CLARRHMOS
Clinical Arrhythmia Model Simulator
a description language and simulator for clinical models of myocardial electrophysiology

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August 26, 1999

Contents

This paper describes the Clarrhmos simulation program and the associated tools. It is addressed to clinicians and researchers with sufficient computer skills. It is an evolving document, following or anticipating developments of Clarrhmos. This particular copy is about Clarrhmos V2.2 as released at 23rd of April 1999

1 Introduction

Clinicians explain the electrocardiographic findings of a patient by formulating hypotheses on the anatomical and physiopathological changes in the myocardium, and on how these changes lead to the sequence of depolarisation and repolarisation which produces the observed surface electrocardiogram.

This explanation, which we call *the clinical model* is formulated in qualitative and semiquantitative terms, such as "refractory period is much increased in the lesion area, thus leading to a region of functional block, thus to reentry as the mechanism of the ventricular tachycardia". Whether for a theoretically possible increase in refractory period, on the assumed or theoretically possible size of the affected region in the actual patient, given his (patient's) actual anatomic sizes of the heart structures, reentry would in fact take place is not known.

1.1 What is Clarrhmos

Clarrhmos is a computer language for building a computer representation of the clinical model and a simulator which can compute the myocardial activation and repolarisation sequence and electrograms.

The associated program CLARRHVIEW provides for the visualisation of the simulated activation and repolarisation sequences and of the ECGs.

1.2 Purposes of Clarrhmos

Clarrhmos was designed initially to be used for:

- verification of the theoretical soundness of certain types of hypotheses on arrhythmic mechanisms
- exploration of the use of computer representations of clinical models of heart electrophysiology for the optimisation of the management of individual patients
- graphical illustration of the generic mechanisms commonly formulated for arrhythmias and conduction disturbances—largely with educational applications

1.3 What Clarrhmos does not

Clarrhmos does not describe the real pathological changes in the heart, which are unknown—the clinician has electrocardiograms and other indirect data and tries to infer what the pathological changes might be—nor does it represent the way in which pathological changes actually lead to the ECG, as these way are also unknown, but some currently accepted theories on it.

Thus, if a CLARRHMOS model is built which actually leads to the expected electrocardiogram, this means that, under the currently accepted theories on ECG signal genesis (actually those coded in Clarrhmos), the pathological constellation implied by the model *would lead* to the observed ECG.

Nevertheless, while CLARRHMOS cannot *proove* wheather a given explanation is valid for the observed ECG it can be used to check for both the qualitative and quantitative consistency of an explanation (a theory for an observed behaviour), potentially to a degree of precision inaccesible to plain judgement.

1.4 Overview

The Clarrhmos simulator takes a description of the heart or of some structures of the heart built by the user, and computes the state of polarization/depolarization of every small region of it and the overall effect of cells' polarization on the electrogram.

For the purposes of simulation, the myocardial structures are decomposed in small regions, of equal volume and cubic shape, named "simulation cells". Typically, they would have a volume of 0.1–1 mm^3. Every simulation cell is considered to have homogenous electrophysiological properties, and to depolarize and repolarize solidarily.

The spatial placement of the cells, their properties and the way in which they interact with external factors make up *the anatomic model.* As just mentioned, in every anatomic model a set of external factors are defined (presumably such as digoxin blood level, vagal tonus and the like) and the way in which every cell is affected and responds to changes in these factors.

The actual values which the external factors take in time, other external effects, such as pacing or electric shock, the spatial placement of the ECG electrodes, and a random seed, together with the anatomic model, constitute a complete set of data from which the behaviour of the model can be computed. These elements, which are not intrinsic to the myocardium, are called *simulation environment.*

CLARRHMOS is the main simulation program. It reads the textfiles describing at least one anatomic model and one simulation environment and produces a simulation film. The simulation film is a computer representation of the state of the simulation cells, millisecond by millisecond (or, eventually, in coarser time units) for the whole simulation duration; it also includes the electrocardiogram on every lead which was defined in the simulation environment.

CLARRHVIEW is the simulation results viewer. It lets the user see the sequential myocardial activation maps on screen. It is a program of some complexity, as the computer screen is bidimensional, and the anatomic model is tridimensional, and as the user must be able to see only a selection of what actually resulted from the simulation.

2 The anatomic model

The anatomic model contains of a set of *anatomic model definitions.* Each of the definitions is represented in the text file that describes the anatomic model by means of a paragraph written between paranthesis "`()`". For each type of element in the anatomic model there is a special kind of paragraph—a paragraph with specific rules of writing.

Please note that in the following discussion we will call the simulation cells, simply *cells.* The actual histological cells in the real myocardia do never appear in our discussion.

2.1 Global parameters

The global parameters characterize a given model as a whole. They are:

time-unit is the duration of the smallest time interval taken into consideration during simulation, for example 1ms;

size-unit is the size of the simulation cell, for example 1mm (which means the simulation cell would have 1 cubic mm in volume);

x-size, y-size, z-size are the number of size units on the 3 dimensions of the model inside which all the anatomic elements described in the anatomic model find their place; the x dimension goes from the right of the patient to the left, the y goes superior to inferior, and z goes from posterior to anterior;

2.2 Cell category

A cell category is a class of cells that may model, for example, the atrial cells, or the M ventricular cells, or the subendocardial cells, or the perisinusal cell or any other type of tissue in the heart which is electrophysiologically homogenous, but is to be distinguised in the model—as a group, from the rest of the myocardium.

2.2.1 Cell parameters

Every cell in the model belongs to one category. For each cathegory the following parameters can be specified:

duration of action potential phases the duration of each of the five phases of the action potential of the given cell in the most typical state (i.e. when the pacing rate of external pacemakers is 60/min, and all the external factors are at the basal level); the sum of these durations gives the intrinsic pacing interval of the cell; the last of the intervals must be very large in order to simulate the lack of intrinsic pacing activity for the normal working myocardium.

phase levels the amplitude of the transmembrane potential at the beginning of each of the action potential phases.

activation delay is the time interval between the depolarization of the cell—provided it is not refractory—by a neighbouring cell (the start of the cell's cycle) and the moment in which it becomes able to depolarize its neighbours; the ration between the size unit and the activation delay gives the speed of the depolarisation front in that part of the myocardium;

activation end is the time interval between the start of the cycle and the moment when the cell ceases to be able to depolarize its neighbours;

refractoriness end is the moment in the cell's cycle when it ceases to be refractory to external impulses;

afterdepolarization probability is the probability for the cell to depolarise again during phase 3 of the action potential.

factor relevance relevance of external or internal factors on actual parameters

factor effect (see below): functions for the influence of internal or external factors on actual parameter computation

2.2.2 Cell variability inside categories

When a cell which belongs to a given cell category is created, the values of the baseline parameters of the cell, and the factor relevance coefficients are generated from the values of the cell category.

Nevertheless, current arrhythmogenic theories sometimes rely on inhomogeneities of the cardiac tissue. For example, it is known that the vagus nerve does not inervate all regions of the atria, or even of the sinus node the same. It would be counterproductive to describe an imaginary pattern of changes by means of a large number of cell categories. Thus we provided a mechanism to specify variability of basic parameters and relevance coefficients.

In the categories, one may specify every parameter or relevance coefficient to have a fixed numeric value, in which case it will have that value for every cell in the category.

Values can also be generated randomly, with parameters of the random distribution specified by the user for each base parameter in part. Only one distribution is supported which is a "delimited bi-halfnormal". The parameters given by the user are the mean μ and two dispersions σ_0 and σ_1. The probability density of the generating a value x for the parameter is:

$$p(x) = \begin{cases} \nu N_{\mu,\sigma_0}(x) \text{ if } \mu - \sigma_0 < x < \mu \\ \nu N_{\mu,\sigma_1}(x) \text{ if } \mu + \sigma_1 > x \geq \mu \\ 0 \text{ if } x > \mu + \sigma_1 \\ 0 \text{ if } x < \mu + \sigma_0 \end{cases}$$

Where $N_{\mu,\sigma}(x)$ is the normal probability density and ν is a correction for the missing ends of the normal half-distributions which is about 1.42. This allows generating random values with a skewed distribution which can be described in an intuitive manner and which limit the range of the parameters.

2.3 External and internal factors

The values specified for each cell when the model is defined are called the *baseline parameters*. The values of the parameters taken into account during simulation may be equal to the baseline ones or may be computed on the spot, taking them into account. For example, in most tissues, the duration of the phases of the action potential change with the duration of the previous cycle length for that cell (or with earlier cycle lengths). Also other factors such as drug concentrations or neurovegetative tonus can influence the actual action potential shape and the other parameters. Thus, by default at the beginning of phase 0 , the simulation program recomputes the *actual parameters* from the baseline ones and other variables, as described below.

The calculation of the actual parameters is done by taking into account the values of the *external factors,* such as digoxin level, oxigenation level and so on, and of the *internal factors* of the cell. Internal factors are either predefined (such as the previous cycle length) or can be defined by the user.

The external and the internal factors are represented in the computer as numbers, stating their value—in an arbitrary unit of measure. For each factor we must:

- declare the factor (name, unit of measure) in the anatomic model
- define the values of the factor at various sampling points in time, in the simulation environment
- define, optionally for any type of cell, the influence of the factor to each of the parameters (the contribution of the factor to the calculation of the actual parameters from baseline parameters).

2.3.1 Calculation of factor value

The values of internal factors (that is, internal to the cells) evolve independently for each cell which has them. Each external factor exists in one version for the whole model.

2.3.2 Calculation of factor effect

There are two sets of coefficients taken into account when computing the actual parameters from the baseline ones.

One consists of a coefficient which has one value for every cell and every external or internal factor, and which tells how much is the factor relevant to the cell. For example, it may tell that the cell is vagally inervated, or that the cell is placed in a region in which oxygenation changes. This coefficient is called *coefficient of relevance of the factor for the cell.*

For every factor and for every cell category, there is a *transfer function,* which tells how does each factor influence every parameter of cells in that category. The functions used for this purpose are from a class named *limited linear transfer functions.* There are four function arguments, named $\psi_0 < \psi_1$, $\tau_0 < \tau_1$. When the value of the factor is less than ψ_0 then the value of the function is τ_0. When the value of the factor is more than ψ_1 then the value of the function is τ_1. When the value of the factor is between ψ_0 and ψ_1 the value of the function varies linearly between τ_0 and τ_1.

For every cell, the factors are applied as follows: every factor is multiplied by the relevance coefficient for the cell. Then, the τ value for the result of applying the relevance coefficient to the factor is computed for every parameter in the cell. Then, for every parameter, the product of these τ values is computed and the result is multiplied with the basic value of the parameter, thus resulting the value of the actual parameter. This is repeated at the initiation of every cycle for every cell.

The *baseline value of a factor with respect to a cell* is the value for which the τ of the factor for the cell is 1.0.

2.4 The heart anatomy

The anatomic model consists of the spatial placement of the cells of different categories. Cells are placed as paralelipipedic blocks of cells, called *cell blocks* or simply *blocks.*

The blocks are defined in some order inside the model. The order is

important. When two blocks overlap the cells in the last specified block replace the cells in the blocks with which it overlaps.

Inside a block, all the available space is considered filled with cells. Every cell is considered linked (in the sense that it can transmit its depolarization state to) every other cell with which it has an adjacent face.

When two blocks are specified to be immediately adjacent, then links are "forged" between the cells of different blocks that come into close contact. The same is true between blocks that replace parts of other blocks because of overlapping and the remains of the overlapped blocks.

> OBSERVATION. In theory, it is possible to build a cardiac representation which replicates the actual heart of a patient exactly, by the use of many small blocks. Nevertheless, the actual shape of the heart is usually unknown and changing, and the level of resolution of our models is not detailed enough to make such an exact description worthwhile. Instead, one should take care to preserve the general topology of the heart (for example, the fact that the posterior arterial wall is connected near its middle with the anterior one) and to approximate as close as possible the distances between the various structures (for example between the SA node and the AV node). The general shape of the electrocardigrafic waves, their succession and variability will be reproduced by such approximate anatomy—but not their exact shape and amplitude.

3 Simulation environment

For every anatomic model, multiple simulations are possible for the following reasons:

1. within the permited range of variation, the actual values of the baseline parameters may be selected in a very large number of ways; in every simulation, one combination of them is selected randomly;
2. the early afterdepolarization of any cell takes place randomly (its probablity is a property of every cell), and the actual incidence will

vary from a simulation to the next; these afterdepolarizations may be lead to complex electrophisiological phenomena in the anatomic model, later;

3. any anatomic model can be simulated under various conditions of fluctuation of the external factors; it is typical to see how the results of the simulation change when a drug is added;

4. some external events, such as the application of an electric shock or of local pacing, may be applied at various moments to the same model, or not be applied at all;

5. after a simulation one may desire to read the results of the simulation using different ECG electrode placements;

A combination of some or all of these variables valid for a given anatomic model, define a *simulation environment*. The principles of specifying these external conditions are described in this section.

3.1 Random seed

The generation of cell parameters and coefficients inside the permited levels of variation, and the decision upon the occourence of random events such as the early afterdepolarizations are governed by a series of "pseudorandom" numbers. This is a list of numbers which, when examined, do not show any rule of variation, that is there is no obvious or simple way of finding out what the next such number will be. Yet, they are *pseudo*random because it is possible to reproduce the whole series exactly, by specifying a small amount of information called *random seed*.

In other words, despite the extensive generation of random values in the cord model (all cell parameters—within the ranges set by their cathegories, and in every cycle to see if the afterdepolarizations occur) the whole simulation will be reproduced exactly if the random seed is preserved untouched and, of course, the anatomic model and the external conditions are also unchanged. If it is changed no matter how little, the probability dependent parameters, coefficients and events change, all, in a completely unpredictable way—but within their ranges of variation.

What is more, if some other external parameters are changed, such as the placement of electrodes or an external factor, and the simulation is run again, with the same random seed, the change of the external factor will take place over the conditions as for the simulation with conditions unchanged.

The random seed in clarrhmos is specified by a string of characters (letter, digits, special signs) and a number. For example "`Clarrhmos 2.0 is a great program.`" and 1000. The series of pseudorandom numbers is obtained by assigning fixed codes to the characters and then combining the codes arrhythmetically ad infinitum. The number is the number of combinations which are done and ignored before the actual pseudorandom numbers begin to be used. There should not be less than 5 characters in the string, and more than 55 are useless. The number should be between 1000 and 30000.

3.2 External factor values

The variation of the external factors is specified by a list of pairs of numbers; the first number is a moment in time, the second number is the value of the factor at that moment. The actual value of the factor is computed at every moment by linear interpolation between the values. The moment 0 is considered to have the value of the first specified moment and the value for the last moment specified is considered to last indefinitely, unchanged.

3.3 External events

For the moment, there are two types of events: electrical shock and pacing. Electrical shock will depolarize all the cells simultaneously. Pacing will depolarize the cells in a given region of the myocardium—if they are not in refractory state.

Electrical shock is described by the moment of it's appearance.

Pacing is described by the region in which it is given (a paralelipiledic region), the moment of the first impulse and the rate of pacing.

3.4 Electrodes

For the moment, there are only bipolar electrodes. They are placed in pairs in space, and they are given names by the user. They are descibed by their names, their polarity and their spatial coordinates.

3.5 Output clauses

Output clauses specify the output required from the simulation program. The simplest form is used for the production of a simulation results file (.simr file) on the standard output, and consists of specifying the rate of ECG output and the rate of activation frame output. Absence of these output clauses means nothing is generated on the standard output.

4 Input file syntax for version 2

The rules of writing every paragraph are described together with every anatomic model definition. The rules are described using two kinds of elements: non-terminal syntactic elements, and terminal syntactic elements.

For example, when we write `cell-category` we mean that the user should type exactly the characters `cell-category`, as in the rule. This is a *terminal syntactic element.*

When we write `<number>` we mean that the user will have to type, instead of `<number>` a number—of his choice—such as 1.3 or 8. This is a *non-terminal syntactic element.*

In order to distinguish, in the rules below—which are called *syntactic rules*—the terminal from the non-terminal syntactic elements, the non-terminal ones are written between angle brackets—which are never used in the terminal ones. The non-terminal syntactic elements will be called, for shortness, *non-terminals*, while the terminal ones will be called *teminals.*

```
<letter>               ::= A | ... | Z | a | ... | z
<digit>                ::= 0 | .. | 9
<special-sign>         ::= - | _ | & | % | ...

<graphic-char>         ::= <letter> | <digit> | <special-sign>

<integer>              ::= <digit>*
<number>               ::= [-]<digit>*[.<digit>*]
<subunit-number>       ::= 1[.0] | 0.<digit>*
<symbol>               ::= <letter><graphic-char>*
<string>               ::= "<graphic-char>*"
```

4.1 The anatomic model

This section specifies the syntax rules for the description of the anatomic model.

4.1.1 External factors

The external factors are described by means of the syntax:

```
<external factor spec> ::= (external-factor <external factor name>
                                             [ <comment> ]
                                             [:unit <symbol>]
                                             [:range (<min> <max>)]
                                             :baseline-value <number>
                           )
<external factor name> ::= <symbol>
<min>                  ::= <number>
<max>                  ::= <number>
<comment>              ::= <string>
```

4.1.2 Cell category

Cell category specification has the following syntax:

```
<cell category spec>   ::= (cell-category <cell category name>
                                  [ <comment> ]
                                  :phase-durations  (<dv> <dv> <dv>
                                                     <dv> <dv>)
                               [  :phase-levels     (<volt> <volt>
                                                     <volt>
                                                     <volt> <volt>) ]
                                  :refractory       (<dv> <dv>)
                                  :active           (<dv> <dv>)
                                  :EAD-probability  <pv>
                                  :LAD-probability  <pv>
                                  :max-LAD-chance   <dv>
                                 {:affected-by <factor-interaction>}* )

<factor-interaction>   ::= (<factor-name> [:relevance <probability>]
                                  :phase-durations  (<lltf> <lltf>
                                                     <lltf>
                                                     <lltf> <lltf>)
                                [ :phase-levels     (<lltf> <lltf>
                                                     <lltf>
                                                     <lltf> <lltf>) ]
                                  :refractory       (<lltf> <lltf>)
                                  :active           (<lltf> <lltf>)
                                  :EAD-probability  <lltf>
                                  :LAD-probability  <lltf>
                                  :max-LAD-chance   <lltf>)

<dv>                   ::= <duration> | (binormal-duration <duration>
                                                           :plus <duration>
                                                           :minus <duration>)

<pv>                   ::= <probability> | (binormal-probability
                                                 <probability>
                                                 :plus <probability>
                                                 :minus <probability>)

<volt>                 ::= <number>

<duration>             ::= <number> | (<number> <time-unit>)
<dimension>            ::= <number> | (<number> <dim-unit>)
<probability>          ::= <subunit-number>

<time-unit>            ::= us | ms | s | min | h
<dim-unit>             ::= angs | um | mm | cm | m

<lltf>                 ::= (LLTF <psi-0> <psi-1> <tau-0> <tau-1>)

<psi-0>                ::= <number>
<psi-1>                ::= <number>
```

```
<tau-0>                ::= <number>
<tau-1>                ::= <number>

<probability>          ::= <number>
```

The anatomic model is specified with the following syntax:

```
<anatomic-model>       ::= (anatomy <anatomic-model-name>
                                    [ <comment> ]
                                    :size-unit <number>   ; microns
                                    :time-unit <number>   ; microseconds
                                    :left-to-right      <dimension>
                                    :up-to-down-size    <dimension>
                                    :back-to-front-size <dimension>
                                    <cell-block> *)

<anatomic-model-name>  ::= <symbol>

<cell-block>           ::= (cell-block <x0> <x1> ; left to right
                                       <y0> <y1> ; up to down
                                       <z0> <z1> ; back to front
                                       <cell-category-name> )

<x0>                   ::= <dimension>
<x1>                   ::= <dimension>
<y0>                   ::= <dimension>
<y1>                   ::= <dimension>
<z0>                   ::= <dimension>
<z1>                   ::= <dimension>
```

4.2 Simulation Environment

The simulation environment will be described using the following syntax:

```
<simulation>           ::= (simulation <simulation-name>
                                       [ <comment> ]
                                       :on-anatomy <anatomic-model-name>
                                       :random-seed <string> <integer>
                                       :start-moment <duration>
                                       :end-moment   <duration>
                                     { :ECG-electrode-pair <electrodes-name>
```

```
                                        (<x0> <y0> <z0>)
                                        { (<x1> <y1> <z1>) |
                                              microelectrode } }*
                                    { :factor-values <factor-name>
                                                     <factor-description> }*
                                    { :electric-shock <e-s-description> }*
                                    { :pacing <pacing-description> }* )

<electrodes-name>       ::= <symbol>

<factor-description>    ::= ( { <duration> <number> }* )
<e-s-description>       ::= <duration>
<pacing-description>    ::= ( ( <x0> <y0> <z0> )
                              ( <x1> <y1> <z1> )
                              { single-impulse <at> } |
                              { impulse-train  <at> <period> } )

<at>                    ::= <duration>
<period>                ::= <duration>

<x0>                    ::= <dimension>
<y0>                    ::= <dimension>
<z0>                    ::= <dimension>

<x1>                    ::= <dimension>
<y1>                    ::= <dimension>
<z1>                    ::= <dimension>
```