Lab-on-a-chip in The Netherlands

How can the development be understood and what can be expected of the future?

October, 2012

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Science and Innovation Management
Master thesis
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Acknowledgements

This thesis marks the completion of the master Science and Innovation Management. In addition, it is the end product of more than six years of study at the University of Utrecht. To realize this master thesis, I have been supported by many people, whom I would like to thank here.

First of all, I would like to thank Prof. Ellen Moors, my thesis supervisor, for her support and feedback during the process of this research. Her insights have greatly contributed to this thesis.

Second, I would like to thank Prof. Harro van Lente for his willingness to be the co-supervisor and his feedback on the research approach.

Further, I would like to thank the interviewees for their willingness to participate in this research. In addition, I would like to thank Colette Bos for her feedback on the results.

Last, I would like to thank my girlfriend, family and friends for their support and understanding during this research.

Abstract

Nanotechnology based lab-on-a-chip devices facilitate faster, cheaper and more accurate analyses than conventional measurement techniques. In addition, they provide the opportunity for direct analyses at location, such as a patient's home. Besides medical applications, lab-on-a-chip devices can be used for bacteria detection in the food industry, monitoring environmental pollution and continuously screening of chemical processes. However, despite these advantages and various application possibilities, the market does not take off. This hampering development of nanotechnology based lab-on-a-chip devices is the focus of this research. One of the frontrunners in lab-on-a-chip is The Netherlands due to a strong electronics sector and high quality research in life sciences. In addition, the Dutch government is investing heavily in public-private programs, such as NanoNextNL, to stimulate the development of lab-on-a-chip. Although the investments have resulted in the production of nanotechnology based lab-on-a-chip devices, the development of lab-on-a-chip is also hampered in The Netherlands. This research aims to understand this development with the research question being: "*How can the development of lab-on-a-chip in The Netherlands be understood within the period 1990- present and what can be expected of the future?*".
First, scientific literature on lab-on-a-chip technologies has been studied in order to identify the different technologies which served as a mapping tool for categorizing the various developments of lab-on-a-chip in The Netherlands. Hereafter, an event analysis has been conducted for lab-on-a-chip technologies in general, which served to sketch the Dutch lab-on-a-chip landscape with its most important development processes and the actors involved. The most important actors in The Netherlands, derived from this event analysis, were categorized according to this distinction based on the lab-on-a-chip technology they relate to. Next, a detailed event analysis has been conducted per technological development pathway, to describe a narrative per technological development pathway and to reveal differences in the particular development processes. The Technological Innovation System (TIS) approach served as a heuristic tool in detecting these development processes. Lastly, each technological development pathway has been investigated in terms of the interpretations by the actors involved of lab-on-a-chip technology to reveal differences with respect to the socio-technical development of each technology. The theory of Social Construction Of Technology (SCOT) approach was used to study this socio-technical development. The combination of the TIS and SCOT analysis served as the framework this study used to understand the development of each lab-on-a-chip technological development pathway present in The Netherlands. This understanding is visualized with a technology roadmap in which past, current and future developments are depicted.
The results show that seven different types of lab-on-a-chip technology can be distinguished in The Netherlands, i.e. 1. Capillary driven, 2. Pressure driven, 3. Centrifugally driven, 4. Electrokinetically driven, 5. Droplet based, 6. Free scale non-contact dispensing (FSNCD) based and 7. Magnetically driven. With regard to the hampered development of lab-on-a-chip devices, the combined results of the TIS and SCOT analysis show that the electrokinetically driven lab-on-a-chip technological development pathway is the only development pathway that experiences this hampered development. Thus, the general idea that markets for lab-on-a-chip are not taking off is, based on this research, only visible within the electrokinetically

driven lab-on-a-chip technological development pathway. The general idea is influenced by the fact that electrokinetically driven chips experience the most attention due to its promises for a decentralized healthcare. However, these same promises are presently perceived by the general public as being too radical when fully implemented, hence hampering the further implementation of this technology. As the results of the other lab-on-a-chip technologies show, this hampered development is not visible, also because some development pathways are in an early stage of development. Two more further developed lab-on-a-chip technologies are the capillary driven and pressure driven chips, which are less visible to the general public. These technologies do not experience this hampered development. The capillary driven chips circumvent the decentralization issue by applying the technology to other industries, such as the food industry, or by developing chips designed to operate within the present centralized healthcare system. For the pressure driven chips, the decentralization issue is entirely circumvented by producing chips designed for integration in chemical processes or destined for chemical research.

Comparing the developments it is expected that the pressure driven and capillary driven lab-on-a-chip technological development pathways will experience the least development difficulties in the near future. The electrokinetically driven lab-on-a-chip technology will mostly be implemented in niche markets if the different perceptions on the decentralization aspects are not settled. The droplet based and FSNCD based lab-on-a-chip technologies are expected to experience less difficulties, because the development is directed to specific fields of scientific research. However, the early phase of development these technologies are currently in, makes anticipating on the future development difficult. This is even more the case for the magnetically driven lab-on-a-chip technologies, for which no sensible expectations could be given. Lastly, it is expected that the centrifugally driven lab-on-a-chip technology will not further develop.

Contents

1. Introduction

"*There is plenty of room at the bottom*" was an invitation by Richard Feynman (1959) to enter a new and promising field of research; nanotechnology. The value of nanotechnology lies in its potential for improvements within an enormous amount of applications, for example within the automotive industry, electronics, energy and the medical sector (Siegrist *et al*., 2008). Nanotechnology is fundamentally different to larger scale technologies, because matter on the nanoscale can assume different physical and chemical properties than the same material at a larger scale (Robillard, 2010). Therefore, the technology enables intervention at a smaller scale, opening the possibility of next-level miniaturization, which could ultimately lead to immense transformations (Compano, *et al.*, 2006; Malanowski and Compano, 2007; Loveridge *et al*., 2008; Siegrist *et al*., 2008). The value of nanotechnology lies in this potential for improvements on a small scale within an enormous amount of applications, because it is the basis for technological solutions and combinations across a range of industrial problems (Linton and Walsh, 2004; Kautt *et al*., 2007; Hyungsub and Mody, 2009; Freitas, 2010). Nanotechnology promises a wide range of fundamental changes to many research fields and industries, revolutionizing applications such as detecting and treating diseases (Robillard, 2010), monitoring and protecting the environment, producing and storing energy, molecular engineering (Drexler, 1986a; Walsh, 2004) and building complex structures for electronic circuits or airplanes (Huang *et al*., 2004). Nanotechnology is therefore likely to enable the next wave of Schumpeter's creative destruction (Wonglimpiyara, 2005). This potential has been recognized and acknowledged by several scientific scholars, public institutes and businesses. Many scholars have studied the development of nanotechnology and its promising applications (e.g. Roco, 2003; Huang *et al*., 2004; Busch, 2008). However, the commercial and social understanding of the implications of the technology lag behind the scientific appreciation of its possibilities. This has a hampering influence on the development of nanotechnology (Islam and Miyazaki, 2010), making the commercial and social understanding of the implications interesting to study.

Due to its potential, economic experts expect the worldwide nanotechnology market to explode (Selin, 2007). Where this worldwide market encompassed 147 billion dollars in 2007, the size of the market is estimated to be 3100 billion dollars in 2015 (Lux Research, adapted from Rijksoverheid, 2012). This implies that growth rates of over 2100% will be achieved in eight years. The greatest contribution to this growth is expected to come from the application of nanotechnology in biotechnology and health. This emerging discipline combines nanotechnology and medicine in order to develop improved and new therapies by modification of atoms and molecules for interaction with human cells (Boulaiz *et al*., 2011). The demand for this field of nanotechnology is growing by more than 17% each year (Mousa and Bharali, 2011). Based on the development of the technology and the increasing demand, it is expected that the application of nanotechnology in the healthcare sector will make up for more than half of the pharmaceutical products in the near future (Lux research, 2006). An important application of nanotechnology in this context is the so-called lab-on-a-chip. This application of nanotechnology is based on microfluidic technology and is expected to create a

worldwide market of sixteen billion dollars in 2017 (Yole, 2012). These lab-on-a-chip devices have as advantages: fast analyses, low consumption of reagents and cost reductions (Yole, 2012). With these devices, one can establish earlier and better diagnosis of molecules, diseases and disorders, because nanotechnology provides an improved way of testing for indicators of, for instance, diseases or toxic compounds (Boenink, 2009). These indicators are sought at the biochemical level, for instance, on the size scale of DNA or proteins. In case of diagnostics, lab-on-a-chip can detect the earliest signs of a disease before any signs of sickness are being expressed. So, nanotechnology based lab-on-a-chip devices make earlier and improved diagnoses possible. An example would be the measurement of protein enzymes in blood, which are specific for dead heart tissue and thus indicate the occurrence of a heart attack. Previously, the levels of these protein enzymes in blood were too low to measure, which was the reason that many patients were wrongly sent home by doctors. However, due to the advances in nanotechnology, these measurements are improved and can even been done within a few minutes. Lab-on-a-chip integrates several laboratory functions on a chip which can be as small as a few square millimeters in size (Ghallab and Badawy, 2010). The chip can perform preparation, purification, storage, mixing and detection amongst other functions (Boulaiz *et al*., 2011). In addition to the example of cardiac enzymes, the chip can measure countless other values from a drop of blood, within a few minutes without the necessity of an expert. This technology can be used in hospitals, but more interesting; it provides the opportunity for direct diagnosis *anywhere*. This type of diagnostics, as the name suggests, allows for direct measurements at the location, such as at the patient's home. Lab-on-a-chip technology is not confined to the medical applications. As it is a container concept for microfluidic measurements on a chip (Tüdos *et al.*, 2001), other application fields could be, for instance, bacteria detection in the food industry, monitoring environmental pollution and continuously screening of chemical processes. Thus, lab-on-a-chip's greatest expectations are within healthcare (Philips Research, 2005), however, the technology can be used for all kinds of purposes, enabling more efficient measurements.

However, despite these advantages, there is a general feeling that the market does not take off yet (Yole, 2012). This hampering development of nanotechnology based lab-on-a-chip technologies is the focus of this research. One of the possible causes is that nanotechnology itself, is not free of risks. For instance, nanoparticles might cause problems inside the body due to their relatively large surface area compared to their mass (Bawarski *et al*., 2008). In addition, pulmonary toxicity and the ability to cross the blood-brain barrier might be problematic (Lam *et al*., 2002; Warheit *et al.* 2004). Because the risks of nanoparticles are still unclear, further investigation on these aspects of nanotechnology is needed (Vandeberg, 2012). So, the nanotechnology lab-on-a-chip market seems to experience a sub-optimal development and there are uncertainties around the safety of nanotechnology in general. However, lab-on-a-chip is less affected by these safety issues, because in this application area the nanoparticles interact with molecules or cells outside the human body (Wagner *et al.*, 2006). Another factor influencing the development of lab-on-a-chip are responsibility issues. For instance, the possibility of direct blood analyses anywhere may lead to a decentralized point-of-care healthcare system (Strategic Research Agenda Nanotechnology, 2008). In this case, as the name suggests, healthcare is provided at the patients' location rather than the

other way around. This could make healthcare more efficient and promises more freedom for patients, however, the responsibility of accurate diagnoses and sound decisions shifts from doctors to the patients or the developers of the products (Strategic Research Agenda Nanotechnology, 2008). Such possibilities could pose responsibility issues for lab-on-a-chip development. Accordingly, this study aims to increase the understanding of lab-on-a-chip development.

1.1 Lab-on-a-chip in The Netherlands

One of the frontrunners in lab-on-a-chip, as well as nanotechnology in general is The Netherlands. In terms of nanotechnology patents, for example, The Netherlands was, next to the Republic of Korea, the fastest growing country in 2003 (Huang *et al.*, 2004). In the case of lab-on-a-chip in particular, The Netherlands have a good starting position due to a strong electronics sector and high quality research in life sciences (Walhout *et al.*, 2010). As a matter of fact, The Netherlands is ranked seventh worldwide in terms of publications in the Lab on a Chip Journal, and has a history in research on nanotechnology and lab-on-a-chip in particular. Notable research programs focusing on nanotechnology and lab-on-a-chip as a subprogram are, for example, NanoNed (2004-2010) and NanoNextNL (as of 2011). Respectively 235 million and 250 million euro's were invested in these research programs by the Dutch government and industry (NanoNed, 2006; NanoNextNL, 2012a). Important to mention here is that these investments have contributed to the international position of The Netherlands in terms of scientific output, not so much in terms of development of lab-on-a-chip (Rijksoverheid, 2012).

Thus, the Dutch government is investing heavily in public-private programs to stimulate the development of lab-on-a-chip. On the one hand this happens because of the high expectations of the chips in general, as described above. On the other hand, the technology addresses the current Dutch problem of increasing chronic diseases, decreasing medical personnel and increasingly high public demands (Walhout *et al.*, 2010). Although the investments have resulted in the production of nanotechnology based lab-on-a-chip technologies, also for The Netherlands the development of lab-on-a-chip technologies is hampered (Walhout *et al.*, 2010). Currently, in The Netherlands, lab-on-a-chip technologies are in the emerging phase of development. This means that lab-on-a-chip is still mostly present within 'the scientific world', or research and development, and has not been fully embedded in society yet (Van Merkerk, 2007). At least not in a crystallized form. As a consequence, uncertainties around the future development of lab-on-a-chip exist, i.e. multiple paths of development are still possible. Current Dutch application fields of lab-on-a-chip range from on-site testing of environmental pollution to solving crimes or detecting (remnants) of life on Mars. In addition, there is the field of medical point-of-care diagnostics which is expected to change radically by lab-on-a-chip. These potential application fields, and uncertainties involved, are influenced by the multiple expectations and visions of lab-on-a-chip, presented both in the scientific realm as well as within society. Therefore, the future development of lab-on-a-chip technologies is to a large extent dependent on these expectations and visions of relevant actors (Van Merkerk and Van Lente, 2005).

1.2 Research questions

Lab-on-a-chip is thus expected to comprise multiple technologies, promising great opportunities for amongst others healthcare. However, lab-on-a-chip experiences a less than expected development. Unraveling the factors that counteract the development of different lab-on-chip technologies are, thus, of importance. In order to understand the development of lab-on-a-chip technologies in The Netherlands, a system perspective is chosen. In this research, the framework of Technological Innovation Systems (TIS) is used, because it takes a dynamic perspective on the development of emergent technological innovation systems. Moreover, the framework distinguishes several structural components of an innovation system, such as the technology itself, the actors involved, networks, institutions and the underlying infrastructure, which influence the development of the system at some point (Hekkert *et al.*, 2007). This framework of development processes in combination with structural components is used as a heuristic tool in order to identify the hampering and inducing processes of the development of lab-on-a-chip technologies in the Netherlands. However, due to the emergent and uncertain nature of lab-on-a-chip, the research approach should account for the different expectations and visions of the actors involved on lab-on-a-chip technology and applications. Therefore, solely performing a TIS analysis will only provide insight in the development of the emerging lab-on-a-chip technologies at the system level. Because lab-on-a-chip has not been fully embedded in society yet, the shaping of lab-on-a-chip within the minds of the actors involved provides additional insight in the development of the emerging lab-on-a-chip technologies. In order to account for these multiple development possibilities caused by the different expectations and visions of relevant actors, a broader view is necessary to encompass the social-technical interplay that shapes the development of the technology. This broader view is achieved by including the socio-technical development, using the Social Construction Of Technology (SCOT) approach. This theory assumes that technological development is an open process and that the outcome is dependent on the social context of the technology (Bijker *et al.*, 1987). As a consequence, each relevant social group has different interpretations of lab-on-a-chip, leading to multiple development pathways of the lab-on-a-chip technologies. As long as this interpretive flexibility exists, closure on the meaning of lab-on-a-chip is postponed, as is the embedment in society.

In order to understand the development of the lab-on-a-chip technologies in the Netherlands, first the technological background of lab-on-a-chip is studied in order to understand the different technological developments that are labeled as ‘lab-on-a-chip’. Moreover, a TIS approach is necessary for each lab-on-a-chip technology to understand the structural development and, in combination, a SCOT approach is needed to include the social-technical interplay that shapes each technology. The combination of the TIS and SCOT analysis serves as the framework this study uses to understand the development of each lab-on-a-chip technological development pathway present in The Netherlands. This understanding is visualized with a technology roadmap in which past, current and future developments are being depicted. For this research, a time horizon of 1990-present is chosen, as the beginning

of the 1990s marks the start of fundamental research on lab-on-a-chip technologies in The Netherlands. Hence, the central question is:

How can the development of lab-on-a-chip in The Netherlands be understood within the period 1990- present and what can be expected of the future?

To answer this central question, three sub-questions are formulated;

What are the different lab-on-a-chip technologies and which development pathways exist within the Dutch lab-on-a-chip landscape?

Which hampering and inducing processes have influenced the development of lab-on-a-chip technologies in The Netherlands?

Which interpretations of lab-on-a-chip have influenced the developments of lab-on-a-chip technologies in The Netherlands?

1.3 Justification

This research is scientifically relevant first of all, because it provides new insights in the dynamics of the development of lab-on-a-chip technologies in The Netherlands. Furthermore, for innovation studies the application of the TIS approach on, amongst others, the healthcare sector is relevant, because up until now the TIS approach has been mainly applied to technologies not coping with the challenges of the healthcare sector. This sector is expected to be different, because lengthy development trajectories involving (pre)clinical trials and regulatory approvals are necessary for market introduction. Moreover, lab-on-a-chip requires regulatory and infrastructural changes due to the revolutionary character of the chips. This is where the combination with a SCOT analysis is expected to provide additional understanding of the variety of developments and the related interpretations of the technologies of the actors involved.

In addition, this research is relevant for society, because lab-on-a-chip can, for example, lead to more accurate monitoring of the environment and food, and to earlier, more accurate diagnosis of diseases. In addition, lab-on-a-chip technologies provide the possibility of diagnosis of diseases which nowadays cannot be detected, such as Alzheimer plaques (Wagner *et al.,* 2006). Improved detection and the subsequently curing of diseases greatly benefits society. Furthermore, the possibility of mobile lab-on-a-chip devices circumvents the necessity of a centralized system for all kinds of measurements. For instance, monitoring food for bacteria, measuring blood values or measuring toxic compounds in the air could now take place instantly and anywhere. As for patients who currently suffer from diseases that demand frequent or permanent hospitalization, this promises more freedom, thereby increasing their welbeing (Walhout *et al.,* 2010). Furthermore, lab-on-a-chip provides a solution to the Dutch problem of increasing chronic diseases, decreasing medical personnel and increasingly high public demands (Walhout *et al.,* 2010). In addition, reduction of costs of analyses decrease due to the time and transport savings (Wagner *et al.,* 2006). This would result in more efficient means of detection and in the case of healthcare; a more efficient healthcare system.

1.4 Structure of the report

Chapter 2 focuses on the theoretical foundation of this research. First of all an overview of the TIS and SCOT theory is provided. After the theoretical background is discussed, chapter 3 presents the research methodology. Firstly, the general design of the research is described, followed by the means of data collection and analysis. Next, the quality of the research methodology is discussed. Chapter 4 describes the results of this research in detail, followed by the conclusions and the answer to the central research question in chapter 5. Chapter 6 discusses the findings of this research.

2. Theory

In order to understand the development of lab-on-a-chip technologies in The Netherlands, both a system perspective and a societal perspective is required. This system perspective is achieved with the framework of Technological Innovation Systems (TIS), because it takes a dynamic perspective on the development of emergent technological innovation systems. The perspective of an innovation system was introduced by Freeman (1987). An innovation system is being defined as the network of institutions in public and private sectors whose activities and interconnections initiate, import and diffuse new technologies (Freeman, 1987). Further development of the theory of innovation systems resulted in several perspectives by setting different boundaries for the system; National Innovation Systems (NIS), Regional Innovation Systems (RIS) and Technological Innovation Systems (TIS), comprising actors, networks and institutions (Hekkert *et al.,* 2007). In addition, these systems share a focus on the historical, institutional and learning aspect of the innovation system. The theory of NIS is applicable to nations only, whereas the TIS approach focuses on a specific emergent technology, irrespective of national boundaries.

Figure 1 presents a schematic, heuristic model of a NIS (Kuhlmann and Arnold, 2001). The figure presents the several components, and their relations, that constitute a typical innovation system. These components are actors, organizations and institutions, assigned to different parts of the system (demand, industrial system, intermediaries, education and research, the political system, infrastructure and framework conditions). In short, the political system consists of the national and regional governments, the effective governance and the policies on research and technological development. The political system affects the framework conditions and the education and research within the innovation system, because many of the research institutes such as universities are controlled by the government. Moreover, the political system influences the infrastructure through their policies. In turn, the infrastructure supports the education and research, and the industrial system. The industrial system consists of the companies present in the innovation system and interacts with education and research, sometimes supported by intermediary organizations. Lastly, the industrial system, and education and research interact with the demands of consumers and intermediate producers. This model can be useful as a guide in mapping the current structure of the Dutch lab-on-a-chip technological innovation systems.

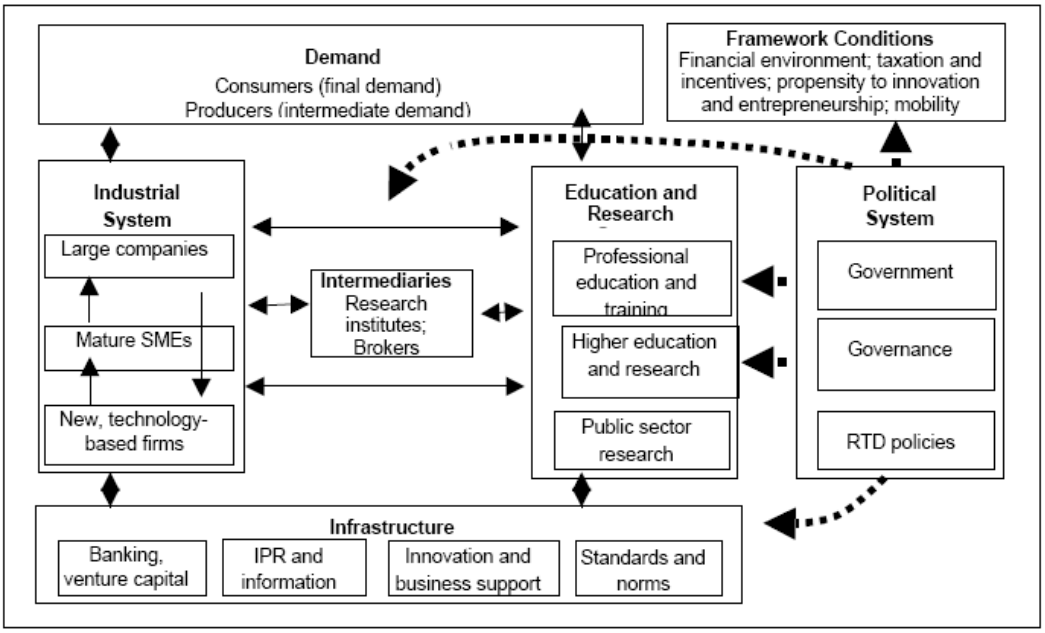

Figure 1. A model of a National Innovation System (adapted from Kuhlmann and Arnold, 2001).

As Negro (2007) and others showed, a TIS analysis could be useful for studying the development, diffusion and implementation of an emergent technology over time, such as a the lab-on-a-chip technologies. TIS was firstly defined as "A dynamic network of agents interacting in a specific economic/industrial area under a particular institutional infrastructure and involved in the generation, diffusion, and utilization of technology" (Carlsson and Stankiewicz, 1991, p. 93). This innovation system consists of actors, networks and institutions (Carlsson *et al.,* 2002). Actors are the individuals, companies, government agencies and research institutions having their own competences and role in the innovation system (Hekkert *et al.*, 2004). Networks are the linkages between the actors, enabling the transfer of knowledge and other resources within the innovation system (Jacobsson and Johnson, 2000). Institutions are the regulations, norms, routines and values that make up the rules of the game (Edquist, 2005). Hekkert *et al.* (2007) extended this perspective by defining several system functions, providing more insight into the dynamic aspect of the system rather than solely mapping the particular technological landscape and its structural elements. These functions of technological innovation systems focus on processes that are considered to be important for the development of a technology. The various system functions as defined by Hekkert *et al.* (2007) will be described briefly. The seven functions distinguished are;

- Entrepreneurial Activities
- Knowledge Development
- Knowledge Diffusion through Networks
- Guidance of the Search
- Market Formation
- Resource Mobilization
- Creation of legitimacy/counteract resistance to change

'Entrepreneurial Activities' is considered as an important process for the development of every innovation system, (Hekkert *et al.*, 2007), because the entrepreneur converts promising

ideas into products or services, hereby setting the first step in the development of an industry. Entrepreneurs can be new entrants to the industry as well as innovating incumbent companies.

Because learning is at the core of innovation, 'Knowledge Development', such as R&D, is also considered to be an important process for the development of an innovation system (Hekkert *et al.*, 2007). That is, knowledge is regarded as the most fundamental resource, which leads to learning as being the most important process (Lundvall, 1992). Therefore, knowledge development is a requirement for the development of an innovation system.

'Knowledge Diffusion through Networks' is of importance, because without the diffusion of knowledge, the development of an innovation system remains absent (Hekkert *et al.*, 2007). In order to diffuse knowledge, networks are a prerequisite. Within networks, the exchange of knowledge is possible, but more importantly: networks facilitate interaction. Interaction, in turn, may create new knowledge by learning, but also by using.

'Guidance of the Search' is an important process within the development of an innovation system, because it leads to a focused development (Hekkert *et al.*, 2007). This focus is dependent on, for instance, expectations, demands or goals. The result of this focus is that the available resources are appointed in the same direction, hereby facilitating a more efficient development of the innovation system.

'Market Formation' is an important process in the development of an innovation system. Because the competition in existing markets is often too strong for emerging technologies to settle, the creation of protected markets is of importance for the emerging technology to develop (Hekkert *et al.*, 2007). Activities protecting these emerging technologies are, for instance, the formation of niche markets or providing advantages for the emerging technologies by favorable policies or tax incentives.

'Resource Mobilization' is an important process for the development of emerging technologies, because without resources development cannot take place (Hekkert *et al.*, 2007). In more detail, financial and human resources are the input for all activities within the innovation system.

Last, the creation of legitimacy or the counteracting resistance to change is an important process within the innovation system, because without legitimacy, the emergent technology will not be accepted within the incumbent regime, or the emergent technology will not overthrow this incumbent regime (Hekkert *et al.*, 2007). Hence, legitimacy paves the way for the innovation system to mature. The opposite is true for counteracting resistance by, for instance, incumbent parties. If there is significant counteracting resistance to the emergent technology, the emerging innovation system will not mature.

The fulfillment of all these system functions is of importance for the further development, performance and success of the innovation system. However, the interaction between these processes is also considered important. Thus, the identification of the fulfillment of these system functions as well as their interactions explain the development of an emergent technology, in this case the lab-on-a-chip technologies. Therefore, this research focuses on

these hampering and inducing processes that affect the development of the lab-on-a-chip technological innovation systems in The Netherlands.

In order to operationalize the system functions into more detailed hampering and inducing processes, the classification scheme of Negro (2007), as seen in Table 1, is used. This classification scheme of Negro (2007) applies to the seven system functions regarded as important for the development of an emergent technology. The signs in column to the right indicate whether this process is a hampering (-) or an inducing (+) process.

Table 1. Operationalization of the seven system functions (adapted from Negro et al.,2009).

Function	Indicator	Sign
Function 1: Entrepreneurial activities	Project started	+
	Project stopped	-
	Organizations entering the market	+
	Organizations leaving the market	-
Function 2: Knowledge development	Research projects	+
	Technological projects	+
	Development projects	+
	Desktop studies on the technology	+
Function 3: Knowledge diffusion through networks	Workshops	+
	Conferences	+
	Reports	+
	Platform	+
	Roadmap	+
Function 4: Guidance of search	Regulations by the government	+
	Deficit of government regulations	-
	Specific tax regimes	+
	Deficit of tax regimes	-
	Positive opinions of experts	+
	Negative opinions of experts	-
	Positive expectations of experts	+
	Negative expectations of experts	-
Function 5: Market formation	Regulation programs	+
	Lack of regulation programs	-
	Stimulation programs	+
	Lack of stimulation programs	-
	Environmental standards	+
	Lack of environmental standards	-
	Specific favorable tax regimes	+
	Lack of specific favorable tax regimes	-
Function 6: Resources mobilization	Subsidies for and investments in the technology	+
	Lack of subsidies for and investments in the technology	-
	R&D subsidy programs	+
	Lack of R&D subsidy programs	-
Function 7: Creation of legitimacy	The technology is promoted by organizations, government	+
	Lack of promotion by organizations, government	-
	Lobby activities for the technology	+
	Lobby activities against the technology	-
	Positive opinions of experts branch organizations	+
	Negative opinions of experts branch organizations	-

This framework of development processes in combination with structural components of Figure 1 are used as a heuristic tool in order to identify and map the hampering and inducing processes of the development of lab-on-a-chip technologies in the Netherlands, as well as the important structural components. In combination, these development processes and structural components provide insight in the development and composition of the Dutch lab-on-a-chip landscape. More importantly, in combination, these development processes and structural components provide insight in the development of each lab-on-a-chip technology in The Netherlands. However, these system functions and structural components provide insights on the development of the technologies at the system level only.

Because lab-on-a-chip technologies are still in their emerging phase, a lot of uncertainties revolve around the actual developments, hence also around the actual innovation system. The path of development is, thus, still flexible. Since, technology and society mutually influence each other (Bijker *et al.,* 1987), insights in the socio-technical interplay provide additional understanding of the development of the different lab-on-a-chip technologies. In order to capture this interplay, the system perspective described above needs to be complemented with a perspective on societal embedment. When studying technological development, it is useful to have such a broader view, because it considers the flexible aspect of the development pathways (Van Merkerk, 2007). As mentioned in the introduction, this broader perspective is achieved by including a social constructivist approach, applying the theory of social construction of technology (SCOT). Pinch and Bijker (1984) introduced the Social Construction of Technology (SCOT), which focuses on the mutual dependence of technology and society by studying the influence of relevant social groups on technological development. These relevant social groups are actors, such as individuals, institutions and organizations, that each share a particular meaning of the purpose of the technology, which is the artifact (Pinch & Bijker, 1984). Moreover, the SCOT approach assumes that technological development is an open process and that the outcome is dependent on the social context of the technology (Bijker *et al.,* 1987). In this way, the success of a technology or artifact can be explained by studying the social context, rather than economic or political factors. This social context varies in terms of differing expectations and visions of the technology. Hence, multiple socio-technical pathways may be present at the same time. As a consequence, each relevant social group may have different interpretations of and attribute different meanings to the technology, leading to multiple development pathways of the lab-on-a-chip technology. This interpretive flexibility is possible, because technological artifacts are culturally constructed and interpreted. This flexibility in how people interpret artifacts results in flexibility in how artifacts are being developed (Pinch and Bijker, 1987). Interestingly, the artifact or technology does not exist without the meaning attributed to it by the relevant social groups. In this sense, the technology is shaped by the social context defining its purpose of existence. This is the socio-technical development of a technology. In general, four categories of social groups can be identified; producers, users, advocates and bystanders (Humphreys, 2005). In short, the producers have a direct economic/organizational stake in the technology, users are directly interested in the technology in order to improve their lives, advocates have a more distant relation to the technology, nonetheless a political stake and bystanders indirectly value and judge the technology on the basis of their own social or moral stake (Humphreys,

2005). In this research, these general categories of relevant social groups can be subdivided into researchers, engineers and investors as producers, hospitals, doctors, patients and health care insurers as users and policy-makers, lobbyists and advocacy groups including religious groups as advocates. For the bystanders, this category can be subdivided into every social group contributing to the social construction of the technology, by for instance verbal communication on the topic. Understanding the meaning and interpretations these relevant social groups address to lab-on-a-chip provides insights into the development of each lab-on-a-chip technology in The Netherlands.

In conclusion, the combination of the TIS and SCOT analysis serves as the framework this study uses to gain insight in the development of each lab-on-a-chip technological development pathway present in The Netherlands. Ultimately, the results of this combination provide the answer to the central research question, including the expectations on future developments of these lab-on-a-chip technological development pathways. To visualize the answer to this central research question, the technology roadmap of Rinne (2004) is used. Technology roadmaps provide a time-directed visualization of relationships between technologies, products and markets (Rinne, 2004). For lab-on-a-chip technological development pathways, Figure 2 will be filled in according to the results of this study, both for the past development of each development pathway as well as for the expected future development of each development pathway.

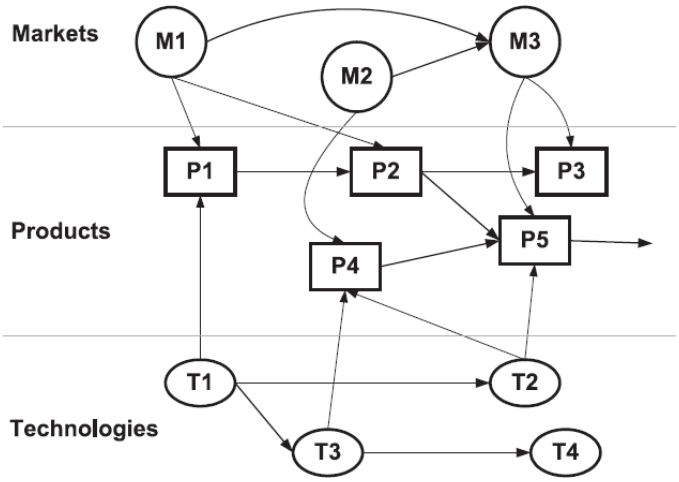

Figure 2. An example of a technology roadmap (adapted from Rinne, 2004).

3. Methodology

In order to answer the central research question *"How can the development of lab-on-a-chip in The Netherlands be understood within the period 1990- present and what can be expected of the future?"* and its sub-questions, data on the development of the lab-on-a-chip technologies in The Netherlands is necessary. This chapter describes the methodology followed in this research. First, decisions regarding the research approach will be given. Hereafter, this chapter will follow the order of research questions as provided in the introduction. Firstly the methodology followed to answer the first sub-question will be described, followed by the methodology of the second and third sub-question. Since the answer to the central research question is a combination of the answers to these sub-question, no additional method to answer this question is described. Lastly, the methodology followed to assure the quality of this research is described.

3.1 Research design

To gain understanding in the development of lab-on-a-chip technologies, The Netherlands is chosen, because this country has a good starting position due to a strong electronics sector and high quality research in life sciences (Walhout *et al.,* 2010). More importantly, although the investments have resulted in the development of lab-on-a-chip applications, the general idea is that the developments are hampered (Walhout *et al.,* 2010). For this case a time horizon of 1990-present is chosen, since around 1990 the knowledge development on lab-on-a-chip technologies started internationally (Manz *et al.,* 1990). A qualitative approach is chosen since this is an explorative case study in which most of the data will be literature sources describing descriptive, rather than numerical, developments and interpretations of the actors involved. In addition, because this is an explorative case study research, the data gathered from the literature sources will be triangulated and supplemented with data retrieved from interviews with the actors involved in the development of lab-on-a-chip technologies. The content of these interviews and the interviewees are displayed in Appendix A.

3.2 The Dutch lab-on-a-chip landscape

In order to answer the first sub-question "*What are the different lab-on-a-chip technologies and which development pathways exist within the Dutch lab-on-a-chip landscape?"*, firstly, scientific literature on lab-on-a-chip technologies have been collected through the Lab on a Chip Journal. This journal is the scientific publication platform for the particular research field of lab-on-a-chip. Therefore, it is assumed that the contents of the Lab on a Chip Journal is representative for the scientific developments of lab-on-a-chip technology. The aim of this methodological step is to create a number of lab-on-a-chip technological categories which could serve as a mapping tool for categorizing the various developments of lab-on-a-chip in The Netherlands. The variety of possible fluid transport technologies for lab-on-a-chip serves as the distinction in this categorization. The outcome of this literature study will be verified during the interviews.

Secondly the lab-on-a-chip landscape will be studied in order to gain some initial understanding of the Dutch lab-on-a-chip landscape, with its most important developments

and actors. The methodological approach to study the hampering and inducing processes during the development of the lab-on-a-chip technologies in The Netherlands is the event history analysis, based on Negro (2007). This methodology consist out of seven sequential steps, which are:

- Literature search
- Database classification
- Allocation to functions
- Summary data and graphical representation
- Historical storyline
- Identification of hampering and inducing mechanisms
- Triangulation of results

Next to the identification of the most important hampering and inducing events, this TIS analysis serves as an initial study to map the most important actors involved. The components mentioned in Figure 1 should be specified for the lab-on-a-chip landscape. This will be done by, firstly, conducting a literature search. This first step of the event history analysis refers to the collection of data through journals via Scopus, newspapers via LexisNexis, reports and websites related to lab-on-a-chip in The Netherlands. Searching for "lab-on-a-chip" in Dutch sources comprise the bulk of the data. In addition, events relating the development mechanisms of lab-on-a-chip landscape are chronologically listed in a database. Next, this database will be structured in terms of categorizing the events. Thirdly, these events will be assigned to the hampering and inducing processes of the system functions as described in the previous chapter and Table 1. Fourthly, adding up all the collected events per hampering and inducing process of a system function generates an overview of the data. Fifthly, the historical narrative of the innovation system shapes the context and content of the events. This narrative assists in understanding the development of the lab-on-a-chip landscape. The last step of the data collection in this sketch of the Dutch lab-on-a-chip landscape will be triangulation of the data with interviewees. These interviews will be semi-structured, meaning that the purpose is both verifying the events gathered in the previous steps as well as gathering new data in terms of events not gathered from the literature sources and events interpreted differently by the interviewee. Analyzing the resulting narrative, allows the researcher to qualitatively identify hampering and inducing processes. The last step of the event history analysis, verifying the results of this method with the actors involved with lab-on-a-chip, strengthens the analysis or reveals irregularities. In other words, analyzing the input provided by the interviewees could reveal additional events or contribute to the understanding of the development of the Dutch lab-on-a-chip landscape.

Hereafter, the most important developers of lab-on-a-chip knowledge and applications present in this lab-on-a-chip landscape will be analyzed in terms of their lab-on-a-chip technology. This lab-on-a-chip technology will be derived from patents, scientific publications and company websites of these most important actors. They are grouped according to the categorization resulting from the first methodological step of this sub-question. The result is an overview of the number of development activities per lab-on-a-chip technology. This

overview, in combination with the narrative and the figure of the lab-on-a-chip landscape, comprise the answer to the first sub-question.

3.3 Development processes of lab-on-a-chip technologies

The second sub-question *"Which hampering and inducing processes have influenced the development of lab-on-a-chip technologies in The Netherlands?"* will be studied in the same way as the sketch of the Dutch lab-on-a-chip landscape. The difference is that for this methodological step, each lab-on-a-chip technological development pathway will be studied separately to enable the detection of differences in hampering and inducing processes between the developments of each lab-on-a-chip technological development pathway. These lab-on-a-chip technological development pathways and its developers of lab-on-a-chip knowledge and applications are provided by the overview resulting from the methods followed to answer the first sub-question. Thus, for each lab-on-a-chip technological development pathway, the event history analysis of Negro (2007), as described in the previous section, is conducted. Due to unwillingness of the actors involved to participate in this research, the last step of the event history analysis, the triangulation of results with the actors involved, is only conducted for the two most widely developed lab-on-a-chip technologies in The Netherlands. The results of these steps is an overview of the development processes per lab-on-a-chip technological development pathway in The Netherlands and provides the answer to the second sub-question.

3.4 The socio-technical development of lab-on-a-chip technologies

The third sub-question *"Which interpretations of lab-on-a-chip have influenced the developments of lab-on-a-chip technologies in The Netherlands?"* will be answered by studying the interpretations of the actors involved for each of the lab-on-a-chip technological development pathways. This step is conducted to capture the socio-technical development of each lab-on-a-chip technology. The SCOT approach provides guidelines on how to reach closure when different relevant social groups are involved in shaping a technology (Pinch & Bijker, 1984). However, this research focuses particularly on the different ways of perceiving lab-on-a-chip by the actors involved and how this has contributed in shaping and developing the technologies in The Netherlands, rather than how to reach closure. In order to distinguish between different types of the actors involved, the classification of Humphreys (2005) is used.

In order to study these interpretations of lab-on-a-chip, interviews are conducted within the specific lab-on-a-chip technological development pathways. Due to unwillingness of the actors involved to participate in this research, these interviews are only conducted for the two most widely developed lab-on-a-chip technologies in The Netherlands. In the other cases, interpretations of the actors involved present in news articles, scientific publications, patents, company websites etc. were used to derive the various interpretations of lab-on-a-chip technology. These interpretations of the technology provide additional insight in the way lab-on-a-chip is developing and might even reveal a fixed direction of development, which would make predictions about future developments and closure a possibility. In the end, the insights gained through these methodological steps are used to answer this third sub-question.

3.5 Quality of the research

In order to assure the quality of this research, several criteria have to be met. The following criteria are based on Yin (2003 and 2009). First of all, construct validity refers to whether or not the data input and the theoretical output correlate. In other words, do the means of data collection suit the theoretical intentions. Construct validity can be increased with source triangulation, using multiple sources of evidence, and investor triangulation, using different perspectives on the data (Yin, 2003). Source triangulation is achieved by using scientific publications, press releases, interviews and other actor specific sources as data input for this study. Investor triangulation is achieved by discussing the data with different types of lab-on-a-chip experts. Secondly, internal validity refers to the established causality. Since this research is explorative of nature, the general understanding of developments is regarded as more interesting that testing these causal relations. Third, external validity refers to the extent to which this research can be generalized. Because this research uses a case study design and applies to the development of lab-on-a-chip technologies in The Netherlands only, the external validity is difficult to establish (Yin, 2009). Last, there is the reliability of the research. This refers to the ability of replication of this research (Yin, 2009). The reliability of this research is increased by good documentation and clarification of methodological steps during this research. The database used for this research is included in Appendix B and C in order for other researchers to be able to view the data. In addition, the interviewees are asked to reflect on the statements derived from the conversation by the interviewer, hereby reducing the researcher subjectivity during the research.

4. Results

In order to answer the central research question, "*How can the development of lab-on-a-chip in The Netherlands be understood within the period 1990- present and what can be expected of the future?*", several steps of data collection have been conducted and subsequently analyzed. First, scientific literature on lab-on-a-chip has been studied in order to identify the different technologies which can serve the fluid transport on a lab-on-a-chip. This is useful since it provides the distinction between the various technological development pathways. Hereafter, an event analysis has been conducted for lab-on-a-chip technologies in general, which served to sketch the Dutch lab-on-chip landscape with its most important development processes and actors involved. The most important actors involved in The Netherlands, derived from this event analysis, are categorized according to this distinction based on the lab-on-a-chip technology they relate to. Next, a detailed event analysis has been conducted per technological development pathway, to reveal differences in the particular developmental processes. Lastly, each technological development pathway has been investigated in terms of the interpretations by the actors involved of lab-on-a-chip technology to reveal differences with respect to the socio-technical development of each technology. The results of these methods will be described in this chapter.

4.1 Developmental possibilities of lab-on-a-chip technology

As a first step in answering the central research question *"How can the development of lab-on-a-chip in The Netherlands be understood within the period 1990- present and what can be expected of the future?"* one must know what the different lab-on-a-chip technologies are. As the technology is still very much in its development phase, there is no finite list of technologies and components to incorporate in a chip. On the other hand, there is no finite list of technologies and components to incorporate in a laboratory either. These elements depend to a large extent on the application area. In other words, the list of techniques, components, materials etc. a company can choose from to develop its chip is long and getting longer. However, starting the development of each lab-on-a-chip from scratch again would make no sense in terms of time and R&D intensity. Therefore, it is expected that some standardizations in terms of lab-on-a-chip toolboxes have been developed or will be in the future (Haeberle and Zengerle, 2007). These standardizations are distinct in the principle of fluid transport. The lab-on-a-chip toolboxes, or technologies, that a developer can choose from, are the technologies being presented in this section. Hereafter, one can use these different lab-on-a-chip technologies for the categorization of the actual lab-on-a-chip developments in The Netherlands.

4.1.1. Capillary driven lab-on-a-chip technology

One of the first lab-on-a-chip technologies identifiable in literature is the capillary driven test strip, or lateral flow assays (Morgan *et al.*, 1996). Although these strips have been known to diagnostics since the 1960s in, for example, diabetes and pregnancy testing (Lambert and Johnson, 1962), ongoing miniaturization of these test strips have resulted in the entrance of the nanotechnology domain. The driving force of this lab-on-a-chip technology is the passive

transportation of liquid driven by capillary forces within the capillaries of a layer. This force is achieved by having a lower capillarity in the input zone or reservoir than in the output zone. The samples are mostly directly loaded in a reservoir from where the fluids are sucked into the underlying layer. This lab-on-a-chip technology is for instance suitable for on-the-spot blood measurements due to the direct loading of the reservoir with a drop of blood from the fingertip (Clark *et al.*, 2002). Further down the capillary strip, reactions can take place and subsequently detection of the particular sample particles can be performed. The results can be read by optical markers such as fluorescent markers which give a signal after the sample fluid has passed the immobilized markers in the detection zone. Another read out possibility is color signals and even read out with the naked eye belongs to the possibilities. The capillary forces stop the liquid transport through the fleece once the end is fully wetted.
The strength of this technology lies in the possibility to perform cheap, on-site measurements without the necessity of any energy supply. Therefore, applications based on the capillary driven technologies range from test strips used in developing countries (Yager *et al.*, 2006) to the detection of the Legionella bacteria in water systems (Horng *et al.*, 2006). In particular, capillarity driven lab-on-a-chip devices are of great use for point-of-care, because they pass the need for additional energy sources. Therefore, it is expected that this type of technology will be of great importance for point-of-care innovations (Eijkel and Van den Berg, 2006). However, the simplicity of this technology is also its drawback; the chips give in on detection accuracy, if detection is without additional energy sources, and the reusability is limited (Haeberle and Zengerle, 2007).

4.1.2. Pressure driven lab-on-a-chip technology

Another promising lab-on-a-chip technology is that of the pressure driven microfluidics (Fredrickson and Fan, 2004). As the name suggests, these chips are actively driven by pressure. Fluids are pumped through the channels and controlled by valves and mixers. Because this is an active process, the controlling of the fluids can be very precise, making this technology suitable for all kinds of measurements. For instance, the lab-on-a-chip devices can be integrated in larger systems to control or measure fluids. More complex, complete micro-reactors could be designed, controlling the mixing and measuring of numerous different channels. Additionally, these chips are, with pneumatic actuation, suitable for portable applications with battery or hand powered sources (Sia *et al.*, 2004). Another promising example of pressure driven technology is that of soft lithography. With this technology, all necessary components could be integrated into one single elastomer of polydimethylsiloxane (PDMS) (Xia *et al.*, 1996; Haeberle and Zengerle, 2007). This elastomer is cheap, but still powerful compared to silicon or glass. Application of PDMS on lab-on-a-chip mostly results in the construction of channels and valves only.

4.1.3. Centrifugally driven lab-on-a-chip technology

A different approach to develop lab-on-a-chip devices is based on centrifugal forces. This approach dates back to the 1960s (Anderson, 1969; Burtis *et al.*, 1972; Gorkin *et al.*, 2010) and is now further developed to operate on the nanoscale (Madou and Kellogg, 1998; Duffy *et al.*, 1999; Ekstrand *et al.*, 2000; Madou *et al.*, 2001). The driving centrifugal force is actuated

by rotation of a disk on which the channels are constructed. One of the biggest advantages of this lab-on-a-chip technology is that parallel processing can be achieved by as many as one hundred times on one disk (Haeberle and Zengerle, 2007). This could, for instance, be beneficial for drug screening, where reactions can take place one hundred fold with the same amount of sample and reagent fluids. On these disks, valves could be incorporated to control and mix fluids. One could independently open or close valves, but this process could also be automated for one particular kind of analysis. In that case, the resistance of the valves should be equal to a particular rotation frequency. Once the frequency of rotation is increased to this level, the valves automatically open facilitating further liquid flow (Gorkin *et al.,* 2010). Three kind of valves could be used for this purpose. First there is the geometric capillary valve, which is a narrow piece of channel keeping the liquid in place due to the energy barrier present in this part of the channel which prevents the meniscus of the fluid from breaking. At least until the rotation frequency produces a smaller radial outward force than the force on the meniscus. Another valve for centrifugal lab-on-a-chip devices is achieved by applying a hydrophobic coating on the channel walls. This will prevent the liquid from continuing down the channel until the radial outward force is greater than the hydrophobic counterforce. The third type of valve is the hydrophilic siphon valve. Below a critical frequency the right meniscus proceeds beyond the third bend hereby draining the channel (Gorkin *et al.,* 2010). Thus, all processes on the 'lab-on-a-disk' can be controlled by the rotation frequency only, making this another advantage of this technology. A disadvantage, however, is that as soon as any additional measuring or sensing is required, the rotating aspect results in technical difficulties (Gorkin *et al.,* 2010). In addition, the critical frequencies of the valves described above are fixed and therefore only suitable for one type of measurement. So the possibilities for application are limited once the disk is manufactured (Haeberle and Zengerle, 2007).

4.1.4. Electrokinetically driven lab-on-a-chip technology

Unlike the lab-on-a-chip technologies described above, the electrokinetically driven technology, in which the fluid is actuated electrically, is of particular interest for lab-on-a-chip due to the increased surface tensions gained with a greater surface to volume ratio. This advantage combined with the simple necessity of electrodes as a driving force makes electrokinetic systems an accurate and simple lab-on-a-chip technology (Harrison *et al.,* 1992; Manz *et al.,* 1992; Effenhauser *et al.,* 1993; Harrison *et al.,* 1993; Haeberle and Zengerle, 2007). The analysis is focused on chemical compounds which are separated via electrophoresis in the channels. The fluid transport in such channels can take place in several ways. First there is the electroosmotic flow, which is actuated by a negatively charged surface of the channel material, such as glass or silicon (Dutta *et al*., 2002). This creates a surplus of positively charged fluids at the channel walls. Once the channel is electrically activated, the positively charged molecules move towards the negative end of the channel. These positively charged molecules can then be measured for all kinds of tests. Next to electroosmotic flow, the fluid inside the channels will be attracted to either one of the electrodes if they contain electrically charged molecules. The velocity of this fluid propulsion is directly linked to the charge and size of the molecules and thus serves as the distinction between different molecules. This kind of fluid actuation is called electrophoresis (Harrison *et al.,* 1992; Manz

et al., 1992; Effenhauser *et al.,* 1993; Harrison *et al.,* 1993; Haeberle and Zengerle, 2007). If the particles inside the channels are uncharged, dielectrophoresis can temporarily charge them with a non-uniform electrical field (Haeberle and Zengerle, 2007). This approach is more suitable for biochemical analyses (Morgan *et al.,* 1999). Next to the accuracy of electrokinetic lab-on-a-chip technology, the chips are also fast and efficient due to the pulse free initiation of the fluid and the high surface to volume ratio facilitates parallelization of tests with small sample volumes (Haeberle and Zengerle, 2007). However, this same surface to volume ratio means that highly accurate detection technologies are necessary. In addition, gas bubbles can occur due to the electrolysis of the fluid, decreasing the accuracy of the tests, because this disturbs the fluid distribution within the channel. However, the biggest disadvantage of electrokinetically driven lab-on-a-chip technology is the necessity of a high voltage energy source, making point-of-care applications less feasible.

4.1.5. Droplet based lab-on-a-chip technology

In addition to these technologies, there is the droplet based lab-on-a-chip technology. The principle behind this technology is the use of droplets as reaction confinements (Haeberle and Zengerle, 2007; Huebner *et al.,* 2008; Lin *et al.,* 2008). These droplets are isolated in for instance air or oil. The generation of droplets with membranes is also possible (Vogelaar *et al.,* 2001). Because the droplet itself is the reactor, multiple droplets on a chip facilitates parallel analysis with a low amount of sample and reagent fluids. Two kinds of droplet based lab-on-a-chip devices exist, the channel based and the planar surface based chip. These channel based chips are pressure driven and facilitate droplet generation, manipulation and transportation in a single motion. They rely on a two phase fluid flow which result in sample fluid or droplets and carrier fluid plugs into the channels. These droplets and plugs flow through the channels when pressure is being applied (Cheow *et al.,* 2007). The planar surface based chips consist of droplets on a two dimensional chip which can be moved arbitrarily. These chips are actuated either by electrowetting or surface acoustic waves. In the case of the electrowetting actuated chips, the droplets are moved by applying voltage to the surface on which the droplets are being placed. Given the amount of voltage and the electrical charge of the droplets the movement of the droplets can be controlled precisely (Lee *et al.,* 2002; Mugele *et al.,* 2005). The alternative to this type of planar surface based chips is using surface acoustic waves for fluid transport (Wixforth, 2003). These mechanical waves move over the hydrophobic surface of the chip with amplitudes of only a few nanometers. Advantages of these droplet based chips are first of all the small liquid volumes necessary for analysis. In addition, incubation and storage of liquids is possible within the droplets. The planar surface chips have the particular advantage of flexibility, since the moving of droplets is free in a two dimensional space. Moreover, these chips do not require any moving parts, resulting in cost benefits (Haeberle and Zengerle, 2007)

4.1.6. Free scale non-contact dispensing based lab-on-a-chip technology

Another lab-on-a-chip technology, the free scale non-contact dispensing (FSNCD) based chips, allows for the delivery of liquids as free droplets into planar substrates, conventional containers, such as wells, or any other target (Haeberle and Zengerle, 2007). This technique is

closest to the conventional laboratory routines, where assays are conducted by performing repetitive pipetting steps. However, in this case the volumes of the liquid dispensed are accurate to the nanoscale. Thus a single chip can contain up to thousands of parallel assays with different droplet or compartment sizes and an individual controllability (Ingham *et al.*, 2010). Opposite to these advantages are the high fabrication costs of the dispensing chips.

4.1.7. Magnetically driven lab-on-a-chip technology

Lastly, one can distinguish the magnetically driven chip technology. Magnetics offers a few advantages compared to the other chip technologies. For instance, actuation of the fluid within the channels can also be initiated with an external magnet (Pamme, 2006). This leads to possibilities such as isolating biomolecules that are attached to magnetic particles inside the chip with an external magnet. Also, in contrast to electrokinetically driven chip technology, magnetism is not affected by increased surface charges, pH, ionic concentrations or temperature (Pamme, 2006). Nowadays, magnetic forces are incorporated in chip technology in various ways. They are used to manipulate particles within the fluid, mostly with an external magnet. Since this is not necessarily a sophisticated approach and the devices can be mobile, magnetic lab-on-a-chip technology can be fabricated at low cost and serve on-site detections (Pamme, 2006). In addition, the magnetic forces can be used to transport, separate and sort magnetic and non-magnetic compounds, the latter more difficult to realize, within the channels. A possibility of such a fluid transport is magnetically activated artificial cilia, leading to fluid propulsion in the direction the cilia move (Khaderi *et al.*, 2011). The incorporation of more sophisticated electromagnetic parts within the chips also belongs to the possibilities, thereby increasing the fabrication costs as well as the quality of the detection due to more precisely controlled magnetic fields (Pamme, 2006). Thus, the advantages and disadvantages of this technique depend on the decision for either low-cost, simple and portable magnetic chips or high-cost, high quality and energy source dependent electromagnetic chips.

4.1.8. Conclusion

In conclusion, there is a large variety of lab-on-chip technologies, with each technology having its distinctive advantages and disadvantages, making no type of lab-on-a-chip technology perform better than the other. To sum it up, an overview of the technologies is provided in Table 2. This overview serves as the distinction between the differing types of lab-on-a-chip technologies for the remainder of this chapter. In the next section, the actual developments of lab-on-a-chip in The Netherlands will be categorized according to this overview. One has to bear in mind that these are standardizations in terms of lab-on-a-chip technologies, i.e. applications of lab-on-a-chip might be related to a few of these technologies. For instance, one can incorporate magnetic measurement on a lab-on-a-chip on which fluid transport takes place by capillary forces. Thus, these different lab-on-a-chip technologies can be interrelated, however, this is entirely dependent on the developer, which shows the unique characteristics of each lab-on-a-chip application.

Table 2. Lab-on-a-chip technologies.

Technology	**Description**	**Advantages**	**Disadvantages**
Capillary driven lab-on-a-chip technology	Passive transportation of fluids driven by capillary forces within the capillaries of a layer	Cheap, on-site measurements without the necessity of any energy supply	The simplicity of the chip results in a relatively lower accuracy, without additional energy sources
Pressure driven lab-on-a-chip technology	Fluids are pumped through the channels and controlled by valves and mixers	Flexible and configurable chips Efficient and accurate	Dependent on pressure source
Centrifugally driven lab-on-a-chip technology	Actuation by rotation of a disk on which the channels are constructed	Parallel processing Controllable with rotation frequency	Rotating aspect makes additional measurements difficult and each disk is suitable for one type of measurement only
Electrokinetically driven lab-on-a-chip technology	Applying voltage to the fluids results in measuring the distinctive surface tensions of the molecules inside the channels	Increased surface tensions with smaller scale measurements Accurate, relatively cheap, fast and efficient due to the pulse free initiation of the fluid and the high surface to volume ratio	Gas bubbles may develop Necessity of a high voltage energy source
Droplet based lab-on-a-chip technology	The use of droplets as reaction confinements	Parallel analysis, precise controllability, small fluid volumes, incubation and storage of fluids possible, no moving parts necessary	The channel design is fixed for one type of measurement Droplets on planar surfaces results in evaporation and finally instability of hydrophobic and hydrophilic coatings
FSNCD based lab-on-a-chip technology	Delivery of fluids as free droplets into planar substrates, conventional containers or any other target	Parallel assays with different droplet sizes and an individual controllability	High fabrication costs
Magnetically driven lab-on-a-chip technology	Fluid is actuated either with an external or internal magnet.	Possibility of low-cost, simple and portable chips or high-cost, high quality and energy dependent chips	Non-magnetic particles are more difficult to detect

4.2 Sketching the Dutch lab-on-a-chip landscape

In order to gain understanding of the development of lab-on-a-chip in general, key events during this development give more insight in the current situation of lab-on-a-chip in The Netherlands. As mentioned in the methodology, explorative interviews and LexisNexis data are used as primary data sources for the collection of these events. At the end of this section, the key events are appointed to the System Functions as described in the theoretical chapter. Categorizing these events in this manner provides insight into the development, diffusion and implementation of an emergent technology (Negro, 2007; Hekkert *et al.,* 2007). Important to note is that this event analysis also serves as an initial study on the relevant actors involved in lab-on-a-chip developments in general.

4.2.1 Historical narrative of the Dutch lab-on-a-chip landscape

"Following the trend towards smaller channel inner diameter for better separation performance and shorter channel length for shorter transport time, a modular construction of a miniaturized 'total chemical analysis system' is proposed" (Manz *et al.,* 1990, p. 244). These total chemical analysis systems were termed by Manz *et al.,* (1990) as µTAS or MicroTAS (Micro Total Analysis Systems). Although this event occurred outside The Netherlands, it marks the start of knowledge development within The Netherlands on these MicroTAS. Since 1994, MicroTAS conferences, scientific conferences devoted to this field of research, are being held all over the world. The first edition, however, was held in and initiated by The Netherlands, with the first chairmen being prof.dr.ir. Piet Bergveld and prof.dr.ir. Albert van den Berg (FutureChemistry, 2012). This conference eventually led to a technology push of MicroTAS (FutureChemistry, 2012). After some years of research, around the turn of the century, nanotechnology, including lab-on-a-chip technologies, were said to be innovations of importance for The Netherlands' future due to the opportunities it provides (Vandeberg, 2012). According to the University of Twente, University of Amsterdam, Technical University Delft, Technical University Eindhoven, University of Groningen, University of Nijmegen, University of Wageningen and TNO, nanotechnology will create an enormous market for The Netherlands within 25 years and due to the head start in research in this field, this poses great opportunities for The Netherlands (Trouw, 22-3-2003). On the basis of this expectation, the project NanoImpuls was started in 2003. The Dutch Ministry of Economic Affairs appointed 23 million euro's to the project, next to the 23 million euro's invested by the industry; was carried out by the above listed knowledge institutes and coordinated by Technology Foundation STW (Trouw, 22-3-2003). One of the four research themes was Nanofluidics, focusing on the control of fluids on the nanoscale, with which chemical reactions could be performed on a chip (Trouw, 22-3-2003). Noticeable is that the term lab-on-a-chip has become more popular than MicroTAS (Van Merkerk, 2005). First, the technology was used by analytical chemists to miniaturize existent analyses by integrating several laboratory functions on a chip (Van Merkerk, 2005). However, with the broadening of the research field, around 1995 the term lab-on-a-chip became more popular, since this term implies a broader application area and appeals to those outside the scientific community, thereby increasing the visibility of the technology (Van Merkerk, 2005). As from 2001 onwards the research field has its own scientific journal; Lab on a Chip Journal. However,

more important is that the expectation that nanotechnology will create an enormous market for The Netherlands within 25 years marks the active search into the possibilities for The Netherlands. Based on this expectation, as of 2005, the next research program on the possibilities of nanotechnology was started, as is the case with NanoImpuls (Vandeberg, 2012). This program, NanoNed, was a research consortium initiated by (NanoNed, 2006):

- MESA+, University of Twente (secretary)
- Kavli Institute of Nanoscience, Delft University of Technology
- CNM, Technische Universiteit Eindhoven
- BioMade/MSC+, University of Groningen
- IMM, Radboud University Nijmegen
- BioNT, Wageningen University and Research Centre
- Photonics Group, Universiteit van Amsterdam
- TNO Science and Industry
- Philips Electronics Nederland

The Dutch government has granted the consortium 95 million euro's in the form of a BSIK subsidy in 2005 (Besluit Subsidies Investeringen Kennisinfrastructuur/ Decree on subsidies for investments in the knowledge infrastructure), financed with the revenues from natural gas. In addition, together with funds inherited from NanoImpuls and financial support of the consortium partners, the total budget of NanoNed was over 235 million euro's (NanoNed, 2006). Most of the research was done at the MESA+ Institute for Nanotechnology at the University of Twente and possibilities of lab-on-a-chip technologies were part of this research (Vandeberg, 2012). Prof.dr.ir. Albert van den Berg led this research on lab-on-a-chip and received a NWO Spinoza Prize for his research in 2009.

During the NanoNed program, NanoNed, FOM (Foundation for Fundamental Research on Matter) and STW (together NNI: Nederlands Nano Initiatief/ Netherlands Nano Initiative) were asked by the Dutch Cabinet to write a Strategic Research Agenda Nanotechnology (SRA) for the period 2010-2020 (NanoNed, 2009; Vandeberg, 2012). Prof.dr.ing. Dave Blank was the author of this SRA (2008), which focused on the current position of nanotechnology in The Netherlands, on which future developments are important and how to achieve these both organizationally and financially. This document was crucial for all nanotechnologies in The Netherlands, because it was the basis for the design of subsequent programs (Vandeberg, 2012). For instance, financial resources were addressed to NanoLabNL, founded by NanoNed in 2005 (NanoNed, 2006), to strengthen the infrastructure of nanotechnology with clean room facilities in 2009 (NanoNed, 2010). Also founded on the basis of SRA Nanotech is NWO-Nano (NanoNed, 2010). This program, again managed by STW, grants subsidies to excellent fundamental and application oriented nanotechnology research projects and business plans. After this these projects are being guided by STW. Nanomedicine is one of the four themes of NWO-Nano (2009). Lastly, in 2009, the Cabinet awarded 125 million euro's from the Economic Structure Enhancing Fund (FES) to the High-Tech Systems and Materials Program 'Towards a sustainable open innovation ecosystem' to be used for research in the field of micro- and nanotechnology and to develop new micro- and nanotechnology based applications (NanoNed, 2010). Moreover, the participating companies invested more than 60

million euro's in the program as did the participating universities and knowledge institutes. In total 250 million euro's has been invested in the program, which was based on the SRA Nanotech (NanoNed, 2010). The program gave rise to NanoNextNL in 2011. This project, involving 136 parties from the academic world, medical centers, other institutes and commercial companies, is the biggest innovation project in The Netherlands ever since, facilitating nanotechnology research (Vandeberg, 2012). The project is subdivided into ten research themes, which are in turn subdivided into numerous programs (NanoNextNL, 2012b);

- Risk Analysis and Technology Assessment
- Energy
- Nanomedicine
- Clean Water
- Food
- Beyond Moore
- Nano materials
- Bio-nano
- Nano fabrication
- Sensors and actuators

Both the themes 'Sensors and actuators' and 'Nanomedicine' involve lab-on-a-chip technologies. Moreover, the theme focusing on risk analysis and technology assessment may involve lab-on-a-chip technologies. Lab-on-a-chip is on the one hand subject to this risk analysis, but, on the other hand, might also assist in identifying risks (Vandeberg, 2012). Considering the consumers' opinion on nanotechnology and lab-on-a-chip, a recent survey of Llowlab on Lowlands festival visitors showed that around 80% of the visitors had a positive opinion of nanotechnology and around 70% had a positive opinion of lab-on-a-chip (Bos, 2012). So, although the actual risks have not been identified yet, there seems to be an overall positive opinion of nanotechnology and lab-on-a-chip among bystanders.

On a smaller scale, a lot of individual activities can be identified. Since these are ultimately appointed to a particular lab-on-a-chip technological development pathway, in this section they will only be screened to identify the most relevant actors for the development of lab-on-a-chip in general in order to gain insight in the overall landscape. An important market introduction of lab-on-a-chip for The Netherlands was, first of all, Micronit Microfluidics in 2000 (FEM Business, 11-6-2005), because this company, with its business-to-business strategy, provided the technological basis for many successive Dutch lab-on-a-chip developers (Van Merkerk, 2012). Other lab-on-a-chip market introductions of importance are Medimate in 2005 (Het Financieele Dagblad, 20-12-2005), C2V in 2008 (Het Financieele Dagblad, 16-2-2008), Senzair in 2008 (Dagblad Tubantia/Twentsche Courant, 18-6-2008) and Blue4Green in 2010 (Staijen, 2012). Next to these companies, other important sources of knowledge on lab-on-a-chip came from Ostendum (Het Financieele Dagblad, 26-5-2009), FutureChemistry (FutureChemistry, 2012), LioniX (Dagblad Tubantia/Twentsche Courant, 19-12-2007) and more importantly; the BIOS Lab-on-a-Chip Group of the University of Twente (Van Merkerk, 2012), Philips Research (Van Merkerk, 2012), Kavli Institute of

Nanoscience of Delft University of Technology and BioNT of Wageningen University and Research Centre (Spits, 11-9-2009). In addition, events such as the yearly STW congresses and the gatherings of NanoNextNL were important (Vandeberg, 2012). These meetings consist of different compositions participants: all parties involved, per theme, per program or even smaller groups. This ensured maximal knowledge diffusion between the participants. Bigger meetings result in the exchange of totally different ideas and perspectives on problems, solutions and goals. For collaborations, research shows that groups consisting of three to four parties were an optimal composition (Vandeberg, 2012). In addition, knowledge diffusion was increased with the foundation of Micronit Microfluidics, producing lab-on-a-chip devices for other lab-on-a-chip developers, thereby increasing the diffusion of lab-on-a-chip itself (Van Merkerk, 2012). Next to the investments in the overarching research programs such as NanoNextNL, smaller investments took place. For example, Zilveren Kruis Achmea subsidized Medimate in 2007 (De Twentse Courant Tubantia, 21-12-2007). In addition, Nano4Vitality invests in Senzair (Het Financieele Dagblad, 20-6-2008). Also, STW subsidizes application oriented research through the NWO-Nano program, in which companies and researchers can apply for support. Only the best proposals are being granted, based on a peer-review process (Vandeberg, 2012). Lastly, important users of lab-on-a-chip products are, at present, patients and farmers using the technology for point-of-care diagnostics (Vandeberg, 2012) and other companies integrating the technology into chemical processes (FutureChemistry, 2012a). However, as the survey of Llowlab showed, the bystander's opinion of lab-on-a-chip seems to be an overall positive one, leading to the expectation that lab-on-a-chip will increase its foothold in society. To what extent and how this implementation is going to be designed it is important to look at the uncertainties that hamper the development of applications of lab-on-a-chip (Vandeberg, 2012).

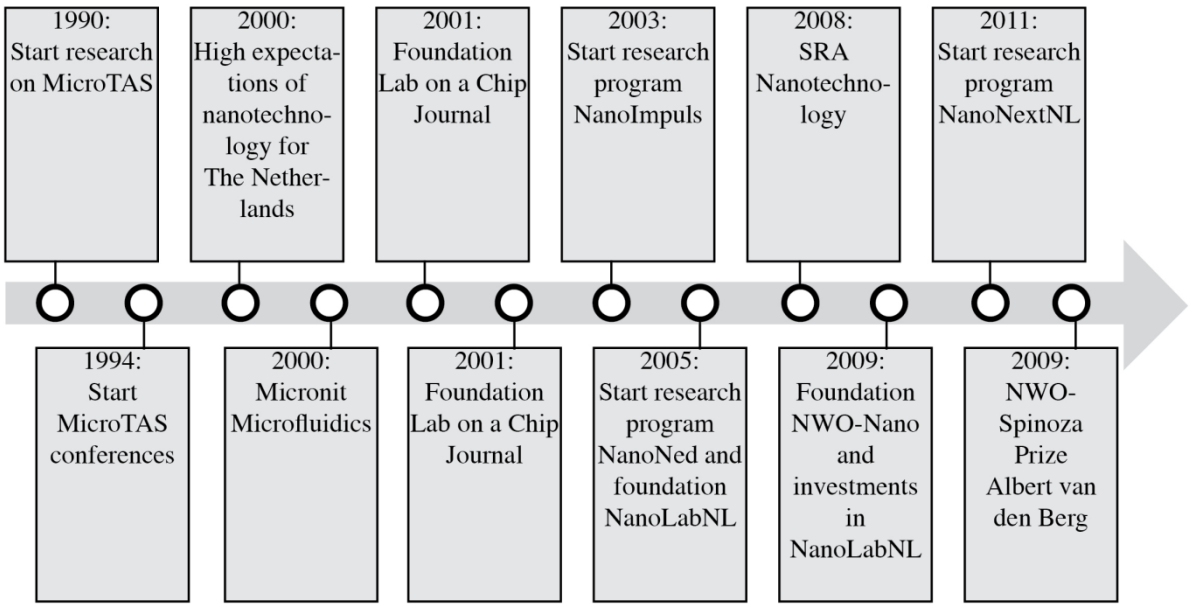

Figure 3. Timeline of the most important events in the history of the Dutch lab-on-a-chip landscape.

4.2.2. The Dutch lab-on-a-chip landscape

All in all, narrative described above provides a sketch of the lab-on-a-chip landscape in The Netherlands. Figure 3 displays all these key events in chronological order. Viewing this timeline of key events one can distinguish several different development processes in the history of the Dutch lab-on-a-chip landscape. First of all, knowledge development is conducted since the early 1990s, with highlights being the NanoNed and NanoNextNL research programs. This knowledge development is accompanied by conferences such as MicroTAS and the gatherings organized by NanoNextNL, facilitating knowledge diffusion. Along this knowledge development, lab-on-a-chip enjoys legitimacy with events such as the Lab on a Chip Journal, devoted to lab-on-a-chip research only, important themes within the national research programs, the NWO Spinoza Prize for prof.dr.ir. Albert van den Berg and the positive opinion consumers seem to have of lab-on-a-chip. Another important process during the history of the Dutch lab-on-a-chip landscape is the publication of the Strategic Research Agenda Nanotechnology in 2008, providing a search guide for all nanotechnologies in The Netherlands. Furthermore, this document formed the basis of the national nanotechnology infrastructure, with the most important support of resources coming from the NWO-Nano subsidizing program and the NanoLabNL facilities. As described in the narrative above, uncertainties around the actual risks of nanotechnology exist. This has prevented the establishment of standards and norms of nanotechnology products. This has no impact on the knowledge development of nanotechnology in general, but it creates uncertainties around the extent of implementation and configuration of nanotechnology products. It has a negative impact on the formation of markets within the lab-on-a-chip landscape (Vandeberg, 2012). Thus, clarifications on these safety and configuration issues are needed in order for the Dutch lab-on-a-chip landscape to develop successfully. Another factor influencing the development of lab-on-a-chip are responsibility issues. Moreover, for instance, the possibility of direct blood analyses anywhere may lead to a decentralized point-of-care healthcare system (Strategic Research Agenda Nanotechnology, 2008). In this case, as the name suggests, healthcare is provided at the patients' location rather than the other way around. This could make healthcare more efficient and promises more freedom for patients, however, the responsibility of accurate diagnoses and sound decisions shifts from doctors to the patients or the developers of the products (Strategic Research Agenda Nanotechnology, 2008). Such possibilities could pose responsibility issues for lab-on-a-chip development. Furthermore, lab-on-a-chip technologies are currently in the emerging phase of development. This means that lab-on-a-chip is still mostly present within 'the scientific world', or research and development, and has not been fully embedded in society yet (Van Merkerk, 2007). At least not in a crystallized form. As a consequence, uncertainties around the future development and implementation of lab-on-a-chip exist.

However, as described in the previous section, there is not one lab-on-a-chip technology. Therefore, the results of this landscape sketch cannot lead to conclusions on the functionality of lab-on-a-chip in The Netherlands. As mentioned, this narrative served as a first step in mapping the activities related to all lab-on-a-chip technologies in The Netherlands, as well as the most important actors involved with all the technologies and the lab-on-a-chip

infrastructure present in The Netherlands. With the results of this narrative however, a schematic overview of the Dutch landscape in which all lab-on-a-chip technologies are embedded could be sketched. Figure 4 shows this lab on a chip landscape.

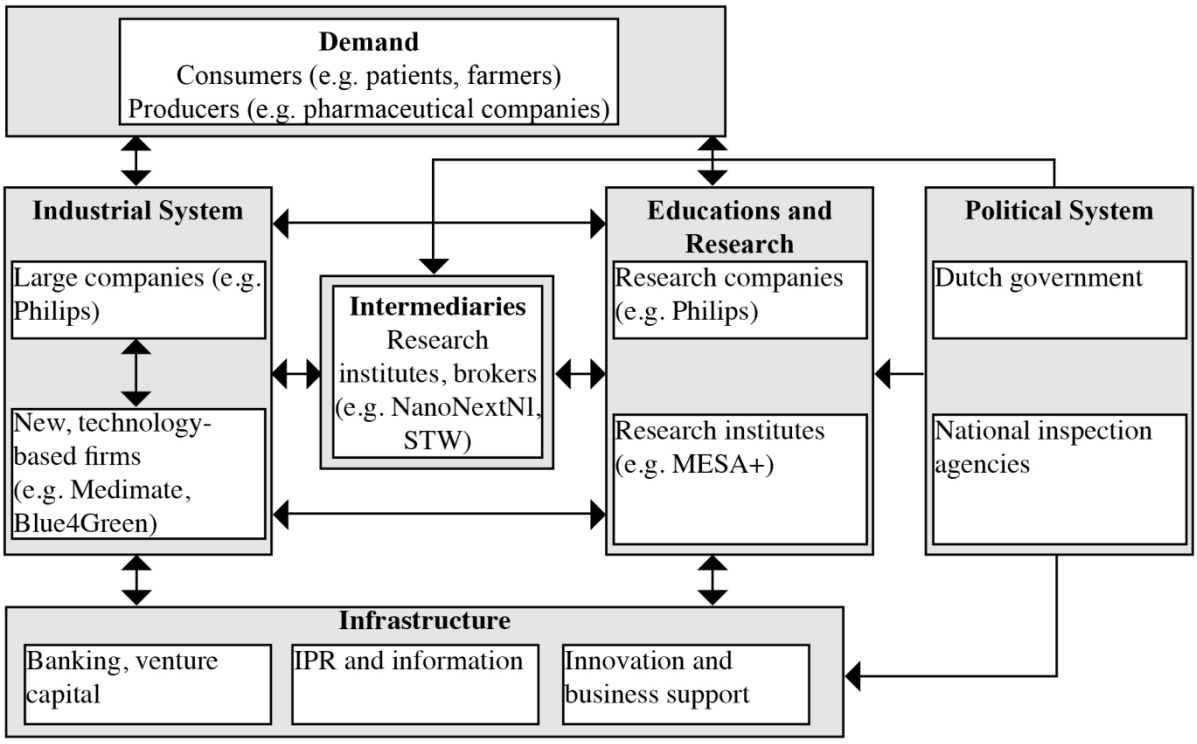

Figure 4. The Dutch lab-on-a-chip landscape.

4.3 Lab-on-a-chip developments in The Netherlands

As has been mentioned before, there is not one lab-on-a-chip technology in The Netherlands, but there are multiple ones. The categorization of lab-on-a-chip technologies provided in section 4.1 serves as a mapping tool for the lab-on-a-chip developments in The Netherlands. Literature study on the scientific publications in the Lab on a Chip Journal originating from The Netherlands as well as patent publications and company websites, including news articles, brochures, poster presentations etc., of relevant companies participating in the research programs NanoNextNL, Nano4Vitality, MicrofluidicsNL and the MESA+ Institute for Nanotechnology have provided the boundaries for this mapping of developments. This study resulted in the distribution of development activities for all seven lab-on-a-chip technologies in The Netherlands displayed in Table 3. For a more detailed description of the companies and research institutes involved and their developments, see Appendix D.

Table 3. Lab-on-a-chip developments in The Netherlands.

	Capillary driven chips	Pressure driven chips	Centrifugally driven chips	Electrokinetically driven chips	Droplet based chips	FSNCD based chips	Magnetically driven chips
Aquamarijn							X
Axxicon			X				
Blue4Green				X			
Bronkhorst High-Tech		X					
C2V	X						
Capilix				X			
Chemtrix		X					
Delft University of Technology		X		X	X		
Eindhoven University of Technology	X						X
Flowid		X					
Future Chemistry		X					
LioniX		X		X		X	
Medimate				X			
Microdish						X	
Micronit Microfluidics		X		X	X		
Nanomi					X		X
Ostendum	X						
Philips Healthcare	X	X		X			X
Radboud University Nijmegen		X			X		
Sentron				X			
Senzair				X			
University of Groningen				X		X	X
University of Leiden				X			
University of Twente	X	X		X	X		X
Wageningen University and Research Centre				X	X		
Total	**5**	**10**	**1**	**13**	**6**	**3**	**6**

At this point the first sub-question, *"What are the different lab-on-a-chip technologies and which development pathways exist within the Dutch lab-on-a-chip landscape?"*, can be answered. As Table 3 shows, all seven lab-on-a-chip technologies in the field of

nanotechnology for lab-on-a-chip in The Netherlands are being pursued. However, the number of developers of knowledge and applications of these seven lab-on-a-chip technologies shows differences per lab-on-a-chip technological development pathway. The Netherlands is mostly active in the electrokinetically driven lab-on-a-chip technology (eight companies and five research institutes) as well as the pressure driven lab-on-a-chip technology (seven companies and three research institutes). For the capillary driven lab-on-a-chip technology (three companies and two research institutes) and the droplet based lab-on-a-chip technology (two companies and four research institutes), knowledge development takes place in relatively fewer companies and research institutes in The Netherlands. More or less equally distributed is the development of magnetically driven lab-on-a-chip technology (three companies and three research institutes), yet there is even less distributed activity in FSNCD based lab-on-a-chip technology (one company and two research institute) and in lab-on-a-chip devices driven by centrifugal forces (one company). But what is the reason for this uneven distribution of development? In the next section, the answer to this question is sought in the differences in development processes of each of these seven lab-on-a-chip technological development pathways.

4.4 Development processes of lab-on-a-chip technologies

In order to gain better understanding in the development processes of the emerging lab-on-a-chip technologies, key events during their development give more insight in the current situation. Therefore, the second sub-question is phrased as: *"Which hampering and inducing processes have influenced the development of lab-on-a-chip technologies in The Netherlands?"*. As mentioned in the methodology, interviews and LexisNexis have been used as the primary data sources for the collection of these events. In addition, press releases of the companies, website information or scientific publications have been used as sources for the collection of these events. Since this research distinguishes seven different kinds of lab-on-a-chip rather than one technology, investigating the seven system functions for lab-on-a-chip in general would not be very insightful for understanding the variety of developments. Therefore, this section describes the key events for each of the technological development pathways to enable reflection on the development processes per particular lab-on-a-chip technological development pathway.

4.4.1. The emerging Dutch capillary driven lab-on-a-chip innovation system

As described in section 4.2, capillary lab-on-a-chip technology was one of the first to appear in scientific literature (Morgan *et al.,* 1996). However, the first publication originating from The Netherlands appeared in 2006 (Eijkel and Van den Berg, 2006), describing the possibilities of the technique for lab-on-a-chip devices. After this point in time, more Dutch publications appear focusing on this technology. Most of them affiliated with Philips Research and Eindhoven University of Technology (Derks *et al.,* 2006; Bruls *et al.,* 2009). This research led to the application of the technology to the detection of cocaine, marihuana and morphine within a drop of saliva. This chip is intended to be used by the police (NRC Handelsblad, 20-12-2008). This is in concordance with the positive opinion of Cor Kuijten, narcotic specialist for the Dutch police force. He states that Philips' lab-on-a-chip technology

is useful for roadside drug screening, because the chips are portable and diagnose within minutes. Such an equivalent to roadside alcohol screening was not possible before (NRC Handelsblad, 20-12-2008). In addition to this, Philips Research was developing a chip that could detect proteins and smaller molecules and is intended for various applications in healthcare (NRC Handelsblad, 20-12-2008). An example of such a chip has been developed in cooperation with the Amsterdam Medisch Centrum. They developed a chip that detects troponine, a protein indicating a heart attack, which could be used by ambulance personnel to directly determine the approach, rather than diagnosing the situation upon arrival at the hospital (NRC Handelsblad, 20-12-2008). But there were also pursuits of the technology on a smaller scale. In 2005, C2V developed a capillary lab-on-a-chip, which could detect butane and propane, which are indicators for the presence of gas in the earth's crust. Moreover the chip could be used to detect toxic gasses for chemical companies and even long cancer could be detected in exhaled air (Het Financieele Dagblad, 16-2-2008). In 2008, C2V was granted a patent for their capillary chromatographic device (US2008185342, 2008) and entered the market that same year (Het Financieele Dagblad, 16-2-2008). C2V's chip had several advantages over conventional methods for the described detections; the chips were faster, better and, most importantly, much cheaper. All this led to excitement among the 'big players' in the oil and gas industry and, for instance, also the American ministry of national security intends to use this technology for the detection of toxic gasses (Het Financieele Dagblad, 16-2-2008). Another small company enjoying international attention was Ostendum. In 2007, Ostendum announced the development of a capillary lab-on-a-chip which can detect viruses within minutes (C2W, 3-7-2007). In 2010 as well as 2011, Ostendum was granted a patent for their capillary lab-on-a-chip. These developments led to international attention, with, for instance, Forbes ranking the development amongst the thirteen most amazing new nanotechnologies (Forbes, 2007). In addition, in 2011, Ostendum won the Young Technology Award, which is a prize for promising young companies (De Twentse Courant Tubantia, 17-12-2011). From 2012 onwards, Ostendum's chip has been envisioned to be utilized for the detection of a virus within the human body within minutes and even for the detection in which stage of development the virus is (De Telegraaf, 7-2-2012). In addition, the chip could be used to measure the presence and amount of bacteria in meat, dairy products and other types of food (De Telegraaf, 7-2-2012). These expectations created a huge demand for such a technology in both the medical world and the food industry (De Telegraaf, 7-2-2012). For instance, as of 2009, Ostendum started a cooperation with Zwanenberg Food Group to develop a chip for the detection of viruses in food (Innofood, 15-6-2009).

In conclusion, several key events took place during the development of the emerging Dutch capillary lab-on-a-chip innovation system. First of all, there is the knowledge development within the research institutes of BIOS Lab-on-a-Chip Group as well as Eindhoven University of Technology and Philips Research. On the smaller scale there is knowledge development conducted by C2V and Ostendum. These developments gave rise to entrepreneurial activities of Philips, C2V and Ostendum. These market introductions were accompanied with promising expectations and investments in the technology. Demand for the technology is for instance high in the medical world, food industry, gas industry and for toxic compounds and narcotic detections. Further development of the technology is hereby legitimized. This is also visible in

the processes of resource mobilization, such as the Young Technology Award for Ostendum and the cooperative developments of Philips Healthcare with the Amsterdams Medisch Centrum and of Ostendum with Zwanenberg Food Group. Besides the gatherings for lab-on-a-chip in general of research programs, such as NanoNextNL, no information is available on events of knowledge diffusion for capillary lab-on-a-chip in particular. In a similar way, processes of guidance of search do not seem to take place, other than the Strategic Research Agenda Nanotechnology which had impact on the guidance of search for all nanotechnologies. As far as market formation is concerned, this is not detectable in the historical narrative. As described in the sketch of the Dutch lab-on-a-chip landscape, uncertainties around the actual risks and implementation of nanotechnology have prevented the establishment of standards and norms of nanotechnology products. This has no impact on the knowledge development of nanotechnology in general, but it creates uncertainties around the extent of implementation and configuration of nanotechnology products. This has a negative impact on the formation of markets within the lab-on-a-chip innovation system (Vandeberg, 2012). Thus, clarifications on these safety and configuration issues are needed in order for the Dutch capillary lab-on-a-chip innovation system to be successful. Responsibility issues regarding a decentralization of analyses do not seem to play a major role in this lab-on-a-chip innovation system, since the consumer is not the direct user of these lab-on-a-chip devices. Further, processes addressing knowledge diffusion as well as guidance of search for capillary lab-on-a-chip technology in particular are necessary in order for a single Dutch capillary lab-on-a-chip innovation system to become successful. Otherwise, without knowledge diffusion, the entrepreneurial activities within the system are individual initiatives and are being developed separately (Van Merkerk, 2012).

4.4.2. The emerging Dutch pressure driven lab-on-a-chip innovation system

The first publication on pressure drive lab-on-a-chip technology originating from The Netherlands is from the year 1996 (Hulsman *et al.,* 1996), describing two pressure driven injectors for flow analysis systems. From this point onwards, more Dutch publications appear, most of them affiliated with the MESA+ Institute. In addition, there is a separate research group within the MESA+ Institute, the Mesoscale Chemical Systems Group, focusing on chip technologies for chemical reactions. This research group is led by prof. dr. Han Gardeniers and is cooperating, on this topic, with the Radboud University Nijmegen. Knowledge development on pressure driven lab-on-a-chip already led to the foundation of the companies Chemtrix in 2008 (NRC Handelsblad, 22-12-2008), Flowid in 2008 (Flowid, 1-7-2008) and FutureChemistry in 2008 (FutureChemistry, 2012). These companies developed chip applications for pharmaceutical and chemical companies which use pressure driven chips as microreactors for flow chemistry experiments and to research chemical reactions. These microreactors have as advantages cost reductions and increased safety (FutureChemistry, 2012). An important event in the industry of these microreactors was the introduction of FutureChemistry's complete system for flow chemistry in 2009. This led to a focus shift from research on configurations of the system to research on the reactions within the system. This complete system for flow chemistry marks the start of market formation (FutureChemistry, 2012). Next to these microreactor chips, FutureChemistry provides courses on flow

chemistry, because the know-how is absent in the industry as well as missing from universities' courses (FutureChemistry, 2012). In 2008, the Dutch companies Micronit Microfluidics, FutureChemistry and Flowid announced the start of a cooperation named Access2Flow (FutureChemistry, 9-10-2008). Together, the three companies will offer a new generation of microreactor systems that enable chemists to quickly perform reactions on an industrial scale. Moreover, knowledge diffusion takes place in the form of the Flow Chemistry Society in 2010 (FutureChemistry, 2012), aiming to enhance appreciation as well as implementation into everyday practice by providing scientific publications in the Journal of Flow Chemistry in 2011 (FutureChemistry, 2012). Other notable events in the history of the Dutch pressure driven lab-on-a-chip innovation system are the start of a cooperation of FutureChemistry and Scheringh-Plough in 2008 (FutureChemistry, 18-9-2008; Het Financieele Dagblad, 19-9-2008) and the investment in FutureChemistry by PPM Oost (FutureChemistry, 18-9-2008). In addition, Flowid received a STW Valorization Grant in 2008 (Flowid, 12-12-2008).

In conclusion, several key events took place during the development of the Dutch pressure driven lab-on-a-chip innovation system. First of all, knowledge development is conducted mostly within the MESA+ Institute, especially by the Mesoscale Chemical Systems Group, and the Radboud University Nijmegen. This knowledge development provided the core technology of several start-ups, which in turn conducted knowledge development themselves. To ensure knowledge diffusion, education on the technology is being provided by FutureChemistry. In addition to the larger research programs, such as NanoNextNL, smaller co operations exists, like for instance, Access2Flow and the Flow Chemistry Society. Resources mobilization processes took place in the form of investments and subsidies. However, the process of guidance of search is not present in the narrative above. This is because the creation of revenue is presently most important. Later on, future prospects can serve as developmental guidelines. Therefore, presently, companies should be flexible towards adjustments of the products (FutureChemistry, 2012). In the case of market formation, as with the general lab-on-a-chip landscape, no such processes seem to be taking place. As described in the sketch of the Dutch lab-on-a-chip landscape, uncertainties around the actual risks of nanotechnology have prevented the establishment of standards and norms of nanotechnology products. This has no impact on the knowledge development of nanotechnology in general, but it creates uncertainties about the extent of implementation and configuration of nanotechnology products. This has a negative impact on the formation of markets within the lab-on-a-chip innovation system (Vandeberg, 2012). Responsibility issues arising out of a decentralization of analyses do not seem to play a major role for this lab-on-a-chip technology, since these lab-on-a-chip devices are used by professionals. Lastly, the process of legitimacy creation is visible in the narrative, for instance with the introduction of a separate journal and research group focusing on this technology. Yet public promotion of the technology does not seem to be taking place. An explanation for this is that microreactors are a tool, an internal technology for chemical reactions. They are not directly visible to the general public (FutureChemistry, 2012). In line with this explanation is that the users and customers of this technology are mostly large chemical and pharmaceutical companies. They would like to investigate what the benefits of this technology are, as is visible in the

cooperation of FutureChemistry with Schering-Plough, motivated by the possibility to investigate the benefits (FutureChemistry, 19-8-2008). All in all, for this innovation system to further develop, specific guidelines for the direction of development are desirable as well as clarifications on standards and norms.

4.4.3. The emerging Dutch centrifugally driven lab-on-a-chip innovation system

For the development of the Dutch centrifugal lab-on-a-chip innovation system, no processes could be identified. The only Dutch developer of centrifugal lab-on-a-chip technology is Axxicon, which hasn't published any articles or press releases on the technology, nor is this the case with articles on Axxicon. In addition, Axxicon is not affiliated with research programs such as NanoNextNL. Therefore, no insight has been gained in the understanding of the development of centrifugal lab-on-a-chip technology in The Netherlands.

4.4.4. The emerging Dutch electrokinetically driven lab-on-a-chip innovation system

The first Dutch publications related to electrokinetic lab-on-a-chip technology appeared as of 2002 (Chmela *et al.*, 2002) and have been mostly conducted and published within the University of Twente. For instance, in the case of the Lab on a Chip Journal, 23 out of the 29 Dutch publications originate from the University of Twente, the MESA+ Institute in particular. Moreover, prof. dr. ir. Albert van den Berg and prof. dr. Jan Eijkel each contributed to eleven of those articles. In addition, there is a separate research group within the MESA+ Institute, the BIOS Lab-on-a-Chip Group, focusing on the development of lab-on-a-chip technology for (bio)medical and environmental applications. This research group is led by prof. dr. ir. Albert van den Berg. The BIOS Lab-on-a-chip Group, and prof. dr. ir. Albert van den Berg, are regarded as very important for the knowledge development for electrokinetic lab-on-a-chip technology (Staijen, 2012). In addition, Van den Berg received the NWO Spinoza Prize for his research on lab-on-a-chip in 2009 (NRC Handelsblad, 9-6-2009). This knowledge development already led to the foundation of, among others, the following start-ups: Medimate in 2005 (Het Financieele Dagblad, 20-12-2005), Senzair in 2008 (Het Financieele Dagblad, 20-6-2008) and Blue4Green in 2010 (De Twentse Courant Tubantia, 13-11-2010). All these companies are based in the Twente region. These companies developed chips for blood analyses (Medimate and Blue4Green) and breath analyzers (Senzair). Prior to their market introduction, Blue4Green also started a cooperative project with De Graafschap Dierenartsen in which their product was tested on 1500 cows (Staijen, 2012; De Twentse Courant Tubantia, 15-6-2009). Another important entrepreneurial project is the chip LioniX is developing for the European Space Agency which will be used for the detection of biological material on Mars (Dagblad Tubantia/Twentsche Courant, 19-12-2007). As mentioned in section 4.1, these systems provide advantages over conventional methods by enabling fast, efficient and high quality measurements anywhere. This has raised high expectations of the technology, visible in, for instance, the NWO Spinoza Prize, the interested European Space Agency and the numerous investments in the technology. Moreover, the point-of-care market has a big, direct impact on the society, leading to more media attention and investments (FutureChemistry, 2012). A notable one is the subsidy for Medimate of healthcare insurer Zilveren Kruis Achmea (De Twentse Courant Tubantia, 21-12-2007),

motivated to invest in Medimate's chip for point-of-care lithium measurements for manic depressives, because they are convinced that these chips increase the quality of patients' lives and decrease the number of hospitalizations due to lithium poisoning (Het Financieele Dagblad, 5-2-2008). Next to the directly involved users of the technology, such as the farmers in the case of Blue4Green, and the healthcare insurers and manic depressives in the case of Medimate, the general public is also positive towards the technology. A survey of Llowlab 2012 showed an overall positive opinion of Lowland visitors towards nanotechnology (around 80%), and around 70% towards lab-on-a-chip in particular (Bos, 2012). Although within this survey no distinction was made between the different types of lab-on-a-chip technology, the lab-on-a-chip present at Llowlab 2012 was an electrokinetic chip and the example used to illustrate the possibilities of lab-on-a-chip technology was that of Medimate. So, multiple events took place that promote the technology. In addition, Van den Berg is a spokesman for the technology, providing lectures, such as at Lowlands University, working on a futuristic children's book on the impact of nanomedicine, facilitated by electrokinetic lab-on-a-chip technology, on healthcare (Vandeberg, 2012). Knowledge diffusion of electrokinetic chip technology takes also place in, for example, the meetings of the NanoNextNL theme 'Nanomedicine', as well as the meetings of one of its programs 'Nanofluidics for lab-on-a-chip', led by Van den Berg. There are also smaller events of knowledge diffusion, such as the self-organized meetings of Blue4Green with veterinarians and farmers (Staijen, 2012). Moreover, Blue4Green shares practical knowledge and skills with Medimate and Micronit Microfluidics (Staijen, 2012).

In conclusion, several key events took place during the development of the Dutch electrokinetic lab-on-a-chip innovation system. One can distinguish several different processes in the history of the emerging Dutch electrokinetically driven lab-on-a-chip innovation system. First of all, knowledge development is conducted mostly within the MESA+ Institute, especially by the BIOS Lab-on-a-chip Group. This knowledge development provided the core technology of several start-ups, which in turn conduct knowledge development themselves. Examples are Medimate, Senzair and LioniX. To ensure knowledge diffusion, the larger research programs, such as NanoNextNL, have special programs dedicated to nanotechnology for lab-on-a-chip. In addition, smaller initiatives for knowledge diffusion exist, with for example the collaborations between Blue4Green, Medimate and Micronit Micofluidics, but also knowledge diffusion towards potential users, such as the self-organized meetings of Blue4Green with veterinarians. Another important activity for the process of knowledge diffusion as well as promotion of the technology are the public lectures of Van den Berg, since he functions as a spokesman of the technology and his accessibility makes him a real promoter (Vandeberg, 2012). Next to these events related to the process of legitimacy creation, one can detect positive expectations of current users of the technology as well as the positive opinion Lowlands visitors have of electrokinetic lab-on-a-chip devices. In addition, a key event in the creation of legitimacy is the NWO Spinoza Prize for Van den Berg in 2009. An effect of this created legitimacy is visible in the numerous investments in the technology. Also future prospects of the technology are high, with aspects such as point-of-care and self-control of patients belonging to the possibilities. Although these guiding prospects can already be implemented into markets such as healthcare, as for example with

Medimate's chip, this is not extensively happening. As described in the landscape sketch, uncertainties around the actual risks of nanotechnology have prevented the establishment of standards and norms of nanotechnology products. This has no impact on the knowledge development of nanotechnology in general, but it creates uncertainties around the extent of implementation and configuration of nanotechnology products. This has a negative impact on the formation of markets within all lab-on-a-chip innovation systems (Vandeberg, 2012). In addition, possibilities such as point-of-care measurements and ultimately self-control of patients raise responsibility issues for these lab-on-a-chip devices regarding the accurate diagnosis and treatment. These responsibility issues are particularly unbeneficial for electrokinetic lab-on-a-chip technologies and, thus, also the development of the electrokinetic innovation system (Staijen, 2012). Therefore, it is expected that in the near future the technology will only be implemented in niche markets (Staijen, 2012). Noteworthy is that these responsibility issues are not the case for Blue4Green. The responsibility issues apply less to the animal care sector, leading to a larger scale implementation than electrokinetic chips applied to human health. Note that almost all developments take place in the Twente region, making this more or less a regional innovation system. An explanation for this strong regional development is the positive entrepreneurial climate, positive collaboration environment, clean room facilities, high-tech factory for production, vivid and enthusiastic researchers such as prof.dr.ir. Albert van den Berg (Vandeberg, 2012). Although most development processes are taking place within this system, for this innovation system to further develop, issues regarding responsibility of correct diagnosis require clarification for the further implementation of this technology in healthcare.

4.4.5. The emerging Dutch droplet based lab-on-a-chip innovation system

The first Dutch publications related to droplet based lab-on-a-chip technology appear as of 2006 (De Jong *et al.,* 2006). However, since membrane technology forms the basis for this technology, related knowledge development started earlier (Vogelaar *et al.,* 2001). Most of this research on membrane technology as well as the generation of droplets is conducted by the MESA+ Institute, as well as the Wageningen University and Research Centre and Radboud University Nijmegen. Few companies are also contributing to this knowledge development, being Aquamarijn (as of 2001) and Nanomi (as of 2003). As mentioned, as of 2006, research on the generation of droplets for lab-on-a-chip technology started. Again most of this research is conducted in the BIOS Lab-on-a-chip Group, the Wageningen University and Research Centre and a special research group of the Radboud University Nijmegen, the Wilhelm Huck Group. The Wilhelm Huck Group was created in 2007 and conducts research on droplet generation. These three universities are also collaborating on this research topic (De Jong *et al.,* 2006). The companies Aquamarijn and Nanomi also develop knowledge on the generation of droplets. In addition to these, Delft University of Technology is to a lesser extent active with research on droplets. Altogether this knowledge development has not yet led to entrepreneurial activities for droplet based chips. Aquamarijn and Nanomi do offer the possibility to produce various droplets for lab-on-a-chip applications, yet the introduction of actual chips has still to come. One notable application of the technology is however a chip developed by dr. Floor Wolbers at the BIOS Lab-on-a-chip Group. In 2007, Wolbers

developed a chip that detects the effectiveness of various drugs for cancer within the droplets of the chip (Dagblad Tubantia/ Twensche Courant, 19-6-2007). It is expected that this will increase the quality of cancer treatment and the quality of life, since the most suitable treatment is established in vitro with a chip, rather than in vivo and not knowing a priori what the most effective treatment for the patient is (Vrij Nederland, 31-1-2009). In 2008, Wolbers received the Overijssel PhD Award for her chip (De Twentse Courant Tubantia, 29-11-2008).

In conclusion, several key events took place during the development of the Dutch droplet based lab-on-a-chip innovation system. One can distinguish several different processes in the history of the emerging Dutch droplet based lab-on-a-chip innovation system. First of all, the process of knowledge development is the most dominant process in this system. The three most active Dutch universities in this respect are collaborating in order to enable knowledge diffusion. However, entrepreneurial activities have yet to take place. Except for the chip of Wolbers, no applications of the technology on lab-on-a-chip exists. However, this droplet based lab-on-a-chip has considerable advantages for cancer treatment, creating legitimacy for this application. This is also visible in the award the scientist received for her research. All in all, droplet based lab-on-a-chip technology is still very much in its development phase. Most of the activities take place within research institutes and although Aquamarijn and Nanomi are generating the droplets, the introduction of droplet based lab-on-a-chip technology has not yet happened.

4.4.6. The emerging Dutch FSNCD based lab-on-a-chip innovation system

The first publication on FSNCD chip technology originating from The Netherlands is from the year 2004 (Andersson and Van den Berg, 2004), describing novel developments in microfluidics for tissue engineering and future opportunities. Two years later, another article of Andersson and Van den Berg (2006) appears, providing ideas on applications of FSNCD chips and questioning the reason for the absence of biologists in this particular research field. More knowledge development takes place, mostly within the BIOS Lab-on-a-chip Group as well as the Wageningen University and Research Center and the NIZO Food Research. This research at the Wageningen University and Research Center led to the foundation of the start-up of Microdish in 2008 (De Gelderlander, 16-6-2010). Microdish develops chips which are used for microorganism culture, being more flexible, faster and more efficient for cell cultivation, control and subsequent measurements than conventional petri-dishes (Ingham *et al.*, 2010). In 2008, dr. Colin Ingham, inventor of the technology, won the Zilveren Zandloper prize for Biotechnology for the development of Microdish´s chip (Microdish, 2012).

In conclusion, several key events took place during the development of the Dutch FSNCD lab-on-a-chip innovation system. One can distinguish several different processes in the history of the emerging Dutch FSNCD based lab-on-a-chip innovation system. First of all, knowledge development takes place within the research institutes of BIOS Lab-on-a-chip Group, University of Groningen and Wageningen University and Research Center. However, events regarding knowledge diffusion is not present in this narrative. In fact, the absence of biologists in this knowledge development process in questioned (Andersson and Van den Berg, 2006). Yet, in 2008 the process of entrepreneurial activities started with the start-up

Microdish. Their chip possesses advantages over conventional methods, hereby making the further pursuit of this technology legitimized. In 2008, the inventor of the technology even won a prize for the Microdish technology. Nonetheless, the Dutch FSNCD lab-on-a-chip innovation system is still predominantly in its development phase.

4.4.7. The emerging Dutch magnetically driven lab-on-a-chip innovation system

The first publication on magnetic lab-on-a-chip technology originating from The Netherlands (MESA+ Institute) is from the year 2005 (Wensink *et al.*, 2005), describing the reaction kinetics with a magnetic lab-on-a-chip. Another important publication is that of the development of magnetic, artificial cilia for fluid propulsion in 2008 (Den Toonder *et al.*, 2008). This knowledge development collaboration between Philips Research and Eindhoven Universtity of Technology, was the start for the exploration of this new method for fluid transport. Other publications follow (Farhni *et al.*, 2009; Khaderi *et al.*, 2011), also the result of collaborations between Philips Research and Eindhoven University of Technology, and in the last case, also Zernike Institute for Advanced Materials of the University of Groningen. Despite these collaborative knowledge developments, no entrepreneurial activities have taken place with the emerging magnetic lab-on-a-chip innovation system. Note that Philips have developed a capillary driven lab-on-a-chip in which the detection of the sample fluid is done magnetically. In addition, Nanomi provides the possibility to generate droplets coated with magnetic nanoparticles which can label specific compounds and through this, serve as a tool for detection. However, lab-on-a-chip devices driven by magnetic forces, such as with the artificial cilia, have not been developed yet.

In conclusion, several key events took place during the development of the Dutch magnetic lab-on-a-chip innovation system. One can distinguish several different processes in the history of the emerging Dutch magnetically driven lab-on-a-chip innovation system. First of all, the first development of a magnetically driven chip in 2004, but more importantly is the development of fluid propulsion with magnetically actuated cilia in 2008. From this point onward, knowledge development on this topic has increased and knowledge development collaborations are formed to enable knowledge diffusion. However, due to the absence of all the other processes of importance for the development of an innovation system, the current magnetic lab-on-a-chip innovation system is still at the beginning of its development phase.

4.4.8. Conclusion

After this event analysis, the second sub-question *"Which hampering and inducing processes have influenced the development of lab-on-a-chip technologies in The Netherlands?"* can be answered. Comparing the development processes of the different emerging lab-on-a-chip innovation systems, one can detect differences in the fulfillment of the seven development processes, i.e. also in the performance of the innovation systems. First, within the capillary lab-on-a-chip innovation system, knowledge diffusion, guidance of search and market formation lack behind. As a result, without knowledge diffusion, the entrepreneurial activities within the system are individual initiatives and are developed separately. Nonetheless, expectations of these applications are high and development advances. Also because these chips enable multiple applications with a single chip. As for the pressure driven lab-on-a-chip

innovation system, low visibility of the products led to the creation of a micro reactor subculture, with its own meetings and journal. As a consequence, a lot of collaborations takes place and because the risk and configuration issues apply less to the large chemical and pharmaceutical companies which integrate the product in their systems, the size of the market is relatively big. Therefore, the development of this innovation system is relatively advanced. The electrokinetic lab-on-a-chip innovation system has the most development processes. It is a well-coordinated, mostly regional innovation system, however, responsibility issues generate uncertainties affecting the market formation of this system. Nonetheless, the most entrepreneurial activities take place in this innovation system. The regional competitive advantage of the Twente region plays an important role in the advances of the development of this innovation system. The droplet based innovation system is mostly involved with knowledge development. Although no negative processes occur, the development of this technology is still in its earliest phase. A similar scenario is the case for the FSNCD based lab-on-a-chip innovation system. Knowledge development is still the dominant development process in the system, preventing the innovation system to further develop. The least developed innovation system is that of the magnetic lab-on-a-chip technology. Only knowledge development is taking place.

All in all, the innovation system of the pressure driven and electrokinetically driven lab-on-a-chip technology are most developed in terms of development processes. A confirmation for this, is the uneven distribution of activities in the previous section. Yet, the various interpretations of relevant actors of the lab-on-a-chip technologies are also important to understand, since it is expected that the socio-technical interplay also influences the actual development of these technologies. This will be studied in the next section.

4.5 Socio-technical development of lab-on-a-chip technologies

By phrasing the third sub-question as *"Which interpretations of lab-on-a-chip have influenced the developments of lab-on-a-chip technologies in The Netherlands?"*, socio-technical development aspect of the lab-on-a-chip technologies is studied. In order to gain understanding in these various interpretations of the emerging lab-on-a-chip technologies, each development pathway has been investigated in terms of interpretations of relevant social groups of lab-on-a-chip technology to reveal similarities and differences with respect to the socio-technical development of this technology. These interpretations are derived from actor's statements in publicly available sources such as company profiles, published scientific articles, company brochures and posters, and media appearances. Conducting interviews with the actors involved is, ultimately, the best source for analyzing these interpretations. This population of relevant actors per development trajectory is determined by the outcome of the innovation system analyses. This section describes these different actor's interpretations on lab-on-a-chip technologies in order to enable reflection on the socio-technical development per lab-on-a-chip technological development pathway present in The Netherlands.

4.5.1. Interpretations of capillary driven lab-on-a-chip technology

The biggest developer of capillary lab-on-a-chip technology is Philips. Philips is developing their lab-on-a-chip for healthcare with the aim of delivering lab-equivalent test results at the point-of-care, within minutes and more efficient than conventional methods (Philips, 2012). Their motivation is based on the trend of decentralized treatment and testing towards a more patient-friendly care, at the patient's bedside. Important characteristics of such a chip are, next to the portability, rapid diagnosis, robustness, accurateness and disposability (Philips Research, 2005). In addition, the configuration of the reader should be user friendly (Philips, 2012). It is predicted that within 10 years, because of the implementation of these characteristics in the chip, complex in vitro diagnostic blood assays will have shifted from laboratory to near patient settings. However, future applications should have the right symbioses between in vivo and in vitro diagnostics. In addition, many applications outside the health sector are possible where speed and ease of use are of importance (Philips, 2012). Think for instance, of the application of the technology to the detection of cocaine, marihuana and morphine within a drop of saliva (NRC Handelsblad, 20-12-2008). This is also what the intended user, the Dutch police force, is expecting from lab-on-a-chip technology. Cor Kuijten, narcotic specialist for the Dutch police force states that Philips' lab-on-a-chip technology is useful for roadside drug screening, because the chips are portable and diagnose within minutes. Such an equivalent to roadside alcohol screening was not possible before (NRC Handelsblad, 20-12-2008).

Another widely applicable capillary lab-on-a-chip is developed by C2V. Making the detection of butane and propane less complex and less expensive was the aim of C2V (Het Financieele Dagblad, 16-2-2008). Because the application of lab-on-a-chip in the gas sector means that the conventional, half a million euro's, instruments are bypassed, important characteristics their lab-on-a-chip should possess are high quality and robustness (Het Financieele Dagblad, 16-2-2008). In the near future, the chip could be used to detect toxic compounds at lower costs than conventional methods. This provides a solution for, for instance, the American Ministry of National Security, which now have an affordable tool to detect toxic compounds (Het Financieele Dagblad, 16-2-2008). Once C2V has further developed, they aim for the healthcare market with similar chips detection the presence of longue cancer in exhaled breath (Het Financieele Dagblad, 16-2-2008).

The last developer of capillary lab-on-a-chip technology, Ostendum, also produces a widely applicable chip. This company develops chips for the detection of bacteria, viruses, yeasts, biomarkers and so on. This translates into two broad application areas: the healthcare sector and the food industry (De Telegraaf, 7-2-2012). For these markets, point-of-care or on-site measurements are the most important characteristics the chips should have (Ostendum, 2012). However, for the healthcare sector, implementation of these chips have not been realized yet. In case of the food industry, Ostendum started a cooperation with Zwanenberg Food Group. The Zwanenberg Food Group is motivated for this cooperation because of the on-site measurements possible with the chip, in addition to a decrease in costs, complexity and time per measurement; "The newly developed machine can help detect pathogenic organisms 'on the spot'," according to Erik Vliek, Director of Quality Assurance/Research & Development

at Zwanenberg. “The present methods are expensive, complicated and time-consuming, as they take a number of days to establish whether or not meat contains viruses or bacteria, for example.” (Zwanenberg Food Group, 12-6-2009).

In conclusion, the various actors’ interpretations of capillary lab-on-a-chip technology seems to be directed towards on the spot measurements. With the exception of C2V at this moment, the developers value portability as a characteristic of these types of lab-on-a-chip, and so do the respective users. Another similarity is the perceived problem per industry. All three developers recognize the inefficiency of previous methods as the problem their chip addresses, and so do the users. In addition, presently or in the future, healthcare seems to be an application area for capillary lab-on-a-chip technology. Another similarity in the interpretation of what capillary lab-on-a-chip technology is, although not explicitly mentioned as an important characteristic by the developers, is the widely applicability of the chips. All three chip developers produce chips which can perform multiple detections on the same chip.

4.5.2. Interpretations of pressure driven lab-on-a-chip technology

Starting on the side of the most influential research institute, the Mesoscale Chemical Systems Group, focuses on lab-on-a-chip technologies for chemical reactions. In other words, the Mesoscale Chemical Systems Group perceives the purpose of pressure lab-on-a-chip technology to be the application to chemical reactions. Continuing to the most influential start-ups, Chemtrix, Flowid and FutureChemistry, these companies developed lab-on-a-chip applications for pharmaceutical and chemical companies which use pressure chips as microreactors for flow chemistry experiments and to research chemical reactions (FutureChemistry, 2012). In particular, Chemtrix aims for reactors that produce continuous chemical reactions, which are safer and more efficient than conventional reactors (Chemtrix, 2012). This efficiency and safety aspect is also aimed for by Flowid, in addition to unique process controllability (Flowid, 2012). In addition to these start-ups, Bronkhorst High-Tech is a company that develops liquid mass flow chips, stating that quality of the product, fast and accurate measuring and small liquid volumes are the most characteristics of the chips for them (Bronkhorst High-Tech, 2012). Micronit Microfluidics, a supplier of, among others, pressure driven lab-on-a-chip technology, states to that the highest quality is the most important aspect of their chips. This is similar FutureChemistry’s company vision that the chips “should be used to improve the safety and efficiency of chemical processes” (FutureChemistry, 2012). In the case of knowledge diffusion, similar goals are pursued; within the cooperation of Access2Flow (Micronit Microfluidics, FutureChemistry and Flowid) the goal is the development of a new generation of microreactor systems that enable chemists to quickly perform reactions on an industrial scale (FutureChemistry, 9-10-2008). Yet, the only specific user identifiable in the event analysis, Scheringh-Plough, agreed to cooperate in order to explore FutureChemistry’s technology in order to investigate its benefits (Radboud University, 18-9-2008). No interpretations regarding the most important characteristics of such a chip or the expectations are known. However, FutureChemistry perceives robustness, reliable, not easily obstructed, cheap and widely applicable as the most important characteristics of these chips (FutureChemistry, 2012). In addition, based on customer desires, the targeted price per chip is five to ten euro’s. In the near future, it is expected that

universities and graduate schools provide courses on flow chemistry and that the technology is implemented in the systems of all top twenty chemical and pharmaceutical companies for research and production of chemical compounds (FutureChemistry, 2012). With respect to these interpretations of the technology, no irregularities are experienced within FutureChemistry's direct environment.

All in all, the various interpretations by the actors involved of pressure driven lab-on-a-chip technology are directed towards producing chemicals and the analysis of these chemical reactions. It is expected that this technology will substitute for the conventional methods for these reactions, since the relative inefficiency of these methods is perceived as the problem pressure driven lab-on-a-chip technology addresses. This leads to the application of this technology to the chemical and pharmaceutical industry, as well as the academic world.

4.5.3. Interpretations of centrifugally driven lab-on-a-chip technologies

The only developer of centrifugal lab-on-a-chip technologies, Axxicon, mentions that "highest performance requirements" and "state-of-the-art measuring" are important characteristics of their chip technology (Axxicon, 2012). However, since Axxicon is the only actor known in this innovation system, insight on the socio-technical development of centrifugal lab-on-a-chip technologies is limited.

4.5.4. Interpretations of electrokinetically driven lab-on-a-chip technologies

To start with the first Dutch market introduction of an electrokinetic lab-on-a-chip technology, Micronit Microfluidics pursued this type of technology, because of the expectation of superior quality measurements (Micronit Microfluidics, 2012). Whereas Capilix values the lab quality results, but perceives fast analysis and on-site measurements as more important characteristics (Capilix, 2012). Capilix' foresees the water market as the most important market for this technology, even though it could be used for various applications. Senzair perceives the purpose of these lab-on-a-chip technologies to be to increase the quality of healthcare, both in diagnosis as less invasive treatments (Senzair, 2012). Therefore, Senzair developed a chip detecting information on a patient's internal state present in exhaled air. This chip is expected to facilitate "point-of-care breath analysis, offering a potential revolution in disease diagnosis and treatment guidance" (Senzair, 2012). Taking this interpretation of point-of-care as the purpose of electrokinetic lab-on-a-chip technology one step further is Medimate. Next to the possibilities of improving diagnostics and making healthcare more efficient, the biggest promise of the technology is the possibility of point-of-care diagnosis and ultimately, self control of healthcare, according to the founders of Medimate (Dagblad Tubantia/Twentsche Courant, 10-1-2006). In addition, disposability of the chips and easy to use are important characteristics that lab-on-a-chip technology should have (Dagblad Tubantia/Twentsche Courant, 10-1-2006). In the near future, these chips should cost a couple of euro's, making them disposable (Dagblad Tubantia/Twentsche Courant, 10-1-2006). Other expected applications with Medimate's chip are other diseases which require frequent measurements of blood values, such as with the electrolyte balance of heart patients (Dagblad Tubantia/Twentsche Courant, 10-1-2006). Also with these measurements, the promise of self control of health care is perceived as the most important purpose of lab-on-a-chip technology,

enabling the development of a new, decentralized healthcare system. This promise of self control of health care is also regarded as important by the patient organization for manic depressives and stakeholders (patiëntenvereniging voor Manisch Depressieven en Betrokkenen). This is the result of a survey Medimate conducted within this patient organization (Medimate, 2012). In addition, healthcare insurer Zilveren Kruis Achmea included Medimate's chip in its healthcare package, motivated to invest in Medimate's chip for point-of-care lithium measurements for manic depressives, because they are convinced that these chips increase the quality of patients' lives and decrease the number of hospitalizations due to lithium poisoning (Het Financieele Dagblad, 5-2-2008). Recall that previously, the patients had to go to a physician or hospital to measure their lithium concentration. Self diagnosis, thus, creates a lot of freedom for these patients. However, as pointed out before, this raises responsibility issues regarding correct diagnosis and treatment. This is reflected in the important aspects of lab-on-a-chip technology Lowlands visitors mentioned when given the example of Medimate (Bos, 2012). Most of them had a positive opinion regarding the technology due to important possibilities such as fast and less invasive diagnoses (Bos, 2012). However, when the responsibility issue was pointed out, the majority was not sure to what extent the self control aspect should be pursued. The current, centralized healthcare system was preferred, leading to the preference of point-of-care diagnoses to a moderate extent (Bos, 2012). Blue4Green circumvents these responsibility issues by applying the technology to the animal care sector, where money is the common denominator (Staijen, 2012). Blue4Green perceive electrokinetic lab-on-a-chip technology as a means to address the problem of the increasing human population, demanding increasingly more food, leading to more pressure on the veterinary industry. In addition, animal welfare is gaining attention on the political agenda. Blue4Green's chip enables point-of-care animal diagnosis, making earlier and accurate treatment of diseases possible with a less invasive method. Both also contributing to animal welfare (Staijen, 2012). Besides this point-of-care aspect of the chips, Blue4Green values the user friendliness of their chips. This characteristic came forth out of close cooperation with De Graafschap Dierenartsen in which the prototype was tested on 1500 cows (De Twentse Courant Tubantia, 15-6-2009; Staijen, 2012). Feedback from the users showed that fast and accurate diagnosis at the point-of-care in a user friendly configuration are characteristics perceived to be important by those users (Staijen, 2012). Due to this trial project, the interpretations of the technology of Blue4Green and its users are therefore well adjusted. In addition, Blue4Green does not have to cope with the responsibility issue applicable to human healthcare chips. Therefore, this specific electrokinetic lab-on-a-chip is in a further stage of development than the others (Staijen, 2012). Because, as the Llowlab survey shows, for the other applications the responsibility issue is not easily solved, it is expected that the electrokinetic lab-on-a-chip technology in the near future will only be implemented in niche markets, such as the diagnostics for manic depressives (Staijen, 2012).

In conclusion, the interpretations by the actors involved of electrokinetic lab-on-a-chip technology is mostly directed towards on the spot measurements, albeit in different industries. Point-of-care is in case of the healthcare sector regarded as the most promising aspect of the technology. Medimate even interprets the possibility of a new, self control diagnosis, decentralized healthcare system as the most important promise of the technology. However,

stabilization on the extent of implementing this point-of-care possibility greatly varies among social groups. In more detail, those directly involved with the technology value the aspect of self control, however, the general public prefers the centralized organization of healthcare. Because of these responsibility issues, it is expected that most applications of electrokinetic lab-on-a-chip technologies will be implemented in niche markets (Staijen, 2012). An example in which interpretations of relevant stakeholders are similar, and thus stabilized, is the case of Blue4Green. This is confirmed by the further development of this type of electrokinetic lab-on-a-chip technology. Lastly, although not explicitly mentioned as an aspect of electrokinetic lab-on-a-chip technology, note that most applications of these type of chips are addressed at one type of measurements.

4.4.5. Interpretations of droplet based lab-on-a-chip technology

Since this type of lab-on-a-chip technology is still waiting to enter the market, the interpretations by the actors involved of the technology is at this moment mostly affected by the interpretation of the researchers. One notable application of the technology is however a chip developed by dr. Floor Wolbers. This application addresses the problem of ineffective cancer treatment since individuals react differently to different types of treatment. Wolbers' research enables the establishment of the most effective treatment a priori and in vitro, greatly benefitting the quality of patients' lives (Vrij Nederland, 31-1-2009). This first application of droplet based lab-on-a-chip technology contributes to the promise of personalized healthcare.

4.4.6. Interpretations of FSNCD based lab-on-a-chip technology

As is the case with the socio-technical development of droplet based lab-on-a-chip technology, the socio-technical development of the FSNCD based lab-on-a-chip technology is mostly dependent on the interpretation of researchers. One of these interpretations of researchers is shaped by the opportunity to perform tissue engineering (Andersson and Van den Berg, 2004). Another interpretation of researchers is in an article questioning the absence of biologists in this research theme (Andersson and Van den Berg, 2006), hereby implying that they expect this type of lab-on-a-chip technology to be suitable for biological research. In 2008, the first biological application of FSNCD lab-on-a-chip technology was introduced to satisfy "the strong need to develop faster, more automatable methods of growing and assaying cells" (Microdish, 2012). Perceived important characteristics of such an application are disposability and the possibility to perform a massive number of parallel assays (Microdish, 2012). In conclusion, the socio-technical development of FSNCD lab-on-a-chip technology is influenced by the interpretation that this technology suits biological research. For instance, one perceived problem is the need for faster, more automatable methods for cell cultivation.

4.4.7. Interpretations of magnetically driven lab-on-a-chip technology

Since there are no applications of magnetic lab-on-a-chip technology yet, and research on the subject is not in a stage in which interpretations of opportunities, expectations or purposes of the technology are would make sense. Therefore, the socio-technical development of magnetic lab-on-a-chip technology is not visible in this stage of development.

4.4.8. Conclusion

At this point, the third sub-question *"Which interpretations of lab-on-a-chip have influenced the developments of lab-on-a-chip technologies in The Netherlands?"* can be answered. Considering the socio-technical development of the different lab-on-a-chip technologies, differences in the interpretations between the technologies as well as within a development trajectory exists. Also, the relevant social groups, i.e. producers, users, advocates and bystanders, differs per lab-on-a-chip technology. For the capillary lab-on-a-chip technology, the possibility of on the spot measurements is mostly regarded as an important characteristic. In addition, the purpose of these chips is interpreted as addressing the relatively inefficient conventional methods. However, the application areas in which the technology should be implemented differs per application; healthcare, gas sector and food industry. Last, the different applications of the technology each enable multiple types of measurements with the same chip. The relevant social groups for this technology were the three companies as producers and hospitals, the Dutch police force and the food and gas industry as the most important users. Interpretations regarding pressure driven lab-on-a-chip technology show no interpretive flexibility; the purpose of the technology is the production of chemicals and the analysis of these reactions and the expectations of the technology all relate to the implementation of this technology into chemical and pharmaceutical companies as well as into academic research. Because these chips are envisioned to substitute complex chemical processes, quality aspects of the chip are perceived as the most important characteristics. So, for this type of lab-on-a-chip technology, closure has taken place on the interpretation of what important aspects of the technology are, which purpose the technology should serve and in which application area this should take place. The most important relevant social groups were the companies as producers and chemical and pharmaceutical companies as well as chemical researchers as the most important users. Since Axxicon is the only actor known in this particular innovation system, insight on the social influences of centrifugal lab-on-a-chip technologies is limited. Nonetheless, the most important characteristic of these chips is perceived to be related to the quality of the measurements. Accordingly, Axxicon, as the producer, is also the only relevant social group for this lab-on-a-chip technology. The interpretations of what electrokinetic lab-on-a-chip should be used for, mostly relates to on the spot measurements. For the application of the technology on healthcare, point-of-care diagnoses is regarded as the most promising possibility of the technology. However, interpretive flexibility exists in this context. Medimate and its users, for instance, foresee a decentralization of the healthcare sector due to the possibility of self control diagnosis. Although this is a promising possibility, uncertainties with respect to the extent of implementation of this self control diagnosis leads to interpretive flexibility. Therefore, different opinions on these responsibility issues prevent closure on the form of application of these point-of-care diagnostics. An exception is Blue4Green, with its point-of-care chip for the veterinary industry. Because these responsibility issues do not apply here, closure on the form of application is achieved, enabling the further development of this electrokinetic lab-on-a-chip technology. On the other hand, the further development of the other point-of-care chips is presently hampered, confining these technologies to niche markets. The most important relevant social groups for this lab-on-a-chip technological development pathway

were the companies as the producers, Albert van den Berg as advocate, the participants in the Llowlab research as bystanders and patients and farmers as the most important users. Although droplet based lab-on-a-chip is still in its knowledge development phase, the development of Wolbers' chip raises promising expectations for personalized healthcare. At this moment, the most important relevant social groups for this lab-on-a-chip technological development pathway are the researchers as the producers and as the users in the future. Also still predominantly in its development phase, the FSNCD lab-on-a-chip technology seems to develop in the direction of microbiology and cell cultivation in particular. Expectations for this application are high, since it is perceived to be problematic that there is a need for faster, more automatable methods of growing and assaying cells. This leads to important chip characteristics such as the possibility to perform numerous parallel assays. At this moment, the most important relevant social groups for this lab-on-a-chip technology are the researchers and Microdish as the producers and researchers as the users. Lastly, since there are no applications of magnetic lab-on-a-chip technology yet, and research on the subject is not in a stage in which interpretations of opportunities, expectations or purposes of the technology are would make sense.

So how do these development trajectories compare in terms of social-technical interplay of technology, and interpretations of the actors involved? The interpretations of the pressure driven lab-on-a-chip technology have stabilized. Therefore, the socio-technical development of this technology induces the further development of pressure driven lab-on-a-chip technology. In the case of the capillary lab-on-a-chip technology, interpretations on what the technology is in terms of capabilities and what problem it should address are stabilized. However, the application areas currently differ, although healthcare is envisioned to be an application area for all capillary lab-on-a-chip technologies. This interpretive flexibility prevents closure on the technology, hampering the establishment of one *single* capillary lab-on-a-chip technology. Yet even more different interpretations exist with respect to electrokinetic lab-on-a-chip technology. Although point-of-care is the common promise, interpretive flexibility exists around the configuration of this point-of-care possibility. With the exception of Blue4Green, this prevents the applications from leaving the niche markets and maturing. In the case of the other lab-on-a-chip technologies, the process of the socio-technical development cannot be compared due to the early phase of development. One can, however, detect differences in expected application areas: environmental monitoring and, in the long run, healthcare for capillary chips, chemical processes for pressure driven chips, healthcare for electrokinetic chips, research on personalized medicine for droplet based chips and microbiology and cell cultivation for FSNCD chips. Next to the socio-technical interplay, which affect the development of the different lab-on-a-chip technologies, these different expected application areas account for the existence of multiple innovation systems for lab-on-a-chip in The Netherlands.

5. Conclusions

The aim of this research was to gain understanding in the development of lab-on-a-chip in The Netherlands. Two problematic aspects of this development were studied. First, since lab-on-a-chip is a container concept for multiple technologies enabling analyses on a chip, the technological background of lab-on-a-chip was studied to untangle the variety of developments in The Netherlands that are labeled as lab-on-a-chip. With the distinction of lab-on-a-chip technologies, the development of each type of lab-on-a-chip technology in The Netherlands has been studied in terms of development processes and its socio-technical development. This development was investigated in order to understand the second problematic aspect of lab-on-a-chip development; despite intensive knowledge production and investments in the technologies, the actual development of lab-on-a-chip applications is being hampered. With this understanding of the development processes and socio-technical development per lab-on-a-chip technology the central research question "*How can the development of lab-on-a-chip in The Netherlands be understood within the period 1990-present and what can be expected of the future?*" can be answered. This chapter provides the answer to this question by combining the answers to the three sub-questions of this research. At the end of this chapter, besides answering the central research question, expectations on the near-future development of each type of lab-on-a-chip technological development pathway in The Netherlands will be provided.

5.1 Lab-on-a-chip technologies in The Netherlands

The first sub-question, "*What are the different lab-on-a-chip technologies and which development pathways exist within the Dutch lab-on-a-chip landscape?",* focuses on the technological categorization of lab-on-a-chip development possibilities as well as the distribution of the actual development of lab-on-a-chip in The Netherlands according to this categorization. Based on an extensive literature study on the technological possibilities of lab-on-a-chip, it can be concluded that there are seven distinct fluid transport technologies being used for lab-on-a-chip, including 1) capillary driven, 2) pressure driven, 3) centrifugally driven, 4) electrokinetically driven, 5) droplet based, 6) free scale non-contact dispensing based (FSNCD) and 7) magnetically driven. Each driving technology has its distinctive advantages and disadvantages, making no type of lab-on-a-chip technology perform better than the other. Capillary driven lab-on-a-chip technology enables passive fluid transportation, making it a cheap technology and because of the passive transport principle, this technology enables on-site measurements. Pressure driven lab-on-a-chip technology is based on actively pumping fluid through the channels, controlled by valves and mixers. This technology enables accurate, efficient and flexible lab-on-a-chip devices. With centrifugally driven lab-on-a-chip technology, fluid transport is realized by the rotation frequency of the 'lab-on-a-disk'. This technology enables parallel processing and controllability by the rotation frequency only. Electrokinetically driven lab-on-a-chip technology enables measurements based on surface tensions of molecules inside the channels that have been electrokinetically actuated. The increased surface tensions with smaller scale measurements result in accurate, fast and efficient electrokinetically driven lab-on-a-chip devices. With the droplet based lab-on-a-chip

technology, the droplets function as reaction confinements, enabling parallel analysis and incubation and storage of fluids. The FSNCD based lab-on-a-chip technology enables parallel assays with different measurements and individual controllability by the delivery of fluids into planar substrates or containers. Lastly, with the magnetically driven lab-on-a-chip technology fluids are being actuated magnetically. This enables low-cost, simple and portable lab-on-a-chip devices. This categorization of lab-on-a-chip technologies and their characteristics provides the categorization for mapping the developments that are collectively termed as 'lab-on-a-chip'.

With this distinction of lab-on-a-chip technologies, the actual developments of lab-on-a-chip in The Netherlands have been mapped during the period 1990-now. It can be concluded that within The Netherlands electrokinetically driven as well as pressure driven lab-on-a-chip devices are dominant in terms of distributed development; respectively thirteen and ten actors are active with the technology. For magnetically driven as well as droplet based lab-on-a-chip devices, six actors are active with the development. Capillary driven lab-on-a-chip devices are developed by five actors, whereas there are only three actors involved in the development of FSNCD based lab-on-a-chip technology and one actor is involved in the development of centrifugally driven lab-on-a-chip technology in The Netherlands. Thus, when using the distinction of lab-on-a-chip technologies as a mapping tool for the lab-on-a-chip developments in The Netherlands, the result is an uneven distribution of actors active in the development per lab-on-a-chip technology.

5.2 Understanding the current state of lab-on-a-chip development in The Netherlands

In order to understand this uneven distribution of development activities, a Technological Innovation System (TIS) analysis has been conducted per lab-on-a-chip technology to identify hampering and inducing processes that have affected the development of that particular technological pathway; *"Which hampering and inducing processes have influenced the development of lab-on-a-chip technologies in The Netherlands?"*. Next to these development processes, the socio-technical development of each lab-on-a-chip technology has been studied using a Social Construction Of Technology (SCOT) analysis in order to be able to further understand this uneven distribution of development within The Netherlands; *"Which interpretations of lab-on-a-chip have influenced the developments of lab-on-a-chip technologies in The Netherlands?"*. The interpretations of lab-on-a-chip are central in this analysis, since the outcome of technological development pathway depends on this social context of interpretations, expectations, visions and opinions of the actors involved. The stage of development each lab-on-a-chip technological development trajectory is in, can then be better understood by combining the results of the TIS and SCOT analysis.

In case of the capillary driven lab-on-a-chip technological development pathway, the TIS analysis shows that knowledge development, entrepreneurial activities and promotion of the technology are the most common development processes. However, knowledge diffusion, guidance of search and market formation lag behind, making the development of this technology poorly coordinated, resulting in isolated pursuits of capillary driven lab-on-a-chip devices. However, the SCOT analysis shows that the interpretations per application of this

technology are stable. The relevant social groups for this technology are the companies as producers and the hospitals, the Dutch police force and the food and gas industry as the most important users. The possibility of on the spot measurements is regarded as an important characteristic by Philips, Ostendum and the users of their applications. In addition, the purpose of these chips is interpreted by all three developers and their (envisioned) users as addressing the relatively inefficient conventional methods. However, the application areas in which the technology should be implemented differs per application; healthcare for Philips, gas sector for C2V and food industry for Ostendum. Therefore, individually, these applications of capillary lab-on-a-chip technology do not experience hampering of developments. But there is no emerging of just one capillary driven lab-on-a-chip innovation system.

In the case of the pressure driven lab-on-a-chip technological development pathway, the innovation system is much further developed than the capillary driven lab-on-a-chip innovation system. Low visibility for the general public of the products led to the creation of a micro reactor subculture, with its own meetings and a journal. As a consequence, a lot of collaborations take place between the Dutch developers of knowledge and applications. And because the risk and configuration issues apply less to the large chemical and pharmaceutical companies which integrate the product in their systems, the size of the market is relatively big. Therefore, the development of this innovation system is relatively advanced. The most important relevant social groups are the companies as producers and chemical and pharmaceutical companies as well as chemical researchers as the most important users. Interpretations of the developers and present users regarding pressure driven lab-on-a-chip technology show no interpretive flexibility; the purpose of the technology is the production of chemicals and the analysis of these reactions and the expectations of the technology all relate to the implementation of this technology into chemical and pharmaceutical companies as well as into academic research. Because these chips are envisioned to substitute complex chemical processes, quality aspects of the chip are perceived as the most important characteristics by all present relevant social groups, i.e. chemical and pharmaceutical companies and researchers. So, for this type of lab-on-a-chip technology, closure has taken place between the developers and present users on the interpretation of what important aspects of the technology are, which purpose the technology should serve and in which application area this should take place. Based on the combination of TIS and SCOT analysis, it can be concluded that this innovation system is maturing; it is a well-coordinated system with a development inducing socio-technical interplay. Moreover, due to the superior efficiency of these chips in comparison to conventional methods and the relatively irrelevance of the risk, configuration and responsibility issues for the large pharmaceutical and chemical companies, the implementation of this type of lab-on-a-chip technology is more or less straightforward.

For the centrifugally driven lab-on-a-chip technological development pathway, the TIS and SCOT analysis show that this technology is barely developing. Only one application of this technology in The Netherlands is known and no development processes or interpretations of the technology by other actors than the developer could be detected. Accordingly, Axxicon, as the producer, is also the only relevant social group for this lab-on-a-chip technology. The

most important characteristics relate to high-quality measurements, as perceived by the only developer.

In the case of the electrokinetically driven lab-on-a-chip technological development pathway, the TIS analysis shows that it is a well-developed and coordinated emerging innovation system. Compared to the other lab-on-a-chip innovation systems, it has the most inducing development processes due to its technology promises and visibility to the general public. It is a well-coordinated, mostly regional innovation system, however, responsibility issues regarding correct diagnoses in a decentralized healthcare system generate uncertainties influencing the market formation of this system. Nonetheless, the most entrepreneurial activities take place in this innovation system. The regional competitive advantage of the Twente region plays an important role in the advances of the development of this innovation system. Based on the SCOT analysis, however, interpretive flexibility exists between the developers of the technology and the general public regarding the implementation of the point-of-care possibilities of this technology. The most important relevant social groups for this lab-on-a-chip technological development pathway are the companies as the producers, Albert van den Berg as an advocate, the participants in the Llowlab research as bystanders and patients and farmers as the most important users. Medimate and its users (e.g. people suffering from a bipolar disorder), for instance, foresee a decentralization of the healthcare sector due to the possibility of self-controlled diagnosis. Although this is a promising possibility, uncertainties with respect to the extent of implementation of this self-controlled diagnosis leads to interpretive flexibility. Different opinions amongst the general public, and amongst the developers and current users of the technology on these responsibility issues prevent closure on the form of application of these point-of-care diagnostics. An exception is Blue4Green, with its point-of-care chip for the veterinary industry. Because such responsibility issues do not apply here, closure on the form of application has been achieved, enabling the further development of this electrokinetic lab-on-a-chip technology. However, the further development of the other point-of-care chips is presently being hampered, confining these technologies to niche markets. Therefore, despite the relatively extensive development and coordination of this technology, for the majority of electrokinetic lab-on-a-chip devices the development of actual applications is being hampered by the interpretive flexibility on the form of implementation.

For the droplet based lab-on-a-chip technological development pathway, the TIS analysis shows that the development is mostly focused on knowledge development. Although no hampering processes occur, the development of this technology is still in its earliest phase. At this moment, the most important relevant social groups for this lab-on-a-chip technological development pathway are the researchers as the producers and as the users in the future. Because the interpretations by the actors involved of the technology is at this moment mostly affected by the interpretation of the researchers, the SCOT analysis could only reveal the direction of knowledge development. This knowledge development is mostly focused on the promise of personalized healthcare. Based on these results, it can be concluded that this technology is in its development phase and that the researchers' interpretation of the

technology is related to the promise of personalized healthcare. At this stage, no hampering processes as well as interpretive flexibility could be detected.

For the FSNCD based lab-on-a-chip technological development pathway, a similar scenario is the case for the innovation system; knowledge development is still the dominant development process in the system, preventing the innovation system to develop further. The FSNCD based lab-on-a-chip technology seems to develop in the direction of microbiology and cell cultivation in particular. At this moment, the most important relevant social groups for this lab-on-a-chip technology are the researchers and Microdish as the producers and researchers as the users. Expectations of the researchers for this application are high, since it is perceived to address the need for faster, more automatable methods of growing and assaying cells. This leads to important chip characteristics such as the possibility to perform numerous parallel assays. Based on these results of the TIS and SCOT analysis, it can be concluded that this technology is still in its development phase in which interpretations of the technology are directed to cell cultivation and other microbiological assays. At this stage, no hampering processes as well as interpretive flexibility could be detected.

In the case of the magnetically driven lab-on-a-chip technological development pathway, the TIS analysis shows that, compared to the other lab-on-a-chip technologies, the magnetically driven lab-on-a-chip innovation system is the least developed. At this moment, only knowledge development is taking place. And, since there are no applications of magnetic lab-on-a-chip technology yet, and research on the subject is not in a stage in which interpretations of opportunities, expectations or purposes of the technology would make sense, the SCOT analysis did not result in insight in this aspect of development. Therefore it can only be concluded that this technology is still in its earliest development phase and, at this point, no hampering processes as well as interpretive flexibility could be detected.

In conclusion, based on the combination of the results of the TIS and SCOT analysis, the pressure driven lab-on-a-chip technology experiences the most inducing development in terms of development processes and socio-technological development. For the capillary driven lab-on-a-chip technology, the combination of results also shows an inducing development. Although one cannot speak of the development of one innovation system, on an individual basis the applications are well-developed in terms of development processes as well as the socio-technical development. A hampered development is visible in the case of the electrokinetically driven lab-on-a-chip technological development pathway. While the structural development of this technology is the most extensive, the interpretive flexibility regarding the implementation of the possibility of point-of-care and self-control healthcare is hampering the further implementation of this technology in society. The other technologies are not yet in a stage of development in which insights on the structural and social development dynamics could be gained.

At this point, the central research question "*How can the development of lab-on-a-chip in The Netherlands be understood within the period 1990- present and what can be expected of the future?*" can be answered. Firstly, in order to understand the development of the Dutch lab-on-a-chip technologies, one should take a technological perspective on the concept 'lab-on-a-

chip'. By doing so, seven different types of lab-on-a-chip technology can be distinguished. When using these technologies as a framework for mapping the development lab-on-a-chip activities in The Netherlands, it turns out that these are unevenly distributed. The variety of technologies is being further explored by taking a social perspective, focusing on the meanings to and interpretations, expectations et cetera of the actors involved. The results show that the different application areas envisioned are at least part of the cause of this variety; food and environmental monitoring, and healthcare for capillary chips, chemical processes for pressure driven chips, healthcare for electrokinetic chips, research on personalized medicine for droplet based chips and microbiology and cell cultivation for FSNCD based chips. In order to better understand this uneven distribution of developments, the development of these technologies is studied with a TIS and SCOT analysis. This combination is valuable in understanding the emergent development of lab-on-a-chip, because the TIS analysis takes a dynamic perspective on the development of emergent technological innovation systems and unravels the hampering and inducing developmental processes. Because lab-on-a-chip has not been fully embedded in society yet, a SCOT analysis is necessary to study the socio-technical interplay within each lab-on-a-chip technological development pathway. The results show that with regard to the hampered development of actual lab-on-a-chip applications, the electrokinetically driven lab-on-a-chip technological development pathway is the only development pathway that experiences this hampered development. Thus, the general idea that markets for lab-on-a-chip are not taking off is, based on this research, only visible within this technological development pathway. This general idea is influenced by the fact that electrokinetically driven chips experience the most attention due to their promises for healthcare. However, these same promises are presently perceived by the general public as being too radical when fully implemented, preventing the further implementation of this technology. As the results of the other lab-on-a-chip technologies show, this hampered development is not visible, also because some development pathways are at an early stage of development. Two further developed lab-on-a-chip technologies are the capillary driven and pressure driven chips. Although less extensively developed and less visible to the general public, these technologies do not experience this hampered development. In the case of the capillary driven chips, this issue is being circumvented by applying the technology to other industries, such as the food industry, or by developing chips designed to operate within the present centralized healthcare system, such as Philips is doing. For the pressure driven chips, the point-of-care possibility is entirely being circumvented by producing chips designed only for integration in chemical processes or destined for chemical research.

All in all, the variety of lab-on-a-chip developments in The Netherlands is caused by a variety of technological possibilities for these chips as well as different application areas being envisioned. The current state of developments is best understood by combining insights on structural and social development per technology. This way, it can be concluded that the various lab-on-a-chip technological development pathways in The Netherlands are in general being induced in terms of this structural and social development. Exceptions are the healthcare applications of electrokinetic chips. The general idea that lab-on-a-chip markets are not taking off is understandable in combination with the fact that electrokinetic lab-on-a-chip

devices have a well-developed innovation system and, due to their promises for healthcare, are most visible to the general public.

5.3 Expectations of future lab-on-a-chip developments

At this point, the second part of the central research question, "*How can the development of lab-on-a-chip in The Netherlands be understood within the period 1990- present and what can be expected of the future?*", can be answered. Based on the results and the conclusions above, providing expected near-future developments of the Dutch lab-on-a-chip technological development pathways is possible.

In the case of the capillary driven lab-on-a-chip technological development pathway, it is expected that the current applications of the technology will experience no difficulties in the near future. Although this is a loosely coupled system, each application is developing well, with already a lot of interest from users. Moreover, these applications enable multiple types of analyses with the same chip. On the one hand, this makes this technology interesting to develop for larger companies, such as Philips. On the other hand, this makes this technology applicable to multiple markets, hereby increasing the chances of further development. Lastly, it is expected that Philips' chip will experience extensive point-of-care use within the current healthcare system, because Philips perceives the promise of a decentralized healthcare system to be too radical (Philips, 2012). Therefore, their chips are designed to be implemented within the current healthcare system, i.e. serve as fast, initial tests in hospitals upon which further decisions are to be taken. Because this does not conflict with the current set-up of the Dutch healthcare system and the interpretations of lab-on-a-chip of the general public, no difficulties are to be expected after the market introduction of these chips in 2013. It is predicted that within 10 years, due to the implementation of these characteristics in the chip, complex in vitro diagnostic blood assays will have shifted from laboratory to near patient settings (Philips, 2012).

As for the pressure driven lab-on-a-chip technological development pathway, it is expected that the current applications of the technology will experience extensive implementation within the chemical and pharmaceutical industry in the near-future (FutureChemistry, 2012). In fact, these chips have already gained the interest of large chemical and pharmaceutical companies. Therefore it is expected that the implementation of this technology in these industries will only increase (FutureChemistry, 2012).

Since the centrifugally driven lab-on-a-chip technology has only one developer in The Netherlands and it experiences no interests from other companies or public media and does not have a particular application area, based on this research, it is expected that this type of lab-on-a-chip technology will not mature.

In the case of the electrokinetically driven lab-on-a-chip technological development pathway, it is expected that the applications of this technology on healthcare will experience difficulties with implementation (Staijen, 2012). Since the perspective of a decentralized healthcare system is regarded as important by the developers, but interpreted as too radical by the general public, this lab-on-a-chip technology is not expected to experience large scale

adoption in healthcare. However, the application of this technology developed by Blue4Green does not experience these conflicting interpretations, leading to the expectation that this chip will be extensively implemented in the veterinary industry (Staijen, 2012).

Due to the early stage of development, it is more difficult to anticipate the developments of the droplet based lab-on-a-chip technology. One can, however, detect a perceived application area, i.e. research for personalized medicines (Dagblad Tubantia/ Twensche Courant, 19-6-2007; Vrij Nederland, 31-1-2009). Since the application of this technology is directed to scientific research and since this technology gives rise to a new field of research, it is not expected that the further development of this technology encounters difficulties in terms of development processes or the socio-technical development.

Similarly, the early stage of development of the FSNCD based lab-on-a-chip technology makes it more difficult to anticipate on future developments. One can, however, detect a perceived application area, i.e. microbiological research (Andersson and Van den Berg, 2006). Since the application of this technology is directed to scientific research and since this technology enables more efficient research than the conventional methods for microbiological research, it is not expected that the further development of this technology encounters difficulties in terms of development processes or the socio-technical development.

Lastly, in the case of the magnetically driven lab-on-a-chip technological development pathway, expectations of further developments are even more difficult since, currently, only fundamental research is taking place. Therefore, the further development of this technology is still too flexible. Presently, this flexibility prevents sensible anticipation on the future of this technology in The Netherlands.

Comparing these expectations, it is to be expected that the pressure driven and capillary driven lab-on-a-chip technological development pathways will experience the least difficulties in the near future. The electrokinetically driven lab-on-a-chip technology will mostly be implemented in niche markets unless the interpretive flexibility on the point-of-care aspects of producers and bystanders is settled. The droplet based and FSNCD based lab-on-a-chip technologies are expected to experience less difficulties, because the development is directed to specific fields of scientific research. However, the early phase of development these technologies are currently in, makes anticipation of the future development difficult. This is even more the case for the magnetically driven lab-on-a-chip technological development pathway, for which no sensible expectations could be described. Lastly, it is expected that the centrifugally driven lab-on-a-chip technology will not further develop.

In order to give an overview of the conclusions, Figure 5 provides the lab-on-a-chip technology roadmap, visualizing the historical and present development of lab-on-a-chip in The Netherlands, as well as the expected near-future development for the lab-on-a-chip technologies, products and markets.

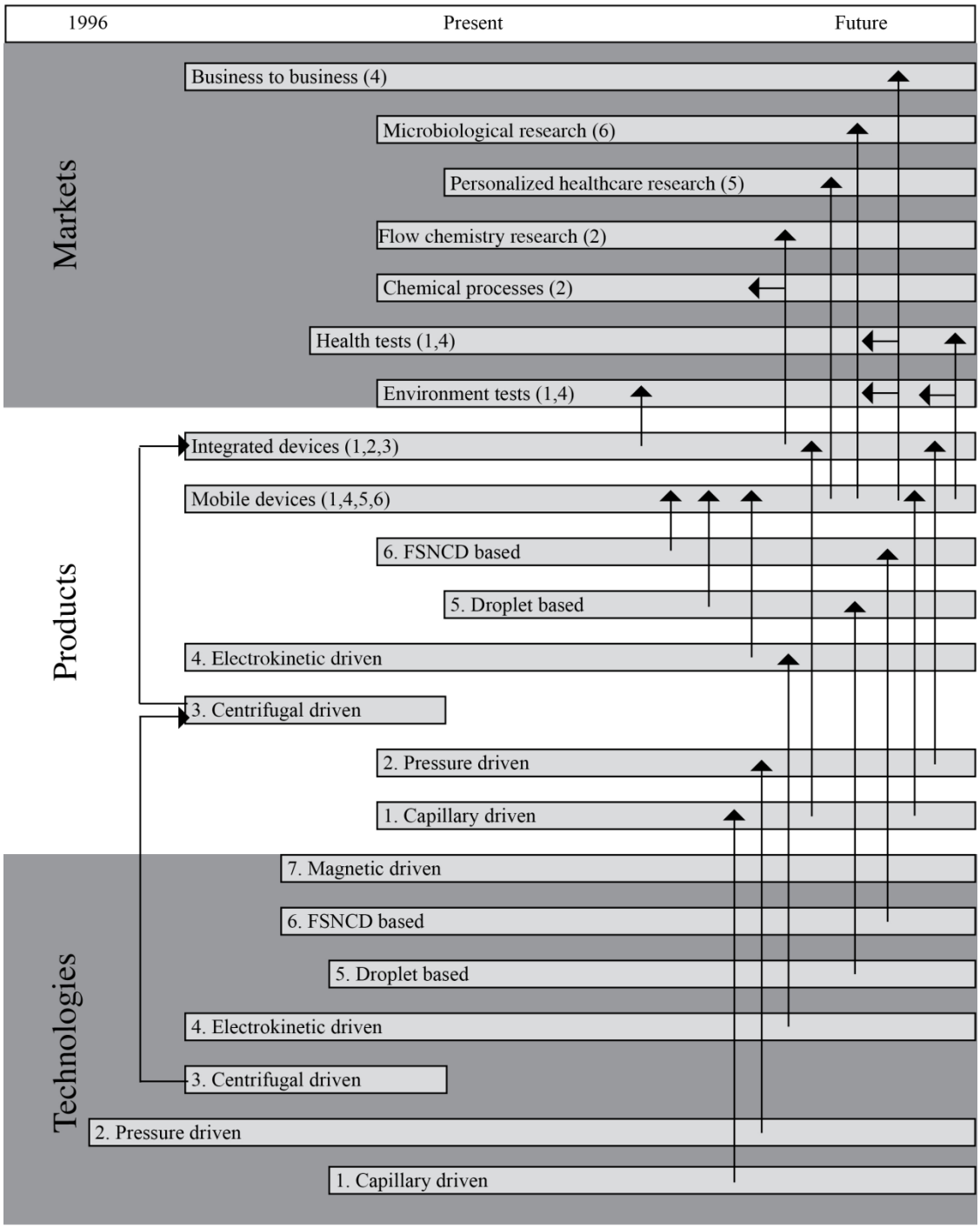

Figure 5. The Dutch lab-on-a-chip technology roadmap.

6. Discussion

This research focused on the development of lab-on-a-chip applications in The Netherlands. The aim of this research was to gain understanding in the development of lab-on-a-chip in The Netherlands by focusing on two problematic aspects of this development; first, lab-on-a-chip is not just one technology, but a container concept for multiple technologies enabling analyses on a chip and second, despite extensive knowledge production and investments in the technologies, the actual development of lab-on-a-chip applications is being hampered. The developments of lab-on-a-chip technology in The Netherlands have been mapped by firstly conducting a literature study to subdivide the container concept 'lab-on-a-chip' into several lab-on-a-chip development trajectories. Next, the development of each lab-on-a-chip technology has been studied by conducting a Technological Innovation System (TIS) analysis and a Social Construction Of Technology (SCOT) analysis. This chapter will discuss whether or not this research was theoretically and methodologically sound and whether or not the results are adequate for understanding lab-on-a-chip developments in The Netherlands. Moreover, this chapter will compare this research with other studies as well as discuss starting points for further research.

6.1 Theoretical and methodological reflection

By aiming to understand the various developments of lab-on-a-chip in The Netherlands, the first methodological step was to understand the variety of lab-on-a-chip technologies by conducting a literature study. It is assumed that the Lab on a Chip Journal, scientific publication platform for this research field, is representative for the scientific developments of lab-on-a-chip technologies. Due to the limited time available for this research, this assumption could not be checked with studying related journals. Nonetheless, the outcome of this literature study, the technological distinction of the various lab-on-a-chip development trajectories, was checked with the interviewees and confirmed to be recognizable.

As a second step in answering the first sub-question, the Dutch landscape of lab-on-a-chip in general was sketched to gain some initial understanding of the most important developments and actors. A TIS analysis was chosen, because this approach accounts for the emergent nature of lab-on-a-chip technology, by focusing on development processes that are considered to be important for emergent technologies to mature. Categorizing these processes provides insight in the development, diffusion and implementation of an emergent technology (Hekkert *et al.*, 2007; Negro, 2007). Rather than mapping the causality within this innovation system as well as the fulfillment of development processes over time, the TIS approach was used as a heuristic tool for identifying the actors involved and the most important hampering and enabling processes for lab-on-a-chip technology in The Netherlands. The primary data sources for this methodological step were written material and explorative interviews with key stakeholders in the field. Noteworthy here is that for LexisNexis the term 'lab-on-a-chip' was searched for in the Dutch articles. Hence, articles related to lab-on-a-chip, but not explicitly mentioning this container concept were not included in this research. In addition, as it turned out, much of these articles are related to electrokinetic lab-on-a-chip technology.

However, in combination with the explorative interviews, the results could be combined to get an adequate overview of the most important aspects of lab-on-a-chip in The Netherlands.

During the literature study on the variety of lab-on-a-chip technologies, it was decided that the variety of fluid actuation technologies should function as the categorization to understand the variety of lab-on-a-chip technologies. One could also decide to focus on, for instance, the variety in application areas or the mechanism of analyzing. In the case of the application areas as the categorizing characteristic, the understanding of the development of lab-on-a-chip technologies would decrease since the technologies are still very much in their development phase. This means that application areas have not yet been fully crystallized. Moreover, as with the capillary driven lab-on-a-chip technology, multiple application areas suit the same chip. In the case of the mechanism of analyzing as the categorizing characteristic, the understanding of the development of lab-on-a-chip technologies would decrease since multiple analyzing mechanisms could be implemented on the same chips, serving the same application areas. For instance, Philips chose to analyze the actuated fluids magnetically. However, the analysis might as well have been conducted electrically, with a laser, color dying the sampled compounds etc. In addition, the analysis of for instance reactions on droplet based and FSNCD based chips could be conducted with the naked eye. Therefore, the decision for fluid actuation mechanisms as the categorizing characteristic for lab-on-a-chip technologies in The Netherlands suits the purpose of this literature study best.

The outcome of this literature study, i.e. the distinction between seven technologically different lab-on-a-chip devices, served as the tool for mapping the lab-on-a-chip activities in The Netherlands. Practical experience with this technological framework showed that all producers of knowledge or applications of lab-on-a-chip in The Netherlands could be categorized within this framework. Noteworthy is that this population of developers was confined to the participants in the research programs of NanoNextNL, Nano4Vitality and MicrofluidicsNL. In addition, the Dutch articles on lab-on-a-chip present on LexisNexis were used as the delineation of the research population. Hence, it is expected that this research population does not include all Dutch producers of knowledge or applications of lab-on-a-chip. This uneven distribution of activities has been confirmed by the interviewees to be representative for the current situation of lab-on-a-chip development in The Netherlands. Moreover, the lab-on-a-chip articles derived from LexisNexis did not lead to the inclusion of additional producers of knowledge or applications. Therefore, it can be concluded that the distribution of developments regarding the lab-on-a-chip technologies presented in this study is representative for the actual development distribution in the Netherlands. Furthermore, based on the confirmation through LexisNexis, it can be concluded that the most important producers of lab-on-a-chip knowledge and applications have been included in this research. The allocation of the included actors to the different lab-on-a-chip technologies was based on patents, scientific publications and, if these were not present, company websites. Because no difficulties occurred during this allocation, the technological framework is thought to function well in order to map the variety of development trajectories that fall under the container concept ‘lab-on-a-chip’.

The next methodological step, the TIS analysis, has proven to be more difficult. Due to the emergent nature of the various lab-on-a-chip technologies identified, only a few events regarding the individual development processes could be detected through LexisNexis (125 articles). Keeping in mind that the events in these articles are distributed over seven different development trajectories, other sources of data were necessary to complement this analysis. The interviews as well as press releases of the companies selected proved valuable in complementing the data. In addition, the interviews were used to verify the selected events from LexisNexis and press releases. Although these data gave insights in the development of each lab-on-a-chip technology, a higher willingness of companies to participate in this research via interviews would have led to more insight in these development dynamics. Nonetheless, the two most developed lab-on-a-chip technologies have been complemented with data from interviews. In addition, two interviews on lab-on-a-chip in general have been conducted in order to gain understanding of the context of lab-on-a-chip in The Netherlands. Another interview with a company active with the third most developed lab-on-a-chip technology, the capillary driven chips, was especially aimed for. However, this could not be realized.

The last methodological step was the SCOT analysis for the identification of the various meanings to and interpretations, expectations of the actors involved in the different lab-on-chip development trajectories. Since lab-on-a-chip technologies are predominantly in the developmental phase, interpretations of the technologies in terms of purpose, important features, expected application areas etc. are abundant. However, since the actors involved detected during the TIS analysis served as the input for the SCOT analysis, this methodological step is subject to the same delineation flaws as the TIS analysis. Thus, social groups not mentioned by interviewees, press releases and on LexisNexis could not be included in this research. Nonetheless, the SCOT analysis proved rich enough in interpretations to enable conclusions on the socio-technical development per lab-on-a-chip technological development pathway. Important to note is, however, that in most instances, the relevant social groups could not be questioned personally. Due to time limitations, the SCOT analysis was mostly based on other sources than interviews with the actors involved. This means that the analysis of interpretations of the relevant social groups is dependent on the interpretation of the researcher and that this research is susceptible to biased interpretation of data.

In order to answer the central research question, the results of the TIS and SCOT analysis were combined. This combination proved valuable in understanding the emergent development of lab-on-a-chip, because the TIS analysis takes a dynamic perspective on the development of emergent technological innovation systems. And because lab-on-a-chip has not been fully embedded in society yet, a SCOT analysis is necessary to study the shaping of lab-on-a-chip taking the various meanings and interpretations of the actors involved into account. Only by combining these results the suitability of the theories became apparent. If this research would have focused on the development processes per technology only, this would have led to the understanding that electrokinetically driven lab-on-a-chip technologies are best developed in The Netherlands, to be followed by pressure driven and capillary driven

chips. If this research would have focused on the societal developments per technology only, this would have led to the understanding that pressure driven lab-on-a-chip technology is best developed in The Netherlands, to be followed by capillary driven and electrokinetically driven chips. Combining of the theories both emphasizes the importance of development processes for an emergent technology to further develop and the importance of stable socio-technical interplay for an emergent technology to further develop. This is in line with previous studies underlining the importance of social influences in technological development (e.g. Bijker, 1995; Geels, 2002; Rip & Schot, 2002; Geels & Schot, 2007). Given the uncertain, emergent nature of the lab-on-a-chip technologies, the variety of application fields as well as the variety of social interpretations, the combination of a TIS and SCOT analysis is most suitable to understand the development of these technologies. Therefore, the combination of a TIS and SCOT analysis provided also the basis for answering the second part of the central research question; the expectations of future developments.

The answer to the central research question has been visualized in a technology roadmap. It was intended that this visualization would also display relations between the different lab-on-a-chip technologies and enable comparisons in terms of suitability for a specific application area. These relations between the different lab-on-a-chip technologies could not be included, because the different lab-on-a-chip technologies are not per definition related. For instance, Philips had developed a capillary driven lab-on-a-chip device on which the read-out mechanism is magnetic. So, for this application, these two technologies are related. However, in the case of the other capillary driven lab-on-a-chip devices, magnetism plays no role. The comparison in terms of suitability for a specific application area could not be realized, because the different, and often early, phase of development of the different lab-on-a-chip technologies prevents thorough comparisons in terms of suitability for a specific application area. This could be investigated in the future, when the different lab-on-a-chip technological development pathways have emerged to a larger extent.

What does this methodological reflection show in terms of construct validity, internal validity, external validity and reliability? Construct validity refers to whether or not the data input and the theoretical output correlate. In other words, do the means of data collection suit the theoretical intentions? Construct validity can be increased with source triangulation, using multiple sources of evidence, and investor triangulation, using different perspectives on the data . In this study, the construct validity was increased by triangulation of multiple sources (scientific publications, press releases, interviews and other actor specific sources). In addition, the construct validity was increased by triangulation of the results with experts. During the interviews with experts, next to the verification of results found in the TIS and SCOT analysis, underlying assumptions and motives were asked about in order to gain different perspectives on the data and create a better in-depth understanding of the development of lab-on-a-chip. Moreover, the final results were checked by a fellow student. Noteworthy is that the construct validity is negatively affected by selection bias. For this research, selection bias occurred by focusing on the Lab on a Chip Journal for the establishment of the technological framework. Moreover, the delineation of the research population was based on lab-on-a-chip developers participating in NanoNextNL, Nano4Vitality and MinacNed and mentioned in

Dutch sources on LexisNexis. This selection affected the delineation of the TIS analysis, which, in turn, affected the delineation of the SCOT analysis. Although this selection delineation is based on the assumption of importance, which was verified during the interviews, this has a decreasing effect on the construct validity of this research. The internal validity refers to the causality that has been established. This can be checked by testing the causal relations with innovation theory. However, since this research is explorative of nature, the general understanding of developments was regarded more interesting than testing causal relations. The external validity refers to the extent to which this research can be generalized. This criterion can be met by comparing the results with similar studies. However, due to the explorative nature of this research, similar studies could not be found. More specifically, the technological framework used in this research to map the lab-on-a-chip developments has never been applied to The Netherlands. An earlier TIS analysis applied on multiple lab-on-a-chip development pathways could not be found, let alone such a study for The Netherlands. This is similar for the SCOT analysis. All in all, a comparison of the development of lab-on-a-chip technologies in The Netherlands could not be found. Last, the reliability of the research refers to the ability of replication of the research and is achieved by gathering data as close to the source as possible. The reliability of this research is maintained by documenting the process of data collection and data analysis as described in the methodology. However, because of the allocation of developers to a particular lab-on-a-chip technology, the identification of events and the allocation to development processes, and the mostly indirect analysis of interpretations of relevant social groups, in general the reliability is dependent on the subjective interpretation of the researcher.

6.2 Relevance of this research

This research is relevant for society, because, as described in the introduction, lab-on-a-chip technologies offer next-level efficiency for all kinds of analyses. Furthermore, the possibility of mobile lab-on-a-chip devices circumvents the necessity of a centralized system for these analyses. This leads to other benefits for society, such as further cost reductions due to savings in time, transport and human resources necessary for these analyses. Moreover, for healthcare, these possibilities could address the problem of increasing chronic diseases, decreasing medical personnel and increasingly high public demands (Walhout *et al.*, 2010). As for patients which currently suffer from diseases that demand frequent or permanent hospitalization, this promises more freedom, hereby increasing their wellbeing. Thus, this research, which focused on the understanding of the development of lab-on-a-chip technologies in The Netherlands, is socially relevant because insights gained from this research could be used for decision making during the development of lab-on-a-chip technologies in The Netherlands. Moreover, this would induce the development of some lab-on-a-chip technological development pathways, but might also lead to the decision to stop some developments and focus on the more promising technologies. All in all, the most important social contribution of this research is the understanding of the current situation of lab-on-a-chip technological development pathways in The Netherlands in terms of structural and socio-technical development processes.

This research is scientifically relevant, first of all, because this research has shown that the combination of a TIS and SCOT analysis is useful for understanding the early development of emergent technologies both in structural and social aspects. Future research could build upon this experience in cases of early development of emergent technologies. In such a situation, this combination of theories helps to explain differences in development, because solely performing a TIS or SCOT analysis might lead to different conclusions. This would also be the case for lab-on-a-chip in The Netherlands; when performing a TIS analysis only, the results would be more positive for electrokinetically driven chips, whereas the SCOT analysis would reveal otherwise. Furthermore, this research has provided a categorization of seven lab-on-a-chip technologies, which has proven to function as a mapping tool for understanding the development of lab-on-a-chip in The Netherlands. With this categorization of lab-on-a-chip technologies, future research could explore the technological development pathways in more detail. For instance, one could study the process of development in terms of structural and socio-technical processes of one of the lab-on-a-chip technological development pathways more extensively. Moreover, future research could study the interrelations between the distinguished lab-on-a-chip technologies, products and markets as depicted in Figure 5, as well as compare the lab-on-a-chip technologies in terms of suitability for a specific application area. Furthermore, the international lab-on-a-chip developments could be mapped in the same way as has been done in this research. All in all, the most important scientific contribution of this research is the categorization of lab-on-a-chip technologies. Future research on lab-on-a-chip developments can build on this categorization and serve as a first step in studying lab-on-a-chip developments.

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Appendix A: Interviews

Interviewee	Organization	Date	Relation with lab-on-a-chip
Dr. Rens Vandeberg	Technology Foundation STW	14-9-2012	Program officer at NanoNextNL and the program director of NanoLabNL
Dr. Kaspar Koch	FutureChemistry	19-9-2012	Co-founder and Managing Director at FlowChemistry
Eric Staijen Msc	Blue4Green	24-9-2012	Co-founder and Chief Technology Officer at Blue4Green
Colette Bos Msc	University of Utrecht	18-9-2012	Master thesis on nanomedicine and one of the researchers present at Llowlab 2012
Dr. Rutger van Merkerk	UMC Utrecht/Pontes Medical	8-10-2012	Phd-study with lab-on-a-chip as a case

Depending on the relation of the interviewee with lab-on-a-chip, the questions below were altered or left out.

Dutch interview questions

Welkom en voorstellen

Korte toelichting van de master en relatie met het onderzoek

Toelichting onderzoek

Vragen of het interview opgenomen mag worden

Algemene vragen

Wat is uw functie en hoe lang bekleedt u deze functie al?

Wat is uw academische achtergrond?

Wat is uw relatie met lab-on-a-chip binnen Nederland?

- Wat zijn uw verrichtingen?
- Wat zijn uw doelen?
- Wat zijn uw verantwoordelijkheden?
- Heeft u een keer een cruciale rol gespeeld?

Lab-on-a-chip innovatie systeem plaatje voorleggen, klopt dit?

- Kloppen de verschillende technologieën? Welke mist u?
- Kloppen de geïdentificeerde bedrijven? Welke mist u?

- Welke actoren spelen de belangrijkste rol? En waarom?
- Kloppen de verbanden?
- Welke regelgeving en onderliggende infrastructuur zijn van belang?
- Ontbreekt er nog iets in het plaatje?

Bedrijfsgerelateerde vragen

Zou u de drijvende kracht van uw lab-on-a-chip classificeren als capillair, druk, centrifugaal, elektrisch, magnetisch of is uw lab-on-a-chip gebaseerd op druppels of een plaat met aparte reactiekamers?

Of is er een andere kracht werkzaam aan de basis van uw technologie?

Wat is, volgens u, de rol van uw bedrijf voor lab-on-a-chip?

- Wat houdt deze rol precies in?
- Wanneer was uw bedrijf belangrijk voor lab-on-a-chip?
- Op welke manier was uw bedrijf belangrijk voor lab-on-a-chip?

Interpretatie van lab-on-a-chip

Wat zijn, volgens u, de belangrijkste eigenschappen die een lab-on-a-chip moet bezitten?

Wat verwacht u van lab-on-a-chip in de toekomst?

Wat is, volgens u, het doel van lab-on-a-chip? Met andere woorden, waar is lab-on-a-chip voor nodig?

Welke sociale groepen zijn betrokken bij uw technologie?

Waarom zijn deze groepen, volgens u, betrokken bij uw technologie?

Ervaart u verschillen in de antwoorden van bovengenoemde vragen binnen uw bedrijf of binnen uw netwerk?

- Wat zijn deze verschillen?
- Met welke actoren verschilt u hierin in mening?

Ontwikkelingsprocessen

Toelichting TIS-analyse

Ondernemersactiviteiten

Welke belangrijke ondernemersactiviteiten, zoals marktintroductie, hebben plaatsgevonden tijdens de ontwikkeling van lab-on-a-chip?

- Wanneer vonden deze gebeurtenissen plaats?
- Hoe is het gesteld met het ondernemingsklimaat van lab-on-a-chip?

Hebben er al belangrijke negatieve gebeurtenissen plaatsgevonden? Denk aan het opheffen van een bedrijf of het stoppen van een project.

Welke ondernemersactiviteiten verwacht u in de toekomst? Denk aan andere producenten, andere type producten of toepassingen.

Kennisontwikkeling

Welke belangrijke gebeurtenissen hebben plaatsgevonden met betrekking tot kennisontwikkeling, zoals onderzoeksprojecten, technologische projecten, ontwikkelingsprojecten en studies over lab-on-a-chip?

- Wanneer hebben deze gebeurtenissen plaatsgevonden?
- Waar vindt onderzoek naar lab-on-a-chip vooral plaats? (universiteiten, bedrijven, onderzoeksinstituten).
- Spelen patenten een belangrijke rol voor lab-on-a-chip? Zo ja, waarom, welke?
- Welke specifieke kennisontwikkelingen in de afgelopen 10-20 jaar zijn belangrijk geweest voor de ontwikkeling van lab-on-a-chip? Bijvoorbeeld specifieke onderzoeksresultaten, technologische ontdekkingen.
- Is er een gebrek aan specifieke kennis dat het succes van lab-on-a-chip applicaties belemmert? Zo ja, welke kennis en waar zou toekomstig onderzoek zich op moeten richten?

Kennisdiffusie

Welke belangrijke gebeurtenissen hebben plaatsgevonden met betrekking tot kennisdiffusie? Denk aan workshops, conferenties, rapporten, platforms.

- Wanneer hebben deze gebeurtenissen plaats gevonden?

Wat zou u graag anders willen zien met betrekking tot kennisdiffusie binnen uw netwerk?

Welke partijen, actoren zijn hoofdzakelijk betrokken bij deze kennisverspreiding?

Waar ligt de nadruk op congressen, workshops etc. en is deze nadruk door de tijd heen veranderd?

Sturen van ontwikkeling

Welke regulaties van de overheid, belastingsmaatregelen en positieve meningen van experts zijn, volgens u, belangrijk geweest voor het sturen van de ontwikkeling van lab-on-a-chip? En waarom?

Hoe worden huidige reguleringen ervaren door verschillende betrokken partijen? Wat voor impact heeft regelgeving op de sector?

Wat zou u graag anders zien bij de regulaties van de overheid, belastingsmaatregelen en de betrokkenheid van experts? En waarom?

Hoe zijn, volgens u, in het verleden de verwachtingen geweest met betrekking tot de ontwikkeling van een markt voor lab-on-a-chip?

Wat zouden overheden beter kunnen doen met betrekking tot de regelgeving rondom lab-on-a-chip?

Wat zouden overheden ter ondersteuning van lab-on-a-chip kunnen doen?

Marktformatie

Welke regulatieprogramma's, stimulatieprogramma's, specifieke belastingmaatregelen en andere manieren om marktformatie te stimuleren zijn volgens u belangrijk voor de marktformatie van lab-on-a-chip?

Hoe is het gesteld met de bereidheid tot inversteren in lab-on-a-chip bedrijven?

Wat zijn de voornaamste stimulerende ontwikkelingen geweest op marktformatie voor lab-on-a-chip?

- Waarom?
- Wat had beter gekund?

Wat zijn de voornaamste belemmerende ontwikkelingen geweest op marktformatie voor lab-on-a-chip?

- Waarom?
- Wat had beter gekund?

Wat voor effect hebben deze belemmerende en stimulerende ontwikkelingen gehad op de bereidheid tot investeren in lab-on-a-chip?

Mobilisatie van middelen

Welke subsidies voor en investeringen in de technologie, alsmede R&D subsidie programma's zijn volgens u belangrijk geweest voor de ontwikkeling van lab-on-a-chip?

Hoe zit het met de mobilisatie van ervaren personen of tastbare middelen, zoals ondersteunende instrumenten?

- Vindt u deze middelen afdoende?

Creatie van legitimiteit

Welke promotie- of lobbyactiviteiten voor of tegen de technologie hebben plaatsgevonden?

Welke positieve meningen van experts zijn volgens u van invloed geweest op de ontwikkeling van lab-on-a-chip?

Welke negatieve meningen van experts zijn volgens u van invloed geweest op de ontwikkeling van lab-on-a-chip?

Zijn er incidenten geweest met betrekking tot lab-on-a-chip? Zo ja, wat is de invloed hiervan geweest op de markt?

Hoe staat volgens u de consument tegenover lab-on-a-chip?

Hoe is het gesteld met de geloofwaardigheid van lab-on-a-chip?

Zijn er vanuit de industrie activiteiten ondernomen om het imago te verbeteren? Zo ja, Welke?

Zijn er gebeurtenissen van buitenaf, bijvoorbeeld de media, die invloed hebben gehad op het imago van de nanotechnologie in zijn geheel?

Wat vindt u van de rol van wetenschappers, politiek, media met betrekking tot lobbyactiviteiten rondom lab-on-a-chip?

Algemeen

Wat zijn volgens u de sterke punten van lab-on-a-chip binnen Nederland? Denk aan technologisch, beleidsmatig, hoe bedrijven met elkaar omgaan, op markten opereren etc.. En waarom?

Wat zijn de zwakke punten van lab-on-a-chip binnen Nederland en waarom?

Hoe kan de markt voor lab-on-a-chip succesvoller worden gemaakt volgens u?

Afsluitend

Heeft u nog aanvullende opmerkingen of vragen naar aanleiding van dit onderzoek naar lab-on-a-chip technologieën in Nederland?

Weet u nog andere partijen of personen die aan te raden zijn om te interviewen?

Wilt u graag een verslag van dit interview ontvangen?

Appendix B: Data event analysis

Entrepreneurial activities

If an article described an event related to the market introduction of a company or lab-on-a-chip application, it was assigned to this development process.

Source	Date	Titel
FEM Business	11-6-2005	Tech-special: Goud van eigen bodem
Het Financieele Dagblad	20-12-2005	Nanotechnologie biedt hulp aan manisch-depressieven
Het Financieele Dagblad	16-2-2008	Dwerg uit Twente is vastbesloten de giganten te verslaan
Dagblad Tubantia/Twentsche Courant	18-6-2008	UT: deelname in bedrijf dat ziektes vaststelt
Flowid press release	1-7-2008	Flowid first TU/e STW spin-off
FutureChemistry press release	18-9-2008	Schering Plough as Launching Customer
FutureChemistry press release	9-10-2008	Cooperation makes microreactor technology accessible to fine-chemistry and pharmacy
NRC Handelsblad	22-12-2008	Met alleen mooie ideeën verdien je niks; Op Chemelot kunnen startende chemiebedrijven gedijen tussen de grote concerns
De Gelderlander	16-6-2010	De Vos in de prijzen
De Twentse Courant Tubantia	13-11-2010	Hoe het de vorige winnaars verging
Het Financieele Dagblad	5-11-2011	Innovaties

Knowledge development

If an article described an event related to the progress or outcome of research on lab-on-a-chip, it was assigned to this development process.

Source	Date	Titel
Trouw	22-3-2003	Beta's negeerden maatschappelijke belangen ; Exacte vakken; Wetenschapsraad kan kloof met burger dichten
Dagblad Tubantia/Twentsche Courant	10-1-2006	Technieken waarmee patienten zelf medicijnen kunnen toedienen
Twentsche Courant	11-6-2006	'Crime-lab' op een bankpasje
Dagblad Tubantia/ Twensche Courant	19-6-2007	Effect kankermedicijnen straks beter te meten
C2W	3-7-2007	Virusverklikker op een chip
Dagblad Tubantia/Twentsche	19-12-2007	Zoeken naar leven op Mars

Courant		
Het Financieele Dagblad	16-2-2008	Dwerg uit Twente is vastbesloten de giganten te verslaan
Flowid press release	1-7-2008	Flowid first TU/e STW spin-off
Het Financieele Dagblad	19-9-2008	Radboud spin-off werkt met Schering-Plough
NRC Handelsblad	20-12-2008	Magnetische minilabs
Het Financieele Dagblad	26-5-2009	Spin-off Universiteit Twente ontwikkelt snelle virusdetector
De Twentse Courant Tubantia	15-6-2009	Blue4Green zet chip in tegen 'droogstand' koe
Innofood	15-6-2009	Ostendum werkt samen met Zwanenberg aan detectiesysteem voor ziekteverwekkers
Spits	11-9-2009	Snelle soatest in ontwikkeling; Nanotechnologie maakt goedkoper onderzoek mogelijk
De Gelderlander	16-6-2010	De Vos in de prijzen
De Twentse Courant Tubantia	13-11-2010	Hoe het de vorige winnaars verging
Het Financieele Dagblad	5-11-2011	Innovaties
De Telegraaf	7-2-2012	Chip spoort bacterie en virus op; Snelle diagnose kan levens redden

Knowledge diffusion

If an article described an event relating to the diffusion of lab-on-a-chip, either in the form of tacit and documented knowledge or in the form of lab-on-a-chip products, it was assigned to this development process.

Source	**Date**	**Titel**
Twentsche Courant	18-9-2008	Twentse hightech voor iedereen
FutureChemistry press release	9-10-2008	Cooperation makes microreactor technology accessible to fine-chemistry and pharmacy
Dagblad De Pers	21-1-2010	Debat op de vierkante micrometer De nanokaravaan; Nanotechnologie 'Eerlijk zijn over kansen en risico's'
Twentsche Courant	27-1-2012	Kleine chip in grote koffer

Guidance of search

If an article described an event related to regulations of the government, specific tax regimes or opinions and expectations of experts, it was assigned to this development process.

Source	**Date**	Titel
Leeuwarder Courant	18-3-2005	Welten wil KNMI voor criminaliteit
Trouw	30-7-2005	Stukje kauwgum meer waard dan getuigenverklaring
Dagblad Tubantia/Twentsche Courant	10-1-2006	Technieken waarmee patienten zelf medicijnen kunnen toedienen
NRC Handelsblad	20-12-2008	Magnetische minilabs
Vrij Nederland	31-1-2009	De hypothese; Floor Wolbers
Het Financieele Dagblad	26-5-2009	Spin-off Universiteit Twente ontwikkelt snelle virusdetector
Nederlands Dagblad	4-12-2010	Fabriekje op mijn aanrecht
NRC.NEXT	15-11-2011	High-tech snufjes in de topsport
De Telegraaf	7-2-2012	Chip spoort bacterie en virus op; Snelle diagnose kan levens redden

Market formation

If an article described an event related to regulation programs, stimulation programs, environmental standards or specific favorable tax regimes, it would be assigned to this development process. However, no such events could be detected in literary sources.

Resources mobilization

If an article described an event related to subsidies for and investments in the technologies or R&D subsidy programs, it was assigned to this development process.

Source	**Date**	**Titel**
Trouw	22-3-2003	Beta's negeerden maatschappelijke belangen ; Exacte vakken; Wetenschapsraad kan kloof met burger dichten
De Twentse Courant Tubantia	21-12-2007	Steun Achmea voor mini-lab
NRC Handelsblad	30-1-2008	Alsof er in Enschede een rotsblok op de weg valt; Universiteit Twente investeert fors in nanotechnologie
Het Financieele Dagblad	20-6-2008	Lab-on-a-chip
Twentsche Courant	15-8-2008	Miljoenenbijdrage voor diagnose in zakformaat
FutureChemistry press release	18-9-2008	Schering Plough as Launching Customer
De Twentse Courant Tubantia	29-11-2008	Geldprijzen voor UT-onderzoekers

Flowid press release	12-12-2008	Flowid recieves STW Valorization Grant
Twentsche Courant	24-2-2009	Blue4Green vat de veeziektes bij de horens

Creation of legitimacy

If an article described an event related to the promotion of the technologies, lobby activities related to the technologies or opinions of experts, it was assigned to this development process.

Source	**Date**	**Titel**
Dagblad Tubantia/Twentsche Courant	10-1-2006	Technieken waarmee patienten zelf medicijnen kunnen toedienen
Forbes	4-6-2007	13 Amazing New Nanotechnologies: Real-time virus testing
Dagblad Tubantia/ Twensche Courant	19-6-2007	Effect kankermedicijnen straks beter te meten
Het Financieele Dagblad	5-2-2008	Een lucratieve combinatie
Het Financieele Dagblad	16-2-2008	Dwerg uit Twente is vastbesloten de giganten te verslaan
Het Financieele Dagblad	20-6-2008	Lab-on-a-chip
FutureChemistry press release	9-10-2008	Cooperation makes microreactor technology accessible to fine-chemistry and pharmacy
De Twentse Courant Tubantia	29-11-2008	Geldprijzen voor UT-onderzoekers
Flowid press release	12-12-2008	Flowid recieves STW Valorization Grant
NRC Handelsblad	20-12-2008	Magnetische minilabs
Vrij Nederland	31-1-2009	De hypothese; Floor Wolbers
Het Financieele Dagblad	26-5-2009	Spin-off Universiteit Twente ontwikkelt snelle virusdetector
NRC Handelsblad	9-6-2009	Spinozapremies voor drie bèta's
Zwanenberg Food Group press release	12-6-2009	Zwanenberg Food Group closely involved in development of super speedy virus detector
De Twentse Courant Tubantia	13-11-2010	Hoe het de vorige winnaars verging
De Twentse Courant Tubantia	17-12-2011	Ostendum wint Young Technology Award
De Telegraaf	7-2-2012	Chip spoort bacterie en virus op; Snelle diagnose kan levens redden

Appendix C: Data socio-technical analysis

Source	Date	Specification
Andersson and Van den Berg	2004	Microfabrication and microfluidics for tissue engineering: state of the art and future opportunities. *Lab on a Chip Journal* 4, 98–103
Andersson and Van den Berg	2006	Where are the biologists? *Lab on a Chip Journal* 6, 467–470
Aquamarijn	2012	Retrieved from http://www.aquamarijn.nl/company_info.php, last visited 7-9-2012
Axxicon	2012	Retrieved from http://www.axxicon.com/PDF's/cs%20Leaflet%20Microfluidics%20final.pdf, last visited 7-9-2012
Bos	2012	Interview
Bronkhorst High-Tech	2012	Retrieved from http://www.bronkhorst.com/en/products/liquid_flow_meters___controllers/, last visited 7-9-2012
Capilix	2012	Retrieved from http://www.capilix.com/aboutcapilix/, last visited 7-9-2012
Chemtrix	2012	Retrieved from http://www.chemtrix.com/technology, last visited 7-9-2012
Dagblad Tubantia/Twentsche Courant	10-1-2006	Technieken waarmee patienten zelf medicijnen kunnen toedienen
De Telegraaf	7-2-2012	Chip spoort bacterie en virus op; Snelle diagnose kan levens redden
Flowid	2012	Retrived from http://www.flowid.nl/about%20us/index.html, last visited 7-9-2012
FutureChemistry	2012	Interview
FutureChemistry press release	9-10-2008	Cooperation makes microreactor technology accessible to fine-chemistry and pharmacy
FutureChemistry press release	18-9-2008	Schering Plough as Launching Customer
Het Financieele Dagblad	16-2-2008	Dwerg uit Twente is vastbesloten de giganten te verslaan
Het Financieele Dagblad	5-2-2008	Een lucratieve combinatie
Innofood	15-6-2009	Ostendum werkt samen met Zwanenberg aan detectiesysteem voor ziekteverwekkers
Medimate	2012	Retrieved from http://www.medimate.com/missie, last visited 7-9-2012
Microdish	2012	Retrieved from http://www.microdish.nl/products/, last visited 7-9-2012
Micronit Microfluidics	2012	Retrieved from http://www.micronit.com/footer/technologies/microfluidics/chip-electrophoresis/, last visited 7-9-2012 Retrieved from http://www.micronit.com/footer/technologies/microfluidics/droplet-generation/, last visited 7-9-2012
Nanomi	2012	Retrieved from http://www.nanomi.com/Corporate.html, last visited 7-9-2012
NRC Handelsblad	20-12-2008	Magnetische minilabs

Ostendum	2012	Retrieved from http://www.ostendum.com/Ostendum_A4flyer.pdf, last visited 7-9-2012
Philips	2012	Retrieved from http://www.business-sites.philips.com/magnotech/about/index.page, last visited 7-9-2012
Philips Research	2005	Interview with head researcher, retrieved from research data gathered by R.O. van Merkerk (2007)
Sentron	2012	Retrieved from http://www.sentron.nl/sensors/isfet-ph-sensors/, last visited 7-9-2012
Sentron	2012	Retrieved from http://www.sentron.nl/sensors/isfet-ph-sensors/, last visited 7-9-2012
Senzair	2012	Retrieved from http://www.senzair.nl/technologies/characterstics.html, last visited 7-9-2012
Staijen	2012	Interview
Vrij Nederland	31-1-2009	De hypothese; Floor Wolbers
Zwanenberg Food Group press release	12-6-2009	Zwanenberg Food Group closely involved in development of super speedy virus detector

Appendix D: Developments of lab-on-a-chip in The Netherlands

Actor	Description	Sources
Aquamarijn	Aquamarijn develops high flux, precision microfiltration membranes. During, new applications came across: the membranes enabled the generation monodisperse droplets. These droplets can be used for droplet bases lab-on-a-chip devices.	Retrieved from http://www.aquamarijn.nl/company_info.php, last visited 18-10-2012. Retrieved from http://www.aquamarijn.nl/micro_fluidics.php, last visited 18-10-2012.
Axxicon	Axxicon produces high-tech precision injection moulds and is the world leader in standardized mould systems for the production of optical discs for data storage. In addition, Axxicon has extensive knowledge and experience in micro moulding, which enables them to manufacture lab-on-a-chip consumables in cooperation with life sciences- and diagnostics companies	Retrieved from http://www.axxicon.com/company_profile.aspx, last visited 18-10-2012. Retrieved from http://www.axxicon.com/PDF's/cs%20Leaflet%20Microfluidics%20final.pdf, last visited 18-10-2012
Blue4Green	Blue4Green is developing technology for better and faster methods to diagnose diseases in animals. Blue4Green's technology enables veterinary professionals to diagnose on the spot. The chips enabling these measurements is an electrokinetically driven lab-on-a-chip device.	Retrieved from http://blue4green.com/en/about-us/, last visited 18-10-2012. Retrieved from http://blue4green.com/en/products/farmchip/, last visited 28-10-2012
Bronkhorst High-Tech	Bronkhorst High-Tech offers a product range of thermal mass flow meters and controllers. The most recent development is a series of ultra-compact, chip-sensor based instruments for gas flow and pressure measurement and control.	Retrieved from http://www.bronkhorst.com/en/about_us/company_profile/, last visited 18-10-2012. Retrieved from http://www.bronkhorst.com/en/products/liquid_flow_meters___controllers/, last visited 18-10-2012
C2V	In 2005, C2V developed a capillary lab-on-a-chip, which could detect butane and propane, which are indicators for the presence of gas in the earth's crust. Moreover the chip could be used to detect toxic gasses for chemical companies and even longue cancer could be detected in exhaled air.	US2008185342, 2008 Het Financieele Dagblad, 16-2-2008
Capilix	Capilix has developed a technology that integrates on-line analysis and capillary electrophoresis technology. This enables on-line chemical analysis of industrial water process with lab quality results.	NL1038266, 2008 Retrieved from http://www.capilix.com/aboutcapilix/, last visited 18-10-2012. Retrieved from http://www.capilix.com/wp-content/uploads/Poster_Capilix_Aquatech2011.pdf, last visited 18-10-2012.
Chemtrix	Chemtrix has developed a product portfolio of continuous flow systems suitable for reaction screening and production.	EP2429696, 2012 Retrieved from http://www.chemtrix.com/technology, last visited 18-10-2012.

Delft University of Technology	Various lab-on-a-chip research topics receive attention at this university. The most important are pressure driven, electrokinetically driven and droplet based lab-on-a-chip technology.	Guijt *et al.*, 2003 Parikesit *et al.*, 2005 Ziemecka *et al.*, 2011 Lefortier *et al.*, 2012
Eindhoven University of Technology	Various lab-on-a-chip research topics receive attention at this university. The most important are capillary driven and magnetically driven lab-on-a-chip technology.	Rebrov *et al.*, 2009 Ranzoni *et al.*, 2010 Khaderi *et al.*, 2011 Park and Anderson, 2012
Flowid	Flowid is specialized in implementing flow technology for chemical production purposes. Flowid designs and optimizes processes with flow chemistry.	Retrieved from http://www.flowid.nl/about%20us/index.html, last visited 18-10-2012
FutureChemistry	FutureChemistry is a worldwide technology leader in flow chemistry. They develop, implement and sell microreactor hardware and procedures for optimizing and screening chemical reactions and processes.	Retrieved from http://www.futurechemistry.com/about-us.html, last visited 18-10-2012
LioniX	LioniX is a leading co-developer, manufacturer and provider of microfluidic products and components for its original equipment manufacturer customers. Most of these lab-on-a-chip devices are driven electrokinetically. However, other types of chips are also produced by LioniX, being: pressure driven and FSNCD based lab-on-a-technology.	NL1021269, 2004 Martinez Vazquez *et al.*, 2008 Crespi *et al.*, 2009 Dongre *et al.*, 2010 Retrieved from http://www.lionixbv.nl/aboutlionix.html, last visited 18-10-2012. Retrieved from http://www.lionixbv.nl/solutions.html, last visited 18-10-2012.
Medimate	Medimate develops healthcare solutions for healthcare professionals, patients, and researchers by using electrokinetically driven lab-on-a-chip technology. Medimate offers solutions by taking decentralized measurements or self monitoring the concentrations in the blood level.	WO2008141659, 2008 Floris *et al.*, 2010 Retrieved from http://www.medimate.nl/medimate-uk, last visited 18-10-2012. Retrieved from http://www.medimate.nl/mission, last visited 18-10-2012.
Microdish	MicroDish is dedicated to improve microbial culture through the design, manufacture and use of microengineered culture chips and nanoscale reagents by making use of a planar, compartmentalized lab-on-a-chip devices.	Ingham *et al.*, 2010 Retrieved from http://www.microdish.nl/index.php?pagekey=microdish, last visited 18-10-2012.
Micronit Microfluidics	Micronit Micofluidics has been manufacturing glass-based lab-on-a-chip products for more than ten years. Micronit Microfluidics has extensive experience in microfluidics and is a key supplier of microfluidic devices to life sciences and chemistry markets. Micronit Microfluidics offers droplet based, electrokinetically driven and pressure driven lab-on-a-chip devices	Retrieved from http://micronit.com/footer/technologies/microfluidics/droplet-generation/, last visited 18-10-2012. Retrieved from http://micronit.com/footer/technologies/microfluidics/chip-electrophoresis/, last visited 18-10-2012. Retrieved from

		http://micronit.com/footer/technologies/microfluidics/micromixing/, last visited 18-10-2012.
Nanomi	Nanomi is specialized in the development of functional emulsions and micro- and nanospheres. This enables the production of monodisperse droplets and particles, which can be used for droplet based lab-on-a-chip devices.	US2007227591, 2007 Dijke *et al.*, 2009 Retrieved from http://www.nanomi.com/Corporate.html, last visited 18-10-2012.
Ostendum	Ostendum is currently developing a portable biosensor for the detection of bacteria, viruses, yeasts and biomarkers. The platform for these measurements is capillary driven lab-on-a-chip technology.	WO2010090514, 2010 Retrieved from http://www.ostendum.com/, last visited 18-10-2012. Retrieved from http://www.ostendum.com/xprod1.html, last visited 18-10-2012.
Philips	Philips is developing Minicare, a handheld testing platform, with the aim of providing physicians with blood test results at the point-of-care. Once a droplet of sample is applied to the cartridge the sample is automatically drawn in by capillary forces. Hereafter, magnetic nanoparticles detect the target molecules.	Retrieved from http://www.business-sites.philips.com/magnotech/about/index.page, last visited 18-10-2012. Retrieved from http://www.business-sites.philips.com/magnotech/technology/index.page, last visited 18-10-2012.
Radboud University of Nijmegen	Various lab-on-a-chip research topics receive attention at this university. The most important are pressure driven and droplet based lab-on-a-chip technology.	Bai *et al.*, 2010 Bauer *et al.*, 2010 Shim *et al.*, 2011 Theberge *et al.*, 2012
Sentron	Sentron is specializing in the development, production and application of pH measurements. Sentron has developed a comprehensive line of quality meters and probes for glass-free pH measurement.	Retrieved from http://www.sentron.nl/about-us/, last visited 18-10-2012. Retrieved from http://www.sentron.nl/sensors/isfet-ph-sensors/, last visited 18-10-2012.
Senzair	Senzair was founded to realize the development of new biosensors and to integrate these in breath solutions. In 2012, Senzair was granted a patent for their electrokinetically driven lab-on-a-chip device.	NL2005714, 2012 Retrieved from http://www.senzair.nl/about/senzair.html, last visited 18-10-2012.
University of Groningen	Various lab-on-a-chip research topics receive attention at this university. The most important are electrokinetically driven, FSNCD based and magnetically driven lab-on-a-chip technology.	Homsy *et al.*, 2005 Kraus *et al.*, 2006 Jellema *et al.*, 2009 Khaderi *et al.*, 2011
University of Leiden	Various lab-on-a-chip research topics receive attention at this university. The most important are electrokinetically driven lab-on-a-chip technology.	Podszun *et al.*, 2012
University of Twente	Various lab-on-a-chip research topics receive attention at this university. The most important are capillary driven, pressure driven, electrokinetically driven, droplet based and magnetically driven lab-on-a-chip	Homsy *et al.*, 2005 Valero *et al.*, 2005 Eijkel and Van den Berg, 2006 Salieb-Beugelaar *et al.*, 2009 Segerink *et al.*, 2010

	technology.	Vangelooven *et al.*, 2010 Segerink *et al.*, 2011
Wageningen University and Research Centre	Various lab-on-a-chip research topics receive attention at this university. The most important are electrokinetically driven and droplet based lab-on-a-chip technology.	Fox *et al.*, 2005 Van Dijke *et al.*, 2009 Baraban *et al.*, 2011 Krebs *et al.*, 2012