CAUSAL RELATIONS IN EPIDEMIOLOGICAL RESEARCH. CONSEQUENCES OF EVALUATING DEGREES OF COMPLEXITY AND NON-LINEARITY

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Causal relations may be extremely difficult to infer from epidemiological studies. Standard approaches to evaluation of causality as the famous 9 points of Bradford Hill [1] or others have not offered the epidemiologist any solution to this problem. As discussed in standard textbooks as Rothman &Greenland [1], causal mechanisms may be of extremely complex nature. Moreover, there is a major difference between what epidemiologists discuss when inferring from results in epidemiological studies to the real biological causal mechanisms. In most cases, the real biological mechanisms remain obscure or unknown.

We have often assumed that causal relation can be investigated using results from various studies with some degree of consistency under various conditions. However, the problem still remains if we fail to address the biological causal mechanisms. As long as we only measure effects and relate them to variables of more or less biological relevance, we work under the so-called black box paradigm. If we were only concerned about interpretation of the date from an observational or experimental study, this would not necessarily represent any major problem. As our main aim of epidemiology of a subject is to understand biological mechanisms in order to try to influence them through intervention in society, we also have to address this.

A lot of the philosophical background for discussions of causation has been from physics. We often forget that we often in biology do not work with the kind of direct causation as found in physics. Biology mainly uses a conceptual framework where explanations are more important than causality. The evolutionary theory of Darwin is a good example of such an overall explanatory theory, where our aim is not to predict what happens but to explain what has happened.

Most epidemiological work will be with the overall aim to try to predict “what happens if we do..”. In its extreme form, prediction is used in various risk assessment models, where epidemiological data are often used to establish prediction models in areas where predictions are perhaps impossible to defend. We must remember that nonlinear processes never repeat themselves, and that there is a limit to how much we can trust previous information when producing predictions.

The key to understanding biological processes is the term complexity. In this context I use the term as modern system researchers use the term, meaning non-linear systems with different levels of feedback systems. A high level of feedback structures often means a high level of stability. To put it short -- many or most biological systems belong to this group of systems [2]. Metabolic pathways are excellent examples of systems stabilized by feedback systems. A range of other examples from biology can be found in recent literature [2-4]. Modern system theory [2] also tells us that biological systems may be stable over time if they are of a sufficient complexity. A complex system under stress may undergo sudden changes if brought out of balance by external forces (discontinued equilibrium).

Rothman & Greenland [1] mentions briefly that causal models may contain approaches using both chaos theory and quantum mechanics. This may perhaps seem a bit speculative, but if we try to look into how we assume that our “disease mechanisms” operate, we realize that our basic starting point is that causal mechanisms are linear. As long as we want to make predictions relevant for the external population, our only possible starting point is that unknown or known factors operate in similar ways as in our study.

Given a non-linear system, a non-measurable change of a factor might have been the initial condition for developing a disease or changing the status of a herd or ecological system. At the same time, a system of certain complexity may be extremely robust to major changes in causal factors. This is well known in ecological studies, where systems may be stable over time until a sudden and unpredictable change occurs.

In epidemiology, the most typical example of non-linear systems is in the epidemiology of infectious diseases. Moreover, it is easy to see that infectious disease dynamics also typically possess the sensitivity to initial conditions typically seen in non-linear or chaotic systems. As also stated in reference books [5], infectious disease dynamics may be extremely complex. Some infectious diseases of animals are, however, of low complexity. Examples may include acute diseases with only one host and no external reservoir. Other infections involving several species, vectors and survival in the environment are of more complex nature, and thus often difficult to predict.

Perhaps the most striking feature of non-linear systems, are their reluctance to allow any long-term predictions. The practical consequence for infectious diseases is that we can easily model the initial stage of the spread of an infectious agent, but will often run into problems when trying to predict the long-term behavior of a system. Reliable detailed predictions can only be made for linear systems of low complexity, but simple nonlinear systems may also be extremely unstable. The prediction time horizon needed in risk assessments may be irrelevant for many complex biological systems.

In daily life we meet the situation through a large number of conflicting results from published epidemiological studies. The first reflection on this should not be that the conflicts appear due to different designs or statistical techniques, but simply that it a logical consequence of the many non-linear disease processes we encounter. Only very simple causal pathways can be studied in a way that repeated observational studies give the same results. Not only do we experience different risk estimates or variance, but also the direction of effect may be different. An inducing factor may suddenly pop up as a protective factor in a later study.

We have often assumed that many problems will be solved if we would be able to measure the extra-variance linked to herds or other clusters and thus use a more or less “true” statistical estimate to solve the puzzle. Given non-linear and complex causal mechanisms, this will not necessarily help us much.

The discussion about causal criteria has been a major topic in the field of epidemiology. Perhaps we should address the problem in a slightly different way. If we assume different ways of interpreting/ predicting systems of low and high complexity, we may be able to better distinguish between different ways to design and interpret our epidemiological studies.

Table 1. Hypothetical categories of complexity and non-linearity and possible consequences epidemiological research.

	Low complexity	High complexity
Low level of non-linearity	Simple causal pathways, but may be unstable due to low level of complexity	Stable systems, high level of correspondence between study results
High level of non-linearity	Often unstable systems. Causal pathways possible to identify and study in detail.	Conflicting study results. Only option is to break down and study parts of causal pathways

The main message in Table 1 is that we are in trouble when we are studying disease mechanisms of high complexity and high level of non-linearity. The only option here is to break down and study parts of the pathways separately. Throughout time we may hope that we will understand the whole set of mechanisms involved – but not predict what happens on the individual level.

For lower levels of non-linearity we have better hopes, but we must still remember that predictable results may be more common in complex systems than in systems of low complexity.

1 Rothman KJ, Greenland S. Modern Epidemiology. 2nd ed. 1998, Philadeplphia: Lippincott-Raven Publishers.

2 Bar-Yam Y. Dynamics of complex systems. 1997, Reading, Mass.: Addison-Wesley..

3. Liebovitch LS. *Fractals and chaos. Simplified for the biological sciences.* 1998, New York: Oxford University Press.

4. Prigogine I, Stengers I. *The end of certainty : time's flow and the laws of nature*. 1997, New York: Free Press. IX, 228 s.

5. Anderson, R.M. and R.M. May, Infectious diseases of humans : dynamics and control. Oxford science publications. 1991, Oxford: Oxford University Press.