Modelling and robust estimation of AV node function during AF

Relatore: Prof. Luca MAINARDI
Correlatori: Valentina CORINO, Frida SANDBERG, Prof. Leif SÖRNMO

Tesi di Laurea di:
Luca IOZZIA Matr. 787341
Gennaro GAROLDI Matr. 787540

Anno Accademico 2013-2014
Contents

1. Introduction 7

2. Medical Background 9
   2.1 Cardiac Anatomy and Physiology 9
   2.2 The cardiac conduction system 11
   2.3 Channel cell mechanisms (action potential generation) 13
   2.4 Electrocardiography 16
   2.5 Atrial Fibrillation 19
      2.5.1 Diagnosis and Classification 21
      2.5.2 Treatment 22
   2.6 Atrioventricular node anatomy 25
      2.6.1 Dual pathway 26

3. Mathematical Background 29
   3.1 Poisson Process 29
   3.2 Maximum Likelihood Estimation 30
   3.3 Optimization Algorithms 31
      3.3.1 Simulated Annealing 33
      3.3.2 Generalized Pattern Search 34
   3.4 Lambert Function 35

4. Methods 37
   4.1 Previous mathematical AV node models 37
      4.1.1 Mangin’s model 37
      4.1.2 Cohen’s model 40
      4.1.3 Lian’s model 42
   4.2 Corino’s model 44
      4.2.1 Description of the model 44
   4.3 Modified model 53

5. Results 65
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1</td>
<td>Simulation</td>
<td>65</td>
</tr>
<tr>
<td>5.1.1</td>
<td>Data Exploration</td>
<td>65</td>
</tr>
<tr>
<td>5.1.2</td>
<td>Relationship between $\gamma$ and $\hat{\alpha}$</td>
<td>68</td>
</tr>
<tr>
<td>5.1.3</td>
<td>Simulation Results</td>
<td>72</td>
</tr>
<tr>
<td>5.1.4</td>
<td>Inversion</td>
<td>74</td>
</tr>
<tr>
<td>5.2</td>
<td>Real data</td>
<td>76</td>
</tr>
<tr>
<td>5.2.1</td>
<td>Real data results</td>
<td>77</td>
</tr>
<tr>
<td>6.</td>
<td>Discussions</td>
<td>82</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>2.1</td>
<td>Pathway of blood flows through the heart and lungs [6].</td>
<td>9</td>
</tr>
<tr>
<td>2.2</td>
<td>Haemoglobin dissociation curve [7]. Torr is non-SI unit, equal to [mmHg].</td>
<td>11</td>
</tr>
<tr>
<td>2.3</td>
<td>Examples of myocyte cells obtained from microscopes [8].</td>
<td>11</td>
</tr>
<tr>
<td>2.4</td>
<td>SA node action potential, the threshold values trigger AP generation [9].</td>
<td>12</td>
</tr>
<tr>
<td>2.5</td>
<td>General geometric conduction system [10].</td>
<td>13</td>
</tr>
<tr>
<td>2.6</td>
<td>APs along the path of cardiac conduction system [14].</td>
<td>15</td>
</tr>
<tr>
<td>2.7</td>
<td>The cardiac action potential [15].</td>
<td>16</td>
</tr>
<tr>
<td>2.8</td>
<td>APs develops along the cardiac conduction system. All these contributes are visible on the ECG as P wave, QRS complex and T wave [6].</td>
<td>17</td>
</tr>
<tr>
<td>2.9</td>
<td>Wave and interval definitions of two consecutive heart-beats [16].</td>
<td>18</td>
</tr>
<tr>
<td>2.10</td>
<td>12-Lead ECG placement standard [17].</td>
<td>18</td>
</tr>
<tr>
<td>2.11</td>
<td>Comparison of ECG tracks during normal rhythm (upper image) and AF (lower image) [18].</td>
<td>20</td>
</tr>
<tr>
<td>2.12</td>
<td>ECG during Atrial Fibrillation [20].</td>
<td>21</td>
</tr>
<tr>
<td>2.13</td>
<td>ECG shows the transition from AF-state to the normal rhythm [24].</td>
<td>24</td>
</tr>
<tr>
<td>2.14</td>
<td>Details of the AV nodal region. The so-called slow and fast conduction pathways are indicated by the arrows (their size was increased to allow the reader to visualize the tortuosity of the conduction pathway) [26].</td>
<td>25</td>
</tr>
<tr>
<td>3.1</td>
<td>Given the interval time t, N(t) represents the number of randomly in time arrivals.</td>
<td>29</td>
</tr>
<tr>
<td>3.2</td>
<td>Example 2-D of a general optimization problem [35].</td>
<td>32</td>
</tr>
</tbody>
</table>
3.3 Example of convergence of pattern search finding the global minimum. At each step, represented by the different figures (a), (b), (c), (d), the cross is looking for the direction, underlined by the red spot (see the transition between (c) and (d)) that lets a decrease of the function \( f(x_k) \). When no such increase or decrease in any one parameter further improved the fit to the experimental data, the step size is halved (see (d)), and the process is repeated, [38]. . . . . . . . . . . . . . . . 35

3.4 The two real branches of \( W(x) \). The first dashed line is \( W_0(x) \); the second continuous line is \( W_{-1}(x) \) [39]. . . . . . . . . . . . . . 36

4.1 Representation of the model. An atrial impulse arriving at the AV node is conducted to the ventricles with a conduction time equal to \( AV_i \) leading to the ventricular activation \( V_i \). The refractory time following this beat is initially \( \theta_i \). An atrial impulse \( A_1 \) arriving at the AV node at a time interval \( AA_1 \), following the first beat is blocked leading to a prolongation of the refractory period to \( \theta_i + \Delta \), where \( \Delta = \Omega \Delta_{std} + \Delta_{mean} \) and \( \Omega \) is a normally distributed random number. The next atrial event \( A_2 \) comes in after the expiration of the new refractory period, and it is thus conducted through the AV node to the ventricles with a conduction time \( AV_{i+1} \) which is a function of the recovery time \( RT = AA_1 + A_1 A_2 - AV_i \) [3]. . . . . . . . . . 38

4.2 Observed histogram of VV intervals in one patient. (B) Best fit using the simulated time series without concealed conduction in the model of Shrier. (C) Best fit with the inclusion of concealed conduction \( \Delta_{mean} \) in the model of Jorgensen. (D) Best fit using the Mangin model. . . . . . . . . . . . . . . . 39

4.3 Plot of autocovariance coefficients of RR interval sequences during normal sinus rhythm (a) and during AF (b) [4]. . . . . 41

4.4 Transmembrane potential of hypothetical AV junction cell. The action potential of duration \( \tau \), marks the period during which the AV node is refractory. During the phase 4 the AV node depolarizes spontaneously by constant \( \dot{V}_4 \), and each arrival atrial impulse creates a step-wise depolarization that adds an amount equal to \( \Delta V \). When the threshold \( V_T \) is reached, a new action potential starts [4]. . . . . . . . . . . . . . . . . . . . . . . . . . . 41
4.5 The phase-IV depolarization of AVJ is modulated by random AF impulses, and can be excited by the VP-induced retrograde wave. The excitation of AV node starts a refractory period, the end of which starts the recovery time [5]. 43
4.6 Model of the AV node showing the generator of atrial impulses arriving to the splitter node dividing the two pathways. 45
4.7 Probability of an atrial impulse to be blocked by the slow (black solid line) and the fast (grey dashed line) pathway. \(\tau_1\) = deterministic part of refractory period of the slow pathway, \(\tau_{p1}\) = maximum prolongation of the slow pathway, \(\tau_2\) = deterministic part of refractory period of the fast pathway, \(\tau_{p2}\) = maximum prolongation of the fast pathway 46
4.8 Simulated RR interval histogram during atrial fibrillation. Set parameters: \(\lambda = 9.09\) Hz, \(\tau_1 = 0.1s, \tau_2 = 0.4s, \tau_{p1} = 0.1s, \tau_{p2} = 0.15s, \alpha = 0.7\). Simulated time registration: 27 minutes 49
4.9 Comparison between the RR series histogram, the theoretical PDF and the experimental PDF. Set of parameters: \(\lambda = 6.25Hz, \tau_1 = 0.1s, \tau_2 = 0.2s, \tau_{p1} = 0.05s, \tau_{p2} = 0.1s, \alpha = 0.4\); while the set of estimated parameters: \(\tau_1 = 0.1s, \tau_2 = 0.1981s, \tau_{p1} = 0.0466s, \tau_{p2} = 0.1041s, \alpha = 0.4214\) 50
4.10 Comparison between the RR series histogram, the theoretical PDF and the experimental PDF. Set of parameters: \(\lambda = 6.25Hz, \tau_1 = 0.1s, \tau_2 = 0.2s, \tau_{p1} = 0.05s, \tau_{p2} = 0.08s, \alpha = 0.2\); while the set of estimated parameters: \(\tau_1 = 0.0988s, \tau_2 = 0.2790s, \tau_{p1} = 0.0496s, \tau_{p2} = 0.0817s, \alpha = 0.1854\) 50
4.11 (a) Comparison between the RR series histogram, the theoretical PDF and the experimental PDF. Set of parameters: \(\lambda = 5.25Hz, \tau_1 = 0.1s, \tau_2 = 0.35s, \tau_{p1} = 0.05s, \tau_{p2} = 0.08s, \alpha = 0.8\); while the set of estimated parameters: \(\tau_1 = 0.1010s, \tau_2 = 0.3569s, \tau_{p1} = 0.0455s, \tau_{p2} = 0.0694s, \alpha = 0.8087\) 51
4.12 Comparison between the RR series histogram, the theoretical PDF and the experimental PDF. Set of parameters: \(\lambda = 8.25Hz, \tau_1 = 0.15s, \tau_2 = 0.35s, \tau_{p1} = 0.05s, \tau_{p2} = 0.1s, \alpha = 0.6\); while the set of estimated parameters: \(\tau_1 = 0.1497s, \tau_2 = 0.3498s, \tau_{p1} = 0.0496s, \tau_{p2} = 0.5969s, \alpha = 0.1854\) 51
4.13 PDF for different \(\Delta\tau(a), \alpha(b), \lambda(c), \tau_p(d)\). In (d) each curve is represented for different settings of \(\tau_{p1}\) and \(\tau_{p2}\): (i) \(\tau_{p1} = 0.05s\) and \(\tau_{p2} = 0.08s\); (ii) \(\tau_{p1} = 0.08s, \tau_{p2} = 0.13s\); (iii) \(\tau_{p1} = 0.12s, \tau_{p2} = 0.16\). Set parameters: \(\tau_1 = 0.1s, \tau_2 = 0.34s, \alpha = 0.7, \lambda = 6.25Hz, \tau_{p1} = 0.1s, \tau_{p2} = 0.15s\) 52
4.14 Modified model of AV node inserting the parameter \( \gamma \) at the entrance to split the atrial impulses between the two pathways.

4.15 a) RR intervals histogram obtained by the Corino’s model with the set of parameters: \( \lambda = 6.25 Hz, \tau_1 = 0.1s, \tau_2 = 0.28s, \tau_{p1} = 0.07, \tau_{p2} = 0.12s, \alpha = 0.64 \); b) RR intervals histogram obtained by the \( \gamma \)-model with the set of parameters: \( \lambda = 6.25 Hz, \tau_1 = 0.1s, \tau_2 = 0.28s, \tau_{p1} = 0.07, \tau_{p2} = 0.12s, \hat{\alpha} = 0.64 \).

4.16 Mismatching between the Corino’s model PDF and the RR intervals histogram generated by the \( \gamma \)-model.

4.17 Comparison of RR intervals histogram created by (a) Corino’s model and (b) \( \gamma \)-model with the following parameters setting: \( \tau_{p1} = 0s, \tau_{p2} = 0s, \lambda = 6.25 Hz, \tau_1 = 0.1s, \tau_2 = 0.28s, \alpha = \hat{\alpha} = 0.64 \).

4.18 a) Probability distribution of ventricular activations generated by non-blocked atrial impulses passed only through the slow pathway using (a) Corino’s model and (b) \( \gamma \)-model. Parameters setting: \( \lambda = 6.25 Hz, \tau_1 = 0.1s, \tau_2 = 0.28s, \tau_{p1} = 0s, \tau_{p2} = 0s, \alpha = \hat{\alpha} = 0.64 \).

4.19 a) Probability distribution of ventricular activations generated by non-blocked atrial impulses passed only through the fast pathway using (a) Corino’s model and (b) \( \gamma \)-model. Parameters setting: \( \lambda = 6.25 Hz, \tau_1 = 0.1s, \tau_2 = 0.28s, \tau_{p1} = 0s, \tau_{p2} = 0s, \alpha = \hat{\alpha} = 0.64 \).

4.20 a) Superimposition of the RR intervals histogram generated by (a) the \( \gamma \)-model and (b) Corino’s model with the PDF (solid line) generated by the previous model considering only the slow pathway. Parameters setting: \( \lambda = 6.25 Hz, \tau_1 = 0.1s, \tau_2 = 0.28s, \tau_{p1} = 0s, \tau_{p2} = 0s, \alpha = \hat{\alpha} = 0.64 \).

4.21 Graphical representation of Corino’s model for the generation of RR series.

4.22 Graphical representation of \( \gamma \)-model for the generation of RR series.

4.23 The atrial impulse AI(1) is the first atrial impulse arriving at \( t > \tau_1 \). The probability to pass through the slow pathway is signed with the symbol \( \times \), while the probability to be blocked is signed with symbol \( \circ \). The “tree” goes on every time the single atrial impulse is blocked.
4.24 Superimposition of RR histogram generated by the $\gamma$-model and the PDF calculated in Eq. 4.20 considering only the slow pathway, using the parameters setting: $\lambda = 6.25Hz$, $\tau_1 = 0.1s$, $\tau_2 = 0.28s$, $\tau_{p1} = 0s$, $\tau_{p2} = 0s$, $\hat{\alpha} = 0.64$.

4.25 Superimposition of RR intervals histogram generated by the $\gamma$-model considering both the slow pathway and fast pathway, and the built PDF according to the Eq. 4.17. Parameters setting: $\lambda = 6.25Hz$, $\tau_1 = 0.1s$, $\tau_2 = 0.28s$, $\tau_{p1} = 0s$, $\tau_{p2} = 0s$, $\hat{\alpha} = 0.64$.

4.26 Graphical representation of $\gamma$-model inserting the refractory periods $\tau_1$, $\tau_2$ and the respective prolongation times $\tau_{p1}$ and $\tau_{p2}$.

4.27 Superimposition of RR intervals histogram generated by the $\gamma$-model and the built PDF according to the Eq. 4.17. Parameters setting: $\lambda = 6.25Hz$, $\tau_1 = 0.1s$, $\tau_2 = 0.28s$, $\tau_{p1} = 0.07s$, $\tau_{p2} = 0.12s$, $\hat{\alpha} = 0.81$.

5.1 (a) Trend of $\hat{\alpha}$ for different values of $\gamma$ when $\lambda = 8.77Hz$, $\Delta\tau_p = 0s$ and $\Delta\tau = [0 - 0.4]s$; (b) trend of $\hat{\alpha}$ for different values of $\Delta\tau$ when $\lambda = 8.77Hz$, $\Delta\tau_p = 0s$ and $\gamma = [0.1 - 0.9]$.

5.2 (a) Trend of $\hat{\alpha}$ for different values of $\gamma$ when $\lambda = 8.77Hz$, $\Delta\tau = 0s$ and $\Delta\tau_p = [0 - 0.21]s$; (b) trend of $\hat{\alpha}$ for different values of $\Delta\tau_p$ when $\lambda = 8.77Hz$, $\Delta\tau = 0s$ and $\gamma = [0.1 - 0.9]$.

5.3 Each curve is $\hat{\alpha}$ trend depending on $\lambda$ when $\Delta\tau = 0.17s$ $\Delta\tau_p = 0s$ and $\gamma = [0.1 - 0.9]$.

5.4 Scatter plot of (a) parameter $A$ and (b) parameter $B$, depending on respectively the parameter $\gamma$ and the product of $\lambda\gamma$, fixing $\Delta\tau_p = 0$. In (a) the parameter $A$ is the complementary of the input parameter $\gamma$; in (b) there is a positive correlation between the parameter $B$ and the frequency with which the atrial impulses arrives to the slow pathway.

5.5 The graphic representation of $C$ depending of $\gamma$ (a) and $\lambda$ (b), referred to the equation 5.6, studied for different values of $\gamma$ and $\lambda$, establishing $\Delta\tau = 0$. Both curves in (a) and (b) have the same random behaviour; in (a) each curve represents a different $\lambda$; in (b) each curve represents a different $\gamma$.

5.6 Trends of the derived $\hat{\alpha}$ (dashed lines) and actual $\hat{\alpha}$ (solid lines) depending on the difference between the two prolongation times ($\Delta\tau_p$). Each curve corresponds to a different value of $\gamma$ that was varied from 0.1 to 0.9.
5.7 Trends of the derived $\tilde{\alpha}$ (dashed lines) and actual $\hat{\alpha}$ (solid lines) depending of the difference between the two refractory periods ($\Delta \tau$). Each curve corresponds to a different value of $\gamma$ that was varied from 0.1 to 0.9. . . . . . . . . . . . . . . . 73

5.8 (a) Estimated $\tilde{\alpha}$ depending on $\gamma$; (b) estimated $\gamma$ through the inverted eq. 5.13, depending on $\tilde{\alpha}$. Parameter setting common for both graphs: $\Delta \tau = 0.2s$, $\Delta \tau_p = 0.07s$, $\lambda = 8.57Hz$. . . 76

5.9 Patient 1: comparison $\alpha$ (a) and $\gamma$ (b) for each treatment. . . 78

5.10 Patient 2: comparison $\alpha$ (a) and $\gamma$ (b) for each treatment . . 78

5.11 Patient 1: Superimposition of $\alpha$ (solid line) and $\gamma$ (thick line) during baseline (a), and Metoprolol (b), Diliziasem (c), Verapamil (d), Carvedilol (e) treatments. . . . . . . . . . . . . . . . 79

5.12 Patient 2: Superimposition of $\alpha$ (solid line) and $\gamma$ (thick line) during baseline (a), and Metoprolol (b), Diliziasem (c), Verapamil (d), Carvedilol (e) treatments. . . . . . . . . . . . . . . . 79

5.13 Patient 1: Comparison along the 24h recording of all estimated parameters and derived $\gamma$ during baseline. . . . . . . . 80

5.14 Patient 2: Comparison along the 24h recording of all estimated parameters and derived $\gamma$ during baseline. . . . . . . . 81
## List of Tables

2.1 Major ionic species contributing to the resting potential of cardiac muscle cells [6] ........................................... 14
2.2 Complications enhanced in the overview of Kirchhof et al. [19]. ................................. 20
2.3 Classification drugs .................................................. 23

5.1 Set of parameters used in the simulation ........................................... 65
5.2 Estimation of the parameters $A$ and $B$ by using the MLS, for different set of parameters $\gamma, \lambda, \Delta \tau$. ................................. 70
5.3 Absolute error and RMSE between the $\hat{\alpha}$ obtained using Eq. 5.7 and the actual value $\tilde{\alpha}$ ................................. 74
5.4 Demographic characteristics and cardiovascular history in the study population ................................. 77
Abstract

**Objective:** The purpose of the present thesis is to enrich the robustness of a statistical atrioventricular (AV) node model during atrial fibrillation (AF). The model takes into account electrophysiological properties as the two pathways, their refractory periods and concealed conduction; these pathways are located between sinoatrial (SA) and AV node. It is highly desirable understanding of the AV node function, in order to achieve optimal arrhythmia management for those patients affected by AF, which is the most common arrhythmia. **Methods:** The simulation has been improved by introducing a new parameter that represents the probability of an impulse arriving at either one of the two pathways. Exploration data has been conducted keeping fixed a set of parameters while varying one of them. **Results:** The model concerns a relationship between the probability of an atrial impulse passing through (output parameter, $\alpha$) and choosing (input parameter, $\gamma$) either one of two pathway. To test its accuracy and precision mean absolute error (MAE) and root mean square error (RMSE) have been calculated for different $\gamma$, obtaining, $MAE = 3.8 \pm 8.2023 \times 10^{-4}$ and $RMSE = 1.59 \pm 0.87 \times 10^{-2}$. Moreover, an investigation has been conducted on real data to verify the proposed relationship using estimated parameter made by the proposed model. Dataset consists 24-h Holter recordings on 31 patients, for each patient there is a baseline and 4 different treatments recordings. The results showed that the standard deviation of introduced parameter presents a greater stability in 58% of recordings, and t-test has given a not significant difference. **Conclusion:** This study indicates that the proposed relationship can be used to calculate the input parameter $\gamma$, given estimated parameter $\alpha$. However, a more stability of the parameter $\gamma$ has not been noticed.

**Index terms:** Atrial Fibrillation (AF), atrioventricular node (AV node), Carvedilol, Diltiazem, dual pathways, Holter recordings, maximum likelihood estimation (MLE), minimum least squares (MLS), metoprolol, refractory period, RR intervals, statistical modeling, Verapamil.
Sommario

**Background:** La fibrillazione atriale (FA) rappresenta l’aritmia più comune [1]. Durante la FA si hanno molteplici foci ectopici negli atri che danno origine ad un’attività disorganizzata di impulsi elettrici atriali (300-600 bpm) diretti al nodo atrioventricolare (AV), con principale conseguenza il possibile aumento della frequenza ventricolare (140-220 bpm). La FA è spesso associata a palpitazioni, svenimento, dolori al petto, infarto, sebbene a volte possa essere asintomatica.

L’aumento di casi di FA può essere associato all’invecchiamento della popolazione e ad un aumento dell’incidenza delle malattie cardiovascolari. Durante la FA il nodo AV assume il ruolo di filtro in grado di bloccare un numero elevato di impulsi atriali che arriva secondo un’attività caotica e irregolare. Sebbene le proprietà elettrofisiologiche del nodo AV influenzino il ritmo ventricolare durante la FA, esse non sono tuttavia valutate nella corrente pratica medica. La ragione è da ricercare: 1) mancata possibilità di utilizzare il protocollo di pacing durante FA; 2) assenza di investigazioni di tipo non invasivo.

**Scopo:** Lo scopo della seguente tesi è l’implementazione di un modello statistico che studi la funzione del nodo (AV) durante la FA mediante acquisizione non invasiva dell’informazione utile.

**Struttura del lavoro:** La prima parte del lavoro ha riguardato lo stato dell’arte delle fisiologia del cuore, andando a focalizzare l’attenzione sul sistema di conduzione cardiaco, in particolar modo sull’anatomia del nodo AV. La conduzione del singolo impulso atriale può avvenire attraverso due vie di conduzione preferenziali: lo “slow pathway” e il “fast pathway”. Essi sono distinti sia da un punto di vista fisiologico che anatomico, e sono contraddistinti rispettivamente lo “slow pathway” da una velocità di conduzione lenta ma con un più breve tempo di refrattarietà, mentre il “fast pathway” da una velocità di conduzione più elevata ma con un periodo di refrattarietà maggiore. E’ stato approfondito lo studio della “concealed conduction”, secondo cui il blocco di un impulso atriale prematuro può causare un aumento della refrattarietà del medesimo nodo AV. In ultima analisi si é approfondita la patologia della FA, includendo la diagnosi, le classificazioni e i trattamenti clinici adot-
La seconda parte del lavoro ha riguardato l’applicazione di un modello del nodo AV sviluppato precedentemente da Corino et al. [2]. I parametri che lo caratterizzano sono i seguenti: 1) frequenza con cui gli impulsi atriali arrivano al nodo AV; 2) tempi di refrattarietà e rispettivi periodi di elongazione (causati dal fenomeno della “concealed conduction”) dello “slow pathway” e “fast pathway”; 3) probabilità con cui un impulso atriale passa attraverso uno dei due percorsi. Dal momento che il seguente modello applicato su dati reali genera in alcuni casi una stima dei parametri instabile lungo il periodo di registrazione, abbiamo deciso di apportare una modifica al modello al fine di avvicinarci maggiormente alle proprietà elettrofisiologiche del nodo AV. Per tale ragione abbiamo inserito un nuovo parametro $\gamma$ che tiene conto della probabilità con cui ciascun impulso atriale sceglie il rispettivo percorso lungo il nodo AV. Di conseguenza il nostro lavoro è stato così suddiviso: 1) analisi delle differenze apportate sul nuovo modello in fase di simulazione; 2) ricerca della relazione esistente tra $\gamma$ e la probabilità $\alpha$ con cui gli impulsi atriali non bloccati attraversano uno dei due percorsi preferenziali per diventare attivazioni ventricolari.

**Metodi:** Il lavoro di simulazione e di stima è stato svolto completamente su Matlab.

*Simulazione:* Gli impulsi atriali arrivano al nodo AV secondo un processo Poissoniano di frequenza $\lambda$. Ciascun impulso ha una probabilità $\gamma$ di scegliere la via di conduzione “slow pathway”, mentre probabilità $(1 - \gamma)$ di selezionare il “fast pathway”. In entrambi i percorsi, il periodo di refrattarietà e rispettivo tempo di elongazione vengono descritti da due funzioni a tratti $\beta_1(t)$ e $\beta_2(t)$. Gli impulsi passanti in uscita dai due percorsi rappresentano una serie di attivazioni ventricolari che si distribuiscono secondo un processo Poissoniano disomogeneo di intensità $\lambda \beta(t)$.

*Stima:* Il metodo di stima dei parametri del modello utilizzato è il metodo di massima verosimiglianza (MLE).

*Relazione $\gamma - \alpha$: *Relativamente allo studio della relazione esistente tra la probabilità di input e la probabilità di output si è optato per una esplorazione sperimentale dei dati, utilizzando la minimizzazione degli scarti quadratici (MLS) per trovare il "fitting" della curva sperimentale.

**Risultati:** E’ stata trovata la relazione che intercorre tra la probabilità $\gamma$ di scegliere lo "slow pathway", e la probabilità $\alpha$ con cui un impulso può passare attraverso il medesimo percorso. La validità della relazione sperimentale è stata confermata mediante il calcolo dell’errore medio assoluto
(MAE) e l’errore quadratico medio (RMSE) calcolati come medie di tutti gli errori commessi nella stima di $\hat{\alpha}$ teorico: $MAE = 3.8 \pm 8.2023 \times 10^{-4}$ e $RMSE = 1.59 \pm 0.87 \times 10^{-2}$. L’applicazione sui dati reali del modello ha consentito di ottenere la stima dei parametri su cui si è applicata la relazione sperimentale. Il dataset consiste in registrazioni Holter di 24-h su 31 pazienti, per ciascuno dei quali vi è una registrazione in baseline e 4 differenti registrazioni per 4 trattamenti farmacologico. I risultati ottenuti mostrano una tendenza della deviazione standard del parametro $\gamma$ ad essere più stabile nel 58% delle registrazioni, mentre il t-test ha evidenziato nessuna significativa differenza tra i due parametri $\alpha$ e $\gamma$.

**Conclusioni:** Lo studio presentato indica che è possibile determinare la probabilità di ingresso $\gamma$, dato il parametro stimato $\alpha$ mediante l’applicazione del modello.
List of acronyms

*Action Potential, AP*
*Adenosine triphosphate, ATP*
*Atrial Fibrilaton, AF*
*Atrial Impulse, AI*
*Atrioventricular node, AV node*
*Effective Refractory Period, ERP*
*Electrocardiography, ECG*
*Direct Current, DC*
*Function Refractory Period, FRP*
*Joint Probability Function, JPF*
*Maximum Likelihood Estimation algorithm, MLE algorithm*
*Mean Absolute Error, MAE*
*Minimum Least Square algorithm, MLS algorithm*
*Probability Density Function, PDF*
*RATe control during Atrial Fibrillation, RATAF*
*Root Mean Square Error, RMSE*
*Simulated Annealing, SA*
*Sinoatrial node, SA node*
Atrial fibrillation (AF) is the most common arrhythmia [1]. During AF the normal regular electrical impulses generated by the sinoatrial node (SA node) are no longer the pacemaker. In fact multiple ectopic foci exist in the atria, giving origin to disorganized atrial electrical impulses (300-600 beats/minute), and leading to irregular arrival to the atrioventricular (AV) node and thus usually to faster ventricular rate (140-220 beats/minute). AF is often associated with palpitations, fainting, chest pain, stroke, or congestive heart failure, but it may also be asymptomatic. The most important associated risk is the stroke, which is caused primarily by clots forming in the atria. The rise in the prevalence of AF can be predominantly attributed to ageing of the population and to a higher incidence of cardiovascular diseases. The first symptom of arrhythmia can be verified by taking the pulse, while the diagnosis and classification of AF is provided by electrocardiogram (ECG) where it is feasible to notice the presence of AF-events, like absence of P waves and irregular ventricular rate.

During AF the AV node plays a relevant role in order to block many of atrial impulses that arrive according to an irregular and chaotic activity. Although the electrophysiological properties of the AV node influence the ventricular response during AF, they are not routinely evaluated in clinical practice. The reason for not evaluating AV node electrophysiological properties is that a pacing protocol is not applicable in AF and non invasive methods are not available yet. A few mathematical models have been proposed, both invasive (e.g. Mangin model [3]) and non-invasive (e.g. Cohen model [4] and Lian model [5]) to better understand the AV node behaviour. The present thesis is based on a previous study made by Corino et al. [2] whose aim has been to develop a model of the AV node during the AF, whose parameter could be estimated from the ECG signal. From the ECG, the generation of RR intervals histogram is obtained, thanks to which the estimation of parameters of the model is developed using maximum likelihood method.
These parameters take into account the general electrophysiological properties of the conduction system: (1) presence of dual AV nodal pathways; (2) relative refractory periods of the pathways; (3) prolongation time due to the concealed conduction phenomenon. In some examples, the results, when applying the method on real data, present a high variability in some estimated parameters.

Starting from this point, the purpose of the thesis is to enrich the robustness of the model, by the introduction of a new parameter that is more correlated to the physiological characteristics of the AV node. The expected result is the relationship between the new parameter and the parameters estimated by the previous model.

The ECG signals, on which the evaluation of the results has been done, are taken from the RATAF database where it was recorded a 24-hour Holter ECG for each patient affected by AF. The registrations have been achieved for each of the four drugs administration (Metoprolol, Verapamil, Carvedilol and Diltiazem) and one recording without.

The first part of the thesis, Ch. 2, contains the medical background useful to be introduced in the argument of the cardiac conduction system. In Sec. 2.5 the attention is focused on the pathophysiology of AF including diagnosis, classification and treatment. Afterwards there is an overall explanation of the AV node anatomy on which the thesis is based on. In the next Ch. 3 there is a description of the main algorithms used in the model (maximum likelihood estimation, simulated annealing and generalized pattern search), as well as the theory of Poisson process and the Lambert function. The second part of the thesis contains the description of the adopted method, Ch. 4. After a brief introduction of some previous mathematical models, including the implementation of Corino’s model, schematic representation of the modified model is present. Ch. 5 describes the results obtained on the simulations, Sec. 5.1, and on real data, Sec. 5.2, applying the new model. Finally Ch. 6 contains discussions and conclusion.
Chapter 2

Medical Background

In the present chapter a general description of the cardiac anatomy and physiology is described. In the next sections the reader is introduced to the cardiac conduction system, focusing the attention on AF and its aspects on the AV node.

2.1 Cardiac Anatomy and Physiology

The heart couches in the center of the thoracic cavity and is hanging by its attachment to the great vessels within a fibrous sac known as the pericardium. It is possible to consider the heart as "double pump": the gross anatomy of the right heart pump is considerably different from that of the left heart pump, performing their function in different districts, yet the pumping principles of each are primarily the same[6].

![Fig. 2.1: Pathway of blood flows through the heart and lungs [6].](image)

The heart is composed by four chambers, the two upper chambers are
the atria while the remaining lower are ventricles. The ventricles are closed chambers surrounded by muscular walls, and the valves, that separate them from the atria, are structurally designed to allow flow in only one direction, i.e. from the atria to the ventricles. The cardiac valves passively open and close in response to the direction flow according to the pressure gradient across them. The function of the heart is to pump oxygenated and de-oxygenated blood at fixed ratio and pressure values, according to body requests, thus maintaining homeostasis which is the ability or tendency to maintain internal stability in an organism to compensate for environmental changes. Describing the pathway of blood, it flows through the chambers of the heart, as it is indicated in Fig. 2.1. The venous blood (with low oxygen level) returns from the systemic organs to the right atrium via the superior and inferior venae cavae. Then it passes through the tricuspid valve into the right ventricles and from there it is pumped through the pulmonary valve into the pulmonary artery. After passing through the pulmonary capillaries, the oxygenated blood returns to the left atrium through the pulmonary veins. The flow of blood then passes through the mitral valve into the left ventricle and is pumped through the aortic valve into the aorta. After that the systemic blood circulation begins [6]. During circulation, venous and arterial blood does not mix, indeed it flows in separated vessels. The gas exchange happens at the level of the capillary vessels and alveoli pulmonary, under particular conditions of partial pressure of $P_{O_2}$. This phenomenon is due to haemoglobin structure [7]. Observing the saturation of haemoglobin curve, in Fig. 2.2, it is comprehensible how it works in different parts of the human body, releasing or linking $O_2$ molecules. Indeed, those areas with high $P_{O_2}$ value can be categorized as pulmonary alveoli where the haemoglobin links with $O_2$ molecules. Viceversa, areas with a low value correspond to those organs where haemoglobin releases oxygen.

The cardiac anatomy is composed mainly by muscle cells (myocytes), see Fig. 2.3. Muscle cells are similar to the other somatic cells (they contain common organelles) but distinct as they also include an elaborate protein scaffold that is anchored to the cell membrane. Force generation by proteins within the matrix leads to the contraction of the cells and pumping of blood by the heart. Force is produced primarily along the long axis of the cell. Most of the internal volume of myocytes is devoted to a cytoskeletal lattice of contractile proteins whose liquid crystalline order gives rise to a striated appearance under the microscope. As with other cell types, the bilayer membrane contains a collection of ion channels and ion pumps and receptor proteins. In addition, the membranes of cardiac muscle cells contain proteins designed to connect cardiac myocytes to one another as both mechanical and electrical partners.
2.2 The cardiac conduction system

The effective pump-action of the heart requires a precise coordination of the mechanical and electrical contractions. This is accomplished via the cardiac conduction system, see Fig. 2.5. Contractions of each cell are normally started when electrical excitatory impulses generate along their surface membranes. In the healthy heart, the normal site for initiation of a heartbeat is within the "sinoatrial node" (SA node). The SA node is located in the right atrium in the heart and serves as the natural pacemaker. These pacemaker cells manifest natural depolarizations and are thus responsible for initiating the normal cardiac rhythm. Here specialized muscle cells have a membrane oscillator, which always spontaneously generates repetitive action potentials (AP), shown in Fig. 2.4.

The electrical activity of these cells is characterized by a slow depolarization of the membrane potential (mV), the pacemaker potential, which is responsi-
Fig. 2.4: SA node action potential, the threshold values trigger AP generation [9].

ble for triggering each AP. The steepness of this pacemaker potential defines the frequency of the cardiac rhythm. This rhythmic activity is related to the interplay between a number of channels and the $\text{Na}^+ / \text{Ca}^{++}$ exchanger. The main currents beard by these different components can be divided into two groups, depending on whether they contribute to the pacemaker or the AP. After initial SA nodal excitation, depolarization spreads throughout the atria. It is generally accepted that: (1) the spread of depolarizations from nodal cells can go directly to adjacent myocardial cells; (2) preferentially ordered myofibril pathways allow this excitation to rapidly traverse the right atrium to both the left atrium and the AV node. It has been shown that there are three preferential anatomic conduction pathways from the SA node to the AV node [4], see Fig. 2.14. These pathways are microscopically identifiable structures, appearing to be preferentially oriented fibres that provide a direct node-to-node pathway.

More specifically, the anterior tract is described as extension from the front part of the sinoatrial node, dividing into the so called Bachman’s bundle (bearing impulses to the left atrium) and a second tract that dips along the interatrial septum which unites to the anterior part of the AV node. The middle (or Wenckebach’s) pathway boosts from the superior part of the SA node, passes posteriorly to the superior vena cava, then unites the anterior bundle as it enters the AV node. The third pathway is defined as being posterior (Thorel’s) which is considered to extend from the inferior part of the SA node, passing through the crista terminalis and the Eustachian valve nearby the coronary sinus to enter the posterior portion of the AV node [11]. At the ending of atrial depolarization, the excitatory signal reaches the AV node. This excitation arrives to these cells via the aforementioned atrial ways, with
the final excitation of the AV node generally described as occurring via the slow or fast pathways, see section 2.6.1. Following AV nodal excitation, in normal sinus rate, the fast pathway conducts impulses to the "His bundle". After leaving the bundle of His, the normal wave of cardiac depolarization spreads to both the left and right bundle branches; these pathways lead depolarization to the left and right ventricles, respectively. Finally, the signal essentially travels through the remnant of the Purkinje fibers and the ventricular myocardial depolarization spreads.

2.3 Channel cell mechanisms (action potential generation)

The contraction mechanism is spread out to the others cardiac muscle cells by AP, whose electrical activity is fundamental to have a normal function and, due to the properties of the cell membrane, takes advantage of selectively passing charged species from inside to outside and vice versa. Most cells build a charge gradient using the action of ion pumps, ion selective channels and Adenosine Triphosphate-dependent ion pumps (ATP-dependent ion pumps). The charge difference across a membrane creates an electrical potential, defined as the resting membrane potential of the cell. In the resting state, the inner part of the cell carries a negative charge relative to the exterior interstitial environment. The energy connected through the discharging of this potential is usually coupled with cellular functions. In excitable cells, temporally changes in the electrical potential (so the APs is like a "bo-
lus" that goes through nervous system) are used to either communicate or to work. Importantly, in the myocyte, AP is required to initiate the process known as excitation contraction coupling. The extracellular fluid has an ionic composition similar to that of blood serum. The total intracellular concentration of calcium is higher, but much of it is bound to proteins or sequestered in organelles (mitochondria, sarcoplasmic reticulum). Hence, free myoplasmic concentrations are very low and expose in the micro-molar range in Tab. 2.1. ATP-dependend ion pumps, ion-specific channel proteins, and ion exchange proteins are all required to maintain the potential difference in ion concentrations. This separation of charged species across a resistive barrier (the cell membrane) generates the electrical potential ($E_{ion}$) mentioned above. For each ionic species, the value of this potential can be calculated using the Nernst equation [12]:

$$E_{ion} = -\frac{RT}{zF} \ln \frac{[\text{outside}]}{[\text{inside}]}$$  \hspace{1cm} (2.1)

where $R$ is the gas constant, $T$ is the temperature expressed in K degrees, $z$ is the valence of the ion (charge and magnitude), and $F$ is the Faraday constant. The membrane potentials of living cells depend on the concentrations of the other major ion species on both sides of the membrane as well as their relative permeabilities. To determine the overall membrane potential ($E_m$), a modified Goldman–Hodkin–Katz equation [13] is used to take into account the equilibrium potentials for individual ions and the permeability (conductance) of the membrane for each species such that:

$$E_m = \frac{g_{Na}}{g_{tot}} E_{Na} + \frac{g_K}{g_{tot}} E_K + \frac{g_{Ca}}{g_{tot}} E_{Ca}$$ \hspace{1cm} (2.2)

where $g_{Na}$ is the membrane conductance for sodium (Na), $g_K$ is the membrane conductance for potassium (K), $g_{Ca}$ is the membrane conductance for calcium (Ca), $g_{tot}$ is the total membrane conductance, $E_{Na}$ is the equilibrium potential

<table>
<thead>
<tr>
<th>Ion</th>
<th>Inside (mM)</th>
<th>Outside (mM)</th>
<th>Ratio of inside/outside</th>
<th>$E_{Eions}$* (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>15</td>
<td>14</td>
<td>9.7</td>
<td>+60</td>
</tr>
<tr>
<td>Potassium</td>
<td>150</td>
<td>4</td>
<td>0.027</td>
<td>-94</td>
</tr>
<tr>
<td>Chloride</td>
<td>5</td>
<td>120</td>
<td>24</td>
<td>-83</td>
</tr>
<tr>
<td>Calcium</td>
<td>$10^{-7}$</td>
<td>2</td>
<td>$2 \times 10^4$</td>
<td>+129</td>
</tr>
</tbody>
</table>

Tab. 2.1: Major ionic species contributing to the resting potential of cardiac muscle cells [6].
for sodium, \( E_K \) is the equilibrium potential for potassium, and \( E_{Ca} \) is the equilibrium potential for calcium. Evaluation of Eq. 2.2 using the values in 2.1 and the conductance values for sodium, potassium, and calcium results in a membrane potential of -90 mV. In Fig. 2.6 the variations of AP along the whole path are shown. Taking as example the various phases of ventricle

![Fig. 2.6: APs along the path of cardiac conduction system [14].](image)

AP, see Fig. 2.7, they are associated with changes in the flow of ionic currents across the cell membrane. Atrial and ventricular cardiac muscle cells have an extremely rapid initial transition from the resting membrane potential to depolarization. Deepening as the channels allow charge movements, the AP generation is composed by five phases:

**phase 0**
During the closing of K-channels, the Na-channels open and there is a large-amplitude, short-duration inward Na-current.

**phase 1**
It is defined as a small initial re-polarization. The opening of the L-type calcium channels causes a calcium influx and is balanced by the potassium efflux via the now open K-channels.
2. Medical Background

2.4 Electrocardiography

An ECG describes the electrical activity of the heart recorded by electrodes placed on the body surface. The voltage variations measured by the electrodes are caused by the APs of the excitable myocytes as they make the cells contract. The resulting heartbeat in the ECG is manifested by a series of waves whose timing and morphology convey information which are used...
for diagnosing diseases. A group of cells simultaneously depolarizing can be seen as an equivalent current dipole associated with a vector. The vectors describe the time-varying position, orientation and magnitude of the dipole and can be summed to give a dominant vector describing the main direction of the electrical impulse, see Fig. 2.8.

Depending on the location of the electrode the resulting wave can be positive or negative, associated with a vector directed towards or away from the electrode respectively. Referring to a healthy ECG, as shown in Fig. 2.9, it is possible to distinguish the most important T waves.

**P wave**
- It represents atrial depolarization.

**QRS complex**
- It is composed by three waves which correspond to ventricular depolarization; following the order we have the depolarization of three heart regions: inter-ventricular region (Q wave), left ventricle apex (R wave), basal region and posterior left ventricle (S wave).

**T wave**
- It represents re-polarization of ventricles.

**U wave**
- As T wave, it has low amplitude value. It represents the re-polarization...
**Fig. 2.9:** Wave and interval definitions of two consecutive heart-beats [16].

**Fig. 2.10:** 12-Lead ECG placement standard [17].
of papillary muscles.

The diagnosis of cardiac pathologies is based on the morphology of these waves. Besides, not only the single waves take into account, but also specific time interval between them. This impulse is recorded by a set of leads which have a standard position on the body surface. Up to twelve different leads are used when taking an ECG. The Fig. 2.10 shows a standard placement of 12-leads, according to specific locations:

- **V1** - 4th intercostal space, right of sternum;
- **V2** - 4th intercostal space, left of sternum;
- **V3** - Midway between V2 and V4;
- **V4** - 5th intercostal space, mid-clavicular line;
- **V5** - 5th intercostal space, between V4 and V6;
- **V6** - 5th intercostal space, mid-axillary line;
- **RA** - Also called AVR, along right arm;
- **LA** - Also called AVL, along left arm;
- **RL** - Also called AVR, Proximal to right ankle;
- **LL** - Proximal to legt ankle.

### 2.5 Atrial Fibrillation

Atrial fibrillation is the most common arrhythmia [1]. During AF multiple foci are present in the atria, thus the electrical impulses in the upper chambers of the heart become chaotic and cause an irregular heartbeat. This irregular atrial depolarization causes the P waves to disappear on the ECG, where the baseline becomes fibrillating (f waves). The AV node has a very important role because it is bombarded by atrial impulses, and its role as filter becomes fundamental. Though the heart rate is irregular and usually faster than normal sinus rhythm. In general, the diagnosis is made on the basis of the irregularity of the ventricular rhythm and the absence of P waves on the ECG, see Fig. 2.11.

The rise in the prevalence of AF can be predominantly attributed to ageing of the population and to a higher incidence of cardiovascular diseases. Stroke
is the most debilitating complication of AF, being associated to hypercoagulable state, structural abnormalities in the fibrillating atria, and relative blood stagnation. The irregular heartbeat can result in heart palpitations along with a variety of symptoms such as fatigue. When the heart is not pumping blood effectively, blood can stagnate and clot. If the clots break apart and travel to the brain, they can cause a stroke, which represents one of worst consequence linked to AF. Table 2.2 reports the most important complications parameters caused by AF.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Relative changing in AF patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Death rate doubled</td>
</tr>
<tr>
<td>Stroke</td>
<td>Stroke risk increased</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>Hospitalizations are frequent in AF patients and may contribute to reduced quality of life.</td>
</tr>
<tr>
<td>Quality of life and exercise capacity</td>
<td>Wide variation according to AF classification and presence of other pathologies</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td>Wide variation according to AF classification and presence of other pathologies</td>
</tr>
</tbody>
</table>

*Tab. 2.2: Complications enhanced in the overview of Kirchhof et al. [19].*
2.5.1 Diagnosis and Classification

The fast and irregular atrial activity may be not clearly visible in low quality recordings (high noise level), in which case the diagnosis is essentially made on the irregularity of the ventricular complexes, see Figure 2.12. The presence of AF as the basic rhythm of the recording makes the ECG interpretation much more difficult, because the appearance of the next ventricular complex cannot be foreseen [20]. As it has been said above, the electrocardiographic diagnosis of AF is given by the presence of rapid atrial activity which is irregular (more than 400 bpm), while ventricular activity appears with QRS complexes separated by RR intervals which are completely irregular. AF can be the basic rhythm or it may be present in long or short episodes, alternating with another basic rhythm, usually the sinus rhythm.

There is a well-accepted classification, as it shows the next description according to the guideline [21]:

Paroxysmal AF

The word paroxysmal means recurring sudden episodes. It means that sporadic episodes of AF come and go. The presence of each episode comes on suddenly, but will stop without treatment within a week (more commonly within two days). So each episode stops just as suddenly as it starts and the heartbeat goes back to a normal rate and rhythm. For this reason the interval time between each paroxysmal episode can vary widely from patient to patient. Although paroxysmal AF means that it will stop on its own, some patients with symptomatic
paroxysmal AF take treatment as soon as the AF develops, to stop it as quickly as possible.

**Persistent AF**
This means AF that lasts longer than seven days and is unlikely to revert back to normal without treatment. However, the heartbeat can be reverted back to a normal rhythm with cardioversion treatment. Persistent AF tends to be recurrent so it may come back again at some point after successful cardioversion treatment.

**Long-standing persistent**
AF has lasted for more than one year when it is decided to adopt a rhythm control strategy.

**Permanent AF**
This means that the AF is present long-term and the heartbeat is not reverted back to a normal rhythm. This may be because treatments were tried and were not successful. Patients with permanent AF are treated to bring their heart rate back down to normal, but the rhythm remains irregular. Permanent AF is sometimes called established AF.

Another important phenomenon is the *remodelling* [22]. Any persistent change in atrial structure or function constitutes atrial remodelling. There are two types of remodelling: electrical and structural. The former is reversible situation due to high atrial rhythm. The AP nature is characterised by shorter length and, as well as, shorter speed conduction making easy reentry mechanisms. The latter is not reversible because during the prolonged arrhythmia a lost of atrial muscle tissue and diffused fibrosis among the atria occurs. Thus the connections are compromised leading to a lower propagation speed. From a clinical point of view, atrial remodelling may switch the duration of AF, hence the patient could pass though the previous classes, e.g. from paroxysmal to persistent AF.

### 2.5.2 Treatment

During AF the AV node receives continuously irregular atrial impulses that create shorter and more irregular RR intervals than during normal sinus rhythm. Thanks to the AV node, the impulses are mostly blocked and they cannot reach the His bundle. Nowadays there are two principal ways to manage the arrhythmia: to restore and to maintain sinus rhythm, or to let AF to continue avoiding rapid ventricular rates. The former is called rhythm control, while the latter is rate control.
2. Medical Background

Restoration of sinus rhythm

The management of AF passes through the restoration of rhythm whose consists to apply one the methodology:

1. Pharmacological cardioversion;

2. Electrical cardioversion;

3. Ablation.

The pharmacological cardioversion makes use of administration of antiarrhythmic drugs to stop the AF episode. The pharmacological cardioversion is more effective on patient with paroxysmal AF and it is achieved by the use of drugs shown in Tab. 2.3.

The different pharmacological classes act on cell channels, in particular:

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Disopiramid, Procainamid, Chinidina</td>
</tr>
<tr>
<td>Ib</td>
<td>Lidocaina, Mexiletina</td>
</tr>
<tr>
<td>Ic</td>
<td>Flecaïnide, Propafenone</td>
</tr>
<tr>
<td>II</td>
<td>Propanololo, Metoprolol</td>
</tr>
<tr>
<td>III</td>
<td>Amiodarone, Bretilio, Dofetilde, Ibutilide, Sotalol</td>
</tr>
<tr>
<td>IV</td>
<td>Verapamil, Diltiazem</td>
</tr>
</tbody>
</table>

Tab. 2.3: Classification drugs.

Class Ia drugs blocks $Na^+$, prolonging action potential and reducing the conduction speed; Class Ib reduces action potential and modestly the action potential duration; Class Ic drugs increase the refractory time and as well as they have same effect of Class Ia drugs; Class II drugs block the receptors $\beta$-adrenergic ($\beta$-blockers); Class III drugs act blocking $K^+$-channels; Class IV drugs block $Ca^{++}$-channels. Specifically, Class I and III are mostly used for the pharmacological cardioversion therapy whose includes antithrombolytic treatment according to the high risk of AF patients.

Electrical cardioversion is applied in those cases where the arrhythmia is classified as persistent [23]. This technique concerns a therapeutic dose of electric current to the heart at a specific moment in the cardiac cycle. Two electrode pads are connected by cables to a machine which the ECG displays and defibrillates. The scope of this technique is to depolarize as much as possible of myocardium, stopping the current rhythm and allowing to sinus rhythm to be restored. An electrical cardioversion event looks as shown in
Fig. 2.13, where an irregular rhythm is recorded before the electrical shock which restores the regular sinus rhythm.

The catheter ablation should be reserved for patients with AF which remains symptomatic despite optimal medical therapy. The ablation is an invasive procedure, which usually includes the use of radio-frequency energy. This energy, warming the cardiac tissue, induces a definitive "scar" which changes the arrhythmogenic substrate, blocking ectopic foci to propagate in the atria.

Fig. 2.13: ECG shows the transition from AF-state to the normal rhythm [24].

Rate control

The rate control during AF is broadly defined as prevention of inappropriately rapid and irregular ventricular rates during AF without making any specific attempt to restore and maintain sinus rate. Rate control in AF has three aims: control of the heart rate at rest, control of the heart rate during activity, and regularization of the heart rate. Control of the ventricular rate is a crucial goal of pharmacological management of AF. The combination of drugs to be given to a patient is obviously based on the classified AF and presence of other heart diseases.

Usually, it is considered by medical staff a long-term treatment. The main motivation to initiate rate control therapy is relief of AF-related symptoms. β-blockers and calcium-antagonists, class II e IV in Tab. 2.3, are used to control the ventricular rate. Their effects do not act on AF electro-physiologic characteristic, but they slow down AV node conduction.

All of them achieve the same goal which prevents very high ventricular rate during AF. Their main difference concerns the efficacy and applicability. AF occurring in patients with little or no underlying cardiovascular disease can be treated with almost any rate-control drugs. Most patients with AF will receive β-blockers initially for rate control. Amiodarone is reserved for those who have failed treatment with other rate-control drugs or have significant structural heart disease. However, the presence of another heart disease can shift the pharmacological treatment to another therapy.
2.6 Atrioventricular node anatomy

The AV node is located in the so-called "floor" of the right atrium, in the center of Koch’s Triangle, over the muscular part of the AV septum, and inferior to the membranous septum. The AV node has the main role of delaying atrial impulses by approximately 0.12 s. This $\Delta$ in the cardiac pulse is extremely important, as it ensures that the atria have ejected their blood in the ventricles. In the normal heart the cardiac impulse is generated in the SA node and is conducted through the atrial myocardium to the AV node. The compact AV node is a complex histological structure, which consists of a loose transitional zone of cells extending into the surrounding atrial myocardium [25]. These transitional cells are situated in the triangle of Koch, where two pathways arise for the conduction of the impulse: a fast pathway, located anteriorly and in close proximity to the His bundle, and a slow pathway, situated posteriorly and inferiorly to the compact node. The fast pathway conducts more rapidly, usually with a relatively longer refractory period, whereas the slow pathway conducts more slowly, with a shorter refractory period. This section will be characterized by a deeper exposition of AV node characteristics and its conduction properties.

*Fig. 2.14:* Details of the AV nodal region. The so-called slow and fast conduction pathways are indicated by the arrows (their size was increased to allow the reader to visualize the tortuosity of the conduction pathway) [26].
2.6.1 Dual pathway

As previously mentioned, one of the more intriguing behaviours of the AV conduction is the so-called dual pathway AV node electrophysiology. This term is used in reference to two different wavefronts that propagate from the atria to the His bundle, one with a shorter effective refractory period (ERP) and another with a longer (ERP) (i.e. slow and fast pathways respectively). This phenomenon was described during 1950s by Preston and collaborators [27], and nowadays the role that fast and slow pathways play in the conduction from the atria to the His bundle has still many hypothesis. The demonstration of the existence of two pathways has been well documented by N. Mazgalev et al. [28] that has performed invasive studies using 10 rabbit during AV node reentrant tachycardias. According to their model, the AV node is a bilayer structure supported by two wavefronts. An earlier wavefront (fast) that propagates via the transitional cell envelope, and a later wavefront (slow) propagates via the deeper inferior nodal extensions. They have studied the AV node potential depending on the distance measured in time between two consecutive atrial impulses (A1A2). The decrease of A1A2 was associated with a decrease in AV node potential with consequent AV node block, suggesting that the available driving force was unable to generate full depolarization. When A1A2 was shortened to threshold value, the presence of a delayed component, representing the later and stronger slow wavefront, let the restoration of the conduction, and a full AP.

The slow and fast pathways are physiologically and anatomically distinct routes to the AV node. The slow pathway traverses the isthmus between the coronary sinus and the tricuspid annulus and has a shorter effective refractory period but a longer conduction time compared to the fast pathway. The collocation of the fast pathway is usually in the interatrial septum, and it is characterized by a faster conduction rate and a longer effective refractory period. During the sinus rhythm the normal conduction happens along the fast pathway, but during pathologies like AF, possible premature beats are often conducted through the slow pathway, since the fast pathway can be refractory at these rates. More specifically, the dual characteristics can be revealed through an electrophysiological study, performing a S1-S2 pacing protocol. In this procedure, a stimulus (S1) of constant duration and amplitude was given and after followed by a second stimulus (S2) of varying duration and amplitude. At each step, the S1-S2 interval is reduced until conduction block in the fast pathway occurs due to the long refractory period [28].

During AF the time between two atrial activations is shorter than the refractory period of AV nodal cells. Consequently, the AV node works as a filter,
blocking some atrial activations and limiting the number of ventricular beats according to the phenomenon of concealed conduction. The way in which this natural filter works, and how it could be used to perform efficient rate control therapies, remains not completely understood.

Concealed Conduction

It has well documented that an impulse entering the AV node can sometimes fail to traverse it completely. Langerdorf [29] used for the first time the term "concealed conduction" to describe "the presence of incomplete conduction coupled with an unexpected behaviour of the subsequent impulse". At the beginning the use of this term was restricted to define: "(1) partial or incomplete forms of anterograde and/or retrograde AV conduction block in which an atrial impulse did not generate a distal response but had influences on impulses that followed it"; (2) "abortive AV node conduction of a premature atrial impulse blocked in both directions causing first or second degree AV block". Over the years, it was discovered that the blocked impulses brought to a general increase refractoriness of the same AV node, whose conduction time is delayed by these following characteristics: strength, direction, form, number and sequence of the fibrillatory impulses that reach the AV node. Accordingly, this activity is underlined by fast irregular ventricular rhythm during AF.

Electrotonic modulation and decremental conduction

The mechanism controlling the concealed conduction is still controversial. According to Hoffamn’s [30] previous work, the AV node is "the site for slow and continuous conduction of electrical impulses from the atrium to the His bundle". The effects that may be developed by the crossing of the impulses across the AV node are a progressively increasing threshold, a decreasing amplitude and because of the raising rate of the AP there would be a gradual decrease of activity of the regions responsible for depolarizing more distal tissues. However Meijler et al. [31] confuted the decremental conduction existence bringing different considerations. At first it is quite clear that the AV conducting system should be regarded as highly heterogeneous and discontinuous. Moreover, it is incompatible with the modern electrophysiological properties and with the electrophysiographic features recorded in patients with AF. So a new idea was proposed, linked to the existence of electrotonic modulation of AV node propagation by atrial impulses blocked within the AV node, responsible in the irregular rhythms noticed in patients with AF. While in decremen-
tal conduction the amplitude of the AP decreases gradually until it dissipates completely, unable to excite tissues ahead of it, in electrotonic transmission, the AP stops at the site of block. Thanks to the local circuit, there will be a passive membrane depolarization whose amplitude decays with the distance, as function of the resistive properties of the tissues involved.

Meijler has explained the presence of "after effects" on the propagation of subsequent impulses, when the concealed conduction happens. When an impulse is blocked in the AV node, a subthreshold depolarization for cells distal to the site of block verifies. Therefore the inhibition of amplitude brought by the subthreshold depolarization will affect the second AV node subthreshold response (defined as electrotonic effects). The whole effect produces a delay or even a blockade in the transmission of the subsequent impulses.
Chapter 3
Mathematical Background

In this chapter there is an overview of the mathematical knowledge necessary for the implementation of the AV node model.

3.1 Poisson Process

The Poisson process is defined as a stochastic process that counts the number of arrivals $N(t)$ occurred in the finite interval time of length $t$ with a mean rate $\lambda$ defined as intensity, see Fig. 3.1. The function $N(t)$ obeys to the Poisson distribution:

$$P\{N(t) = n\} = \frac{(\lambda t)^n}{n!} \exp\{-\lambda t\}$$  (3.1)

where $\lambda t$ is the mean of events that will occur during the time $t$. If the intensity $\lambda$ is constant, the process is called homogeneous, otherwise if $\lambda(t)$ is time-dependent, the process is an inhomogeneous Poisson process, and the average arrival rate in the interval time $[0;t]$ of the Poisson process will be:

$$\mu(t) = \int_0^t \lambda(\tau) d\tau,$$  (3.2)

The Poisson process has some peculiar properties that are described below.

**Memoryless property:** An $X$ process can be characterized by *memoryless property* if:

$$Pr\{X > t + x\} = Pr\{X > x\}$$  (3.3)
Considering $X$ as the waiting time until some given arrival, the equation 3.3 states that, given that the arrival has not occurred by time $t$, the distribution of the remaining waiting time is the same as the original distribution, so the remaining waiting time has no ‘memory’ of previous waiting. This property implies that the arrivals are distributed randomly in time, thus assuring their statistically independence.

Assuming this property, the probability that the first arrival $X_1$ occurs after time $t$ is given by a decreasing exponential controlled by $\lambda$:

$$Pr\{X_1 > t\} = Pr\{N(t) = 0\} = e^{-\lambda t} \tag{3.4}$$

**Random selection:** If a random selection is made from a Poisson process with intensity $\lambda$ such that each arrival is selected with probability $p$, independently of the others, the resulting process is a Poisson process with intensity $p\lambda$.

**Random split:** If a Poisson process with intensity is randomly split into two subprocesses with probabilities $p_1$ and $p_2$, where $p_1 + p_2 = 1$, then the resulting processes are independent Poisson processes with intensities $p_1 \lambda$ and $p_2 \lambda$.

### 3.2 Maximum Likelihood Estimation

The method of maximum likelihood (MLE) [32] corresponds to many well-known estimation methods in statistics. MLE is a preferred method of parameter estimation in statistics and is an useful tool for many statistical modeling techniques.

Let define $y = (y_1, ..., y_m)$ as a random sample vector from an unknown population. The aim of this algorithm is represented by the set of parameters that generate the most likely sample. Here, each population has correspondent probability distribution and with each probability distribution an unique parameter. Defined $p(y|\theta)$ as the probability density function (PDF), it specifies the probability of observing data vector $y$ given the parameter $\theta$. The parameter $\theta = (\theta_1, ..., \theta_k)$ is a vector in a multi-dimensional parameter space.
3. Mathematical Background

Assuming all elements $y_i$ of $y$ are statistically independent, second to theory of probability, the PDF for the data $y = (y_1, ..., y_m)$ given the parameter vector $\theta$ can be expressed as a production of PDFs for individual observations:

$$p(y = (y_1, y_2, \ldots, y_n)|\theta) = p(y_1|\theta) \ast p(y_2|\theta) \ast \ldots \ast p(y_m|\theta) = \prod_{i=1}^{m} p_i(y_i|\theta)$$ (3.5)

Denoting the inverse problem: *Given the observed data and a model of interest (set of parameters), find the one PDF, among all the probability densities that the model describes, that is most likely to have produced the data*. It is useful to work with the natural logarithm of the likelihood function, the so-called *log–likelihood* function:

$$\log p(y|\theta) = \sum_{i=1}^{m} \log p_i(y_i|\theta)$$ (3.6)

The final solution is given by the maximization of Eq. 3.5, obtaining formally,

$$\hat{\theta} = \arg\max_{\theta} \left\{ p(y|\theta) \right\}$$ (3.7)

The value $\hat{\theta}$ is called the maximum likelihood estimate of $\theta$. The solution to the equation may not have a close form solution because of the complexity of the model (high parameter number), therefore it becomes necessary to solve the problem numerically (see next section). Below, MLE properties are listed:

**Consistency.** The sequence of MLEs converges in probability to the value being estimated [33].

**Asymptotic normality.** As the sample size increases, the distribution of the MLE tends to the Gaussian distribution with mean $\theta$ and covariance matrix equal to the inverse of the Fisher information matrix [33].

**Efficiency.** It achieves the Cramér–Rao lower bound when the sample size tends to infinity. This means that no consistent estimator has lower asymptotic mean squared error than the MLE (or other estimators attaining this bound) [34].

### 3.3 Optimization Algorithms

In general, an optimization problem can be express as:

$$z = \arg\min_{x \in X} \left\{ f(x) \right\}$$
where:

- $X$ array of admissible solutions;
- $f(x)$ target function to minimize (or maximize).

Discerning the difference between local and global maximum, we say that a specific $x^* \in X$, we will have:

- $f(x^*) \geq f(x)$, $\forall x \in \varepsilon(x)$, where $\varepsilon(x)$ is part of $X$ (Local);
- $f(x^*) \geq f(x)$ $\forall x \in X$ (Global).

![Fig. 3.2: Example 2-D of a general optimization problem [35].](image)

For non-deterministic polynomial-time hard (NP-hard), computationally burdensome, usually it is necessary to apply heuristic methods for reaching the solution. We can divide the procedure in two iterative techniques: building and improving. The first is geared to find an admissible solution; while the second, starting from the admissible solution previously found, iteratively applies a function, converging to the local maximum. The main problem, given by heuristic algorithm, is the "local solution trap", which can be bypass using proper converging procedure that allows to accept worse solutions. During the thesis work, we have mainly used the two following algorithms, focusing on them because they represent the best solution (according to the estimation) we obtained. As the most part of iterative algorithms of minimization (or maximization), numerically algorithms suffer about: presence of local
minima, long computational time (if the observation number is considerable high). It is also truth that given a certain number of parameters to estimate, the computational increase proportionally to number of parameters. In Fig. 3.2, a bidimensional example shows the research of the optimal solution (global minimum).

### 3.3.1 Simulated Annealing

As above mentioned, there are two techniques to find the solution. The success possibility often increases using metaheuristics techniques, as simulated annealing (SA) [36]. It is based on the analogy between the hardening physic process and the solving of combinatorial optimization problems. Hardening involving heating and controlled cooling of a material to increase the size of its crystals and reduce their defects. Both are attributes of the material that depend on its thermodynamic free energy. Heating and cooling the material affects both the temperature and the thermodynamic free energy which are differently correlated. While the same amount of cooling leads the same amount of decrease in temperature, it will lead a bigger or smaller decrease in the thermodynamic free energy based on the rate which it occurs, with a slower rate producing a bigger decrease. The notion of slow cooling is implemented in the SA algorithm as a slow decrease in the probability of acceptance worse solutions as it explores the solution space. Indeed, accepting worse solutions is property of metaheuristics because it allows a wider search for the optimal solution. Describing in summary the macro-steps, we would have:

**Initialization:**

Initial guess point \( S \);

**Move definition:**

Define the operation to find a random \( S' \) solution around the current solution;

**Accepting the move:**

Assess whether \( S' \) the solution can be the new current solution, so \( S' \rightarrow S \), applying the following accepting probability:

\[
P = \begin{cases} 
1 & \Delta f \leq 0 \\
\frac{1}{e}\left(\frac{\Delta f}{T}\right) & \Delta f \geq 0 
\end{cases}
\]

**Cooling schedules:**

It represents all control parameters of SA. In general, it is composed by:
initial control parameter \((T_0)\), allowing all transitions to be accepted at the starting point; final control parameter \((T_f)\), no transition is accepted; transition number \(L_k\) for each value \(T_k\) and decremental law \(T\); they are correlated to ensure a quasi-equilibrium condition for each \(T\) value changing.

### 3.3.2 Generalized Pattern Search

The patternsearch is a direct search method for solving non linear optimization problems [37], it means that it does not use derivatives or approximations of derivatives to solve the problem:

\[
\min_s f(x),
\]

where \(x \in \mathbb{R}^n f : \mathbb{R}^n \rightarrow \mathbb{R}\). A subset of the direct search algorithms, class called pattern search, share a structure that makes unified convergence analysis. The general form of optimization is given by an initial guess at a solution \(x_0\) and an initial choice of a step length parameter \(\Delta_0 > 0\). The algorithm can be explained as following:

For \(k = 0,1,...,\)

i) Check for convergence;

ii) Compute \(f(x_k)\);

iii) Determine a step \(s_k\) using exploratory moves \((\Delta_k, P_k)\), where \(\Delta_k\) is the step-length control parameter and \(P_k\) is the pattern;

iv) If \(f(x_k) > f(x_k + s_k)\), then \(x_{k+1} = x_k + s_k\), otherwise \(x_{k+1} = x_k\);

v) Update \((\Delta_k, P_k)\).

The pattern \(P_k\) is defined by two components, a real nonsingular basis matrix \(B\) and a generating matrix \(C_k\), where the columns of \(C_k\) must contain a core pattern represented by \(M_k\) and its negative \(-M_k\). The pattern \(P_k\) is then defined by the columns of the matrix \(P_k = BC_k\), therefore the steps are of the form \(s_k = \Delta_k Bc_k\), where \(c_k \in C_k\).

The hypothesis required by the exploratory moves are:

i) \(s_k \in \Delta_k P_k \equiv \Delta_k BC_k\);

ii) If \(\min \{ f(x_k + y), y \in \Delta_k B[M_k, -M_k]\} < f(x_k), \) then \(f(x_k + s_k) < f(x_k)\).

The second hypothesis claims that if descent can be found for any one of the \(2n\) steps defined by the core pattern, the exploratory moves returns a step that gives a simple decrease and the iteration is considered successful. If the iter-
ation is *unsuccessful*, it is required to reduce the current step-length control parameter $\Delta_k$, which has the effect of refining the restriction, called rational lattice, over which the search is conducted. The process will be repeated until some suitable stopping criterion is satisfied.

The advantages of the algorithm are given by the mild conditions on both the *exploratory moves* and the $\Delta_k$ update to guarantee global convergence. There is no requirement that the step should be defined by the core pattern, nor that $2n$ steps must be evaluated, or even that the step returned gives the greatest decrease possible.

\[ x = W(x)e^{W(x)} \]  \tag{3.8}
In case of real $x$, for $\frac{1}{e} \leq x < 0$ there are two possible real values of $W(x)$, see Fig. 3.4. The branch satisfying $-1 \leq W(x)$ is called the principal branch ($W_0(x)$) and the branch satisfying $W(x) \leq -1$ the negative branch denoted as $W_{-1}(x)$. The negative branch goes to $-\infty$ as $x \to 0$, while the principal branch grows slowly but unbounded for $x \to \infty$. The Lambert W function solves any equation of the canonical form $C = xe^x$. The base of the exponential can be a generic number $b$, so, given the equation $xb^x = C$, the solution of the inverted equation is:

$$x = \frac{W(C\log b)}{\log b} \quad (3.9)$$
The present chapter provides an overview of previously proposed mathematical models of the AV node conduction system. The non invasive model proposed by Corino et al. [2] is thoroughly described since this thesis is based on it. The section describes the principal modifications that have been implemented to the previous model.

4.1 Previous mathematical AV node models

Some mathematical models have been proposed to study the AV nodal electrophysiological characteristics. The models can be estimation models, (cf. Mangin model in Sec 4.1.1), or simulation models, (cf. Cohen model in Sec 4.1.2 and Lian model in Sec 4.1.3). The clinical information used by the models could be divided in invasive or non-invasive. The invasive information can be useful for the simulation models to have a comparison of the results, while the estimation models apply this information to obtain the estimated parameters. Estimation models take into account the most important electrical properties of AV node, summarizing them with the model parameters. The main problem related to this approach is the simplification needed to describe the AV node. Simulation models of the AV node describe in more details the electrophysiological dynamics. However, because of the high number of model parameters, they are not suited for robust estimation. In the following paragraph a review of the existing models is presented.

4.1.1 Mangin’s model

Mangin et al. [3] studied the effect of metoprolol and amiodarone drugs on atrial and ventricular activity during AF by epicardial recordings in 10 postsurgical patients. The aim of the work was proposing a mathematical model of the AV node, extracting parameters able to describe the drug effects on AV nodal physiology during AF. The study is based on the relationship between the AV nodal conduction time and the preceding recovery interval. Accord-
ing to the model, the conduction time is associated with a sequence of conducted beats through an iterative series. The model accounts the concealed conduction (see section 2.6.1), improving the previous hypothesis, brought by Jorgensen et al. [40], that each blocked beat leads to a fixed increment in the refractory period. Mangin et al. modified this assumption, supported by recorded data. Since atrial activations show different degrees of penetration of the AV node, due to their time-variability and conduction pathway chosen, it is reasonable, according to them, to estimate the prolongation of the refractory period brought by blocked beats using a normal distribution. The increment in the refractory period due to a blocked beat \( i \), is:
\[
\Delta = \Omega_i \Delta_{std} + \Delta_{mean}
\]  
where \( \Omega_i \) is a normally distributed random number with mean zero and standard deviation 1. Following a conducted beat, the refractory period is reset to \( \theta \) and subsequent blocked beats lead to a prolongation of the refractory period see Fig. 4.1. This hypothesis has been confirmed by comparing the results of

![Fig. 4.1: Representation of the model. An atrial impulse arriving at the AV node is conducted to the ventricles with a conduction time equal to \( AV_i \) leading to the ventricular activation \( V_i \). The refractory time following this beat is initially \( \theta_i \). An atrial impulse \( A_1 \) arriving at the AV node at a time interval \( AA_1 \), following the first beat is blocked leading to a prolongation of the refractory period to \( \theta_i + \Delta \), where \( \Delta = \Omega \Delta_{std} + \Delta_{mean} \) and \( \Omega \) is a normally distributed random number. The next atrial event \( A_2 \) comes in after the expiration of the new refractory period, and it is thus conducted through the AV node to the ventricles with a conduction time \( AV_{i+1} \) which is a function of the recovery time \( RT = AA_1 + A_1 A_2 - AV_i \) [3].

their simulation to the results of simulations of previous three models of the
AV node, see Fig. 4.2. At first the Shrier model is presented, in which the concealed conduction is not taken into account. Observing the Fig. 4.2(b) the model does not give a good agreement with the observed ventricular activity in patients with AF, confirmed by the low value of the probability $P$ (defined as the significance level of t-test), for which the cumulative distribution function of the simulated ventricular activations has a low probability to be the same of the experimental ventricular activations. In Fig. 4.2(c) the concealed conduction is added, so that the concealed beat leads to an equal increment in the refractory period, as proposed by Jorgensen et al.. The probability P is higher, but the histogram results multi-modal (Fig. 4.2(c)). However, allowing the concealed beats to have different effects in the increment of refractory period, the agreement between the observed histogram and the simulated histogram increases to the probability P=0.95 (Fig. 4.2(d)).

![Fig. 4.2: Observed histogram of VV intervals in one patient. (B) Best fit using the simulated time series without concealed conduction in the model of Shrier. (C) Best fit with the inclusion of concealed conduction $\Delta_{\text{mean}}$ in the model of Jorgensen. (D) Best fit using the Mangin model.](image)

The conclusion to which they arrived was that the drugs effects have led a decrease in ventricular activity, but no marked changes in the atrial activity.
So changes in ventricular rate are conducted by alterations in the properties of the AV node, rather than changes in the atrial activity. The main limitation of this model is linked to its nature. Since it is an approximation of the physiological AV node, it is not easy to estimate the errors relative to the parameters. So the relationship between variations in conduction through the AV node and the parameters is still unknown. Moreover, their intention to predict the time of occurrence of every ventricular contraction is not possible, because of the stochastic nature of the penetration of atrial activity into AV node during AF.

4.1.2 Cohen’s model

The non-invasive model exposed by Cohen et al. [4] has been proposed for the genesis of RR intervals fluctuations during AF and accounts for the statistical features of the RR interval sequence. The AV node is considered as an electrically active cell with defined electrical properties, like refractory period and automaticity. During AF a turbulent electrical activity makes atrial impulses arrive randomly in time with higher frequency (called \( \lambda \)) compared to the sinus rhythm. Atrial impulses are assumed to arrive according to a Poisson process. The AV node model represents the temporal and spatial summation of the electrical activity of all cells of the AV node. It means that all blocked atrial impulses are summed in time and the AV node does not initiate a new refractory period until after the next ventricular activation has occurred.

Cohen has studied the statistical properties of RR interval, discovering the statistical independence of each other during AF. Indeed, focusing the attention on autocovariance coefficients of RR intervals values, during normal sinus rhythm the correlation of RR intervals is over delays of 25 ms, while during AF the autocovariance is close to zero for index \( i \geq 2 \), see Fig. 4.3. In the Fig. 4.4 the transmembrane potential of the AV node is shown. According to this model, there is a time \( \tau \) during which the AV node is completely refractory, that means it is not excitable to the stimulation of atrial impulses. At the beginning of phase 4 the transmembrane potential is at its resting potential value \( V_R \). During this phase there are two different ways of transmembrane potential increase: (1) spontaneously rise with a rate equal to \( \dot{V}_4 \); (2) discrete increase \( \Delta V \) due to atrial impulse arrival during this period. The threshold \( V_T \) could be reached by the result of stepwise depolarizations due to atrial impulses, and spontaneous phase 4 depolarization. After this value the AV node starts to fire by creating a new action potential.

In Cohen’s model the amplitude \( \Delta V \) has two different meanings: (1) it reflects the sustained stepwise depolarization made by the single cells; (2) it
4. Methods

**Fig. 4.3:** Plot of autocovariance coefficients of RR interval sequences during normal sinus rhythm (a) and during AF (b) [4].

**Fig. 4.4:** Transmembrane potential of hypothetical AV junction cell. The action potential of duration $\tau$, marks the period during which the AV node is refractory. During the phase 4 the AV node depolarizes spontaneously by constant $\dot{V}_4$, and each arrival atrial impulse creates a step-wise depolarization that adds an amount equal to $\Delta V$. When the threshold $V_T$ is reached, a new action potential starts [4].
4. Methods

represents also the spatial coherence of this activity. Therefore during normal sinus rhythm, a synchronous depolarization wavefront arrives at the AV node with $\Delta V = V_T - V_R$, permitting one-to-one AV conduction. During AF, there will be the loss of spatial coherence in atrial depolarization that will cause a decreasing in $\Delta V$ amplitude. As the degree of spatial disorganization increases, $\lambda$ raises with the widespread of many parallel inputs to AV node.

The first mathematical model proposed by Cohen takes into account four parameters:

1. $\lambda$ is the frequency of atrial impulses that arrive at the AV node;
2. $\Delta V/(V_T - V_R)$ is the relative amplitude of the atrial impulses during phase 4;
3. $\dot{V}_4/(V_T - V_R)$ is the relative rate of phase 4 depolarization of the AV node;
4. $\tau$ is the refractory period of the AV node.

One property not underlined by the Fig. 4.4 is the time required by impulses to pass through the AV node. However, according to Cohen’s model, since there is the hypothesis of random arrival in time of atrial impulses to the AV node, the RR interval distribution during AF is not influenced by a randomly conduction delay of atrial impulses. Therefore it is not necessary to consider the conduction delay in analyzing the predicted RR intervals histogram.

To test their model, Cohen compared the experimental histogram of RR intervals obtained from patients in chronic AF to the prediction model. They showed that the model was able to predict both unimodal RR intervals histograms, and multiple peaks in the histogram. However two of the four parameters described, $\Delta V/(V_T - V_R)$ and $\dot{V}_4/(V_T - V_R)$, can be uniquely determined only when at least two peaks were present in the histogram. This happens because these two parameters serve to determine the positions of the two peaks. Moreover, the model estimates unphysiological values of the parameter $\lambda$, ranging between 5 Hz and 116 Hz. Finally, although the model is statistical in nature, no statistical parameter estimation procedure has been devised. Instead, the model parameters were determined from the RR series using an ad hoc procedure.

4.1.3 Lian’s model

Lian et al. [5] have proposed an AF-ventricular pacing model. It could be considered as an extension of Cohen’s AF model accounting more detailed electrophysiological characteristics like ventricular pacing (VP), bidi-
Fig. 4.5: The phase-IV depolarization of AVJ is modulated by random AF impulses, and can be excited by the VP-induced retrograde wave. The excitation of AV node starts a refractory period, the end of which starts the recovery time [5].

rectional physiological conduction delays, and electrotonic modulation in the AV node. As [4], the AV node can be activated due to combined effect of two phenomena: 1) spontaneous phase-IV depolarization; 2) AF bombardments. In addition, the AV node can also be activated by the invasion of a VP-induced retrograde wave. As illustrated in Fig. 4.5, the activation of the AVJ starts a refractory period $\tau$, during which the AVJ is non-responsive to stimulation by both the AF impulses and the VP-induced retrograde waves. When the AV node refractory period ends, $V_m$ returns to the resting potential, $V_R$, and starts a linear increase at a rate $dV/dt$. Each time an atrial impulse reaches the AV node during phase-IV, $V_m$ is increased by a discrete amount $\Delta V$. On the other hand, if the AV node is penetrated by a VP-induced retrograde wave during phase-IV, $V_m$ is brought to $V_T$ immediately. The AV node recovery time, $T_R$, is defined as the interval between the end of the last AV node refractory period and the current AV node activation time. In this model both the conduction delay $AVD$ and the refractory period $\tau$ are considered recovery time-dependent ($T_R$). In more detail, the relationship between the refractory period $\tau$ and the recovery time $T_R$ is:

$$\tau = \tau_{\text{min}} + \tau_{\text{ext}} \left(1 - \exp\left(-T_R/\tau_{\text{ext}}\right)\right) \quad (4.2)$$

where $\tau_{\text{min}}$ is the shortest AV node refractory period when $T_R = 0$, and $\tau_{\text{ext}}$ is the maximum value assumed by the refractory period when $T_R \to \infty$. It is also feasible to set the dependence between the AV delay $AVD$ and the recovery time $T_R$:

$$AVD = AVD_{\text{min}} + \alpha \exp\left(-T_R/\beta\right) \quad (4.3)$$
where $AVD_{min}$ is the minimum AV delay when $T_R \to \infty$, $\alpha$ is the maximum extension of AV delay when $T_R = 0$, and $\beta$ is the time constant.

The concealed conduction of atrial impulses is influenced by the electrotonic modulation, as described in section 2.6.1. Each atrial impulse blocked by the AV node generates a prolongation of refractory period. The prolongation is modulated by the electronic modulation and depends on two variables: timing and strength of the blocked impulse. Considering this phenomenon, the ventricular rate depends on opposite events:

1. Atrial frequency rate whose increasing frequency provokes a more rapid ventricular rate;

2. the concealed atrial impulses frequency can prolong the AV node refractory period and potentiate the AV block.

So the ventricular rate could depend on the electrotonic modulation level. If it is stronger, the ventricular rate could be slower than atrial frequency impulses, otherwise there will be the opposite event. The strength of this model is that it is taking account for most statistical properties of RR intervals during AF. The weakness is the difficulty to use a simultaneous search over all the sixteen model parameters. They suggest to reduce the dimension of the search space by deriving some baseline parameters independently, and thereafter trying to conduct a search, with the reduced space, to achieve quantitative data [5].

### 4.2 Corino’s model

This section focuses on the previous model made by Corino et al. [2] and [41]. The model introduced in this thesis models the AV node during AF through ECG-based estimation method [2], taking into account the main electrophysiological properties of the AV node, namely the presence of dual AV pathways, their refractory period and the phenomenon of concealed conduction.

#### 4.2.1 Description of the model

According to the model, series of atrial impulses arrive randomly in time at the AV node following a Poisson process with mean rate equal to $\lambda$ (see Fig. 4.6 for a schematic representation). The AV node is considered as a lumped structure which takes into account the concealed conduction, relative refractoriness and existence of dual pathways. Therefore, for each atrial impulse there are two ways to reach the AV node: the slow and the fast pathway. The
first atrial impulse arriving after a ventricular activation has a probability $\alpha$ of
taking the slow pathway, whereas a probability $(1 - \alpha)$ to take the fast path-
way. The following atrial impulses take the same pathway chosen by the first
one, until one of them is non-blocked and becomes a ventricular activation.
The presence of the feedback lets to reset the previous choice related to the
taken pathway. In this way, the output probability, related to the number of
ventricular activations that occur along the slow pathway, is equal to the input
probability $\alpha$ for which the atrial impulses get the pathway with the shorter
refractory period.

The refractory period is characterized by deterministic time $\tau$, when the

\[ \beta_i(t) = \begin{cases} 
  0 & \text{if } 0 < t < \tau_i \\
  \frac{t - \tau_i}{\tau_{pi}} & \text{if } \tau_i \leq t < \tau_i + \tau_{pi} \\
  1 & \text{if } t \geq \tau_i + \tau_{pi} 
\end{cases} \quad (4.4) \]

Fig. 4.6: Model of the AV node showing the generator of atrial impulses arriving to
the splitter node dividing the two pathways.

AV node is completely refractory to stimulation by atrial impulses, and by a
stochastic part $\tau_p$, where the transmembrane potential increases uniformly to
allow the impulse passing. Thus during the interval time $[\tau, \tau + \tau_p]$, caused
by concealed conduction and/or relative refractoriness, the probability to pass
is linearly increasing. After the time $\tau + \tau_p$ called maximally prolonged re-
fractory period, no impulse is blocked, see Fig. 4.7. Because of the presence
of dual pathways, there are two different refractoriness properties, $\tau_1$ and $\tau_{p1}$
for the slow pathway and $\tau_2$, $\tau_{p2}$ for the fast pathway. The slow pathway is
characterized by the refractory period $\tau_1$, assumed to be minor than $\tau_2$.
It is possible to define mathematically the refractoriness of the $i$th pathway ($i = 1; 2$) by the positive-valued function $\beta_i(t)$:
where $t$ represents the time elapsed from the last ventricular activation, $\tau_i$ is the $i$th refractory period and $\tau_{pi}$ is the $i$th prolongation time. During the maximally prolonged period, the probability to pass by impulse increases by linearly way. The distribution of non-blocked atrial impulses happens along an inhomogeneous Poisson process with the intensity function $\lambda \beta(t)$. Since the conduction time is included in the function $\beta_i(t)$, the ventricular activation coincides with non-blocked atrial impulse, so also ventricular activations occur as inhomogeneous Poisson process with the same intensity function. The probability density function (PDF) of the arrival time of the $n$th non-blocked impulse, defined by $t_n$ has the following equation [2]:

$$p_t(t_n) = \frac{\lambda \beta(t)}{(n-1)!} \left( \int_0^t \lambda \beta(\tau) d\tau \right)^{n-1} \exp \left\{ - \int_0^t \lambda \beta(\tau) d\tau \right\}$$

(4.5)

Since a ventricular activation immediately follows the first non-blocked atrial impulse reaching the AV node, the PDF of the time between consecutive ventricular activations, denoted as $x$, is:

$$p_x(t_1) = p_x(x) = \lambda \beta(x) \left\{ - \int_0^x \lambda \beta(\tau) d\tau \right\}$$

(4.6)
Because of the existence of dual pathways, \( p_x(x) \) is composed by two components:

\[
p_x(x) = \alpha p_{x,1}(x) + (1 - \alpha) p_{x,2} \tag{4.7}
\]

Combining the time-dependent refractoriness function \( \beta(t) \) with the equation

\[
p_{x,i}(x) = \begin{cases} 
0 & \text{if } 0 < x < \tau_i \\
\frac{\lambda(x - \tau_i)}{\tau_p} \exp \left\{ -\frac{\lambda(x - \tau_i)^2}{2\tau_p} \right\} & \text{if } \tau_i \leq x < \tau_i + \tau_p \\
\lambda \exp \left\{ -\frac{\lambda \tau_p}{2} - \lambda(x - \tau_i - \tau_p) \right\} & \text{if } x \geq \tau_i + \tau_p
\end{cases} \tag{4.8}
\]

where \( x \) represents the RR interval. Using the property of statistical independence between consecutive ventricular activations declared in section 4.1.2, the joint probability function is given by:

\[
 p_x(x_1, x_2, \ldots, x_M) = \prod_{m=1}^{M} p_x(x_m) = \prod_{m=1}^{M} (\alpha p_{x,1}(x_m) + (1 - \alpha) p_{x,2}(x_m)) \tag{4.9}
\]

where \( p_{x,1}(x_m) \) and \( p_{x,2}(x_m) \) are obtained by the equation 4.8.

**Estimation**

The estimation of the arrival rate \( \lambda \) is determined independently of the model parameters that characterize the ventricular activity, by deriving the dominant AF frequency from the ECG. The atrial activity is extracted from the ECG using spatiotemporal QRST cancellation, after which the AF frequency is tracked on a short-term basis using a method based on a hidden Markov model. An estimate of \( \lambda \) is given by the median value of the AF frequency estimates computed over the analysed ECG segment length [2]. The estimation of the model parameters related to dual AV nodal pathways and refractory period prolongation contained in the vector:

\[
\theta = [\tau_1 \tau_2 \alpha \tau_{p1} \tau_{p2}] \tag{4.10}
\]

is conducted by jointly maximizing the log-likelihood function respect to \( \theta \) as following:

\[
\hat{\theta} = \arg \max_\theta \log p_x(x_1, x_2, \ldots, x_M | \theta; \lambda), \tag{4.11}
\]
with

\[
\log p_x(x_1, x_2, \ldots, x_M | \theta; \lambda) = \log \prod_{m=1}^{M} p_x(x_m | \theta; \lambda) \\
= \sum_{m=1}^{M} \log(\alpha p_{x,1}(x_m | \theta; \lambda) + (1 - \alpha)p_{x,2}(x_m | \theta; \lambda))
\]

(4.12)

Since no closed-form solution could be found for \( \hat{\theta} \), combined with the fact that the gradient is discontinuous, different optimization algorithms were explored to numerically optimize the log-likelihood function 4.12. The following optimization algorithms were explored:

1. the algorithm Nelder-Mead that finds the minimum of a scalar function of several variables, starting at the point \( x_0 \);
2. the algorithm ’simulated annealing’ is a probabilistic metaheuristic approach to find a good approximation to the global minimum of a given function in a large search space, see section 3.3.1;
3. the algorithm ’patternsearch’ that is a direct search method for solving non linear optimization problems, see section 3.3.2. Since the patternsearch has been found as the most fast computational algorithm, we decided to use it as optimization algorithm.

Some examples

By using the described AV node model, RR series can be simulated and the RR intervals histograms are created in order to understand the probability distribution of RR intervals of different lengths given a fixed set of parameters, see an example in Fig. 4.8. The purpose of the application of the AV node model was related to observe:

1. The graphical matching between the simulated RR intervals histogram and the theoretical PDF given the same set of parameters;
2. The graphical matching between the theoretical PDF and the PDF built through the estimated set of parameters.

Different parameters settings were used for the simulation summarized in the following:
4. Methods 49

Fig. 4.8: Simulated RR interval histogram during atrial fibrillation. Set parameters: 
\[ \lambda = 9.09 \text{ Hz}, \tau_1 = 0.1 \text{s}, \tau_2 = 0.4 \text{s}, \tau_{p1} = 0.1 \text{s}, \tau_{p2} = 0.15 \text{s}, \alpha = 0.7. \] Simulated time registration: 27 minutes.

1. \( \lambda \) is the arrival rate of atrial impulses to the AV node: \((5.5 \pm 1.5) \text{Hz}\);
2. \( \tau_1 = (0.2 \pm 0.03) \text{s} \) and \( \tau_2 = (0.3 \pm 0.1) \text{s} \);
3. \( \tau_{p1} = (0.08 \pm 0.1) \text{s} \) and \( \tau_{p2} = (0.11 \pm 0.04) \text{s} \);
4. \( \alpha \in [0 - 1] \);
5. \( nAI \) is the number of atrial impulses arriving at the AV node during the registration time \( t = \frac{nAI}{\lambda} \). The variation is from 7000 to 15000 impulses.

The obtained results show that there is a good overlapping between the simulated RR intervals histogram, the theoretical PDF and the estimated PDF, see Figs. 4.9 and 4.10, 4.11, 4.12.

The result obtained is that the PDF, created by the proposed model, follows correctly the histogram.

The main evidence underlined by the PDF is the bimodality characteristic due to the presence of dual AV nodal pathways. Fig. 4.13 shows how the PDF changes its shape when the estimated parameters \( \Delta \tau = (\tau_2 - \tau_1), \alpha, \lambda, \tau_{p1}, \tau_{p2} \) are modified. Improving \( \Delta \tau \) the second peak is shifted to rightside. If \( \Delta \tau \) is close to 0.1 s the two peaks are hardly distinguished, whereas the \( \alpha \) variation modifies the weight given to peaks. If \( \alpha \) is less than 0.5, the first peak is less emphasised, otherwise there would be the opposite behaviour.
4. Methods

Fig. 4.9: Comparison between the RR series histogram, the theoretical PDF and the experimental PDF. Set of parameters: \( \lambda = 6.25 Hz \), \( \tau_1 = 0.1 s \), \( \tau_2 = 0.2 s \), \( \tau_{p1} = 0.05 s \), \( \tau_{p2} = 0.1 s \), \( \alpha = 0.4 \); while the set of estimated parameters: 
\( \tau_1 = 0.1 s \), \( \tau_2 = 0.1981 s \), \( \tau_{p1} = 0.0466 s \), \( \tau_{p2} = 0.1041 s \), \( \alpha = 0.4214 \).

Fig. 4.10: Comparison between the RR series histogram, the theoretical PDF and the experimental PDF. Set of parameters: \( \lambda = 6.25 Hz \), \( \tau_1 = 0.1 s \), \( \tau_2 = 0.28 s \), \( \tau_{p1} = 0.05 s \), \( \tau_{p2} = 0.08 s \), \( \alpha = 0.2 \); while the set of estimated parameters: 
\( \tau_1 = 0.0988 s \), \( \tau_2 = 0.2790 s \), \( \tau_{p1} = 0.0496 s \), \( \tau_{p2} = 0.0817 s \), \( \alpha = 0.1854 \).
Fig. 4.11: (a) Comparison between the RR series histogram, the theoretical PDF and the experimental PDF. Set of parameters: $\lambda = 5.25\, Hz$, $\tau_1 = 0.1\, s$, $\tau_2 = 0.35\, s$, $\tau_{p1} = 0.05\, s$, $\tau_{p2} = 0.08\, s$, $\alpha = 0.8$; while the set of estimated parameters: $\tau_1 = 0.1010\, s$, $\tau_2 = 0.3569\, s$, $\tau_{p1} = 0.0455\, s$, $\tau_{p2} = 0.0694\, s$, $\alpha = 0.8087$.

Fig. 4.12: Comparison between the RR series histogram, the theoretical PDF and the experimental PDF. Set of parameters: $\lambda = 8.25\, Hz$, $\tau_1 = 0.15\, s$, $\tau_2 = 0.35\, s$, $\tau_{p1} = 0.05\, s$, $\tau_{p2} = 0.1\, s$, $\alpha = 0.6$; while the set of estimated parameters: $\tau_1 = 0.1497\, s$, $\tau_2 = 0.3498\, s$, $\tau_{p1} = 0.0496\, s$, $\tau_{p2} = 0.5969\, s$, $\alpha = 0.1854$. 
with $\alpha$ larger than 0.5. The extreme $\alpha$ values [0 1] produce the disappearance of one of two peaks. The AI frequency $\lambda$ is proportionally correlated to peaks height. Rising $\lambda$ the first peak is more affected to increase its value.

The last graph is showing different $\tau_p$ and $\tau_{p2}$ settings. The influence on PDF is evident by enlarging shape peaks.

**Fig. 4.13:** PDF for different $\Delta \tau$ (a), $\alpha$ (b), $\lambda$ (c), $\tau_p$ (d). In (d) each curve is represented for different settings of $\tau_p$: (i) $\tau_{p1} = 0.05s$ and $\tau_{p2} = 0.08s$; (ii) $\tau_{p1} = 0.08s$, $\tau_{p2} = 0.13s$; (iii) $\tau_{p1} = 0.12s$, $\tau_{p2} = 0.16$. Set parameters: $\tau_1 = 0.1s$, $\tau_2 = 0.34s$, $\alpha = 0.7$, $\lambda = 6.25Hz$, $\tau_{p1} = 0.1s$, $\tau_{p2} = 0.15s$. 
4.3 Modified model

The application of the Corino et al. model on real data generates a high variability of the estimated parameters during the 24-h ECG recordings, in particular regarding the probability $\alpha$.

The input probability splitting the atrial impulse between the slow pathway and the fast pathway was equal to the output probability to pass through either one of the two pathways. A modification of the model is here proposed, as shown in Fig. 4.14. The new model has a new parameter $\gamma$ that represents the probability of an impulse to arrive at the slow pathway. The probability of conduction, defined $\hat{\alpha}$, different from the input probability $\gamma$, is estimated from the model as the ratio between the number of atrial impulses passed through the slow pathway and the total number of atrial impulses passed through both the slow pathway and the fast pathway.

![Fig. 4.14: Modified model of AV node inserting the parameter $\gamma$ at the entrance to split the atrial impulses between the two pathways.](image)

The first part of the study has been conducted to understand the changes that have been brought by the new model in the RR intervals histogram. Using the same parameters settings for the Corino’s model and the so called $\gamma$-model, it is worth to notice a great difference in the shape of the RR intervals histogram, see Fig. 4.15. Hence the main problem is the impossibility to apply the same PDF built through the Corino’s model [see Eq. 4.8] on the histogram created by the $\gamma$-model, see Fig. 4.16.

In order to define the new PDF, an initial simplification was applied:

1. The prolongation times $\tau_{p1}$ and $\tau_{p2}$ were set equal to 0s;

2. The two histograms relative to the ventricular activations passed through the slow pathway and the fast pathway were studied separately.

Fig. 4.17 shows the RR histograms obtained using Corino’s model and $\gamma$-model, with the same parameters setting. A significant difference can be
4. Methods

Fig. 4.15: a) RR intervals histogram obtained by the Corino’s model with the set of parameters: \( \lambda = 6.25Hz, \tau_1 = 0.1s, \tau_2 = 0.28s, \tau_{p1} = 0.07, \tau_{p2} = 0.12s, \alpha = 0.64 \); b) RR intervals histogram obtained by the \( \gamma \)-model with the set of parameters: \( \lambda = 6.25Hz, \tau_1 = 0.1s, \tau_2 = 0.28s, \tau_{p1} = 0.07, \tau_{p2} = 0.12s, \hat{\alpha} = 0.64 \).

Fig. 4.16: Mismatching between the Corino’s model PDF and the RR intervals histogram generated by the \( \gamma \)-model.
4. Methods

Fig. 4.17: Comparison of RR intervals histogram created by (a) Corino’s model and (b) $\gamma$-model with the following parameters setting: $\tau_{p1} = 0s$, $\tau_{p2} = 0s$, $\lambda = 6.25Hz$, $\tau_1 = 0.1s$, $\tau_2 = 0.28s$, $\alpha = \hat{\alpha} = 0.64$.

noted in the two histograms. Figs. 4.18(a) and (Fig. 4.18(b)) represent the series of RR intervals using the two different models (Corino’s model and $\gamma$-model), whose non-blocked atrial impulses are passed only through the slow pathway.

The RR intervals histogram, represented in Fig. 4.18(b), appears to be

Fig. 4.18: a) Probability distribution of ventricular activations generated by non-blocked atrial impulses passed only through the slow pathway using (a) Corino’s model and (b) $\gamma$-model. Parameters setting: $\lambda = 6.25Hz$, $\tau_1 = 0.1s$, $\tau_2 = 0.28s$, $\tau_{p1} = 0s$, $\tau_{p2} = 0s$, $\alpha = \hat{\alpha} = 0.64$.

more extended and its amplitude is lower compared to the histogram in Fig.
4. Methods

Fig. 4.19: a) Probability distribution of ventricular activations generated by non-blocked atrial impulses passed only through the fast pathway using (a) Corino’s model and (b) $\gamma$-model. Parameters setting: $\lambda = 6.25 Hz$, $\tau_1 = 0.1 s$, $\tau_2 = 0.28 s$, $\tau_{p1} = 0 s$, $\tau_{p2} = 0 s$, $\alpha = \hat{\alpha} = 0.64$.

4.18(a). This observation means that the RR intervals of the new model along the slow pathway are longer than the previous model and the presence of a peak that accounts the most occurred RR interval is less evident.

The same procedure was applied on the fast pathway. Figs. 4.19(a), (b) represent the histograms of non-blocked atrial impulses that passed through the fast pathway using the Corino’s model and the $\gamma$-model. Unlike the slow pathway, the distribution of RR intervals between the Fig. 4.19(a) and the Fig. 4.19(b) appears very similar, thus the PDF $p_{x,1}$, calculated in Corino’s model (see Eq. 4.7), could fit the RR intervals histogram created by the $\gamma$-model.

As a confirmation of our hypothesis, we decided to apply the two PDF, calculated by the Corino’s model, $p_{x,1}$, $p_{x,2}$ (see Eq. 4.7) to the histograms of the new model representing respectively the slow pathway and the fast pathway, see Fig. 4.20(a) and 4.20(b). The PDF $p_{x,1}$ is not able to fit the respective histogram, while, as our hypothesis, the PDF $p_{x,2}$ has a good matching to the respective histogram. The first conclusion is that the PDF of impulses passing through the fast pathway is the same of Corino’s model.

The next step of our work was to find the new PDF describing the distribution of RR intervals passed through the slow pathway in the $\gamma$-model. For that reason we decided to understand the differences in RR interval generations between the two models. Starting from the Corino’s model in the hypothesis $\tau_{p1}$ and $\tau_{p2}$ equal to $0 s$, the function $\beta_i(t)$ that describes the respective
Fig. 4.20: a) Superimposition of the RR intervals histogram generated by (a) the $\gamma$-model and (b) Corino’s model with the PDF (solid line) generated by the previous model considering only the slow pathway. Parameters setting: $\lambda = 6.25Hz$, $\tau_1 = 0.1s$, $\tau_2 = 0.28s$, $\tau_{p1} = 0s$, $\tau_{p2} = 0s$, $\alpha = \hat{\alpha} = 0.64$.

Refractoriness of the slow and fast pathway is:

\[
\beta_1(t) = \begin{cases} 
0 & \text{if } 0 < t < \tau_1 \\
1 & \text{if } t \geq \tau_1
\end{cases} \quad (4.13)
\]

\[
\beta_2(t) = \begin{cases} 
0 & \text{if } 0 < t < \tau_2 \\
1 & \text{if } t \geq \tau_2
\end{cases} \quad (4.14)
\]

A graphical representation of the present model is described in Fig. 4.21. Assuming that the first atrial impulse $AI(1)$, arriving after a ventricular activation, chooses to take the slow pathway according to probability $\alpha$, all the following atrial impulses $AI(2)$ and $AI(3)$ take the same pathway. It means that the ratio between the number of atrial impulses taking the slow pathway and the total number of atrial impulses is equal to the ratio between the non-blocked atrial impulses passed through the slow pathway and the total non-blocked atrial impulses; thus the input probability is equal to the output probability. Therefore the two PDF can be considered independent, weighed for the probability $\alpha$ for the slow pathway and $(1 - \alpha)$ for the fast pathway. In the new model, the great difference is that the input probability $\gamma$ is responsible to split each atrial impulse. To better understand the new model, a graphical representation of the two pathways was created, see Fig. 4.22. It is possible to describe the single generation of ventricular activation:
4. Methods

Fig. 4.21: Graphical representation of Corino’s model for the generation of RR series.

Fig. 4.22: Graphical representation of γ-model for the generation of RR series.
1. \( t < \tau_1 \): The first two atrial impulses AI(1) and AI(2) cannot pass since the arrival time occurs during the slow and fast pathway refractory periods;

2. \( \tau_1 < t < \tau_2 \): The third atrial impulse AI(3) takes the fast pathway that is still not active \((\beta_2(t) = 0)\). Finally the fourth atrial impulse takes the slow pathway and arrives at \( t > \tau_1 \), so it is not blocked.

The study of the distribution of the atrial impulses arriving during the time window \([\tau_1 - \tau_2]\) becomes important to understand the generation of the single RR event. Therefore we consider the last atrial impulse AI(0) arriving along the time \( t < \tau_1 \), see Fig. 4.23. The first atrial impulse AI(1) arrives at

![Fig. 4.23: The atrial impulse AI(1) is the first atrial impulse arriving at \( t > \tau_1 \). The probability to pass through the slow pathway is signed with the symbol \( \times \), while the probability to be blocked is signed with symbol \( \circ \). The “tree” goes on every time the single atrial impulse is blocked.](image)

The probability to pass through the slow pathway is signed with the symbol \( \times \), while the probability to be blocked is signed with symbol \( \circ \). The “tree” goes on every time the single atrial impulse is blocked. Time \( t > \tau_1 \), and it has:

1. probability \( p = \gamma \) to take the slow pathway and to pass through the slow pathway and to become the next ventricular activation;

2. probability \( p = 1 - \gamma \) to take the fast pathway and to be blocked.

If the first atrial impulse AI(1) is not passed, the second atrial impulse AI(2) has:

1. probability \( p = (1 - \gamma)\gamma \) to take the slow pathway and to pass through the slow pathway and to become the next ventricular activation;

2. probability \( p = (1 - \gamma)^2 \) to take the fast pathway and to be blocked.
Hence the $n-AI$ atrial impulse will have:

1. probability $p = (1 - \gamma)^{n-1} \gamma$ to take the slow pathway and to pass through the slow pathway and to become the next ventricular activation;

2. probability $p = (1 - \gamma)^n$ to take the fast pathway and to be blocked.

So the probability of the single atrial impulse to pass through the slow pathway during the time window $[\tau_1 - \tau_2]$ is:

$$p(AI(n)) = \gamma(1 - \gamma)^{n-1}$$ (4.15)

Since a ventricular activation follows immediately the passed atrial impulse, the Eq. 4.15 describes the probability distribution of the single ventricular activation to pass during $[\tau_1 - \tau_2]$.

If we extend the study to a registration time $T$, it is possible to define the probability distribution of RR intervals that fall in the time window $[\tau_1 - \tau_2]$. Defined $n$ as the number of atrial impulses arriving during the time window $[\tau_1 - \tau_2]$ with frequency equal to $\lambda$, and $k$ as the number of atrial impulses passing through the slow pathway, the RR intervals that pass through the slow pathway are distributed according to the binomial probability $B(n, \gamma)$:

$$P(k) = \binom{n}{k} \gamma^k (1 - \gamma)^{n-k}$$ (4.16)

Under the hypothesis of large $n$ ($n \geq 100$), it is possible to consider the limit of the binomial distribution as a Poisson process $P(\lambda \gamma)$. Considering that the number of atrial impulses occurs along the registration time $T$, it is possible to insert the mean arrival rate $\lambda = \frac{n}{T}$ for which the Poisson process is $P(\lambda \gamma)$.

If the atrial impulse arrives at the $AV$ node along time $t > \tau_2$ similar considerations to the Corino’s model must be done. Both the functions of refractoriness $\beta_1(t)$ and $\beta_2(t)$ are set to 1. Therefore, all the atrial impulses $n_{AI}$ arriving at time $t > \tau_2$ become ventricular activations, and the probability to take the slow pathway is equal to the probability to pass through the same pathway equal to $\hat{\alpha}$, whereas $1 - \hat{\alpha}$ is the probability to pass through the fast pathway equal to the probability to take the fast pathway itself.

The PDF $p_x(x)$ that describes the whole model is still influenced by the dual nature of AV node:

$$p_x(x) = \hat{\alpha} p_{x,1} + (1 - \hat{\alpha}) p_{x,2}$$ (4.17)

where $p_{x,1}$ is the PDF regarding the slow pathway and the $p_{x,2}$ the PDF regarding the fast pathway. The PDF $p_{x,1}$ is composed by two inhomogeneous Poisson process with different intensity function:
Fig. 4.24: Superimposition of RR histogram generated by the \( \gamma \)-model and the PDF calculated in Eq. 4.20 considering only the slow pathway, using the parameters setting: \( \lambda = 6.25 \text{Hz}, \tau_1 = 0.1s, \tau_2 = 0.28s, \tau_{p1} = 0s, \tau_{p2} = 0s, \hat{\alpha} = 0.64. \)

1. \( \lambda \gamma \beta_1(t) \) if \( \tau_1 < t < \tau_2; \)

2. \( \lambda \beta_1(t) \) if \( t \geq \tau_2. \)

where \( \beta_1(t) \) is the same described in Eq. 4.13. Hence the \( p_{x,1} \) is given by:

\[
p_{x,1}(x) = \begin{cases} 
0 & \text{if } 0 < x < \tau_1 \\
\lambda \gamma \exp \{ -\lambda \gamma (x - \tau_1) \} & \text{if } \tau_1 \leq x < \tau_2 \\
\lambda \exp \{ -\lambda \gamma (\tau_2 - \tau_1) - \lambda (x - \tau_2) \} & \text{if } x \geq \tau_2
\end{cases} \tag{4.18}
\]

under the hypothesis of \( \tau_{p1} \) and \( \tau_{p2} \) equal to 0. In Fig. 4.24 the good matching of the new computation of PDF on the RR histogram generated by the \( \gamma \)-model is represented, considering only the slow pathway.

Regarding the fast pathway the function \( \beta_2(t) \) is the same in Eq. 4.14. Considering the Eq. 4.6, it is possible to write the modified PDF, under the hypothesis of \( \tau_{p1} = \tau_{p2} = 0s \), for the fast pathway:

\[
p_{x,2}(x) = \begin{cases} 
0 & \text{if } 0 < x < \tau_2 \\
\lambda \exp \{ -\lambda (x - \tau_2) \} & \text{if } x \geq \tau_2
\end{cases} \tag{4.19}
\]
The result of the calculated PDF $p_x(x)$ is shown in Fig. 4.25.

The second step regarded the insertion of prolongation periods $\tau_{p1}$ and $\tau_{p2}$.

**Fig. 4.25**: Superimposition of RR intervals histogram generated by the $\gamma$-model considering both the slow pathway and fast pathway, and the built PDF according to the Eq. 4.17. Parameters setting: $\lambda = 6.25 HZ$, $\tau_1 = 0.1 s$, $\tau_2 = 0.28 s$, $\tau_{p1} = 0 s$, $\tau_{p2} = 0 s$, $\hat{\alpha} = 0.64$.

In Fig. 4.26 a graphical representation has been introduced to clarify the model. During the time window $[\tau_1 - \tau_2]$, the probability of passing through the slow pathway by the atrial impulse through the slow pathway is split in two events:

1. Zone A: $\tau_1 < t < \tau_1 + \tau_{p1}$. The probability to pass increases linearly according to the function $p_{1,A} = \frac{t - \tau_1}{\tau_{p1}}$;

2. Zone B: $\tau_1 + \tau_{p1} \leq t < \tau_2$. The probability to pass is equal to 1.

Both events occur according to an inhomogeneous Poisson process with intensity $\lambda \gamma \beta_1(t)$, where $\beta_1(t)$ is the same described in Eq. 4.4. The PDF
4. Methods

*Fig. 4.26:* Graphical representation of $\gamma$-model inserting the refractory periods $\tau_1$, $\tau_2$ and the respective prolongation times $\tau_{p1}$ and $\tau_{p2}$.

$p_{x,1}(x)$ of the slow pathway is so modified:

$$p_{x,1}(x) = \begin{cases} 
0 & \text{if } 0 < x < \tau_1 \\
\lambda \gamma \frac{(t - \tau_1)}{\tau_{p1}} \exp \left\{ -\lambda \gamma \frac{(x - \tau_1)^2}{2 \tau_{p1}} \right\} & \text{if } \tau_1 \leq x < \tau_1 + \tau_{p1} \\
\lambda \gamma \exp \left\{ -\frac{\lambda \gamma \tau_{p1}}{2} - \lambda \gamma (x - \tau_1 - \tau_{p1}) \right\} & \text{if } \tau_1 + \tau_{p1} \leq x < \tau_2 \\
\lambda \gamma \exp \left\{ -\lambda \gamma (\tau_2 - \tau_1) - \lambda (x - \tau_2) \right\} & \text{if } x \geq \tau_2 
\end{cases}$$

(4.20)

Regarding the fast pathway, the PDF $p_{x,2}(x)$ is the same of equation 4.8 described in Corino’s model section. By using the equation 4.17 the PDF $p_x(x)$ has been overlapped on the RR intervals histogram created by the $\gamma$-model, and a good matching has been noticed, see Fig. 4.27.

The research of the relationship between the output probability $\hat{\alpha}$ and the input probability $\gamma$ becomes important for two main reasons:

1. The previous model generates unstable $\alpha$ estimations on real data. Our hypothesis is that the probability $\gamma$ represents the probability of arriving at the slow pathway;

2. The $\gamma$-model estimates the RR histogram using the parameter vector $\theta = [\tau_1 \ \tau_2 \ \tau_{p1} \ \tau_{p2} \ \hat{\alpha}]$. However it is necessary the $\gamma$ estimation to calculate the PDF $p_{x,1}$ of the slow pathway.

Therefore, the relationship between $\alpha$ and $\gamma$ let to estimate $\gamma$ known $\hat{\alpha}$. The section of Results investigates the trend of $\gamma$ depending on $\hat{\alpha}$. 
Fig. 4.27: Superimposition of RR intervals histogram generated by the $\gamma$-model and the built PDF according to the Eq. 4.17. Parameters setting: $\lambda = 6.25 Hz$, $\tau_1 = 0.1s$, $\tau_2 = 0.28s$, $\tau_{p1} = 0.07s$, $\tau_{p2} = 0.12s$, $\hat{\alpha} = 0.81$. 
Chapter 5

Results

This chapter presents: i) the experimental study of $\hat{\alpha}$ trend depending on the input parameters; ii) the analysis of the experimental law, followed by the confirmation of the equation by studying the mean absolute error and the root mean square error; iii) the inversion of the law and its application on real data.

5.1 Simulation

Different parameters settings were used to simulate RR-series, see Tab. 5.1. For each parameters setting, a 30 min RR interval series was simulated. The parameter $\lambda$ was incremented with 0.5 Hz step, the step-size of $\Delta \tau$ and $\Delta \tau_p$ was 0.01 s, and the probability $\gamma$ varied with 0.1 step.

<table>
<thead>
<tr>
<th>Inputs</th>
<th>Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda$</td>
<td>5 – 10 [Hz]</td>
</tr>
<tr>
<td>$\Delta \tau$</td>
<td>0 – 0.5 [s]</td>
</tr>
<tr>
<td>$\Delta \tau_p$</td>
<td>0 – 0.2 [s]</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0 – 1</td>
</tr>
</tbody>
</table>

*Tab. 5.1: Set of parameters used in the simulation*

5.1.1 Data Exploration

To study the relationship between $\hat{\alpha}$ and $\gamma$, a simplification was adopted, defining:

1. $\Delta \tau = \tau_2 - \tau_1 > 0s$ is the difference between the fast pathway with longer refractory period and the slow pathway with shorter refractory period;
\[ \Delta \tau_p = \tau_{p2} - \tau_{p1} \] as difference between the two prolongations. Since the prolongation time \( \tau_p \) indicates the concealed conduction phenomenon, both conditions \( \tau_{p1} < \tau_{p2}, \tau_{p2} < \tau_{p1} \) are possible, hence \( \Delta \tau_p \) can be either \( > 0 \text{s} \) or \( < 0 \text{s} \).

The choice of the above mentioned parameters was done to reduce the number of influencing parameters, thus it was studied only the variation due to the difference between the two refractory periods and the respective prolongations. Besides the two differences enhance the dependence between the two pathways. In the following paragraphs the trend of \( \hat{\alpha} \) is shown depending on two parameters and fixing the other ones.

**Trend of \( \hat{\alpha} \) depending on \( \gamma \) and \( \Delta \tau \)**

The parameter \( \lambda \) is kept constant and \( \Delta \tau_p = 0 \text{s} \) while varying \( \gamma \) and \( \Delta \tau \).

The mathematical function that describes the relative refractoriness of the \( i \)th pathway can be simplified to:

\[
\beta_i(t) = \begin{cases} 
0 & \text{if } 0 < t < \tau_i \\
1 & \text{if } t \geq \tau_i 
\end{cases} \quad (5.1)
\]

In Fig. 5.1(a) each curve represents the variation of \( \hat{\alpha} \) fixing \( \Delta \tau \) for different \( \gamma \) values, while in Fig. 5.1(b) the parameter \( \hat{\alpha} \) has been studied depending on \( \Delta \tau \) and each curve indicates a different fixed \( \gamma \) parameter. From the graphs it is worth noticing that:

1. \( \hat{\alpha} \) increases with \( \gamma \) (see Fig. 5.1(a)), because increasing the probability to choose the slow pathway, a greater number of atrial impulses passes through the same one, increasing \( \hat{\alpha} \);

2. increasing \( \Delta \tau \) the curve will be shifted towards higher values of \( \hat{\alpha} \) (Fig. 5.1(a)). The explanation is intuitive: in the time window \([\tau_1 - \tau_2]\), the time-dependent refractoriness of the slow pathway \( \beta_1(t) = 1 \), while for the fast pathway \( \beta_2(t) = 0 \). Hence the atrial impulse can pass through the slow pathway, whereas it is blocked in the fast pathway. Therefore, increasing the difference \( \Delta \tau \), the probability \( \hat{\alpha} \) of the atrial impulse to pass through the slow pathway increases, as can be observed in Fig. 5.1(b) too.

Regarding the Fig. 5.1(a): (1) focusing on curves with \( \Delta \tau > 0 \text{s} \) an exponential relationship between \( \hat{\alpha} \) and \( \gamma \) is observed; (2) the asymptotic value 1 assumed
5. Results

by the parameter $\hat{\alpha}$ corresponds to the maximum value of $\gamma$.
In Fig.5.1(b) it is evident that for the initial value $\Delta \tau = 0s$ the parameter $\hat{\alpha}$ is equal to the input parameter $\gamma$, because the two functions $\beta_1(t)$ and $\beta_2(t)$ are characterised by the same parameters, so the probability to be conducted by one of the two pathway is the same to the probability to choose one of them.

Fig. 5.1: (a)Trend of $\hat{\alpha}$ for different values of $\gamma$ when $\lambda = 8.77Hz$, $\Delta \tau_p = 0s$ and $\Delta \tau = [0-0.4]s$; (b) trend of $\hat{\alpha}$ for different values of $\Delta \tau$ when $\lambda = 8.77Hz$, $\Delta \tau_p = 0s$ and $\gamma = [0.1 - 0.9]$.

Trend of $\hat{\alpha}$ depending on $\gamma$ and $\Delta \tau_p$

Establishing $\Delta \tau = 0s$ and fixing $\lambda$, $\Delta \tau_p$ was inserted (studying the condition $\tau_{p2} > \tau_{p1}$). The probability function $\beta_i(t)$ that describes the respectively refractoriness period of slow/fast pathway is thus modified:

$$\beta_i(t) = \begin{cases} 
0 & \text{if } 0 < t < \tau_i \\
\frac{t}{\tau_{pi}} & \text{if } \tau_i \leq t < \tau_i + \tau_{pi} \\
1 & \text{if } t \geq \tau_i + \tau_{pi}
\end{cases} \tag{5.2}$$

In the Fig. 5.2(a) different curves of $\hat{\alpha}$ depending on $\gamma$ for different values of $\Delta \tau_p$ are shown, while in Fig. 5.2(b) the trend of $\hat{\alpha}$ is represented varying $\Delta \tau_p$ and each trend is shown changing $\gamma$.

The observations are similar to the previous section:

1. $\hat{\alpha}$ increases with $\gamma$ (see Fig. 5.2(a)), because increasing the probability to choose the slow pathway, a greater number of atrial impulses pass through the same one, increasing $\hat{\alpha}$;

2. increasing $\Delta \tau_p$ the curve will be shifted towards higher values of $\hat{\alpha}$ (Fig. 5.2(a)). In the time window between $\tau_{p1}$ and $\tau_{p2}$, the probability
\( \beta_1(t) \) is equal to 1, while for the fast pathway \( \beta_2(t) \) is inferior to 1. Hence the atrial impulse can pass through the slow pathway, whereas it is blocked in the fast pathway. Therefore, increasing the difference \( \Delta \tau_p \), the probability \( \hat{\alpha} \) of the atrial impulse to pass through the slow pathway increases, as can be observed in Fig. 5.2(b) too. However in Fig. 5.2(b) \( \hat{\alpha} \) trend looks less influenced by the parameter \( \Delta \tau_p \) compared to \( \Delta \tau \). During the interval \([\tau_{p1} - \tau_{p2}]\), \( \beta_1(t) = 1 \), but \( \beta_2(t) \) is not equal to 0, so there is a probability equal to \( \frac{t}{\tau_{pi}} \) that the atrial impulse could pass from the fast pathway. Therefore the probability \( \hat{\alpha} \) is less altered by \( \Delta \tau_p \) compared to the dependence on \( \Delta \tau \).

Fig. 5.2: (a) Trend of \( \hat{\alpha} \) for different values of \( \gamma \) when \( \lambda = 8.77Hz \), \( \Delta \tau = 0s \) and \( \Delta \tau_p = [0 - 0.21]s \). (b) Trend of \( \hat{\alpha} \) for different values of \( \Delta \tau_p \) when \( \lambda = 8.77Hz \), \( \Delta \tau = 0s \) and \( \gamma = [0.1 - 0.9] \).

Trend of \( \hat{\alpha} \) depending on \( \gamma \) and \( \lambda \)

The last analysis regards the dependency of \( \hat{\alpha} \) on the occurrence frequency of atrial impulses \( \lambda \), setting to fixed value \( \Delta \tau \) and \( \Delta \tau_p = 0s \). In Fig. 5.3 \( \hat{\alpha} \) increases with \( \lambda \) because the interval time among the atrial impulses is getting lower, so the probability of a single atrial impulse to fall in the interval \([\tau_1 - \tau_2]\) increases.

5.1.2 Relationship between \( \gamma \) and \( \hat{\alpha} \)

The research of the relationship between the "theoretical" \( \bar{\alpha} \) and \( \gamma \) has been conducted by using Minimum Least Squares (MLS) algorithm, so that the whole analysis has been established following the next steps:
5. Results

Fig. 5.3: Each curve is $\hat{\alpha}$ trend depending on $\lambda$ when $\Delta \tau = 0.17s$ $\Delta \tau_p = 0s$ and $\gamma = [0.1 - 0.9]$.

1. Assumption of exponential equation, which has been suggest by the different trends studied in the Sec 5.1.1;

2. Introducing limits $0 < \tilde{\alpha} < 1$ because $\tilde{\alpha}$ is a probability;

3. Setting bounds for the refractory periods $\tau_1$, $\tau_2$ and the respective prolongations $\tau_{p1}$ and $\tau_{p2}$ to the physiological range as shown in Sec 5.1;

4. Analysis of estimated coefficients obtained using the MLS.

Depending on $\Delta \tau$ and setting $\Delta \tau_p = 0$ to simplify the study, we have suggested an exponential law for the description of the counted $\hat{\alpha}$ trend depending on the time $\Delta \tau$, see Fig. 5.1(a):

$$\tilde{\alpha}(\Delta \tau, A, B | \Delta \tau_p = 0) = 1 - Ae^{-B\Delta \tau}$$

(5.3)

where $\tilde{\alpha}$ is the estimation of the probability $\hat{\alpha}$, while $A$ and $B$ represent the coefficients that are estimated by MLS see Tab. 5.2. As mentioned in point 2), it has been inserted the asymptote 1 to which $\tilde{\alpha}$ can converge. The parameter $A$ is easily solved. Enforcing $\Delta \tau = 0$, it was pointed out in sec 5.1.1 that the output parameter is equal to the input one, so:

$$\tilde{\alpha}(\Delta \tau = 0) = \gamma = 1 - A;$$

$$A = 1 - \gamma$$

(5.4)

so the parameter $A$ is the complementary of $\gamma$.

In Fig. 5.4(a) a negative correlation between the parameter $A$, obtained by
<table>
<thead>
<tr>
<th>Set parameter</th>
<th>A</th>
<th>B</th>
<th>1 − γ</th>
<th>λγ</th>
</tr>
</thead>
<tbody>
<tr>
<td>γ = 0.2, λ = 10.67 Hz, Δτ = 0.2</td>
<td>0.7891</td>
<td>2.1240</td>
<td>0.8</td>
<td>2.1349</td>
</tr>
<tr>
<td>γ = 0.2, λ = 7.43 Hz, Δτ = 0.2</td>
<td>0.7993</td>
<td>1.4863</td>
<td>0.8</td>
<td>1.4869</td>
</tr>
<tr>
<td>γ = 0.2, λ = 5.51 Hz, Δτ = 0.2</td>
<td>0.7992</td>
<td>1.0304</td>
<td>0.8</td>
<td>1.1020</td>
</tr>
<tr>
<td>γ = 0.5, λ = 10.67 Hz, Δτ = 0.2</td>
<td>0.5004</td>
<td>5.3237</td>
<td>0.5</td>
<td>5.3374</td>
</tr>
<tr>
<td>γ = 0.5, λ = 7.43 Hz, Δτ = 0.2</td>
<td>0.4953</td>
<td>3.700</td>
<td>0.5</td>
<td>3.7174</td>
</tr>
<tr>
<td>γ = 0.5, λ = 5.51 Hz, Δτ = 0.2</td>
<td>0.5027</td>
<td>2.7294</td>
<td>0.5</td>
<td>2.7550</td>
</tr>
<tr>
<td>γ = 0.7, λ = 10.67 Hz, Δτ = 0.2</td>
<td>0.2992</td>
<td>7.4702</td>
<td>0.3</td>
<td>7.4690</td>
</tr>
<tr>
<td>γ = 0.7, λ = 7.43 Hz, Δτ = 0.2</td>
<td>0.2980</td>
<td>5.1575</td>
<td>0.3</td>
<td>5.2010</td>
</tr>
<tr>
<td>γ = 0.7, λ = 5.51 Hz, Δτ = 0.2</td>
<td>0.3033</td>
<td>3.9263</td>
<td>0.3</td>
<td>3.8570</td>
</tr>
</tbody>
</table>

Tab. 5.2: Estimation of the parameters $A$ and $B$ by using the MLS, for different set of parameters $γ$, $λ$, $Δτ$. 
5. Results

Fig. 5.4: Scatter plot of (a) parameter $A$ and (b) parameter $B$, depending on respectively the parameter $\gamma$ and the product of $\lambda \gamma$, fixing $\Delta \tau_p = 0$. In (a) the parameter $A$ is the complementary of the input parameter $\gamma$; in (b) there is a positive correlation between the parameter $B$ and the frequency with which the atrial impulses arrives to the slow pathway.

MLS algorithm, and the independent variable $\gamma$ has been discovered. This is a confirmation of the eq. 5.4. Regarding the parameter $B$, a positive correlation has been found with the mean arrival rate $\lambda \gamma$ of atrial impulses that enter in the slow pathway, see Fig. 5.4(b). Therefore the equation is:

$$\tilde{\alpha}(\gamma, \Delta \tau, \lambda | \Delta \tau_p = 0) = 1 - \left[ (1 - \gamma)e^{-\lambda \gamma \Delta \tau} \right]$$

(5.5)

The following step has been to consider the elongation times ($\Delta \tau_p \neq 0$), reproducing the same procedure and setting in this case $\Delta \tau = 0$. Since the obtained trend between the counted $\tilde{\alpha}$ and $\gamma$ looks still an exponential (see Fig. 5.2), it has been used the same structure of the equation 5.5, changing only the exponential argument. Setting the equation:

$$\tilde{\alpha}(\gamma, \Delta \tau_p, \lambda | \Delta \tau = 0) = 1 - \left[ (1 - \gamma)e^{-\lambda \gamma C \Delta \tau_p} \right]$$

(5.6)

$C$ was obtained by MLS, varying the variables $\gamma$, $\Delta \tau_p$ and $\lambda$. In our opinion the parameter $C$ is a weighing parameter of $\Delta \tau_p$, that is obtained as the average of different $C$ values depending on $\gamma$ and $\lambda$, see Fig. 5.5. The average calculated is equal to 0.5.

To complete the relationship between $\tilde{\alpha}$ and $\gamma$, the influence of the parameter
\[ \Delta \tau_p \] was added to the refractory period \( \Delta \tau \), leading to:

\[
\bar{\alpha}(\gamma, \Delta \tau, \Delta \tau_p, \lambda) = 1 - \left[ (1 - \gamma) e^{-\lambda \gamma \frac{\Delta \tau + \Delta \tau_p}{2}} \right]
\]

Fig. 5.5: The graphic representation of \( C \) depending on \( \gamma \) (a) and \( \lambda \) (b), referred to the equation 5.6, studied for different values of \( \gamma \) and \( \lambda \), establishing \( \Delta \tau = 0 \). Both curves in (a) and (b) have the same random behaviour; in (a) each curve represents a different \( \lambda \); in (b) each curve represents a different \( \gamma \).

5.1.3 Simulation Results

Recalling the relationship between \( \bar{\alpha} \) and \( \gamma \):

\[
\hat{\alpha} = 1 - \left[ (1 - \gamma) e^{-\lambda \gamma \frac{\Delta \tau + \Delta \tau_p}{2}} \right]
\]

Figs. 5.6 and 5.7 show the comparison between the derived probability of \( \bar{\alpha} \) obtained using above equation and the actual \( \hat{\alpha} \) obtained in the simulations, as a function of \( \Delta \tau \) and \( \Delta \tau_p \), respectively. It can be noted that the actual trend of \( \hat{\alpha} \) follows the derived \( \bar{\alpha} \).

The mean absolute error (MAE, Eq. 5.8) and the RMSE (Root Mean Square Error, Eq. 5.9) were calculated to confirm our result, which are shown in Tab. 5.3. We used both in order to analyse the variation in the errors in a set of estimations. Indeed, MAE is an average magnitude without considering their direction, evaluating the accuracy of the measurement, while RMSE is
5. Results

Fig. 5.6: Trends of the derived $\tilde{\alpha}$ (dashed lines) and actual $\hat{\alpha}$ (solid lines) depending on the difference between the two prolongation times ($\Delta \tau_p$). Each curve corresponds to a different value of $\gamma$ that was varied from 0.1 to 0.9.

Fig. 5.7: Trends of the derived $\tilde{\alpha}$ (dashed lines) and actual $\hat{\alpha}$ (solid lines) depending on the difference between the two refractory periods ($\Delta \tau$). Each curve corresponds to a different value of $\gamma$ that was varied from 0.1 to 0.9.
5. Results

<table>
<thead>
<tr>
<th>$\gamma$</th>
<th>$MAE$</th>
<th>$RMSE$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0029 ± 0.0005</td>
<td>0.0000 ± 0.00000</td>
</tr>
<tr>
<td>0.1</td>
<td>0.0033 ± 0.0005</td>
<td>0.0422 ± 0.00752</td>
</tr>
<tr>
<td>0.2</td>
<td>0.0031 ± 0.0006</td>
<td>0.0493 ± 0.00958</td>
</tr>
<tr>
<td>0.3</td>
<td>0.0033 ± 0.0007</td>
<td>0.0487 ± 0.00930</td>
</tr>
<tr>
<td>0.4</td>
<td>0.0035 ± 0.0007</td>
<td>0.0451 ± 0.00850</td>
</tr>
<tr>
<td>0.5</td>
<td>0.0047 ± 0.0008</td>
<td>0.0397 ± 0.0069</td>
</tr>
<tr>
<td>0.6</td>
<td>0.0038 ± 0.0008</td>
<td>0.0328 ± 0.0049</td>
</tr>
<tr>
<td>0.7</td>
<td>0.0038 ± 0.0009</td>
<td>0.0257 ± 0.0009</td>
</tr>
<tr>
<td>0.8</td>
<td>0.0045 ± 0.0010</td>
<td>0.0186 ± 0.0018</td>
</tr>
<tr>
<td>0.9</td>
<td>0.0045 ± 0.0011</td>
<td>0.0111 ± 0.0006</td>
</tr>
<tr>
<td>1.0</td>
<td>0.0045 ± 0.0013</td>
<td>0.0000 ± 0.00000</td>
</tr>
</tbody>
</table>

Tab. 5.3: Absolute error and RMSE between the $\tilde{\alpha}$ obtained using Eq. 5.7 and the actual value $\alpha$.

a quadratic scoring rule which measures the average magnitude of the error. Since the errors are squared before they are averaged, the RMSE gives a relatively high weight to large errors. This means the RMSE is most useful when large errors are particularly undesirable.

$$MAE = \frac{\sum_{i=1}^{m} |\hat{\alpha}_i - \tilde{\alpha}_i|}{m}$$ \hspace{1cm} (5.8)

$$RMSE = \sqrt{\frac{\sum_{i=1}^{m} (\hat{\alpha}_i - \tilde{\alpha}_i)^2}{m}}$$ \hspace{1cm} (5.9)

Below the two index of errors are shown:

$$\bar{MAE} = (3.8 \pm 0.8202) \times 10^{-3}$$

$$\bar{RMSE} = (1.59 \pm 0.87) \times 10^{-2}$$

5.1.4 Inversion

Since the purpose of the thesis is to calculate the parameter $\gamma$, it is necessary to invert the equation 5.7 in order to study $\gamma$ depending on the parameters.
In order to invert, it is necessary to refer to the Lambert function, defined in Sec 3.4 as the multivalued inverse of the function:

\[ y = f(W) = W(x)e^{W(x)} \]  

(5.10)

As described in sec. 3.4, the Lambert function has two branches; in this study we used the principal branch \((W_0(x))\) for which \(W(x) \geq -1\). To invert Eq. 5.7 it is fundamental to arrive at the simplified form 5.10.

Assuming:

\[ z = 1 - \gamma; \Delta T = \Delta \tau + \frac{\Delta \tau_p}{2} \]

the equation will be:

\[ \tilde{\alpha} = 1 - ze^{-\lambda(1-z)\Delta T} \]  

(5.11)

Bringing the parameters non-dependent from \(z\) to the left side of the equation:

\[ \tilde{\alpha}' = ze^{\lambda z \Delta T} \]

where \(\tilde{\alpha}' = (1 - \tilde{\alpha})e^{(\lambda \Delta T)}\). Changing the base \(b = e^{(\lambda \Delta T)}\) it is possible to arrive to the compact form similar to the (1.2):

\[ \tilde{\alpha}' = zb^z \]  

(5.12)

Using the Lambert function property described in the article [42] the solution \(z\) is:

\[ z = W(\tilde{\alpha}') \]

if the base of the exponential \(b \equiv e\). However in this case \(b \not\equiv e\), so it needs to use the property described in [42], for which:

\[ z = \frac{W(\tilde{\alpha}' \log(b))}{\log(b)} \]

So, the final equation is:

\[ z = 1 - \gamma = \frac{W((1 - \tilde{\alpha})e^{(\lambda \Delta T)} \log(e^{(\lambda \Delta T)}))}{\log(e^{\lambda \Delta T})} \]

\[ \gamma = 1 - \frac{W((1 - \tilde{\alpha})\lambda \Delta Te^{(\lambda \Delta T)})}{\lambda \Delta T} \]  

(5.13)

In Fig. 5.8 the graphical dependence between the input and output probability is represented. In Fig. 5.8(a) it is shown the dependence of \(\tilde{\alpha}\), obtained by the eq. 5.7, on \(\gamma\), whereas in Fig. 5.8(b) the dependence between \(\gamma\), obtained by the inverted eq. 5.13, and the estimated \(\tilde{\alpha}\).
5. Results

(a) Fig. a

(b) Fig. b

Fig. 5.8: (a) Estimated $\tilde{\alpha}$ depending on $\gamma$; (b) estimated $\gamma$ through the inverted eq. 5.13, depending on $\tilde{\alpha}$. Parameter setting common for both graphs: $\Delta \tau = 0.2s$, $\Delta \tau_p = 0.07s$, $\lambda = 8.57Hz$

5.2 Real data

Data collected in the RATe control in Atrial Fibrillation (RATAF) study were analyzed in this work. The RATAF study was a prospective, randomized, investigator-blind, crossover study designed to compare four drug regimens (metoprolol, diltiazem, verapamil, and carvedilol) used to reduce the ventricular heart rate in patients with permanent AF. Each drug was given for more than three weeks to ensure an adequate period of washout of the previous treatment and steady-state plasma concentrations. Before starting the first treatment and at the last day of each of the 4 treatment periods, 24-h Holter recordings were made. The regional ethics committee and the Norwegian medicines agency approved the study, registered at www.clinicaltrials.gov (clinical trial no. NCT00313157) and conducted in accordance with the Helsinki Declaration. Each patient provided written informed consent before any study-related procedures were performed. The clinical characteristics of the patients are shown in Table 5.4. Data analysis was conducted on those patients which recordings have sufficient quality along the 24h. Therefore, the analysis was carried out on 31 patients, containing 155 recordings.

Starting by the following formula:

$$\gamma = 1 - \frac{W((1 - \tilde{\alpha})\lambda \Delta T \exp(\lambda \Delta T))}{\lambda \Delta T}$$

The probability of $\gamma$ has been calculated applying the above formula on es-
5. Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>42/18</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 ± 9</td>
</tr>
<tr>
<td>AP duration (months)</td>
<td>11(2 − 121)</td>
</tr>
<tr>
<td>BMI</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25</td>
</tr>
</tbody>
</table>

*Tab. 5.4: Demographic characteristics and cardiovascular history in the study population*

Estimations realized by the model, so that a comparison between $\alpha$ and $\gamma$ was possible.

5.2.1 Real data results

The first part of the analysis has regarded the calculation of the mean and standard deviation values of $\alpha$ and $\gamma$, respectively $\sigma_\alpha$ and $\sigma_\gamma$. It has been found that $\sigma_\gamma$ is resulted lower than $\sigma_\alpha$ in 58% of the analysed recordings. It is important to have an understanding of the values as a whole, hence it has been calculated the mean values assumed respectively by $\alpha$ and $\gamma$.

$$\bar{\sigma}_\alpha = 0.1857$$
$$\bar{\sigma}_\gamma = 0.1813$$

In order to assess the difference between $\alpha$ and $\gamma$, it has been carried out t-test on $\sigma_\gamma$ and $\sigma_\alpha$ for all recordings, which has confirmed the non-significant difference between $\alpha$ and $\gamma$. Indeed, the $\sigma_\gamma$ presents approximately the same value of $\sigma_\alpha$.

It is now interesting to show some example which enhances the difference between $\alpha$ and $\gamma$ and behaviour. For this purpose two patients are exposed. The Figs. 5.9 and 5.10 show as $\gamma$ gives a better result in terms of interquartile range, and confirm the usual lower values of $\gamma$, according to Eq. 5.7. The two boxplots show on right the probability of $\alpha$ while on the left the probability of $\gamma$. Deepening the analysis, the superimposition between $\alpha$ and the derived $\gamma$ (Figs.5.11 and 5.12) shows an expected results, according to the $\alpha$ and $\gamma$ standard deviations. Indeed, the two behaviours have almost the same trend, $\gamma$ follows $\alpha$. This similar tendency between $\alpha$ and $\gamma$ is explained mainly by the presence of a small $\Delta \tau$, indeed if $\Delta \tau \approx 0$ and $\Delta \tau_p \approx 0$, then $\alpha = \gamma$.

Substantially $\gamma$ trend is characterised by a lower value, which is explainable observing the Fig. 5.8 that show the tendency of $\gamma$ to have a smaller than $\alpha$. 

Fig. 5.9: Patient 1: comparison $\alpha$ (a) and $\gamma$ (b) for each treatment.

Fig. 5.10: Patient 2: comparison $\alpha$ (a) and $\gamma$ (b) for each treatment.
Fig. 5.11: Patient 1: Superimposition of $\alpha$ (solid line) and $\gamma$ (thick line) during baseline (a), and Metoprolol (b), Diliziasem (c), Verapamil (d), Carvedilol (e) treatments.

Fig. 5.12: Patient 2: Superimposition of $\alpha$ (solid line) and $\gamma$ (thick line) during baseline (a), and Metoprolol (b), Diliziasem (c), Verapamil (d), Carvedilol (e) treatments.
This is due to atrial impulses enter preferentially into the slow pathway, which is characterised by lower refractory period facilitating the passing of atrial impulses into slow pathway, increasing $\alpha$, see Fig. 4.14. Instead, referring to Eq. 5.6, $\Delta \tau_p$ value is weighted by a constant $C$ equals to $1/2$, which prevents an exponential increasing too quick of $\gamma$. Hence, $C$ coefficient prevents an overestimation of $\gamma$. However, analysing the real data the difference $\Delta \tau_p$ is not contained in the simulated interval ($0 - 0.2$ sec), that it means $C$-value may have a different value. It is noticeable that in some sample $\gamma$ assumes an higher amplitude of $\alpha$, especially observing the trend of $\tau_{p1}$ and $\tau_{p2}$ in both Fig.s 5.13 and 5.14. This phenomenon is observable in 5.14, referring to the prolongations. Indeed interval by interval, the difference $\Delta \tau_p$ may reach values close or higher than $0.5$ Sec Hence, increasing of $\Delta \tau_p$ may lead to a constant $C \neq 0.5$.

![Fig. 5.13: Patient 1: Comparison along the 24h recording of all estimated parameters and derived $\gamma$ during baseline.](image)
Fig. 5.14: Patient 2: Comparison along the 24h recording of all estimated parameters and derived $\gamma$ during baseline.
Chapter 6

Discussions

The aim of the present thesis was to modify the Corino’s model in order to achieve a representation of the AV node closer to its electrophysiological properties. Previously, the probability of taking either one of the two pathways was equal to the probability of passing through. In this way the relative refractoriness of the two pathways did not have a relevant influence on the input distribution of the atrial impulses. In the modified model (the \(\gamma\)-model) the two functions \(\beta_1(t)\) and \(\beta_2(t)\) modify the assumption of equal probabilities. Therefore the simulated RR histogram changes, especially the shape of RR intervals distribution along the pathway with shorter refractory period (slow pathway) that becomes wider and lower compared to the simulated RR histogram of Corino’s model. Indeed during the time window \([\tau_1 - \tau_2]\) the generation of ventricular activation is prolonged by the refractoriness of the fast pathway. Moreover, since the two probabilities are significantly different, the understanding of the relationship between the parameter \(\hat{\alpha}\) and the parameter \(\gamma\) is necessary.

We found the relationship between \(\gamma\) and \(\hat{\alpha}\) at first empirically and then it was proved by the study of MAE and RMSE, calculated between the actual \(\hat{\alpha}\) and the derived \(\tilde{\alpha}\), that reach the order of magnitude of \(10^{-3}\). In the investigation of the law, the only parameter that has been not found completely stable is the parameter \(C\) that represents the weighing coefficient of \(\Delta\tau_p\). It is discovered to be time-dependent from \(\Delta\tau_p\). To fix this variability, the parameter \(C\) was calculated as the average of different \(C\) coefficients varying the parameters \(\Delta\tau_p\) and \(\lambda\). To improve the accuracy of the estimation it was imposed \(\Delta\tau_p < 0.2s\), bound physiologically accepted. A future improvement will be to better understand the dependence of the parameter \(C\) from \(\Delta\tau_p\).

Regarding the clinical applications, we are proposing a model that takes into account the general electrophisiological properties of the AV node by using a non-invasive tool as the ECG. We propose to estimate the input probability \(\gamma\) that lets to evaluate the number of atrial impulses that arrive at one of the
two pathways during AF. This information may be useful to localize ectopic foci, on which the clinician can intervene by ablation. Therefore our model can be inserted as a supporting tool for the ventricular rate control during the AF treatment.

The result obtained in the present thesis is that the parameter $\gamma$ is not significantly more stable than the output probability $\alpha$, contrasting the hypothesis that was made at the beginning of our work. An explanation of this result is that the variability with which the atrial impulses arrive at the pathway is intrinsic of AV node properties.

To conclude this study presents a statistical method for a quantitative analysis of AF. A previous model was initially implemented, accomplishing all characteristic such as dual nodal pathways, concealed conduction and relative refractoriness taken into account. These aspects are modelled and estimated as the probability of the atrial impulse to pass through the slow pathway, the difference in refractory period between the two pathways and the maximum prolongation. The simulation has been improved introducing a new parameter that represents the probability of an impulse choosing either one of the two pathways.

To test its accuracy and precision the mean absolute error (MAE) and root mean square error (RMSE) for different $\gamma$’s has been calculated. Obtaining, $MAE = (3.8 \pm 0.82023) \times 10^{-3}$ and $RMSE = 0.0159 \pm 0.0087$, calculated as average among all errors.

Moreover, the relationship on dataset was tested on 24-h Holter recordings. The results showed that the standard deviation of introduced parameter presents a greater stability in 58% of recordings. It has been carried out a t-test on the two standard deviations that enhances a not significant difference.

This study indicates that the relationship opens a new approach for the study of AF. There are certain aspects of the relationship that need improvements, e.g. a more robust C coefficient for weighing the difference of the maximum prolongations.


[19] Kirchhof P.; Auricchio A; Bax J; Crijns H; Camm J; Diener HC; Goette A; Hindricks G; Hohnloser S; Kappenberger L; Kuck KH; Lip GY; Olsson B; Meinertz T; Priori S; Ravens U; Steinbeck G; Svernhage E; Tijssen J; Vincent A; Breithardt G. “Outcome parameters for trials in atrial fibrillation: executive summary”. In: Eur Heart Journal vol 28 (2007), pp. 2803–2817.


