Electro motive drug administration

Aarts, Jos

Published: 01/01/1995

Document Version
Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

- A submitted manuscript is the author's version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

Citation for published version (APA):
Electro Motive Drug Administration

A study on uniformity and efficiency

Jos Aarts

identiteitsnr: 327022
WFW-rapport: 95.093

Stageverslag behorende bij de 2e stage van de studierichting Werktuigkundige Medische Technologie, Technische Universiteit Eindhoven (TUE).

Deze stage is verricht bij de afdeling Fysica van de Klinisch Fysische Dienst van het Catharina Ziekenhuis te Eindhoven (CZE).

Begeleiders: A. J. Aarends (CZE)
A. Hendrikx (CZE)
P. Bovendeerd (TUE)
Preface

At the end of 1993 a novel treatment method for a number of bladder pathologies was offered by TD Medical (Eindhoven, Holland) to Dr. Hendrikx, urologist at the Catharina Hospital (Eindhoven, Holland) for evaluation. TD Medical is the Dutch representative for Physion (Mirandola, Italy), who developed this method called Electro Motive Drug Administration, EMDA®.

The Physics group, a sub-division of the Clinical Physics Department of the Catharina Hospital evaluated this method. Within the framework of my practical work (Biomechanical Engineering, Eindhoven University of Technology) I was involved in this evaluation.
Summary

The drug mass flow into the bladder wall through intravesical infusion of a drug solution and subsequent passive diffusion of the drug into the bladder wall is slow. Enhanced penetration of the drug might be obtained by electromotive drug administration which is the active diffusion of ionized drug molecules into the bladder wall due to the Coulomb force experienced by the application of an electric field.

In this study the spatial distribution of the drug administration over the bladder wall and the effect of ions other than the drug ion (competitive ions) on the efficiency of drug administration have been studied. Studies on electromotive drug administration described in literature reveal no satisfactory information on these subjects. Therefore, in this study numerical models have been developed to obtain this information.

The distribution of the drug administration over the bladder wall was investigated using a 2D mathematical (finite element) model. In the model iontophoresis was the sole mode of transport. Geometrical and conductivity properties of bladder cavity, bladder wall, surrounding tissues and skin were considered. Modelling results suggest the following conclusions. A low specific conductivity of the bladder content and/or bladder wall improve uniformity of the drug distribution. Placing a second skin electrode at the dorsal side of the body increases uniformity also, placing the intravesical electrode eccentric in the bladder has no significant effect on the uniformity. Experimental data on the overall conductivity of the mucosa layer of the bladder wall are needed to do more accurate predictions on the uniformity.

Furthermore, the relative contribution of the drug ions to the electric current in relation to the contribution of other (competitive) ions present has been modeled for the bladder content using a 1D electric circuit. Due to continuous influx of urine the relative contribution of drug ions to the electric current decreases during the treatment, which decreases effective treatment time. The length of the effective treatment time is increased by a large starting volume of intravesical solution, a low flow rate of urine influx, a high concentration and mobility of the drug ions present in the intravesical solution and low concentrations and mobilities of competitive ions.

An animal experiment is suggested to measure the value of the bladder wall conductivity and to investigate the role of capacitive effects and electroporation on the drug administration. Furthermore, this experiment can also be used the study the overall effect of parameters that may improve the uniformity and efficiency of the drug administration.
Contents

Chapter 1: Introduction 1

Chapter 2: Methods to determine the drug administration 3

2.1 Introduction 3
2.2 Experimental setups 4
2.2.1 Studies on cadaveric tissue 4
2.2.2 Animal tests 5
2.2.3 Patient studies 6
2.3 Methods of measurement 6
2.3.1 Radiolabeled drug studies 6
2.3.2 Dye studies 7
2.3.3 Pain scores 7
2.4 A numerical method to determine drug administration 8

Chapter 3: Transport modes for charged and uncharged particles 9

3.1 Passive diffusion 9
3.2 Iontophoresis 10
3.2.1 Conductivity 10
3.2.2 Capacity 11
3.3 Electro-osmosis and subsequent transport of uncharged particles 12
3.4 Electroporation 13

Chapter 4: Anatomy of the bladder 14

Chapter 5: Spatial distribution of electromotive drug administration 17

5.1 Introduction 17
5.2 A 2D model for the drug transport in the pelvis 17
5.2.1 Transport mode: Iontophoresis 17
5.2.2 Material property: the specific conductivity 18
5.2.3 Geometric properties: the anatomical model 18
5.2.4 Boundary conditions: the placement of the electrodes 20
5.3 The theory of electrodynamics 20
5.3.1 The electrodynamics of a 1D situation 20
5.3.2 The electrodynamics of a 2D situation 22
5.4 The numerical solution method 23
5.5 Parameter variations 25
5.6 Results 27
5.7 Discussion 32
5.8 Conclusions 36
Chapter 6: The impact of competitive ions on the efficiency of electromotive drug administration

6.1 Introduction
6.2 Competitive ions
6.3 Materials and methods
6.4 Results
6.5 Conclusions

Chapter 7: Conclusions and recommendations

7.1 Spatial distribution
7.2 Competitive ions
7.3 The use of an animal experiment in further investigations
7.4 An animal test
7.4.1 Recommendations to obtain information of use to our models
7.4.2 Method of measurement
7.4.3 Recommendations to improve uniformity and efficiency

References

Appendices

Appendix I Derivation of the equation describing the 2D electrodynamics
Appendix II The use of the software packages Sepran and Matlab
Chapter 1: Introduction

Conventional administration of drugs for various urologic pathologies involving the bladder wall is usually performed via the systemic route. The concern about this method is toxicity (in relation to other vital organs) due to the high concentrations which are required to achieve an effective therapy for bladder wall pathologies.

In recent years, intravesical infusion and subsequent passive diffusion of various agents into the bladder wall has become an accepted therapeutic procedure. This method can be used for a number of urological pathologies and other purposes. For example local anesthesia in case of a biopsy/transurethral resection (TUR) or interstitial cystitis (e.g. lidocaine), staining of bladder tumors (diagnostic agents), relapsing bacterial infections of the bladder (antibiotic agents), in case of a spastic or neurologic bladder (anti-cholinergic agents) and for prevention of bladder cancer, confined to the inner surface of the bladder wall. In this last case the infusions are applied as a preventive measure (almost always following an initial TUR of tumors) and not as a treatment of endoscopically detectable tumors, particularly not for invasive tumors [PHY 94, Ste 94].

The mode of drug transport in this method is passive in nature. The rate of drug transport from within the bladder cavity into the bladder wall mainly depends upon the existence of a drug concentration gradient over the bladder wall and the diffusion coefficient of the bladder wall. Because the great majority of patients are not anuric, the urine flowing into the bladder continuously dilutes the drug solution so that the drug concentration gradient and therefore the drug diffusion rate decreases progressively with time. In addition urinary output varies greatly between patients and for the same individual at different moments. Diffusion rates of the drug can vary by at least 300% from treatment to treatment.

Furthermore, the urothelium, covering the inner surface of the bladder wall, is the least permeable endothelial membrane in the body (i.e. low diffusion coefficient), which results in a very low drug diffusion rate. Intravesical infusion and subsequent passive diffusion results in a small and varying amount of drug administered to the bladder wall.

A method, called Electromotive Drug Administration, is proposed to achieve a higher and more precise transport rate of drugs into the bladder wall. Furthermore, this method is claimed to have the highest drug deposition at the lesion site and a uniform drug deposition over the surrounding tissue of the bladder wall.

In this method the drug solution is again infused into the bladder cavity. However the transport rate is enhanced by the application of an electric field. This electric field is applied by placing a spiral electrode in the centre of the bladder cavity and a dispersive electrode on the ventral side of the body. The following electrokinetic phenomena can play a role in the enhancement of the transport rate by means of an electric field.

**Iontophoresis:** If the drug molecules are ionised upon solution these drug ions experience a force in the electric field which causes them to move. The diffusion into the urothelium under the influence of a force other than a concentration gradient is called active diffusion.

**Electrophoresis:** If the dissolved drug is not ionised itself but the solution does contain certain ions, iontophoresis, as described above, induces transport of water because of its electric dipole (electro-osmosis). This in turn induces an enhanced penetration of non-ionised solutes, associated with the bulk movement of water.

**Electroporation:** The application of an electric field can cause an increase in the permeability of biological membranes. There can be increased passive transport of drugs due to concentrations gradients because the value of the diffusion coefficient has been increased.
Introduction

We have taken a closer look at two aspects of the method of electromotive drug administration.

- The spatial distribution of the drug deposition over the bladder wall. Placing only one dispersive electrode on the ventral side of the body may set limitations to the level of uniformity of drug deposition that can be achieved.

- The impact of competitive ions on the efficiency of the drug deposition. There are a number of ions other than the drug ions present in the body. First of all the dissolved drug separates into the drug ion and a counter ion. Furthermore, the influx of urine enlarges the amount of other ions in the bladder cavity. In addition, the body itself is an ocean of ions. Under the influence of an electric field these ions move through the body, constituting an electric current. The amount of drug administered to the bladder wall depends upon the ability of the drug ions to move through the body in relation to the other ions. That is why these ions are called competitive ions.

We have studied a number of papers on methods to determine the drug deposition in order to find information about the two aspects mentioned above. These methods are discussed in chapter 2. In this discussion we will restrict ourselves to some comments on these methods in relation to our study only. Finally, we present in this chapter yet another way of determining the drug transport. In order to answer our questions we will analyze the method of electromotive drug administration using relative simple mathematical models. These models will be described more extensively further on. To keep these mathematical models simple a great number of assumptions are made about the electrokinetic phenomena that play a role in the drug transport and the anatomy of the bladder and the surrounding tissues. In chapter 3 we will first describe the phenomena that may play a role in the transport. In chapter 4 we will give a brief description of the anatomy. On the one hand this gives an idea of the simplifications made in the models, on the other it is useful for the discussion of and the conclusion about the results. In chapter 5 the spatial distribution of the electromotive drug administration is studied. The impact of competitive ions on the efficiency of electromotive drug administration is the subject of chapter 6. Both aspects can be treated separately, however, their effects on the drug administration can be superimposed. The general conclusions and recommendations about the method of electromotive drug administration are the subject of chapter 7.
Chapter 2: Methods to determine the drug administration

2.1 Introduction

Our study of literature revealed a number of papers on ways of determining the effect of iontophoresis on the amount of drug administered to the skin and the bladder wall. In this chapter we will, more specifically, look at the possibilities and/or limitations of these methods to determine the spatial distribution of the drug deposition and the effect of competitive ions on the drug deposition.

Two aspects of these methods that are of specific interest to us will be discussed separately: the experimental setup and the actual measurement/quantification of the drug deposition. We have made this distinction because most measuring methods are not restricted to a certain type of experimental setup and, therefore, can be used in different experiments (Table 2.1). The different experimental setups can be grouped as follows:

- studies on cadaveric tissue
- animal studies
- patient studies (clinical trials)

The experimental setup mainly determines whether it is possible to study the spatial distribution or impact of competitive ions. However, to examine the results of these experiments the amount of drug administered must be measured in some way. In addition, this method of measurement can influence the information that can be obtained from the experiment. Different measuring methods were used, which can be classified from quantitative to more qualitative methods:

- radiolabeled drug studies
- dye studies
- pain scores

The different experimental setups are discussed in paragraph 2.2. The methods of measurement are discussed in paragraph 2.3. Finally, in paragraph 2.4, we present yet another way of determining and quantifying the drug administration, which will be explained in the following chapters and which is of specific value in case uniformity analysis is required, like in intravesical applications.

Table 2.1: Methods to determine the drug administration. Different measuring methods can be used for different types of experimental setups. In this table the papers are denoted that were used in our study of literature.

<table>
<thead>
<tr>
<th>MEASURING METHODS</th>
<th>EXPERIMENTAL SETUP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cadaveric tissue</td>
</tr>
<tr>
<td>radiolabeled drug</td>
<td></td>
</tr>
<tr>
<td>dye</td>
<td>[Lug 93]</td>
</tr>
<tr>
<td>pain score</td>
<td></td>
</tr>
</tbody>
</table>
2.2 Experimental setups

2.2.1 Studies on cadaveric tissue

Cadaveric human bladders were used in preliminary qualitative experiments (case/control study) to assess iontophoretic penetration of dye substances into the bladder wall, as compared to passive penetration [Lug 93]. In the control experiments staining of tissue generally involved only the outermost layers of the urothelium. In sharp contrast, application of iontophoresis resulted in penetration of all dyes tested through full-thickness urothelium and often into the underlying lamina propria and muscularis tissues. However, the placement of the electrodes in these experiments differs from that in the clinical application (Fig. 2.1). The dispersive electrode was placed directly on the bladder wall instead of on the skin. The spiral electrode in the centre of the bladder cavity was replaced by a cup shaped electrode placed on some part of the inner surface of the bladder wall. The cup was filled with a dye solution. This configuration can not be used to determine the drug deposition over the bladder wall, because the treatment is confined to the small area underneath the electrode (± 6 cm²). Furthermore, because the bladders in these experiments were excised from the body it is not possible to study the effect of competitive ions others then the counter ions that originate by dissolving the dye (e.g. ions present in urine). In addition, because of time variations between death and excision, it was realized that the specimens would demonstrate differences in urothelial permeability and that all bladders would be more permeable than those under in vivo conditions. More general, the electric characteristics of tissue alter following death [Duc 90]. This has to be taken into account when using values of material properties obtained from measurements on cadaveric tissue.

Studies on cadaveric tissue can only be used as preliminary, qualitative investigations, to study the feasibility of facilitating drug delivery by means of iontophoresis.

Figure 2.1: Schematic representation of dye studies in cadaveric bladders. The treatment is confined to a small area, which makes it impossible to study the distribution of the dye over the bladder wall. The effect of competitive ions can not be studied either because the bladder is excised from the body (from: Lug 93).
2.2.2 Animal tests

Rhesus monkeys were used in a series of animal studies to obtain precise information about iontophoretic delivery of radiolabeled dexamethasone to the skin and underlying tissues. [Gla 80]. Again the results show an increased amount of drug transferred into the tissues by means of iontophoresis in comparison to passive diffusion. These experiments, although well suited to study the general effect of electromotive drug administration, are useless (no urine influx, different tissue properties and geometry) in studying specific aspects of its application in urology.

Another animal experimental setup is suggested to study iontophoresis in the bladder [Gri 95]. The generic model, using dogs of about 15-20 kg, has the following features, which indeed makes it possible to study the drug distribution and impact of competitive ions.
- The intravesical electrode used in this experiment is the same spiral electrode used in the clinical application discussed later on (Fig. 2.2). The dispersive electrodes are placed on the anterior abdominal wall. This configuration enables the investigation of the drug distribution over the bladder wall.
- Because of the in vivo situation the material properties are unaltered and it is possible to study the effect of urine influx (i.e. competitive ions).
- After the treatment the bladder is excised and divided into 6 sections, which can be examined separately by means of one of the measuring methods discussed in the next paragraph, to determine the drug distribution over the bladder wall. These different sections are:
  1. Anterior and posterior walls
  2. Two lateral walls
  3. Dome and bladder neck

Animal tests can be used to obtain more precise information about iontophoretic drug delivery, because of their in vivo nature. A disadvantage of animal tests is the difference in the geometry of the bladder and the tissue properties between animals and humans. Furthermore, a surgical procedure is necessary to access the urethra because the canine urethra is smaller than the human urethra.

![Figure 2.2: The spiral electrode applied in the animal test [Gri 95] resembles the one used in the clinical application. This situation makes it possible to study the spatial distribution and the effect of the influx of urine, containing competitive ions, from the ureters (from: Lug 93).](image-url)
2.2.3 Patient studies

A patient study was done to provide a preliminary clinical assessment of the efficacy of iontophoretic local anesthesia applied to the bladder wall [Lug 93]. Thirty six patients diagnosed with recurrent neoplasia of the bladder were entered into the study. All were treated with iontophoretic local anesthesia, and 28 of the subjects (9 female, 19 male, aged 50-78 years) underwent biopsy-coagulation or resection of tumor(s) or both. It was this cohort of patients in whom results were evaluated. The method of measurement used was a pain score (par 2.3.3). Initially, it was planned to match experimental subjects with a control group. However the first 6 patients of this control group all described their pain as moderate and commencing on severe; therefore, this approach was abandoned, which left 22 experimental subjects remaining in the study. Of the 22 experimental subjects, 16 recorded their pain sensations as none to minor. The other 6 patients reported their pain as severe to intolerable. This might be the result of a non uniform drug distribution, but correlation between lesion site and pain score was not performed. The advantage of patient studies is that the experimental setup equals the clinical application. However, an objective measurement of the amount of drug administered to the bladder wall is more difficult then in an animal study or a study on cadaveric tissue. The effect of the method of measurement on the use of an experiment in determining the drug deposition will be discussed in the next paragraph. The ultimate validation of the effect of electromotive drug administration is probably a controlled, double blind patient study in which careful selection of patients and controls warrants reliable conclusions. Locations of biopsies within this population should be evenly distributed over the bladder sphere.

2.3 Methods of measurement

2.3.1 Radiolabeled drug studies

One way of quantifying the drug deposition in a certain tissue is by means of the administration of a radiolabeled drug to that tissue and the measurement of the activity of that tissue after the treatment. Tritium-labeled dexamethasone sodium phosphate ($D_m$Na-P) was used to quantify the amount of dexamethasone penetrating the skin and subcutaneous tissues through iontophoresis [Gla 80]. The experimental setup of this study is discussed in paragraph 2.2.2. The total amount of drug administered was determined by measuring the specific activity of the drug solution before and after the treatment. In addition, the amount of drug administered to the different types of tissue (from the skin to the bony structure) were measured also. The different tissues underlying the skin were dissected slice by slice and frozen. These layers were weighed, and then analyzed in a scintillation counter to determine the amount of drug per gram of wet tissue. Of course this method can also be used to determine the amount of drug administered to different regions of a certain tissue to examine the spatial distribution of the drug administration. An advantage of this method is that quantitative figures of the drug mass concentration can be obtained. This makes it possible to get an objective picture of the drug distribution over the bladder wall and precise quantities of the amount of drug administered. A disadvantage of the method is that the bladder has to be excised to examine the drug distribution, which makes it impossible to use in patient studies. Other examples of radiolabeled drugs are $0.3\mu Ci\ 125I$-labeled insulin [Chi 88] and $14C$-labeled lidocaine $10\mu Ci$ [Gri 95].
2.3.2 Dye studies

Use of different dyes and additional concentrations in determining the amount of drug administered to the bladder wall is described. For instance methylene blue (0.1%), gentian violet (0.1%), mitoxantrone (0.04%), and doxorubicin (0.1%) in [Lug 93] and methylene blue (2.0%), hematoporphyrin (0.5-1%) and doxorubicin (0.05%) in [Gri 95]. The general procedure in dye studies is as follows: a dye is used as a model or substitute for a specific drug. The relevant properties (mobility, ion charge) of the dye in relation to iontophoresis have to be the same as that of the drug. In addition, iontophoresis is applied to the tissue of interest (skin, bladder wall). After a period of time the treatment is stopped and the treated areas are washed. The tissue is excised, sectioned and examined by light or photo microscopy for density and depth of dye penetration. The examination of the drug deposition is based on visual inspection, which is less quantitative then measuring the specific activity of the tissue. In addition, the eye observes on a logarithmic scale which makes it hard to determine the density of the dye on a linear basis. Using the depth of penetration, in terms of the number of stained cell layers gives a more quantitative figure. However, there is no quantitative relation between this figure and the actual drug mass deposition. Again to determine the in vivo drug deposition by means of a dye study the bladder has to be excised afterwards.

2.3.3 Pain scores

The effect of iontophoresis on local anesthesia of human bladders was determined by pain scores [Lug 93]. Patients were treated with iontophoretic local anesthesia and underwent biopsy-coagulation or resection of tumor(s) or both. All endoscopic manipulations were scaled on a graduated scale from minimal to most vigorous. The patients were asked to respond to the manipulations by means of the following simple scoring system. The pain caused by their intravenous cannulation was to be standardised as moderate, and the pain caused by manipulation as none, minor, moderate (equivalent to intravenous cannulation) or severe (= failure). This method is even more subjective. In addition, it is impossible to say anything about the amount of drug administered in terms of mass concentrations. Furthermore the drug distribution is not studied by determining the effect of electromotive drug administration in a systematic way (i.e. in some well chosen points), these points are determined by the arbitrary location of the tumors.

From these paragraphs we have seen that patient studies have (as can be expected) the best resemblance with the clinical application. However, it is hard to determine the effect of the treatment in a quantitative way and at short notice. The only situation in which information about the effect of iontophoresis can be obtained directly is the iontophoretic administration of local anesthesia and successive biopsy and/or resection of tumor(s) as describe above. In other applications (e.g. controlling inflammations or tumors) the effect of iontophoresis on drug administration can not be seen directly. One can only say if the patient is cured after a period of time. This makes a patient study less appropriate to determine the amount of drug administered. To study the spatial distribution and the impact of competitive ions precise quantification of drug deposition is necessary. From the methods of measurement discussed in par. 2.3 the method using radiolabeled drugs is the most quantitative. In that case the bladder has to be excised, which is generally impossible in case of a patient study.
Methods to determine the drug administration

An alternative is an animal test. However, because of the disadvantages of an animal model and the fact that the animal has to be sacrificed we choose to try yet another way to determine the spatial distribution and the impact of competitive ions.

2.4 A numerical method to determine drug transport

In chapter 3 and 4 the most important phenomena for the transport of charged and uncharged particles and the anatomy of the bladder and the surrounding tissues will be discussed. From this we can build a physical model to describe the drug transport through successive tissues. In addition, this model can be translated into a set of mathematical equations which can be used to calculate the drug transport. The values of the drug and tissue parameters (concerning the properties in relation to drug transport) in these equations are derived from in vitro measurements. As said before these values may differ from the values in the in vivo situation. In addition, to get to this set of equations and to solve them a number of assumptions have to be made, which reduces the resemblance between the model and reality. However, the advantage of a numerical method is that it is very simple to study the effect of different parameters (i.e. different drugs, geometry, tissue parameters) and differences in the values of the parameters, which can lead to a better understanding of the drug transport. This information can be used to develop an improved experimental setup for animal tests. We will use this method to study the spatial distribution of the drug over the bladder wall (chapter 5) and the impact of competitive ions on the efficiency of the drug deposition (chapter 6). The two subjects are studied separately because their mathematical formulation and in addition, the way in which the equations are solved differ from each other. The results, however, can be combined to give some insight into the method of electromotive drug administration (chapter 7).
Chapter 3: Transport modes for charged and uncharged particles

A number of electrokinetic phenomena which account for the transport of charged and uncharged particles (the drug molecules can either be ionised or non-ionised upon solution) in the presence of an electric field were mentioned in the introduction. These phenomena will be described in this chapter. From the introduction we also know that under normal conditions passive diffusion is negligible. However, when electroporation (one of the electrokinetic phenomena) may occur under the influence of the electric field, a tissue becomes more permeable. In addition, passive diffusion may again play a more prominent role in the transport of particles. That is why this mode of transport is described in this chapter also.

The human body is very complex, therefore, the phenomena mentioned here will certainly not be the only ones that cause the transport of particles. However, these are the most important and most frequently mentioned in other studies.

The reason why these phenomena are described here is that they can be combined to form a physical model, which then can be used to compute the transport of the particles (drug ions) through a certain tissue (the bladder wall) numerically. As a first approximation a model can be used in which only a few of these phenomena are accounted for. Subsequently such a model can be extended by taking into account more of the phenomena that will be discussed below.

3.1 Passive diffusion

The transport of charged and/or uncharged particles in a certain direction in this phenomenon depends upon the existence of a concentration gradient \((\Delta C/\Delta x)\) for that particle in that direction (Eq. 1). The concentration gradient is the driving force, which causes particles to flow from a region with a high concentration to a region with a lower concentration (this explains the negative sign). Furthermore, the rate of transport \(\Phi_D\) [mole/sec] depends upon the diffusion coefficient \(D\) of a certain tissue for a certain particle [Ste 94].

\[
\Phi_D = - D \frac{\Delta C}{\Delta x}
\]  

(1)

The diffusion coefficient of a tissue may differ for different types of particles. A high diffusion coefficient of a tissue for a certain particle means that this particle can move through a certain the tissue more easily than a particle for which the diffusion coefficient is low. Which, under equal concentration gradients, results in a higher transport rate for the first type of particle.
Transport modes

3.2 Iontophoresis

In an electric field a particle with a certain charge experiences a force. The charged particles in our situation are positively and negatively charged ions (drug ion, its counter ion and other ions present in the body). A positive ion experiences a force in a direction opposite to that of the negative ions. If the particle is free to move through a solution or tissue, it will flow in the direction of this force, thereby constituting an electric current (current = movement of charge/charged particle(s)). This is the basic principle of iontophoresis [Ste 94]. Iontophoresis is a form of active diffusion, i.e. the transport of particles through a certain tissue is influenced by a force other than a concentration gradient. In this paragraph we will address the movement of particles in terms of an electric current in stead of a mass flow because we are looking at an electric phenomenon. The relation between the electric current and the actual mass flow of the drug ion is given by Faraday's law (Eq. 2).

\[
\phi_d = \frac{I}{zF}
\]  

where \( I \) is the total current, \( t_c \) represents the proportion of electrical current carried by the drug ion compared to the proportion of current carried by all ions in solution. \( \phi_d \) is the current constituted by the drug ions [Coulomb/sec]. \( z \) is the valency of the drug ion to be delivered. \( F \) is the Faraday constant, \( zF \) is the charge of one mole of drug ions [Coulomb/mole]). So \( \phi_d \) represents the amount of drug administered per unit time in moles.

The solution or tissue through which the ion moves offers a resistance to this movement. Since we focus on the movement of an ion and not on the resistance offered thereto, we use the reciprocal of the resistance, the conductivity. The conductivity will be discussed in paragraph 3.2.1. There are also ions that are confined to a certain region of space, e.g. ions within the cells of a certain tissue or at the surface of a rather impermeable membrane. These ions also experience a force in the electric field which causes them to move within their own region of space. In addition, these ions influence the electric field and thereby the electric current through the body. This effect is called the capacitive effect and will be discussed in paragraph 3.2.2.

3.2.1 Conductivity

As said before the solution or the tissue through which an ion moves offers a resistance to this movement. The reciprocal of this resistance is the conductivity of that tissue. A high conductivity means that the ion is able to move through the tissue rather easily, i.e. the force needed to generated this current (the electric field) may be small. A low conductivity means that a large force is necessary to generate a current through the tissue.

The conductivity \( G \) of a certain tissue for a certain ion depends on both the tissue and the ion (Eq. 3).

\[
G = \sigma \frac{A}{L}
\]  

where \( \sigma \) is the conductivity of the tissue, \( A \) is the cross-sectional area, and \( L \) is the thickness of the tissue.
Firstly, the conductivity depends on geometric parameters of the tissue. The conductivity of a tissue with cross sectional area $A$ and length $L$ (Fig. 3.1) is directly proportional to the cross sectional area of the tissue volume through which the ion moves. The larger the cross sectional area the easier the ions can move through this region of space. The conductivity is inversely proportional to the distance $L$ the ion has to move; the longer the way they have to travel the higher the force required to maintain the electric current.

![Figure 3.1](image)

**Figure 3.1:** The geometric parameters of a tissue influencing the conductivity. The conductivity $G$ is directly proportional to the cross sectional area $A$ and inversely proportional to the length $L$.

Secondly, the conductivity $G$ depends on the specific conductivity $\sigma$ of the tissue for a certain ion (a material parameter). The specific conductivity of a tissue may differ for different types of ions. It can be seen as the product of the mobility of the ion in a certain tissue and the charge density of the ions free to move. A high mobility means that the ions move relatively easy through the tissue. The mobility of the particles depends on many factors (e.g. viscosity of the solution and effective radius of the ion), which makes it very hard to calculate except for simple models [Web 88].

### 3.2.2 Capacity

Not all ions present in the body are free to move, there are also ions that are confined to a certain place, e.g. ions within the cells of a certain tissue or ions that arrive at the surface of a rather impermeable membrane. These ions can not contribute to a DC current, but the are able to influence this current. When no external electric field is applied the nett charge density inside a cell or on the boundary of a membrane is zero. If an electric field is applied there will be accumulation of charge which again influences the external field, and therefore the electric current. This effect is called the capacitive effect. The way in which the charge is accumulated inside a cell and the effect this has on the current differs from that in case of a impermeable membrane (e.g. the urothelium) only in relation to the scale.
Transport modes

Polarization of the cells in a tissue

In tissue under normal conditions the nett charge density inside a cell is zero. In addition, there is a certain equilibrium between the ions inside and outside the cells. The ions are not exactly confined to the cell, but the amount of ions that go out is same as the amount of ions that go in, so nett there will be a certain amount of ions confined to the cell. Under the influence of an external field the negative charged ions in the cell tend to move to the positive electrode and the positive charged ions tend to move to the negative electrode. This distribution of ions causes an electric field itself (polarization) with a direction opposite to the external field and therefore reducing the magnitude of the nett field. In addition, this reduces the magnitude of the electric current across the tissue, governed by the conductivity. Because the intracellular ions are confined to a certain space, they do not contribute to the current through the tissue.

The accumulation of charge on the surface of a rather impermeable membrane

The accumulation or depletion of charge on the surface of a membrane is due to the impermeability of the membrane. For instance, when a certain type of ion constituting for the current in a certain tissue arrives at the membrane, that is very impermeable for that ion, the ions will accumulate. However, the current is remained constant by increasing the magnitude of the external field (making use of a current generator). The ions on the other site of the membrane will constitute for this current, which leads to a depletion of that type of ion at the other boundary of the membrane. Notice that there might be no actual current, and in addition transport of drug ions, through the membrane, only an accumulation of charge over the membrane (a depletion of positive charge is equal to an accumulation of negative charge). There might be a very small electric current through the membrane. This current can consist of ions already present in the membrane or a small amount of ions that penetrates the membrane, because it is not absolutely impermeable. This situation is equivalent with charging a capacitor, with the leakage current representing the small amount of drug ions that penetrate the membrane. An advantage of the accumulation of charge at the surface of a membrane is that this results in an increased concentration gradient over the membrane, which makes passive diffusion more effective.

3.3 Electro-osmosis and subsequent transport of uncharged particles

The phenomenon mentioned in this paragraph plays a role in the transport of uncharged particles, which is of interest if the solvent drug is not ionised. The solution containing these particles, however, also has to contain a certain amount of ions. Like with normal iontophoresis these additional ions move under the influence of an external electric field (thereby constituting a certain current). In addition, because of the electric dipole of water it is attracted by these ions and therefore moves along with these ions. This phenomenon is called electro-osmosis. Because water molecules capture other particles in an hydration shell, the movement of water induces the movement of other charged and uncharged particles. This mode of transportation can enhance the penetration of these uncharged particles into a tissue in relation to the penetration due to passive diffusion only.
3.4 Electroporation

This phenomenon, like the previous one only has an indirect influence on the transport of charged and uncharged particles. The basic principle of this phenomenon is that the permeability of the membrane is increased, which may result in an increased passive transport of drugs along concentrations gradients because the value of the diffusion coefficient (D) has increased. The way in which the diffusion coefficient is altered is not exactly clear. Different mechanisms have been mentioned in literature. One possibility is the following [Chi 88]. Under the influence of an electric field a current is generated, again the ions constituting this current do not have to be the ones we are interested in. This may alter the molecular arrangement of rather impermeable membrane components, which could yield some changes in tissue permeability. In other words the movement of uncharged particles by means of passive diffusion is enhanced by the movement of charged particles by means of iontophoresis.

Another possibility is the formation of voltage dependent pores [Pat 83, Jun 83]. One can imagine the following might take place. Under normal conditions the cells of the membrane lay close together (Fig. 3.2a), which results in a low permeability. When an electric field is applied the cells become polarized, as described in paragraph 3.2.2, and in addition repel each other (Fig. 3.2b). This way pores may arise in the membrane (like Venetian blinds opened up) which results in an increased diffusion coefficient.

![Figure 3.2: A simple model for voltage dependent pore formation a) The configuration of the cells make the membrane very impermeable. b) Under the influence of an electric field, channels are formed due to the repulsion of neighboring cells.](image-url)
Chapter 4: Anatomy of the bladder

The anatomy of the bladder and the surrounding tissues is rather complex. The anatomic model used in the numerical method to determine the spatial distribution of the drug administration is relatively simple, i.e. a number of assumptions have been made. To form an idea of the complexity of the structures and geometry we will briefly describe the bladder and its position in the pelvis. Abstract derived from [Hin 93].

The geometry of the bladder

When empty the bladder appears to have five surfaces: a superior surface (the dome of the bladder), a posterior surface that forms the base of the bladder, an anterior surface and two anterolateral surfaces (Fig. 4.1). When distended, the bladder becomes more spherical with only the base and the neck remaining fixed.

![Figure 4.1: The geometry of the bladder, consisting of five surfaces of the bladder. The bladder becomes more spherical upon distension. The bladder is surrounded by a great number of structures and organs.](image-url)
The structure of the bladder wall

The inner surface of the bladder is covered with vesical 'mucosa' (urothelium), continuous with that of the ureters and the urethra, which is made up of transitional epithelium (Fig. 4.2A). This layer is thrown into folds as the bladder empties. However, over the trigone, it is flat and free of folds as would be expected from its situation on a surface that does not appreciably change dimensions (see below). On vesical distention, the epithelial cells are capable of extreme flattening. With intercellular gaps of 15 Å and intracellular channels of 10 Å, the urothelium is the least permeable endothelial membrane in the body [Ste 94]. The mucosa is fixed to the underlying muscularis by a very sparse lamina propria. The lamina propria has a loose structure that is rich in elastic tissue.

The muscularis (detrusor muscle) of the bladder consists of separate coarse bundles of smooth muscle (Fig. 4.2A and 4.2B). The muscle bundles of the internal layer run in longitudinal direction. The middle layer has more or less circularly orientated fibers that form rings around the bladder wall from apex to base. The outer layer of the detrusor is found on the anterior and posterior aspects in wide bundles that run in a generally longitudinal direction; on the lateral walls, this layer is less clearly distinguishable. Over much of the bladder body, the bundles change planes and directions, and they interlace so that a single fiber may continue through all three layers. This arrangement is functionally suited to coordinate contraction in all directions to achieve uniform reduction of the surface area during voiding.

Figure 4.2: A) The structure of the bladder wall consisting of three layers: transitional epithelium (mucosa), lamina propria and the muscularis. The muscularis itself also consists of three layers: an internal and an outer longitudinal layer and a middle circular layer. B) The three bundles of smooth muscle forming the muscularis of the bladder wall. The structure of the bladder base is somewhat different. However, it is also made of smooth muscle. This part is called the trigone.

The bladder base joins the vesical neck, the point where the bladder connects to the urethra, and the ureteral orifices, the connections to the ureters (Fig. 4.1) and, in addition, it has the function to retain and release urine. This is why the bladder base is the least distensible portion of the bladder. Therefore, the bladder base is structurally distinct from the bladder body. It consists, however, of smooth muscle also and is called the trigone. It can be split into two parts: the superficial and the deep trigone (Fig. 4.2B). The deep trigone is continuous with the middle circular layer of the detrusor muscle.
The position of the bladder in the pelvic cavity

The bladder is sited within the true pelvis, the cylindrical cavity within the bony pelvis, bounded posterior by the sacrum and the coccyx, lateral by the ischium and anterior by the pubis (Fig. 4.3). Besides the bladder there are a number of other structures and organs present in the pelvis. The bladder is surrounded by a number of muscles and overlying fascia (e.g. the Obturator internus muscle, the levator ani muscle and the Gluteus maximus muscle). Organs present are: the rectum, the urethra and the ureters in both the male and the female, the prostate, seminal vesical and ampulla of vas deferens in the male (Fig. 4.1) and the uterus, the cervix and the vagina in the female. In addition, there are also blood vessels, nerves and ligaments present (Fig. 4.1). The whole is separated from the external world by skin and possible underlying fatty tissue.

Figure 4.3: A transverse section of the pelvis, showing the eccentric position of the bladder in the pelvic cavity and the surrounding structures and organs (male).
Chapter 5: Spatial distribution of electromotive drug administration

5.1 Introduction

In this chapter we will look at the spatial distribution of the electromotive drug administration to the bladder wall. More specific, we will study the effect of the placements of the electrodes, the geometry of the bladder, its position in the pelvis, and the values of drug and tissue parameters on the spatial distribution.

To study these effects we will approach the subject in the way described in paragraph 2.4. First we build a model (par. 5.2), in this model we define which mode of transport we want to take into account, which material parameter plays a role in this transport mode, the geometric parameters (i.e. the anatomical model) and the boundary conditions (i.e. the placement of the electrodes).

Then we have to translate this model into a set of mathematical equations which can be used to calculate the drug distribution over the bladder wall. To do this we use the theory of electrodynamics (par. 5.2). At first a 1D situation is explained (par. 5.2.1), which helps to understand the formulation of the mathematical equations for the 2D situation of our model and the results obtained from that model (par. 5.2.2). Although a 3D model is needed to account for the total drug distribution, important conclusions can already be drawn from the 2D situation. Therefore we will not extend this to a 3D model in this study. The equations obtained from paragraph 5.3 in combination with the geometry and boundary conditions of paragraph 5.2 are to complicated to solve analytically. Therefore, a numerical solution method is used to solve the problem. We used the software package Sepran [Sep 93] that uses the finite element method. In paragraph 5.4 we will briefly describe how the finite element method works. The way in which the mathematical formulation, the anatomical geometry and the boundary conditions have to be implemented in the software package is described in appendix II.

As said in paragraph 2.5 the advantage of a numerical method is that it is very easy to study the effect of different parameters and differences in the values of these parameters on the drug distribution. Paragraph 5.5 gives an overview of these parameter variations. In paragraph 5.6 the results of these calculations are presented. These results are discussed in paragraph 5.7. The conclusions about the uniformity of the electromotive drug administration by this numerical method are formulated in paragraph 5.8.

5.2 A 2D model for the drug transport in the pelvis

5.2.1 Transport mode: Iontophoresis

In this chapter we will only study the spatial distribution of drugs that ionize upon solution. Therefore, from the transport modes described in chapter 3 we will take into account iontophoresis only. Electro-osmosis plays a role in the case of non-ionized drug molecules. Electroporation and successive passive diffusion enhancement may play a role in the transport of charged particles. However, because the exact mechanism is unknown it can not be modeled. Furthermore we will only look at the conductivity of a tissue for charged particles. Capacitive effects are left out of consideration, which is formally correct only at the onset of the treatment because nett charge accumulation takes time to build up.
Because the drug is ionized we will, in this chapter, use the electric current density (instead of the mass flow) as a measure for the transport rate. The mass flow is proportional to the current density (Eq. 1, par 3.1), therefore, the electric current density distribution over the bladder wall equals the mass flow.

From paragraph 3.1.1 we know that the conductivity $G$ of a tissue for a certain ion depends upon the specific conductivity $\sigma$ (a material parameter) and geometry of the tissue (geometry parameters).

5.2.2 Material property: the specific conductivity

Since competitive ions are the subject of chapter 6 and we are interested in the distribution of the total current to which drug mass flow is proportional in this chapter only, each tissue will be assigned only one 'mean' value for the specific conductivity. This mean value can be interpreted as a combination of the conductivities of all ions present. In addition, the multi layered tissue consisting of organs and other structures surrounding the bladder is assigned a single value for the specific conductivity. Furthermore these conductivities are assumed to be isotropic, that is they have the same value in all directions within the tissue. This is a simplification, as it is known that muscle fibers, for example, are not isotropic conductors.

5.2.3 Geometric properties: the anatomical model

From chapter 4 we have seen that the anatomy of the pelvis is very complex. Besides the bladder there are a number of other organs/structures present in the pelvis. In addition, the organs consist of different types of tissues. Modelling all these components may be feasible but laborious. Therefore, we will simplify the anatomy. In fact this simplification will have its effect on the spatial distribution of the electric field (and therefore the current distribution). Our arguments to start with this simplified geometrical mode are:

- If this simplified model reveals no uniformity deviations in drug deposition it will be necessary to check whether this also holds in a more detailed model, approximating human anatomy better.
- If however it does reveal significant uniformities, it can be regarded highly unlikely that these non uniformities will be compensated for by a fortuitous geometrical arrangement of structures/organs present.
- The simple geometry allows us to analyze the impact of several factors (drug solution conductivity, urine influx, membrane resistance, electrode position) on the spatial distribution of the drug. Using this geometry results can be understood and interpreted more easily instead of when we use a more detailed model.
- It is difficult to describe the exact shapes, dimensions and the structure of the components, and their relation to each other (this would require a 3D model). In addition, all these factors may vary due to anatomic variation. Furthermore, the conductivity values of these tissues/components are not available and it is not possible to measure them within the framework of this study.

We will now describe how the anatomy of the pelvis is modelled.

Since we use a 2D model we will look at a cross section of the pelvis at the level of the bladder, perpendicular to the vertical axis of the human body. The contour of the body is presumed to be cylindrical, so the cross sectional area is circular. The diameter of the body is chosen 35 cm (Fig. 5.1).
The geometry of the bladder changes with the influx of a fluid (e.g. urine or a drug solution), becoming more spherical as the bladder fills. While we are interested in the situation in which the bladder is filled, it may be considered being approximately spherical and therefore circular upon cross section. The diameter of the bladder is chosen to be 7 cm which corresponds with an intravesical (spherical) volume of 180 ml. The bladder is sited at the ventral side of the body. Therefore, the centre of the bladder is placed 10 cm ventral to the centre of the body. Structure of the bladder wall is rather complex consisting of layers of smooth muscles oriented in different directions, the trigone (smooth muscle of the bladder base), the continuations of the bladder with the ureters and urethra and an overlying very impermeable membrane (the urothelium). We will divide the bladder into two parts based on the difference in conductivity: the urothelium and the surrounding tissues (mostly muscles). The urothelium is modelled as a 2 mm thick layer. This value is an arbitrary choice, the most important point is that it is much more smaller than the other dimensions. The muscles of the bladder wall together with the other tissues surrounding the bladder are modeled as one compartment and given one "mean" value of conductivity. The skin, in fact the stratum corneum, the low permeable part of the skin is again modeled separately (2 mm, for this value the same argument holds as for the urothelium) and is modeled only at the site of the dispersive electrode.

**Figure 5.1**: The anatomical model
5.2.4 Boundary conditions: the placement of the electrodes

The method of electromotive drug administration uses an electric field to enhance the drug deposition. This electric field is applied through the placement of two electrodes. The placement of these electrodes affects the shape of the electric field and therefore the drug distribution. As a reference we use the configuration shown in figure 5.1. The spiral electrode is placed in the centre of the bladder. The electrode is circular upon cross section (diameter of 1 cm). The dispersive electrode is placed on the skin modeled at the ventral side of the body. (In Fig. 5.1 the electrode is not visible because in the anatomical model defined in Sepran, the value for the voltage of this electrode is prescribed on the boundary-line between the skin and the electrode. The electrode does not have to be modeled itself.) In our study we chose the spiral electrode to be positive (anode) and the dispersive electrode to be negative (cathode) In reality this would be the situation for positive drug ions.

5.3 The theory of electrodynamics

As said in the introduction we will first take a look at the transport of ions through subsequent tissues, by means of iontophoresis, in one dimension only (par. 5.2.1). The electrodynamics of this situation are equivalent to a conductor network. (This is equal to a resistor network, however, the tissues are thought of as conductors in stead of as resistors, since we are interested in the movement of the ions through the tissue instead of the resistance offered thereto.) The transport of ions (i.e. an electric current) can be calculated using simple equations. In our model we have to deal with transport of ions in two dimensions (par. 5.2.2). In that case, the conductor network can no longer be used. However, the mathematical equations that describe the transport of ions in a 2D situation can be derived from the equations of the conductor network.

5.3.1 The electrodynamics of a 1D situation

In a 1D situation the ions move through a tissue in one (spatial) dimension only. In the other two dimensions the tissue is infinitely extended or has the same cross sectional area everywhere. If we further assume that the value of the specific conductivity is the same everywhere in the tissue, the movement of ions through this tissue can be modeled as an electric current through a conductor (Fig 5.2).

![Figure 5.2: The movement of ions through a tissue is modeled as an electric current through a conductor. The voltage V represents the driving force, causing the ions to move. The current I represents the electric current constituted for by the moving ions. The total conductivity G of the conductor is determined by the geometric properties A (cross section) and L (length) and the specific conductivity \( \sigma \) of the tissue.](image)
The voltage $V$ over the chain represents the driving force which causes the ions to move from A to B thereby constituting an electric current. This current is represented by the current $I$ through the chain. The relation between the voltage $V$ over and the electric current $I$ through the conductor is governed by Ohm’s law (Eq. 1).

$$I = GV$$  \hspace{1cm} (1)$$

In this equation the driving force for the electric current is the voltage $V$ over the conductor. However, the actual force is the electric field strength. The electric field strength is given by the voltage $V$ over the conductor divided by the length $L$ of the conductor. The conductivity $G$ of the conductor represents the total conductivity of the tissue for the ions moving from B to C. As mentioned in chapter 3 the conductivity depends on the specific conductivity $\sigma$ of the tissue for a certain type of ion (a material property) and the cross section $A$ and length $L$ of the "channel" through which the ions move from A to B (geometric properties) (Eq. 2).

$$G = \sigma \frac{A}{L}$$  \hspace{1cm} (2)$$

The movement of ions through subsequent tissues can be modeled by placing more conductors in series, each conductor representing the conductivity of a different layer of tissue (Fig. 5.3).

**Figure 5.3:** The movement of ions through subsequent tissues can be modeled by conductor network. Each conductor representing the conductivity of a different tissue layer. Since there is no accumulation of charge the current $I$ is the same through all tissues.
Because capacitive effects have not been taken into account (steady state) there is no accumulation of charge. This means that the current $I$ is the same at every cross section in the 1D network. In that case the relation between the voltage $V$ over and the current $I$ through the conductor network becomes (Eq. 3):

$$I = \frac{G_1 G_2}{G_1 + G_2} V$$  \hspace{1cm} (3)

So the total current through subsequent tissue layers is determined by the conductivities of both tissues.

### 5.3.2 The electrodynamics of a 2D situation

In a 2D model we want to study the movement of ions through a cross section of the pelvis at the level of the bladder to determine the effect of the geometry on the current distribution over the bladder wall. In terms of the conductor network this means that we have to extend the 1D situation to a number of parallel chains of series of conductors so the ions are not confined to move in one dimension only but are free to move over the whole surface. In addition these parallel chains have to be connected to each other so that the ions can follow the route of the least resistance towards the surface electrode. In fact the ions can move in any direction, so the number of parallel chains and additional conductors we have to take into account should also be infinite. To account for this infinite number of possible pathways we have to abandon the conductor network and use a mathematical formulation (discrete versus continuous representation). The mathematical equations describing the transport of ions in a 2D situation can be derived from the simple equations used in the conductor network. The derivation of these equations is given in appendix I. Here we will restrict ourselves to the notation of the final result of this derivation, the equation we have to solve (Eq. 4).

$$\nabla \cdot (-\sigma \nabla V) = 0$$  \hspace{1cm} (4)

with

$$\nabla = \frac{\partial}{\partial x} \sigma_x + \frac{\partial}{\partial y} \sigma_y$$  \hspace{1cm} (4a)

For simple geometric situations this equation can be solved analytically. However, for our anatomical model, with different values of the specific conductivity $\sigma$, and the boundary conditions (prescribed values of the voltage $V$ at the electrode sites) this has to be done numerically using a numerical solution method.
5.4 The numerical solution method

The problem has to be solved numerically, therefore, we use the numerical software package Sepran. The solution method used in this package is the finite element method. In this paragraph we will briefly describe how this method works [Ste 84]. The practical implementation of the equation, the geometry and the boundary conditions in the software package are described in appendix II.

Equation 4 (par. 5.3.2) holds for all points in the tissue. However, in the finite element method, the voltage \( V \) (the degree of freedom), is calculated at a finite number of points in space, the so called nodes. In between these nodes, the voltage is calculated by interpolation of the nodal point values. To this end, nodes are grouped into elements. Different types of elements can be used, determining the way in which the interpolation is done. In this study we use triangular elements, consisting of three nodes. Within the element, the voltage values are obtained by linear interpolation of the three nodal point values. The distribution of the nodal points and subsequent elements over the geometry is called the mesh generation (Fig 5.4).

![Figure 5.4: The mesh generation. The anatomical model is filled up with nodal points (cross sections) and subsequent elements. Four surfaces can be distinguished: the bladder cavity, the bladder wall, the body and the skin. The nodal points on the surface-lines between two surfaces are used as nodal points in both surfaces. The open circle in the centre of the bladder is the anode.](image-url)
The voltage $V$ in the body can be plotted using equipotential lines, i.e. lines that connect points with the same value (Fig 5.5).

Figure 5.5: The voltage $V$ in the body. Equipotential lines are plotted from 0 V (skin electrode) to 1 V (electrode in the centre of the bladder) with an increment of 0.05 V (20 lines). Most lines are within the skin (i.e. the voltage drop in the skin is high because of the high resistance of the skin)

We are not interested in the voltage $V$ but in the electric current density $J$. Therefore, at first the electric field strength (a derivative of the voltage, appendix I) has to be calculated. The electric field strength can be calculated and plotted by Sepran also (appendix II, Fig 5.6).

Figure 5.6: The vector field of the electric field strength. The electric field strength is plotted in the bladder cavity only. The amplitude of the vector represents the magnitude of the electric field, the direction of the vector represents the direction of the electric field.

In addition, to obtain the distribution of the normal component (i.e. perpendicular to the bladder wall) of the electric current density over the bladder wall some operations have to be done on the electric field strength. These operations have been done with another software package: Matlab (appendix II). The results obtained are plotted in par 5.6.
5.5 Parameter variations

With the model discussed in this chapter we want to study the spatial distribution of the electric current density over the bladder wall. More specific, we want to study the effect of some parameters on this distribution by means of parameter variation. To carry out these parameter variations we need a reference. As reference we will use the anatomic model described in paragraph 5.2. The values of the conductivities of the different tissues in this model are denoted in table 5.1. This table also contains the position of the electrodes.

Table 1: The reference (REF), conductivities and placement of the electrodes.

<table>
<thead>
<tr>
<th>conductivity $\sigma$ [mS cm$^{-1}$]</th>
<th>placement of electrodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>cavity</td>
<td>wall</td>
</tr>
<tr>
<td>6.10</td>
<td>2</td>
</tr>
</tbody>
</table>

The parameters we want to vary are:
- the conductivity within the bladder cavity.
  The conductivity of the bladder cavity changes due to the influx of urine during the treatment.
- the conductivity of the bladder wall.
  The exact value of this conductivity is unknown, therefore we want to calculated the drug distribution over a wide range of conductivities.
- the placement of the electrodes.
  Changing the positions of the electrodes, changes the boundary conditions of the problem, thereby changing the electric field and subsequent the drug distribution.

The other parameters, the conductivity of the body and the skin, are kept the same in all calculations.

The different values of the conductivity of the bladder cavity are obtained from conductivity measurements on the intravesical solution during an animal test (par. 6.4), starting from a pure dye solution (start of the treatment), via a mixture of dye and urine (the end of the treatment) to pure urine (before the treatment). These values are listed in table 5.2.

Table 5.2: The different values of the conductivity of the bladder cavity used to study the effect of this conductivity on the drug distribution over the bladder wall.

<table>
<thead>
<tr>
<th>parameter</th>
<th>conductivity of the bladder cavity [mS cm$^{-1}$]</th>
<th>number</th>
</tr>
</thead>
<tbody>
<tr>
<td>values:</td>
<td>0.23</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>6.10 (REF)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>33.3</td>
<td>3</td>
</tr>
</tbody>
</table>
The different values of the conductivity of the bladder wall were unknown. Therefore, the values used in the calculations are chosen arbitrarily to study the effect over a wide range of conductivity values.

Table 5.3: The different values of the conductivity of the bladder wall.

<table>
<thead>
<tr>
<th>parameter: conductivity of the bladder wall [mS cm(^{-1})]</th>
<th>number</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (REF)</td>
<td>1</td>
</tr>
<tr>
<td>0.2</td>
<td>2</td>
</tr>
<tr>
<td>0.02</td>
<td>3</td>
</tr>
<tr>
<td>0.002</td>
<td>4</td>
</tr>
</tbody>
</table>

We have evaluated the following configurations of electrode placements as boundary conditions for the problem (table 5.4). Starting point was the placement described in par 5.2, i.e. the anode in the centre of the bladder and the cathode at the ventral side of the body. We then, subsequent, placed the anode eccentric, 1.5 cm toward the dorsal side of the bladder, or a second identical cathode at the dorsal side of the body. In both situations we left the position of the cathode resp. anode the same. Finally we combined both situations.

Table 5.4: The different configuration of electrode placements.

<table>
<thead>
<tr>
<th>parameter: placement of the electrodes</th>
<th>voltage [V]</th>
<th>number</th>
</tr>
</thead>
<tbody>
<tr>
<td>anode: centric</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>cathode: ventral</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>anode: eccentric</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>cathode: ventral</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>anode: centric</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>cathode: ventral &amp; dorsal</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>anode: eccentric</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>cathode: ventral &amp; dorsal</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>anode: centric</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>cathode: ventral &amp; dorsal</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
5.6 Results

In this paragraph we will show the results of the calculations on the different parameters mentioned in paragraph 5.5. Each parameter will be plotted in a different chart. The numbers in the charts refer to the different values of a calculated parameter, these numbers can also be found in the final columns of the tables in paragraph 5.5.

The definition of the axis in the charts of this paragraph is as follows:

**Vertical axis:** the normal component of the electric current density \( J \) (i.e. normal to the bladder wall) in mA/m. This unit, which is the result of the 2D model, is explained in appendix I. It is equivalent to the more common unit Ampère per square metre \([A/m^2]\) in the 3D situation.

**Horizontal axis:** the position on the bladder wall in degrees; 0° represents the ventral side of the bladder, 180° represents the dorsal side.

Electric current density distribution over the bladder wall for the reference (REF).

![Graph showing electric current density distribution over the bladder wall for the reference (REF).](image)

**Figure 5.4:** The electric current density distribution over the bladder wall in the reference situation. The electric current density is the highest at the ventral side of the body (0°) and gradually decreasing towards the dorsal side (180°).
Electric current density distribution for different values of intravesical conductivity.

The uniformity becomes worse as the conductivity of the solution increases. Values of conductivity 1) 0.23 mS/cm 2) 6.10 mS/cm 3) 33.3 mS/cm.

Figure 5.5: The effect of the conductivity of the intravesical solution on the electric current density.
Electric current density distribution for different values of bladder wall conductivity.

The effect of the conductivity of the bladder wall on the electric current density distribution. Again the uniformity becomes worse as the value of the conductivity of the bladder wall increases. Values of conductivity: 1) 2 mS/cm 2) 0.2 mS/cm 3) 0.02 mS/cm 4) 0.002 mS/cm.

Figure 5.6: The effect of the conductivity of the bladder wall on the electric current density distribution. Again the uniformity becomes worse as the value of the conductivity of the bladder wall increases. Values of conductivity: 1) 2 mS/cm 2) 0.2 mS/cm 3) 0.02 mS/cm 4) 0.002 mS/cm.
Electric current density distribution for different placements of electrodes.

Figure 5.7: The effect of the placement of the electrodes. 1) Reference situation. 2) eccentric anode; local effect, little effect on the difference between the maximum and minimum value of the electric current density. 3) second dispersive cathode; effect over a broader part of the bladder wall, decreasing the difference between max. and min. value of the current density. 4) combined effect of 2 and 3. 5) same configuration as 3. However, with a higher voltage drop over the second cathode and the anode than over the ventral cathode and the anode, to compensate for the eccentric position of the bladder.
Finally we will add an extra column to the tables of paragraph 5.5 in which we denote the ratio between the maximum and the minimum value of the electric current density; the uniformity ratio.

**Table 5.5:** The uniformity ratio the different values of the conductivity of the bladder cavity.

<table>
<thead>
<tr>
<th>parameter: conductivity of the bladder cavity [mS cm(^{-1})]</th>
<th>number</th>
<th>uniformity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>values: 0.23</td>
<td>1</td>
<td>1.45</td>
</tr>
<tr>
<td>6.10 (REF)</td>
<td>2</td>
<td>8.59</td>
</tr>
<tr>
<td>33.3</td>
<td>3</td>
<td>17.02</td>
</tr>
</tbody>
</table>

**Table 5.6:** The uniformity ratio for different values of the conductivity of the bladder wall.

<table>
<thead>
<tr>
<th>parameter: conductivity of the bladder wall [mS cm(^{-1})]</th>
<th>number</th>
<th>uniformity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>values: 2 (REF)</td>
<td>1</td>
<td>8.59</td>
</tr>
<tr>
<td>0.2</td>
<td>2</td>
<td>5.16</td>
</tr>
<tr>
<td>0.02</td>
<td>3</td>
<td>1.65</td>
</tr>
<tr>
<td>0.002</td>
<td>4</td>
<td>1.09</td>
</tr>
</tbody>
</table>

**Table 5.7:** The uniformity ratio for different configurations of electrode placements.

<table>
<thead>
<tr>
<th>parameter: placement of the electrodes</th>
<th>voltage [V]</th>
<th>number</th>
<th>uniformity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>values: anode: centric, cathode: ventral</td>
<td>1</td>
<td>1</td>
<td>8.59</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anode: eccentric, cathode: ventral</td>
<td>1</td>
<td>2</td>
<td>7.20</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anode: centric, cathode: ventral &amp; dorsal</td>
<td>1</td>
<td>3</td>
<td>2.23</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anode: eccentric, cathode: ventral &amp; dorsal</td>
<td>1</td>
<td>4</td>
<td>2.55</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anode: centric, cathode: ventral &amp; dorsal</td>
<td>1</td>
<td>5</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.7 Discussion

In this paragraph we will try to explain the results of our calculations on the effect of the studied parameters on the distribution of the electric current density over the bladder wall. We thereto compare two extreme "routes" through the body and intuitively explain why the one may enjoy the preference over the other, thereby giving rise to a certain amount of non uniformity of the current distribution. These two routes are (Fig. 5.4):

I A straight line directly from the anode to the cathode.

II A line starting in the opposite (dorsal) direction, eventually bending back towards the cathode at the ventral side of the body.

Figure 5.4: The two extreme routes (I and II) through the body, that will be used to explain why the one may enjoy the preference over the other.

The electric current density distribution in the reference situation (REF).

The reference situation is described in table 5.1. From the results in par. 5.6 we have seen that the electric current density in the reference situation is non uniform. This electric current distribution is calculated with equation 4 (par. 5.3.2). From this equation we see that this distribution is determined by the specific conductivities \( \sigma \) (material property) of the different tissues, the geometry of the anatomic model (geometric properties) and the boundary conditions (prescribed values of the voltage \( V \)).

If we only look at the two routes mentioned above we can again model them as a 1D conductor network consisting of a series of conductors (Fig. 5.3). Where B and C are the anode and cathode respectively, the voltage \( V_{BC} = 1 \)V and \( G_1 \) and \( G_2 \) are the conductivities of the bladder cavity and the body.
Spatial distribution

The bladder wall is not modeled separately because the specific conductivity of the wall is the same as that of the body in the reference situation. The bladder wall will be added below, which makes it possible to see the effect of the individual parameters.

The total conductivity of the conductor network (par. 5.3.1) is given by (Eq. 5):

$$ G_{tot} = \frac{G_1 \cdot G_2}{G_1 + G_2} \tag{5} $$

In the electric analogue the specific conductivity and the geometry are combined in the conductivity $G$ of the conductors in the circuit. The conductivity $G_i$ is the same for both routes, because the length and the specific conductivity are the same within the bladder cavity. However, $G_{\text{II}}$ is higher than $G_{\text{I}}$ because the length of route II through the body is longer than that of route I. Therefore, $G_{\text{tot,II}}$ is higher than $G_{\text{tot,I}}$. (And, $G_{\text{tot,II}}$ is higher than $G_{\text{II}}$).

The electric current through the chain is given by (Eq. 1.):

$$ I = G_{tot} \cdot V \tag{1} $$

So $I_II$ is larger than $I_I$, constituting the non uniformity of the current distribution. The magnitude of the non uniformity depends on the difference between the lengths of the routes in the body. However, this only holds because the whole body is assigned only one value for the specific conductivity. In that case one may say that the ions take the shortest route. The course of the electric current density over the bladder wall confirms this relation. The current density decreases from the ventral to the dorsal side of the bladder. The ions take the route of the least resistance (the resistance is the reciprocal of the conductivity). The effect of different tissues with different specific conductivities within the body will be addressed later.

The effect of the value of the conductivity of the intravesical solution

From the results on the calculations with different values for the intravesical conductivity we see that the non uniformity becomes greater as the conductivity increases. From the above we have seen that the non uniformity is, in fact, determined by the length of the route through the body. However, the effect of this difference on the magnitude of the uniformity is influenced by the conductivity within the bladder. This can again be shown looking at the two extremities.

If $G_1 \gg G_2$ the total conductivity $G_{tot}$ becomes (Eq. 6):

$$ G_{tot} = \frac{G_1 \cdot G_2}{G_1} = G_2 \tag{6} $$

In this situation the total conductivity is mainly determined by the conductivity of the body. While $G_2$ is different for both routes (proportional to pathlength) the electric current distribution is non uniform.
If \( G_1 \ll G_2 \) the total conductivity becomes (Eq. 7):

\[
G_{\text{tot}} = \frac{G_1}{G_2} = G_1
\]

In this situation the total conductivity is determined mainly by the conductivity of the bladder cavity. This conductivity is the same for both routes, thereby diminishing the non uniformity.

The effect of the value of the conductivity of the bladder wall

From the results on the calculations with different values for the specific conductivity of the bladder wall we see the same effect as above: the higher the specific conductivity of the bladder wall the greater the non uniformity. The reason for this is similar. When the conductivity of the bladder wall is small in comparison to the other conductivities the total conductivity is mainly determined by this layer. While this conductivity is the same for both routes (same length and specific conductivity) this reduces the non uniformity.

We have seen that a low conductivity of both the bladder cavity and wall reduces the non uniformity. However, a low conductivity also means that the amount of the electric current decreases (in the calculations we have used a constant value for the voltage between the anode and the cathode) and therefore, the total amount of drug administrated. The amount of the electric current can easily be adjusted by increasing the voltage between the anode and the cathode, so that the total current can be kept constant. That is why a current generator is applied in the clinical application.

The effect of the placement of the electrodes.

First we will take a look at the effect of placing the anode eccentric in the bladder cavity. So far the length of both routes in the bladder wall were the same. By placing the anode eccentric (towards the posterior side) in the bladder cavity the length of route II in the bladder cavity is smaller then that of route I. This reduces the difference in the lengths of the total routes and therefore the difference in the total conductivities. However because the bladder cavity is small in comparison to the body and the anode can not be placed to close too the bladder wall the effect on the total length of the route is small. From the results we see that the effect is confined to a small region at the dorsal side of the bladder wall. The differences in the distances between the anode and the lateral side and ventral side respectively are to small to be effective. However, when the specific conductivity of the bladder cavity is low this effect may become bigger because the total conductivity is then determined more by the conductivity of the bladder cavity and therefore, also more by the difference in the length of the routes in the bladder cavity.
Spatial distribution

By placing a second dispersive cathode at the dorsal side of the body the second route changes. The ions do not have to "bend" back towards the ventral side of the body. They can move to the dorsal cathode in a straight line (like the first route). This greatly reduces the length of route II. However, because the bladder itself is positioned eccentric in the body there is still a difference in the length of the routes and therefore a certain amount of non uniformity. Because the ions at the lateral sides of the bladder may also move to the dorsal cathode the effect on the uniformity of this second electrode is experienced over a broader region of the bladder wall then in the case of the eccentric anode.

The non uniformity, caused by the difference in the length of the routes (isotropic tissue conductivities, may be decreased by placing the dispersive electrode far from the intravesical electrode (e.g. on the upper leg). In that case the possible routes from the intravesical to the dispersive electrode are almost the same in length. Validation requires a 3D model.

The "expected" effect of non homogeneities in the body

So far we have modeled the body as consisting of one tissue with one value for the specific conductivity. In that case the non uniformity of the electric current distribution is mainly determined by the length of the route through the body, with the size of the effect depending on the specific conductivities of the body, the bladder wall and cavity. This is a simplification of reality. We will now say something about the effect of other tissues/organs present in the body. These effects have not been calculated, but we are able to give some comments on this subject by looking at the model.

Firstly, let us look at the effect of a small tissue within the body with a high specific conductivity, for instance a blood vessel [Duc 90]. When the conductivity of the surrounding tissue is lower the ions will move through the blood vessel. Because the dimensions of the vessel are relatively small this has no great influence on the length of a certain route of the ions through the body. So the influence of a small tissue with a high conductivity on the electric current distribution is small.

Secondly, there may be a certain tissue (e.g. an organ) with a specific conductivity that differs (higher or lower) from that of the one used in the calculations. Such a tissue may have an effect on the electric current distribution. To understand this one has to notice that the shortest route is not always the route of the least local resistance. For instance a short route through a tissue with a low specific conductivity (high resistance) may be preferable to a long route with a high specific conductivity (low resistance). Modeling such tissues may alter the electric current distributions calculated with our model.

However, there are two reasons why we can use our results to study the electric current distribution.
- These tissues/organs are present in the whole body (as well at the dorsal side as at the ventral side). Although they will influence the distribution, it is unlikely that this will lead to a more uniform distribution. This means that the amount of non uniformity in our calculations may well be an underestimation rather than an overestimation of the uniformities clinically manifest.
- When the specific conductivities of the bladder cavity and bladder wall are low compared to that of the body the electric current distribution over the bladder wall is mainly determined by these conductivities.
5.8 Conclusions

Reference geometry

1) The electric current density distribution over the bladder wall in the reference situation is far from uniform. The ratio between the maximum and minimum value of the electric current density, the uniformity ratio, is 9. This reference situation is a worst case situation. That is, a high specific conductivity for the bladder content and bladder wall and one dispersive electrode at the ventral side of the body.

Effect of the specific conductivity

2) A low specific conductivity within the bladder cavity improves the uniformity of the electric current density distribution. Our model shows a uniformity ratio of 1.5 for a specific conductivity of 0.23 [mS/cm] versus a ratio of 9 for \( \sigma = 6.10 \) [mS/cm] and a ratio of even 17 for \( \sigma = 33.3 \) [mS/cm] (table 5.5).

3) A low conductivity of the bladder wall also improves the uniformity of the distribution. In our model the uniformity ratio varies from 9 for a specific conductivity of 2 [mS/cm] to a ratio of 1.1 for a specific conductivity of 2x10^3 (table 5.6).

4) Although a low conductivity improves uniformity, it decreases the total amount of electric current. This can easily be adjusted by using a current generator, in which case higher voltages are required.

Effect of the placement of the electrodes

5) Placing the anode eccentric in the bladder (towards the dorsal side) has only a local effect on the electric current distribution. It increases the amount of electric current at the dorsal side of the bladder. However, it does not significantly alter the uniformity ratio: 7 in case of an eccentric anode versus 9 in the reference situation. Furthermore, placing the anode too close to the bladder wall may be dangerous (burns).

6) Placing an extra cathode at the dorsal side of the body affects the electric current density over a broader region of the bladder wall. In addition, it decreases the uniformity ratio (uniformity ratio: 1.5), which means an improved uniformity.

7) Placement of the dispersive electrode far from the intravesical electrode (e.g. on the upper leg) may improve the uniformity of the drug distribution. Validation requires a 3D model.
Assumptions of the model

8) The anatomic model is a simplification of the real situation. However, the non-uniformity resulting from our calculations is not likely to be an overestimation. On the contrary, modeling more structures/organs may well decrease the uniformity of the current density distribution rather than increasing it. The same argument holds for the assumption of isotropic specific conductivities for the different tissues.

9) The exact value of the bladder wall conductivity is unknown. Therefore, the effect of the bladder wall on the uniformity is studied over a wide range of arbitrarily chosen values for the bladder wall conductivity.

10) These calculations are based on iontophoresis as mode of transport only. Furthermore, accumulation of charge, which limits its validity to the onset of the experiment only, and electroporation have not been taken into account.

11) The model can be used to draw more or less qualitative conclusions with respect to the uniformity and the magnitude of the drug administration over the bladder wall only.
Chapter 6 The impact of competitive ions on the efficiency of electromotive drug administration

6.1 Introduction

In this chapter the effect of the presence of ions, other than the drug ions, on the amount of drug administered to the bladder wall (i.e. the amount of drug that passes through the mucosa) will be discussed. These other ions are referred to as competitive ions and consist of ions already abundantly present in the body, for instance K⁺, Na⁺ en Cl⁻ (co-ions) and ions that originate from dissolving the drug (counter-ions). The question we want to answer is: does significant presence of co- and counter-ions in the bladder content importantly reduce the efficiency of intravesical electromotive drug administration?

6.2 Competitive ions

All present ions, positively or negatively charged, contribute to the current, and can be considered as parallel channels (Eq. 1).

\[ I_{tot} = I_{drug} + I_{counter} + I_{co-ion} \] (1)

which can also be written as (Eq. 2):

\[ I_{tot} = \alpha I_{tot} + \beta I_{tot} + \gamma I_{tot} \] (2)

Where \( \alpha, \beta \) and \( \gamma \) reflect the percentages of the current carried by the drug-ions, counter ions and co-ions respectively: \( \alpha + \beta + \gamma \) equals 1. The factors \( \alpha, \beta \) and \( \gamma \) can be different for the different types of tissue that the current passes through. We are specifically interested in the distribution over the respective ion channels, of the current entering the mucosa, from which we can derive the amount of drug administered to the bladder wall. Local drug deposition rate (mg/min) at the bladder wall is proportional to the local current density (mA/cm²) of drug ions. The fraction of the current not carried by drug ions but flowing through other ion channels is not useful, in the sense that it does not contribute to drug deposition. The drug mass flow rate, which is the amount of drug administered to the bladder wall per unit time, becomes (Faraday’s law; Eq. 3).

\[ \phi_D = \frac{60 \alpha I_{tot} M}{z F} \] (3)

With \( \phi_D \) = the amount of drug administered per unit time [mg/min], \( \alpha I_{tot} \) = fraction of the total current through the mucosa carried by the drug-ions [mA], \( M \) = the molecular weight of the drug [g/mol], \( z \) = the valence of the drug ion [-], \( F \) = the Faraday constant (charge per mol monovalent ions) [C/mol]
A simple model is used to calculate the distribution of the current over the different ion channels described by the fractions $\alpha$, $\beta$ and $\gamma$ (from equation 2). This analysis however is done for the *bladder content only*. The reasons for this choice are:
- It is the starting point for the drug transport towards the target tissue;
- It is the only compartment of which the content can be controlled to a reasonable extent. Conditions at onset of EMDA treatment can be quite accurately defined;
- It is the only compartment of which the content and constituents are easy accessible; analysis of - for instance - mucosa tissue constituents is more invasive because of required biopsies.
- It is in the bladder compartment that a disturbance of optimal conditions can be expected due to inevitably present urine influx.
- Samples were available to us from an animal test (par. 6.3) which can be used for our purpose which is to estimate the impact of urine influx on EMDA-efficiency.

To analyze the current distribution we make use of a simple one dimensional electric analogue. Different ions are present in a compartment that can contribute to the current. The total current through this compartment can be seen as parallel branches through these different ion channels. The ion channels can be modelled as parallel conductors in the electrical analogue, each having a conductivity corresponding to the conductivity of the compartment content for that specific ion.

In the bladder cavity the competitive ions are:
- the drug ion
- the drug counter ion
- the ions present in urine entering the bladder
- the ions present in the drug solvent

A further assumption we make is that the bladder content is a homogeneous mixture. As we are only interested in the current distribution through the bladder cavity into the bladder wall, just for convenience we assign one overall conductivity for combined ion channels in the bladder wall and one overall conductivity for surrounding tissues plus skin layer. The one dimensional electric analogue is shown in figure 6.1, showing three conductors in parallel constituting the bladder content compartment, in series with one overall conductor for the mucosa layer and one overall conductor representing the tissues surrounding the bladder and the skin layer covered by the surface electrode.

**Figure 6.1**: One dimensional electric analogue to analyze the current distribution over the different ion channels in the bladder content: drug ions, co-ions and counter ions. The bladder wall (mucosa) and the other surrounding tissue layers (including the skin) are represented as one overall ion channel.
From this circuit we see that for the bladder content:

\[ I_{\text{tot}} = I_{\text{drug}} + I_{\text{co-ion}} + I_{\text{counter}} \]  \( \text{(1)} \)

The current through a column of conducting material \( i \) is given by (Eq.4, Fig 5.2):

\[ I = \sigma \frac{A}{L} V \]  \( \text{(4)} \)

Of course the actual geometry of the bladder compartment is far from column shaped, it is roughly spherical. For our purpose this is of no relevance, since for each ion channel \( A, L \) and \( V \) are the same. With equation 1 and 4 we get (Eq. 5).

\[ I_{\text{tot}} = (\sigma_{\text{drug}} + \sigma_{\text{co-ion}} + \sigma_{\text{counter}}) \frac{A}{L} V \]  \( \text{(5)} \)

Equation 4 also holds for the total current through the compartment which gives us the following equation for the voltage \( V \) over the tissue (Eq. 6).

\[ V = \frac{I_{\text{tot}}}{A_{\text{tot}}} \cdot \frac{L_{\text{eff}}}{A_{\text{eff}}} \text{ with } \sigma_{\text{tot}} = \sigma_{\text{drug}} + \sigma_{\text{co-ion}} + \sigma_{\text{counter}} \]  \( \text{(6)} \)

and with \( L_{\text{eff}}/A_{\text{eff}} \) representing the ratio of effective length over effective area.

We can then write equation 5 as follows (Eq. 7)

\[ I_{\text{tot}} = \frac{\sigma_{\text{drug}}}{\sigma_{\text{tot}}} I_{\text{tot}} + \frac{\sigma_{\text{co-ion}}}{\sigma_{\text{tot}}} I_{\text{tot}} + \frac{\sigma_{\text{counter}}}{\sigma_{\text{tot}}} I_{\text{tot}} \]  \( \text{(7)} \)

Looking back at equation 2 we see that (Eq. 8).

\[ \alpha = \frac{\sigma_{\text{drug}}}{\sigma_{\text{tot}}}, \quad \beta = \frac{\sigma_{\text{co-ion}}}{\sigma_{\text{tot}}}, \quad \gamma = \frac{\sigma_{\text{counter}}}{\sigma_{\text{tot}}} \]  \( \text{(8)} \)

Or in words: the fraction of the current conducted through a certain ion channel is directly proportional to the ratio of the conductivity of this ion-channel substance to the sum of the conductivities of the mixture components.
As the volume fraction of urine in the bladder compartment starts at zero (after flushing) and increases with time, these fractions change with time. At the start of current application, just after flushing and filling of the bladder compartment with the drug solution the fraction $\gamma$ representing the fraction of the current conducted through urine-minerals can be practically zero. After some yet unknown interval it may approach unity, in case of poorly conducting drug ions and drug counter ions. The conductivity is proportional to the ion concentration.

If we assume constant urine influx at a flow rate $F_{\text{urine}}$ (in ml/min) we can write for the conductivity of the urine ion channel (Eq. 9):

$$\sigma_{\text{urine}}(t) = \text{Vol. fraction}_{\text{urine}} \cdot \sigma_{\text{urine undiluted}}$$

with

$$\text{Vol. fraction}_{\text{urine}} = \frac{F_{\text{urine}} \cdot t}{V_0 + F_{\text{urine}} \cdot t}$$

The same holds for the time dependent conductivity of the drug ion channel:

$$\sigma_{\text{drug}}(t) = \text{Vol. fraction}_{\text{drug}} \cdot \sigma_{\text{drug undiluted}}$$

with

$$\text{Vol. fraction}_{\text{drug}} = \frac{V_0}{V_0 + F_{\text{urine}} \cdot t}$$

with $F_{\text{urine}}$ = the flow rate of the influx of urine

$\Delta t$ = the time interval in which the volume increases with $\Delta V$

$V_0$ = initial bladder volume, at $t=0$

6.3 Materials and methods

We can use measured values for the conductivities and volume fractions of the different components to calculate the fractions $\alpha$, $\beta$ and $\gamma$.

From an animal test comparable to the one described in paragraph 2.2.2 we obtained two series of liquid samples. One series of dog A that received EMDA-treatment, and a series of the control dog B in which no current was applied.

The samples available for each of the two dogs (A and B) are:

1) 'pure' urine, drained from the bladder before flushing (U).
2) dye solution (0.1 % gentian-violet, solved in water) as used to fill the bladder after flushing (D). This dye was used as a substitute for the drug to study the effect of electromotive drug administration (dye study).
3) mixture of dye and urine drained from the bladder directly after a treatment of 10 min
4) dedi water, used to complete 25 ml standard volumes required for conductivity measurements (W)
Conductive ions

Conductivities of these 25 ml samples were measured at 21.5 ° Celsius, using an AC conductivity meter WTW LF535.

The conductivities of the undiluted samples were then calculated using the following equation (Eq. 11):

\[
G_{\text{undiluted}} = (G_{\text{diluted}} - G_{\text{water}} \frac{V_{\text{water}}}{V_{\text{tot}}}) \frac{V_{\text{tot}}}{V_{\text{undiluted}}}
\]

\(V_{\text{tot}} = 25 \text{ ml} \) (standard volume for conductivity measurements). Then the mixtures (samples A3 en B3) were examined to determine the relative contribution of the different components to the conduction. First the volume fractions were calculated, which, together with the values for the undiluted conductivities, substituted in equations 9 and 10 result in the conductivity values of the dye and the urine in the mixture samples. With these values the relative contributions of the drug and urine ions to the total current can be calculated from equation 8.

### 6.4 Results

**Table 6.1:** Measured conductivity values of the samples (diluted with dedi-water to obtain a standard volume of 25 ml required for conductivity measurements; column 4) and the undiluted conductivity values, corrected for this dilution (column 5). The conductivity of dedi-water (\(G_{\text{water}}\)), necessary to calculate the undiluted conductivities, is also measured. Sample code: A and B stand for dog A and dog B respectively. The numbers 1, 2 and 3 indicate the components of the sample (par 6.3).

<table>
<thead>
<tr>
<th>Sample code</th>
<th>Components</th>
<th>Volume undiluted ml</th>
<th>Conductivity G diluted mS/cm</th>
<th>Conductivity G undiluted mS/cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>W</td>
<td>dedi-water (W)</td>
<td>25</td>
<td>0.0013</td>
<td>0.0013</td>
</tr>
<tr>
<td>A1</td>
<td>urine (U)</td>
<td>25</td>
<td>47.60</td>
<td>47.60</td>
</tr>
<tr>
<td>B1</td>
<td>urine (U)</td>
<td>13.9</td>
<td>25.50</td>
<td>45.86</td>
</tr>
<tr>
<td>A2</td>
<td>dye (D)</td>
<td>9.9</td>
<td>0.125</td>
<td>0.31</td>
</tr>
<tr>
<td>B2</td>
<td>dye (D)</td>
<td>8.9</td>
<td>0.083</td>
<td>0.23</td>
</tr>
<tr>
<td>A3</td>
<td>mixture (W+D+U)</td>
<td>15.8</td>
<td>1.47</td>
<td>2.33</td>
</tr>
<tr>
<td>B3</td>
<td>mixture (W+D+U)</td>
<td>17</td>
<td>4.15</td>
<td>6.10</td>
</tr>
</tbody>
</table>
Table 6.2: absolute and relative contribution (columns 4 and 5) to the conductivity of bladder content (drained immediately post treatment).

<table>
<thead>
<tr>
<th>sample</th>
<th>component</th>
<th>volume fraction</th>
<th>absolute contribution to conduction [mS/cm]</th>
<th>relative contribution to conduction [-]</th>
</tr>
</thead>
<tbody>
<tr>
<td>treated dog A3</td>
<td>urine (U)</td>
<td>0.04</td>
<td>1.90</td>
<td>0.86 (γ)</td>
</tr>
<tr>
<td></td>
<td>dye (D)</td>
<td>0.96</td>
<td>0.30</td>
<td>0.14 (a+β)</td>
</tr>
<tr>
<td>control dog B3</td>
<td>urine (U)</td>
<td>0.13</td>
<td>5.96</td>
<td>0.97 (γ)</td>
</tr>
<tr>
<td></td>
<td>dye (D)</td>
<td>0.87</td>
<td>0.20</td>
<td>0.03 (a+β)</td>
</tr>
</tbody>
</table>

The relative contributions denoted in the final column are the factors $\alpha + \beta$ (the conductivities of the dye ion and its counter ion cannot be measured separately) and $\gamma$ of equation 2. For dog A we find $\alpha + \beta = 0.14$ and $\gamma = 0.86$. For dog B we find $\alpha + \beta = 0.03$ and $\gamma = 0.97$. That is, after 10 min most of the current is constituted for by the co-ions present in the urine.

### 6.5 Conclusions

#### Dye ions

1) The selected dye (0.1 % gentian-violet, solved in water) is a poor electric conductor: ± 0.3 mS/cm (i.e. ± 150 x worse than urine).

#### Effect of co-ions (urine influx)

2) Continuous influx of urine in the bladder creates a significant current bypass. A small volume fraction of urine (± 10 %), which occurred already within 10 minutes after flushing can already conduct the bulk of the electrical current (± 90 %). This means that the amount of dye ions transported into the bladder wall, and therefore, the dye administration decreases.

#### Effect of counter ions

3) The relative contribution of the dye (D) calculated in table 6.2 is in fact the combined contribution of the dye ions ($\alpha$) and their counter ions ($\beta$). This means that the relative contribution of the dye itself is even less ± 10 %.

#### Assumptions of the model

4) The distribution of the electric current over the different ion channels as calculated in this chapter refers to the bladder content only.
Chapter 7: Conclusions and recommendations

In this chapter we give an overall picture of the results of our study and recommendations for further investigation. In paragraph 7.1 we recapitulate the conclusions obtained from the results of calculations on the spatial distribution of electromotive drug administration and give recommendations on how to improve the model used for these calculations. In paragraph 7.2 the same is done for the impact of competitive ions. In paragraph 7.3 we argue the use of an animal experiment in further investigations. In paragraph 7.4 we give recommendations on an animal experiment that is of use at this stage of the study.

7.1 Spatial distribution

The distribution of the drug administration over the bladder wall was investigated using a 2D mathematical (finite element) model. In the model iontophoresis was the sole mode of transport. Geometrical and conductivity properties of bladder cavity and wall, surrounding tissues and skin were considered. The uniformity of the electric current density, which is proportional to the drug mass flow, was expressed in terms of the uniformity ratio, defined as the ratio between the maximum and minimum value of the electric current density.

Conclusions

In the study we started with a reference situation. The uniformity ratio for this reference situation was 9, which means that the electric current distribution over the bladder wall is non uniform. This situation is a worst case situation. We used a high specific conductivity of the bladder content conductivity (the specific conductivity at the end of the EMDA-treatment in a animal test, table 5.2) and a high specific conductivity of the bladder wall conductivity (arbitrary choice due to the lack of a measured value).

A low specific conductivity of the bladder content and/or bladder wall improved uniformity of the current density distribution (conclusions 2 and 3, par 8.5). Placing a second dispersive electrode at the dorsal side of the body increased uniformity also, placing the intravesical electrode eccentric in the bladder wall had no significant effect on the uniformity (conclusions 5 and 6, par 8.5).

The values for the specific conductivity of the bladder content are realistic values, obtained from the measurement of the specific conductivity of the intravesical solution at the begin and the end of the treatment in an animal test. The bladder content showed an increase in conductivity from 0.23 to 6.10 \([\text{mS/cm}]\), due to the influx of urine. This increased the uniformity ratio calculated with our model from 1.5 to 9 (i.e. the uniformity decreased).

Because of lack of data on the specific conductivity of the bladder wall we investigated, using the model, the effect of a variation of this conductivity over three orders of magnitude. These calculations showed that for a low specific conductivity of the bladder wall (e.g. 1/10th of the specific conductivity of the bladder content at the start of the treatment) the uniformity ratio was 2. The calculations were made for a high conductivity of the bladder content (the end of the treatment), using one dispersive electrode only (i.e a worst case situation). This means that if the bladder wall indeed has a high resistance...
Conclusions and recommendations

(which is very likely because the mucosa is the least permeable tissue in the body)
uniformity is guaranteed within a certain range (maximum uniformity ratio of about 2).

Recommendations

Experimental data on the overall resistance of the mucosa layer (in different drug solutions to be used in electromotive drug administration) are needed to do more accurate predictions on the uniformity and the magnitude of the electric current density.

It is unclear yet, whether capacitive effects and electroporation are that important, that they should be incorporated in the present model. The expected effects are discussed in paragraph 3.1.2 and 3.3 respectively.

7.2 Competitive ions

Besides the magnitude of the electric current density, it is also important to know the relative contribution of the drug ions to this current in relation to the contribution of other (competitive) ions present. We have modeled this distribution for the bladder content using a 1D electric analogue in which three channels were modeled representing the competitive ions. The competitive ions in the bladder content are: the drug ion, the drug counter ion and the ions present in the urine entering the bladder.

Conclusion

Due to the continuous influx of urine the relative contribution of the drug ions to the electric current decreases during the treatment. This decreases the effective treatment time. The length of the effective treatment time is determined by:
- the relative mobilities of the ions present in the intravesical solution
- the concentration of drug ions in the intravesical solution
- the starting volume of intravesical solution
- the flow rate of urine influx

An illustration of the effect of competitive ions on the effective treatment time can be obtained from the calculations on our model. In this model the conductivity values and volume fractions for the different ions in the bladder content were obtained from an animal test (par 6.3). In this animal test a dye was used instead of a drug. Our calculations showed that a small volume fraction of urine (± 10 %), which occurred already within 10 minutes after flushing already conducted the bulk of the electrical current (± 90 %). Thus the continuous influx of urine in the bladder creates a significant current bypass.

Recommendation

The distribution of the current over the different ion channels calculated in chapter 6 holds for the bladder content only. When entering a subsequent tissue this distribution might change. The changes in quantities as concentration, electric field strength and pH are governed by basic laws of physics. Assistance on further investigations with respect to this subject is offered by the Department of Chemical Engineering, Section Instrumental Analysis, Eindhoven University of Technology).
7.3 The use of an animal experiment in further investigations

In chapter 2 we said that the results of our study might be used to propose an animal test in which uniformity and efficiency can be improved by information obtained from our study. However, we believe that at this stage it is not useful to do such an animal test. From our study it has become clear to us that electromotive drug administration is a very complex process. That is, the uniformity, the magnitude of the electric current density and the relative contribution of the drug ions to this current depend on a number of parameters. For some of these parameters we do not know their exact effect or their interactions. At this moment it is better to further investigate the items recommended in the previous paragraphs. This way it may be possible to eliminate uncertainties about the contribution of certain parameters to the drug administration. By doing so a more specific experimental setup for a future animal test with less unknown parameters can be used to verify the uniformity and efficiency of electromotive drug administration. General disadvantages of an animal test will always be the different physiology, tissue properties and bladder geometry of an animal and the fact that access to the bladder is hindered due to a smaller urethra.

At this moment we suggest the following. In paragraph 7.1 it is recommended to measure the value of the bladder wall conductivity. To obtain reliable data these measurements have to be conducted within one hour after excision because electrical characteristics of tissue alter following death [Duc 90]. It is disproportional to sacrifice an animal to obtain the conductivity value of the bladder wall only. However, this animal can also be used to obtain further information on the role of other transport modes in electromotive drug administration. Finally, this experiment can be used to study the overall effect of parameters that may improve the uniformity and efficiency of the drug administration. In the next paragraph recommendations are given with respect to the such an animal test.

7.4 An animal test

In this paragraph recommendations are given for an animal test that we believe to be of use at this moment. These recommendations are related to obtaining information of use to our models (par. 7.4.1), a quantitative way of measuring the drug administration (par. 7.4.2) and, finally, recommendations on how we, at this moment, think that the uniformity and efficiency can be improved (7.4.3).

7.4.1 Recommendations to obtain information of use to our models

- Bladder wall conductivity.

  Measurement of the bladder wall conductivity to obtain a more accurate value that can be used in the 2D model.
Conclusions and recommendations

Transport modes

- In our model we only took into account iontophoresis. In an animal test other transport modes can occur, and in that respect the results of the animal test are a better indication for the value of electromotive drug administration in clinical application. What is seen is the overall effect of all transport modes. An idea of which transport mode does contribute to the drug administration can be obtained as described in the recommendations below. If we know that other transport modes play an important role our models have to be expand.

- It is recommended to plot the current I and the voltage V of the current generator(s) during the treatment. An increase in the voltage V at constant current may be due to capacitive effects at the mucosa. This only holds if there is no influx of urine, so ureters have to be blocked and if the amount of drug in the intravesical solution is large in relation to the amount of drug deposited. Otherwise capacitive effects may be underestimated or even overlooked.

- It is possible to verify the effect of electroporation. Therefore, one has to use a radiolabeled drug solution (ionized upon solution) in relation with a dye solution (not ionized). The drug ions will penetrate the mucosa due to iontophoresis and if electroporation occurs passive diffusion. The driving force for the dye is passive diffusion only and therefore it only shows enhanced penetration into the mucosa if electroporation does occur.

7.4.2 Method of measurement

- To determine the amount of drug administered it is important to have a quantitative method of measurement. The best method is to use a radiolabeled drug.

- It is very important to make sure that the radiolabeled drug solution, used to determine the amount of drug deposition, has the same mobility as the drug solution used in clinical application.

- To study the distribution of the drug administration over the bladder wall it is important to divide the bladder in different sections (par 2.2.2)

- A radiolabeled measuring method requires preparation of thin slices (slice thickness < penetration depth), using a microtome, parallel to the bladder wall in order to obtain depth profiles of radiolabeled drug distribution and a scintillation counter to measure the activity of the tissue.

- Integral drug mass deposition over the whole bladder can easily be calculated from specific activity values of the intravesical solution pre and post treatment.

- Special precautions related to the use of radioactivity are required.

- Proper conservation of the excised bladder is of vital importance. Redistribution of radionuclides after excision must be prevented.
7.4.3 Recommendations to improve uniformity and efficiency

**Electrode placement**

- Uniformity of electric current distribution may be improved by placing a second dispersive electrode, with additional current generator at the dorsal side of the body. By applying equal currents one realizes an equal amount of total electric current towards the ventral and dorsal side of the bladder. In that case the voltage needed to constitute this current is higher in the dorsal situation. From our calculations we have seen that increasing the voltage over the anode and the dorsal cathode with a factor two (in relation to the voltage over the anode and the ventral cathode) resulted in an uniformity ratio of 1.5 where this ratio was 2.5 for the situation in which the voltage was the same for both dispersive electrodes.

- Uniformity can be improved even further by applying more electrodes around the body. This leaves the dome and the base as spots with minimum drug deposition.

- Due to the risk of burns and the small effect on the uniformity of an eccentric intravesical anode, the anode should be placed in the centre of the bladder cavity.

**Conductivity of the bladder content**

- A low conductivity of the bladder content and bladder wall improve the uniformity. However, the conductivity of the bladder content is the only one that can be controlled and therefore the only one that can be used to improve uniformity. A low conductivity of the bladder conductivity can be obtained by using a low drug concentration in the intravesical solution. Higher voltages are applied by the current generator to obtain a constant electric current. Attention has to be paid to the electric safety of the animal.

**Effective treatment time**

- Urine influx strongly reduces the efficiency of electromotive drug administration (effective treatment time < 10 min. in the animal test described in chapter 6). Therefore, the influx of urine, or more specific the ions present in the urine, must be restricted as well as possible. This results in a longer effective treatment time.

- The effect of the influx of urine can be reduced by:
  - A large starting volume of intravesical solution
  - A high starting concentration of drug ions, i.e. a high conductivity of the intravesical solution (see also the next item)
  - Reducing the flow rate of urine. There are a number of possible ways to do this:
    - Decreasing urine production medicinal.
    - Blocking the ureters with a belt around the body or clipping the ureters itself.
    - Blocking the orifices of the ureters using a biodegradable gel instead of an intravesical drug solution (suggested by the Department of Chemical Engineering, Section Instrumental Analysis, Eindhoven University of Technology, Eindhoven).
Conclusions and recommendations

- A contradiction arises when using a high starting concentration of drug ions to reduces the effect of urine ions as competitive ions. By increasing this concentration of drug ions the conductivity of the intravesical solution increases also, which worsens the uniformity of the drug distribution.

General remark

- The combined effect of eliminating urine influx and the use of low conductive intravesical solutions results in an optimum in the uniformity and efficiency of electromotive drug administration. Uniformity can be further improved by the placement of the electrodes. If the conductivity of the bladder wall is very low the uniformity is guaranteed by the bladder wall and the intravesical drug concentration may be increased to decreases the effect of the influx of urine on the effective treatment time. However, at this point value of the bladder wall conductivity is unknown. Therefore it is highly advisable to measure the conductivity value of the bladder wall (see par. 7.4.3).
References

- Griffith, D. Proposed model for animal test. Personal communication, 1995
Appendix I

Derivation of the equation describing the 2D electrodynamics

From paragraph 5.3.1 we have seen that the relation between the voltage $V$ over and the electric current through a conductor is governed by Ohm’s law (Eq. 1).

$$I = GV$$  \hspace{1cm} (1)

From paragraph 5.3.2 we have seen that to describe the transport of ions through the body, the number of conductors should be infinite. That is the dimensions of the conductors ($A$ and $L$) will become infinitesimal small. This means that instead of the current $I$, the voltage $V$ and the conductivity $G$ one has to speak of the current per unit of area (the current density $J$), the voltage per unit of length (the electric field strength $E$) and the specific conductivity $\sigma$. The specific conductivity is the material property of the total conductivity $G$. For the conductor in figure 5.2 this means:

$$J = \frac{I}{A}$$  \hspace{1cm} (2)

$$E = \frac{V}{L}$$  \hspace{1cm} (3)

and

$$\sigma = G \frac{L}{A}$$  \hspace{1cm} (4)

Substituting these definitions in Ohm’s law results in the following equation (Eq. 5):

$$J \cdot A = \sigma \cdot \frac{A}{I} \cdot E \cdot I$$  \hspace{1cm} (5)

It can be easily seen that all geometric properties vanish from this equation which results in the point form of Ohm’s law (Eq. 6).

$$J = \sigma \cdot E$$  \hspace{1cm} (6)

Notice that in this formulation the current density and the electric field strength have become vectors in the three dimensional space. In this situation the specific conductivity should be a tensor to account for non isotropic material behaviour (with respect to the conductivity). However, we assume the tissues to be isotropic. In that case the tensor becomes a scalar and the direction of the electric current density is equal to the direction of the electric field strength.
Appendix I

In this study we are interested in the two dimensional situation, considering a cross section of the pelvis at the level of the bladder. In that case the current density is defined as the current per unit of length (Ampère per meter, Eq. 7).

\[ J = \frac{I}{L} \]  \hspace{1cm} (7)

instead of the current per unit of surface (Ampère per meter\(^2\), Eq. 8).

\[ J = \frac{I}{A} \]  \hspace{1cm} (8)

Both are referred to as current density.

\[ \nabla \cdot J = 0 \]

\[ - \frac{\partial J_x}{\partial x} + \frac{\partial J_y}{\partial y} = 0 \]  \hspace{1cm} (9)

The divergence of the current density is zero. This means that the change of J in the x direction plus the change of J in the y direction is equal to zero. Physically this equation states that there is no nett accumulation of charge (assumed in par. 5.1). If capacitive effects are present in intravesical iontophoresis, this equation holds for the first instant only, as long as no net charge accumulation has been produced at the mucosa surface.

Figure 1.1: The definition of the current density. In a 2D situation, the current over a surface, the current density is defined as the current per unit of length. In the 3D situation, the current through a certain volume, the current density is defined as the current per unit of surface.

In discussing the conductor series network we said that the current was the same in each conductor, what comes out of one conductor goes into the subsequent conductor. In the 2D situation this holds for every point in the body. The mathematical formulation of this situation is as follows (Eq.9):

\[ \nabla \cdot J = 0 \]  \hspace{1cm} (9)
Appendix I

It is the distribution of this current density we are interested in. To determine this we compute the direction and amplitude of the driving force of the electric current, that is the electric field strength $E$. Actually it is better to speak of an electrodynamic field, because the field is the result of moving charge instead of static charges. From equation 6 we see that the direction of the current density vector is the same as that of the electrodynamic field vector. The amplitude of the current density is the conductivity $\sigma$ times the amplitude of $E$. To compute $E$ we substitute equation 6 in 9 (Eq. 10):

$$\bar{\nabla} \cdot \sigma \vec{E} = 0$$  \hspace{1cm} (10)

Furthermore we use the relation between the actual driving force $E$ and the voltage $V$. From the electric analogue we know that $E$ is equal to the voltage over a certain distance divided by that distance $L$. For an infinitesimal small length this relation becomes (Eq. 11).

$$E = -\nabla V = -(\frac{\partial V}{\partial x} \vec{e}_x + \frac{\partial V}{\partial y} \vec{e}_y)$$  \hspace{1cm} (11)

We substitute this equation 11 in equation 10 (Eq. 12).

$$\bar{\nabla} \cdot (-\sigma \nabla V) = 0$$  \hspace{1cm} (12)

This is the equation we have to solve, which gives the potential field.
Appendix II

The use of the software packages Sepran and Matlab

The solution method used in the software package Sepran to solve the problem is described in paragraph 5.4. The practical implementation of the equation, the geometry and the boundary conditions in the software package are described in this appendix. We will not go extensively into the details of the program, but merely comment on aspects that are relevant in the context of this report. Detailed documentation on Sepran is available in the Sepran manual [Seg 93].

We will first take a look at how the anatomic model (par. 5.2) is subdivided into a number of elements and nodes: the mesh generation. Then we will describe the implementation and solving of the actual equation: the main program. Finally we will describe the postprocessing on this solution, partially executed by subroutines in the main program and partially by the program Matlab, to obtain results that can be easily interpreted.

The mesh generation

The mesh generation is executed by a standard Sepran program: sepmesh (written in Fortran). In an inputfile (listing II.1) the user has to define the geometry, i.e. a number of surfaces representing the different tissues in the anatomic model (based on differences in conductivity), and the type of elements that have to be generated. For the definition of the geometry the user must define the main points necessary for the generation of curves. These curves can then be combined to form the surfaces. In Sepran a number of standard elements are available. The element we use is a triangle with three nodal points (Fig. II.1),

![Figure II.1: The element used to solve the problem numerically. The degree of freedom (the voltage V) is calculated in the nodal points. Within the element, the voltage values are obtained by linear interpolation of the three nodal point values.](image)

which means that the degree of freedom (in our study the voltage V) is assumed to vary linearly over the boundaries of the element. This is denoted in the inputfile by the additive 3 (shape number of the element) in the definition of the surfaces. In addition, the curves that form the boundaries of a surface are part of the elements too, therefore one has to add the additive 1 in the definition of the lines, which means that the lines are linear. The accuracy of the method depends partially on the size of the elements in relation to the dimensions of the total geometry. More and smaller elements result in more accurate modelling but is computational more demanding. The size of the elements can implicitly be defined by giving the number of elements you want on the curves of a surface. This is denoted by nem = 1 which means the number of elements on a curve is i. This together
with the length of the curve determines the size of the elements. In most of the applications it is not necessary to have small elements all over the geometry. You define small elements in regions where you expect large variations in the solution of the degree of freedom (the bladder and the ventral side of the body) and large elements where you expect the variations to be small (dorsal). Finally the program generates the mesh distribution.

**Listing II.1: Inputfile for the meshgenerator.**

```plaintext
MESH2D
  coarse(unit=0.010)
  points
    p1=(0.0,0.175,3.0)
    p2=(0.0,0.1,1.0)
    p3=(0.0,-0.075,1.0)
    p4=(-0.0,-0.110,1.0)
    p5=(-0.0,-0.145,1.0)
    p6=(-0.049,-0.168,1.0)
    p7=(0.049,-0.168,1.0)
    p8=(0.0,0.175,1.0)
    p9=(0.0,0.105,1.0)
    p10=(0.0,0.115,1.0)
    p11=(-0.049,-0.170,1.0)
    p12=(0.049,-0.170,1.0)
    p13=(0.0,-0.073,1.0)
    p14=(0.0,-0.147,0.2)
  curves
    c1=arc1(p1,p6,p2)
    c2=arc1(p6,p8,p2,nelm=5)
    c3=arc1(p8,p7,p2,nelm=5)
    c4=arc1(p7,p1,p2)
    c5=cline1(p8,p14)
    c6=arc1(p5,p3,p4,nelm=50)
    c7=arc1(p3,p5,p4,nelm=50)
    c8=cline1(p5,p10,nelm=15)
    c9=arc1(p10,p9,p4,nelm=10)
    c10=arc1(p9,p10,p4,nelm=10)
    c11=cline1(p6,p11,nelm=1)
    c12=arc1(p11,p12,p2,nelm=10)
    c13=cline1(p12,p7,nelm=1)
    c14=arc1(p14,p13,p4,nelm=60)
    c15=arc1(p13,p14,p4,nelm=60)
    c16=cline1(p14,p5,nelm=1)
  surfaces
    s1=general3(c3,c4,c1,c2,c5,-c15,-c14,-c5)
    s2=general3(c6,c7,c8,-c10,-c9,-c8)
    s3=rectangle3(N=10,M=1,-c3,-c2,c11,c12,c13)
    s4=general3(c14,c15,c16,-c7,-c5,-c16)
  meshsurf
    selm1=s1
    selm2=s2
    selm3=s3
    selm4=s4
  plot(plotm=10d0,yfact=1d0,jmark=5,numsub=0)
end
```
The main program

The main program is used to build a set of linear equations necessary to solve the problem. One writes this program using standard subroutines available in Sepran. We will not go into the details of how these subroutines work (The main program is listed at the end of this appendix, listing II.4). It is more interesting to look at the inputfile for this program (listing II.2). In the inputfile one first of all has to define the sort of problem one wants to solve. This depends on the equation one wants to solve and the type of elements used. In Sepran prepared solutions for a number of standard problems are available.

The equation we want to solve (equation 1).

$$\nabla \cdot (\sigma \nabla V) = 0 \quad (1)$$

is a second order elliptic differential equation with one degree of freedom of which the general notation is (Eq. 2):

$$-\nabla \cdot (\alpha \nabla c) + \sigma \cdot \nabla c + \beta c = f \quad (2)$$

The degree of freedom c corresponds to the voltage V in our equation. Furthermore, the element we use is a linear triangle. The standard problem definition number for this situation is 100. This has to be defined for each surface in the block PROBLEM...END. In addition, the boundary conditions must be defined. There are two types of boundary conditions: essential boundary conditions and natural boundary conditions.

An essential boundary condition means that the degree of freedom, the voltage V, is prescribed on some part of the boundary. In our situation these are the curves constituting the electrodes. The curves on which essential boundary conditions are present are defined in the block PROBLEM...END, their values are defined in the block ESSENTIAL BOUNDARY CONDITIONS...END, the values are 1 V (anode) and 0 V (cathode) respectively. The value 0 does not have to be specified (default).

Natural boundary conditions are boundary conditions concerning the derivative of the degree of freedom. In our case that is the electric field E (equation 11, appendix I). While the area outside the body contour can be seen as an insulator the normal component of the electric field equals zero. For this problem this is also a default situation and therefore this natural boundary condition does not have to be defined on the body surface explicitly. In the block COEFFICIENTS...END the coefficients of equation 2 have to be defined. By comparing equation 1 and 2 we see that the values for the coefficients u, $\beta$ and f equal zero. These coefficients do not have to be defined (default). The coefficient $\alpha$ corresponds to the conductivity $\sigma$. For each element group the value of $\alpha$ equals the conductivity of the tissue represented by that element group.
set time on
set warn on
set output on

PROBLEM
types
elgrp1, (type = 100)
elgrp2, (type = 100)
elgrp3, (type = 100)
elgrp4, (type = 100)

essential boundary conditions
curves0(c12)
curves0(c9,c10)

END

COEFFICIENTS
elgrp1 (nparm = 7)
  coef1 = (value = 2d0)
  coef3 = coef1
elgrp2 (nparm = 7)
  coef1 = (value = 6.1d0)
  coef3 = coef1
elgrp3 (nparm = 7)
  coef1 = (value = 0.2d-1)
  coef3 = coef1
elgrp4 (nparm = 7)
  coef1 = (value = 0.2d1)
  coef3 = coef1

END

OUTPUT
write 2 solutions

Listing II.2: inputfile for the main program: the problem definition.

The solution of the differential equation results in a value for the voltage in each nodal point. However, we are not interested in the voltage but in the direction and amplitude of the electric current density. Therefore, we have to postprocess the solution. With the subroutine derive it is possible to calculate the direction and amplitude of the electric field in each nodal point. Both solutions can be plotted, the voltage as contour lines connecting nodes with the same voltage and the electric field strength as a vector field (subroutines plotcl and pictvc). For further processing another program (Matlab) is used. Therefore we print the values of the electric field strength (subroutine prinr), while we are primarily interested in the distribution over the bladder wall we will only print the values at the nodal points of the curves representing this wall. This results in an matrix of n rows (n the number of nodal points) and 5 columns: the number of the node, the x and y coordinate and the x and y component of the electric field strength.
Matlab is very well suited for calculations on matrices. In Matlab we have written a simple program to calculate the actual electric current density, normal to the bladder wall, over the bladder wall (listing II.3). The program transforms the x and y component of the electric field strength into a normal component (perpendicular to the bladder wall). In addition, these values are multiplied with the conductivity to obtain the electric current density. Finally these results are plotted in a chart, with on the x axis the position on the bladder wall, in degrees (0 degrees is the ventral side of the bladder, 180 degrees is the dorsal side), and on the vertical axis the normal electric current density.

```
Eveld=input('Eveld = eveldn: ');
coor=[Eveld(:,2) Eveld(:,3)];
coorl=coor(1:51,:);
coorm=coor(52:100,:);
coore=coor(101:,:);
phip=(pi/2)+atan((coorp(:,2)+0.1l)./(coorp(:,1)));
phim=(3*pi/2)+atan((coorm(:,2)+0.1l)./(coorm(:,1)));
phie=(5*pi/2)+atan((coore(:,2)+0.1l)./(coore(:,1)));
phi=[phip
     phim
     phie];
phigr=phi*(180/pi);
sigma=input('waarde sigma: '); 
ldicht=sigma*[Eveld(:,4) Eveld(:,5)];
Iflux=(-ldicht(:,2).*cos(phi))+(ldicht(:,1).*cos(pi/2-phi));
plot(phigr,Iflux)
```

**Listing II.3**: Matlab program. This program is used to calculate and plot the normal component of the electric current density as a function of the position on the bladder wall.
Appendix II

Listing II.4: The main program.

c * opslaan waarden veldsterkte op de blaaswand
    ichois = 1
    number = 0
    icurvs(1):=6
    icurvs(2):=6
    icurvs(3):=7
    text = 'E-veld'
call
    prinr(ichois,kmesh,kprob,isol(1,2),number,icurvs, $text,idum)
c * plotten van de resultaten
c* equipotentiaallijnen
number=1
    jsmoot=1
    ncntln=20
    contin(1)=100
    do 10 i = 1, 20
        contin(i+5) = 0.0 + 0.05*i
    continue
    plotf1(number,kmesh,kprob,isol(1,1),contin,ncntln,plotfm, $yfact,jsmoot)
c* vectorveld electrische veldsterkte (in de blaas)
idgf1=1
idgf2=2
    yfact=1d0
    factor=0d0
    jkader=0
    jmax=1
    xmin=-0.045
    xmax=0.045
    ymin=-0.155
    ymax=0.055
call
    plotvc(idgf1,idgf2,isol(1,2),isol(1,2),kmesh,kprob, $plotfm,yfact, factor)
c * wegschrijven van de oplossing
call output(kmesh,kprob,isol)
c * afsluiten sepran
call finish(0)
end