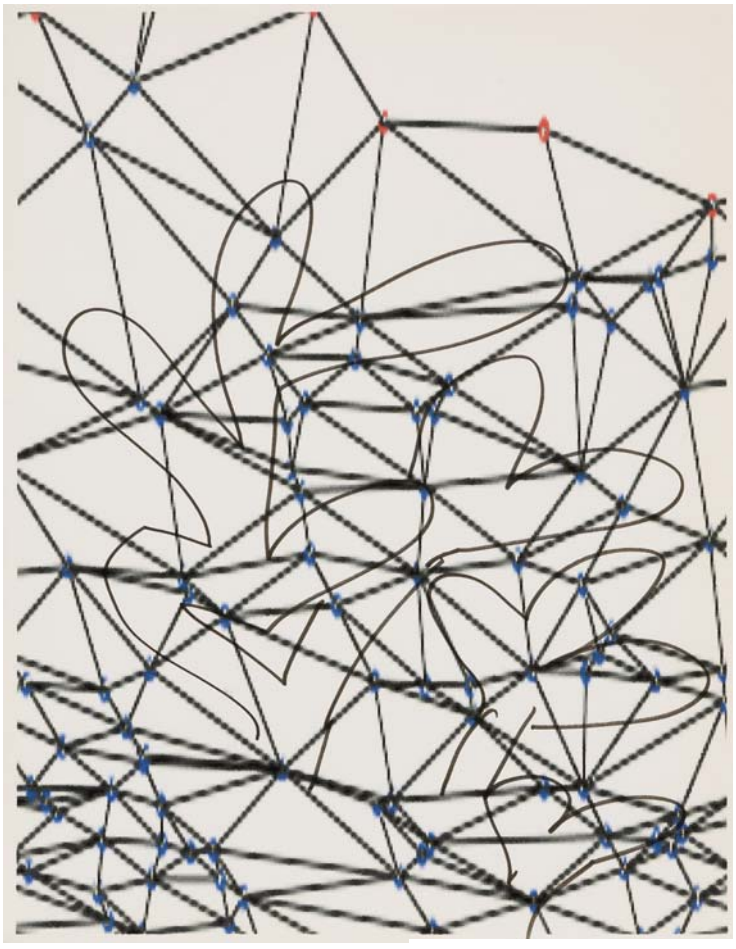
First European Advanced Seminar in the Philosophy of the Life Sciences

Causation and Disease in the Postgenomic Era

PROGRAM and ABSTRACTS



Hosted by the Brocher Foundation
Hermance (Geneva), Switzerland, September 6 - 11, 2010

Monday, September 6

13:30 Welcome

14:00 **Giovanni BONIOLO** (Milano),
Could mechanisms and the philosophy of cartoon biology vanish?
Marco NATHAN (New York), *Comment*
Discussion

15:30 Break

16:00 **Jean GAYON** (Paris),
Function, Disease and Overcapacity: Causation in a non-normal world
Miles MACLEOD (Altenberg), *Comment*
Discussion

18:30 Optional concert at Eglise St Germain
Maurice STEGER and the Ensemble LA CIACCONA
Misic baroque for 'flûte à bec'

Tuesday, September 7: BOUNDARIES

09:00 **Hillel BRAUDE** (Montreal),
Linking Pain and Pathos: Revisiting the Causal Problematic in Clinical Medicine through Affective Neuroscience
Lara Katharina KUTSCHENKO (Mainz),
Why Classify Diseases?

10:30 Break

11:00 **Paolo MAUGERI** (Milan) and **Alessandro BLASIMME** (Milan),
Modelling Cancer and the Problem of Disanalogy
Thomas PRADEU (Paris), *Comment*
Discussion

12 :30Lunch

14:00 **John DUPRE** (Exeter),
Emerging Sciences and New Conceptions of Disease
Francesca MERLIN (Montreal and Paris), *Comment*
Discussion

15:30 Break

16:00 **Lisa GANNETT** (Halifax),
Context Matters: A Local Epistemology of "Race"
Kathryn TABB (Pittsburgh), *Comment*
Discussion

Wednesday, September 8: CAUSATION

09:00 **Pierre-Olivier METHOT** (Exeter and Paris),
From the 'Law of Declining Virulence' to the 'Trade-off Model': Using Historical Epistemology to Assess a Shift in the Concept of Virulence and Disease

Susanne BAUER (Berlin),
Between Complexity and Restriction, Modelling Causation in Epidemiology

10:30 Break

11:00 **Christophe MALATERRE** (Paris),
Downward Causation in Cancer Research: the Experimental Evidence?
Federica RUSSO (Canterbury), *Comment*
Discussion

12 :30Lunch

14:00 **Giuseppe TESTA** (Milan),
Taming Through Codes: the Notion of Epigenetic Code in Disease Causation
Antonine NICOGLOU (Paris), *Comment*
Discussion

15:30 Break

16:00 **Michael ESFELD** (Lausanne), and **Christian SACHSE** (Lausanne)
Philosophical Theories of Causation and Biological Functions
Cristian SABORIDO (Leioa), *Comment*
Discussion

17:30 Dinner break

18:30 **Sandra MITCHELL** (Pittsburgh), will be held at the CMU
Philosophical Reflections on Robustness and Gene-Environment Interaction in Complex Disease

20:45 Concert at Eglise St Germain
Pierre-Louis Rétat and the ensemble CHIOME D'ORO
La sémantique dramaturgique dans la music : le Théâtre du Monde ou le clair-obscur, baroque music

Thursday, September 9: MECHANISMS

09:00 **Steeves DEMAZEUX** (Paris),
Promises and Limits of Mechanistic Explanation in Psychiatry
Fridolin GROS (Milan),
The Limits of Mechanistic Explanation in Molecular Biology

10:30 Break

11:00 **Frédérique THERY** (Paris),
Ontological Diversity of Molecular Mechanisms: Towards a Typology
Philippe HUNEMAN (Paris), *Comment*
Discussion

12:30 Lunch

14:00 **Ken WATERS** (Minneapolis),
Why DNS-Centered Biological Sciences Succeed
Robert MEUNIER (Milan), *Comment*
Discussion

15:30 Free afternoon

Friday, September 10: COMPLEXITY

09:00 **Adam BOSTANCI** (Cambridge),
From RNA Interference (RNAi) to RNA Silencing: the Biomedical Significance of Small RNAs and of Sequence-specific Interactions between Nucleic Acids
Marta BERTOLASO (Rome),
Hierarchies and Causal Relationships in the Interpretative Models of the Neoplastic Process

10:30 Break

11:00 **Marie Isabel KAISER** (Muenster),
The Diversity of Explanatory Reduction in Biology
Maria CEREZO (Murcia) and **Elsa MURO** (Navarra), *Comment*
Discussion

12:30 Lunch

14:00 **Annick LESNE** (Paris),
Genetic Risk and the Roll of Gene-Evironment Interplay in Complex Diseases: How Modelling Could Help? The Example of Crohn Disease
Mila PETROVA (Exeter), *Comment*
Discussion

15:30 Break

16:00 **Werner CALLEBAUT** (Altenberg),
Multiscale Modelling of Biological Phenomena, Dynamic Mechanistic Explanation, and Scientific Perspectivism
Bartolomiej SWIATCZAK (Milan), *Comment*
Discussion

Saturday, September 11

09:00 **Bernardino FANTINI** (Geneva),
Biological specificity and the causative role of genetic information
Norberto SERPENTE (London), *Comment*

10:30 Break

11:00 **Staffan MÜLLER-WILLE** (Exeter) and **Maria KRONFELDNER** (Bielefeld),
Final Discussion and *Outlook*

12:30 Light lunch and departure

Eglise de St. Germain, Mercredi 8 septembre, 20h45

Ensemble Chiome d'Oro

Capucine Keller - *soprano*

Elisabeth Opsahl, Liselotte Emery - *cornets à bouquin et flûtes à bec*

Saskia Birchler, Pavel Amilcar - *violons*

André Cortesi - *flûte traversière renaissance*

Marc Durollet - *violoncelle*

Etienne Galletier - *théorbe et guitare*

Pierre-Louis Rétat - *clavecin, orgue et direction*

Le théâtre du monde ou le clair-obscur
La sémantique dramaturgique dans la musique

Francesco TURINI (1595-1656)	« Sonata 2 a tre »
Sigismondo d'India (1583-1629)	« Cruda Amarilli »
Marco UCCELLINI (1603-1680)	« La Luciminia Contenta »
Sigismondo d'India (1583-1629)	« Piangono al pianger moi »
Claudio MONTEVERDI (1567-1643)	« Illustratevi o Cieli », Ulisse
Sigismondo d'India (1583-1629)	« La tra 'l sangue e le morti »
Francesco CAVALLI (1602-1676)	Atto 3, scena 1, La Doriclea
Marco UCCELLINI (1603-1680)	« La Prosperina »
Sigismondo d'India (1583-1629)	« Tu parti, ahi lasso »
Francesco TURINI (1595-1656)	Sonata sopra la Monica
Francesco CAVALLI (1602-1676)	Lamento de Procris, Gli amor di Apolo e Dafne
Girolamo KAPSBERGER (1580-1651)	« Arpeggiata »
Claudio MONTEVERDI (1567-1643)	« Amore », Poppea

ABSTRACTS

Giovanni BONIOLO (Milano),
Giovanni.boniolo@ifom-ieo-campus.it
Could mechanisms and the philosophy of cartoon biology vanish?

In this talk I propose a perspective on molecular interactions which could be thought of, if one likes it, as a farewell to the mechanistic talk.

Jean GAYON (Paris),
gayon@noos.fr
Function, Disease and Overcapacity: Causation in a non-normal world

To be communicated

Hillel BRAUDE (Montreal),
Hillel.braude@mail.mcgill.ca
Linking Pain and Pathos: Revisiting the Causal Problematic in Clinical Medicine through Affective Neuroscience

In his genealogical study, *The Birth of the Clinic*, Michel Foucault suggests that modern medicine has succeeded in freeing itself from the causal problematic and the limitations of etiological reasoning. Similarly, Georges Canguilhem claims that medical science is founded upon the duty to assist individuals even if that requires violating the rational, critical pursuit of knowledge. In other words, the scientific requirement of tracing causal relations is less significant than the moral duty to heal. Foucault presents an epistemological rupture with causality and Canguilhem a moral one. Yet, these critiques are related in that both are founded on linear notions of causality. The epistemological and moral issues around causality find an additional nexus in the neuroscience of pain and suffering. The ethics principle of beneficence receives its force from the duty to remove pain and relieve suffering. Contemporary neuroscience is beginning to map the psychological and neural correlates of the affective dimension of pain. The relation between pain and suffering is better understood in terms of circular, rather than, linear notions of causality. This suggests the possibility of combining the epistemological and moral dimensions of causality in a theory of clinical reasoning that does not have to jettison completely notions of causality and the rational pursuit of knowledge.

Lara Katharina KUTSCHENKO (Mainz),
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Why Classify Diseases?

Sound scientific classification is regarded to be an analytical framework that unambiguously defines and systematises key objects of inquiry. It may be used as causal taxonomy if it is coherent with essential theoretical assumptions, thus enabling researchers to explain and predict events (e.g., chemical reactions by means of the periodic table of elements). In medicine, reasoning about *diseases* seems to be indispensible given that a vast amount of current knowledge and practices relies on it. However, the heterogeneous character of diseases challenges their suitability as unambiguous units of classification. Hence, the question arises in how far medical classification allows for causal reasoning. The aim of this talk is to re-assess the rationale of classifying diseases: Medical classifications, I argue, mediate between research approaches and clinical practice with regard to a common, though complex and fuzzy, subject area. To characterise how this works, an analysis of current

classification in use, such as the International Statistical Classification of Diseases and Health-Related Problems, will serve as a starting point. In particular, disease classifications maybe used in quite different ways, namely as resources for practice to standardise diagnoses and codify communication, as resources for research in epidemiology or clinical trial design, and as objects of research in revision processes of classification systems. In focusing on the interconnection between the heuristic role of classifying diseases, the referential function of standardised classification systems, and their broad pragmatic use in health-care administration, I will outline a new approach of characterising the epistemic specificity of medical classification.

Paolo MAUGERI (Milan) and **Alessandro BLASIMME** (Milan),
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Modelling cancer and the problem of disanalogy

So far the philosophical literature on the use of animal models in the biomedical sciences has focused on the analogy between the organisms used as models and the target system. Accordingly, the relevant issues have generally revolved around the notion of representativeness in light of evolutionary distance and on the epistemic value of extrapolations from animals to humans. Given the fact that there are always disanalogies between the model and the target system, some commentators have argued that extrapolations from animals to humans are bound to fail. In particular, they claim that disanalogies due to different evolutionary histories are always causally relevant. Thus, life sciences are epistemically warranted at using them only as heuristic devices, and never as valid tools for causal explanations or for testing hypotheses about human diseases. This approach, we maintain, should be reformed. Current experimental practices enabled researchers to control causally relevant disanalogies between the animal model and the target system according to specific epistemic needs. Although, disanalogies cannot be completely removed in the model – it would otherwise be a *replica* rather than a model – those that are causally relevant to the phenomenon under investigation, can be interfered with at the molecular level. In order to illustrate these features, we will present the cancer stem cell hypothesis as a case study. We will show how successful modelling of human cancer in "humanized mice" points towards an accurate causal understanding of the disease.

John DUPRE (Exeter),
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Emerging Sciences and New Conceptions of Disease

Various developments in contemporary biology are changing our conception of an organism, and hence our conception of what it is for an organism to malfunction, or become diseased. In particular, developments in microbiology are indicating close causal relations between multicellular organisms and their microbial symbionts that suggests that, for many purposes, they should be seen as parts of one polygenomic organism. Dysfunctional development, metabolism, and immunity in humans may all on occasion be due to symbionts rather than failures originating in 'human' cells. Insights from epigenetics suggest a much deeper influence of the environment on physiological development than has often been supposed, and problematise traditional assumptions about the distinction between endogenous and exogenous pathogenesis.
In this talk I shall consider some of the changes in our conception of the human organism consequent on such scientific developments, and make some suggestions about how this might influence our understanding of disease.

Lisa GANNETT (Halifax),
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Context Matters: A Local Epistemology of "Race"

In this paper, I defend a local epistemology of "race" within the context of human population genetics/genomics. By "race", I mean the various overlapping group categories of classification used by researchers (i.e. not just what many consider as race, but also geographical location, ethnicity, nationality, aboriginal status, religion, etc.). I begin with Longino's account of local epistemology as she articulates it alongside her defence of pluralism in science. On Longino's account, the diverse goals motivating researchers in population genetics/genomics promote expectations of a local epistemology of "race". In contrast to the metaphysical pluralism espoused by Cartwright and Dupré, Longino's approach is entirely epistemological. Despite being sympathetic to Longino's disinclination to metaphysical theorizing, I argue that a local epistemology of "race" finds support in the world. Building on Beatty's evolutionary contingency thesis, and based on the ontological claims of theories central to population genetics/genomics, I emphasize the contingency of patterns of human genome diversity and the support for pluralism and a local epistemology of "race" that results. The failure of natural kind theorizing to do what many expect of it when it comes to debates about the scientific legitimacy of "race" in biomedicine (e.g. concerning researchers' use of census categories in the US) provides further support for pluralism and an epistemology of "race" that is local not global. Such debates have resulted in the recommendation that biogeographical ancestry (BGA) be used instead of "race", but I argue that this ignores the ways in which context matters in BGA's emergence as both concept and technology. BGA's value as a global category of classification in population genetics/genomics is negated by its origins in a set of diverse US-based interests—social and commercial as well as scientific—in forensics, gene mapping, pharmaceutical development, and direct-to-consumer genealogy testing. I conclude with examples from Atlantic Canada that help to illustrate what a local epistemology of "race" might look like instead.

Pierre-Olivier METHOT (Exeter and Paris),
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From the 'law of declining virulence' to the 'trade-off model': using historical epistemology to assess a shift in the concept of virulence and disease

For nearly a century bacteriologists and medical researchers contended that the degree of virulence (i.e. disease severity) in any given host-pathogen association would gradually decrease as a consequence of the process of evolution by natural selection. For instance, Frank MacFarlane Burnet held the view that 'if both host and parasite are to survive, a mild, rather long-lasting infection' [...] 'is the most advantageous relationship for both' (Burnet 1953). Accordingly, highly virulent associations were considered as being 'recent and still imperfect development of host-parasite relation' (Chandler 1940). The widespread belief in such evolutionary trend toward commensalism – labelled the 'law of declining virulence' by Theobald Smith (1904) – contributed to shape an 'ecological vision' (Anderson 2004) of infectious diseases. From the late 1970s, however, Smith's hypothesis came under scrutiny and a new picture of host-pathogen relationship began to emerge. On the one hand the rejection of the process of adaptation as being 'for the good of the species' by evolutionary biologists during the 1960s undermined the rationale of the avirulent hypothesis. On the other, with the use of mathematical models epidemiologists showed that the degree of virulence would not necessarily decrease with time, as the previous model postulated. To the contrary, depending on the selective pressures and the modes of transmission virulence will either increase, decrease or become stabilized. Using the methodology of historical epistemology this paper examines this shift by focusing of the work of Smith and the critics that were progressively raised against his evolutionary model of virulence, until its final replacement by the 'trade-off model' in the mid-1980s. It is argued that this change of hypothesis was

accompanied by an important shift in the concept of disease itself. In effect, whereas the avirulent hypothesis conceptualized disease as being a contingent phenomenon, that is, as a 'biologic misinterpretation of borders' (Thomas 1972), the trade-off model indicates that there are no a priori grounds for thinking that disease prevalence will naturally decline in a law-like fashion. Overall, the history of the concept of virulence illustrates the close, but often neglected, relationship between evolutionary thought, medicine and disease throughout the twentieth century.

Susanne BAUER (Berlin),
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Between complexity and restriction. Modelling causation in epidemiology

Epidemiologists often view the history of epidemiology as the "evolution of our ideas as to disease causation". This paper aims at a history that does not focus on ideas but takes its point of departure in practices and tools. I look in particular into the use of visual tools – such as causal maps and arrow diagrams – that mediate between conceptual considerations in study design to the actual statistical modelling. Drawing on both published material and participant observation, the presentation focuses on those numerical and visual techniques that transform the complex disease aetiologies into workable models for epidemiological hypothesis testing. Based on inference testing, epidemiologists test for statistical "associations" between exposure and disease; in order to assess causality, epidemiologists then refer to a set of criteria, first formulated by Bradford Hill in the 1960s and continually developed since then. With genomic epidemiology, novel modelling techniques strive to account for multiple levels and pathways. This contribution will follow various ways to cope with complexity via visual tools from risk factor epidemiology to postgenomics.

Christophe MALATERRE (Paris),
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Downward Causation in Cancer Research: the Experimental Evidence?

The etiology of cancer tumors is often equated with the search for mutated genes, be they oncogenes and tumor suppressor genes that result in abnormal cell proliferation (e.g. Weinberg 1998). However, alternative research programs advocate, rather, to seek the causes of cancer not at the molecular level of the genes but at the tissue level: far from being a faulty gene, the real cause of carcinogenesis would consist in a disrupted tissue organization with downward causation effects on cells and cellular components (e.g. Sonnenschein & Soto 1999, 2008). In this contribution, I ponder how to make sense of such downward causation claims. Adopting a manipulationist account of causation (Woodward 2003), I argue that such claims cannot be taken literally: I propose rather that they be interpreted as artefacts stemming from causal coarse graining. However, I also argue that such downward causation claims might point at particularly interesting structural and dynamic properties of causal networks, and that such properties are crucial to our understanding of causation in complex systems.

Giuseppe TESTA (Milan),
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Taming Through Codes: the Notion of Epigenetic Code in Disease Causation

In this paper I examine the notion of the 'histone code', tracing its recent emergence, its overlaps and differences with the notion of 'genetic code', and the ways in which it is being used to explain complex phenotypic traits, including several diseases. The explanatory framework of the histone code predicts that various combinations of post-translational modifications (PTM) on histones represent molecular signals that guide the recruitment of

PTM-specific effectors and thereby direct a range of specific biological outputs. As such, the histone code hypothesis is part of a larger effort in current biology, that aims at tracing a variety of cellular phenotypes to defined arrays of PTM on many cellular proteins. The attempt to map the manifold functions of the key tumor suppressor p53 onto its full range of PTM is a paradigmatic example of this research trajectory. To this end, a variety of experimental systems were employed. I start by analyzing the conflicting results that emerged from the studies on p53 insofar as they highlight the main epistemic quandaries and the interpretive opportunities and constraints that arise as a result of framing PTM as codes. I then compare the results on the p53 'code' of PTM to the current problems in 'cracking' the histone code, highlighting the key methodological differences between these two fields of inquiry and their implications. The result of this comparison forms then the basis to scrutinize the salient epistemological, technical and discursive resources that underlie the notion of 'histone code' and to define the extent to which it represents merely a useful metaphor or a compelling and rigorous analogy.

Michael ESFELD (Lausanne) and **Christian SACHS** (Lausanne)
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Philosophical Theories of Causation and Biological Functions

The paper argues for a causal-dispositional view of biological functions by contrast to an etiological one, embedding that view within a general theory of causation that is based on acknowledging causal properties. I show how that view paves the view for regarding biological properties as being causally efficacious.

Sandra MITCHELL (Pittsburgh),
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Philosophical Reflections on Robustness and Gene-Environment Interaction in Complex Disease

Understanding the causality associated with complex biological systems raises challenges for scientists, clinicians and philosophers. Take, for example, the genetics of major depressive disorder. Most genes associated with psychiatric diseases are non-Mendelian, rather the causal structure involves multiple causes at multiple levels of organization. There is an influential study supporting the interaction of genes with the environment in generating MDD in adults (Caspi, et. al. 2003) and yet there are other studies to suggest that the interaction effect has not been replicated (Risch, et. al. 2009). Feedback structures are central to the robustness of biological systems, and yet in disease the complex dynamics of feedback can generate an amplified negative effect. These types of complex behaviors require us to rethink some deep rooted assumptions about causal inference from experimental intervention and about the character of causality itself. In this lecture I will explore these philosophical issues.

Steeves DEMAZEUX (Paris),
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Promises and Limits of Mechanistic Explanation in Psychiatry

The philosophical basis of psychiatric taxonomy since 1980 has been the promotion of an “atheoretical” – i.e. a purely descriptive – clinical approach. This decision was part of a heuristic strategy which aimed at fostering epidemiological studies as well as neurobiological investigation on mental disorders. However, such a strategy, which tries to push psychiatry closer to the medical model, has not been very fruitful so far. Actually, none of the more than 200 labels included in the DSM-IV remains uncontroversial inside the field of psychiatry. Even the most “sacred symbols” of psychiatry, as schizophrenia or depressive disorder, still raise questions about their scientific validity and their causal underpinnings. In my

presentation, I will try to show why the ‘mechanization project’ as well as the ‘naturalization project’ (Murphy, 2006) cannot be successful for resolving the most important disagreements in psychiatry. First, empirical findings and epidemiological studies tend to increase rather than decrease the gap between the clinical perspective (accepted descriptions of the surface symptoms of mental disorders) and the explanatory perspective (idealized models of underlying mechanisms). Second, surface features of mental disorders are inescapably normative, and this point undermines the pretensions of psychiatry to rely on purely scientific explanations of mental disorders. Third, evolutionary psychology over the past 20 years has produced a more complex and ambivalent picture of what should count as a mental disorder.

Fridolin GROS (Milan),
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The Limits of Mechanistic Explanation in Molecular Biology

In recent years, mechanistic explanations have attracted increasing attention from philosophers of science. In particular, it has been argued that mechanistic explanations are the model of choice for the biological sciences. Instead of directly invoking fundamental laws of nature, mechanistic explanations describe how regularities in biological systems can be understood in terms of components and their interactions. Whereas traditional models of nomological explanation rely on strong properties of natural laws, mechanistic explanations are able to describe regularities that are essentially contingent and susceptible to failure. However, the conception of mechanistic explanation in biology rests on underlying assumptions that often are not made entirely explicit. It presupposes that the causal flows generating living processes show very robust regularities and only leave their habitual tracks in case of malfunction. However, it is not a general property of complex systems to be "mechanistically" reducible in that way. In order to detect the limits of the mechanistic view it is necessary to adopt a more general perspective. I argue that such a perspective can be provided by describing mechanisms within the framework of dynamical systems. Clearly, the idea of representing biological systems as dynamical systems is not new; however, due to the lack of experimental support, it has for the most part been a rather speculative endeavor. Drawing on recent work by systems biologists I show how high-throughput methods might be able to embed this theoretical framework in experimental practice.

Frédérique THERY (Paris),
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Ontological Diversity of Molecular Mechanisms: Towards a Typology

Whereas philosophers interested in mechanistic explanations usually emphasize the common properties shared by mechanisms, I believe that this issue is better tackled from the angle of diversity. My thesis is that the multiplicity of experimental procedures and techniques developed in connection with the shift to postgenomics has led to point out an ontological mechanistic diversity. Such a diversity is apparent regarding multiples aspects of molecular mechanisms, and is successfully grasped by mechanisms involving non-coding RNAs. First, the number of components of a mechanism, as well as the structure of the interactions (motifs) between these components, vary between mechanisms. The notion of motif, which is a key notion in systems biology, is intertwined with mechanistic explanations, and is helpful to classify mechanisms with respect to their structure. Second, quantitative elements (such as the concentration of components) are increasingly frequently integrated into mechanistic descriptions, in addition to qualitative descriptions. Molecular processes are indeed more and more investigated with high quantitative resolution. The resulting data reveal that the quantitative aspect of molecular mechanisms can exhibit different modalities. Third, dynamic features bring a new layer of complexity to mechanistic explanations. The term 'dynamics', as used by biologists, has different meanings, leading to categorize molecular mechanisms according to their dynamic characteristics. Such an investigation also questions the pertinence

of integrating dynamic features into mechanistic explanations. Fourth, recent studies suggest that mechanisms can exhibit stochastic behaviors. I suggest to distinguish between different kinds of mechanistic irregularities. The ontological diversity of mechanisms stems from the long evolutionary history that shaped these mechanisms, reminding us of the necessity to articulate mechanistic explanations with evolutionary explanations.

Ken WATERS (Minneapolis),
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Why DNS-centered Biological Sciences Succeed

The extraordinary success of DNA-centered research in genetics, cell biology, and developmental biology (GCD) has led many researchers and funding agencies to believe that DNA-centered research into the causes of complex diseases will also be successful. Yet, so far at least, genomic epidemiology has not succeeded. I will show that expectations were raised by mistaken ideas about why DNA-centered approaches in GCD have been so successful. I will extend my recent work on difference making causes and on scientific practices in gene-centered sciences to explain why the causal features of DNA that make DNA-centered approaches in GCD so successful are not the causal features required of DNA for genomic epidemiology to be successful. Understanding why DNA-centered practices work, when they do, helps us understand the kind of knowledge these practices produce and the kinds of situations in which these practices are likely to succeed.

Adam BOSTANCI (Cambridge),
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From RNA Interference (RNAi) to RNA Silencing: the Biomedical Significance of Small RNAs and of Sequence-specific Interactions between NucleicAcids

The 2006 Nobel Prize in Physiology or Medicine was awarded to Andrew Fire and Craig Mello "for their discovery of RNA interference - gene silencing by double-stranded RNA". In recent work, I have carried out a survey of the history of the broader research field that began with the discovery of RNA interference (widely known as RNAi) and that I call 'RNA silencing'. This historical survey was carried out alongside an examination of the patent applications that cover the seminal discovery by Fire and Mello, as well as patent applications that cover subsequent important findings in RNA silencing, in particular by the Tuschl group. In this paper, I will initially sketch the picture and some of the questions that emerge from this historical research. I then consider philosophical issues in claims about the broader importance of RNA interference and silencing for biomedicine. In particular, I examine (1) the relationship between RNA silencing and the central dogma of molecular biology, which is often cited in representations of RNA interference for broader audiences (drawing for example on work by Rosenberg, 2006) and(2) what RNA silencing means with respect to gene-centrism and with respect to the notion of a research tool (as discussed for example by Waters, 2006). I also examine and evaluate (3) the expectations about therapeutic use of RNA interference and silencing and (4) what my analysis can tell us about claims by biotechnology companies that are active in this area. Although I am critical of common representations of RNA interference, I also aim to also provide a positive assessment of the significance of RNA interference and RNA silencing in the context of contemporary biology.

Marta BERTOLASO (Rome),
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Hierarchies and causal Relationships in the Interpretative Models of the Neoplastic Process

The current view of the neoplastic process is that it is not a static circumstance, but an evolving molecular and cellular process, so that the high heterogeneity of phenotypes among different tumours, and even among cancer cells within the same tumour, is another feature of cancer that clearly has to be taken into account.
The aim of this paper is to present a critical analysis of the kind of biological systems identified in the two main interpretative theories of cancer (i.e. *Somatic Mutation Theory* and *Tissue Organization Field Theory*) to explain cancer heterogeneity and its temporal dynamics. Despite the huge amount of data collected through the reductionist perspective in cancer research, which considers tumours as a genetic and cellular disease, no unique causal relationships have been identified to account for cancer origin, progression and heterogeneity. New interpretative theories and models have been challenging the traditional reductionism, moving towards systemic perspectives.
Arguments related to the hierarchical organization of the organism are in both approaches used to account for the neoplastic process, while their explanations diverge due to their opposing epistemological presuppositions. Instead of using a bottom-up explanatory approach, most of them propose that neoplasia should be analyzed at higher levels of biological organization, as a phenomenon arising from the disruption of complex tissue organization where top-down causality play a central explanatory role. However I will show that these reductionist and systemic perspectives are not alternatives in explaining the neoplastic process as they address two different kinds of undetermination and illustrate the reason why their methodological approaches can eventually converge.

Marie Isabel KAISER (Muenster),
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The Diversity of Explanatory Reduction in Biology

Reduction is a topic on which there have been intense and long-standing disputes since philosophy of biology emerged. And these disputes are far from over. On the contrary, reduction seems to be a very important element of actual biological research practice and a frequently discussed subject also within biology itself. Even systems biologists – who claim that their research is explicitly non-reductive and "whole-istic" (Chong/Ray 2002) – spend much time on talking about reduction. Often, however, it remains unclear what, exactly, is meant by references to the allegedly reductive character of biological research and hence the discussion is prone to suffer from ambiguities and misunderstandings. Thus, it is particularly pressing to think about the topic of reduction philosophically and to analyze what exactly 'reduction' in biology means. In order to do this, different *types of reduction* need to be kept apart: ontological, methodological, theory reduction and explanatory reduction. In my talk I focus on the latter which also lies at the heart of the actual reductionism debate in the philosophy of biology. The main aim of my talk is to clarify the concept of reduction in the context of biological explanations, that is, to give an *account of explanatory reduction*. This involves three different tasks: (1) identifying the units of the relation of reduction, (2) elaborating on the reductive character of this relation and (3) explaining how this account can help to capture and shed light on the diverse biological research practice.

Annick LESNE (Paris),
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Genetic Risk and the Rold of Gene-evironment Interplay in Complex Diseases: How Modelling Could Help? The Example of Crohn Disease

Genome-wide association studies comparing the presence of tens of thousands of single nucleotide polymorphims (SNPs) in large cohorts of more than a thousand patients to their distribution in paired cohorts of controls have been recently conducted for several diseases, in particular Crohn disease (an inflamatory bowel disease whose incidence has grown by a factor of ten, up to 1/1000, in developed countries in the last half century). They evidenced more than a hundred of alleles significantly associated with the disease, but with very small odds ratio, between 1.1 and 2 (the largest is around 4 in the case of Crohn disease). I will discuss these results, which point to the absence of any one-to-one association, by far: having a ``wrong'' gene variant is neither necessary nor sufficient for the appearance of the disease, and some control subjects could even have more risk alleles than some patients. Genome-wide association studies thus strongly challenge the notion of risk allele in case of complex diseases (i.e. non Mendelian disorders). Certainly environmental factors play an essential role in complex diseases, in a complicated and non linear interplay with genetic factors. The notion of genetic predisposition of a subject, and presumably the very notion of a ``cause'' for such diseases have to be reevaluated. I will briefly present how we are addressing these issues within a network viewpoint, accounting for the observed nonlinear, non-sequential, and context-dependent causality. In the context of public health, a proper evaluation of genetic risk is essential at two levels. At the individual level, with the hope of developing personal medicine based on genetic profiling. At the population level, to make correct predictions about the future incidence of a disease and decide on efficient preventive actions and policies.

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Multiscale Modelling of Biological Phenomena, Dynamic Mechanistic Explanation, and Scientific Perspectivism

My lecture is inspired by microbiologist Carl Woese's dictum that "a society that permits biology to become an engineering discipline, that allows that science to slip into the role of changing the living world without trying to understand it, is a danger to itself" (Woese 2004: 173). From a societal perspective, any adequate understanding of health and disease in the postgenomic era will require us to go beyond 'esoteric' scientific knowledge ("mode one"), let alone engineering knowledge that heavily depends on "kludges" as evidenced by synthetic biology, systems biology, etc., and take into account knowledge sustained by more diverse and inclusive social relations ("mode two") as well (Barnes 2003). The theses I will develop and defend in my lecture are: (1) In terms of the "causation" referred to in the title of our seminar, the new *mechanistic philosophy of science* developed by Bechtel, Cartwright, Craver, Darden, Glennan, Machamer, Wimsatt, and others offers the most plausible account of explanation and understanding available for philosophical reflection on biomedicine today. It reflects on the explanatory endeavor most practicing scientists in the field focus on—the (reductionist) decomposition of mechanisms into component parts and operations. But it should pay more attention to the converse ('systemic') endeavor of recomposing components into a mechanism organized so as to produce the phenomenon targeted for explanation. "Real biological mechanisms exhibit complex orchestration of operations in real time, often involving one or more feedback processes and non-linear interactions among operations" (Bechtel 2010). DST (= dynamical systems theory, not to be confused with something else!) points the way. (2) *Multiscale modeling*, which I (Callebaut 2009) define as any kind of modeling, computational or other, that includes components from two or more levels of the scientific ontological hierarchy (from the quantum-mechanical to the ecological) of (biological) organization and/or multiple time scales (from, say, the 1 μs characteristic of

Brownian motion to the 10^9 s of a human lifetime), is an ideal test case for the new mechanicism. Although multiscale modeling originated in computer science, engineering, metereology, and physics and is still peripheral to biomedicine at present, multiscale models of, say, angiogenesis, the physiological process involving the growth of new capillary blood vessels from pre-existing ones (Qutub et al. 2009) will arguably become more prominent in biomedicine as well. (3) *Scientific perspectivism* is the appropriate philosophical stance to deal with a number of epistemological, methodological, and ontological challenges that modelers of complex, multiscale phenomena are facing. Perspectivism (Leibniz, Nietzsche, I would add William James…) is the philosophical position according to which one's access to the world through perception, experience, and reason is possible only through one's own perspective and interpretation. Scientific perspectivism extends this position to *scientific* observation and theorizing.

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Biological specificity and the causative role of genetic information.

Since the very beginning of the 'molecular revolution' in the early '50s, genetics and genomics have made intensive use of metaphors based on information, language and communication. The epistemological status of these metaphors is rather problematic. In same cases, they are used as simple models or images, as rhetorical tools, but in other contexts they play a fundamental role in the explanatory structure.
The lecture will explore historically the construction of the language of molecular biology, analyse the epistemological status of the linguistic metaphors and suggest that information in biology should be considered as a specific form of causality, responsible for the production of biological specificity.

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Final Discussion and Outlook

In the final session we will summarize the threads of the discussion and identify loose ends.

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