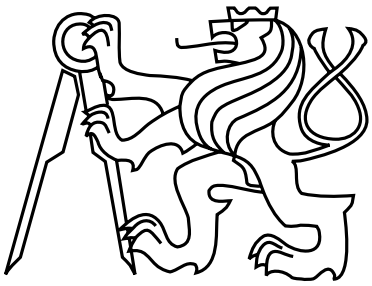
Czech Technical University in Prague
Faculty of Electrical Engineering
Department of Cybernetics



Bachelor thesis

Statistical Analysis of Bipolar Patients

Chanh Nguyen Huu

Supervisor: Ing. Daniel Novák, Ph.D.

Study Programme: Electrical Engineering and Information Technology

Field of Study: Cybernetics and Measurement

January 6, 2012

Acknowledgements

I would like to thank Daniel Novák, my supervisor, for his suggestions and constant support during writing of this bachelor thesis.

Declaration

I hereby declare that I have completed this thesis independently and that I have listed all the literature and publications used.
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In Prague on January 6, 2012 Chanh Nguyen Huu

Czech Technical University in Prague
Faculty of Electrical Engineering

Department of Cybernetics

BACHELOR PROJECT ASSIGNMENT

Student: Chanh Nguyen Huu

Study programme: Electrical Engineering and Information Technology

Specialisation: Cybernetics and Measurement

Title of Bachelor Project: Statistical Analysis of Bipolar Patients

Guidelines:

1. Perform state of art of bipolar disorder.
2. Analyze movement activity of bipolar patients. Aggregate movement activity results with analysis and results of psychiatric questionnaires.
3. Evaluate and test the methodology on patients siffering from bipolar disorder.

Bibliography/Sources:

[1] Jones, S.H.; Hare, D.J.; Evershed, K.: Actigraphic Assessment of Circadian Activity and Sleep Patterns in Bipolar Disorder. Bipolar Disord 2005:7(2): 176-186.
[2] Bauer, M.; Grof, P.: Temporal Relation Between Sleep and Mood in Patients with Bipolar Disorder. Bipolar Disord 2006;8:160-167

Bachelor Project Supervisor: Ing. Daniel Novák, Ph.D.

Valid until: the end of the summer semester of academic year 2011/2012

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prof. Ing. Vladimír Mařík, DrSc.
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Dean

Prague, April 7, 2011

České vysoké učení technické v Praze
Fakulta elektrotechnická

Katedra kybernetiky

ZADÁNÍ BAKALÁŘSKÉ PRÁCE

Student: Chanh Nguyen Huu

Studijní program: Elektrotechnika a informatika (bakalářský), strukturovaný

Obor: Kybernetika a měření

Název tématu: Statistická analýza pacientů trpící bipolární poruchou

Pokyny pro vypracování:

1. Seznamte se s problematikou bipolární poruchy.
2. Navrhněte metodu analýzy pohybové aktivity bipolárních pacientů. Navrženou metodiku zkombinujte s psychiatrickým vyhodnocením pomocí dotazníků.
3. Validujte vyvinutou metodiku na souboru minimálně 10 probantů.

Seznam odborné literatury:

[1] Jones, S.H.; Hare, D.J.; Evershed, K.: Actigraphic Assessment of Circadian Activity and Sleep Patterns in Bipolar Disorder. Bipolar Disord 2005:7(2): 176-186.
[2] Bauer, M.; Grof, P.: Temporal Relation Between Sleep and Mood in Patients with Bipolar Disorder. Bipolar Disord 2006;8:160-167

Vedoucí bakalářské práce: Ing. Daniel Novák, Ph.D.

Platnost zadání: do konce letního semestru 2011/2012

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V Praze dne 7. 4. 2011

Abstract

This bachelor thesis deals with study of bipolar disorder and analysis of objective data from actigraphy. The case study of long-term recordings of two patients is presented. The thesis goal is to predict relapse using Approximate Entropy and Circadian Rhythms Instability. Parameters IV and IS of Circadian Rhythms Instability methods described the change of patient status before the bipolar event. However, the relapse prediction couldn't be performed accurately.

Keywords: Approximate Entropy, Circadian Rhythms Instability, prediction

Abstrakt

Tato bakalářská práce se zabývá studií bipolární poruchy a analýzou objektivních dat získané z aktigramu. Práce se zabývá studii dlouhodobým záznamem dvou pacientů. Cílem této bakalářské práce je použití dvou metod Aproximativní entropie a Cirkadiánní rytmu nestability pro predikci relapsů. Hodnoty parametů IV a IS u metody Cirkadiánního rytmu nestability popisují změnu stavu pacienta před a po relapsi. Niceméně, predikce relapsů nemohly být přesně určeny.

Klíčová slova: Aproximativní Entropie , Cirkadiánní rytmus nestability, predikce

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Chapter 1

Introduction

This bachelor thesis deals with analysis and processing the data of patients, who suffer from bipolar disorder. The main goal of the study is the prediction of patient's relapse. Bipolar disorder is a kind of the mental illness which causes unexpected changing of moods which are recognized as mania or depression. According to doctors and scientists the bipolar disorder has its origin in genetic.

Currently there is no rigorous procedure for the permanent cure. A patient suffering from bipolar disorder has to visit regularly his doctor who monitors a patient's condition by a subjective questionnaire. The question-form consists of 18 questions in which the patient chooses his actual mental condition. Based on the results of the questionnaire, the doctor can recognize coming mania or depression. It is possible to stabilize the patient's mood by administering him appropriate dose of medications.

My study focuses on a new method for predicting patient's relapses in order to prevent possible patient hospitalization. The method called Approximate Entropy makes use of data which are collected by an actiwatch attached to the wrist like a classic wristwatch. This device records actual patient's physical activity which may give a clue about the possible relapse. In contrast to a subjective questionnaire, it provides objective actigraphy data. Thus my work inheres in processing and comparing data before and after known relapses.

In the bachelor thesis I assess the data of 2 patients who sufficiently collaborated on the research. Patient no.1 have been participating in this study for more then 3 years, patient no.6 for more than 1 years.

This study is divided into 6 sections starting with Introduction. The 2nd section is a description of the bipolar disorder's symptoms, causes, treatments and drugs. The third section describes the definition and implementation of the methods, backed up by several examples. The next section deals with actigraphy and preparing data preprocessing. Section 5 is dedicated to data analyses and descriptions of the results. The last section contains the conclusion and outlines future directions.

Chapter 2

Bipolar disorder

2.1 What is the bipolar disorder?

Bipolar disorder, also known as manic-depressive illness, is a brain disorder that causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks. Symptoms of bipolar disorder are severe. Bipolar disorder symptoms can result in damaged relationships, poor job or school performance, and even suicide. But bipolar disorder can be treated, and people with this illness can lead full and productive lives.

Although bipolar disorder is a disruptive, long-term condition, you can keep your moods in check by following a treatment plan. In most cases, bipolar disorder can be controlled with medications and psychological counseling (psychotherapy) [13].

Bipolar disorder is not easy to spot when it starts. The symptoms may seem like separate problems, not recognized as parts of a larger problem. Some people suffer for years before they are properly diagnosed and treated. Like diabetes or heart disease, bipolar disorder is a long-term illness that must be carefully managed throughout a person's life.

Bipolar disorder often develops in a person's late teens or early adult years. At least half of all cases start before age 25. Some people have their first symptoms during childhood, while others may develop symptoms late in life.

2.2 The symptoms of bipolar disorder?

People with bipolar disorder experience unusually intense emotional states that occur in distinct periods called "mood episodes." An overly joyful or overexcited state is called a manic episode, and an extremely sad or hopeless state is called a depressive episode. Sometimes, a mood episode includes symptoms of both mania and depression. This is called a mixed state. People with bipolar disorder also may be explosive and irritable during a mood episode.

Extreme changes in energy, activity, sleep, and behavior go along with these changes in mood. It is possible for someone with bipolar disorder to experience a long-lasting period of unstable moods rather than discrete episodes of depression or mania.

A person may be having an episode of bipolar disorder if he or she has a number of manic or depressive symptoms for most of the day, nearly every day, for at least one or two weeks. Sometimes symptoms are so severe that the person cannot function normally at work, school, or home.

Bipolar disorder is divided into several subtypes. Each has a different pattern of symptoms. You can see symptoms reflect a range of moods in fig.2.1 .

2.2.1 Manic phase of bipolar disorder

Signs and symptoms of the manic or hypomanic phase of bipolar disorder can include:

- Euphoria
- Inflated self-esteem
- Poor judgment
- Rapid speech
- Racing thoughts
- Aggressive behavior
- Agitation or irritation
- Increased physical activity
- Risky behavior
- Spending sprees or unwise financial choices
- Increased drive to perform or achieve goals
- Increased sex drive
- Decreased need for sleep
- Easily distracted
- Careless or dangerous use of drugs or alcohol
- Frequent absences from work or school
- Delusions or a break from reality (psychosis)
- Poor performance at work or school

2.2.2 Depressive phase of bipolar disorder

Signs and symptoms of the depressive phase of bipolar disorder can include:

- Sadness
- Hopelessness
- Suicidal thoughts or behavior
- Anxiety
- Guilt
- Sleep problems
- Low appetite or increased appetite
- Fatigue
- Loss of interest in activities once considered enjoyable
- Problems concentrating
- Irritability
- Chronic pain without a known cause
- Frequent absences from work or school
- Poor performance at work or school

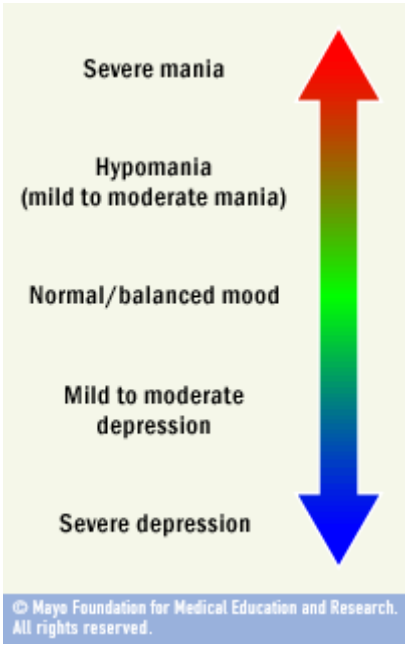

Figure 2.1: Changing of moods

2.2.3 Types of bipolar disorder

- Bipolar I disorder: Mood swings with bipolar I cause significant difficulty in your job, school or relationships. Manic episodes can be severe and dangerous.
- Bipolar II disorder: Bipolar II is less severe than bipolar I. You may have an elevated mood, irritability and some changes in your functioning, but generally you can carry on with your normal daily routine. Instead of full-blown mania, you have hypomania — a less severe form of mania. In bipolar II, periods of depression typically last longer than periods of hypomania.
- Cyclothymic disorder: Cyclothymic disorder, also known as cyclothymia, is a mild form of bipolar disorder. With cyclothymia, hypomania and depression can be disruptive, but the highs and lows are not as severe as they are with other types of bipolar disorder.[9]

2.2.4 Other signs and symptoms of bipolar disorder

- Seasonal changes in mood: As with seasonal affective disorder (SAD), some people with bipolar disorder have moods that change with the seasons. Some people become manic or hypomanic in the spring or summer and then become depressed in the fall or winter. For other people, this cycle is reversed — they become depressed in the spring or summer and manic or hypomanic in the fall or winter.
- Rapid cycling bipolar disorder: Some people with bipolar disorder have rapid mood shifts. This is defined as having four or more mood swings within a single year. However, in some people mood shifts occur much more quickly, sometimes within just hours.
- Psychosis: Severe episodes of either mania or depression may result in psychosis, a detachment from reality. Symptoms of psychosis may include false but strongly held beliefs (delusions) and hearing or seeing things that aren't there (hallucinations).[25] [24]

2.3 Causes of bipolar disorder

The exact causes of bipolar disorder is unknown for doctors and scientists, but they think and believe that there are many factors seem to be involved in causing and triggering bipolar episodes. The factors involved are thought to be a complex mix of physical, environmental and social factors.

2.3.1 Genetics

Bipolar disorder tends to run in families, so researchers are looking for genes that may increase a person's chance of developing the illness. Genes are the "building blocks" of heredity. They help control how the body and brain work and grow. Genes are contained inside a person's cells that are passed down from parents to children. [15]

Children with a parent or sibling who has bipolar disorder are four to six times more likely to develop the illness, compared with children who do not have a family history of bipolar

disorder. However, most children with a family history of bipolar disorder will not develop the illness.

Genetic research on bipolar disorder is being helped by advances in technology. This type of research is now much quicker and more far-reaching than in the past. One example is the launch of the Bipolar Disorder Phenome Database, funded in part by NIMH. Using the database, scientists will be able to link visible signs of the disorder with the genes that may influence them.

So far, researchers using this database found that most people with bipolar disorder had: [21]

- Missed work because of their illness
- Other illnesses at the same time, especially alcohol and/or substance abuse and panic disorders
- Been treated or hospitalized for bipolar disorder.

The researchers also identified certain traits that appeared to run in families, including:

- History of psychiatric hospitalization
- Co-occurring obsessive-compulsive disorder (OCD)
- Age at first manic episode
- Number and frequency of manic episodes.

Scientists continue to study these traits, which may help them find the genes that cause bipolar disorder some day.

But genes are not the only risk factor for bipolar disorder. Studies of identical twins have shown that the twin of a person with bipolar illness does not always develop the disorder. This is important because identical twins share all of the same genes. The study results suggest factors besides genes are also at work. Rather, it is likely that many different genes and a person's environment are involved. However, scientists do not yet fully understand how these factors interact to cause bipolar disorder.

2.3.2 Brain function and functioning

Brain-imaging studies are helping scientists learn what happens in the brain of a person with bipolar disorder.[28] [29] Newer brain-imaging tools, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), allow researchers to take pictures of the living brain at work. These tools help scientists study the brain's structure and activity.

Some imaging studies show how the brains of people with bipolar disorder may differ from the brains of healthy people or people with other mental disorders. For example, one study using MRI found that the pattern of brain development in children with bipolar disorder was similar to that in children with "multi-dimensional impairment," a disorder that causes symptoms that overlap somewhat with bipolar disorder and schizophrenia. [6] This suggests

that the common pattern of brain development may be linked to general risk for unstable moods.

Learning more about these differences, along with information gained from genetic studies, helps scientists better understand bipolar disorder. Someday scientists may be able to predict which types of treatment will work most effectively. They may even find ways to prevent bipolar disorder.

2.3.3 Environmental

Evidence suggests that environmental factors play a significant role in the development and course of bipolar disorder and those individual psychosocial variables may interact with genetic dispositions.[26] [2]

For example some teens, stresses such as a death in the family, their parents' divorce, or other traumatic events could trigger a first episode of mania or depression. Sometimes, going through the changes of puberty can set off an episode. In girls, symptoms can be tied to their monthly menstrual cycle. [8]

2.4 Diagnosing bipolar disorder

If your GP (general practitioner) suspects that you have bipolar disorder, they will usually refer you to a psychiatrist (a medically qualified mental health specialist). If there is a risk that you could harm yourself as a result of your illness, your GP will arrange for you to have an immediate appointment.[11]

2.4.1 Specialist assessment

At your appointment you will be assessed. The psychiatrist will ask you a number of questions to determine whether or not you have bipolar disorder and, if you have, what treatments will be most suitable for you.

During the assessment, you will be asked about your symptoms and when you first experienced them. The psychiatrist will also ask you about how you usually feel leading up to and during an episode of mania or depression, and whether you have had thoughts about harming yourself.

The psychiatrist will also want to find out about your medical background and your family history, to determine whether any of your relatives have had bipolar disorder. If someone else in your family has the condition, the psychiatrist may wish to talk to them. However, they will ask for your agreement before doing so.

2.4.2 Other tests

Depending on your symptoms, you may also require tests to see whether you have a physical problem, such as thyroid disease.

If you have bipolar disorder, you will need to visit your GP on a regular basis for a physical health check. As well as having bipolar disorder, you may have other health problems, and any medication prescribed for you may have side effects. For example, putting on weight is a common side effect of medication that is used to treat bipolar disorder.

2.4.3 Advanced directives

If you are diagnosed with bipolar disorder, it is important that you discuss your condition with the psychiatrist so you are fully involved in the decisions about your treatment and care.

However, in some cases - for example, where a person's symptoms become severe - it may not be possible for them to make an informed decision about their care, or to communicate their needs. In such situations, it may be possible to draw up an advanced directive.

An advanced directive is a set of written instructions that state what treatments and help you want (or do not want) in advance in case you cannot communicate your decisions at a later stage. Your GP or psychiatrist will be able to provide you with further help and advice about this.

2.5 Treatments and drugs

Bipolar disorder requires lifelong treatment, even during periods when you feel better. Treatment is usually guided by a psychiatrist skilled in treating the condition. You may have a treatment team that also includes psychologists, social workers and psychiatric nurses. The primary treatments for bipolar disorder include medications; individual, group or family psychological counseling (psychotherapy); or education and support groups.

- Hospitalization: Your doctor may have you hospitalized if you are behaving dangerously, you feel suicidal or you become detached from reality (psychotic).
- Initial treatment: Often, you'll need to begin taking medications to balance your moods right away. Once your symptoms are under control, you'll work with your doctor to find the best long-term treatment.
- Continued treatment: Maintenance treatment is used to manage bipolar disorder on a long-term basis. People who skip maintenance treatment are at high risk of a relapse of symptoms or having minor mood changes turn into full-blown mania or depression.
- Substance abuse treatment: If you have problems with alcohol or drugs, you'll also need substance abuse treatment. Otherwise, it can be very difficult to manage bipolar disorder.[20]

2.5.1 Medications

A number of medications are used to treat bipolar disorder. If one doesn't work well for you, there are a number of others to try. Your doctor may suggest combining medications for maximum effect. Medications for bipolar disorder include those that prevent the extreme highs and lows that can occur with bipolar disorder (mood stabilizers) and medications that help with depression or anxiety.[3] [23]

Medications for bipolar disorder include:

- Lithium
- Anticonvulsants
- Antipsychotics
- Antidepressants
- Symbyax
- Benzodiazepines

2.5.2 Psychotherapy

Psychotherapy is another vital part of bipolar disorder treatment. Several types of therapy may be helpful. These include:

- Cognitive behavioral therapy
- Psychoeducation
- Family therapy
- Group therapy

2.5.3 Hospitalization

In some cases people with bipolar disorder can benefit from hospitalization. Getting psychiatric treatment at a hospital can help keep you calm and safe and stabilize your mood, whether you're having a manic episode or a deep depression. Partial hospitalization or day treatment programs also are options to consider. These programs provide the support and counseling you need while you get symptoms under control. [4]

Chapter 3

Methods

I use two methods Approximate Entropy (ApEn) and Circadian rhythm (CiRh).

3.1 Approximate Entropy (ApEn)

Several studies have reported evidence of chaotic processes appearing in psychiatric conditions, including bipolar disorder [7], schizophrenia[16] and depression[17]. These findings suggest that non-linear approaches to the analysis of longitudinal data from patients with bipolar disorder may provide information not apparent from traditional statistics.

The mathematical techniques used for the detection of non-linear complex systems arose from the physical sciences, where very long time series of data with consistent patterns are typically available for analysis. However, biological time series are characterized by high levels of noise[12], restricted amount of data available and problems with non-stationarity [5]. Recently refined non-linear measuring techniques are more applicable.

In 1991, Pincus introduced approximate entropy (ApEn), a model-independent statistic to quantify regularity in time series data [18], which is well suited for the short, noisy datasets available for physiologic data. ApEn measures regularity or the predictability that a pattern in a time series remains the same on incremental comparisons. In contrast, the standard deviation statistic measures variability around a mean without regard to the order of data in a time series.

ApEn is defined by three input parameters [27]:

$$ApEn(N, m, r) \tag{3.1}$$

Where m ... specifies the pattern length, r ... defines the criterion of similarity and N ... number of elements in the data series (sequence).

3.1.1 Algorithm for approximate entropy

Fix m, a positive integer, and r, a positive real number. Given a time-series of data *u(1)*, *u(2)*, ..., *u(N)*, from measurements equallyspaced in time, from a sequence of vectors *x(1)*, *x(2)*, ..., *x(N - m + 1)* in R^m, defined by *x(i) = [u(i), u(i +1, ..., u(i + m - 1))]*. Next, define for each i, $1 \leq i \leq N - m + 1$,

$$C_i^m(r) = (number \quad of \quad "j" \quad such \quad that \quad d[x(i), x(j)] \leq r)/(N - m + 1) \tag{3.2}$$

We must define *d[x(i), x(j)]* for vectors *x(i)* and *x(j)*.We define:

$$d[x(i), x(j)] = max_{k=1,2,...,m}(|u(i + k - 1) - u(j + k - 1)|) \tag{3.3}$$

From the $C_i^m(r)$, define

$$C^m(r) = (N - m + 1)^{-1} \sum_{i=1}^{N-m+1} C_i^m(r) \tag{3.4}$$

and define

$$\beta = \lim_{r \to 0} \lim_{N \to \infty} \log C^m(r)/r \tag{3.5}$$

The assertion is that for m sufficiently large, β_m is the correlation dimension. Such a limiting slope has been shown to exist for the commonly studied chaotic attractors.

Define

$$\Phi^m(r) = (N - m + 1)^{-1} \sum_{i=1}^{N-m+1} \log C_i^m(r) \tag{3.6}$$

Fix m and r in Eq.4.6; define

$$ApEn(m, r) = \lim_{N \to \ infty} [\Phi^m(r) - \Phi^{m+1}(r)] \tag{3.7}$$

Given N data points, we implement this formula:

$$ApEn(N, m, r) =^m (r) - \Phi^{m+1}(r) \tag{3.8}$$

If we find similar patterns in a rate time series, ApEn estimates the logarithmic likelihood that the next intervals after each of the patterns will differ (i.e., that the similarity of the patterns is mere coincidence and lacks predictive value). Smaller values of ApEn imply a greater likelihood that similar patterns of measurements will be followed by additional similar measurements. If the time series is highly irregular, the occurrence of similar patterns will not be predictive for the following measurements, and ApEn will be relatively large. [19] [22]

These properties are shown on two examples with regular periodic sinusoidal signal in fig.3.1 and irregular signal with noise in fig.3.2. Signal in fig.3.1 has very small value of ApEn and it is very good predictable than signal in fig.3.2 where value of ApEn is higher.

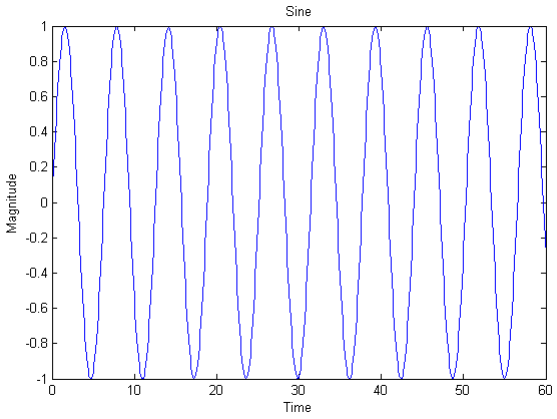

Figure 3.1: Sine: ApEn = 0.021

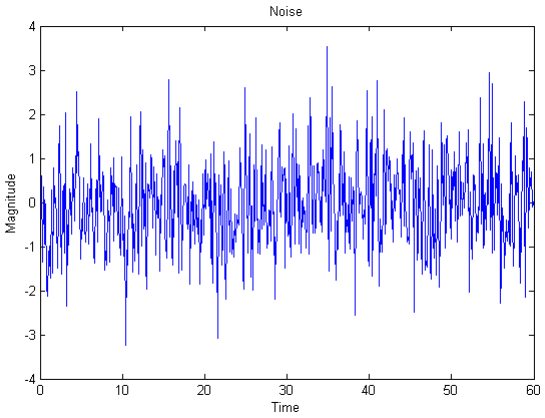

Figure 3.2: Noise: ApEn = 0.672

3.2 Circadian Rhythms (CiRh)

It has been proposed that patients with bipolar disorder have abnormally shifted or arrhythmic circadian systems. The term "circadian" refers to a time frame of "about 1 day" and captures an interesting feature of the circadian clock, namely, that it runs slightly longer or shorter than 24 hours. Evolution has endowed us with a biological system that is highly responsive to zeitgebers("timegivers")—stimuli in the environment that cue the system so that our circadian rhythms become synchronized with the activity in the world around us. Our system is particularly sensitive to the zeitgeber light.

An active process known as entrainment keeps our system aligned with external time and allows it to shift as the balance of light and dark varies across the seasons and as we travel from one time zone to another. It is an incredibly simple yet intricately orchestrated system. The "master clock" is located in the suprachiasmatic nucleus (SCN) in the anterior hypothalamus.

The SCN governs all circadian rhythms and is supplemented by a large number of peripheral clocks across organs and cells [1]. When the system is in harmony, it is fully synchronized by the SCN. But this harmony across systems can be easily lost at various junctures, including

between the SCN and external time and between the SCN and different organs in the body. For the latter, each clock is differentially sensitive to zeitgebers. The SCN is very responsive to light, the clock in the liver is very sensitive to food, and clocks in muscle are sensitive to exercise. So there are many inputs that can influence and contribute to harmony and dysregulation.

Several studies have suggested that bipolar disorder is characterized by enhanced light sensitivity. For example, in a recent study light was administered in the morning or at midday to nine depressed women with bipolar disorder. Three of the four who received light in the morning developed a mixed state, and the other responded well. Four of the five who received midday light responded well. It is possible that the greater impact in the morning reflects an increased sensitivity of the photoreceptors in the eye.

3.2.1 Circadian Rhythm instability

Circadian rhythm instability was operationalised using a nonparametric method of activity data analysis. Circadian data is commonly modeled using a 1-cycle-per-day, cosinor curve fitting technique. However, modeling based on cosinor functions often provide a relatively poor fit when applied to activity data. The 24-hour pattern in activity appears to approximate more closely a square-like wave than a cosinor function [14].

Van Someren developed a nonparametric method of data analysis that does not rely on the assumptions associated with cosinor curve fitting [30]. This method of activity data analysis has been applied across a wide range of populations, including patients with Alzheimer's disease, patients with seasonal affective disorder and in your case patients with BD.

For the present study nonparametric variables describing the 24-hour pattern in activity were used for hypothesis testing. Given the significant concerns regarding the suitability of cosinor model fitting to 24-hour activity data, these curve parameters were not used for hypothesis testing.

3.2.2 Nonparametric technique

Three measures of circadian rhythm instability can be derived from the nonparametric technique described by Van Someren [31]. Relative Amplitude (RA), Intradaily Variability (IV), and Interdaily Stability (IS).

3.2.2.1 Relative Amplitude (RA)

RA describes the strength of the activity rhythm based on the difference between the most active 10-hour period (the period of 10 consecutive hours within the 24-hour day with the highest average level of activity; M10) and the least active 5-hour period (the period of 5 consecutive hours within the 24-hour day with the lowest average level of activity; L5), relative to an estimation of total activity (i.e., M10 + L5).

A higher ratio indicates a stronger and more stable rhythm. The difference between M10 and L5 is expressed relative to an estimation of total activity in order to standardize between-person differences in activity levels. Individual preferences for different types of activities (e.g., running vs. Platiny chess) mean that standardized amplitude is a more valid reflection

of activity rhythm strength. Vigorous types of exercise can increase the level of activity and amplify the raw amplitude independent of an improvement in rhythm strength and stability.

The equation for computing RA:

$$RA = \frac{M10 - L5}{M10 + L5} \tag{3.9}$$

3.2.2.2 Intradaily Variability (IV)

IV provides an indication of rhythm fragmentation, reflecting the frequency of rest/activity transitions in a given 24-hour period. It is calculated as the ratio of the mean squares of the difference between consecutive hours and the mean squares around the 24-hour mean. A higher IV ratio indicates greater rhythm fragmentation and reduced stability of the activity rhythm.

The algorithm for computing IV:

$$IV = \frac{n \sum_{i=2}^{n} (x_i - x_{i-1})^2}{(n-1) \sum_{i=1}^{n} (x_i - \bar{x})^2} \tag{3.10}$$

3.2.2.3 Interdaily Stability (IS)

IS provides an indication of the strength of coupling between the activity rhythm and the presumed 24-hour exogenous zeitgeber pattern. It is calculated as the ratio between the variance of the average 24-hour pattern around the mean and the variance of the overall activity pattern across multiple days. A lower IS ratio indicates reduced stability in the activity rhythm.

The computational algorithm for IS:

$$IS = \frac{n \sum_{h=1}^{p} (\bar{x}_h - \bar{x})^2}{p \sum_{i=1}^{n} (x_i - \bar{x})^2} \tag{3.11}$$

Where:

n ... total number of data,
p ... total number of data per day,
$\bar{x}_h$ ... hourly means,
$\bar{x}$ ... is the mean of all datas,
x_i ... invidual data points.

Chapter 4

Data pre-processing

The following chapter describes the main steps that were necessary for data processing. The work concentrates on individual data analysis of two patients. Although at first sight one can argue that the number of patients is not sufficient, the study makes use of long-term data which are very difficult to acquire. This is a classical type of a medical case study in which two types of data exist. One source of data are abjecvitely acquired by measuring physical activity. The second source of data are obtained by patient itself filling. However, I only focus on the objective data.

4.1 Actigraphy

Actigraphy is an objective, ambulatory monitoring method for tracking a patient's sleep/wake activity patterns over time. Monitoring was performed with an actigraph device fig.4.1. The actigraph device is worn continuously like a standard wristwatch.

It is non-invasive and can be worn easily 24/7 by almost all the patients, thus it can be used in the comfort of the patient's own home for multiple days and nights. The device is especially useful when self-reporting is not an option as with patients who cannot accurately or reliably self-report sleep information.

The actigraphy analysis provides sleep schedule variability, sleep quantity and quality statistics, and daytime activity patterns for weeks at a time. It has been widely used and well validated in the field of sleep research for years. The long-term data collected from the home environment by actigraphy also provides sleep efficiency, total sleep time and sleep start and end times not available from any other methods. For these reasons the actigraphy is used to detect movement activity of patients with bipolar disorder. [10]

4.1.1 Actigraphy of patients

The actigraphy of both patients are showed in fig.4.2 and fig.4.3 . These are the charts of patients with an overall record since the start of testing when they have put the actiwatch on.

The table tab.4.1 describes data properties of both patients.

The monitoring of data were not continuos due to two sources of failures apperead during data acquisition:

Figure 4.1: Wrist actiwatch

Patient number	Start date	Stop date	Sampling frequency	Number of samples	New sampling frequency	New number of samples
1	6.11.2006	21.8.2009	120s	733 630	-	-
6	31.5.2007	17.8.2008	30s	1 279 771	120s	319 943

Table 4.1: Information table for testing data

1. Shutdown due to a low battery
2. Zero activity caused by not wearing the actiwatch

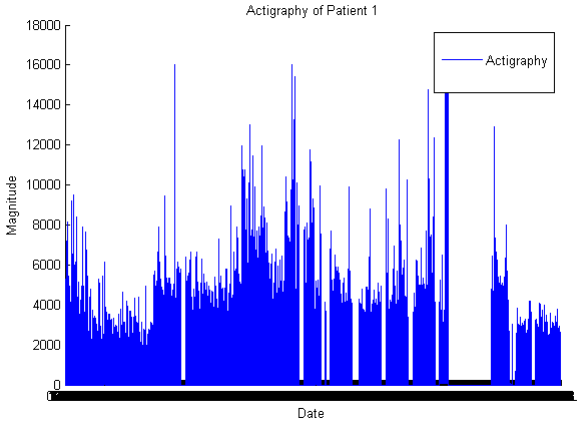

Figure 4.2: Actigraphy data. Patient number 1 (P1)

An example of recorded data for patient no.1 is shown in fig.4.2. This record includes mainly shorter interruptions and only one longer discontinuity of several months has been detected for 3 years.

For better visibility a weekly record was chosen in fig.4.4 (a calculating window of 7 days) in which a very regular cycle is apparent. Depending on the progression of the week it is

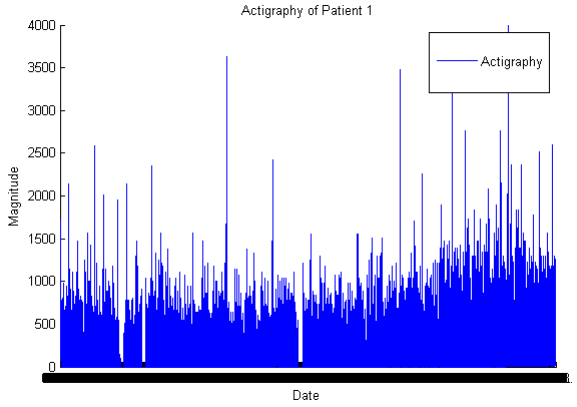

Figure 4.3: Actigraphy data. Patient number 6 (P6)

estimated that the very low magnitudes embody nights while the large magnitudes represent patient's activity during days.

The other actigraphy charts of patient no.6 can be found in Appendix C.1

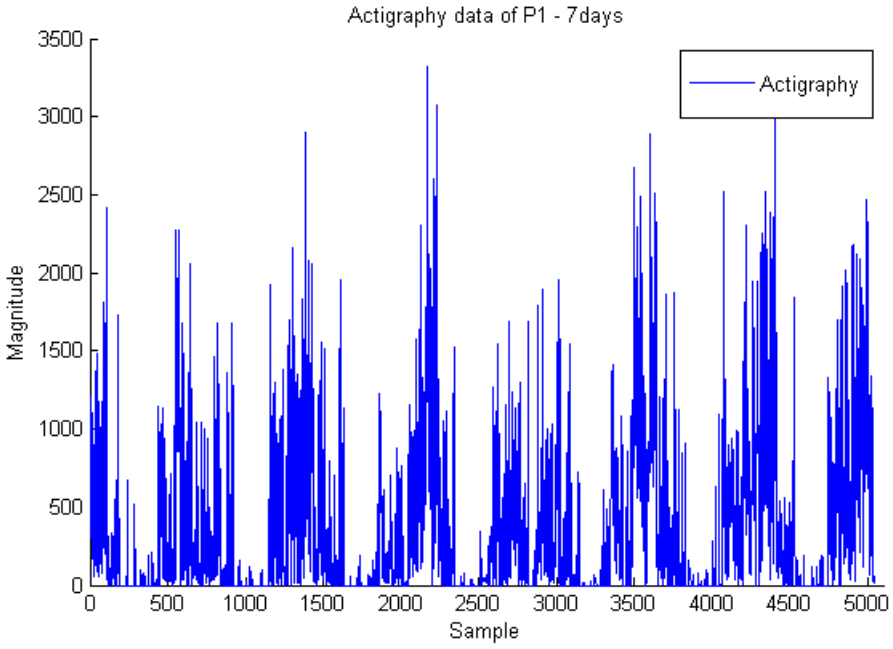

Figure 4.4: Actigraphy data of 7 days. Patient number 1 (P1)

Chapter 5

Results

The results of relapse prediction are presented in this chapter. We expected some differences in values of two selected measures (Approximative Entropy and Circadian Rhythm) comparing data before and after relapse. The study worked with various lengths of the before relapse (BR) and after relapse (AR) windows length of 7, 14, 30 or more days. However, the time for prediction of relapse were constant (the prediction parameter (PP) is always 3 or 7 days) as well as the time for returning into a stable mood (the stabilizing parameter (SP) is always 5 days). If there was a failure of data, I set the SP with a length of 5 days within the first valid data. Finally, the results in fig.5.1 are presented for PP 3 days and SP of 5 days.

Regarding CiRh, the figures are depicted for RA, IS and IV parameters. I can only set the lengths of windows and compare results' outputs parameters of CiRh. Properties of parameters Ra, IS and IV are described in section 3.2.2. It was necessary to remove data from actigraphy which contain 3 hours of idle in 24 hours interval due to inaccuracy of the method CiRh. The testing window for testing CiRh is always 7 days.

Why I compared data before and data after relapses? Again, the main underlying hypothesis is that that patient's behaviour will be different before and after relapses. The BR behaviour will be more chaotic and irregular in comparison to the AR behaviour which is expected to stabilize after hospitalization or drug administration. Thus the final value of ApEn BR is ideally bigger than the final value of ApEn AR.

In this bachelor thesis I tried to predict relapses using prediction length 3 and 7 days. Therefore I compared various lengths of windows before and after relapses. The results of the methods are presented for patient no.1 only. The results of patient no.6 are described in Appendix C.2.

5.1 Results of ApEn

The results for ApEn are depicted for different configuration of three variables N, r and m which govern the ApEn function behavior. First, the parameter m was fixed and parameter r changed. There are no big differences between the after onset and before onset of the bipolar event as it is demonstrated in fig.5.2 and fig.5.3

Finally, the variables r, m were fixed to the combinations in which r=*0,1*; m=*3* or r=*0,15*; m=*2*. In the continual figure fig.5.4 these two combinations of parametrs are collated. Compared to the ApEn of the parametrs r=*0,1* and m=*3*, the final ApEn of the variables r=*0,15* and m=*2* is higher.

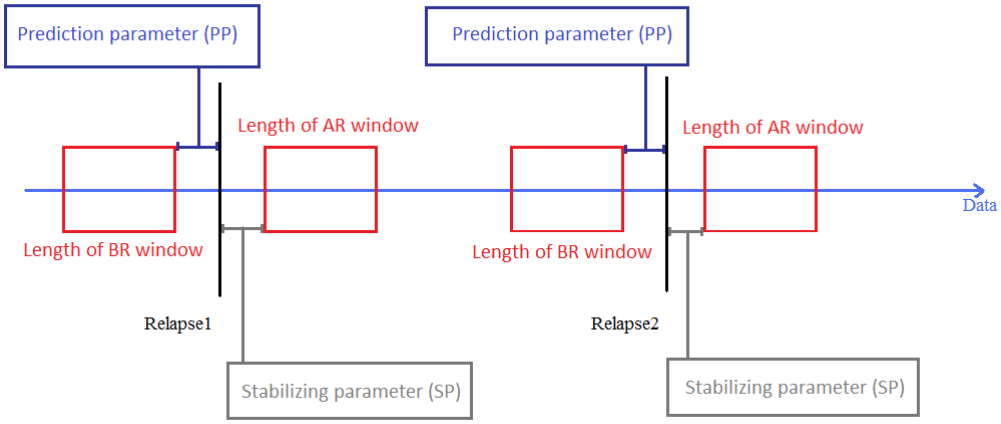

Figure 5.1: Caltulation windows

In the figures fig.5.5 there are presented results for the PP of 3 days and the SP of 5 days with two combinations of parameters m and r. The length of BR windows is 7 days. (For other combinations of PP, BR and AR windows you can see Appendix A). Generally there are no large differences between data before and data after. However, in some cases we can see that the final value of ApEn before relapse is lower than final value of ApEn after relapse even though the opposite result is expected.

The bar charts in fig.5.6 shows the values of differences between data before and data after relapse.

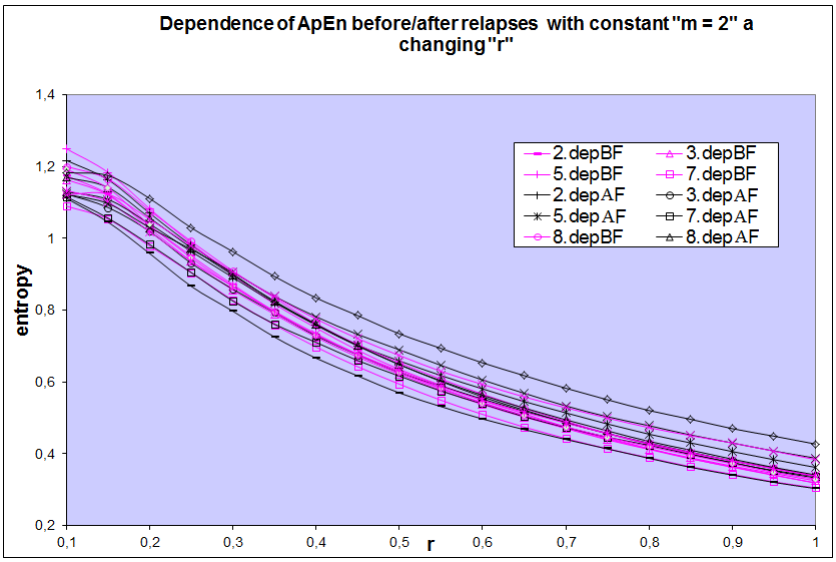

Figure 5.2: Compare data BF and AF 3days before: m = 2

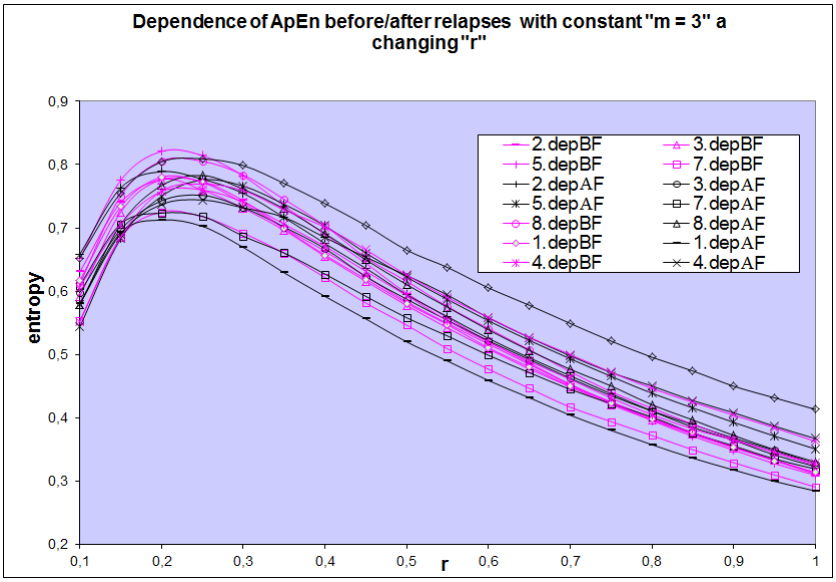

Figure 5.3: Compare data BF and AF 3days before: figure m = 3

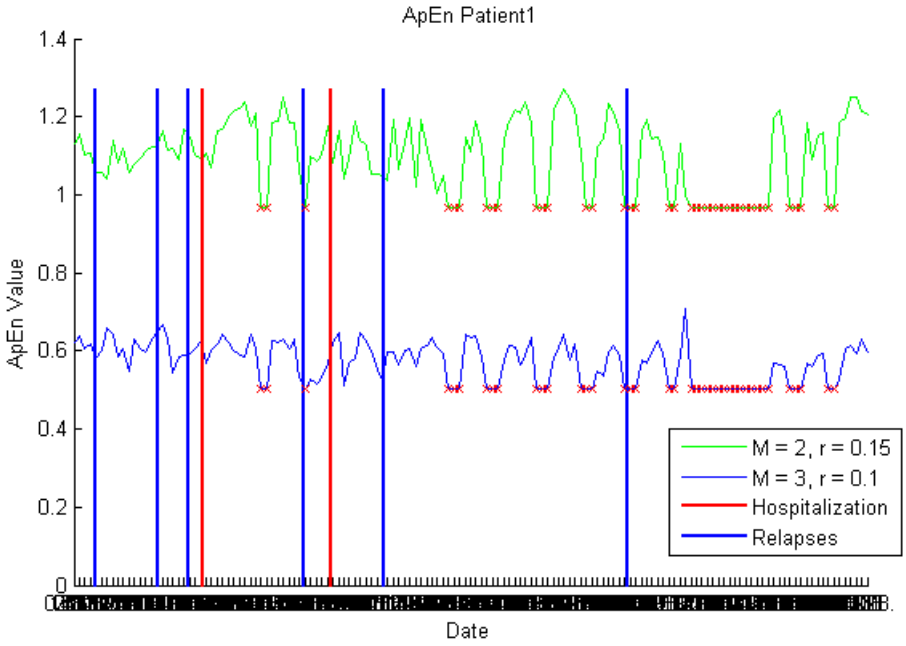

Figure 5.4: P1: Continual with both combination of parameters

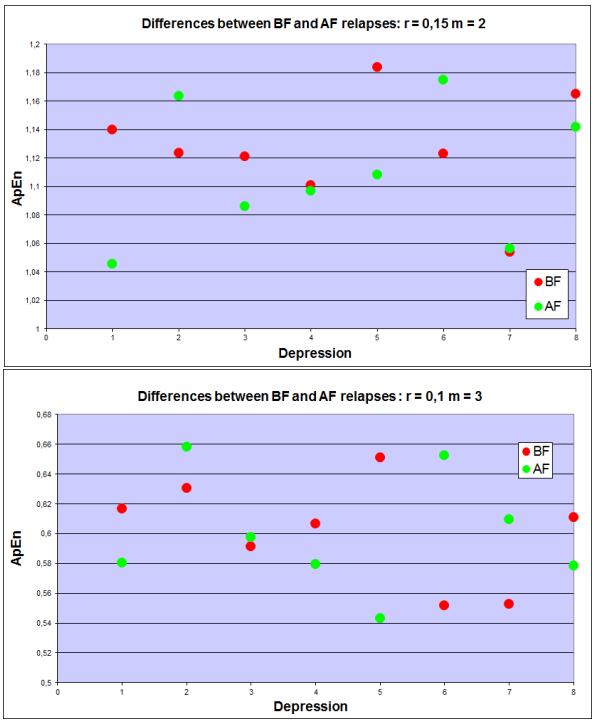

Figure 5.5: Differences between BF and AF - 3days before: figure m = 2 and figure m = 3

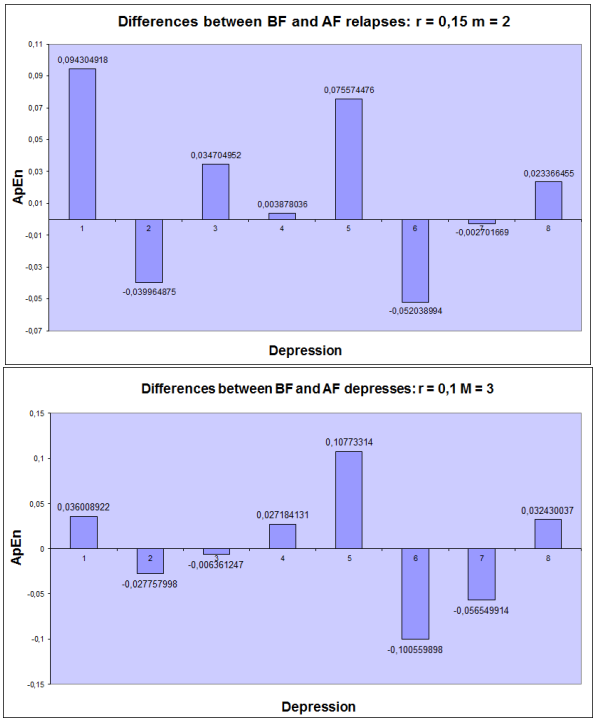

Figure 5.6: Value of Differences between BF and AF - 3days before: figure m = a and figure m = 3

5.2 Results of CiRh

By the CiRh method, the parameters RA, IV and IS were analyzed. The data including 3 hours of inactivity and more were removed. For the purpose of the method I created continual figures with calculation windows of 7 days. So each sample represents 7 days of testing data.

The results of parameter IV is depicted in fig.5.7. As stated in section 3.2.2.2, a higher IV ratio indicates greater rhythm fragmentation and reduced stability of the activity rhythm.

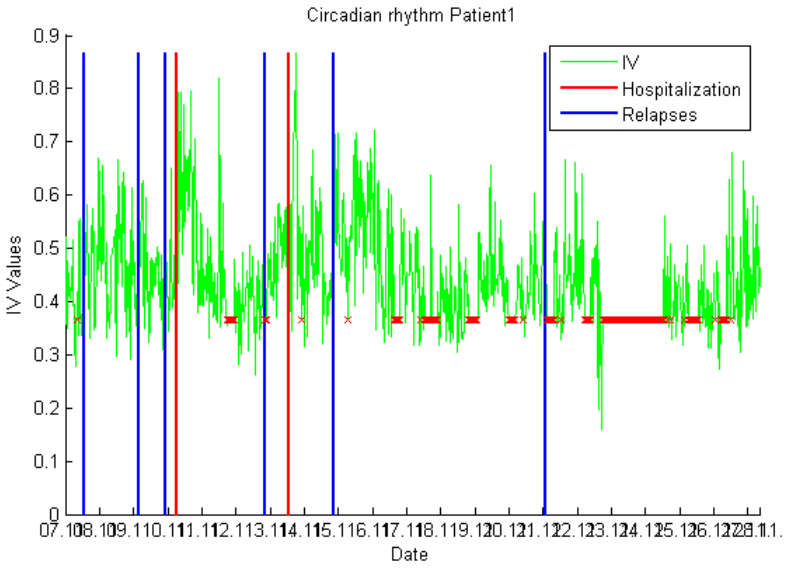

Figure 5.7: Parameter IV

As mentioned in section 3.2.2.3, a lower IS ratio indicates reduced stability in the activity rhythm. Fig.5.8.

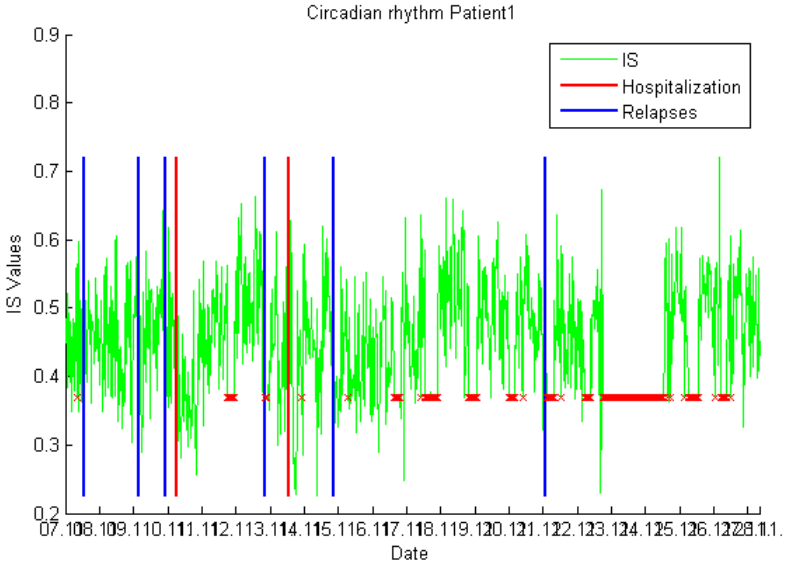

Figure 5.8: Parameter IS

RA parameter defines a difference between M10 and L5 and its higher ratio indicates a stronger and more stable rhythm as it is described in section 3.2.2.1. As can be noted in fig.5.9, there is asymptotic behavior approaching to value 1.

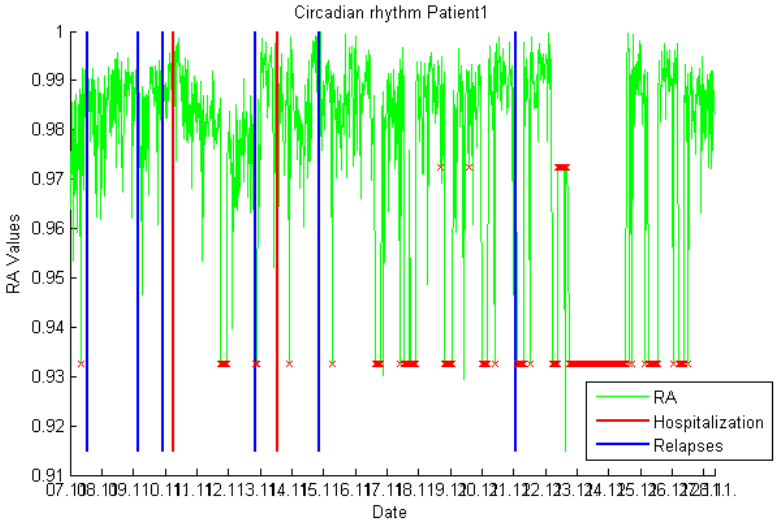

Figure 5.9: Parameter RA

In the figures below, there are presented results of paremeters IV (fig.5.10), IS (fig.5.11) and RA (fig.5.12) for relapse no.1 with this corresponding settings: the PP of 3 days, the SP of 5 days and BR and AR windows of 7 days. The results of CiRh parameters BR and

AR are compared. Relapse no.1 was chosen due to the biggest difference between parameters BR an AR.

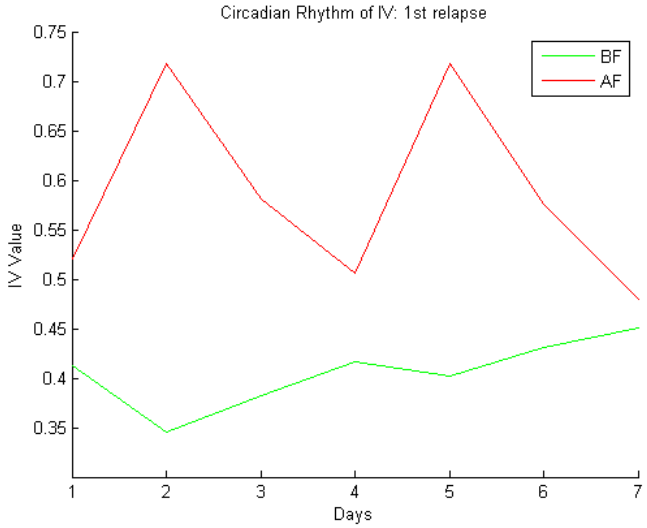

Figure 5.10: Parameter IV: Compare data before and after relapse - window of 7 days

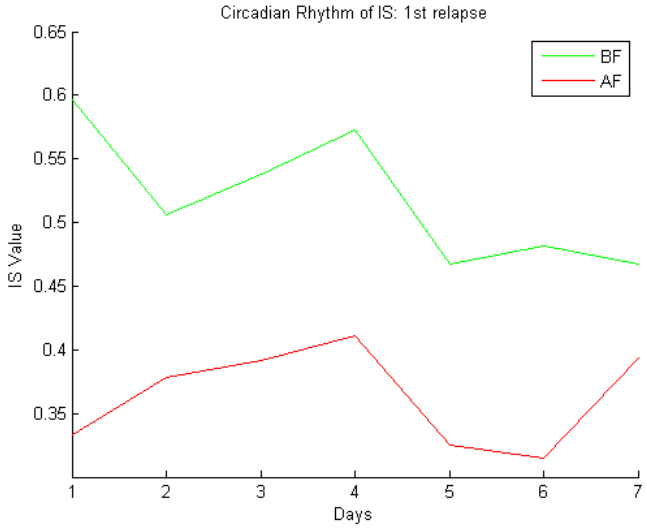

Figure 5.11: Parameter IS: Compare data before and after relapse - window of 7 days

Other graphs for patient no.1 are included in Appendix B.1.

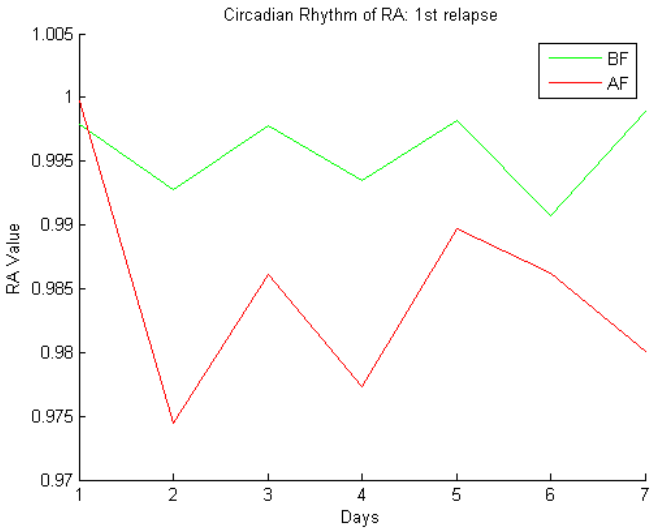

Figure 5.12: Parameter RA: Compare data before and after relapse - window of 7 days

Chapter 6

Conclusion

In this bachelor thesis the goal was to predict relapses of patients suffering from bipolar disorder. Two methods were applied: Aproximative Entropy and Circadian Rhythm.

Parameters of ApEn m and r were varied in order to find optimal value settings. The ApEn was calculated for different length of calculation window before and after relapse. The results for various long calculation windows are very similar for various combinations of parameters m and r. Therefore the optimal parameters m and r was chosen according the greatest difference of resulting ApEn measure. The combination *m=2*, *r=1,5* and combination *m=3*, *r=1* prove to have the greatest differences in comparison with other combinations. As a conclusion, ApEn in this case is not very suitable for predicting relapses. There are not differences settings of 3 or 7 days as prediction parameter. Next problem was data failure when ApEn measure is very sensitive to missing data.

Regarding the CiRh methodology, the window calculation length was set to 7 days in all cases. Results of parameters RA, IV and IS show in most cases that there is difference before and after bipolar event. For example value IV before relapse are generally lower than after relapse as can be seen in fig.5.10. The results of parameters IV and IS are very surprising indicating that the patient no.1 has more stable organization of the circadian rest-activity rhythm before relapses than after relapses.

Results of parameters IV and IS during relapses correspond to the definitions describing above (section 3.2.2). Parameter RA has very high values indication that the stability of CiRh is high except of two relapses. Differences between each relapses are very small and the values of each relapses are very high except two relapses (1st and 5th) which are smaller compared to other relapses.

As future direction, I propose to correlate the processed data as described above with subjectively acquired data. Further point would be enhancement of our database where more data will offer clearer insight on possibility of relapse prediction.

Bibliography

[1] W.-J. A. Chronobiology and mood disorders. Dialogues Clin Neurosci 2003; 5:315—325.

[2] L. Alloy, L. Abramson, S. Urosevic, P. Walshaw, R. Nusslock, and A. Neeren. The psychosocial context of bipolar disorder: Environmental, cognitive, and developmental risk factors. Clinical Psychology Review 25 (8). (December 2005): 1043–75.

[3] C. Andreescu and a. et. Complementary and alternative medicine in the treatment of bipolar disorder. A review of the evidence. Journal of Affective Disorders. 2008;110:16.

[4] T. Becker and R. Kilian. Psychiatric services for people with severe mental illness across western europe: what can be generalized from current knowledge about differences in provision, costs and outcomes of mental health care? Acta Psychiatrica Scandinavica Supplement 429 (429).2006 : 9–16.

[5] P. Faure and H. Korn. Is there chaos in the brain? i. concepts of non-linear dynamics and methods of investigation. C R Acad Sci III 2001; 324: 773–793.

[6] N. Gogtay, A. Ordonez, D. Herman, K. Hayashi, D. Greenstein, C. Vaituzis, M. Lenane, L. Clasen, W. Sharp, J. Giedd, D. Jung, I. Nugent, A. Toga, E. Leibenluft, P. Thompson, and J. Rapoport. Dynamic mapping of cortical development before and after the onset of pediatric bipolar illness. J Child Psychol Psychiatry. 2007 Sep;48(9):852-862.

[7] A. Gottschalk, M. Bauer, and P. Whybrow. Evidence of chaotic mood variation in bipolar disorder. Arch Gen Psychiatry 1995; 52: 947–959.

[8] L. Grandin, L. Alloy, and L. Abramson. Childhood stressful life events and bipolar spectrum disorders.
`http://guilfordjournals.com/loi/jscp/`,Volume 31, 2012: 0736-7236.

[9] A. H.S. Kaplan sadock's comprehensive textbook of psychiatry. lippincott williams wilkins:philadelphia. Mood Disorders: Clinical Features. in Sadock BJ, Sadock VA (ed). (2005).

[10] http://www.learnactiware.com. Actigraphy.
`http://www.learnactiware.com/documentation/actigraphybrochure.pdf`,
Accessed on Jan.,012.

[11] http://www.nhs.uk. Bipolar disorder - diagnosis.
`http://www.nhs.uk/Conditions/Bipolar-disorder/Pages/Diagnosis.aspx/`,
Accessed on Jan.,012.

[12] M. Huber, H. Braun, and J. Krieg. Effects of noise on different disease states of recurrent affective disorders. Biol Psychiatry 2000; 47: 634–642.

[13] R. Kessler, P. Berglund, O. Demler, R. Jin, K. Merikangas, and E. Walters. Lifetime prevalence and age-of-onset distributions of dsm-iv disorders in the national comorbidity survey replication. Arch Gen Psychiatry. 2005 Jun;62(6):593-602.

[14] W. Nelson, J. Tong, Y. L.and Lee, and F. Halberg. Methods for cosinorrhythmometry. Chronobiologia 1979; 6: 305-323.

[15] J. Nurnberger and T. Jr. Foroud. Genetics of bipolar affective disorder. Curr Psychiatry Rep. 2000 Apr;2(2):147-157.

[16] M. Paulus, M. Geyer, and D. Braff. Use of methods from chaos theory to quantify a fundamental dysfunction in the behavioural organization of schizophrenic patients. Am J Psychiatry 1996; 153: 714–717.

[17] L. Pezard, J. Nandrino, B. Renault, and et al. Depression as a dynamical disease. Biol Psychiatry 1996; 39: 991–999.

[18] S. Pincus, I. Gladstone, and R. Ehrenkranz. A regularity statistic for medical data analysis. J Clin Monit 1991; 7: 335–345.

[19] S. Pincus and A. Goldberger. Physiological time-series analysis: What does regularity quantify? Am J Physiol 1994;266(Heart Circ Physiol):H1643-H1656.

[20] R. Post. Bipolar disorder in adults: Maintenance treatment. `http://www.uptodate.com/home/index.html/`, Accessed Jan. 3, 2012.

[21] J. Potash, J. Toolan, J. Steele, E. Miller, J. Pearl, P. Zandi, T. Schulze, L. Kassem, S. Simpson, V. Lopez, D. MacKinnon, and F. McMahon. The bipolar disorder phenome database: a resource for genetic studies. Am J Psychiatry. 2007 Aug;164(8):1229-1237.

[22] S. Ryan, A. Goldberger, S. Pincus, J. Mietus, and L. Lipsitz. Gender and age-related differences in heart rate dynamics: Are women more complex than men? J Am Coll Cardiol 1994;24:1700-1707.

[23] J. Sarris and a. et. Bipolar disorder and complementary medicine: Current evidence, safety issues, and clinical considerations. The Journal of Alternative and Complementary Medicine. 2011;17:881.

[24] C. Schneck, D. Miklowitz, J. Calabrese, M. Allen, M. Thomas, S. Wisniewski, S. Miyahara, M. Shelton, T. Ketter, J. Goldberg, C. Bowden, and G. Sachs. Phenomenology of rapid-cycling bipolar disorder: data from the first 500 participants in the systematic treatment enhancement program. Am J Psychiatry. 2004 Oct;161(10):1902-1908.

[25] C. Schneck, D. Miklowitz, S. a. A. M. Miyahara, S. Wisniewski, L. Gyulai, M. Allen, M. Thase, and G. Sachs. The prospective course of rapid-cycling bipolar disorder: findings from the step-bd. Am J Psychiatry. 2008 Mar;165(3):370-7; quiz 410.

[26] A. Serretti and L. Mandelli. The genetics of bipolar disorder: genome 'hot regions,' genes, new potential candidates and future directions. Molecular Psychiatry 13 (8).(August 2008): 742–71.

[27] P. S.M. Approximate entropy as a measure of system complexity. Proc Natl Acad Sci USA 1991; 88: 2297–2301.

[28] J. Soares and J. Mann. The anatomy of mood disorders–review of structural neuroimaging studies. Biol Psychiatry. 1997 Jan 1;41(1):86-106.

[29] J. Soares and J. Mann. The functional neuroanatomy of mood disorders. J Psychiatr Res. 1997 Jul-Aug;31(4):393-432.

[30] E. J. W. Van Someren, A. Kessler, M. Mirmiran, and D. F. Swaab. Indirect bright light improves circadian rest-activity rhythm disturbances in demented patients. Biological Psychiatry 1997; 41: 955-963.

[31] E. J. W. Van Someren, D. F. Swaab, C. C. Colenda, W. Cohen, W. V. McCall, and P. B. Rosenquist. Bright light therapy: improved sensitivity to its effects on rest-activity rhythms in alzheimer patients by application of nonparametric methods. Chronobiology Internationa 1999; 16(4): 505-518.

Appendix A

Patient number 1 (P1)

A.1 Figures of ApEn: Window before relapses - 3days; parameters -> m = 2, r = 0.15

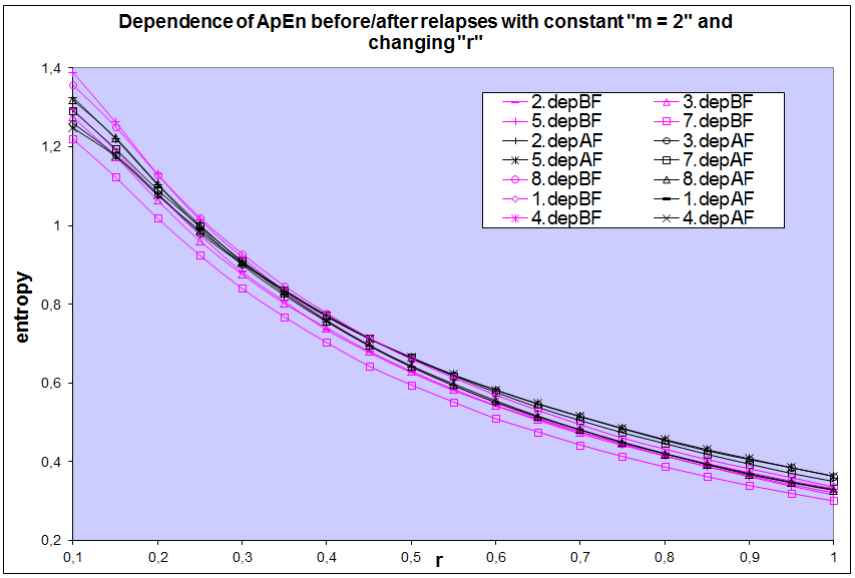

Figure A.1: ApEn: Compare data BD and AF relapses - 14days

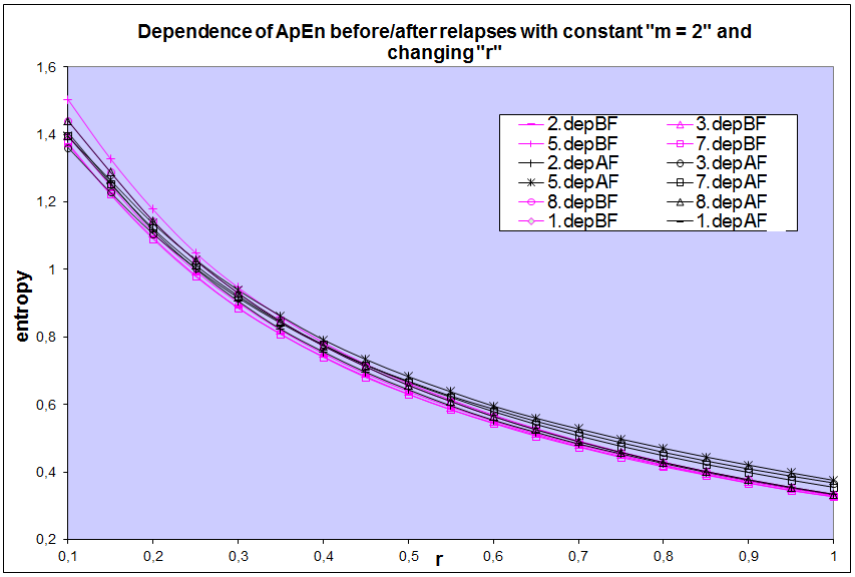

Figure A.2: ApEn: Compare data BD and AF relapses - 30days

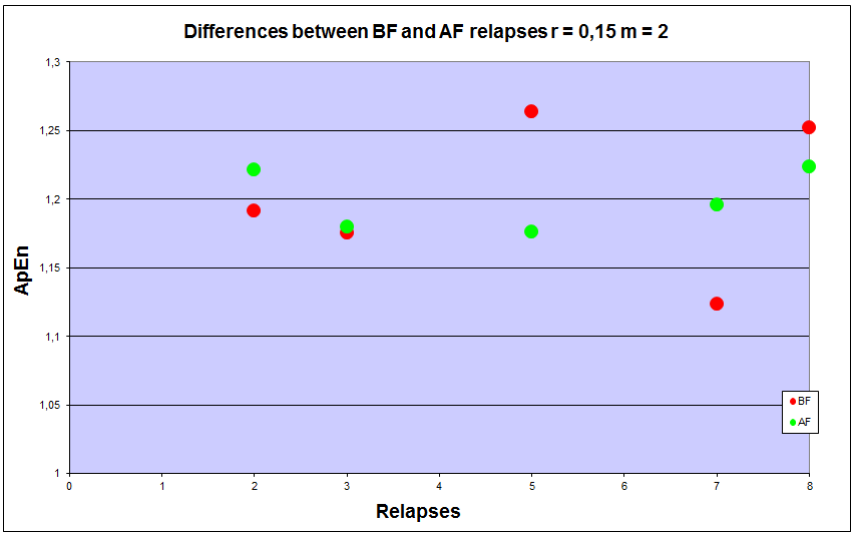

Figure A.3: ApEn: Differences between BD and AF relapses - 14days

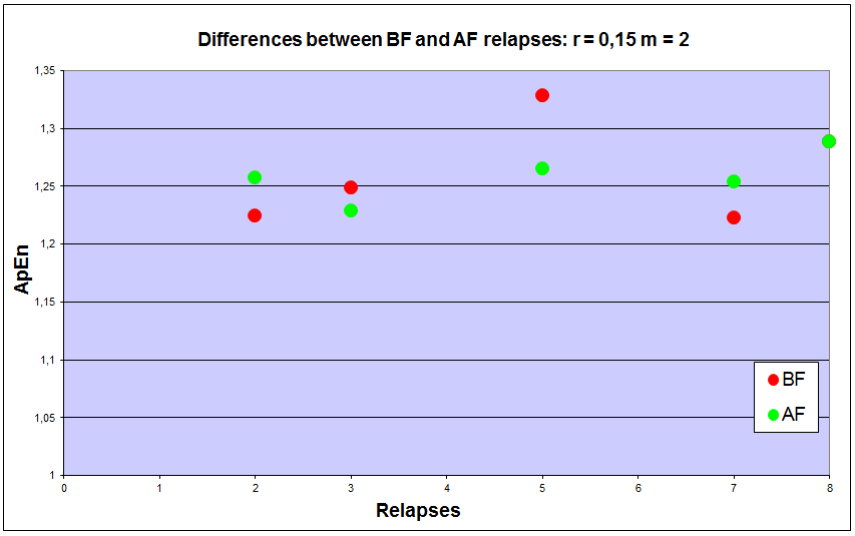

Figure A.4: ApEn: Differences between BD and AF relapses - 30days

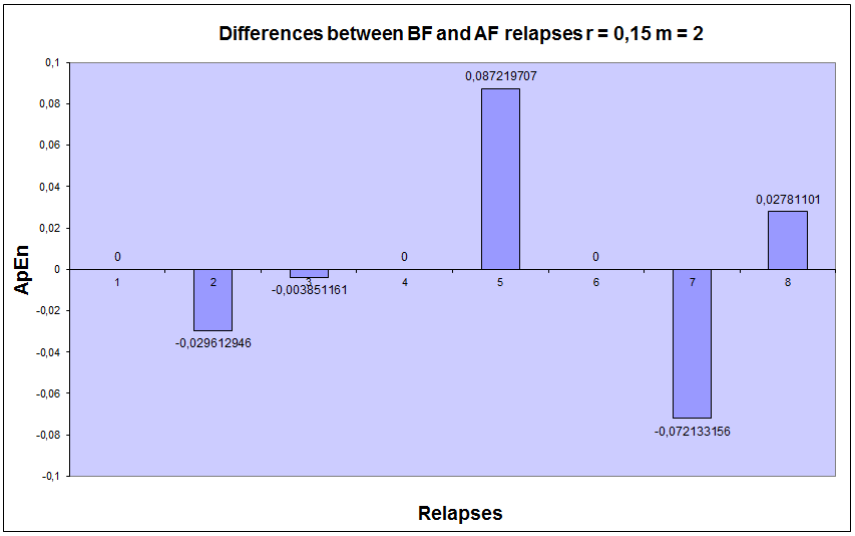

Figure A.5: ApEn: Value of differences between BD and AF relapses - 14days

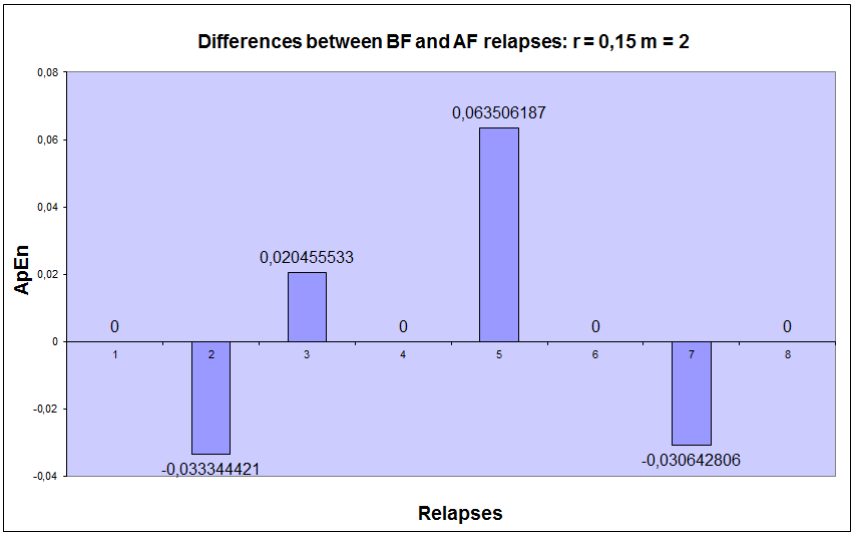

Figure A.6: ApEn: Value of differences between BD and AF relapses - 30days

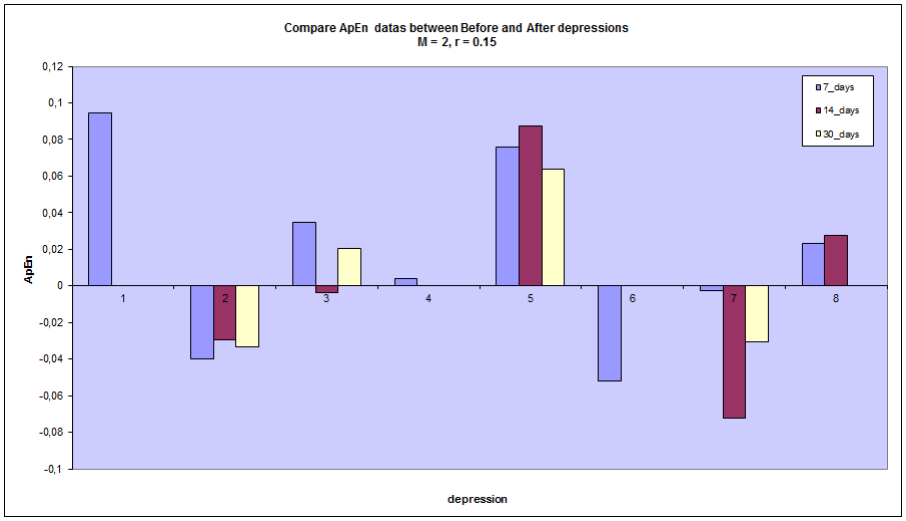

Figure A.7: ApEn: Value of differences between BD and AF relapses - 7/14/30days

A.2 Figures of ApEn: Window before relapses - 3days; parameters -> m = 3, r = 0.1

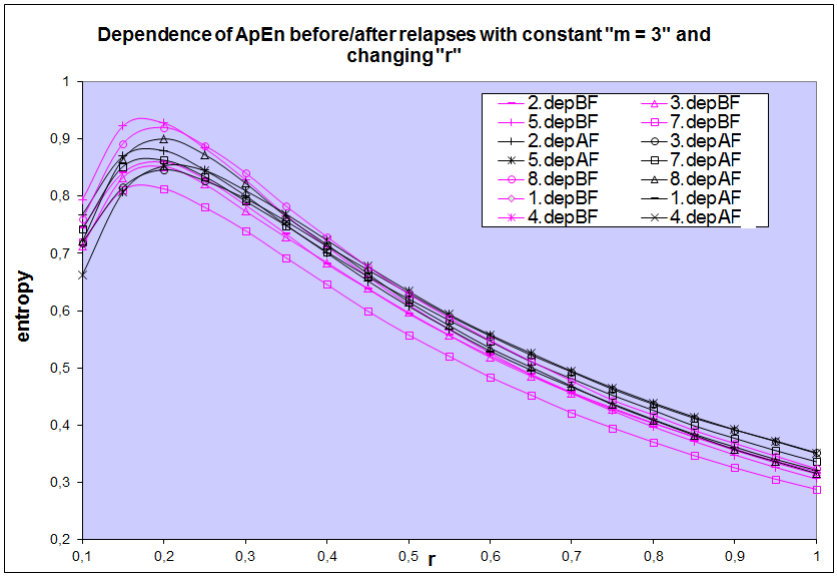

Figure A.8: ApEn: Compare data BD and AF relapses - 14days

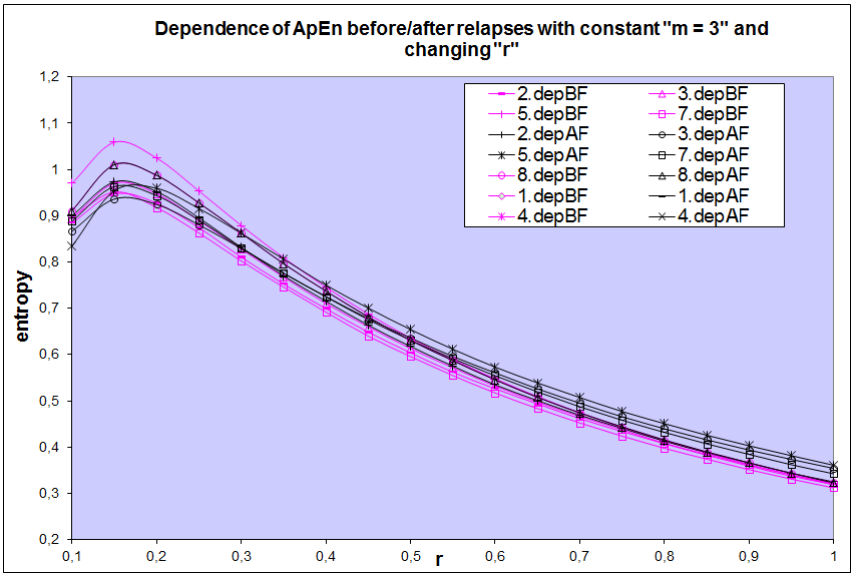

Figure A.9: ApEn: Compare data BD and AF relapses - 30days

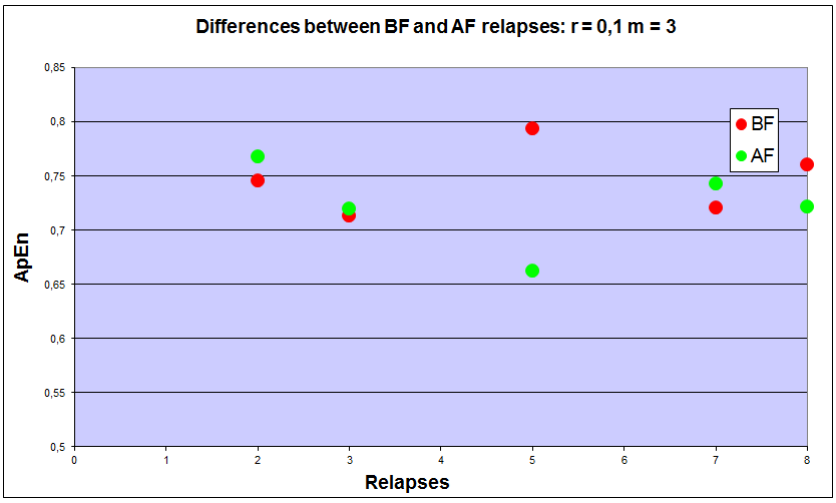

Figure A.10: ApEn: Differences between BD and AF relapses - 14days

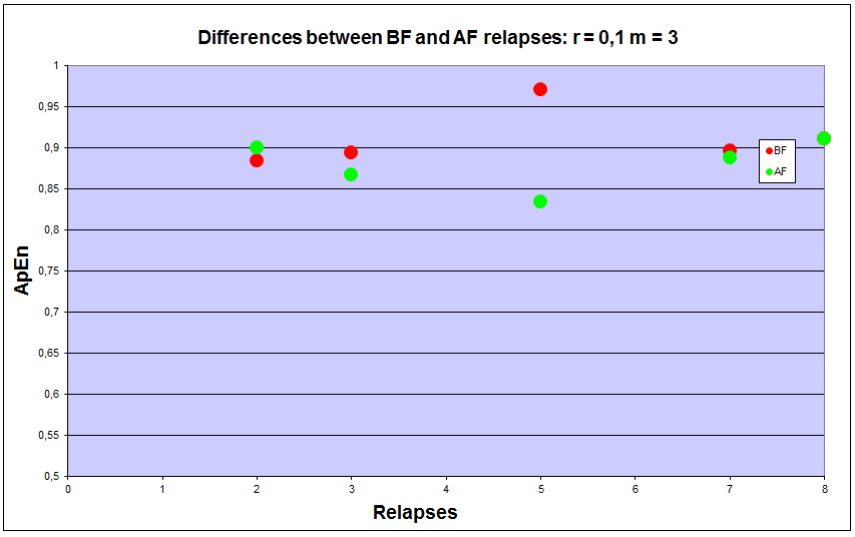

Figure A.11: ApEn: Differences between BD and AF relapses - 30days

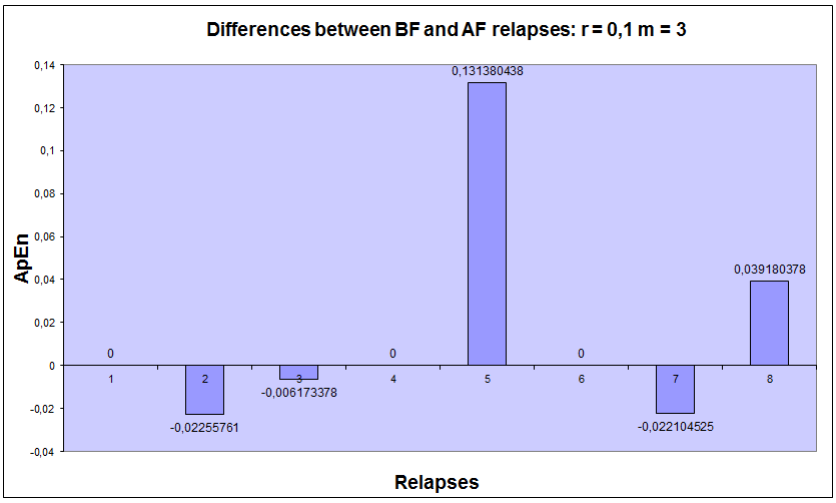

Figure A.12: ApEn: Value of differences between BD and AF relapses - 14days

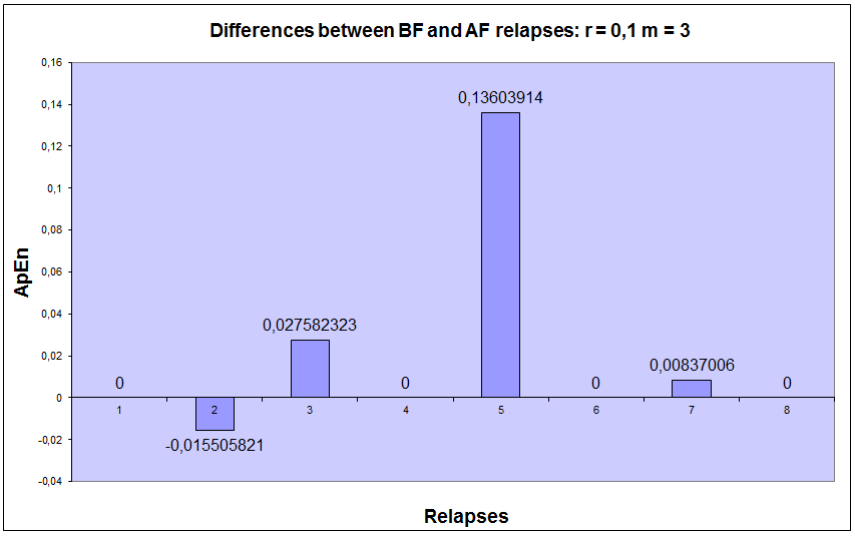

Figure A.13: ApEn: Value of differences between BD and AF relapses - 30days

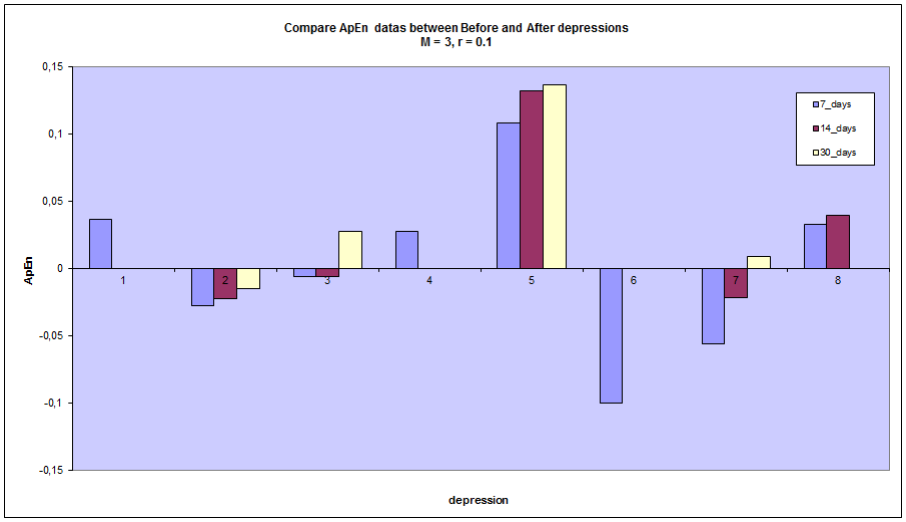

Figure A.14: ApEn: Value of differences between BD and AF relapses - 7/14/30days

A.3 Figures of ApEn: Window before relapses -7days; paremeters -> m = 2, r = 0.15

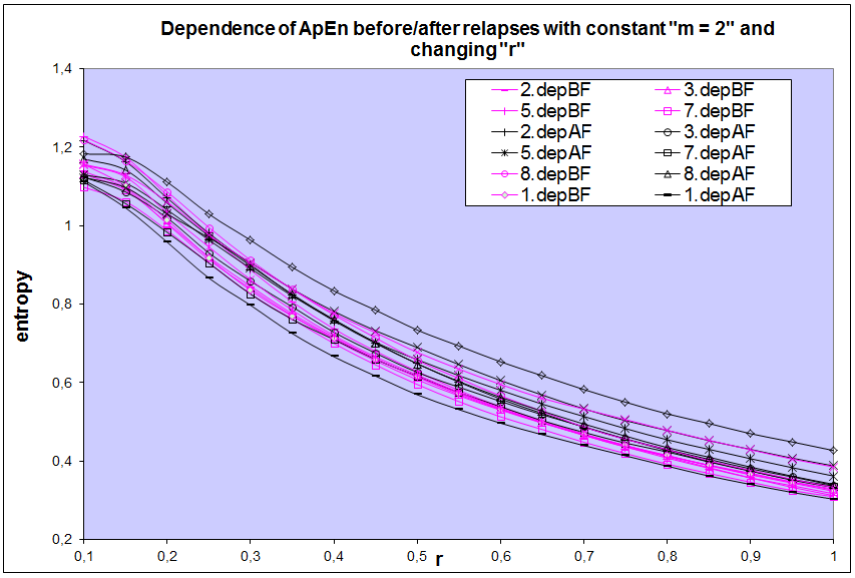

Figure A.15: ApEn: Compare data BD and AF relapses - 7days

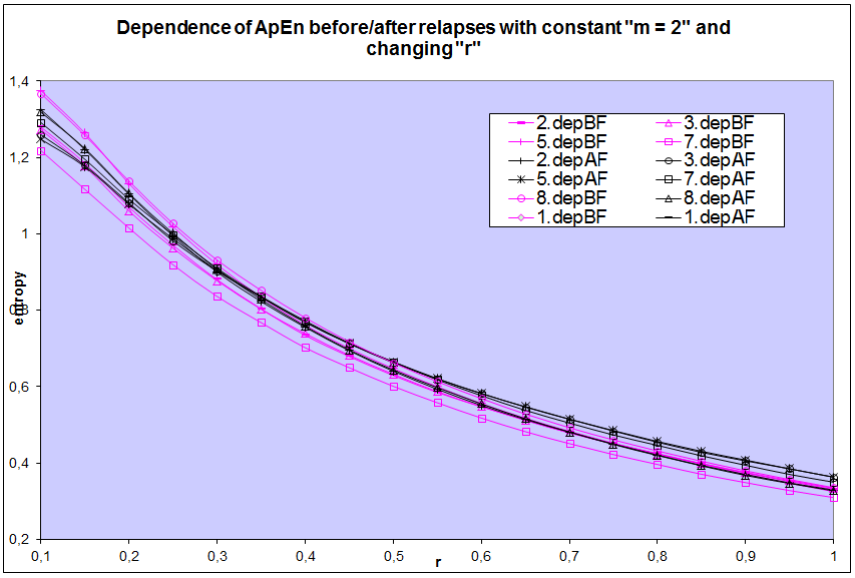

Figure A.16: ApEn: Compare data BD and AF relapses - 14days

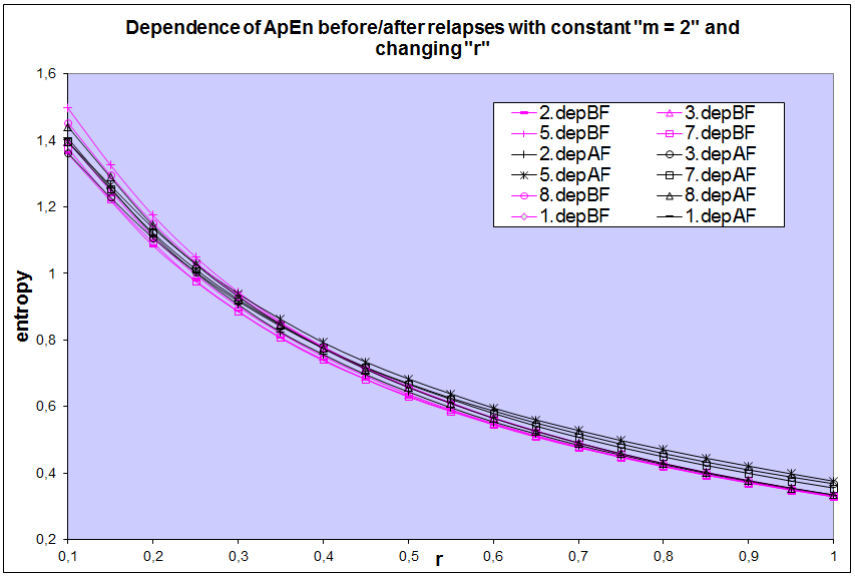

Figure A.17: ApEn: Compare data BD and AF relapses - 30days

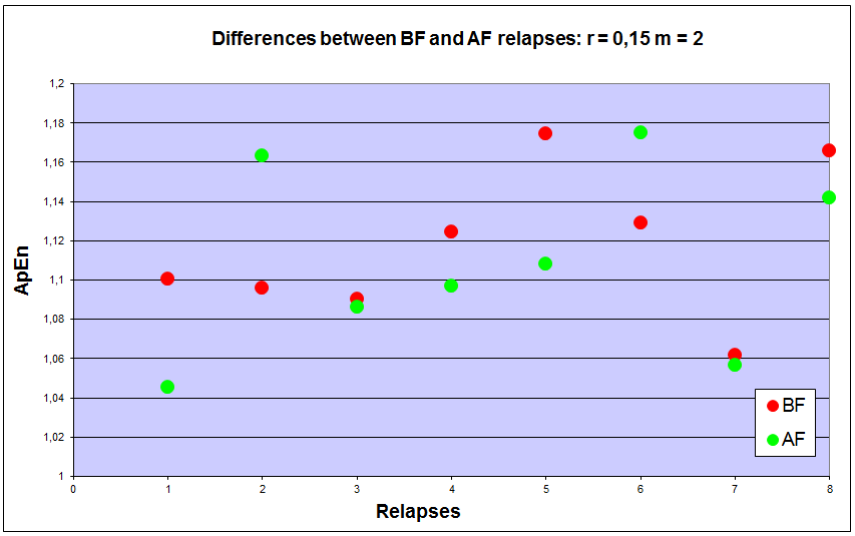

Figure A.18: ApEn: Differences between BD and AF relapses - 7days

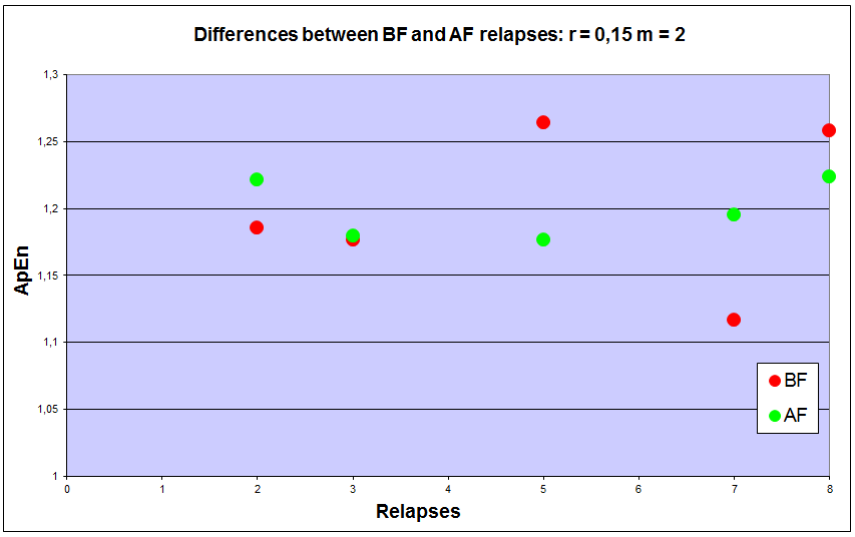

Figure A.19: ApEn: Differences between BD and AF relapses - 14days

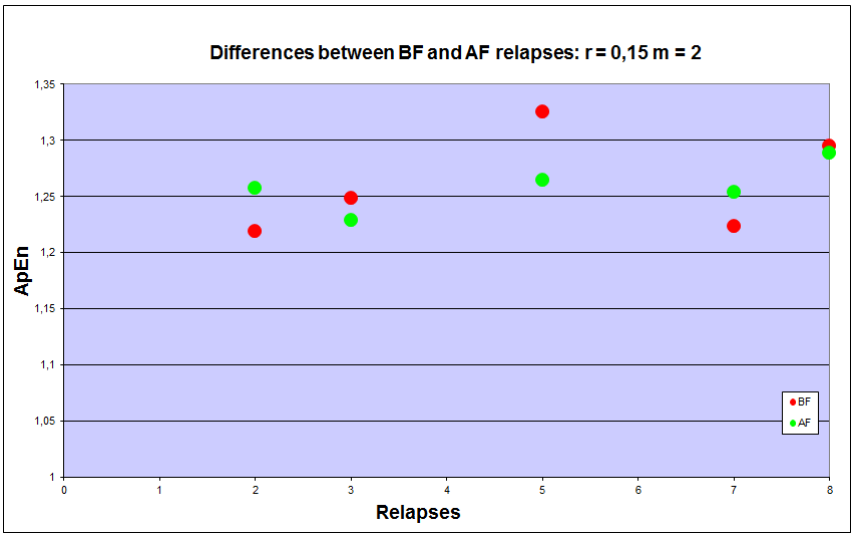

Figure A.20: ApEn: Differences between BD and AF relapses - 30days

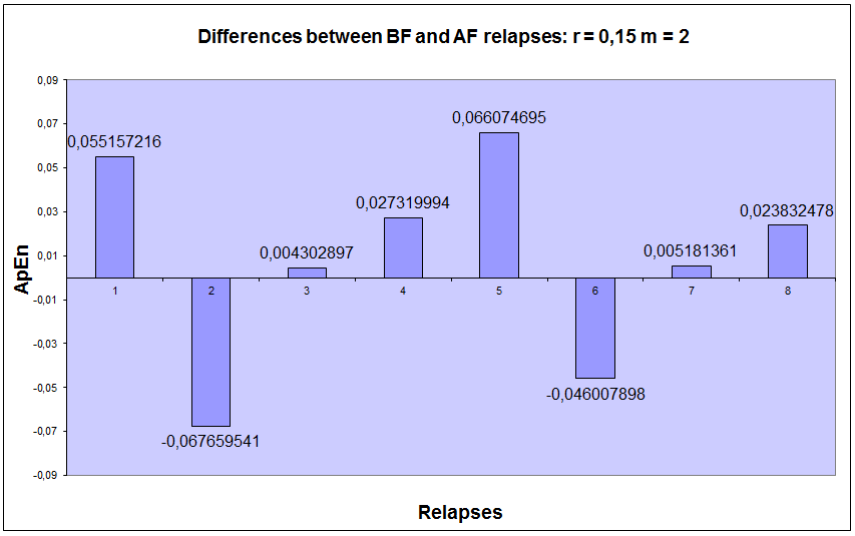

Figure A.21: ApEn: Value of differences between BD and AF relapses - 7days

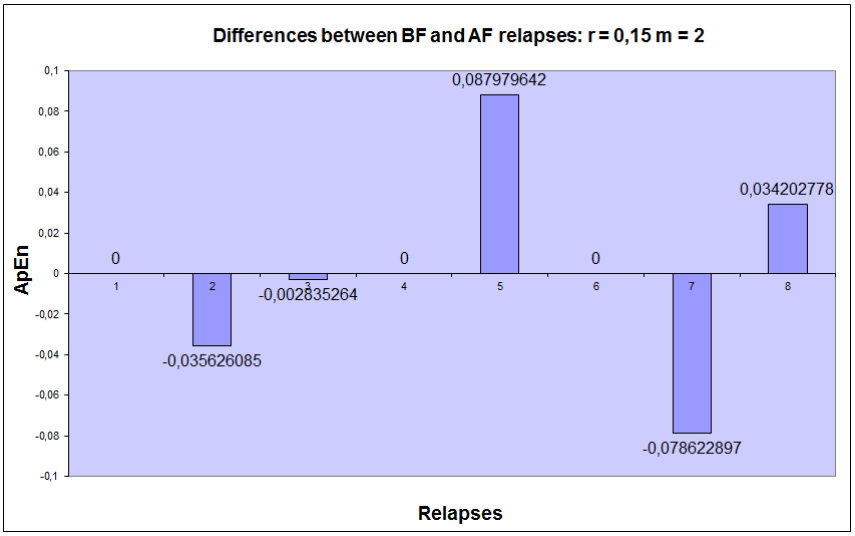

Figure A.22: ApEn: Value of differences between BD and AF relapses - 14days

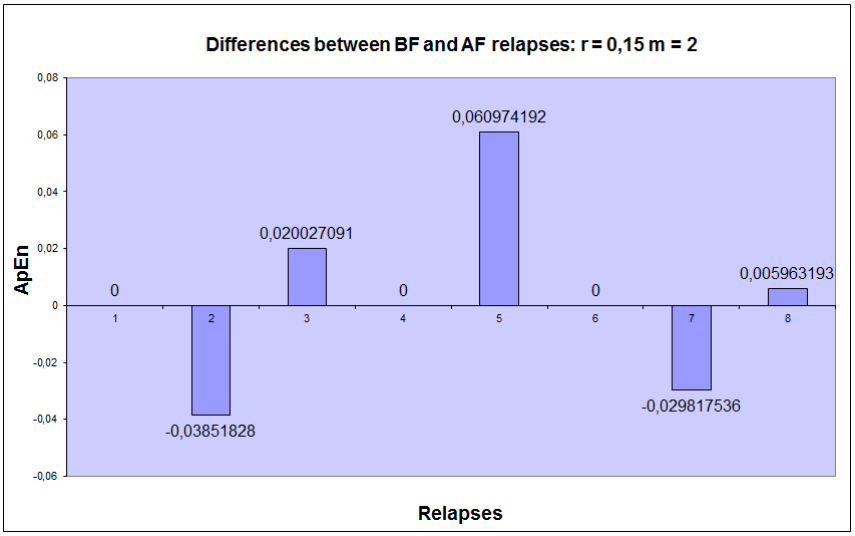

Figure A.23: ApEn: Value of differences between BD and AF relapses - 30days

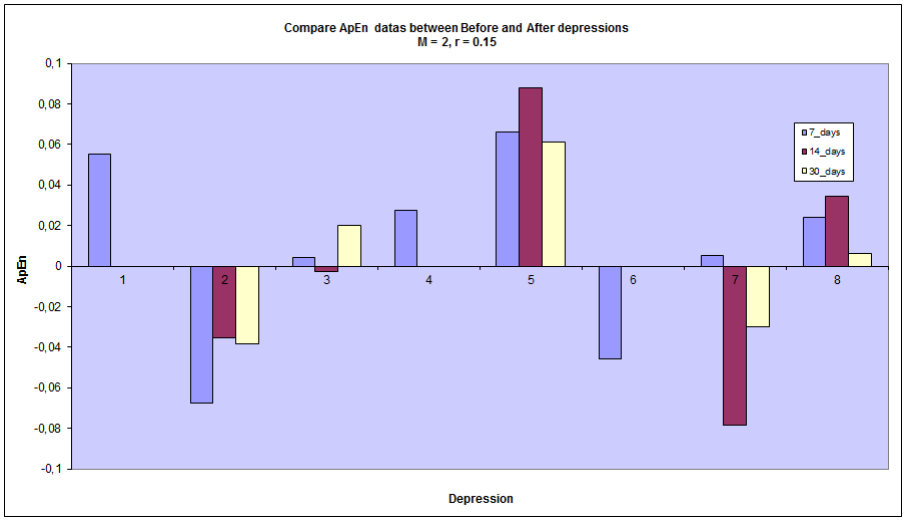

Figure A.24: ApEn: Value of differences between BD and AF relapses - 7/14/30days

A.4 Figures of ApEn: Window before relapses -7days; paremeters-> m = 3, r = 0.1

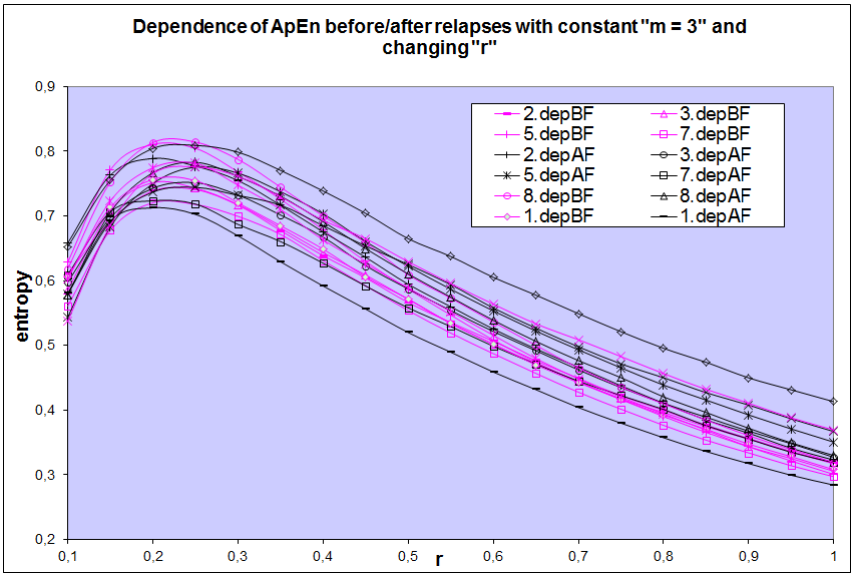

Figure A.25: ApEn: Compare data BD and AF relapses - 7days

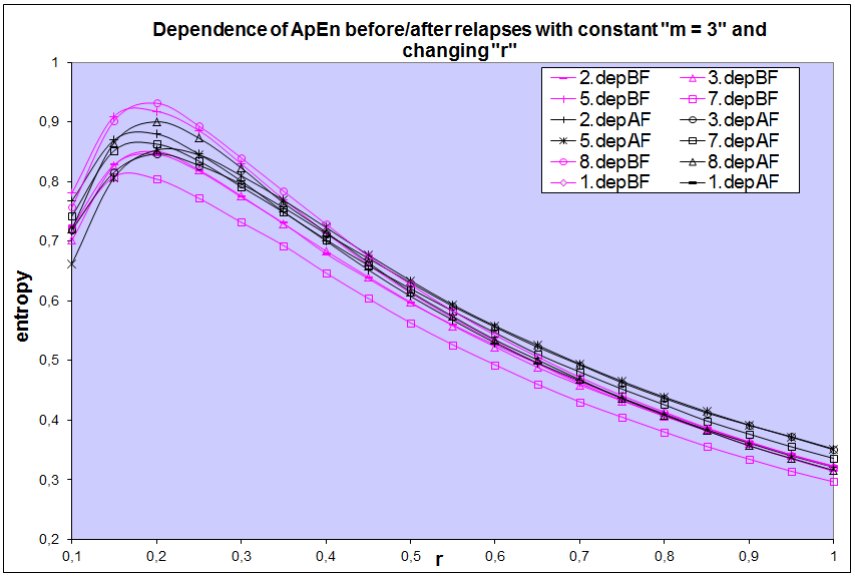

Figure A.26: ApEn: Compare data BD and AF relapses - 14days

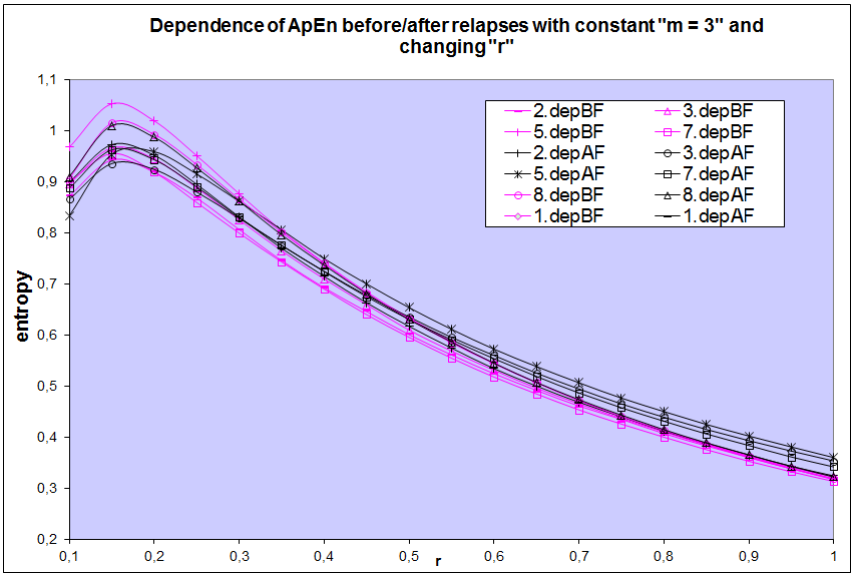

Figure A.27: ApEn: Compare data BD and AF relapses - 30days

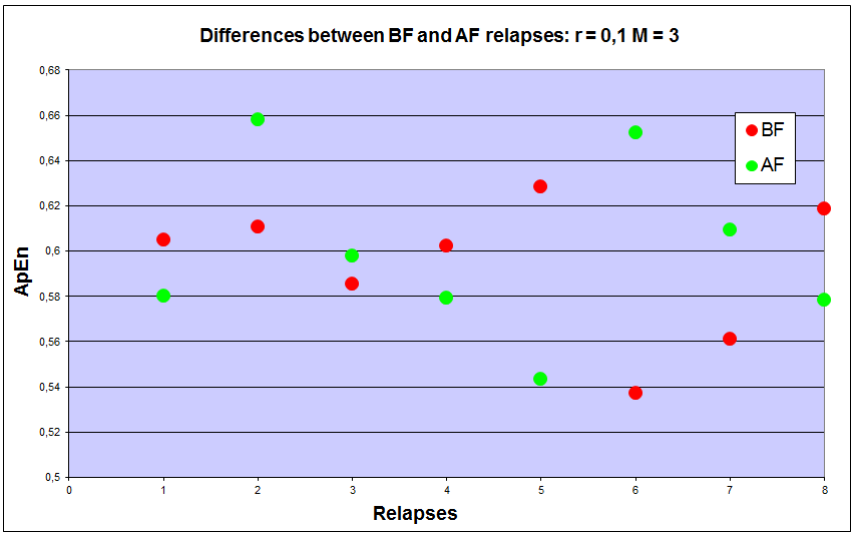

Figure A.28: ApEn: Differences between BD and AF relapses - 7days

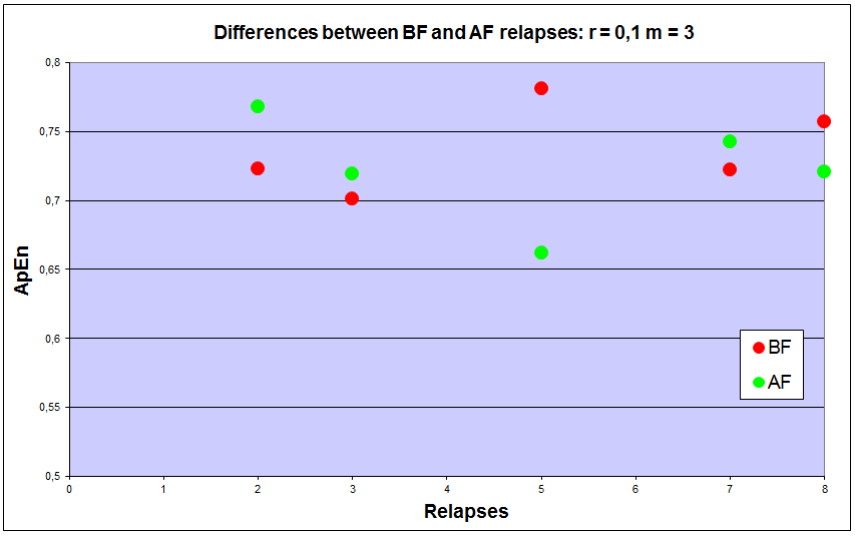

Figure A.29: ApEn: Differences between BD and AF relapses - 14days

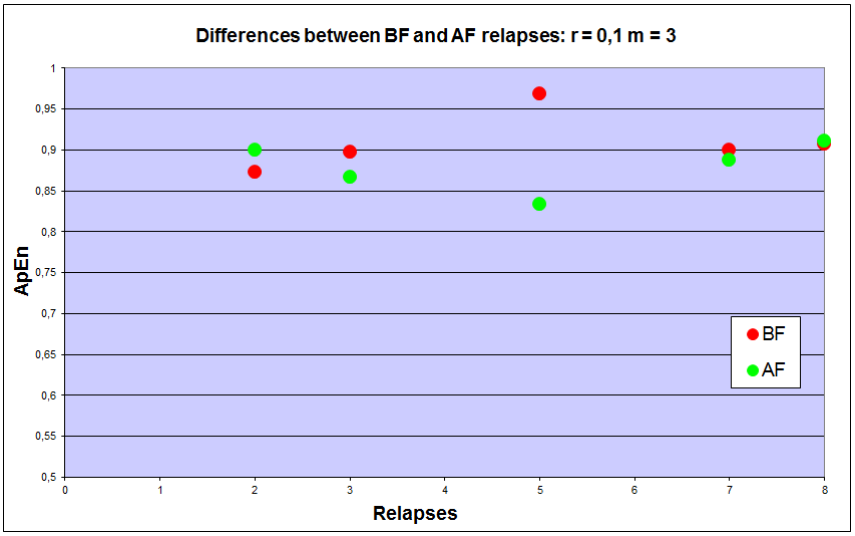

Figure A.30: ApEn: Differences between BD and AF relapses - 30days1

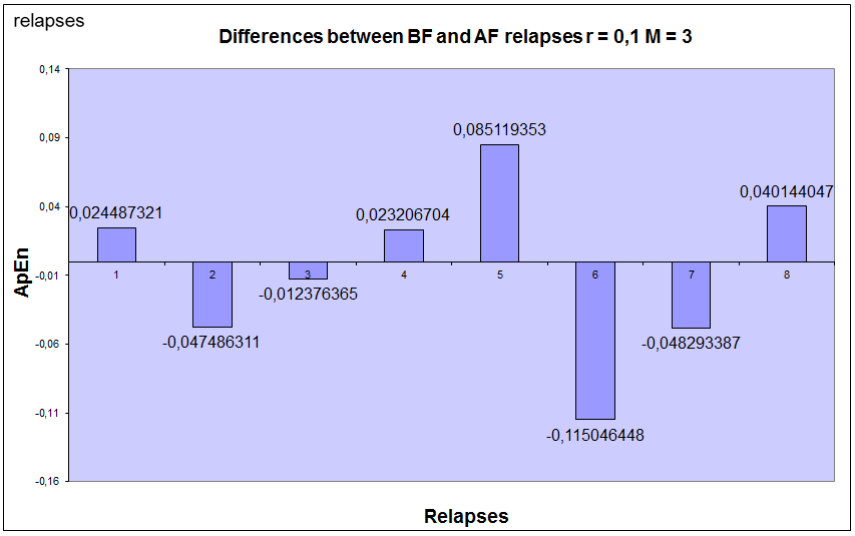

Figure A.31: ApEn: Value of differences between BD and AF relapses - 7days

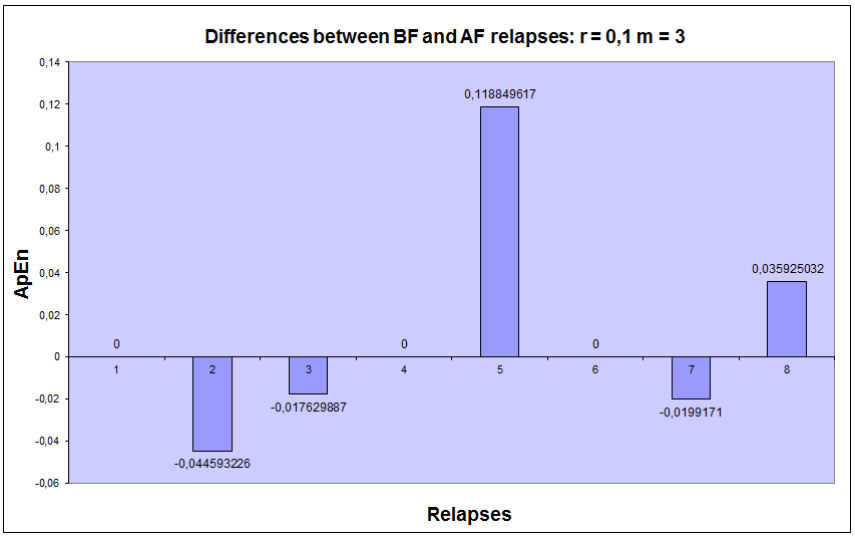

Figure A.32: ApEn: Value of differences between BD and AF relapses - 14days

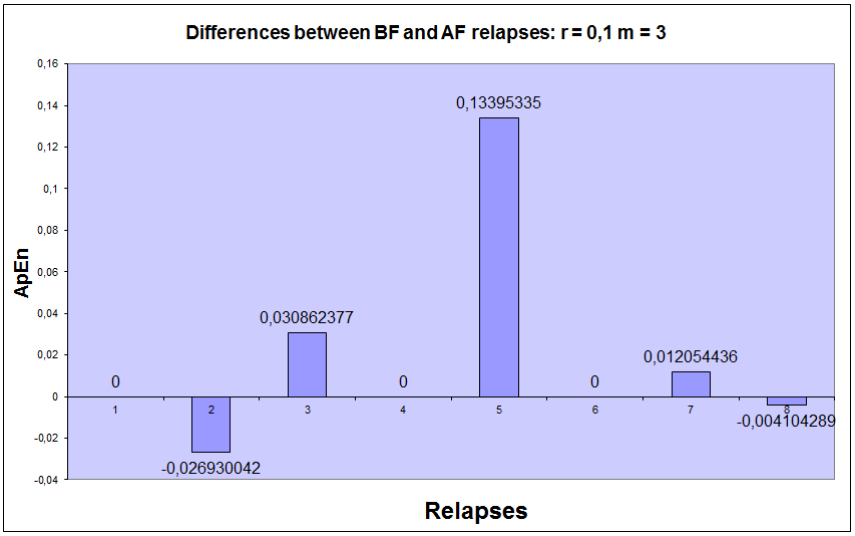

Figure A.33: ApEn: Value of differences between BD and AF relapses - 30days

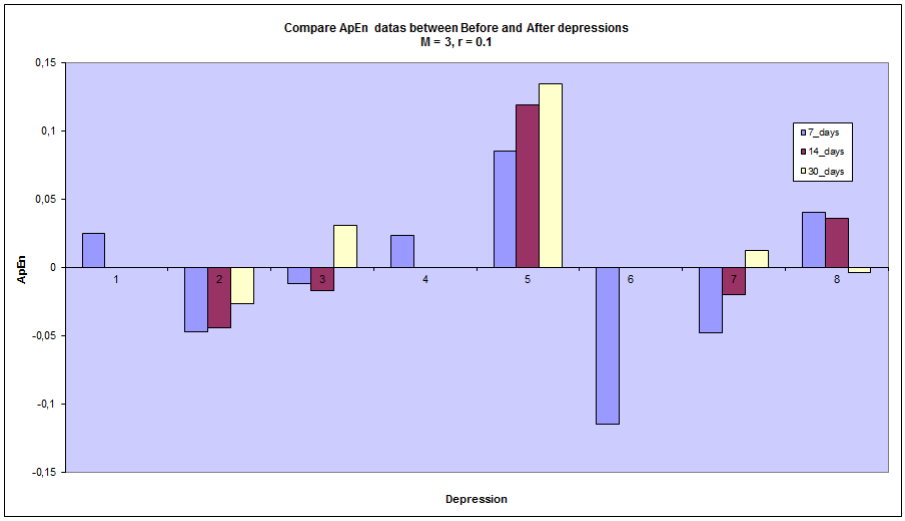

Figure A.34: ApEn: Value of differences between BD and AF relapses - 7/14/30days

Appendix B

Figures of CiRh - Patient 1

B.1 Continual figure

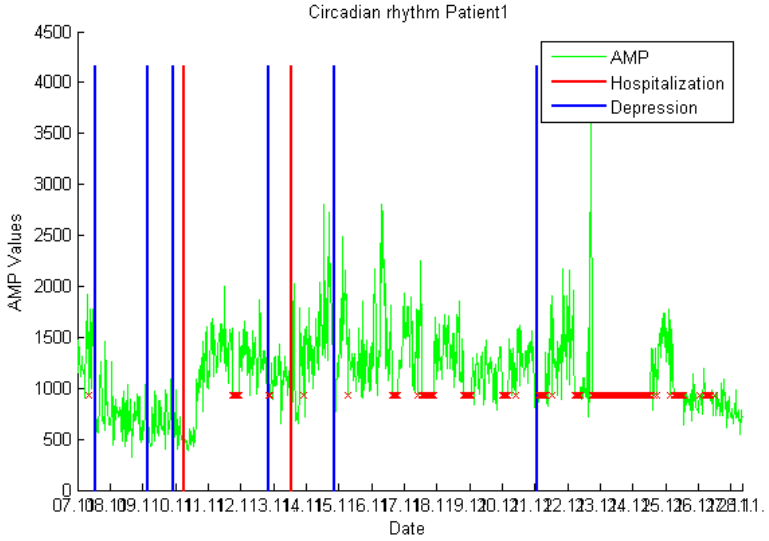

Figure B.1: CiRh: Parameter AMP

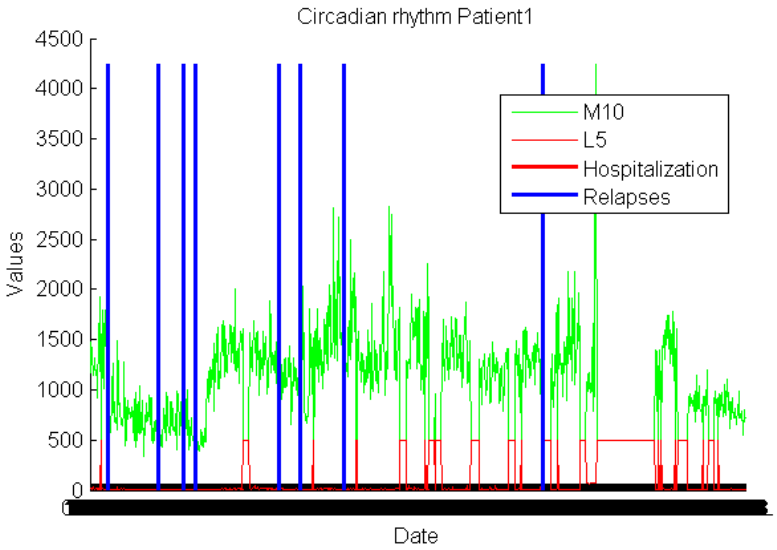

Figure B.2: CiRh: Parameters M10; L5

B.2 Figures of CiRh: Compare data BR and AR -> 1st relapse

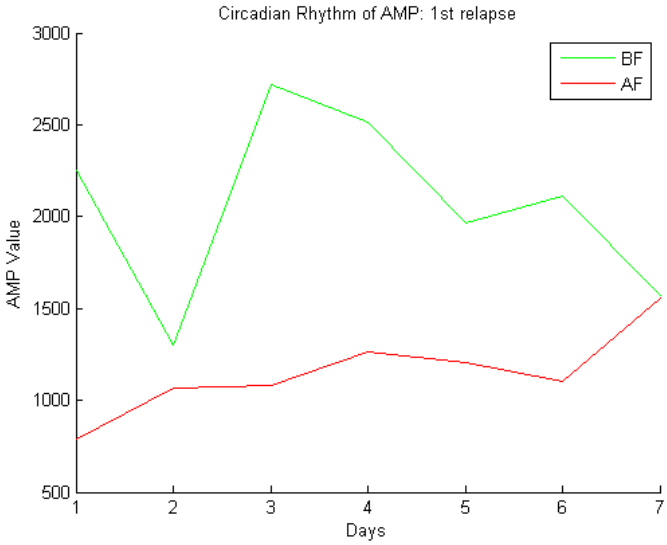

Figure B.3: CiRh: Parameter AMP - 1st relapse

B.3 Figures of CiRh: Compare data BR and AR -> 2nd relapse

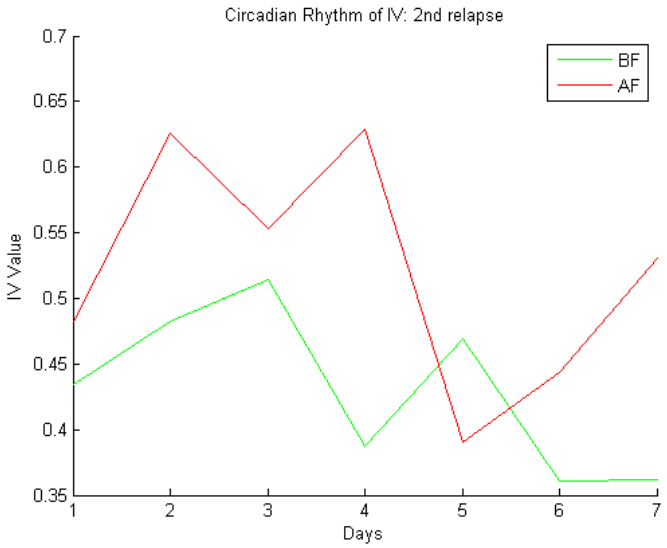

Figure B.4: CiRh: Parameter IV- 2nd relapse

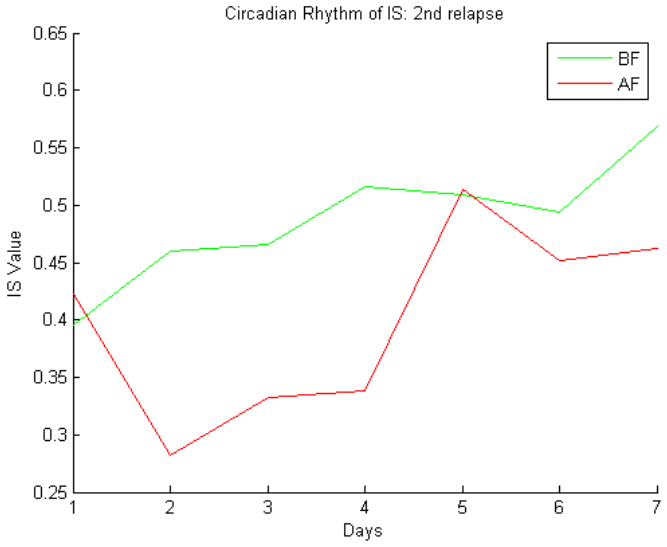

Figure B.5: CiRh: Parameter IS - 2nd relapse

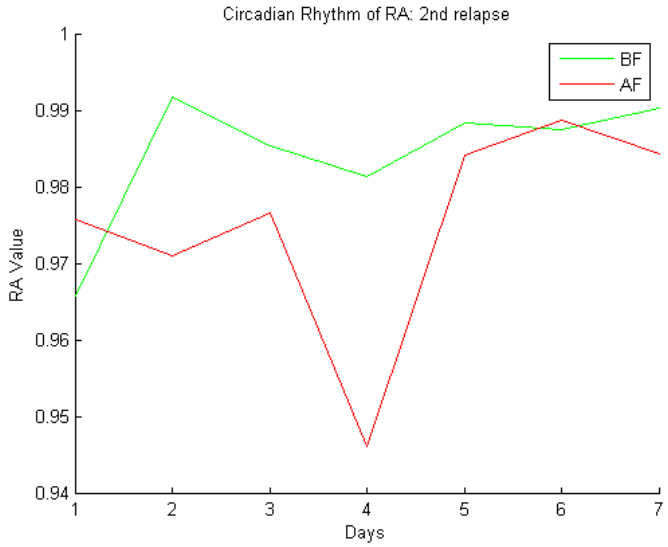

Figure B.6: CiRh: Parameter AR - 2nd relapse

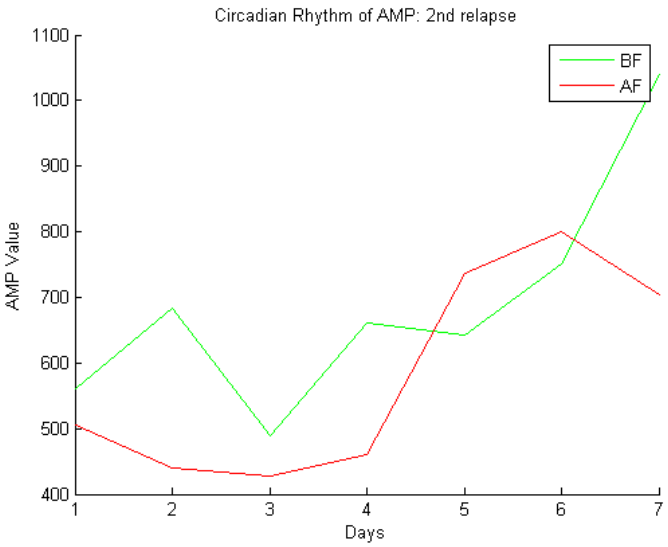

Figure B.7: CiRh: Parameter AMP - 2nd relapse

B.4 Figures of CiRh: Compare data BR and AR -> 3rd relapse

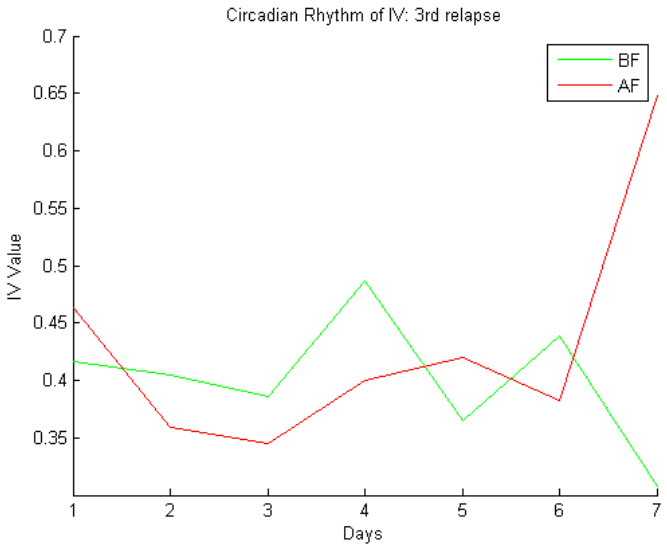

Figure B.8: CiRh: Parameter IV - 3rd relapse

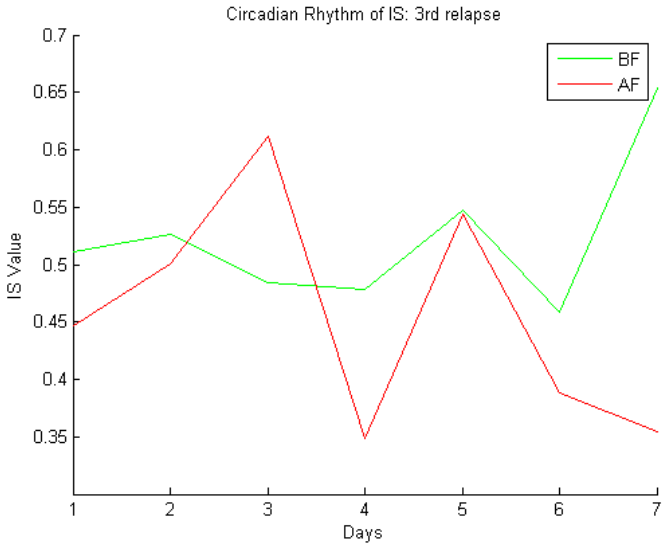

Figure B.9: CiRh: Parameter IS - 3rd relapse

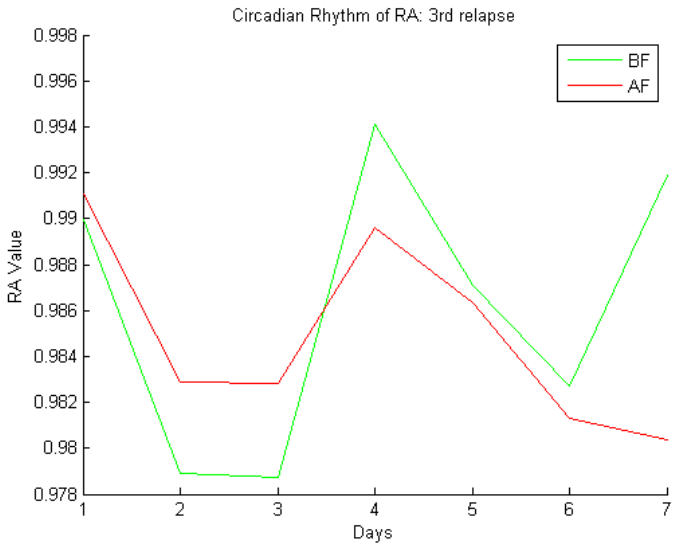

Figure B.10: CiRh: Parameter AR - 3rd relapse

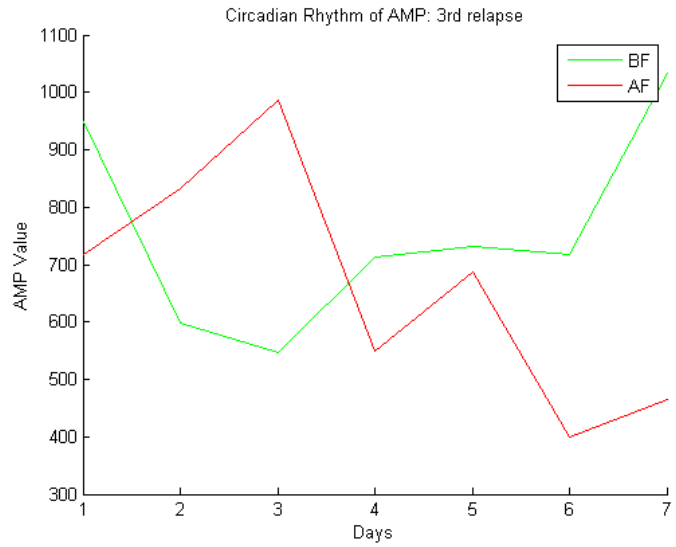

Figure B.11: CiRh: Parameter AMP - 3rd relapse

B.5 Figures of CiRh: Compare data BR and AR -> 4th relapse

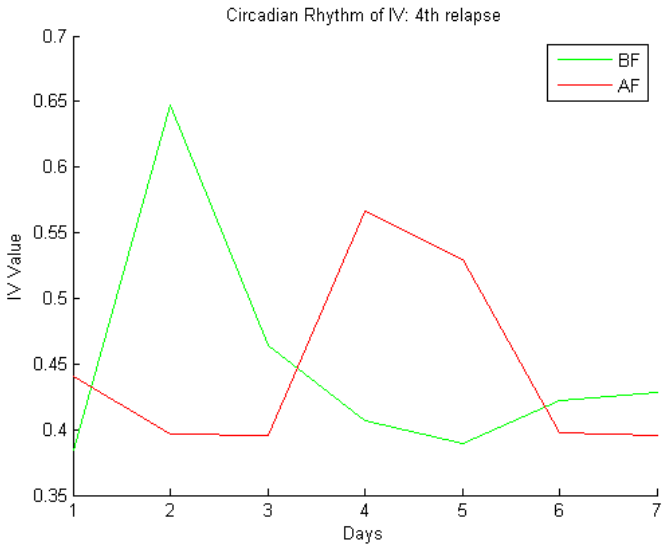

Figure B.12: CiRh: Parameter IV - 4th relapse

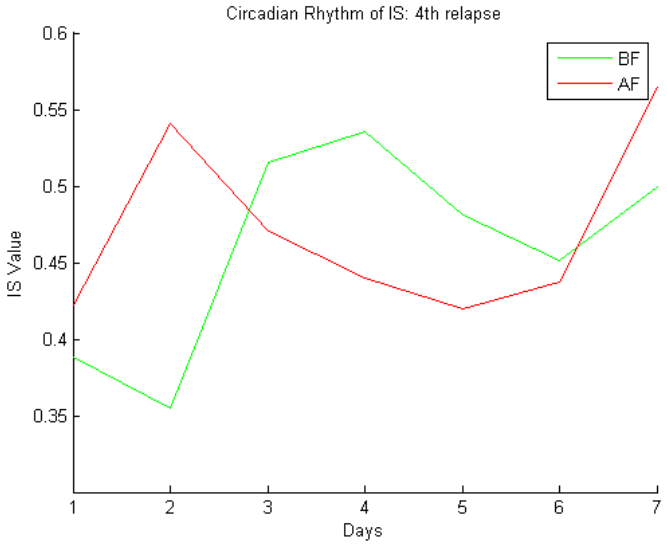

Figure B.13: CiRh: Parameter IS - 4th relapse

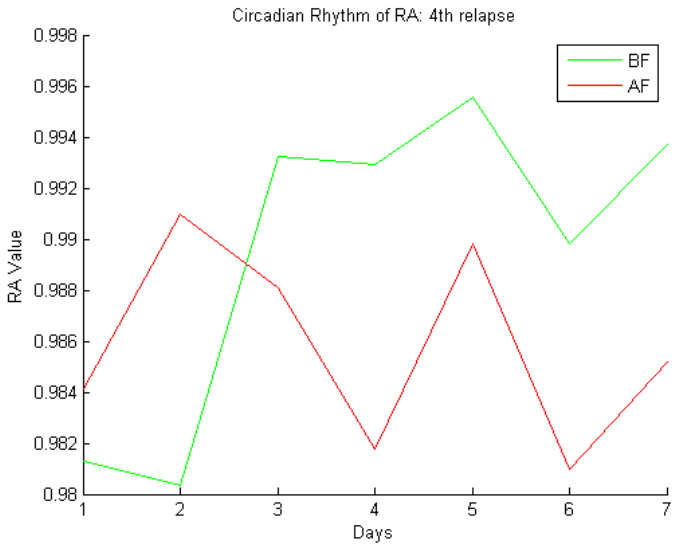

Figure B.14: CiRh: Parameter AR - 4th relapse

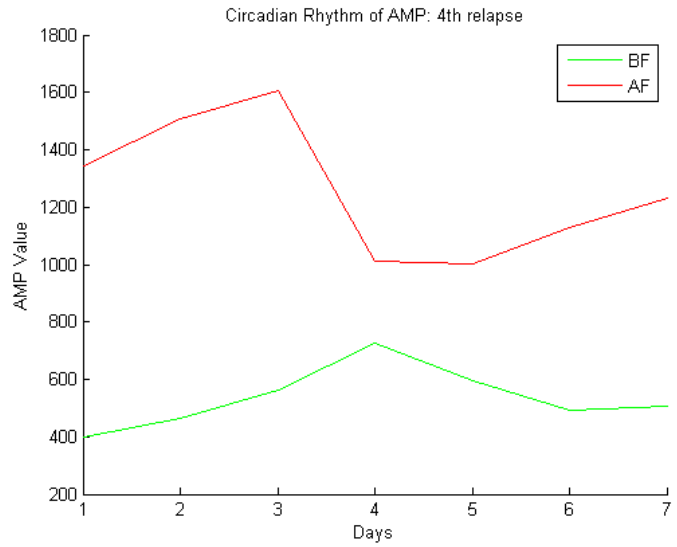

Figure B.15: CiRh: Parameter AMP - 4th relapse

B.6 Figures of CiRh: Compare data BR and AR -> 5th relapse

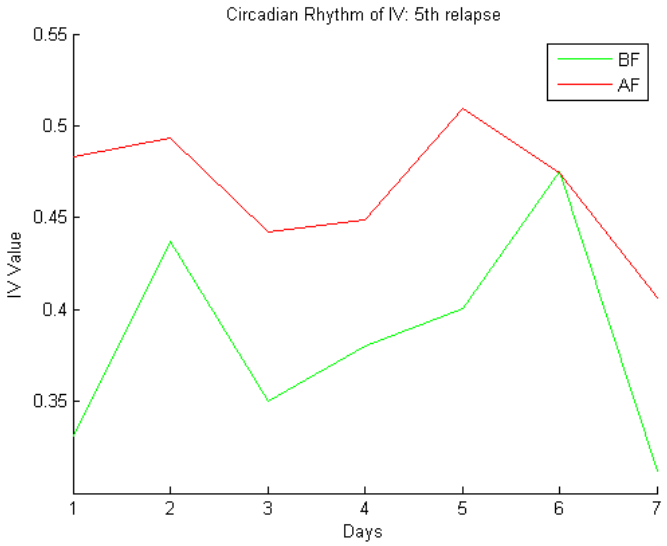

Figure B.16: CiRh: Parameter IV - 5th relapse

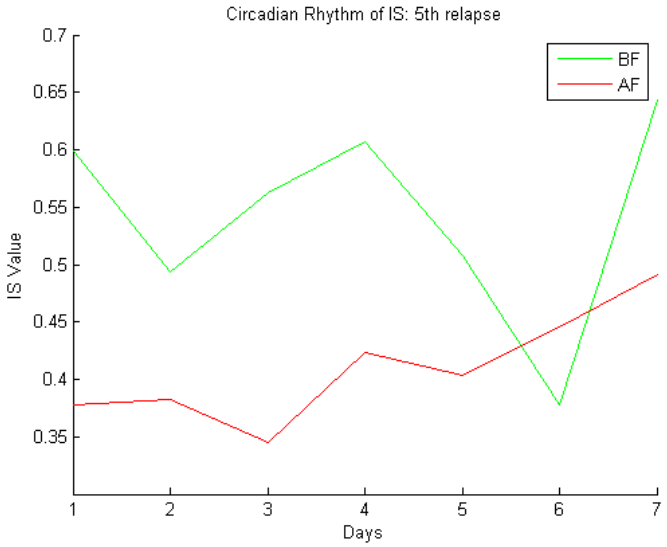

Figure B.17: CiRh: Parameter IS - 5th relapse

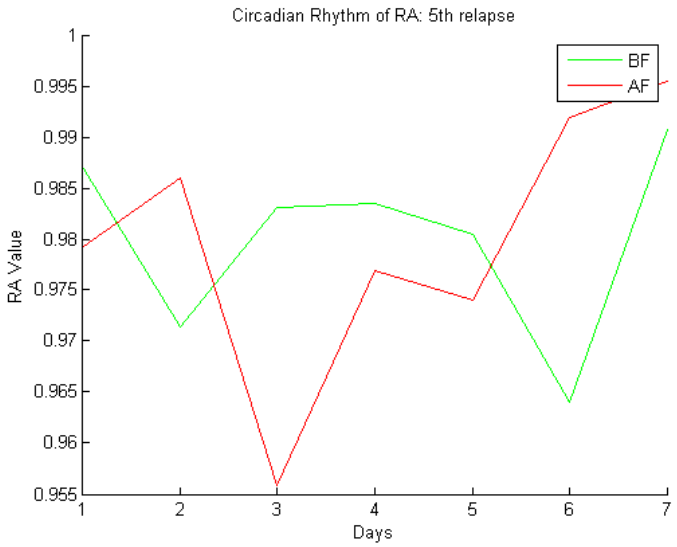

Figure B.18: CiRh: Parameter AR - 5th relapse

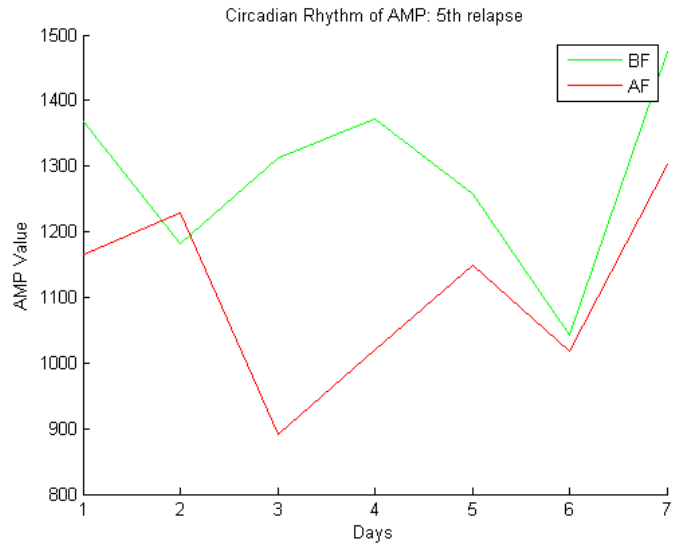

Figure B.19: CiRh: Parameter AMP - 5th relapse

B.7 Figures of CiRh: Compare data BR and AR -> 6th relapse

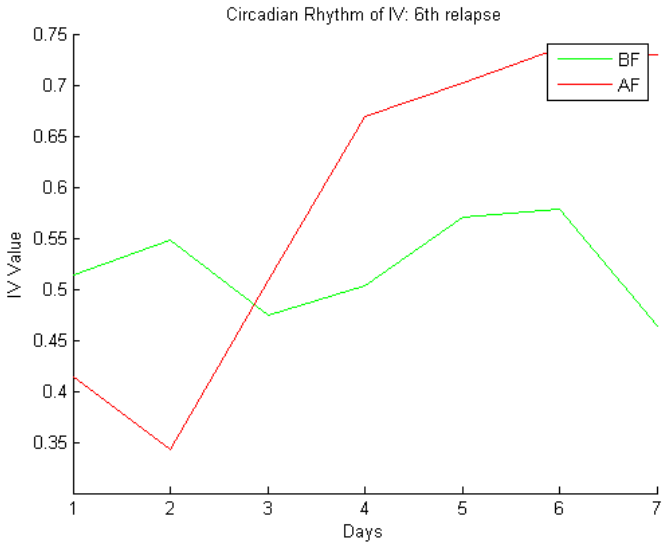

Figure B.20: CiRh: Parameter IV - 6th relapse

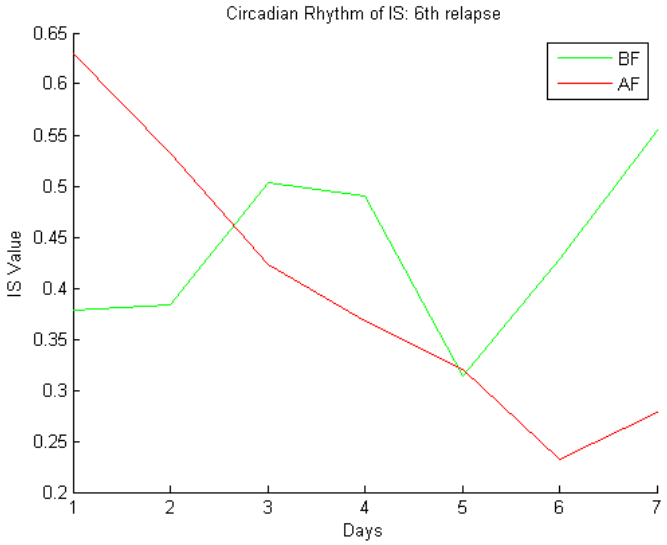

Figure B.21: CiRh: Parameter IS - 6th relapse

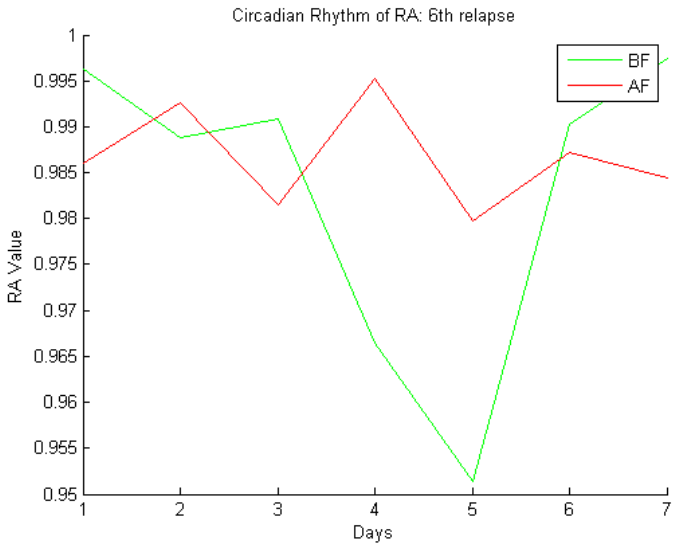

Figure B.22: CiRh: Parameter AR - 6th relapse

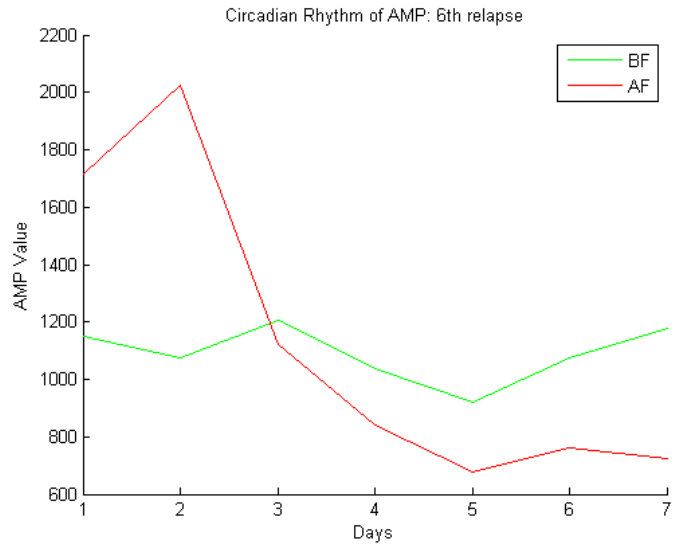

Figure B.23: CiRh: Parameter AMP - 6th relapse

B.8 Figures of CiRh: Compare data BR and AR -> 7th relapse

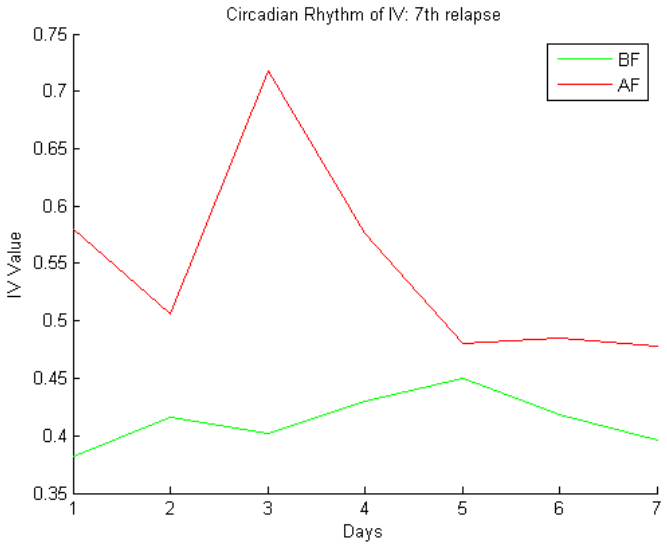

Figure B.24: CiRh: Parameter IV - 7th relapse

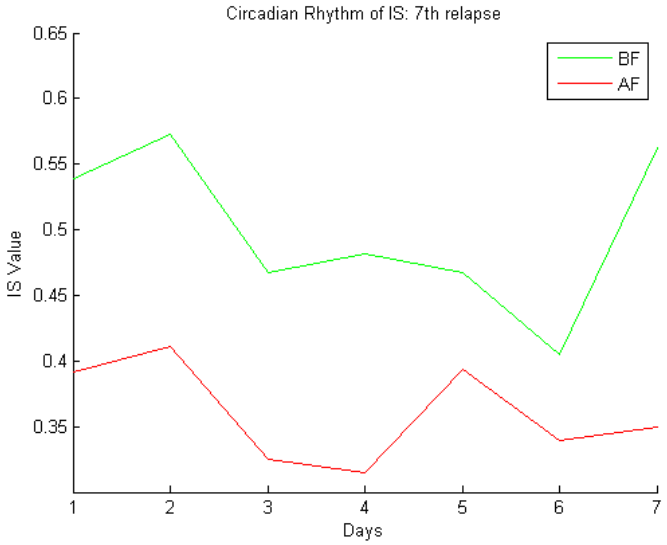

Figure B.25: CiRh: Parameter IS - 7th relapse

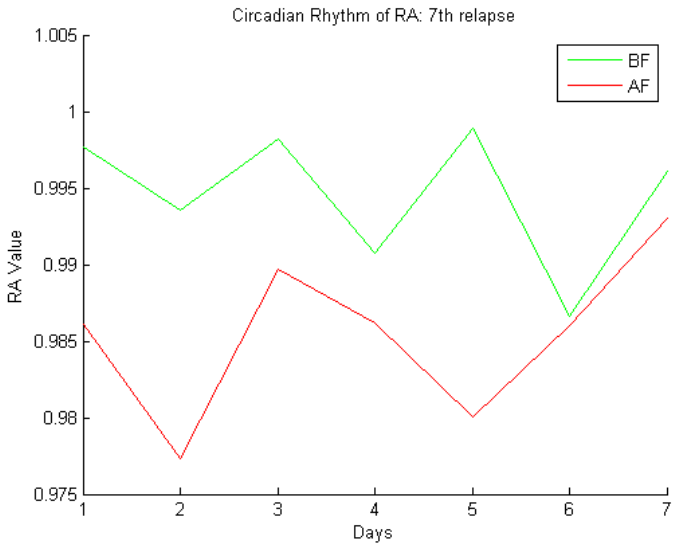

Figure B.26: CiRh: Parameter AR - 7th relapse

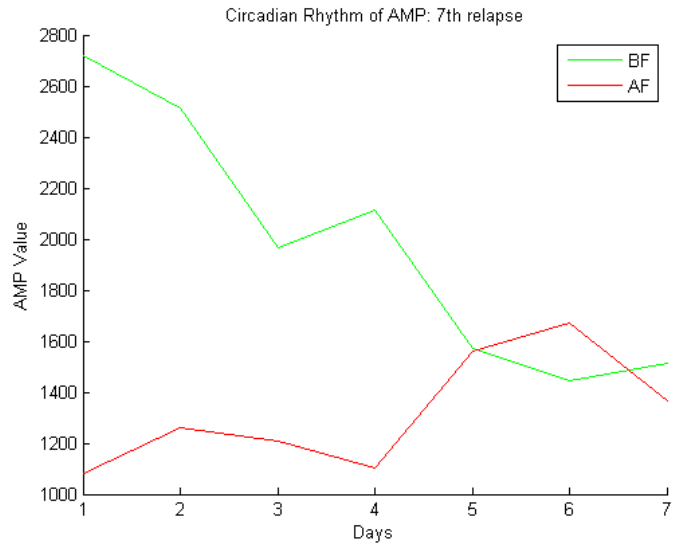

Figure B.27: CiRh: Parameter AMP - 7th relapse

Appendix C

Patient number 6 (P6)

C.1 Actigraphy of P6

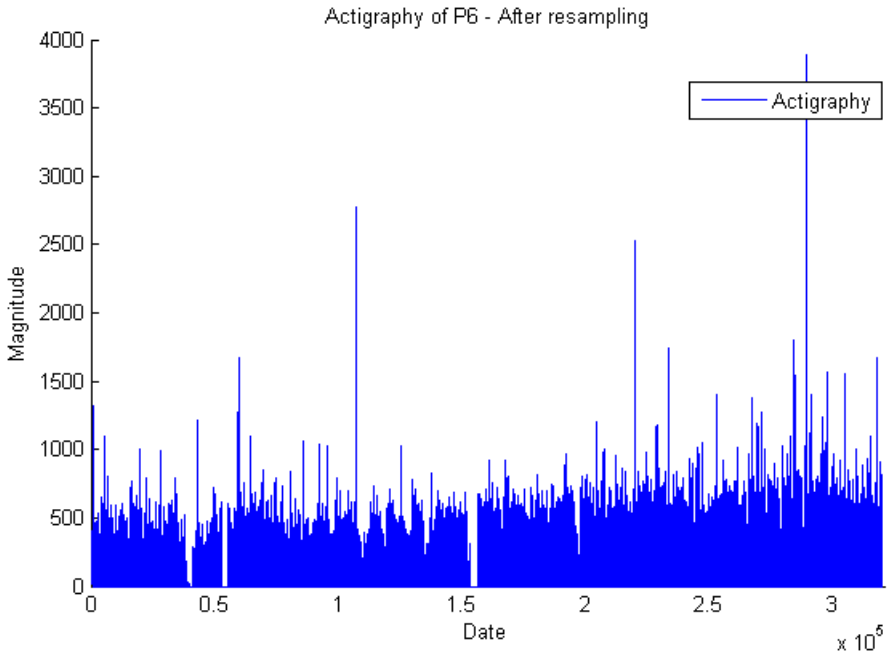

Figure C.1: Actigraphy data after resampling. Patient number 6 (P6)

C.2 Figures of ApEn: Window before relapses - 3days; parameters -> m = 2, r = 0.15

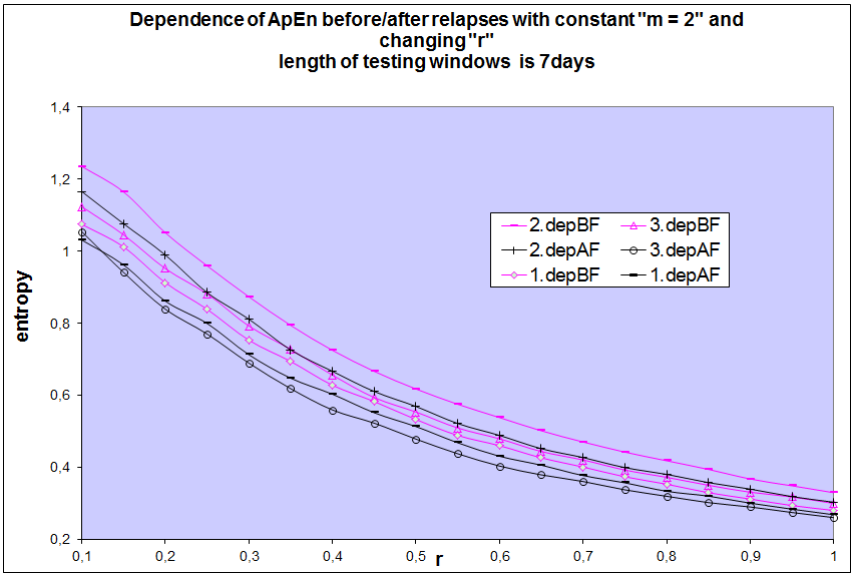

Figure C.2: ApEn: Compare data BD and AF relapses - 7days

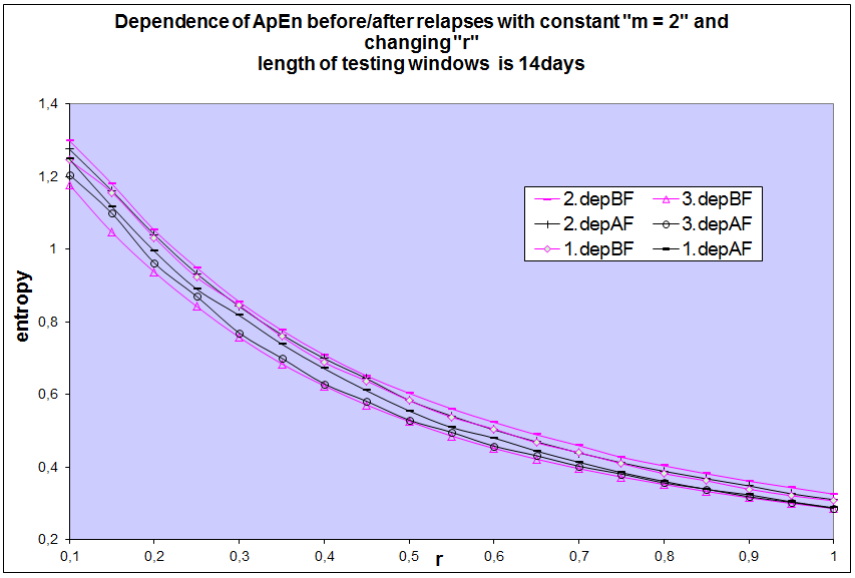

Figure C.3: ApEn: Compare data BD and AF relapses - 14days

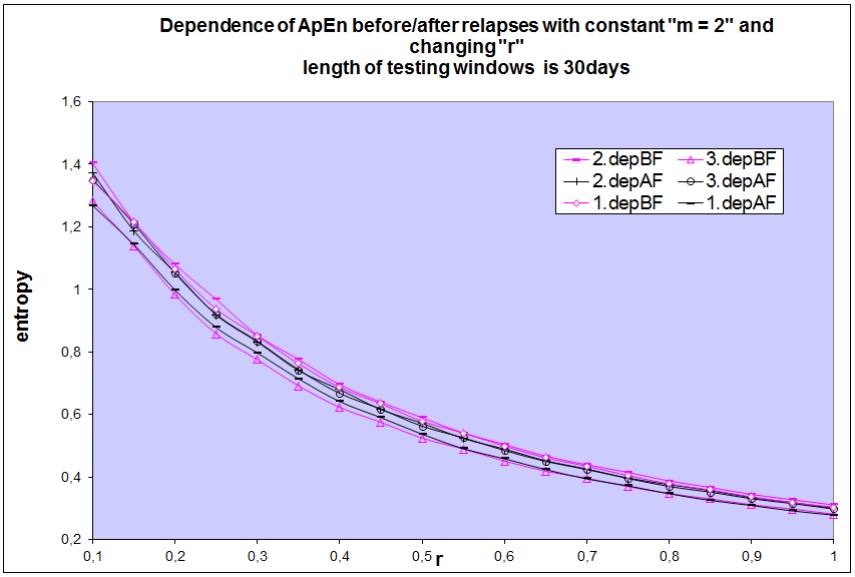

Figure C.4: ApEn: Compare data BD and AF relapses - 30days

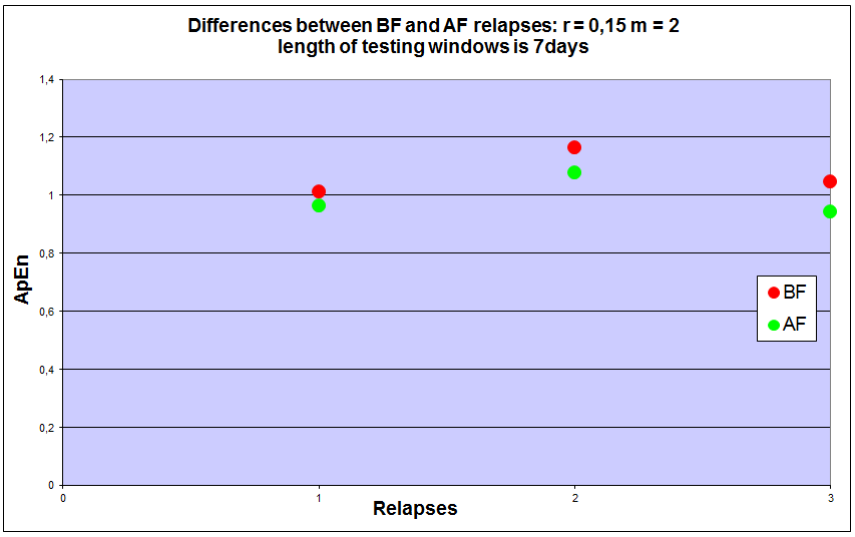

Figure C.5: ApEn: Differences between BD and AF relapses - 7days

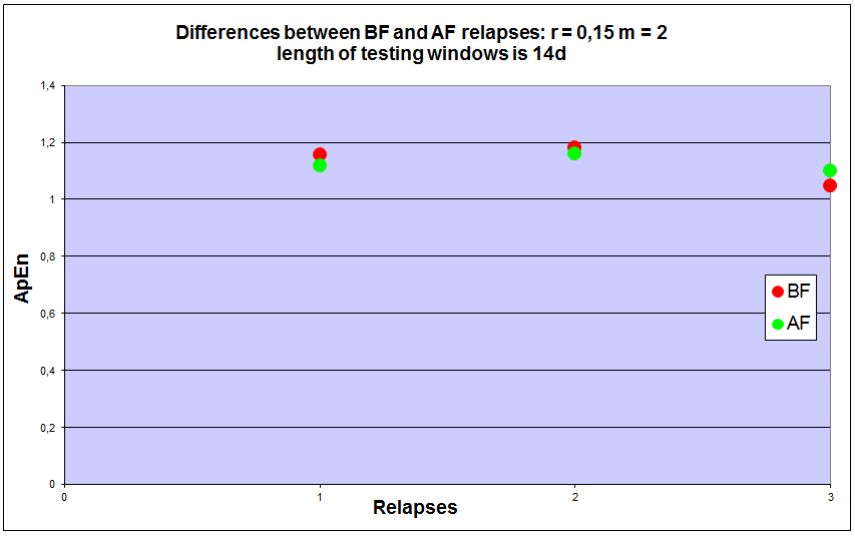

Figure C.6: ApEn: Differences between BD and AF relapses - 14days

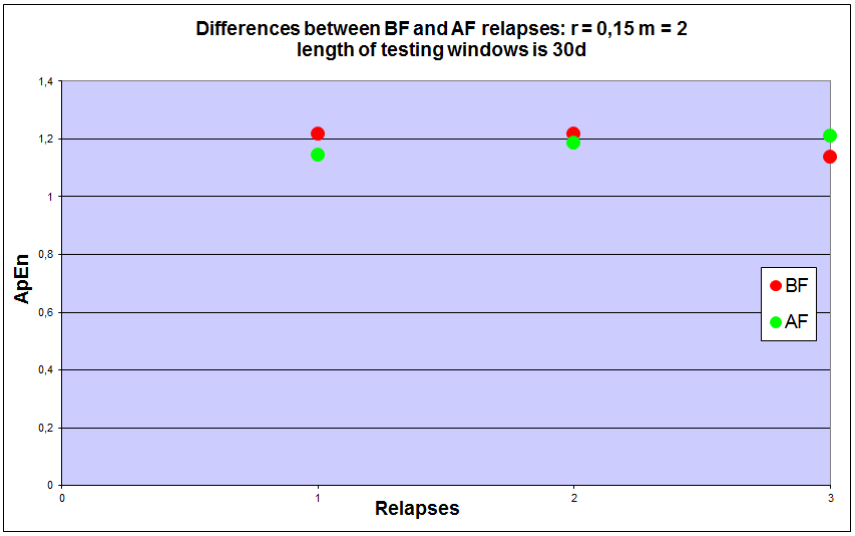

Figure C.7: ApEn: Differences between BD and AF relapses - 30days

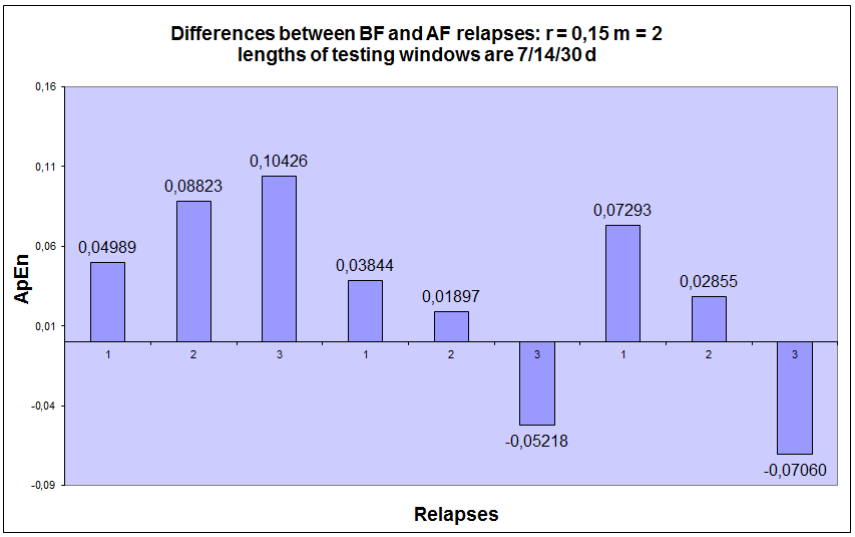

Figure C.8: ApEn: Value of differences between BD and AF relapses - 7/14/30days

C.3 Figures of ApEn: Window before relapses - 3days; parameters -> m = 3, r = 0.1

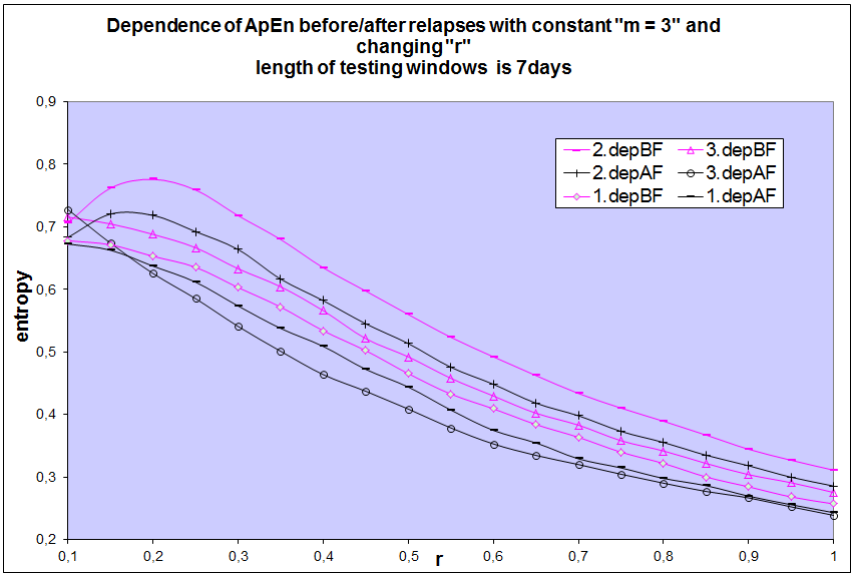

Figure C.9: ApEn: Compare data BD and AF relapses - 7days

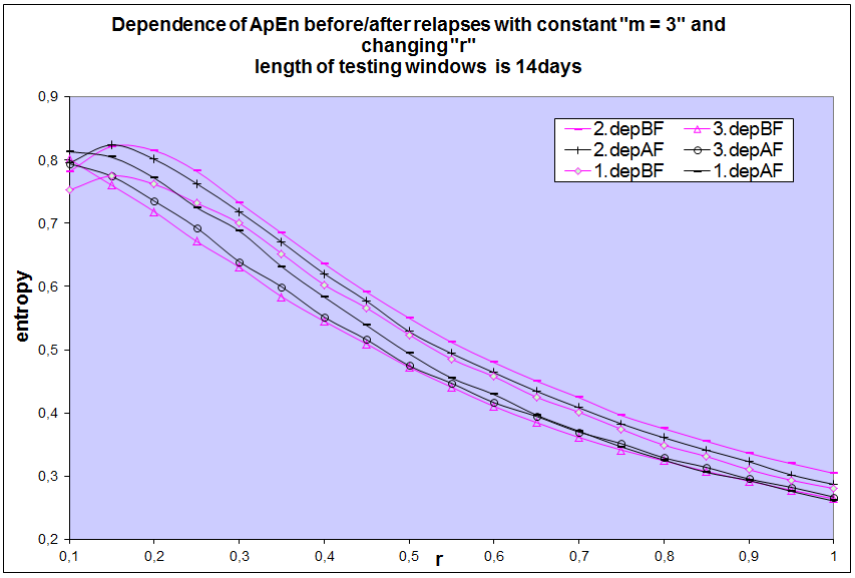

Figure C.10: ApEn: Compare data BD and AF relapses - 14days

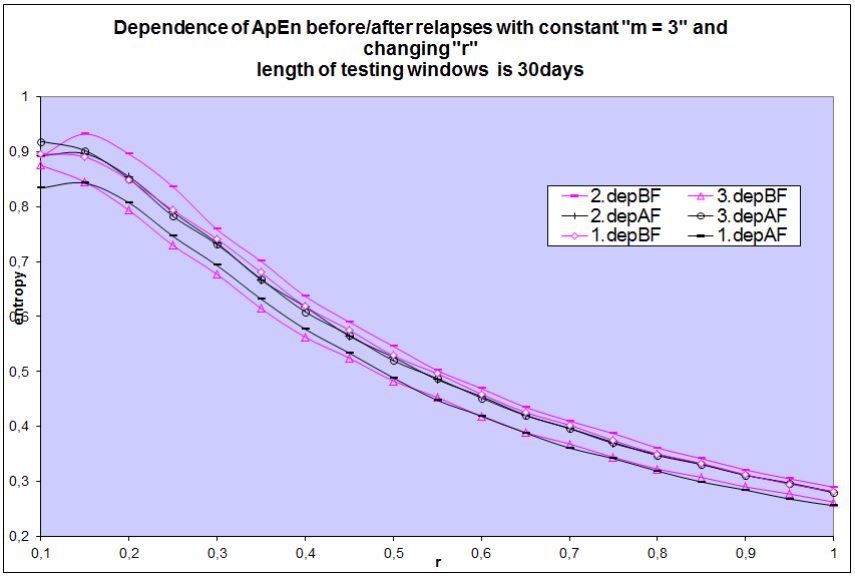

Figure C.11: ApEn: Compare data BD and AF relapses - 30days

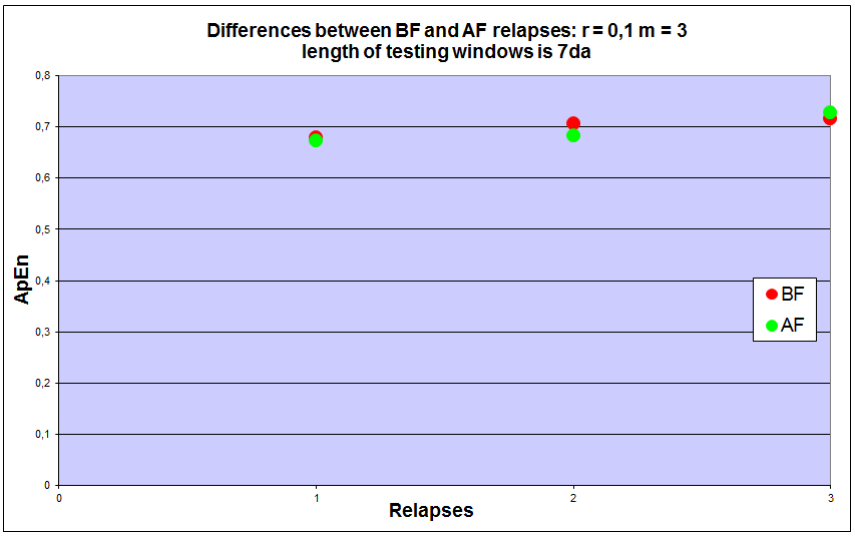

Figure C.12: ApEn: Differences between BD and AF relapses - 7days

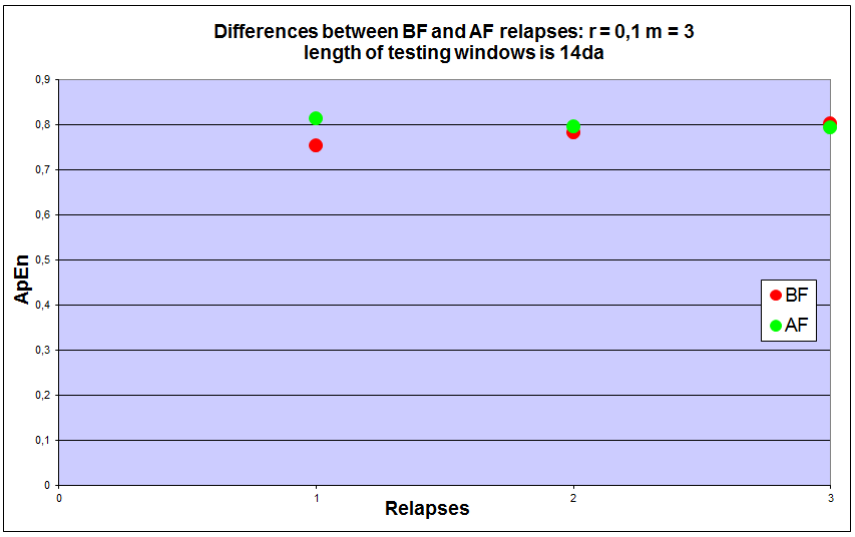

Figure C.13: ApEn: Differences between BD and AF relapses - 14days

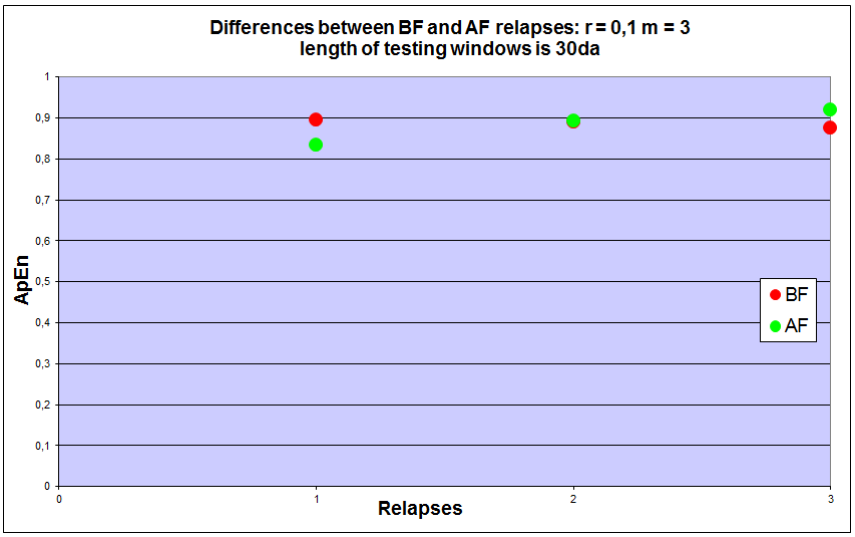

Figure C.14: ApEn: Differences between BD and AF relapses - 30days

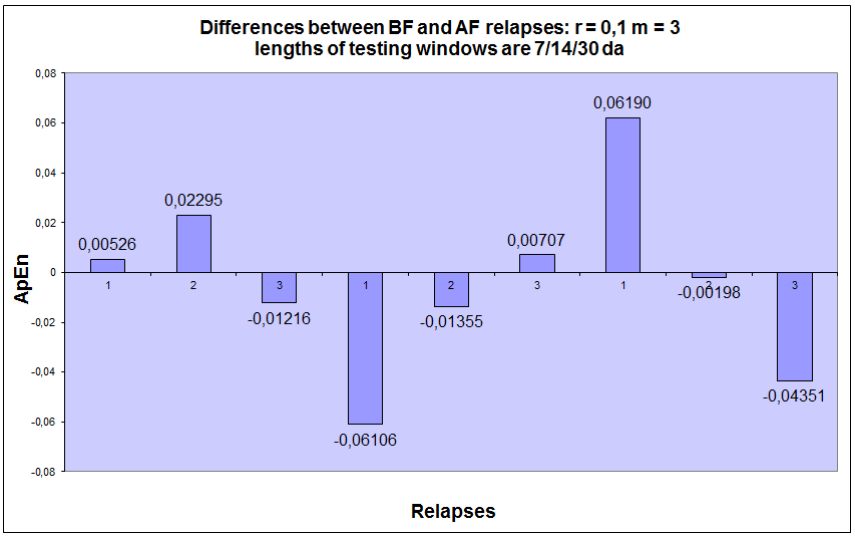

Figure C.15: ApEn: Value of differences between BD and AF relapses - 7/14/30days

C.4 Figures of ApEn: Window before relapses - 7days; parameters -> m = 2, r = 0.15

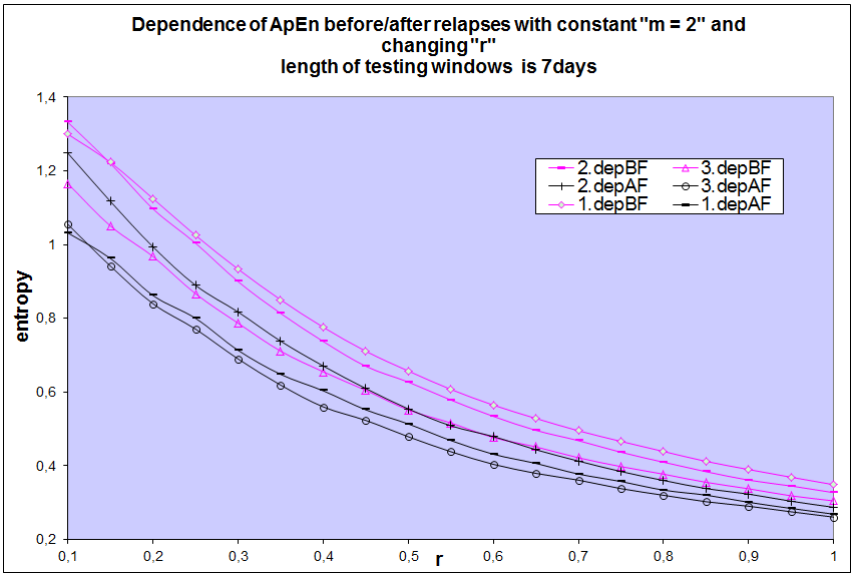

Figure C.16: ApEn: Compare data BD and AF relapses - 7days

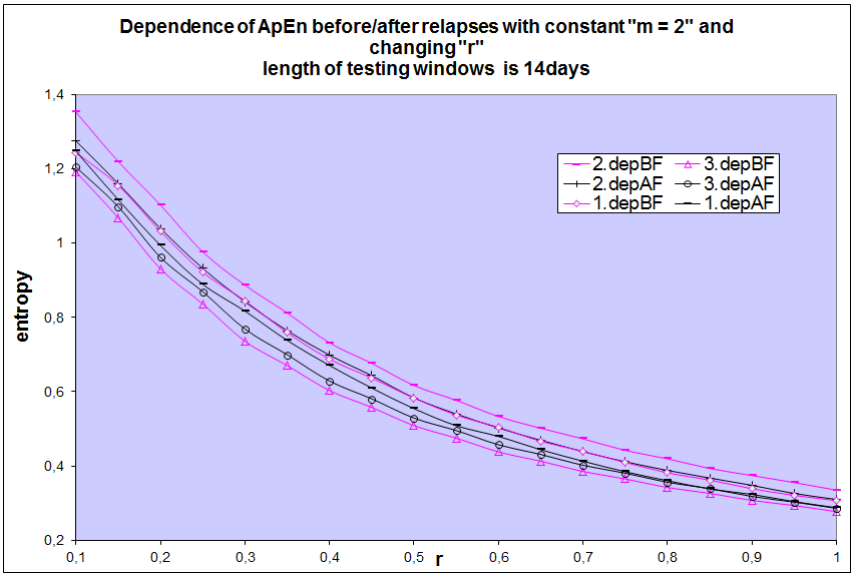

Figure C.17: ApEn: Compare data BD and AF relapses - 14days

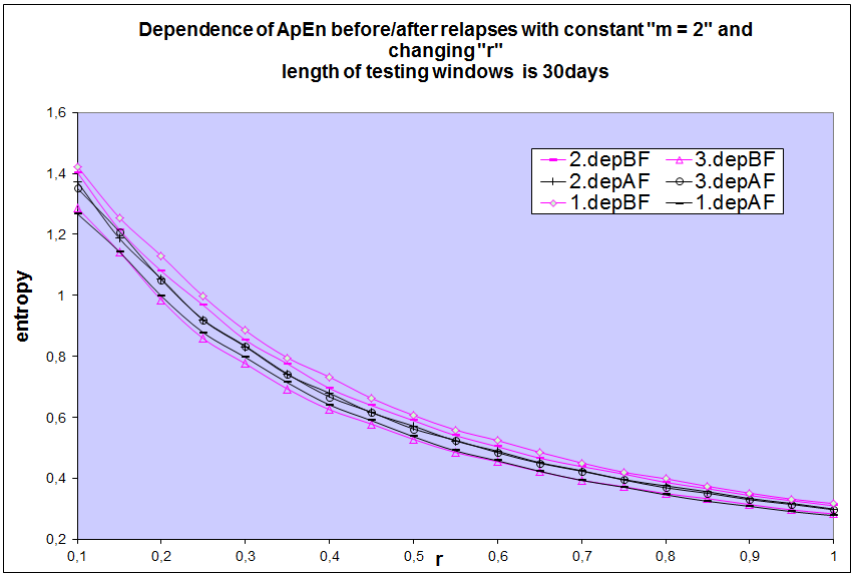

Figure C.18: ApEn: Compare data BD and AF relapses - 30days

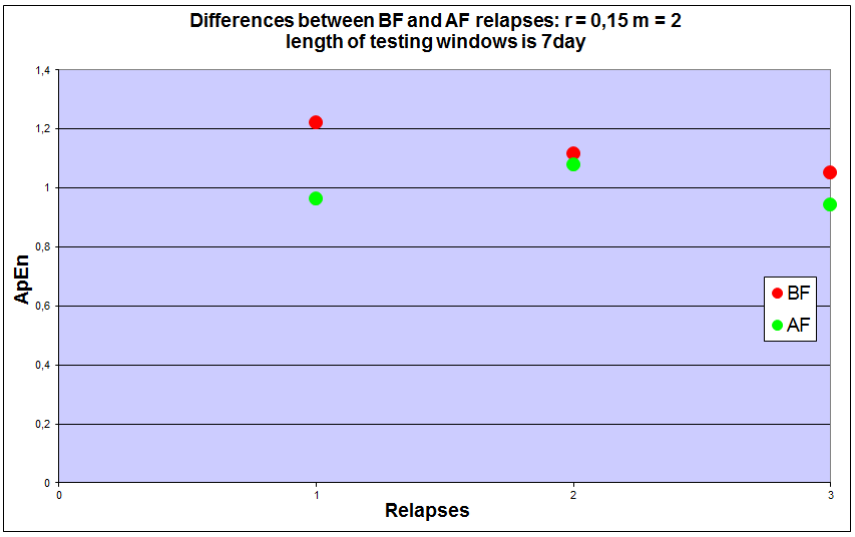

Figure C.19: ApEn: Differences between BD and AF relapses - 7days

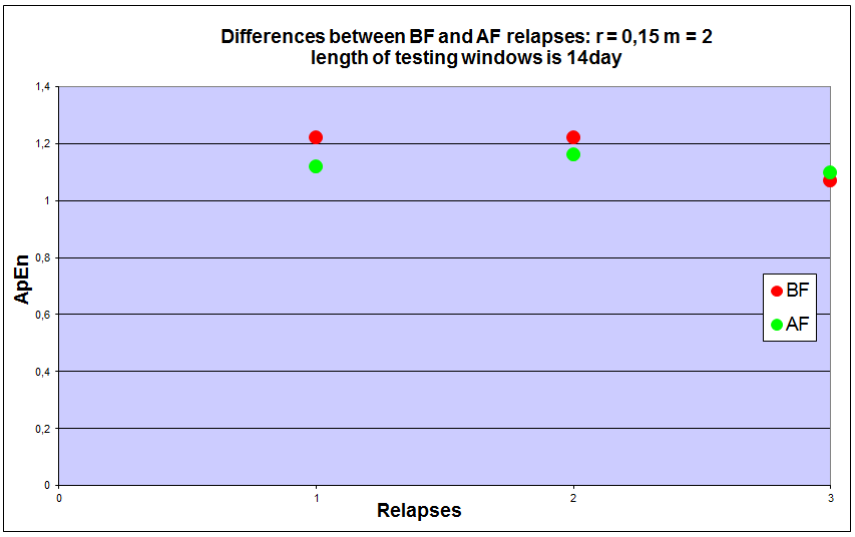

Figure C.20: ApEn: Differences between BD and AF relapses - 14days

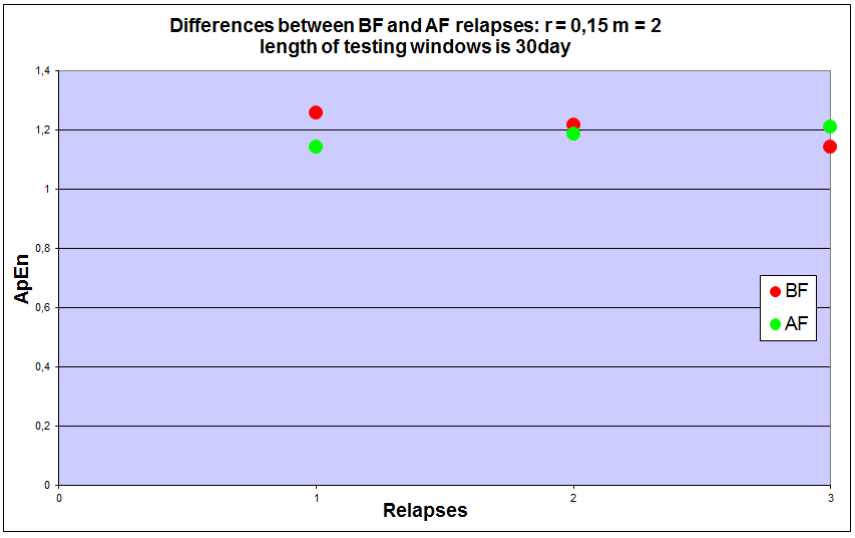

Figure C.21: ApEn: Differences between BD and AF relapses - 30days

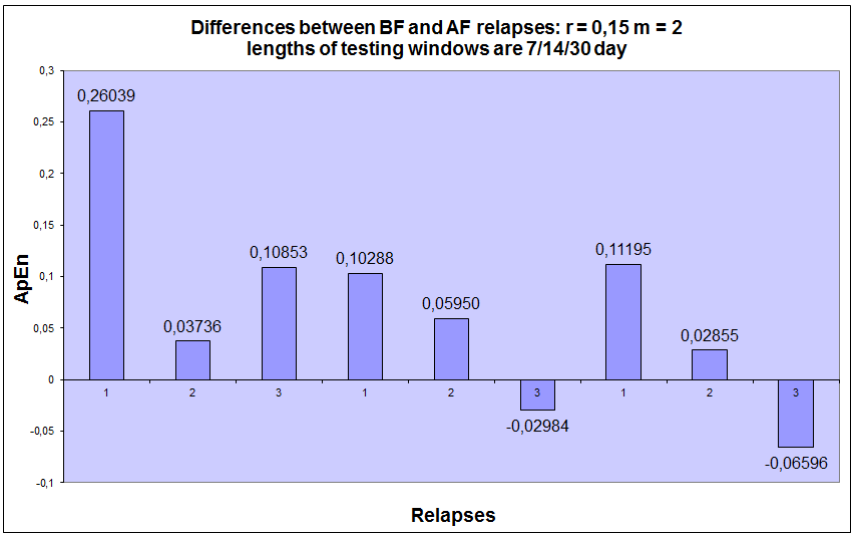

Figure C.22: ApEn: Value of differences between BD and AF relapses - 7/14/30days

C.5 Figures of ApEn: Window before relapses - 7days; parameters -> m = 3, r = 0.1

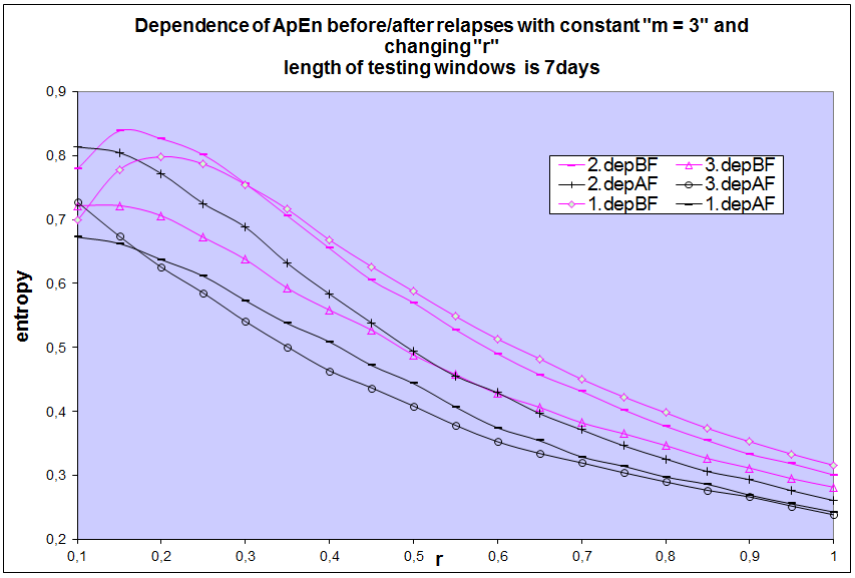

Figure C.23: ApEn: Compare data BD and AF relapses - 7days

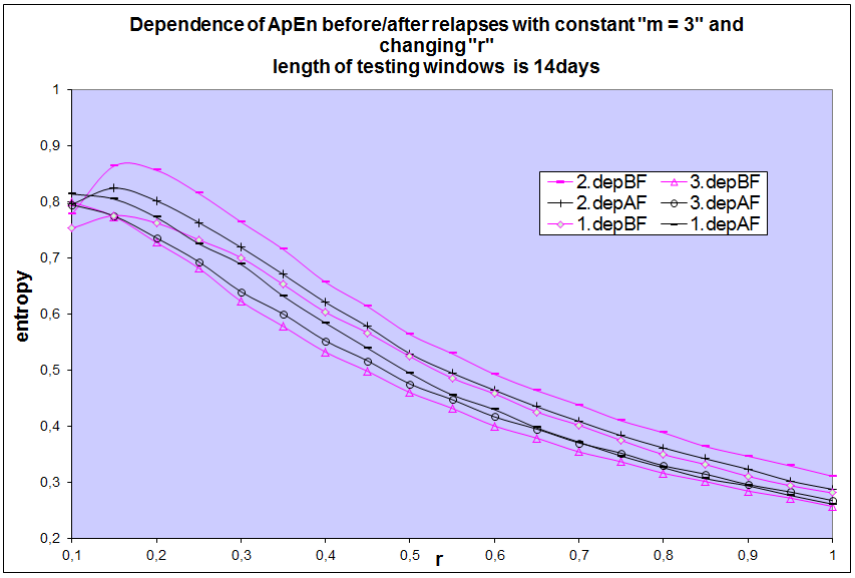

Figure C.24: ApEn: Compare data BD and AF relapses - 14days

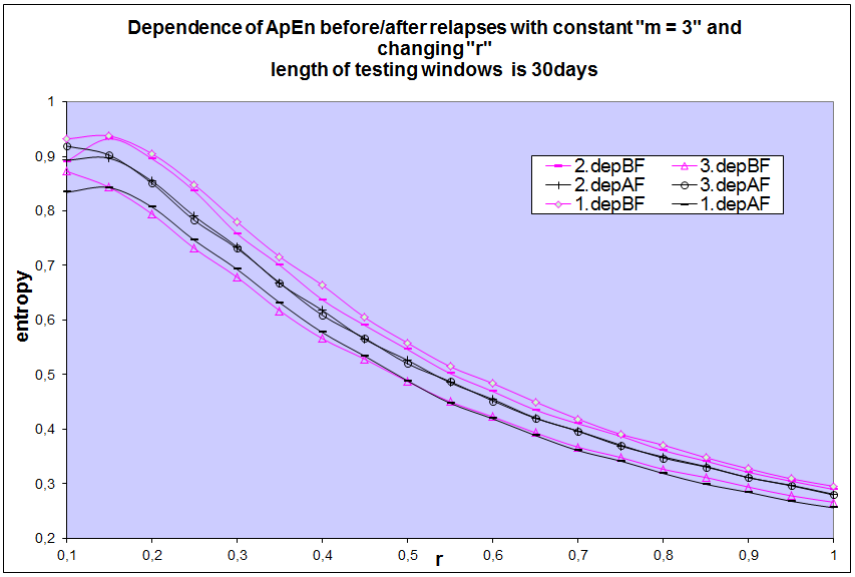

Figure C.25: ApEn: Compare data BD and AF relapses - 30days

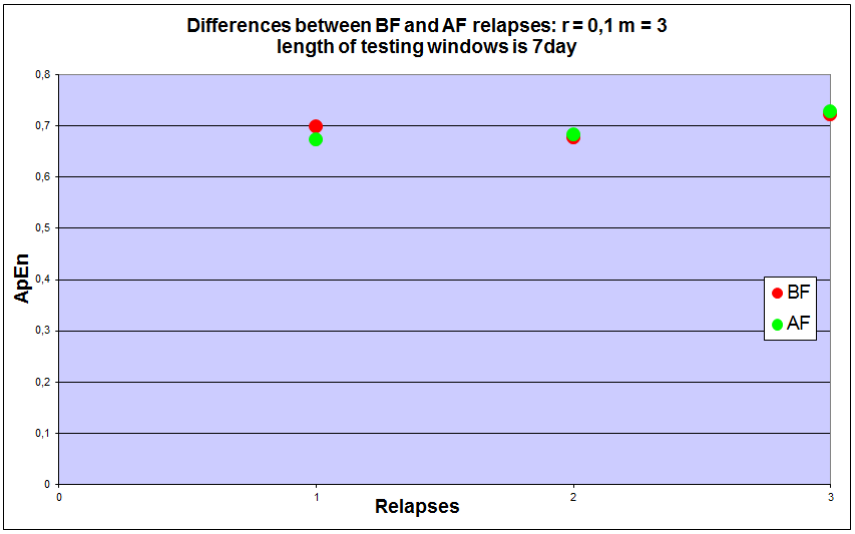

Figure C.26: ApEn: Differences between BD and AF relapses - 7days

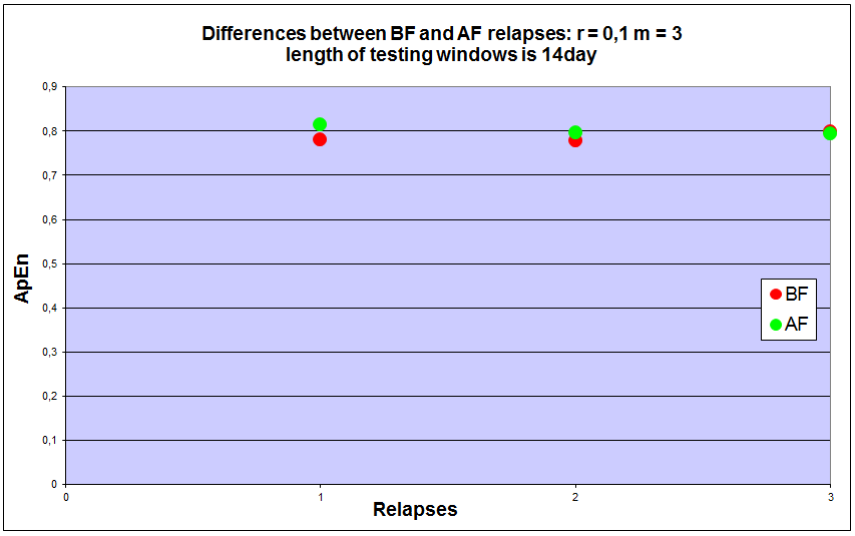

Figure C.27: ApEn: Differences between BD and AF relapses - 14days

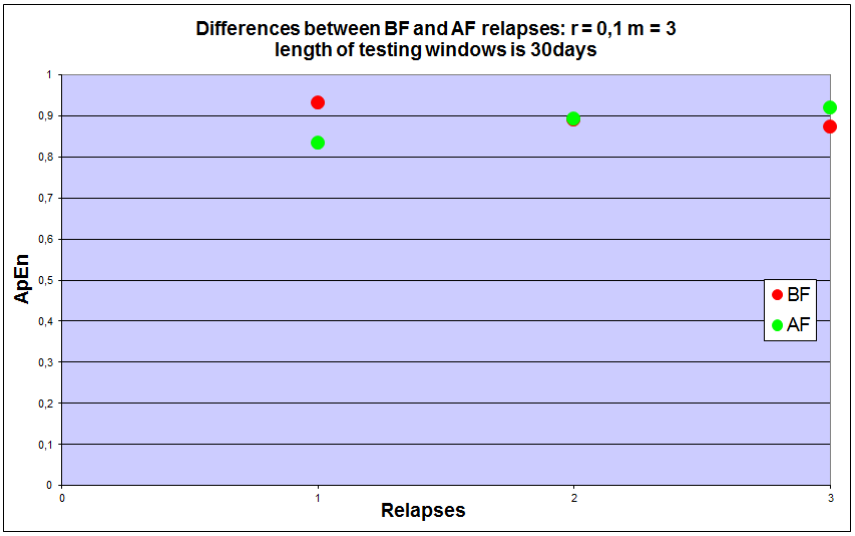

Figure C.28: ApEn: Differences between BD and AF relapses - 30days

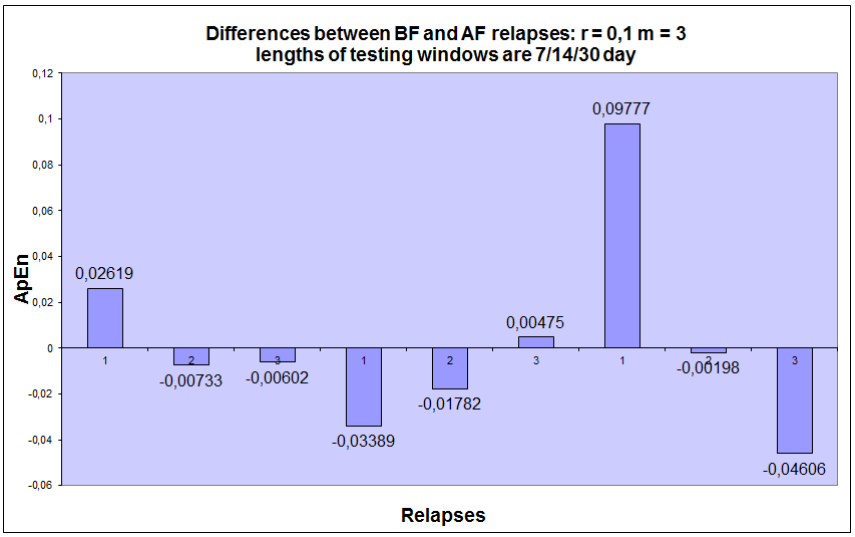

Figure C.29: ApEn: Value of differences between BD and AF relapses - 7/14/30days

Appendix D

Figures of CiRh - Patient 6

D.1 Continual figure

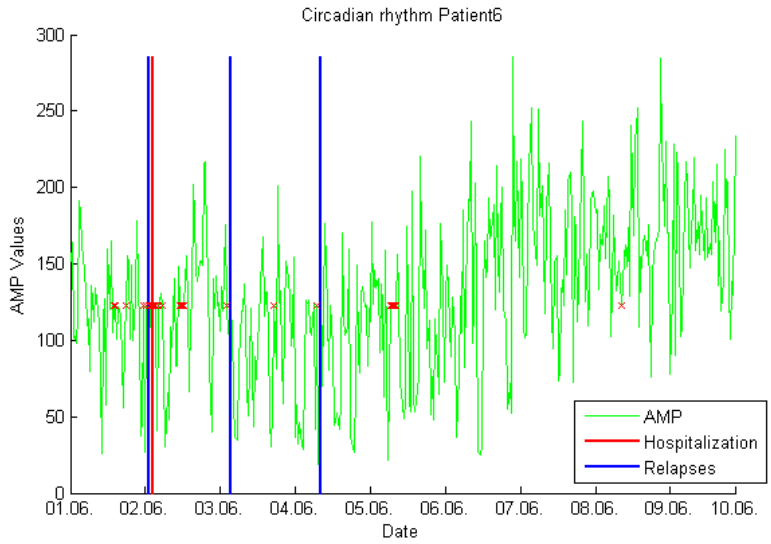

Figure D.1: CiRh: Parameter AMP

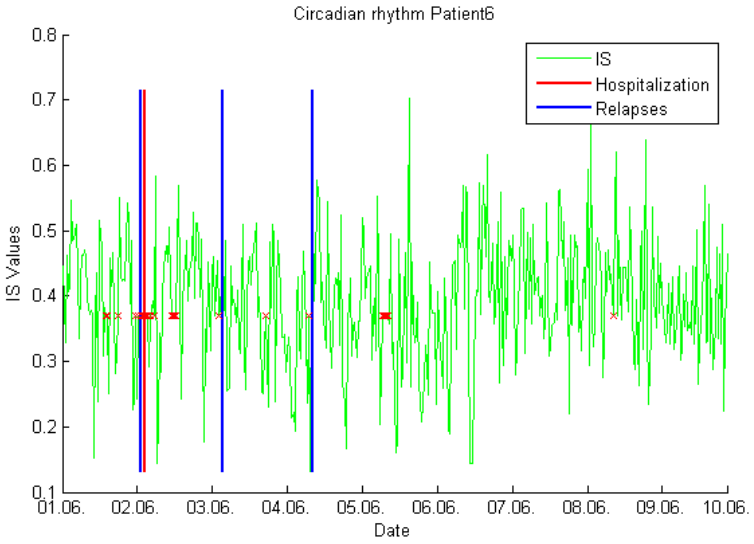

Figure D.2: CiRh: Parameter IS

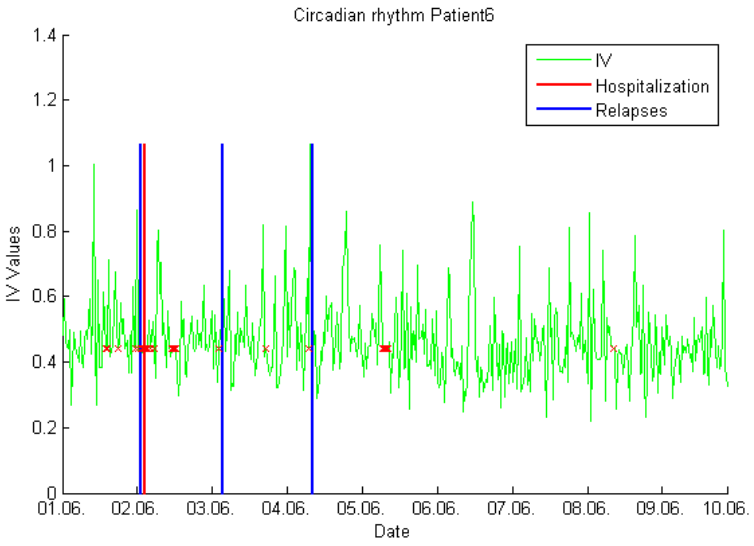

Figure D.3: CiRh: Parameter IV

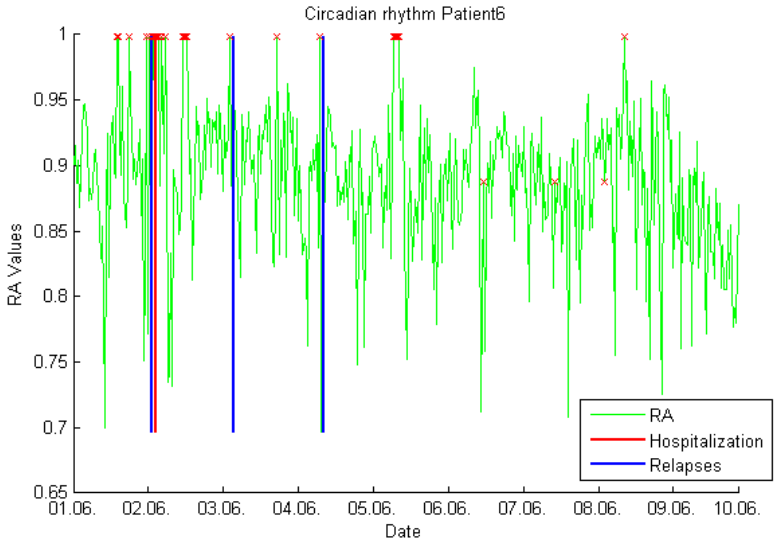

Figure D.4: CiRh: Parameter RA

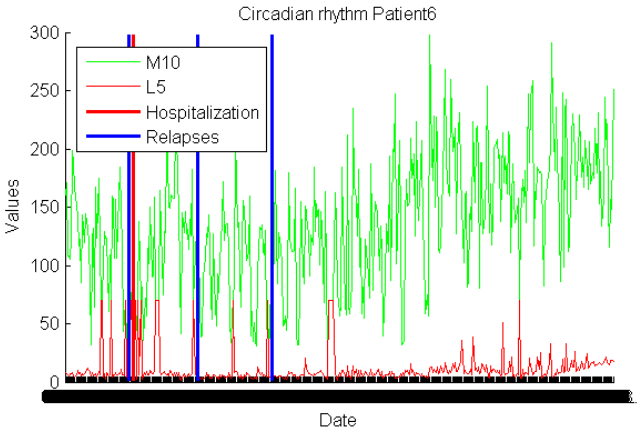

Figure D.5: CiRh: Parameters M10; L5

D.2 Figures of CiRh: Compare data BR and AR -> 1st relapse

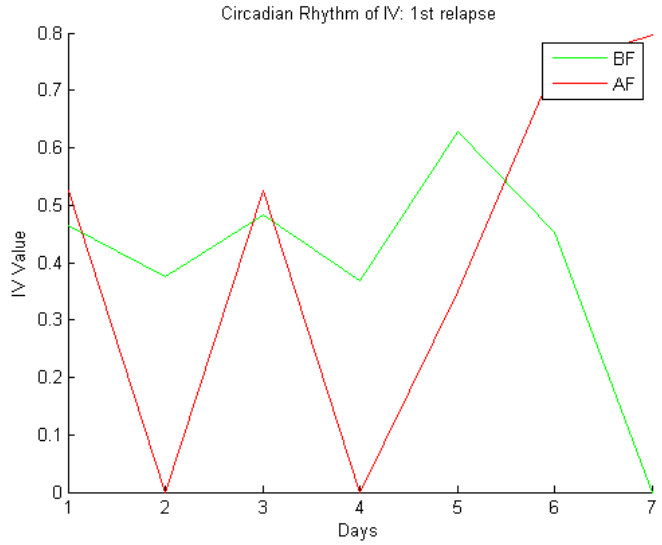

Figure D.6: CiRh: Parameter IV - 1st relapse

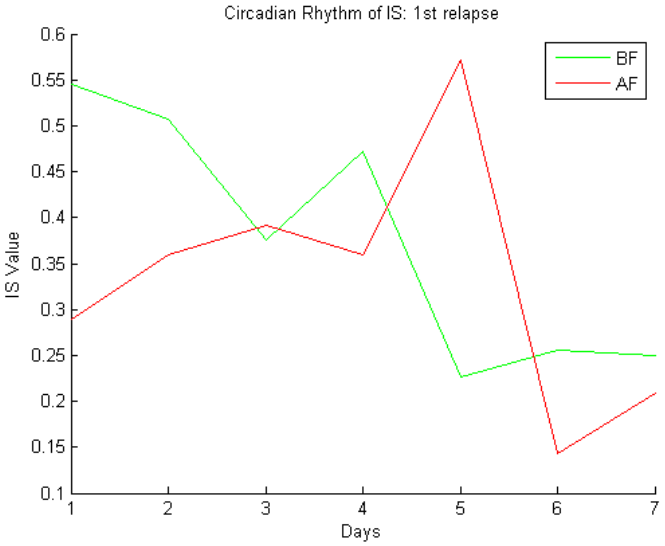

Figure D.7: CiRh: Parameter IS - 1st relapse

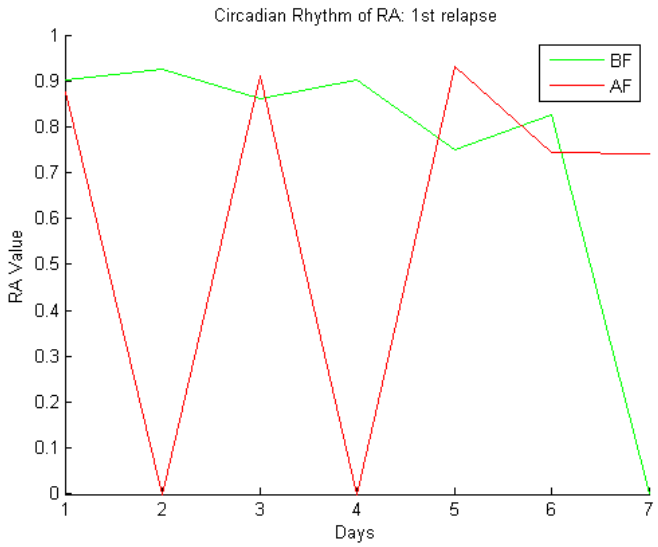

Figure D.8: CiRh: Parameter RA - 1st relapse

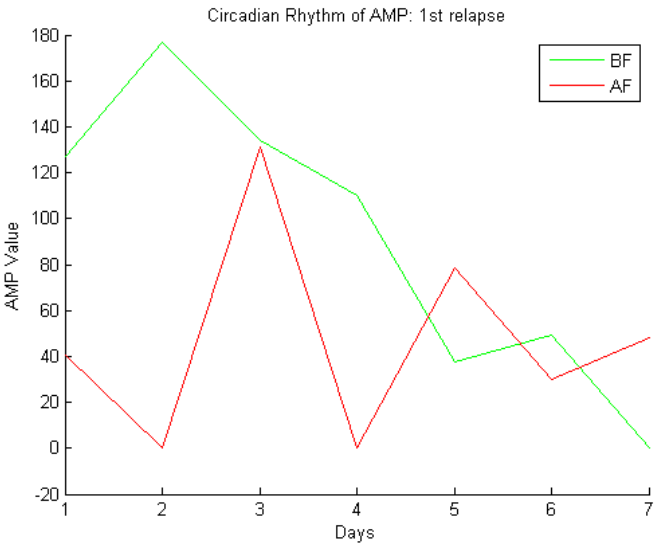

Figure D.9: CiRh: Parameter AMP - 1st relapse

D.3 Figures of CiRh: Compare data BR and AR -> 2nd relapse

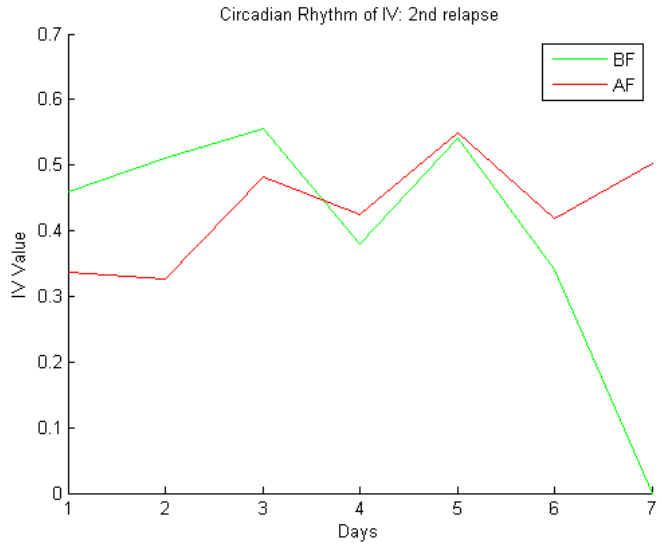

Figure D.10: CiRh: Parameter IV - 2nd relapse

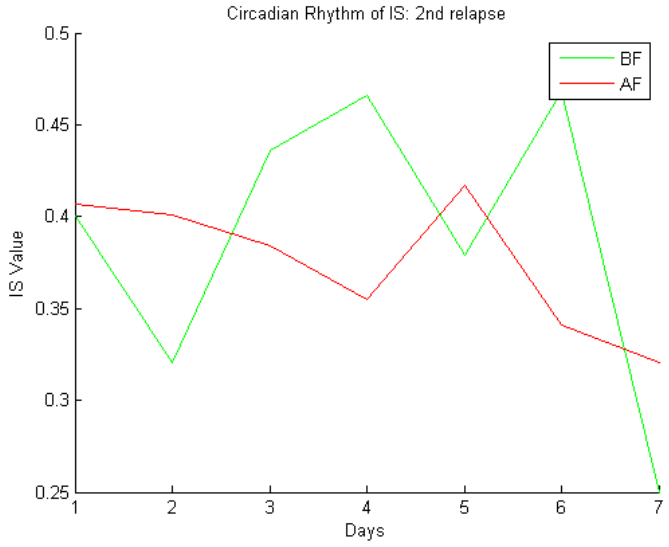

Figure D.11: CiRh: Parameter IS - 2nd relapse

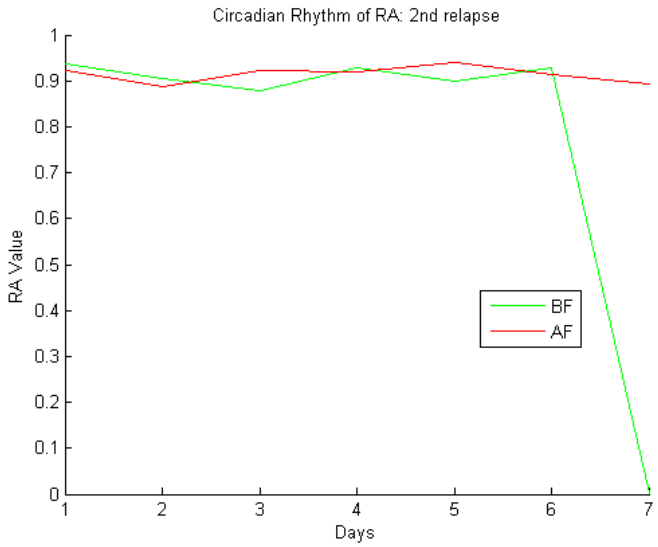

Figure D.12: CiRh: Parameter RA - 2nd relapse

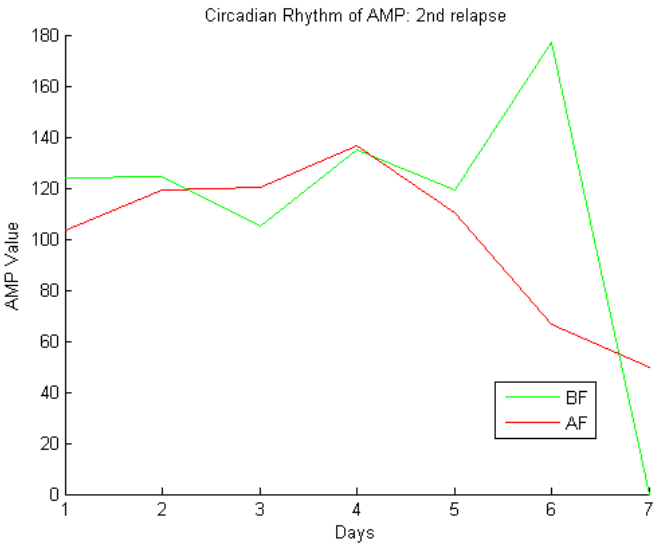

Figure D.13: CiRh: Parameter AMP - 2nd relapse

D.4 Figures of CiRh: Compare data BR and AR -> 3rd relapse

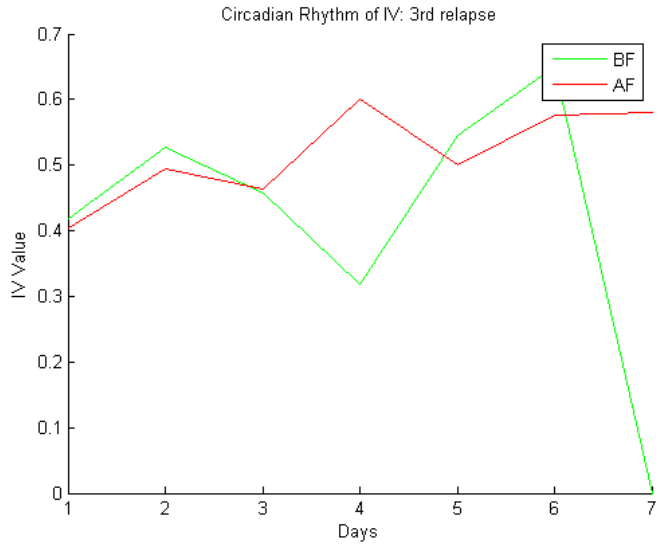

Figure D.14: CiRh: Parameter IV - 3rd relapse

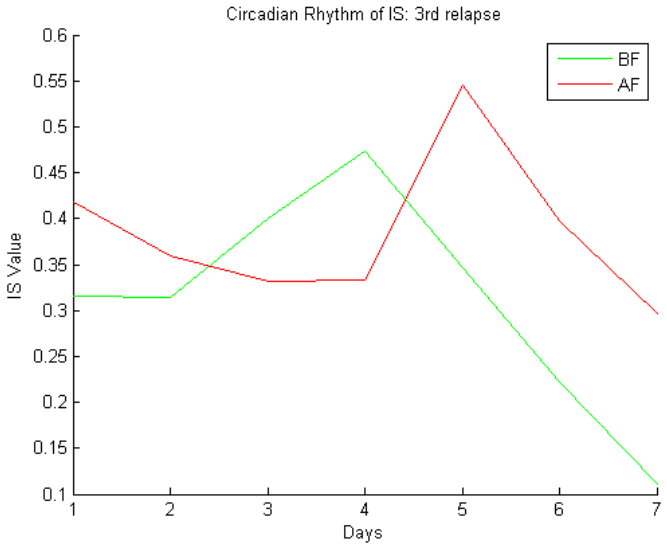

Figure D.15: CiRh: Parameter IS - 3rd relapse

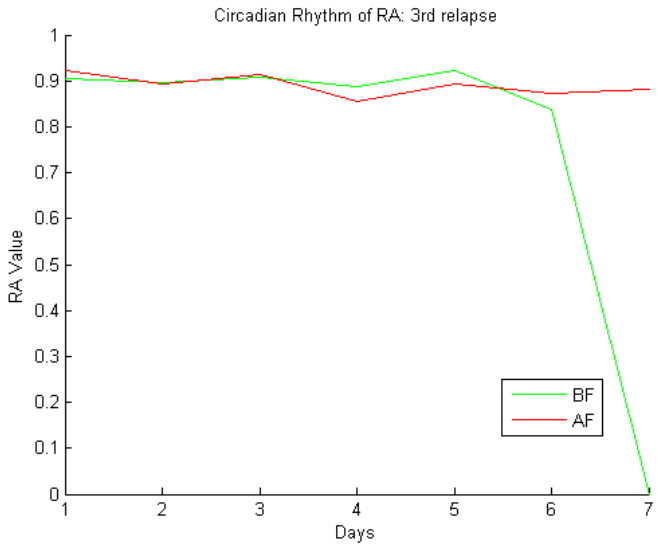

Figure D.16: CiRh: Parameter RA - 3rd relapse

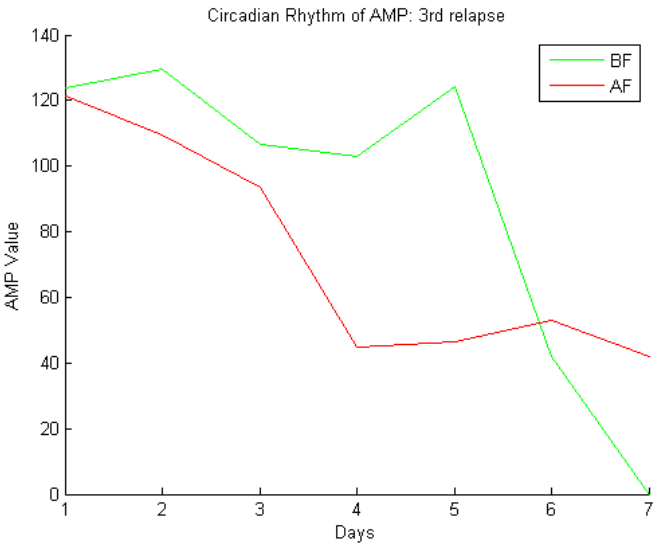

Figure D.17: CiRh: Parameter AMP - 3rd relapse