_2} = \frac{\frac{r \cdot w_o + r \cdot E_{r1} \cdot w_a}{w_o + r \cdot w_a}}{\frac{r \cdot w_o + r \cdot E_{r1} \cdot w_a}{w_o + r \cdot w_a} + \frac{(1-r) \cdot w_o + (1-r) \cdot E_{r2} \cdot w_a}{w_o + (1-r) \cdot w_a}} \tag{9}$$

The overall probability that a naive agent adopts T_1 at a given time is thus

$$\begin{aligned} P(T_1 \text{ adopted}) &= 1 \cdot r^n + 0 \cdot (1 - r)^n + (1 - r^n - (1 - r)^n) \cdot q \\ &= (1 - q) \cdot r^n - q \cdot (1 - r)^n + q \end{aligned} \tag{10}$$

The obvious exceptional cases here, $r = 0$ (no T_1 individuals in the parental generation) and $r = 1$ (no T_2 individuals in the parental generation) yield 0 and 1, respectively. It isn't easy, however, to obtain general insight from Eq. (10) due to the unwieldy nature of q. The relationship between $P(T_1$ adopted) and various parameters are thus explored using a numerical method, as shown in Fig. 3.

The following observations are noted. First, reassuringly, the probability of adopting T_1 is higher when the parental population has more T_1 individuals (larger r), as it is more likely that T_1 individuals are selected as models.

Second, as the realized efficacy of T_2 (E_{r2}) increases, the probability of adopting T_1 decreases, but the rate of decrease is slow when the weight of observed technological practice is large, which makes sense because a large w_a means a relatively small w_o, or the weight of observed outcome; if naive individuals don't pay much attention to the outcome, efficacy won't matter very much.

Third, when individuals weigh more on observed outcomes ($w_a = 0.1$), the probability of adopting T_1 has a nuanced relationship with n. If we only consider cases where T_1 is superior ($E_{r1} > E_{r2}$), $P(T_1$ adopted) decreases with n when most individuals in the parental generation possess T_1 ($r = 0.9$) yet increases with n when T_2 individuals are the majority ($r = 0.1$). This suggests that the suppression of inferior treatment depends on the population composition and the number of models picked. We will return to this point and the role of n in the next section.

Simulation of Technological Adoption Dynamics with the Placebo Effect

The above analytic results assume that the realized efficacy of treatments is given and fixed. The population dynamics would be more interesting once we include the placebo effect and allow realized efficacy to be endogenously determined. That is, individuals' treatment outcomes are a function of not only the treatment's baseline efficacy E_b but also the magnitude of the placebo effect. To this end, I construct an agent-based simulation with agents' life cycle specified in Sect. 2.3., and examine the relative frequency of T_1 individuals after a certain time under various parameter combinations.

A full exploration of parameter space is shown in Fig. 4. Note that because the population size is relatively small, fixation of either T_1 or T_2 occurs rather often, and therefore "T_1 frequency" on y axis can also be viewed as the probability that T_1 or T_2 reaches fixation (if T_1 reaches fixation in a given run, it will have a T_1 frequency of 1).

The most apparent pattern, of course, is that the end-point frequency of T_1 individuals at generation 200 decreases as the baseline efficacy of the invading treatment increases

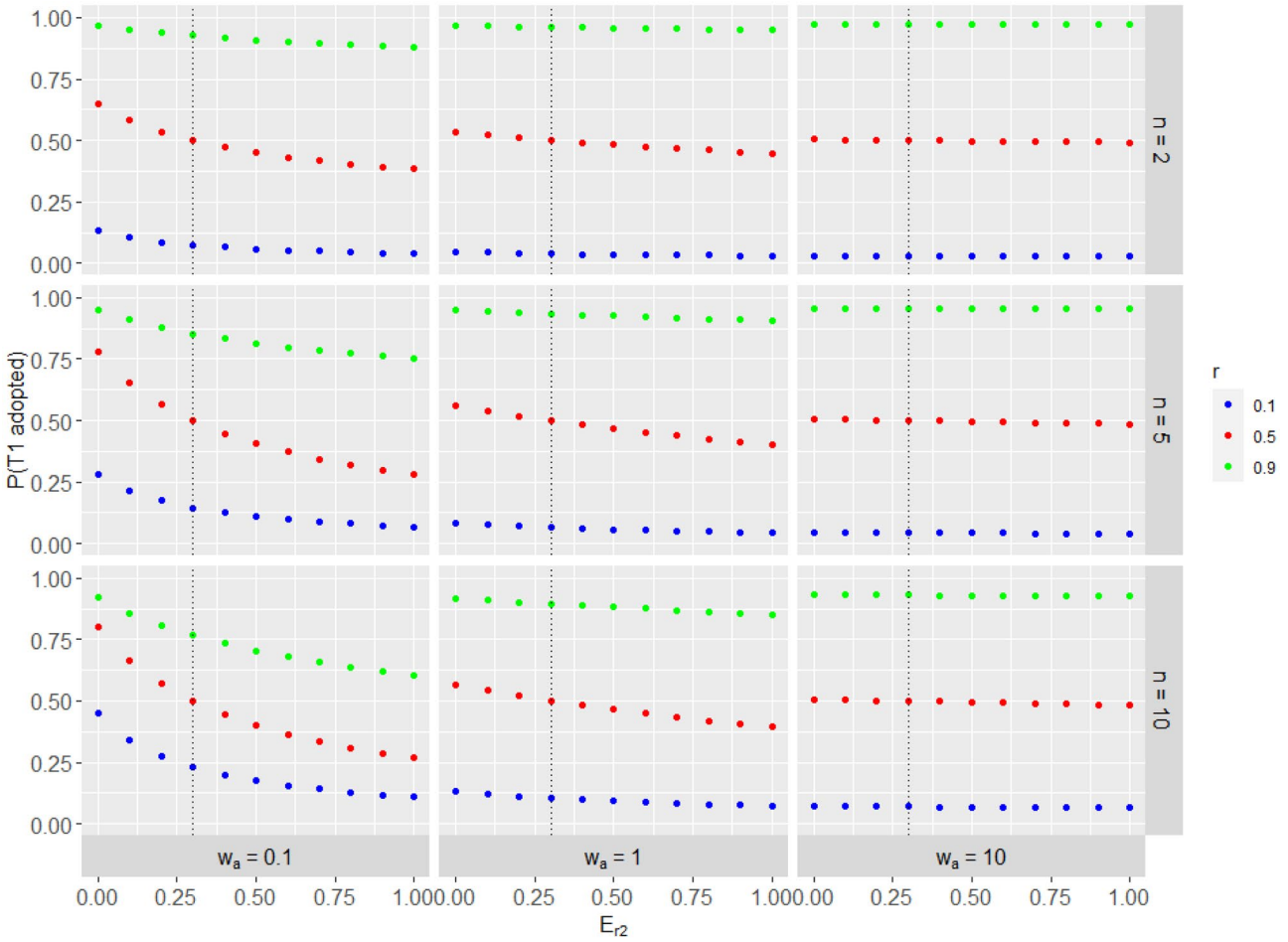

Fig. 3 Relationship between E_{r2}, w_a, r, n and the probability of adopting T_1. The realized efficacy of T_1 (E_{r1}), is fixed at 0.3 (dotted line) and weight for the observed outcome w_o is fixed at 1

across all conditions. This result makes intuitive sense; the more the invading treatment is objectively better (i.e., larger E_{b2}), the more likely it will spread in the population. This pattern is least pronounced, however, when w_a is extremely large ($w_a = 100$), as when agents entirely rely on observed action and ignore outcome, the efficacy of the invading treatment does not matter. The role of the placebo effect, on the other hand, is subtle and more dependent on specific parameter combinations. First, the placebo effect always makes the adoption of new technology less likely when it has lower baseline efficacy than that of the existing treatment ($E_{b1} < 0.3$), as indicated by the relatively high frequency of T_1 individuals. This is because the degree to which a belief may benefit from the placebo effect depends on its initial magnitude, and since the initial belief for the invading treatment is 0, existing treatments benefit more from the placebo effect. Additionally, the disadvantage of the invading treatments is exacerbated by the fact that they are objectively inferior (small E_{b2}). Since most individuals in the starting population possess T_1, sampling more individuals as models and weighing more on action makes belief in the efficacy of T_1 even stronger. Therefore, the suppression of inferior treatment is most pronounced when the number of models picked n is large and the weight of observed action w_a is moderately large. As mentioned, extremely large w_a renders the placebo effect unimportant; on the other hand, when w_a is very small (meaning w_o is relatively large), the placebo effect also does not make noticeable difference when the invading treatment has lower baseline efficacy. The intuition here is that a firm reliance on observed efficacy already suppresses inferior technology, and the placebo effect does not add much.

Second, when the invading treatment is objectively superior ($E_{b1} < E_{b2}$) the presence of the placebo effect may enhance the adoption of the invading treatment when n is large and w_a is of intermediate magnitude, and the invading technology's baseline efficacy is only moderately larger than that of the existing technology. For example, in the case of $n = 10$ and $w_a = 1$ (bottom middle graph), The frequency of T_1 individuals is lower in the presence of the placebo effect ($\beta = \beta_1 = 0.5$) compared to no placebo effect ($\beta = \beta_1 = 0$)

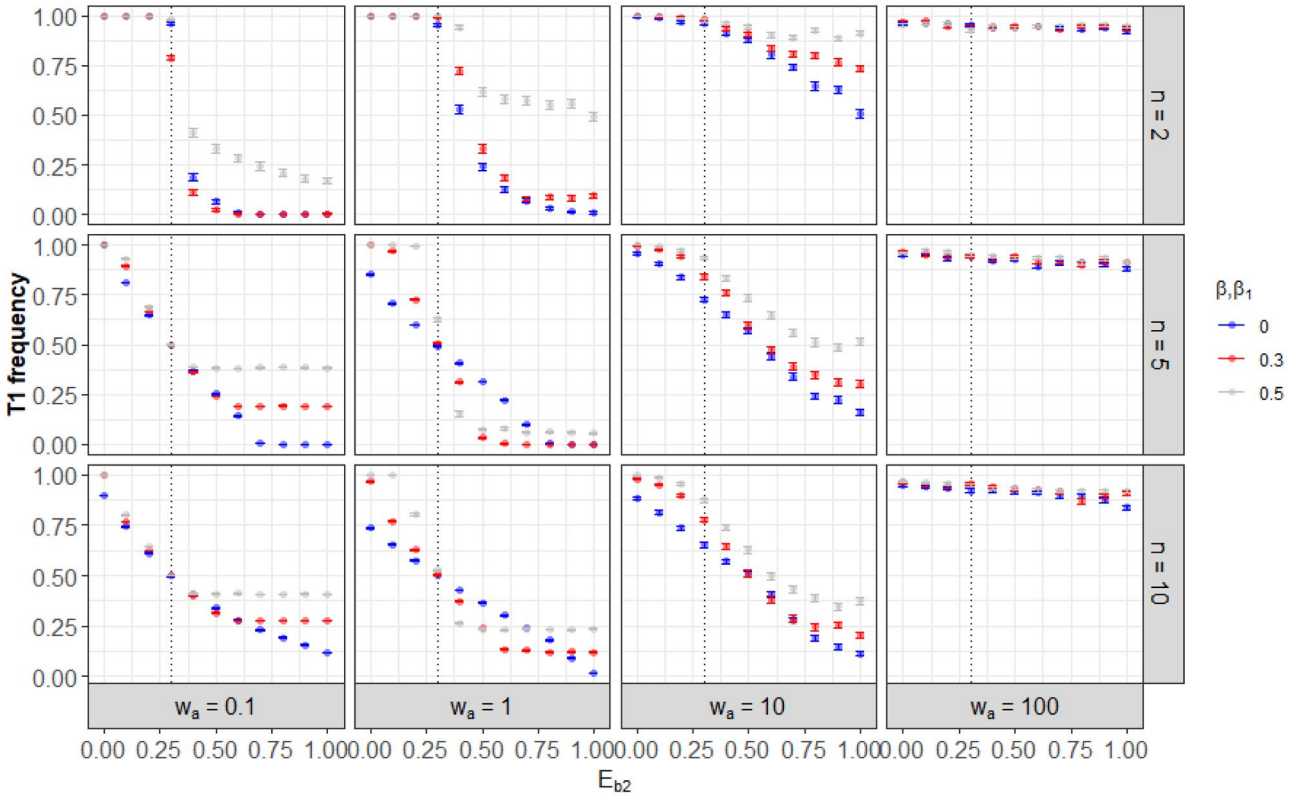

Fig. 4 Frequency of T_1 individuals at generation 200 under different parameter settings. The initial population ($N = 200$) consists of 95% T_1 individuals and 5% T_2 individuals and is kept at a constant size. Baseline efficacy of the existing technology (E_{b1}) is fixed at 0.3 (dotted line) and weight for the observed outcome w_o is fixed at 1. β and β_1 are set to be the same to represent the overall magnitude of the placebo effect. Error bars represent 95% confidence interval for 500 independent simulation runs

when E_{b2} is within a particular range, i.e., $0.3 < E_{b2} < 0.7$. Why is this? Recall that the superior invading treatment can also benefit from the placebo effect because individuals' subjective belief of its efficacy will gradually increase and may eventually reach an equilibrium that is higher than that of the existing treatment. In other words, superior technology will quickly spread in the population in the presence of a large placebo effect once it gets over the initial hurdle. What we observe in the simulation is that this occurs when agents weigh both observed action and observed outcome similarly ($w_a = w_o = 1$). The intuition here is that weighing heavily on action makes the evolutionary dynamics like the Hardy–Weinberg equilibrium situation and the placebo effect would play little role; on the other hand, weighing heavily on outcome paradoxically benefit the existing technology as agents' initial belief in it is high and therefore has higher realized efficacy under the placebo effect. The ceiling effect occurs, however, when the magnitude of the placebo effect and baseline efficacy of the invading technology gets sufficiently large and the probability of the invading technology spreading (lower T_1 frequency) does not further increase with increasing E_{b2}.

Lastly, there is a very noticeable effect of several models picked (n) on the adoption of superior invading technology. When agents heavily weigh observed outcomes (left column in Fig. 4), large n neither suppresses inferior technology nor enhances the adoption of superior technology to the same degree as small n. This is the direct result of how agents construct their belief (see Eq. (7) and (8)) regarding the efficacy of T_1 and T_2; when observed outcomes dominate belief construction, p_1 and p_2 are effectively the same as realized efficacy E_{r1} and E_{r2}, and the proportion of models who practice T_1 and T_2 is largely ignored. When the number of models picked is large, most agents will experience a mixture of T_1 and T_2 individuals in their model set, and because agents don't pay much attention to observed action, the inferior technology paradoxically enjoys an advantage: since action faithfully reflects belief (an agent is more likely to practice T_1 if his subjective belief in T_1 is higher), exclusively focusing on outcome loses much valuable information and increases the probability of adopting the inferior treatment. There are two solutions: one is to decrease the number of models picked (reduce the chance of having a mixture of T_1 and T_2 models) and the other is to increase the weight attached to observed action. This rather counter-intuitive result is independent

of the placebo effect and of particular importance from an evolutionary perspective, as it suggests that there may be an optimal balance between weights of the two information sources, w_a and w_o (Hong, unpublished). To maximize the probability of adopting the better treatment, the best strategy is to take both action and outcome into belief construction.

Discussion

The Puzzle of Ineffective Medical Treatment

As the French philosopher and essayist Michel de Montaigne famous claimed, "there are men on whom the mere sight of medicine is operative." In fact, nearly all traditional medicine relied on our minds' self-suggestive power to some degree (Hunter, 2007). Therefore, our understanding of pre-RCT medical practices and our conception of rationality for people in traditional societies would be woefully incomplete without accounting for the existence of the placebo effect. If we view traditional healing practices as strictly ineffective, their cross-cultural and historical persistence presents an evolutionary puzzle. Why would people practice often costly rituals which achieve no better than chance? Although people may engage in these healing practices for various social and religious reasons, these practices are still deeply puzzling from an instrumental perspective. Horton (1967) forcefully argues against symbolistic interpretations of these traditional practices; according to his argument, there is no fundamental difference between a traditional healer and a western scientist regarding the scope and objective of their practices: both offer explanations, predictions, and control of worldly events. Although a general theory of why people practice ineffective technologies may be difficult to achieve, a focus on the placebo effect in the domain of medical practice may render seemingly ineffective treatments less puzzling. Many shamanistic healing practices, for example, are suggested to have a non-trivial placebo component (Humphrey, 2018). If we temporarily suspend our methodological commitment to randomized, controlled trials, many of the healing practices do "work", and it is to the patients' advantage to engage in these practices and believe in their efficacy.

As already mentioned, many factors contribute to the magnitude of the placebo effect and the eventual therapeutic outcome. In this paper, I have focused on the cultural transmission of efficacy information in anecdotal stories and observed action, which creates a reciprocal relationship between belief and efficacy. In my stylized model, I show that the realized efficacy of some treatments may be higher than its baseline efficacy, and treatments in which individuals do not have much initial confidence will experience an increase in realized efficacy over time as individuals become more convinced of its effectiveness and eventually reach some equilibrium. In the model, the transmission of cultural information occurs through distinct generations, yet depending on the frequency of the treatment practice, multiple belief-efficacy reinforcing cycles can occur within an individual's lifetime, and equilibrium may be reached even faster than the model suggests.

Transmission Biases in Technological Adoption and the Role of the Placebo Effect

The population dynamics of technological adoption have been theoretically examined in classic cultural evolution literature (Boyd & Richerson, 1985; Boyd et al., 2013). Like many other forms of cultural variants, technological practices are subjected to the same transmission biases as beliefs and values, yet they are distinct in that technologies are, by definition, means to some end. People use technologies to achieve various objectives, and it is very likely the outcomes of the technology affect the probability of their adoption. The existence of payoff biased transmission has ample empirical support: Human children have been shown to pay attention to their models' payoffs when making copying decisions (Vale et al., 2017), and even pigeons were suggested to fail to copy their conspecific tutors' food-finding techniques if the tutors obtain smaller rewards than themselves (Giraldeau & Lefebvre, 1987).

At the same time, frequency-biased social learning strategies may still play a role. Technologies that frequently yield negative results can still prevail in a society if the fact that they are practiced by many individuals in a community is taken as evidence for their validity. Many ethnographers have alluded to this factor to explain the persistence of magic and divination: failure to produce promised outcomes often do not disillusion either the practitioners or the observers (Culwick et al. 1935); rather, these failures may be explained away by appealing to incidental technical malfunction, unfulfilled-ritual requirements, or a lack of skill of the diviner (Annus, 2010).

Humans likely possess a suite of learning strategies. Though individual learning and different social learning rules are often portrayed as distinct strategies used in different contexts (Wood et al., 2013), they can be employed simultaneously (Laland, 2004). In a way, the second model is an attempt to combine frequency-dependent transmission and payoff biased transmission (see Eq. (9)) into a single decision-making process by explicitly modeling belief formation. The model shows that although the placebo effect often creates an incumbent advantage and suppresses the invasion of new, potentially superior medical technologies, it can nonetheless enhance the adoption of new treatments when individuals weigh both

observed action and observed outcome roughly equally. This result provides a more nuanced understanding of the conditions under which advantageous cultural variants may spread. For example, when the placebo effect is present, an existing treatment often has higher realized efficacy and thus an exclusive focus on outcome may make it difficult for the invading technology to overcome the initial disadvantage.

One implication here is that certain medical practices may "get stuck" in the population not because individuals do not care about efficacy but because these practices do achieve substantial efficacy due to the placebo effect. Therefore, the successful invasion of a new treatment may require particular circumstances such as exceptionally high baseline efficacy or some boost in the initial confidence of its efficacy induced by other socio-cultural factors and transmission biases such as prestige bias (Henrich & Gil-White, 2001).

My model also highlights the importance of weighing both action and outcome in making optimal trait adoptions decisions. It is easy to understand why ignoring outcome information reduces the probability of adopting the better trait, but what is less obvious is that ignoring observed action also leads to sub-optimal decisions. Because both action and outcome carry useful information regarding the efficacy, the technological variants, genetic and cultural selection likely favor substantial weight for both information sources. Note that as it stands, this paper only examines the population dynamics under specific assumptions and does not analyze the evolutionarily stable strategies regarding what types of belief updating and trait adoption decision rules maximize fitness. Previous authors have suggested that different learning strategies should be viewed as operating within a single inferential process (Heyes, 1994; Plotkin, 1988), and the weight that people attach to different information sources are subject to natural selection (Perreault et al., 2012). For example, Perreault and colleagues (2012) analyze a model where agents try to infer the correct environmental state based on social and non-social cues and find that social cues are preferred when changes in the environment are slow. My model contributes to this literature by emphasizing the role of the placebo effect and how the belief construction process affects the adoption of superior medical technology.

Finally, it should be noted that this paper does not provide evolutionary rationales for the existence of the placebo effect and takes it as a given. Research on the evolution of the placebo effect remains scant, but see Humphrey's (2002) proposal that the placebo effect evolved as a way to optimally allocate limited resource (our body's immune response is more likely to occur when the expectation of recovery is high), and Trimmer's et al. (2013) formalization of this idea. My model, however, does suggest a new possibility for understanding the evolutionary benefit of the placebo effect in the context of technological evolution: most obviously, the placebo effect always suppresses the invasion of inferior medical technology and may even enhance the adoption of superior treatment in certain situations. Future work may be devoted to exploring the evolutionary dynamics of the placebo effect from this perspective.

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Code Availability Code used for simulation is available at https://github.com/kevintoy/placebo_effect

Declarations

Conflicts of Interest None.

References

Annus, A. (2010). *Divination and Interpretation of Signs in the Ancient World*. *Oriental Institute Seminars*.

Aschwanden, H., & Cooper, U. (1987). Symbols of death: an analysis of the consciousness of the Karanga. In *Shona heritage series* (p. 389). Gweru, Zimbabwe: Mambo Press. https://ehrafworldcultures.yale.edu/document?id=fs05-021

Bianchi, C. C. (1989). *Gubida illness and religious ritual among the Garifuna of Santa Fe, Honduras: an ethnopsychiatric analysis*. Ann Arbor, Mich.: University Microfilms International. https://ehrafworldcultures.yale.edu/document?id=sa12-016

Boyd, R., Richerson, P., & Henrich, J. (2013). The cultural evolution of technology: Facts and theories. In P. J. Richerson and M. H. Christiansen (Ed.), *Cultural Evolution: Society, Language, and Religion*. MIT Press. http://www2.psych.ubc.ca/~henrich/pdfs/Boyd Richerson Henrich The cultural evolution of technology 7.pdf. Accessed 26 March 2019

Boyd, R., & Richerson, P. J. (1985). *Culture and the evolutionary process*. University of Chicago Press.

Culwick, A. T. (Arthur T., Culwick G. M., M., & Kiwanga, T. (1935). *Ubena of the Rivers*. London: G. Allen & Unwin, Ltd. https://ehrafworldcultures.yale.edu/document?id=fn31-001

Day, T., & Bonduriansky, R. (2011). A Unified Approach to the Evolutionary Consequences of Genetic and Nongenetic Inheritance. *The American Naturalist*. https://doi.org/10.1086/660911

De Craen, A. J. M., Kaptchuk, T. J., Tijssen, J. G. P., & Kleijnen, J. (1999). Placebos and placebo effects in medicine: Historical overview. *Journal of the Royal Society of Medicine*. https://doi.org/10.1177/014107689909201005

De Craen, A. J. M., Tijssen, J. G. P., De Gans, J., & Kleijnen, J. (2000). Placebo effect in the acute treatment of migraine: Subcutaneous placebos are better than oral placebos. *Journal of Neurology*. https://doi.org/10.1007/s004150050560

Evans-Pritchard, E. (1937). *Witchcraft, oracles and magic among the Azande*. Clarendon Press.
Faasse, K., & Petrie, K. J. (2016). From Me to You: The Effect of Social Modeling on Treatment Outcomes. *Current Directions in Psychological Science*. https://doi.org/10.1177/0963721416657316
Giraldeau, L. A., & Lefebvre, L. (1987). Scrounging prevents cultural transmission of food-finding behaviour in pigeons. *Animal Behaviour*. https://doi.org/10.1016/S0003-3472(87)80262-2
Hammami, M. M., Al-Gaai, E. A., Alvi, S., & Hammami, M. B. (2010). Interaction between drug and placebo effects: A cross-over balanced placebo design trial. *Trials*. https://doi.org/10.1186/1745-6215-11-110
Harrell, S. (1983). *Belief and unbelief in a Taiwan village*. Ann Arbor, Mich.: Xerox University Microfilms. https://ehrafworldcultures.yale.edu/document?id=ad05-011
Henrich, J., & Boyd, R. (1998). The Evolution of Conformist Transmission and the Emergence of Between-Group Differences. *Evolution and Human Behavior*. https://doi.org/10.1016/S1090-5138(98)00018-X
Henrich, J., & Gil-White, F. J. (2001). The evolution of prestige: Freely conferred deference as a mechanism for enhancing the benefits of cultural transmission. *Evolution and Human Behavior*. https://doi.org/10.1016/S1090-5138(00)00071-4
Henrich, J., & McElreath, R. (2003). The Evolution of Cultural Evolution. *Evolutionary Anthropology*. https://doi.org/10.1002/evan.10110
Heyes, C. M. (1994). Social learning in animals: Categories and mechanisms. *Biological Reviews of the Cambridge Philosophical Society*. https://doi.org/10.1111/j.1469-185X.1994.tb01506.x
Hong, Z. (2016). Combining Conformist and Payoff Bias in Cultural Evolution: An Integrated Model for Human Decision Making. Under review.
Hong, Z. & Henrich, J. (2021). The cultural evolution of epistemic practices: the case of divination. *Human Nature* (forthcoming).
Horton, R. (1967). African Traditional Thought and Western Science. *Africa*. https://doi.org/10.2307/1158253
Hróbjartsson, A., & Gøtzsche, P. C. (2010). Placebo interventions for all clinical conditions. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD003974.pub3
Humphrey, N. (2002). Great expectations: the evolutionary psychology of faith- healing and the placebo effect. In *The mind made flesh*.
Humphrey, N. (2018). Shamans as healers: When magical structure becomes practical function. *The Behavioral and Brain Sciences*. https://doi.org/10.1017/S0140525X17002084
Hunsley, J., & Westmacott, R. (2007). Interpreting the magnitude of the placebo effect: Mountain or molehill? *Journal of Clinical Psychology*. https://doi.org/10.1002/jclp.20352
Hunter, P. (2007). A question of faith. Exploiting the placebo effect depends on both the susceptibility of the patient to suggestion and the ability of the doctor to instil trust. *EMBO Reports*. https://doi.org/10.1038/sj.embor.7400905
Kaptchuk, T. J. (1998). Intentional Ignorance: A History of Blind Assessment and Placebo Controls in Medicine. *Bulletin of the History of Medicine*. https://doi.org/10.1353/bhm.1998.0159
Kaptchuk, T. J., Goldman, P., Stone, D. A., & Stason, W. B. (2000). Do medical devices have enhanced placebo effects? *Journal of Clinical Epidemiology*. https://doi.org/10.1016/S0895-4356(00)00206-7
Kaptchuk, T. J., & Miller, F. G. (2015). Placebo effects in medicine. *New England Journal of Medicine*. https://doi.org/10.1056/NEJMp1504023
Kirmayer, L. J. (1994). Improvisation and authority in illness meaning. *Culture, Medicine and Psychiatry*. https://doi.org/10.1007/BF01379449
Laland, K. N. (2004). Social learning strategies. *Learning and Behavior*. https://doi.org/10.3758/bf03196002
Lancy, D. F., Bock, J., & Gaskins, S. (2010). *The anthropology of learning in childhood*. Rowman Altamira.
Misra, S. (2012). Randomized double blind placebo control studies, the "gold Standard" in intervention based studies. *Indian Journal of Sexually Transmitted Diseases*. https://doi.org/10.4103/0253-7184.102130
Miton, H., Claidière, N., & Mercier, H. (2015). Universal cognitive mechanisms explain the cultural success of bloodletting. *Evolution and Human Behavior*. https://doi.org/10.1016/j.evolhumbehav.2015.01.003
Murdock, G. P. (1980). *Theories of Illness a World Survey*. University of Pittsburgh Press. https://philpapers.org/rec/MURTOI. Accessed 28 March 2019
Perreault, C., Moya, C., & Boyd, R. (2012). A Bayesian approach to the evolution of social learning. *Evolution and Human Behavior*. https://doi.org/10.1016/j.evolhumbehav.2011.12.007
Plotkin, H. C. (1988). *The role of behavior in evolution*. MIT press.
Shapiro, A. K. (1969). Iatroplacebogenics. *International Pharmacopsychiatry*. https://doi.org/10.1159/000468855
Sigerist, H. E. (Henry E. (1951). *A history of medicine.* Oxford University Press. https://global.oup.com/academic/product/a-history-of-medicine-9780195050790?cc=us&lang=en&. Accessed 30 March 2019
Smith, E. W., & Dale Andrew Murray, d. 1919. (1920). *Ila-speaking peoples of Northern Rhodesia: vol. 1*. London: MacMillan and Co. https://ehrafworldcultures.yale.edu/document?id=fq06-001
Trimmer, P. C., Marshall, J. A. R., Fromhage, L., McNamara, J. M., & Houston, A. I. (2013). Understanding the placebo effect from an evolutionary perspective. *Evolution and Human Behavior*. https://doi.org/10.1016/j.evolhumbehav.2012.07.004
Turnbull, C. M. (1965). *Wayward servants: the two worlds of the African Pygmies*. Garden City, N.Y.: The Natural History Press. https://ehrafworldcultures.yale.edu/document?id=fo04-002
Tylor, E. B. (1871). *Primitive culture: researches into the development of mythology, philosophy, religion, art, and custom* (Vol. 2). J. Murray.
Vale, G. L., Flynn, E. G., Kendal, J., Rawlings, B., Hopper, L. M., Schapiro, S. J., et al. (2017). Testing differential use of payoff-biased social learning strategies in children and chimpanzees. *Proceedings of the Royal Society b: Biological Sciences*. https://doi.org/10.1098/rspb.2017.1751
Vickers, A. J., Vertosick, E. A., Lewith, G., MacPherson, H., Foster, N. E., Sherman, K. J., et al. (2018). Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. *Journal of Pain*. https://doi.org/10.1016/j.jpain.2017.11.005
Waber, R. L., Shiv, B., Carmon, Z., & Ariely, D. (2008). Commercial features of placebo and therapeutic efficacy. *JAMA - Journal of the American Medical Association*. https://doi.org/10.1001/jama.299.9.1016
Wartolowska, K. A., Feakins, B. G., Collins, G. S., Cook, J., Judge, A., Rombach, I., et al. (2016). The magnitude and temporal changes of response in the placebo arm of surgical randomized controlled trials: A systematic review and meta-analysis. *Trials, 17*(1), 589.
Wood, L. A., Kendal, R. L., & Flynn, E. G. (2013). Whom do children copy? Model-based biases in social learning. *Developmental Review*. https://doi.org/10.1016/j.dr.2013.08.002