Causality in the Life Sciences

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Foreword
For many years, the standard textbook on philosophy of science for students in the life sciences at both the University of Aarhus and the University of Copenhagen was Videnskabsteori for de biologiske fag (Eng. Philosophy of the Life Sciences, Andersen et al 2006). However, developments in both philosophy of science and the universities mean that the book now needs updating. Until an updated version is available, this note serves as an alternative, updated version of the book’s chapter 5 on causality.

The author is grateful to the authors of the original book for inspiration and to Trine Dich and Sune Holm for comments to earlier versions of this text.

Reading the text
The text is divided into seven sections interrupted by four textboxes containing longer examples and philosophical rabbit holes. You can skip the boxes if you want, but if you dive in, you might find that they go deep.

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1 Scientists seek knowledge of causal relations

One of the aims of science is to construct knowledge of causal relations, and thereby increase our understanding of how different parts of nature and society interact. We seek this understanding for its own sake, but also to strengthen our ability to manipulate nature and society for our own purposes. For instance, scientists seek to understand the causes of diseases in humans and animals in order to find possible causes of their cure (treatment), or even their prevention. They also seek to understand the fundamental workings of cells, organisms and ecosystems by mapping the causal interactions among their parts. They do this partly because they simply want to know, but partly also to learn more about how they can be preserved, saved, or changed depending on our interests.

Because investigating causal relations is an important part of what scientists do, it is also important to understand the methodological challenges related to this effort, and to be skilled in assessing the credibility of claims about causal relations. To this end, this note will dive into the notion of causation to help you understand the practical challenges related to investigating and assessing claims about causation.

2 Causes, background conditions, and causal chains

Here is a little challenge for you: find something – an event, a change, whatever you want – that has only one cause. Describe it to your classmates, and see if they agree that there is truly only one cause at play. At first glance, this seems like a simple task. We are used to talking about causes in the definite singular – the cause of X is Y. Rhinovirus is the cause of the common cold. Lack of stimulation causes stress among domestic animals. Jane had a mutation in the gene BRCA1 that caused her to develop ovarian cancer. All of these claims seem to say that there was only one cause at play. However, if we look closer, it is more complicated than that. Strictly speaking, the common cold is caused by an interaction between rhinovirus and other things or processes. These other factors include the mucous membranes and the immune system. Furthermore, although rhinovirus is involved in the majority of common colds, other virus infections, including some adenoviruses, can also result in the common cold. Similar considerations apply to the other examples mentioned above. Thus, although we often talk about the cause of something, we should perhaps be talking about a cause.
To be more precise, we can distinguish between a causal factor and a causal complex (Fig. 1). Rhinovirus is a causal factor for the common cold in the sense that it can interact with other factors to produce the common cold. The combination of these factors we call a causal complex. There may be several different causal complexes that can produce the same effect. In the case of the common cold, there is one involving the rhinovirus, mucous membranes, and an insufficient reaction from the immune system. Another causal complex involves adenovirus, mucous membranes, and the immune system. This means that even if we break one causal complex by removing one of the necessary factors, e.g. the rhinovirus, we will not completely remove the effect (the common cold), since the effect is also produced by other complexes.

2.1 Causes and background conditions

It seems reasonable to say that both rhinovirus and adenovirus are causes of the common cold, partly because they are factors in causal complexes that lead to the disease. But what about having a head? Is that a cause of the common cold? If we follow the logic above, we seem forced to say yes. All the causal complexes we can think of leading to the common cold involve the interaction between parts of the head and other factors. If we remove a person’s head, that person will never catch a cold again. So by the logic of Fig. 1 having a head is a cause of the common cold, eating is a cause of hunger (since you have to be alive to be hungry, and you eventually die if you do not eat), and Big Bang is a cause of everything. Some will object that this is absurd. If you ask any expert about the causes of hunger, none of them is going to mention eating. Similarly, no expert will mention having a head as a cause of the common cold. Such factors seem more appropriately described as background conditions that we take for granted. Of course, people with colds have heads, and of course, hungry people have not (yet) died of hunger.

When we investigate causal relations, we always do it in a certain setting, which can be described as a set of background conditions. Whether a factor is placed in the foreground as a causal factor or in the background as a background condition largely depends on the researchers’ aims and interests. Causal factors can change during a study, so the more of these we focus on, the more complex the study
becomes. Background conditions, on the other hand, are generally assumed to be fixed over the course of the investigation. Fixing background conditions can thus reduce the complexity of the study, but also limit the applicability of the results. In an investigation of the causes of the common cold, for instance, researchers can choose to assume as a background condition that the immune system is functioning “normally” and investigate whether different types of viruses can induce the common cold. This allows the researcher to focus on the virus infection as a causal factor for the common cold, but it also limits the applicability of the results to people who, to a good approximation, have a “normally” functioning immune system.

Because they can affect the interpretation of the study, important assumptions about background conditions must be carefully described. Particularly if part of the study is to recreate these in an artificial environment like a laboratory or to reproduce them in a sample population (See Section 6). If a study indicates that there is a causal relation between two factors under one specific set of background conditions, an important part of the discussion of the results will be how dependent they are on these. This may be a topic for another investigation, where factors that were considered background conditions in the previous study take centre stage and are investigated as causal factors.

The distinction between causes and background conditions illustrates that it is not logic or nature alone that determines whether or not something is a causal factor. This is, at least partly, determined by our interests.

2.2 Causal chains

Causes come in chains. Mutations in the gene BRCA1 are a causal factor for ovarian cancer in the sense that they are translated into a dysfunctional protein, which in turn is transported to the relevant cells where they enter a complex interaction with other molecules and organelles to eventually produce the disease. Being a factor far down the chain, the mutation is an indirect causal factor for ovarian cancer, as opposed to direct causal factors that are found immediately before the effect. However, this does not automatically mean that the mutation is a less important causal factor.
In some cases, it is important to know where in the chain a certain causal factor is, and molecular biologists are generally very interested in understanding pathways. Causal chains often branch out in the sense that one factor leads to multiple effects (see Fig. 2). The protein created based on the reading of a mutated gene may, for instance, have effects in multiple parts of the body. Intervening early in a causal chain may therefore have unintended effects. On the other hand, it is in some cases easier to intervene on the indirect causes. For instance, lack of stimulation is no doubt an early factor in a complex causal chain that leads to stress in domestic animals, but in most cases, it is easier to intervene at this early stage than intervening on the more direct causal factors.

**Box 1: Mechanisms**

Some causal chains are coordinated and stable producing the same effect over and over again. Examples include the production of ATP molecules through photosynthesis (see front page), the cardio-vascular system pumping oxygen around your body, and the changing seasons triggering migrations of wild animals. Textbooks in the life sciences are full of diagrams depicting such mechanisms performing essential functions at different levels of organisation (cell, organism ecosystem), and much research goes into mapping them. Some philosophers take this interest in mechanisms to be one of the features that, from a methodological perspective, set the life sciences apart from, for instance, the physical sciences that focus more on describing general mathematical laws (see e.g. Bechtel & Abrahamsen [2005]).
3 Causation and probability

The shift from talking about a single cause to talking about multiple causal factors that interact in chains has far-reaching consequences. It even affects the structure of your education! The shift implies that we can no longer assume that X is a cause of Y if and only if the presence of X is always followed by the presence of Y and the presence of Y is always preceded by the presence of X. Infections with rhinovirus are not always followed by a cold (in fact most are not, the immune system prevents it), and a cold is not always preceded by an infection with rhinovirus. Rather, infections with rhinovirus increase the probability of getting a cold. The important thing here is not that the probability increases. There is also a causal relation between enrichment for domestic animals and stress, but in this case, the enrichment decreases the probability of developing stress. The important thing is that abandoning the idea of the cause in favour of multiple causal factors, implies that causation and probability become intimately linked. This means that we cannot achieve the important aim of being able to understand, investigate and assess claims about causation without becoming skilled in understanding, investigating and assessing claims about probability. An important reason why most science students have to take a course in statistics (which is partly based on probability theory) is therefore that it provides tools for studying causal relations.

3.1 From factors to variables

Statisticians do not describe causal relations as relations among factors as we have done so far. Instead, they describe causal relations as a relation between variables. We follow this tradition below. Variables are mathematical symbols – x, Y, z – that we introduce in our descriptions of the world as placeholders for something that can change. The shift from talking about factors to talking about variables does not mean that we are suddenly claiming that it is mathematical variables, not physical objects, that interact causally. We need not read any fundamental claims about the nature of reality into this shift, but rather see it as a convention based on practicality. Letting x denote the presence of a rhinovirus infection, and y the presence of a common cold and describing the causal relation between the virus and the disease as a relation between x and y has some practical advantages. In particular, it makes the tools of mathematics easier to apply. If we want, we can write the claim that the presence of a rhinovirus infection increases the probability of a common cold as an inequality:

\[ P(y = \text{present}|x = \text{present}) > P(y = \text{present}|x = \text{not present}) \] (1)

and manipulate it using mathematical theories of probability, which might teach us something new.

As we will explore further in Sec. 5, the relation between probability and causation is not straightforward. Having yellow fingernails increases the probability of developing lung cancer. I could define variables and write an inequality exactly like equation 1 that they would satisfy, and yet, there is not causal connection between yellow fingernails and lung cancer – only a correlation. When two variables correlate, a change in one is systematically associated with a change in the other. For instance,
a positive correlation means that when one variables goes up, so does the other. If two variables are causally connected, they correlate, but *not all correlated variables are causally connected*. Distinguishing between causal relations and mere correlations can be very difficult in practice but before we explore this further, we must define more precisely, what it means for two variables to be causally connected.

**4 A definition of a causal factor**

Philosophers and scientists have pondered the nature of causality for millennia. Among other things, they have tried to come up with a precise definition of what it means for something to be a cause of something else. They are yet to arrive at a consensus. Many competing definitions exist, and some argue that the idea of finding one definition that captures all the different ways in which we talk about causation is futile.

Although there is no consensus, some definitions are more influential than others. One of the most influential recent definitions in relation to the life sciences is due to the American philosopher James Woodward. Woodward’s definition is based on the simple idea that the characteristic feature of a causal connection is that if you manipulate the cause, the effect will also change. This idea implies that a good way to investigate whether $X$ is a causal factor for $Y$ is to intervene on $X$ and see if it results in a change in $Y$. Woodward turned this basic idea into a formal definition presented in his book *Making Things Happen* from 2003. Here we look at version tailored to the life sciences. It reads:

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$X$ causes $Y$ if and only if there are background circumstances $B$ such that if some (single) intervention that changes the value of $X$ (and no other variable) were to occur in $B$, then $Y$ or the probability distribution of $Y$ would change.

(Woodward 2010, p. 290)

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To understand this definition in detail, we need to understand what an intervention is. In his book, Woodward devotes an entire chapter to the topic, and much of the discussion on the definition has centered on this term. We can summarize this discussion by saying that intervention should be understood as an *idealized experimental intervention* described in the next section.
4.1 Idealised experimental interventions

Put simply, an idealised experimental intervention on a variable, \( C \), gives the experimenter complete control over the value of \( C \) throughout the course of the experiment without affecting any other (relevant) variables. More specifically, Woodward (2016) sets up four criteria that an idealised experimental intervention, \( I \), performed to investigate the possible causal relation between a variable \( C \) and an effect variable \( E \) must fulfil:

1. \( I \) must determine the value of \( C \) throughout the experiment.
2. \( I \) must not affect \( E \) through a route that does not go through \( C \).
3. \( I \) must not be caused by changes in variables that are causally connected to \( E \) except through \( C \).
4. \( I \) must not affect any variable causally connected to \( E \) except through \( C \).

If an intervention fulfilling these criteria performed under background conditions \( B \) on \( C \) would result in a change in the value or probability distribution of \( E \), then \( x \) is causal factor for \( E \) under \( B \).

To unpack the criteria, consider Fig 5.

**Figure 5:** If the intervention, \( I \), on a variable \( C \) is to be ideal, \( I \) must only affect the effect variable \( E_i \) through \( C \). Relations like the ones illustrated in blue may not be present.
Criterion 1 says that the intervention should grant the experimenter complete control over the value of $C$ throughout the experiment. If the experiment, for instance, consists in changing the participants’ diet, it should grant the experimenter complete control over what the participants eat. That does not necessarily mean that all the food has to come from the experimenter, but the experimenter must be able to compensate exactly for any input from sources that are not part of the intervention. We can imagine, for instance, an experiment testing how the amount of calcium in dairy cows’ diet affects a specific effect by adding calcium to the food they eat in the stables. These cows may also eat grass outside in the field and get calcium through this route, but then the experimenter should then be able to exactly compensate for this intake by adding less calcium to the served food, if the intervention is to fulfil the first criterion. The purpose of this criterion is, of course, that it allows the experimenter to know the exact value of $C$ throughout the experiment, which is necessary to be able to say with certainty that changing the value of $C$ to a specific value changes the probability distribution of the effect variable in a specific way.

Where the first criterion allows the experimenter to know exactly what the value of the potential causal variable is, the remaining three criteria ensure that the experimenter knows exactly what change, if any, the intervention resulted in.

The second criterion says that the intervention must not affect the effect variable through a route that does not go through $C$. For instance, if an investigator wants to test whether a change in the design of the pens in a kennel reduces the dogs’ stress level, this must be done in a way where the monitoring of the animals’ stress level is not in itself stressful. Otherwise, there will be uncertainty about the exact change in stress level the intervention has caused.

Similarly, the third criterion says that the causes of the intervention must not affect the parts of the causal chain that comes after the variable that is under consideration as a potential causal variable. For instance, if an experimenter wants to test whether a change in a specific gene can result in a specific change in the phenotype, the test should not be done in a way that affects the folding of the proteins constructed from the edited gene, e.g. by accidentally introducing reactive chemicals to the cell.

Finally, the fourth criterion says that an ideal intervention should not change the value of any other causally relevant variables. Returning to rhinovirus and the common cold as an example, an investigation of the relation between these should be done in a way that does not affect the function of the mucous membranes or the presence of adenovirus.

Interventions fulfilling Woodward’s four criteria are called *idealised* interventions for good reason: They are impossible to knowingly perform in practice. We can strive to get as close to the ideal as possible, and document the process thoroughly, but there will always be uncertainty about whether all four criteria are fulfilled. Consider, for instance, the fourth criterion. To know that this is fulfilled, we must, in principle, have a complete overview of all the causal chains that include the effect variable,
and how each link in these chains is affected by the intervention. In practice, this is not possible, especially not for complex biological systems. So, although we can argue that we have taken all the variables we can think of into account, we can never be sure that we have covered all of them. Consider also that striving towards fulfilling one criterion can sometimes be counterproductive in fulfilling others. Aspiring to fulfil criterion 1, for instance, we could conduct the experiment under highly controlled laboratory conditions, but doing so might take us further away from fulfilling criterion 3 because the highly controlled environment is likely to change the influence of relevant variables. This means that there may not be a single best way to design an experiment: two different designs can score high relative to different criteria and be limited relative to others. In such cases, the best solution may be to perform both studies and combine the results (See Section 6.3)

When assessing the quality of such studies it is similarly important to understand some of the most common challenges that real studies of causal relations face, and how and to what extent they can be faced. This is the topic of the final two sections.

Box 3: “Causal talk” in research papers

Researchers rarely state their understanding of causality explicitly. In fact, they often avoid the word cause entirely. Instead, they speak of associations, relations or correlations, or say that something can increase or decrease something else. Sometimes this is just a matter of taste and tradition; they might as well have used the word cause. In other cases, researchers avoid talking about causes because they are very careful not to overstate their results. As we shall see below, all causal connections are a form of association or correlation. However, not all correlations and associations are based on a causal relation. Many researchers are well aware of this and take care not to claim that they have found a causal relation if they are not sure. When assessing the credibility of a claim, it is therefore important to pay attention to the precise way it is presented. On the one hand, we cannot criticize an author for claiming without proper justification to have found a causal relation if the author made no such claim. On the other hand, an author can make a claims about causal relations without using the word cause, e.g. by suggesting that we can manipulate an effect by manipulating some factor that is ‘associated’ with it.

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Box 3 (continued): “Causal talk” in research papers

Consider the following example taken from a research article reviewing the available literature on the effects of tail docking on the frequency of tail biting among domestic pigs (Sutherland & Tucker 2011).

To begin with, the authors state that:

“To date, the cause of tail biting has been difficult to identify, but a considerable number of risk factors are known, including the environment (floor type, stocking density, ventilation, lack of enrichment […]), nutrition […], gender […], genetics […], tail length […], and health status.” (p. 180)

Here, the authors seem to want to make an explicit distinction between “the cause” of tail biting and “risk factors” for tail biting. This is not uncommon (Goddiksen 2018), although the distinction is commonly made between causes (in plural) and risk factors. Turning specifically to (lack of) enrichment as a risk factor, the paper continues:

“Enrichment can influence tail biting behaviour. […] Providing pigs with straw or other rooting materials appears to more effectively reduce tail biting behaviour compared to provision of environmental enrichment in the form of toys. […] Indeed, the probability of tail biting was reduced by approximately 50% when pigs were provided with light amounts of straw. […] However, the provision of straw or other rooting materials does not necessarily assure that tail biting behaviour will be eliminated […]” (p. 180-181)

Here, the authors seem to describe a relation much like the relation between rhinovirus and the common cold mentioned above. However, whereas we described the relation between rhinovirus and the common cold as causal, the authors here seem to insist that lack of enrichment is not a cause of tail biting. Possibly, this is because they seem to think that a factor can only be a cause if it is the cause, and if removing the cause removes the effect entirely. This would be a simplified view of causation, and it is contradicted in the paper’s conclusion, where the authors state that tail biting is “complicated and multi-factorial” (p. 184).

In the end, we are left uncertain about why the authors insist on treating lack of enrichment as a risk factor and not a cause and with a reminder that not all talk about causes involves the word cause. Whenever a relation is presented to be something like a causal relation, it is relevant to bring out the tools presented below to assess the reliability of the claims made about the relation.
5 Causation, correlation and confounding

In 2012, the New England Journal of Medicine printed a note by American doctor Franz Messerli entitled “Chocolate Consumption, Cognitive Function, and Nobel Laureates”. The center of the piece was the figure shown below (Fig 6). It shows that there is a correlation between per capita chocolate consumption per year in a given country and the number of people born in said country having received a Nobel Prize divided by the number of current residents counted in 10s of millions.

Figure 6: The correlation discovered by Messerli between chocolate consumption and Nobel laureates per 10 million people in a given country. From Messerli (2012).

As mentioned above, this observation does not necessarily mean that these two variables are causally connected in the sense defined in Sec. 4. If we look hard enough, and with a bit of skill, we can find very many variables that correlate, even though we have reason to believe that there is absolutely no causal connection between them (Fig 7).
Messerli was well aware of this. He wrote:

“Of course, a [statistically significant] correlation between X and Y does not prove causation but indicates that either X influences Y, Y influences X, or X and Y are influenced by a common underlying mechanism. However, since chocolate consumption has been documented to improve cognitive function, it seems most likely that in a dose-dependent way, chocolate intake provides the abundant fertile ground needed for the sprouting of Nobel laureates. Obviously, these findings are hypothesis-generating only and will have to be tested in a prospective, randomized trial.” (p. 1563)
Messerli’s list of possible interpretations can be illustrated as follows:

\[ X \rightarrow Y \quad X \leftarrow Y \quad X \quad Y \quad Z \]

**Figure 8:** If we observe a correlation between variables \( X \) and \( Y \), it could mean (A) that \( X \) is a causal factor for \( Y \), but before we can draw this conclusion, we must rule out three other possibilities: Random correlation (Fig. 7), reverse causality (B) and confounding (C).

To this, we must add an additional possible interpretation, namely that the correlation Messerli found was just like the ones shown in Fig 6: Random correlations, that disappear if more data is included. However, Messerli had actually already taken this possibility into account. How he did that can be read from Fig 6 by those who can remember their statistics course.

As far as we know, no one took up Messerli’s challenge to test his hypothesis in a “prospective, randomized trial”. However, three Belgian researchers responded to Messerli’s study by showing that there is an even stronger correlation between the number of IKEA stores per 10 million people in a country and the number of Nobel laureates per 10 million (Maurage, Heeren & Pesenti 2013). So perhaps going to IKEA is an even better (though perhaps less pleasant) way to improve your chances of a Nobel Prize than eating a lot of chocolate? Probably not. Their point was rather that we should be very careful when reading causality into a correlation. Most likely, the relation discovered by Messerli is of type (C) illustrated in Fig 8. The Belgian researchers showed that both chocolate consumption and the chance of receiving a Nobel Prize depends on the gross domestic product per capita of a person’s country of birth: People who live in rich countries eat more chocolate (partly because they can afford to), and are more likely to receive a Nobel Prize (possibly because rich countries have better educational systems).

The possibility of confounding, random correlation and reverse causation must be considered whenever we investigate causal relations, and as we shall see in the next section, a lot of effort has gone into designing research methods that allow researchers to exclude these possibilities.
6 Investigating causal relations

Following Woodward’s definition, it is easy in theory to investigate causal relations: To test if a variable, $x$, is a causal factor for $y$, simply perform an ideal experimental intervention on $x$ sufficiently many times to see if it changes the probability distribution of $y$, and if so, by how much. However, as already noted, this is impossible to do perfectly in practice. Real experiments always deviate in one way or another from Woodward’s ideal. This introduces uncertainty about how to interpret the results. It is important that you understand which uncertainties can arise from what types of investigations, as it will help you both perform your own investigations and assess the credibility of investigations performed by others.

6.1 Real controlled experiments

The closest we come to Woodward’s ideal experimental interventions are real experimental studies. Experimental studies can be done in many different ways, but by definition (Andersen et al 2006, Ch. 6) they share the characteristic that the experimenter manipulates the variable that is under investigation as a potential causal factor. Of course, the experimenter may not always succeed in changing the variable by the desired amount (if at all) and may accidentally change the value of other (potentially confounding) variables in the process.

We perform experiments in order to see if the intervention on the potential causal factors produces a change in the probability distribution of the effect variable. Changes are always relative to a baseline. So, in order to assess the change, we need to know what the probability distribution of the effect variable would have been under the exact same background conditions, if we had not made the intervention. If we do not have this knowledge prior to the intervention, we will have to obtain it by making a controlled experiment, that is, an experiment where we compare the effect of an intervention on individuals in an intervention group, relative to individuals in a control group that is, in principle, identical to the control group on all relevant variables except the one under investigation as a causal factor. A major source of uncertainty in controlled experiments is of course that we cannot always be sure whether the control and intervention groups are sufficiently similar. This is especially true if the experiment takes place in an environment where there is less control over the background conditions, or if the number of individuals in the two groups is relatively small.

One way to make reliable experiments is therefore to use a very large number of individuals (experiments with medicines, for instance, can involve thousands of patients), that are randomly divided into control and intervention groups, making the experiment a Randomized Controlled Trial (RCT). Randomly assorting the individuals into control and intervention groups minimises the risk that the experimenter will make biased groups, e.g. by putting all the strongest individuals into one group, and using a large number of individuals minimises the risk that such bias is created accidentally and increases the chance that any variation in background conditions present in the intervention group, will
also be present in the control group. Furthermore, if the participants are properly selected, using a larger number of individuals ensures that the experiment captures a broader range of the background conditions present in the relevant population, making it easier to translate the results of the experiment into a result about the population (Fig 9).

Figure 9: To move from an RCT performed on a sample population to a result about the wider population of interest, we must at least be able to argue that the relevant variation in background conditions was conserved through the sampling and assortment.

Another way to make experiments more reliable is to conduct the randomized controlled experiment in an environment where there is a high degree of control over the relevant background conditions - typically in a laboratory. This makes it easier to argue that the background conditions were identical for both the control and intervention groups. This can be a very good approach, but it also has limitations. First, there can be a trade-off between control over background conditions and the realism of these background conditions (See Box 4). The laboratory can be a highly controlled environment, but also a very artificial one in the sense that the background conditions in the laboratory can be very different from those found in the natural environment that we want to say something about. So even though the controlled laboratory environment can allow us to say something with relative certainty about causal relations, this knowledge will, initially at least, only be about causal relations under the background conditions that are found in the laboratory. Whether these results also apply to other environments, animals in the wild for instance, may not be clear from the laboratory results, but may have to be investigated separately.
Box 4: Are neonicotinoids a risk to wild pollinators?

Neonicotinoids are a group of pesticides that kill small insects by attacking their central nervous system. Once commonly used in field crops, they have been largely banned in the EU since 2013 because they were found to be a likely causal factor for *Colony Collapse Disorder* (CCD), in which worker bees abandon their hive and the entire colony eventually dies. Between 2007 and 2012, there was a dramatic increase in CCD in both Europe and North America leading to serious worries about the health of not just bees but the entire ecosystem that bees play a vital role in as pollinators. Since CCD mainly occurs in highly cultivated areas, pesticides were suspected to be causal factors from early on. Neonicotinoids in particular came under suspicion because of their mode of action and widespread use. To assess whether neonicotinoids could be a causal factor for CCD, researchers performed laboratory experiments where worker bees were exposed to high, but sub-lethal, doses of pesticide and monitored for their ability to navigate back to their hive. It was concluded that neonicotinoids could impair bees’ ability to navigate, and the European Food Safety Authority therefore advised the EU Commission to ban most uses of neonicotinoids.

Before the decision was made, there was some debate about the results that the suggested ban was based on. Banning one pesticide will almost always lead to an increase in the use of other pesticides. It is therefore important not to ban relatively safe pesticides based on a mere suspicion of them posing a risk to bees because it can lead to an increase in the use of pesticides that are known to pose a risk to the environment. Critics of the ban of neonicotinoids argued that this was exactly what was about to happen. They argued that a ban on neonicotinoids would likely lead to an increase in the use of pesticides called pyrethroids which were well known to be harmful to both birds, fish and *bees* if exposure is sufficiently high. Interestingly, the critics of the ban did not question the laboratory results. They questioned their relevance in the ongoing debate.

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An additional challenge for laboratory studies is that some species, including humans and large animals, are ill suited to be kept under controlled laboratory conditions for longer periods of time. Other species are hard to experiment on because our understanding of them is limited. It is therefore common to seek knowledge about causal relations in one species (humans for instance) by performing experiments on model organisms from another species (rats for instance). Again, this can be a very beneficial approach because it removes some kinds of uncertainty but choosing to experiment on model organisms also introduces new kinds of uncertainty because the results may have to be translated from one species to another.

**Box 4 (continued): Are neonicotinoids a risk to wild pollinators?**

The experiments showing that neonicotinoids could impair bees’ ability to navigate were performed by putting drops of pesticide on a glass plate and placing the bee on top of it. This would lead the bee to be exposed to a high dose of the pesticide through multiple pathways. Under these conditions, both proponents and critics agreed that neonicotinoids could impair the bees’ ability to navigate. However, the critics argued that this result on its own had little relevance for the discussion of what was causing wild bees to abandon their hives. Wild bees rarely land in a puddle of pesticide. They absorb it though the nectar and pollen they collect from flowers. This not only means that the way the bees are exposed in the wild is likely different from the way they were exposed in the laboratory, the amount of pesticide they are exposed to is also likely different. Critics therefore cautioned that more research was needed before it could be concluded that neonicotinoids played an actual causal role in CCD, and until this knowledge was available, we should not ban a pesticide that was thought to be unsafe, partly because it would lead to an increase in the use of pesticides that were known to be unsafe.

In the end, the critics did not convince the Commission. Neonicitinoinds were banned for a five year period, and further research was initiated. In 2018, following a court case where the main manufacturers of neonicotinoids tried to argue that the ban was illegal because it lacked scientific basis, the ban was made permanent based on the research available at the time.

For further details on the initial ban, see Cressey (2013).
6.2 Observational studies

Often, it will not be possible to explore a potential causal relation through experiments. If we think back to Messerli’s hypothesis about the causal relation between chocolate intake and winning a Nobel prize, this seems incredibly difficult to test in an experiment. It would probably require following a large group of people over a long period of time, ensuring that one group ate plenty of chocolate, while the other did not, and at the same time ensuring, that both groups received, on average, the same education and opportunities. Not only would this be difficult and expensive; it would probably also be unethical to intentionally intervene on so many people’s diet for so many years only to see if it affects their chance of receiving a Nobel Prize, especially given the uncertainty that would be associated with the result.

Speaking more generally, well-performed experiments are very well suited to assess causal relations, but it will often be either unethical or impractical (or both) to test a specific hypothesis about a causal relation though an experiment. Instead, we can choose to test it through an observational study. There are many types of observational studies (Goddiksen, Nielsen & Sandøe 2017), but they share the characteristic that the investigator does not intervene on the variable under investigation as a potential causal factor. Instead, she compares individuals for which the variable has different values for some external reason. For instance, she could investigate the effect of exposing humans to neonicotinoids (see Box 4) by comparing farmers working with the pesticide to similar people who do not.

Since the intervention on the potential causal variable is not performed by the investigator in observational studies there is generally more uncertainty on exactly when the intervention occurred (if at all), exactly how much the variable was changed, and whether other variables were changed in the process. Knowing exactly when the potential causal variable was changed and when the effect occurred is important. The cause always precedes the effect, so this information is used to rule out the possibility of reverse causation (Fig 7). Knowing how much the potential causal variable was changed is important if we want to understand the details of the causal connection – e.g. whether there are trigger values in the causal variable under which the effect will not occur. Knowing whether other variables were changed in the process of changing the causal variable is of course important in order to be able to rule out confounding (Fig 7). To compensate for these uncertainties, investigators can try to gain more control over potentially confounding variables by controlling the environment (potentially at the cost of the realism of the study) and/or increase the number of individuals in the study in the hope that having a lot of data will enable them to control for the different uncertainties using statistics.
6.3 Combining studies

Since no single study of a causal relation is perfect, it can be useful to combine multiple studies to get a better basis for assessing the relation. There are at least two reasons for this:

1. Studies using different methods can have different weaknesses. In combination, they can therefore partly compensate for each other’s weaknesses. Laboratory experiments, for instance, can sometimes be hard to translate into a result about the world outside the controlled laboratory. Observational studies performed out in the field will on the other hand, have uncertainty about possible confounding that the controlled laboratory experiment does not have. So, in combination, a well performed experiment and a well performed observational study may be better than each study on its own.

2. Studies using the same method can also sometimes partly compensate for each other’s weaknesses. As we saw above, controlled experiments aim to have identical background conditions for the control and intervention groups. The way we typically try to achieve this is by making both groups large enough to ensure that differences “average out”. Of course, a single study with, say, a thousand participants may not succeed in doing so. However, if it is combined with four other studies using the same method in a meta-analysis of data from five thousand participants we may be closer to the ideal, and the meta-analysis will therefore be more reliable than the individual studies.

There is a lot more to say about how studies can be combined to produce results that are more reliable than the individual studies on their own, but that is the topic of another note (Goddiksen, Nielsen & Sandøe 2017).

7 Summary

Constructing knowledge of causal relations is an important aim of research. As an academic you should therefore be able to assess the reliability of claims about causal connections and to some extent be able to design your own studies. To this end, it is useful to have reflected on the nature of causation.

Two variables are causally connected under a given set of background conditions if and only if an idealised experimental intervention on one variable would lead to a change in the value or probability distribution of the other.

Unfortunately, we cannot knowingly perform idealised experimental interventions in practice. Real interventions are always associated with some degree of uncertainty about possible changes to confounding variables, and whether an effect was actually observed. Much of the uncertainty stems from the need of a baseline to compare with. To know whether an intervention has caused a change in an effect variable, we must know what the value of the effect variable would have been if the intervention had not occurred. This often implies the comparison of an intervention and a control group.
that should not only be (on average) identical on all relevant background conditions, but also representative of the population under study. These two conditions can be hard to obtain simultaneously.

Different types of studies deviate from idealised experimental interventions in different ways (Sec. 6). Common to all types of studies is that they generate a dataset which may show that two variables correlate. Based on this correlation, and the design of the study, the researcher must argue that there is a causal connection in nature or society. To do so convincingly, the researcher must rule out at least four alternative interpretations:

1. The observed correlation is random.
2. The observed correlation is due to a confounding variable.
3. The observed correlation derives from a causal connection present under different background conditions than those present in the relevant parts of nature/society.

Finally, to argue that the direction of the causal connection is from X to Y, the researcher must rule out the possibility that:

4. The observed correlation derived from a causal connection, but the connection goes from Y to X.

Conversely, when you assess the credibility of a causal claim, you should consider whether the author has convincingly ruled out these alternatives. Depending on the design of the study, it may be easy to rule out some of these alternatives. If there is a clear delay between cause and effect, alternative 4 is easily ruled out, and alternative 1 is routinely ruled out using statistical methods. Alternatives 2 and 3, on the other hand, are trickier to rule out simultaneously, because there is often a trade-off between the control over confounding variables needed to rule out alternative 2, and the realism needed to rule out alternative 3. A single study may therefore not be enough to convince you that two variables are causally connected, but a combination of studies might.
References and further reading

References in the text
Frederiksberg: Biofolia


Other useful texts on causality
Woodward’s definition is only one among many. For an overview see: Broadbend, A. (n.d.). Causation. *The Internet Encyclopaedia of Philosophy*. Available at: https://iep.utm.edu/causatio/ [accessed Oct 2021]

American doctor and statistician Bradford Hill formulated a list of criteria to be used when identifying causal relations through correlations: Hill A. (1965). The Environment and Disease: Association or Causation?. *Proceedings of the Royal Society of Medicine, 58*(5), 295–300.