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Micro Model of Human Heart Arrhythmias

Theoretical models: Macro vs. Micro

Group 3 Members

Jeffrey Burkham
Koray Duhbaci
Manu Gupta
Rahul Raja Padinjarekovilakom

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Introduction

The general behavior of the heart as a pump used to force the blood to the cardiovascular system. The heart is contained in the pericardium, a membranous sac consisting of an external layer of dense fibrous tissue and an inner serous layer that surrounds the heart directly. The heart consists of two sides and four chambers; each of the four chambers of the heart is different from the others because of its functions.

The heart is endowed with a specialized system for generating rhythmical impulses to cause rhythmical contraction of the heart muscle and for conducting these impulses rapidly throughout the heart. When this system functions normally, the atria contract about one sixth of a second ahead of the ventricles, which allows extra filling of the ventricles before they pump the blood through the body. Another special importance of this system is that is allows all portions of the ventricles to contract almost simultaneously, which is essential for effective pressure generation in the ventricular chambers.

Unfortunately, though, this rhythmical and conduction system of the heart is very susceptible to damage by heart diseases and other ailments. The consequence is often a bizarre heart rhythm or abnormal sequence of contractions of the heart chambers, and the pumping effectiveness of the heart is often affected severely, even to the extent of causing death.

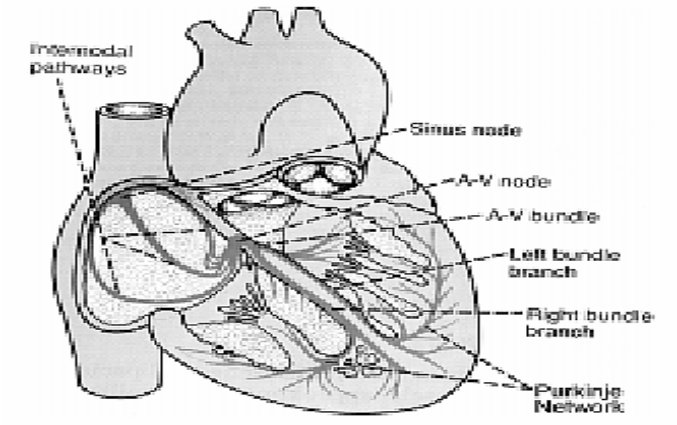


Figure 1. The conductive system of the heart

The rate and the rhythm of the heart are controlled by the *sinus node* (also called *sinoatrial or S-A node*), which is a nerve bundle situated in the wall of the right atrium. The sinus impulse leaves the SA node and spreads through the atrial muscle causing its contraction; this atrial activation is reflected by the P wave of the electrocardiogram. The sinus impulse eventually reaches the *AV node* (*atrio-ventricular node*), which is another nerve bundle situated in the right atrium above the valve and just right to the inter atrial wall after a delay at the AV node. The impulse travels down the *AV branch*, *bundle branches* and *Purkinje network* causing ventricular contraction reflected as the QRS complex of the electrocardiogram. The parts of the conductive system of the heart are shown in Figure1.

The Electrocardiogram

The *electrocardiogram* (EKG or ECG) provides a record of electrical events which occurred within the heart, and is obtained from electrodes placed on the surface of the body. An EKG is thus a plot of the time-dependence of charging potential differences between electrodes on the body surface. A typical EKG is shown in Figure 2.

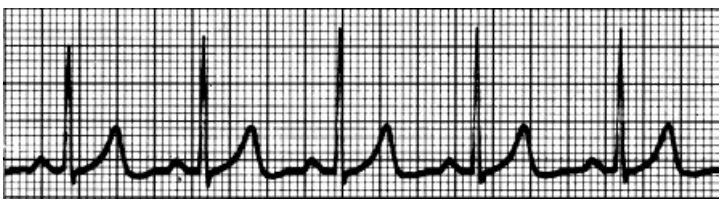


Figure 2. ECG recorded from body surface

The Macro Model

The characteristic features of normal sinus rhythm:

- The heartbeat rate is between 60 and 100 beats per minute, the pattern is regular.
- QRS complexes are narrow < 0.08 second.
- Each T wave is followed by a P wave.
- The P wave is positive in Lead 2.
- There is fixed 1-to-1 relation between P waves and QRS complexes.
- The PR interval is normal.

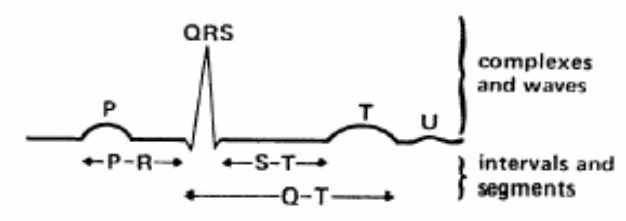


Figure 3. A Normal Sinus Rhythm

Modeling the P, T and U Waves

The P, T, and U waves are modeled as Gaussian curves. The equation of the curve is:

$f(t) = A \exp[-(t-t_0)^2 / \sigma^2]$

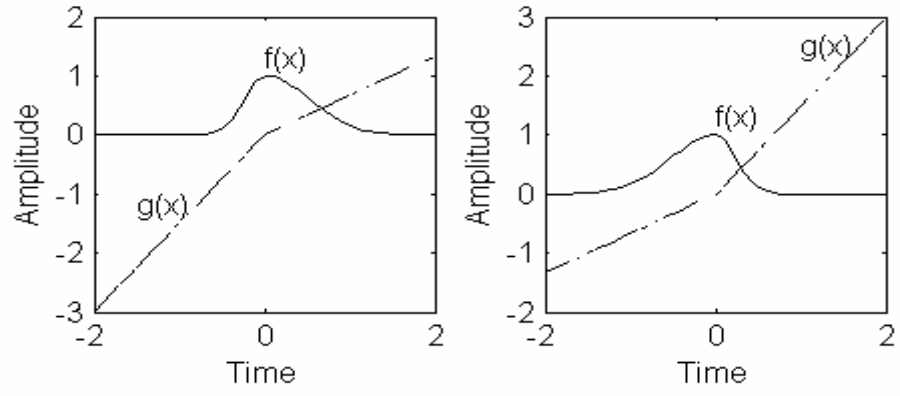
Where A is the amplitude of the wave, σ is the standard deviation, and t_0 is the time point of the maximum of the wave. In order to allow curves to be non-symmetric, the so-called slant parameter ξ has been introduced. The equation of the curve becomes:

$f(t) = A \exp[-g^2(t-t_0) / \sigma^2]$

where

$g(t) = \exp(\xi)t , t>0$
$= 1 / \exp(\xi) t , t<0$

Examples of the curves are shown in Figure 4. The dashed line is a graph of *g* function, while the solid one is a graph of the *f* function.



(a) **(b)**

Figure 4. The slant parameter (a) ξ = –0.4, (b) ξ = 0.4

For the above figure, $A = 1$; $\sigma = 0.5$; $t_0 = 0$
The parameters of each of the P, T, and U waves are:

- A the amplitude of the wave
- σ the standard deviation
- t_0 the time point of the peak of the wave
- ξ the slant

Modeling the F Waves

There are no P waves during the atrial flutter but the atrial electrical activity occurs as "sawtooth" shaped F waves. Those waves are modeled as a first derivative of Gaussian curves. The equation of the curve is:

$$f(t)=-A[(t-t_0) / \sigma^2] \exp[-(t-t_0)^2 / \sigma^2]$$

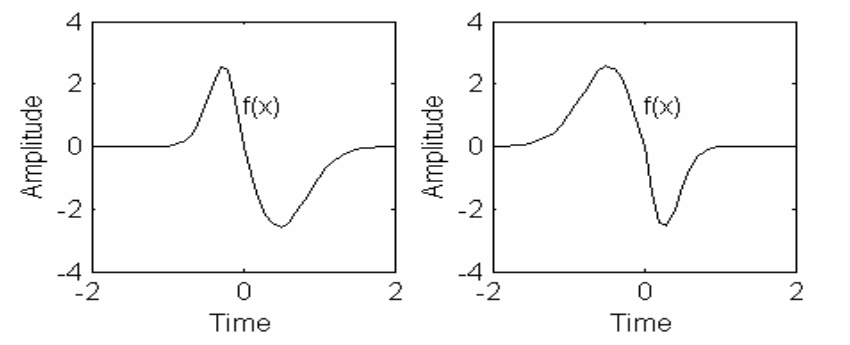
The slant parameter ξ has been introduced analogously to the slant parameter of the P wave. The equation of the curve becomes:

$$f(t)=-A[g(t-t_0) / \sigma^2] \exp[-g^2(t-t_0) / \sigma^2]$$

where

$$g(t)=\exp(\xi)t , \; t>0$$
$$= 1 / \exp(\xi)t , \; t<0$$

Examples of the curves are shown in Figure 5. The solid line is a graph of the *f* function.



(a) **(b)**

Figure 5. The slant parameter (a) ξ = - 0.3, (b) ξ = 0.3

For the above figure $A = 3$; $\sigma = 0.5$; $t_0 = 0$

The parameters of each of the F waves are:

- A the amplitude of the wave
- σ the standard deviation
- t_0 the time point of the peak of the wave
- ξ the slant

Modeling the QRS Complex

The QRS complex is modeled as three Gaussian curves, where the amplitudes of Q and S waves are of opposite sign to the amplitude of the R wave.

The parameters of each QRS complex are:

- A_Q the amplitude of the Q wave
- A_R the amplitude of the R wave
- A_S the amplitude of the S wave
- σ the standard deviation
- t_0 the time point of the peak of the waves
- ξ the slant equals 0

Example of the modeled QRS complex is show in Figure 6. The parameters are: $A_Q = -5$, $A_R = 100$, $A_S = -15$, $\sigma = 0.5$, $t_0 = 0$.

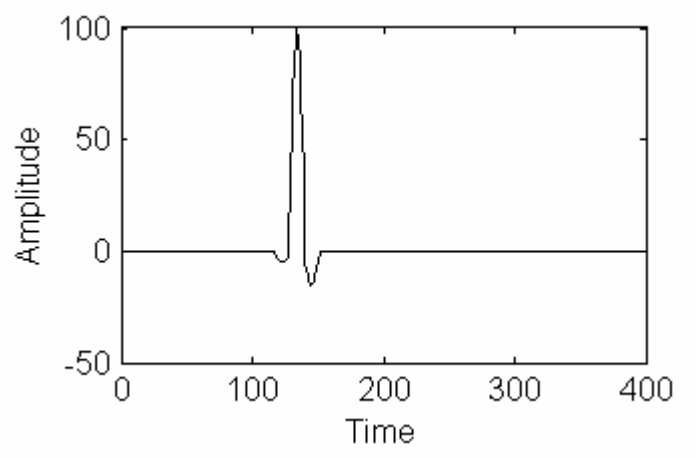


Figure 6. An example of a modeled QRS complex

Implementation of Arrhythmias

Definition of Arrhythmias

The six basic blocks of information that characterize arrhythmias are:

1. The rate of the arrhythmia
2. The pattern, or regularity, of the arrhythmia
3. Whether a QRS complex has normal or abnormal conduction
4. Whether atrial activity is present
5. What type of atrial activity is present?
6. How the atrial activity is related to the ventricular activity.

The simulator program can generate waveforms of various arrhythmias, using an ASCII Tab delimited file that appears as a table. Each row of the table corresponds to one heartbeat.

The columns of the table are:

- Pamp the amplitude of the P wave
- Famp the amplitude of the F wave which is observed during atrial flutter instead of P wave
- Pwidth the width in milliseconds of the P or F wave in the middle height
- Pslant the slant parameter of the P or F wave (see Chapters 10.1. and 10.2.)
- PRint the interval between the peaks of the P wave and the QRS complex
- Qamp the amplitude of the Q wave
- Ramp the amplitude of the R wave
- Samp the amplitude of the S wave
- Rwidth the amplitude in milliseconds of the R wave in middle height
- RRint the interval between the peak of the P wave and the peak of the P wave from the following heartbeat (the name is somewhat misleading because it is *not* the interval between QRS complexes)
- Tamp the amplitude of the T wave
- Twidth the width in milliseconds of the T wave in the middle height
- Tslant the slant parameter of the T
- RTint the interval between peaks of the QRS complex and the T wave
- Uamp the amplitude of the U wave
- Uwidth the width in milliseconds of the U wave in the middle height
- Uslant the slant parameter of the U wave
- TUint the interval between peaks of the T wave and the U wave

Pamp	Famp	Pwidth	Pslant	PRint	Qamp	Ramp	Samp	Rwidth	RRint	Tamp	Twidth	Tslant	RTint	Uamp	Uwidth	Uslant	Tuint
8	0	20	-0.1	120	5	100	15	10	750	30	52	0.5	290	2	30	0	150
8	0	20	-0.1	120	5	100	15	10	750	30	52	0.5	290	2	30	0	150
8	0	20	-0.1	120	5	100	15	10	750	30	52	0.5	290	2	30	0	150
8	0	20	-0.1	120	5	100	15	10	750	30	52	0.5	290	2	30	0	150
8	0	20	-0.1	120	5	100	15	10	750	30	52	0.5	290	2	30	0	150
8	0	20	-0.1	120	5	100	15	10	750	30	52	0.5	290	2	30	0	150
8	0	20	-0.1	120	5	100	15	10	750	30	52	0.5	290	2	30	0	150
8	0	20	-0.1	120	5	100	15	10	750	30	52	0.5	290	2	30	0	150

Table 1. A table for Normal Sinus Rhythm

By adjusting this table and passing the values in it to the above modified Gaussian equations, it is possible to simulate different arrhythmias.

The Micro Model

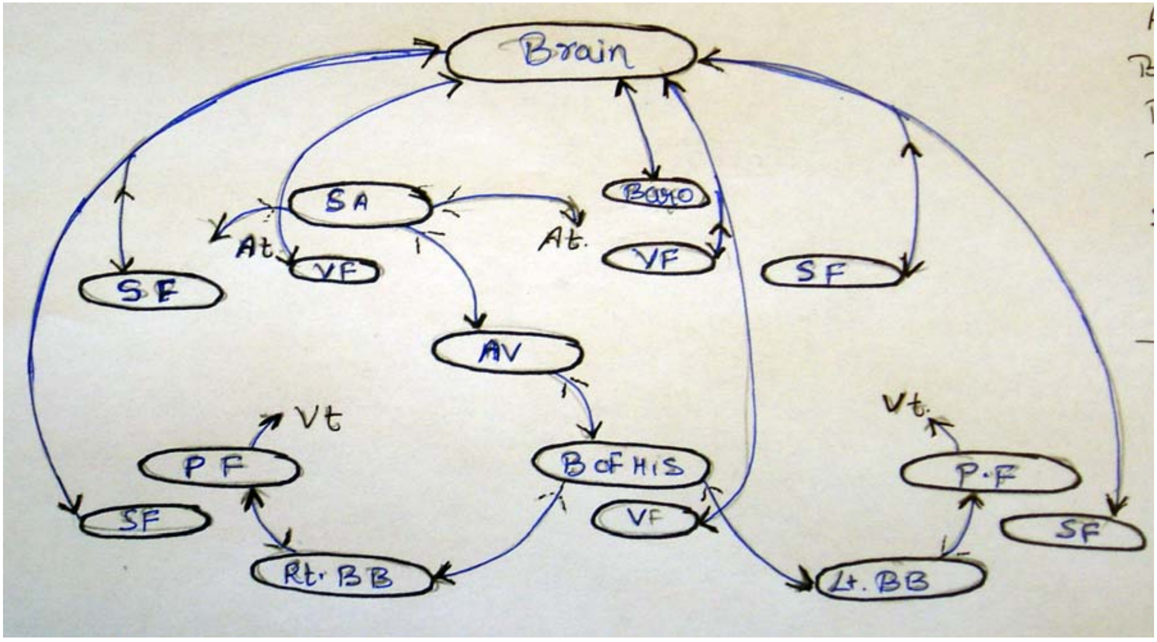


Figure 7. Agent Interaction in Micro Model

	Abbr.	**Agent**
1.	SA	Sinoatrial node
2.	AV	Atrioventricular node
3.	G of His	Bundle of His
4.	BB	Bundle branch
5.	PF	Purkinje fiber
6.	SF	Sympathetic fiber
7.	VF	Vagal fiber
8.	Baro	Baroreceptors
9.	Brain	Brain

The agents are programmed with functionality of their need.
They work in coordination; if they refuse to coordinate, arrhythmia can occur.
They may stop working, depending on the inputs.
The agent ‘brain’ is programmed to send commands to the other agents to act accordingly.
Input can be given to this system, e.g., stress (to brain), blood condition, damaged heart muscle, blood pressure, etc.
Medical statistics can be utilized which determine and quantify mental and physical conditions, and their results and interactions.

An increasing number of discrete input conditions (t=0) will improve model accuracy, and broaden model generalization.

SA node	Junction of RA and superior vena cava
AV node	septum (septum divides heart vertically)
Bundle of His	both interior wall and septum
Purkinje Fibers	myocardium
Vagal fibers	aorta, bundle of His, and branches
Sympathetic fibers	within walls of the atria (4 ventricles)

Rate is controlled by frequency at which the SA node generates impulses.
Heart rate can be affected indirectly, such as diet, respiration, body temperature, blood chemistry, sleep, etc.
Pressoreceptors or (baroreceptors) – arch of aorta and carotidal sinus (alters vagal tone).

Macro vs. Micro Models

Macro models

Macro models of the heart and its operation today yield state information. For instance, typical state information is presented graphically as an electrocardiogram (EKG/ECG) trace. The doctors have an idea what a specific malfunction (e.g., a bradycardia arrhythmia) looks like in general, and if the patient's EKG at some future point exhibits characteristics of it, the doctor will proscribe treatment that she has been taught is appropriate, given the patient's whole-health status.

Existing medical macromodels of the heart and heartbeat can describe a "normal" heartbeat, and can even describe state of an abnormal heart (e.g., ventricular fibrillation). However, they cannot predict future states, except in very vague (e.g., generalized) terms which are not patient-specific. Further, macro heart models do not yield transitory states (e.g., as a function of time). And perhaps tellingly, macro models do not yield predictive diagnostic results. Doctors rely on their own judgment, intuition, peer discussion, and experience to interpret patient history (e.g., the EKG a few minutes ago) in order to "predict" the future (patient illness).

Micro models

In contrast to the macro model, a micro model of the heart can simulate arrhythmias which are patient-specific, and which are a continuous function in the time domain. As a quick example, a fibrillating heart is injected with a stimulant. What is the biological response in 10 seconds? In 30? Does the patient die at 45 seconds if the dosage exceeds a given threshold? What will be the EKG during the next five minutes, heartbeat by heartbeat?

However, the doctor does not currently have a micromodel available that can be run to simulate either the causes and respective effects leading from the healthy EKG (let's call it "State A", Figure 8) to the current bradycardia ("State B"), and has no simulation available to test her "best guess" treatment to solve the "State B" malfunction. In other words, she cannot test (or play out some "what-if" scenarios) for various courses of medication and treatment to determine the optimum (or at least more optimal) treatment.

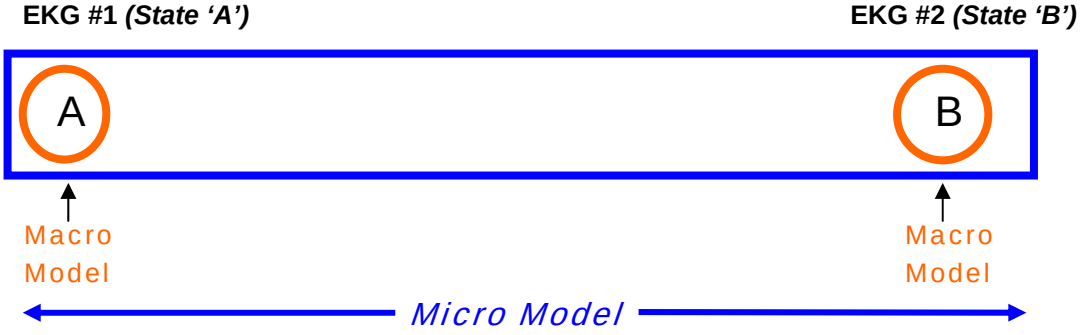


Figure 8. Macro vs. Micro Model

The microsim model of the heart can describe not just state A and state B, but the intermediate states, and can be used to extrapolate (predict) future states. This is a great advantage of micro vs. macro, in context of modeling the heart (and its arrhythmias).

In typical words of doctors of today who do not have the micorsimulation available, "I'm going to proscribe these pills. Take one each day with a meal in the morning, don't smoke or drink alcohol, don't get in stressful situations, don't fly any spacecraft, and come see me in two weeks. If you have any sudden pains, go to the nearest hospital and call me immediately." Translated, the doctor does not know for sure what will happen. If you die, well she did her best, and will get paid anyway. From the patient's point of view, it would be nice if the doctor was sure about her treatment and prognosis. With a good microsim, there would be less guesswork and more certainty.

Benefits of developing an operational microsim of the heart are not just medical treatment for patient-specific conditions, but optimize treatments (e.g., best possible, even in hindsight), uniform diagnosis and treatment (less art, more science), and less regional treatment variations relying on the 'skill' of doctor. Ideally, 100 doctors should all decide the same (optimum) course of treatment. Variations are indicative of sub-par treatment (unless all are equally effective/noneffective).

Alternative Methods Considered

We considered four other methods to create the microsim we proposed.

Heart as a "black box"

We spent much time researching the feasibility of modeling the heart as an independent organ (e.g., a "black box"). The model would be down to the cellular level, and have many hundreds of thousands of external inputs, many of which would, themselves, be macromodeled, most likely in differential form. However, inputs would also exist in discreet form, such as patient history and patient state information (at the start of the sim run).

An advantage to this method is that a transitory model of other organs would not be necessary, as only input effects to the heart model (the black box) would be necessary. Organ and body interactions would be modeled with statistical data and/or macro equations, and could combine interactive effects before introduction into the domain of the black box (the heart micromodel). Though this would be very complicated to properly model, it would be closed (e.g., finite), and thus suitable to even today's pseudo-parallel Von-Neuman computer architectures. Computational power is possible today, but the power necessary is approximately equivalent to present day model of Earth's magnetic fields, where a single full iteration requires six months on fastest supercomputers.

However, the main impediment is not computational, but clinical. Present day medical understanding is still rather limited, even at the basic cellular level of charge generation, refractory periods, etc. Even the function of the U-wave is not fully agreed upon by doctors. The world of high-resolution EKGs is just opening up for medical research. What this means is that many complex interactions are not yet suitably macro modeled.

Heart as part of whole-body system

A second alternative is to model the entire body functionally, with heart as subject of study. The heart would not be an isolated "black box." It would be a cellular model with inputs from other organs and bodily interations. Potential accuracy increased, particularly extension of predictive windows. The whole-patient study would be a great benefit, especially to "unusual" cases.

However, some of the same limitations are present in this model as in the black box model. Most importantly, present-day medical understanding is limited, even in the other body organs -- especially the brain (which just happens to control the heart). The necessary level of computer power is increased: it is

roughly equivalent to the continuing attempts to completely model of earth's weather state, and accurately predict weather (even on the smallest scale), planet-wide. In other words, even if the clinical understanding of all the human body which interacts with the heart were understood, computationally it is still not feasible -- yet.

The analogy model

A third approach at developing a workable microsim model was the "Analogy" model. This was, in effect, a back-propogated effort to use existing micro models known to work, and extrapolate analogously in the medical domain of the heart. However, this approach seemed to yield an inadequate micro model of the heart (because of gaps in the analogy), though certain analogies (like comparing the topology of Sweden to the topology of the electrical system of the heart) did seem to help the group gain a general feel for the micro-model concept.

The expert system

The fourth alternative we considered was based on the "Expert" system, which is already in use by many doctors at various levels. The expert system takes various input conditions, and searches a database and/or a set of heuristics exhaustively, then produces one or more "answers" to the input conditions. In simple forms, it is used to detect drug interactions, offer diagnosis from observed symptoms, etc. But the key is that it is still state-driven, and an expert "simulation" would involve inputting many states. In other words, it is not readily ported to simulations in a continuous time domain, and by its nature, is diagnostic. So although it might perhaps appear to unsavvy observers that a simulation would "run" based on this method, in fact the underlying mechanism would not be a simulation!

Conclusion

The basic micro-model of the heart we presented is possible to construct with today's medical understanding and computational capabilities. Accuracies will improve as clinical understating of the multi-variate parameter interactions between the agents we described become more understood. In particular, the emerging research into the meaning of the relatively new high-resolution EKGs are defining detail about the operation of the heart that has heretofore eluded medical science. As these interactions are understood and quantified, they can be modeled, and input into the heart microsim, and thus broaden the use of the microsim (e.g., cover more and more medical diagnostic instances), as well as increasing its usefulness as a predictive tool for patients and doctors.