Knowledge production in experimental molecular medicine

Primers for a reflexive life knowledge.

Kunnskapsproduksjon i eksperimentell molekylær medisin

Primerar for ein refleksiv livskunnskap.

Thesis submitted for partial fulfilment of the degree Master of Philosophy.

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The real is never "what one might believe"; it is what one should have been thinking. Empirical knowledge is lucid only after the event, after the apparatus of reasoning has been set in motion.

- Gaston Bachelard 1938 (1969) *The Formation of the Scientific Mind* p.13.

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Samandrag.

Eksperimentell molekylær medisin har dei siste 60 åra vakse til å bli ei stor grein innan dei medisinske vitskapane. Eksperimentell molekylær medisin studerer korleis dei biologiske makromolekyla protein, karbohydrat, nukleinsyrer (DNA) og lipid påverkar helse og sjukdom. Kunnskapen frå den eksperimentelle molekylære medisinen har forma vår forståing av liv og av sjukdom.

I denne studien har eg stilt spørsmålet om korleis eksperimentell molekylær biologi produserar kunnskap. For å kaste lys over denne problemstillinga har eg diskutert to linjer innan vitskapsfilosofien og medisinen. Den første er korleis Claude Bernard i den tidlige Franske positivismen si ånd utvikla eksperimentell medisin som vitskap. Den andre linja eg har diskutert kan representerast av tenkjerar som Gaston Bachelard, Bruno Latour, og Hans-Jörg Rheinberger. Dei peika på at dei sosiale, teknologiske og historiske faktorane som spelar inn i kunnskapsproduksjonen.

Eg har freista å gi ei forståing av eksperimentell molekylær medisin som integrerer sosiale, teknologiske og materielle faktorar. Den eksperimentelle tilnærminga til liv og helse er mogleggjort av eit syn på liv som utelukkande bygd opp etter fysiokjemiske lover. Det eksperimentelle arbeidet er teoretisk-praktisk, og det eksperimentelle systemet dannar ei teoretisk-materiell matrise av forståing der nye fenomen kan dannast. Kva eksperiment som skal gjerast, og dermed kva kunnskap som skal produserast, er ei avveging mellom ulike praktiske og taktiske omsyn. Forskarane vil søke å maksimere produksjonen av viktige vitskaplige utsegner. Dei vitskaplige utsegnene vert gitt verdi etter om dei er meir eller mindre relevante for vitskaplige og medisinske målsetjingar.

Det andre spørsmålet eg har stilt i denne oppgåva er om ein filosofisk refleksjon over kunnskapsproduksjonen kan føre til ein vitskaplig sjølvrefleksjon, kritikk, og endring av kunnskapsproduksjonen. Georges Canguilhem har vist korleis vitskaplige omgrep opnar for nye vitskaplige spørsmål, forståingar og teoriar. Canguilhem utvikla omgrepet "biologisk normativitet" - at det levande grunnleggande kjenneteiknast av at det ikkje er likegyldig til sin eigen tilstand. På bakgrunn omgrepet "biologisk normativitet" dette har eg forsøkt å diskutere korleis molekylær medisin kan endrast ved å legge meir vekt på å forstå korleis molekylærbiologiske fenomen fungerar i ein biologisk og medisinsk kontekst.

Aim of study.

In thousands of molecular medicine research laboratories in the world people are every day crouching over their experiments. Every year governments and private organizations direct large amounts of funding into these laboratories with the hope that their scientific work shall bring health and prosperity. Every year the number of research papers indexed at the biomedical database PubMed has been steadily increasing, passing 800.000 per year in 2008[1].

During the latter 60 years this companionship between medicine and molecular biology that is molecular medicine has yielded not only new types of diagnosis and therapy. It has sparked debates concerning ethical, political, and philosophical dimensions, such as what it is to be human, and what possibilities there are there and should there be for intervening in life. R. Reininger claimed that our image of the world is always a display of values[2]. The position of experimental molecular medicine in our society is also a reflexion of the view of life and health in our society.

The focal point for this study is the process by which by the researchers produce knowledge in experimental molecular medicine. My main question raised is: *how does the researcher produce knowledge within the field of experimental molecular medicine*. I am myself a researcher within the field of molecular medicine. Every morning I head for the laboratory/office for new experiments, new hypotheses, and reading papers; training in conducting experiments in order to gain relevant and trustable knowledge. Therefore, a second question in this work is: *can a philosophical reflection over the knowledge production in experimental molecular medicine go into a self-reflection and change of the knowledge production itself?*

The objects of study for molecular medicine are the biological macromolecules defined as proteins, nucleic acids, carbohydrates, and lipids, and how these relate to human health and disease. Experimental molecular medicine is based upon the presupposition that the

[1] http://preview.ncbi.nlm.nih.gov/pubmed/

[2] "Unser Weltbilt is immer zugleich ein Wertbilt", Reininger, R., *Wertphilosophie und Ethik Die Frage nach dem Sinn des Lebens als Grundlage Einer Wertordnung*, 1939. Vienna-Leipzig, Braümuller, p. 29. Quoted in Canguilhem 1991 p. 179.

physiochemical workings of the biological macromolecules are relevant for the state of the organism. Knowledge about the organism at a molecular level will thus be relevant for prevention and treatment of disease. This frames and motivates experimental molecular medicine as a knowledge-producing activity.

This object of study of experimental molecular medicine brings with it some important characteristics. First, the high complexity of biological systems makes generalizations and predictions difficult in biological sciences. The planning and interpretation of experiments is dependent on the specific knowledge about the particular phenomenon studied. Molecular medical knowledge takes the form of an elaborate network of statements about particular phenomena rather than a system of principles and laws. Secondly, the medical notions of "health" and "disease" show that it is not life itself that is the object of study. It is rather the pathological states, and how these can be detected, prevented and cured.

The methodological principle for studying life at the molecular level in experimental molecular medicine is the controlled experiment. Experiments are designed on the background of observations and previous knowledge. There are some considerations that I will emphasize connected to the experimental approach. First, the experimental setups used to study life at a molecular level are themselves are technological results of a scientific process, and thus they *embody scientific concepts*. Secondly, the experimental approach is just that: an approach. It produces a certain type of knowledge, and which further shape the resulting understandings about the molecular level of organisms. Thirdly, the experimental process is a practical process. Therefore the process of knowledge production is dependent on the performance of the scientists, and the output of the process is dependent on the choices, priorities and organization of the practical process.

Taken together, this emphasizes the importance of understanding knowledge production in experimental molecular medicine as a *theory-practice*: it is theory and practice at the same time. The theoretical knowledge within the field is shaped by the experimental approach, and the experimental process which directly involves the theoretical knowledge. The theory is value-laden through the connection to medicine, and this further affects choices and decisions in the experimental conduct. In order to understand the knowledge production of experimental molecular medicine we need concepts that can capture its hybrid characteristics. In this work I will try to give a description of experimental molecular

medicine that captures these hybrid aspects: how is experimental molecular medicine constituted as an approach for studying life and disease? What is the relation between theory and practice, and how is the scientific conduct performed in order to produce statements about the world?

In part 1 I will present some thinkers that have addressed the question of how knowledge is produced in the experimental life sciences. The development of medicine as a scientific discipline has been connected, at least in France, to positivist philosophy. I will therefore briefly describe positivist philosophy and its connection to the development of medicine, before I go more into detail on how Claude Bernard established the principles of experimental medicine as a scientific approach. Further, I will give a short overview of some thinkers that criticized the positivist approach to science, and emphasized the historical, situated and subjective aspect of scientific work, before I look at how Steve Woolgar & Bruno Latour, and Hans-Jörg Rheinberger have studied the practice of experimental molecular medicine. This presentation of is neither a purely historic nor systematic presentation. The aim is rather to give a context for the discussions, problems, and approaches presented in this work. I will end part 1 by discussing these works with respect to the questions raised in the aims of this work.

If scientific activity is specific, context-dependent, and situated, a source of important addressing specific scientific cases is an important source of insights. In part 2 I will present a case study of a work within experimental molecular medicine, namely the NAT-research group at the University of Bergen. This case study is not chosen randomly: I am myself working within this project. As I am myself an actor and a stakeholder in the project, I am aware that this will color my study. On the other hand I have detailed knowledge about the field and the process. Indeed, seeing the long-standing tradition of self-reflection in philosophy of science, this subjectivity and involvement will also hopefully yield some interesting perspectives.

In the part 3 I will use the case study from part 2 and the theories presented in part 1 to try to give an account of how knowledge is produced within the field of experimental molecular medicine. More specific, I will try to understand how the preconditions of experimental molecular medicine are tied together with the practical-theoretical process of knowledge production, and what kind of knowledge is the output of this process. I will try to develop

some of the notions and theories given in part 1 to formulate the experimental approach of molecular medicine as a value-laden, situated theory-practice co-produced together with a certain view of life and disease.

An understanding of experimental molecular medicine as both practices, knowledge production, and world views, will enable us to intervene in the theory-practice in order to reflect upon the values and views that exist within the field. In part 4 I will address the second question of this thesis, namely whether a philosophical reflection over experimental molecular medicine can go into a critical reflection and intervention of the science itself. To address this, I will first discuss how Canguilhem develops the notion of normativity of life as an alternative to the reductionistic emphasis of the experimental medicine. Secondly, I will discuss whether there exists conceptions of life in the molecular life sciences that address what Canguilhem calls the original aspects of life. Thirdly, I will see whether these conceptions together with Canguilhems normative biology can form the basis for a re-thinking of the experimental life sciences, before I in part 5 will come with a conclusion of the work.

1. Philosophy of the experimental life sciences.

The laboratory as a place for conducting controlled experiments emerged in the mid-19th century. The laboratory proved itself fruitful in generating new knowledge about organisms. In the 20th century technological developments made it possible to study organisms at a sub-cellular level, and molecular biology emerged as a scientific discipline. In addition to the technological basis, molecular biology included elements from genetics, biochemistry, microbiology, physics, chemistry, and informatics. The development of molecular biology was closely attached to medicine, continuing the laboratory tradition from experimental medicine (Rheinberger, 1990).

I will start by drawing up two lines of understanding science which are both important for understanding the development of experimental molecular medicine as a science, and for understanding how the scientific activity is socially, technologically and practically constituted. The first line of thought is represented by the early French positivism. The positivism of Comte and others was concerned with describing a scientific rationality, where the scientific conduct is governed by logical and rational principles. This positivism was connected to the establishment of several of the natural sciences in the 19th century, including medicine. It is therefore interesting with respect to how experimental molecular medicine gained its foundation and legitimacy. The other line of thought is that part of philosophy in the 20th century that pointed at scientific knowledge production as a social activity situated in particular places at particular times. The works of Gaston Bachelard, Michel Polanyi, and Michel Foucault exemplifies this line. These works problematize the view of science as a rational activity that produces objective knowledge about the world. They show several of the values, practical aspects and social mechanisms that constitute scientific work as a temporally and spatially situated activity. Indeed, it is these works that have highlighted the hybrid aspect of science.

In the following of part 1 I will go more into detail of some thinkers that address the problems raised in the above presented lines of thought. In order to understand the basis of experimental molecular medicine I will go through the principles of experimental medicine, as formulated by the physician Claude Bernard in "Principles of experimental medicine". Further, I will briefly go through how thinkers like Ludwik Fleck, Gaston Bachelard,

Georges Canguilhem, and Michel Foucault developed a philosophy where science was seen as a historical, situated and context-specific activity, and where the knowledge produced by the scientific activity was a result of multiple social, material, and technological factors. The conduct of experimental molecular medicine as knowledge producing activity will be addressed by going through the work "Laboratory Life" by Bruno Latour & Steve Woolgar. In this work Latour & Woolgar describe some social and rhetorical factors that are part of the knowledge producing process. They problematize how a social and situated process gives rise to what the participants of this process call "true statements about the world. Then, we will look at how the philosopher Hans-Jörg Rheinberger investigates how the practice and technology of experimentation is connected to the body of knowledge in order to produce new knowledge. In the end of part 1 I will summarize the presented works and how they contribute to the aim of this study, namely to get an understanding of how experimental molecular medicine produces knowledge.

1.1 Positivism.

1.1.1 Positivism and the development of medicine as a scientific discipline.

Positivism[3] can be described as "a philosophical system that holds that every rationally justifiable assertion can be scientifically verified or is capable of logical or mathematical proof, and that therefore rejects metaphysics and theism"[4]. Thus, positivism holds rationalism and logic as central to thought. Positivism was closely connected to the development of the natural sciences, and these sciences were seen as the prime example of a rational, systematic, and logical understanding of the world. (Gutting, 2001 p. 8).

The positivist approach was challenged during the mid 20th century, but its influence is still seen in later attempts to define rules of scientific reasoning and logic, found for example in rationalist philosophy and in what has been called "the received view" (Suppe, 2000). Also, as science has grown, several scientists and pundits (e.g. Francis Crick[5] and Richard

[3] The French philosopher *August Comte* (1798-1857) coined the term “positivism”. Comte was a central figure within what is called the first wave of positivism that emerged in France during the first half of the 19th century.

[4] New Oxford American Dictionary in Apple Dictionary Version 2.1.3, 2005-2009 Apple Inc.

[5] «You», your joys and your sorrows, your memories and your ambitions, your sense of personal identity and free will, are in fact no more than the behavior of a vast assembly of nerve cells and their associated molecules". Crick F., 1994. *The Astonishing Hypothesis. The Scientific Search for the Soul*, Charles Scrib- ner’s Sons, New York.

Dawkins (Dawkins, 2006)) have taken positivist-like positions. Thus, positivism continues to have a significant influence on the debate around the status and role of science and scientific knowledge.

Medicine as a scientific discipline was established in the late early/mid 19th century. The problem of medicine was that it had a long tradition of craftsmanship, but it lacked systematic understanding and the ability to predict observations. In France, several philosophers and medical doctors tried to develop a scientific foundation for medicine. Among these were Pierre-George-Jean Cabanis, August Comte and Claude Bernard. Positivism was one of the philosophical movements that engaged in the establishment of a medical rationality (de Cuzzani, 2003). An important factor in this process was the objectification of disease. Through the introduction of several types of apparatus, such as the stethoscope, the focus of the clinician was changed from the "subjective" symptoms of the patient to the "objective" signs of the disease (de Cuzzani, 2003 p.32). Such signs could be systematically analyzed, and this led the way to the laboratory as a place for scientific medical analysis. In order to establish a scientific and objective medicine, Bernard proposed the controlled experiment as approach for obtaining medical knowledge. For Bernard the controlled experiment represented a material analysis, and the only way the scientist in a logical and controlled manner could get knowledge from the object of study.

1.1.2 Claude Bernard and the principles of experimental medicine.

Claude Bernard (1813-1878) was a French physiologist who is known for his major discourse on scientific method, "An Introduction to the Study of Experimental Medicine" (1865) (Bernard, 1957)[6]. He revolutionized medical science by developing a scientific experimental methodology based on a strict marriage between physiology and the underlying laws of physics and chemistry. Thus he was an important figure in establishing medicine as an experimental science. It is this role that makes Bernard a suitable starting point for this study.

[6] I have in this section based my discussion of the work of Bernard on "An introduction to the Study of Experimental Medicine". As my aim has been to draw out, present, and discuss some concepts and aspects of the philosophy of Bernard that are recurrent throughout the text of Bernard, I have of practical reasons not given the citations to the exact sections, page numbers etc. throughout the text (except when direct citations are used). This is also the case for some other works I have presented in detail in this thesis, where this is indicated.

Bernard stated that the scientific goal of medicine is the same as for all sciences: to understand the laws of the phenomena so as to foresee, vary, or master these phenomena. For medicine more specifically, the aim is to conserve health and cure disease. This leads to the three branches of medicine, namely physiology: the study of normal conditions of life and health, pathology: the study of morbid conditions and the prevention of these, and therapeutics: the cure of disease with medical agents. For medicine to be scientific it needs to be founded on physiology, have a comparative method, and take an analytical form (Bernard, 1957 p. 2). Both pathology and therapeutics shall rest on the same foundation: experimental physiology.

The experimental method was for Bernard to submit ideas to experience, where the only form for reliable explanations were material causality - cause and effect in physiochemical relations. Today this is a presupposition for experimental medicine, but at Bernard's time, this was not obvious. Vitalistic views commonly held at the time stated that the phenomena of living organisms were due to forces that were qualitatively different from physiochemical laws; they were due to vital forces within the organism. From this vitalistic view, experimental intervention in the organism would disturb the vital forces and thus destroy the quality of life itself. Such interventions would therefore be of no sense to medicine. But Bernard held that the spontaneous properties of organisms were a result of *underlying physiochemical mechanisms* (Bernard, 1957 p. 61). Rather than terminating the enquiry of a phenomenon due to vital forces, the physician should perform an experimental intervention to unravel the underlying causes of the phenomenon. If medicine wanted to be scientific, biology had to be absolutely deterministic, using controlled experiment as its method.

Bernard pointed at the experiment rather than the clinical observation as the scientific foundation of medicine. Observation in the clinic is not sufficient for unveiling the true causes of physiological functions or pathological states. The observation needs to be reformulated into a question that can be tested experimentally (Bernard, 1957 p. 12). Where the observer studies phenomena as nature shows them without varying their conditions, the experimenter disturb the phenomena in order to make them present themselves *in ways nature does not show them.* Doing an experiment is always an intentional act that produces a disturbance of the phenomena that are studied. By designing an experimental setup the experimenter will make nature reveal itself, and she/he will get the answer to the posed question and an explanation of the observation. Thus, an observation sparks an idea, which is

posed as a question, and the question is tested by a controlled experimental comparison. In this way the experimental method subjects the physician's ideas to experience in an ordered manner.

According to Bernard, observation and experiments are two of the elements in scientific enquiry. In addition to observation and experiments the scientist needs ideas and facts. As mentioned above, the experimental intervention must start with an idea or question posed on the basis of an observation. From the observation the formulation of an idea is done through a kind of intuition where the experimenter catches sight of probable explanations for the observations. These explanations are on the previous knowledge within the field. Ideas and observations are, together with facts and experiments, the elements that build the scientific method. Facts are the necessary materials for thinking about nature. The facts are obtained by experiments. Ideas are given their content by facts, and the ideas makes up the statements about nature that embody science. A scientific hypothesis is a scientific idea that is controlled experimentally. Reasoning gives form to ideas so that the facts produced from the experiments leads back to an idea, which again can be tested experimentally. The experimentally derived fact in itself is nothing without a connected idea that gives an understanding of the phenomenon.

Importantly, the experimenter must not let the preconceived idea be too dominating: the experimental output alone should determine whether the idea is correct or not. This is indeed a point that Bernard stresses: man has a tendency for making generalizations and for clinging to his ideas. One should therefore be aware of the "fake men of science" that create general theories and systems without subjecting them to experimental testing. Man does not contain within himself the knowledge and criterion of external things, and the systematic experience - the experiment must therefore be the sole authority to which all ideas must be subjected and tested (Bernard, 1957 p. 28). Through the experimental process, mans pride is lessened as he sees that the objective reality of things will forever be hidden. The scientific truth, which is the one the scientist can grasp, is the relations between things. Unravelling these relations is the goal of all sciences. Interesting with respect to the historical epistemology of Bachelard and Canguilhem, Bernard claims that the experimental truths rest upon unconscious conditions in the scientific rationality and thinking, and they can therefore only be known in their relation to the present state of science. No matter how novel or great their ideas are, scientists and their ideas is always a product of their time.

Bernard's caution towards generalities also transfers to how medical and biological phenomena are described. There is a pitfall, he says, in giving the words used to describe phenomena too much emphasis. They do not have meaning in themselves except for the phenomena they refer to. If words are put before the phenomena they describe, they bear with them generalizations, systems and doctrines, promoting personal views. For Bernard, and I will claim that this is a widespread view in the natural sciences, the material is seen as the primary. How the material is expressed or represented in some way through language is secondary. That does not mean that it is not important. Nor does it mean that Bernard has a naïve view on the relation between the objects of study and how they are described or represented by language and symbols.

The deterministic program is not unproblematic for Bernard. Phenomena always appear as a result of relations with their environment. For organisms this environment can both be the external environment or the *milieu interieur,* the internal environment, of the organism. Indeed, the internal environment is an important notion for Bernard. Bernard used the internal environment to explain the spontaneous phenomena of organisms. Organic phenomena seemed spontaneous, but they were the result of the physiochemical mechanisms made possible by the internal environment of the organism (Bernard, 1957 p. 61). Also, the internal environment in different parts of the organisms makes possible the study of constituents of the organism independent of the organism as a whole. This is a presupposition for the experimental intervention. But, when the experimenter intervenes with an organism the internal environment will to some extent be disrupted. It is only for the sake of ease in the experimental analysis that the experimenter breaks up the organism.

When we wish to understand the true physical quality and significance of the phenomenon, claims Bernard, we should always refer to its role in the whole. After the experimental analysis one should synthetically reconstruct the total organism in thought, reuniting and ordering the parts determined by analysis. But this process is indeed not simple additions or subtractions, but rather synthesis of complex units. When studying life one should therefore include the study of the organic environment. Bernard here touches upon what separates biology and medicine from chemistry and physics: the vital creation that unfolds through both evolution and the specific life of an organism (Bernard, 1957 p. 93). This is not a re-introduction of vital forces, for although complex, organisms are nothing more than

physiochemical properties. It is the *organization* of living organisms makes them qualitatively different from the non-living.

Complexity makes analysis difficult. Even simple deductions are uncertain. The experimental analysis aims at disassociating these phenomena in order to reduce them to simpler relations. But despite this there is always insufficiency in an experimental setup. The experimenter is dependent on a good experimental setup in order to do adequate tests. Indeed, it is the skill of the trained experimenter to design and perform good experimental setups. For this, the laboratory is a necessary condition. It is a place for withdrawal, where the experimenter can analyze phenomena in a setting disentangled from their complex context.

According to Bernard, the skill of experimental physiology is only learned in laboratories. I interpret this as an emphasis on experimental medicine as craftsmanship, where the practical factors of experimental performance are necessary for an adequate outcome. The material analysis of Bernard has been a tremendous success, leading from physiology to cell biology, and further on to the molecular biology of the 20th century. In establishing a method and approach to study life, Bernard also established a certain view of life: the physiochemical. Although Bernard states the importance of totality and organization in organisms, his experimental method is an approach that mostly produces knowledge of the constituents of biological phenomena. The view of Bernard that the cause of biological phenomena is found in underlying physiochemical processes has had a large influence on medicine. These are some of the aspects of the work of Bernard that were problematized by Georges Canguilhem and will be more thoroughly handled in part 4.

1.2 Situatedness and subjectivity of scientific activity.

Until 1950s theories inspired by positivism (logical positivism) were the leading philosophy of science in the English-speaking world. Today its influence persists. Stephen Hawking wrote recently:

"Any sound scientific theory, whether of time or of any other concept, should in my opinion be based on the most workable philosophy of science: the positivist approach put forward by Karl Popper and others. According to this way of thinking, a scientific theory is a mathematical model that describes

and codifies the observations we make. A good theory will describe a large range of phenomena on the basis of a few simple postulates and will make definite predictions that can be tested… If one takes the positivist position, as I do, one cannot say what time actually is. All one can do is describe what has been found to be a very good mathematical model for time and say what predictions it makes." (Hawking, 2001 p31)

But from the middle of the last century there was an increasing interest in looking at science as a historical and social activity. Several lines of thought, both from scientists and philosophers in Anglo-American and French philosophy, addressed the situated aspects of scientific knowledge production.

1.2.1 Subjectivity and incommensurability.

One of the earliest works describing the situatedness of knowledge production was Ludwig Fleck's "The Genesis and Development of a Scientific Fact" (Fleck, 1976)[7]. The first English translation of this book was published in 1976, then with a foreword of Thomas Kuhn. A central notion in the work of Fleck was the *thought collective*; knowledge was produced in a social environment through a specific "thought style". Thus, the knowledge was not only a product of rational and logical investigations of the world, but also of the social process in the scientific community.

Another early book that criticizes the positivist position of science is "Science, Faith and Society" (1946), by Michael Polanyi (Polanyi, 1964). He argues that positivism fails to recognize the role that subjectivity plays in the practice of science. Later Polanyi developed the concept of *tacit component* of science (Polanyi, 1958). According to Polanyi, there scientific knowledge depends to a large extent on the idiosyncratic and practical craftsmanship of scientific investigation. Through a subjective process the scientist goes into the theoretical-practical situation that constitutes a scientific work. Through investing time and effort in a field, and embodying skills through tacit knowledge, the scientist gets committed to the area of study. This commitment makes it possible to further pursue interesting problems and creating a focus that is needed to resolve complex problems, but also creating a way of thinking, a "personal knowledge". Thus, for Polanyi, scientific knowledge is decentralized and, at least partly, discontinuous. A branch of science can in

[7] *Entstehung und Entwicklung einer wissenschaftlichen Tatsache. Einführung in die Lehre vom Denkstil und Denkkollektiv* Schwabe und Co., Verlagsbuchhandlung, Basel, 1935.

this way develop a framework for conducting and understanding science that is incommensurable with respect to other branches.

The landmark event in the debate of philosophy of science in the English-speaking world was the notion of paradigm shifts, as developed by *Thomas Kuhn*, widely used far beyond philosophical circles. In his work from 1962, "The Structure of Scientific Revolutions" (Kuhn, 1996) Kuhn attacks the view of the positivists that science is a rational activity. Kuhn draws upon both Polanyi's description of the idiosyncratic and practical aspects of science, as well as Ludwik Fleck's notion of "thought collectives" that maintain certain thought styles (Fleck, 1976). If one studies the history of science, said Kuhn, one will find periods of developed science followed by breaks with the established scientific paradigm, and a development of a new scientific understanding that is incommensurable with the previous understanding. Science has throughout history existed as different paradigms, with different presuppositions, values, problems, and methods.

1.2.2 Historical epistemology in French philosophy.

In the first half of last century, an autonomous reflection on sciences was developed in France; it originated from a critical reflection on science's historical development. Schematically, this position can be summarized in this way: since the philosophy of science is a reflection on theoretical and experimental procedures of science, it must take as its starting point the history of science. (de Cuzzani, 2003 p. 61) Therefore, thirty years before Kuhn, Gaston Bachelard thematized the historical and situated characteristics of science in a series of books, including "Le nouvel esprit scientifique" (1934; English translation, 1984) and "La philosophie du non" (1940; English translation, 1964), (Bachelard, 2006; Bachelard, 1988).

Bachelards work was structured as case studies of concrete scientific situations, where knowledge of both scientific detail and historical and philosophical theory played equally important roles. Bachelard claimed that science was a rational activity, but using case studies he showed how there was different local scientific rationalities within different fields, or even within one field at different times. He pointed at the discontinuities in scientific history: science is not a steady process of increase in knowledge. For science to progress there must be epistemological breaks where new scientific understandings break with the logic and presuppositions of the previous understanding. The philosopher of science must go into

detail in specific scientific cases in order to give an adequate philosophical account of science (Rheinberger, 2005).

Bachelard also emphasized the role of technology in the scientific work. Instrumentation used in experiments is the result of previous scientific work, and therefore theories are embodied into technological devices. Instruments are theories materialized, and new scientific findings are given concrete reality in a "technique of realization" in what Bachelard called *phenomenotechnique*. As scientific theories are materialized in the apparatus of scientific enquiry, theory testing cannot be separated from theory. Rather, the scientist uses technology to *invent* phenomena. Thus, technology is not a by-product of scientific activity, but the theoretical-material part of the matrix of understanding that enables the production of new material-theoretical phenomena. Technology is used unite theoretical conceptions of material phenomena and the matter of interest. This enables the scientist to manipulate the matter so to produce or construct new phenomena (Rheinberger, 2005). Rather than revealing truths about nature, scientist create their own objects, and these objects gain their meaning only within the understanding and approach of the particular science (Castelão-Lawless, 1995).

George Canguilhem in the wake of Bachelard, developed a epistemological history of science (Lecourt, 1975 p. 163). According to Canguilhem the task of the philosopher of science is to try to reconstruct the sciences according to each science own history. Canguilhem argues that the history of science is a particular form of history, because its subject is a special kind of object: the historicity of the scientific problems (de Cuzzani, 2003 p. 83). The fact that the scientific problems are historical, involves that they cannot be conceived independent of the historical research process. An important insight for this is that there is a relationship between the conception of the world that is established by the science, and the approach that is used by the scientists to study the world. The task of philosophy of science consists in discovering and analyzing the problems posed or evaded, resolved or dissolved by the actual practice of scientists. To accomplish this task Canguilhem proposes an epistemological investigation of the historicity of the production of scientific concepts. As formulated by Lecourt:

"It is understandable that Georges Canguilhem should have concentrated his attention on the condition of appearance of concepts, i.e., ultimately, on the conditions which make problems formulatable." (Lecourt, 1975 p.173)

Concepts permit to formulate scientific questions and theories represents the scientific answers. Moreover, Canguilhem argues that one and the same concept can take place in different theories (Gutting, 2001 p. 229).

Michel Foucault (1926-1984) inspired by both Bachelard and Canguilhem (Gutting, 2001) p. 86) developed Bachelard's notion of epistemological breaks into a project of showing that concepts and practices that present themselves as a-historical necessities are historical and contingent. Foucault described this project as an effort to discover the unconsciousness of our knowledge, and also to see how breaks with the established discourses could take place at particular times and places (Gutting, 2001 pp. 258-288).

It was important for Bachelard, Canguilhem, and Foucault to study the historical and social conditions for knowledge production. Foucault calls the works of Bachelard and Canguilhem *historical epistemology* (Utaker, 2009). In a culture there will be certain views of what type of knowledge is important and how this knowledge should be obtained or produced. This will constitute what types of questions are asked at a given times, and what practices which are developed to meet these questions. Investigating concrete cases of scientific activity and how this activity was constituted at a given place at a given time would both show both how the activity emerged, was sustained, and also how it decreased or was replaced at a later time.

Foucault investigated the conditions of knowledge production. In a Kantian line, Foucault claims that there are forms that make possible the production of certain types of knowledge. For Kant these forms are *a priori* universal, and they determine the validity of statements; for Foucault they are *a priori* relative to that which is conditioned. Foucault here sets up two types of conditions for the production of a statement: the existence conditions, that make it possible for a statement to be formulated at all, and the validity conditions that determine whether the statement is true or false (Utaker, 2009). Indeed, both Bachelard and also Canguilhem show that the forms of knowledge production are relative, and to point at how the existence conditions and validity conditions are established, exercised, and changed.

1.3 Understanding experimental molecular medicine as a hybrid activity.

Throughout the 1960s and 1970s a wave of thinkers elaborated on the historical and situated aspects of science. Several of these drew upon anthropology and sociology for understanding science itself and the role that it plays in western culture. This led to a commonly held social-constructivist view of science: where the positivists had stated that science dealt with a-historical necessities, the social-constructivist view questioned whether anything in science could be explained by reference to necessities in the material world (Lübcke, 2003 p. 267). An example of such works is "Laboratory Life" by Bruno Latour and Steve Woolgar.

Bruno Latour's philosophical development is also characteristic for a trend in this tradition of philosophy of science. From the social constructivist position in his early works, he later tries to see how material agency plays a part in the both social and material activity of scientific practice (Latour & Woolgar, 1986; Latour, 1993). Other thinkers that have thematized the role of material agency in the social, technological and situated scientific process is Ian Hacking, Hans-Jörg Rheinberger and Andrew Pickering (Hacking, 1983).

In his work "The Mangling of Practice - Time, Agency, and Science" (Pickering, 1997) Pickering tried to give an account of the interplay between scientific practice and material agency. Pickering picks up a thread from Bachelard, who claimed that material agency revealed itself through resistances. Pickering describes the experimental process as a process of accommodation, resistance, and tuning: the scientist has a hypothesis, an anticipation or an idea that he/she wants to investigate. An experimental setup is made to arrange the material agency in such a way that it can give information about this hypothesis, idea or anticipation. If no sense can be made out of the activity of the material agency, the scientist has encountered a resistance stemming from a shortcoming in the understanding of the matter. From this the scientist has to evaluate and change his/hers understanding, tune the experimental setup, and try a new accommodation. This process is repeated until the scientist is able to obtain meaningful information from the material.

I will in the rest of this section discuss the role of social, technological, and rhetorical factors in the concrete research process of experimental molecular medicine. I will do this through a presentation of the work "Laboratory Life - The Construction of Scientific Facts" by Steve Woolgar and Bruno Latour (Latour & Woolgar, 1986), before I give a closer look at the

experimental system as a system of knowledge production through a presentation of Hans-Jörg Rheinbergers work "Towards a History of Epistemic Things - Synthesizing Proteins in the Test Tube" (Rheinberger, 1997).

1.3.1 Laboratory Life: an anthropologist visits the laboratory.

When Laboratory Life was published in 1979 it was one of the first anthropological works studying science as a cultural activity. The work was a case study of the laboratory of Roger Guillemin, later a Nobel laureate in medicine, at the Salk Institute in LaJolla, California. The background for the study was the impression that western anthropology had detailed knowledge about other cultures, but that central activities within our own civilization had not been studied with the same methods (Latour & Woolgar, 1986 p. 17). One had separated science from the social, as if science was naturally and rationally given. There had been few efforts to investigate the methods and activities that lead to the production of knowledge as cultural phenomena.

One of the problems of studying one's own culture is that that it is easy to unknowingly accept the premises of the activity, and in that way masking some of the constituting cultural factors of the activity. To protect the cultural perspective Latour & Woolgar decided to not accept that natural science was about the truth. They rather took an outside perspective, seeing science as a purely social activity that could be studied in the same way as other social activities. In this way they could avoid that the “truth” could trump any analysis of choice, relations, and decisions (Latour & Woolgar, 1986 p.29).

One of the main questions that is investigated in is Laboratory Life is: how does a process dependent on certain people handling a certain type of instruments at a certain place in a certain time in history, end up producing statements that are supposed to be eternal facts about the world? How do such particular social situations and processes produce eternal pure facts? To understand this Latour & Woolgar started by giving a naïve description of the practical laboratory activity (Latour & Woolgar, 1986 p. 45). The people in the laboratory are doing craftsmanship, treating material, reagents, and machines in regulated practices and configurations. The output of the process comes in the form of inscriptions (graphs, diagrams etc.) made by the machines. These inscriptions are then interpreted as a direct indication of the substance that is studied, and taken as evidence for or against certain ideas, concepts, or theories. From the interpretations of these first inscriptions new inscriptions are

made. These are called scientific papers, and include both graphical and written inscriptions. In the scientific paper the scientists make claims about how nature is. The participants of the laboratory view the production of scientific papers the main goal of their activity. Thus the laboratory can be seen as a place for literary inscription.

The phenomena that are manifested through the inscriptions are made possible by a certain material configuration, in the form of experimental setup and a specific sequence of events, as made possible by the experimenter. This, says Latour & Woolgar, is what Bachelard calls phenomenotechnique: the manifestation of phenomena by their construction through material techniques (Latour & Woolgar, 1986 p. 63). An important aspect of the phenomenotechnique is that the material setups used for creating new phenomena themselves contain theories and assumptions. A model system or a machine used for analysis has also been the subject of scientific debate. The inherent theoretical understanding of the material setup is what forms a "matrix of understanding" of the material under study, in which new phenomena can be understood and given meaning. The strength of the laboratory is exactly that it contains the specific configuration of technology and knowledge designed for the purpose of bringing forth specific material phenomena in such a matrix of understanding. The laboratory allows for analysis and making distinctions, for the choice of one statement over another. The laboratory thus forms a reality that does not have its counterpart in the world outside the laboratory, but is specifically situated in the laboratory.

An important point Latour & Woolgar make here is that the relation between statements and facts are inverted in the laboratory culture. The scientists in the case study view the experimental work as a process of revealing the truth about nature. Once the truth has been revealed, the way it was revealed is uninteresting. As the theories and assumptions contained in the experimental setup often are well established and agreed-upon, they are seen as true descriptions of the world, and therefore not questioned. The experimental result coming out from the manipulation of the experimental setup can then also be seen as a direct and true description of the substance that is studied. Latour & Woolgar, on the other hand, claim that the truth is a consequence rather than the foundation of laboratory work (Latour & Woolgar, 1986 p. 183). The truth is a part of the social process. The image we have of the world is a result of the science that we use to say something about the world. In this perspective, the way such an image is produced becomes an integral part of the understanding we have of the

world. It is no longer possible to view facts as eternal and pure statements of the world. They are entangled in human activity.

This further emphasizes the importance of looking at the concrete fact-producing processes, both the material and intellectual. Latour & Woolgar find that the thought processes of the scientists in the laboratory do not differ from those that are found in daily life. They conclude that there is no specific scientific rationality, and that rather, scientists seem scientific because they are scientists. A scientific discussion is usually a mixture of different aspects and interests. This can be due to that that the theoretical, descriptive and technical are closely interwoven in the laboratory setting. Indeed, it is in this theoretical-material landscape that scientists think, plan, and navigate. Here, Latour & Woolgar follow Heidegger in that "gedanke ist Handwerk" (Latour & Woolgar, 1986 p. 171).

In order to get pure facts about nature from this process, there must be a work of purification where the "dirty" hybrid nature of the laboratory that produces the statements is washed off. Latour & Woolgar ascribe this purification both to the inversion between statements and facts, as was described above, and to the rhetorical aspect of the research process. The research process, they claim, can be viewed as a stepwise rhetorical process of justification of statements. The functional intention of the literary inscriptions produced by the scientists is to produce statements, and to persuade the reader that the statements are true. Important parts of the argument are the figures and tables that represent experimental results. When there are no more reasons to doubt the statements put forward in the text, it is said to “be about facts”. "Laboratory Life" identifies five types of statements in literary inscriptions (Latour & Woolgar, 1986 p. 65):

Type 5: Taken-for-given facts.

Type 4: Accepted knowledge.

Type 3: Statements about other statements, where modalities are included

Type 2: Statements and suggestions derived from more accepted knowledge.

Type 1: Speculations.

In the rhetorical process of showing something as true, the scientists attempt to transform statements from lower to higher types. In order to go to a higher type the scientist must connect the statement both to earlier statements and to, most importantly, trustworthy experimental inscriptions. In this process of transformation the facts lose their social, technological, and historical references. From being one plausible alternative among other plausible alternatives, statements go through an ontological change and acquire fact status. The other alternatives are rendered false. The fact stands alone as a true and pure statement about nature.

When choosing one fact among alternative statements the scientists also face the danger that the fact they chose should be found to be an “artifact”. That is, that they cannot argue in a convincing manner that their statement is a fact. When a fact is “de-masked” as an artifact, a process of deconstruction steps in. All of the technical and social processes leading up to the fact become visible as reasons for this fact being wrongly chosen.

To summarize, "Laboratory Life" describes the laboratory as a place for the construction of facts through a practical-theoretical configuration that allows for ordering experience and choosing between different statements about the world. The relation between the world and the fact is inverted so that the fact is viewed as deducted from true nature itself, while for Latour & Woolgar "true nature" is rather a product of the scientific activity. The inversion makes it possible for the scientists to remove the fact from the situated context of its production through a rhetorical process of argumentation. This is done both by experiments and by connecting it to previous knowledge within the field.

An interesting question that "Laboratory Life" ask, but leaves unanswered, is why the illusion of the fact as purely objective is upheld? Indeed, it is not enough to show that something is an illusion. One must also show why this illusion is necessary (Kant, 1998) in (Latour & Woolgar, 1986 p. 175).

1.3.2 Hans-Jörg Rheinberger: the phenomenotechnique of experimental molecular medicine.

In his work "Towards a History of Epistemic Things – Synthesizing Proteins in the Test Tube" (Rheinberger, 1997) Hans-Jörg Rheinberger looks more closely on experimental systems, and on how novel objects come into existence in such systems. Rheinberger uses the work of the medical doctor and biochemist Paul Zamecnik as a case for describing how experimental systems are used to produce and describe novel objects. Zamecnik and his co-workers are known for the identification and description of the key constituents and mechanisms of protein synthesis during the late 1940s and the 1950s. An important point for Rheinberger, which we also have seen for Latour & Woolgar, is that knowledge production is situated at a certain time and place. But where "Laboratory Life" from this highlighted the social and cultural aspect of scientific work Rheinberger emphasizes the historical and technological aspect of scientific work.

Rheinberger lean on the notion of Bachelard of phenomenotechnique: technologies embody scientific concepts. In his investigations of the experimental work of Zamenick he describes the experimental system as a matrix of understanding which both has a theoretical and a material part (Rheinberger, 1997 p. 29). The technological entities harbor scientific concepts that make it possible to think within the material system: how the various technological constituents will relate to and react to various scientific phenomena of interest. Importantly, the experimental logic of the system, the knowledge to produce fecund and interpretable experimental setups, to perform them, and to interpret and judge them, is dependent on the practical-theoretical and tacit skill of the experimenter. This connects the theoretical and the material part of the previous knowledge within the fieldto the object of study and the concrete material situation of designing and performing the experiment. As new epistemic things are created in this system, they contain within them the concepts of their production. They are phenomenotechical.

The technical conditions of the experimental system determine the realm of possible representations of epistemic things. The more the experimenter learns to think within the system through a practical rationality, the better the system comes to realize its intrinsic capacities. But also, as the system is designed to capture the unknown and unforeseen, it harbors within it more capacities then the researcher knows. Through this, new spaces of

experience and new kinds of rationalities are created, where the system both is a space for representation, and a materialization of concepts and theories.

Rheinberger characterizes the field of scientific knowledge as a field where what is known and what is beyond imagination is permanently reoriented and reshuffled (Rheinberger, 1997 p.11). Rheinberger calls the objects of science, which are produced experimentally and implemented in the system, "epistemic things". Every new epistemic thing that is created in the system is a result of the knowledge already established in the system. At the same time the new entities will lead to new understandings of the previous knowledge. New information or understanding about a phenomenon or a context of phenomena will substitute the old understanding. Rheinberger calls this a Derridaean principle of supplementarity: a process of epistemic displacement where everything is intended as a substitution or addition that will reconfigure the system.

Rheinberger follows Bernard in that experimental knowledge is relational. What one tries to register in the experimental system are specific differences. Through defining a field where differences can be registered, the experimental system gradually acquires contours, creates resonance between different representations, and conveys manageable meanings. An experimental system that is organized such that the production of differences becomes the orienting principle creates a subversive movement in the sense of a dislocation of epistemic entities. The experimental system oscillates from processes of stabilization and subversion: phases of representation of new resonances and organizing entities, and phases of confirming and stabilizing demonstration (Rheinberger, 1997 p. 80). In this way, a continuous process of deconstruction and re-signification upholds the fecundity of an experimental system. New traits and entities are included in the system, and the system changes organization to include the new traits. As long as the system is capable of producing distinctions, specific differences, it will move on.

The experimental systems are arrangements that allow for the production of cognitive, unprecedented, spatiotemporal singularities and events. For this reason, the system cannot be to rigidly defined. A rigid system would not be able to produce unforeseen events, while if the system is too open, the experimenter cannot make sense of the data registered in the system. This experimental openness is also reflected in a theoretical indeterminacy: as the scientist cannot to rigidly anticipate the unknown he/she must be sensitive to unforeseen

signals from the experimental system (Rheinberger, 1997 p. 14). It is not theory on one hand and practice on the other hand. “Deriving” ideas from the material of observation, and “imposing” ideas upon the material represented is in this process inextricably connected. In this both material and theoretical situation the experimenter aims at achieving *resonances* in the matter of study.

This notion of resonance points at some element that can be stabilized - something giving resonance. This is the epistemic thing. Rheinberger is careful not to assess a positive value to the epistemic resonances. Even though talking about resonance of things, he avoids describing them as “truth” or “reality" in a positive fashion. The reality of epistemic things lies in their resistance, their capacity to turn around the preconceived anticipation and understanding. Rheinberger here follows Bachelard and Pickering in that the world shows itself through its resistances. Also Michael Polanyi has taken a similar position. Polayni proposed that it is the capacity of things to reveal themselves in unexpected ways that shows that they are an aspect of reality. To trust a thing that we know is real is also to admit that we cannot fully describe it by our conception of it, and that it therefore always will continue to manifest itself in new ways in the future (Polanyi, 1965) quoted in (Rheinberger, 1997 p. 23). The reality of the epistemic things lies in this capacity to turn around our previous understanding. The resonance or resistance does not need not to be absolute or eternal. It is enough that it can carry the system to some new step.

Science aims at creating new spaces of representation - at increasing the limits of experience. Biological macromolecules cannot be registered by our senses directly. We obtain knowledge about them through the traces they leave in the spaces of representation, for example as the measurement of radioactive signal from a radioactively labeled protein. Such material traces, or representations, Rheinberger calls graphemes. Rheinberger here draws on Van Fraassen and Sigmand:

“Representation of an object involves producing another object which is intentionally related to the first by a certain coding convention which determines what counts as similar in the right way” (Van Fraassen & Sigman, 1993) quoted in (Rheinberger, 1997 p. 103).

Thus, when something is represented within the experimental system, this representation is also dependent on a conception of how the representation works. This conception is governed by the understanding of the experimental system itself. Resulting from this,

scientific activity is an endless production of traces, constantly searching for resonances that again change the previous understanding in a process of stabilization and subversion. The references for such a system of endless production of are neither things in themselves nor social constructions or paradigms, but rather internal referents consisting of previous knowledge and theories and of other experimental systems. There is not a dichotomy between representation and reality. The experimental system is itself a product of such a process of representation. The measurement of radioactivity through a Geiger teller is itself a product of the representation of entities within particle physics. Rheinberger can here be understood as making an immanent ontology, where he starts out by saying that entities are represented through traces in spaces of representation. Ending up by saying that there is nothing but traces and representations and how they relate to each other (Rheinberger, 1997 p. 104).

1.3.3 The laboratory as producer of knowledge.

In their works presented here, Latour & Woolgar and Rheinberger describe the processes where knowledge is produced in the laboratory. But they manage to show how *cultural* and *social* aspects of experimental molecular medicine affect the knowledge production: how facts are produced from an internal logic of sign-systems, various experimental inscriptions, negotiations, and rhetoric processes. Latour & Woolgar talks about the processes through which decisions are made, and through which a fact is established, which they call micro-processes. But they do not clarify why exactly one explanation is chosen before another. On this point both Latour and Rheinberger have a quite near-sighted view: something is important because it adds to the fecundity of the system. Maybe the main factor determining the importance of experimentally produced facts are what Latour addresses in his later work "The Pasteurisation of France" (Latour, 1988), namely that they can be translated out of the laboratory and into a setting of for example the clinic. The value of new epistemic entities will be evaluated with respect to some means outside of the experimental system itself.

I would emphasize the importance of the factors robustness and relevance in the knowledge production. Choosing a statement about the subject of study needs to be robust and trustworthy. Thus, trustworthiness will be of importance, for example as described in Laboratory Life where the trustworthiness of a fact was based on the experimental setup. With respect to relevance, the statement claims to have some sort of relevance outside itself,

it claims to be part of a context, wide or narrow. Thus it claims some sort of continuum in causality, identification, representation or similarity to a context outside itself. Thus, for a statement to be made, one needs to have some basis for robustness and relevance.

The premise and strength of the laboratory is that it is a place of simplifying and modeling life. To be able to single out causalities, there is a trade-off between durability and relevance of statements. We here touch upon the problem of generality of biological statements, as have been addressed by both Bernard and Canguilhem: due to the complexity of biological systems, one cannot assess a generality to statements without producing new statements that are as equally well durable about that particular case in that particular context. One cannot transfer statements and judgments from one model system to another without a new process of validation in the new context. Still, the laboratory approach has led to numerous clinical applications, thus there is a work of what Latour would call translation (Latour, 1988) translating the knowledge from the laboratory into the clinic. What is the basis of relevance for experimentally produced knowledge? The shortcoming with Rheinberger lies in the relevance: he concentrates on how knowledge is produced in its concrete setting, and he also gives account for how it is stabilized and made durable within the experimental systems. But he does not account for how this stabilized entity is translated into knowledge that can be used outside the laboratory.

1.4 Summing up and approaching.

The two lines of thought presented here are both central for understanding science as it is conducted today. The early positivists were important for establishing medicine as a scientific discipline, and the positivists tried to create a rational and systematic foundation for the sciences. The natural sciences bear with them a positivistic ambition of a systematic and rational description of the natural world. This ambition can take the form of a belief that science *is* a direct, rational, logical and systematic representation or description of the natural world, or it can take the more moderate form of an ambition to make a systematic and internally coherent understanding of the object of study.

The historical epistemology of Bachelard and Canguilhem showed the importance of going into detail in the practical scientific work in order to show how scientific rationalities vary with time, place, and situation. In the light of this view the positivistic approach becomes

problematic. Also, Bachelard emphasized how the scientific knowledge production takes place in a theoretical-material field of phenomenotechnique. Michel Polanyi further described how this local scientific activity has a large individual and tacit component. Later sociologists and philosophers of science, such as Bruno Latour and Andrew Pickering, have further tried to work out the relationship between the social enterprises that are the sciences, and their objects of study in the material world.

In the works of Bernard, Latour & Woolgar, and Rheinberger we have seen several important factors that play a part in the experimental molecular medicine. The problems that are investigated are somehow connected to human health, and they are investigated experimentally at the molecular level of the organism. The challenge of experimental molecular medicine is to draw sound conclusions from the complexity of the object of study. This is handled through a thoroughly elaborated experimental system of material analysis. Through the experimental setup, where meaning is given to new phenomena through an internal system of referents, the scientist intervenes with the matter of study, and in response he/she meets resistances or resonances. Through a process of accommodation, resistances are sought overcome, and through a process of stabilization, resonances are sought stabilized and further connected to the system of referents, and in the end purified as statements about the material world. As a result of the new knowledge, the system of referents will re-organize to include the new entity in the network.

Along the way in this process, decisions and evaluations are continuously made. These are dependent on both the quality and outcome of the experiments, but also on the evaluation of the experiments with relation to the system of referents, both technical and theoretical. The fact-production process is to a large extent singular and situated: there is not a general approach for making an experiment work. This does not necessarily mean that the knowledge is singular and situated, but that in the process of mangling one does not know in advance under which circumstances one can achieve resonance. As Rheinberger notes, this situation of fumbling is a characteristic of the research process. This fluidity implies however, that there is a process of translation and justification required to show that the epistemic things and the knowledge-claims about them are relevant also outside the laboratory. This has been called the in *vivo-in vitro* problem (Strand, 2003).

The processes of formulating medical problems, constructing an experimental setup for solving them, conducting and evaluating experiments, stabilize and formulate findings, and translate findings to a relevant solution of the problem are gathered in a theoretical-practical process. I will take my enquiry of knowledge production in experimental molecular medicine along the lines of historical epistemology. Rather than to address scientific knowledge production in a general manner, it is indeed necessary to specify the scientific tradition of interest. Medicine has its own history of establishing itself as a science. Molecular medicine both has its own methodological and theoretical history and its implication on what life and disease is, and the experimental methodology brings with it important phenomenotechnological considerations. The knowledge production must be understood as both social, material, technological, value-laden, and practical.

In the positions handled above I have not been able to find a satisfactory take on the, to borrow an expression from Latour (Latour, 1993), *hybrid* aspects of experimental molecular medicine. Bernard establishes the experimental method, but he does not seem to recognize, as noted by Canguilhem, that this method also represent a certain perspective on life. Rheinberger addresses the internal dynamics of fact production, while Latour & Woolgar present some of the cultural dynamics surrounding the process. In order to get an integrated understanding of experimental molecular medicine these concepts and notions have to be developed into an understanding that is theoretical, practical, material, and value-laden. It is this that I will try to develop in the rest of this work. What perspective on life determines the experimental method as approach, and the molecular level as a meaningful level for medical investigations? How is the experimental work governed and conducted in order to produce knowledge relevant for human health, and how does the resulting knowledge live up to the aims of the science?

Bearing Bernard's words in mind, we should try to avoid becoming false men, not only of science, but also of philosophy of science. As I have emphasized the singularity of experimental research, we will now turn to this game of hide-and-seek between human and material agency: we will go to the laboratory[8].

[8] Import to add: we will also go to the office next to the laboratory, where projects are planned and articles read.

2. Case study: The NAT-group.

I will now go on to look at a concrete case, namely the NAT/Thyroid research group (from here on termed the NAT-group) at the Department of Molecular Biology and the Department of Surgical Sciences at the University of Bergen (UiB), Norway. I am myself a researcher at this group, where I have taken both a master's degree and a PhD-degree[9].

I will first give a short general introduction to the NAT-group's history and context, before I proceed to investigate a specific project within the group, namely the identification and characterization of the human protein N-α-acetyltransferase complex C (hNatC). My focus will be on the individual and practical aspect of the research process.

2.1 The context of NAT resarch.

2.1.1 A short history of the NAT-group.

Johan Lillehaug, professor in molecular biology at University of Bergen, and Jan Erik Varhaug, specialist in endocrine surgery at Haukeland University Hospital and professor at Department of Surgical Sciences, initiated the Thyroid-group as an effort to identify genes and/or gene products involved in the development of thyroid tumors. Such genes and gene products could then further be described with respect to treatment of thyroid cancer. The method used was to remove thyroid cancer tumors from patients by surgery, and subsequently analyze them using molecular biology tools in the laboratory. In the analysis they looked for genes that were higher or lower expressed in the thyroid tumors, as compared to normal thyroid tissue from the same patient. Among several genes found up- or down-regulated, three were found particularly interesting and chosen for further characterization. One of these was the N-α-acetyltransferase human (NATH) (Fluge et al., 2002).

The NATH gene was found over expressed in thyroid carcinomas. The gene encoded the NATH protein, a protein previously un-described in humans. Works on the yeast homologue of NATH, Nat1, had showed that the protein was part of an enzymatic complex named the

[9] Professor Johan R. Lillehaug and Dr. Thomas Arnesen have read, commented on, and approved the case description as it is given here.

NatA complex (protein N-α-acetyltransferase complex A). This complex catalyzed the chemical protein modification N-α-acetylation (Polevoda & Sherman, 2003). Protein modifications are considered crucial in regulating the biological function of proteins. N-α-acetylation was one of the most common protein modifications in eukaryotic organisms, but besides this not much was known about this particular modification. So NATH seemed to be a protein with a large potential for novel and interesting findings. On the basis of this, Varhaug and Lillehaug applied for funding of a PhD-position at the Norwegian Cancer Society to further investigate the NATH gene and protein[10].

The stipend was given to Thomas Arnesen. Arnesen described NATH as a part of the human NatA complex (hNatA) (Arnesen et al., 2005). Also, projects were initiated to identify other protein N-α-acetyltransferases (NATs) in humans, independent of Thyroid cancer. The work on N-α-acetyltransferases shifted from studying the role of NATH in thyroid cancer, to a more general characterization of protein N-α-acetylation and the proteins that catalyzed this reaction.

With Arnesen the project started growing in manpower, including technical apprentices, technicians, master students, and PhD-students. I myself started as a master student at the group in 2005. In 2006 Arnesen himself continued as a post-doctor at the group. In addition two PhD-students at the group and several master students worked on the project. This enabled both the initiation of several and more ambitious projects, and the build-up of specialized methodological expertise within the group.

The following years, from 2006 to 2009, the group continued to build momentum. It expanding its international network through arranging meetings for groups involved in the field of protein N-α-terminal acetylation and developing cooperation with these groups (Arnesen, 2009)(Arnesen et al., 2009), recruiting more PhD-students and master students. It produced a series of articles on other proteins in the NAT protein family (Evjenth et al., 2009; Starheim et al., 2008, 2009).

From 2010 and onward can be said to mark a new phase for the NAT-work, as Arnesen received a grant from the Norwegian Research Council for the establishment of an

[10] In total, three PhD-projects were initiated on the basis of gene candidates from the work of Fluge, each addressing one candidate gene. NATH was one of these three.

independent research group. While the first period (late 1980's to 2000) was a period for developing a topic of study and a project profile, the second period was a period where several independent projects lived side by side (2001-2005/6). In the third period the NAT-project continued and the NAT-group expanded and developed momentum (2006-2009), the fourth and present period can be said to mark the start of a period where the phase will try to define itself as a larger research-group with a certain ambition level. This is both marked by an increase in the number of PhD-students and post-docs in the group, and a change in research group organization, with the NAT-group being an independent research group of Arnesen, separated from the research group of Lillehaug (spring 2010).

2.1.2 The medical perspective of NAT-research.

The NAT-group is situated at the Department of Molecular Biology at the Faculty of Mathematics and Natural Sciences at the University of Bergen. The Department of Surgery has been involved in defining medical problems and supplying the group with clinical material in the form of tumor samples. More specifically, the medical discipline connected to the NAT-group is oncology or tumor biology. Importantly, although being defined as molecular biology as such, the group has a medical perspective[11]. As we have seen in part 1, the distinction between medicine and biology brings some central considerations, and I have therefore used the term "molecular medicine" to describe the topic of the group. The medical perspective is further emphasized through the funding of the group from institutions such as Norwegian Health Region West and The Norwegian Cancer Society.

The connection to oncology sets a perspective on the work of the group: the relevance of biological macromolecules with respect to cancer. Something that is highly relevant for oncology is important/valuable/"good", and something that is irrelevant for oncology is irrelevant/unvalued/"bad". This again is decisive for what questions we ask, what problems we pursue, and what experiments we conduct. It is not the biological macromolecules *per se* that we are studying; it is their involvement in human disease. NATH was chosen because it was over expressed in thyroid cancer. Protein N-α-acetylation was further pursued due to

[11] The Department of Molecular Biology at UiB was started in 1996 at the Faculty of Mathematics and Natural Sciences, and consisted then of a number of group from different departments and faculties that all fell within a definition of molecular biology. Lillehaug was then situated at the Faculty of Medicine, UiB, where he had done molecular biology research related to Thyroid cancer. According to Lillehaug (personal communication) an important reason for starting a department of molecular biology at the faculty of natural sciences was to gain more independence from the medical sciences, and thus make possible a more autonomous molecular biology at UiB.

both this link to cancer, and to that it was widespread and poorly understood. It had a high potential for providing medically relevant findings.

Such scientific goals are changeable, and evaluations are made with respect to what directions the project has a potential. One could say that it is sufficient for the group that the findings are relevant for *something*. Such a change in perspective can be seen in the group as it went from clinical oncology to more general molecular biology. But as the group has commitments to funding sources and employers (for example Health Region West), such changes in focus cannot be done without at the same time arguing for the relevance of such a change. And also, a change in focus also often means a change in methodology and knowledge, thus one must be sure that this investment is worth it. Following from this, one would expect that at least major changes follow a somewhat conservative dynamic. In the case of the NAT-group it can be tempting to speculate that the change in focus from clinically related thyroid work to more general molecular biology also was connected with the development of an independent research group with a new leadership.

2.2 The hNatC project part 1: Initial characterization.

Until 2005 the group had worked mostly on the hNatA protein complex. In yeast a NatC protein complex had also been described (Polevoda & Sherman, 2001). Arnesen did a search on the Entrez Human Genome Database[12], where he found that there existed genes for predicted human homologues to the three subunits of the yeast NatC complex in the human genome. From this prediction he formulated the hypothesis that there also existed a human NatC complex (hNatC). The aim of my study as a master student was to identify the subunits of the hNatC complex. I also continued work on the hNatC complex into my PhD-work.

I will here not address every aspect of the hNatC-project. Rather, I will describe some parts of the process that are philosophically interesting. As for today (August 2011), the project can be divided in three phases where three main questions have been addressed. The first question when the project was started was that of identity: what are the constituents of the hNatC complex? The second question was that of relevance: "is hNatC important for human cells?" The third question, which is the one addressed in the current work of the project, is

[12] A database predicting all possible translated human proteins from the human genome based on knowledge about gene expression and translation of RNA into proteins (http://www.ncbi.nlm.nih.gov/).

that of function: what is the function of hNatC? This latter question will be further addressed in 2.3. Here I will look at the questions of identity and relevance, and how they went on to form the first hNatC-paper of the group, published in 2009 (Starheim et al., 2009).

2.2.1 What are the subunits of hNatC?

As mentioned above, Arnesen formulated a hypothesis based on database predictions: there existed a human NatC complex. Based on the assumption that the homologues of the yeast NatC subunits were the proteins that was most conserved throughout evolution, three candidates were chosen, one for each yeast NatC-subunit. In the database they had the names NAT12, MAK10, and LSM8. Now, the hypothesis had to be experimentally verified since database-predictions are not considered proof for the existence of a complex.

The task I was given as a master student was to 1) experimentally investigate if these predicted human homologues could form a complex, 2) if they were associated with ribosomes (as had been shown as an important part of the function in yeast), and 3) if they displayed enzymatic activity. If so, we had identified a hNatC complex. This would be a finding represented novelty in the human field, and could form the basis for wider knowledge of NATs in human. I will here go through the first point: the investigation of whether the predicted human homologues formed a complex. A summary of the experimental procedure described here is given in figure 2.1.

While I initiated the work on NAT12, MAK10, and LSM8, a paper was published presenting a vertebrate NatC complex (a complex in Zebrafish and rat) (Wenzlau et al., 2006). Using these identified NatC subunit proteins as query sequences in the human genome, I obtained two different top-candidates for hNatC subunit complexes: NAT5 (a homologue of NAT12), and LSMD1 (a homologue of LSM8). This meant that for two of the subunits of hNatC, I had two candidates that had to be tested (Figure 2.1).

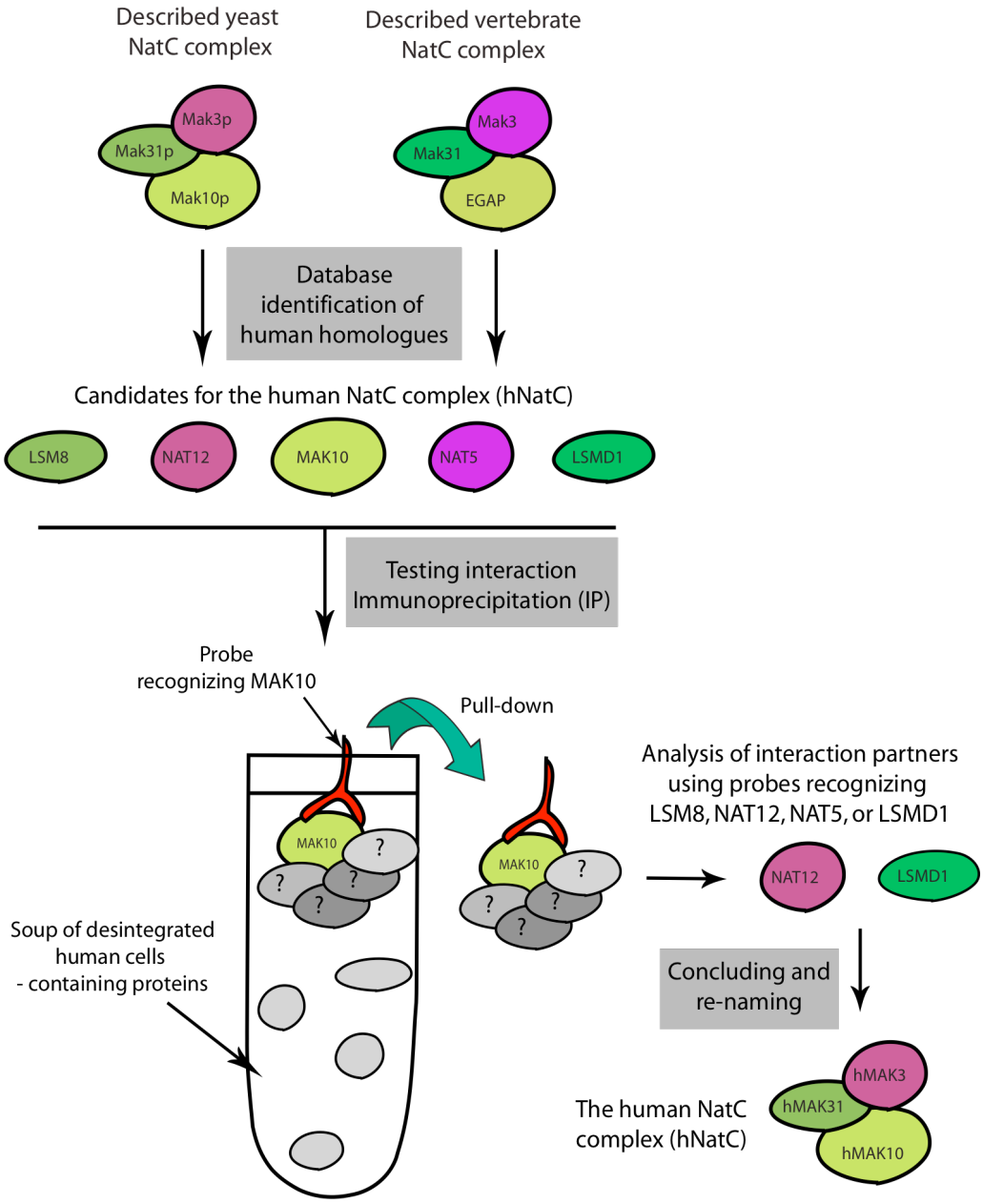

Figure 2.1: Experimental setup for identifying subunits of the hNatC complex by immunoprecipitation.

I used the method immunoprecipitation to investigate which of the candidates interacted to form a complex. This experiment was decisive for choosing one alternative over others when deciding what should be defined as the subunits of the hNatC complex. The basis for this experiment is that one collect cells, typically from an artificially cultured cell culture, crush the cells, and then use a probe to pull out a protein x from the cell soup (called a homogenate). Proteins that interact with protein x in the soup will then be pulled along with

protein x. If one is interested in investigating if protein y is an interaction partner of x, one can analyze the pull-down complex with a probe recognizing protein y. If the probe recognizes y in the pull-down complex, one can conclude that x and y somehow interacts. Importantly, one should also compare with a control-protein z that is not expected to interact with x. As for most experimental setups immunoprecipitation contains many factors that give rise to modalities. The conditions for crushing cells, the interaction between probe and protein, the physiological conditions of the pull-down, and the conditions of analysis of the pull-down complex are all factors that need tuning.

In my case, I was to investigate which of the candidates LSM8, MAK10, NAT12, NAT5, and LSMD1 interacted to form a protein complex. Several different setups were tried with various results. Some pullouts did not yield any interaction partners at all, and some pullouts pulled out all proteins tested, included the negative control protein. Some setups showed pullout of various candidates, but they were not always reproducible. It took many rounds of tuning before I succeeded to design a setup that showed interactions between MAK10, NAT12, and LSMD1, as compared to the negative control. It took further rounds of tuning to reproduce the result. In addition to this setup additional alternative setups were needed to verify the interactions. On the basis of about 60 experiments over 2 years, we concluded that NAT12, MAK10, and LSMD1 were the subunits of the hNatC complex. The proteins were re-named after their yeast homologues (e.g. the human homologue of Mak3p is human MAK3, termed hMAK3, with the prefix h- indicating species (human)).

2.2.2 What is the relevance of hNatC?

We had identified a novel human protein complex. But did this complex actually have any biological role? We investigated this by removing the proteins in the hNatC complex from the cell, and looking at different phenotypes resulting from this depletion. "Phenotype" is defined as "the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment"[13]. In molecular medicine this environment can often be the internal environment of the organism, and the phenotype is understood as how the genes manifest themselves in the organism. One thus looks at the state of the organism and on the characteristics of particular processes in the organism. The phenotype

[13] New Oxford American Dictionary in Apple Dictionary Version 2.1.3, 2005-2009 Apple Inc.

experiments were performed by PhD-student Darina Gromyko. She depleted the identified hNatC protein subunits in the cell in a process called knockdown, and then used various setups to look at various cellular consequences of the depletion. Although she did not remove the *genes* when depleting the hNatC subunits, but only inhibited the expression of the genes, the consequences of the depletion are still called a phenotype.

The number of measurable potential phenotypes of protein depletion of a protein x is enormous even on single-cellular level, and they range from general phenotypes such as reduced growth and cell death, to small modifications of specific proteins involved in particular cellular functions. Which phenotypes one decides to investigate is thus a choice of interest. As described above, our group had a cancer perspective, and thus Gromyko investigated if cellular processes known to be involved in the development of cancer cells were altered after hNatC depletion. Thus, when we found it important to investigate whether hNatC had any relevance, we investigated whether the complex had any effect on cancer-related processes.

The processes she investigated were cell growth, cell division cycle, and a type of programmed cellular death called apoptosis. Her findings were that when hNatC subunits were depleted, the cells grew somewhat slower. Cell division was not affected, but there was an increase in percentage of cells that had initiated apoptosis. We interpreted these phenotypes as signs of hNatC being necessary for the normal well being of the cells in cell culture. Apoptosis is considered a way for the organism to regulate the number of cells, and remove damaged cells. A hallmark of cancer cells is that they are cells that fail to go into apoptosis. Thus, inducing apopotosis in cancer cells is a way to kill cancer cells. Therefore, the finding that depletion of hNatC induced apoptosis was interesting for us in a cancer perspective: it opened for the possibilities that hNatC either potentially could be inhibited as a part of cancer treatment, or that hNatC could be a factor contributing to the resistance of going into apoptosis in cancer cells.

It is a long way from cell culture to clinical application, and even though we proposed a possible role for hNatC in cancer development or treatment, this role was highly hypothetical. Thus, the relevance of the complex was an interesting cell biology observation with respect to the central and important process of apoptosis, and a weak suggestion of a link to cancer.

2.2.3 Making the article.

"Now", Lillehaug said one day, "we have to start thinking paper". At this time my master thesis was just finished. I had identified the three subunits of the hNatC complex, and showed that they interacted with each other and with the ribosome. The subunits of our work were somewhat different than the ones presented in the previous article on the NatC complex in vertebrates. All these factors increased the novelty of the study - we had something. It could become a good piece of work! So, what did we need to do to make the story good?

When we started to formulate the article, we also started to formulate which experiments were needed for getting the work published at a certain journal-level. The presentation of a novel enzymatic complex was novel, but in itself not that interesting if we could not show a cellular relevance of this complex. At this time the work on cellular relevance (as presented in 2.2.2) had not been initiated. Thus the relevance of the complex became an area of focus, and further initiated the above-described work by Gromyko. In addition to a general relevance in the form of a phenotype, Arnesen suggested that if we had a specific example of a protein that was acetylated by hNatC, and this had consequences for that protein, then the *story* would become significantly stronger. Thus, the formulation of an article is also a formulation of a narrative, a story. Indeed, it was often repeated by Lillehaug that we should not leave to many potential questions, to many angles of attack, for the reviewers of the journal.

As a tentative outline of the manuscript was formulated, I also started working on making my experimental results more *presentable* (that was: doing experiments over again for making prettier images, cleaner signals from immunoprecipitation experiments etc.) as a beautiful image was considered more psychologically convincing than an ugly picture. It would take two more years from the start of formulating the hNatC manuscript before the article would be published in the journal Molecular and Cellular Biology (at that time impact factor 6.8).

2.3 The hNatC project part 2: What is the function of hNatC?

I will now go on to describe the hNatC project as it has developed after the publication of 2009. There is an methodological difference between the description of this part of the project, and the description given in part 2.2: while the former description was on projects already conducted and concluded, this part of the project is still on-going, and the result of the process is still open.

2.3.1 What is the question?

After finishing the work of publishing the first paper, we (Lillehaug, Arnesen and me) decided that the hNatC project could be interesting to pursue further. There were two main reasons for this. On one hand the phenotypes were interesting: they had clinical and cell biological potential. On the other hand it was an area with little competition, and thus we were hopefully allowed to develop the project without the fear of being scooped in the competition of getting our findings published. We decided further to concentrate on hNaa30p, and leaving hNaa35p and hNaa38p behind. This was due to practical considerations in terms of labor: focusing on only the catalytic subunit rather than all three allowed for more thorough work on hNaa30p. Biologically it was the hNaa30p-specific acetylation that was of particular interest. If this was connected to the hNatC complex or not was of less importance as the first goal was to find some specific function at all that could be connected to one specific NAT.

The project now went into a phase where several hypotheses and topics were raised as potential continuations of the first article. The questions raised in this period was raised both on the basis of the work already conducted (as a direct continuation), on the basis of potential links pointed at in the literature, and on curiosity ("this was an interesting idea - let's try it!"). These enquiries often took the form of "let's see if there is something here". The different questions that were raised were pursued in various degrees. One question, the question of a connection between hNatC and cellular nutrition sensors was especially thoroughly investigated, as there was strong indications in the literature that hNatC did affect cellular nutrition response. Could hNaa30p have a function in the regulation of nutritional balance in the cell? If we were able to confirm this experimentally hNatC would have been connected to an area of large biological and medical relevance. Therefore, even as we did

not manage to obtain any consistent results about a role of hNatC in cellular nutrition sensing, we continued tuning these experiments for 2 years.

When going back looking at various project descriptions (table 2.1) it is clear to me that there was a large fluctuation of what the project actually should be about.

Gradually, the questions we raised became more and more connected to showing a role for hNaa30p with respect to various cellular processes. The underlying question was: what was the function of hNaa30p with respect to such processes? "Function" can be defined as “an activity or purpose natural to or intended for a person or thing”[14]. It is an “activity”: process, movement, transitive. It is a “purpose”, thus it is grounded in something outside itself. It is “natural” or “indented”, thus it is normative. To assess a function to a biological entity is to make a normative statement about the activity of the entity as seen from the context. As the discussion between Arnesen, Lillehaug, and me progressed, it became clear that we had to define what kind of function we were looking for. The molecular enzymatic function of hNaa30p was to perform acetylation, and to modify proteins. The cellular function of hNaa30p we knew little about, but this could potentially be several different independent functions connected to different cellular localizations and pathways[15]. And further on, hNaa30p could have a physiological function or even a social function.

So the question became: what is the cellular function of hNaa30p? From here it was possible to take many ways. To get some hints we looked at what was known about Naa30p and NatC in the literature. The results we had from the first paper showed lack of growth and cell death, so one possibility was to look at factors connected to growth and cell death, and see if these somehow for example could be potential hNaa30p-substrates. The problem with this was that decreased cell growth and cell death can result from a number of processes, often being the endpoint of a general state of stress in the cell. We therefore figured that finding

[14] New Oxford American Dictionary in Apple Dictionary Version 2.1.3, 2005-2009 Apple Inc.

[15] hNatC can have evolved into local functions that are independent of each other. Or it may have one particular cellular function that can give a statement of the form “the cellular function of hNatC is f(x)”. As one cannot know this, one cannot know what experimental observations can be connected to each other, and what must be seen as independent phenomena. Also, when talking about phenotypes and functions, one must beware of primary effects, secondary effects etc. hNatC may affect something that again puts of a chain of events in the complex cellular system. Some of these events can be closely tied to hNatC functions, while other events may happen more as a consequence of other events. The interesting question is then of course: if large parts of the cellular system potentially are affected by a protein, how far into this system could one stretch the notion of "cellular protein function" for it to still make sense? If everything somehow affects everything, than definitions are indeed floating.

specific cellular functions from hNaa30p with regard to cell growth and cell death/cell survival could potentially be a tough job.

Table 2.1 - Questions raised as potential continuations of the NatC project in the period after first publication.

Month-year	**Question**	**Investigated?**
August 2008	Are there more subunits in the hNatC complex?	Initiated but terminated due to technical difficulties.
August 2008	Does hNatC affect cellular nutrition sensors?	Thoroughly investigated, but without positive result.
September 2008	Through which mechanism is cell death mediated after hNaa30p-depletion?	Thoroughly investigated, positive results.
September 2009	Does hNatC influence organelle organization?	Several experiments initiated, positive results.
May 2010	Does hNaa30p change cellular localization after cellular stimulation?	Pilot experiments, positive results, but terminated.
September 2010	Does hNaa30p influence cellular nutrition balance responses?	Thoroughly investigated, technical difficulties/negative results.

But, as already mentioned, hNatC could have many functions. To show all of them were not only practically hard, it is also theoretically impossible as one never know what one doesen't know. So we should be satisfied if we could propose *one* cellular function of hNatC.

A question that crystallized itself during this period was the question of organelles: did hNatC influence organelle organization[16]? This question seemed for me to attract itself several other exiting and interesting questions: organelles were involved in a wide array of processes in the cell and in the organism. It had biological and medical potential, it could be connected to our previous findings, and there was potential novelty. The next question was what we should try to observe after intervention. Again, several different alternatives were possible (Figure 2.2). As several links in the literature and databases pointed at the spatial organization of organelles, I decided to look at organelles through microscopy in hNaa30p-depleted cells. This task was formulated as a master thesis, and a master student (Thomas Kalvik) started working on this in September 2009.

[16] As the pitfalls of subjectivity are present in this self-analysis of my scientific work, it is especially present here, where I give reasons for decisions in my own self-designed project. But I will try, and as covering one part usually unveils a different; should I fail to reveal the substantial about the project I may reveal something substantial about myself.

And indeed, when depleting hNaa30p from cells, Kalvik observed changes in the organelle organization of the cells. The result was repeated, and he counted the number of cells where the organelle organization had changed in hNaa30p-depleted cells as compared to a control, and the change was statistically significant. In addition he managed to show the effect of hNaa30p depletion on a protein involved in organelle organization (Kalvik, 2010). We had findings, and they were stabilized!

The findings that hNaa30p somehow affected organelle organization could be the cellular function we were hoping for, what Pickering would call a bridgehead for further research (Pickering, 1997).

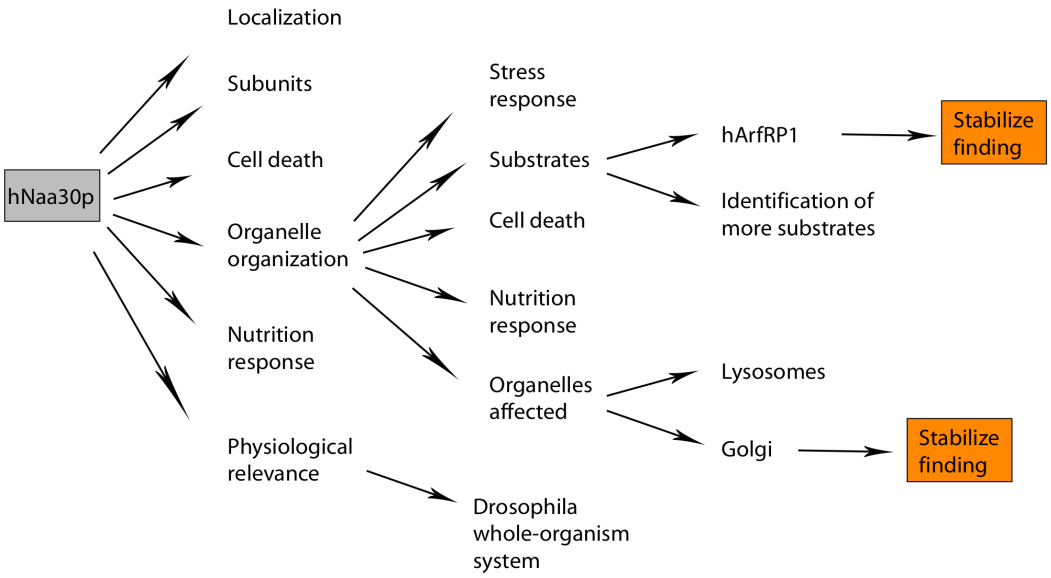

Figure 2.2 Alternatives for possible routes of enquiry, February 2011.

In January 2011 I started drafting a manuscript, where the data we had so far was included. And as I wrote the manuscript and got feedback from the co-authors, it became painstakingly clear to me that I did not have data that supported the statements I wanted to make. It was not that the data contradicted the statements it was rather that we lacked the experimental data that supported the statements that I wished to make. The advice was clear: what statements were the most important, which experiments were needed to address these statements, and what was realistic within a given time frame?

As for today, effort is put into conducting more experiments that can investigate the role of hNaa30p in organelle organization.

3. How does the researcher produce knowledge?

The main question raised in the aim of this study was: how does the researcher produce knowledge within the field of experimental molecular medicine? In part 1 I presented several thinkers who have addressed this question but which did not, in my opinion, give an adequate account of the process in its entirety. It was this process I set forth to understand. As the fact production of experimental biology and medicine reflects the complexity of its study matter, in part 2 I followed the advice from Bernard and Rheinberger and looked at a concrete case of experimental work, namely the work of the NAT-group at the University of Bergen. In this part I will use the works presented in part 1 and the case presented in part 2 to make a philosophical reflection understand how knowledge is produced in experimental molecular medicine. Why does the NAT group conduct the work that we do in the way that we do, and what kind of knowledge do we strive to produce?

I will first identify some of the conditions for the existence of the NAT-group and their work, and how these existence conditions come to constitute the conditions for validity of statements in the experimental context. I will then look at the temporal organization of the research project, and look at knowledge production as a *process*, before I describe the practical conduct of the experiments as a theory-practice where theory and practice is embedded in the process of knowledge. Last, I will point at some methodological problems that affect the knowledge produced in experimental molecular medicine.

3.1 Conditions of experimental knowledge.

Worldviews, and thus also approaches for studying the world, are situated. They change with time and place. They are maintained in what Ludwik Fleck called "thought collectives" (Fleck, 1976 p.44), and what Foucault called epistemes (Foucault, 2006). In these collectives a conception of the world is developed, develops, and maintains what Foucault called discourses (Foucault, 2009), which further determines what is thinkable. It is within discourses in thought collectives that the conditions for different forms of activities and knowledge can be found.

What are the conditions for the knowledge produced by the NAT-group? Canguilhem, Rheinberger, and Latour & Woolgar emphasized that knowledge production is an activity

that is historical and situated: certain societies produce certain practices at certain places at certain times. This produced specific types of knowledge. A question following from this is: what conditions at these places and times make the research activity and the resulting knowledge come about? More precise in the case of experimental molecular medicine: what are the conditions that lead to the material analysis as an adequate and widespread approach for solving medical problems?

As briefly described in the introduction, Foucault distinguished between existence conditions and validity conditions (Utaker, 2009). The existence conditions are the conditions allowing a certain type of activity or discourse to arise at a certain time and place at all, and the validity conditions are the conditions for determining the validity of statements within this activity. I here want to look at what can be some of the existence conditions and validity conditions that constitute the material analysis of experimental molecular medicine, as exemplified by the existence and work of the NAT-group.

3.1.1 Existence conditions of experimental molecular medicine.

The most recent white Paper on Research from the Norwegian Government, "Forskningsmelding no. 30, 2008-2009: Klima for forskning" (Climate for research) (Kunnskapsdepartementet, 2009) provides cultural and instrumental reasons for research. The cultural reasons include the development of civilization and culture and the inherent curiosity of humans. The instrumental reasons are to provide solutions that make it possible to improve society, solve problems, and facilitate economical growth. When a certain type of research is supported and funded one of the reasons is a belief that this type of activity, more than other types of activity (that is not funded or supported) will improve our culture and society, provide solutions to problems, and facilitate economic growth. It will be for the general good of society to a degree that it is worth prioritizing over other options[17]. As it is stated in the Paper of Research:

"The development within molecular and gene technology gives us increased information about the patient and the disease's genetic portraits. There are large expectations for tailor-made treatment, which will give larger efficiency and reduction in side effects. Modern biotechnology, in cooperation

[17] Here it is important to differ between the normative intentions of research and health policy, and how these are realized through practical politics. I here merely wish to point at that there exist a *trust* in experimental molecular medicine not only within the research community itself, but in the Norwegian society in a broader sense.

with information and communication technology, and nanotechnology, puts us in a better position for prevention and treatment of diseases." (Kunnskapsdepartementet, 2009 p. 44, my translation)

Medicine comes in many forms, and experimental molecular medicine is one of several approaches for achieving health and economical benefits on the basis of medical activity. Molecular medicine seeks to explain the causalities of disease at a molecular level, and through this develop methods of prevention, diagnosis, and treatment. This experimental approach to medicine can be seen as a continuation of Bernard's material analysis. Bernard's claim was that all biological phenomena could be understood exclusively through physiochemical properties in what I will call a physiochemical immanence. Therefore, one should not stop the enquiry with reference to for example vitalistic laws; one should further pursue the material analysis.

This physiochemical approach is inspired from classical physics (up to Heisenberg and Bohr), which could be said to have a determinist and mechanistic worldview. It has indeed been seen in parts of molecular biology a belief that the whole of biology could be "explained" in terms of chemistry and physics[18] (Rommetveit, 2007 p. 41). The current position of experimental molecular medicine research in western societies is such that it no longer has to argue to justify for its existence. The view of life as physiochemical and understandable by material analysis is widely accepted.

From the view that life follows physiochemical laws, combined with the Darwinian theory of descent from a common ancestor (Darwin, 2003) it also follows a view of a continuity of life. Whether it is in genetic information storage, protein models, human cell culture, laboratory mice, or the human organism, it is asserted that the organisms are homologous, that is: similar due to ancestry, both within and across species. They are built up of the same constituents and they work by variations over the same mechanisms. Thus, we shall add the view of a continuity of life as another existence condition of experimental molecular medicine. This is not to say that results from bacterial experiments automatically are valid in human organisms. Rather, it is the assumption is that they somehow will or may be relevant.

[18] Rommetveit points at that the claim of totality was a characteristic of classical physics that was later abandoned in physics, but continued in molecular biology. It is indeed interesting to note that one rarely find explanations in molecular biology going beyond framework of classical physics (For an exception of this: Fleming G.R. & Scholes G.D., 2004. Physical chemistry: quantum mechanics for plants, *Nature***.** Sep 16;431(7006):256-7.).

In the case of the NAT-group the work was initiated as a multi-disciplinary project, where material from the clinic was to be analyzed in the laboratory, and then the knowledge from the laboratory could be transferred back to the patient in the form of diagnosis or treatment. Underlying this approach there are two important presuppositions. First, it is assumed that the laboratory analysis will reveal some of the causalities of disease, and secondly that the work done in the laboratory on model systems such as human and bacterial cell cultures, will yield relevant explanations. In this we see the two suppositions of physiochemical immanence and continuity of life.

One may speculate if it is the promise of full causal understanding of life that makes experimental molecular medicine appealing. From Canguilhem's philosophy we have that a certain approach to life also reflects a certain view of life. Perhaps the view of life in these sciences could be found in this promise of causal understanding of life. As Bernard claims: if we have the causal explanation of a phenomenon, the use of statistics is absurd (Bernard, 1957 p. 136). The reductionist experimental molecular biology bears within itself the promise that chaos and multiplicity of life can and should be fully explained and thus controlled. In this material worldview, where the divine has retracted and there is nothing but physical laws, human understanding fills the resulting void. When the full causal understanding of the organism is known, the tailor-made treatment of disease can finally be a reality.

This makes the existence of the NAT-group understandable: the expensive, time-consuming production of facts, years of work that are summed up in a 13-pages research article (in the case of the hNatC article) (Starheim et al., 2009) are made possible by the view of life as fully explainable. The effort will pay off, sooner or later, in the form of direct health benefits.

3.1.2 Validity conditions of experimental molecular medicine.

The validity conditions are the conditions for determining the validity of statements within a field. The existence conditions constitute what is thinkable in the field of experimental molecular medicine, and thus frame the validity conditions. The existence conditions in the form of the physiochemical immanence give a unique status to the experiment as a way to gain knowledge about organisms. Thus, the experiment is the validity condition for experimental molecular medicine. The outcome of the experiment determines whether a

statement is valid or not. In the case of the identification of the hNatC subunits, the database prediction of a human NatC complex was not enough to make the statement "there exists a hNatC complex" valid. An experimental enquiry was needed to determine the validity of the statement. As we managed to register specific differences in the experimental setup, these were used to determine whether there existed a NatC-complex or not.

The validity of the statement is further determined by the quality of the experimental setup: is the setup appropriate to do the intended determinations? Is the immunoprecipitation experiment adequate for determining if there exists an hNatC complex or not? As Rheinberger describes, the experiment is designed to register specific differences. The fear of the researchers is that as the method aims at showing specific differences there may be unknown variables that give "unspecific differences". For example, we used a method for depleting hNaa30p in order to see what happens when hNaa30p is lacking in the cell. But we cannot know whether the method used for depleting hNaa30p specifically also can have other effects that are not shared by the control. If the setup is found invalid the conclusions from the setup are also invalid. The problem is that the experimental setups do not have any absolute frames of reference. The references used are internal controls and other experimental setups, which both are relative controls constituted by the same existence conditions as the experiment itself. When Latour mentions the fear of a statement being dismissed and undressed as an artefact, it is the questioning of whether the output of the setup actually gives this information. Indeed, this may explain the obsessive focus on methodology that is found within experimental life science.

3.2 The project as organizational structure.

I have now described some of the presuppositions for the existence of the experimental approach to life. Experimental molecular medicine has grown from a belief that knowledge is needed to address problems of health and well-being, that this knowledge is the knowledge about underlying causes originating in the physiochemical properties of living beings, and that material analysis of the molecular build-up of living systems will provide answers to the problems. This has further led to the formation of the practical-theoretical field of experimental molecular medicine, where the experimental setup is the main authority in the production of facts. Thus, the process of fact-production is a *practice* where the

theoretical knowledge within the field, the facts derived from earlier experiments, the embodiment of theories in technology, and the practical skill of the experimenter are tuned to capture new epistemic objects.

This process is both theoretical and practical. The knowledge production is dependent on the skill, knowledge, and *work* of people. Latour & Woolgar and Rheinberger have given us understandings of this knowledge production as both social and practical. In this process, it is of utmost importance for the scientists to *organize* the scientific process. At any moment in the research process the possible ways for further enquiry are numerous, as so are the possible factors that can be included in the enquiry. As experimental work is both costly, time consuming, and labor demanding, following any of these ways will require large efforts. The scientists therefore needs to focus and define their work, and economize their time.

Important in this respect is the comment of Rheinberger that experimental work oscillates between subversion and confirmation. In order to facilitate new understanding and objects, the experimental process must be subversive. In order to produce statements, it must stabilize and confirm objects or entities. The challenge is to find a balance between the phases of subversion and confirmation: to organize what Pickering calls the dialectic process of accommodation and resistance that is the mangling of practice (Pickering, 1997). What I here wish to show is that these processes and acts of subversion, accommodation, and stabilization, are sought controlled and organized. To do this I will establish some notions that can describe the organizational aspects of the research process, a process that is at the same time practical, theoretical, tactical, and situated.

3.2.1 Projects as narratives.

As we have seen from the case studies, the theoretical-practical processes proceeds differently for the different cases. Rather then in a "linear" fashion of encountering a problem, raising a question related to this problem, proposing a hypothesis as an answer to the question, performing an experiment to test the hypothesis, interpreting the result from the experiment, and using this to solve the problem, these stages can co-exist in an entangled relationship. This includes ideas, hypothesis and theories, experiments and interpretations, but also decisions and evaluations about what paths to follow, what is practically feasible, and how resources should be distributed. This loosely organized process I will term a

research *project*. The thesaurus[19] gives several definitions of "project", among which are plan, program, enterprise, venture, proposal, idea, concept scheme, assignment, piece of work, all of which indeed are involved in the process that forms a scientific project.

Defining something as a project makes possible for the scientists a certain narrative, a certain scope and delineation of objects of study and the work done on these. I here use the term narrative as a cognitive structure with a certain coherence that allows the parts to fit into a whole, and the whole to be constituted by the parts. There are several factors that influence the organization of a research project.

1. The *known and potential epistemic phenomena* that the project relates to through claiming that the project is about these phenomena. The known and potential epistemic phenomena create focus for the work of the group as the work is aimed at these objects. For the here-described case, the main phenomenon is the hNatC complex. This organizes sub-goals such as identification of the hNatC complex, relevance of the hNatC complex, and function of the hNatC complex. The epistemic phenomena (I here deliberately use "phenomena" instead of Rheinbergers "objects" or "things" as this also captures processes and relations) that are the centre of the work can change as long as the work serves some purpose worth pursuing. Jerome Ravetz has explained this by distinguishing between scientific goals, such as identifying a protein complex, and purposes, such as curing cancer or accumulating knowledge. As long as the scientific purposes are found meaningful, the drift of goals is less problematic (Ravetz, 1996). The epistemic phenomena that are involved in the concrete research goals be maintained as long as they are potent motors for maintaining a fecund project.

As an example of this was the effort to find a causal relation between hNatC and nutrient response: if we had managed to see such a relation the factors of nutrient response would take a major role in the further work of the hNatC project. The purpose of the work could then be shifted towards questions about metabolic regulation of cellular activity, which indeed is an interesting field! But, as we did not manage to show such a relation this enquiry was aborted.

[19] New Oxford American Dictionary in Apple Dictionary Version 2.1.3, 2005-2009 Apple Inc.

2. The *value field* as defined by human health and pathology. The perspective of health and pathology organizes choices through adding values to different alternatives. Alternatives that are (potentially) more related to human health and pathology than other similar alternatives will be prioritized. They will be prioritized with respect to value laden organizing entities in the value field. This can also take an indirect form through considerations of biological relevance. When something is important for the state of the organism or cell it is assumed that it will also be relevant for health and disease.

When seeing the different questions posed in the process of formulating the functional part of the hNatC complex, we see that the research project is somewhat promiscuous with respect to how the relevance to health and pathology takes form. It is enough that it is relevant, preferentially to cancer. But if it is relevant to neurological diseases, that will be the focus instead. Thus, the relevance for health and disease governs choices that are made, but it also forms a reserve that the scientists can draw upon when claiming the importance of their work. The relevance for health and disease is indeed what Ravetz would call a purpose of the work.

3. The *experimental system* used to perform the work. Rheinberger claims that the process of knowledge production within experimental life science starts with choice of experimental system. In many situations the choice of system and the formulation of problems is a reciprocal process. The choice of experimental system will depend on what problems one is interested in pursuing, but also the experimental system at hand affects what problems are posed. This latter point is important, as the establishment of an experimental system is one of the largest investments a scientist makes. Establishing infrastructure, knowledge, and methodology of an experimental system is both expensive and laborious. The establishment of a model system may thus more often lead to that the model system affects the questions posed rather than the other way around.

As Rheinberger describes, different experimental model systems have different opportunities and limitations. The experimental model used in the hNatC project was human cell-culture. This system was available at the group before the project was initiated. The strength of this system is that it is of human origin, it is relatively simple to handle, and it has a lower complexity as compared to vertebrate whole-organism systems such as mouse. The limitations are that the simplicity goes on behalf of the physiological relevance, it is more

complex than for example systems such as yeast, and it is not that easily manipulated as for example fruit fly (*Drosophila melanogaster*). The human cell culture system is thus a trade-off between relevance and simplicity.

For the researchers it is therefore necessary to address the questions that make use of the power of the chosen model system in a best possible manner. In addition, it is important to see what the model system cannot say anything about NatC. The complex had already been studied in yeast. Studies in human cell lines could add knowledge about the role of NatC in human cell biology, and possibly relevance of the NatC complex with respect to human disease. What the human cell line system could *not* do was to give valid statements about links to human disease, or about roles of NatC in a physiological perspective. To further address the physiological role of Naa30p we in spring of 2011 initiated studies of Naa30p in *Drosophila melanogaster*.

4. *Practical-tactical considerations* of what can be done within certain frames of time and effort. As the production of knowledge through experimental work is laborious and financially expensive, considerations are made to manage time and resources with respect to point 1) and 2) above. Driving factors are funding and competition within the field (pressure to publish first etc.). Experimental work is also framed both by length of employment of the researchers, often ranging from a few months to 4-5 years for the active experimenters. In most employments there are demands for outcome in the form of publications, thesis or similar.

This aspect of research-organization is relevant for the politics of research, publication, and education, and could indeed be the subject for a thesis on its own. Latour & Woolgar has addressed the tactical and career-oriented considerations involved in research in the section "Cycles of credit" in "Laboratory life" (Latour & Woolgar, 1986 chapter 5). What I rather want to emphasize here is that these factors affect what kind of knowledge is produced. One possible outcome of the above-presented situation is that researchers do not start projects with a long time frame and an uncertain outcome, but rather go for quick and safe projects (see for example (Alon, 2009) for a reflection over project design).

As for our case study, the decision of starting to study the hNatC complex was not only a decision about studying hNatC. It was also a choice of a topic that could give a master-

thesis, a research paper, and possibly go into a PhD-thesis within realistic limits of time and cost. Initially, the work of studying the hNatC complex followed the same path as was used for the studies of the hNatA complex: immunoprecipitation, studying cell growth and cell death etc. Thus, the scope of the project was loosely considered to be identification and initial biological characterization, a work that was possible to do within appropriate time frames, with low investments into new methodology, possible to do for a master-student (later PhD-student).

5. The *expected outcome* of the research process. The main outcome of the scientific activity of the group is new descriptions and understandings of molecular biological phenomena and constituents, and tools and technology related to these. This can include chemical compounds for use in research or therapy, methods for clinical application such as markers for diagnosis and prognosis or targets for therapy, and patents. But also more general outputs such as increased knowledge within the field. These are all factors that determine the aims and goals for the research - they are involved in determining the value field. But perhaps a bit surprising (at least for non-academics) is that if one is to determine from the daily activity, the main focus for the research group is to publish scientific papers containing scientific statements. The scientific paper indeed has a very strong position and status within the scientific community, although it is only a medium for reporting the activity of the laboratory. This brings us to the next point, namely the rhetorical structure of knowledge.

6. The *rhetorical* structure of knowledge. The work and findings of the group is mainly presented in the form of a scientific paper. The process through which the paper is evaluated, namely the peer-review-process, strengthen Latour's & Woolgar's claim that the scientific process also is a rhetorical process. By this I do not mean rhetorical in the sense that the scientist creates an illusion. Rather, I follow the Aristotelian definition of rhetoric as "the faculty of observing in any given case the available means of persuasion" (Aristotle, 2004) Section I.2). It is important for the scientists that the statements they make are presented in a convincing manner. The ethos is established by a proper presentation of the authors as researchers (institutions and affiliations), and the proper scientific language. Fleck here points at the importance of presenting statements in a manner that is recognized by the thought collective. Tapping into the scientific mood and genre of the thought style will immediately awaken a feeling of trust and recognition by the reader (Fleck, 1976 p.145). Also, the research process will often be presented as a rational and logical process. This may

also give an answer to why the purification of facts is necessary: when claiming to speak about the truth the scientist wins authority. Logos is provided by a connection between statements and validity conditions through reference to trustable experimental setups. Patos may perhaps be found in the insisting that the presented statements are objectively true statements about nature.

The rhetorical aspect of science also includes to the use of narratives. Narratives are used in two ways: as a cognitive structuring of knowledge for the scientists themselves, and as a coherent presentation of their work to others. First, a narrative can work as a cognitive structure that provides a context for the statements produced (Starheim, 2010). The narrative will differ from concepts or theories by that it includes the self-understanding of activity of the scientist. It is how the scientists, in Latour & Woolgar's words, give meaning to their work. A narrative in our case study can be the following: "N-α-acetylation is one of the most common protein modifications in eukaryotes. Still, no one understands the function of it! Our group is unraveling the function of this modification in humans. It turns out that it has potentially important implications for human health".

Secondly, when scientific statements are presented to others (in the form of publications or similar) narratives are deliberatively used to make the scientific work more convincing. Often, a scientific paper will present scientific experiments and findings in a logical order, tied together with "... and then we ...", or "to investigate this ...". But this logical structure is often more a chronology added in retrospect; where as the work itself often is more trial and error. This does not mean that there cannot be coherence in a work. But it is often the case that this coherence is more obvious at later stages of a project. Some thinkers, like Thomas Kuhn and Paul Feyerabend has distinguished between a context of discovery, where a phenomena does not have to be presented in a rational and logical manner, and a context of justification, where the phenomenon is to be stabilized, explained and characterized in a rational manner (Hoyningen-Huene, 2006; Feyerabend, 1996 p. 147). The reasons why scientific work is presented in narratives can be several. It is easier to both understand findings when they are presented in coherence. It is harder to find angles of criticism when the canvas of the narrative is stretched. Also, it defines the limits of what the statements claim and do not claim, it creates a delineation that is coherent for the whole of the presented work.

The narrative presentation of knowledge plays an important role in shaping the experimental process. Even though experiments are not planned with respect to a narrative presentation of the outcome of the experiment, the narrative will start to affect the choice of experiments as potential narratives starts to emerge from the results of the experiments. In the example of hNatC, the choices of performing cell growth and cell death experiments was done after the complex was identified in order to be able to expand the narrative to also involve a more direct indication of relevance to human health and disease. This is, indeed, to "start thinking paper". Hence the proverb that "when writing your thesis, the last thing you write is the aim of the study". This is due to that you don't know how the narrative will look like until you know the parts that constitute this whole.

This process of creating what Jerome Bruner called *narrative facts* (Bruner, 1998) is indeed an important factor of what Latour calls the purification of facts: the process of changing the epistemic status of an epistemic object or trace into a valid statement about nature. In creating the narrative, the important is chosen before the less important.

Through these factors the project is a way of organizing the research process on different levels, from the different projects that individual lab members have, to the project of the group as a whole. It delineates different focuses from other, it makes possible to focus interests and efforts, use time and resources in a more efficient way, build up a more clear-cut and defined expertise, and make up a self-understanding.

3.2.2 Openness and closedness of the scientifc process.

Rheinberger describes the experimental system as oscillating between phases of subversion and stabilization. There are phases when novel entities are searched for, and there are phases when such entities are stabilized - reproduced, controlled, and formulated. I suggest that this subversion and stabilization is a consequence of a dynamic in the research process, namely that the degree of *openness* and *closedness* varies throughout the process. What I am trying to capture with these notions is the evaluation of alternatives at given points of time in the project process: what alternatives are considered realistic paths to follow at different stages in the process.

In the research process, there are a hypothesis-generating phases, where various alternatives are formulated - processes of opening up, phases of evaluation, weighting, and testing

alternatives, and phases of focusing on a few alternatives in order to stabilize findings. As mentioned previously, these phases does not necessarily follow a linear progression, but they affect the process through constituting the priorities that are made continuously throughout the process. In an open phase a hypothesis-generating experiment can be chosen before experiments of repeating a possible finding. In a closed phase emphasis is put on confirming and stabilizing an epistemic object.

Pickering touches upon this dynamic. He describes scientific knowledge as representational chains that capture and frame material agency through various concepts. This process he views as a cultural extension that can be lead in different directions. The first phase of the extension he call bridging: an open-ended phase where the scientist(s) "tentatively fixes a vector of cultural extension to be explored". During the second phase, transcription, established moves from previous systems and procedures are moved into the new space of cultural extension, whereas in the third phase, filling, the new system is completed on the basis of the bridgehead and the accommodation of procedures to the new system (Pickering, 1997 p.117). For Pickering, the first phase is one of association, the second is the one where material agency is the active part (performance of experiment), and the third phase is the interpretation. In the second and third phase the scientist tries to frame material agency by accommodating and interpreting the resistances of the material agency. Although these conceptions bear similarities to my notions of openness and closedness, they describe a more immanent level of the actor-agency relation. Included in the notions of openness and closedness is that that the enquiry towards material agency also is an investment, and that there is at any time a large number of possible ways to direct the enquiry. Thus the concrete decisions that are being made are also dependent on practical-tactical considerations.

The stages of openness and closedness are quite different for the identification-project and the functional project described in the case study. Some projects can be considered more “safe” than others, with methods and biological knowledge more stabilized. Examples of this are the identification of subunits of hNatC. Here, we had a pretty good idea about how the conclusion could look like in advance. As for the task of functional characterization, the research process has been quite different. Figure 2.2 illustrates the different degrees of openness and closedness in the hNaa30p-function project. Where the project of identification started with a clear hypothesis and ended with giving the findings from this hypothesis, the functional project have to a large extent been about finding out what the project should be

about; defining alternatives, choosing between these, and again seeing what new alternatives this opened for. The projects in themselves from the beginning harbored different degrees of openness. This does not mean that every project goes from an open to a closed state, or proceed in a planned manner. In the identification project we also considered doing experiments that would open for potentially finding other subunits for the hNatC complex. This would further lead to a process of studying these. But as opening up a research process will beg for a subsequent process of stabilizing and thus a longer time perspective, we prioritized stabilizing of the subunits we had already started studying.

The continuous evaluation of the research process with regard to openness and closedness is indeed a skill of the trained project leader. Keeping a process open may lead to several novel findings, but it can also lead to stagnation due to lack of focus. Keeping the process too closed, embarking only on projects where the result and relevance can be predicted in advance can merely amount to the filling obvious gaps of knowledge within a field. Such works may indeed be necessary - it was necessary for us to show that there was an hNatC-complex in humans before we started further studies. But as such findings does not, in the words of Rheinberger, lead to major rearrangements of the knowledge, a group that only does such work will not set the agenda within a field.

Again it is indeed worth raising the question of whether the current situation of research, with high levels of competition, demands for publication, efficiency, and short-term employments and funding drive researchers towards more closed states of research. If such were the case, this would go on behalf of the subversive, creative and inventive sides of research, as these are the more risky and open phases of the research process. On a macro-level one might see experimental molecular science moving towards a self-reinforcing direction, where consensus is sought on behalf of a critical attitude.

3.3 Experimental work is a thought-practice.

In the previous chapters I described the presupposition of experimental knowledge production and the organization of this knowledge production. I will now focus on the concrete experimental research situation. To avoid an overly strict dichotomy between mental and practical operations I will use the notion of *thought-practice* to describe the concrete experimental work. The reason for this is that in experimental molecular medicine

mental and practical operations both have the same objects and they are intrinsically entangled to each other and to their objects. Theories are intrinsic in the technology and practice of experimentation through phenomenotechnology (Castelão-Lawless, 1995), and the theories are shaped by the practice for example through the process of mangling (Pickering, 1997). Furthermore, it is important to note that experimental molecular medicine has a craftsmanship-aspect that includes implicit and explicit knowledge (what Michel Polanyi called the tacit dimension of experimental work (Polanyi, 1958)), trained hands, and a practical organization of conduct. Equipped with the concept of thought-practice I will now try to give a description and understanding of the concrete situation of experimental knowledge production in molecular medicine.

3.3.1 From the known to the unknown: the relation to previous knowledge.

As presented in 3.1.2 the experiment is a central source and argument of knowledge production in experimental molecular medicine. When designing an experiment one aims at using the known to capture the unknown. From the network of established knowledge, one can know what one doesn't know. From the knowledge of manipulation and technology, one can know how to get expand into fields of this "known unknown". Rheinberger describes this movement into the unknown as both conservative, in the sense that the new is framed and made possible by the known, and subversive, as the new will change the understanding of the previously known. All knowledge will be dependent on previous knowledge, and all new phenomena will, through resistances and unanticipated characteristics, somehow change the previous knowledge and understanding. This leads to a change and re-interpretation of the scientific knowledge that can be both conscious and unconscious.

Thus, the new knowledge produced is at least partly dependent on our prior understanding, and on what new knowledge can be anticipated. In the research process such anticipations can take the form of what is called "links", that is vague hints and loosely connected relations in the body of knowledge, pointing at some vague correlation or crossing point or tangent. My use of the term "link" is similar both to Pickering's use of the term "linkage" Pickering describes scientific knowledge as "representational chains ascending and descending through layers of conceptual multiplicity and terminating in captures and framings of material agency, with the substance and alignments of all the elements in these chains formed in mangling". Scientific questions are developed as associations and linkages

along these representational chains (Pickering, 1997 pp.100-101). Also Ludwik Fleck has described this use of previous knowledge for the production of new phenomena with his terms active and passive linkages, where the active linkage is the stipulation from the existing knowledge into an understanding of the object of study, and the passive linkage is the assumed unknown interconnections in the object of study that can constrain and resist and direct the understanding of the object of study (Fleck, 1976 p. 95; Cohen, Schnelle, & Fleck, 1986 p. xxx).

The work of finding a function of the hNatC complex has largely consisted in looking for and testing links. An example of such a link was the encounter of organelle-related terms when looking for processes connected to hNatC function in databases and literature. The literature and knowledge of the field makes in this way up a network that the researcher uses for the formulation of problems, ideas, and hypothesis. This relation to a network of knowledge gives intertextuality an important role. Statements that are produced in an experimental work are produced with relation to both the experimental setup and output, and to the previous statements in the field. The connection between the theoretical and the material is made possible by the phenomenotechnical properties of the experimental system. This creates a theoretical-material matrix of understanding.

The relation of a particular experiment to previous knowledge is both one of practice to more general theory, and of practice to specific knowledge about specific cases. The hNatC work relates to the specific work that is done on NatC in yeast. In addition one can say that it also relates to general theories such as the central dogma of molecular biology (information transfer from DNA-RNA-protein) and evolutionary theory. Indeed, there are a number of general concepts in molecular biology and medicine, but instead of taking for example a mathematical or an axiomatic form they take the form of descriptive statements with high generality, such as "changing the structure of a protein will affect the function of the protein". Interestingly, as general concepts are taken for granted, they are often "silent". This may be the reason behind the claim that biology does not have many general theories and concepts as compared to more mathematically based sciences such as physics. Thus, the experimenter has two kinds of relations to previous knowledge: a conscious relation to the specific experimental works that relate to his/hers work, and an unconscious relation to the taken-for-granted concepts and facts in the field (the level-5-statements of "taken-for-granted facts" in the hierarchy of Latour & Woolgar). Knowing specificities and examples of general

workings of the system allows the researcher to think within the network, and in this way get anticipations of links, raise questions etc.

3.3.2 Chain of thought-practice.

The process of thought-practice is harbored within the scientific community, where individuals alone and in cooperation perform the theoretical-practical operations. Thus, the personal abilities will affect the research conduct. I will here mention some factors that impact the individual scientist's performance of the experimental thought-practice.

The scientist's familiarity with the existing knowledge within the field determines which questions that can actually be raised, what scenarios that can be imagined. Also important here is to have an understanding of the knowledge. This is necessary to see links and possibilities, and to separate the important from the less important. Such understanding must also include an understanding of the experimental systems. As the experimental systems harbor certain understandings of material agency, the researcher must connect the technological knowledge to the knowledge within the field in order to organize the material agency for the emergence of new epistemic things.

What is actually done of the planned experiments is dependent on the ability to conduct experiments. Most experiments do not lead directly to scientific findings. In many cases the experimental work is a process of trying to make an adequate setup for registering the specific differences of interest. This depends on the skills of the scientist. A trained experimenter will be able to reach a point of deciding setup faster than an untrained experimenter, who often will have problems with getting reproducible signals from the setup (as an example, the first year of my work on immunoprecipitation of hNatC mostly consisted in trying to actually do an immunoprecipitation).

Whether a setup works is further dependent on whether any resonance can be achieved with the material of interest. The setup and intervention of an experiment depends on the understanding of the material of study and an anticipation of a certain reaction from the material as a response to the intervention. But the material of study can react in unexpected manners - it is an agency not under full control of the researcher. In such cases, the understanding of the material lacks to capture some characteristics that make it behave in such and such manner. The unexpected reaction must be in a conceivable form, for if not the

behavior will simply not be understood. If it can be conceived within the framework of articulation and understanding of the material, then the scientist can draw the reaction into the network of knowledge and use this to create a new understanding or new questions that can be the subject of experimental enquiry. It is this process that Andrew Pickering calls the mangling of practice: a process of accommodation, material resistance, and tuning of the experimental setup for a new accommodation and the framing of material agency (Pickering, 1997). Through this process, the material of study affects the research process in a non-random manner. But since it manifests itself in a "negative" manner, it cannot be fully described as one does not know what one does not know. Thus, the formulation of an understanding will not be a direct representation of a material state.

The relation between mental and practical operations is to a large extent dependent on the particular situation. The idea, question, or hypothesis, is used to make an experimental setup that can capture a specific difference that can in some way give information back to the idea or question. This can take the form of a defined question, a loose enquiry, or for some experiments not even much of a preconceived idea, as the point of the experiment is to give rise to new ideas. Rheinberger describes such conceptual indeterminacy as a necessary characteristic of the scientific process as it provides the necessary flexibility to keep the project in touch with a fecund and relevant problem-field: to keep up-to-date with and define the border between described and unknown.

On this basis the experimental scientist designs projects, formulates questions, and plans experiments. And it is here we can see how the creativity of individuals applies to scientific work. As the path forward is dependent the understanding the creation of an understanding of the previous knowledge, the questions that a scientist manage to raise depends on the intellectual and creative work done on this body of knowledge. This is most apparent when encountering extraordinary original scientific works. One such example is Francis Crick's formulation of the central dogma of information transfer in molecular biology (Crick, 1970).

3.3.3 The experiment detects specific differences.

The aim of the experimental setup is to, with Rheinbergers words, create a space of representation where specific differences between epistemic objects are manifested. These differences must be of such a manner that they can give an answer to a posed question. Of the given hNatC candidate proteins, which of them interacted to form a complex? The

immunoprecipitation experiment addressed the binding properties of the proteins. The difference in binding properties was the specific difference of interest.

The experiment is based upon the manipulation of a more or less controlled matrix of physiochemical parameters and biological constituents in such a way that differences are manifested within the matrix. A research experiment will aim at manifesting hitherto un-manifested differences. In order for the differences to be interpretable, the setup needs to be designed in a *constrained* manner so that the differences produced are *specific*. Ideally, all variables relevant for the outcome of the experiment should be known so that the outcome will be unequivocal. As I described in the section about validity conditions of experimental knowledge, it is the ability of the experiment to show specific differences between material identities that makes the material analysis a fecund producer of scientific knowledge. Therefore, the choice of experimental system - the definition of the matrix, is crucial for the questions asked.

Here one can draw the line of reasoning from Bernard to Rheinberger: the knowledge we derive from the experiment is relational. Through bringing forth specific differences it separates one identity from another. This relation between difference and identity constitutes the epistemic things that resonance in the experimental system. A difference cannot resonance in itself, but two identities can give resonance in different ways: they manifest themselves as different traces in the system.

The philosophy of difference, as seen in various versions with Derrida and Deleuze among others (Deleuze, 1994; Derrida, 2005) can be seen as a critique of the traditional priority of identity that traditionally was given in European metaphysics after Aristoteles[20]. Rheinberger, and also Latour in later works, has showed that this philosophy of difference is well applicable to experimental dynamics. Rheinberger gives a Derridean account for his notion of difference in experimental systems (Rheinberger, 1997 p. 76). Here I will not go more thoroughly into the philosophy of difference, but constrain myself to saying that difference and relations are both fundamental categories for how new entities manifest

[20] As a remark on the side I will suggest that giving one priority over another veils the identity-difference-relation as a composite notion, in this relation identity constitutes difference and reciprocal. That does not mean that difference does not have a central place in practical enquiries into the unknown, for what is the "unknown" other than an identity of absence - a bank of fog where nothing is seen before contours - differences - can be made out in the gray, contours made out of identities.

themselves in experimental systems, and they practical and applicable notions for understanding how an experimental setup is designed.

3.4 Some methodological problems of experimental molecular medicine.

3.4.1 Blind zones in experimental knowledge produciton.

There are some aspects inherent in the methodology and approach of experimental molecular medicine and life science that shapes the knowledge in such a manner that we can expect certain types of knowledge to go on behalf of other types. I will here mention two such aspects.

The narrow specificity of phenomenotechnological tools. The methods within molecular biology and medicine often aim at expanding our range of perception through representing for our senses entities that we cannot directly perceive. A functional protein cannot be seen by the naked eye. Neither can a regular human cell. As the entities are represented through a method, this creates a layer of epistemic uncertainty to the represented as it also means that we have no frame of reference to the things represented except for the methods themselves. If we were studying butterflies, we could be pretty sure that butterflies exist, as far as our senses gives us information about the world around us. When studying enzymes, we can be pretty sure that these exist, as far as our methods give information about the world around us, and we have an adequate understanding of these methods. This understanding is more uncertain as it contains several points of suppositions than direct perception. In the case of the immunoprecipitation we presuppose the existence of cells, proteins, antibodies with binding capacities, the effect of different salts and detergents in the washing process, polymerisation capacity, electrical fields, and charge in the analysis process. This is indeed not unique for molecular medicine and biology, but the point is that it makes the knowledge within the field more abstract as it is dependent on technical-theoretical understanding, and more uncertain as it is dependent on this understanding.

It is in this light the description Rheinberger give of experimental setups is interesting. He describes the design of experimental setups as creating new spaces of representation. For Rheinberger, a certain type of knowledge is made possible by the methods that allow for the representation of entities. Molecular biology was only possible after the development

technologies such as the electron microscope, radioactive isotopes, and genetic models. Prior to these technologies, one had no possibility of perceiving sub-cellular entities.

In his work "Representing and Intervening" Ian Hacking discusses this as an aspect of scientific observation (Hacking, 1983). Hacking's point is that observation comes in many forms. Although an experimental system is dependent on a set of theory, one may very well do observations in the system that intuitively spark interest, without putting to many theoretical assumptions into a spark of curiosity. But maybe more interesting in our case, Hacking claims that it is the disunity of science that allows for such mediated observations. The theories behind electric charge or plastic polymerization are not something we directly include in our understanding of the hNatC complex. Rather, we use one batch of theoretical assumptions within one field to observe another field with its own batch of theoretical assumptions. Assuming that the assumptions of the different fields somehow are relevant for each other.

My point is that often, what is manifested in an experimental system is very specific: the method only gives us information about that which we design the experiment to capture. The representations of entities through a method create a "blindness" as we cannot know what the method does not capture or see. The immunoprecipitation of hNatC subunits made it possible to determine if some of the chosen proteins formed a complex. It did not give us information about whether there were more subunits in such a complex, if the registered complex was a functionally important one, etc. The above-presented problem of confirming versus revoking results must be seen as a coming from this. The easiest conclusions to draw from an experiment are specific confirming conclusions, thus favoring a certain type of observations in the knowledge production.

This makes the knowledge within molecular biology and medicine sensitive to changes in understanding. It should also lead to extra precautions in the application of experimental knowledge, as there is an extra layer of uncertainty and bias in the knowledge.

This blindness has consequences for the interpretation of experimental output. There is an asymmetry between the status of confirmative and revoking statements, or positive and negative results, resulting from experimental output. I will here define a negative result as a result that does not produce a trace in the space of representation of the experimental system.

Doing the immunoprecipitation experiment, we could register that we had immunoprecipitated hMAK3 and hMAK31 together with hMAK10. This showed that however little generality could be ascribed to such an interaction it nevertheless *could happen* in a human model system. In the case of NAT5 we did not detect hNAT5 in the hMAK10 immunboprecipitates. But making a statement about the interaction, or the lack of interaction between hNAT5 and hMAK10, is more complicated. We could not know we did not detect hNAT5 in the immunoprecipitates was due to methodological limitations, that the proteins did not interact in this cell type, that the proteins did not interact in this cell state, or that they actually never interact. The only statement we could make was that in this setup, under these experimental conditions, we could not detect hNAT5 in the hMAK10 immunoprecipitate.

This is an example of what I will call counter-Popperian argumentation. Popper proposed the falsification requirement for scientific statements: a scientific statement is a statement that can be falsified, and all hypotheses should be formulated in such a manner that they can be falsified (Lübcke, 2003). In the case of the immunoprecipitation experiment the reasoning is opposite: if we manage to show that an interaction can happen (as compared to the controls) in some biological setting, this forms the basis for the scientific statement "proteins x and x can interact". If they fail to interact in other setups, this does not falsify the first result as biological systems and experiments are dependent on the experimental conditions. On the other hand, if we fail to see an interaction between x and x (or more specific: if we do not register a trace in the experimental system), this is not a falsification as we cannot know the reason for the lack of trace. To further complicate things, the initial immunoprecipitation experiments did not register interactions between MAK10 and any of the tested proteins. Still we continued to repeat the experiment and tuning the experimental conditions until we managed to obtain a reproducible specific interaction. In a Popperian line of thought this is indeed almost absurd, but in the line of Pickering this is the process of mangling: the tuning of the experiment with respect to resistances in the material agency. We do not know whether the interaction represents something general or rather something more specific or rare.

Topology of the value field. As mentioned in section 4.1.2 the view of a disinterested science is hardly a realistic description. In order to sort and evaluate knowledge, it will always be evaluated with respect to something. It is positioned in what I called a value field. The result

of this is that our knowledge about biological systems centers on entities and processes known to be valuable in the established value field. The topology of the value field will be dependent on the knowledge within the field, and of the understanding of what is important. The field will contain trajectories of phenomena, processes, theories and approaches that will attract new work through the dynamics of intertextualism: scientists will connect their work to entities that are already considered important in order to borrow importance to their own statements. If these become too dominant, they can go on behalf of other approaches. The conception of life and disease, and the methodology to study these, affect how one within a research field tries to accomplish the medical aims. As a result of the analytic approach of experimental molecular biology, that can be said to better at producing knowledge about constituents than at understanding biological systems, some phenomena are the subject of enormous amounts of attention. It could be that this focus on biological constituents go on behalf of an understanding of how biological systems react to and functions to states that the organism experience as normal or pathological.

Taken together, these "blind zones" become important to consider when the knowledge produced in experimental life sciences shall be translated to other contexts. It brings us to the problem of validity and relevance of the experimental life-knowledge.

3.4.2 Validity and relevance of experimental life-knowledge.

When claiming the validity of a statement an important aspect is the limits of the validity: valid with respect to what? This will depend on what the statement claims. The statement "there exists a human NatC complex" aims at being valid with respect to the particular experimental system. The statement "the human NatC complex is a target for cancer treatment" aims at being valid with respect to patient treatment in a clinical setting. The validity of these statements both have to be tested experimentally, the first by setting up an experiment of the type described above, the second by clinical tests and so forth.

This may seem straightforward if statements actually were separated in a clear-cut manner. But as there is implied medical relevance in the work of the NAT-group, the statement "there exists a human NatC complex" is also committed to having medical relevance. Why did we put effort into identifying a hNatC complex? Because it is medically relevant. The reason why it is medically relevant is that it is needed for normal cell growth, and removing it leads

to cell death. But this finding of potential medical relevance was done after the work of identification was done. Still, medical relevance was anticipated.

Here I find a problem with the analysis of Rheinberger. He shows how epistemic things are produced in an experimental system, but he does not give account for how the implied validity with respect to relevance to life in general, and health in specific. The dynamic of the case that Rheinberger describes in "Towards a history of epistemic things" follows the same logic as we see in the NAT-project: one start out with a clinical problem, and one goes out on a 20 years venture of analysing sub cellular constituents. The possible findings are presupposed to be relevant for the initial clinical problem. Is this due to a belief that any information will be relevant for life in some way or another? Indeed it is not often one hears scientists dismiss their work as irrelevant (although there may be many reasons for this).

The experimental analysis, its inherent reductionism, and its presupposed relevance may reveal some blind spots in the experimental culture. Canguilhem criticizes the experimental analysis for removing what is essential about life, namely the state of the organism. When studying a protein, it is how the protein relates the organism as a whole that makes it meaningful to talk about the protein in a pathological sense. In the process of isolating, modeling, and analysis, the experimental molecular biologist has removed himself from the environment, organization, and totality of the organism. But the validity of statements from a specific experimental system must be translated back to the biological context, and as we have seen, this translation is not straightforward. This translation is not only in the form of clinical applications such as medicines, prognostic markers etc, based upon research, such as are found specialized in the field called "translational research". It is also concepts, facts, and rationales formulated within the field of research. And it contains the "blind zones" as described in previous section.

Indeed, translation takes place constantly. But the premise that material analysis is an adequate starting point of such a translation brings with it some theoretical considerations that Strand formulated as the *in vitro/in vivo* problem (Strand, 2003): when statements are moved from an analytic molecular biological setting into a clinical setting, it is moved to a more complex system. How the statement will relate to this system cannot be predicted in a straightforward manner. We cannot predict how the biological phenomena will relate to the biological context.

3.5 Summary: the theory-practice of experimental life knowledge.

In this part I have attempted to give an account of how experimental molecular medicine produce knowledge. I have done this through looking at how conceptions, practices, values, social structures, individual capability, experimental systems, and social contexts interplay to produce statements about nature. My approach has been a near-sighted one, as it has been important for me to make a philosophical reflection that has been closely connected to the concrete scientific conduct. In this way I have aimed at accommodating the philosophical conceptions with concrete practice.

The existence conditions for the experimental approach is the view that organisms can be understood exclusively through physiochemical laws, that the molecular constituents of living organisms forms the basis for health and disease, and that material analysis in the form of the controlled experiment will give us knowledge about diagnosis, prevention, and cure of disease. The controlled experiment further forms the validity condition for deciding whether statements about the molecular workings of organisms are true or not.

As the experiment play an important role, the knowledge production to a large extent takes a practical approach, where the performance of the experiment is crucial for it to form the basis of statements. The performance of the experiment is dependent on individual skill, time, effort, and economical resources. Thus, there is a need to prioritize what experiments to, what kind of knowledge to produce. The choices made are dependent on factors such as the self-understanding of the group with respect to what is their subject of study, the expected outcome of the experiment as compared to expected effort, the expected relevance for health and disease - the position of the statements in the value field, and considerations with respect to publication, lengths of employment and similar. In this sense the knowledge produced is also a product of practical considerations.

The need for making priorities throughout the research process is also reflected in the temporal dynamic of the research. As the experimental system can take both stabilizing and destabilizing function, that is that the experimenter can use the experimental system both to register new phenomena, resistances and differences, but also to stabilize and frame these phenomena through constructing more experimental setups aiming at the production of the

same phenomenon, and repeat these, the researcher has also a choice of whether he/she should open up the experimental system or close it in.

The concrete experimental situation is a thought-practice where the experimenter works within a theoretical-material matrix of understanding, where the technological and material constituents are given theoretical understandings. This allows the researchers to think within the matter, and thus be able to produce new phenomena. The experimental system creates spaces of representation, where new phenomena are represented in a manner that can be understood within the matrix of understanding. In this situation the material agency can react or manifest itself in ways that the researchers had not anticipated on the background of their previous understanding. This will then represent a resistance to their understanding, and through a process of tuning they will try to adapt their theoretical-practice. The scientists will adjust their understanding of the phenomena *and* the experimental setup for studying it in a manner so that the experimental output can be used to determine the validity of a statement about the phenomenon.

Experimental molecular medicine thus creates knowledge within a physiochemical, analytical matrix of understanding and practice. The concrete knowledge that is produced is the result of the theoretical-material understanding, the value field of medicine, the topology of the value field as a result of the relation between theory-practice and values, practical and tactical experimental considerations, and resistances in the material.

4. Re-thinking the theory-practice of molecular medicine.

In part 3 I developed an understanding of the knowledge production in experimental molecular medicine that aimed to capture the *hybrid* aspect of this knowledge production. One of the central insights from that discussion is that there is a connection between the conception of life and the approach chosen to study life. The aim of this work was first to reflect upon the knowledge production within this scientific field, and secondly to see if such reflection opens for a reflexive life knowledge. I will here address the second question: can the philosophical reflection of knowledge production in experimental molecular medicine be developed into a reflexivity within the science itself, that can change the practice of that specific science?

With regard to the second aim I would like to emphasize that since experimental molecular medicine is a theory-practice, a development of conceptions must be done simultaneously as the development of an approach. There must be a co-production of theory and practice, and this theory-practice needs to go through the process of mangling to develop and find its form.

In this part I discuss how a re-thinking of the conceptions of life can open for new types of molecular medicine. First, I will see how George Canguilhem from his critique of the material analysis develops his concept of normativity as a central aspect of life. Secondly, I discuss what conceptions of life and health except for the physiochemical-analytic theory-practice that can be found in the molecular life sciences. Last I will see whether there exist alternative lines of thought that can be tied together with the work of Canguilhem, this in order to form an alternative to the physiochemical-analytic theory-practice.

4.1 Georges Canguilhem: the normativity of life.

The importance of the works of Canguilhem in this context is twofold. First, through his criticism of Bernard, Canguilhem reveals some of the conditions that made possible the experimental approach, and he shows that the conditions and approach are intrinsically connected. This aspect of the philosophy of Cangilhem can form a basis for a self-reflective theory-practice within the science itself, where values, presuppositions, conceptions, and

practice can be included in the same reflective thought-practice. Secondly, through handling both the conceptions of life *and* discussing the approaches used for studying life Canguilhem also opens for a simultaneous re-thinking of the conceptions and the approaches. As was mentioned in part 1, Canguilhem states that scientific concepts are used as tools to pose scientific questions. Scientific concepts can be used in different scientific contexts to open for new ways of understanding. The development and use of concepts raise questions, and these questions find their explanation in the form of scientific theories (Resch, 1992 p. 180). An example is the import of the term "information" from informatics to molecular biology, which led to the theory of genetic information storage and information transfer. Thus, if we want to re-think the scientific theory-practice and develop new ways of scientific thinking, an important part of the job is the development and discussion of scientific concepts.

Maybe the most important insight from Canguilhem with respect to the development of scientific concepts is the notion of biological *normativity* as characteristic of life. Here, I will discuss two of his works, namely "The Normal and the Pathological" (Canguilhem, 1991), where he analyzes the sciences of physiology and pathology, and "Knowledge of Life" (Canguilhem, 2008), where he looks at biology and the study of life in general. Through a discussion of these works I will see how Canguilhem develops the concept of normativity as an alternative to Bernard's concept of normality, and thus creates a new frame of reference for understanding health and disease.

4.1.1 Conceptions of normality and pathology.

In his work "The Normal and the Pathological" (Canguilhem, 1991) from 1943 (and expanded in 1966) Canguilhem performed a historical analysis of medicine, where he traced the medical concepts and approaches, and how these were constituted. Medicine, stated Canguilhem, came from a therapeutic need. Disease had always had a strong impact on the life of humans, and throughout the history of medicine the conceptions of disease and therapy took various forms.

The positivists had a statistical understanding of pathology. For Bernard, the relation between the normal and the pathological state was a homogenous one (Bernard, 1957 p. 146). The pathological state was a quantitative modification of the normal state, and every pathological state had a corresponding normal state (Bernard, 1877). But Canguilhem asked: if the pathological state is merely a quantitative modification of the normal state, where can

we draw the objective border between normal and pathological? For Bernard the normal was a constant frame of reference, but defining the normal in itself was not easy. Indeed, said Canguilhem, Bernard aimed at creating an objective pathology, but he did it through a conception of normality and pathology that abandoned the originality of normality and pathology in life. There is a qualitative difference between a normal and a pathological state. For the organism a pathological state is something qualitatively different from a normal state (Canguilhem, 1991 pp. 87-88).

To understand how the pathological state differs qualitatively from the normal one, Canguilhem proposed we have to understand disease on the level of the total individual (Canguilhem, 1991 p. 108). The pathology manifests itself to the organism in the sense that the organism's standards of living are somehow restricted. An alteration that does not lead to restriction will not in itself be seen as pathological. Thus, being sick leads to a qualitative change of life for the diseased (de Cuzzani, 2004).

The state of disease as a restriction points at an important characteristic of life, namely that life is not indifferent to its state. In this lies the *normativity of life*. Canguilhem creates a conception of life: life is normative. It is something to which its state is *not indifferent to itself* (Canguilhem, 1991 p. 129). The biological normativity is an activity of the organism itself.

The organism maintains its norm with respect to an environment. Organisms can live in environments that are more or less suitable. "Health" is a state where the organism manages to control and maintain its own norm within the environment it lives. The pathological state is marked by a change that makes it impossible for the organism to maintain its norm. Thus, it is biological normativity constitutes the existence of normal and pathological states in medicine. The biological normativity separates the life sciences from other natural sciences. There is no pathology for a quark; there is no pathology in chemistry or physics. The experience of pathological states can only be evaluated in terms of the relation between the environment and the organism's adaptation to the environment: how does the organism react to disadvantageous states, and what are the margins of tolerance for change in state and environment (Canguilhem, 1991 p. 197)? The organism has a margin of tolerance for the inconsistencies of the environment, and can thus be healthy even when the environment changes.

Science describes the environment in terms of theoretical abstractions. But a living creature does not live among natural laws and abstractions. It lives among events that vary by these laws, in a world of possible events and unexpected resistances. The living being recognizes health only on the level of experience: in the opportunities in and tolerance of the environment. Humans feel healthy when they not only can tolerate the environment, but also affect it and themselves; when they are "more than normal", when they are able to establish new norms, new ways of life[21]. Humans feel diseased when they are hindered in this ability to affect their own life, when they are restricted. Thus, health and disease does not differ by biochemical properties, but by biological value.

As medicine deals with health and pathology, medicine itself becomes a normative activity. Medicine must be understood as an effort of the human organism to manipulate with the potential states of the human organism in order to achieve more beneficial states. It is the spontaneous effort of the living being to dominate life and the environment, and organize this according to its values as a living being. It is here medicine find its meaning as a scientific activity. The development of therapy is a development of approaches for changing the state of the organism into a state where it better can maintain its norms. This is not a complete restoral of a "normal" state, as the organism will always be affected of its earlier states. To be cured is rather to develop new physiological constants and organizations for the organism to maintain a beneficial state (de Cuzzani, 2003 pp. 122-128).

After defining normativity as a central aspect of life, the next question for Canguilhem was: does the experimental approach address these aspects of life? When the context is so important, in what sense are the laboratory standards appropriate to serve as the norm for the functional activity of the living being outside the laboratory? Canguilhem states that the functional norms of the living being, as they are examined in the laboratory, are only meaningful within the framework of scientific operative norms. The laboratory itself constitutes a novelty that cannot be directly interpreted back into the original environment of the organism. Animals subjected to experiments in a laboratory setting are put in a state of artificial pathology. The laboratory as an environment itself establishes new norms. The

[21] This conception of the normal bears resemblances to Sartre's conception of freedom, as presented in Being and Nothingness. Sartre here explains freedom as the ability to constitute a new meaning for oneself as a self (Gutting 2001 p. 139). For both Canguilhem and Sartre it is the transcendence of ones earlier self that is central for the normativity or freedom of the individual, respectively.

material analysis gives observations about different states of the organism, and these states can be said to more or less be associated with a pathological state on an organism level. But for a cell in a human body it gives as little sense to talk about a pathological state. As Canguilhem puts it:

"To look for disease at the level of cells is to confuse the plane of concrete life, where biological polarity distinguishes between health and disease, with the plane of abstract science, where the problem gets a solution" (Canguilhem, 1991 p. 223).

As the material analysis does not address the basic medical problem it should not be the basis of medicine. To understand the qualitatively different experience of disease, we must understand the conditions under which organisms are able to maintain their norms, their normativity. Rather than to split up and analyze the underlying constituents of organisms in physiochemical terms, one should aim at a life science that understands the original normative aspects of organisms.

4.1.2 Life science and the characteristics of life.

In the work "Knowledge of Life" (Canguilhem, 2008) from 1952 and expanded in 1965 and 1992, Canguilhem addresses the topic of life science in relation to life more in general than in "The Normal and the Pathological". What are the characteristics of the living, and what demands does these put on the sciences that have the living as their object?

Canguilhem starts with describing science itself as a part of the normative activity of life. The motivation for enquiring knowledge is a search for security through reduction of obstacles. With the construction of theories through a process of assimilation we can re-organize the human life and its relation to the world. The universal relation between human knowledge and living organization is shown through the relation between knowledge and human life. It is this perspective that allows humans to attribute value to facts: *by distinguishing those facts that have a real relation to the organism from those that are indifferent to it* (Canguilhem, 2008 p. xx).

As described in "The Normal and the Pathological" the life sciences reflect their object of study. The authenticity of biological knowledge lies in that the biological concepts form a kind of mimesis where they are designed to represent and describe the organism. This mimesis can be said to be due to some special problems stemming from the complexity of

the biological, leading to some methodological considerations that need to be taken into account in the life sciences (Canguilhem, 2008 pp. 11-15):

1. Specificity. The specificity of an observed biological phenomenon limits all logical generalizations in ways that cannot be foreseen. Thus, there are reservations in all generalizations made about organisms.

2. Individualizations. Organisms are individuals, and they vary. This makes it challenging to find representative objects of study.

3. Totality. Given that an organism is a totality that is changed with every attempt of removal: it possible to analyze what determines a phenomeon by isolating it?

4. Irreversibility. Organisms have irreversibility to them: they develop and change with time. This makes chronological extrapolation and prediction hard.

The individuality of organisms, together with the irreversibility of biological phenomena, limits the possibility to repeat and reconstruct the conditions of a certain phenomenon. With the points 1-4 given above in mind Canguilhem again rises the question of whether the experimental physiochemical approach to biology gives us the most important answers about life. Will the knowledge resulting from experimental medicine give us an understanding of the original aspects of life, and of health and disease as normative states?

Through the physiochemical approach Canguilhem argues that biology devaluates its own specificity. If one wants to capture the originality of life, it would have to be through the originality of the total experience. The physiochemical sciences have determined laws between objects without a point of reference. But as organisms are not indifferent to their state due to their inherit normativity, the relation between the milieu, both internal and external, is important for understanding the organism itself. It is the living being's experiences with the milieu that gives meaning for the organism. It is this totality of relations between the organism and milieu that must be the frame of reference for knowledge of life.

Canguilhem brings forth the term vitalism to restore the independence of biology. The term vitalism is problematic as it was used for the special vital forces that Bernard fought against with the physiochemical approach. Canguilhem does not claim that there are such special natural laws for life. On the contrary he opposes such views. But the meaningful aspect of

vitalism, he says, is to look for meaning in the relation between life and science: life science. Canguilhem's vitalism is to look for the specific aspects of life that lies in life's polarity, normativity, and organization.

This vitalism is anti-reductionist. A living being cannot be reduced to a crossroad of influences alone. It has its own meaning, and for the organism this meaning is *being*. Where as a machine would verify the norms of predictability, the living acts in accordance with indeterminism: it tolerates changes in the internal and external environment, and it lives by improvisation. These are necessary qualities for an organism, because an organism does not live in a world of abstract natural laws. It lives in a world of unforeseeable events and variations that occur in accordance with natural laws. From this point of view, meaning is an appreciation of values in relation to needs such as hunger or survival. For the organism that experiences the needs they are irreducible, and therefore an absolute system of reference. "Vitalism" is an expression of the self-identity of life within the living being that is conscious of life (Canguilhem, 2008 p. 62).

4.1.3 A normative life science?

From Bernard and Canguilhem we see that the complex and normative nature of biology and experimental molecular medicine sets the agenda for how these sciences should be understood. I will here discuss how Canguilhem, through the establishment of normativity as a central characteristic of life[22] also proposes a new conception of life, and a new life science.

Bernard's solution to biological complexity, and to the medical aim of curing disease, is the controlled experiment: we don't know what nature will look like before we have tested it, and the adequate method is the controlled analytic experiment. Bernard defines the boundaries of the experimental system by defining relevant and irrelevant factors: physiochemical properties are to be considered. Vital forces in the meaning of soul and similar, is not to be considered.

Bernard's description gives a scientific practice that both claims fecundity and validity, and that can be readily translated to practical work in other laboratories. This is indeed a great

[22] I here use the term "life" to designate what Canguilhem call "le vivant" ("the living").

strength of Bernard's work. But the problem with this experimental reductionism is, in my opinion, that what was an approach, has turned into a dogma. For Bernard, biological systems could be explained fully by the underlying constituents and processes. Still, he was no full reductionist as he claimed that the organization of constituents in organic systems makes living organisms qualitatively different than the non-living. But a tendency in molecular biology and medicine has been to claim that a phenomenon can be fully understood by, or *reduced* to, the underlying constituents. One might say that since Bernard's grasp on totality was so much weaker than his proposed method of analysis, the practical-theoretical philosophy of Bernard pointed out the direction of reductionism. Bernard warned about generalizers who did not know the specificities of biology. But in the heyday of experimental molecular medicine many experimenters themselves have become generalizers of methodology and concept. This may stem from a lack of self-awareness in Bernard's work: that his method itself contained values, interests, and a certain perspective. In establishing a methodology that is adequate for studying life, Bernard also establishes a certain view of life. It is this that Canguilhem points at in his analysis of experimental medicine.

The strength of Canguilhem is his analysis of concepts: the principle of normativity of life and how this is reflected in medicine. Medicine becomes a normative science, where the special characteristics of life, namely normativity and totality, set the perspective in which medicine is conducted. Canguilhem criticizes Bernard's material analysis for being to reductionistic, and not take into account the organic totality in which health and disease makes sense. This is indeed a relevant criticism, and Canguilhem points at how life science would benefit from a larger emphasis on the totality of the organism.

But in this we find some of the problems of Canguilhem's work: in developing a new view on life and disease, he also claims that this begs for a new life science. This life science should reflect the perspective of totality on health and disease. He draws the consequence of the interplay between how we view the world, and what values constitute this view. Canguilhem is not so much interested in how knowledge is produced in experimental medicine as in what kind of knowledge should be produced. But Canguilhem does not suggest how this could be dealt with practically. He sheds little light over the concrete process of knowledge production, and about how the road to the proposed new life science should be built. As Canguilhem does not go into the practical aspects of medical and

biological knowledge production, he also fails to raise his propositions of a new life science as a feasible alternative to Bernard's program, at least for the experimental life sciences.

4.2 The tension between the reductionist approach and the complexity of life.

The material analysis with its inherent reductionism has had a strong influence on molecular medicine and the experimental life sciences. I have here tried to see how the experimental life sciences, although based on the material analysis, have tackled the complexity of biological systems. My suggestion is that even though there is a widespread view that the life sciences should be mechanical, analytical, and physiochemical, the life sciences has developed conceptions and practices to deal with the complexity and originality of life.

4.2.1 There is a tension between the reductionistic and the integrative understanding within the molecular life sciences.

There have been many attempts to define life, also in the age of molecular life science. Phenomena such as viruses have problematized what could be called living or not. Often, attempts of defining life list some characteristics that organisms must fulfill to be considered a living organism. For example, Nealson & Conrad list these characteristics that a phenomenon must have in order to be living: i) a structure for conversion of energy into a biologically useful form, ii) a unique chemistry associated with the structure (for terrestrial life this chemistry is carbon-based), iii) replication with fidelity, iv) evolution, v) energy consumption of energy for the building of its (complex) structure, vi) means to escape its own metabolic end-products (Nealson & Conrad, 1999). Koshland takes a somewhat different approach, suggesting seven kinetic and thermodynamic pillars of life: 1) Program, a plan that describes the ingredients and the kinetics of the living system, 2) improvisation, the ability to change the program in order to meet the events of the environment (it is here meant on the level of evolution of a group of individuals through mutation and selection), 3) compartmentalization in order to maintain the arrangement and kinetics of the system, 4) energy - life involves reactions that consume energy, 5) regeneration in order to compensate for thermodynamic and material loss, for example in the form of import of chemical substrates or mechanisms for maintenance of structure, 6) adaptability to the surroundings, as for example searching for food when deprived of nutrients, 7) seclusion, that is specificity

of constituents in order to allow for necessary reactions within the volume of the organism (Koshland, 2002).

As I suggested in 3.1, one of the presuppositions of experimental molecular medicine is a belief that life and disease can be understood by its underlying physiochemical properties. This is reflected in the examples above by the emphasis on a distinct chemistry, the importance of chemical specificity, and the use of physiochemical terminology in the formulation of the characteristics. But in these examples we also see other conceptions of life that does not fit with a reductionistic understanding. Notions such as improvisation, replication and organization do not directly translate to a mechanical or physiochemical explanation. Such notions refer to organisms as organized and complex entities, and they do not have corresponding concepts within the inorganic sciences (as I know of). Thus, although the reductionistic approach has had a large impact within the experimental molecular life sciences, *and* for how these sciences understand themselves, there are other less pronounced conceptions of life within the experimental molecular life sciences. There is thus a co-existence between explaining life at a physiochemical level and the *need for specific concepts and understandings* that capture the complex organization of living systems.

Rheinberger gives a striking example of the surprises that comes with complexity in biological systems, namely the introduction of information theory in genetics and molecular biology during the 1950s. Rheinberger quotes Mahlon B. Hoagland in that a vocabulary that included expressions from information theory formulated a new and clearer understanding of the field (Rheinberger, 1997 p. 157). In order to take the understanding from the analyzed constituents to the biological function, a leap in conceptual understanding was needed. This new understanding was the formulation of a synthesis that included another level of organization that the participating constituents. It did not come directly from the disciplines related to experimental molecular medicine or biology itself. Rather, the concepts came from informatics theory, cybernetics, and physics. The concepts of information transfer came from information theory, the notions of organisms as self-regulatory systems came from cybernetics (Rheinberger, 1990). In "What is life" from 1944 Erwin Schrödinger proposed that biological traits that were inherited from one generation to the next had to be stored in the physical structure of the organism, and that this structure somehow specifically was transferred to the next generation (Schrödinger, 1992 p. 61). Crick pointed at this as an

influence for his work on the DNA-structure (Rheinberger, 1990). This work of getting an understanding of what is today considered basic constituents and principles of molecular biology required a leap of conceptual understanding. The explanation of the biological macromolecules in terms of information storage and transfer introduces notions and conceptions that cannot be reduced to a lower level of complexity. There is a qualitative difference between the organization of the biological macromolecules in their biological context, and their building blocks. This difference is unique for living organisms. At the core of biological reductionism, organization plays a leading part.

Michel Polanyi has argued that such irreducible leaps are found between many levels of biological organization (Polanyi, 1968). This is the background for the many disciplines of biology that analyze biological systems on different levels: molecular biology, cell biology, histology, physiology, embryology, ecology etc. They deal with different levels of biological organization. One cannot fully understand the molecular biological phenomena without seeing it in its biological context - an enzyme as part of a pathway or a cell as part of a tissue. And one cannot understand biological systems without seeing them as ways for the organism to maintain life in a world of more or less unprecedented events.

4.2.2 Life science has developed approaches to tackle the originality of life.

Due to the originality of life, Canghilhems list some methodological considerations in the life sciences (section 4.1.2) that cause problems for a strictly reductionistic experimental approach. As presented in the last section, the molecular life sciences have developed more conceptions of life than the reductionistic and mechanical. I will here discuss how the points of Canghuilhem has been addressed practically in the molecular life sciences, before I in the next section see if these practices have a critical potential for the re-thinking of experimental molecular medicine.

1. Specificity. The specificity, or more precise the functional specificity, of biological phenomena is reflected in the need to confirm statements experimentally. A biological phenomenon may be structurally similar in different contexts (e.g. the expression of a particular gene), while the functional specificity (the role and effect of that gene in the different context) may differ. The elaborate experimental effort within biology can be seen as a necessity in order to tackle the functional specificity of biological phenomena.

2. Individualisation. The individualization of organisms, both on a species and organism level, has been considered a factor that adds to the problems of general concepts. This has been met by standardized model systems, as so to allow for comparing. But as nature appears far from standardized this leads to a problem when considering the generality of the phenomena. There is indeed a tension between the need for standardization and the individualization of organisms, as well as the need to know the generality of an observed phenomenon. This can be done either by investigating the phenomena with respect to the general concepts that actually exist within the field qualitatively by a specific experiment, or quantitatively by the use of statistics. Alternatively, the individual nature of the phenomena is interesting itself, something that especially in medicine brings forth the large literature of case studies.

The individual nature of organisms has also given rise to projects such as the 1000-genomes project (Africa, 2010), as well as the registration of genetic variations in the Single Nucleotide Polymorphism database[23]. The enterprise of personalized medicine can be viewed as a practical and clinical effort of tackling the individual nature of life and disease (see for example (Offit, 2011)). The aim of personalized medicine is to have sufficient knowledge of the causal factors of disease for each patient in order to tailor the treatment for each patient. For example, as the development and progression of cancer is a highly individual process, personalized cancer treatment would target not the cancer as a cell growth phenomenon *per se*, but rather target the concrete process of cancer development in that individual patient. In personalized medicine the dream of a full causal understanding of life takes a clear manifestation[24]. But also, personalized medicine is an acknowledgement of the individual nature of organisms, and of the causes and progression of states that become pathological for the individual organism. Thus, individualization is a problematic, but not un-addressed, aspect of life science.

3. Totality. As an organism can be said to represent a totality that will be changed when disturbed, how can biological phenomena be studied by analysis? This is one of Canguilhem's main points of criticism against the experimental approach. Totality, or studying organisms as systems has been a focus within the relatively new area of the

[23] http://www.ncbi.nlm.nih.gov/snp

[24] For an example from Norwegian scientists: http://www.forskning.no/artikler/2011/mai/288166

molecular life sciences that is called systems biology[25]. The rise of systems biology as a sub-discipline has been enforced by large amount of experimental data that can be produced with current molecular biological techniques (allowing more variables to be studied simultaneously), the development of computer technology for modeling and integrating data, and theoretical biological works that has pointed on the need for a systematic understanding of biology (Hood, 2003; O'Malley & Dupré, 2005). This will be further handled in section 4.3.

4. Irreversibility. The irreversibility, or I will call the temporal specificity of organisms is the foundation of disciplines such as developmental biology (on a species-plane) as well as evolutionary biology (in the sense that evolution is an unidirectional process where the current state is directly dependent on previous states and events). We may say that organisms are temporally specific/organized, and that this organization is irreversible. Also, within the handling of model systems and molecular studies time plays a role. For model systems, the age of the organism must be considered. For molecular studies temporal processes such as cell cycle and circadian rhythms, and enzyme kinetics are all important subjects of study.

Biology and medicine has thus dealt with many of the characteristics of their study organisms. On this level biology and medicine reflect the originality of life and organisms through two understandings of life: one that emphasizes the physiochemical aspect, with focus on the causal mechanics of constituents, and one that sees the need to tackle the characteristics of life through an understanding of organization, context, and adaptation to the life-world of the organism. These conceptions often exist side by side, both shaping the conduct of the life sciences.

4.3 Towards a new theory-practice of molecular medicine.

Through stating that that the conceptions of the study object and the approach for studying this, is connected, Canghuilhem shows that through a critical analysis of the concepts it is possible to develop new conceptions, and perhaps new approach and practices based on these new conceptions. In this way the room for critical re-thinking is increased within the

[25] The study of biological contexts at various levels has a long history within other biological sciences such as for example ecology, which study the relations between organisms and their physical environment (Apple Dictionary Version 2.3.2 Apple 2005-2009).

science. As the approach and conception is no longer seen as a rational or naturally given, it opens for a discussion and de-stabilization of the conditions of the knowledge production. Canghuilhem, Latour & Woolgar, Bachelard and Rheinberger give tools for putting the thought collective in perspective, for destabilizing the presuppositions of the knowledge production, and for creating spaces for intervention into the theory-practice.

But why should the concepts of normality and disease, concepts that only are valid on the level of the total organism, be important for the molecular life sciences? The notion of normativity brings in a new perspective for which to understand biological systems, also on a sub-cellular and molecular level. If biological systems have developed into maintaining the normative state of the organism, we need an understanding of how the biological systems work at various organizational levels to do just this. What characterizes a molecular biological system that can react, buffer and tackle changes in environment, sudden events, damages and dangers?

On the basis of Canguilhems critique of experimental medicine, and his development of the concept of normativity, I would suggest that experimental molecular medicine put a larger emphasis on understanding molecular constituents as functional parts of biological systems that have developed to maintain certain states of the organism. This means understanding how sub-cellular systems vary, react to, and buffer the events in the life of an organism. With respect to pathology it means understanding what state the systems are in when the organism has an experience of disease, and what mechanisms exist for restoring a desired state. When connecting the experience of disease on an organism-level with the molecular dynamics one will avoid a "molecular pathology" as one on a molecular level only will deal with different states of systems. On this level one cannot talk about "error" as this introduces values and meanings into a biological level of organization where such concepts do not make sense. On the molecular level there is only variation.

The medical meaning must only be given with respect to the experience of disease of the individual. The frame of reference is not a "normal" or "abnormal" state, but rather *the way the organism manages or fails to manage its normativity*. The challenge will be to determine how biological systems are organized for the organism to maintain desired states. As biological systems have developed into tackling such conditions, this also affects the understanding of pathology. How much disturbance, variation, and change can a biological

system take before the organism experiences a pathological situation? Emphasizing the system and the context, also on a molecular level, will change the trajectories for relating phenomena to health and disease within the field. A phenomenon will be valued with respect to how it relates to the biological context, by whether it is important or indifferent for the biological system. In this way, state and normativity can become an organizing principle for experimental molecular medicine.

Another point is that to understand a molecular phenomenon in a context, there must be ways to transfer a phenomenon into different contexts. If NatC were studied in cell culture, how would the conclusions from that study translate into a tissue or organ-context, or to an individual context within personal medicine? Here, systems-to-systems understanding is needed. One might say that these are not molecular problems in themselves, but if we want to understand the parts and the whole, as is the goal for molecular medicine, these are the problems that are at the core of the medical aim of molecular medicine.

Which methods will develop as good tools for studying life and health as a normative activity is beyond the scope of this work, as it is best handled in the development of the theory-practice through mangling (thereby the subtitle of this work: *primers* for a reflexive life knowledge). I will here only briefly suggest some possibilities. Important for these is that if they are to work as forces generating new thought-practices, they must succeed at becoming fecund trajectories within the medical value field.

Experimentally, although challenging, the focus should change from single-constituent analysis to system-state understanding. The problem here, maybe even more than with single-constituent-studies, is the problem of generality and singularity. When understanding systems and states, there is a tension between the individual organization and a more general understanding of systems. Personalized medicine bears within itself an emphasis of disease as an individual state. Understanding how individuals can vary with respect to the organization of the biological systems can give understanding of how systems can be built and can vary to maintain a norm within different frames of variation.

As was mentioned above, systems biology has developed as a sub-field that put emphasis on molecular and cellular context. An increased emphasis on totality and context, and the approaches used to study this, will change both the conception of biological systems as

conceptions of understanding and methods for studying biological systems are developed. (O'Malley & Dupré, 2005). Developing modeling tools for understanding experimental data is a potentially important supplement to experiments.

The concept of normativity can be used as the basis for asking new questions in molecular medicine. By making normativity an organizing principle for biological systems, this begs for an understanding of how the biological systems are constructed to maintain the norm of the organism. Molecular medicine should therefore aim at studying how biological systems react to disturbance and variation, how they are constructed to meet the unanticipated events that make up the life of an organism, and what states underlies and connects to a pathological experience for the organism.

5. Conclusion.

Experimental molecular medicine has developed into a major scientific discipline. It has during the last 60 years had significant impact on health, and disease, and on the understanding of life. The introduction of molecular biological understandings and methods into many medical disciplines can indeed be called a paradigm shift of medicine. This work has both been a philosophical investigation of the knowledge production within experimental molecular medicine, and an effort to open experimental molecular medicine to a reflexive development of its concepts and approaches.

Experimental molecular medical knowledge production is a hybrid activity.

The main aim of this study was to investigate how experimental molecular medicine produces knowledge. To address this I first discussed how Claude Bernard proposed the experimental approach as method for producing knowledge about the physiochemical processes underlying health and pathology. I then discussed how the historical epistemology described scientific activity as situated and conditional. From the works of Canguilhem, Rheibnerger, Latour& Woolgar and others, it became clear to me that the knowledge production is a hybrid activity. Worldviews, presuppositions, values, practical and tactical considerations, material agency, experimental systems and individual capability all participate to shape the resulting knowledge. *In order to understand how knowledge is produced in experimental molecular medicine we must understand how these factors work together in a hybrid process*.

From the works presented in part 1 I did not get a sufficient integrative understanding of the hybrid aspect of knowledge production. In my opinion, *there was a need to develop conceptions that could be used to simultaneously involve the above-mentioned aspects in an understanding of experimental molecular medicine*. In order to address this, I used the conceptions presented in part 1, and a reflection over my own experimental work (part 2) to develop concepts and an understanding of the conditions, organization, and conduct of experimental molecular medicine, and of the knowledge that it produces.

Even though I in this reflection tried to maintain some general lines of understanding, using specific cases will lead to a polyphony in the philosophical understanding of the scientific

work. It is as if the de-coherence of the scientific process itself is reflected in the philosophical enquiry. I believe that if other examples had been chosen as case studies, the outcome and conclusions of the philosophical work would also look different. This may go in behalf of the general overview, but it also emphasizes the claim of Bachelard and Rheinberger that instead of general understandings of science we should look for the local rationalities in scientific conduct. These local rationalities are also a result of the polyphony of our understanding of the world. When trying to conceive such rationalities or knowledge-producing customs by philosophical reflection we should try to avoid overly generalizing concepts.

In part 3 I develop an understanding of experimental molecular medicine as a theory-practice. Experimental molecular medicine is based upon the physiochemical conception of life. The controlled experiment is the main argument for determining whether statements about the world are true or not. The experimental process is a process of mangling; where the scientists tune their experimental setups and theoretical understandings in order to accommodate the resistances the material agency gives in the system. Through the *theoretical-material matrix of understanding* of the experimental system and the knowledge surrounding it, scientists try to stabilize phenomena that can form the basis for making statements about the world. Through this process of mangling the theoretical-material matrix of understanding is constantly re-organized to include new and unanticipated understandings.

The experimental process is a practical activity that demands time, effort and resources. In order to focus their work, scientists create a self-understanding of their work as a "*research project*" with a certain scope and certain. In the process of planning experiments, different economical, practical, rhetorical, and technical considerations are balanced. I emphasize two factors that affect which experiments and questions are pursued. The first is the variation of the *openness and closedness* in the project process. In order to efficiently produce new and robust statements the researchers must balance their project between subversive and hypothesis-generating phases, and phases of stabilizing phenomena and building support for statements. The second aspect is the *value field* of medicine. I have developed the concept of value field to describe the effect scientific aims have on the value that is ascribed to scientific statements. For medicine the value field is defined by health and disease: statements that are relevant for health and disease are considered more valuable than facts

that are irrelevant to health and disease. The concept of value field differs from a regular concept of relevance in that there may exist several aims in the same field, and the scientists *position* their work after one or more of these. In order to increase the value of their statements, scientists can attempt to connect their statements to established valuable knowledge within the field. In this manner *trajectories* are created and enforced within the field. Such trajectories can be seen as trend-topics and buzzwords throughout the scientific community.

The concept of normativity can point to a new theory-practise in molecular medicine.

The second question posed in this work was whether a philosophical reflection over the knowledge production in experimental molecular medicine could lead to self-reflection and a subsequent change of the theory-practice within experimental molecular medicine itself? In part 4 I investigate whether Canguilhem's concept of biological normativity can open for new questions and understandings within experimental molecular medicine. I suggest that it is indeed possible to make normativity a central concept in the understanding of health and disease. If we see health and disease as constituted by the ability of the organism to maintain certain norms, normativity will form a trajectory within the value field of molecular medicine. Biological systems and phenomena must be given value with respect to whether they affect the ability of the organism to maintain a desired norm. *To understand how organisms maintain their norms we need an understanding of how biological systems, also on the molecular level, are constructed to meet the challenges throughout the life of the organism*. The development of such an understanding must come from a theoretical-practical process of mangling that take the biological normativity as its organizing principle.

Some general considerations of this work.

This work started as a philosophical enquiry, but as it developed the works of biology and philosophy got more and more entangled. Conceptions from the philosophical reflection appeared as useful tools for planning, explaining and conducting my experimental work, and the experimental work and experience shaped the philosophical understanding of knowledge production. The work took a truly trans-disciplinary form.

Being a practitioner of the life sciences, I have found many works, including Latour and Canguilhem, hard to apply to the theoretical-practical experimental life sciences. They do

not readily translate into the theory-practice of the experimental work. This has perhaps not been the aim for these works. But in my opinion, they then also loose relevance, and they make a divide between the philosophy of sciences and the sciences themselves that neither parts should be satisfied with.

In his later work "We have never been modern" Latour mentions the post-modern view of knowledge as local and de-coherence (Latour, 1993). In the same work he argues for that de-coherence veils the fact that different forms of knowledge are woven together in the social and political field. Latour states that as the different fields of knowledge have, mediation is needed to show how for example natural science affects the way we live our lives and conceive the world. Scientific activity and power needs to be challenged in its conceptions, values, and consequences. Therefore, an integrative understanding of the knowledge production is needed,

In this sense, this work has also been a work of mediation. It has been an aim that this work should be as interesting and relevant to read both for philosophers and biologists. If I have succeeded I am not to judge, but I am not in doubt that the philosophy of science that was presented in the introduction of this work is *important* both to science and to society, but that significant amounts of its potential remains to be unleashed before it is readily *translated into the practice-language of scientific theory-practice*. Trans-disciplinary work is needed to develop scientific activity in such a way that it benefits from the insights of philosophy of science.

In a famous quote, Marx claimed that philosophers interpret the world, but the aim is to change the world. Heidegger argued against this, saying that to change the world we must have a certain interpretation of it[26]. To this I will add, in all modesty, that intervention is a powerful way of changing interpretations. Experimental molecular medicine has changed the way we understand health and disease, the way we see ourselves as living beings, and our view of life in general. These changes come both through the ethical and political debates surrounding the field, but maybe most of all they come from the constant enrolment and production of new phenomena of life into the phenomenotechnical field of molecular life

[26] http://www.youtube.com/watch?v=jQsQOqa0UVc

science. This emphasizes the importance of a reflection over science that includes both the conditions, conceptions, practices, theories, and results of scientific activity.

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