Causality and Noncompliance in Drug Testing

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Abstract

We present the basics for the language of causality the do-calculus, introduced by Pearl. We show how traditional DAGs can be used to convey causality relations and discuss the difference between experimental and artifically generated data. We go over the analysis of compliance for drug testing from Pearl and Chickering and discuss the problems with a posterior distribution for a non-identifiable quantity. We provide additional graphs to get some insight into the Gibbs sampling used.

1 Introduction

I have heard tell that the people of two villages once destroyed one another, because of a drop of honey. [...] He stopped at the shop of an oilman and offered him the honey for sale and he bought it. Then he emptied it out of the skin, that he might see it, and in the act a drop fell to the ground, whereupon the flies flocked to it and a bird swooped down upon the flies. Now the oilman had a cat, which sprang upon the bird, and the huntsmans dog, seeing the cat, sprang upon it and slew it; whereupon the oilman sprang upon the dog and slew it, and the huntsman in turn sprang upon the oilman and slew him.

One Thousand and One Nights, translated by Sir Richard Burton

One of the most important lessons to be learned in statistics in that correlation does not imply causality. Statistics do not make claims about causality, and they would be rather useless if it were not for the fact that we can sometimes supply the intuition to deduce some form of causal relations responsible for the observed correlations. In this paper we will look at a language, the *do-calculus*, whose purpose is to serve as a formal tool to perform causal deductions symbolically.

As we should expect, it does not answer previously unanswerable questions and it does not magically inject causal meaning into data. Like everything else in mathematics, it is only a formal tool to attack larger problems by organizing our thoughts properly and communicating them effectively.

We start in section 2 by introducing the basic tools of causality required to understand the material. We assume that the reader is relatively confortable with graphical models used in Bayesian inference. In section 3 we explain the purpose of [Pea00] and [CP97] in the context of drug testing, we reproduce their results and we provide some additional graphs that, we think, offer an interesting way to visualize their Gibbs sampling.

2 Basic principles of causality

The most natural way to construct a DAG representing a joint distribution over some variables is to ask in what order would Nature assign their values, and on what quantities those variables depend at the moment that they are sampled. We can use our causal intuition to supply basic independance assertions about the variables and then the d-separation machinery to deduce the unintuitive relationships.

Consider the popular example involving clouds C, a sun-powered sprinkler S, rain R and potentially wet grass W. Before any mention of the parameters involved in the joint distribution we can easily sketch the little diagram in Figure 1a. Other valid DAGs can be identified (see Figure 1b,c) and they are just as good in terms of modeling statistical correlations and independance relationships.

However, if we were to ask what would happen if we were to intervene by turning off the sprinkler manually, or by pouring a tank of water on the grass, only DAG (a) would be useful because

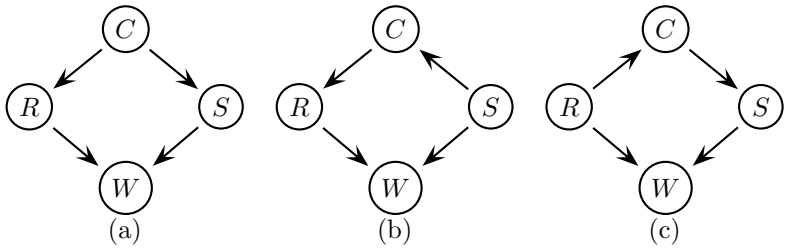


Figure 1: (a) The DAG based on causal intuition. (b) & (c) The equivalent DAGs in terms of the conditional independance relations encoded. Those three DAGs are equivalent when we model statistical correlation, but they are not equivalent when DAGs are used to model a causal mechanism allowing interventions.

it describes more than statistical correlations : it describes the mechanism by which the objects really influence each other.

Pearl points out in [Pea00] that we are already attributing a special meaning to 1 (a), often preferring it over the alternatives (b), (c) even in the context of modeling correlation. He argues that a new formal language is needed to describe the concept of interventions.

The basic operation featured in his *do-calculus* is an intervention on a node X in a given DAG, denoted by $\text{do}(X = x)$. It corresponds to removing of all arrows going into X, treating $X = x$ as an observed variable and performing the usual Bayesian inference on the resulting graph. We can perform interventions on any number of nodes in addition to having observed or hidden nodes as usual.

Interventions are defined in terms of a particular DAG to which we will refer here as the "causal graph". We select a causal graph that represents sufficiently well, in our judgement, the process by which Nature generates the samples. If such a graph can be found, the *do-calculus* interventions will match the potential real-life interventions. This provides us a powerful symbolic machinery to model the unintuitive consequences of real-life interventions.

Returning to the example of the wet grass, we compare in figure 2 the causal model, the effects of $do(S = s)$, the effects of $do(W = w)$ and the usual conditional distribution with $W = w$. The formulas for the pdfs are the following :

$$
\begin{array}{lrcl}
\text{(a)} & p(C,R,S,W) & = & p(C)\ p(R|C)\ p(S|C)\ p(W|R,S) \\
\text{(b)} & p(C,R,W|do(S=s)) & = & p(C)\ p(R|C)\ p(W|R,S=s) \\
\text{(c)} & p(C,R,S|do(W=w)) & = & p(C)\ p(R|C)\ p(S|C) \\
\text{(d)} & p(C,R,S|W=w) & \propto & p(C)\ p(R|C)\ p(S|C)\ p(W=w|R,S)
\end{array}
$$

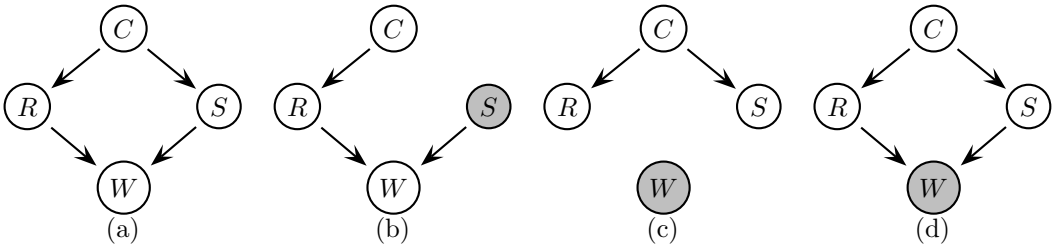


Figure 2: (a) The original causal model. (b) After performing the intervention $do(S = s)$. (c) After performing the intervention $do(W = w)$. (d) Comparing with simple conditioning on $W = w$.

The delicate issue is whether or not we can find such a graph in which *do-calculus* interventions correspond to real-life interventions. In some artificial settings, the correspondance can be perfect, but in most experimental settings, the best that we can hope for are causal graphs that are useful.

Consider the typical Bayesian models where we define a joint distribution by means of a DAG $\mathcal{G}$ and we decide to sample from the joint in the usual order specified by the arrows $\mathcal{G}$. We can

define interventions as little clamps put on particular nodes that refrain the sampling algorithm from changing the value of those nodes to anything else than specified values. In that case, the interventions can be modeled perfectly by *do-calculus* by using $\mathcal{G}$ as the causal graph.

2.1 Identifiability

When we have access to a causal graph that can answer queries about interventions, we can compute quantities of the form $p(A|B, do(C))$ by performing the intervention operations described previously. We cut the arrows going into C and then we perform the usual Bayesian graphs inference to evaluate $p(A|B, C)$ in the resulting graph.

When such a quantity involving *do-calculus* can be translated into an expression involving only classical probabilities, the quantity is said to be *identifiable*.

When we have access to a causal graph that models interventions perfectly, all quantities are identifiable. However, there are situations in which no such causal graph exists, even in a artificial setting. A simple example can be constructed from the wet grass scenario. Suppose that we were only interested in the variables R, S and knew nothing about the existence of C, W. In the traditional correlational DAG setting, we can write down the joint distribution of R, S as either $R \rightarrow S$ or $R \leftarrow S$. Note that, by using the correct causal model involving the four variables, we have that $p(S|do(R)) = p(S)$ and $p(R|do(S)) = p(R)$. We should get that from any valid causal model with two variables as well, if one exists.

Assuming (to reach a contradiction) that there exists a causal model with only the nodes S, R, it has to be either $R \rightarrow S$ or $R \leftarrow S$. If it was $R \rightarrow S$, we would get that $p(S|do(R)) = p(S|R)$. However, we know that $p(S|R) \neq p(S)$ so this causal model with two variables is wrong. Having $S \rightarrow R$ leads to a similar contradiction. The problem is that, although a DAG with R, S is a proper tool to model the correlations between R, S, it is insuffisant to capture the richness of the interactions of R, S in the original context where we allow interventions.

There are situations where we have knowledge about limited parts of the actual causal graph that Nature uses to generate the data and we can still evaluate quantities involving *do* interventions. In [Pea00], special dotted arrows are used to refer to the existence of hidden variables that are common ancestors to some of the nodes of interest. Rules are introduced to evaluate when quantities are *identifiable* despite the presence of hidden variables not explicitly represented in the causal graph.

The drug testing scenarios presented in [CP97] and [Pea00] deal with a situation in which the quantity of interest named $ACE(X \rightarrow Y)$ is not identifiable, but where we can nevertheless establish bounds for that quantity using linear optimization. It is also possible in that situation to use Gibbs sampling to obtain a posterior distribution of $ACE(X \rightarrow Y)$, but as we are dealing with a quantity not identifiable, we have to be careful in interpreting the results.

3 Modeling compliance in drug testing

3.1 The setting

In [Pea00] and [CP97] is presented an experimental drug testing setting in which the experimenters can supply a certain drug to patients but cannot force them to take it. The patient does have to report if he took it or not, and at the end of the experiment his health condition is evaluated. The three variables are labeled by Z, X, Y, corresponding to

the patient is given the drug ($Z = 1$) or not ($Z = 0$),
the patient is takes the drug ($X = 1$) or not ($X = 0$),
the patient is heals the drug ($Y = 1$) or not ($Y = 0$).

The experimenter has to rely on his good judgement to select reasonable threshold values to represent the final condition of the patient as 0 or 1, and to determine how much of the treatment

should have been undergone by the patient before it qualifies as 1. The premiss of this model is that there will be a strong connection between the decision of the patients to take the drug or not and their potential recovery.

Comparing $p(Y = 1|X = 1)$ and $p(Y = 1|X = 0)$ is not a good measure of effi ciency for the treatment. As Chickering and Pearl explain it so well in [CP97] :

> The major source of difficulty in managing and analyzing such experiments has been the subject noncompliance. For example, a subject in the treatment group may experience negative side effects and will stop taking the drug. Alternatively, if the experiment is testing a drug for a terminal disease, a subject suspecting that he is in the control group may obtain the drug from other sources. Imperfect compliance poses a problem because simply comparing the fractions as above may provide a misleading estimate for how effective the drug would be if applied uniformly to the population. For example, if those subjects who refused to take the drug are precisely those who would have responded adversely, the experiment might conclude that the drug is more effective than it actually is.

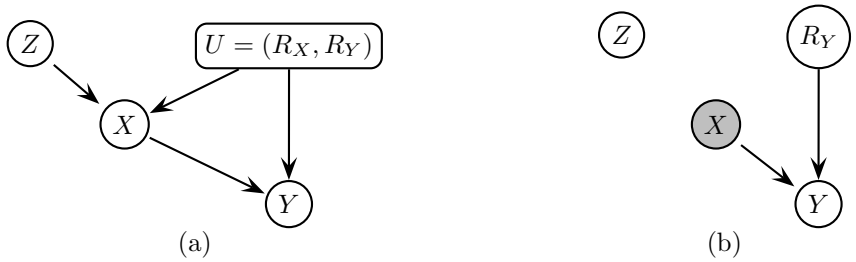


Figure 3: (a) The causal model with the unknown hidden variables U expressed as a joint (R_X, R_Y). (b) The causal model after performing $do(X)$.

The causal model used is shown in figure 3. Its par ameters are chosen to be such that, given the state of the latent variables U, there is a deterministic mapping from Z to X and from X to Y. The randomness comes from the fact that the latent variables are unobserved. There are only 16 possible pairs of mappings so the complete space of possible latent variables U can be expressed as a joint distribution $(R_X, R_Y) \in \{0, 1, 2, 3\}^2$ where R_X and R_Y are used to classify the patients in four possible categories each.

$R_X = 0$: the patient never takes the drug $(X = 0)$
$R_X = 1$: the patient takes the drug iff given $(X = Z)$
$R_X = 2$: the patient does the opposite of what is asked $(X = 1 - Z)$
$R_X = 3$: the patient always takes the drug $(X = 1)$
$R_Y = 0$: the patient never recovers $(Y = 0)$
$R_Y = 1$: the patient recovers iff he takes the drug $(Y = X)$
$R_Y = 2$: the patient recovers iff he does not take the drug $(Y = 1 - X)$
$R_Y = 3$: the patient always recovers $(Y = 1)$

We are assuming here that the patients can find access to the treatment on their own, whether it's because they are willing to get the drug elsewhere or because there is some sort of flexibility in the experiment. In any case, the choice not to rule out these possibilities is a penalty on our predictive power and not a limiting hypothesis that narrows the applications of the model. The object of the study is to find the "average causal effect of X on Y", written as $ACE(X \to Y)$. This quantity is defined to be

$$\begin{aligned} ACE(X \to Y) &= p(Y = 1|do(X = 1)) - p(Y = 1|do(X = 0)) \\ &= [p(R_Y = 1) + p(R_Y = 3)] - [p(R_Y = 2) + p(R_Y = 3)] \\ &= p(R_Y = 1) - p(R_Y = 2) \end{aligned}$$

The goal is to find $ACE(X \to Y)$ using experimental data D in the form of samples $\{(Z_i, X_i, Y_i)\}_{i=1}^n$. This is where [Pea00] and [CP97] split. The first uses the samples to estimate $p(X, Y|Z)$ and then,

defining constraints on (R_X, R_Y) based on those MLE estimates, solves two linear optimization problems to obtain an upper and lower bound on $ACE(X \to Y)$.

The second, however, points out that estimating $p(X, Y|Z)$ from small samples might not be a good idea. Indeed, the approach detailed in [Pea00] has no way of signaling how uncertain are the bounds given because it uses the data only to find an MLE. It does not give a posterior distribution and would have no good prior if we had one. In [CP97], Chickering and Pearl explain how Gibbs sampling can be used to sample effectively on the conditional distribution of R_X, R_Y given the data collected in the experiment. From those samples of R_X, R_Y we can not only estimate $ACE(X \to Y)$, but we can get a posterior distribution.

We will omit the details of the linear optimization approach and refer the reader to [Pea00]. The Gibbs sampling method is covered in the next section.

3.2 Gibbs sampling for posterior $ACE(X \to Y)$

Here we go over some of the examples from [Pea00] and [CP97] to reproduce their results. They use two real datasets from the medical literature and one artificially generated dataset that has the special property of having only one possible value for the $ACE(X \to Y)$. Their datasets are summarized in tables with the frequency counts for the possible values of $X, Y|Z$.

To recover datasets we sample a number n of triplets of the same relative frequency. This only garantees that we will be asymptotically close to those frequencies. We enumerate the possible discrete states that can be taken by U as $\{1, 2, \ldots, 16\}$ and we assume that all U_i are drawn from a multinomial distribution with parameter $q \in \mathbb{R}^{16}$.

We treat that parameter q as a random variable Q and we put a Dirichlet prior of hyperparameter $\alpha = (\alpha_1, \ldots, \alpha_{16})$ on it. We get the causal graph in figure 4. The only interventions that we will study are on Z and X and they should match real-life interventions sufficiently well.

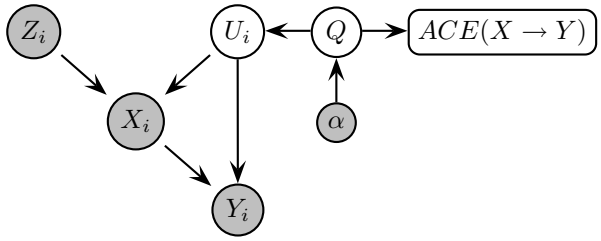


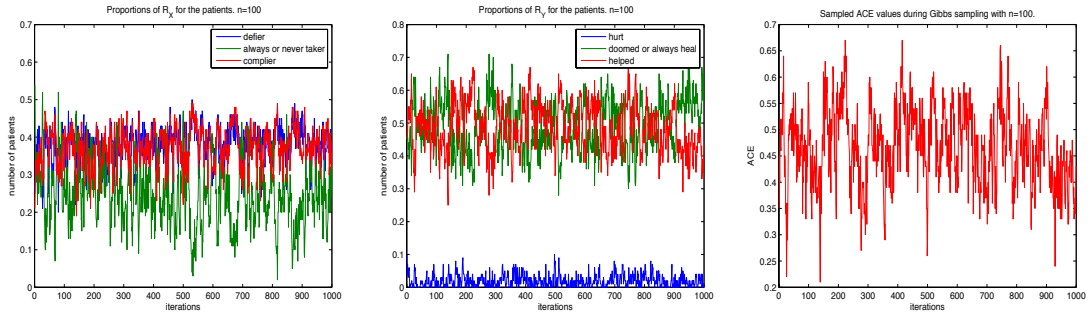
Figure 4: The causal model that generates the data $D = \{(Z_i, X_i, Y_i)\}_{i=1}^n$, denoted with a plate notation. The value $ACE(X \to Y)$ can be computed deterministically with a value $Q = q$, but we will only have access to a posterior distribution on Q.

We are interested in approximating $p(Q|D)$ where $D = \{(Z_i, X_i, Y_i)\}_{i=1}^n$. This is done using Gibbs sampling on $p(Q, U_1, \ldots, U_n|D)$, keeping a record on the values of Q sampled. We alternate between sampling from the two following distributions :

$$\begin{aligned} p(U_1, \ldots, U_n|D, Q = q) &= \prod_{i=1}^{n} p(U_i|Z_i, X_i, Y_i, Q = q) \\ p(Q|U_1 = u_1, \ldots, U_n = u_n, D) &= \text{Dirichlet}(\alpha_1 + N_1, \ldots, \alpha_{16} + N_{16}) \end{aligned}$$

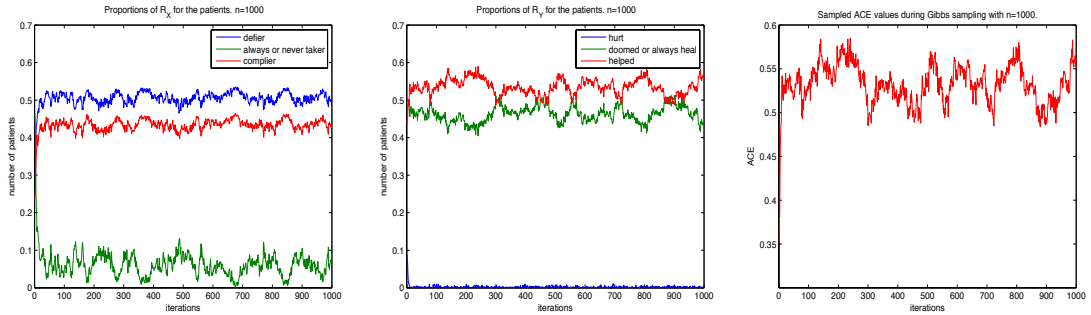
where N_t is the number of patients whose observed variables (Z_i, X_i, Y_i) are compatible with the patient type $U_i = t$. For example, if N_7 is the number of patients who are defiers $(R_X = 2)$ and would heal iff given the medication $(R_Y = 1)$, then N_7 is equal to the number of instances of $(1, 0, 0)$ or $(0, 1, 1)$ in D.

There is an arbitrary decision to be made concerning the order in which the 16 states of $U = (R_X, R_Y)$ are enumerated, but as long as we are consistent in our implementation and we compute $ACE(X \to Y)$ from the values of Q properly, we can omit the details of the implementation.



(a) (b) (c)

Figure 5: Different categories of patients assigned during Gibbs sampling. We have sampled $n = 100$ patients from a distribution that should produce an identifiable ACE of 0.55 .



(a) (b) (c)

Figure 6: Different categories of patients assigned during Gibbs sampling. We have sampled $n = 1\ 000$ patients from a distribution that should produce an identifiable ACE of 0.55 .

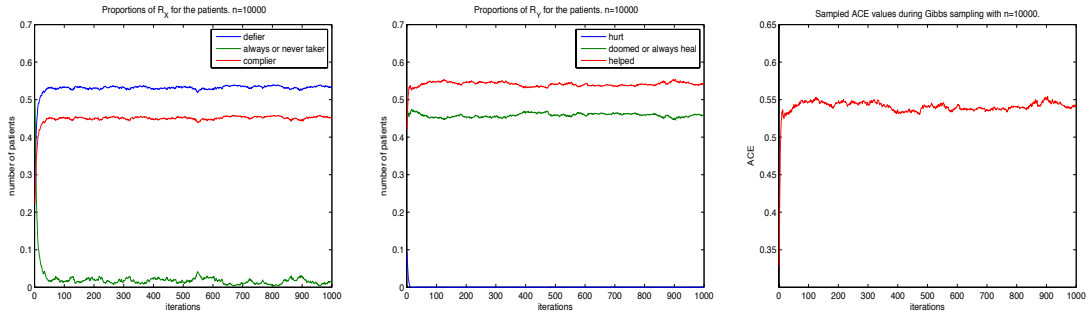
3.3 Practical results

We consider here two of Pearl's example cases given in [Pea00]. The first case is an artificial setting in which the relative frequencies are chosen to imply that $ACE(X \to Y) = 0.55$. Results for different sample sizes are found in figures 5, 6 and 7. When we produce a sample of experimental data to be used for Gibbs sampling, we get relative frequencies that differ a bit and, as shown in figures 5c, 6c, the sampled values for the posterior $ACE(X \to Y)$ are around 0.55. When we get enough data, we see in figure 7c that the posterior $ACE(X \to Y)$ is very close to 0.55.

We decided to have a look at the states of the hidden variables U_i attributed to the patients during Gibbs sampling. This allows us to get a better intuition about the meaning of the experimental data. In figures 6b, 7b we can start to see how the only possible conclusion from the data is that no one is hurt by the treatment. We can also see that there is a large portion of the people who healed and would not have if it had not been for the treatment. The rest are people whose recovery was not affected by the treatment. The part (a) of figures 5, 6, 7 are hard to interpret and were included just for curiosity's sake.

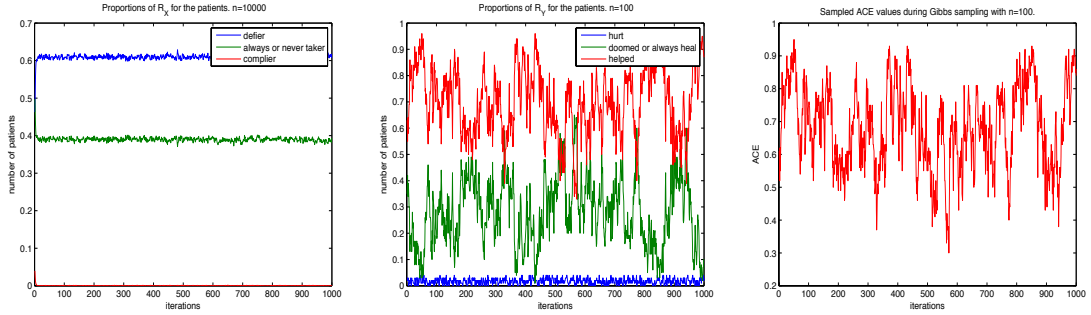
The next case is one where it can be established with linear optimization (see [Pea00]) that $ACE(X \to Y) \in [0.38, 0.78]$. Results for different sample sizes are found in figures 8, 9 and 10. Again we used experimental samples generated from a frequency table. We have to be careful when interpreting the values sampled from the posterior $ACE(X \to Y)$. The "true" $ACE(X \to Y)$ is computed from the hidden value of Q, but for one set of experimental data, there are often infinitely many possible values of Q that could have generated the data. There are 15 free parameters defining Q and only 6 parameters are required to describe the distribution $X, Y|Z$ (we usually assume that we have the same number of $Z = 0, 1$).

In figures 5, 6, 7 we saw that we could get closer to the true value of $ACE(X \to Y)$ by having more data, but in the case of figures 8, 9, 10, that quantity $ACE(X \to Y)$ is not identifiable. Having more patients will not help.



(a) (b) (c)

Figure 7: Different categories of patients assigned during Gibbs sampling. We have sampled $n = 10\ 000$ patients from a distribution that should produce an identifiable ACE of 0.55 .



(a) (b) (c)

Figure 8: Different categories of patients assigned during Gibbs sampling. We have sampled $n = 100$ patients from a distribution that should produce an unidentifiable ACE in $[0.38, 0.78]$.

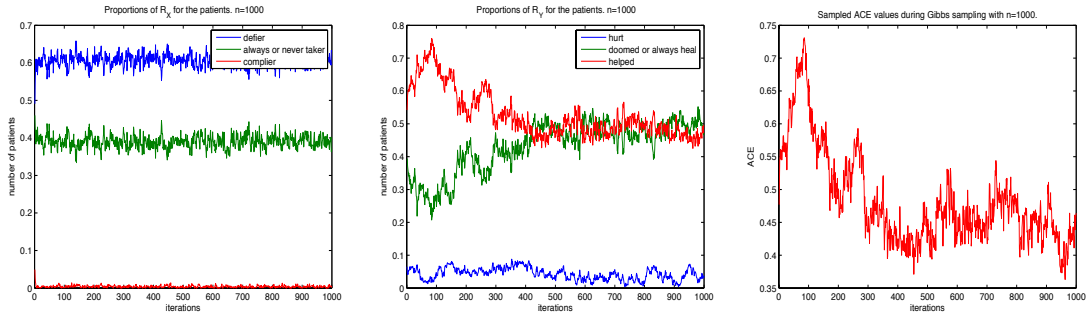
The value of Q that can produce $ACE(X \to Y) = 0.38$ correponds to a situation in which the majority of the patients distributed as

32%	$R_X = 0, R_Y = 0$	never take the drug, and will always die whether they take it or not
47%	$R_X = 1, R_Y = 1$	comply with the assigned treatment, and are healed iff they take the drug.

On the other side, the value of Q that can produce $ACE(X \to Y) = 0.78$ correponds to a situation where

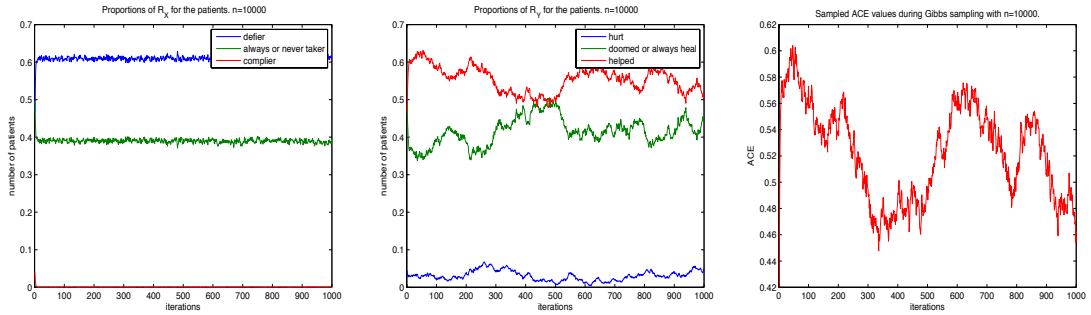
32%	$R_X = 1, R_Y = 0$	comply with the assigned treatment, and will always die whether they take the drug or not
47%	$R_X = 1, R_Y = 1$	comply with the assigned treatment, and are healed iff they take the drug.

Both of those are equally good at explaining the observed data. Any posterior distribution for $ACE(X \to Y)$ becomes a consequence of the way that the prior on Q compromises between the two (or infinitely many more) explanations.



(a) (b) (c)

Figure 9: Different categories of patients assigned during Gibbs sampling. We have sampled $n = 1\ 000$ patients from a distribution that should produce an unidentifiable ACE in $[0.38, 0.78]$.



(a) (b) (c)

Figure 10: Different categories of patients assigned during Gibbs sampling. We have sampled $n = 10\,000$ patients from a distribution that should produce an unidentifiable ACE in $[0.38, 0.78]$.

The graphics presented here use a prior of $\alpha = (1, \ldots, 1)$, but other priors are also valid. Selecting a good prior is hard because of the complexity of the relations encapsulated in U. The fact that many patients are "defiers" ($R_X = 2$) in figures 8, 9 and 10 has more to do with their initial reaction to the treatment than their rebelious personalities. If the drug was hard to obtain, or if avoiding the assigned treatment required much efforts, we could imagine selecting a prior to encode this belief.

We should note, too, that $ACE(X \rightarrow Y) \in [0.38, 0.78]$ is still a strong result. The choice of examples presented in this paper suggests that the values for $ACE(X \rightarrow Y)$ are always high, but when we sample values of Q from a Dirichlet distribution with $\alpha_1 = \ldots = \alpha_{16}$, we get an average of 0 for $ACE(X \rightarrow Y)$.

We can also see that although $ACE(X \rightarrow Y)$ was not identifiable in figures 8, 9 and 10, we got in the first graphs (a) a concentrated posterior distribution for the number of defiers/compliers. That itself leads to interesting questions about the treatment being studied.

Finally, we should note that the value $ACE(X \rightarrow Y)$ that we studied in this paper is used to evaluate how many more people would recover if we applied the treatment ($do(X = 1)$) to everyone. Even with a positive $ACE(X \rightarrow Y)$, it might still be smarter to let people have their own say, thought such a thing might not always be possible (ex : water fluoridation). A patient with a strong averse reaction to a treatment might not care if the treatment is going to have positive (or negligible) effects for 99% of his neighbors.

These questions fall outside the scope of the current review. We refer again the reader to [Pea00] that offers basic methods to evaluate certain counterfactual statements.

The choice of $ACE(X \rightarrow Y) = p(R_Y = 2) - p(R_Y = 3)$ as the object of study is also arguable. We are all familiar with what "twice as many chances of succeeding" means, but an increase of 5% in probabilities has to be put in context. Having 1% more chances of winning the lottery is enormous, but having 1% more chances of winning a meaningless one-time coin flip is negligible. The current definition of the $ACE(X \rightarrow Y)$ is convenient when considering the effects of a policy change on a population to determine how many more individuals would be positively affected. But when X involves a significant cost, $ACE(X \rightarrow Y)$ needs to be put into context. We would readily pay \$100 to have an increase of +1% in absolute odds for the lottery, going from 0% to 1%.

References

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[Pea00] J. Pearl. *Causality: Models, Reasoning, and Inference*. Cambridge University Press, 2000.