Surface steam sterilization:

Steam penetration in narrow channels

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Aan mijn ouders

Contents

Chapter 1

Introduction

1.1 Background

Infection prevention is applied in health care facilities, pharmaceutical, and food industries, to prevent patients, staff, and environment from contamination with microorganisms. Sterilization is part of infection prevention in the health care system. Its necessity became evident over time [1–5]. Already in the stone age, in Mesopotamia, Egypt, ancient Latin America and Asia, surgery with instruments was performed [6–9]. However, cleaning, disinfection and sterilization of instruments was not addressed until Antonie van Leeuwenhoek (1632−1723)[10] described viable organisms. Viable organisms can be defined as organisms that are alive, capable of living, developing, or germinating under favorable conditions. Pasteur (1822−1885)[11], and Koch (1843−1910)[12] recognized that (viable) microorganisms are the carriers of diseases. It was Semmelweis (1818−1865), however, who showed the relation between hand washing and infections of patients [13]. Lister (1827−1912) discovered the relation between infection of patients and medical instruments. He introduced the concept of aseptic working and the use of sterile instruments [14]. Later on, it was discovered that microorganisms are not able to travel by themselves [15, 16]. They need a carrier, such as a liquid, a person, air borne particles, or instruments to move from one location to another. After the mechanism of transport of micro-organisms was better understood, protection of staff, patients and environment became a more important issue.

Nowadays, social hygiene is widely implemented, e.g., in restaurants and food industries with a Hazard Analysis Critical Control Point (HACCP) [17]. In health care industries and facilities infection prevention became a key issue, e.g., in dental practices, hospitals and pharmaceutical industries (see appendix A.1). Decontamination has become an essential part of infection prevention. Three levels of decontamination are recognized: cleaning, disinfection and sterilization. It can be applied on floors, worktables, surgical instruments, and medicines in closed containers [18–20]. Cleaning is rinsing and washing of the visible dirt or contamination, e.g., hand washing and rinsing of surgical instruments. Items may still be contaminated after washing. Disinfection is deactivating most of the microorganisms. It can be applied on surfaces such as working tables and endoscopes that do not penetrate the human natural barriers, e.g., the skin [15]. Disinfection can be done with a liquid disinfectant [21] or exposure to an elevated temperature [22]. Also after disinfection items may still be contaminated. Generally accepted definitions for washing and disinfection are not found in the literature. Viable microorganisms may still be present after washing and disinfection. The highest level of decontamination is sterilization. Sterile is defined as ‘free of all viable organisms’ [18–20], an accepted and respected definition in health care industry and facilities worldwide [23, 24]. Sterilization

became an essential step in the process of producing sterile medical devices [15, 25]. The term medical device has a broad definition (see inset on page 2). In this thesis, unless otherwise indicated, a medical device is limited to items that are steam sterilized, such as surgical instruments.

Definition of a Medical Device
The definition of a medical device as given in the Medical Device Directive (93/42/EEC)[25]:

medical device means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

In health care facilities steam sterilization is the most frequently applied sterilization method for reusable medical devices. Such devices may vary from textiles used during surgery to complex surgical instruments. All surfaces of these medical devices that can come into contact with the environment have to be sterile. For textiles this means all surfaces of the individual fibers, and for instruments all inner- and outer-surfaces that may come into contact with the environment. Therefore this method of sterilization is referred to as surface sterilization. In practically every hospital and in many dental and general practitioner offices worldwide steam sterilizers are used for surface sterilization of medical devices. Steam sterilizers are derived from domestic food cookers, invented in 1679 by Denis Papin (1647−1712). Chamberlain (1851−1908), working with Louis Pasteur, was the first to use elevated pressure for sterilization purposes (1879).

Arrhenius (1859-1927) presented the first models of thermally activated processes in the 1920s. His Arrhenius law is still in use as a basis for calculations of the killing rate of organisms in food industry, pharmaceutical industry, and health care. Until about the 1980s, various studies on killing mechanisms of organisms and sterilization have been published [26–30]. Especially in the late 1950s and beginning of the 1960s there has been a lot of activity in this field of research in the UK [31–37]. After this period the number of publications on steam sterilization was decreasing, possibly because steam sterilization was sufficiently specified for the items to be sterilized. At that time, the bulk of the items

to be sterilized in hospitals were textiles, whereas the medical instruments did hardly change. Nowadays, textiles are being replaced by disposable solutions and, consequently, their use in hospitals reduces.

Since 1990, Minimally Invasive Surgery (MIS) or laparoscopic surgery is developing rapidly. MIS has the advantage that the surgical intervention on the patient is less severe than with open surgery, resulting in a reduction of recovery and healing time and a decrease of the discomfort for a patient [38–40]. An economical side effect is a reduction of costs for patients, hospitals and insurance companies [41–43]. Instruments used for MIS may contain narrow hollow channels, i.e., channels with a radius in the order 1 mm and lengths in the order of 1 m. Establishing surface steam sterilization conditions on the inner surfaces of such channels requires that the air that is initially present in the channel is replaced by steam [31]. This replacement appears to be far from trivial during steam sterilization, as will be demonstrated in the chapters 6, 7 and 8 of this thesis.

Steam sterilization appears to be relatively safe, fast, well accepted by public opinion, and economically interesting compared to alternative sterilization methods (see chapter 2). Nevertheless, changes in items to be sterilized and the possibilities created by the application of modern techniques are not always satisfactorily addressed or researched [44–47]. In this respect we mention the necessary physical conditions and parameter measurements and steam penetration in narrow channels. In this thesis several of these points will be addressed.

Unnecessarily long sterilization times
Exposure times for steam sterilization are specified [31], e.g. 134 °C for 3 minutes. In this temperature-time combination for sterilization with saturated steam, safety margins are already included. Nevertheless, frequently exposure times longer than 3 minutes are applied, up to even 7 minutes or more. Exposure of medical devices to sterilization conditions for such a long time promotes unnecessary wear out of these devices and involves excessive use of energy and water. Consequently, unnecessary costs may be initiated.

1.2 Current status of surface steam sterilization

To achieve minimal acceptable levels of infection prevention in health care facilities and industry, standards and legislation are developed. This is done on a national, European, and worldwide scale. Although standards are often interpreted as state of the art, they merely address minimum requirements. Unfortunately, not all standards or legislation for steam sterilization are scientifically or evidence based [48–50]. Where possible and available, biological, chemical, or physical data are used to develop the standards. However, when insufficient data is available within the standardization committees, one tries to achieve a consensus between the participating members. Such a consensus can be based on definitions, opinions and discussions. Standards for surface steam sterilization are no exception to this procedure [51–53]. Evidently, this may introduce a false sense of safety or even unsafe situations for patients, staff and environment. Also it may result in unnecessary costs, for example, extra treatment of infected staff and patients and cleaning

costs for contaminated environment. On the other hand, it may give rise to deterioration of medical devices and energy costs resulting from unnecessarily long exposure times of these devices to elevated temperatures (see inset pages 3 and 4).

Prions
Diseases such as Creutzfeld Jacob (CJD) and variant Creutzfeldt-Jakob (vCJD) are related to prions. In the literature prions are described as wrongly folded proteins [54]. Because prions, like proteins, are not viable organisms, they are not included in the definition of 'sterile' [18–20, 23, 24]. However, like toxic matter, prions on instruments may harm people and should not be present on medical instruments used on patients. In the literature we have not found conclusive evidence that prions are made harmless in a steam sterilization process.
Regardless the above, in several health care facilities steam sterilization processes e.g., 121 °C for 30 minutes or 134 °C for 18 minutes [55], are applied on medical devices which are possibly contaminated with prions. This may introduce a false sense of safety. A better solution might be to remove prions from medical instruments before sterilization, like done with toxic matter. Another option might be to adjust the current definition for 'sterile' and include not only viable organisms but also harmful matter.

In the literature and standards minimum requirements for steam sterilization are specified for surface steam sterilization [31, 51]. These time-temperature combinations are specified as minimum requirements under the assumption that saturated steam is present on all surfaces to be sterilized. In these time-temperature combinations the temperature is assumed to be constant. Often aqueous medicines disintegrate at elevated temperatures and the specified time-temperature [56–58]. In these cases the so-called F-value theory may be used to limit the exposure time to elevated temperatures but also to optimize the sterilization process. This theory comprises a mathematical model to calculate the equivalent of the time-temperature combination of an accepted sterilization process [18, 59]. Basically this calculation is an integration of the killing of organisms over time. The F-value is calculated from the moment that sterilization conditions are present, e.g., at temperatures of 105 °C and higher. For example, an accepted and standard time-temperature combination for aqueous medicines in closed ampules is 120 °C for 20 minutes. In this case the reference value is $F_{20\,\mathrm{min}}^{120\,^\circ\mathrm{C}}$ and is called the F_0-value. With the mathematical model the 'F-value' of an actual process is calculated from behavior of the temperature as function of the time. The calculated F-value should be equal or larger than the $F_{20\,\mathrm{min}}^{120\,^\circ\mathrm{C}}$-value (20 minutes). Currently a similar method is used to calculate the disinfection period in washer-disinfectors in hospitals [22, 60, 61] and is called the A_0-concept or A-value method. Unfortunately, it is not documented in the literature on which temperature domain the F-, and A-values can be applied, because in these methods the killing rate of organisms is linearized around a certain reference temperature. In chapter 5 the F-value theory is discussed in more detail. It is shown that the currently used methods can be extended in a straightforward way to the entire temperature region of interest.

Although it is difficult to prove that insufficient sterilization may cause infection, contaminations of patients by instruments have been reported in the literature [1–5, 15, 62–

68]. Also it has to be noted that the incubation time before symptoms of a contamination show up makes it difficult to identify the contamination source. This may lead to unnecessary discomfort and costs (see inset page 5). If a contamination occurs, patients generally consult a General Practitioner (GP) for treatment without knowing or identifying the source where they were contaminated. This illustrates also that the relation between sterilization and infection prevention is often difficult to quantify. Possibly, not all incidents are published because their cause was not identified, or they are undocumented because of privacy and legislation, or for less ethical reasons. Fortunately, a tendency is noticed that health care facilities are implementing patient surveillance systems and systems to monitor (track and trace) medical devices. In the patient file the medical devices used on the patients are registered, making it easier to recognize relations between infections of patients, used medical devices and sterilized batches of these devices. An additional economical advantage for the health care facility is that these monitoring systems can be used to manage, control and schedule preventive maintenance of medical devices and the equipment used for decontamination.

Choice of an effective steam sterilization process
A steam sterilization process suitable for non wrapped, solid instruments, is called a type N process [52]. A sterilizer equipped with N processes costs about € 2,000.–. A steam sterilization process to sterilize wrapped porous loads is called a type B process [52]. Steam sterilizers equipped with these processes cost about € 4,000.–, roughly € 2,000.– more. In dentist treatments hollow instruments are often used, e.g., hollow drills for implantology and re-usable multi-function syringe tips [69]. According to standards a type B processes should be used for this type of devices. If a type N process would be used to sterilize these hollow devices a patient may be contaminated during a dentist treatment. Not taking the discomfort for the patient into account, the costs for treatment are at least € 30.–; € 20.– for the consultation of a dentist or general practitioner, and € 10.– for the medicines. This hollow instrument may remain contaminated and form a source of contamination and risk for patients. Again not taking the discomfort into account, after 70 contaminations with this device or other devices a sterilizer with a type B process would be profitable. One should note that oral herpes is a relatively harmless infection compared to for example a hepatitis infection. Obviously, the return of investment for more severe infections will be much faster and the discomfort for the patients will be substantially reduced. Because the contaminated patients usually go to a general practitioner for treatment and not to the actual place of the contamination, a patient surveillance system could make this issue better visible for patients, dentists and insurance companies.

If surface steam sterilization is applied, it should be done in an effective and reproducible way. In this thesis, effective means that all surfaces are exposed to steam sterilization conditions for a predetermined time. With reproducible is meant that each time a sterilization cycle is executed, the conditions on all surfaces are similar to the runs before. When steam faces barriers, establishing steam sterilization conditions on surfaces becomes more difficult. Barriers can be porous loads, the wrapping of instruments to be sterilized, or instruments with cavities, such as devices with narrow channels. For these

items replacement of air by steam may require additional attention [52].

It is remarkable that criteria for steam sterilization differ depending on the geographical position, whereas the aim is the same. As an example we mention the performance requirements of the steam penetration test [32] (appendix A.2). The requirements for such a test in Europe [70] and the USA [71] differ essentially, whereas the objective, production of sterile medical devices, is the same. It is also remarkable that criteria [51, 52] for large and small steam sterilizers differ, although in both types of sterilizers similar items may be sterilized [49]. It is likely that microorganisms behave similar all over the world, and therefore procedures, processes and standards for sterilization should be similar worldwide as well.

Summarizing, with a better understanding of surface steam sterilization, suboptimal processes can be optimized, resulting in an improvement of steam sterilization processes, global differences in criteria can be reduced, and a false sense of safety can be avoided. More important, effective sterilization introduces less infections of patients, staff and environment, and decreases costs.

1.3 Outline of this thesis

This thesis aims to contribute to the fundamental understanding of surface steam sterilization, steam sterilization processes and penetration of steam in medical instruments with narrow channels during such processes.

In chapter 2 the basic concepts of surface steam sterilization, steam sterilizers and sterilization processes are reviewed. This chapter also briefly addresses the current standards for steam sterilization. It is followed by chapter 3, a survey on the validation status of 197 steam sterilizers in Dutch hospitals, in 2001 and 2002. The results of this survey showed that only 40 % of the hospitals in this survey did fulfill the claims they made with respect to their steam sterilization. All these claims were made based on standards. This initiated the study reported in chapter 4, in which we investigated to which extent these steam sterilization standards cover steam sterilization conditions as specified in the literature. The study shows that monitoring and validation of steam sterilization processes based on temperature and pressure measurements[1] is only valid in specific situations. In the literature an alternative method for monitoring, the F-value theory, is described. In chapter 5 the limitations of the original F-value theory are discussed and an improved model is proposed. This modified model can be applied over a broader temperature range. However, even if the sterilization conditions are satisfied within the sterilizer chamber itself, this does not necessarily imply that all types of loads can be properly sterilized. For instance, with the development of MIS instruments more surgical instruments contain hollow narrow channels. Steam penetration in these channels appears to be far from trivial. In chapter 6 a model for steam penetration in narrow channels in the absence of condensation is discussed, where special attention is given to the effect of non-condensible gases (NCGs). In chapter 7 experiments are presented that were performed to quantify the

[1] In this method a so-called theoretical temperature is calculated from the measured pressure [72]. In the standards [51] criteria are given to which extent the measured temperatures and this theoretical temperature should agree.

sensitivity to NCGs of a commercially available instrument to assess steam penetration, together with a theoretical model to explain these experimental results. In this model condensation is assumed to be dominant. Both models in chapters 6 and 7 are quasi one-dimensional and quasi isothermal. In chapter 8 a two dimensional and non-isothermal theoretical model is discussed. In the last chapter 9 the conclusions, discussions, and an outlook are given.

> Chapters 3, 4, 5 and 6 of this thesis are papers that have been published or submitted, which are included in their original form. Consequently, some overlap between parts of these chapters is unavoidable.

Chapter 2

Steam sterilization

'Free of all viable organisms' is worldwide accepted as the definition for sterility of medical devices [18–20, 23, 24]. To prove that a medical device is actually sterile it has to be tested. During this testing the item is handled and manipulated and cannot be considered sterile anymore. Consequently testing sterile items before use is pointless and even impossible. Therefore a statistical approach was and is necessary. Favero [73] described how the statistical definition of sterility originated, how it evolved and how the concept of the Sterility Assurance Level (SAL) developed over time and is applied in practice. Currently, the European standard EN 556 [23] defines 'For a terminally-sterilized medical device to be designated "STERILE", the theoretical probability of there being a viable microorganism present on/in the device shall be equal to or less than 1×10^{-6}.' A largely similar concept is the SAL, which is defined as 'the probability of a single viable microorganism occurring in or on a product after sterilization' [53]. To meet the sterility requirement the value of the SAL should be 10^{-6} or less. It can be stated that worldwide the accepted statistical definition is 'Sterility of medical devices is defined as the chance of finding a viable organism in or on a medical device being 1 in 1,000,000 or less'.

Statistical definition of 'sterile'
In principle, the statistical definition of 'sterile' [23] could be interpreted as that at most 1 of 1,000,000 sterilized items may contain a viable organism [46]. However, it is obvious that the surface of, for instance, 10^6 scalpels is much smaller than that of 10^6 orthopedic drills. Therefore this definition contains a 'sliding' scale with respect to the actual surface area.
Apart from this, there is an ongoing discussion whether the actual sterilization process should always reduce the amount of viable organisms by a factor of 10^6 [46, 47]. When the definition 'free of viable organisms' is accepted and is applicable to the medical devices, all steps to produce a sterile item should be considered. In hospitals, these steps often include washing, disinfection and sterilization. Each step leads to a certain reduction of the amount of viable organisms. If before sterilization an item would already be free of viable organisms, it might be considered sterile. However, it is not wrapped and can get recontaminated during handling, transport and storage (see appendix A.3). Nevertheless, if the initial contamination before the actual sterilization process is known, that process might be adjusted accordingly. Standards for sterilization allow for such an approach [53].

Often sterilization is associated with inactivation of organisms rather than removing [20]. Although viable organisms can be separated from a fluid by filtration, this is often not considered as sterilization. Filters can start leaking and filtration does not kill organisms. Exposing organisms to deadly conditions will inactivate or destruct them. A

possible classification of different sterilization methods can be based on the temperature: low temperature sterilization, i.e., sterilization at temperatures below 100 °C, and high temperature sterilization, at temperatures above 100 °C. Examples of low temperature sterilization are ethylene oxide sterilization, formaldehyde-, hydrogen peroxide-, plasma-, ozone-, and irradiation sterilization. Examples of high temperature sterilization are dry heat and steam sterilization. Another basis for classification of sterilization methods could be the mechanism of killing the viable microorganisms, such as oxidation, intoxication, destroying vital cell structures. Oxidizing sterilization methods[1] are hydrogen peroxide, ozone, and dry heat sterilization, intoxicating methods[2] are ethylene oxide and formaldehyde, and examples of sterilization methods based on changing vital cell structures[3] are irradiation and steam sterilization.

Steam sterilization in dental offices
Dry heat sterilization temperatures are typically above 150 °C. At a specified temperature, exposure times are specified to produce sterile items, e.g., at 160 °C the exposure time is 2 hours (see table 2.2). The complete process cycle of a dry heat sterilization process, with warming up and cooling down, will take over 3 hours. A typical exposure time for items processed in steam sterilization at 134 °C is 3 minutes. A complete steam sterilization cycle will be ended in about 1 hour. Energy costs of dry heat sterilization are higher than those of steam sterilization. In addition, MIS and complex instruments, e.g., hand-pieces for dentistry, are often made of different parts, consisting of different materials with different thermal expansion characteristics. Most plastics and polymers used in a medical device will deform irreversibly at temperature above 140 °C. In a medical device different materials may be welded together, or moving within each other, e.g., the turbine to drive the drill in a dentist hand-piece. The higher the temperature, the bigger the difference in expansion of the various materials, and the faster the wearing out of the expensive medical device. Obviously, compared to dry heat sterilization, steam sterilization will safe time, energy, wearing out of instruments, and therefore costs in dental practices.

It is important to realize that sterilization is only possible if the organisms are in contact with the sterilization agent or 'sterilant'. However, as mentioned above, sterilized items should not be touched or handled anymore after sterilization. Consequently, devices have to be protectively wrapped before sterilization to prevent re-contamination after sterilization. Protection can be done by wrapping the devices before sterilization in a micro biological barrier, for instance sheets of crepe, or by packing in a container (see appendix A.3). Obviously the sterilant must be able to penetrate through the wrapping.

Every sterilization method has its advantages and disadvantages. Nevertheless, all sterilization methods have the ability to kill and are therefore by definition hazardous. A sterilant can be even classified carcinogenic, e.g., formaldehyde [74]. This concerns not

[1] Sterilization methods in which oxygen out of the environment is used to 'burn' the viable organisms which are present.

[2] Sterilization methods in which the viable organisms are poisoned.

[3] Sterilization methods which irreversible change the vital cell structures necessary for life, e.g., DNA strings.

only the target group but also the operators of a sterilizer and its environment. Depending on the specific situation the most effective and safest sterilization method should be chosen (see inset page 10). In pharmaceutical and food industries, for example, items are sterilized only once before being transported to the end-user. During the transport from industry to end-user heavy wrapping is necessary to prevent re-contamination but also to protect the devices and their micro biological barriers from damaging. Consequently, sterilization methods in industries have to be able to penetrate the heavy transport wrapping in order to come into contact with viable microorganisms. Irradiation and ethylene oxide have good penetration capabilities and are more often applied in industries than in health care facilities.

Industrial sterilization is performed at the end of a production line and no or only limited reprocessing is performed. On the other hand, in health care facilities, e.g., hospitals and dental practices, sterilization of re-usable medical devices such as surgical instruments and hand-pieces is performed frequently. Reprocessing of re-usable medical devices can be classified as an expertise. To perform the reprocessing and sterilizing of medical devices efficiently and by experts, a so called Central Sterile Supply Department (CSSD, appendix A.4) can be found in the larger health care facilities.

In health care facilities worldwide steam sterilization is the most generally applied sterilization method for various reasons. First, the bulk of reusable medical devices can be processed in it. Second, compared to other sterilization methods it is the least hazardous for staff and environment and is therefore socially accepted. Third, the working mechanism of steam sterilization is fairly well understood and described in the literature [18–20]. Fourth, alternative methods demand extra safety requirements [75, 76]. These extra requirements can be hardware, such as sensors, and monitoring systems for locations and staff, written procedures for operating the machine, including safety and calamity procedures, and even requirements for specialized staff to operate the sterilizer. Finally, steam sterilization has economical advantages compared to other sterilization methods.

The result of a sterilization process depends on the combination of the sterilizer, process, load, loading pattern (placement of the instruments in the sterilizer) and wrapping. In this chapter the surface steam sterilization conditions (section 2.1) and steam quality (section 2.2) will be addressed, followed by the explanation of the working principle of a steam sterilizer (section 2.3) and steam sterilization processes (section 2.4). Over time standards for steam sterilization have been developed and published [23, 51, 53, 70, 71, 77–80]. In section 2.5 these will be reviewed briefly.

2.1 Surface steam sterilization conditions

Steam sterilization is generally applied in two ways: sterilization of aqueous liquids in closed containers and surface steam sterilization. Regardless the method the killing mechanism is coagulation [28]. Without the proteins organisms are not viable and cannot live. Coagulation requires energy and water [20, 28, 81]. Before coagulation can take place the protein string has to be broken up into smaller chains. In steam sterilization processes for aqueous liquids in closed containers the steam is used to heat up the liquid in the container. By heating up the aqueous liquid hydro-sulphide ions and smaller peptide chains

may be detached from the proteins [81, 82]. Like water molecules these hydro-sulphide ions and peptide chains are bipolar. Therefore, these detached ions and chains can move through the water to new other locations within the organism. At these locations new bonds between the molecules are formed, the actual coagulation. These new bonds are different from the original bonds and are generally harder and irreversible. Because these newly formed molecules differ from the proteins chains, life and viable life is destroyed [20, 28, 81, 82]. In this thesis coagulation is defined as the irreversible change and hardening of the protein chains of a microorganism.

In aqueous environments the water content of cell structures is optimal for sterilization. However, contamination of medical instruments occurs on the surfaces of these devices. Before being exposed to surface steam sterilization, the amount of water in the viable organisms on these surfaces depends on the type of organism and the environmental conditions [26, 83]. If only exposed to elevated temperatures with insufficient water in the organism, ions and peptide chains may not be detached and able to relocate. However, the steam is not only supplying the energy for increasing the temperature. Steam condenses on colder surfaces and provides a condense layer. This layer establishes the necessary wet environment to transport the ions and peptides to other locations to form new irreversible bonds.

Chaufour et al. [84] showed that items have to be cleaned before surface sterilization. A layer of organic material or dirt can prohibit the creation of sterilization conditions. Apart from this, when biologically incompatible materials such as endotoxines are introduced in a patient, the patient may develop an infection. In aqueous steam sterilization the amount of incompatible materials is often controlled with aseptic processes. However, on a surface of a medical device the amount of such materials has to be reduced as much as reasonably achievable before sterilization. Cleanliness of surfaces after cleaning processes is not trivial, especially not for the inner surfaces of channels in medical devices [85–87]. In such cases sterilization is the final security that no viable organisms are brought into a patient.

Sterilization can be defined as establishing sterilization conditions and maintaining these for a predetermined time. Surface steam sterilization conditions are specified as sterilization of clean surfaces with saturated steam at a predetermined temperature. The only time-temperature combinations for surface steam sterilization with saturated steam found in the literature are those of the Working Party on Pressure-Steam Sterilizers of the Medical Research Council [31]. In table 2.1 these combinations are presented together with the time-temperature relations determined for sterilization of aqueous liquids by Perkins [88].

2.2 Steam quality

In steam sterilization of aqueous liquids in containers the steam does not come into direct contact with the liquid. As long as the liquid reaches the predetermined temperature sterilization will occur. For surface steam sterilization the quality of the steam is more important, because the steam will be in contact with the surfaces that have to be sterilized. In steam sterilization two aspects of steam quality can be distinguished. First the

composition of the steam. Presence of contaminants may result in deposits on surfaces in contact with the steam. Deposits of contaminants may lead to coloration and even to malfunctioning of instruments, such as stiff or blocked hinges, or leaking valves of a sterilizer. In extreme cases deposits could even be transferred to a patient. Therefore minimum requirements are suggested for maximum values of contaminants in feed water, steam and condense of the steam [51].

Perkins		MRC	
time (minutes)	temperature (°C)	time (minutes)	temperature (°C)
2	132	3	134
8	125	10	126
12	121	15	121

Table 2.1: Time-temperature data sets for sterilization of aqueous liquids of Perkins [88] and the time-temperature combinations for steam from the Working Party on Pressure-Steam Sterilizers of the Medical Research Council in the UK [31].

The second aspect of the steam quality is the amount of non condensible gases (NCGs). It is reported in the literature that heat transfer by condensation of steam in the presence of NCGs is substantially smaller than that by condensation of pure steam [89, 90]. This reduction may slow down the heating of loads with very high heat capacities, but in principle, this effect can be taken into account by allowing some extra time for the load to heat up. A more serious issue is that current time-temperature combinations for steam sterilization are based on the reported findings of Perkins [88] (table 2.1). Perkins' time-temperature combinations find their origin in the study of Precht [81]. In the study of the 'Working party on pressure-steam sterilizers' of the Medical Research Council it was assumed that organisms exposed to 100 % or saturated steam behave the same as organisms emerged in an aqueous liquid [31]. This results in similar temperature-time combinations for aqueous liquid and surface steam sterilization. However, it was reported in this study that in hospitals 'The quality of steam is known to vary with the degree of saturation, the amount of water-fog carried in it, and the amount of air it contains'. This basically means that the steam in hospitals is not always saturated. Because of these phenomena the Working Party adapted the results of Perkins [88] with safety margins (table 2.1). A rationale for the size of these margins has not been given.

Actually, the effectivity of killing organisms with steam compositions other than saturated steam or dry heat has, to our knowledge, not been reported. This may be the reason why steam sterilization processes performed with non saturated steam are considered as dry heat sterilization processes. In this respect it is remarkable that standards allow a small percentage (3 to 3.5 %) of NCGs in steam [51, 91]. The relation of this value to the actual presence of sufficient condensate on the surface of the items to be sterilized or to the validity of the time-temperature combinations given in table 2.1 is not clear. It is also not documented whether these values incorporate any experimental uncertainties in the measurements of temperature and pressure in the sterilizer chamber.

surface steam sterilization		dry heat	
time (minutes)	temperature (°C)	time (minutes)	temperature (°C)
-	-	60	170
-	-	120	160
-	-	150	150
-	-	180	140
3	134	-	-
10	126	-	-
15	121	overnight	121

Table 2.2: Time-temperature data sets for steam [31] and dry heat [19] sterilization.

2.3 Steam sterilizer

Surface steam sterilization is performed in steam sterilizers. These sterilizers come in many sizes and shapes, but the working principle and the essential parts are similar. Surface steam sterilization can be best (most effective and reproducible) performed in a vacuum assisted steam sterilizer, which is schematically shown in figure 2.1. A modern steam sterilizer has a double wall, called a jacket. In the jacket steam can be submitted with the purpose to heat up the inner side of the jacket.[4] By keeping the jacket at a temperature of about 0.5 to 1 °C higher than the chamber temperature, no condense will be formed on the jacket. By valves in the supply lines the steam inlet into the jacket and sterilizer chamber can be controlled independently. Both steam inlets are connected to the steam supply. To avoid direct steam impact on the processed load, a baffle plate is mounted in front of the chamber steam inlet. To pump the gases and possibly water condense out of the sterilizer chamber, a vacuum pump is installed in the drain line. Between the sterilizer chamber and the vacuum pump a valve is present, which is essential to prevent that potentially contaminated water, vapor or gas can flow back into the sterilizer chamber. When air is submitted it will be filtered with a High-Efficiency Particulate Air (HEPA) filter to avoid re-contamination of loads. At least one door is available to load and unload the sterilizer. To avoid that batches of sterilized and unsterilized loads intersect, sterilizers can be equipped with a loading and an unloading door (GMP, appendix A.4). NCGs should not be able to leak into the chamber. To prevent leaks via the doors gaskets are mounted.

Two pressure sensors are mounted on the sterilizer chamber and two temperature sensors, often Pt100s, are mounted in the drain of the sterilizer chamber. One pressure and one temperature sensor form a set. One set of senors is used for the control of the sterilizer. The second set is used for independent monitoring and registration of the processes. Modern steam sterilizers are pressure controlled because pressure can be controlled easier, more accurate and faster than temperature. If the gas in the sterilizer chamber is saturated steam, a so called theoretical temperature can be calculated from the pressure [72]. This

[4] Smaller sized steam sterilizers do not always have a jacket. In these cases the independent heating of the inside of the jacket can be performed with an alternative method, e.g., electrical heating.

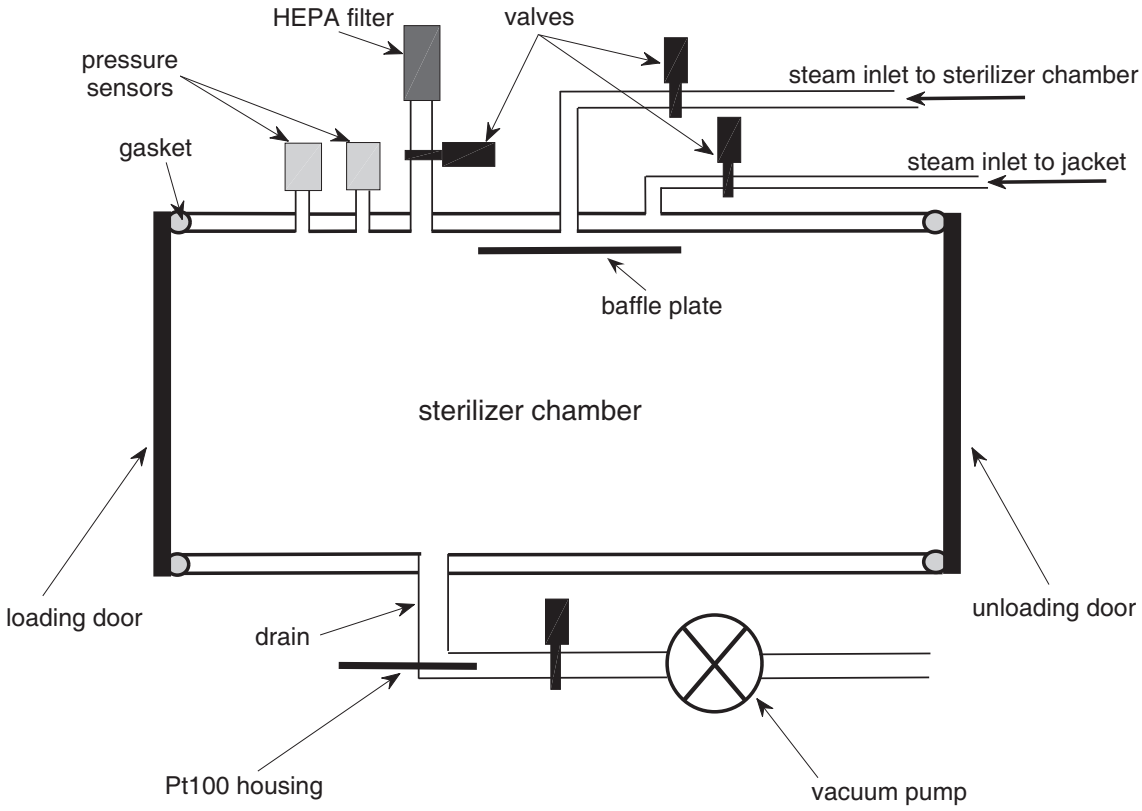

Figure 2.1: Schematic representation of a vacuum assisted steam sterilizer.

temperature can be compared with the measurements by the temperature sensor in the controller. Based on the input from the control sensors the valves, pump and doors are controlled by a controller that contains preprogrammed sterilization cycles, i.e., the sterilization processes. A steam sterilizer often has about 5 preprogrammed processes. The monitoring pressure and temperature sensors are installed for an independent check to ensure that the process is running correctly. Often readings of the monitoring and of the control sensors are presented in a display or indicator[5] on the sterilizer and are registered in a graph or digitally, to print a hard-copy.

To load the sterilizer and to keep the load at its desired position during a process, items to be sterilized are placed in so called nets, trays or baskets. Inside the sterilizer precautions are made to fix the specific loading system. The loading systems are also used to prevent direct contact of the load with the sterilizer jacket and doors. In larger sized sterilizers trolleys may be used for loading and unloading purposes.

Steam for a sterilizer can be provided by a central boiler in a facility or by dedicated steam generators. As outlined in section 2.2, steam quality is important for an effective and reproducible surface steam sterilization process. Nowadays dedicated steam gener-

[5]In decontamination the term 'indicator' can refer to biological, chemical and physical indicators. Biological Indicators (BIs) are devices which contain a specified number and species of microorganisms that have to be killed after a process [77]. Chemical Indicators (CIs) are indicators based on a chemical reaction which gives information on a decontamination process [79]. Physical indicators are indicators that use physical measurements to obtain information on a decontamination process.

ators are preferred because they offer better possibilities to control the steam quality, in particular, the amount of NCGs in the steam. Frequently, the steam generation is considered as part of the sterilizer. Reducing and avoiding contaminants and NCGs in the steam sterilizer starts with the water used for feeding the steam generator. Contaminants can be separated from the feeding water in various ways, e.g., reversed osmosis, filtration, distillation or combinations of these techniques. Once the contaminants are removed the water may still contain NCGs. NCGs found in feeding water are environmental gases such as carbon dioxide (CO_2), nitrogen (N_2) and oxygen (O_2), typically. Especially carbon dioxide (CO_2) may dissolve in water and appear as a NCG again during steam generation. In steam sterilization degassing of the feeding water can be done, for instance, with a so-called 'break-tank'. Before the water is supplied into the actual steam generator it is kept in a closed reservoir at 95 °C or higher for a certain minimum time. Gases will dissolve from the water, resulting in limited amounts of NCGs remaining in the feeding water for the actual steam generator or boiler.

2.4 Surface steam sterilization process

In surface steam sterilization processes all surfaces that can be in contact with the environment have to be exposed to steam sterilization conditions. These processes consist of three phases, which are depicted in figure 2.2. Before the start of the actual sterilization phase (phase II in figure 2.2) all initially present air has to be replaced by saturated steam, which has to be maintained for a predetermined time. Time-temperature combinations for saturated surface steam sterilization are listed in table 2.1. After the sterilization phase the sterilizer has to come to a safe state to open (phase III). For surface steam sterilization this means that the pressure in the sterilizer chamber has to be equal to the environmental pressure and the load has to be dry. If the chamber pressure is sub-atmospheric, the sterilizer cannot be opened because the door will be sucked against the sterilizer, whereas in case of a super-atmospheric pressure a door may open too fast, causing injury to the operator. Loads have to be dry because most, if not all, microbiological barrier systems are considered to be not a barrier for microorganisms when they are wet (appendix A.3).

In the conditioning phase or phase I several methods can be applied to replace initially present air by steam [69]. These methods are sketched in figure 2.3. Depending on the type of load that has to be sterilized a particular process can be chosen [52]. Flushing processes are the most simple (figure 2.3-A). A pressure vessel with a steam inlet and a gas outlet is loaded. After closing the door or lid, steam injection is started. The gas outlet is slightly opened. Gas initially present in the sterilizer will be replaced by steam while the aimed pressure is being reached. This kind of sterilizers have similarities with pressure cookers. A disadvantage of these flush processes is the difficulty to determine if all air is replaced by steam and, consequently, to recognize the start of the sterilization phase. This jeopardizes the reproducibly of the process and is often camouflaged by extending the sterilization phase. Another disadvantage is that wrapped instruments cannot be sterilized in these flush processes, because it cannot be guaranteed that steam penetrates wrappings effectively and reproducibly (see appendix A.3). Also sterilized loads may still be wet after the process because of the limited drying capacities of the sterilizer. If this process is used for sterilization of medical devices it is necessary to immediately use the

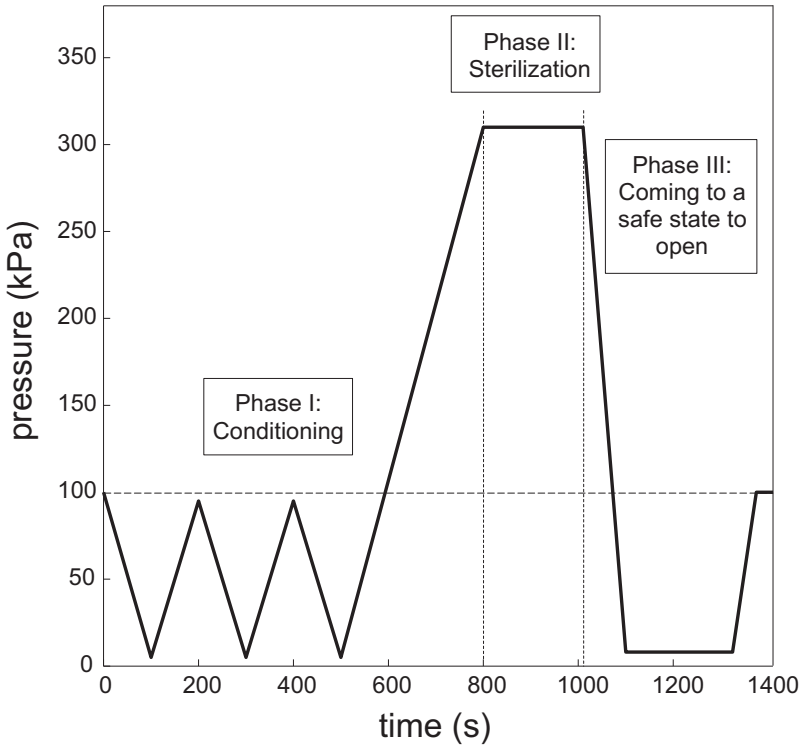

Figure 2.2: The three typical phases of a steam sterilization process. Phase I or conditioning phase: replacing air by water vapor, steam. At the end of this phase all surfaces present in the sterilizer are exposed to saturated steam at a predetermined temperature. Phase II or sterilization phase: the actual sterilization phase. After establishing the sterilization conditions the predetermined time has to elapse. Phase III or bringing the sterilizer to a safe state to open: the load is dried and the pressure is equalized with the environmental pressure.

devices after opening and at the location of the sterilizer. Basically, because of these disadvantages flush processes are only appropriate for sterilization of aqueous liquids in closed containers and to prevent cross contamination of non wrapped and non hollow (massive) instruments. Although these processes are still used in health care facilities in daily practice, it was recommended already in 1965 not to use them for general and dentist practices [92].

Air replacement by steam with super-atmospheric steam pulses (figure 2.3-B) is considered to be more effective than flushing. In these processes, steam is injected into the sterilization chamber up to a certain specific pressure. After reaching this pressure level the steam valve is closed and the outlet valve is opened until a certain pressure level above atmospheric pressure level is reached. This 'steam pulsing' is repeated several times. After the final gas outlet, the pressure in the steam sterilizer is brought to the steam sterilization pressure and kept constant for the sterilization time (phase II, figure 2.2). When the sterilization time has elapsed the outlet is opened again and the pressure in the steam sterilizer is equalized to the environmental pressure. Although the steam penetration of these processes is better than that of flushing processes, the degree of steam penetration in loads, especially loads with narrow hollow channels, is limited [93].

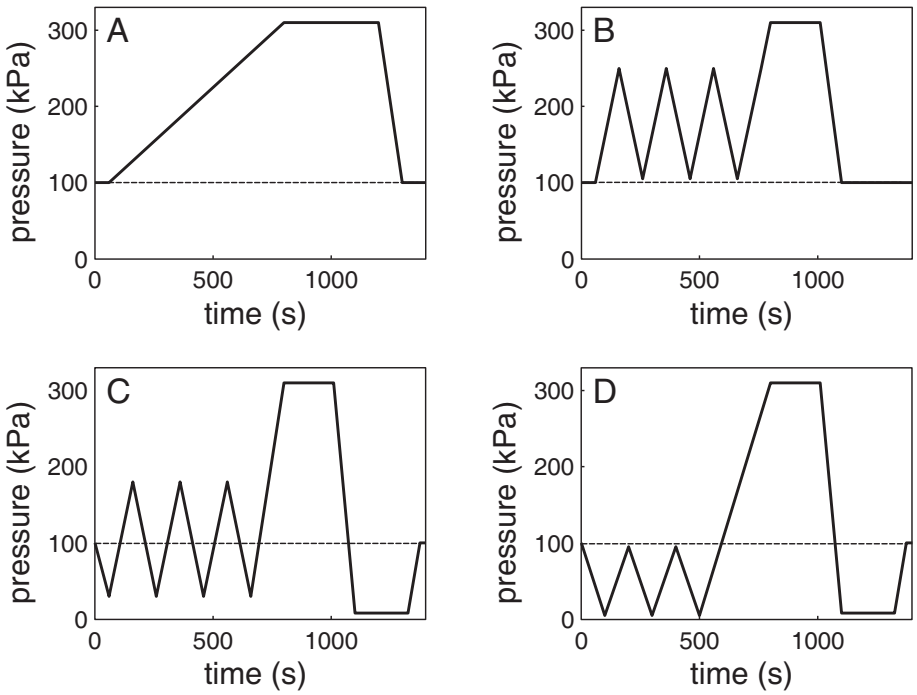

Figure 2.3: Schematic representation of various sterilization processes. The horizontal line at 100 kPa represents the atmospheric pressure. A) Flush process. B) Super-atmospheric pulsing. C) Trans-atmospheric pulsing. D) Sub-atmospheric pulsing [52].

Vacuum assisted steam sterilization processes are the most reproducible (figure 2.3-D) and are most frequently used in hospitals. With these processes it is possible to reduce the pressure below atmospheric pressure. With the possibility to create sub-atmospheric pressures, gas mixtures can be sucked out of wrapped nets, porous loads and cavities in instruments. The corresponding processes are considered to be able to sterilize all kinds of loads. If the vacuum pump of a sterilizer is not able to reach deep vacuum, e.g., lower than 7 kPa, trans-atmospheric pulsing is sometimes applied (figure 2.3-C).

2.5 Standards

For medical devices minimum requirements are specified by governments. In Europe the minimum requirements for medical devices are specified in the Medical Device Directive (MDD) [25]. Although the title of the MDD suggests that it is a directive, it has the same status as legislation. The MDD basically states that what is claimed should be proven and documented. Consequently, if it is claimed that a medical device is sterile, sterility has to be proven and documented. The simplest method to show that sterility can be claimed in Europe is to use harmonized standards. It is accepted that when the applicable standards for sterility are met a medical device is sterile. A list of harmonized standards for Europe is published by the European Committee for Standardization.[6] In

[6]http://ec.europa.eu/enterprise/policies/european-standards/harmonised-standards/medical-devices/index_en.html, last accessed 31 August 2013.

this list not only European standards are found but also ISO standards. ISO standards are published by the International Organization for Standardization[7] and have the status of being worldwide standards. Based on the Lisbon Agreement (1989) and the Vienna Agreement (1991) European member states use the ISO standards[8] if the standard is accepted by Europe and ratified by that member state.

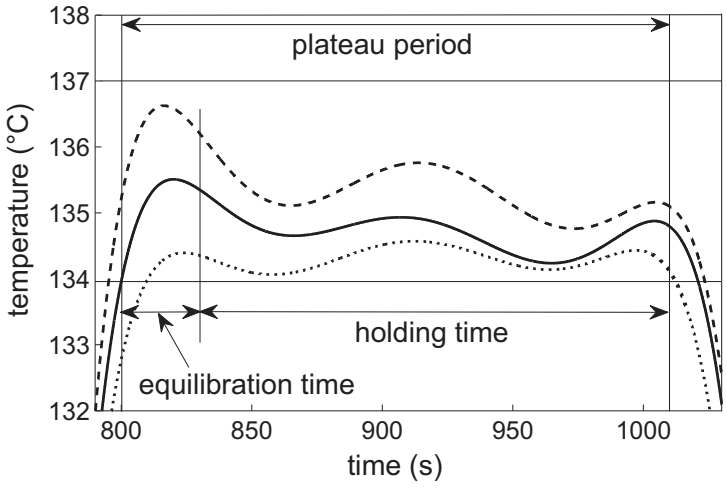

Figure 2.4: The sterilization phase (phase II, figure 2.2) or plateau period, which can be divided in the equilibration time and the holding time [51]. The equilibration time starts when the temperature calculated from the pressure reaches 134 °C. After the equilibration time all measured temperatures should be within a 2 °C band between 134 and 137 °C. For a sterilizer with a volume smaller than 800 l the equilibration time is maximum 15 s, for sterilizers larger than 800 l the maximum is 30 s. This results in a plateau period of 3.5 minutes for sterilizers larger than 800 l.

Standards are published by standards institutes and can be on a national (country) and international (European (EN) or worldwide (ISO)) level. A Work Group (WG), consisting out of experts in the specific field, prepares a draft standard. When accepted by the standards institute it can be published as a new standard and it will be enforced for a period of time. Basically two types of standards can be distinguished. First, product standards, which describe and define a product, such as the European standard EN 285 for large steam sterilizers [51]. Second, process standards, which describe the actual process or procedure. An example of a process standard is the ISO 17665 part 1 [53] for steam sterilization. A third kind of document is a guidance document. This is not a standard but an informative document with the aim to clarify a standard, e.g., the guidance ISO 17665 part 2 [94] clarifies the ISO 17665 part 1 [53].

Obviously, a standard can only specify minimum requirements and the state-of-the-art of that specific moment in time. If evidence is not available or complete at the moment of preparing the standard it may reflect consensus between members of the WG, based on opinions. Since research and developments are ongoing and insights and knowledge

[7] www.iso.org, last accessed 31 August 2013.

[8] http://www.cen.eu/boss/supporting/Reference%20documents/cooperation/Pages/default.aspx, last accessed 31 August 2013

change. An example is the ongoing discussion on the statistical definition of sterility [46, 47] (see inset page 9). It is likely that standards are outdated after a certain time. To keep standards as close as possible to the state-of-the-art after their publication it is necessary to periodically revise them. A typical time period for revision is 5 years. Would an immediate adjustment be necessary an amendment can be used [51, 95, 96]. Although standards cannot continuously be state-of-the-art, they are necessary to make processes and machines comparable and to define the relevant terminology. To prevent that standards would impair or stop development and innovation they cannot be design restrictive. For surface steam sterilization processes this means that only the sterilization phase (phase II) and the final result, dry loads, can be defined. The method to establish sterilization conditions during phase I (figure 2.2) or how to dry the load during phase III cannot be specified in standards.

As shown in section 2.1, the presence of condensate at the surfaces to be sterilized is essential for steam sterilization. When NCGs are present sterilization conditions cannot always be guaranteed. NCGs can be introduced in a sterilizer chamber by several causes, such as a leak in the sterilizer or its appendages (figure 2.1), insufficiently deep vacuum in combination with insufficient steam injection during phase I (figure 2.2), and NCGs in the steam caused by poor steam generation (section 2.2). For practical reasons modern steam sterilizers are controlled using pressure (section 2.3). In the standards pressure and temperature criteria for steam sterilization processes are specified [51–53]. For example, in figure 2.4 the so-called plateau period is plotted for a 134 °C surface sterilization process. The plateau period is divided in the equilibration time and the holding time, i.e., the actual sterilization phase. During this period all temperatures in the loadable space of the sterilizer may differ at most 2 °C from the theoretical temperature calculated from the pressure. If a gas is compressed too rapidly an adiabatic temperature overshoot may occur. To loose the extra amount of energy an equilibration time of 15 s is allowed for a sterilizer with a chamber volume of less than 800 l. For sterilizers with a volume equal or larger than 800 l the equilibration time is 30 s. To protect the load from excessive temperatures a maximum temperature for a process is defined. This temperature is the aimed sterilization temperature, e.g., 134 °C, plus 3 °C. Possibly the rationale for this maximum temperature is that many plastics used in surgical material will permanently deform at temperatures above 140 °C. For this reason steam sterilization is often preferred above dry heat sterilization[9] (see inset page 10). For processes at 121 °C a similar 3 °C excess temperature is defined, resulting in a maximum temperature of 124 °C, probably also to protect items to be sterilized, e.g., fit-prostheses and respirator material.

Standards for steam sterilization discriminate between large and small sterilizers. In Europe small sterilizers are defined as sterilizers with a loadable space of $30 \times 30 \times 60$ cm or smaller than 60 l [52]. All sterilizers with a larger loadable space are considered as large sterilizers [51]. Three types of processes are identified for steam sterilizers [52]. These processes are listed in table 2.3. A typical 'B' or large sterilizer process has sub- or trans-atmospheric pulses in the conditioning phase (figure 2.3-D). A flush process or a process with super-atmospheric pulsing is a type 'N' process (figure 2.3-A and -B). Depending on

[9] Although not suitable to sterilize medical devices, dry heat sterilization has its application in laboratories and pharmaceutical industries. It is an effective method for burning/oxidizing pyrogen material of surfaces of glass-work and solid metal objects, leaving clean and deposit free surfaces.

Type	Description of intended use
B	The sterilization of all wrapped or non-wrapped, solid hollow load product type A and porous products as represented by the test loads in this standard.
N	The sterilization of non wrapped solid products.
S	The sterilization of products as specified by the manufacturer of the sterilizer including non wrapped solid products and at least one of the following: porous products, small porous items, hollow load products type A, hollow load products, single wrapped products, multiple-layer wrapped products.

Note 1: The description identifies ranges of products and test loads
Note 2: Non wrapped sterilized instruments are intended either for immediate use or for non sterile storage, transport and application (e.g., to prevent cross infection).

Table 2.3: Table 1: Types of sterilization processes given in the standard EN 13060 [52].

the load S-processes can contain parts from flush, super- and sub-atmospheric processes (figure 2.3).

Steam sterilizers comprise mechanical parts and software. Just like any other machine a sterilizer can break down. To judge the functioning of a sterilizer the essential parameters should be monitored. For steam sterilization these are the degree of saturation of steam, the temperature and the time. Current steam sterilizers only measure and control pressure, temperature and time. In chapter 4 it will be shown that the accuracies of the measurements of temperatures and pressure which are currently specified in the standards [51] are not sufficient to determine small amounts of NCGs in a steam sterilization process. This makes adequate monitoring of each sterilization process and periodical validation of the combination of sterilizer, process, load, loading pattern and wrapping a necessity.

Chapter 3

A validation survey of 197 hospital steam sterilizers in The Netherlands in 2001 and 2002

Steam sterilization is the most common method of sterilization used in hospitals and by companies sterilizing for hospitals. This study validated 197 steam sterilizers with respect to technical condition, various production processes and routine control tests, according to the European standards for steam sterilization. Overall, only 40 % of the validated steam sterilizers met the standards. We recommend that adequate measures need to be taken, based on the comments in the validation reports, in order to guarantee the sterility of processed medical items.

This chapter has been published in the Journal of Hospital Infection 59: 126–130, 2005.[1]

3.1 Introduction

Sterilization methods for medical devices, equipment, textiles and re-usable items have been developed to prevent infection due to contamination of such materials. In health care facilities, steam sterilization is the most common sterilization method used. Various types of steam sterilizers or autoclaves are available with different steam sterilizing processes [69, 95, 97, 98]. A steam sterilizing process has to be effective and reproducible and must be validated [25]. Failure of steam sterilizing processes, lack of routine control tests to monitor the steam sterilization processes on a daily basis, and non-validated changes in the steam sterilizer itself may result in a non-sterile product [99]. This implies that the various sterilization processes, loads, loading patterns and wrapping materials have to be validated. Validation provides documented evidence that after steam sterilization, a sterile product with predetermined specifications and quality characteristics is obtained [95, 97, 98]. In addition, validation results can be used for correct interpretation of data from the daily routine control tests, e.g., the air leakage test[2] and the steam penetration

[1] In the literature no more recent study addressing the same topic than the survey reported in this chapter is found, suggesting that no significant changes have occurred during the last decade. At this moment the Dutch RIVM (National Institute for Public Health and the Environment, Ministry of Health, Welfare and Sport (http://www.rivm.nl/English, last accessed 31 August 2013) is performing a study on sterilizers in Dutch hospitals. The results are expected to be published in the second half of 2013.

[2] A procedure described in the standards [51] to test if the air leak into a sterilizer is below the specified maximum.

test[3] [95, 97, 98, 100]. To our knowledge, no data are available in the literature from a validation survey of hospital steam sterilizers. Here, we report the results of 197 validation programs on steam sterilizers in The Netherlands during the period 2001–2002.

3.2 Materials and methods

3.2.1 Steam Sterilizers

In total, we validated 197 steam sterilizers in The Netherlands during the period 2001–2002. These steam sterilizers represented 18 brands and 93 types. Among these were 182 large steam sterilizers with a loadable space of one standard unit ($30 \times 30 \times 60$ cm) [95, 98] or more and 15 small sterilizers with type B processes. A type B process is defined as a process by which wrapped as well as non-wrapped, solid, hollow and porous items can be sterilized [98]. All steam sterilizers were used to sterilize medical equipment, textiles and various other medical devices. Of the 197 validated steam sterilizers, 186 were located in 71 (63 %) of the 112 Dutch hospitals. Of these 186 sterilizers, 174 were situated in 71 central sterile supply departments (CSSDs) and 12 were situated in eight operating theaters (OTs). The remaining 11 steam sterilizers were used by four (66 %) of the six Dutch companies that perform steam sterilization for hospitals on a commercial basis. The median age of the CSSD steam sterilizers in the survey group was 9 years; the oldest was 24 years old. The OT steam sterilizers had a median age of 10 years; the oldest was 12 years old. Company steam sterilizers had a median age of 10 years; the oldest was 13 years old.

3.2.2 Validation program

During the two-year survey, each steam sterilizer was validated once, either initially or revalidated. An initial validation means that a steam sterilizer is validated for the first time, either because the steam sterilizer was new or because it was subject to a change in process, load, loading pattern, wrapping material or procedure since a previous validation. Revalidation means that the steam sterilizer was initially validated before 2001 and that processes, loads, loading patterns, wrapping materials and procedures were not changed. In the previous 10 years, all revalidated steam sterilizers were validated at least once a year. Prior to each validation, a validation program was prepared by the head of the CSSD, OT or company in co-operation with the validation project leader, who was an engineer from KW2 B.V. (Amersfoort, The Netherlands). In the validation program, the reason for validation and the relevant standards used were indicated. Steam sterilization processes to be validated were sterilization at 121 °C for 15 min and at 134 °C for 3 min. Furthermore, the validation program included a document study of each steam sterilizer and an inspection of the technical condition according to the standards [95, 97, 98]. The technical condition included the general construction of the steam sterilizer, the devices

[3] A standardized test to check on a daily basis if the steam penetration capacities in the conditioning phase and the exposure to sterilization conditions in the actual sterilization phase are meeting the requirements in the standards (see also appendix A.2).

used for the process display and registration, and the pressure gauge attached to the steam sterilizer chamber.

3.2.3 Measurements of the production processes of the steam sterilizers

The production processes were validated with specified loads. Temperatures were measured with type K thermocouples (Eurotherm, Voorburg, The Netherlands). The thermocouples were inserted into the steam sterilizer and placed on pre-assessed positions in the sterilizer chamber and load. An Endress+Hauser type PMC130 or PMC133 pressure sensor (Endress+Hauser, Weil am Rhein, Germany) was connected to the steam sterilizer chamber for pressure measurements [95, 98]. The sensors for temperature and pressure measurements were connected to a Chessel recorder type 4200 or 4250 (Eurotherm, Durrington, West Sussex, UK). The recorder was connected to a computer with validation software (KWvers5, KW2 B.V., Amersfoort, The Netherlands). The complete validation sets used were calibrated according to international standards [95, 97, 98].

3.2.4 Measurements of the daily routine control tests

The routine control tests that were performed daily were part of the validation program. Both the air leakage test and the steam penetration test (see appendix A.2) were validated according to the standards [95, 97, 98]. In the air leakage test, the pressure was measured as a function of the time to measure the exposure time. Steam penetration in the 182 large steam sterilizers was tested using the standardized Bowie & Dick (B&D) test [95, 97, 98]. Once-a-day indicator sheets were used (Propper, Long Island City, NY, USA). In the 15 small steam sterilizers, the standard B&D test package did not fit. Therefore, measurements in these steam sterilizers were made with a disposable B&D test package, the B&D type steam penetration test pack 2000 (Interster International, Wormerveer, The Netherlands) or the TST single-use B&D type test pack (Albert Browne Ltd., Leicester, UK). The user decided which disposable package was used. The wrapping of each B&D indicator sheet listed the required temperature, the period of time for which the indicator had to be exposed to 100 % saturated steam, and the color change of the indicator.

3.2.5 Evaluation of the data

A validation engineer of KW2 B.V. carried out the validation program and prepared the validation report. The validation project leader evaluated the final report.

3.2.6 Statistics

Differences between the results of the validations of steam sterilizers located in the CSSDs, OTs and companies were compared using a Chi-square test [101]. The same test was used to compare the results from the initial validations and re-validations.

	Hospital steam sterilizers			Company		Total	
	CSSD*		OT**	steam sterilizers			
Validation	a†/tot‡	(%)	a†/tot‡	a†/tot‡	(%)	a†/tot‡	(%)
Initial	11/19	(58)	0/1	2/2	(100)	13/22	(59)
Revalidation	60/155	(39)	0/11	5/9	(56)	65/175	(37)

* Central sterile supply department.
** Operating theater.
a† Number of steam sterilizers meeting the requirements of the standards [95, 97, 98].
tot‡ Total number of steam sterilizers validated.

Table 3.1: Number of hospital and commercial steam sterilizers meeting the standards of an initial validation or a revalidation.

3.3 Results

In total, 13 of the 22 initially validated steam sterilizers (59 %) and 65 of the 175 revalidated steam sterilizers (37 %) met the standards (table 3.1). The company steam sterilizers performed better ($P < 0.025$) than the hospital steam sterilizers. None of the OT steam sterilizers achieved satisfactory results (table 3.1). The technical condition of the 22 initially validated steam sterilizers was significantly better ($P < 0.05$) than that of the 175 revalidated steam sterilizers (table 3.2). In total, 127 production processes in the 22 initially validated steam sterilizers were validated. A production process did not meet the standards in one (5 %) CSSD steam sterilizer (table 3.2), because the 2 °C temperature band was exceeded. In the 175 revalidated steam sterilizers, 835 production processes were validated. Inadequate results were obtained with 31 (18 %) steam sterilizers (table 3.2). Both the 2 °C and 3 °C temperature bands were exceeded in 25 steam sterilizers, the 2 °C temperature band in three steam sterilizers and the 3 °C temperature band in one steam sterilizer. In addition, the actual steam sterilization time was too short in one steam sterilizer, and in another sterilizer, the load was wet after a sterilization process. The validation results of the routine control processes of the initially validated steam sterilizers were better ($P < 0.05$) than those of the revalidated steam sterilizers (table 3.2). The results of the air leakage test were unsatisfactory in four (18 %) of the 22 initially validated steam sterilizers and in 12 (7 %) of the 174 revalidated steam sterilizers (table 3.3). Steam penetration tests of initially validated steam sterilizers showed better results than those of the revalidated steam sterilizers (table 3.3).

3.4 Discussion

Validation data of steam sterilizers are important for the purpose of guaranteeing the sterility of the processed items, but data from validation surveys of steam sterilizers in hospitals are lacking. Our two-year survey, including 63 % of the steam sterilizers used in Dutch hospitals and Dutch companies involved in steam sterilization of hospital devices and items, showed that only 78 (40 %) of the 197 steam sterilizers met the requirements

of the various validation tests. These requirements were formulated by the European Committee for Standardization [95, 97, 98]. Although in the European standards, small and large steam sterilizers are described separately, the same validation tests are recommended. In our survey of 15 small and 182 large sterilizers, the findings from validations of the small and large steam sterilizers did not differ significantly. Only 13 (59 %) of the 22 initially validated steam sterilizers and 65 (37 %) of the 175 revalidated steam sterilizers met the requirements of the validation program. Although a large variation in the age of the steam sterilizers was present, no relationship was found between age and validation results. The data of the 11 validated company steam sterilizers were significantly better ($P < 0.05$) than the data of the 186 hospital steam sterilizers. Apparently, commercial competition between companies leads to the search for recommended improvements. In addition, companies are audited by the hospitals for which they perform the sterilization or by an institute providing them with the required certificates. The results from validations of the OT steam sterilizers unambiguously indicate that the quality of these steam sterilizers must be improved. In conclusion, only 78 (40 %) of the 197 validated steam sterilizers in our two-year survey met the standards. This may imply that not all steam sterilized items reach the sterility standard that is guaranteed or expected. We recommend that improvements, based on the comments in the validation reports, are carried out, particularly for OT steam sterilizers.

Acknowledgement

The authors thank the validation engineers and project leaders of KW2 B.V. for their co-operation and for access to the validation data on steam sterilizers.

Table 3.2: Number of initially validated and revalidated steam sterilizers meeting the standards for the technical condition, the production processes, and the routine control processes.

	Hospital steam sterilizers				Company steam sterilizers		Total	
	CSSD*		OT**					
Validation	a†/tot‡	(%)	a†/tot‡	(%)	a†/tot‡	(%)	a†/tot‡	(%)
Initial								
- Technical condition	15/19	(79)	1/1	(100)	2/2	(100)	18/22	(82)
- Production process	18/19	(95)	1/1	(100)	2/2	(100)	21/22	(95)
- Routine control processes	13/19	(68)	0/1		2/2	(100)	15/22	(68)
Revalidation								
- Technical condition	114/155	(74)	3/11	(27)	7/9	(78)	124/175	(71)
- Production process	126/155	(81)	10/11	(91)	8/9	(89)	144/175	(82)
- Routine control processes	96/155	(62)	1/11	(9)	7/9	(78)	104/175	(59)

* Central sterile supply department.

** Operating theater.

a† Number of steam sterilizers meeting the requirements of the standards [95, 97, 98].

tot‡ Total number of steam sterilizers validated.

Table 3.3: Number of validated steam sterilizers with an air leakage test and a steam penetration test meeting the standards.

	Hospital steam sterilizers				Company steam sterilizers		Total	
	CSSD*		OT**					
Validation	a†/tot‡	(%)	a†/tot‡	(%)	a†/tot‡	(%)	a†/tot‡	(%)
Initial								
- Air leakage test	16/19	(84)	0/1		2/2	(100)	18/22	(82)
- Steam penetration test	16/19	(84)	0/1		2/2	(100)	18/22	(82)
Revalidation								
- Air leakage test	143/154§	(93)	10/11	(91)	9/9	(100)	162/174§	(93)
- Steam penetration test	97/155	(63)	1/11	(9)	7/9	(78)	105/175	(60)

* Central sterile supply department.

** Operating theater.

a† Number of steam sterilizers meeting the requirements of the standards [95, 97, 98].

tot‡ Total number of steam sterilizers validated.

§ In one steam sterilizer the air leakage test was not available.

Chapter 4

Review of surface steam sterilization for validation purposes

Sterilization is an essential step in the process of producing sterile medical devices. To guarantee sterility, the process of sterilization must be validated. Because there is no direct way to measure sterility, the techniques applied to validate the sterilization process are based on statistical principles. Steam sterilization is the most frequently applied sterilization method worldwide and can be validated either by indicators (chemical or biological) or physical measurements. The steam sterilization conditions are described in the literature. Starting from these conditions, criteria for the validation of steam sterilization are derived and can be described in terms of physical parameters. Physical validation of steam sterilization appears to be an adequate and efficient validation method that could be considered as an alternative for indicator validation. Moreover, physical validation can be used for effective troubleshooting in steam sterilizing processes.

The content of this chapter has been published in the American Journal of Infection Control 36: 86–92, 2008.

4.1 Introduction

Sterilization is an integral part of producing sterile medical devices in hospitals and other health care environments. Because sterilization is not directly measurable, other techniques must be applied to prove that medical devices have in fact been sterilized. If the sterilization conditions are defined, a validation can be performed either with indicators (chemical or biological) or physically (see footnote page 15). We will argue that physical validation can be a useful alternative for indicator validation.

The term *sterile* is defined as free of all viable organisms [19, 20]. This can be achieved by removal, inactivation, or destruction of all forms of viable life that are present. The removal of organisms can be done by filtration. Inactivation or destruction of viable organisms can be done by exposing them to deadly conditions (e.g. oxidation, intoxication) or by destroying cell structures necessary for life, (i.e., the DNA or protein structures). It is pointless to test a sterile item on sterility before use, because once tested the product is not sterile anymore. Favero [73] described how the statistical definition of sterility is used in practice and how the concept of the Sterility Assurance Level (SAL) evolved over time. The worldwide accepted definition for sterility for medical devices is defined as the chance of finding a viable organism in or on a medical device to be at most 1 in 1,000,000 or a SAL of at most 10^{-6}. The SAL is defined as the probability of a single viable microorganism occurring in or on a product after sterilization [53].

Every sterilization process based on killing has three phases. The first phase is creating sterilization conditions, the second phase is the actual exposure of all object(s) to be sterilized to these conditions, and the third phase is used to bring the sterilizer to a safe state to be opened and to remove the object(s) out of the sterilizer. It is generally accepted that medical devices are sterile if the combination of sterilizer, sterilization process, load, wrapping method, and distribution of the load within the sterilizer chamber (the loading pattern) yield the desired sterilization conditions in and/or on the medical devices for a predetermined period. The validation is the documented procedure for obtaining, recording, and interpreting the data required to establish that a process will consistently yield a result complying with predetermined specifications [53]. Before a validation is performed, a validation program is composed. This program includes the reason for validation, the identification and location of the sterilizer, and the standards to be used. Within the standards, criteria are described for the technical condition of a steam sterilizer, including the general construction, the devices used for the process display and registration, and the sterilization process itself.

The most generally applied sterilization method for medical devices worldwide is steam sterilization. In contrast to North America [102] and the developing countries [103], where physical validation of steam sterilization is not frequently applied in hospitals, physical validation is used in Europe (e.g., the United Kingdom, Sweden, Belgium, Germany, and the Netherlands)[104]. In this chapter, we discuss a physical validation of the steam sterilization processes that can be performed efficiently and economically in hospitals and other health care environments.

4.2 Sterilizing conditions of aqueous liquids and surface steam sterilization

Without complete protein strings, an organism cannot live. The killing mechanism of sterilization of aqueous liquids is destroying the protein strings by coagulation. Coagulation[1] is the irreversible change and hardening of the protein chains of the microorganisms and requires energy and water [20, 81]. In a typical sterilization process for aqueous liquids in a closed container, the liquid is exposed to a temperature of 121 °C for 15 minutes or 120 °C for 20 minutes. The elevated temperature supplies the energy to remove hydro sulfide ions and smaller peptide chains from the proteins [82]. The bipolar water molecules provide a mechanism by which the hydro sulfide ions and peptide chains (both of which are also bipolar) can be transported to other locations within the organism. At these locations, new irreversible and harder bonds between these entities are formed. The amount of water in the cells depends on the type of organism and the environmental conditions [26, 83]. This amount may be insufficient to transport the molecules that are removed from the proteins. Water in the direct environment of the organisms can supply the additional required water for coagulation.

Surface steam sterilization conditions are similar to those for aqueous liquid sterilization. Therefore, the conditions on the surfaces to be sterilized must be identical to the conditions in the aqueous liquid. This means that all surfaces to be sterilized have to be

[1] See section 2.1 for some more details of this process.

wet and brought to the predetermined temperature. To establish these conditions in a reproducible way, all the air in a surface steam sterilizer has to be replaced by water vapor before the start of the actual sterilization phase, and the steam in the sterilizer chamber must not be superheated.[2] Furthermore, the surfaces must be clean, so the steam and condensation have access to all surfaces to be sterilized. Chaufour et al. [84] have shown that cleaning before sterilization is essential.

In 1937, Savage [26] studied temperature tolerance bands for reproducible surface steam sterilization conditions. He found that with 100 % saturated steam at 105 °C, the temperature margin was less than 1 °C, but as the temperature rises, the margin becomes wider, e.g., at 110 °C the temperature margin in the sterilizer might be larger than 8 °C in the range from 110 to 118 °C without losing the killing efficacy of the process. One of his conclusions was that if the temperature derived from the saturated steam pressure exceeds 132 °C, no temperature margins have to be observed. The Working Party on Pressure Steam Sterilizers of the Medical Research Council in 1959 [31] and Joslyn in 1991 [19] noted that this latter conclusion is questionable, but did not define a temperature band with appropriate criteria. Instead, the Medical Research Council used the time-temperature combinations reported by Perkins [88] but added safety margins to account for deviations in steam quality among different steam sterilizers. In table 4.1, three values of Perkins and those of the Medical Research Council concept are presented. The time-temperature combinations defined by the Medical Research Council are still in use for steam sterilization [105, 106].

Perkins		MRC	
time (minutes)	temperature (°C)	time (minutes)	temperature (°C)
2	132	3	134
8	125	10	126
12	121	15	121

Table 4.1: Three recommended time-temperature combinations of the Working Party on Pressure steam sterilizers of the Medical Research Council [31], derived from time-temperature combinations for saturated steam sterilization reported by Perkins [88].

A gas or vapor can be heated within a large range of temperatures. If the time-temperature combinations of the sterilization of aqueous liquids are to be used for surface steam sterilization, it is necessary to verify whether saturated steam is present in the sterilizer chamber and on the surfaces to be sterilized. Therefore, the degree of saturation of the water vapor in a steam sterilization process has to be determined. In a production steam sterilizer, no direct measurements of the degree of saturation of the steam are performed. These measurements appear to be too inaccurate, too slow, or too expensive to implement in such a sterilizer. Alternative physical methods to determine the degree of saturation of the steam are an air detector [95] or to use the pressure-temperature relation ($p - T$ relation) of saturated steam [72, 107]. An air detector may be useful for

[2] In sterilization processes, superheated steam should be not considered as steam because its characteristics are closer to dry heat than to saturated steam.

routine control, but it is not suitable for process control or validation purposes. It does not accurately quantify the degree of saturation or the degree of superheating of steam. Using the $p - T$ relation [72] a theoretical temperature (T_p) can be calculated from the measured pressure (Fig. 4.1). If T_p is compared with the measured temperature(s) in the sterilizer chamber (T_c), three situations may occur:

- T_c equals T_p (100 % saturated steam is present in the sterilizer chamber),
- T_c is lower than T_p (the steam is supersaturated),
- T_c is higher than T_p (the steam is superheated).

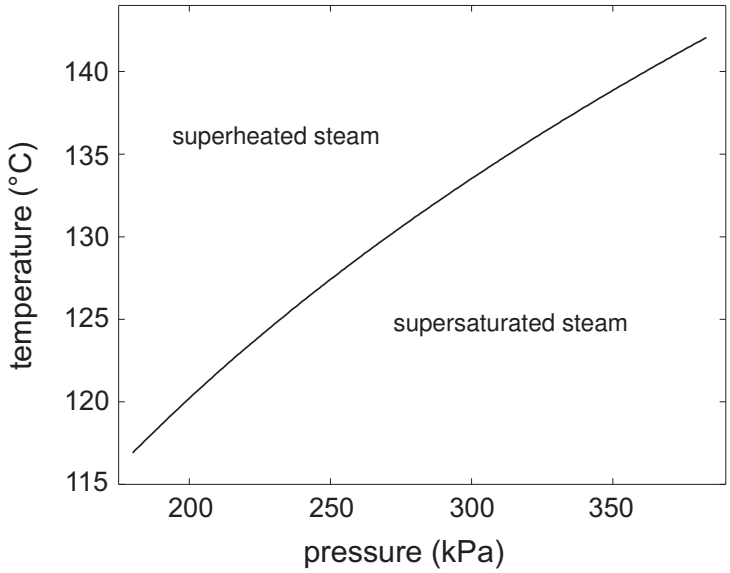

Figure 4.1: Theoretical temperature of 100 % saturated steam (T_p) calculated from the pressure (p) [72]. Above the curve the steam is superheated and below the curve the steam is supersaturated (often called wet steam).

If T_c equals T_p an ideal situation for surface steam sterilization is established. The water vapor present in the sterilizer chamber is on the coexistence curve of the water and the vapor phase (Fig. 4.1). The surfaces are wet and warmed up to the aimed temperature. Supersaturated steam ($T_c < T_p$) is not a direct problem with respect to the surface steam sterilization conditions, but it may lead to other problems not discussed here (e.g., wet loads after the sterilization process has been completed). Moreover, at lower temperatures the sterilization time will be longer. Superheated steam in a steam sterilizer chamber ($T_c > T_p$) has to lose its surplus of energy before it can condense on colder surfaces. This extra energy loss may be realized by warming up surfaces, evaporating water from surfaces, or even by extracting water out of viable cells. The amount of water in the cells may become lower than required for coagulation [83], without the possibility to supply additional water. A second problem of superheated steam is that energy transfer from a vapor to a surface is less efficient than energy transfer by condensation, which slows down the sterilization process. For an optimal steam sterilization process T_c should be equal

or lower than T_p ($T_c \leq T_p$). According to the findings of Savage [26], an elevation of T_c equal to 1 °C is allowed at 105 °C. Because no other results are found in the literature, we assume that the maximum elevation of the chamber temperature is 1 °C above T_p, resulting in $T_c \leq T_p + 1$. The allowed temperature elevation found by Savage, which we will generalize as ΔT_{ns}, may be caused by the presence of non-condensible gases or by the super-heating of the steam. At 134 °C, a temperature elevation of 1 °C corresponds to 9 kPa, and at 140 °C it corresponds to 10 kPa (Fig. 4.1) [72].

4.3 Validation of steam sterilization processes

To validate a steam sterilizer, it must be proven that the steam sterilization conditions described in the previous section are met throughout the sterilizer chamber and that the exposure times are realized in an effective and reproducible way. If this is the case, all the surfaces of the medical devices are efficiently and reproducibly sterilized. Therefore, a set of processes to be validated is defined in the validation program, containing the combination of the sterilizer, the process, the load, the loading pattern, and the wrapping. For example, in a setting in which textiles and instruments are being steam-sterilized at 121 °C for 15 minutes, the set of processes for the initial or first validation (or performance qualification) could include an air leakage test to prove that the sterilizer is air-tight; a steam penetration test (see appendix A.2) to provide information for the daily monitoring of the steam penetration of the steam sterilizer; an empty load; 50 % and 100 % instrument loads; 50 % and 100 % textile loads; and 50 % and 100 % mixed loads. With the data of the production processes, all other load compositions within the matrix presented in table 4.3 can be sterilized. In production chains in the industry, each load to be sterilized may be identical. In that case, the validation program can be simplified to steam penetration test, air leakage test, empty load, and the specified load, the latter test being repeated three times.

Air leakage test			
Steam penetration test			
Textile load	0 %	50%	100%
Mixed load	-	50%	100%
Instrument load	-	50%	100%

Table 4.2: Example of a validation program for a sterilizing program at 121 °C for 15 minutes for textiles, instruments, and mixed loads. Because the empty chamber is validated for textiles, it has not to be validated again for the instrument and mixed loads. The wrapping method, loading, and loading pattern are documented. Compositions of loads different from the validated loads can be sterilized by means of interpolation of the matrix of textile, mixed loads, and instrument loads. The matrix of production processes shows that all validations are performed on 0 %, 50 %, and 100 % loads, i.e., in triplicate.

4.3.1 Number of positions to be measured

Sterilization conditions must be obtained for any surface that is to be sterilized. To achieve this in a reproducible way, the sterilization conditions must be established throughout the sterilization chamber. To be sure that this is the case, sufficient positions must be measured. The number of positions should be chosen such that it allows the determination of the most extreme temperatures (hottest and coldest positions) as well as the temperatures at the positions of the control sensors. To determine the pressure in the sterilizer chamber and to assess the performance of the pressure sensor of the steam sterilizer, one independent sensor measuring the pressure is sufficient. For instance, in general [97] it is sufficient to use one thermo-sensor per 100 l with a minimum of 6 for temperature measurements and one sensor for pressure measurements.

4.3.2 Temperature requirements

When indicators are used for the validation, the humidity (H), temperature (T), and time (t) are important. To guarantee the accuracy of these parameters, the handling of the indicators must be specified by the manufacturer, together with the specification of the storage conditions and the interpretation method (e.g., incubation time and color change). If these specifications are not given, the indicator cannot be used for validation purposes.

For physical validation, only the measured temperatures (T), pressure (p), and time (t) are available to judge the process. To assure aqueous sterilizing conditions with saturated steam, the measured temperatures should satisfy the relation $T_c \leq T_p + \Delta T_{ns}$. Inaccuracies in the measured temperatures T_{mc} in the chamber and in the theoretical temperature T_{mp} calculated from the measured chamber pressure must also be taken into account. This yields the condition:

$$T_{mc} \leq T_{mp} - \Delta T_{mc} - \Delta T_{mp} + \Delta T_{ns}, \tag{4.1}$$

where ΔT_{mc} and ΔT_{mp} denote the uncertainties in T_{mc} and T_{mp}, respectively. To be able to use a certain time-temperature relation, the minimum temperature in the steam sterilizer must remain above the aimed sterilization temperature T_a:

$$T_{mc} \geq T_a + \Delta T_{mc}. \tag{4.2}$$

To protect the medical devices against excessive temperatures, a maximum temperature T_{md} may be defined, but this is of no importance for the steam sterilization conditions. Equations 4.1 and 4.2 are plotted in Fig. 4.2 for $T_a = 134\,^{\circ}\mathrm{C}$ and $\Delta T_{ns} = 1\,^{\circ}\mathrm{C}$. This figure shows that this region grows wider at higher temperatures and with improving validation equipment.

4.3.3 Entrapped air

Medical devices, particularly hollow instruments such as endoscopes and packages with textiles, may contain entrapped air. At the positions where entrapped air is present, the steam sterilization criteria cannot be established. During the sterilization phase the entrapped air will diffuse to other positions. At these positions, the steam sterilization

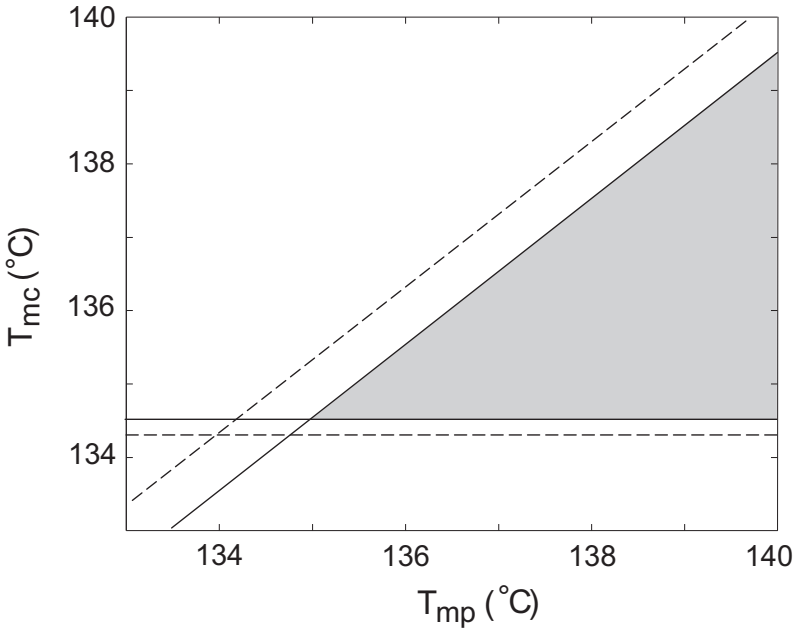

Figure 4.2: Temperature tolerance bands for steam sterilization with 100 % saturated steam at 134 °C. The allowed temperature elevation introduced by non-condensible gases or superheating of steam ΔT_{ns} equals 1 °C. The temperature T_{mp} calculated from the pressure [72] is plotted on the horizontal axis. For inaccuracies of 1 kPa in the pressure and 0.5 °C in the temperature the solid horizontal line is the minimum temperature that should be measured ($T_{mc,min} > T_a + \Delta T_{mc}$). The other solid line is the maximum temperature ($T_{mc,max} \leq T_{mp} - \Delta T_{mc} - \Delta T_{mp} + 1$) that should be measured. The gray area represents the region in which surface steam sterilization conditions can be assured. The dashed lines represent the limits for inaccuracies of 0.5 kPa and 0.3 °C in pressure and temperature, respectively.

conditions can be impaired. It is obvious that the removal of entrapped air out of hollow medical devices needs special attention. This point will be addressed in more detail in the chapters 6, 7 and 8 of this thesis.

4.3.4 Sampling rate

To determine whether the steam in the sterilization phase is 100 % saturated, T_{mp} and T_{mc} are compared in physical validation measurements. Although the pressure and temperature changes during the actual sterilization phase are small, during the air removal phase (the phase before the sterilization phase) the changes are in the order of 1 kPa/second or even faster. To be able to monitor these changes with an accuracy of 1 kPa, the response time τ_p of a pressure sensor used for validation purposes should be 1 second at most, according to the standard [95]. To determine whether the steam at the start of the sterilization phase is 100 % saturated, it must be possible to compare T_{mp} and T_{mc} in the air removal phase. To enable a direct comparison between T_{mp} and T_{mc}, the response time of the temperature sensors τ_T, should be similar to that of the pressure sensor (i.e., 1 second at most [95]). Apart from this, the readings of all sensors should be performed

at the same sampling frequency, preferably at the same moment. To satisfy the Nyquist criterion [108, 109], a requirement for correct sampling, the sampling interval τ_s, should be at least a factor of 2 smaller than τ_p and τ_T and, consequently, the sampling rate of the validation equipment should be 2 Hz or faster.

A sampling rate is not applicable for bioligical and chemical indicators (see footnote page 15).

4.4 Criteria in standards

According to the standards, the actual sterilization time in sterilization processes is the exposure time [110] or the holding time [53, 95]. This time starts immediately after the equilibration time, the time given to reach an equilibrium in the sterilizer chamber. In European and ISO standards, the equilibration and holding time together form the plateau period.

The standard EN-ISO 17665 part 1 [53] does not specify temperature bands for steam sterilization processes. It is the intention of the Technical Committee 198 Work group 3 (ISO-TC198-WG3) to specify these criteria in the standard EN-ISO 17665 part 2 [94].

In the North American standard for hospital sterilizers [110], all measured temperatures should differ no more than 3 °C from the sterilization temperature. The accuracy of the monitoring systems should be equal or better than 1 °C and for the pressure the inaccuracy may be 3 % of the full scale reading. Inaccuracies for validation systems are not specified. In addition, a direct relation between the measured temperatures and the pressure is not given.

Using the EN 285 standard [95], all temperatures measured during the holding time must be within a band between the aimed sterilization temperature T_a and $(T_a + 3\ \mathrm{K})$; for example, if the aimed sterilization temperature is 134 °C, all temperatures must have values between 134 °C and 137 °C. For sterilization processes in small (type S) steam sterilizers [98], the upper limit for $T_a = 134$ °C equals 138 °C. The justification for the defined 3- and 4-K bands [95, 97, 98] is the protection of the items and products to be sterilized against high temperatures. Apart from these conditions, all measured temperatures should be within a 2-K band at any moment during the holding time, as is also stated in the ISO 17665 standard [53]. The theoretical temperature is considered as a measured temperature. No further specifications other than the duration are given for the equilibration time.

Analysis of the tolerance bands for the holding time given in the standards shows that sterilization conditions based on those of aqueous liquids cannot be guaranteed. For example, with the given inaccuracies, a measured temperature of 134 °C can actually be 133.5 °C and a measured temperature of 136 °C may be 136.5 °C, resulting in an actual temperature band of 3 °C. If the theoretical temperature is taken into account and a pressure of 305 kPa is measured, T_p may be 134 °C. Because in this example the actual temperature could be 136.5 °C, this results in a band of 2.5 °C. Both tolerance bands exceed the value $\Delta T_{ns} = 1$ °C given by Savage [26]. This is illustrated in Fig. 4.3, where some temperature regions allowed by the standards [95, 97, 98] are compared to the limits for steam sterilization conditions derived in the present study. This figure clearly shows

that steam sterilization conditions cannot be guaranteed.

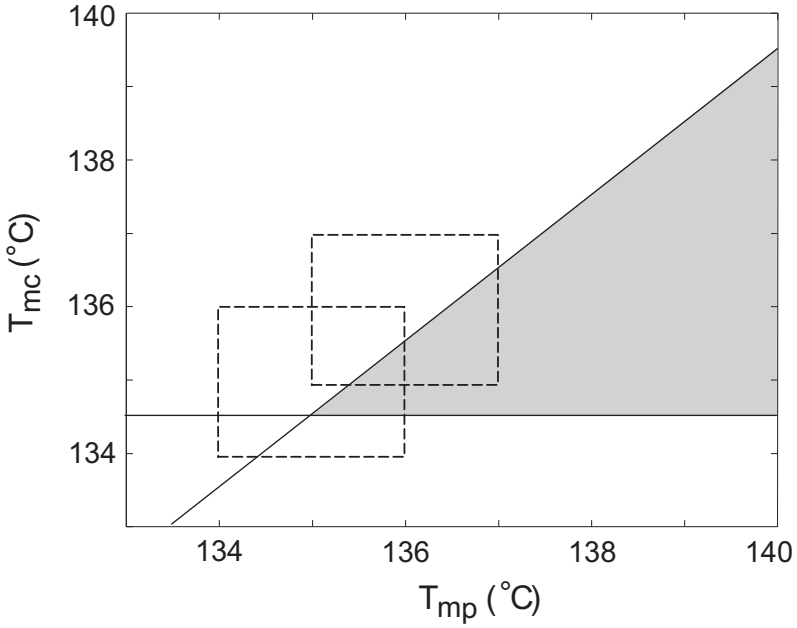

Figure 4.3: Temperature tolerance bands for steam sterilization with 100 % saturated steam at 134 °C. T_{mp} represents the temperature calculated from the measured pressure [72], whereas T_{mc} represents the temperature measured in the sterilizer chamber. The experimental inaccuracies in the pressure and temperature are 1 kPa and 0.5 °C, respectively. The gray area represents the region in which steam sterilization conditions can be assured. The dashed boxes illustrate some regions that are allowed according to the European standards [95, 97, 98].

In the standards [95, 97, 98] an exception with respect to these general 2 K and 3 K tolerance bands is made for the thermometric small load test [95]. In this test, the temperature measured above a standard test pack [95] should not exceed the temperature measured at a reference measurement point of the sterilizer chamber by more than 5 K during the first 60 s and by more than 2 K during the remaining period. No rationale has been found for this exception. The North American standards [110–112] do not explicitly address non-condensible gases.

The European standard [95] allows 3.5 % (V/V) non-condensible gases to be present in the steam, which will result in a pressure raise. From the pressure raise, the temperature elevation of T_p can be calculated [72], which amounts to approximately 1.2 °C at 134 °C. In the European standard, no additional criteria are specified with respect to T_p. The present study, however, indicates that in figure 4.2 the boundary relating the upper limit of T_{mc} to T_{mp} should be shifted by 1.2 °C to higher values of T_{mp}.

The North American standards [110] give no specification for the sampling rates of the measurements. The European standard [95] specifies for the sterilizer equipment a sampling rate of at least once per 2.5 s (0.4 Hz) for the temperature, and at least once per second (1 Hz) for the pressure. The response time for temperature (τ_{90}) is 5 s, tested in water, which is twice the temperature sampling time. In section 4.3.4 it is explained why, during validation of the processes, a sampling frequency 2 Hz is preferred for all sensors.

4.5 Discussion

The main objective of sterilization is to obtain sterile objects. To assure sterile objects after a sterilization process, validation is essential. If the theory for aqueous liquid sterilization is applied to surface steam sterilization, a straightforward set of criteria can be defined (see equations 4.1 and 4.2). Although this makes physical validation possible, in many countries validation of steam sterilization processes is performed with indicators. An advantage of using indicators compared with physical validation is the simplicity of use. On the other hand, physical validation yields more insight in the sterilization process itself.

European standards used for the development of indicators for steam sterilization specify the accuracies of the steam sterilizer to be used [100, 113] – for example, the accuracy of the temperature must be better than 0.5 °C and the accuracy of the pressure better than 2.5 kPa. The ISO standards (ISO 11140-2 and ISO 18472) on this topic are not yet available or published as standard. For the development of indicators for steam sterilization, the North American standard [111] requires an accuracy of the temperature better than 0.5 °C and an accuracy of the pressure better than 3.4 kPa (0.5 psia). The European standards are therefore a little more strict than the North American standard. Although these specifications for the development of indicators may be comparable with the physical requirements for validation, it is obvious that an indicator cannot be more accurate than the equipment used for its development. Furthermore, the integrity of an indicator can only be guaranteed if the storage and handling is performed according to the specifications given by the manufacturer. If biological indicators are used, the incubation time of the indicators will inevitably take time. Consequently, the validation results or, in daily practice, clearance of the sterilized loads will be delayed until the results of the indicators are available. Apart from this, a disadvantage of indicators is that they only provide a one sided test. This implies that in case of a problem, the information given by indicators will often not be sufficient for trouble shooting.

If the set of physical requirements described earlier is used for validation measurements, surface steam sterilization conditions can be guaranteed. Moreover, physical measurements provide detailed information on the reproducibility and efficacy and can be used for trouble shooting. Because modern steam sterilizers are controlled on the basis of physical parameters (e.g., temperature, pressure, and time), it is recommended that these parameters be monitored and validated. This will lead to better insight into the sterilization process and hence a possible cost reduction. If an independent check is required on the effectiveness of the sterilization processes that are validated, indicators can be added.

Finally, it is recommended that the criteria described in standards are based on well-established microbiological and physical models. Only then can discrepancies within standards for steam sterilization be eliminated.

Chapter 5

Temperature dependence of F-, D- and z-values used in steam sterilization processes

The minimum exposure time F for a decontamination process at a certain temperature is usually calculated from an empirical model with the decimal reduction time D and the temperature resistance coefficient z as parameters. These are implicitly assumed to be independent of temperature. Using a microbiological approach, it is shown that also D and z depend on temperature, indicating that the usual models provide only reliable results in a limited temperature region. The temperature dependence of F resulting from this approach describes the available experimental data very well. Safety margins to assure sterility can be included in a straightforward way. The results from the present approach can be used to safely optimize decontamination processes. The corresponding mathematical model can be implemented rather directly in process control systems. Our results show that for steam sterilization and disinfection processes the values of F predicted by the usual models largely underestimate the required minimum exposure times at temperatures below 120 °C. This has important consequences for the optimization of such processes.

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5.1 Introduction

To obtain sterile products, items have to be sterilized. To compare different decontamination processes, in practice a description in terms of minimum exposure times F is used [18, 19, 22, 59, 61]. The value of F at a certain temperature is the minimum time that the organisms, present in or on an item, have to be exposed to a hostile environment to assure sterility of the item. Worldwide, sterility of medical devices is defined as the chance of finding a viable organism in or on a medical device to be at most 1 in 1,000,000 or a Sterility Assurance Level (SAL) of at most 10^{-6} [23, 53, 73, 114, 115]. Already many decades ago, Perkins reported temperature-time combinations for sterilization of aqueous liquids [88]. A few years later, the Working Party on Pressure Steam Sterilizers of the Medical Research Council [31] adjusted these values to steam sterilization with 100 % saturated steam by including safety margins [31]. The resulting temperature-time combinations are still in use, e.g. 121 °C for 15 min and 134 °C for 3 min. For a given temperature and time the value of F for a process can be calculated. This value should be equal to or

larger than that corresponding to an accepted temperature-time combination, in order to assure sterility.

Apart from comparing steam sterilization processes, F-values are used to optimize such processes, in order to safe time, energy, money, or to reduce the exposure time of thermo-labile products to high temperatures. In most cases the exposure time to high temperatures is made as short as possible. This is done by taking into account the contribution of each part of the sterilization process to the inactivation of the organisms.

To calculate the value of F for other temperatures than those reported in the literature, empirical models are used with the decimal reduction time D (min) and the temperature resistance coefficient z (°C) as parameters. Values of D and z can be found in the literature [18, 19, 59]. From calculations based on an Imaginary Micro Organism (IMO) concept and using the temperature-time combination of 120 °C for 20 min [31], Van Asten and Dorpema obtained $D = 3.33$ min and $z = 17$ °C [59]. With this reference point they calculated generic temperature-time combinations for other temperatures. Values for D and z can also be calculated from two accepted temperature-time combinations. Using the values given by the MRC [31], 121 °C for 15 min and 134 °C for 3 min, one obtains $D = 2.5$ min and $z = 18.6$ °C. The values for F reported in the literature do not seem to be very consistent [18, 31, 59, 88]. Therefore, we thought it worthwhile to investigate whether a straightforward microbiological approach can be used to obtain a reliable prediction for the temperature dependence of F. The theoretical framework is presented in the next section. In the subsequent section the predictions of the resulting model are compared with experimental temperature-time combinations [88], the combinations given by the MRC [31], and the behaviour of F resulting from the two models mentioned above. The chapter will be concluded with a discussion.

5.2 Theory

It is generally accepted that the most essential mechanism for sterilization of aqueous liquids is coagulation[1]; the irreversible change and hardening of the protein chains of the micro-organisms [20]. This process can be described in terms of chemical reaction kinetics [116, 117] , in which the inactivation of organisms is given by

$$\frac{dN}{dt} = -kN, \tag{5.1}$$

with N the number of organisms, t the time, and k the specific inactivation constant for an organism. If the conditions required for steam sterilization are satisfied [118], the inactivation is identical to that in aqueous liquids, in which case the temperature dependence of k obeys the Arrhenius law:

$$k = A \exp\left(-\frac{E_a}{RT}\right), \tag{5.2}$$

In this equation A represents a constant, E_a the activation energy for the inactivation reaction (J mol^{-1}), R the universal gas constant (8.31 J mol^{-1} K^{-1}), and T the temperature

[1] See section 2.1 for some more details of this process.

(K). If the population of organisms is exposed to a constant temperature, the number of living organisms after a certain time can be obtained from equation 5.1:

$$N_e = N_0 \exp(-kt) \quad \text{or} \quad \ln N_e - \ln N_0 = -kt, \tag{5.3}$$

with N_0 the initial number of organisms[2], N_e the number of organisms that have survived the sterilization process, and t the time that has elapsed since the start of the sterilization process. This equation shows that the time required to achieve sterility does not only depend on k but also on the initial number of organisms. In papers on sterilization theory [27] and in the pharmaceutical industry [18–20], the $^{10}\log$ (referred to as log) is often used instead of the natural logarithm. In that case, equation 5.3 reads:

$$N_e = N_0\, 10^{-k't} \quad \text{or} \quad \log N_e - \log N_0 = -k't, \tag{5.4}$$

where $k' = k/\ln(10)$.

Often, a sterility criterion (S) is defined as $S = \log(N_0/N_e)$. Substitution of this criterion in equation 5.4 shows that S is equal to the product $k't$. The minimum time (F) to satisfy the sterility criterion can be calculated with:

$$F = \frac{1}{k'} \log\left(\frac{N_0}{N_e}\right) = \frac{1}{k'} S. \tag{5.5}$$

The decimal reduction time D is defined as the time needed to reduce the number of organisms by a factor of 10, e.g., if $N(0) = N_0$ at $t = 0$, then at $t = D$ the value $N(D) = N_0/10$. Equation 5.4 shows that

$$D = 1/k' = \ln(10)/k \tag{5.6}$$

and the inactivation of a process can be written as:

$$\log N_e = -\frac{1}{D} t + \log N_0. \tag{5.7}$$

This equation illustrates that the inactivation can be represented by a straight line in a graph with a logarithmic N-axis [27, 121, 122]. By substituting equation 5.6 in equation 5.5 the minimum exposure time (F) for a given sterilization criterion S can be expressed as:

$$F = D \log\left(\frac{N_0}{N_e}\right) = DS. \tag{5.8}$$

The decimal reduction time $D = \ln(10)/k$ depends on the environment conditions. Since in sterilization of aqueous liquids the temperature dependence of k is exponential (see equation 5.2), D has a similar temperature dependence. In the literature [19, 30, 59, 123] the temperature dependence of D is described by a temperature resistance coefficient z (°C), the temperature increase required to reduce D by a factor of 10 with respect to its value D_{ref} at a temperature T_{ref}:

$$\log D = -\frac{1}{z}(T - T_{\text{ref}}) + \log D_{\text{ref}}, \tag{5.9}$$

[2] In the literature and standards N_0 is often taken equal to 10^6 [77, 119, 120]. It is not clearly defined whether this number reflects the number of organisms on a surface, in a volume, or on a set of items.

or,

$$\log\left(\frac{D}{D_{\text{ref}}}\right) = -\frac{1}{z}(T - T_{\text{ref}}). \tag{5.10}$$

This equation shows that with a known value of z and a known D_{ref} at a certain temperature T_{ref}, values of D at other temperatures can be calculated. If z would be independent of temperature, a plot of $\log(D)$ against T would yield a straight line with a slope equal to $-1/z$. This approximation of D is represented by the dashed line in figure 5.1. By substituting equation 5.10 into equation 5.8 the required exposure time (F) at a given temperature can be calculated:

$$F = F_{\text{ref}} \times 10^{(T_{\text{ref}} - T)/z}, \tag{5.11}$$

where F_{ref} is the minimum exposure time at $T = T_{\text{ref}}$.

In principle, D and z may be different for different types of micro-organisms. This complication was taken into account in a straightforward way by Van Asten and Dorpema, who developed the so-called IMO concept [59]. The IMO is by definition the most resistant micro-organism for the sterilization method used. By using the values for D and z corresponding to this organism, a safety margin in the sterilization time is implemented.

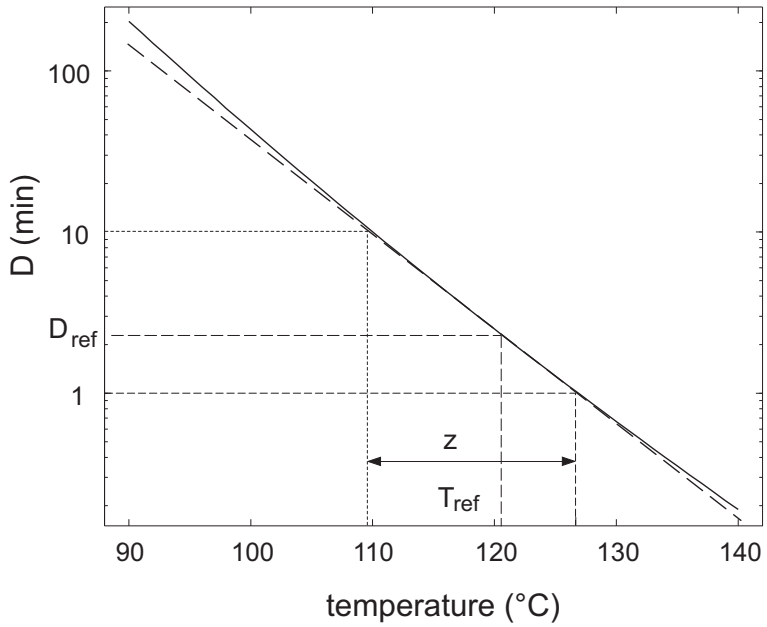

Figure 5.1: Temperature dependence of the decimal reduction time D. The resistance coefficient z (°C) is defined as the temperature increase needed to reduce D by a factor of 10. The dashed line reflects the approximation in which z is independent of temperature. The solid curve reflects the actual variation of the the decimal reduction time D, with $T_{\text{ref}} = 121\,°\text{C}$ and $z_{\text{ref}} = 17\,°\text{C}$, yielding a resistance coefficient z that depends on temperature.

A disadvantage of the traditional definition of the temperature resistance coefficient z (equation 5.9) is the implicit temperature dependence of this coefficient. This means that z values reported in the literature should only be used in a limited range of sterilization temperatures around the temperature T_{ref} at which z has been determined. This can be

demonstrated as follows. If we combine equations 5.2 and 5.6, the decimal reduction time D can be written as:

$$D = \frac{\ln(10)}{A} \exp\left(\frac{E_a}{RT}\right). \tag{5.12}$$

Because equation 5.2 is expressed in the absolute temperature (K), all temperatures have to be expressed in K.

The derivative of equation 5.12 with respect to temperature is given by:

$$\frac{dD}{dT} = \frac{\ln(10)}{A} \exp\left(\frac{E_a}{RT}\right)\left(-\frac{E_a}{RT^2}\right) = -D\left(\frac{E_a}{RT^2}\right). \tag{5.13}$$

For an arbitrary temperature T_{ref} this equation can be written as:

$$\frac{d\log(D)}{dT} = -\frac{1}{\ln(10)}\left(\frac{E_a}{RT_{\text{ref}}^2}\right). \tag{5.14}$$

This equation describes the slope of a plot of $\log(D)$ against T at a temperature T_{ref}. Since, by definition, this slope is equal to $-1/z$ (see equation 5.9), it follows that

$$z = \frac{T_{\text{ref}}^2 R \ln 10}{E_a}. \tag{5.15}$$

This equation shows that z depends on the square of the (absolute) temperature. Since z is not constant, the temperature increase to reduce D by a factor of 10 is also not constant. This is illustrated in figure 5.1, where the solid curve reflects a typical variation of D with temperature calculated from equation 5.12. The dashed line represents a linearization of this curve, corresponding to the traditional definition of z, which is obviously only valid in a temperature region close to T_{ref}. If the actual temperature T differs significantly from a temperature T_{ref}, at which a z value has been documented, equation 5.15 shows that the actual z value may be obtained using:

$$z(T) = z(T_{\text{ref}})\left(\frac{T^2}{T_{\text{ref}}^2}\right). \tag{5.16}$$

This is illustrated in figure 5.2, where we used a standard model reported in the literature [59]: $T_{\text{ref}} = 120\,^{\circ}\text{C}$ (393 K) and $z_{\text{ref}} = 17\,^{\circ}\text{C}$. Alternatively, the temperature dependence of D can be expressed in T_{ref} and D_{ref} using equation 5.12. This yields

$$\ln\left(\frac{D}{D_{\text{ref}}}\right) = \frac{E_a}{R}\left(\frac{1}{T} - \frac{1}{T_{\text{ref}}}\right). \tag{5.17}$$

Substitution of equation 5.15 gives:

$$\log\left(\frac{D}{D_{\text{ref}}}\right) = \frac{T_{\text{ref}}^2}{z(T_{\text{ref}})}\left(\frac{1}{T} - \frac{1}{T_{\text{ref}}}\right). \tag{5.18}$$

In contrast to the usual description of sterilization processes, equations 5.16 and 5.18 are valid in the entire temperature region in which equation 5.2 can be applied.

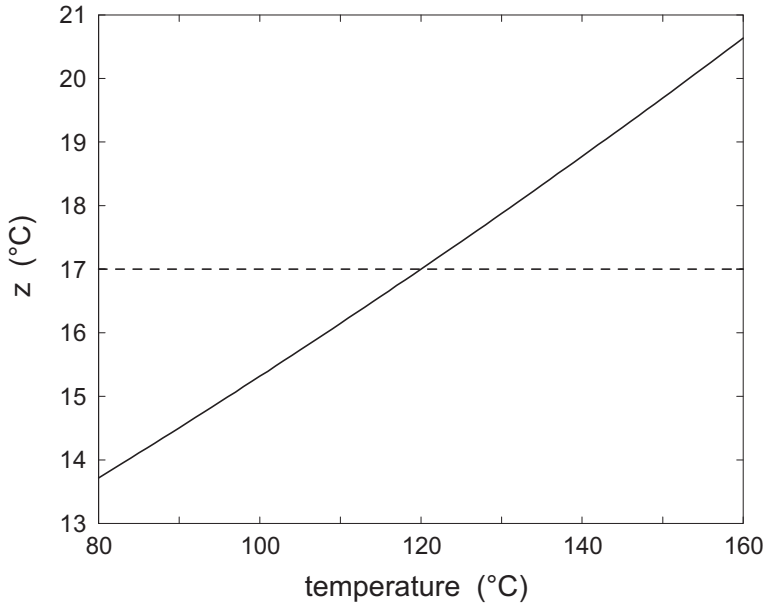

Figure 5.2: Variation of the resistance coefficient z with temperature. The horizontal dashed line represents the constant value $z = 17\,^{\circ}\mathrm{C}$ used in various theoretical models [18, 19, 59]. The solid curve represents $z(T)$ calculated from equation 5.16, using $T_{\mathrm{ref}} = 120\,^{\circ}\mathrm{C}$ and $z_{\mathrm{ref}} = 17\,^{\circ}\mathrm{C}$.

5.3 Results

As already mentioned in section 5.1, the temperature-time combinations required to assure sterility in aqueous liquids reported by Perkins [88] are still the basis of the present sterility criteria for steam sterilization processes. To test to what extent the theory described in section 5.2 can be a useful extension of the traditional description in terms of D and z, we fitted the data of Perkins by the following equation:

$$\ln\left(\frac{F}{F_{\mathrm{ref}}}\right) = \frac{E_a}{R}\left(\frac{1}{T} - \frac{1}{T_{\mathrm{ref}}}\right), \tag{5.19}$$

which can be obtained directly from equation 5.17 for any arbitrary value of the sterility criterion S (see equation 5.8). Since the experimental errors in the experiments of Perkins are not given, they are estimated from the precision of the reported values, i.e., an uncertainty of 1 °C in the temperature and 0.5 to 1 min in the time. In figure 5.3 the results of this procedure are shown. The data of Perkins are denoted by the black squares. The solid curve is a fit of equation 5.19 to these data. It is evident that this equation describes the data very well. For a reference temperature $T_{\mathrm{ref}} = 120\,^{\circ}\mathrm{C}$ (393 K) the fit yields an inactivation temperature $E_a/R = 2.643 \times 10^4$ K and $F_{\mathrm{ref}} = 14.38$ min. One should note that the choice of T_{ref} in equation 5.19 is arbitrary. For instance, by taking $T_{\mathrm{ref}} = 134\,^{\circ}\mathrm{C}$ (407 K) an equivalent description of the data is obtained for the same inactivation temperature and $F_{\mathrm{ref}} = 1.423$ min. Values for F_{ref} at different values of T_{ref} are directly related by equation 5.19.

The Working Party on Pressure Steam Sterilizers of the MRC has added safety margins to the data of Perkins to assure sterility for steam sterilization processes [31]. The

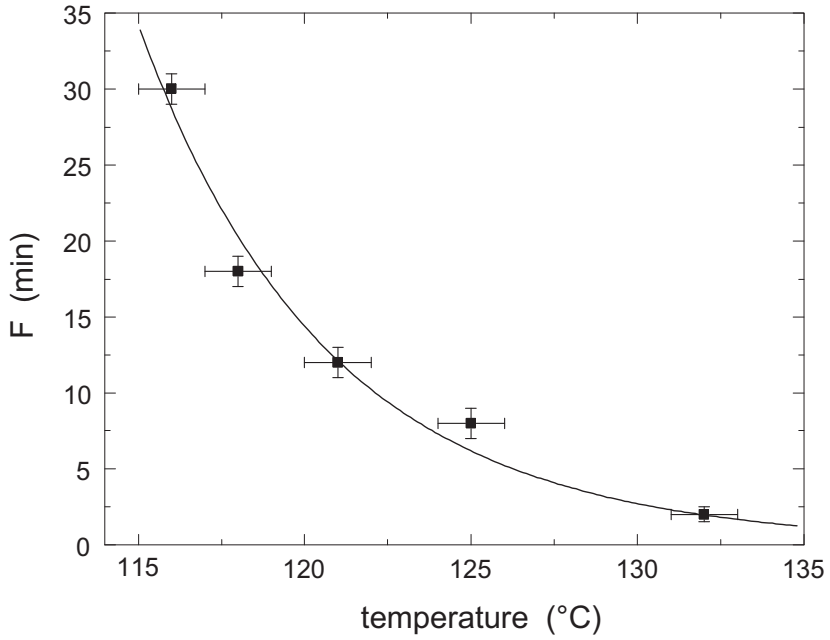

Figure 5.3: Time-temperature combinations to achieve sterility for aqueous liquids given by Perkins [88] (black squares) and a fit of equation 5.19 to these data. The initial number of organisms N_0 is taken equal to 10^6.

corresponding temperature-time combinations are denoted by the open circles in figure 5.4. This figure shows that, in terms of exposure time, the safety margin at 121 °C equals 25 %, increasing via about 90 % at 126 °C to about 110 % at 134 °C. The MRC states that these safety margins have been included to allow for deviations in steam quality [31], but no rationale is given for their magnitude, in particular, the large relative increase at higher temperatures. These temperature-time combinations have no direct relation with a microbiological inactivation process. Nevertheless, several theoretical models based on the MRC temperature-time combinations have been developed and are used in practice, as already mentioned in section 5.1. Two of these are included in figure 5.4. The dashed curve represents a model with $T_{\text{ref}} = 120\,°\text{C}$, $F_{\text{ref}} = 20$ min and $z = 17\,°\text{C}$ (see equation 5.11), whereas the dotted curve represents a model with $T_{\text{ref}} = 121\,°\text{C}$, $F_{\text{ref}} = 15$ min and $z = 18.6\,°\text{C}$. Inspection of the figure shows that both models describe the MRC temperature-time combinations reasonably well and respect adequate safety margins between 120 and 135 °C. However, at temperatures below about 115 °C, the values of F following from these models drop below those resulting from the fit to the data of Perkins, where no safety margins have been included. We will return to this point below.

From a microbiological point of view, adding safety margins to the data of Perkins can be done in two ways. First, one might increase the sterility criterion S, which results in a proportional increase of the minimum exposure time, as can be seen from equation 5.8. This is reflected by the dashed curve in figure 5.5, where we used the fit of equation 5.19 to the data of Perkins and increased F_{ref} by 50 %. This value was chosen because it yields the best description of all three temperature-time combinations given by the MRC. If we would have chosen an increase of F_{ref} by 100 %, an excellent description of

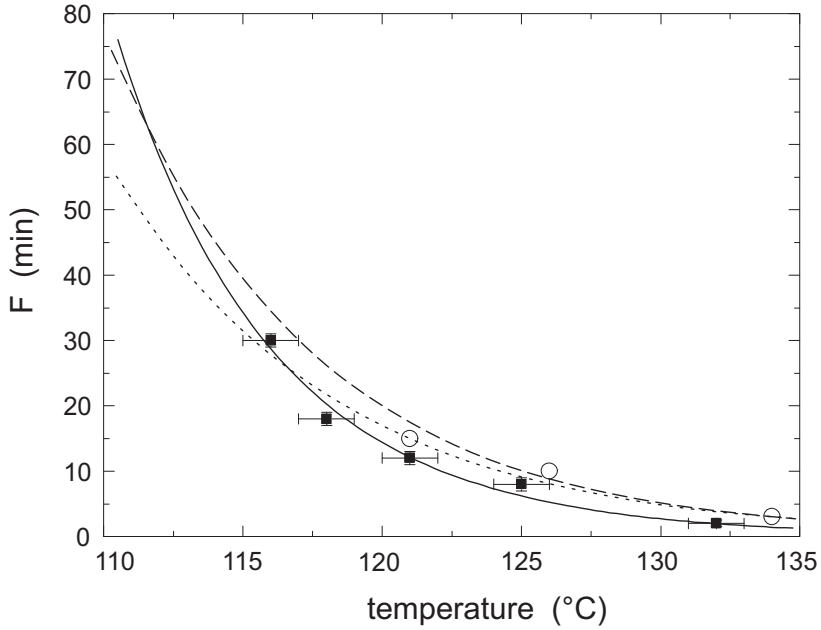

Figure 5.4: Various time-temperature combinations used in steam sterilization processes. The black squares represent the data reported by Perkins [88], the open circles represent those given by the MRC [31]. The solid curve is a fit of equation 5.19 to the data of Perkins. The dashed curve represents a theoretical model with $F_{\text{ref}} = 20$ min, $T_{\text{ref}} = 120\,^{\circ}\text{C}$, and $z_{\text{ref}} = 17\,^{\circ}\text{C}$, the dotted curve represents a theoretical model with $F_{\text{ref}} = 15$ min, $T_{\text{ref}} = 121\,^{\circ}\text{C}$, and $z_{\text{ref}} = 18.6\,^{\circ}\text{C}$.

the MRC temperature-time combinations at 126 and 134 °C would have been obtained, but the value of F at 121 °C would have been overestimated by 60 %. This illustrates the somewhat arbitrary magnitude of the safety margins introduced by the MRC. Second, one might increase the inactivation energy of the most resistant micro-organism. This approach, however, results in exposure times that increase much faster with decreasing temperatures than the temperature-time combinations given by the MRC. As an example, we included in figure 5.5 the fit of equation 5.19 for $T_{\text{ref}} = 134\,^{\circ}\text{C}$ to the data of Perkins, where we increased the activation energy by 30 % (dotted curve). Also this value was chosen because it yields the best description of all three temperature-time combinations given by the MRC. In view of these results we conclude that the most adequate way to add safety margins is by increasing the sterility criterion S and, consequently, F_{ref} by about 50 %. We will refer to this description (dashed curve) as F_{theor}.

In general, steam sterilization processes are optimized as much as possible, in order to safe time, energy, money, or to reduce the exposure time of thermo-labile products to high temperatures. In most cases the exposure time to high temperatures is made as short as possible. This is done by taking into account the contribution of each part of the sterilization process to the inactivation of the organisms. For a part of the process at temperature T_i during a time interval Δt_i it follows from equation 5.7 that

$$\log\left(\frac{N_0^i}{N_e^i}\right) = \frac{\Delta t_i}{D(T_i)}, \tag{5.20}$$

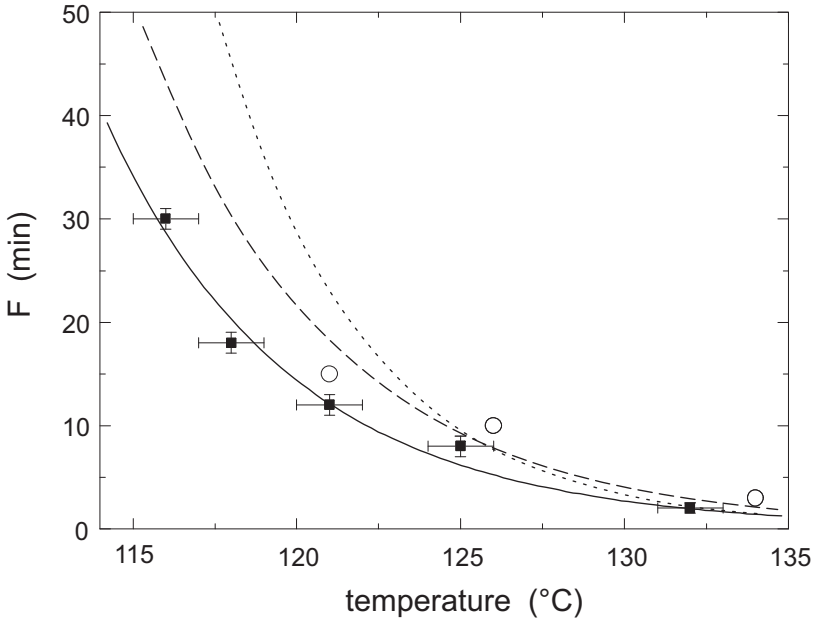

Figure 5.5: Various time-temperature combinations that might be used for steam sterilization processes. The black squares represent the data reported by Perkins [88], the open circles represent those given by the MRC [31]. The solid curve is a fit of equation 5.19 to the data of Perkins. The dashed curve reflects the effect of increasing the sterility by 50 %, the dotted curve represents the effect of increasing the inactivation energy by 30 %.

where N_0^i and N_e^i denote the number of organisms at the start and the end of the time interval t_i, respectively. For the entire process (time intervals i to N) this gives

$$\log\left(\frac{N_0}{N_e}\right) = \sum_{i=1}^{N} \frac{\Delta t_i}{D(T_i)}. \tag{5.21}$$

For any chosen value of the sterility criterion S the decimal reduction time $D(T_i)$ at a certain temperature can be expressed in the minimum exposure time $F(T_i)$ at that temperature (see equation 5.8), which yields

$$S_{\text{process}} = \log\left(\frac{N_0}{N_e}\right) = S\sum_{i=1}^{N} \frac{\Delta t_i}{F(T_i)}. \tag{5.22}$$

From this equation it can be seen that a process meets the sterility criterion if $S_{\text{process}} \geq S$, or

$$\sum_{i=1}^{N} \frac{\Delta t_i}{F(T_i)} \geq 1. \tag{5.23}$$

The sum in this equation can be evaluated as follows. The process is divided in sufficiently small time intervals Δt_i. From the temperatures T_i during these time intervals the values $F(T_i)$ are calculated using equation 5.19 with appropriate values of the parameters F_{ref} and T_{ref}.

If we compare figures 5.4 and 5.5 it is clear that in the temperature range between 121 and 134 °C both F_{theor} introduced above and the two models mentioned above represent the MRC temperature-time combinations with an acceptable degree of accuracy. At lower temperatures, however, the latter two models predict minimum exposure times that are much lower than those resulting from a microbiological approach. If the $F(T)$ relations for these models would be used to evaluate the sum in equation 5.22, the contribution of the low-temperature parts of the process to the inactivation would be overestimated. In such cases it cannot be guaranteed that the chosen sterility criterion is actually satisfied. The errors in the calculations will be most pronounced for processes that involve temperatures below 115 °C during significant time intervals.

5.4 Discussion

Although the minimum exposure times F calculated according to various empirical models [18, 19, 59] are in line with the reported experimental data of Perkins [88] and the MRC [31], the results presented in this chapter show that these methods should only be applied in the temperature region between 121 and 134 °C. Moreover, it is shown that these calculations are only valid within a limited temperature range close to some reference temperature (T_{ref}), because the parameters D and z used in these calculations actually vary with temperature. Consequently, the parameters D_{ref} and z_{ref} used to calculate the value of F must be chosen close to the used T_{ref}, and should be available in the literature or determined from experiments close to T_{ref}.

This limited temperature range is a major disadvantage of the current methods to calculate values of F and may lead to incorrect conclusions and even to a false sense of safety. For instance, when sterilization temperatures are located significantly below T_{ref}, the calculated exposure times to sterilization conditions appear to be too short. This error may be very pronounced for sterilization processes in which the items are warming up and cooling down slowly.

The straightforward microbiological approach presented in this chapter to calculate $F(T)$ by equation 5.19 perfectly describes the available experimental data [88]. The resulting mathematical model contains only two independent parameters and can be implemented in a similar way as the generally used empirical models [18, 19, 59]. There is no need to improve the description by using a double Arrhenius function, such as the log $R - fa_t$ function [124], which involves up to five adjustable parameters. By increasing the sterility criterion S by 50 % the model gives a fair overall description of the temperature-time combinations of the MRC [31]. It has the major advantage that it is applicable in the entire temperature range where the Arrhenius equation can be applied. For sterilization of aqueous liquids or surface steam sterilization this temperature range extends at least from 115 to 134 °C, as is shown by the perfect fit of our model to the data of Perkins. As long as the dominant killing process is coagulation, which is basically a mechanistic process, the Arrhenius equation remains valid. To investigate this point in detail, it may be worthwhile to supplement the data of Perkins with data at temperatures between, e.g. 105 and 115 °C.

The model can be implemented rather directly in the computer program used to collect

and analyse the data during validation and monitoring of a sterilization process. Another advantage of the use of this model is that no false sense of safety is introduced and products are not exposed to high temperatures longer than necessary. This will result in sterilized products, saving energy and costs.

In its present simple form, our model cannot directly be used to optimize the thermal preservation cycles used in the food industry (see, for instance, [125]). Various experiments on the death kinetics of some microorganisms that are relevant for food product quality show significant deviations from log-linear behaviour, in the form of 'shoulders', lags and tails [124]. If data on the death kinetics of all relevant micro-organisms would be available from controlled experiments in the entire temperature range of interest, a mathematical model might be developed following the approach presented in this chapter, but it would be far more complex.

Chapter 6

Penetration of water vapor into narrow channels during steam sterilization processes

In surgery medical devices are used that should be sterile. To obtain surface steam sterilization conditions in hollow medical devices (e.g. endoscopes), sufficient water vapor should be present in the narrow channels in these devices during sterilization. In this chapter a model to calculate the water vapor distribution in narrow channels during steam sterilization processes is presented. The narrow channels in the devices are modeled as tubes with one open and one closed end. The model is restricted to isothermal situations in which no condensation takes place. To validate the model, the time evolution of the water vapor density at the closed end of a test tube is quantified by a pilot experiment based on infrared light absorption measurements. A stainless steel test tube was used with a length of 54 cm, an inner radius of 1.5 mm, and a wall thickness of 0.5 mm. These dimensions are comparable to the channels in medical instruments. Both the model calculations and the experiments show that for a wide range of sterilization process parameters the vapor density near the closed end of the tube is insufficient for steam sterilization. Despite the simplicity of the model, a fair overall agreement is found between the model predictions and the experimental results. This agreement can be improved significantly by an empirical modification of the boundary conditions at the open end of the tube. Our calculations show that the tube length is the most important parameter. Some possible changes of the process parameters to increase the water vapor concentration at the closed end of the tube are addressed briefly.

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6.1 Introduction

Medical devices used for minimal invasive surgery may contain narrow channels (e.g. endoscopes). The diameter of these channels is in the order of one millimeter, the length is in the order of one meter. Often these instruments are steam sterilized before use in surgery. Although the sterility of the minimal invasive instruments is of utmost importance, little or no information can be found on this topic, either in the literature or from manufacturers or users of these instruments. The aim of this study is to investigate whether during a steam sterilization process the inner surface of the channels in these medical devices is actually exposed to sterilization conditions.

Surface steam sterilization conditions are derived from sterilization of aqueous liquids, in which the mechanism for the killing of organisms is coagulation[1] of proteins. Coagulation requires energy and a wet environment [20, 82, 126]. In an aqueous liquid sterilization process the temperature rise provides the energy. Water present in the liquid provides the required wet environment. In surface steam sterilization steam may provide both the energy and the water. In the literature [19, 31, 88], European and ISO standards [51, 52] surface steam sterilization conditions are described. These imply the presence of saturated steam at a predetermined temperature-time combination.

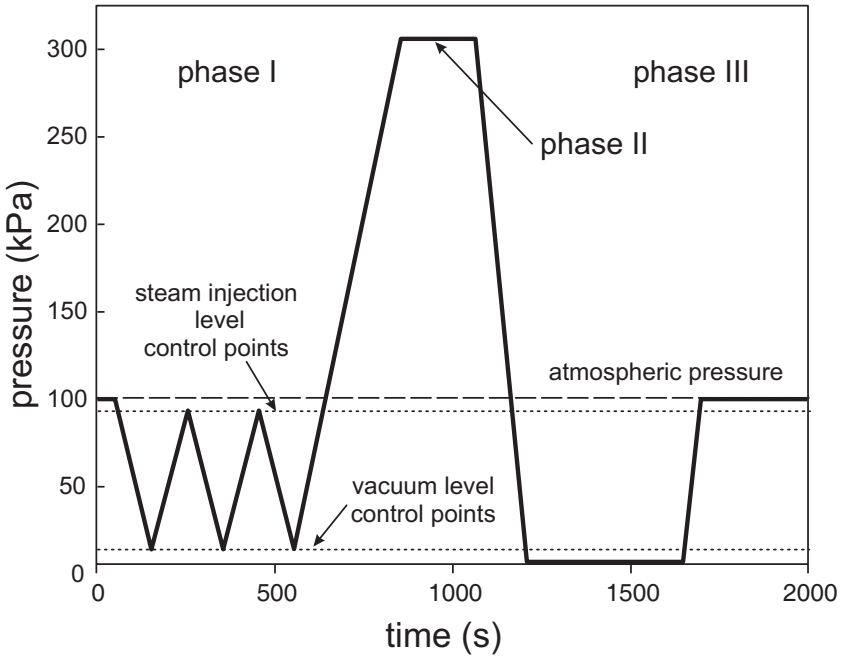

Figure 6.1: Schematic pressure curve of a surface steam sterilization process. Phase I: replacement of air by water vapor; Phase II: actual sterilization phase involving a predetermined combination of temperature and pressure during a certain time; Phase III: returning the steam sterilizer to a safe mode and drying of the load.

Every surface steam sterilization process can be divided in three phases, which are presented schematically in figure 6.1. During phase I the air is replaced by saturated steam, whereas phase II is the actual sterilization period. During phase III the steam sterilizer is brought into a safe state to be opened. Often this phase is also used to dry the steam sterilized loads. To achieve steam sterilization conditions, the air in the steam sterilizer chamber, including the air in all narrow channels, should be replaced completely by steam before the start of the actual sterilization phase (phase II).

Steam penetration in narrow channels in stationary situations has been studied by Young [119] and Young et al. [127]. However, a description of steam penetration in narrow channels during dynamic processes like surface steam sterilization has not yet been reported. Because of the dynamic character of the process and the time-dependent boundary conditions, the problem can not be solved analytically.

[1]See section 2.1 for some more details of this process.

In this chapter we present a model that describes the water vapor distribution in a tube during the first and second phase of a generic steam sterilization process. In section 6.2 the physical model and its applicability will be discussed. Experiments with a tube with one open and one closed end have have been performed to validate some of the model predictions. Section 6.3 describes the experimental setup. The results of the experiments are compared with the corresponding model predictions in section 6.4. Finally, in section 6.5 the results are discussed and some improvements of the model and the generic sterilization process are suggested.

6.2 Physical model

The process of surface steam sterilization consists of heat transfer and the complete replacement of air in the steam sterilizer chamber by steam. To obtain surface steam sterilization conditions on the inner surface of the tube the steam has to penetrate the tube to replace the air. According to the European standard [51] a minimum steam fraction of 0.965 is required.

Figure 6.2 schematically presents the model used in this chapter. A steam supply is connected to the chamber via a steam inlet. To be able to remove gases out of the chamber an outlet with a vacuum pump is connected to the chamber. Valves in the inlet and outlet can be opened and closed. Pressurization of the sterilizer chamber is achieved by the injection of steam by opening the steam inlet while the outlet is closed. Evacuation is achieved by pumping away the gas mixture present in the chamber while the steam inlet is closed. Initially, only air is present in the steam sterilizer chamber and the tube. The process in the sterilizer chamber is assumed to be ideal: instantaneous mixing of the gases occurs, resulting in a homogeneous gas distribution throughout the sterilizer chamber.

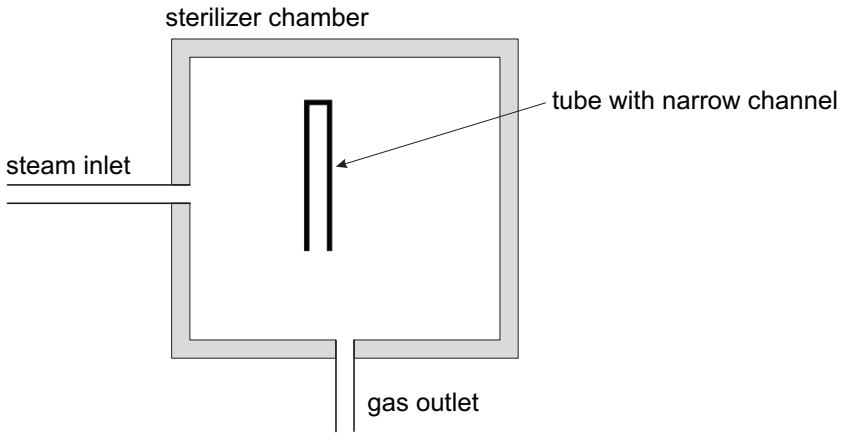

Figure 6.2: Schematic representation of the model used in the computations. During pressurization steam is injected and the outlet is closed (see figure 2.1). During evacuation the inlet is closed, the vacuum pump is switched on and the outlet is opened. A tube with a narrow channel is positioned in the steam sterilizer chamber, the closed end up and the open end down. The tube has no direct thermal contact with the wall.

A medical device with a narrow channel to be sterilized is modeled as a tube positioned in the sterilizer chamber (figure 6.2). The tube is open at one end ($x = 0$) and closed at the other end ($x = L$). The inner radius of the tube is a. The wall of the steam sterilizer chamber is kept at a constant temperature higher than the condensation temperature of the steam. Hence no condensation will take place on the wall. At the conditions that occur during a steam sterilization process the gas (air) and water vapor act as ideal gases [72, 107]. Therefore the pressure is related to the partial densities ρ_g and ρ_v and the temperature T by:

$$p = p_v + p_g = \rho_v R_v T + \rho_g R_g T, \tag{6.1}$$

where R_i is the specific gas constant of component i and the subscripts v and g represent water vapor and gas, respectively. The total density ρ equals $\rho_v + \rho_g$.

At each chamber pressure increase, i.e. during steam inlet, the spatially averaged gas density ρ_g in the chamber remains constant. At each chamber pressure decrease, the composition of the gas-vapor mixture in the chamber does not change. As a consequence the changes of the composition in the chamber with time are directly related to the pressure $p(t)$.

Next we consider the convection-diffusion process in the tube. In this study only tubes with large aspect ratios are considered ($L \gg a$). The Reynolds number of the flow in the tube ($Re = 2\rho a V/\eta$, with ρ the density ($\mathrm{kg\,m^{-3}}$), V the velocity ($\mathrm{m\,s^{-1}}$), η the viscosity ($\mathrm{Pa\,s}$)) is smaller than 50. Also the relative pressure difference over the length of the tube ($(\Delta p)_L/p$) is much smaller than unity. Under these conditions the flow inside the tube is locally described by the Poiseuille equation [128]:

$$\overline{u} = -\frac{a^2}{8\eta}\frac{\partial p}{\partial x}, \tag{6.2}$$

with $\overline{u}$ the velocity ($\mathrm{m\,s^{-1}}$) averaged over the cross-section of the tube and p is the pressure (Pa). The pressure and the water and gas densities in the tube satisfy the ideal gas law (equation 6.1). The conservation of mass in the tube is given by [128]:

$$\frac{\partial \rho}{\partial t} + \frac{\partial(\rho\overline{u})}{\partial x} = 0. \tag{6.3}$$

Fick's law [128] describes the relation between the diffusion flux and the concentration gradients. Using this law the equation for the conservation of mass of component i becomes [128]:

$$\frac{\partial \rho_i}{\partial t} + \frac{\partial \rho_i \overline{u}}{\partial x} = \frac{\partial}{\partial x}\left(\rho D^* \frac{\partial(\rho_i/\rho)}{\partial x}\right). \tag{6.4}$$

D^* is a modified diffusion coefficient, which appears because of the radial dependence of the velocity (Taylor dispersion) [129, 130]. Using the dimensionless Péclet number (Pe) and time (ϵ):

$$Pe = \frac{a\overline{u}}{D}, \quad \epsilon = \frac{Dt}{a^2}, \tag{6.5}$$

the modified diffusion coefficient can be determined [129, 131, 132]. The typical diffusion coefficient (D) for water vapor in air is in the order of 10^{-5} $\mathrm{m^2\,s^{-1}}$ at atmospheric conditions. The radius (a) of a modeled tube is typically 1 mm. Depending on the x-position in

the tube and the pressurization or evacuation rate of the sterilizer chamber, the velocity in the tube can vary from 0 to about 0.2 $\mathrm{m\,s^{-1}}$ and hence Pe can vary from 0 to about 20. With the given values of D and a, ϵ is in the order of $10t/\mathrm{s}$. In a typical steam sterilization process the duration of a pressurization and evacuation cycle is larger than 10 s and hence $\epsilon > 100$. For these values of Pe and ϵ the Aris solution is a valid approximation to modify the diffusion coefficient [128, 132]:

$$D^* = D + \frac{a^2\overline{u}^2}{48D} = D\left(1 + \frac{Pe^2}{48}\right). \tag{6.6}$$

The diffusion coefficient D depends on the temperature and pressure [133]:

$$D(p,T) = D_{ref}\left(\frac{T}{T_{ref}}\right)^{\frac{3}{2}}\frac{p_{ref}}{p}, \tag{6.7}$$

where $D_{ref} = 2.4 \times 10^{-5}\ \mathrm{m^2 s^{-1}}$ denotes the reference diffusion coefficient at $T_{ref} = 313$ K and $p_{ref} = 100$ kPa [72].

The usual steam sterilizer chambers have a volume larger than 10^{-3} $\mathrm{m^3}$, whereas volumes of the tubes relevant for the present study are smaller than 10^{-5} $\mathrm{m^3}$. As already mentioned above, the gases in the chamber are assumed to mix instantaneously to a homogeneous distribution. The disturbance of $p(t)$ and $\rho_i(t)$ at the open end ($x = 0$) of the tube may therefore be neglected and the boundary conditions for the tube at $x = 0$ become:

$$p(0,t) = p(t)\,, \quad \rho_i(0,t) = \rho_i(t), \tag{6.8}$$

where $p(t)$ and $\rho_i(t)$ refer to the quantities in the sterilizer chamber, and $p(x,t)$ and $\rho_i(x,t)$ to those within the tube.

The set of equations (6.2–6.4, 6.6 and 6.7) describes the problem of penetration of water vapor into the tube. Together with the boundary conditions (equation 6.8) this set of equations is solved numerically using the standard `pdepe` routine of Matlab®.

The wall thickness of the tube used in our experiments is 0.5 mm and it is made of stainless steel. Condensing steam on the outside of the tube heats up the wall of the tube. The time constant for heat transfer through the wall to heat up the inner surface can be estimated from

$$t_w = w^2 c_p \rho_w / \lambda, \tag{6.9}$$

where w [m] is the wall thickness, c_p [$\mathrm{J\,K^{-1}kg^{-1}}$] is the heat capacity of the wall material, ρ_w [$\mathrm{kg\,m^{-3}}$] is the density, and λ [$\mathrm{W\,m^{-1}K^{-1}}$] is the heat conductivity of this material. Using typical values for the heat conductivity and heat capacity, the time constant for heat transfer through the wall to heat up the inner surface appears to be in the order of 0.05 s. During the first phase of the sterilization process the penetration of water vapor in the tube is dominated by the pressurization and evacuation of the sterilization chamber. Consequently, the imposed velocity at the open end of the tube is less than 0.02 $\mathrm{m\,s^{-1}}$. During pressurization condensation may occur on the inner wall of the tube up to several mm from the open end, where the temperature is still below that of saturated steam at the actual sterilization chamber conditions. This process is not taken into account in the model, but the region in which it may have an effect corresponds to only 1 % of the length of the tube.

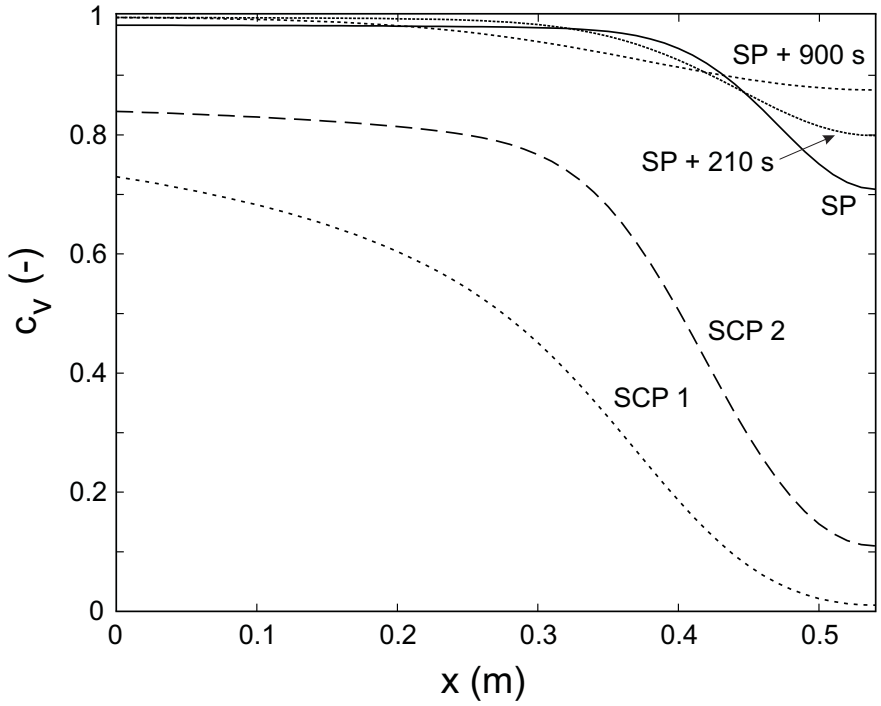

Figure 6.3: Calculated water vapor distribution c_v in a tube that is positioned as indicated in figure 6.2 during a generic process depicted in figure 6.1. The process has Vacuum Control Points (VCPs) of 20 kPa and Steam injection Control Points (SCPs) of 99 kPa. The tube has a length $L = 54$ cm, a radius of 1.5 mm and a wall thickness of 0.5 mm. The open and closed end of the tube correspond to $x = 0$ and $x = L$, respectively. The behavior of $c_v(x)$ is given at both SCPs, the start of the sterilization phase (SP), and 210 s and 900 s later.

With the model mass fractions or concentrations of vapor and air can be calculated as a function of position and time. As already mentioned above, for steam sterilization the water vapor concentration in the tube, $c_v(x,t) = \rho_v(x,t)/\rho_{v=100\,\%}$, is an important parameter. In figure 6.3 the calculated behavior of $c_v(x)$ is plotted for both Steam Injection Control Points (SCPs), the start of the sterilization phase (SP), and for times 210 s and 900 s later. This figure shows that after each evacuation and subsequent pressurization cycle the vapor concentration at $x = 0$ has increased. This is a result of the dilution of the residual air in the chamber, which is rather significant at this rather high value of the Vacuum Control Points.

After the first evacuation, upon pressurizing the sterilization chamber with steam, a mixture with a relatively high c_v enters the tube and drives the residual air towards a small region near the closed end. During this process the front between the mixture and the residual air broadens because of diffusion (the diffusion length $\sqrt{Dt}$ at $t = 100$ s is in the range of $5 - 15$ cm, see equation 6.7), but only a small amount of steam penetrates until the closed end of the tube. Nevertheless, after the subsequent evacuation the residual mixture in the tube will contain a certain fraction of vapor. During each subsequent pressurization cycle, the steam penetration in the tube increases, partly because of the increasing value of c_v in the sterilization chamber, but mainly because after the preceding evacuation cycle the vapor fraction in the residual mixture in the tube is higher.

After pressurization to 308 kPa, the spatial distribution of c_v within the tube gradually broadens during phase II, again showing the effect of diffusion. It is obvious that for this process the steam sterilization condition $c_v > 0.965$ is not realized in a large part of the tube at the start of phase II, the vapor fraction being lowest at $x = L$. In section 6.5 we will discuss how the process parameters can be adapted to increase this fraction.

We like to note that variations in the values of the diffusion coefficient by a factor of two had no significant effect on the numerical results. Variations of the values of the viscosity and the radius of the tube had hardly any effect. Only below a tube radius of 10 μm, where viscosity effects become more important, the results started to deviate significantly from those presented in figure 6.3. As may be expected, the vapor fraction at the closed end decreases significantly when the pressure of the Vacuum Control Points (VCPs) or the lube length is increased.

6.3 Experimental

It is far from trivial to measure the water vapor concentration in a harsh environment like a steam sterilizer chamber, which implies an extremely humid atmosphere with temperatures up to 140 °C and pressures up to 350 kPa. Additional limitations occur because we aim to perform measurements within a narrow tube without affecting the flow of the gas mixture, which requires the inner diameter of this tube to be constant. Preliminary experiments using capacitive techniques to measure the dielectric permeability of the gas mixture were unsuccessful because the capacitive probe fully corroded already after a few process cycles. Therefore we constructed a setup based on the large absorption of infrared light of certain wavelengths by H_2O molecules. This setup is presented schematically in figure 6.4.

It basically consists of a tube with one closed and one open end, which can be positioned in a steam sterilizer. At the closed end of the tube infrared light with a wavelength of either 1.45 μm or 1.30 μm is transmitted through the tube in the radial direction via an optical fiber system. For this system 0.37 NA Hard Polymer Clad Multimode Fibers (T21S31, ThorLabs) are used, which can withstand temperatures up to 150 °C and are mechanically robust. As light sources infrared LEDs (L7850 and L7866, Hamamatsu) are used. The transmitted light is detected with a InGaAs PIN photodiode (G8370, Hamamatsu). The absorption is deduced by comparing the intensities of the transmitted light at both wavelengths. Since the absorption by water vapor at 1.45 μm is almost an order of magnitude larger than that at 1.30 μm, this procedure largely suppresses effects caused by scattering of light within the tube or efficiency variations of the optical system. The relation between the measured absorption and the water vapor concentration was obtained from calibration measurements, which will be discussed below.

A Lautenschläger type 3119/4STE test sterilizer (Cologne, Germany) with a volume of 342 l was used for the experiments. This test sterilizer, its water treatment and steam generation are described elsewhere [134]. Before each experimental session the system consisting out of the sterilizer and the test tube with sensor was heated up to the aimed sterilization temperature. Test programs used for the experiments were preprogrammed and uploaded in the controller of the test sterilizer. To ensure that the inner tube and

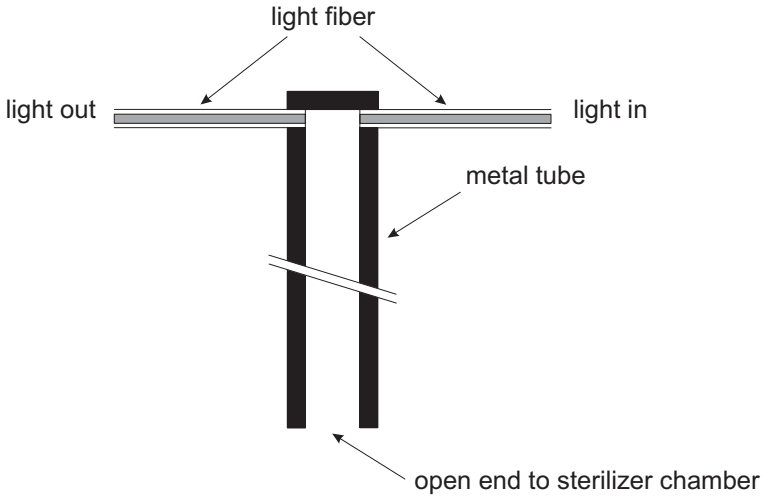

Figure 6.4: Schematic representation of the test tube with water vapor sensor. The tube has an open and a closed end. It is positioned with the closed end pointing upwards in the test sterilizer and the open end downwards. At the closed end of the tube ($x = L$) an infrared light beam is emitted into the tube via a glass fiber. At the opposite side of the tube a second fiber is receiving the light that is transmitted through the gas mixture in the tube.

sensor were dry at the start of an experiment, the sterilizer chamber with the tube including the sensor was evacuated to a pressure lower than 5 kPa and kept for 15 minutes at that pressure, before an experiment was started.

The absorption $\alpha(t)$ was obtained from

$$\alpha(t) = \frac{I(1.30) - I(1.45)}{I(1.30)}\,, \tag{6.10}$$

where $I(1.30)$ and $I(1.45)$ represent the output voltages of the detector for wavelengths of 1.30 μm and 1.45 μm, respectively. To relate the values of $\alpha(t)$ to the amount of water vapor, a two-point calibration of the system has been performed.The value of α measured after switching on the system in the laboratory (environmental relative humidity 30 %) was set to zero by balancing the light intensity of both LEDs. Placing the system in a sterilizer chamber that was subsequently evacuated to about 5 kPa did not result in a significant shift of the zero offset; also pressurizing the chamber with air did not have a noticeable effect. Next, two processes were performed that according to the model would result in nearly 100 % saturated steam at the closed end of the tube at the start of the sterilization phase. These will be described in the next section.

6.4 Results

Two processes that according to the model would result in nearly 100 % saturated steam at the closed end of the tube at the start of the sterilization phase are a generic process as depicted in figure 6.1 with Vacuum Control Points (VCPs) of 5 kPa and Steam injection

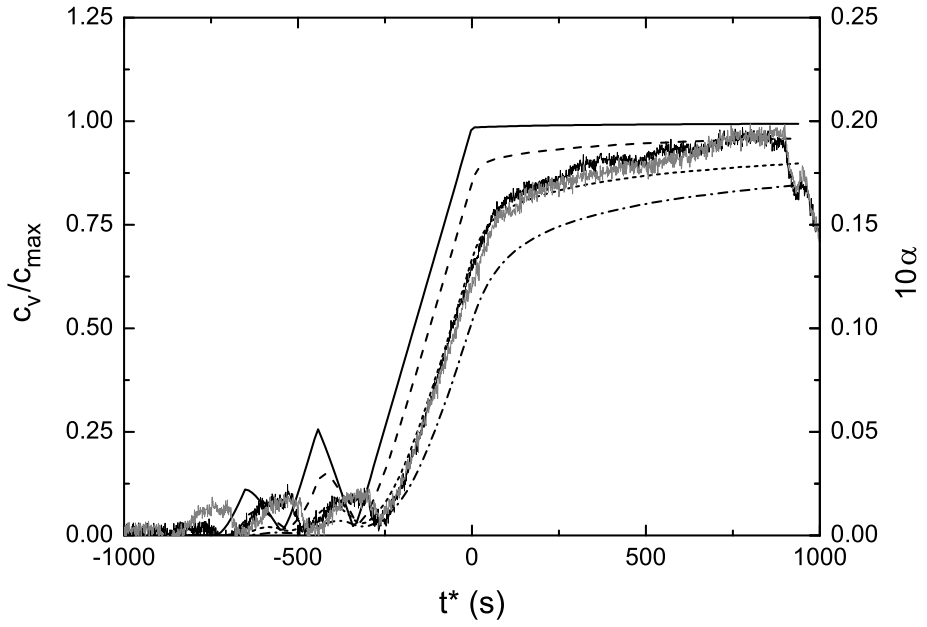

Figure 6.5: Experimental data for a process with 3 VCP's of 5 kPa (black) and a process with 4 VCP's of 10 kPa (grey). The solid black curve denotes the model prediction for the first process. The predictions of the adapted model are denoted by the dashed, dotted, and dashed-dotted curve for $\tau = 30$, 60, and 90 $\mathrm{s\,m^{-1}}$, respectively.

Control Points (SCPs) of 99 kPa and a similar process with VCPs of 10 kPa and one additional evacuation and pressurization cycle. The experimentally measured values of the water vapor fraction during these processes are presented in figure 6.5. For ease of comparison, the time for the individual processes in the plot is shifted such that the start of the sterilization phase corresponds to $t^* = 0$.

The data for both processes during phase II are very similar, as predicted by the model. However, they show a significant time lag with respect to the model prediction for the generic process, which is represented by the solid black curve. Since this time lag is much larger than the response time of the water vapor sensor, which is less than 1 s, it most likely originates from the assumptions made in the model. In particular, the boundary conditions based upon immediate and perfect mixing of the vapor and the residual air in the sterilization chamber and the absence of condensation and subsequent evaporation near the entrance of the tube are rather drastic simplifications. These differences from ideal model behavior will most likely slow down the water vapor penetration towards the closed end of the tube. Therefore these effects were included in an empirical way by relaxing the rigid boundary conditions given in equation 6.8 to

$$\rho_i(0,t) = \rho_i(t) - \tau f_i(0,t), \tag{6.11}$$

where $f_i(0,t)$ denotes the flux of component i at the open end of the tube and the parameter τ is an inverse velocity. These conditions implement an additional barrier

or delay near the entrance of the tube. The results of this modified model for the generic process with three Vacuum Control Points (VCPs) of 5 kPa are included in figure 6.5 for $\tau = 30$, 60, and 90 $\mathrm{s\,m^{-1}}$. The dotted curve ($\tau = 60\ \mathrm{s\,m^{-1}}$) agrees much better with the experimental data than the original model prediction. The results of the modified model for the process with VCPs of 10 kPa and one additional evacuation and pressurization cycle are not plotted, since they correspond within 2 % with the results for the other process. In the figure the normalized value of c_v is equal to 50α, which yielded the best overall agreement between the data and the corresponding model predictions and satisfied the condition that the experimental values of c_v/c_{max} remained below the maximum value of unity. We estimate the accuracy of this calibration factor to be better than 5 %. This factor will be used for all other experiments described in this chapter.

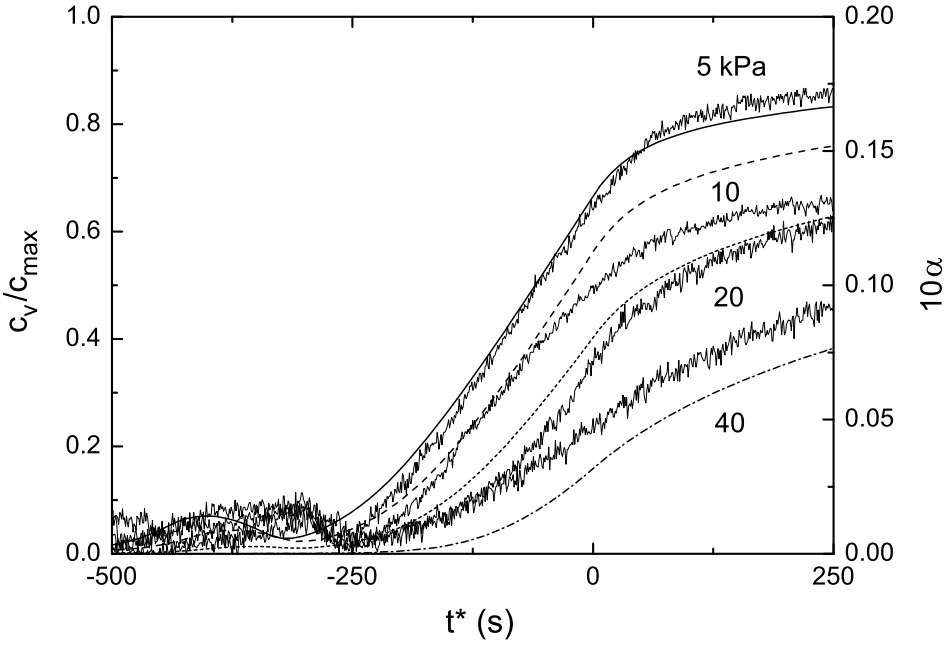

Figure 6.6: Moisture concentration at the closed end of the test tube as a function of time for generic processes with VCP's of 5, 10, 20, and 40 kPa, respectively. The corresponding results of the modified model are represented by the solid, dashed, dotted, and dashed-dotted black curves. The time for the individual processes has been shifted such that $t^* = 0$ corresponds to the start of the sterilization phase.

According to the literature [31] and standards [51] sterilization conditions should be kept for 3 min. Upon reaching the sterilization pressure often an adiabatic temperature overshoot appears. For sterilizers with volumes of over 800 l standards allow up to 30 s equilibration time for this overshoot to relax [51]. Since the sum of these two times (210 s) is relevant for practical applications we limited the time of phase II in the next set of experiments to 250 s. Three generic processes were performed, with VCPs of 10, 20, and 40 kPa, respectively. The SCPs of all processes were fixed at 99 kPa, whereas the speed of inlet of steam and outlet of the gas mix was set to 0.9 $\mathrm{kPa\,s^{-1}}$.

The experimentally measured water concentration at the closed end of the tube is plotted in figure 6.6 for these processes, together with the data for the process with VCPs of 5 kPa presented in figure 6.5. The corresponding predictions obtained from the model with relaxed boundary conditions are included also. Inspection of this figure shows that both the data and the model reveal that the steam penetration drastically decreases when the VCPs increase. On average, the model describes the data rather well, although the individual processes show deviations ranging up to $0.1 c_v/c_{max}$ during the sterilization phase. Apart from uncertainties in the model predictions, various experimental factors have a large impact on the actual steam penetration. Variations of the VCPs of 1 kPa and variations of the speed of evacuation and pressurization of the sterilization chamber of 5 % cause variations in the data up to 7 %. On the other hand, the water vapor sensor showed an offset drift after exposure to saturated steam at high temperatures, which was in first order corrected for at the start of each measurement. Also gradual sensitivity variations up to about 5 % were observed. These probably result from small movements of the inner part of the fiber with respect to its jacket. After repeated exposure of the optic fiber sensor to conditions occurring during generic steam sterilization processes, microscopic images of the end surface of the fibers showed a small outward displacement of the core with respect to the jacket. We will return to this point in section 6.5.

6.5 Discussion

We performed both numerical computations and experiments on the water vapor fraction near the closed end of a narrow tube, mimicking the channel present in instruments used for minimal invasive surgery, during a generic steam sterilization process. Our results indicate that for a wide range of steam sterilization process parameters, the water vapor fraction near the closed end of the tube is insufficient for steam sterilization. Both the experimental data and the model predictions show that the water vapor fraction may be increased by lowering the pressure to which the sterilization chamber is evacuated before the actual sterilization phase or by increasing the number of evacuation cycles. Our experiments, however, suggest that for a tube length L of about 0.5 m it may be problematic to reach the value of 0.965, given in the standards [51]. To obtain some information about the steam penetration for other values of L, we performed model calculations for tube lengths up to 1 m. The results for a process with three VCPs of 10 kPa are presented in figure 6.7 for both the original and the modified model.

Inspection of this figure shows that the vapor fraction decreases significantly for increasing tube lengths. The model with $\tau = 60\ \mathrm{s\,m^{-1}}$, which gives the best agreement with the experimental data, indicates that already for tube lengths above 20 cm the water vapor concentration drops below 0.965. The model with $\tau = 0$, which seems to reflect a very optimistic limit, indicates that this occurs above tube lengths of about 40 cm. It is obvious that modifications of the generic steam sterilization process are necessary to properly sterilize many instruments used for minimal invasive surgery. In this respect we like to note that diffusion of water vapor towards the closed end of the tube (and air towards the open end) is crucial for reducing the air fraction. This diffusion can be made more effective by increasing the time of the various cycles of phase I, in which the load in the sterilization chamber is not yet exposed to sterilization conditions. This might, for

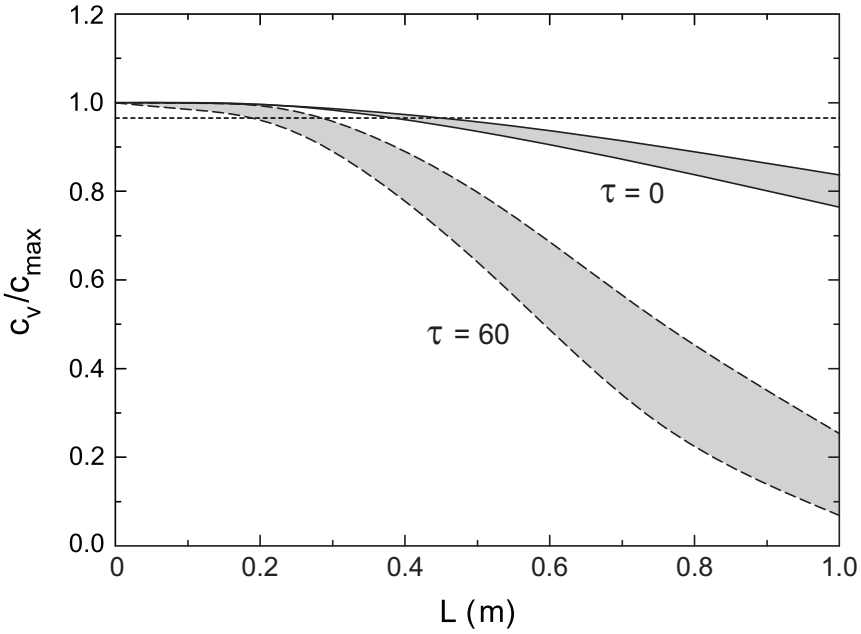

Figure 6.7: Calculated vapor concentration at the closed end of a tube as a function of the tube length for a generic process with VCP's of 10 kPa. The results of the models with rigid ($\tau = 0$) and relaxed ($\tau = 60$) boundary conditions are represented by gray areas, representing the evolution of the vapor concentration during the sterilization phase ($t^* = 0$: lower boundary, $t^* = 210$ s: upper boundary). The horizontal dashed line represents the minimum vapor concentration required for steam sterilization [51].

instance, be implemented by adding a constant pressure plateau at the vacuum level and steam injection control points.

As mentioned in section 6.1, little or no quantitative information on steam penetration in tubes is found in the literature. Therefore, we compared our simulations with the results of Young [119] and Young et al. [127] for static situations. In their experiments, which were confined to tubes with a length to diameter ratio (L/d) between 5 and 20, they observed that with increasing L/d ratio the steam penetration decreases, which qualitatively agrees with our simulations. A more detailed quantitative comparison with their results is not possible, because they were not able to measure the steam fraction within the tube, and therefore had to use a correlation between results of biological experiments and temperature measurements.

The only measurements of steam penetration in a narrow tube during a non-static process reported in the literature are those of Kaiser and Görman [135]. They performed experiments in which a tube was connected to a measuring chamber, incorporating a chemical indicator. With respect to the water vapor fraction at the closed end of the tube as a function of tube length L they observe the same qualitative variations as found in this study. However, in contrast to other experimental and theoretical studies [119, 127] and our simulations, they conclude that with increasing radius a of the tubes the steam penetration *decreases*. The physical origin of this counterintuitive tendency is not clear. We like to note, however, that in the experimental setup used in [135] the net volume of the measuring chamber (about 200 μl) is comparable to or very large with respect

to the volume of the actual test tube ($1.5 - 300$ μl). Such a large additional volume at the dead end of the test tube will have a dramatic effect on the pressurization and evacuation dynamics, which depends on the tube geometry. For this reason, this setup is not representative for the medical devices that are used in practice and modeled in our simulations.

The experimental setup described in section 6.3 enabled us to measure the water vapor concentration at the closed end of a narrow tube without disturbing the flow pattern. To our knowledge, no comparable measurements have been reported yet. The observed zero offset drift and sensitivity variations of the measurements can probably be reduced by using other types of optical fibers or changing their mechanical attachment to the test tube. Apart from this, a more straightforward calibration of the sensor may be achieved by using a tube length below 10 cm, in which the vapor concentration during phase II of a generic process will be almost unity. In this respect we like to note that the use of the sensor without a tube in a sterilization process appeared to be problematic, since in that configuration condensing droplets on the fiber ends induce very large irregular absorption signals.

It is obvious that various extensions may improve the accuracy of the current model. For instance, a finite heat capacity of the wall and its effect on the condensation and evaporation inside the tube during a non isothermal steam sterilization process may be included. On the other hand, since the tube length L is a very dominant parameter, experiments for various tube lengths will probably give information on modifications that are actually necessary to enable the use of the model as a tool to calculate the steam penetration in practical situations. This will be a topic of future studies.

Chapter 7

Measuring non condensible gases during steam sterilization processes

In surgery medical devices are used that should be sterile. To obtain surface steam sterilization conditions, not only in the sterilizer chamber itself but also in the loads to be sterilized, the amount of non condensible gases (NCGs), for instance air, should be very low. Even rather small fractions of NCGs (below 1 %) seriously hamper steam penetration in porous materials or devices with hollow channels (e.g. endoscopes). Traditional steam penetration tests have not been developed for the latter type of instruments and often yield results of limited use. One of the instruments which according to the manufacturer can detect the presence of residual NCGs in a reliable and reproducible way is the 3M^{TM} Electronic Test System (ETS). In this paper a physical model is presented that describes the behavior of this instrument during a typical steam sterilization process. This model has been validated by experiments in which known fractions of NCGs were introduced in a sterilizer chamber in which an ETS was placed. Despite several approximations made in the model, a good agreement is found between the model predictions and the experimental results. Our calculations reveal that the ETS is very sensitive to residual NCGs that are present in the sterilizer chamber before sterilization. These NCGs indeed impair the steam penetration in hollow channels. However, the ETS is also very sensitive to NCGs present in the steam supplied to the sterilizer, of which the effect on steam penetration is much smaller. The consequences of these observations for the use of the ETS in practical applications are addressed briefly.

7.1 Introduction

Sterilization of medical devices is a crucial part of preventing device-related infections in hospitals. Worldwide, steam sterilization is the most applied sterilization method for surface sterilization of surgical instruments. Surface steam sterilization conditions are derived from sterilization of aqueous liquids, in which the mechanism for the killing of organisms is coagulation[1]. Coagulation requires energy and a wet environment [20, 82, 104]. In an aqueous liquid sterilization process the added energy is used to raise the temperature. Water present in the liquid provides the required wet environment. In surface steam sterilization steam may provide both the energy and the water. In the literature [19, 31, 88] and in European and ISO standards [51, 52] surface steam sterilization conditions are described. These imply that 100 % water vapor has to be present on the surface at a certain temperature for a certain time [31, 104], for example, saturated steam at

[1]See section 2.1 for some more details of this process.

134 °C for 3 minutes. To establish these conditions, the air that is initially present in the sterilizer chamber has to be replaced by saturated steam. This should occur during the first phase of a sterilization process, which is illustrated in figure 7.1. During the second phase, the sterilization phase, the established sterilization conditions have to be maintained for a certain time. During the third phase the sterilizer is brought to a safe state to be opened. In production processes this means that the load has to be dry and that the pressure in the sterilizer chamber is equal to ambient pressure.

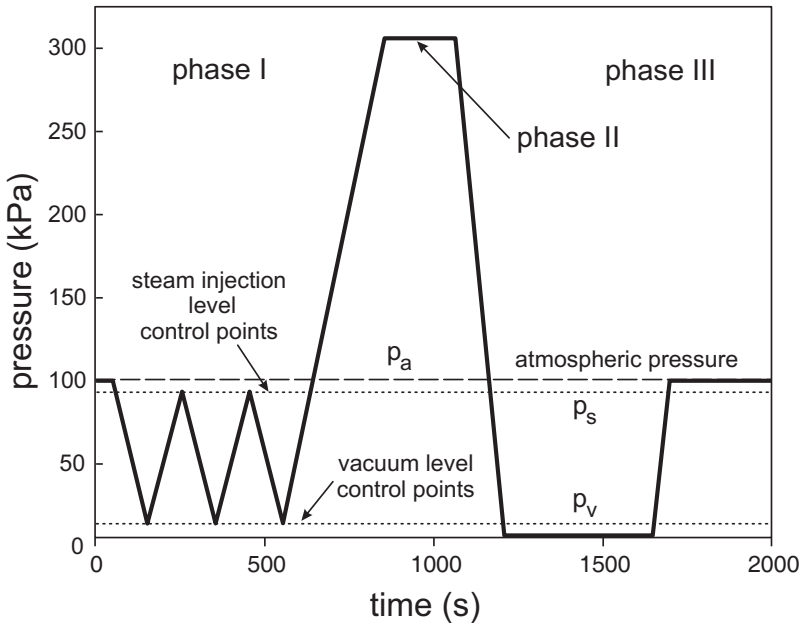

Figure 7.1: The three phases of a steam sterilization process. Phase I, conditioning phase: air present in the sterilizer chamber is replaced by steam and the aimed sterilization temperature is reached. To this end the sterilizer chamber is evacuated several times down to a pressure p_v and subsequently filled with steam to a pressure p_s. Phase II, sterilization phase: the actual sterilization period. Phase III, coming to a safe state to open: the pressure is brought to ambient pressure and the load is dried.

To check if during a process steam sterilization conditions are or have been met in the sterilization chamber, various techniques are available, each with their specific advantages and disadvantages. Most generally used in practice are physical measurements of temperature and pressure [51, 53], or measurements based on biological [77, 78] or chemical [79] indicators.

If small amounts (about 1 % or more) of non condensible gases, like air, are present in the sterilization chamber at the start of the sterilization phase, steam sterilization conditions may still be met on the surfaces of the load that are exposed directly to the steam [19, 20, 31], but the penetration of steam in, for instance, porous materials or narrow channels might be seriously impaired. A possible lack of steam penetration was already recognized half a century ago, and led to the development of the Bowie and Dick (B&D) steam penetration test [32]. This original steam penetration test uses a chemical indicator to judge the penetration of steam through a pack of porous textile towels (see appendix A.2).

Since the introduction of the B&D test in 1963 textile loads are less frequently present, whereas loads with surgical instruments have gradually become more common. Furthermore, during the last two decades Minimal Invasive Surgery (MIS) has developed rapidly. Instruments used for MIS often contain hollow channels with diameters of 1 mm or smaller and lengths up to over 1 m. The inner surfaces of these channels have to be sterilized as well. Unfortunately, a direct measurement of the steam penetration in such channels is not (yet) possible in practice. Recently, we have performed model calculations and experiments on a test tube mimicking the channels present in medical instruments [136]. This study revealed that a significant fraction of the commonly used sterilization processes may fail to reduce the amount of NCGs to a level which is sufficiently low for sterilization of the inner part of such instruments. Since no direct relation has been found between the results of a B&D test and the amount of NCGs in the sterilizer chamber, alternative methods for the detection of residual amounts of NCGs to assess the performance of a sterilizer or sterilization process would be very helpful.

The concentration of NCGs can be derived indirectly from the steam saturation, which can be calculated from the measured temperature and pressure, but this approach is rather inaccurate for small concentrations of NCGs [118].[2] On the other hand, small amounts of air can in principle be measured accurately by an Oxygen Analyzer. This instrument, however, has the drawback that it is generally designed to measure a dry gas mixture at a constant (often rather high) temperature. Hence it cannot be used to measure the gas mixture in the sterilizer chamber directly, because this mixture contains a largely varying amount water vapor and varies in temperature between room temperature and about 410 K. Therefore samples of the gas mixture should be taken, which next have to be analyzed at a fixed temperature. This hampers a real-time monitoring of the fraction of NCGs. An alternative approach is to measure parameters that are very sensitive to the presence of small amounts of NCGs, like the speed of condensation and the resulting heat transfer from steam to surface (see for instance [137, 138]). This latter approach is implemented in a commercially available test device, the ETS (3M$^{\text{TM}}$, Neuss, Germany), but detailed physical specifications of this instrument are not reported. In this chapter a physical model is presented that describes the behavior of this instrument during a typical steam sterilization process. This model has been validated by experiments in which known fractions of NCGs were introduced in a sterilizer chamber in which an ETS was placed. The chapter is organized as follows. In section 7.2 the principle of the ETS will be outlined. The physical modeling of this instrument will be described in section 7.3. The experimental procedure and the results of our measurements will be presented in section 7.4. In section 7.5 the model predictions will be compared with the data and the model parameters will be evaluated. The chapter will be concluded with a discussion in section 7.6, where also the added value of the ETS in practical sterilization processes will be addressed briefly.

[2] In figure 4.3 the temperature tolerance bands for steam sterilization with 100 % saturated steam at 134 °C are presented for representative experimental inaccuracies in the pressure and temperature. A large part of the regions reflecting the experimental measurements is outside the gray area where sterilization conditions are established according to the standards [51, 94, 95, 97, 98]. This shows that, using these standards, direct measurements of temperature and pressure are insufficient to ensure saturated steam conditions in the sterilizer chamber.

7.2 Principle of the ETS

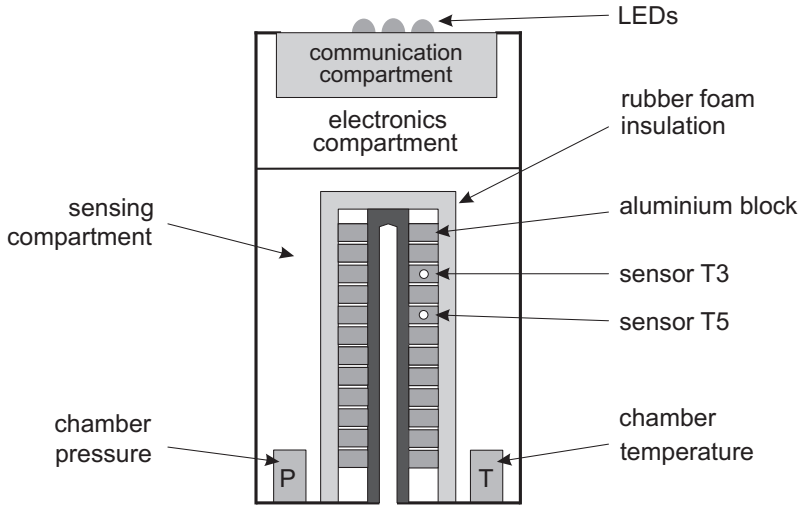

Figure 7.2: Schematic diagram of the sensing unit of the Electronic Test System (ETS, 3M^{TM}, Neuss, Germany). The LEDs (Light-Emitting Diodes) on top of the unit indicate the status and the overall results of a penetration test and can provide an optical link to download the measured data into the ETS software. The lower compartment contains a Liquid Crystal Polymer (LCP) tube, which is open at the bottom end and closed at the top end. Twelve aluminum blocks are attached to this tube. The LCP tube with these blocks is insulated from the rest of the unit by a foam rubber cylinder. Between the aluminum blocks, rubber O-rings are mounted to ensure that mainly horizontal heat transfer will occur in these blocks. The pressure in the sterilizer chamber is measured with the sensor P and the chamber temperature with the sensor T. Sensors T3 and T5 measure the temperature in the corresponding aluminum blocks, counted from the top down.

The sensing unit of the ETS is schematically depicted in figure 7.2. Before the start of a penetration test process the ETS is at room temperature. During the process a mixture of steam and air will enter the Liquid Crystal Polymer (LCP) tube of the ETS. The heat capacity of the aluminum (Al) blocks that are attached to the outer side of this tube is so large that they warm up very slowly. Hence the wall of the tube will have a lower temperature than the gas mixture entering the tube. Consequently, the steam will condense on the wall of the LCP tube. The condensate runs off the wall towards the bottom of the tube, where it leaves the ETS. This condensation will establish a continuous flow of steam (and air) into the LCP tube during the process until the end of the sterilization phase (in figure 7.1, phases I and II). Air flowing with the steam into the tube will not condense and can only leave via the open end of the tube by diffusion. However, diffusion is a very slow process compared to the flow initiated by the condensing steam on the wall. Therefore, in the tube air will accumulate and the concentration of steam will substantially decrease. This effect will be more pronounced towards the closed end (top) of the tube, where so much air can be present that the steam will not be able to penetrate until this end.

Because the aluminum blocks are well isolated from the outer part of the ETS, the temperature increase of these blocks is directly related to the energy transfer from the gas mixture to the wall of the LCP tube. This energy transfer is dominated by the latent heat that is released during condensation of the steam. The presence of even small amounts of air will significantly reduce the heat transfer. Therefore it is expected that the temperature increase of an aluminum block closer to the top of the LCP tube (T3, figure 7.2) is smaller than that of a lower block (T5). This effect will be larger when more air is present in the sterilizer chamber.

All temperature sensors are Pt100s with a resolution of 0.01 °C and an accuracy of 0.2 °C. The resolution and accuracy of the pressure measurements are 0.1 and < 0.3 kPa, respectively.

7.3 Physical model

Figure 7.3 schematically illustrates the model of the ETS used in our computations. The inner LCP tube is open at one end ($z = 0$) and closed at the other end ($z = L_{\text{tube}}$). The radius of the tube is r. Only the open end of the LCP tube is in contact with the sterilizer chamber. The process in the sterilizer chamber is assumed to be ideal: instantaneous mixing of the water vapor and air occurs, resulting in a homogeneous gas distribution throughout the sterilizer chamber.

We will now successively consider the flow of the gas mixture in the tube, the condensation process and the temperature variation of the aluminum blocks. Since the flow of the gas mixture is modeled in a way largely similar to that presented in [136], some details will be omitted here.

At the conditions that occur during a steam sterilization process the gas (air) and water vapor act as ideal gases [72, 107]. Therefore the pressure is related to the partial densities ρ_g and ρ_v and the temperature T by:

$$p = p_v + p_g = \rho_v R_v T + \rho_g R_g T, \tag{7.1}$$

where R_i is the specific gas constant of component i and the subscripts v and g represent water vapor and gas, respectively. The total density ρ equals $\rho_v + \rho_g$.

Since the Reynolds number of the flow in the tube ($Re = 2\rho V a/\eta$, with ρ the density ($\mathrm{kg\,m^{-3}}$), V the velocity ($\mathrm{m\,s^{-1}}$), η the viscosity (Pa s)) is smaller than 100 and the relative pressure difference over the length of the tube ($(\Delta p)_L/p$) is much smaller than unity, the flow inside the tube is locally described by the Poiseuille equation [128]:

$$\overline{u} = -\frac{r^2}{8\eta}\frac{\partial p}{\partial z}, \tag{7.2}$$

with $\overline{u}$ the velocity ($\mathrm{m\,s^{-1}}$) averaged over the cross-section of the tube and p the pressure (Pa). The conservation of mass in the tube is given by [128]:

$$\frac{\partial \rho}{\partial t} + \frac{\partial(\rho\overline{u})}{\partial z} = 0. \tag{7.3}$$

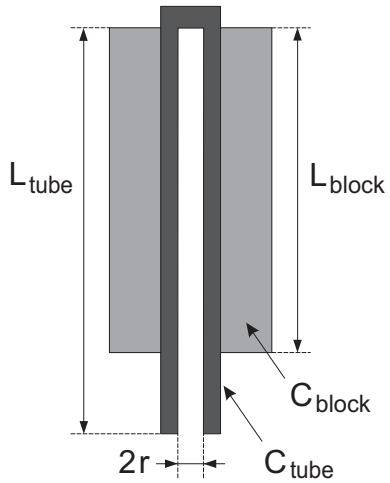

Figure 7.3: Schematic representation of the model used in the computations. The inner channel of the ETS is modeled as a cylindrical tube with a constant radius r and length L_{tube}. The 12 aluminum (Al) blocks are approximated by a second tube with length L_{block} and an effective heat capacity C_{block}, in which the distance between the original Al blocks is taken into account. The heat conductivities of this tube in the axial and radial direction are taken zero and infinitely large, respectively. The heat conductivities of the LCP tube in the radial and axial direction are used as model parameters. The part of the LCP tube in contact with the outer tube is assumed to be thermally shunted in the axial direction by the original Al blocks, which increases the effective axial heat conductivity of the LCP tube in that region by about a factor of 10. All dimensions are taken from an ETS identical to the one used in our experiments.

Using Fick's law [128] the equation for the conservation of mass of component i can be written as:

$$\frac{\partial \rho_i}{\partial t} + \frac{\partial \rho_i \overline{u}}{\partial z} = \frac{\partial}{\partial z}\left(\rho D^* \frac{\partial(\rho_i/\rho)}{\partial z}\right). \tag{7.4}$$

D^* is a modified diffusion coefficient, which appears because of the radial dependence of the velocity (Taylor dispersion). For the range of parameter values appropriate to the present model it can be approximated by [129, 132]:

$$D^* = D + \frac{a^2 \overline{u}^2}{48 D}. \tag{7.5}$$

The diffusion coefficient D depends on the temperature and pressure [133]:

$$D(p,T) = D_{\text{ref}} \left(\frac{T}{T_{\text{ref}}}\right)^{\frac{3}{2}} \frac{p_{\text{ref}}}{p}, \tag{7.6}$$

where $D_{\text{ref}} = 2.4 \times 10^{-5}$ m^{2}s^{-1} denotes the reference value of D at $T_{\text{ref}} = 313$ K and $p_{\text{ref}} = 100$ kPa [72].

The chamber of the sterilizer used in our experiments has a volume of 0.340 m^3, whereas the inner channel of the ETS has a volume of about 3×10^{-6} m^3. The disturbance of $p(t)$ and $\rho(t)$ at the open end ($z = 0$) of LCP tube of the ETS is therefore neglected

and the boundary conditions at $z = 0$ are:

$$p(0,t) = p(t)\,, \quad \rho_i(0,t) = \rho_i(t), \tag{7.7}$$

where $p(t)$ and $\rho_i(t)$ refer to the quantities in the sterilizer chamber, and $p(z,t)$ and $\rho_i(z,t)$ to those within the tube.

Measurements with a thermocouple inside the ETS showed that the gas temperature during the sterilization phase (figure 7.1) decreases from 407 K at $z = 0$ to about 380 K at $z = L_{\text{tube}}$. During the evacuation of the sterilizer chamber during phase I the gas temperature decreases to about 323 K. To keep the model manageable, however, we have described the flow of the gas mixture within the tube by an isothermal process, at a temperature corresponding to that at the open end of the tube during the sterilization phase. This approximation was also motivated by preliminary calculations, based on the experimentally observed temperature increase of the Al blocks resulting from condensation of water vapor inside the LCP tube of the ETS. These calculations revealed that the latent heat of the condensing water vapor dominates all other terms in the energy balance of the gas-liquid system within this tube. Of course, one might argue that since the relative pressure difference over the length of the tube is very small, a temperature decrease towards the end of the tube would imply an increase of the density of vapor and air. As such this is correct, but this increase (of about 10 %) will hardly affect the condensation rate, which depends primarily on the wall temperature of the tube, the partial vapor pressure and the air fraction.

Next, we consider the condensation process of the water vapor. We will model this process as film condensation and use standard Nusselt boundary layer theory [128]. This theory predicts a film of condensate running down along the inner wall of the tube with a thickness $\delta(x)$ given by

$$\delta(x) = \left[\frac{4k(T_{\text{sat}} - T_{\text{w}})\mu x}{\rho_f(\rho_f - \rho_g)g h_{fg}}\right]^{1/4}. \tag{7.8}$$

In this equation k is the thermal conductivity of liquid water (0.68 $\text{Wm}^{-1}\text{K}^{-1}$ in the temperature range of interest), T_{sat} the saturation temperature of the vapor, T_w the wall temperature, ρ_f and ρ_g the density of the fluid and vapor, respectively, μ the dynamic viscosity of liquid water (0.28×10^{-3} Pa s) and g the gravity constant (9.8 m s^{-2}). The parameter h_{fg} is the specific latent heat of water vapor (2160 kJ kg^{-1}). The distance from the top of the film is denoted by $x = L_{\text{tube}} - z$. The density of water is taken as 940 kg m^{-3}, where the variation of about 3 % in the temperature range of interest is neglected. The vapor density ρ_g is less than 1 % of ρ_f, so it is neglected in the calculation of δ.

The local heat flux $q(x)$ to the wall of the tube is given by

$$q(x) = \frac{k(T_{\text{sat}} - T_{\text{w}})}{\delta} = \left[\frac{k^3\rho_f(\rho_f - \rho_g)g h_{fg}}{4\mu}\right]^{1/4} (T_{\text{sat}} - T_{\text{w}})^{3/4} x^{-1/4}. \tag{7.9}$$

Inserting the numerical parameter values and the radius of the LCP tube of the ETS (3 mm) in this equation we obtain the following expression for the local heat transfer per meter through the wall of the tube:

$$q_m(z) = P_m(T_{\text{sat}} - T_{\text{w}})^{3/4}(z - L_{\text{tube}})^{-1/4}, \tag{7.10}$$

where for an ideal film $P_m = 163$ W/m. Note that both T_{sat} and T_w depend on z.

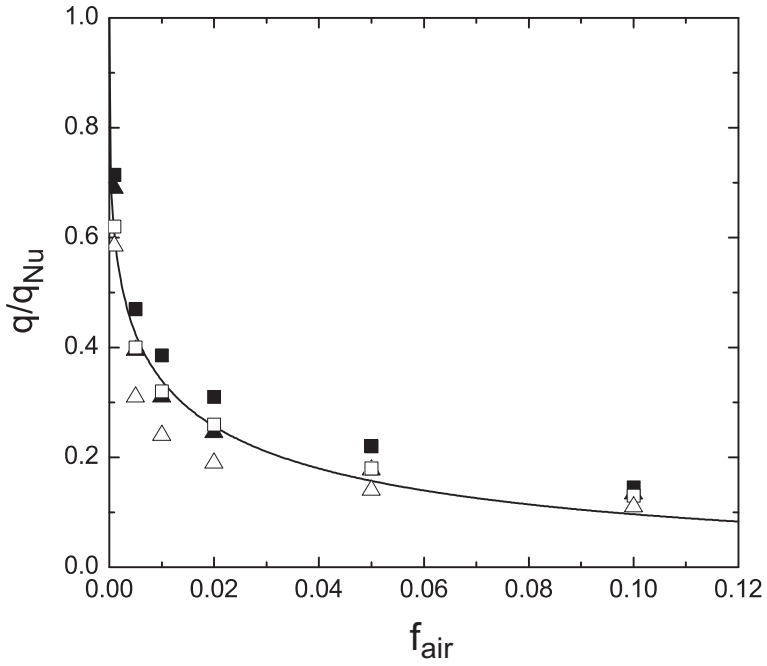

Figure 7.4: Reduction of the heat transfer from condensing steam by the presence of a certain fraction of air: $f_{\mathrm{air}} = \rho_{\mathrm{air}}/(\rho_{\mathrm{air}} + \rho_{\mathrm{vapor}})$ [137]. Black and open symbols denote the data for temperatures of 100 °C and 82 °C, respectively. Squares represent data for $T_{\mathrm{sat}} - T_w = 5\,^{\circ}\mathrm{C}$, triangles those for $T_{\mathrm{sat}} - T_w = 15\,^{\circ}\mathrm{C}$.

The presence of NCGs has been shown to reduce the heat transfer by condensation dramatically [89, 137–140]. Basically this is caused by the development of a layer with a large fraction of NCGs near the surface of the condensate, through which vapor molecules have to diffuse before they can condense. As an example, we have plotted the relevant data calculated by Minkowycz and Sparrow [137] in figure 7.4. The other cited studies yielded results which generally agree with these data within about 20 %. For computational purposes, we have approximated the data by an empirical curve. We chose an expression of the form

$$q/q_{Nu} = \exp(-C f_{air}^{1/3}), \tag{7.11}$$

with $f_{\mathrm{air}} = \rho_{\mathrm{air}}/(\rho_{\mathrm{air}} + \rho_{\mathrm{vapor}})$ and $C = 5$, since this simple expression nicely describes the very steep behavior for small air fractions. Various alternatives were found to be satisfactory as well, although computationally more expensive. The value of q'_m obtained by combining equations 7.10 and 7.11 is divided by the latent heat of condensation of water vapor and added as a sink term for ρ_v in equation 7.4.

Finally, we consider the temperature of the tubes depicted in figure 7.3. The time constant for heat transfer through the wall of the LCP tube to heat up its outer surface or the Al blocks can be estimated from

$$t_w = w^2 c_p \rho_w / \lambda, \tag{7.12}$$

where w $[m]$ is the wall thickness, c_p $[\mathrm{J\,K^{-1}kg^{-1}}]$ the heat capacity of the wall material, ρ_w $[\mathrm{kg}\,m^{-3}]$ the density, and λ $[\mathrm{W\,m^{-1}K^{-1}}]$ the heat conductivity of this material. Using typical values for the heat conductivity and heat capacity, the time constant for heat transfer through the wall appears to be in the order of 2 s. Since the relevant times in a sterilization process are two orders of magnitude larger, we simplified the problem by assuming a lumped circuit, where the heat capacity is concentrated on the outer side of the LCP tube. The temperature T_e of this outer side can be described by

$$\frac{\partial T_e}{\partial t} = \frac{k_{\mathrm{LCP},z} A_{\mathrm{LCP},z}}{C_{\mathrm{tot}}} \frac{\partial^2 T_e}{\partial^2 z} + q_m. \tag{7.13}$$

The term $k_{\mathrm{LCP},z}$ denotes the heat conductivity of the LCP tube in the axial direction and $A_{\mathrm{LCP},z}$ is its cross sectional area. C_{tot} represents the heat capacity per meter of the system (inner tube only for $z < (L_{\mathrm{tube}} - L_{\mathrm{block}})$ or both tubes for larger values of z), whereas the term q_m is the heat of condensation discussed above. The heat capacity of Al, which varies about 7 % in the temperature range of interest, was fitted by a second order polynomial.

The local value of the temperature T_{sat} was calculated from the partial air vapor pressure $p_v = p \times (\rho_v R_v)/(\rho_v R_v + \rho_g R_g)$ using the conversion equations given in [107]. The temperature of the inner wall T_w was eliminated from the calculations by combining equation 7.10 with the equation describing the heat transfer through the wall:

$$q_m = h_{\mathrm{LCP},r}(T_w - T_e), \tag{7.14}$$

where $h_{\mathrm{LCP},r}$ represents the heat transfer coefficient per meter in the radial direction.

Summarizing, the set of equations (7.2–7.6) together with the the boundary conditions (equation 7.7) and the sink term for ρ_v describes the flow of the vapor-air mixture in the ETS. The condensation is modeled by equation 7.10, 7.11 and 7.14. The temperature variation of the LCP tube and the Al blocks is modeled by equation 7.13, where the initial temperature is estimated from the experimental data. The resulting set of 3 second order PDE's is solved numerically using the standard `pdepe` routine of Matlab®. This routine solves initial-boundary value problems for parabolic elliptic PDE's in one dimension. The numerical solution was obtained at 150 equally spaced grid points along the LCP tube and for every 0.5 s up to 650 s.

7.4 Experimental

For the experiments a Lautenschläger type 3119/4STE test sterilizer (Cologne, Germany) with a volume of 340 L is used. Details of this sterilizer and its steam supply can be found in [134]. Figure 7.5 shows a typical result for a process during which hardly any None Condensible Gases (NCGs) were present in the sterilization chamber. The data presented in this figure indicate that the temperature of the aluminum blocks in the ETS gradually rises from about 25 °C at the start of the final inlet of steam ($t \approx 210$ s) to about 80 °C at the end of the sterilization phase ($t \approx 530$ s). The temperature increase of T3 (near the closed end of the LCP tube) is slightly smaller than that of T5 (more distant from the closed end).

The same process was repeated in the other experiments, but now a known volume of air was injected in the sterilizer chamber just before the final inlet of steam. This volume is calibrated as cm^3 at room temperature (295 K). For each air volume the experiment was repeated three times. From the reproducibility of these experiments the error is estimated to be about $0.01\,^{\circ}C\,s^{-1}$. The observed values of dT/dt for T3 and T5 are plotted in figure 7.6 versus the injected volume of air. Inspection of this figure shows that when no air is injected, the temperature of T3 and T5 increases at about the same rate at the start of the sterilization phase. When air is injected, the temperature increase of T3 drops significantly below that of T5, corroborating the entrapment of air near the closed end of the LCP tube of the ETS.

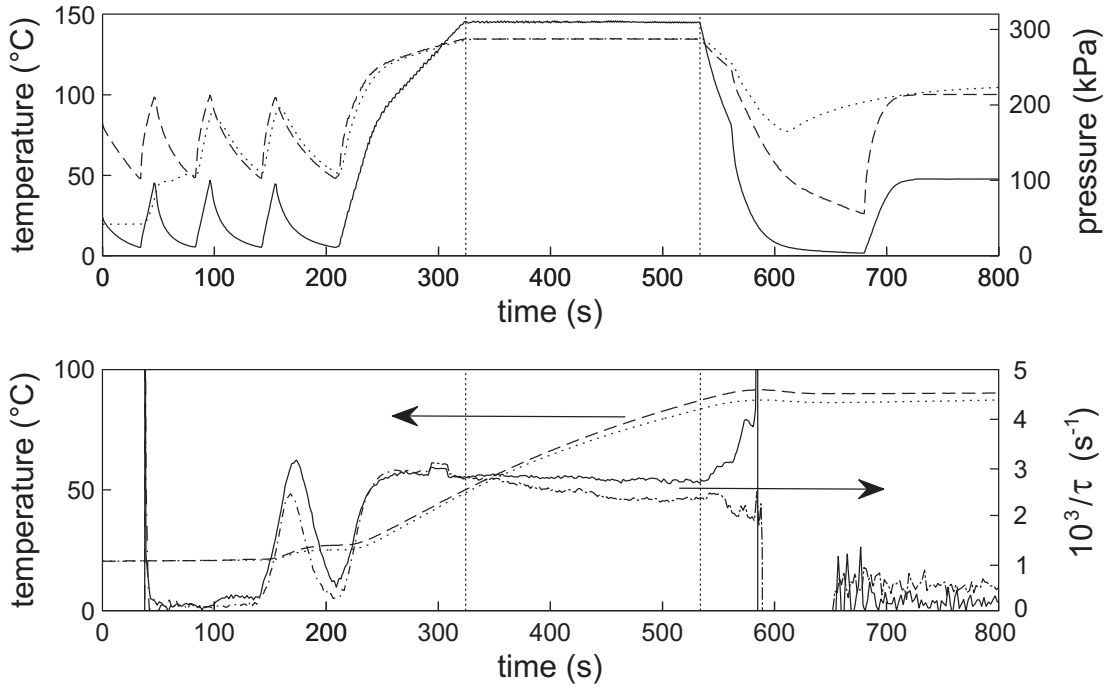

Figure 7.5: Example of data measured by an ETS during the experiments. In the upper plot the solid curve denotes the pressure and the dotted curve the temperature, both measured in the sterilizer chamber. The dashed curve denotes the so-called theoretical temperature, the temperature calculated from the pressure [72]. The start and end of the sterilization phase are denoted by vertical dotted lines. The lower plot shows the measured temperature of T3 and T5 (see figure 7.2), denoted by the dotted and dashed curves, respectively. From these temperatures an inverse time constant τ^{-1} is derived, which for each block i is equal to $(dT_i/dt)/(T_{\text{chamber}} - T_i)$. The behavior of these τ^{-1}-values is denoted by the dashed-dotted and solid curve for T3 and T5, respectively.

We like to note that the highest amount of injected air (about 900 cm^3) corresponds to a concentration of only about 0.25 % in the sterilizer chamber. Inspection of the data presented in figure 7.6 shows that in principle air fractions down to about 0.05 %, present during a sterilization process, can be clearly detected by an ETS.

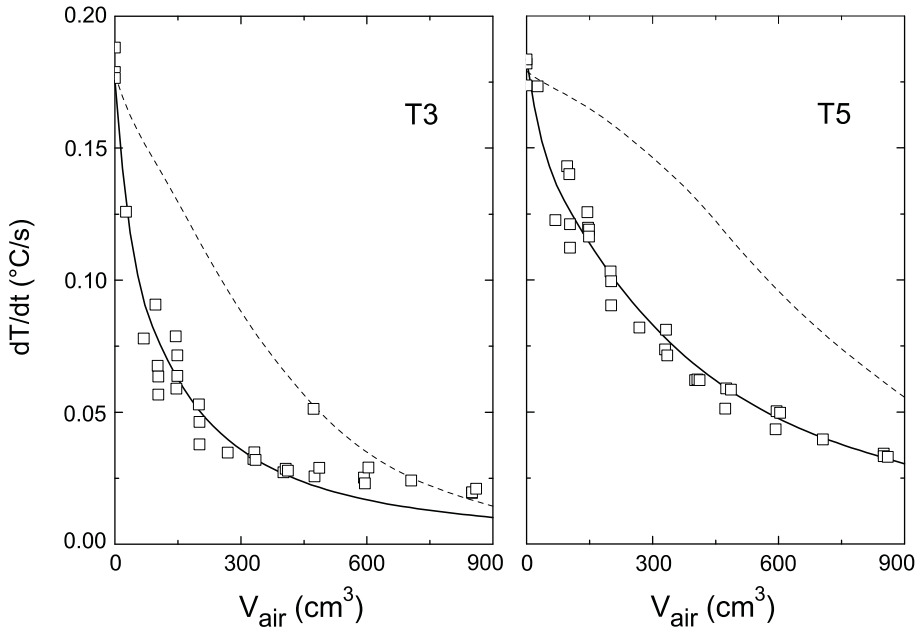

Figure 7.6: Temperature change per unit of time (dT/dt) at the positions of T3 and T5 of the ETS (see figure 7.2) as a function of the volume of air injected just before the final inlet of steam. The derivatives dT/dt are calculated at the start of the sterilization phase. The open squares denote the experimental data, the dashed and solid curves reflect the corresponding model predictions assuming ideal and non-ideal film condensation, respectively.

7.5 Results

Because the model outlined in section 7.3 describes a situation where uninterrupted condensation occurs at the inner wall of the LCP tube, it is used to calculate the behavior of the ETS during the period between the final steam inlet and the end of the sterilization period. During phase I of the process the sterilizer chamber is successively evacuated and pressurized with steam. We assume that the injected steam contains no residual air and that no condensation occurs in the sterilizer chamber. In that case the air fraction f_a just before the final inlet of steam is given by $f_a = (p_v/p_a)(p_v/p_s)^2$ if no additional air is injected (the pressures p_a, p_v and p_s are defined in figure 7.1). The total air density, together with the value of p_v and the temperature T_e at this moment, specify the initial situation.

The data presented in figure 7.5 show that without injection of air the aluminum blocks in the ETS are heated at a rate of on average $0.16\,^{\circ}\mathrm{C\,s^{-1}}$ between the start of the final steam inlet and the end of the sterilization phase. From the volume of the twelve Al blocks (4.5 $\mathrm{cm^3}$ per block) a heat capacity of about $130\,\mathrm{J\,K^{-1}}$ is found, and hence the heat supplied by the condensation of vapor is roughly 21 W over a length $L_{\mathrm{block}} = 0.093$ m. If we integrate equation 7.10 over the tube, we obtain a value $T_{\mathrm{sat}} - T_w \approx 0.6\,^{\circ}\mathrm{C}$ and a heat transfer coefficient of the LCP tube $h_{\mathrm{LCP},r} \approx 2\ \mathrm{W\,K^{-1}m^{-1}}$. This would imply that the difference between the wall and gas temperature is very small compared to the temperature drop across the wall of the LCP tube. In that case the heat transfer to the Al blocks would almost fully be determined by the heat conduction of the inner tube and changes in the

condensation process resulting from NCGs would be largely suppressed. The results for this situation are represented by the dashed curves in figure 7.6. Inspection of this figure shows that the qualitative characteristics of the experiments are described correctly, i.e. the decrease of dT/dt at increasing air fractions, which is much more pronounced for T3 than T5. It is obvious, however, that the experimentally observed decrease of dT/dt at small values of $V_{\rm air}$ is much larger than predicted by the model.

The LCP tube of the ETS can fairly accurately be described as a cylindrical channel with a diameter of 6 mm, centered in a square rod with transverse dimensions 8.2×8.2 mm^2. If we take the heat conductivity of a typical polymer, which is in the order of 0.5 W m^{-1}K^{-1}, we obtain an estimate $h_{{\rm LCP},r} \approx 9$ W K^{-1}m^{-1}, which is more than a factor of 4 higher than the value inferred above. Since the heat conductivity of LCP may be even higher, the description of the condensation process by ideal film condensation at the entire inner surface of the LCP tube is probably too much simplified. Actually, inspection of the inner wall of the tube revealed twelve equidistant milled ridges in the axial direction with a height of about 0.3 mm, which may give rise to preferential condensation on only a part of the surface. For this reason $h_{{\rm LCP},r}$ was chosen such that the best agreement with the experimental data was obtained, whereas P_m was adjusted such that for $V_{\rm air} = 0$ the value of dT/dt was equal to that observed in our experiments. It appeared that the value for $h_{{\rm LCP},r}$ is not very critical; the above estimate of 9 W K^{-1}m^{-1} resulting in a value $P_m = 7.2$ W m^{-1} was satisfactory. This value of P_m suggests that the actual condensation process is about a factor 20 less effective than ideal film condensation.

The heat conductivity $k_{{\rm LCP},z}$ of the LCP tube in the axial direction, defined in equation 7.13, can be used to optimize the difference in the behavior of T3 and T5. For larger values of $k_{{\rm LCP},z}$ the behavior of T3 and T5 becomes more similar, for smaller values the difference is largest. The best agreement with the experimental data was obtained for $k_{{\rm LCP},z} \approx 1.5$ W m^{-1}K^{-1}. This is somewhat larger than expected for a typical polymer, although not unrealistic for LCP. Apart from this, the heat conductivity in the axial direction may be enhanced by various contributions that are not included in the model. In this respect we like to note that the heat transfer via the air between adjacent Al blocks in the ETS (figure 7.2) already adds 50 % to the value calculated for the tube alone. The resulting behavior of dT/dt for T3 and T5 is represented by the solid curves in figure 7.6. Inspection of this figure shows that our model describes the data for both temperature sensors simultaneously within experimental inaccuracy, except for the data for T3 at high values of $V_{\rm air}$. We like to note, however, that by small readjustments of the two independent fitting parameters the deviations in this region can be reduced, at the cost of introducing a small error elsewhere.

7.6 Discussion

We have demonstrated experimentally that an instrument which has been proposed to assess the steam penetration during a steam sterilization process is very sensitive to even small concentrations of NCGs. Using a rather simple and straightforward physical model, the response of this instrument to additional volumes of air injected in the sterilizer chamber at the start of the final steam inlet can be described very well.

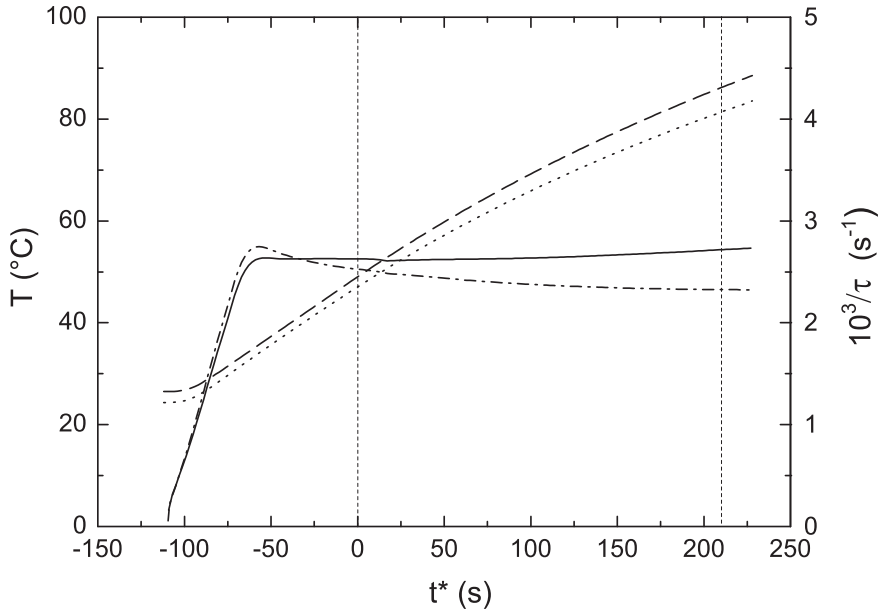

Figure 7.7: Calculated behavior of the temperature variation of T3 and T5 and the inverse relaxation times $\tau_i^{-1} = (dT_i/dt)/(T_{\text{chamber}} - T_i)$ for each block i for the situation corresponding to the experimental data presented in figure 7.5. The start and end of the sterilization phase are denoted by vertical dotted lines. The temperature variations of T3 and T5 are denoted by the dotted and dashed curves, respectively. The behavior of τ_i^{-1} is denoted by the dashed-dotted and solid curve for T3 and T5, respectively. The time t^* denotes the time with respect to the start of the sterilization phase.

As already discussed above, we have included the effect of the presence of NCGs on the condensation heat transfer by fitting an empirical curve to a set of numerical results reported in the literature (see figure 7.4). Inspection of this figure shows that the reduction of the heat transfer depends on both T_{sat} and T_w, the reduction being larger as T_{sat} or T_w decreases. In the temperature region of interest, these variations appear to have only a minor effect on the results of our model, in the sense that they can be largely compensated by small adjustments of the model parameters $h_{\text{LCP},r}$ and $k_{\text{LCP},z}$.

One of the simplifications of our model is the implicit assumption of a more or less stationary condensate film on the inner wall of the LPC tube in the ETS. This implies that condensation will occur as soon as $T_{\text{sat}} > T_{\text{wall}}$, which condition is already satisfied at a pressure of about 10 kPa during the final steam inlet, corresponding to about 2 s after the start. At that moment, however, no sufficient vapor has already entered the tube to create a condensate film as described by equation 7.8. Using the parameter values given in the preceding sections and assuming that all vapor flowing into the tube will condense, the time to create such a film can be estimated to range between 15 and 40 s. Since it is not known how the initial film formation in the LCP tube with its particular geometry occurs, we included this effect in first order by assuming that the parameter P_m in equation 7.10 grows linearly with time until the film has formed.

To illustrate the effect of this refinement, we will now consider not only the situation at the start of the sterilization phase, but use our model to calculate the behavior within

a larger time interval, covering the region of figure 7.5 from the start of the final steam inlet to the end of the sterilization phase. The variation of the temperature of T3 and T5 can be calculated straightforwardly. For the calculation of $\tau_i^{-1} = (dT_i/dt)/(T_{\text{chamber}} - T_i)$ for each block i we took the chamber temperature derived from the partial vapor pressure (equation 7.1) using the conversion equations given in [107]. This temperature is also referred to as theoretical temperature [51], which is given by the dashed curve in the upper part of figure 7.5. These calculations revealed that the behavior of τ^{-1} during the sterilization phase can be predicted reasonably well by the original model, but the predicted behavior just after the start of the final steam injection is too high by a factor of two. If we include a film formation time of 20 s, we obtain the temperature variation of T3 and T5 and the behavior of τ_i^{-1} plotted in figure 7.7. These results rather nicely agree with the data presented in figure 7.5. We like to note that the experimental data also reveal a time delay of about 20–30 s between the start of the final steam injection and the start of the temperature increase of the Al blocks. Although this agreement may be somewhat fortuitous, this time is comparable to that used to refine our model. The adjustment of P_m during the first 20 s appeared to have only a small effect on the results of our calculations of dT/dt plotted in figure 7.6.

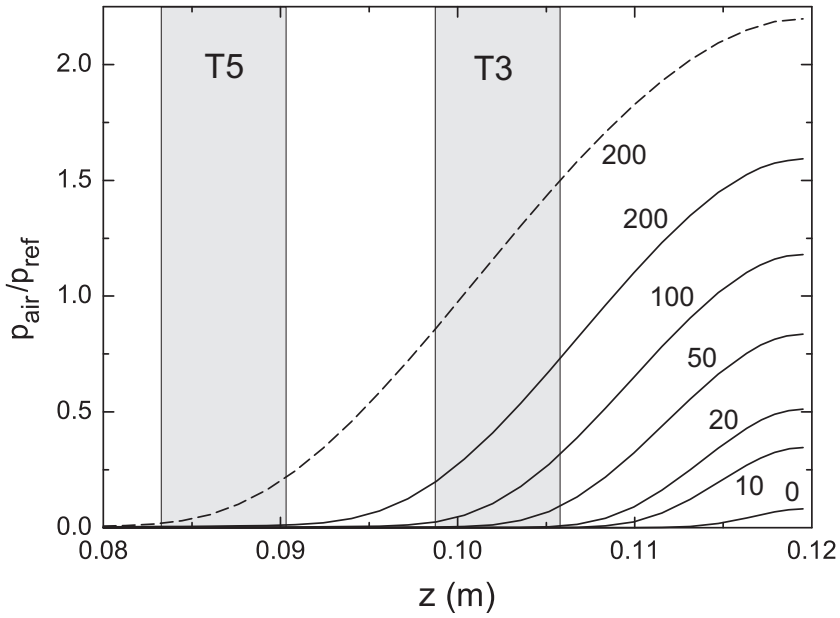

Figure 7.8: Partial air pressures normalized to $p_{\text{ref}} = 100$ kPa as a function of position in the inner channel of the LCP tube of the ETS. The pressures at the start of the sterilization phase are given by the solid curves, which are labeled according to the volume of additional air V_{air} injected in the sterilizer chamber. The dashed curve denotes the partial air pressure for $V_{\text{air}} = 200$ cm^3 at the end of the sterilization phase. The gray areas represent the position of the Al blocks T3 and T5. Note that only the upper part of the inner channel is depicted.

The high sensitivity of an ETS to the presence of NCGs in the sterilizer chamber results from the accumulation of air at the end of the LCP tube. This is illustrated very nicely by the calculated results plotted in figure 7.8. This figure also reveals that the accumulation of air continues during the sterilization phase. In our model it is assumed

that the fraction of air in the sterilizer chamber does not change from the start of the final steam inlet to the end of the sterilization phase, since the volume of the sterilizer chamber is about five orders of magnitude larger than that of the inner channel of the LCP tube. In principle this is correct, but the amount of air injected in the sterilizer chamber is limited and the ETS extracts much more air from the chamber than estimated from the volume of the LCP tube alone. From the data presented in the figure and the radius of the LCP tube it can be inferred that for an injected air volume of 200 cm^3 (at 100 kPa) roughly 1.4 cm^3 has been accumulated in the tube at the end of the sterilization phase, which will only have a minor effect on the model. From the figure it can also be deduced that changes of the positions of T3 and T5 have a large effect on the measured temperatures. In this respect one should note that our model assumes that the heat transfer by condensation is measured locally, whereas in reality it is averaged over the thickness of an individual Al block (7.1 mm). Possible errors resulting from this approximation are most likely compensated by the choice of the fitting parameters.

Both our experiments and model calculations reveal that the ETS is very sensitive to residual NCGs that are present in the sterilizer chamber before the final inlet of steam. If the values of τ^{-1} of T3 and T5 are significantly lower than their values in the absence of NCGs and τ_3^{-1} is substantially lower than τ_5^{-1}, the steam penetration in long hollow channels may be impaired significantly, as has been shown in [136]. The present model, however, can also be used to calculate the effect of small fractions NCGs that are present in the steam supplied to the sterilizer, which frequently occurs in practical situations. In such cases the values of τ^{-1} given by the ETS will also drop significantly, although the effect on steam penetration in hollow channels is much smaller or negligible, since the steam entering the channel is not blocked by air entrapped in the tube. This implies that measurements with an ETS do not give unambiguous information on the steam penetration in this type of loads, and should be supplemented with additional data on, for instance, the steam quality. Nevertheless, the present study shows that the ETS very likely represents a worst case scenario for steam penetration.

Chapter 8

Finite Volume Modeling of steam penetration during sterilization processes

8.1 Introduction

In chapter 6 steam penetration in a narrow channel during a generic sterilization process is discussed. The behavior of the air-vapor mixture is described by a quasi one-dimensional model, in which condensation is neglected. In chapter 7 a largely similar system with uninterrupted condensation is modeled. Obviously these two models describe extreme cases. In daily practice many items, such as channeled surgical instruments, will have a behavior in between these two extreme cases and both condensation and evaporation may occur on the surfaces of these items. In a model of steam sterilization of these items it necessary to calculate the pressure, temperature, the gas composition and the amount of condensate at all locations of the system at any time during a sterilization process. These aspects increase the complexity of the model, because during such a process condensate may be changing its location, for example by gas flows over the condensate and by gravitational forces. To be able to locate the condensate and to describe the behavior of the air-vapor mixture in the radial direction of a channel a model has to comprise at least two dimensions but preferably three. Recently, a project is started to develop a model that finally should include all these aspects. In this chapter the first developments within this project are presented: air and vapor transport in a non-isothermal, two-dimensional space, steady state system, including a condensation and evaporation mechanism.

Obviously, the system cannot be solved analytically. Consequently, a numerical method and software application have to be used. We have not been able to identify a software application that appreciates all the aspects necessary to model the steam penetration in narrow channels during a steam sterilization process. An application that already includes several of the aspects of the problem and provides a platform to implement the missing aspects is the software application Plasimo [141, 142]. Another advantage of this Finite Volume Method (FVM) based application is that possibilities for extending the model to other sterilization methods, such as ethylene oxide and even plasma, are possible as well.

In section 8.2 the definitions, governing equations, boundary conditions and initial conditions which describe the condensation and evaporation will be introduced. In section 8.3 the used numerical software application Plasimo is discussed briefly. In section 8.4 some preliminary results are presented. A discussion of the current developments and an outlook is given in section 8.5.

8.2 Governing equations

In steam sterilization processes different gases, such as water vapor, nitrogen and oxygen are present and, consequently, the situation has to be described by a multicomponent system. In the model the Stefan-Maxwell equation is used to calculate the diffusion velocities of the various components. To calculate the bulk flow properties, the Navier Stokes equation is used. These two equations, together with the heat balance equation, are used to calculate the composition of the gas, velocity, pressure and temperature. On the surfaces of solid matter condensation and evaporation can take place. The Hertz-Knudsen equation is used to describe this process. When the mass flux of water vapor during the condensation and evaporation processes is known the gas composition can be calculated, but the release of latent heat also has a thermal effect. Clearly, all equations are coupled. In this section first the used definitions are given. Next, the conservation of mass, momentum and energy is discussed, followed by the boundary conditions and initial conditions. Much of the derivations and considerations in this section are based on the work and thesis of Beks-Peerenboom [141, 143–145].

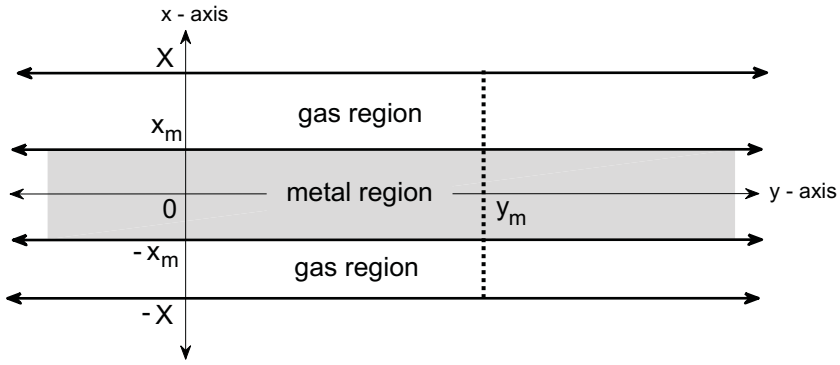

Figure 8.1: A metal plate in a gas region. The z-axis is oriented perpendicular to the surface. Both the y- and z-axis extend into infinity and are symmetry axes. The metal region extends from $0 \leq x \leq x_m$ and the gas region from $x_m < x \leq X$. The origin (0,0,0) is the symmetry point.

8.2.1 Definitions

In a gas region, e.g., the region between x_m and X in figure 8.1, the mass density of gas component i can be expressed as

$$\rho_i = m_i n_i, \tag{8.1}$$

in which m_i represents the mass of particles of gas component i, and n_i the number density of this gas component. The total mass density in the gas region is equal to the sum of the mass densities of the individual components,

$$\rho = \sum_i \rho_i. \tag{8.2}$$

The mass fraction of component i is defined as

$$y_i = \frac{\rho_i}{\rho}. \tag{8.3}$$

Hence, by definition the mass fractions sum up to unity,

$$\sum_i y_i = 1. \tag{8.4}$$

Equations 8.2, 8.3 and 8.4 show that the composition can be expressed in number densities, mass densities or mass fractions.

Over the gas region the mass averaged or barycentric velocity field ($\vec{v}$) is defined as

$$\vec{v} = \sum_i y_i \vec{u}_i, \tag{8.5}$$

where $\vec{u}_i$ is the averaged velocity of particles of component i. For each component, the diffusion velocity ($\vec{v}_i$) is defined as the velocity of that component relative to the mass average velocity,

$$\vec{v}_i \equiv \vec{u}_i - \vec{v}. \tag{8.6}$$

From the definition of the mass averaged velocity field it follows that

$$\sum_i y_i \vec{v}_i = \sum_i y_i \vec{u}_i - \sum_i y_i \vec{v} = 0. \tag{8.7}$$

Further on in this chapter this equation will be used as a constraint to solve the set of the Stefan-Maxwell equations.

Dalton's law describes that the sum of the partial pressures yields the total pressure

$$p = \sum_i p_i. \tag{8.8}$$

In the pressure range (0 to 350 kPa) and temperature range (0 to 150 °C) of steam sterilization processes the various components can be described as ideal gases [72]

$$p_i = n_i k_b T, \tag{8.9}$$

with k_b Boltzmann's constant (1.3807×10^{-23} J/K).

8.2.2 Conservation of mass

Mass conservation on the component level can be described by the continuity equation [128, 141]

$$\frac{\partial \rho_i}{\partial t} + \nabla \cdot \rho_i \vec{u}_i = m_i S_i, \tag{8.10}$$

where S_i is the production rate of the i-th component per unit volume. It is assumed that no condensation and no gas production will occur in the gas region, which simplifies this mass conservation equation to

$$\frac{\partial \rho_i}{\partial t} + \nabla \cdot \rho_i \vec{u}_i = 0. \tag{8.11}$$

Summation of all components in a gas region yields the mass continuity equation

$$\frac{\partial \rho}{\partial t} + \nabla \cdot \rho \vec{u} = 0. \tag{8.12}$$

8.2.3 Conservation of momentum

The conservation of momentum is described by the Navier Stokes equation [128]

$$\frac{\partial \rho \vec{u}}{\partial t} + \nabla \cdot (\rho \vec{u} \vec{u}) = -\nabla p + \nabla \cdot \bar{\bar{\pi}} - \rho \vec{g}. \tag{8.13}$$

On the left hand side of the equation the first term describes the increase of momentum per unit volume and the second term the rate of momentum addition by convection per unit volume. The right hand side represents the pressure gradient, the viscosity terms and the gravitational force. The first term describes the force exerted by the pressure on the control volume and the second term is the viscous force on the control volume. The tensor $\bar{\bar{\pi}}$ represents the Stokes viscous stress tensor ([128], page 81 and appendix B). In the system considered here the gases are assumed to act as Newtonian fluids. This makes it possible to write the term $\nabla \cdot \bar{\bar{\pi}}$ in equation 8.13 as $\mu \nabla^2 \vec{u}$, with μ the dynamic viscosity (Pa s).

In the gas region the Stefan-Maxwell equations are used to calculate the velocity of the components relative to the mass averaged velocity

$$\vec{d_i} = \sum_j f_{ij} (\vec{v_i} - \vec{v_j}). \tag{8.14}$$

In this equation $\vec{d_i}$ represent the *diffusion driving forces* (m^{-1}) and f_{ij} the *friction* ($\mathrm{s\,m}^{-2}$) of particles j on particle i. As already mentioned above, equation 8.7 is used as a constraint to solve this set of equations.

The barycentric flow field ($\vec{u}$) is calculated in conjunction with the pressure from the Navier Stokes equation and the continuity equation (equation 8.12). Additionally, the total mass averaged velocity is calculated. For the Navier Stokes equation the total mass density is not altered and used as input.

8.2.4 Conservation of energy

For the complete system, gas region and solids, the conservation of energy can be written in terms of the component's specific enthalpy h_i ($\mathrm{J\,kg}^{-1}$) [141]

$$\frac{\partial}{\partial t} (\rho y_i h_i) + \nabla \cdot (\rho \vec{v} y_i h_i) + \nabla \cdot \vec{q_i} + \bar{\bar{\pi}}_i : \nabla \vec{v} - \vec{v} \cdot \nabla p_i = Q_i. \tag{8.15}$$

In this equation $\vec{q_i}$ ($\mathrm{J\,m}^{-2}\mathrm{s}^{-1}$) is the conductive heat flux of component i and Q_i ($\mathrm{J\,m}^{-3}\mathrm{s}^{-1}$) the heat source of that component. If it is assumed that the specific heat of each component is constant over the applied temperature domain its specific enthalpy can be written as

$$h_i = h_i^0 + c_{p,i} T, \tag{8.16}$$

with h_i^0 the specific enthalpy ($\mathrm{J\,kg}^{-1}$) at a reference temperature T_0 (K), $c_{p,i}$ the specific heat of the i-th component ($\mathrm{J\,kg}^{-1}\mathrm{K}^{-1}$) and T the actual temperature. In case it is

assumed that $c_{p,i}$ is not a constant, a more accurate relation for $c_{p,i}(T)$ could be implemented. All components have locally the same temperature. A single energy balance is solved for the mixture. Summation over the component heat balance equations results in

$$\frac{\partial}{\partial t}\left(\sum_i \rho y_i h_i\right) + \nabla \cdot \left(\sum_i \rho \vec{v} y_i h_i\right) = -\nabla \cdot \vec{q} - \bar{\bar{\pi}} : \nabla \vec{v} + \vec{v} \cdot \nabla p + Q, \tag{8.17}$$

where $\vec{q}$ is the heat flux caused by conduction and Q an energy source. Substitution of equation 8.16 in this equation and using the continuity equation 8.12 and Fourier's law of heat conduction ($\vec{q} = \lambda \nabla T$, with λ the thermal conductivity ($\mathrm{Wm^{-1}K^{-1}}$) [128]), yields

$$\frac{\partial}{\partial t}\rho\, c_p T + \nabla \cdot \vec{v}\, c_p T - \nabla \cdot (\lambda\, \nabla T) = -\bar{\bar{\pi}} : \nabla \vec{v} + \vec{v} \cdot \nabla p + Q. \tag{8.18}$$

In this equation we have introduced $c_p = \sum_i y_i c_{p,i}$.

8.2.5 Boundary and initial conditions

In steam sterilization processes devices are positioned in a gas region as schematically illustrated in figure 8.1. To obtain a solution of the equations given above boundary conditions and initial conditions have to be imposed. They include the gas composition, pressure, velocity, and temperature. Both sets of conditions are addressed in this section.

Gas composition

At the open boundary of the system, the *inlet*, the gas composition is imposed. The relevant gases present are water vapor (H_2O), nitrogen (N_2), and oxygen (O_2). The constant values of these components are imposed as Dirichlet conditions, e.g., 0.8 % N_2, 0.2 % O_2, and 99.0 % H_2O. Because of the symmetry of the problem, the gas conditions are identical in adjacent gas regions (at $y = 0$ and $y = y_m$ in figure 8.2) and the flux in the y-direction will be zero. At the interface between the solid material and the gas region condensation and evaporation may occur. As a first approximation, the evaporation and condensation are described with the Hertz-Knudsen relation [146]

$$\Gamma_s = S_{cond} - S_{evap} = \frac{p^* - p_s}{\sqrt{2\pi m\, k_b T}}, \tag{8.19}$$

in which Γ_s represents the net condensation rate per unit of area and time, S_{evap} the evaporation source and S_{cond} the condensation source, p^* the partial pressure of the water vapor, and p_s the saturation pressure of water at the temperature T. The water vapor flux resulting from condensation and evaporation will change the gas composition in the gas region and with that also the velocity of the components in the gas region.

We like to note that many subtle features of the actual condensation-evaporation process are not included in equation 8.19. Among these are the temperature variation in the condensate film and the temperature step at the liquid-vapor interface [147]. In a later stage, these effects may be accounted for empirically by using the Hertz-Knudsen-Schrage relation [148] or by using results from, e.g., statistical rate theory [149].

Pressure and velocity

The boundary conditions for pressure and velocity are coupled. Patankar [150] distinguishes two possibilities:

- The pressure is specified on the boundaries: a Dirichlet condition. In that case, the derivative of the velocity is set to zero. The gas can only flow perpendicular through a surface, e.g., the inlet.
- The normal velocity (or its normal derivative) is specified: the pressure equation does not depend on the boundary pressure. In this case the boundary pressure is set using interpolation ('second-order Neumann').

For tangential velocity components, Dirichlet conditions can be used at walls (no-slip) and at the inlets (forward flow). On symmetry boundaries homogeneous Neumann conditions can be used.

On solid walls, the normal mass flux is dictated by the rate at which mass is transferred to the boundary. In the present case, the normal mass flux $\rho\vec{v}\cdot\vec{n}$ is dictated by the net condensation rate, as expressed by equation 8.19. This yields

$$\rho\vec{v}\cdot\vec{n} = m_{water}\Gamma_s \Rightarrow \vec{v}\cdot\vec{n} = m_{water}\Gamma_s\rho^{-1}. \tag{8.20}$$

As such, the component equations (H_2O vapor flux towards the wall) dictate the mass flux and hence the bulk velocity at the wall.

Temperature

Also for the temperature two different boundary conditions can be distinguished:

- A temperature is specified on the boundaries: a Dirichlet condition. In that case, we impose a constant value for the temperature on the boundary, e.g. the inlet.
- Boundaries where similar conditions continue in adjacent regions, e.g., a symmetry axis. In this case, Neumann conditions are imposed for the temperature.

When water vapor condenses on a solid material the latent heat of water vapor will be immediately released to the surface. Vice versa, if evaporation occurs heat will be extracted from the solid material. Using the flux of water vapor described by the Hertz-Knudsen (equation 8.19), the volumetric amount of latent heat (Φ in $\mathrm{J\,m^{-2}s^{-1}}$) can be quantified as

$$\Phi = h_{fg}m_s\Gamma_s, \tag{8.21}$$

in which h_{fg} represents the specific latent heat of water vapor ($\mathrm{J\,kg^{-1}}$) and m_s the net mass of water condensing on the wall. Consequently, the component boundary conditions result in a heat source term in the *interior* of the temperature calculation domain.

The properties and dynamics of the condensate film itself have not yet been included in the model. A condensing water vapor molecule is assumed to leave the gas region and to transfer its latent heat directly to the metal wall (see equation 8.21). This leads to a

decrease of the enthalpy in the gas region by an amount $m_s h_{water}$. Apart from this, the effect of the condensate film on the geometry of the gas region is neglected, since in the relevant practical situations the thickness of the film is more than two orders of magnitude smaller than, e.g., the diameter of the channel in which the gas mixture is present.

Initial conditions

At the start of a calculation the initial conditions of the system have to be defined. For the gas region these include the temperature, pressure, and gas composition. For the solid material these include only the temperature.

8.3 Plasimo

Since the set of equations that govern the system under study cannot be solved analytically, numerical simulations have been performed. As mentioned above the Plasimo modeling toolkit [141, 142] or software application was selected. This application has originally been developed for the simulation of plasma sources and was extended to be able to model neutral gas mixtures as well. For further and future developments it is necessary that the application can be extended with missing aspects, e.g, the behavior of condensate on the surfaces of the solid material and condensation in the gas region. Plasimo offers these possibilities.

Plasimo uses the Control Volume Method, as shown in figure 8.2. It also uses the Gummel iteration method [141, 142]. This means that in an iteration the equations for all quantities are solved consecutively, and iteration continues until the final solution is obtained. In Plasimo, first the temperature field is updated, next the flow variables p and $\vec{v}$ are calculated with the help of the SIMPLE algorithm, and finally the composition is adjusted. For more information we refer to the Plasimo review paper [142].

8.4 Some preliminary results for steam

8.4.1 Metal plate

In a stationary system a metal plate is positioned in a gas region (figure 8.1). The z-axis of the plate is the symmetry axis. Both the y- and z-axis extend to infinity. To calculate a solution a grid is defined in Plasimo (figure 8.2). The metal plate has dimensions $0 < x < 0.07$ m and the gas region $0.07 < x < 0.15$ m. At $x = 0$ the symmetry axis is located and at $x = 0.07$ m the interface between the metal plate and the gas region is present. Initially the temperature of the complete system is 20 °C (293.16 K) with a pressure of 202.07 kPa. In the gas region initially the composition of the gas expressed in fractions is 0.79 nitrogen (N_2), 0.20 oxygen (O_2) and 0.01 water vapor (H_2O). At the inlet boundary ($x = 0.15$ m) three different gas compositions are imposed at 373.16 K (100 °C) and 202.07 kPa. The respective gases are a gas saturated with water vapor, a gas with 5 % over saturation of water vapor, and a gas with 5 % under saturation (see table 8.1).

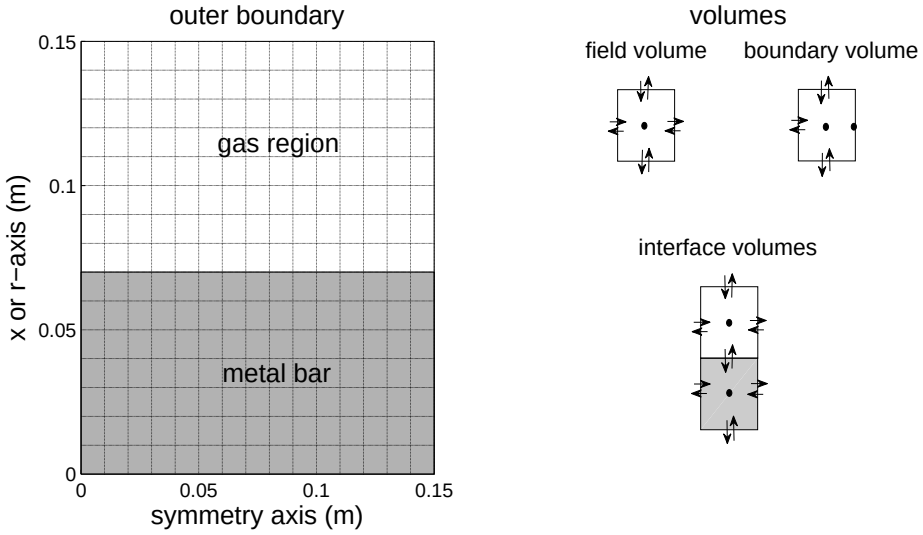

Figure 8.2: At the left the grid of the system representing a metal plate in steam is depicted. Each square represents a volume of the grid. The geometry of the system is similar to that given in figure 8.1. At the right the basic volumes of the grid are depicted. The solid dot in the center of the volumes represent the nodal point in which the scalars, such as pressure, temperature and composition, are calculated. The double arrows are the locations where the fluxes such as energy and velocity components are calculated. In a *field volume* only one nodal point is present, whereas in a *boundary volume* a second nodal point at a boundary of that volume can be present. In this point also the boundary conditions are imposed. In the *interface volumes* the most interesting aspect is the flux between the gas region and the metal, because obviously no gases can flow through the interface.

The steady state solutions for these different gas compositions are presented in figure 8.3. Inspection of this figure shows that when the gas is saturated with water vapor the complete system stabilizes at the temperature imposed on the inlet. In case of a gas with over saturation of water vapor the temperature of the metal plate increases to temperatures higher than the gas temperature imposed on the inlet boundary. This occurs because the water vapor will condense until the saturated water vapor pressure equals the imposed partial vapor pressure (see equation 8.19). As long as condensation occurs to reach equilibrium, heat is transported to the metal (equation 8.21) and the temperature will continue to increase. In practice, however, the plate will not reach a temperature higher than that imposed at the inlet. When over saturation of water vapor would be present (see figure 4.1), condensation would already take place in the volume of the gas

	components (moleculair fractions)		
	water vapor (H_2O)	nitrogen (N_2)	oxygen (O_2)
5 % over saturated	0.55	0.36	0.09
saturated	0.50	0.40	0.10
5 % under saturated	0.45	0.44	0.11

Table 8.1: Gas composition in fractions used in the calculations at 373.16 K and 202.07 kPa.

region until the saturation pressure is established. As already mentioned above, in the present model this volume condensation is not implemented.

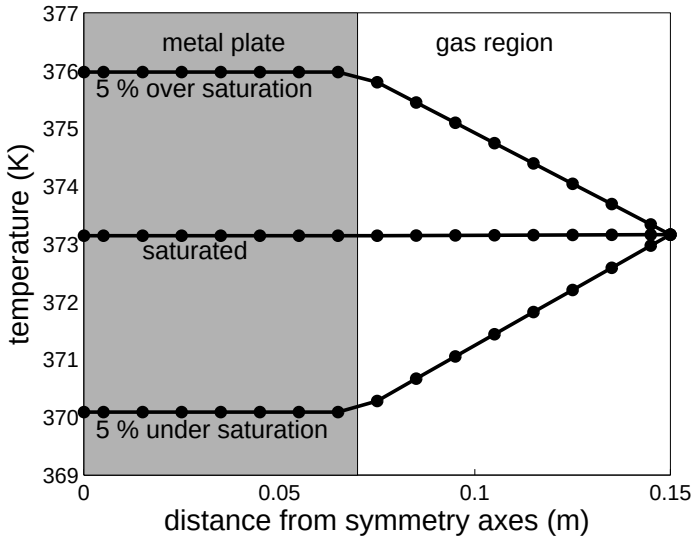

Figure 8.3: Steady state solution of the system presented in figure 8.2 with an initial temperature of 293.16 K and boundary conditions on the open boundaries at $x = 0.15\,\mathrm{m}$ given by $T = 373.16\,\mathrm{K}$ and a pressure of 202.07 kPa. On the inlet boundary ($x = 0.15\,\mathrm{m}$) different gas mixes are imposed with over-, under- and saturated with water vapor as tabulated in table 8.1. The black dots in the curves represent the grid at which the temperature is calculated (figure 8.2).

In case of an under saturated water vapor the results show that the temperature of the metal will not reach the temperature imposed at the inlet boundary (figure 8.3). This occurs because water will evaporate from the surface until the saturation pressure of the water vapor equals the partial vapor pressure in the gas region. The energy needed to evaporate the water is retrieved from the metal. Consequently, the temperature of the metal will decrease. Also this situation cannot occur in practice. Evaporation is only possible as long as condense is present on the wall. In the present model, the amount of condense available for evaporation is not yet limited

When no water vapor is present the metal block will only be heated up or cooled down via Fourier heat conduction. In practice the complete system will reach the temperature imposed at the inlet.

8.4.2 Cylindrical bar with an open channel

In previous chapters (chapters 6 and 7) cylindrical systems and channels were considered because of the similarity of the shape with channels in medical devices. The behavior was described in terms of quasi one-dimensional systems. Plasimo has the possibilities to use cylindrical coordinates, which enables a description of the channel by two spatial coordinates. Extension to more general three-dimensional systems is also possible. To illustrate some possibilities of the current model, calculations of the gas distributions are

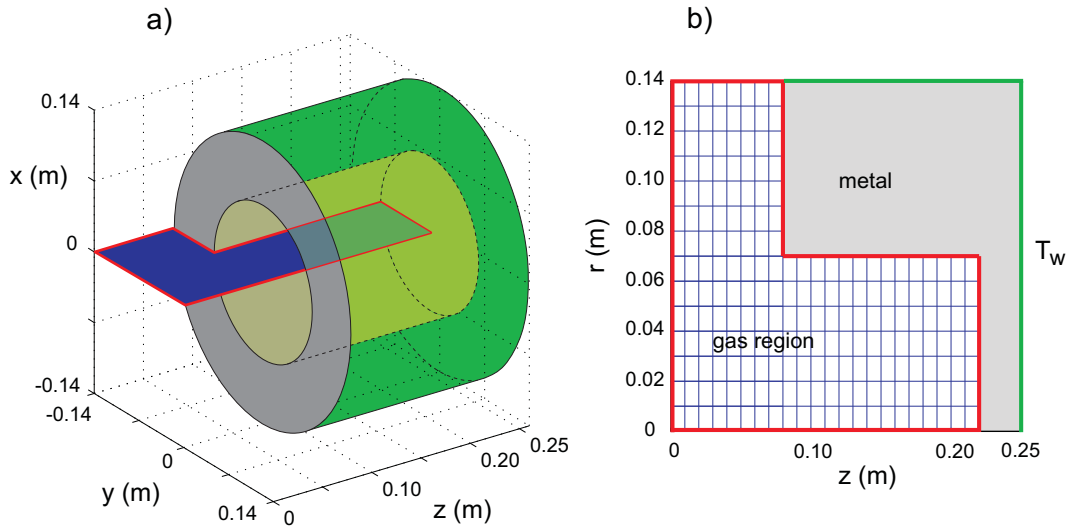

Figure 8.4: Geometry of the cylindrical metal bar with a channel that is open at one end. The blue rectangle represents the grid used for calculation and is given in more detail in figure b. The gas distribution is calculated within the red region.

presented for a cylindrical metal bar with a channel which is open at one side. The bar has a diameter of 0.14 m and a length of 0.17 m. Along its symmetry axis a cylindrical channel is present with a radius of 0.14 m and a length of 0.14 m. The geometry of the system is illustrated in figure 8.4. The open end side of the bar is exposed to a gas mixture. Initially the gas composition in the gas region is similar to the gas used in the previous section: 0.79 N_2, 0.20 O_2 and 0.01 H_2O at 293.16 K and 347 kPa. On the inlet the same pressure is imposed and the gas consists of 0.08 N_2, 0.02 O_2 and 0.90 H_2O at 408.16 K. In the two cases discussed here the variations are limited to changes of the boundary temperature T_w of the outer wall of the cylinder (the green boundary in figure 8.4b). The imposed temperatures are $T_w = 293.16$ K and $T_w = 393.16$ K.

The results of the model calculations reveal large differences in the distribution of the water vapor and the non condensible gases (NCGs, N_2 and O_2) between the cases with $T_w = 293.16$ K and $T_w = 393.16$ K. At $T_w = 293.16$ K the water vapor hardly penetrates the channel. A closer inspection of this situation reveals that in the gas region close to the metal surface at the open end of the cylinder low concentrations of water vapor and high concentrations of NCGs are present. The calculations also show that for $T_w = 293.16$ K the velocities towards the metal surface are higher by up to a factor 2 in the axial direction and up to a factor 1.5 in the radial direction than the corresponding velocities for $T_w = 393.16$ K.

These observations can be explained by the fast condensation of water vapor that occurs for $T_w = 293.16$ K. A lower wall temperature will induce a faster condensation, as predicted by the Hertz-Knudsen equation (8.19). Compared to $T_w = 393.16$ K relatively high water vapor velocities towards the cold metal surface will be established. At the same time NCGs present near the metal surfaces cannot diffuse to locations with lower NCG concentrations because the diffusion velocity is lower than the flow velocity of the gas in the direction of the metal wall. Because of the continuous relatively fast water

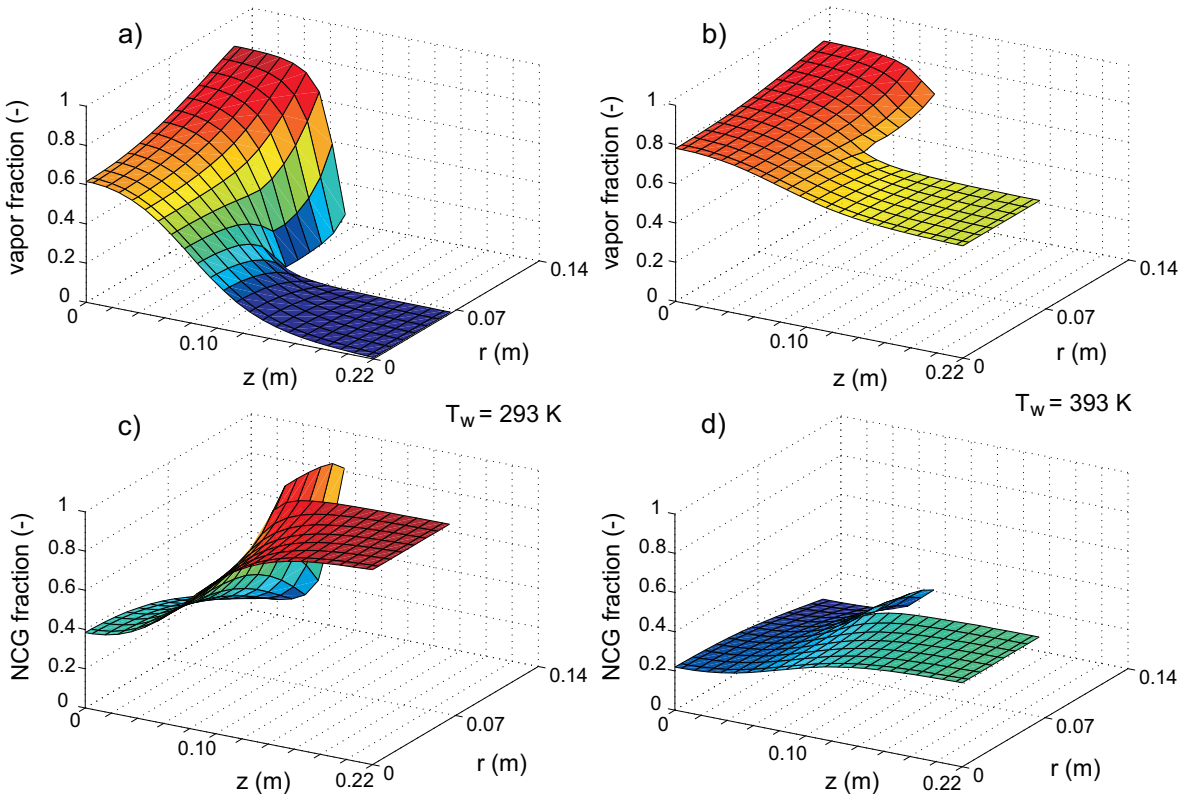

Figure 8.5: Gas distribution within the metal cylinder depicted in figure 8.4. For the calculations all conditions were kept the same except the temperature on the outside boundary of the metal cylinder (T_w). In the figures a) and c) results are presented for $T_w = 293$ K, in the figures b) and d) those for $T_w = 393$ K.

vapor flow to the metal wall hardly any water vapor will diffuse and penetrate into the channel. For $T_w = 393.16$ K the condensation velocity is lower and, consequently, the gas velocities are lower and the water vapor is able to diffuse through the entire gas region including the channel in the metal bar.

8.5 Discussion and outlook

The recently started developments to model surface steam sterilization and steam penetration in steam sterilization processes already comprise a non-isothermal system and a mechanism for condensation and evaporation. Among the possible extensions of the model we specifically mention three-dimensional configurations, time dependent situations, a more refined description of the condensation and evaporation process, some kind of bookkeeping of the amount of condensate, and a mechanism for condensation in the gas region in case of over saturated steam.

Extension to three dimensions is basically already possible but is judged not very useful as long as the condensation and evaporation mechanisms are not addressed adequately. As soon as the time dependence has been implemented, the results of the application can be compared with the results presented in chapters 6 and 7.

Presently, the condensation and evaporation of water is described by the Hertz-Knudsen equation. As already indicated above, a next step might be to refine the model by using the Hertz-Knudsen-Schrage relation [148]. However, the estimates for the coefficients in this equation reported in the literature differ by about two orders of magnitude. In our opinion, computations and experiments on simple, carefully chosen model systems can be used to obtain appropriate values for these coefficients. Next, it might be useful to include the properties and dynamics of the liquid film itself in an empirical way.

If the suggested improvements would be implemented, the model and application could be used to describe steam conditions on surfaces of items in steam sterilization processes. This includes surfaces of channels in items such as medical devices. The results can be compared with values reported in the literature to judge if steam sterilization conditions are actually met (section 2.1 and 2.2).

The software application has a fully modular structure, which gives the possibility to extend the application to other sterilization methods, like ethylene oxide, formaldehyde, hydrogen peroxide, and even plasma sterilization. On the other hand, if an adequate model for condensation and evaporation would be implemented the model could, for example, also be used to model energy transport by steam in heat exchangers used in power plants.

Chapter 9

Discussion and outlook

Sterilization is recognized as an essential part of infection prevention (chapter 1 and 2). In the future, it may become even more essential, because more resistant microorganisms are developing and medicines may not be effective to cure contaminations anymore [151–153]. To develop adequate methods for infection prevention, a fundamental understanding of infection prevention is essential. Because surface steam sterilization is a part of infection prevention and is the most frequently applied sterilization method worldwide, a fundamental understanding of surface steam sterilization is a necessity. Chapter 3 shows that standards for steam sterilization defining the minimum requirements are not always appreciated by hospitals. This raises the question whether the professionals in the field have sufficient knowledge about the steam sterilization process.

Steam sterilization involves two main disciplines; microbiology and physics. Concerning the microbiology, the only useful data set found for steam sterilization is already more than half a century old [31]. The specified time-temperature relations derived from this data set assume that saturated steam is present and contain safety margins that are not justified by experimental data (table 2.1). With the present microbiological knowledge and equipment it may be possible to find a more complete and reliable relation for killing viable organisms based on the degree of humidity, temperature and time. Until the moment that such an improved relation is established the current temperature-time combinations with saturated steam (100 % absolute humidity) have to be respected.

Concerning the physics, the chapters 4 and 5 conclusively show that the current knowledge of surface steam sterilization needs some adjustments. In chapter 4 it is shown that with the currently accepted inaccuracies of the measurements [51] it cannot be ensured that sterilization conditions are satisfied. Various improvements of the relevant procedures and standards are suggested. Chapter 5 shows the limitations of the current F-value theory and contains a suggestion to adjust this theory in a way that extends its applicability to a larger temperature domain. For disinfection processes a similar theory is currently applied, the so called A_0-theory. Also the limitations of this theory can be investigated in a similar way.

In the chapters 6, 7 and 8 it is demonstrated that steam penetration in narrow channels during steam sterilization processes is not trivial. Before roughly 1990 this was no serious problem, because loads to be sterilized consisted mainly of textiles and non-hollow instruments. Since that time, however, complex instruments for Minimal Invasive Surgery, which may contain narrow channels, and other systems with narrow channels are more frequently present. A detailed understanding of steam penetration in these instruments becomes important. The studies presented in these chapters may contribute to such a development. These chapters also show that direct measurements of temperature and pressure alone are not sufficient to ensure that steam sterilization conditions are actually

present in case of complex loads. It appears that also the degree of steam saturation (or the amount of non-condensible gases) has to be determined.

Given the fact that direct measurements of the steam penetration in narrow channels are very complicated, physical models which are able to predict the sterilization conditions in such systems are very useful. Two models presented in this thesis can already be used in developments of channeled surgical instruments, process challenge devices, and steam sterilization processes. Further development of these models can extend their applicability to, for example, other sterilization processes and washing and cleaning processes in health care and food industry. Also in the designing phase of medical instruments and decontamination equipment these models can be used to predict whether the specified sterilization criteria can be reached with a given process or in which way the process should be adapted.

Overall it may concluded that the results of the studies described in this thesis can be used to improve the safety of decontamination processes of medical instruments, which reduces patient discomfort and, at the same time, costs.

Appendices

A.1 Impact of studies

Shortly before the study reported in chapter 3 became available in the public domain a reporter from a daily newspaper picked up this paper [104]. This resulted in a front page article with the head line 'unnecessary danger for infection' [154][1] on Saturday, January 8, 2005. The inspection body in the Netherlands reacted in this newspaper article as follows: 'It is quite possible that 60 % of the sterilizers do not meet the European standards. But that does not mean that the cleaned instruments swarm of pathogens that have survived the whole process. Usually they do not, not even with a sterilizer that does not fully meet the standards'.[2] This publication unleashed a series of publications in virtually all Dutch daily newspapers and many in Belgium. Also national and regional radio stations reported on this topic. A letter [155] referring to this paper was sent to the editor, pointing out that standards [95, 97, 98] are subject to interpretation and are sensitive to changes over time. This stresses the fact that standards are not necessarily state-of-the-art and can or will be outdated by evidence from research (section 2.5). The amount of attention also shows that a broad public is interested in the subject of decontamination of medical devices, because it may affect them or their loved ones.

Also the studies reported in the chapters 4, 5 and 6 have received much interest in- and outside of the field of infection prevention and decontamination. Spin-off studies [49, 50, 134, 156] addressing more directly the daily practice in sterilization initiated discussions and written responses [157–159] in the field of decontamination. An explanation for this large amount of interest could be that people involved, such as staff of CSSDs, or sales persons felt responsible, addressed or sometimes even provoked.

As the aim of this thesis is 'to contribute to the fundamental understanding of surface steam sterilization, steam sterilization processes, and the penetration of steam in medical instruments with narrow channels' (section 1.3), our published work so far has at least started various discussions and reconsiderations of common surface steam sterilization topics. These discussions can be conclusively closed if evidence based information is used to write standards, pharmacopoeias, and legislation, and when such information prevails above opinions and marketing considerations.

A.2 Steam penetration test

In standards steam penetration tests are tests that have to be performed daily before a steam sterilizer is used for production [52, 53, 70, 71, 80, 100]. The intention of such a

[1] Original Dutch title: 'Onnodig gevaar infecties'.

[2] Original Dutch text: 'Het is goed mogelijk dat 60 procent van de sterilisatoren niet aan de Europese normen voldoet. Maar dat betekent nog niet dat de schoongemaakte instrumenten krioelen van de ziekte verwekkers. Die overleven het hele proces meestal niet, ook niet bij een sterilisator die misschien niet helemaal aan de normen voldoet'.

test is to verify if the steam penetration capacity of a sterilization process is similar as before. The original steam penetration test was developed by Bowie and Dick [32] in the early 1960s. It was meant as an easy to build and use test for steam sterilizers in hospitals. It makes use of a defined stack of Huckaback towels. These towels were chosen because they were commonly available in hospitals. In the middle of the stack of towels an unglazed 10 x 8 inch sheet of paper with a St. Andrews cross of chemical indicator tape is positioned. The stack of towels with indicator sheet is placed in the sterilizer and a process is started. After the process the sheet with indicator tape has to be taken out of the textile stack and the color change of the indicator tape has to be judged. When the indicator tape shows an uniform color change the test is considered to be a good or 'pass' result: The sterilizer can be used for production. If not, the sterilizer is not ready for use and adequate action has to be taken.

Basically the purpose of the test is to detect if all non condensible gases (NCGs) are removed from the steam sterilizer chamber before starting the actual sterilization phase and to keep this condition at the aimed temperature until the end of the sterilization phase (see figure 2.2). Common causes of NCGs in a steam sterilizer are:

1. Leaks in the sterilizer. This includes the appendages or ductwork, such as the valves and gaskets (see figure 2.1).
2. Insufficient deep air removal in the conditioning phase of the steam sterilization process (see figure 2.2).
3. NCGs introduced with the steam.

Current steam penetration tests are based on ink [50, 160] or on physical measurements [134] and have to comply with the standards [70, 71, 80, 100]. Such a test does not have to be representative for a load or apecific medical devices.

A.3 Packing of Medical Devices

To ensure sterility of sterilized Medical Devices these either have to be used immediately after opening the sterilizer or have to be protected from re-contamination. In this context immediately means that after opening the sterilizer the sterilized items are instantaneously used in the same room. Most often that is not possible; the item is not immediately used or the sterilizer is located in a different room or even in a different building. In these situations the sterilized items have to be protected to avoid re-contamination with a microbiological barrier but should also be protected against damage during transportation. For Medical Devices such as medicines in glass ampules or bottles the glass forms both the microbiological barrier and the protection against damaging.

Re-usable Medical Devices can be packed individually or in sets. Sets are a combination of medical Devices, such as instruments that are used together in a procedure in surgery. To protect the devices against re-contamination and damage packaging systems are used [161, 162]. It is important to realize that a sterilization agent is only effective when it is in contact with the organism. Therefore the microbiological barrier has to be penetrable for the sterilization agent used. However, the microbiological barrier has to be

intact and not damaged, because a damaged microbiological barrier cannot be considered as a barrier for micro-organisms.

Packaging systems depend strongly on the use of the instrument. Individual instruments are frequently packed in pouches. One side of these pouches may be composed of a material that is easy to penetrate and the other side may contain a foil through which the device can be observed for easy recognition. Single packed instruments can be used in the emergency room or in nursing wards. Instruments used in operating theaters (OTs) have to be presented sterile. In these cases it is recommended to use a two layer system. Such a system can appear in many ways: double wrapped in pouches; a double sheet of cotton, crepe or non woven, or combinations of both; wrapped in a sheet and wrapped in a container.

In daily practice it is often claimed that water permeable wrapping material has to be dry at the moment of opening the sterilizer to prevent recontamination. The argument is that a wet wrapping is not a microbiological barrier. In literature discussions and studies on this topic have been reported [163, 164], but no conclusive results are presented. Most likely because no conclusive studies have been reported, the standards suggest that loads loads should be dry after sterilization [53, 94]. Obviously further studies on the influence and effectiveness of wrapping methods would be worthwhile.

A.4 Central Sterile Supply Department

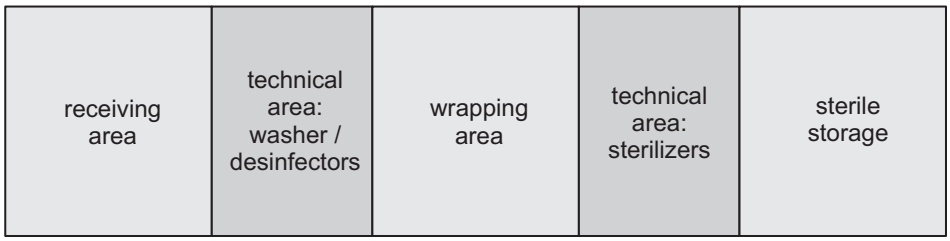

Figure A.1: Schematic layout of a CSSD. Medical devices to be processed arrive in the receiving area. After the first check and registration they are loaded in a washer-disinfector. At the wrapping side the washer-disinfector is unloaded and the instruments are wrapped. The wrapped instruments are loaded in the sterilizer. After the process the sterilizer is unloaded in the sterile storage.

To reprocess used Re-Usable Medical Devices (RUMDs) to sterile medical devices, larger health care facilities have a Central Sterile Supply Department (CSSD, figure A.1). After use of the RUMDs at locations in the facility, such as the operating theaters, emergency rooms and nursing wards, they are transported to the CSSD. Upon arrival in the CSSD the medical devices are checked and registered, followed by washing and disinfection. During washing the (visible) dirt is removed and during disinfection most of the viable organisms are inactivated.

As mentioned in section 1.1, worldwide definitions for washing and disinfection are not available. Chaufour et al. [84] showed the necessity of washing and disinfection

before sterilization. It is also a safety measure to protect the CSSD staff from being contaminated during the handling of the devices, e.g., wrapping of the devices. Generally, automated washing and disinfection is considered to be more reproducible than manual procedures [165, 166]. Most often washing and disinfection is performed in one machine. After washing and disinfection the devices are wrapped in microbiological barrier and a protection against damaging (appendix A.3). After that the devices are sterilized. Once sterilized the wrapped RUMDs are stored in a sterile storage from where they are distributed to locations where they will be used.

To prevent re-contamination and to avoid mixing of processed and not processed medical devices, Good Manufacturing Practicing (GMP[3]) is applied for the processing of medical devices. The GMP institute[4] specifies how to design, specify and practice procedures to minimize errors in production. Applying GMP in a CSSD often implies a one way routing for the medical devices. A medical device goes from stage to stage without going back and without intersecting, or returning to, a former stage. Double-door washer-disinfectors and sterilizers conform to the GMP routing. These machines can be loaded at one ('dirty') side and unloaded at the other ('clean') side.

Many microorganisms that are infectious for living creatures need a carrier to be transported (section 1.1) [15, 16]. This can be an instrument, a liquid or a person, but also an airborne particle. Airborne particles will flow in the direction of the lowest pressure. By applying a pressure hierarchy in a CSSD the air flow can be controlled and with that the flow of potentially contaminated airborne particles. RUMDs arrive in the receiving area of the CSSD. Obviously this area has to be classified as dirty and contaminated. By keeping this area at a lower pressure than the pressure in a facility, airborne particles will flow into this area. Only trained staff with protective clothing is present in this area. Additional potentially contaminated particles entering this area will not increase the risk for the staff. A typical pressure for this area is 5 Pa below environmental or facility pressure. By keeping the wrapping area at a higher pressure than the facility pressure, particles will flow from this area into the receiving area (figure A.1). This helps to prevent re-contamination of the instruments after washing-disinfection and before sterilizing. It can be argued that the sterile storage should be the cleanest area because the sterilized items are stored in there. An overpressure of 10 Pa compared to the facility pressure might be applied. However, it can also be argued that in the sterile storage the instruments are protected against recontamination and that during wrapping the probability of recontamination is the highest. In that case the wrapping area should be at a higher pressure than the storage area; the sterile storage can have an overpressure of 5 Pa and the wrapping area an overpressure of 10 Pa. In the technical areas (figure A.1) the washer-disinfectors and sterilizers are situated, with the loading door in the 'dirty' area and the unloading door in 'clean' area. These technical areas are often considered

[3]GMP refers to the Good Manufacturing Practice Regulations promulgated by the US Food and Drug Administration under the authority of the Federal Food, Drug, and Cosmetic Act. Their regulations, which have the status of a law, require that manufacturers, processors, and packagers of drugs, medical devices, some food, and blood, take proactive steps to ensure that their products are safe, pure, and effective. GMP regulations require a quality approach to manufacturing, enabling companies to minimize or eliminate instances of contamination, mix-ups, and errors.

[4]The GMP institute is a division of the ISPE, the International Society for Pharmaceutical Engineering. http://www.gmp1st.com/ and http://www.ispe.org/, last accessed 31 August 2013.

to be the most dirty areas of the CSSD. These two technical areas might be kept at the lowest level pressure, e.g., 10 Pa below the facility pressure.

To maintain the pressure hierarchy in a CSSD airlocks have to be present between the facility and the receiving area, between the receiving area and the wrapping area, between the wrapping area and the sterile storage, and between the sterile storage and the facility. In practice also the movement of staff has to be implemented in the CSSD layout. Staff members working in a CSSD are wearing special clothing. In the receiving area often protective clothing is used to reduce the risk to contaminate the instruments and the risk of getting contaminated. Because of this special clothing, staff cannot exit the CSSD and enter the hospital without precautions. Therefore areas such as dressing rooms and a coffee room have to be included in the total layout of a CSSD.

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Summary

In health care facilities steam sterilization is an essential part in reprocessing medical devices, especially re-usable surgical instruments. This thesis starts with a short review of the history and basic concepts of surface steam sterilization, steam sterilizers and sterilization processes. Also the current standards for steam sterilization are addressed briefly. Next, a survey of steam sterilization conditions in Dutch hospitals is presented. This survey, which involved 197 steam sterilizers in Dutch hospitals during the time period 2001 and 2002, showed that only 40 % of these sterilizers did satisfy the claims made by the hospitals themselves. These claims were based on and referred to generally accepted standards for steam sterilization. This observation motivated a study that aimed to assess whether steam sterilization conditions are actually established when the current standards for steam sterilization are met. It was found that when these standards are met, steam sterilization conditions as defined in the literature are not necessarily realized. In particular, it was found that monitoring and validation of steam sterilization processes based on temperature and pressure measurements is only valid in specific situations.

An alternative method to monitor sterilization is the F_0-value theory. However, the current theory is only valid within a limited temperature range around a certain reference temperature. The limitations of the current theory are analyzed and an improved F_0-value theory is developed. This modified theory is applicable for steam sterilization within the same temperature interval as the Arrhenius law describing the process governing the killing rate of the microorganisms.

One should realize that even if the sterilization conditions are satisfied within the sterilizer chamber itself, this does not necessarily imply that all types of loads can be properly sterilized. For instance, with the development of Minimal Invasive Surgery more surgical instruments contain narrow hollow channels. Steam penetration in these channels appears to be far from trivial. To assess whether specified surface steam sterilization conditions are met not only in the sterilizer chamber, but also on all surfaces of the items to be sterilized, two models are developed to describe steam sterilization conditions on the inner surfaces of instruments containing narrow hollow channels.

The first model describes a tube with one open and one closed end without condensation on its inner wall during a generic sterilization process. To validate the model, the time evolution of the water vapor density at the closed end inside a representative test tube is quantified by a pilot experiment based on infrared light absorption measurements. Both the model calculations and the experiments show that for a wide range of sterilization process parameters the vapor density near the closed end inside tubes with a length exceeding 25 cm may be insufficient for steam sterilization. Even small amounts of non condensible gases (NCGs) present in the sterilization chamber appear to reduce the steam penetration in such tubes dramatically.

The second model describes a vertical tube with uninterrupted condensation. This model mimics a commercially available instrument which according to the manufacturer can detect the presence of residual NCGs in a reliable and reproducible way. This model has been validated by experiments in which known fractions of NCGs were introduced

in a sterilizer chamber in which such an instrument was placed. Our calculations reveal that the instrument is indeed very sensitive to residual NCGs that are present in the sterilizer chamber before sterilization, but also to NCGs present in the steam supplied to the sterilizer, the effect of which on steam penetration is much smaller.

In both models, specific assumptions are made, which hamper their application to more general cases. Specifically, these models describe quasi one-dimensional situations. Therefore, a pilot study has been performed to improve these models and extend them to two dimensional (axially symmetric) situations. This study is based on a numerical framework in which the thermodynamic and kinetic properties of the vapor and non-condensible gases are taken into account in great detail.

Both the model calculations and the experimental results indicate that, to ensure proper surface steam sterilization of complex loads like modern surgical instruments, not only the pressure, temperature and time should be monitored, but also the amount of non condensible gases.

Throughout the studies described in this thesis it is noticed that the use of standards is necessary for steam sterilization in practical situations. However, the results presented in this thesis indicate that when the requirements given by the current standards are met, it cannot be guaranteed that accepted steam sterilization conditions reported in literature are satisfied. Therefore we conclude that standards should be adjusted such that they become evidence based, where possible.

Samenvatting

In de gezondheidszorg is stoomsterilisatie een belangrijk onderdeel van het reinigen van medische hulpmiddelen voor hergebruik. Dit geldt met name voor herbruikbare chirurgische instrumenten. Dit proefschrift begint met een kort overzicht van de geschiedenis en de basisprincipes van stoomsterilisatie, stoomsterilisatoren en sterilisatieprocessen. Hierbij wordt kort ingegaan op de huidige standaards voor stoomsterilisatie. Vervolgens wordt een inventarisatie gepresenteerd van de status van oppervlakte stoomsterilisatie. Deze inventarisatie betrof 197 stoom-sterilisatoren in Nederlandse ziekenhuizen in de periode van 2001 tot 2002 en liet zien dat slechts 40 % van deze stoomsterilisatoren voldeed aan de eisen die geclaimd werden door de gebruiker, meestal een ziekenhuis. Deze claims waren gebaseerd op en ontleend aan de geldende standaarden. Dit resultaat was een reden om te onderzoeken of er inderdaad stoomsterilisatiecondities aanwezig zijn als aan de eisen uit de standaarden wordt voldaan. Uit deze studie bleek dat, wanneer aan de eisen uit de standaarden wordt voldaan, er niet noodzakelijkerwijs stoomsterilisatiecondities aanwezig zijn zoals deze beschreven zijn in de literatuur. Met name is vastgesteld dat monitoring en validatie van stoomsterilisatieprocessen op basis van direct gemeten temperatuur en druk alleen in specifieke situaties valide is.

Een alternatieve methode om sterilisatie te monitoren is met behulp van de F_0-waarde. De huidige theorie is echter slechts geldig binnen een beperkt temperatuurinterval rond een zekere referentietemperatuur. De beperkingen van de huidige theorie zijn geanalyseerd en een verbeterde F_0-waarde theorie is ontwikkeld. Deze laatste kan worden toegepast op stoom-sterilisatie binnen hetzelfde temperatuurinterval als de Arrhenius wet die de vernietiging van de micro-organismen beschrijft.

Men moet zich realiseren dat zelfs als de gespecificeerde sterilisatiecondities in de sterilisatiekamer zijn bereikt, dit niet noodzakelijkerwijs betekent dat alle soorten ladingen goed gesteriliseerd kunnen worden. Als gevolg van de ontwikkeling van Minimaal Invasieve Chirurgie bevatten bijvoorbeeld steeds meer instrumenten dunne open kanaaltjes. De penetratie van stoom in dit soort kanaaltjes is niet vanzelfsprekend. Om na te gaan of de gespecificeerde oppervlakte stoomsterilisatiecondities niet alleen in de sterilisatiekamer bereikt worden, maar ook op alle oppervlakken van de te steriliseren objecten, zijn twee modellen ontwikkeld die de stoomsterilisatiecondities beschrijven op de inwendige oppervlakken van instrumenten met dunne open kanaaltjes.

Het eerste model beschrijft het gedrag van een buisje waarvan een uiteinde open is en het andere gesloten en geen condensatie op het binnenoppervlak optreedt gedurende een generiek sterilisatieproces. Om het model te testen is een pilot experiment uitgevoerd waarbij de fractie waterdamp aan het gesloten eind in een representatief buisje is bepaald via de absorptie van infrarood licht. Zowel de modelberekeningen als de experimentele resultaten tonen aan dat de fractie waterdamp aan het gesloten einde in buisjes langer dan 25 cm onvoldoende kan zijn voor stoomsterilisatie. Zelfs de aanwezigheid van zeer kleine hoeveelheden Niet-Condenseerbare Gassen (NCG's) in de sterilisatiekamer blijkt de stoompenetratie in dit type kanaaltjes drastisch te reduceren.

Het tweede model beschrijft een verticaal buisje waarin ononderbroken condensatie

optreedt. Dit systeem lijkt op een commercieel verkrijgbaar instrument dat volgens de fabrikant resterende fracties NCG's op een betrouwbare en reproduceerbare manier kan detecteren. Dit model is getest met behulp van experimenten waarbij bewust bekende hoeveelheden NCG's werden ingelaten in een sterilisatiekamer waarin zich een dergelijk instrument bevond. De modelberekeningen tonen aan dat het instrument inderdaad zeer gevoelig is voor resterende fracties NCG's in de sterilisatiekamer aan het begin van de sterilisatiefase, maar ook voor NCG's die aanwezig zijn in de stoom die aan de sterilisator wordt toegevoerd en die een veel kleinere invloed hebben op de stoompenetratie.

Beide modellen bevatten specifieke aannames, waardoor ze niet zonder meer gebruikt kunnen worden voor meer algemene situaties. In het bijzonder beschrijven deze modellen quasi-eendimensionale situaties. Om deze reden is een verkennende studie uitgevoerd om deze modellen te verbeteren en uit te breiden naar tweedimensionale (axiaal symmetrische) situaties. Deze studie is gebaseerd op een numeriek platform waarmee de thermodynamische en kinetische eigenschappen van waterdamp en niet-condenseerbare gassen in detail gemodelleerd kunnen worden.

Zowel de modelberekeningen als de experimentele resultaten tonen aan dat, om de juiste stoomsterilisatiecondities van complexe ladingen zoals moderne chirurgische instrumenten, te kunnen garanderen, niet alleen de druk, temperatuur en tijd gemonitord moeten worden, maar ook de hoeveelheid niet-condenseerbare gassen.

Bij alle studies die in dit proefschrift worden beschreven wordt opgemerkt dat het gebruik van standaards noodzakelijk is voor stoomsterilisatie in de praktijk. De in dit proefschrift gepresenteerde resultaten tonen echter aan dat zelfs als aan de in de standaards vastgelegde eisen wordt voldaan, niet kan worden gegarandeerd dat voldaan wordt aan de stoomsterilisatiecondities die in de literatuur zijn beschreven. Daarom concluderen we dat de standaards zodanig zouden moeten worden aangepast dat deze waar mogelijk gebaseerd zijn op feitelijke waarnemingen.

Publications

Publications as first author

Het steriliseren van tandheelkundige instrumenten
van Doornmalen JPCM, Verschueren M, Rietmeijer AGM, and Dankert J.
Nederlands Tijdschrift voor Tandheelkunde 108, 269 - 272, 2001.

A validation survey of 197 hospital steam sterilizers in the Netherlands
in 2001 and 2002
van Doornmalen JPCM and Dankert J.
Journal of Hospital Infection, 59, 126 - 130, 2005.

Review of surface steam sterilization for validation purposes
van Doornmalen JPCM and Kopinga K.
American Journal of Infection Control, 36, 86 - 92, 2008.

Temperature dependence of F-, D- and z-values used in
steam sterilization processes
van Doornmalen JPCM and Kopinga K.
Journal of Applied Microbiology, 107, 1054-1060, 2009.

Six commercially available Class 6 Chemical Indicators tested
against their stated values
van Doornmalen JPCM and Kopinga K.
Central Service 6, 400-404, 2012.

Penetration of water vapour into narrow channels during
steam sterilization processes
van Doornmalen JPCM, Verschueren M and Kopinga K.
Journal of Physics D: Applied Physics, 46, 065201, 2013.

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Finally to all who contributed to this work but are not mentioned by name, and many names come up while writing this, please accept my apologies but know that I do appreciate your help, support, contributions and efforts.

Joost

Curriculum Vitae

Education

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1990-1994	University of Technology Eindhoven, Applied Physics
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Professional

1995-1998	Coöperatief Adviesbureau Vereniging Krachtwerktuigen u.a. Amersfoort, Team leader Validation & Monitoring
1998-2005	KW2 B.V., Amersfoort (Management buy-out) Manager Validations & Monitoring, Vice president
2005-2008	Bureau Veritas, Amersfoort (acquired KW2 B.V.) Manager of the department In Service Verification
2008-present	3M Deutschland GmbH, Neuss (D), Infection Prevention Division Manager scientific affairs and education sterilization EMEA

Standardization committees

- Member of Dutch Standardization Committee
  'Steriliseren en Steriliteit' (NC 308.081)
- Member CEN Technical Committee 102
  'Sterilizers for medical purposes'
- Member CEN Technical Committee 204
  'Sterilization of medical devices'
- Member of ISO Technical Committee 198
  'Sterilization of health care products'
- Member ISO Technical Committee 210
  'Quality management and corresponding general aspects for medical devices'