CONTEXT, CAUSALITY AND CONSEQUENCES

From robust evidence to timely action in biology, ecology, law and public policy

A public conference

Friday 26 and Saturday 27 November 2021

Preceded by

Critical Scientist Organisations' Meeting
By invitation only
Thursday 25 November 2021 (afternoon)

Annual General Meeting
of ENSSER members
Thursday 25 November 2021 (morning)

All three events are hybrid events,
i.e. they will take place on site in Bern, Switzerland
as well as online

Registration online:
https://us02web.zoom.us/webinar/register/WN_X9hhCNv9QLCFACw8-QiGGA

Registration onsite:
Please contact us at office@ensser.org to see if onsite participation is still available

Organised by

European Network of Scientists for Social and Environmental Responsibility
Critical Scientists Switzerland
Mariolopoulos – Kanaginis Foundation for the Environmental Sciences
Association des amis de la génération Thunberg

Sponsored by

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EMstitut

1. Conference "Context, Causality and Consequences: from robust evidence to timely action in biology, ecology, law and public policy"

"In what circumstances can we pass from this observed association to a verdict of causation?"
"The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association."
"…the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A."
"What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?"
"In occupational medicine our object is usually to take action. (...) we shall wish to intervene to abolish or reduce death or disease."
"All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."

A. Bradford Hill: "The Environment and Disease: Association or Causation?",
Proc. Royal Soc. Med., p. 295 – 300, 1965,
https://doi.org/10.1177/003591576505800503

Keywords: agnotology, ambiguity, causality, cause, co-causal, control, determination, direct cause, effect, evidence, hubris, ignorance, indeterminacy, indeterminism, indirect causes, multi-causality, non-target effect, precaution, Precautionary Principle, precision, probability, risk assessment, target effect, uncertainty

Content of the conference

The understanding of "causes" is at the core of scientific investigations. It underlies all current efforts to face ecosystemic challenges. Physics has framed causality within robust and unifying "conservation principles" (energy, momentum etc.). But how can we understand and verify supposed causal relations within the historicity and diversity of life in a unified manner? How can we scientifically describe the effects which appear to be caused by a chemical or physical event on an ecosystem governed by reproduction and variation and on environments enabling diversity?

A special influence on our notions of causality in biology and ecology is exerted by our advanced reliance on automation, digitization, computers, in-silico models, computational surrogates, artificial intelligence and machine learning. If life-science phenomena are viewed as caused by one or a few selected agents, how does this view align with what can be obtained from a computerized output, with less and less reliance on hands-on experience and human senses for verification?

A paradoxical situation seems to emerge, where this approach appears to enable to flip cause and effect, as exemplified in synthetic biology. Traditionally, say, cloning relied on the appropriate functioning of an entire framework system (environment), such as E. coli, to express a specific gene insert. With the advent of reverse genetics, the same technique is now publicized as being "under the control of the gene" to be expressed. It seems that modeling, and focusing on what one wants to obtain, has shifted the comprehension and understanding of what is cause and effect, demonstrating that the entire framework of causality is not only poorly understood, but little investigated.

When approaching this question from another level, one may ask what the biological influencers of causality are. Is it about material entities (e.g. genes), or also about interactions, relationships, and context (from sub-cellular to ecological)? A unique ability of life is to be able to adapt to a changing environment. So one may ask: what causes habituation

and learning, and in which way do these influence the appearance of causality (in gene expression, disease and other phenomena)?

"Science is the organised attempt to discover how things work as causal systems."[11] But in current biology and ecology every cause has multiple effects and every effect has multiple causes. So at this conference we study notions of multi-causality within complex systems that encompass many variations, in time and space, of the "known" co-causal factors, whilst acknowledging the existence of many other unknown, yet possibly influential variables.

There are some current attempts to re-introduce simple causality, for example, in searches for the particular gene or environmental circumstances that are relevant to a specific biological trait, via genetic modification which is claimed to be "*precise*".

However, other approaches are attempting to identify modifiable co-causal factors within context and time dependent complex biological and ecological systems, factors which enable both life and harms to emerge and which, if removed or reduced in a timely manner, would result in less harm to people and environments.

Such approaches to identifying robust causal inferences in biology, ecology, tort law and public policy on health and environment eschew simplistic dichotomies (e.g. nature/nurture; gene/environment; acute/chronic; effects/adverse effects; statistically significant/insignificant effects; association/causation; valid/invalid arguments) in favour of continuums, or spectrums, along which choices need to be made as to where and when positions on such continuums justify robust causal inferences.

Current approaches to coaxing causality from complexity also include systematic review methodologies; systematic approaches to integrating different evidence streams; and "*inferences to the best explanation*" used in tort law. There are also approaches that render explicit and transparent the often implicit sources of divergent evaluations of the "same" evidence, which can be illustrated historically with: leaded petrol; low dose ionising radiations; and antibiotics as animal growth promoters; and currently with: per- and polyfluoroalkyl substances (PFAS); glyphosate; neonicotinoid insecticides; and electromagnetic fields (EMFs).

These sources of divergent evaluations include (1) different types of paradigms, assumptions and argumentation used; (2) the diverse disciplinary conventions of toxicologists, endocrinologists, epidemiologists, biologists, ecologists, and lawyers; and (3) their value based choices.

Public and stakeholder involvement in helping to identify robust causal inferences for public policy interventions have also been used, sometimes including communities affected by harms. The value of these approaches will be reviewed.

Programme

Friday 26 November 2021

8:30 Registration

9:00 Welcome / Introduction
Prof. Polyxeni Nicolopoulou – Stamati, University of Athens Medical School and chair of ENSSER
Diederick Sprangers MSc, Scientific Coordinator of ENSSER

Moderator: Diederick Sprangers, ENSSER

9:30 **Prof. Giuseppe Longo**, Centre Cavaillès (République des Savoirs), CNRS and Ecole Normale Supérieure, Paris

1 Waddington, C.H. (1943), "The Scientific Attitude", second revised edition, Penguin

Causality and novelty production in biology

Physics has been framing causality in fundamental principles of "conservation" (energy, momentum…); in some cases, the "causal" terminology may be even avoided (a body falls for "symmetry reasons" according to Einstein, which frames/avoids referring to the "cause" – gravitation). These conservation properties gave unity to a diversity of theories, often incompatible with each other (quantum and relativistic fields, but hydrodynamics and known theories of elementary particles as well …).

Causality seems an unavoidable concept in biology: we need to understand how an endocrine disruptor *affects* an organism and if (and possibly how) it may *cause* cancer. Can we frame causality in more general principles? Are the first Darwinian principle, "reproduction with variation", and "enablement" sufficient principles for this purpose? Organisms are not spontaneous self-organization of flows of matter and energy, like hurricanes and flames that are fully described by conservation laws applied to flows, but they are historical objects *using* flows, canalized by self-generated *constraints*. What causes what, then?

10:15 Discussion

11:00 Coffee break

11:30 **Prof. Denis Noble**, University of Oxford
20th century biology got causation in living systems the wrong way round

20th century biology was built on three central dogmas: 1. The Weismann Barrier, which was proposed by the geneticist August Weismann in the late 19th century and then incorporated into the standard theory of evolution, the Modern Synthesis. It forbids any causal influence of the soma on the germ-line cells, the future eggs and sperm. 2. The Central Dogma of Molecular Biology, formulated by Francis Crick in 1958 and 1970, which has been interpreted to forbid any causal effect of protein and other regulatory networks on DNA sequences. Causation is assumed to be only one way DNA --> RNA --> proteins. 3. The assumption that DNA is an auto-replicator, replicating like a crystal, and is therefore the cause of all living processes. 21st century biology has shown that all three assumptions about causation in living organisms have been falsified. The consequences for biology, and for many other disciplines, including economics and sociology, that have been influenced by popularizations of 20th century biology, such as The Selfish Gene, are profound. The fundamentals of biology need rebuilding. So do the consequences for other disciplines that have taken causality in biology for granted. (Noble D (2021) The Illusions of the Modern Synthesis. Biosemiotics. 14, 5-24)

12:15 Discussion

13:00 Lunch

Moderator: Prof. Giuseppe Longo

14:30 **Dr. Siguna Müller**, Kärnten, Austria
Causality and SARS-CoV-2 – new findings that mandate a broader perspective

Based on recent published work, this talk discusses difficulties with, and shortcomings of, more conventional notions of "causality" in the context of SARS-CoV-2 infection and Covid-19 disease. Specific focus will be given to

- The role of structural versus sequence-based approaches and determinants involving infectivity and host range of the virus,
- The relevance of viral presence alone, versus tissue-specific tolerance and immune responses, in the pathogenicity of this virus,
- Beyond-sequence determined factors in the adaptive immune response and their implications for prophylactic treatments.

15:15 Discussion

16:00 Tea break

16:30 **Dr. Thierry Paul**, National Centre for Scientific Research (CNRS) and Sorbonne University, Paris
Causality, indeterminism and all that: a quantum entanglement

In quantum mechanics, repeated measurements of a given quantity (position, energy, ...) on the same system in the same state will not provide the same result: the different consecutive results are randomly distributed according to a probability law depending on the state of the system. This indeterminism is a building block of the quantum paradigm, fully necessary to its consistency, and a source of a lot of

misunderstandings. How can causality be handled in front of this intrinsic indeterminism, intrinsic in the sense that it does not result from a lack of "information"? In fact, the quantum evolution contains two parts, totally disjointed: the first one is the evolution of the wave function driven by a differential equation leading to a natural principle of causality, and the second is the indeterministic phenomenon of measurement, whose random result values are taken from a set of possible ones associated to the wave function. We will discuss precisely the impact of the causality of the first evolution on the indeterministic aspects of the second one. We will show that this impact is far from being complete and we will raise the question: can non-causality be considered as a causality itself?

We will illustrate this question by recent results in quantum information, such as evolution given only by repeated measurements or the surprising quantum Zeno phenomenon.

We will be strictly focused on the mathematical formalism of quantum mechanics – but we will carefully avoid any kind of technicality – hoping that some ideas can be exported to other scientific contexts, and show how it provides peculiarities in the behaviour of "causally" linked natural parameters, for example time and energy.

17:15 Discussion

18:00 End

Saturday 27 November 2021

Moderator: Dr. Ricarda Steinbrecher, EcoNexus, Oxford

9:00 Short welcome and recapitulation

9:05 **David Gee BA**, Centre for Pollution Research and Policy, Brunel University, London
Association <u>and</u> Causation: Bradford Hill's approach to causality in Public Health updated?

In 1965, after 20 years of controversy over whether smoking caused lung cancer, the UK Chief Medical Statistician, Austin Bradford Hill, published his paper on "*Environment and Disease: Association or causation?".* In answering that broad question, refined to *"in what circumstances can we pass from this observed association to a verdict of causation?"* he identified 9 "features", or "aspects", of the available evidence which we could "*especially consider"* when judging whether *"the frequency of undesirable event B will be influenced by a change in the environmental feature A.*

The Bradford Hill approach has been widely adopted in public health (and sometimes in ecology), though with frequent misunderstandings and some distortions. (Cranor, Neutra, Gee, Jurimetrics, 2017). However, should we update the Bradford Hill approach in light of the very different circumstances of 21st century biology/ecology, characterised by non linear, dynamic and complex systems; multi-causal and multi effect features; and often long latencies between exposures and sometimes irreversible harms that require timely interventions if much harm is to be avoided? For example, should we now put **different weights** on any of the 9 features of evidence? **Or reduce them to just 5** as the WHO did with its assessment of the evidence on falling sperm counts and endocrine disrupting chemicals in 2002? Is the **asymmetry** of the 9 features (i.e. if present, they can provide robust evidence for causality, but if absent, they cannot provide robust evidence of non-causality, as Bradford Hill noted) greater or lesser nowadays? Should we use more than the three **different strengths of evidence** for causality that he used to illustrate the need to adopt *"differential standards"* when determining how much case specific evidence to wait for, before acting to prevent harm? This choice of strength of evidence depends, as Hill illustrated, upon the acceptability of living with the plausible consequences of being wrong in acting, or not acting, so as to prevent, or diminish, harm.

Finally, do we now need to use some **standard terms and shared understandings in the language used** to characterise the links between environmental agents A, B, C, …. and effects X, Y, Z, which is often Babylonian!

9:25 Discussion

9:40 **Dr. Maël Montévil**, French National Centre for Scientific Research (CNRS)
Organization, historicity and causality

Two models dominate reflection on causality, namely mechanisms and physics. The former focuses on very local processes, while the latter focuses on ahistorical systems. We argue that neither is a sufficient framework for biology. Instead, in biology, parts of a system collectively maintain each other, which enables us to understand how biological systems maintain themselves. This perspective corresponds notably to autopoiesis and closure of constraints, and is sometimes called organization. In this view, the parts maintain each other, leading to circularities. It implies that a systemic mode of thinking is critical to understand these phenomena. However, they are also historical: the organization they maintain is the singular result of evolution, and they change over time. It follows that causality in biology has two distinct features. First, it has a circular dimension: how do singular organizations maintain themselves? Second, it has to include historical changes: how do we understand the appearance of novelty?

10:25 Discussion

11:00 Coffee break

11:30 **Dr. Elena Rocca**, Centre for Applied Philosophy of Science, Norwegian University of Life Sciences
Difference-maker, mechanism or disposition? How explicating and critically discussing basic assumptions about causality improves scientific evaluations of risk

Risk assessment is traditionally considered as a discipline-specific matter, requiring different tools and approaches depending on the area of application. In the last years, it became clear that this is problematic since different experts give often diverging risk evaluations, even in the cases where there is empirical agreement over the available data. This suggests that scientists base their conclusions on some premises that are not stated explicitly. We called such premises Philosophical BIAS (Basic Implicit Assumptions in Science), of which one important assumption is about the nature of causality, and one strictly connected the nature of complexity. In this talk, I will use cases of environmental risk assessment of oil pollution and GM technologies to show that depending on the basic understanding of causality and complexity scientists evaluate the available evidence of risk differently. In conclusion, I will present our preferred view on causality and explain why it makes a difference in the approach to risk assessment.

12:15 Discussion

12:45 Lunch

Moderator: Dr. Angelika Hilbeck, Swiss Federal Institute of Technology, Zurich

14:15 **Prof. Ana Soto**, Tufts University School of Medicine (Boston), Centre Cavaillès, Ecole Normale Supérieure (Paris) and Institute for Advanced Studies of Nantes
Towards the understanding of biological causality and its application to endocrine disruption

Since the last half of the 19th century biology has undergone a process of theoretical impoverishment. This process started with the introduction of the idea that biology could be reduced to chemistry and physics, and that cells and organisms are analogous to machines. Several other developments in biological thinking intensified this impoverishment further, including the current pervasive use of commercially available kits for assessing biochemical end points, which has fostered technical ignorance; the introduction and analysis of "big data" as a new specialty; and the transfer of the task of finding patterns for the generation of hypotheses to computers and "data scientists".

The adoption of the concept of mechanism as the only acceptable form of causality conflicts with the interdependence between the organism and its parts and the circularity it entails. Both the physicalism introduced in the 19th century and the metaphorical introduction of mathematical theories of information introduced in the 20th century have addressed development, a historical process, with tools designed to study spontaneous phenomena resulting from ahistorical laws. Both the disregard for historicity and the obsession with mechanism have been detrimental to the study of hormonal regulation and endocrine disruptors. Moreover, the search for mechanisms is hindering regulatory processes as scientists are kept busy searching for "adverse outcome pathways".

These problems call for a reappraisal of the philosophical and theoretical frames that are guiding contemporary research. While inert matter requires causes to change states or properties, organisms,

instead, are agentive and thus capable of initiating activity by themselves. Our theoretical framework consists of: (1) the principle of biological inertia or default state that states that the unconstrained state of cells is proliferation with variation and motility. The default state is a cause in biology; by contrast, anything that affects the default state is a constraint; (2) the principle of variation, which accounts for the production of novelty; and (3) the principle of organization by closure of constraints which accounts for robustness and stability. These principles have been successfully used for the understanding of endocrine disruption.

15:00 Discussion

15:35 Tea break

16:05 **Prof. Thomas Vondriska**, David Geffen School of Medicine, University of California, Los Angeles
Genomes, epigenomes and causal inference in multicellularity and human disease

One of the most important problems in biology is how the same genome is used to produce dramatically different behaviors and appearances in the dozens or hundreds of cells that make up a multicellular organism. In addressing this problem, modern biological techniques enable measurement of cellular processes at an unprecedented level of resolution. Some of these processes, like organismal development, appear largely deterministic. Other processes, like disease, arise from a complex interplay of hard-wired cellular functions, random occurrences and cumulative (or sometimes transient) environmental inputs. I will discuss some of the key questions biologists face in understanding how the structure and function of a genome is impacted by the cell type it resides in. I will draw on historical examples and very recent findings to illustrate how our understanding of multicellularity and disease etiology are both driven by an evolving conception of biological causality.

16:50 Discussion

17:25 Final discussion

18:00 Closing words:
David Gee BA, Centre for Pollution Research and Policy, Brunel University, London
Prof. Polyxeni Nicolopoulou – Stamati, University of Athens Medical School and chair of ENSSER

18:15 End

Venue: EventForum, Fabrikstrasse 12, CH-3012 Bern, Switzerland

Online participation: voluntary fee
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On site participation: registration fee
€ 50 (reduced), € 150 (regular), € 250 (solidary). This includes lunch on both days. If the reduced fee is still beyond your financial capacity, please inform us: the fee should not stop anyone from attending. Please transfer the conference fee to our bank account with reference "conference fee" or to our paypal account. Your registration is approved upon reception of the conference fee.

Recording: The entire conference (lectures and discussion sessions, both on site and online) will be recorded and published.

Registration: Please register by email to office@ensser.org (mentioning your name, affiliation, academic degree, country, and if you would like to participate online or onsite) or use the form on our website.
NB By registering, you consent to your image and voice being recorded during the conference and published.

2. Critical Scientist Organisations' Meeting

This meeting is by invitation only. The invitation will be sent separately.

Date:	Thursday 25 November 2021, 14:00 – 18:00 CET
Venue:	Office of Critical Scientists Switzerland Mattenhofstrasse 5, Raum 213 CH-3007 Bern
Information:	Diederick Sprangers, dsprangers@ensser.org

3. Annual General Meeting of ENSSER

This meeting is for ENSSER members only. The invitation will be sent separately.

Date:	Thursday 25 November 2021, 9:00 – 12:00 CET
Venue:	Office of Critical Scientists Switzerland Mattenhofstrasse 5, Raum 213 CH-3007 Bern