A mathematical model to study reentrant cardiac arrhythmias

Citation for published version (APA):

Dassen, W. R. M. (1983). *A mathematical model to study reentrant cardiac arrhythmias*. [Doctoral Thesis, Maastricht University]. Rijksuniversiteit Limburg. <https://doi.org/10.26481/dis.19830310wd>

Document status and date:

Published: 01/01/1983

DOI:

[10.26481/dis.19830310wd](https://doi.org/10.26481/dis.19830310wd)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the 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](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

A Mathematical Model To Study Reentrant Cardiac Arrhythmias

Proefschrift

Ter verkrijging van de graad van doctor in de geneeskunde aan de Rijksuniversiteit Limburg te Maastricht op gezag van de rector magnificus Prof.Dr. H.C. Hemker, volgens besluit van het College van Dekanen in het openbaar te verdedigen in de aula van de Rijksuniversiteit, Tongersestraat 53 te Maastricht, op donderdag 10 maart 1983 des namiddags te vier uur precies.

door

Willem René Marie Dassen geboren te Maastricht.

Promotor: Prof. Dr. Hein J.J. Wellens, Maastricht The Netherlands
Prof. Dr. Rob M. Heethaar, Utrecht The Netherlands
Referenten: Prof. Dr. Harry A.J. Struyker Boudier, Maastricht The Netherlands
Frans J.L. van Capelle PhD, Amsterdam The Netherlands
David L. Ross MB, BS, Sydney Australia

Het verschijnen van dit proefschrift werd mogelijk gemaakt door steun van de Nederlandse Hartstichting en Rescar (stichting ter bevordering van research in de cardiologie)
Maastricht.

To my parents

To Doortje

Contents

Chapter 1.

Introduction	1
1.1 Historical overview	1
1.2 The philosophy behind the model	7

Chapter 2.

Description of the mathematical model used to simulate clinical cardiac electrophysiology	11
2.1 The model	11
2.2 The simulation study	15
2.3 The 35 different segment states	16
2.4 Order of handling	22
2.5 Handling of a segment without changes in electrophysiological parameters or new impulses	24
2.6 The introduction of a new impulse	26
2.7 Consequences of short refractory periods and non constant conduction velocity	29

Chapter 3.

Some simulation studies using the model	43
---	----

Chapter 4.

General discussion	59
4.1 Limitations	59
4.2 Accuracy	66
4.3 Real time application	67
4.4 Clinical applications	67
4.5 Didactical aspects	68

Chapter 5.

Summary	71
Samenvatting	71
Rizzumee	72

Chapter 6.

Appendix I : Handling of a segment	75
------------------------------------	----

Chapter 7.

Appendix II : Introduction of an impulse	89
References	101
Slotwoord	107
Curriculum vitae	109

"The great tragedy of Science -
the slaying of a beautiful hypothesis by an ugly fact"

T.H. Huxley
(1825-1895)
Collected Essays

Chapter 1.

Introduction

1.1 Historical overview

In 1561, the noble Rutgerus of Randwick, mayor of Gennep, Holland, visited his physician Johann Weyer because of palpitations. Dr Weyer described the pulse of Rutgerus of Randwick as having an intermittent rhythm with every third beat a so-called "pulsus caprizans". (1)

Although at that time the interpretation of the pulse and the accompanying prognosis, as described by Galen (2) in the second century were still considered to be valid, Weyer recognised already, that the outcome of a disease not only depended on the characteristics of the pulse but also on the underlying condition of the patient.

Also for this patient, Weyer was right. Rutgerus did not die from his arrhythmia, but recovered after a copious evacuation. He was slain in 1583, murdered by a group of Spanish riders. (3)

Galen's interpretation of the pulse and its prognostic significance remained valid until the 17th century.

But Galen was not the first author interested in the arterial pulsations and their abnormalities.

Already in 500 BC. the art of feeling the pulse was known in China. Approximately in the year 280, a classic treatise on the pulse published in ten volumes was available in China. Roughly at the same time the "Pen tsao" (= System of Medicine) was published. In the sixth century it took Li Shi 30 years to compile it for publication. Using this method location and site of all diseases could be derived by studying the accompanying pulse. (4 - 5)

At the end of the 19th century it was possible to record the mechanical pulse, and to register the electrical activity using the capillary electrometer. (6)

It was not until the beginning of the 20th century, that cardiac rhythm could be studied in a more easy and accurate way.

In 1906 Einthoven, professor in Physiology and Chancellor of the University of Leiden, presented at the occasion of the 331st anniversary of the University his ideas about the use and the advantages of registration of the electrical activation of the heart with the help of the string galvanometer. Using this device he was able to make registrations of good quality. Referring to the fact that the patient in the hospital, and the cardiograph in his laboratory were connected over a long distance by telephone wires (!) the first registrations were named "Telecardiograms". At the same time Einthoven made some interesting remarks about the value of electrophysiological research and its relation to medicine. (7) He stated :

... physiology is no longer only pleasant entertainment, like the reading of a simple novel for a serious reader of scientific literature, but indeed an important and

necessary subject of study....

The introduction of the recording of the electrical activity of the heart by a string galvanometer, was an important step on the long way to clinical electrophysiology of today.

In 1906 Einthoven showed that by using different electrode positions potentials of different morphology could be recorded. He also gave examples of 2:1 atrioventricular block, extrasystoles, bigeminal rhythm and dextrocardia. In the same article he suggested the study of the influence of the administration of drugs on atrioventricular conduction. (8)

Although the electrical registration of human cardiac activity was introduced in the beginning of this century, several decades passed before a more direct approach to the study of rhythm and conduction disturbances in the intact human heart became possible.

Important landmarks in the study of arrhythmias were the introduction of the recording of intra-cardiac potentials by Latour en Puech in 1957 (9) and the combination of intracardiac recordings coupled with programmed stimulation of the human heart by Durrer (10) in 1967. In that study the authors demonstrated in four patients with the WPW syndrome the initiation and termination of circus movement tachycardia by using properly timed electrical stimuli.

This was followed shortly thereafter by the development of a reliable catheter technique to record the His bundle electrogram in the human heart. (11)

The availability of these intracardiac stimulation and recording techniques accelerated the accumulation of knowledge on conduction and rhythm abnormalities in man.

In 1971 Wellens (12) described the use of programmed stimulation of the heart in patients with atrial flutter, AV nodal tachycardia and the pre-excitation syndromes. One year later he reported on the use of this technique in patients suffering from ventricular tachycardia. (13)

In patients suffering from tachycardia clinical electrophysiological studies can be of great help in determining the underlying mechanism of the arrhythmia and the selection of treatment. (14)

These investigations however, are not without risks, relatively unpleasant to the patient, expensive, and time and personnel consuming.(15)

The study and understanding of mechanisms of tachycardias in patients using electrophysiological investigations is difficult because only limited data are available :

- Most patients are investigated only a few times.
- The number of healthy volunteers to study impulse formation and conduction in the normal heart is almost nil.
- Many electrophysiological parameters are influenced by the autonomic nervous system. These changes are difficult to quantify and to control and cannot be reproduced at will. (16)

Because of these limitations and also because of ethical reasons, it is impossible to perform certain studies in the intact human heart, like the effect of chronic drug intoxication on impulse formation and conduction. In such cases the use of an animal model can be of great help. Using such a model it is possible to repeat an experiment several times under well defined laboratory conditions. The fluctuations in sympathetic and vagal tone and their influences on electrophysiological parameters, are however very difficult to control in the intact animal model and extrapolation to the human heart is difficult.

To simulate electrophysiological experiments in a reproducible way, without spontaneous or autonomic fluctuations in any parameter, one can use a mathematical model.

This requires that the investigator describes all different parts of the model and defines the relations between them.

Following a mathematical description, the investigator can use actual values obtained during an electrophysiological study to test the effect(s) of various perturbations on the model. In such a model both the consequences of changes in parameters as selected by the investigator, and the effect of the introduction of extrastimuli can be studied.

By defining basic electrophysiological properties of the model and the induced changes, the investigator will be able to test hypotheses that originate during clinical electrophysiological investigations in man. Also multiple changes and combinations of changes in electrophysiological properties, which can not be investigated during the clinical stimulation study, can now be studied under defined circumstances. While attractive, computer simulation also has its limitations as will be shown later.

The use of a mathematical model to study electrophysiological properties of the heart is not new. Several models have been used to study aspects of cardiac electrophysiology, such as :

- a) Basic cardiac electrophysiology (17 - 26)
 - b) Reconstruction of the electrocardiogram (27 - 41)
 - c) Simulation of the function of some parts of the conduction system of the heart (42 - 45)
 - d) The simulation of the total heart or parts of it, to study mechanisms, observed during clinical electrophysiological studies. (46 - 50)
-
- a) Basic cardiac electrophysiology

Mathematical models have been developed to study the generation of impulses and their conduction to adjacent cells. Some of these models describe quantitatively membrane potentials, propagation of action-potentials and interference between two individual pacemakers. (17-23). Sharp for instance (20), combined numerical methods for solving cable equations and previously published models for membrane properties to simulate cardiac impulse propagation along a unidimensional strand. Decreased excitability and changes in intercellular

coupling could be simulated. All these models were based on data from the cellular level derived from experiments using microelectrode techniques. The contribution by Hodgkin and Huxley (24) on mechanisms of impulse generation and propagation through a core-conductor model of propagation can be considered a standard work, forming the basis for several other models. In their work they introduced a model of an excitable cell on which the so-called Hodgkin-Huxley equations are based.

Recently van Capelle (25) published a study about impulse propagation in a two-dimensional model. In this model sheets consisting of coupled excitable elements were used to simulate arrhythmias. Before simulation starts the geometry of the network, the amount of coupling between elements and the electrophysiological properties of the elements, describing excitability, automaticity, and refractory period are defined. After defining the contour of the sheet of elements, using a joystick and a graphic display of the contour, elements can be removed, leaving holes in the sheet. In the same way connections between elements can be deleted, changed or added and the type of cells of the different elements can be modified. Using the same technique, the site of stimulation and the elements selected to be monitored on the terminal are determined. The activation of each element is recorded on a disk file for further interpretation. Using a sheet of these elements it was possible to simulate both focal and reentrant arrhythmias. The author suggests that the spatial interaction could play an important role in this type of investigations.

It is of interest that many investigators describing impulse propagation concentrated upon intestinal tissue beside cardiac tissue because of its less complicated morphology as compared to the cardiac tissues. (26)

All models so far discussed, describe the heart in its basic state or allow the summation of a small number of elements.

b) Reconstruction of the electrocardiogram.

One of the oldest models to reconstruct the cardiogram was developed by Van der Pol in 1928. (27).

In 1965 Silvester showed in an analog model, that it was possible to simulate the vectorcardiogram. (28). To do so he divided the heart in 20 segments, each containing an independent time varying dipole. This model of a 20-dipole heart was located in an inhomogeneous volume conductor to simulate the torso.

This was followed a few years later by a digital version. (29 - 30) Using these more powerful techniques the resolution was increased considerably. The Purkinje fiber distribution having homogeneous conduction velocity and the sites of first activation determined during animal experiments have to be given to the model. Myocardial lesions of 7-10 mm diameter and 2-3 mm thickness can be recognised in the simulated cardiograms.

In the model designed by Min in 1974, a matrix of relaxation oscillators coupled in two directions was used to describe the electrical activity in smooth muscle like stomach and small intestine. To describe these oscillators a group of non-linear differential equations were applied. This made it possible to simulate the normal

electrocardiogram, some arrhythmias and the use of an external pacemaker. (31) Also in the model of Rosenberg one is able to simulate a number of arrhythmias. (32)

In many of these models designed to reconstruct the surface electrocardiogram, special attention is given to the influence of size and shape of the thorax on the configuration of the electrocardiogram. (33 - 41).

In 1978 Miller presented a digital model for the simulation of body surface electrocardiograms during the ventricular activation and recovery. (33) Using approximately 4000 elements in a three dimensional array, a reconstruction of the ventricles of the heart was made. These 4000 elements were grouped into 23 regions. Data about the excitation sequence and the action potentials were taken from the literature. By summing up all potentials in each region the dipole representing that region can be calculated. By combining these 23 dipoles and assuming the heart to be surrounded by a homogeneous volume conductor with the shape of an adult male torso, the potentials on the surface could be simulated. In the same issue of Circulation Research Miller described the simulation of ischemia and infarction. (34) This was based on the hypothesis that ischemia is reflected by a decrease in the magnitude of the resting potential and changes in action potential duration. By progressively modifying the action potentials in those elements representing the area of ischemia, the electrocardiographic signs of ischemia could be simulated.

Anterior and inferior transmural ischemia and infarction and anterior subendocardial ischemia could be simulated.

Based on the assumption that the ventricles (apart from the septum) have a eccentric spherical configuration, Hori (35) developed a mathematical model of the activation of the ventricles. Like others he divided the ventricle in a number of small elements each containing one dipole. To calculate the behaviour of every dipole data derived during animal experiments were used. In this model a few limitations are present. 1) There is no intraventricular septum. 2) The eccentric spherical model does not duplicate the morphology of the ventricles satisfactory. 3) The conduction velocity in the conduction system and the myocardium is assumed to be constant.

In the model constructed by Ritsema van Eck (37) a much more accurate representation of the morphology of the two ventricles was given.

In this 3-dimensional model the ventricle was reconstructed using 155000 regularly packed rhombododecahedragonal cells, each with a volume of 1.28 mm³. The endocardial surface was covered by a network of Purkinje cells. Each myocardial cell was assumed to be at rest, activated or refractory. The time delay between the activation of adjacent cells represent the conduction velocity. Also in this model laboratory data were used to determine the first sites and times of activation.

In the study of Rudy and Plonsey (38) special emphasis was given to the influence of variations in the location of the heart on the potentials measured at the epicardium. The effect of the surface layer and subcutaneous fat on these potentials was shown to be minimal. In a second study the author (40) used this model of eccentric spheres to determine the influence of a number of factors on the electrocardiogram. They studied the influence of the blood pool on these potentials,

anemia and polycythemia. Low lung conductivity (emphysema), low and high pericardial and myocardial conductivity was simulated and the influence on the electrocardiogram was studied. The influence of low skeletal muscle conductivity, obesity, a thick myocardium protruding into the lung region, increase of myocardial wall at the expense of the blood cavity and finally the position of the heart in the torso was determined.

Ramsey (41) simulated the surface electrocardiogram using potentials directly measured on the epicardial surface instead of using a number of dipoles. To do so 90 electrodes were chronically implanted on the ventricle. Heart to body surface transfer coefficients were derived from the measured geometric coordinates of all the electrodes, assuming a homogeneous volume conductor between the epicardium and the body surface.

In the study by Arntzenius et al (36) several different models designed to reconstruct the heart are discussed.

c) Simulation of the function of some parts of the conduction system of the heart

These models are developed to describe and investigate the function of parts of the cardiac conduction system.

In 1971 Omerca made an analog model of the conduction in cardiac tissue, using a tunnel diode. (42)

This was followed in 1973 by a mathematical description of conduction through the AV Node by Heethaar. (43) To analyse AV nodal conduction an isolated perfused rat heart was stimulated using a variety of impulse sequences such as fixed rates and frequency steps. The response was measured on the left ventricular epicardium. Using these data a mathematical description of the AV node was determined. By stimulating the atrium at a random cycle length, which was longer than the AV nodal refractory period, the ventricular response was determined and compared with the mathematical model. It was shown to be possible to determine the atrial cycle length or the AV nodal conduction time from the ventricular cycle length. After including the influence of refractoriness in the behaviour of the model the influence of blocked impulses can be studied.

It appears that the influence of a blocked impulse and a conducted impulse on the conduction time can be calculated using the same mathematical equations. In this model Wenckebach conduction can be demonstrated. The same author also constructed an analog model of AV nodal conduction to find a physiological explanation for the mathematical relationships found during AV nodal conduction (44-45). A transmission line of coupled excitable cells was used obeying the Bonhoeffer-Van der Poll equations. The reaction of the transmission line on fixed rates of stimulation and frequency steps was compared with the behaviour of the AV node in animal experiments.

d) Simulation of the total heart or parts of it, to study mechanisms observed during clinical electrophysiological studies

Only in this group of mathematical models mechanisms of arrhythmias and relevance of clinical observations can be studied.

In these models the conduction system or parts of it have been simulated. This allows testing of hypotheses from clinical electrophysiological investigations.

To simulate the whole heart one cannot use a model based on a description of impulse propagation between cells. Such a model would be enormous because millions of coupled oscillators have to be taken into consideration. Furthermore during clinical electrophysiological investigations the properties of these cells are not known.

In 1982 Holley used a 3-dimensional model of the ventricles to simulate ventricular tachycardia. (46)

Our group has previously reported on the use of a mathematical model to study factors influencing stability of a circus movement tachycardia. (47- 48) During an invasive electrophysiological investigation in a patient a characteristic pattern of termination of a circus movement tachycardia was observed. Using data on AV nodal conduction, a single purpose model to study this alternation of the tachycardia cycle length prior to termination, was constructed. The findings using this model were compared with the clinical data. Both were in complete agreement. These results were used to verify the behaviour of the model described in this thesis. Using a mathematical model, we also described that some of the criteria advanced as diagnostic for triggered activity as mechanism of a tachycardia, can also be observed in arrhythmias using a reentry circuit.(49)

A major problem with investigations using mathematical models is the need to design a completely new model for every simulation study because new components of circuits involved in conduction of impulses have to be used. It is of interest that all these mathematical models have some parts in common.

To make simulation studies available to a larger field of users, a general model of electrical conduction through the heart was designed.

The specifications and properties of such a model are described in this thesis.

The limitations of such a general simulation model will be discussed also.

1.2 The philosophy behind the model

The aim of this study was to develop a mathematical model to facilitate research in clinical electrophysiology. We therefore wanted to have a model whose structure and components would allow implementation of data derived from clinical studies.

Invasive electrophysiological investigations can be performed for different reasons.

- 1) To localize the site of the abnormality in the conduction system in patients with conduction disturbances.
- 2) To study the mechanisms of tachycardias.
- 3) To select the best medication to protect the patient against the recurrence of arrhythmias.
- 4) To increase our knowledge of the 12 lead electrocardiogram by correlating findings from electrophysiological investigations with the surface electrocardiogram.

In our department clinical electrophysiological investigations are performed as follows:

After local anaesthesia, the femoral vein is punctured and catheters are introduced percutaneously and positioned in the heart under fluoroscopic control. The following locations of the catheter are most often used : 1) the high right atrium, 2) across the tricuspid valve ring to record His bundle electrograms, 3) the coronary sinus to record and stimulate the left atrium, 4) the apex of the right ventricle. To record and stimulate the left ventricular apex, the catheter is introduced retrogradely to the left ventricle using the femoral artery or using a transseptal approach in patients with a patent foramen ovale. Catheters are used for recording the local activity and to deliver electrical stimuli. By using tri- or quadripolar catheters stimulation and registration from one site can be performed simultaneously.

By recording activation times from the different catheters conduction times between the different sites of the heart can be determined. These measurements of conduction times are performed during sinus rhythm and during pacing at different cycle lengths. The relation between heart rate and conduction time can be studied. Using a basic paced rhythm and one extra stimulus, the refractory period of the different parts of the conduction system of the heart can be determined. By using different sites and different stimulation cycle lengths initiation and termination of tachycardias is studied and the influence of medication on arrhythmias evaluated. During the investigation all signals are recorded simultaneously and continuously on 16 channel paper and stored on tape. The paperspeed used (100 mm/s) gives a measurement accuracy of 5 to 10 ms.

During these electrophysiological investigations information of the electrophysiologic properties of the heart at the cellular level does not become available. Also knowledge about the exact topographical and morphological aspects of the conduction system in the patient under study cannot be obtained. This makes it impossible to reproduce the activation of the heart in a way as done in the Ritsema van Eyk model.

Furthermore information about the electrophysiological properties of the intact human heart is limited, because the number of sites of observation using intracardial catheters has to be restricted for practical reasons.

As described, by using catheter techniques one can obtain information about conduction between different sites of the heart. It gives values on conduction velocity and the duration of refractory period of tissue in between the sites of the different cathetertips.

In general: to be useful our model should fulfil the following criteria :

- It should resemble reality as closely as possible, especially in relation to stimulation studies performed in the intact human heart.
- It should be based on a modular concept. This will enable flexibility both in the layout of the conduction pathways, as in the electrophysiological properties of these pathways.
- The behaviour of the model should be logical and understandable.

- Results should be presented in a uniform way, at an acceptable computing speed.

The model described in this thesis has to fulfill the following extra requirements:

- Only data should be used that can be derived from invasive electrophysiological investigations. Not in the first place to be able to reproduce the activation in each patient who undergoes electrophysiological investigation, but to be able to test hypothesis derived from finding during these studies.
- The model should be applicable without special knowledge about handling computers. The program has to collect all input data in a ergonomic way. This input of data and the resulting output of results should be performed using a syntax understandable for clinical electrophysiological investigators.

By constructing the model in this way, not using coupled oscillators (which properties cannot be determined during invasive electrophysiologic investigation) all these conditions can be fulfilled.

Approaching the study of reentry arrhythmias using network analysis techniques makes it possible to translate clinical hypotheses directly into computer language.

In the development of this mathematical model a number of assumptions have been made of which some cannot be tested and other apparently are made arbitrarily. For example the assumed homogeneity of different segments, the absolute refractoriness of an element, (an element is refractory or excitable, there is no state inbetween), the selection of a simulation cycle length of 1 ms and the subdivision of a segment in 100 elements. In this thesis a rationale will be given at the time of making these assumptions.

In the model only tachyarrhythmias on the basis of reentry will be simulated. Other mechanisms of arrhythmias like parasystole can be simulated in the model, but only as an independent source of impulse formation.

Chapter 2.

Description of the mathematical model used to simulate clinical cardiac electrophysiology

- 2.1 The model
- 2.2 Simulation studies
- 2.3 The 35 different segment states
- 2.4 Order of handling
- 2.5 Handling of a segment without changes in electrophysiological parameters or new impulses
- 2.6 The introduction of a new impulse
- 2.7 Consequences of short refractory periods and non constant conduction velocity

2.1 The model

As mentioned in chapter 1 the structure of the mathematical model is based upon observations obtained during invasive clinical electrophysiological studies in man.

During these investigations catheters are introduced into the heart at a number of sites. At these sites the intracardiac electrical activity is recorded and programmed electrical stimulation performed to study conduction between different parts of the heart and the mechanisms of tachycardias.

With the information obtained by these techniques, one can design a network, built of segments, in which the segments represent the pathways between different sites in the heart. In this network we assume that the impulse is able to propagate along the different segments in only anterograde, retrograde, or both directions.

Segment properties depend on the electrophysiological data, measured with help of the catheters. The junctions between the different segments in our model represent the catheter positions used in the patients.

This approach allows the implementation of observations from electrophysiological studies into a mathematical network.

By using information about the electrophysiological properties of the segments in between two junction points as obtained during programmed stimulation of the heart values from clinical electrophysiological studies can be put into the model.

Fig 2.1.1. gives an example from a patient with the Wolff-Parkinson-White syndrome having a left sided accessory pathway between the atrium and the ventricle.

FIGURE 2.1.1.

Legend to figure 2.1.1.

This figure is a schematic drawing of the heart and its conduction system. As shown there are six junction points, representing the catheter positions (open circles) used during the electrophysiological investigation.

The segments are located between the junction points, indicating that conduction between these points in at least one direction is possible. Catheter positions: 1. High Right Atrium; 2. Low Right Atrium; 3. Coronary Sinus; 4. His Bundle region; 5. Right Ventricle; 6. Left Ventricle. Note that on the left side of the heart an accessory pathway is present enabling conduction between atrium and ventricle over this structure.

Definitions

Conduction time in one segment: the time required for an impulse to travel through a segment from one junction point to the next one. These times can be related to the cycle length of the last cycle (so called rate-dependency).

The refractory period of a segment is the longest time interval between two successive impulses during which the second impulse is unable to penetrate into a segment in the same direction.

In the model described hereafter a segment can either be excitable or refractory. No intermediate possibility exists in this model.

In clinical electrophysiology it is very difficult to differentiate between the partially refractory and the complete refractory state. Since the model is only using data that can be derived during these clinical studies, the relative refractory phase has been ignored and only two states are accepted: refractory or excitable.

The segments of the model have homogeneous electrophysiological properties which do not change during the conduction of an impulse through the segment. This does not mean that each impulse through the segment has the same conduction

time or that the segment has always the same refractory period. Both can be changed for example in relation to the rate of impulses going through the model. During conduction through a segment, however, the conduction velocity is considered to be constant.

Although it is rather unlikely that all electrophysiological parameters are distributed homogeneously over a segment, there is no better information available. The properties of a segment, derived during electrophysiologic investigations are also determined over the whole segment independent of the actual distribution of these properties.

The conduction velocity and the refractory period are defined in anterograde as well as in retrograde direction. This is done because electrophysiological properties of parts of the cardiac conduction system can be, and frequently are, different in anterograde and retrograde direction.

Unidirectional block in a segment is represented in our model by inability to conduct in one direction. If unidirectional block would have been represented by extremely slow conduction through a segment, permanent block occurs in the direction opposite to conduction.

An impulse travelling through a segment is followed by a refractory sector. The length of this refractory sector is determined by the time of activation of the first element, the conduction velocity in the segment and the duration of the refractory period. The first activated element is the first one to be excitable again after termination of the refractory period. After a certain period of time following activation of an element, not all elements within a segment will be refractory. The elements activated first can again be excitable. The elements which at a certain time interval are still inexcitable are considered to form a tail of refractoriness.

As soon as the first element becomes excitable again the refractory or excitable state of the segment is defined by the position of the tail. In the same direction, impulse and tail travel with the same velocity.

To define the position of the impulse and the tail, each segment is divided into 100 elements. Element 1 is the first element used, when an anterograde impulse is conducted through the segment. During retrograde conduction element 100 is the first one activated. When an anterograde impulse has reached or passed the element 100, the impulse is considered to have left the segment, leaving behind a certain number of refractory elements.

The subdivision of a segment in 100 elements is arbitrary. By increasing the number of elements the accuracy will only increase if the simulation cycle length decreases with the same magnitude. This procedure will increase computing time. More information on the relation between computing time and resolution is given in paragraph 4.2.

Another important concept of the model is the collision point. If an anterogradely and a retrogradely conducted impulse collide, the collision point within the segment is calculated. This calculation is made by taking into account the old positions of the impulses together with the conduction velocities in both directions.

Usually at both sides of the collision point a part of the segment is refractory. The

collision point is always the last activated element of a segment, and the last one to become excitable again.

Conduction velocities are defined as the number of elements in a segment (100), divided by the conduction times in ms. Conduction velocity is defined both in anterograde (AV) and retrograde (RV) direction.

Conduction distances in each direction are defined as the number of elements passed by an impulse during one simulation cycle, (see below) in each direction. They are also defined anterogradely (AD) and retrogradely (RD).

In the model simulation cycle lengths of 1 ms have been selected arbitrarily. Longer cycle lengths to increase simulation speed, or shorter cycle lengths to increase temporal resolution are possible however.

The best resolution achieved using registrations on paper is 5 till 10 ms. Using a simulation cycle length of 1 ms the model is always more accurate than these registrations.

Segment states.

Every segment is defined by its state and the value of its parameters. In figure 2.1.2. a schematic representation of a segment is presented. An impulse is penetrated in the anterograde direction.

FIGURE 2.1.2.

Legend to figure 2.1.2

This figure shows a segment with an anterogradely partially conducted impulse. The position of the impulse (AP) is indicated by an open circle. The refractory part of the segment is marked by the shaded area. The number one in this figure indicates the first (excitable) element. The time this element will remain refractory represents the refractory state of the segment after a conducted impulse.

AP indicates the position of the impulse in the segment. If the impulse is located at position no 1, it means that the impulse has just entered the segment. If the impulse reaches position 100, or passes it, the impulse is considered to have left the segment and the value of AP returns to zero. An AP value of zero indicates therefore that no impulse is being conducted through the segment.

FIGURE 2.1.3.

Legend to figure 2.1.3

This figure shows a segment with an anterogradely "vanishing" tail. The position of the refractory tail is indicated by an open square. The symbols used in figure 2.1.2 and 2.1.3 will be used in following illustrations. In these illustrations a collision point (CP) will be indicated by a black circle, the position of a retrogradely conducted impulse by RP and the retrograde vanishing tail by RL.

As soon as the time for refractoriness at the first excitable element has returned to zero, some elements will become excitable again during the next simulation cycle. The AL (Anterograde tail) represents the end of the refractory tail after conduction of an impulse. It is processed in the same way as an impulse is processed.

2.2 Simulation studies

A simulation study contains the following five parts.

- 1) Defining the network.
The site and number of junction points are selected. The segments, representing pathways, are located between these junction points.
- 2) Defining the electrophysiological properties of the segment. The properties of the segments are defined, including: conduction velocity, refractory period and ability of an impulse to be conducted into one or both directions.
- 3) Defining the initial state. If at the start of the simulation study the network is not conducting impulses and no segment is (partially) refractory, all segments are in state 1. (see paragraph 2.3).
- 4) The actual computation.
During the simulation process a certain sequence of operations is continuously repeated.
 - a) The first operation is the calculation of the state of each segment after one more cycle. To calculate the new state, the present state and electrophysiological properties of the segment are considered. The different possibilities are described in detail in paragraph 2.5.
 - b) In the second step the introduction of an impulse into a segment is considered. This impulse can be conducted from one segment to a junction point and from there into all the segments that are connected to that junction point. The impulse can also be entered over a free end of a segment, that means a junction point connected to one single segment. Before an impulse can enter a segment a number of conditions have to be fulfilled. In paragraph 2.6 these conditions are listed.
 - c) In the third step the model tests whether or not the electrophysiological properties of one or more of the elements have changed. The possible consequences of a change in electrophysiological parameters are listed in paragraph 2.7.
- 5) Presenting the results.
Results can be presented in three different ways:
 - a) The time of activation of a junction point is given, together with the number of the segment which was conducting this impulse. Also when applicable the occurrence of a collision point is reported. This enables the user to draw ladder diagrams of activation through the conduction system.

- b) After every computational cycle (or a multiple of cycles) all parameters of one or more segments can be printed. This makes it possible to study very accurately the behaviour of a part of the conduction system. The amount of data, however, is too big to use this method over a long period of time.
- c) In special circumstances it is possible to represent the defined network on a high-resolution graphic display. The position of impulses, tails and collision points can be displayed realistically. The amount of work required however, limits this application only to didactical purposes.

2.3 The 35 different segment states

Considering the definitions and limitations as described in detail in paragraph 2.7., only 35 different states of a segment are required to define the possible states of a segment. These states (ST) will be described in more detail below. By limiting the number of states to 35, the structure of the model remains simple and computer time can be reduced.

ST 1. The segment is not electrically activated, there is no impulse within the segment and all elements of the segment are excitable. The segment is able to conduct the next impulse.

ST 2. There is one impulse being conducted anterogradely. This leaves all the elements up to the left junction refractory. Ahead of the impulse all the elements of the segments are excitable.

ST 3. All elements of the segment are refractory as the result of a previous anterogradely conducted impulse. The state of the whole segment is defined by the time period the first activated element on the left side will remain refractory.

ST 4. The last activated elements on the right side of the segment are still refractory. The part on the left side of the segment which was activated earlier is potentially able to conduct a new impulse. The length of the refractory part of the segment is defined by the position of the tail in this segment.

ST 5 This is a combination of the second and the fourth state. A part of the segment is still refractory, caused by a previously anterogradely conducted impulse. At the excitable left side of the segment an impulse has entered the segment. The impulse is conducted anterogradely at a fixed distance behind the tail, since the conduction velocity of the impulse and the tail are considered to be equal

ST 6 This state is essentially identical to the second situation. However the impulse is now being conducted retrogradely through the segment.

ST 7 As in state three all elements of the segment are refractory. In contrast to the third state, this is the result of a previously retrogradely conducted impulse.

ST 8 The left side of the segment is still refractory, because of a previously retrogradely conducted impulse. The right side of the segment is no longer refractory and is potentially able to conduct an impulse retrogradely.

ST 9 A retrogradely conducted impulse follows a tail at a fixed distance, through the again excitable part of the segment on the right side

ST 10 An impulse is conducted both in anterograde and retrograde direction. After a period of time these two impulses will collide and create a collision point, leaving the whole segment refractory on both sides of the collision point.

ST 11 As predicted in state 10 the antegrade and retrograde conducted impulses created a collision point, leaving the whole segment refractory. The refractory period on the left and the right side of the collision point may or may not be equal in length.

ST 12 The left part of the segment, made refractory by a previously antegradely conducted impulse, is able to conduct impulses again at the beginning of the segment. The elements on the right side of the collision point are still completely refractory.

ST 13 This is the reverse of state no 12. Now starting at the right side of the segment some elements are potentially excitable.

ST 14 The elements on the left side of the segment, up to the collision point, made refractory by a previously antegradely conducted impulse, have recovered completely. The elements on the right side of the collision point are still refractory.

ST 15 The reverse of state 14. On the left side of the collision point all elements are still refractory. On the right side, however, all elements are again excitable.

ST 16 Both ends of the segment are again excitable, but on the right side of the collision point some elements are still refractory.

ST 17. Also in this situation both ends of the segment are again excitable. The reverse is shown from state 16

ST 18. While both ends of the segment are excitable, some elements on the left and the right side of the collision point, are still refractory.

ST 19. This situation represents the ultimate one, before the segment can be considered totally electrically excitable again. By definition it will last for only one simulation cycle.

ST 20. Anterogradely an impulse is conducted in the direction of the collision point. Some elements on the right side of this impulse up to the collision point are still refractory. All elements on the right side of the collision point are still refractory, caused by a previously retrogradely conducted impulse.

ST 21. All elements on the left side of the collision point are still refractory. On the right side of the collision point, only some elements are still excitable. At the right end of the segment a new impulse is conducting through the segment in retrograde direction

ST 22. On the left side of the collision point an impulse is conducted in anterograde direction. Between this impulse and the collision point all elements are excitable. On the right side of the collision point all elements are still refractory.

ST 23. On the left side of the segment all elements are *refractory* up to the collision point. On the right side of the collision point an impulse is conducted in retrograde direction. All elements between this impulse and the collision point are excitable.

ST 24. Anterogradely up to the collision point the segment is electrically excitable. Retrogradely there is a refractory tail in between the collision point and a retrogradely conducting impulse.

ST 25. A tail of refractoriness from a previous retrogradely conducted impulse is present on the right side, up to the collision point. Anterogradely an impulse is conducted starting on the left end of the segment.

ST 26. In anterograde direction an impulse follows a tail in the direction of the collision point. On the right side of the collision point all elements are electrically excitable.

ST 27. On the left side of the collision point a tail of refractoriness created by an anterogradely conducted impulse is present. The right side is electrically excitable, apart from an impulse conducted in retrograde direction.

ST 28. Both on the left and on the right side of the collision point some elements are refractory. On the left excitable end an impulse is conducted in the anterograde direction.

ST 29. This is the reverse of situation 28.

ST 30. In this situation, as in the two previous ones, a collision point is present with a refractory tail at both sides. At both excitable ends an impulse is conducted in the direction of the collision point. These impulses are followed by a refractory tail.

ST 31. The refractory tails on the left and the right side of the collision point have disappeared. An anterogradely conducted new impulse followed by a refractory tail has entered the left side of the segment.

ST 32. The reverse of situation 31.

ST 33. The state of the collision point is the same as in situation 31 and 32. There is an collision point without refractory tail at both sides. From both the left and the right side of the segments, an impulse is conducted into the direction of the collision point.

ST 34. Also in this situation two impulses, one conducted in anterograde and one in retrograde direction are occurring. In between there is a collision point with a retrograde refractory tail.

ST 35. This situation is the reverse of situation 34.

2.4 Order of handling.

Possibilities

First we will discuss the handling of impulses, which have been introduced into a segment in an earlier simulation cycle, the handling of the refractory tail and the collision point.

In paragraph 2.6 the introduction of external impulses will be discussed and lastly in paragraph 2.7 the influence of changes in electrophysiological parameters.

The 35 different states are all constructed using three different parameters, an impulse, (i) a tail (t) and a collision point. (c)

To select a uniform order of handling all combinations were considered and one selected (i t c).

Considering three different parameters (i, t, c), six different permutations are possible :

i	i	t	t	c	c
t	c	i	c	i	t
c	t	c	i	t	i

The major decision to make is whether to handle in the final computer program an impulse before or after handling a tail.

If one selects the following sequence of handling: i t c (impulse, tail, collision point), it implies that looking in one direction, the minimum distance between the impulse and the end of the tail is greater than the distance over which an impulse can be conducted in one simulation cycle. Otherwise the impulse, being conducted first, will hit the tail running in front of it, which has not yet been handled.

When we select the sequence t i c : (tail-impulse) this minimum distance is not required because the new position of the tail is determined first.

This minimum distance, which is chosen during the first order of handling, limits the number of possible new states, in this simulation program. An impulse which follows a tail cannot jump over that tail, or over a collision point in the same cycle. For example figure 2.4.1 shows a state of a segment and the possible states that can be reached during one simulation cycle.

FIGURE 2.4.1.

Legend to figure 2.4.1 This figure shows the states that can be reached in one simulation cycle starting from state 20. On the left side all states that can be reached handling the impulse first, are shown. On the right side all possible states using the order - Tail-Impulse- are indicated. Apart from the four states which are common to both cases 20,22,25,28 there are two extra states possible : 11 and 13. In these two situations an impulse conducts over the collision point in the same simulation cycle as the tail preceding this impulse.

This increase in possibilities will increase the complexity and simulation time of the model.

The order of handling impulse-collision point has the consequence that the impulse first hits the collision point and then the model checks whether the collision point can be removed. This only makes a difference if an impulse hits a collision point with no tail at the opposite side. In the latter situation this will be removed in the same cycle.

For the order of handling tail-collision point the order obviously makes no difference.

The differences between these two options is marginal in normal cases. The maximum error in timing is one simulation cycle, which in most simulation studies equals 1 ms.

Following the above considerations the first option was selected, first to handle the impulse, then the tail and finally the collision point.

By defining strictly the order of handling a reproducible and predictable handling of a segment can be performed.

Order of handling selected:

if any : Anterograde Impulse
 Retrograde Impulse
 Anterograde Tail
 Retrograde Tail
 Collision Point

List of abbreviations used:

AP	Anterograde Impulse	$1 \leq AP < 100$
RP	Retrograde Impulse	$1 < RP \leq 100$
AL	Anterograde Tail	$1 \leq AL < 100$
RL	Retrograde Tail	$1 < RL \leq 100$
CP	Collision Point	$1 < CP < 100$
AV	Anterograde conduction velocity	
RV	Retrograde conduction velocity	
AD	Anterogradely conducted distance (number of cells)	
RD	Retrogradely conducted distance (number of cells)	
AT	Anterogradely Refractory Timer. This indicates the time interval, during which element 1 will remain refractory after an anterogradely conducted impulse.	
RT	Retrogradely Refractory Timer. This indicates the time interval, during which element 100 will remain refractory after a retrogradely conducted impulse.	
PD	Proportional displacement. This variable is used to calculate the location of the collision point, taking into account the actual positions of the two colliding impulses and their conduction velocities.	
$PD = \frac{RP - AP}{AD + RD}$		
ARP	Anterograde Refractory Period. This parameter represents the anterograde refractory period of a segment. It can either be constant or rate dependent.	
RRP	Retrograde Refractory Period. Represents the retrograde refractory period.	

2.5 Handling of a segment without changes in electrophysiological parameters or new impulses

In this paragraph the layout of the equations used to calculate the new state of a segment without introducing new impulses will be illustrated.

In all equations the subscript n or $n+1$ represents the $(n)^{\text{th}}$ or $(n+1)^{\text{th}}$ simulation cycle respectively.

To illustrate this layout the handling of two different states will be discussed in detail.

a) State 2 (ST 2)

In state 2 an impulse is being conducted anterogradely through a segment.

In this state an impulse is conducted anterogradely ($AP > 0$), there is no retrogradely conducting impulse ($RP = 0$), there are no anterograde or retrograde tails, nor a collision point. ($AL = 0$, $RL = 0$, $CP = 0$.)

The element excited first is still refractory. ($AT > 0$.) The retrograde refractory timer equals zero. ($RT = 0$.)

$$AP_n > 0 \quad RP_n = 0 \quad AL_n = 0 \quad RL_n = 0 \quad AT_n > 0 \quad RT_n = 0 \quad CP_n = 0$$

First the position of the anterograde impulse after one cycle is determined.

$$AP_{n+1} = AP_n + AD$$

The new position of the impulse equals the old one plus the Anterograde Conduction Distance.

If the impulse reaches or passes the end of the segment (element 100) the variable representing the position of the impulse will be reset to zero ($AP_{n+1} = 0$) and the new state of the segment will be indicated. ($ST_{n+1} = ST\ 3$).

If the impulse does not reach the end of the segment in this simulation cycle these values remain unchanged. ($AP_{n+1} = AP_n$ and $ST_{n+1} = ST\ 2$).

Summarized in computer terms:

$$\begin{array}{ll} \text{IF } (AP_{n+1} \geq 100) & \\ \quad \text{THEN : } AP_{n+1} = 0 & \text{ELSE : } AP_{n+1} = AP_n \\ \quad \quad ST_{n+1} = ST\ 3 & \quad ST_{n+1} = ST\ 2 \end{array}$$

Finally the Anterograde Refractory Timer, indicating the time interval element 1 will remain refractory, is decreased by one.

$$AT_{n+1} = AT_n - 1$$

In the second example a more complicated state will be discussed.

b) State 20 (ST 20)

Again the description of the handling of this state starts with a description of the values of all parameters before the next simulation.

Anterogradely an impulse and a tail are present. ($AP_n > 0$ $AL_n > 0$) The first element is still refractory. ($AT_n > 0$) Retrogradely there is no impulse and no tail present. ($RP_n = 0$ $RL_n = 0$). Element number 100 is still refractory. ($RT_n > 0$). There is a collision point. ($CP_n > 0$)

$$AP_n > 0 \quad RP_n = 0 \quad AL_n > 0 \quad RL_n = 0 \quad AT_n > 0 \quad RT_n > 0 \quad CP_n > 0$$

After one simulation cycle there is still no retrograde impulse. ($RP_{n+1}=0$). The position of the collision point remains constant. ($CP_{n+1}>0$). The new position of the anterogradely conducted impuls equals the old one plus the Anterograde Conducted Distance. ($AP_{n+1}=AP_n+AD$).

The new position of the anterograde conducted tail equals the old position plus the Anterograde Conduction Distance. ($AL_{n+1}=AL_n+AD$).

$$AP_{n+1}=AP_n+AD$$

$$AL_{n+1}=AL_n+AD$$

At this moment the model should check, whether the end of the tail has reached the collision point. If yes this is indicated by resetting the variable describing the position of the anterograde tail ($AL_{n+1}=0$) and by defining the state to be equal to ST 22. If the tail does not reach the collision point these values are not changed.

IF ($AL_{n+1} \geq CP_n$)
 THEN : $AL_{n+1}=0$ ELSE : $AL_{n+1}=AL_{n+1}$
 $ST_{n+1}=ST\ 22$ $ST_{n+1}=ST\ 20$

Thereafter both the Anterograde and the Retrograde Refractory Timers are decreased by one.

$$AT_{n+1}=AT_n-1$$

$$RT_{n+1}=RT_n-1$$

After this decrement it is possible that element 100 is no longer refractory. In that case, if $RT_{n+1}=0$, the retrograde tail is given the value 100. Depending on the state of the segment two different states are possible. If the previous state represented ST 22, the new state will be ST 25. Otherwise the state will be ST 28. If this element is still refractory following this part of the simulation cycle both the values indicating the position of the retrograde tail and the state of the segment remain unchanged.

IF ($RT_{n+1}=0$)
 THEN : $RL_{n+1}=100$ ELSE : $RL_{n+1}=0$
 IF ($ST_{n+1}=ST\ 22$)
 THEN $ST_{n+1}=25$ ELSE : $ST_{n+1}=ST\ 28$

In chapter 6 the handling of all 35 states has been listed.

2.6 The introduction of a new impulse.

The introduction of an impulse into a segment forms the second step in every simulation cycle.

In the first step impulses which have been introduced into a segment during a previous simulation cycle have been handled together with possible tails and

collision points. In the second step the model tests, whether at any of the junction points impulses are considered to be conducted into those segments which are connected to that specific junction point.

This impulse can either be an impulse conducted through an adjacent segment or a new impulse from an internal or external impulse source.

Impulses can only be introduced into a segment from the junction points and not somewhere in a segment.

Because it is possible that during one simulation cycle at both ends an impulse waiting to be conducted into a segment is present, the following must be noted : the state of the segment changes as the result of an anterogradely or retrogradely introduced impulse. Therefore handling the second retrograde impulse requires the new state after handling the first impulse, and not the state of the segment as it was just before the handling of the first impulse.

Before an impulse can enter a segment the following condition must be fulfilled.

The conditions are given for an anterogradely conducted impulse. For a retrograde impulse the values can be derived easily..

The impulse can only penetrate a segment if at the beginning of that segment a number of elements equalling the Anterograde Conduction Distance (AD) does not contain a refractory tail conducting in the same direction. The presence of a collision point in this area, or an impulse in the opposite direction forms no objection against the introduction of an impulse. This free space prevents the impulse from jumping over a preceding tail in the next simulation cycle. If this condition is fulfilled, an impulse is introduced to position one and a timer (the Anterograde Refractory Timer) starts to count down the refractory period of the anterograde junction.

If this condition is not fulfilled, the potential impulse will be ignored.

To define the condition of a segment in cycle $n+1$, based on the situation in cycle n , a fixed procedure of handling is followed.

In the following part the introduction of an impulse in a segment depending on the state of that segment will be described in detail. Using three examples all different possibilities are shown.

Chapter 7 gives a complete description of the procedures used to handle new impulses for each of the 35 possible states.

In the formula used ARP and RRP represent the anterograde and retrograde refractory period respectively. They have been defined separately for each segment and can either be constant or rate dependent.

In the following examples n indicates the situation before, and $n+1$ the situation after the introduction of an impulse into a segment.

Example 1. State 1.

As described in chapter 7 the introduction of a new impulse into a segment starts with a description of the present state.

In state 1. no elements are activated in the segment so all values are by definition equal to zero.

ST 1. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n=0$ $AT_n=0$ $RT_n=0$ $CP_n=0$

All elements are excitable therefore an anterograde impulse can always be introduced into the segment.

The impulse will be introduced to position 1 ($AP_{n+1}=1$) and will set the Anterograde Refractory Timer equal to the Anterograde Refractory Period. ($AT_{n+1}=ARP$). There is still no anterograde tail. ($AL_{n+1}=0$). In retrograde direction all values remain equal to zero. ($RP_{n+1}=0$, $RL_{n+1}=0$, $RT_{n+1}=0$). There is no collision point. ($CP_{n+1}=0$). After the introduction of an anterograde impulse the state of the segment changes into ST 2.

ANT $AP_{n+1}=1$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}=ARP$ $RT_{n+1}=0$
 $CP_{n+1}=0$ $ST_{n+1}=ST\ 2$

Also in retrograde direction an impulse can always penetrate into such a segment. Now the impulse will be introduced to position 100 ($RP_{n+1}=100$) and the Retrograde Refractory Timer will be set equal to the retrograde Refractory Period. ($RT_{n+1}=RRP$). There is no retrograde tail. ($RL_{n+1}=0$). All anterograde values remain zero. ($AP_{n+1}=0$, $AL_{n+1}=0$, $AT_{n+1}=0$) There is no collision point. ($CP_{n+1}=0$). The new state of the segment is ST 6.

RET $AP_{n+1}=0$ $RP_{n+1}=100$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}=0$ $RT_{n+1}=RRP$
 $CP_{n+1}=0$ $ST_{n+1}=ST\ 6$

In the second example the introduction of an impulse in a segment with one refractory end will be discussed.

State 2

The description starts again with a description of the present state.

ST 2. $AP_n>0$ $RP_n=0$ $AL_n=0$ $RL_n=0$ $AT_n>0$ $RT_n=0$ $CP_n=0$

$AT_n>0$ indicates that the first element of the segment is still refractory. New impulses can not penetrate into the segment in anterograde direction and all values remain unchanged.

ANT $AP_{n+1}>0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}=0$ $CP_{n+1}=0$

The introduction of an impulse from the retrograde side of the segment is in this state always possible. The first element (100) is not refractory and there is also no tail which is conducted in retrograde direction.

Therefore after the introduction of an impulse at element 100 the properties of the segment will be as follows:

RET $AP_{n+1}>0$ $RP_{n+1}=100$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}=RRP$
 $CP_{n+1}=0$ $ST_{n+1}=ST\ 10$

Finally in the last example the third and most complicated case will be demonstrated.

State 4.

In this state in anterograde direction a refractory tail is being conducted. Behind this tail at the left side a sector of the segment is again excitable. ($AP_n=0$, $AL_n>0$, $AT_n=0$).

Retrogradely there is no impulse nor tail present. There is no collision point. ($RP_n=0$, $RL_n=0$, $RT_n=0$, $CP_n=0$)

ST 4. $AP_n=0$ $RP_n=0$ $AL_n>0$ $RL_n=0$ $AT_n=0$ $RT_n=0$ $CP_n=0$

Independent of the fact whether an impulse can enter the segment in anterograde direction or not, the values indicating the position of the anterograde tail together with those representing the retrograde values and the collision point remain unchanged.

ANT $RP_{n+1}=0$ $AL_{n+1}>0$ $RL_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}=0$

In this situation one has to check whether an impulse, introduced at element 1, would hit the preceding tail. If so, the impulse will be ignored. If not, the impulse can enter the segment ($AP_{n+1}=1$, $AT_{n+1}=ARP$) and the new state will represent ST 5.

IF ($AL_{n+1}>(1+AD)$)

THEN : $AP_{n+1}=1$

$AT_{n+1}=ARP$

$ST_{n+1}=ST\ 5$

ELSE : $AP_{n+1}=0$

$AT_{n+1}=0$

$ST_{n+1}=ST\ 4$

In retrograde direction impulse introduction is impossible since element 100 is still refractory. ($AL_n>0$, $CP_n=0$).

All values remain unchanged.

RET $AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}>0$ $RL_{n+1}=0$ $AT_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}=0$

2.7 Consequences of short refractory periods and non constant conduction velocity.

So far two major limitations are present in the model.

- 1: As a result of the definitions choosen, leading to the 35 states the conduction time through a segment is shorter than the refractory period of the segment in the same direction.
- 2: The conduction velocity of an impulse or tail travelling through a segment is constant as long as the impulse or its tail are present in any part of the segment.

The consequences of these two limitations are as follows:

Limitation 1. A short refractory period

A conduction time through a segment, shorter than the refractory period of that segment, makes it impossible that two impulses will be conducted in one segment in the same direction.

Eliminating this principle will increase the number of possibilities from 35 to almost infinite making acceptable processing impossible.

If the user is confronted with a situation in which the conduction time is only slightly longer than the refractory period the problem can be solved in some situations by lining up multiple segments, each segment having a conduction time equal to the total conduction time divided by the number of subsequent subsegments. All these subsegments will have the original refractory period.

This division of the original segment into subsegments is only possible if the conduction time through the segment is not a function of the rate at which the impulses enter the segment.

FIGURE 2.7.1.

Legend to figure 2.7.1.

The division of a segment into two subsegments. $T_{segment}$ represents the conduction time through the segment. This solution cannot be used if the conduction time through the segment is rate dependent, for example when simulating tissue with decremental conduction properties like the atrioventricular node.

Fig 2.7.2. shows the function curve of a segment where the conduction time of the segment is a function of the input rate.

FIGURE 2.7.2.

Legend to figure 2.7.2.

The shaded area represents that part of the function curve that can be used during the simulation study. In this part the conduction time is smaller than the refractory period. (Mostly the refractory period will also be rate dependant.)

Before an impulse can enter a segment with rate dependent properties, the actual electrophysiological parameters have to be determined. If conduction time is shorter than the refractory period, the segment can be handled as a normal segment with the appropriate conduction time and velocity. The refractory period of the segment can also be defined as rate dependent. In such a situation the segment can be handled as a normal segment if the conduction time at a certain rate is shorter than the refractory period of the segment at that rate.

If, corrected for the actual rate, the conduction time is not shorter than the refractory period the problem cannot be solved by dividing the segment into subsequent subsegments.

Handling the segment as a normal segment, by dividing the conduction time of the original segment by the number of subsegments (n), the following sub-function curves will apply.

FIGURE 2.7.3.

Legend to figure 2.7.3.

This figure shows a number of rate dependent function curves. The top one ($n=1$) is defined by the equation:

$$\text{Conduction time} = 500 - \text{cycle length}$$

The other curves are derived from this curve by dividing the conduction time at any rate by 2, 3, 4 or 5.

In figure 2.7.4., 2.7.6., 2.7.8., and 2.7.10., using these function curves, the conduction time through 2, 3, 4 or 5 subsegments is indicated.

During a constant rhythm the division of a rate dependent segment into subsegments does not change the performance of the segment. In the following part at a basic rate of 400 ms the response to a premature impulse at 300 ms is studied.

Using these values, we will show, that the behaviour of a premature impulse depends also on the number of subsegments into which a segment has been divided.

On dividing the segment into n subsegments the time sequence of conduction through these subsegments is as follows.

FIGURE 2.7.4.

Legend to figure 2.7.4.

The segment has been divided into two subsegments. The top segment indicates the conduction time during a regular rate of 400 ms. The bottom one shows the response of the subsegments to a premature impulse after an interval of 300 ms.

FIGURE 2.7.5.

Legend to figure 2.7.5.

The first subsegment is confronted with a premature impulse with a coupling interval of 300 ms. This results in a conduction time interval of $200/2 = 100$ ms. This interval is 50 ms longer than the conduction time during the regular rate of 400 ms. So the prematurity of the premature impulse at the second segment is no longer 100 ms, but 100 ms minus the 50 ms extra delay in the first subsegment. (Interval 350 ms for second segment). This gives a total conduction time of 175 ms.

On dividing the segment into three subsegments the following situation appears.

FIGURE 2.7.6.

Legend to figure 2.7.6.

The original segment has been divided into three subsegments. During a regular rhythm of 400 ms the conduction time through the subsegments is 33.33 ms.

The bottom strip indicates, that a premature impulse requires a long period to be conducted through the first subsegment. This delay makes conduction through the next subsegment relatively easier because the extra impulse is arriving less prematurely at this and all the following subsegments.

FIGURE 2.7.7.

Legend to figure 2.7.7.

The impulse is conducted through the first segment in $200/3 \text{ ms} = 66.66 \text{ ms}$. Compared to the conduction time during a regular rate of 400 ms conduction time is 33.33 ms slower. Therefore the prematurity at the second segment is 100 minus 33.33 ms (i.e. 66.66 ms). This results in a conduction time through the second segment of 55.55 ms. Finally this results in a conduction time through the last subsegment of 48.14 ms, giving a total conduction time of 170.33 ms.

After the division in four subsegments the situation is as follows.

FIGURE 2.7.8.

Legend to figure 2.7.8.

In the top panel conduction at constant velocity occurs through the four subsegments. Every segment is passed in 25 ms. The bottom panel shows that conduction gradually improves, during conduction through the subsegments.

FIGURE 2.7.9.

Legend to figure 2.7.9.

Also in this example the increase in conduction time in a subsegment makes the impulse less premature in the following subsegment. In every subsegment the conduction time decreases, but the differences in conduction time between two subsegments decrease also.

Division in five parts gives this result.

FIGURE 2.7.10.

Legend to figure 2.7.10.

The conduction time per subsegment in the top panel numbers 20 ms. In the bottom panel the same mechanism of reduction in conduction time is shown.

FIGURE 2.7.11.

Legend to figure 2.7.11: As in the previous examples, this diagram indicates the decreasing shortening of the conduction time through a row of subsegments. The total conduction time through a segment divided in five subsegments is 167.23 ms. If the segment would be divided into 250 segments the total conduction time would decrease to 163.28 ms.

Limitation 2. Non constant conduction velocity

Fig 2.7.12. shows all situations in which an increase in conduction velocity will be in conflict with the limiting criterion no 2, the consistency of the conduction velocity.

FIGURE 2.7.12.

Legend to figure 2.7.12.

This figure shows the situations in which an increase of conduction velocity could cause mistakes. In these cases it is possible that an impulse is conducted over the position of a preceeding tail or even over a tail and a collision point. These illegal jumps are indicated by arrows

The fact that the impulse is handled before the tail makes it possible in these situations that the calculated position of the impulse will be more distal then the position of the tail or even the collision point.

If one of the situations listed here is present the following extra tests must be performed before a segment can be handled in the way previously described.

$$\text{IF } (AL_n - AP_n) \leq AD \quad \text{then } AD = (AL_n - AP_n) * 0.99$$

$$\text{IF } (RP_n - RL_n) \leq RD \quad \text{then } RD = (RP_n - RL_n) * 0.99$$

(The value 0.99 has been selected arbitrarily.)

By adding this extra restriction it becomes impossible for the impulse to jump over the tail, (i.e. preventing a situation not listed in the 35 possible states. This test only needs to be performed if the AV_{n-1} is not equal to the AV_n , or RV_{n-1} not equal to RV_n .

By using this restriction in conduction velocity to keep the impulse behind the tail, both the impulse and the tail are conducted within a segment at a fixed minimal distance.

Using the model the frequency of occurrence of this phenomenon is very low. During the simulation studies, described in chapter 3, it never occurred.

If an impulse enters in this way into the next segment three situations are possible,

- 1) The new segment has the same properties and this state will continue.
- 2) The refractory period of the new segment is longer and the impulse will block.
- 3) The refractory period of the new segment is shorter and the gap in between the impulse and the tail increases.

If after a change in conduction velocity, the velocity remains constant, the gap between the impulse and the tail will remain at least 101% of the minimally required distance.

This correction in conduction velocity will be indicated to the user by a statement in the output.

TABLE 2.7.1.

Table 2.7.1. represents the situation that can be reached in any cycle if no extra impulse is entered and the electrophysiological properties remain constant.

The columns represent each of the 35 possible states in the n^{th} cycle. Rows represent the possible state in the $(n+1)^{\text{th}}$ cycle.

A black circle indicates the possible state(s) in which a segment will be found in the $(n+1)^{\text{th}}$ cycle, given its state in the $(n)^{\text{th}}$ cycle.

TABLE 2.7.2.

Table 2.7.2. represents the situation that can be reached in any cycle if an extra impulse has entered the segment but the electrophysiological properties remain unchanged .

Like in table 2.7.1., the columns represent each of the 35 possible states in the $(n)^{th}$ cycle. Rows represent the possible state after the introduction of an impulse.

An black square indicates the possible state(s) in which a segment will be found after the introduction of an impulse given its state in the $(n)^{th}$ cycle.

TABLE 2.7.3.

Table 2.7.3. represents the supplemental situation that can be reached in any cycle if no extra impulse is entered and the electrophysiological properties are allowed unlimited changes (see figure 2.7.12.)

Also in this table, the columns represent each of the 35 possible states in the $(n)^{th}$ cycle. Rows represent the state in the $(n+1)^{th}$ cycle that corresponds most with the new state.
 ? indicates the possible state(s) in which a segment will be found in the $(n+1)^{th}$ cycle, given its state in the $(n)^{th}$ cycle.

TABLE 2.7.4.

Table 2.7.4. represents a compilation of all the the situations that can be reached in any cycle.
 The columns represent each of the 35 possible states in the $(n)^{th}$ cycle. Rows represent the possible state in the $(n+1)^{th}$ cycle or after the introduction of an impulse.
 Circles, Squares and ? have the same meaning as in previous tables.

Chapter 3

Some simulation studies using the model

In this chapter we would like to show the results of some simulation studies performed using the previously described model. First a model of the normal cardiac conduction system of the heart will be designed. We will demonstrate how to define the network, and how to enter the electrophysiological properties of the segments, together with the extra stimuli given.

In the second paragraph a previously published simulation study, (47) in which a single purpose mathematical model was used, will be described briefly. The simulation study has been repeated using our model and the results of both methods are compared. As will be shown there is a very good correlation between the original study and the findings using this model.

Finally a more complicated study concerning termination and re-initiation of circus movement tachycardia, due to bundle branch reentry will be described. The last two examples are based on data collected during electrophysiological investigation. Both cases have been published previously.(47-48,50). In these publications patient data, methods and results are given. To get a better understanding of the mechanisms, responsible for these findings, simulation studies were performed.

3.1 The normal conduction system

FIGURE 3.1.1.

Legend to figure 3.1.1.

In this figure the catheter positions used are shown. HRA = High Right Atrium, LRA = Low Right Atrium, CS = Coronary Sinus, His = His Bundle position, RP = Right Purkinje System, LP = Left Purkinje System, RV = Right Ventricle, LV = Left Ventricle.

At the right side all junction points and segments are numbered. One direction of conduction is defined to be anterograde (indicated by arrows).

To simulate the behaviour of the cardiac conduction system the following network is assumed to represent a particular physiological situation in man.

After numbering both the junction points and the segments, and defining an anterograde direction in every segment, the model has been defined completely and can be entered into the computer.

To do this, for every junction point, a list of segments, able to conduct from that junction point, together with the direction, must be entered into the computer.

In our example the list has the following format :

Junction Point	Segment Number	Direction 1=Ant 2=Ret
1	1	1
1	2	1
2	1	2
2	3	1
3	2	2
3	3	2
3	4	1
4	4	2
4	5	1
4	7	1
5	5	2
5	6	1
5	8	1
6	6	2
7	7	2
7	8	2
7	9	1
8	9	2

If for instance between junction point 4 and junction point 5 conduction is only possible in the direction of junction point 5, this has to be indicated by skipping the line 5,5,2.

If a network has been stored previously in the memory of the computer, it does not have to be entered again by hand, but can be reloaded by number.

After the selection of the structure of the network and the number of segments, the anterograde and retrograde conduction velocities and refractory periods have to be defined. If a segment is conducting only in one direction, the parameters defining conduction velocity and refractory period in the opposite direction are of no interest.

In the example shown in figure 3.1.1. the following values for conduction time and refractoriness have been selected:

Table 3.1.1.

SEGMENT	ATime	RTime	ARP	RRP
1	65	65	250	250
2	35	35	250	250
3	40	40	250	250
4	-80	80	270	270
5	40	40	250	250
6	20	20	240	240
7	45	45	250	250
8	25	25	240	240
9	20	20	240	240

Legend to table 3.1.1

ATime and RTime represent the anterograde and retrograde conduction time. ARP and RRP the anterograde and retrograde refractory period. All times are in ms.

One sees that segment number 4 representing AV Nodal conduction has been given a negative conduction time.

This has been done for two reasons:

Firstly the negative sign indicates, that the parameter is not constant, but has a rate dependent conduction time.

Secondly, the value behind the minus sign indicates the conduction time in the first pass through the segment. At that moment, because it is the first pass, the rate at the junction point cannot be determined.

The rate dependent properties of the segment are questioned after the selection of all parameters.

To describe the relation between the rate and the conduction velocity, the two variables a and b in the equation

$$\text{Conduction time} = a * \text{Rate} + b$$

have to be entered.

In this example the selected values are : a = - 0.2 and b =200.

In the same way rate dependent refractoriness can be defined.

After the selection of the network and the electrophysiological properties of the segments, the mathematical model of the conduction system is ready to perform a simulation study.

To start such a simulation study, one or more impulses should be entered into the not activated network. To do so, two methods are presently available :

- First one can induce a basic rhythm of a certain duration, defined by its starting point in time, its interval and its end point in time, together with the

junction point at which the impulses have to be entered into the network.
At multiple junction points regular rhythms can be induced.

- b. Secondly one can select single stimuli and use them either combined with a basic rhythm as an extra stimulus or just as a single impulse.
Again, multiple extra stimuli can be selected, either at the same or at different junction points.

The basic rhythm and the extra stimuli are finally chronologically listed. After every simulation cycle, (in general every millisecond), the clock of the model is compared with the list of points of time previously composed. If they match, at the corresponding junction point an impulse is introduced. The conditions this impulse has to fulfil to be conducted into the segment have been described in chapter 2, paragraph 6.

- c. Thirdly before the actual simulation study starts, the state of one or more segments can be selected to be unequal to zero.

In that case the following parameters have to be defined:

AD, RD, AL, RL, AT, RT, and ST

In this way one can create artificially the situation present after the introduction of an impulse exclusively in one segment.

Although theoretically possible it is less useful to introduce in this way, both an anterogradely and a retrogradely conducted impulse.

The state of multiple segments can be changed in this way.

In the study demonstrated in this example, the following pulse train has been used.

A basic rate starting at point of time 20, with an interval of 600 ms has been selected introducing two impulses. These basic impulses ($t=620$ and $t=1220$ ms) are followed by one premature impulse after 1620 ms. After a compensatory pause the regular rhythm continues after 2420 ms.

All impulses are given at junction point 1.

The last question to be answered is the time (in milliseconds), that the simulation process has to be continued.

After this input, the program starts to simulate conduction through the network.

In most cases the following output layout has been selected:

Junction point	Time of appearance	From segment
xxx	xxx	xxx

The values are shown on a monitor and/or a line printer.

Using the network described in figure 3.1.1. and the parameters listed in table 3.1.1., the reaction of the model on the above described pulse train will be demonstrated.

INTERVAL = 20	INTERVAL = 400
J POINT 1 TIME 20 FROM SEGMENT 0	J POINT 1 TIME 1620 FROM SEGMENT 9
J POINT 3 TIME 55 FROM SEGMENT 2	J POINT 3 TIME 1655 FROM SEGMENT 2
J POINT 2 TIME 95 FROM SEGMENT 1	J POINT 2 TIME 1695 FROM SEGMENT 1
J POINT 4 TIME 135 FROM SEGMENT 4	J POINT 4 TIME 1774 FROM SEGMENT 4
J POINT 5 TIME 175 FROM SEGMENT 5	J POINT 5 TIME 1814 FROM SEGMENT 5
J POINT 7 TIME 190 FROM SEGMENT 7	J POINT 7 TIME 1819 FROM SEGMENT 7
J POINT 6 TIME 195 FROM SEGMENT 6	J POINT 6 TIME 1834 FROM SEGMENT 6
J POINT 8 TIME 200 FROM SEGMENT 9	J POINT 8 TIME 1839 FROM SEGMENT 9
INTERVAL = 600	INTERVAL = 800
J POINT 1 TIME 620 FROM SEGMENT 9	J POINT 1 TIME 2420 FROM SEGMENT 9
J POINT 3 TIME 655 FROM SEGMENT 2	J POINT 3 TIME 2455 FROM SEGMENT 2
J POINT 2 TIME 695 FROM SEGMENT 1	J POINT 2 TIME 2495 FROM SEGMENT 1
J POINT 4 TIME 735 FROM SEGMENT 4	J POINT 4 TIME 2495 FROM SEGMENT 4
J POINT 5 TIME 775 FROM SEGMENT 5	J POINT 5 TIME 2535 FROM SEGMENT 5
J POINT 7 TIME 790 FROM SEGMENT 7	J POINT 7 TIME 2540 FROM SEGMENT 7
J POINT 6 TIME 795 FROM SEGMENT 6	J POINT 6 TIME 2555 FROM SEGMENT 6
J POINT 8 TIME 800 FROM SEGMENT 9	J POINT 8 TIME 2560 FROM SEGMENT 9
INTERVAL = 600	
J POINT 1 TIME 1220 FROM SEGMENT 9	
J POINT 3 TIME 1255 FROM SEGMENT 2	
J POINT 2 TIME 1295 FROM SEGMENT 1	
J POINT 4 TIME 1335 FROM SEGMENT 4	
J POINT 5 TIME 1375 FROM SEGMENT 5	
J POINT 7 TIME 1390 FROM SEGMENT 7	
J POINT 6 TIME 1395 FROM SEGMENT 6	
J POINT 8 TIME 1400 FROM SEGMENT 9	

TABLE 3.1.2.

Table 3.1.2. gives the output after a simulation time of 3000 ms.

Legend to figure 3.1.2.

At time $t=20$ the first impulse is introduced into junction point 1. This point represents a position high in the right atrium, near the sinus node. The impulse conducts through the atrium, through the AV Node in 80 ms and over the two bundle branches to the ventricle.

At $t=620$ a second impulse is introduced and conducts in the same way through the conduction system. A third impulse is given at $t=1220$. At $t=1620$ a fourth impulse is introduced. This impulse will reach the AV Node with a prematurity of 200 ms. This results in an AV Nodal conduction time of 120 ms. The conduction through the rest of the conduction system is identical as in the previous beats. After this premature impulse, a compensatory pause is present. So at $t=2420$, the next sinus impulse appears at junction point 1. This measured from the previous impulse delayed impulse will conduct fast through the AV node in 40 ms. The rest of the conduction system is passed in the usual way.

The following regular impulses will be handled like the first impulse.

NB. In this and following examples sometimes an error of 1 ms can be observed. The reason for this error will be explained in chapter 4.

3.2. Cycle length alternation.

In 1981 we studied the possible role of the AV Nodal function curve as a cause of cycle length alternation, during circus movement tachycardia. (47-48). In these publications two types of AV nodal function curves during tachycardia were used: straight lines of various gradients and representative examples of patient-based AV nodal function curves obtained during clinical electrophysiologic investigations. This was done using a mathematical model of the tachycardia circuit loaded into an Apple II microcomputer. In this model the following assumptions were made:

AA = the tachycardia cycle length

AH = the conduction time through the AV Node and

K = the conduction time through the rest of the circuit. This conduction time was assumed to be constant and rate independent.

and the following basic equation was defined:

$$AA = AH + K$$

The relation between the atrial rate and the AV Nodal conduction time - the AV Nodal function curve -, was varied and the resulting tachycardia was studied. During circus movement tachycardia a fixed point on the AV Nodal function

curve was used, resulting in a constant tachycardia cycle length. A premature impulse given at the atrial side of the AV Node, would shorten the cycle length. This would cause an increase in conduction time through the AV Node. This prolonged conduction time, together with the constant conduction time K through the rest of the circuit formed the new cycle length. This cycle length would be longer than during regular tachycardia. This would cause a faster conduction through the AV Node. The circulating impulse arrived premature at the AV Node and so on.

To study the effect of different AV Nodal function curves upon of the tachycardia cycle length, in that model two groups of function curves were applied.

- Simple first degree polynomials representing the conduction through the AV Node as a function of the stimulus interval. Different slopes could be selected.
- Patient based AV Nodal function curves. These curves were obtained during clinical electrophysiological studies using the extra stimulus technique. An extra stimulus was given in the atrium during a regular paced rhythm. These patients showed cycle length alternation during these investigations.

Using a straight-line relationship between rate and conduction time, three different groups were selected.

- a) Straight line AV Nodal function curves with a gradient = -1
(Slope = 45°)
- b) Straight line AV Nodal function curves with a gradient > -1
(Slope < 45°)
- c) Straight line AV Nodal function curves with a gradient < -1
(Slope > 45°)

The effect of a shortening of the stimulation interval on a tachycardia cycle was studied, using these three different groups.

Secondly patient based function curves were used. Similar findings could be obtained in simulation studies using these patient-based curves. The result of a perturbation of the tachycardia cycle length depended on the slope of the function curve in that point, representing the instantaneous AA interval.

The determination of the relation between the gradient of the AV Nodal function curve, the perturbation of the original tachycardia cycle length and the resulting cycle length alternation, has been repeated using the in chapter 2 described mathematical model of the cardiac conduction system. The results are identical as compared to the findings in the original study.

The network used in this study contains four segments.

FIGURE 3.2.1.

Legend to figure 3.2.1

Model representation of the study of a circus movement tachycardia. It is however possible to represent the conduction through segment 1, 2 and 3 using only one segment considering the refractory period of this new segment is longer than the conduction time through all three segments together.

The following network structure and electrophysiological parameters were entered.

Table 3.2.1.

Definition of the network			Segment	AD	RD	ARP	RRP
JP	Segment	A/R					
1	1	1	1	R	1.25	200	200
1	4	2	2	1.25	1.25	200	200
2	1	2	3	1.25	1.25	200	200
2	2	1	4	1.25	1.25	200	200
3	2	2					
3	3	1					
4	3	2					
4	4	1					

Legend tot table 3.2.1.

JP= Junction Point, A/R: 1 = Anterograde, 2= Retrograde.

AD and RD represent the number of elements passed in one cycle, ARP and RRP are the refractory periods.

R= Rate dependent. In this example the curve has been described by the equation $AH = -AA + 400$

The circulating impulse is introduced into the circuit by changing the state and properties of one segment of the network before the simulation starts.

At position one in segment one an impulse is introduced. By introducing it exclusively in one direction in this segment, and not at the adjacent junction point, a circus movement tachycardia starts.

The results:

Straight line av nodal function curve with a gradient = -1.

Table 3.2.2. shows the effect of perturbation of a circus movement tachycardia using an AV Nodal function curve with a gradient of -1.

J POINT 2 TIME 80 FROM SEGMENT 1	J POINT 1 TIME 1240 FROM SEGMENT 4
J POINT 3 TIME 160 FROM SEGMENT 2	J POINT 2 TIME 1358 FROM SEGMENT 1
J POINT 4 TIME 240 FROM SEGMENT 3	J POINT 3 TIME 1438 FROM SEGMENT 2
INTERVAL = 328	J POINT 4 TIME 1518 FROM SEGMENT 3
J POINT 1 TIME 320 FROM SEGMENT 4	INTERVAL = 358
J POINT 2 TIME 400 FROM SEGMENT 1	J POINT 1 TIME 1598 FROM SEGMENT 4
J POINT 3 TIME 480 FROM SEGMENT 2	J POINT 2 TIME 1648 FROM SEGMENT 1
J POINT 4 TIME 560 FROM SEGMENT 3	J POINT 3 TIME 1720 FROM SEGMENT 2
INTERVAL = 288	J POINT 4 TIME 1800 FROM SEGMENT 3
J POINT 1 TIME 600 FROM SEGMENT 4	INTERVAL = 282
J POINT 2 TIME 719 FROM SEGMENT 1	J POINT 1 TIME 1880 FROM SEGMENT 4
J POINT 3 TIME 799 FROM SEGMENT 2	J POINT 2 TIME 1997 FROM SEGMENT 1
J POINT 4 TIME 879 FROM SEGMENT 3	J POINT 3 TIME 2077 FROM SEGMENT 2
INTERVAL = 355	J POINT 4 TIME 2157 FROM SEGMENT 3
J POINT 1 TIME 959 FROM SEGMENT 4	INTERVAL = 357
J POINT 2 TIME 1000 FROM SEGMENT 1	J POINT 1 TIME 2237 FROM SEGMENT 4
J POINT 3 TIME 1080 FROM SEGMENT 2	J POINT 2 TIME 2280 FROM SEGMENT 1
J POINT 4 TIME 1160 FROM SEGMENT 3	J POINT 3 TIME 2360 FROM SEGMENT 2
INTERVAL = 281	J POINT 4 TIME 2440 FROM SEGMENT 3

TABLE 3.2.2.

FIGURE 3.2.2.

Legend to table 3.2.2. and figure 3.2.2

The reaction of the model on a perturbation of the tachycardia cycle length of 40 ms is shown.

The net result is a stable cycle length alternation with an amplitude equal to the initial perturbation. This alternation will last indefinitely unless the AV Nodal conduction properties change.

Straight line AV Nodal function curve with a gradient > -1.

Using the same network and electrophysiological parameters the function curve has been rotated to a more flat position. The new curve has been described by the equation

$$AH = -0.5 * AA + 240$$

At the rate of the regular tachycardia (320 ms) it represents the same AV Nodal conduction time as in the first example, i.e. 80 ms.

J POINT 2 TIME 80 FROM SEGMENT 1	J POINT 1 TIME 1561 FROM SEGMENT 4
J POINT 3 TIME 160 FROM SEGMENT 2	J POINT 2 TIME 1637 FROM SEGMENT 1
J POINT 4 TIME 240 FROM SEGMENT 3	J POINT 3 TIME 1717 FROM SEGMENT 2
INTERVAL = 320	J POINT 4 TIME 1797 FROM SEGMENT 3
J POINT 1 TIME 320 FROM SEGMENT 4	INTERVAL = 316
J POINT 2 TIME 400 FROM SEGMENT 1	J POINT 1 TIME 1877 FROM SEGMENT 4
J POINT 3 TIME 480 FROM SEGMENT 2	J POINT 2 TIME 1959 FROM SEGMENT 1
J POINT 4 TIME 560 FROM SEGMENT 3	J POINT 3 TIME 2039 FROM SEGMENT 2
INTERVAL = 260	J POINT 4 TIME 2119 FROM SEGMENT 3
J POINT 1 TIME 580 FROM SEGMENT 3	INTERVAL = 322
J POINT 2 TIME 689 FROM SEGMENT 1	J POINT 1 TIME 2199 FROM SEGMENT 4
J POINT 3 TIME 769 FROM SEGMENT 2	J POINT 2 TIME 2278 FROM SEGMENT 1
J POINT 4 TIME 849 FROM SEGMENT 3	J POINT 3 TIME 2358 FROM SEGMENT 2
INTERVAL = 349	J POINT 4 TIME 2438 FROM SEGMENT 3
J POINT 1 TIME 929 FROM SEGMENT 4	INTERVAL = 319
J POINT 2 TIME 994 FROM SEGMENT 1	J POINT 1 TIME 2518 FROM SEGMENT 4
J POINT 3 TIME 1074 FROM SEGMENT 2	J POINT 2 TIME 2598 FROM SEGMENT 1
J POINT 4 TIME 1154 FROM SEGMENT 3	J POINT 3 TIME 2678 FROM SEGMENT 2
INTERVAL = 305	J POINT 4 TIME 2758 FROM SEGMENT 3
J POINT 1 TIME 1234 FROM SEGMENT 4	INTERVAL = 320
J POINT 2 TIME 1321 FROM SEGMENT 1	J POINT 1 TIME 2838 FROM SEGMENT 4
J POINT 3 TIME 1401 FROM SEGMENT 2	J POINT 2 TIME 2918 FROM SEGMENT 1
J POINT 4 TIME 1481 FROM SEGMENT 3	J POINT 3 TIME 2998 FROM SEGMENT 2
INTERVAL = 327	

TABLE 3.2.3.

FIGURE 3.2.3.

Legend to table 3.2.3. and figure 3.2.3

A 60 ms prematurely given impulse at $t=580$ instead of $t=640$ results in cycle length alternation, that damps out rapidly, exactly as expected.

Straight line AV Nodal function curve with a gradient < -1 .

Using the same network and parameters for the third time, the experiment has been repeated using a steep AV Nodal function curve.

With the use of this curve defined by:

$$AH = -1.5 * AA + 560$$

the reaction of the tachycardia cycle length on a perturbation of the rate has been studied.

This curve represents a rotation of the AV Nodal function curve using the same rotation point (AA=320, AH=80) as in the two previous examples.

J POINT 2 TIME 80 FROM SEGMENT 1	J POINT 4 TIME 1182 FROM SEGMENT 3
J POINT 3 TIME 160 FROM SEGMENT 2	INTERVAL = 297
J POINT 4 TIME 240 FROM SEGMENT 3	J POINT 1 TIME 1262 FROM SEGMENT 4
INTERVAL = 320	J POINT 2 TIME 1376 FROM SEGMENT 1
J POINT 1 TIME 320 FROM SEGMENT 4	J POINT 3 TIME 1456 FROM SEGMENT 2
J POINT 2 TIME 400 FROM SEGMENT 1	J POINT 4 TIME 1536 FROM SEGMENT 3
J POINT 3 TIME 480 FROM SEGMENT 2	INTERVAL = 354
J POINT 4 TIME 560 FROM SEGMENT 3	J POINT 1 TIME 1616 FROM SEGMENT 4
INTERVAL = 310	J POINT 2 TIME 1645 FROM SEGMENT 1
J POINT 1 TIME 630 FROM SEGMENT 4	J POINT 3 TIME 1725 FROM SEGMENT 2
J POINT 2 TIME 725 FROM SEGMENT 1	J POINT 4 TIME 1805 FROM SEGMENT 3
J POINT 3 TIME 805 FROM SEGMENT 2	INTERVAL = 269
J POINT 4 TIME 885 FROM SEGMENT 3	J POINT 1 TIME 1885 FROM SEGMENT 4
INTERVAL = 335	J POINT 2 TIME 2040 FROM SEGMENT 1
J POINT 1 TIME 965 FROM SEGMENT 4	J POINT 3 TIME 2120 FROM SEGMENT 2
J POINT 2 TIME 1022 FROM SEGMENT 1	J POINT 4 TIME 2200 FROM SEGMENT 3
J POINT 3 TIME 1102 FROM SEGMENT 2	INTERVAL = 395

TABLE 3.2.4.

FIGURE 3.2.4.

Legend to table 3.2.4. and figure 3.2.4.

A premature impulse with a prematurity of only 10 ms starts the alternation of the tachycardia cycle length.

The amplitude of the perturbation increases and the tachycardia stops after finding one of the segments of the circuit still refractory.

In all these experiments the results are identical to those found using the single purpose model. (47-48)

3.3 Circusmovement tachycardia and the WPW syndrome.

In the last example performed to demonstrate the behaviour of this mathematical model, a combination was made of a branching network and an accessory pathway. (see figure 3.3.1.)

In 1980 we studied a patient with intermittent Wolff-Parkinson-White syndrome and bundle branch reentry, in whom different mechanisms of block of impulse propagation in several reentrant circuits resulted in a major discordance between the "echo-zone" and the "tachycardia-zone". (50) It illustrates the delicate balance in electrophysiological parameters of the segments incorporated in reentry circuits required to initiate and sustain the arrhythmia and the interaction of multiple reentry circuits.

Based on the data found during this investigation a simulation study was performed to explore the relations between conduction velocity, refractory period and the structure of the reentry circuit.

FIGURE 3.3.1.

Legend to figure 3.3.1. This figure shows the network representing parts of the conduction system of the heart, together with an accessory pathway between the ventricle and the atrium on the left side of the heart. The junction points represent the following anatomical sites: 1=Low Right Atrium, 2=His Bundle, 3=Left Ventricle, 4=Coronary Sinus, 5=Right Ventricle. The segments represent: 1=AV Node, 2=Left Bundle, 3=Accessory Pathway, 4=Trans Atrial Conduction, 5=Right Bundle, 6=Transseptal Conduction.

The segments in this network have the following properties:

Segment	ATime	RTime
1	R	100
2	80	80
3	80	80
4	80	80
5	60	60
6	40	40

The refractory periods of these segments are at the beginning of the study so short, that the impulse during circus movement tachycardia never finds a refractory segment in front of it. On the other hand the refractory periods are so long that they are not in conflict with the definitions given in chapter 2 paragraph 7.

During the simulation study the influence of the duration of some refractory periods on the tachycardia will be studied.

At the beginning of the study there is a circus movement tachycardia using segment 1 representing the AV Node, anterogradely and segment 3, representing the accessory pathway, retrogradely.

The circusmovement tachycardia has a rate of 320 ms, which includes an AV Nodal conduction time of 80 ms.

FIGURE 3.3.2.

Legend to figure 3.3.2.

Figure 3.3.2. represents the first revolution of the impulse through the circuit composed of the AV Node, the left bundle, the accessory pathway and the atrium.

FIGURE 3.3.3.

Legend to figure 3.3.3.

Figure 3.3.3. shows the second revolution.

After 320 ms the circuit has been passed once and the impulse starts its second revolution. The impulse will conduct through the AV Node in the same time and would reach junction point no 1 again after 320 ms at $t=640$. But 40 ms earlier, at $t=600$ a premature impulse has been given at junction point 1.

FIGURE 3.3.4.

Legend to figure 3.3.4. This impulse will conduct retrogradely through segment 4 and collide with the circulating impulse. In antegrade direction the premature impulse will conduct through segment 1, representing AV Nodal conduction. Since the impulse is premature the conduction time through the segment is prolonged to 120 ms. The conduction through segment 2,3 and 4 is rate independent, so the impulse will reach the junction point 1, with the same delay of 40 ms.

FIGURE 3.3.5.

Legend to figure 3.3.5.

This results in a conduction time through segment 1 of 40 ms with the impulse arriving at junction point 2 at $t = 1000$. Junction point no 2 has been activated previously at $t = 720$. If the anterograde refractory period of segment 2 is selected to be 310 ms the impulse is not able to penetrate into this segment and left bundle branch block will occur. The impulse is able to enter segment 5 activating the right ventricle and reaching the left ventricle 40 ms later over the transseptal segment.

From junction point 3, segment 2 is activated retrogradely, at the same time the impulse continues to conduct through the accessory pathway retrogradely to the atrium.

Depending on the selected refractory periods in segment no 1 and no 5, the following situation can be simulated:

- If segment 1 is no longer refractory, the impulse will conduct retrogradely and collide with the circulating impulse.
- If the refractory period of segment 5 is sufficiently short in anterograde direction, the impulse can conduct again to junction point 5. If no block occurs in the following segments the circus movement tachycardia will be reinitiated.

J POINT 2 TIME 80 FROM SEGMENT 1
 J POINT 5 TIME 140 FROM SEGMENT 5
 J POINT 3 TIME 160 FROM SEGMENT 2
 J POINT 4 TIME 240 FROM SEGMENT 3
 INTERVAL = 320
 J POINT 1 TIME 320 FROM SEGMENT 4
 J POINT 2 TIME 400 FROM SEGMENT 1
 J POINT 5 TIME 460 FROM SEGMENT 5
 J POINT 3 TIME 480 FROM SEGMENT 2
 J POINT 4 TIME 560 FROM SEGMENT 3
 INTERVAL = 280
 J POINT 1 TIME 600 FROM SEGMENT 3
 J POINT 2 TIME 719 FROM SEGMENT 1
 J POINT 5 TIME 779 FROM SEGMENT 5
 J POINT 3 TIME 799 FROM SEGMENT 2
 J POINT 4 TIME 879 FROM SEGMENT 3
 INTERVAL = 359
 J POINT 1 TIME 959 FROM SEGMENT 4
 J POINT 2 TIME 1000 FROM SEGMENT 1
 J POINT 5 TIME 1060 FROM SEGMENT 5
 J POINT 3 TIME 1100 FROM SEGMENT 6
 J POINT 2 TIME 1180 FROM SEGMENT 2
 J POINT 4 TIME 1180 FROM SEGMENT 3
 INTERVAL = 301
 J POINT 1 TIME 1260 FROM SEGMENT 4
 J POINT 2 TIME 1359 FROM SEGMENT 1
 J POINT 5 TIME 1419 FROM SEGMENT 5
 J POINT 3 TIME 1459 FROM SEGMENT 6
 J POINT 2 TIME 1539 FROM SEGMENT 2
 J POINT 4 TIME 1539 FROM SEGMENT 3
 INTERVAL = 359
 J POINT 1 TIME 1619 FROM SEGMENT 4

J POINT 2 TIME 1660 FROM SEGMENT 1
 J POINT 5 TIME 1720 FROM SEGMENT 5
 J POINT 3 TIME 1760 FROM SEGMENT 6
 J POINT 4 TIME 1840 FROM SEGMENT 3
 INTERVAL = 301
 J POINT 1 TIME 1920 FROM SEGMENT 4
 J POINT 2 TIME 2019 FROM SEGMENT 1
 J POINT 5 TIME 2079 FROM SEGMENT 5
 J POINT 3 TIME 2099 FROM SEGMENT 2
 J POINT 4 TIME 2179 FROM SEGMENT 3
 INTERVAL = 339
 J POINT 1 TIME 2259 FROM SEGMENT 4
 J POINT 2 TIME 2320 FROM SEGMENT 1
 J POINT 5 TIME 2380 FROM SEGMENT 5
 J POINT 3 TIME 2420 FROM SEGMENT 6
 J POINT 2 TIME 2500 FROM SEGMENT 2
 J POINT 4 TIME 2500 FROM SEGMENT 3
 INTERVAL = 321
 J POINT 1 TIME 2580 FROM SEGMENT 4
 J POINT 2 TIME 2659 FROM SEGMENT 1
 J POINT 5 TIME 2719 FROM SEGMENT 5
 J POINT 3 TIME 2759 FROM SEGMENT 6
 J POINT 2 TIME 2839 FROM SEGMENT 2
 J POINT 4 TIME 2839 FROM SEGMENT 3
 INTERVAL = 339
 J POINT 1 TIME 2919 FROM SEGMENT 4
 J POINT 2 TIME 2980 FROM SEGMENT 1
 J POINT 5 TIME 3040 FROM SEGMENT 5
 J POINT 3 TIME 3080 FROM SEGMENT 6
 J POINT 2 TIME 3160 FROM SEGMENT 2
 J POINT 4 TIME 3160 FROM SEGMENT 3
 INTERVAL = 321

TABLE 3.3.1.

FIGURE 3.3.6.

Legend to table 3.3.1. and figure 3.3.6

Table 3.3.1. contains the computer output as described in this paragraph. Figure 3.3.6. shows the ladder diagram derived from this table.

The time of activation of the different junction points is given, together with the segment carrying the impulse. The first considered impulse conducts through the AV node -1.2- in 80 ms. Both ventricles are activated over the bundle branch at their side -5.3-, followed by retrograde conduction back to the left atrium over the accessory pathway -4-. The first cycle is completed in 320 ms. Also the second cycle would take 320 ms, resulting in an activation of junction point 1 at $t=640$. But 40 ms prior a premature impulse has been given to this junction point resulting in a prolonged conduction time of 119 ms. The rest of the circuit is conducting the impulse in the same way as in the first cycle. 240 ms later junction point 1 is activated again. This causes a cycle length of 359 ms corresponding with a AV nodal conduction time of 41 ms. The impulse arrives at the bundle of His at $t=1000$. The left bundle is at this moment still refractory (ARP=310) and the impulse only can conduct over the right bundle, through the ventricular septum and retrogradely into the left bundle branch. At the same time the impulse is conducted through the accessory pathway and reaches the left atrium at $t=1180$. The total cycle length of this cycle becomes 301 ms. After being conducted through the AV node in 99 ms the impulse finds the left bundle again refractory due to the retrogradely conducted impulse. Again the ventricle is activated over the right bundle, through the septum and retrogradely into the left bundle. This prolongation of the AV nodal conduction also prolongs the total cycle length to 359 ms. The AV nodal conduction time in the next cycle shortens to 41 ms and the impulse is conducted again over the right bundle. But now the left bundle is still refractory and does not become penetrated retrogradely in this cycle. In the next cycle starting at $t=1920$ both bundle branches are able again to conduct the impulse anterogradely and a "normal" cycle with a cycle length of 339 resumes. Junction point 2 has been activated at $t=2019$ last and is now activated at $t=2320$. The interval is shorter as the refractory period of the left bundle and another beat with left bundle branch block will occur. The impulse penetrates the left bundle branch retrogradely and junction point 2 is reached at $t=2500$. In the next revolution of the circling impulse junction point 2 is reached at $t=2659$. Starting at this moment a stable circus movement tachycardia with cycle length alternation and left bundle branch block, due to retrograde penetration of the left bundle branch is present.

Chapter 4.

General discussion

In this chapter the following subjects will be discussed:

- A. The limitations of mathematical simulations in general and in our model in particular.
- B. The relation between the time required for a complete simulation study and the resulting accuracy.
- C. The problems and possibilities of the use of the model in real time during clinical electrophysiological investigations.
- D. Clinical applications
- E. Didactical aspects of the use of a mathematical model to simulate electrophysiological phenomena in man.

- A. The limitations of mathematical simulations in general and in our model in particular.

No matter how accurately a mathematical model has been designed, simulation remains an imitation of reality.

Often many relations between different parameters are unknown or not constant in time. Nevertheless the known relations are assumed to represent the behaviour of the different parts of the model.

Every mathematical model designed for simulation purposes, has its own structure and inherent errors. The number and type of errors depends upon the details of the structure of the model. These errors are additional to those introduced because some parameters and relations between parameters may be unknown.

In this model one of the main sources of error results from the fact that the number of elements in each segment is not unlimited. An unlimited increase in the number of elements in each segment would make it impossible to simulate even very simple processes in a short period of time.

In the present model the number of elements over which an impulse travels during one simulation cycle is calculated by dividing the number of elements in each segment (100) by the conduction time in ms.

However an impulse in this model starts at element 1. Conduction through a segment is assumed to have finished when element 100 is reached or passed. It makes no difference whether during the last simulation cycle the impulse just reaches element 100 or passes it (and conducts to an element located more distal than this theoretically last element). This means that only 99 elements are passed in each segment. The error introduced by this fact means that the conduction time resulting from a simulation study can either be greater or smaller than the conduction time selected at the beginning of a simulation study. One way of

controlling this error is to select conduction times less than 100 ms. Then the difference between selected and actually simulated conduction time will remain smaller than 1 ms per segment.

Another method to control error in calculation of conduction time is to start an impulse at element 0. In such a situation the conduction time calculated during the simulation study would always be equal to or longer than the interval selected at the beginning of a study.

A third possible method to overcome this inaccuracy is the following. The fact that only 99 elements must be passed can be compensated by compensating the selected conduction times through a segment by a factor 0.99. The simulation time interval derived using this correction factor is in this situation also equal to or longer than the initially selected values.

Using one of the last two methods, the following error will occur:

If an impulse conducts through a network built of segments with rate independent conduction times, the conduction time through every segment will increase, compared to the actually selected values. The intervals in the mathematical model will vary from those in reality.

In the present model some errors in conduction time will be greater and some smaller than the ones initially selected. The accumulative effect of these errors will tend towards zero.

The following calculations illustrate the magnitude of the error introduced by these three different methods.

Using 91 different selected conduction velocities, (V_{sel}), starting at 1.0 element/ms, increasing in 0.1 ms steps upto 10.0 elements/ms, the following parameters have been calculated.

T_{sel} :	The initially selected conduction time through the segment.
$T_{sel} = 100 / V_{sel}$
T_{sys99} :	The simulated conduction time required to conduct an impulse over 99 segments using the definitions described in chapter 2. This is the time necessary to conduct from element 1 to element 100.
T_{sys100} :	The conduction time required to conduct the impulse over 100 elements.
$T_{sys99/100}$:	The corrected conduction time required to conduct an impulse over 99 . The conduction velocity of the impulse has been multiplied by a factor 0.99.
D1:	The difference between the theoretical conduction time T_{sel} and the simulated conduction time T_{sys99}
D2:	The difference between the theoretical conduction time T_{sel} and the simulated conduction time T_{sys100}
D3:	The difference between the conduction time T_{sys99} and the corrected conduction time $T_{sys99/100}$

Vsel	Tsel	Tsys100	Tsys99/100	Tsys99	D1	D2	D3	Vsel	Tsel	Tsys100	Tsys99/100	Tsys99	D1	D2	D3	
1	100	99	100	100	1	0	0	6	16	66	17	17	17	-34	-34	-34
1.1	90	9	91	91	91	-1	-1	-1	6	1	16	39	17	17	-61	-61
1.2	82	33	83	84	84	-33	-67	-67	6	2	16	12	16	17	12	-88
1.3	76	92	77	77	77	-98	-98	-98	6	3	15	87	16	16	-13	-13
1.4	71	42	71	72	72	-42	-58	-58	6	4	15	62	16	16	-38	-38
1.5	66	66	66	67	67	-66	-34	-34	6	5	15	38	16	16	-62	-62
1.6	62	5	62	63	63	-5	-5	-5	6	6	15	15	16	16	-85	-85
1.7	58	82	59	59	59	-18	-18	-18	6	7	14	92	15	15	-98	-98
1.8	55	55	55	56	56	-55	-45	-45	6	8	14	7	15	15	-3	-3
1.9	52	63	53	53	53	-37	-37	-37	6	9	14	49	15	15	-51	-51
2	50	50	50	51	0	0	0	7	14	28	15	15	15	-72	-72	-72
2.1	47	61	48	48	48	-39	-39	-39	7	1	14	88	14	15	-92	-92
2.2	45	45	46	46	46	-55	-55	-55	7	2	13	89	14	14	-12	-12
2.3	43	47	44	44	44	-53	-53	-53	7	3	13	69	14	14	-31	-31
2.4	41	66	42	42	42	-34	-34	-34	7	4	13	51	14	14	-49	-49
2.5	40	40	40	41	0	0	0	7	5	13	33	14	14	14	-67	-67
2.6	38	46	39	39	39	-54	-54	-54	7	6	13	15	14	14	-85	-85
2.7	37	83	37	38	38	-93	-97	-97	7	7	12	98	13	13	-92	-92
2.8	35	71	36	36	36	-29	-29	-29	7	8	12	82	13	13	-18	-18
2.9	34	48	35	35	35	-52	-52	-52	7	9	12	65	13	13	-35	-35
3	33	33	33	34	34	-33	-67	-67	8	12	5	13	13	13	-5	-5
3.1	32	25	32	33	33	-25	-75	-75	8	1	12	34	13	13	-66	-66
3.2	31	25	31	32	32	-25	-75	-75	8	2	12	19	13	13	-81	-81
3.3	30	3	30	31	31	-3	-7	-7	8	3	12	84	12	13	-84	-96
3.4	29	41	30	30	30	-59	-59	-59	8	4	11	9	12	12	-1	-1
3.5	28	57	29	29	29	-43	-43	-43	8	5	11	76	12	12	-24	-24
3.6	27	77	28	28	28	-23	-23	-23	8	6	11	62	12	12	-38	-38
3.7	27	82	27	28	28	-82	-98	-98	8	7	11	49	12	12	-51	-51
3.8	26	31	27	27	27	-69	-69	-69	8	8	11	36	12	12	-64	-64
3.9	25	64	26	26	26	-36	-36	-36	8	9	11	23	12	12	-77	-77
4	25	25	25	25	0	0	0	9	11	11	11	12	12	11	-89	-89
4.1	24	39	25	25	25	-61	-61	-61	9	1	10	98	11	11	-92	-92
4.2	23	8	24	24	24	-2	-2	-2	9	2	10	86	11	11	-14	-14
4.3	23	25	24	24	24	-75	-75	-75	9	3	10	75	11	11	-25	-25
4.4	22	72	23	23	23	-28	-28	-28	9	4	10	63	11	11	-37	-37
4.5	22	22	22	23	23	-22	-78	-78	9	5	10	52	11	11	-48	-48
4.6	21	73	22	22	22	-27	-27	-27	9	6	10	41	11	11	-59	-59
4.7	21	27	22	22	22	-73	-73	-73	9	7	10	3	11	11	-7	-7
4.8	20	83	21	21	21	-17	-17	-17	9	8	10	2	11	11	-8	-8
4.9	20	4	21	21	21	-5	-6	-6	9	9	10	1	10	11	-9	-9
5	20	20	20	21	0	0	0	10	10	10	10	10	0	0	0	0
5.1	19	6	20	20	20	-4	-4	-4								
5.2	19	23	20	20	20	-77	-77	-77								
5.3	18	86	19	19	19	-14	-14	-14								
5.4	18	51	19	19	19	-49	-49	-49								
5.5	18	18	18	19	19	-18	-82	-82								
5.6	17	85	18	18	18	-15	-15	-15								
5.7	17	54	18	18	18	-46	-46	-46								
5.8	17	24	18	18	18	-76	-76	-76								
5.9	16	94	17	17	17	-96	-96	-96								

TABLE

TABLE 4.1.1.

Table 4.1.1. demonstrates that the differences between the theoretical conduction times and the three calculated conduction times D1, D2 and D3 are always smaller than 1 ms. The difference D1 can have a positive or negative value; the differences D2 and D3 only negative values.

Calculation over these 91 subsequent values gives the following mean error :

$$D1 = 0.248$$

$$D2 = -0.457$$

$$D3 = -0.490$$

The average error using one of these three methodes is very small. There is a small preference for the method used in this study.

In the preceding paragraph the conduction time through a segment was assumed to be not rate dependent. In that case the error in time to conduct through a segment and through a network will be constant.

Fig 4.1.1. shows an example of this situation. One sees a network containing four segments. Together they form a re-entry circuit in which an impulse is circulating clockwise. All values mentioned are derived in the direction of the circulating impulse.

SEGMENT V_{sel} T_{sel} T_{sys99}

SEGMENT	V_{sel}	T_{sel}	T_{sys99}
1	1	100	99
2	1.5	66.6	66
3	5	20	20
4	2	50	50

FIGURE 4.1.1.

Legend to figure 4.1.1. This figure shows a re-entry circuit containing four segments. V_{sel} indicates the selected conduction velocity in elements / simulation cycle. T_{sel} represents the initially selected conduction time, and T_{sys99} shows the conduction time calculated by the model.

Note that all conduction velocities are constant and not rate dependent.

Time required to perform one cycle :

Theoretically : 236.66 ms

Using T_{sys99} : 235.00 ms

The revolution time is slightly shortened, but remains constant.

In another example we will study the behaviour of the same network, after replacing segment 1, by a segment with a rate dependant conduction time. The properties of this segment are equal to the segment used in paragraph 3.2.

FIGURE 4.1.2.

Legend to figure 4.1.2. In this example the conduction time through segment 1 is rate dependent. The relation between the rate and the conduction time is indicated in the left side of the figure.

The conduction time in the direction of the tachycardia in the other segments is as follows :

Segment	ATime	RTime	AD	
1	Rate Dependent	Rate Dependent	Rate Dependent	All values measured in ms.
2	80	80	1.25	
3	80	80	1.25	
4	80	80	1.25	

Through this circuit an impulse is circulating clockwise having a revolution time of 320 ms. By giving a premature impulse at junction point 1, the activation interval of segment 1 shortens to 280 ms. Immediately this will cause a prolongation of the conduction time through this segment of 40 ms to 120 ms. This results in a revolution time of 359 ms causing an acceleration of the conduction velocity resulting in a conduction time through segment 1 of 41 ms. Theoretically this process can continue indefinitely.

After entering this network, the conduction times and refractory periods and the previously mentioned impulses the computer will generate the following output listing. (t=0 indicates the introduction of the premature impulse in segment no 1.)

J POINT 2 TIME 60 FROM SEGMENT 1
 J POINT 3 TIME 160 FROM SEGMENT 2
 J POINT 4 TIME 240 FROM SEGMENT 3
 INTERVAL = 320
 J POINT 1 TIME 320 FROM SEGMENT 4
 J POINT 2 TIME 400 FROM SEGMENT 1
 J POINT 3 TIME 480 FROM SEGMENT 2
 J POINT 4 TIME 560 FROM SEGMENT 3
 INTERVAL = 280
 J POINT 1 TIME 600 FROM SEGMENT 3
 J POINT 2 TIME 719 FROM SEGMENT 1
 J POINT 3 TIME 799 FROM SEGMENT 2
 J POINT 4 TIME 879 FROM SEGMENT 3
 INTERVAL = 359
 J POINT 1 TIME 959 FROM SEGMENT 4
 J POINT 2 TIME 1000 FROM SEGMENT 1
 J POINT 3 TIME 1080 FROM SEGMENT 2
 J POINT 4 TIME 1160 FROM SEGMENT 3
 INTERVAL = 201
 J POINT 1 TIME 1240 FROM SEGMENT 4
 J POINT 2 TIME 1358 FROM SEGMENT 1
 J POINT 3 TIME 1438 FROM SEGMENT 2
 J POINT 4 TIME 1518 FROM SEGMENT 3
 INTERVAL = 350
 J POINT 1 TIME 1598 FROM SEGMENT 4
 J POINT 2 TIME 1640 FROM SEGMENT 1
 J POINT 3 TIME 1720 FROM SEGMENT 2
 J POINT 4 TIME 1800 FROM SEGMENT 3
 INTERVAL = 282
 J POINT 1 TIME 1980 FROM SEGMENT 4
 J POINT 2 TIME 1997 FROM SEGMENT 1
 J POINT 3 TIME 2077 FROM SEGMENT 2
 J POINT 4 TIME 2157 FROM SEGMENT 3
 INTERVAL = 357
 J POINT 1 TIME 2237 FROM SEGMENT 4
 J POINT 2 TIME 2280 FROM SEGMENT 1
 J POINT 3 TIME 2360 FROM SEGMENT 2
 J POINT 4 TIME 2440 FROM SEGMENT 3
 INTERVAL = 283
 J POINT 1 TIME 2520 FROM SEGMENT 4
 J POINT 2 TIME 2636 FROM SEGMENT 1
 J POINT 3 TIME 2716 FROM SEGMENT 2
 J POINT 4 TIME 2796 FROM SEGMENT 3
 INTERVAL = 356
 J POINT 1 TIME 2876 FROM SEGMENT 4
 J POINT 2 TIME 2920 FROM SEGMENT 1
 J POINT 3 TIME 3000 FROM SEGMENT 2
 J POINT 4 TIME 3080 FROM SEGMENT 3
 INTERVAL = 284
 J POINT 1 TIME 3160 FROM SEGMENT 4
 J POINT 2 TIME 3275 FROM SEGMENT 1
 J POINT 3 TIME 3355 FROM SEGMENT 2
 J POINT 4 TIME 3435 FROM SEGMENT 3
 INTERVAL = 355
 J POINT 1 TIME 3515 FROM SEGMENT 4
 J POINT 2 TIME 3560 FROM SEGMENT 1
 J POINT 3 TIME 3640 FROM SEGMENT 2
 J POINT 4 TIME 3720 FROM SEGMENT 3
 INTERVAL = 285
 J POINT 1 TIME 3800 FROM SEGMENT 4
 J POINT 2 TIME 3914 FROM SEGMENT 1
 J POINT 3 TIME 3994 FROM SEGMENT 2
 J POINT 4 TIME 4074 FROM SEGMENT 3
 INTERVAL = 354

J POINT 1 TIME 4154 FROM SEGMENT 4
 J POINT 2 TIME 4200 FROM SEGMENT 1
 J POINT 3 TIME 4280 FROM SEGMENT 2
 J POINT 4 TIME 4360 FROM SEGMENT 3
 INTERVAL = 296
 J POINT 1 TIME 4440 FROM SEGMENT 4
 J POINT 2 TIME 4553 FROM SEGMENT 1
 J POINT 3 TIME 4633 FROM SEGMENT 2
 J POINT 4 TIME 4713 FROM SEGMENT 3
 INTERVAL = 353
 J POINT 1 TIME 4793 FROM SEGMENT 4
 J POINT 2 TIME 4840 FROM SEGMENT 1
 J POINT 3 TIME 4920 FROM SEGMENT 2
 J POINT 4 TIME 5000 FROM SEGMENT 3
 INTERVAL = 287
 J POINT 1 TIME 5080 FROM SEGMENT 4
 J POINT 2 TIME 5192 FROM SEGMENT 1
 J POINT 3 TIME 5272 FROM SEGMENT 2
 J POINT 4 TIME 5352 FROM SEGMENT 3
 INTERVAL = 352
 J POINT 1 TIME 5432 FROM SEGMENT 4
 J POINT 2 TIME 5480 FROM SEGMENT 1
 J POINT 3 TIME 5560 FROM SEGMENT 2
 J POINT 4 TIME 5640 FROM SEGMENT 3
 INTERVAL = 288
 J POINT 1 TIME 5720 FROM SEGMENT 4
 J POINT 2 TIME 5831 FROM SEGMENT 1
 J POINT 3 TIME 5911 FROM SEGMENT 2
 J POINT 4 TIME 5991 FROM SEGMENT 3
 INTERVAL = 351
 J POINT 1 TIME 6071 FROM SEGMENT 4
 J POINT 2 TIME 6120 FROM SEGMENT 1
 J POINT 3 TIME 6200 FROM SEGMENT 2
 J POINT 4 TIME 6280 FROM SEGMENT 3
 INTERVAL = 289
 J POINT 1 TIME 6360 FROM SEGMENT 4
 J POINT 2 TIME 6470 FROM SEGMENT 1
 J POINT 3 TIME 6550 FROM SEGMENT 2
 J POINT 4 TIME 6630 FROM SEGMENT 3
 INTERVAL = 350
 J POINT 1 TIME 6710 FROM SEGMENT 4
 J POINT 2 TIME 6760 FROM SEGMENT 1
 J POINT 3 TIME 6840 FROM SEGMENT 2
 J POINT 4 TIME 6920 FROM SEGMENT 3
 INTERVAL = 290
 J POINT 1 TIME 7000 FROM SEGMENT 4
 J POINT 2 TIME 7109 FROM SEGMENT 1
 J POINT 3 TIME 7189 FROM SEGMENT 2
 J POINT 4 TIME 7269 FROM SEGMENT 3
 INTERVAL = 349
 J POINT 1 TIME 7349 FROM SEGMENT 4
 J POINT 2 TIME 7488 FROM SEGMENT 1
 J POINT 3 TIME 7488 FROM SEGMENT 2
 J POINT 4 TIME 7568 FROM SEGMENT 3
 INTERVAL = 291
 J POINT 1 TIME 7640 FROM SEGMENT 4
 J POINT 2 TIME 7740 FROM SEGMENT 1
 J POINT 3 TIME 7820 FROM SEGMENT 2
 J POINT 4 TIME 7908 FROM SEGMENT 3
 INTERVAL = 340
 J POINT 1 TIME 7988 FROM SEGMENT 4
 J POINT 2 TIME 8040 FROM SEGMENT 1
 J POINT 3 TIME 8120 FROM SEGMENT 2
 J POINT 4 TIME 8200 FROM SEGMENT 3
 INTERVAL = 292

J POINT 1 TIME 8280 FROM SEGMENT 4	J POINT 1 TIME 12461 FROM SEGMENT 4
J POINT 2 TIME 8387 FROM SEGMENT 1	J POINT 2 TIME 12520 FROM SEGMENT 1
J POINT 3 TIME 8467 FROM SEGMENT 2	J POINT 3 TIME 12600 FROM SEGMENT 2
J POINT 4 TIME 8547 FROM SEGMENT 3	J POINT 4 TIME 12680 FROM SEGMENT 3
INTERVAL = 347	INTERVAL = 299
J POINT 1 TIME 8627 FROM SEGMENT 4	J POINT 1 TIME 12760 FROM SEGMENT 4
J POINT 2 TIME 8680 FROM SEGMENT 1	J POINT 2 TIME 12860 FROM SEGMENT 1
J POINT 3 TIME 8760 FROM SEGMENT 2	J POINT 3 TIME 12940 FROM SEGMENT 2
J POINT 4 TIME 8840 FROM SEGMENT 3	J POINT 4 TIME 13020 FROM SEGMENT 3
INTERVAL = 293	INTERVAL = 340
J POINT 1 TIME 8920 FROM SEGMENT 4	J POINT 1 TIME 13100 FROM SEGMENT 4
J POINT 2 TIME 9026 FROM SEGMENT 1	J POINT 2 TIME 13160 FROM SEGMENT 1
J POINT 3 TIME 9106 FROM SEGMENT 2	J POINT 3 TIME 13240 FROM SEGMENT 2
J POINT 4 TIME 9186 FROM SEGMENT 3	J POINT 4 TIME 13320 FROM SEGMENT 3
INTERVAL = 346	INTERVAL = 300
J POINT 1 TIME 9266 FROM SEGMENT 4	J POINT 1 TIME 13400 FROM SEGMENT 4
J POINT 2 TIME 9320 FROM SEGMENT 1	J POINT 2 TIME 13499 FROM SEGMENT 1
J POINT 3 TIME 9400 FROM SEGMENT 2	J POINT 3 TIME 13579 FROM SEGMENT 2
J POINT 4 TIME 9480 FROM SEGMENT 3	J POINT 4 TIME 13659 FROM SEGMENT 3
INTERVAL = 294	INTERVAL = 339
J POINT 1 TIME 9560 FROM SEGMENT 4	J POINT 1 TIME 13739 FROM SEGMENT 4
J POINT 2 TIME 9665 FROM SEGMENT 1	J POINT 2 TIME 13800 FROM SEGMENT 1
J POINT 3 TIME 9745 FROM SEGMENT 2	J POINT 3 TIME 13880 FROM SEGMENT 2
J POINT 4 TIME 9825 FROM SEGMENT 3	J POINT 4 TIME 13960 FROM SEGMENT 3
INTERVAL = 345	INTERVAL = 301
J POINT 1 TIME 9905 FROM SEGMENT 4	J POINT 1 TIME 14040 FROM SEGMENT 4
J POINT 2 TIME 9960 FROM SEGMENT 1	J POINT 2 TIME 14139 FROM SEGMENT 1
J POINT 3 TIME 10040 FROM SEGMENT 2	J POINT 3 TIME 14219 FROM SEGMENT 2
J POINT 4 TIME 10120 FROM SEGMENT 3	J POINT 4 TIME 14299 FROM SEGMENT 3
INTERVAL = 295	INTERVAL = 339
J POINT 1 TIME 10200 FROM SEGMENT 4	J POINT 1 TIME 14379 FROM SEGMENT 4
J POINT 2 TIME 10304 FROM SEGMENT 1	J POINT 2 TIME 14440 FROM SEGMENT 1
J POINT 3 TIME 10384 FROM SEGMENT 2	J POINT 3 TIME 14520 FROM SEGMENT 2
J POINT 4 TIME 10464 FROM SEGMENT 3	J POINT 4 TIME 14600 FROM SEGMENT 3
INTERVAL = 344	INTERVAL = 301
J POINT 1 TIME 10544 FROM SEGMENT 4	J POINT 1 TIME 14680 FROM SEGMENT 4
J POINT 2 TIME 10600 FROM SEGMENT 1	J POINT 2 TIME 14779 FROM SEGMENT 1
J POINT 3 TIME 10680 FROM SEGMENT 2	J POINT 3 TIME 14859 FROM SEGMENT 2
J POINT 4 TIME 10760 FROM SEGMENT 3	J POINT 4 TIME 14939 FROM SEGMENT 3
INTERVAL = 296	INTERVAL = 339
J POINT 1 TIME 10840 FROM SEGMENT 4	J POINT 1 TIME 15019 FROM SEGMENT 4
J POINT 2 TIME 10943 FROM SEGMENT 1	J POINT 2 TIME 15080 FROM SEGMENT 1
J POINT 3 TIME 11023 FROM SEGMENT 2	J POINT 3 TIME 15160 FROM SEGMENT 2
J POINT 4 TIME 11103 FROM SEGMENT 3	J POINT 4 TIME 15240 FROM SEGMENT 3
INTERVAL = 343	INTERVAL = 301
J POINT 1 TIME 11183 FROM SEGMENT 4	J POINT 1 TIME 15320 FROM SEGMENT 4
J POINT 2 TIME 11240 FROM SEGMENT 1	J POINT 2 TIME 15419 FROM SEGMENT 1
J POINT 3 TIME 11320 FROM SEGMENT 2	J POINT 3 TIME 15499 FROM SEGMENT 2
J POINT 4 TIME 11400 FROM SEGMENT 3	J POINT 4 TIME 15579 FROM SEGMENT 3
INTERVAL = 297	INTERVAL = 339
J POINT 1 TIME 11480 FROM SEGMENT 4	J POINT 1 TIME 15659 FROM SEGMENT 4
J POINT 2 TIME 11582 FROM SEGMENT 1	J POINT 2 TIME 15720 FROM SEGMENT 1
J POINT 3 TIME 11662 FROM SEGMENT 2	J POINT 3 TIME 15800 FROM SEGMENT 2
J POINT 4 TIME 11742 FROM SEGMENT 3	J POINT 4 TIME 15880 FROM SEGMENT 3
INTERVAL = 342	INTERVAL = 301
J POINT 1 TIME 11822 FROM SEGMENT 4	J POINT 1 TIME 15960 FROM SEGMENT 4
J POINT 2 TIME 11880 FROM SEGMENT 1	J POINT 2 TIME 16059 FROM SEGMENT 1
J POINT 3 TIME 11960 FROM SEGMENT 2	J POINT 3 TIME 16139 FROM SEGMENT 2
J POINT 4 TIME 12040 FROM SEGMENT 3	J POINT 4 TIME 16219 FROM SEGMENT 3
INTERVAL = 298	INTERVAL = 339
J POINT 1 TIME 12120 FROM SEGMENT 4	J POINT 1 TIME 16299 FROM SEGMENT 4
J POINT 2 TIME 12221 FROM SEGMENT 1	J POINT 2 TIME 16360 FROM SEGMENT 1
J POINT 3 TIME 12301 FROM SEGMENT 2	J POINT 3 TIME 16440 FROM SEGMENT 2
J POINT 4 TIME 12381 FROM SEGMENT 3	J POINT 4 TIME 16520 FROM SEGMENT 3
INTERVAL = 341	INTERVAL = 301

TABLE 4.1.2.

Legend to table 4.1.2.

This reproduction of the computer output shows the junction point reached by an impulse, the time of occurrence and the segment lastly used by this impulse.

The difference between the theoretical cycle length and the calculated one is drawn in figure 4.1.3.

FIGURE 4.1.3.

Legend to figure 4.1.3.

This figure demonstrates that the difference between the calculated simulation time and the theoretically selected time interval is not constant. As a result of a rate dependent segment in the network, the error between expected and simulated circuit time increases after every revolution through the network. After 16000 ms the model is stable and alternates around the tachycardia cycle length with an amplitude of 19 ms and a fixed difference of 21 ms.

- B. The relation between the time required for a complete simulation study and the resultant accuracy.

The model described herein was developed using the Basic computer language and an Apple II microcomputersystem.

During the design of the model the use of this interpreter level language was selected, because program changes could be made easily. One of the big disadvantages of this interpreter level language is its relatively slow calculation velocity. To overcome this problem the model was translated from Basic to Fortran to be used on a VAX370 computer system.

Using this compiler level language instead of Basic, the calculation velocity increased by a factor of approximately 100.

Independent of the selected computer language, the time necessary to simulate a certain process consists of two parts:

The first part indicates

- the time to define the structure of the network,
- the time to define the properties of the different segments and the impulses,
- the time required to produce the results and
- the usertime (i.e. the time elapsed while the system waits for user input).

The second part depends on

- the number of cycles that has to be simulated,
- the number of segments involved,
- the state of these segments and
- the desired accuracy.

If one desires to increase the temporal resolution from 1 ms / segment to 0.1 ms / segment, this goal can be reached by increasing the number of elements in one segment from 100 to 1000 and by multiplying the conduction velocity by 0.1 .

Since this increase in accuracy will not greatly influence time for definition of the network etcetera, the total simulation time will increase by a factor smaller than 10.

Unless one wants to simulate very small segments it is seldom necessary to obtain a temporal resolution of less than 1 ms. The inaccuracy of obtaining input data is in most cases a multiple of the error caused by the number of elements.

C. The problems and possibilities of the use of the model in real time during clinical electrophysiological investigations

One of the most fascinating areas to use this mathematical model is during clinical electrophysiological investigation in man. To make it possible to work in the electrophysiology laboratory the following criteria must be fulfilled. First it would be necessary to have all values required available during the study. Attempts have been made to develop computer systems to detect the potentials at different sites in the heart and to measure conduction intervals between these sites.⁽⁵¹⁾ Many of these systems are able to detect reliable and reproducible potentials during regular rhythms. None of these systems is able to provide the required intervals during the invasive electrophysiological study. During complex arrhythmias automatic calculations of intervals are unreliable and not suitable for use as input in a computer model of conduction in a real time situation.

A second condition that has to be fulfilled is the following. To be able to use the model in real time the simulation velocity must be increased. The time required to simulate a certain process has to be of the same magnitude as the process itself.

If both criteria would be fulfilled, it may be possible for instance to use the computer during the electrophysiological study of patients with tachycardia. Based on the clinical data the model could predict the effect of extra stimuli at different times and locations. These data may be of importance for terminating circus movement tachycardias. Also for the evaluation of programmable permanent pacemakers the model could be a helpful instrument.

At present the criteria required to make these applications possible have not yet been fulfilled. Hopefully in the near future it will become possible to use the model during the electrophysiological investigations as described above.

Two areas where the model can be used already with much success will be described in the following paragraphs.

D. Clinical applications

To initiate clinical circus movement tachycardia three conditions have to be fulfilled:

- A circuit has to be available
- Unidirectional block has to be present.
- Conduction in the circuit has to be slow enough to find excitable tissue ahead of the impulse.

In our mathematical model all these criteria can be realized. Using the model the following clinical aspects of reentrant tachycardia have been studied.

- The influence of the prematurity of the extra stimulus on initiation and termination of reentrant tachycardias. In chapter 3.3 an example of the simulation of termination of a reentrant tachycardia by giving an extra stimulus has been discussed.
- The effect of the administration of medication on a reentrant tachycardia. To do so the influence of this drug on the conduction velocity, ability to conduct and the refractory period of one or more segments has to be defined. Because the model has an internal clock all these parameters can be defined as being time dependent.

In chapter 3.2 the role of the AV nodal function curve as a possible cause of cycle length alternation has been discussed. In a publication describing this relation, the influence of medication on the tachycardia cycle length has also been studied.(47) By movement of the AV nodal function curve to the right, cycle length alternation could be initiated. Movement of the AV nodal function curve in this direction occurs during administration of drugs that increase AV nodal refractoriness. This could explain why these drugs often induce clinical cycle length alternation. Induction of cycle length alternation in the tachycardia model by gradual movement of the AV nodal refractory curve to the right tends to cause a gradual onset of alternation, with a gradual increase in amplitude. This is frequently seen in clinical cycle length alternation.

Finally the influence of the site of stimulation on initiation and termination of reentrant tachycardia can easily be studied. By decreasing the conduction velocity of a segment connecting the site of stimulation and the tachycardia circuit a greater distance can be simulated. The way a second extra impulse abbreviates the time required to terminate a tachycardia can easily be demonstrated. Recently our group published an article to illustrate the mechanisms causing this phenomenon (52).

E. Didactical aspects of the use of a mathematical model to simulate electrophysiological phenomena in man.

This model which was originally designed as an instrument for research in clinical electrophysiology, can also be used for teaching. Education by simulation models offers some important advantages to the student. Independent of the teacher the student can repeat experiments as often as wanted. With each experiment it is possible to change one or more parameters and to study the response of the model to the new conditions.

In the present model some built-in networks are available. The student can study basic electrophysiology such as the properties of the normal cardiac conduction system, conditions required for reentry, and the initiation and termination of reentry tachycardias with programmed extrastimuli.

But these teaching facilities are not limited to the student. Also investigators can use these mathematical models as an objective judge to test their knowledge and understanding.

We believe therefore that the use of simulation models should not be limited to some areas in medicine where it has been accepted already. It deserves to be applied on a much wider scale.

Chapter 5.

Summary

Samenvatting

Rizzumee

Summary

This study describes a mathematical model of the conduction system of the heart. Using this model it is possible to simulate reentrant tachycardias. Also the influence of extra stimuli and drugs on these tachycardias can be studied.

In this way hypotheses can be tested, concerning the mechanism of reentrant tachycardias initiated during programmed electrical stimulation of the heart.

In chapter **one** a short introduction is given to the history of research concerning the causes of rhythm disturbances of the heart. Further a number of simulation models used in cardiac electrophysiology has been reviewed. Finally this chapter ends with an overview of the criteria this model has to fulfil.

In chapter **two** a description of the model is presented. It includes the layout of the model, a description of the parts (segments) used to build the model and a contemplation about the order in which the conduction of an impulse through a segment has to take place. Also in this chapter the equations describing the conduction of an impulse through a segment and the introduction of an impulse into a segment have been illustrated. Finally the consequences of some limitations of the model are discussed.

In chapter **three** three simulation studies are illustrated. The simulation of the normal conduction system of the heart, followed by the simulation of a reentrant tachycardia in a patient with the WPW Syndrome. In the third study an example is given about how a hypothesis derived during clinical investigation, concerning the mechanism of the tachycardia, can be tested.

In chapter **four** special attention is given to the limitations of the model, its accuracy and the possibility of real time use during invasive investigations. It continues with the discussion of some clinical applications and its didactical value.

Chapter **five** contains the summary.

In chapter **six** all equations used to conduct an impulse through a segment are listed.

In chapter **seven** the equations related to the introduction of impulses into a segment are given.

Samenvatting

Deze studie beschijft een wiskundig model van het geleidingssysteem van het hart. Met behulp van dit model is het mogelijk tachycardieën op basis van reentry te simuleren. Ook kan men de invloed van extra stimuli en medicatie op deze tachycardieën nagaan. Zo kan de onderzoeker hypotheses toetsen over het mechanisme van tachycardieën, zoals die zijn opgewekt tijdens invasief

electrophysiologisch onderzoek bij patiënten met reentry tachycardiën. In hoofdstuk **een** wordt een korte inleiding gegeven over de geschiedenis van het onderzoek naar de oorzaken van ritmestoornissen van het hart. Verder wordt een overzicht gegeven van een aantal in de cardiale electrophysiologie gebruikte simulatiemodellen. Het hoofdstuk wordt afgesloten met een omschrijving van de eisen waaraan het in dit proefschrift omschreven model dient te voldoen.

In hoofdstuk **twee** volgt een beschrijving van het model. Aan de orde komen de opbouw van het model, een beschrijving van de bouwstenen (segmenten) waaruit het model is samengesteld en een beschouwing betreffende de volgorde waarin de voortgeleiding door deze segmenten plaatsvindt. Tevens wordt aangegeven volgens welke wetten de voortgeleiding van een impuls door een segment geregeld is, alsmede hoe nieuwe impulsen in de segmenten kunnen worden geïntroduceerd. Tenslotte worden de consequenties van een tweetal beperkingen van het model gedemonstreerd.

In hoofdstuk **drie** worden drie simulatiestudies besproken, te weten de simulatie van het normale geleidingssysteem van het hart, gevolgd door de simulatie van een cirkel tachycardie in een patient met het WPW syndroom. In het derde voorbeeld wordt gedemonstreerd hoe een op grond van klinisch onderzoek ontstane hypothese betreffende het aan een tachycardie ten grondslag liggende mechanisme kan worden getoetst. In hoofdstuk **vier** wordt aandacht besteed aan de beperkingen van het model, de nauwkeurigheid die ermee bereikt kan worden alsmede de mogelijkheden om het model tijdens het invasief onderzoek te gebruiken. Verder komen een aantal klinische toepassingen aan de orde alsmede het gebruik van het model als onderwijsmiddel.

Hoofdstuk **vijf** bevat de samenvatting.

Hoofdstuk **zes** geeft een overzicht van alle vergelijkingen, die gebruikt worden bij de geleiding van een impuls door een segment.

In hoofdstuk **zeven** worden de vergelijkingen gegeven, die bij het introduceren van een nieuwe impuls in een van de segmenten van het model worden toegepast.

Rizzumee

Dit beukske eksplikeert un wiskunstig medel vaan ut geleijingssiysteem vaan ut hart. Met behöllep vaan dit medel is ut meugelik um tachycardiën op basis vaan reentry te simulere. Aoch is ut meugelik de oetwerreking vaan vreuger kaomende hartsleeg en medikaminte op dees tachycardiën noa te kieke. Zoe kin den onderzoeker hiepotese sjekke euver ut mekaniek vaan tachycardiën, wie die weure opgewek bei inwendig elektrofiesiologies onderzoek bei luij met reentrytachycardiën.

In **sjaipiter ein** weurd unne korte inleijing gegeeve euver de gesjiedenis vaan ut onderzoek nao oerzaake vaan hartkloppinge. Weijer weurd un euverzieg gegeeve vaan un aontal in de elektrofiesiologie vaan ut hart gebruikde simulaasie medelle. Ut sjaipiter weurd aofgesloote met un besjrijving vaan vereiste boeaon ut in dit beukske besjreeve medel moot voldoen.

In **sjaipiter twee** steit un besjrijving vaan ut medel. Daorin weurde geneump de samestelling vaan ut medel, un besjrijving vaan de oonderdeile (segmente) boe

oet ut medel besteit, en un fielezofie euver de vollegorde boe in de geleijing door dees segminten verlöp. Aoch weurd verduts wie de geleijing van unnen impuls door zoen segmint geregeld is en wie impulse in de segminten weure ingeveurd. Aon ut ind weure de konsekwinsies van twee beperrekinge van ut medel oetgelag.

In **sjapiter drei** weure drei simulaasieoonderzeuke geëxpliceerd, naomelik de simulaasie van ut gewoene geleijingssysteem van ut hart, dan de simulaasie van unne sirrekel tachycardie van unne mins met de krenkede van Wolff, Parkinson en White. In ut derde veurbeeld weurd getuind wie me unne hiepotese kin sjekke dee oontstande is nao aonleijing van klinies oonderzoek noa ut mekaniek van hartkloppinge.

In **sjapiter veer** weurd aondach geweid aon de beperrekinge van ut medel, wie perseis ut medel werrek en aoch of ut meugelik is bej inwendig oonderzoek ut medel touw te passe. Weijer weure un aontal kliniese touwpassinge geëxpliceerd en aoch of ut medel in ut ónderwies gebruik kin weure.

Sjapiter veif bevat dun rizzumee.

Sjapiter zës gief un euverziech van alle wiskunstige vergeliekinge die gebruik weure bej de geleijing van unnen impuls door un segmint.

In **sjapiter zeve** weurde de vergeliekinge gegeeve die weure gebruik bej de introduksie van unnen neuje impuls in ein van de segminten van ut medel.

Chapter 6.

Appendix I: Handling of a segment

The following equations summarize the handling of the 35 different states if no external impulses are entered into the segment and conduction velocity and refractory period remain constant.

$AP_n, RP_n, AL_n, \dots$ determine the state in the n^{th} simulation cycle.

$AP_{n+1}, RP_{n+1}, AL_{n+1}, \dots$ determine the state in the $(n+1)^{\text{th}}$ simulation cycle.

$ST_n 1, ST_n 2, ST_n 3$ etc represent State 1, 2, 3 etc during the $(n)^{\text{th}}$ simulation cycle.

ST 1. $AP_n=0 \quad RP_n=0 \quad AL_n=0 \quad RL_n=0 \quad AT_n=0 \quad RT_n=0 \quad CP_n=0$

$AP_{n+1}=0 \quad RP_{n+1}=0 \quad AL_{n+1}=0 \quad RL_{n+1}=0 \quad AT_{n+1}=0 \quad RT_{n+1}=0 \quad CP_{n+1}=0$
 $ST_{n+1}=ST 1$

ST 2. $AP_n>0 \quad RP_n=0 \quad AL_n=0 \quad RL_n=0 \quad AT_n>0 \quad RT_n=0 \quad CP_n=0$

$RP_{n+1}=0 \quad AL_{n+1}=0 \quad RL_{n+1}=0 \quad RT_{n+1}=0 \quad CP_{n+1}=0$
 $AP_{n+1}=AP_n+AD$

IF ($AP_{n+1} \geq 100$)
THEN : $AP_{n+1}=0$ ELSE : $AP_{n+1}=AP_n+1$
 $ST_{n+1}=ST 3$ $ST_{n+1}=ST 2$

$AT_{n+1}=AT_n-1$

ST 3. $AP_n=0 \quad RP_n=0 \quad AL_n=0 \quad RL_n=0 \quad AT_n>0 \quad RT_n=0 \quad CP_n=0$

$AP_{n+1}=0 \quad RP_{n+1}=0 \quad RL_{n+1}=0 \quad RT_{n+1}=0 \quad CP_{n+1}=0$
 $AT_{n+1}=AT_n-1$

IF ($AT_{n+1}=0$)
THEN : $AL_{n+1}=1$ ELSE : $AL_{n+1}=0$
 $ST_{n+1}=ST 4$ $ST_{n+1}=ST 3$

ST 4. $AP_n=0$ $RP_n=0$ $AL_n>0$ $RL_n=0$ $AT_n=0$ $RT_n=0$ $CP_n=0$

$AP_{n+1}=0$ $RP_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}=0$
 $AL_{n+1}=AL_n+AD$

IF ($AL_{n+1} \geq 100$)
THEN: $AL_{n+1}=0$ ELSE: $AL_{n+1}=AL_{n+1}$
 $ST_{n+1}=ST\ 1$ $ST_{n+1}=ST\ 4$

ST 5. $AP_n>0$ $RP_n=0$ $AL_n>0$ $RL_n=0$ $AT_n>0$ $RT_n=0$ $CP_n=0$

$RP_{n+1}=0$ $RL_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}=0$
 $AP_{n+1}=AP_n+AD$
 $AL_{n+1}=AL_n+AD$

IF ($AL_{n+1} \geq 100$)
THEN: $AL_{n+1}=0$ ELSE: $AL_{n+1}=AL_{n+1}$
 $ST_{n+1}=ST\ 2$ $ST_{n+1}=ST\ 5$

$AT_{n+1}=AT_n-1$

ST 6. $AP_n=0$ $RP_n>0$ $AL_n=0$ $RL_n=0$ $AT_n=0$ $RT_n>0$ $CP_n=0$

$AP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}=0$ $CP_{n+1}=0$
 $RP_{n+1}=RP_n-RD$

IF ($RP_{n+1} \leq 1$)
THEN: $RP_{n+1}=0$ ELSE: $RP_{n+1}=RP_{n+1}$
 $ST_{n+1}=ST\ 7$ $ST_{n+1}=ST\ 6$

$RT_{n+1}=RT_n-1$

ST 7. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n=0$ $AT_n=0$ $RT_n>0$ $CP_n=0$

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $AT_{n+1}=0$ $CP_{n+1}=0$
 $RT_{n+1}=RT_n-1$

IF ($RT_{n+1}=0$)
THEN: $RL_{n+1}=100$ ELSE: $RL_{n+1}=0$
 $ST_{n+1}=ST\ 8$ $ST_{n+1}=ST\ 7$

ST 8. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n>0$ $AT_n=0$ $RT_n=0$ $CP_n=0$

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $AT_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}=0$
 $RL_{n+1}=RL_n-RD$

IF ($RL_{n+1} \leq 1$)
 THEN: $RL_{n+1}=0$ ELSE: $RL_{n+1}=RL_{n+1}$
 $ST_{n+1}=ST\ 1$ $ST_{n+1}=ST\ 8$

ST 9. $AP_n=0$ $RP_n>0$ $AL_n=0$ $RL_n>0$ $AT_n=0$ $RT_n>0$ $CP_n=0$

$AP_{n+1}=0$ $AL_{n+1}=0$ $AT_{n+1}=0$ $CP_{n+1}=0$
 $RP_{n+1}=RP_n-RD$
 $RL_{n+1}=RL_n-RD$

IF ($RL_{n+1} \leq 1$)
 THEN: $RL_{n+1}=0$ ELSE: $RL_{n+1}=RL_{n+1}$
 $ST_{n+1}=ST\ 6$ $ST_{n+1}=ST\ 9$

$RT_{n+1}=RT_n-1$

ST 10. $AP_n>0$ $RP_n>0$ $AL_n=0$ $RL_n=0$ $AT_n>0$ $RT_n>0$ $CP_n=0$

$AL_{n+1}=0$ $RL_{n+1}=0$

IF ($(RP_n-AP_n) \leq (AD+RD)$)
 THEN: $AP_{n+1}=0$ ELSE: $AP_{n+1}=AP_{n+1}+AD$
 $RP_{n+1}=0$ $RP_{n+1}=RP_{n+1}-RD$
 $CP_{n+1}=AP_n+AD*PD$ $CP_{n+1}=0$
 $ST_{n+1}=ST\ 11$ $ST_{n+1}=ST\ 10$

$AT_{n+1}=AT_n-1$
 $RT_{n+1}=RT_n-1$

ST 11. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n=0$ $AT_n>0$ $RT_n>0$ $CP_n>0$

$AP_{n+1}=0$ $RP_{n+1}=0$ $CP_{n+1}>0$

$AT_{n+1}=AT_n-1$

IF ($AT_{n+1}=0$)

THEN: $AL_{n+1}=1$

ELSE: $AL_{n+1}=0$

$ST_{n+1}=ST\ 12$

$ST_{n+1}=ST\ 11$

$RT_{n+1}=RT_n-1$

IF ($RT_{n+1}=0$)

THEN: $RL_{n+1}=100$

ELSE: $RL_{n+1}=0$

$ST_{n+1}=ST_{n+1}$

IF ($ST_{n+1}=ST\ 12$)

THEN: $ST_{n+1}=ST\ 18$ ELSE: $ST_{n+1}=ST\ 13$

ST 12. $AP_n=0$ $RP_n=0$ $AL_n>0$ $RL_n=0$ $AT_n=0$ $RT_n>0$ $CP_n>0$

$AP_{n+1}=0$ $RP_{n+1}=0$ $AT_{n+1}=0$ $CP_{n+1}>0$

$AL_{n+1}=AL_n+AD$

IF ($AL_{n+1}\geq CP_n$)

THEN: $AL_{n+1}=0$

ELSE: $AL_{n+1}=AL_{n+1}$

$ST_{n+1}=ST\ 14$

$ST_{n+1}=ST\ 12$

$RT_{n+1}=RT_n-1$

IF ($RT_{n+1}=0$)

THEN: $RL_{n+1}=100$

ELSE: $RL_{n+1}=0$

$ST_{n+1}=ST_{n+1}$

IF ($ST_{n+1}=ST\ 14$)

THEN: $ST_{n+1}=ST\ 16$ ELSE: $ST_{n+1}=ST\ 18$

ST 13. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n>0$ $AT_n>0$ $RT_n=0$ $CP_n>0$

$AP_{n+1}=0$ $RP_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}>0$

$RL_{n+1}=RL_n-RD$

IF ($RL_{n+1}\leq CP_n$)

THEN: $RL_{n+1}=0$

ELSE: $RL_{n+1}=RL_{n+1}$

$ST_{n+1}=ST\ 15$

$ST_{n+1}=ST\ 13$

$AT_{n+1}=AT_n-1$

IF ($AT_{n+1}=0$)

THEN: $AL_{n+1}=1$

ELSE: $AL_{n+1}=0$

$ST_{n+1}=ST_{n+1}$

IF ($ST_{n+1}=ST\ 15$)

THEN: $ST_{n+1}=ST\ 17$ ELSE: $ST_{n+1}=ST\ 18$

ST 14. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n=0$ $AT_n=0$ $RT_n>0$ $CP_n>0$

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $AT_{n+1}=0$ $CP_{n+1}>0$

$RT_{n+1}=RT_n-1$

IF ($RT_{n+1}=0$)

THEN: $RL_{n+1}=100$

ELSE: $RL_{n+1}=0$

$ST_{n+1}=ST\ 16$

$ST_{n+1}=ST\ 14$

ST 15. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n=0$ $AT_n>0$ $RT_n=0$ $CP_n>0$

$AP_{n+1}=0$ $RP_{n+1}=0$ $RL_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}>0$

$AT_{n+1}=AT_n-1$

IF ($AT_{n+1}=0$)

THEN: $AL_{n+1}=1$

ELSE: $AL_{n+1}=0$

$ST_{n+1}=ST\ 17$

$ST_{n+1}=ST\ 15$

ST 16. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n>0$ $AT_n=0$ $RT_n=0$ $CP_n>0$

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $AT_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}>0$

$RL_{n+1}=RL_n-RD$

IF ($RL_{n+1}\leq CP_n$)

THEN: $RL_{n+1}=0$

ELSE: $RL_{n+1}=0$

$ST_{n+1}=ST\ 19$

$ST_{n+1}=ST\ 16$

ST 20. $AP_n > 0$ $RP_n = 0$ $AL_n > 0$ $RL_n = 0$ $AT_n > 0$ $RT_n > 0$ $CP_n > 0$

$RP_{n+1} = 0$ $CP_{n+1} > 0$

$AP_{n+1} = AP_n + AD$

$AL_{n+1} = AL_n + AD$

IF ($AL_{n+1} \geq CP_n$)

THEN: $AL_{n+1} = 0$

ELSE: $AL_{n+1} = AL_{n+1}$

$ST_{n+1} = ST_{22}$

$ST_{n+1} = ST_{20}$

$AT_{n+1} = AT_n - 1$

$RT_{n+1} = RT_n - 1$

IF ($RT_{n+1} = 0$)

THEN: $RL_{n+1} = 100$

ELSE: $RL_{n+1} = 0$

$ST_{n+1} = ST_{n+1}$

IF ($ST_{n+1} = ST_{22}$)

THEN: $ST_{n+1} = ST_{25}$ ELSE: $ST_{n+1} = ST_{28}$

ST 21. $AP_n = 0$ $RP_n > 0$ $AL_n = 0$ $RL_n > 0$ $AT_n > 0$ $RT_n > 0$ $CP_n > 0$

$AP_{n+1} = 0$ $CP_{n+1} > 0$

$RP_{n+1} = RP_n - RD$

$RL_{n+1} = RL_n - RD$

IF ($RL_{n+1} \leq CP_n$)

THEN: $RL_{n+1} = 0$

ELSE: $RL_{n+1} = RL_{n+1}$

$ST_{n+1} = ST_{23}$

$ST_{n+1} = ST_{21}$

$AT_{n+1} = AT_n - 1$

IF ($AT_{n+1} = 0$)

THEN: $AL_{n+1} = 1$

ELSE: $AL_{n+1} = 0$

$ST_{n+1} = ST_{n+1}$

IF ($ST_{n+1} = ST_{23}$)

THEN: $ST_{n+1} = ST_{27}$ ELSE: $ST_{n+1} = ST_{29}$

ST 22. $AP_n > 0$ $RP_n = 0$ $AL_n = 0$ $RL_n = 0$ $AT_n > 0$ $RT_n > 0$ $CP_n > 0$

$RP_{n+1} = 0$ $AL_{n+1} = 0$ $CP_{n+1} > 0$
 $AP_{n+1} = AP_n + AD$

IF ($AP_{n+1} \geq CP_n$)
 THEN : $AP_{n+1} = 0$ ELSE : $AP_{n+1} = AP_{n+1}$
 $ST_{n+1} = ST\ 11$ $ST_{n+1} = ST\ 22$

$AT_{n+1} = AT_n - 1$
 $RT_{n+1} = RT_n - 1$

IF ($RT_{n+1} = 0$)
 THEN : $RL_{n+1} = 100$ ELSE : $RL_{n+1} = 0$
 $ST_{n+1} = ST_{n+1}$

IF ($ST_{n+1} = ST\ 11$)
 THEN : $ST_{n+1} = ST\ 13$ ELSE : $ST_{n+1} = ST\ 25$

ST 23. $AP_n = 0$ $RP_n > 0$ $AL_n = 0$ $RL_n = 0$ $AT_n > 0$ $RT_n > 0$ $CP_n > 0$

$AP_{n+1} = 0$ $RL_{n+1} = 0$ $CP_{n+1} > 0$
 $RP_{n+1} = RP_n - RD$

IF ($RP_{n+1} \leq CP_n$)
 THEN : $RP_{n+1} = 0$ ELSE : $RP_{n+1} = RP_{n+1}$
 $ST_{n+1} = ST\ 11$ $ST_{n+1} = ST\ 23$

$AT_{n+1} = AT_n - 1$

IF ($AT_{n+1} = 0$)
 THEN : $AL_{n+1} = 1$ ELSE : $AL_{n+1} = 0$
 $ST_{n+1} = ST_{n+1}$

IF ($ST_{n+1} = ST\ 11$)
 THEN : $ST_{n+1} = ST\ 12$ ELSE : $ST_{n+1} = ST\ 27$

$RT_{n+1} = RT_n - 1$

ST 24. $AP_n=0$ $RP_n>0$ $AL_n=0$ $RL_n>0$ $AT_n=0$ $RT_n>0$ $CP_n>0$

$AP_{n+1}=0$ $AL_{n+1}=0$ $AT_{n+1}=0$ $CP_{n+1}>0$

$RP_{n+1}=RP_n-RD$

$RL_{n+1}=RL_n-RD$

IF ($RL_{n+1} \leq CP_n$)

THEN: $RL_{n+1}=0$

ELSE: $RL_{n+1}=RL_n+1$

$ST_{n+1}=ST_{32}$

$ST_{n+1}=ST_{24}$

$RT_{n+1}=RT_n-1$

ST 25. $AP_n>0$ $RP_n=0$ $AL_n=0$ $RL_n>0$ $AT_n>0$ $RT_n=0$ $CP_n>0$

$RP_{n+1}=0$ $AL_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}>0$

$AP_{n+1}=AP_n+AD$

IF ($AP_{n+1} \geq CP_n$)

THEN: $AP_{n+1}=0$

ELSE: $AP_{n+1}=AP_n+1$

$ST_{n+1}=ST_{13}$

$ST_{n+1}=ST_{25}$

$RL_{n+1}=RL_n-RD$

IF ($RL_{n+1} \leq CP_n$)

THEN: $RL_{n+1}=0$

ELSE: $RL_{n+1}=RL_n+1$

$ST_{n+1}=ST_{n+1}$

IF ($ST_{n+1}=ST_{13}$)

THEN: $ST_{n+1}=ST_{15}$ ELSE: $ST_{n+1}=ST_{31}$

$AT_{n+1}=AT_n-1$

ST 26. $AP_n>0$ $RP_n=0$ $AL_n>0$ $RL_n=0$ $AT_n>0$ $RT_n=0$ $CP_n>0$

$RP_{n+1}=0$ $RL_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}>0$

$AP_{n+1}=AP_n+AD$

$AL_{n+1}=AL_n+AD$

IF ($AL_{n+1} \geq CP_n$)

THEN: $AL_{n+1}=0$

ELSE: $AL_{n+1}=AL_n+1$

$ST_{n+1}=ST_{31}$

$ST_{n+1}=ST_{26}$

$AT_{n+1}=AT_n-1$

ST 27. $AP_n=0$ $RP_n>0$ $AL_n>0$ $RL_n=0$ $AT_n=0$ $RT_n>0$ $CP_n>0$

$AP_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}=0$ $CP_{n+1}>0$

$RP_{n+1}=RP_n-RD$

IF ($RP_{n+1}\leq CP_n$)

THEN: $RP_{n+1}=0$

ELSE: $RP_{n+1}=RP_{n+1}$

$ST_{n+1}=ST\ 12$

$ST_{n+1}=ST\ 27$

$AL_{n+1}=AL_n+AD$

IF ($AL_{n+1}\geq CP_n$)

THEN: $AL_{n+1}=0$

ELSE: $AL_{n+1}=AL_{n+1}$

$ST_{n+1}=ST_{n+1}$

IF ($ST_{n+1}=ST\ 12$)

THEN: $ST_{n+1}=ST\ 14$ ELSE: $ST_{n+1}=ST\ 32$

$RT_{n+1}=RT_n-1$

ST 28. $AP_n>0$ $RP_n=0$ $AL_n>0$ $RL_n>0$ $AT_n>0$ $RT_n=0$ $CP_n>0$

$RP_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}>0$

$AP_{n+1}=AP_n+AD$

$AL_{n+1}=AL_n+AD$

IF ($AL_{n+1}\geq CP_n$)

THEN: $AL_{n+1}=0$

ELSE: $AL_{n+1}=AL_{n+1}$

$ST_{n+1}=ST\ 25$

$ST_{n+1}=ST\ 28$

$RL_{n+1}=RL_n-RD$

IF ($RL_{n+1}\leq CP_n$)

THEN: $RL_{n+1}=0$

ELSE: $RL_{n+1}=RL_{n+1}$

$ST_{n+1}=ST_{n+1}$

IF ($ST_{n+1}=ST\ 25$)

THEN: $ST_{n+1}=ST\ 31$ ELSE: $ST_{n+1}=ST\ 26$

$AT_{n+1}=AT_n-1$

ST 29. $AP_n=0$ $RP_n>0$ $AL_n>0$ $RL_n>0$ $AT_n=0$ $RT_n>0$ $CP_n>0$

$AP_{n+1}=0$ $AT_{n+1}=0$ $CP_{n+1}>0$

$RP_{n+1}=RP_n-RD$

$AL_{n+1}=AL_n+AD$

IF ($AL_{n+1} \geq CP_n$)

THEN: $AL_{n+1}=0$

ELSE: $AL_{n+1}=AL_{n+1}$

$ST_{n+1}=ST_{24}$

$ST_{n+1}=ST_{29}$

$RL_{n+1}=RL_n-RD$

IF ($RL_{n+1} \leq CP_n$)

THEN: $RL_{n+1}=0$

ELSE: $RL_{n+1}=RL_{n+1}$

$ST_{n+1}=ST_{n+1}$

IF ($ST_{n+1}=ST_{24}$)

THEN: $ST_{n+1}=ST_{32}$ ELSE: $ST_{n+1}=ST_{27}$

$RT_{n+1}=RT_n-1$

ST 30. $AP_n>0$ $RP_n>0$ $AL_n>0$ $RL_n>0$ $AT_n>0$ $RT_n>0$ $CP_n>0$

$CP_{n+1}>0$

$AP_{n+1}=AP_n+AD$

$RP_{n+1}=RP_n-RD$

$AL_{n+1}=AL_n+AD$

IF ($AL_{n+1} \geq CP_n$)

THEN: $AL_{n+1}=0$

ELSE: $AL_{n+1}=AL_{n+1}$

$ST_{n+1}=ST_{34}$

$ST_{n+1}=ST_{30}$

$RL_{n+1}=RL_n-RD$

IF ($RL_{n+1} \leq CP_n$)

THEN: $RL_{n+1}=0$

ELSE: $RL_{n+1}=RL_{n+1}$

$ST_{n+1}=ST_{n+1}$

IF ($ST_{n+1}=ST_{34}$)

THEN: $ST_{n+1}=ST_{33}$ ELSE: $ST_{n+1}=ST_{35}$

$AT_{n+1}=AT_n-1$

$RT_{n+1}=RT_n-1$

ST 31. $AP_n > 0$ $RP_n = 0$ $AL_n = 0$ $RL_n = 0$ $AT_n > 0$ $RT_n = 0$ $CP_n > 0$

$RP_{n+1} = 0$ $AL_{n+1} = 0$ $RL_{n+1} = 0$ $RT_{n+1} = 0$

$AP_{n+1} = AP_n + AD$

IF ($AP_{n+1} \geq CP_n$)

THEN: $AP_{n+1} = 0$

ELSE: $AP_{n+1} = AP_{n+1}$

$ST_{n+1} = ST\ 15$

$ST_{n+1} = ST\ 2$

$CP_{n+1} = CP_n$

$CP_{n+1} = 0$

$AT_{n+1} = AT_n - 1$

ST 32. $AP_n = 0$ $RP_n > 0$ $AL_n = 0$ $RL_n = 0$ $AT_n = 0$ $RT_n > 0$ $CP_n > 0$

$AP_{n+1} = 0$ $AL_{n+1} = 0$ $RL_{n+1} = 0$ $AT_{n+1} = 0$

$RP_{n+1} = RP_n - RD$

IF ($RP_{n+1} \leq CP_n$)

THEN: $RP_{n+1} = 0$

ELSE: $RP_{n+1} = RP_{n+1}$

$ST_{n+1} = ST\ 14$

$ST_{n+1} = ST\ 6$

$CP_{n+1} = CP_n$

$CP_{n+1} = 0$

$RT_{n+1} = RT_n - 1$

ST 33.

$AP_n > 0$ $RP_n > 0$ $AL_n = 0$ $RL_n = 0$ $AT_n > 0$ $RT_n > 0$ $CP_n > 0$

$AL_{n+1} = 0$ $RL_{n+1} = 0$ $CP_{n+1} > 0$

$AP_{n+1} = AP_n + AD$

IF ($AP_{n+1} \geq CP_n$)

THEN: $AP_{n+1} = 0$

ELSE: $AP_{n+1} = AP_{n+1}$

$ST_{n+1} = ST\ 23$

$ST_{n+1} = ST\ 33$

$RP_{n+1} = RP_n - RD$

IF ($RP_{n+1} \leq CP_n$)

THEN: $RP_{n+1} = 0$

ELSE: $RP_{n+1} = RP_{n+1}$

$ST_{n+1} = ST_{n+1}$

IF ($ST_{n+1} = ST\ 23$)

THEN: $ST_{n+1} = ST\ 11$ ELSE: $ST_{n+1} = ST\ 22$

$AT_{n+1} = AT_n - 1$

$RT_{n+1} = RT_n - 1$

ST 34. $AP_n > 0$ $RP_n > 0$ $AL_n = 0$ $RL_n > 0$ $AT_n > 0$ $RT_n > 0$ $CP_n > 0$

$AL_{n+1} = 0$ $CP_{n+1} > 0$

$AP_{n+1} = AP_n + AD$

IF ($AP_{n+1} \geq CP_n$)

THEN: $AP_{n+1} = 0$

ELSE: $AP_{n+1} = AP_{n+1}$

$ST_{n+1} = ST\ 21$

$ST_{n+1} = ST\ 34$

$RP_{n+1} = RP_n - RD$

$RL_{n+1} = RL_n - RD$

IF ($RL_{n+1} \leq CP_n$)

THEN: $RL_{n+1} = 0$

ELSE: $RL_{n+1} = RL_{n+1}$

$ST_{n+1} = ST_{n+1}$

IF ($ST_{n+1} = ST\ 21$)

THEN: $ST_{n+1} = ST\ 23$ ELSE: $ST_{n+1} = ST\ 33$

$AT_{n+1} = AT_n - 1$

$RT_{n+1} = RT_n - 1$

ST 35. $AP_n > 0$ $RP_n > 0$ $AL_n > 0$ $RL_n = 0$ $AT_n > 0$ $RT_n > 0$ $CP_n > 0$

$RL_{n+1} = 0$ $CP_{n+1} > 0$

$AP_{n+1} = AP_n + AD$

$RP_{n+1} = RP_n - RD$

IF ($RP_{n+1} \leq CP_n$)

THEN: $RP_{n+1} = 0$

ELSE: $RP_{n+1} = RP_{n+1}$

$ST_{n+1} = ST\ 20$

$ST_{n+1} = ST\ 35$

$AL_{n+1} = AL_n + AD$

IF ($AL_{n+1} \geq CP_n$)

THEN: $AL_{n+1} = 0$

ELSE: $AL_{n+1} = AL_{n+1}$

$ST_{n+1} = ST_{n+1}$

IF ($ST_{n+1} = ST\ 20$)

THEN: $ST_{n+1} = ST\ 22$ ELSE: $ST_{n+1} = ST\ 33$

$AT_{n+1} = AT_n - 1$

$RT_{n+1} = RT_n - 1$

Chapter 7

Appendix II: The introduction of a new impulse

A DESCRIPTION IN THE 35 DIFFERENT STATES

ST 1. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n=0$ $AT_n=0$ $RT_n=0$ $CP_n=0$

ANTEROGRADE

$AP_{n+1}=1$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}=ARP$ $RT_{n+1}=0$ $CP_{n+1}=0$
 $ST_{n+1}=ST\ 2$

RETROGRADE

$AP_{n+1}=0$ $RP_{n+1}=100$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}=0$ $RT_{n+1}=RRP$ $CP_{n+1}=0$
 $ST_{n+1}=ST\ 6$

ST. 2. $AP_n>0$ $RP_n=0$ $AL_n=0$ $RL_n=0$ $AT_n>0$ $RT_n=0$ $CP_n=0$

ANTEROGRADE REFRACTORY

$AP_{n+1}>0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}=0$ $CP_{n+1}=0$

RETROGRADE

$AP_{n+1}>0$ $RP_{n+1}=100$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}=RRP$ $CP_{n+1}=0$
 $ST_{n+1}=ST\ 10$

ST 3. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n=0$ $AT_n>0$ $RT_n=0$ $CP_n=0$

ANTEROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}=0$ $CP_{n+1}=0$

RETROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}=0$ $CP_{n+1}=0$

ST 4. $AP_n=0$ $RP_n=0$ $AL_n>0$ $RL_n=0$ $AT_n=0$ $RT_n=0$ $CP_n=0$

ANTEROGRADE

$RP_{n+1}=0$ $AL_{n+1}>0$ $RL_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}=0$

IF ($AL_{n+1}>(1+AD)$)

THEN : $AP_{n+1}=1$ ELSE : $AP_{n+1}=0$

$AT_{n+1}=ARP$ $AT_{n+1}=0$

$ST_{n+1}=ST\ 5$ $ST_{n+1}=ST\ 4$

RETROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}>0$ $RL_{n+1}=0$ $AT_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}=0$

ST 5. $AP_n>0$ $RP_n=0$ $AL_n>0$ $RL_n=0$ $AT_n>0$ $RT_n=0$ $CP_n=0$

ANTEROGRADE REFRACTORY

$AP_{n+1}>0$ $RP_{n+1}=0$ $AL_{n+1}>0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}=0$ $CP_{n+1}=0$

RETROGRADE REFRACTORY

$AP_{n+1}>0$ $RP_{n+1}=0$ $AL_{n+1}>0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}=0$ $CP_{n+1}=0$

ST 6. $AP_n=0$ $RP_n>0$ $AL_n=0$ $RL_n=0$ $AT_n=0$ $RT_n>0$ $CP_n=0$

ANTEROGRADE

$AP_{n+1}=1$ $RP_{n+1}>0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}=ARP$ $RT_{n+1}>0$ $CP_{n+1}=0$
 $ST_{n+1}=ST\ 10$

RETROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}>0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}=0$ $RT_{n+1}>0$ $CP_{n+1}=0$

ST 7. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n=0$ $AT_n=0$ $RT_n>0$ $CP_n=0$

ANTEROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}=0$ $RT_{n+1}>0$ $CP_{n+1}=0$

RETROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}=0$ $RT_{n+1}>0$ $CP_{n+1}=0$

ST 8. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n>0$ $AT_n=0$ $RT_n=0$ $CP_n=0$

ANTEROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}>0$ $AT_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}=0$

RETROGRADE

$AP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}>0$ $AT_{n+1}=0$ $CP_{n+1}=0$

IF ($RL_{n+1}<(100-RD)$)

THEN: $RP_{n+1}=100$ ELSE: $RP_{n+1}=0$

$RT_{n+1}=RRP$ $RT_{n+1}=0$

$ST_{n+1}=ST\ 9$ $ST_{n+1}=ST\ 8$

ST 9. $AP_n=0$ $RP_n>0$ $AL_n=0$ $RL_n>0$ $AT_n=0$ $RT_n>0$ $CP_n=0$

ANTEROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}>0$ $AL_{n+1}=0$ $RL_{n+1}>0$ $AT_{n+1}=0$ $RT_{n+1}>0$ $CP_{n+1}=0$

RETROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}>0$ $AL_{n+1}=0$ $RL_{n+1}>0$ $AT_{n+1}=0$ $RT_{n+1}>0$ $CP_{n+1}=0$

ST 10. $AP_n>0$ $RP_n>0$ $AL_n=0$ $RL_n=0$ $AT_n>0$ $RT_n>0$ $CP_n=0$

ANTEROGRADE REFRACTORY

$AP_{n+1}>0$ $RP_{n+1}>0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}>0$ $CP_{n+1}=0$

RETROGRADE REFRACTORY

$AP_{n+1}>0$ $RP_{n+1}>0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}>0$ $CP_{n+1}=0$

ST 11. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n=0$ $AT_n>0$ $RT_n>0$ $CP_n>0$

ANTEROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}>0$ $CP_{n+1}>0$

RETROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}>0$ $CP_{n+1}>0$

ST 12. $AP_n=0$ $RP_n=0$ $AL_n>0$ $RL_n=0$ $AT_n=0$ $RT_n>0$ $CP_n>0$

ANTEROGRADE

$RP_{n+1}=0$ $AL_{n+1}>0$ $RL_{n+1}=0$ $RT_{n+1}>0$ $CP_{n+1}>0$

IF ($AL_{n+1}>(1+AD)$)

THEN : $AP_{n+1}=1$	ELSE : $AP_{n+1}=0$
$AT_{n+1}=ARP$	$AT_{n+1}=0$
$ST_{n+1}=ST\ 20$	$ST_{n+1}=ST\ 12$

RETROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}>0$ $RL_{n+1}=0$ $AT_{n+1}=0$ $RT_{n+1}>0$ $CP_{n+1}>0$

ST 13. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n>0$ $AT_n>0$ $RT_n=0$ $CP_n>0$

ANTEROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}>0$ $AT_{n+1}>0$ $RT_{n+1}=0$ $CP_{n+1}>0$

RETROGRADE

$AP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}>0$ $AT_{n+1}>0$ $CP_{n+1}>0$

IF ($RL_{n+1}<(100-RD)$)

THEN : $RP_{n+1}=100$	ELSE : $RP_{n+1}=0$
$RT_{n+1}=RRP$	$RT_{n+1}=0$
$ST_{n+1}=ST\ 21$	$ST_{n+1}=ST\ 13$

ST 14. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n=0$ $AT_n=0$ $RT_n>0$ $CP_n>0$

ANTEROGRADE

$AP_{n+1}=1$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}=ARP$ $RT_{n+1}>0$ $CP_{n+1}>0$
 $ST_{n+1}=ST\ 22$

RETROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}=0$ $RT_{n+1}>0$ $CP_{n+1}>0$

ST 15. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n=0$ $AT_n>0$ $RT_n=0$ $CP_n>0$

ANTEROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}=0$ $CP_{n+1}>0$

RETROGRADE

$AP_{n+1}=0$ $RP_{n+1}=100$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}=RRP$ $CP_{n+1}>0$
 $ST_{n+1}=ST\ 23$

ST 16. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n>0$ $AT_n=0$ $RT_n=0$ $CP_n>0$

ANTEROGRADE

$AP_{n+1}=1$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}>0$ $AT_{n+1}=ARP$ $RT_{n+1}=0$ $CP_{n+1}>0$
 $ST_{n+1}=ST\ 25$

RETROGRADE

$AP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}>0$ $AT_{n+1}=0$ $CP_{n+1}>0$

IF ($RL_{n+1}<(100-RD)$)
THEN: $RP_{n+1}=100$ ELSE: $RP_{n+1}=0$
 $RT_{n+1}=RRP$ $RT_{n+1}=0$
 $ST_{n+1}=ST\ 24$ $ST_{n+1}=ST\ 16$

ST 17. $AP_n=0$ $RP_n=0$ $AL_n>0$ $RL_n=0$ $AT_n=0$ $RT_n=0$ $CP_n>0$

ANTEROGRADE

$RP_{n+1}=0$ $AL_{n+1}>0$ $RL_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}>0$

IF ($AL_{n+1}>(1+AD)$)
THEN: $AP_{n+1}=1$ ELSE: $AP_{n+1}=0$
 $AT_{n+1}=ARP$ $AT_{n+1}=0$
 $ST_{n+1}=ST\ 26$ $ST_{n+1}=ST\ 17$

RETROGRADE

$AP_{n+1}=0$ $RP_{n+1}=100$ $AL_{n+1}>0$ $RL_{n+1}=0$ $AT_{n+1}=0$ $RT_{n+1}=RRP$ $CP_{n+1}>0$
 $ST_{n+1}=ST\ 27$

ST 18. $AP_n=0$ $RP_n=0$ $AL_n>0$ $RL_n>0$ $AT_n=0$ $RT_n=0$ $CP_n>0$

ANTEROGRADE

$RP_{n+1}=0$ $AL_{n+1}>0$ $RL_{n+1}>0$ $RT_{n+1}=0$ $CP_{n+1}>0$

IF ($AL_{n+1}>(1+AD)$)

THEN: $AP_{n+1}=1$

ELSE: $AP_{n+1}=0$

$AT_{n+1}=ARP$

$AT_{n+1}=0$

$ST_{n+1}=ST\ 28$

$ST_{n+1}=ST\ 18$

RETROGRADE

$AP_{n+1}=0$ $AL_{n+1}>0$ $RL_{n+1}>0$ $AT_{n+1}=0$ $RT_{n+1}=0$ $CP_{n+1}>0$

IF ($RL_{n+1}<(100-RD)$)

THEN: $RP_{n+1}=100$

ELSE: $RP_{n+1}=0$

$RT_{n+1}=RRP$

$RT_{n+1}=0$

$ST_{n+1}=ST\ 29$

$ST_{n+1}=ST\ 18$

ST 19. $AP_n=0$ $RP_n=0$ $AL_n=0$ $RL_n=0$ $AT_n=0$ $RT_n=0$ $CP_n>0$

ANTEROGRADE

$AP_{n+1}=1$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}=ARP$ $RT_{n+1}=0$ $CP_{n+1}>0$

$ST_{n+1}=ST\ 31$

RETROGRADE

$AP_{n+1}=0$ $RP_{n+1}=100$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}=0$ $RT_{n+1}=RRP$ $CP_{n+1}>0$

$ST_{n+1}=ST\ 32$

ST 20. $AP_n>0$ $RP_n=0$ $AL_n>0$ $RL_n=0$ $AT_n>0$ $RT_n>0$ $CP_n>0$

ANTEROGRADE REFRACTORY

$AP_{n+1}>0$ $RP_{n+1}=0$ $AL_{n+1}>0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}>0$ $CP_{n+1}>0$

RETROGRADE REFRACTORY

$AP_{n+1}>0$ $RP_{n+1}=0$ $AL_{n+1}>0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}>0$ $CP_{n+1}>0$

ST 21. $AP_n=0$ $RP_n>0$ $AL_n=0$ $RL_n>0$ $AT_n>0$ $RT_n>0$ $CP_n>0$

ANTEROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}>0$ $AL_{n+1}=0$ $RL_{n+1}>0$ $AT_{n+1}>0$ $RT_{n+1}>0$ $CP_{n+1}>0$

RETROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}>0$ $AL_{n+1}=0$ $RL_{n+1}>0$ $AT_{n+1}>0$ $RT_{n+1}>0$ $CP_{n+1}>0$

ST 22. $AP_n>0$ $RP_n=0$ $AL_n=0$ $RL_n=0$ $AT_n>0$ $RT_n>0$ $CP_n>0$

ANTEROGRADE REFRACTORY

$AP_{n+1}>0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}>0$ $CP_{n+1}>0$

RETROGRADE REFRACTORY

$AP_{n+1}>0$ $RP_{n+1}=0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}>0$ $CP_{n+1}>0$

ST 23. $AP_n=0$ $RP_n>0$ $AL_n=0$ $RL_n=0$ $AT_n>0$ $RT_n>0$ $CP_n>0$

ANTEROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}>0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}>0$ $CP_{n+1}>0$

RETROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}>0$ $AL_{n+1}=0$ $RL_{n+1}=0$ $AT_{n+1}>0$ $RT_{n+1}>0$ $CP_{n+1}>0$

ST 24. $AP_n=0$ $RP_n>0$ $AL_n=0$ $RL_n>0$ $AT_n=0$ $RT_n>0$ $CP_n>0$

ANTEROGRADE

$AP_{n+1}=1$ $RP_{n+1}>0$ $AL_{n+1}=0$ $RL_{n+1}>0$ $AT_{n+1}=ARP$ $RT_{n+1}>0$ $CP_{n+1}>0$
 $ST_{n+1}=ST\ 34$

RETROGRADE REFRACTORY

$AP_{n+1}=0$ $RP_{n+1}>0$ $AL_{n+1}=0$ $RL_{n+1}>0$ $AT_{n+1}=0$ $RT_{n+1}>0$ $CP_{n+1}>0$

ST 25. $AP_n > 0$ $RP_n = 0$ $AL_n = 0$ $RL_n > 0$ $AT_n > 0$ $RT_n = 0$ $CP_n > 0$

ANTEROGRADELY REFRACTORY

$AP_{n+1} > 0$ $RP_{n+1} = 0$ $AL_{n+1} = 0$ $RL_{n+1} > 0$ $AT_{n+1} > 0$ $RT_{n+1} = 0$ $CP_{n+1} > 0$

RETROGRADE

$AP_{n+1} > 0$ $AL_{n+1} = 0$ $RL_{n+1} > 0$ $AT_{n+1} > 0$ $CP_{n+1} > 0$

IF ($RL_{n+1} < (100 - RD)$)

THEN: $RP_{n+1} = 100$	ELSE: $RP_{n+1} = 0$
$RT_{n+1} = RRP$	$RT_{n+1} = 0$
$ST_{n+1} = ST\ 34$	$ST_{n+1} = ST\ 25$

ST 26. $AP_n > 0$ $RP_n = 0$ $AL_n > 0$ $RL_n = 0$ $AT_n > 0$ $RT_n = 0$ $CP_n > 0$

ANTEROGRADE REFRACTORY

$AP_{n+1} > 0$ $RP_{n+1} = 0$ $AL_{n+1} > 0$ $RL_{n+1} = 0$ $AT_{n+1} > 0$ $RT_{n+1} = 0$ $CP_{n+1} > 0$

RETROGRADE

$AP_{n+1} > 0$ $RP_{n+1} = 100$ $AL_{n+1} > 0$ $RL_{n+1} = 0$ $AT_{n+1} > 0$ $RT_{n+1} = RRP$ $CP_{n+1} > 0$
 $ST_{n+1} = ST\ 35$

ST 27. $AP_n = 0$ $RP_n > 0$ $AL_n > 0$ $RL_n = 0$ $AT_n = 0$ $RT_n > 0$ $CP_n > 0$

ANTEROGRADE

$RP_{n+1} > 0$ $AL_{n+1} > 0$ $RL_{n+1} = 0$ $RT_{n+1} > 0$ $CP_{n+1} > 0$

IF ($AL_{n+1} > (1 + AD)$)

THEN: $AP_{n+1} = 1$	ELSE: $AP_{n+1} = 0$
$AT_{n+1} = ARP$	$AT_{n+1} = 0$
$ST_{n+1} = ST\ 35$	$ST_{n+1} = ST\ 27$

RETROGRADE REFRACTORY

$AP_{n+1} = 0$ $RP_{n+1} > 0$ $AL_{n+1} > 0$ $RL_{n+1} = 0$ $AT_{n+1} = 0$ $RT_{n+1} > 0$ $CP_{n+1} > 0$

ST 28. $AP_n > 0$ $RP_n = 0$ $AL_n > 0$ $RL_n > 0$ $AT_n > 0$ $RT_n = 0$ $CP_n > 0$

ANTEROGRADE REFRACTORY

$AP_{n+1} > 0$ $RP_{n+1} = 0$ $AL_{n+1} > 0$ $RL_{n+1} > 0$ $AT_{n+1} > 0$ $RT_{n+1} = 0$ $CP_{n+1} > 0$

RETROGRADE

$AP_{n+1} > 0$ $AL_{n+1} > 0$ $RL_{n+1} > 0$ $AT_{n+1} > 0$ $CP_{n+1} > 0$

IF ($RL_{n+1} < (100 - RD)$)

THEN: $RP_{n+1} = 100$	ELSE: $RP_{n+1} = 0$
$RT_{n+1} = RRP$	$RT_{n+1} = 0$
$ST_{n+1} = ST\ 30$	$ST_{n+1} = ST\ 28$

ST 29. $AP_n = 0$ $RP_n > 0$ $AL_n > 0$ $RL_n > 0$ $AT_n = 0$ $RT_n > 0$ $CP_n > 0$

ANTEROGRADE

$RP_{n+1} > 0$ $AL_{n+1} > 0$ $RL_{n+1} > 0$ $RT_{n+1} = 0$ $CP_{n+1} > 0$

IF ($AL_{n+1} > (1 + AD)$)

THEN: $AP_{n+1} = 1$	ELSE: $AP_{n+1} = 0$
$AT_{n+1} = ARP$	$AT_{n+1} = 0$
$ST_{n+1} = ST\ 30$	$ST_{n+1} = ST\ 29$

RETROGRADELY REFRACTORY

$AP_{n+1} = 0$ $RP_{n+1} > 0$ $AL_{n+1} > 0$ $RL_{n+1} > 0$ $AT_{n+1} = 0$ $RT_{n+1} > 0$ $CP_{n+1} > 0$

ST 30. $AP_n > 0$ $RP_n > 0$ $AL_n > 0$ $RL_n > 0$ $AT_n > 0$ $RT_n > 0$ $CP_n > 0$

ANTEROGRADE REFRACTORY

$AP_{n+1} > 0$ $RP_{n+1} > 0$ $AL_{n+1} > 0$ $RL_{n+1} > 0$ $AT_{n+1} > 0$ $RT_{n+1} > 0$ $CP_{n+1} > 0$

RETROGRADE REFRACTORY

$AP_{n+1} > 0$ $RP_{n+1} > 0$ $AL_{n+1} > 0$ $RL_{n+1} > 0$ $AT_{n+1} > 0$ $RT_{n+1} > 0$ $CP_{n+1} > 0$

ST 31. $AP_n > 0$ $RP_n = 0$ $AL_n = 0$ $RL_n = 0$ $AT_n > 0$ $RT_n = 0$ $CP_n > 0$

ANTEROGRADE REFRACTORY

$AP_{n+1} > 0$ $RP_{n+1} = 0$ $AL_{n+1} = 0$ $RL_{n+1} = 0$ $AT_{n+1} > 0$ $RT_{n+1} = 0$ $CP_{n+1} > 0$

RETROGRADE

$AP_{n+1} > 0$ $RP_{n+1} = 100$ $AL_{n+1} = 0$ $RL_{n+1} = 0$ $AT_{n+1} > 0$ $RT_{n+1} = RRP$ $CP_{n+1} > 0$
 $ST_{n+1} = ST_{33}$

ST 32. $AP_n = 0$ $RP_n > 0$ $AL_n = 0$ $RL_n = 0$ $AT_n = 0$ $RT_n > 0$ $CP_n > 0$

ANTEROGRADE

$AP_{n+1} = 1$ $RP_{n+1} > 0$ $AL_{n+1} = 0$ $RL_{n+1} = 0$ $AT_{n+1} = ARP$ $RT_{n+1} > 0$ $CP_{n+1} > 0$
 $ST_{n+1} = ST_{33}$

RETROGRADE REFRACTORY

$AP_{n+1} = 0$ $RP_{n+1} > 0$ $AL_{n+1} = 0$ $RL_{n+1} = 0$ $AT_{n+1} = 0$ $RT_{n+1} > 0$ $CP_{n+1} > 0$

ST 33. $AP_n > 0$ $RP_n > 0$ $AL_n = 0$ $RL_n = 0$ $AT_n > 0$ $RT_n > 0$ $CP_n > 0$

ANTEROGRADE REFRACTORY

$AP_{n+1} > 0$ $RP_{n+1} > 0$ $AL_{n+1} = 0$ $RL_{n+1} = 0$ $AT_{n+1} > 0$ $RT_{n+1} > 0$ $CP_{n+1} > 0$

RETROGRADE REFRACTORY

$AP_{n+1} > 0$ $RP_{n+1} > 0$ $AL_{n+1} = 0$ $RL_{n+1} = 0$ $AT_{n+1} > 0$ $RT_{n+1} > 0$ $CP_{n+1} > 0$

ST 34. $AP_n > 0$ $RP_n > 0$ $AL_n = 0$ $RL_n > 0$ $AT_n > 0$ $RT_n > 0$ $CP_n > 0$

ANTEROGRADE REFRACTORY

$AP_{n+1} > 0$ $RP_{n+1} > 0$ $AL_{n+1} = 0$ $RL_{n+1} > 0$ $AT_{n+1} > 0$ $RT_{n+1} > 0$ $CP_{n+1} > 0$

RETROGRADE REFRACTORY

$AP_{n+1} > 0$ $RP_{n+1} > 0$ $AL_{n+1} = 0$ $RL_{n+1} > 0$ $AT_{n+1} > 0$ $RT_{n+1} > 0$ $CP_{n+1} > 0$

ST 35. $AP_n > 0$ $RP_n > 0$ $AL_n > 0$ $RL_n = 0$ $AT_n > 0$ $RT_n > 0$ $CP_n > 0$

ANTEROGRADE REFRACTORY

$AP_{n+1} > 0$ $RP_{n+1} > 0$ $AL_{n+1} > 0$ $RL_{n+1} = 0$ $AT_{n+1} > 0$ $RT_{n+1} > 0$ $CP_{n+1} > 0$

RETROGRADE REFRACTORY

$AP_{n+1} > 0$ $RP_{n+1} > 0$ $AL_{n+1} > 0$ $RL_{n+1} = 0$ $AT_{n+1} > 0$ $RT_{n+1} > 0$ $CP_{n+1} > 0$

References:

- 1 **Weyer Johann (Wierus)**
Medicarum Observationum Libri II.
Quoted from Collected Works, Amsterdam :917 1660

- 2 **Galen**
Claudii Galeni Opera Omnia.
ed Kühn, Leipzig 1825

- 3 **Bijleveld WJJ, Wijnaendts van Resandt W, Wittert van Hoogland EBFF**
Nederlands Adelsboek.
Van Stockum en Zoon, 's-Gravenhage :204 1916

- 4 **Hübötter F**
Die chinesische Medizin zu Beginn des XX Jahrhunderts und ihr historischer Entwicklungsgang.
Asia Major. Schindler, Leipzig 1929

- 5 **Scherf D, Schott A**
Extrasystoles and allied arrhythmias.
William Heinemann Medical Books Ltd London 1973

- 6 **Wenckebach KF**
Zur Analyse des unregelmässigen Pulses.
Z. klin. Med. 36 1899

- 7 **Einthoven W**
Over de beteekenis der electro-physiologie als een onderdeel van de leer der levensverrichtingen.
EJ Brill Leiden, The Netherlands :32 1906

- 8 **Einthoven W**
Le télécardiogramme.
Arch. int. Physiol. 4 :132 1906

- 9 **Latour H, Puech P**
l'Electrocardiographie Endocavitare
Masson Ed. Paris 1957

- 10 **Durrer D, Schoo L, Schuilenburg RM, Wellens HJJ**
The role of premature beats in the initiation and the termination of supraventricular tachycardia in the Wolff-Parkinson-White syndrome.
Circulation 36 :644 1967

- 11 **Damato AN, Lau SH, Helfant RH, Stein E, Patton RD, Scherlag BJ, Berkowitz WD**
A study of heart block in man using His bundle recording.
Circulation 39 :297 1969

- 12 **Wellens HJJ**
Electrical stimulation of the heart in the study and treatment of tachycardias.
Baltimore, University Park Press 1971

- 13 **Wellens HJJ, Schuilenburg RM, Durrer D**
Electrical stimulation of the heart in patients with ventricular tachycardia.
Circulation 46 :216 1972

- 14 **Wellens HJJ**
Value and limitations of programmed electrical stimulation of the heart in the study and treatment of tachycardias.
George C. Griffith Lecture
Circulation 57 :845 1978
- 15 **Ross DL, Farre J, Bär FWHM, Vanagt EJ, Dassen WRM, Wiener I, Wellens HJJ**
Comprehensive clinical electrophysiologic studies in the investigation of documented or suspected tachycardia.
Time, Staff, Problems and Costs.
Circulation 61 :1010 1980
- 16 **Berne RM**
Handbook of physiology.
Section 2. The Cardiovascular System
Volume I The Heart
Williams & Wilkins Company, Baltimore :581 1979
- 17 **Mann JE, Sperelakis N**
Further development of a model for electrical transmission between myocardial cells not connected by low-resistance pathways.
J Electrcard. 12 :23 1979
- 18 **Salu Y**
Computer simulation of electrical activity of the heart.
J theor Biol. 43 :43 1974
- 19 **Moe GK, Rheinboldt WC, Abildskov JA**
A computer model of atrial fibrillation.
Am Heart J 67 :200 1964
- 20 **Sharp GH, Joyner RW**
Simulated propagation of cardiac action potentials.
Biopys. J. 31 :403 1980
- 21 **Liestol K, Walloe L**
A simulated study of a neuron in a simple muscle control system.
Acta Physiol Scand 109 :463 1980
- 22 **FitzHugh R**
Impulses and physiological states in theoretical models of nerve membrane.
Biophys J 1 :445 1961
- 23 **Owen E, Waring W, Shoji F, Prakash C**
Digital simulation of the membrane voltage and currents in nerve and muscle fibers.
Comp Prog in Biomed 6 :63 1976
- 24 **Hodgkin AL, Huxley AF**
A quantitative description of membrane current and its application to conduction and excitation in nerve.
J. Physiol. 117 :500 1952
- 25 **Capelle FJL v, Durrer D**
Computer simulation of arrhythmias in a network of coupled excitable elements.
Circulation Res 47 :454 1980

- 26 **Robertson-Dunn B, Linkens DA**
A mathematical model of the slow-wave electrical activity of the human small intestine.
Med. and Biol. Engineering. 12:750 1974
- 27 **Pol B v d, Mark j VD**
The heartbeat considered as a relaxation oscillation and an electrical model of the heart.
Philos Mag Suppl 6 :763 1928
- 28 **Selvester RH, Collier C, Pearson R**
Analog computer model of the vectorcardiogram.
Circulation 31 :45 1965
- 29 **Selvester RH, Solomon JC, Gillespie TL**
Digital computer model of a total body electrocardiographic surface map: Adult male torso simulation with lungs.
Circulation 38 :684 1968
- 30 **Selvester RH, Kalaba R, Collier C, Belleman R, Kagiwada RH**
A digital computer model of the vectorcardiogram with distance and boundary effects: simulated myocardium infarction.
Am Heart J 74 :899 1967
- 31 **Min FBM**
Modelvorming van de elektrische activiteit van maag en hart mbv niet lineaire oscillatoren.
Rapport M126 University of Delft 1975
- 32 **Rosenberg RM, Chao CH, Abbott J**
A new mathematical model of electrical cardiac activity.
Math Biosciences 14 :367 1972
- 33 **Miller WT, Geselowitz DB**
Simulation studies of the electrocardiogram I. The normal heart.
Circulation Research 43 :301 1978
- 34 **Miller WT, Geselowitz DB**
Simulation studies of the electrocardiogram II. Ischemia and infarction.
Circulation Research 43 :315 1978
- 35 **Hori M**
Simulation study of QRS-T waves based on an eccentric spherical model of the heart.
Japanese Circulation J 42 :539 1978
- 36 **Arntzenius AC, Schipperheyn JJ, Huisman PH, Kulbertus HE, Ritsema van Eck HJ, Simoons ML, Vinke RVH**
Model studies on activation of the heart.
Europ. J. of Card. 8 :261 1978
- 37 **Ritsema van Eck HJ**
Digital computer simulation of cardiac excitation and repolarization in man.
Thesis. Dalhousy University, Halifax, Nova Scotia, Canada 1972
- 38 **Rudy Y, Plonsey R**
A comparison of volume conduction and source geometry effects on body surface and epicardial potentials.
Circulation Research 46 :983 1980

- 39 **Rudy Y, Plonsey R**
The eccentric spheres model as the basis for a study of the role of geometry and inhomogeneities in electrocardiography.
IEEE Trans Biomed Eng 26:392 1979
- 40 **Rudy Y, Plonsey R, Liebman J**
The effects of variations in conductivity and geometric parameters on the electrocardiogram, using an eccentric spheres model.
Circulation Research 44 :104 1979
- 41 **Ramsey M, Barr RC, Spach MS**
Comparison of measured torso potentials with those simulated from epicardial potentials for ventricular depolarisation and repolarization in the intact dog.
Circulation Research 41 :660 1977
- 42 **Omura Y**
The relationship between the transmembrane action potential and the voltage-time-dependant negative resistance characteristics of the voltage-current curves of excitable pacemaker and non-pacemaker cell membranes.
Trans of the NY Acad of Sc. 33 :467 1971
- 43 **Heethaar RM, Denier van der Gon JJ, Meyler FL**
A mathematical model of A-V conduction in the rat heart.
Cardiovascular Research, 7 :105 1973
- 44 **Heethaar RM, De Vos Burchart RM, Denier van der Gon JJ, Meyler FL**
A mathematical model of A-V conduction in the rat heart II, Quantification of concealed conduction.
Cardiovascular Research, 7 :542 1973
- 45 **Heethaar RM, Denier van de Gon JJ, Meijler FL**
Interpretation of some properties of AV Conduction with the help of analog simulation.
Eur J of Card 1:87 1973
- 46 **Holley L, Goodman AH, Richards DAB, Uther JB**
Computer modelling of the electrical activation of the ventricular myocardium and re-entrant ventricular arrhythmias.
Austr NZ J Med :in press 1982
- 47 **Ross D, Dassen W, Vanagt E, Brugada P, Bar F, Wellens H**
Cycle length alternation in circus movement tachycardia using an atrioventricular accessory pathway. A study of the role of the Atrioventricular node using a computer model of tachycardia.
Circulation 65 :862 1982
- 48 **Dassen W, Ross D, Brugada P, Bar F, Vanagt E, Wellens H**
A computer model for the study of cycle length alternation during tachycardia.
Computers in Cardiology IEEE Computer Society Silver Spring :179 1980
- 49 **Dassen W, Brugada P, Wellens H**
Shortening of the echo-interval with increasing prematurity; a computer model to study its value as differentiating criterion between reentry and triggered activity.
Computers in Cardiology IEEE Computer Society Silver Spring :303 1981
- 50 **Brugada P, Bar FWHM, Vanagt EJ, Wellens HJJ**
Observations on mechanisms of circus movement tachycardia in the Wolff-Parkinson-White syndrome. Role of different tachycardia circuits and sites of block in maintenance of tachycardia.
Pace 4 :507 1981

- 51 **Cooper TB, Hess RC, Litvin Y, MacLean WAH, Powell VG, Siler W, Stanley AWH and Waldrop SE**
A computer system for electrophysiologic studies of cardiac rhythm in humans.
Computers in Cardiology IEEE Computer Society Silver Spring:299 1981
- 52 **Wellens HJJ, Dulk K den, Brugada P**
Pacemaker management of cardiac arrhythmias.
Cardiovascular Clinics :in press 1983

Slotwoord

Het werken met simulatiemodellen in de cardiologie is een fascinerende bezigheid.

Drie factoren maken de Capaciteitsgroep Cardiologie tot een unieke plaats om aan het onderzoek in de electrophysiologie mee te werken.

- In de allereerste plaats de allomaanwezigheid van de stuwende kracht achter de afdeling: professor Hein Wellens. Zonder hem zou dit mathematisch onderzoek op een klinische afdeling nooit plaatsgevonden hebben. Een opsomming wat hij allemaal voor mij gedaan heeft is overbodig, hij weet hoezeer ik hem hiervoor dankbaar ben.
- Op de tweede plaats de crew van het Electrophysiologisch Laboratorium. Deze afdeling die soms vanwege de vele buitenlandse research fellows wat weg heeft van het vreemdelingenlegioen vormt een continue broedstoof voor nieuwe ideeën en onderzoeken. Op deze groep moeten we trots maar ook heel zuinig zijn. Hoewel heel riskant om namen te noemen wil ik toch drie mensen apart vermelden: Jet Beekman, Ton Gorgels en Pedro Brugada.
- Op de laatste maar zeker niet minste plaats de leden van de Capaciteitsgroep Cardiologie. Ondanks het feit, dat het een van de snelstgroeiende groepen binnen de universiteit is blijft het toch een hechte eenheid waarbinnen eenieder zijn eigen subspecialisme kan ontwikkelen. Het is een voorrecht binnen zo'n groep te mogen werken.

Op deze plaats zou ik graag promotor Prof Rob Heethaar, en de referenten Prof Harry Struyker Boudier, Frans van Capelle en David Ross van harte willen bedanken. Voor hun bijdrage aan de voorbereiding en de uiteindelijke vorm van dit proefschrift ben ik hen zeer dankbaar.

En op een voor partners van promovendi bekende laatste plaats zou ik Doortje willen danken voor al het geduld dat je met me hebt gehad als ik 's avonds weer zo nodig aan dit boekje moest gaan werken. Daarom zou ik graag dit boek aan jou op willen dragen.

Maastricht 10 maart 1983

Curriculum vitae

De schrijver van dit proefschrift werd geboren op 13 januari 1953 te Maastricht. Zijn middelbare schoolopleiding(HBS-B) ontving hij aan het St Aloysius College te 's-Gravenhage van 1965 tot 1970. In dat zelfde jaar startte hij de studie Technische Informatica aan de Rheinisch-Westfälische Technische Hochschule te Aken WDL. Na het voltooien van zijn opleiding in 1976 was hij er gedurende bijna twee jaar werkzaam als wetenschappelijk assistent. In 1977 volgde de terugkeer naar zijn oude moederstad en werd hij aangesteld als wetenschappelijk medewerker bij de Capaciteitsgroep Cardiologie waar het onderzoek dat leidde tot dit proefschrift werd verricht.

Layout: Chris Voskamp
Illustraties: W.R.M. Dassen
Druk: Schrijen-Lippertz bv