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EXECUTIVE SUMMARY

The aim of work package **WP4** is to develop methods for the offline and online management, fusion and analysis of multimodal and advanced technology data from social, behavioural, cognitive and physical activities of frailty older people and apply them to manage and analyse new data. Results from the analysis of existing and new data will be also used to create user-profiling virtual models of older people.
The main focus of the deliverable **D4.16** is to develop a clinical state prediction engine that simulates the behaviour of an existing patient model, taking into account up-to-date measurements of physiological factors. This is performed by integrating the results of the different sensors and self-reports (combination of all the acquired data) in order to provide the user with the appropriate feedback. These predictions are used either to alarm the patient in order to prevent adverse events, or to be included as supplemental input to the Decision Support System module. Furthermore, artificial intelligence methods are applied for knowledge discovery from data related to user activity and for physiological classification.

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LIST OF ABBREVIATIONS AND ACRONYMS

(*in alphabetic order*)

DSS	Decision Support System
MIL	Multiple-Instance Learning
UI	User Interface
VPM	Virtual Patient Model
WWBS	Wearable WBan System
WWS	Wearable Wellness System

1 Introduction

Global population has lengthened its life expectancy tremendously over the last few decades. Subsequently, while humans tend to live longer, numerous chronic situations like cardiovascular diseases are found more frequently among them than in the past. In this hypothesis, it is safe to imagine each individual at its late age as a complex patient in need for the consultation of different specialists. Not only, do the national health systems consume an excessive amount of resources to care for the average overaged patient, but also, on the other hand, the quality of life of the latter is impoverished. Therefore, prevention appears to be the absolute and crucial solution. Frailty, the one-word term for our body's state of physical and mental weakness could be explained by the parallel existence of several factors implicating each individual's health status [1, 2]. The first part of this deliverable aims to examine the influence of the inflammation on our health. The role of inflammation in the pathogenesis of frailty has been hypothesized, and so far many studies have been performed in order to understand the mechanism of action underlying this association. Recent studies support this hypothesis and show a clear association between inflammation, frailty, and age-related disease. Chronic inflammation is key pathophysiologic process that contributes to the frailty directly and indirectly through other intermediate physiologic systems, such as the musculoskeletal, endocrine, and hematologic systems. The complex multifactorial etiologies of frailty also include obesity and other age-related specific diseases. This has a semantic effect on quality of life in the later years.

The second part of this deliverable targets the risk assessment platform, which the clinicians can use to monitor the older people and intervene accordingly in case of risks. For this purpose, a FrailSafe Decision Support System (DSS) engine is designed to monitor the older person's vital signs and forward alerts towards clinicians. These alerts are generated when irregularities are observed in the VPM aggregated data or when a short-term event is detected by the online data analysis module.
The last part of the deliverable focuses on the development of a clinical state prediction engine that aims to simulate the behaviour of an existing patient model, taking into account up-to-date measurements of physiological factors. Thus, the system is able to integrate the results of the different sensors and self-reports (combination of all the acquired data) in order to provide the user with the appropriate feedbacks, incentives, and actions. This way several, critical clinical parameters are predicted, such as prediction of frailty level change. These predictions can be used either to alarm the patient in order to prevent adverse outcomes, or to be included as supplemental input to the DSS module. Probabilistic techniques are applied on a provided set of parameters to give probabilistic prediction of specific indicators.

2 Role of inflammation in the pathogenesis of frailty

Inflammation is our natural mechanism of maintaining our body's homeostasis [3]. The occurrence of inflammation is inextricably combined with the exposure of our inner systems to potentially harmful microorganisms, well known as pathogens. However, verified proof reveals that in certain cases, this mechanism falsely targets well-functioning cells of the body too, a situation creating the autoimmune syndromes.

Firstly, triggered by the intervention of inflammatory mediators, vasodilation escalates the blood flow. Simultaneously, increased permeability of the blood vessels results in the leakage of proteins and fluid into the tissue. At this stage, it is evident to the human eye that the area has become red, has increased its temperature and has become swollen. The loss of function is believed to occur in order to avoid the feeling of pain. Afterwards, neutrophils and macrophages take action. Neutrophils migrate outside the blood vessels and adhere first into the tissue with the assistance of chemotactic gradients, which enable them to become attached firmly onto the endothelial cells [4]. Phagocytes have non-specific microbe affinity and efficacy and immediately initiate to extinguish the harmful agent by encapsulating it. Next to arrive are the macrophages, which move slower inside the blood vessel, but, induce a more effective impact than their partners. During the apoptosis of neutrophils, antimicrobial substances, such as NO, OH and H2O2, are released into the blood stream destined to destroy the pathological stimuli. However, their effect is not specialized towards each specific factor, meaning that the surrounding healthy tissue may be damaged. In parallel, this process is enhanced by a group of preformed proteins released into the plasma in an inoperative form, the complement system, which destroys the injurious factor without encapsulating it, but, by simply creating pores on the microbe's cellular surface. At this point, it is important to point out that certain microorganisms and particularly the bacteria have adjusted to this strategy by developing an additional protective surface. In these cases, chemical factors, named opsonins[5] make contact with the macrophage and the microorganism and create a complex. C3b (member of the MAC) and CRP (C-reaction protein) belong to this category [6, 7]. The procedure described above concerns cases where the human body becomes exposed to the harmful factor for the first time.

Human body is so resourceful that it has developed a method of "saving" the different types of pathologic agents. This results to even more immediate and acute response if one "saved" agent enters the human body. In this situation, it is again the macrophages who initiate the process. After encapsulating the agent, they divide it into smaller protein molecules. Subsequently, each molecule gets attached to MHC || proteins and becomes exposed to the cellular surface. At this point, the CD4 cells, through a unique receptor specialized for this specific antigen comes in contact with the macrophage. The connection between the two, is also enhanced by the presence of other proteins found on the cell membrane, while, IL-1 and TNF are produced by the macrophage in order to activate fully the CD4 cells.

The CD4 cells, then, release IL-2 which leads to the increase of their population forming clones and the activation of B cells. B cells are responsible for three major roles [8]. Firstly, they mature into plasmacytes that produce antibodies which enter the blood stream. Each antibody is genetically destined to recognize one and only particular antigen. Secondly, a part of B cells population transforms into memory B cells. Moreover, it is possible that they behave like the macrophage, revealing an injurious antigen to the CD4 cell.

The complex of an antibody and an antigen enables the destructive efficacy of the macrophage.

Inflammation appears to be a mechanism triggered by one single incident and to be completed with the elimination of the pathogen. However, in certain cases it may become established in a particular area of the human body and cause continuously the mentioned symptoms.

Nowadays, science has progressed significantly enough to comprehend most of the extremely specific and complicated steps our body takes to protect itself. Thanks to this, we are able to examine how inflammation contributes among others to frailty. The base of the hypothesis is a linkage between high levels of cortisol and the activation of inflammation markers [9]. It is believed that specifically the incidents of chronic inflammation are responsible for the "weakening" of the individual's stamina [10].

Since it has come to our realization that despite our material wealth, increased access to goods like sterilized water, safely preserved food and advanced drugs, the human population faces an even wider range of health issues seemingly relevant to a series of inflammation incidents, we ought to wonder: why is frailty so common among the population?

The question raised above derives from the simple example of the Galapagos Islands. Even though the islands' biodiversity is under threat from several sources, we cannot help but notice that the Galapagos tortoise has managed to become the longest living of its species. A probable explanation would be that the Galapagos Islands have been a secure and isolated environment in general terms. That is, stress-increasing factors have been almost eliminated and each species has been successfully adjusted to its natural habitat [11].

The example described above brings us to a second question: is anxiety valued sufficiently based on the influence it imposes on our quality of living?

Aiming to reach a reasonable conclusion, it is necessary to evaluate in detail each and every aspect of the majority's way of living that is potentially stress provoking. A balanced psychological status may determine the outcome of everyday life. Nevertheless, depression affects an alarming number of citizens from all social strata. Based on WHO, there are 350 million people from all age groups worldwide suffering from major depression symptoms and over 800000 of them are led to suicide each year. Depression is a mental disorder of which most frequent symptoms consist of uncontrollable sadness, isolation from social activities, inability to concentrate, random emotional fluctuations, constant tiredness and abnormal behaviour [12, 13] .

Such symptoms are also intensified by solidarity -which is, in most times, a conscious personal choice-, financial and social discrepancies like bankruptcy and racism and in certain cases, the unfortunate choice of profession along with inappropriate working conditions. According to studies,, depression seems to affect the female population more often than the males [14].

Secondly, it is essential to take each person's genetic background into account. It is probable that most of the population have inherited altered biochemical paths encrypted into the DNA, resulting to, for example, the abnormally excessive production of cortisol into the blood stream or even, falsely triggering the inflammation factors after no severe threat [15]. This, automatically, leads to general inflammation incidents that target no particular pathogen. In the first case mentioned, the gene defect would be translated as a benign mass in the adrenal glands while, in the second one, the conditions referring to this situation are the autoimmune syndromes, like rheumatoid arthritis [16].

On the other hand, health wise, cardiovascular abnormalities in combination with chronic high blood pressure, hyperlipidemia and diabetes exhaust the resources of the human body [17, 18]. The simultaneous effect of the conditions mentioned may be found in a vast amount of men over the age of 45 and women over the age of 55 (women can be protected thanks to estrogens) and also be linked with genetic predisposition [19]. Such patients are advised to receive medication for life to prevent the formation of atheromatic plaque in the blood vessels and to prolong their life expectancy. Such conditions could develop into constriction of the blood vessels in the extremitions, sudden ischemic and bleeding strokes, aneurisms etc. However, it is common act that not only do they neglect the regular visits to their specialists, but, also, in some cases, they take no action about. Unfortunately, physicians confirm that prevention could be accomplished in condition that citizens are thoroughly informed and educated about the importance of regular check-ups.

The excessive release of cortisol in the blood stream may also contribute to a generalized hormonal alteration. Automatically, the human body will start producing hormones uncontrollably and under no specific mechanisms of action [20]. For example, CRP and PTH will increase, the first one triggering the mechanism of inflammation while, the second one, destructing the bone tissue. This may also lead to loss of appetite and malnutrition. The latter is responsible for not only causing our metabolic rhythms to cease, but it also leads to major muscle tissue loss. It comes as logical conclusion that major bone and muscle tissue loss will result in the so called frailty of the elderly [1].

Furthermore , examining the example of the Galapagos Islands, we ought to point out that throughout history the organisms inhabiting the islands have developed unique ways of surviving [21]. For instance, the iguana of the Galapagos has developed the ability to dive up to 10 metres underwater and feed on sea creatures. Its capacity might be the answer to a previous shortage of food on land, or, a sudden increase in the iguana's population. It is the instinct for survival that led the iguana for food underwater, a plan that proved successful and was later on encrypted into the species'

genome. In this situation, it is clear that there is a positive effect of stress provoking situations too, because they contribute to the progression of species.

As a conclusion, cortisol and inflammation may become an ally to the amelioration of human race, but, they also create numerous health issues, sometimes minor, but others, severe which decrease the quality of life.

3 Risk assessment

Towards enhancing the risk assessment domain, the FrailSafe DSS engine is designed to monitor the older person's vital signs and forward alerts towards clinicians. These alerts are generated when irregularities are observed in the VPM aggregated data (e.g. on heart rate, respiration rate, and blood pressure) or when a short-term event is detected by the online data analysis components (e.g. fall or suicidal text detection). Thus, the DSS can serve as a risk assessment platform, which the clinicians can use to monitor the older people and intervene accordingly in case of risks.

3.1 Generation of alerts

The alerts which are stored in the DSS engine are generated by the offline and online data analysis modules as shown in Figure 1.

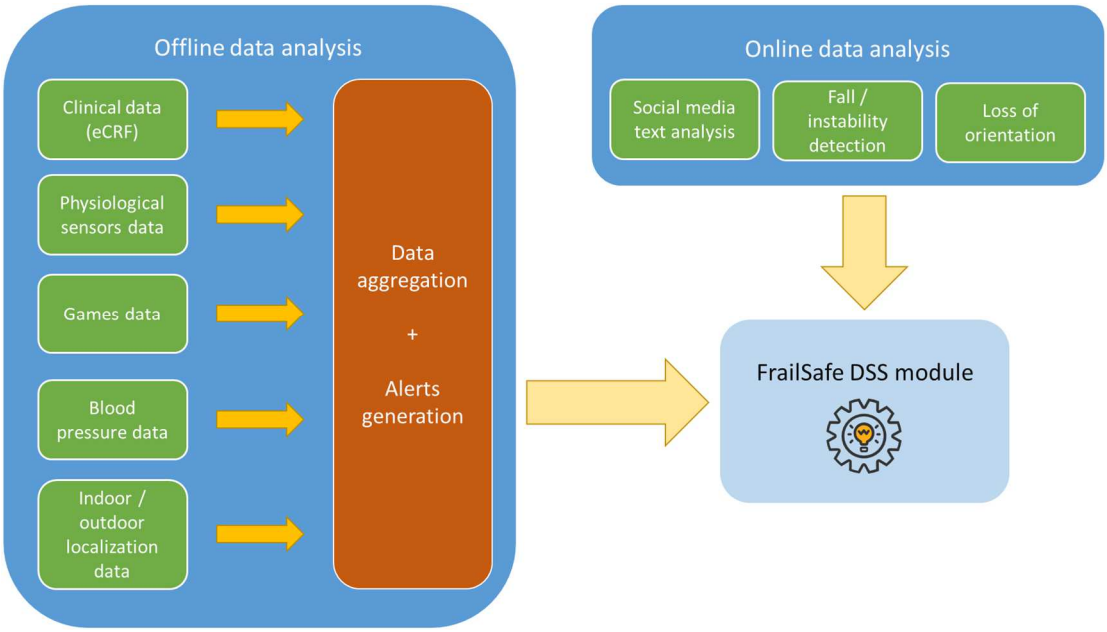

Figure 1: Data aggregation and alert generation from offline and online data analysis.

During the offline data processing, data are being collected from multiple sources and are subsequently summarized with the use of aggregation functions as described in D4.2. Through this procedure the values of the raw and the aggregated data are examined, and alerts are generated if these values are outside of the normal range, as this was defined by the clinicians (Table 1).

Table 1: Normal ranges of measurements per activity.

Measured Entity	Activity	Acceptable Range
Heart Rate	*Standing/sitting/Lying*	*50-100*
Heart Rate	*Walking*	*60-110*

Respiration Rate	*All*	*12-28*
Systolic Blood Pressure	*Standing/sitting*	*100-140*
Diastolic Blood Pressure	*Standing/sitting*	*<90*

While heart rate and blood pressure normal ranges can be applied uniformly to all participants, the respiration rate is something that varies significantly in older people. Currently the above limits are selected based on [22], but in the future they will be personalized for each participant.

The examination of participants' physiological parameters according to these ranges was performed by multiple aspects:

- If the daily average of a participant heart rate or respiration rate falls out of the above ranges while performing an activity, then an alert is generated.
- If the heart rate or the respiration rate of a participant falls out of the normal ranges for a duration of few seconds, then we assume it is an outlier caused by an erroneous measurement. If the duration of abnormal values persists for longer time, then an alert is generated indicating the time period and the average value for the respective period. This type of alert is important, as one participant can e.g. experience normal daily average heart rate but his/her measurements for a specific period of the day could be abnormal.
- If the average daily values of the systolic/diastolic blood pressure fall out of the normal ranges, then an alert is generated for the specific day.
- If the value of the systolic blood pressure for a participant is measured to be under the threshold at any measurement taken, then an alert is generated as it can an indication of hypotension.

The online data analysis components run in real-time and in case they detect any emergency situations they trigger an alarm. The real-time alerts generated are:

a. Social media text alert: It is generated by the social media sensing platform, when it detects suicidal manifestation in a text posted by the participant in his/her social media accounts.
b. Fall detection / instability alert: It is generated by the fall detection android app, when it detects that the participant has fallen or that he/she shows an increased instability.
c. Loss of Orientation alert: It is generated by the respective application, when the participants experiences signs of disorientation in his/her outdoor movement.

3.2 Decision Support System API

The alerts generated by the offline and online data analysis, which are described in the previous section, are sent to the DSS module and are visualized by the DSS UI module. For the purpose of communication between the DSS and the other submodules of the FrailSafe system, an API was created. At the time that this deliverable is written, the API can be accessed by directing the URL in this address:

http://172.16.2.50:5052/dss/

The access is limited to the submodules that are part of the FrailSafe cloud private subnet (as it is defined in the D1.4). The internal structure of the DSS module and the connection with external submodules are depicted in Figure 2.

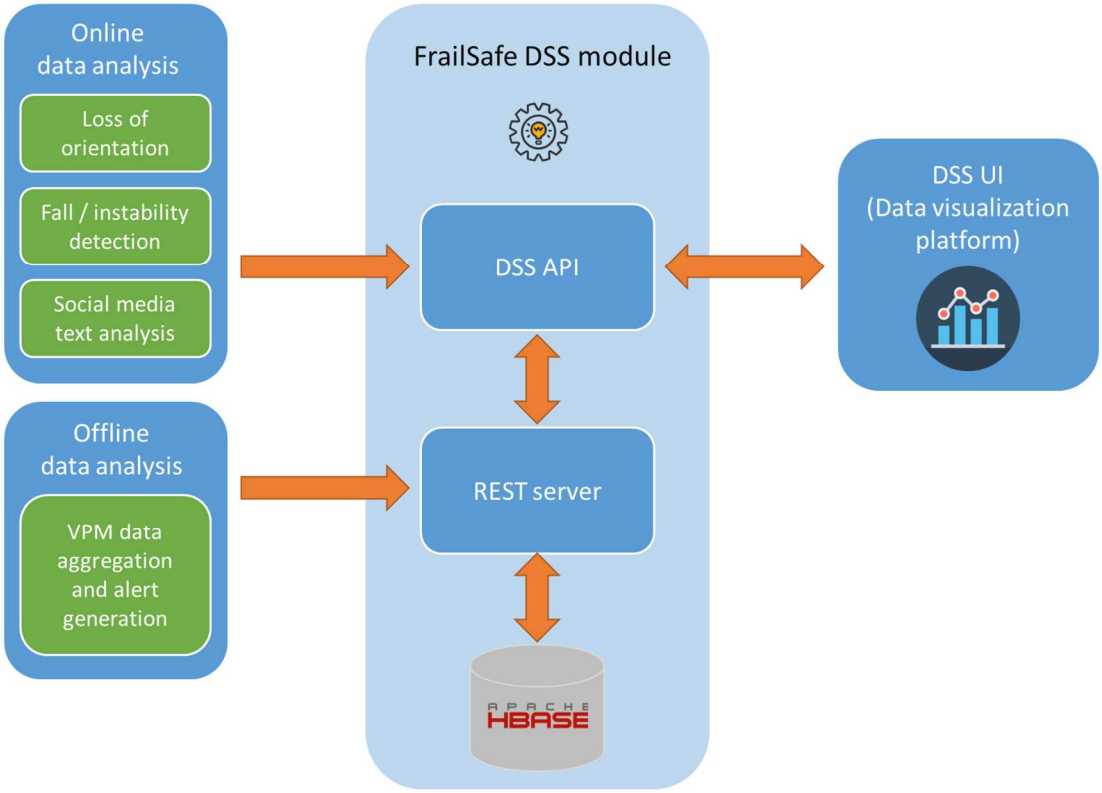

Figure 2: FrailSafe Decision Support System module.

The list of commands that the DSS API allows are the following:

- fetch_all: Fetches a JSON containing all VPM data stored.
- fetch_pid_data/<pid>: Fetches a JSON containing all VPM data stored for one specific participant.

- fetch_pid_date_data/<pid>/<date>: Fetches a JSON containing all VPM data stored for one participant on a specific date.
- fetch_center_data/<cid>: Fetches a JSON containing all VPM data stored for each clinical center.
- fetch_ids: Fetches a JSON containing all participant IDs for whom there are VPM data stored.
- fetch_all_alerts: Fetches a JSON containing all alerts stored.
- fetch_pid_alerts/<pid>: Fetches a JSON containing all alerts stored for one participant.
- fetch_pid_date_alerts/<pid>/<date>: Fetches a JSON containing all alerts stored for one participant on a specific date.
- add_social_alerts/<pid>/<date>: Stores alerts coming from social media analysis.
- add_fall_alerts/<pid>/<date>: Stores alerts coming from fall detection / loss of stability android app.
- add_orientation_alerts/<pid>/<date>: Stores alerts coming from loss of orientation submodule.

The API allows the storing of alerts generated either by the VPM data, or by the real-time data analysis applications (Fall Detection, Loss of Stability, Loss of Orientation and Suicidal Text Detection). These alerts can be classified in three categories, based on the duration of the event detected:

a. Instant alerts, which are produced due to an unusual measurement at a specific time, i.e. elevated blood pressure at a specific time or suicidal manifestation in a text posted in social media.
b. Daily alerts, which are produced when daily user measurements exceed predefined thresholds, i.e. elevated average heart rate for a specific day.
c. Periodic alerts, which are produced due to unusual measurements over a period of time, i.e. elevated breathing rate for one hour.

3.2.1 Example 1: Export all alerts stored in the DSS

Command: GET /fetch_all_alerts

Parameters: No parameters required

Response: Response is a json object containing all alerts

The parameters in the json response are described below:

pid: participant id

date: date of alert

type: Type pf the alert (allowed: daily, instant, period)

from: beginning of alert period in case of period type alert

to: ending of alert period in case of period type alert

time: time of the alert in case of instant type alert

value: alert value

description: description of the alert

activity: activity performed by participants when alert occurred in case of high/low hr or br alerts (values: 1.0 for standing/sitting, 2.0 for lying, 3.0 for walking, 4.0 for walking upstairs, 5.0 for walking downstairs).

Use case:

Request: curl http://172.16.2.50:5052/dss/fetch_all_alerts

Response:


```
{"Results": [
   {
    "data": {
     "activity": "1.0",
     "avg": "7.61180657333",
     "description": "low_br"
    },
    "date": "20161210",
    "from": "20161210T03:39:25.000",
    "pid": "1042",
    "to": "20161210T03:40:09.000",
    "type": "period"
   },
   {
    "data": {
     "description": "high_avg_diastolic",
     "value": "96.5"
    },
    "date": "20170109",
    "pid": "3001",
    "type": "daily"
 },
 {
    "data": {
     "description": "low_systolic",
     "value": "99"
    },
    "date": "20170123",
    "pid": "3033",
    "time": "14:52:00",
```

```
    "type": "instant"
  }
]}
```

3.2.2 Example 2: Store alert data coming from social media analysis

Command: GET /add_social_alerts/<pid>/<date>

Parameters:

<pid>: participant' s id

<date>: datetime of the alert (in format YYYYMMDDTHH:mm:ss)

Response: Response is a json object containing message about the query result.

Use case:

Request: curl -H "Content-Type: application/json" -X POST -d '{"social_media":"facebook", "description":"suicidal_manifistation", "field1": "value1","field2": "value2}' http://172.16.2.50:5052/dss/add_social_alerts/1060/20170909T14:52:00

Response:

```
{
 "message": "Alert for participant with id=1060 and ts=20170909T14:52:00 has been added",
 "status": 200
}
```

3.3 Alert visualization panel

The alerts are visualized by the Decision Support System User Interface (DSS UI) which is described in detail in D5.4 and is part of the Clinical Web Platform. The clinical web platform is the main interface between users (older persons, families, clinicians, researchers) and the underlying FrailSafe database. Through the DSS UI users can view the collected data, according to their access rights, through intuitive visualizations.

The alert visualization tab of the DSS UI, visualizes the alerts produced for the older persons. Currently, the visualizations are table views of the alerts, where three types of alerts are distinguished as described earlier.

The visualization of these alerts in the DSS UI is differentiated based on the type of user that has logged in. The older person can view the alerts generated for him/her as shown in Figure 3, while the clinician is provided with an alert panel for all the older persons he/she is supervising as shown in Figure 4.

The information displayed for each alert includes the older person's ID, the alert description, the date/time of the alert, as well as any other value related to the alert,

e.g. the blood pressure value for a “high blood pressure” alert. In future versions of the DSS UI, the alert visualization tab will also include graphical visualizations of alerts, such as timeline plots, showing the amount of alerts produced through time, etc.

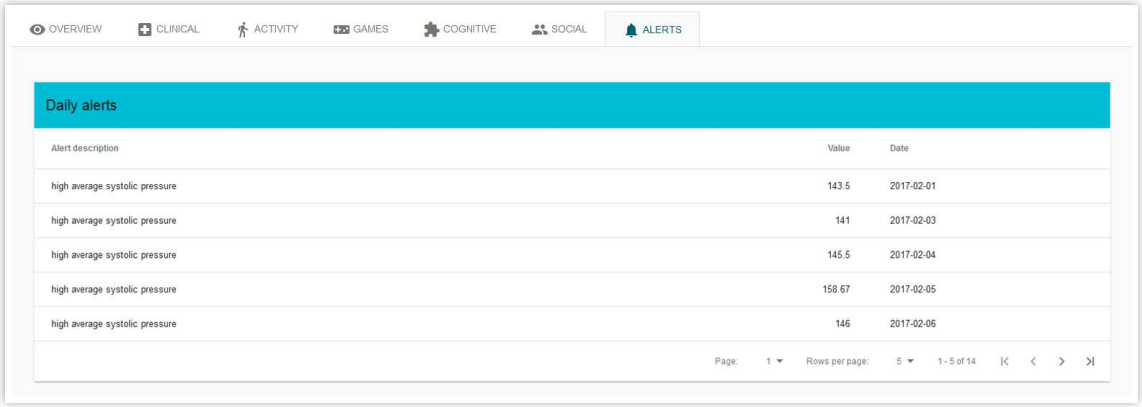

Figure 3: Visualization of alerts in the older person.

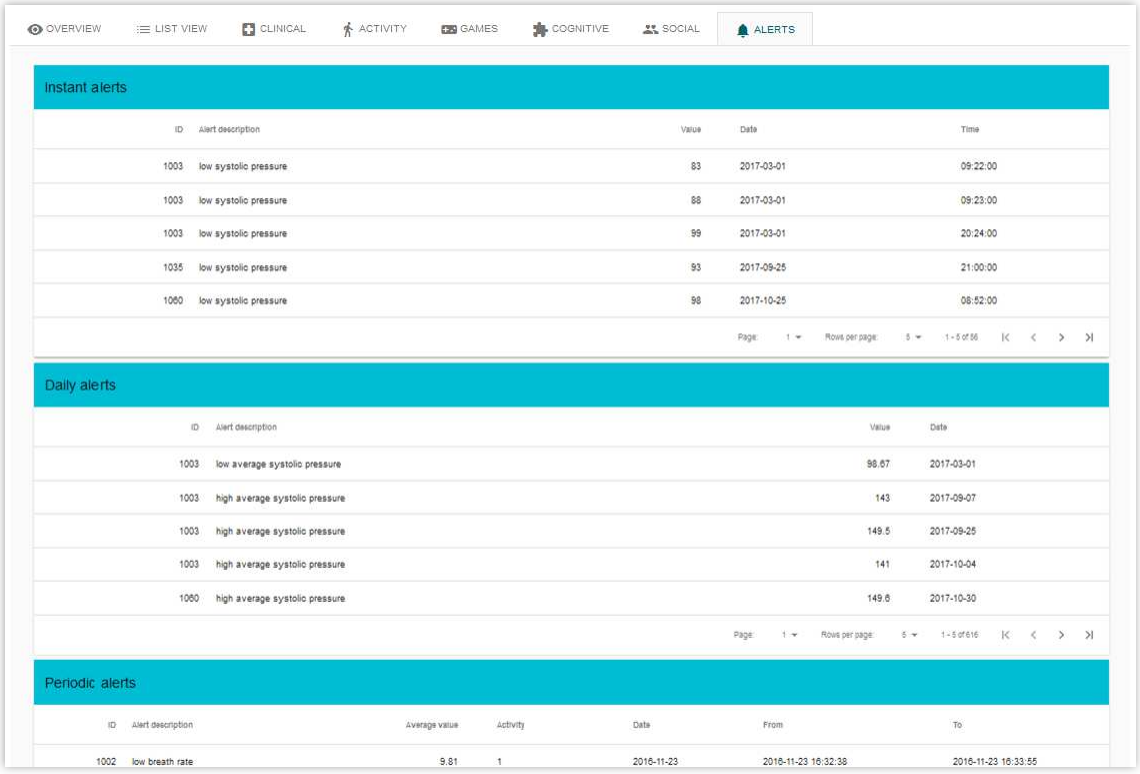

Figure 4: Visualization of alerts in the clinician interface.

4 Clinical State Prediction

4.1 Probabilistic models of frailty by Multi-Instance Learning (MIL) techniques

4.1.1 Background

In many real-life applications collected data come in a format where a single example cannot always be represented as a single feature vector. For example, images depicting several objects, text documents covering several topics or molecules with different conformations having different chemical properties. In all these cases, representing an example as a collection of feature vectors (e.g. patches or segments of an image, paragraphs in a document etc.) is a more efficient way of preserving as more information about an example as possible. On the other hand, this representation needs a more refined level of annotation which means that each of the feature vectors describing an example (i.e. instances) need to be annotated (which is not always possible). Furthermore, there may be instances inside a bag that don't provide any information about the bag's class or even more commonly, instances that are closer related to another class (than the one the whole object belongs to), thus providing misleading information.

To deal with such problems supervised learning techniques have been reformulated and extended to multiple instance learning (MIL) schemes, with the first work appearing in 1997 [23]. In this setting subjects are sets (*bags)*of feature vectors (instances)and labels are provided only for the subjects.

In order to deal with the MIL problem a classifier f_B must be trained which will be able to classify new unseen bags (i.e. collection of instances). According to [24] MIL classifiers can be categorized in three sets: (a) Instance space classifiers, which consider that the discriminative information lies at the instance level, (b) Bag space classifiers, which consider that the discriminative information lies at the bag level and since the bag space is a non-vector space a distance function between bags *D(X, Y)* or a similarity kernel must be defined that can be used to construct the classifier and (c) Embedded Space classifiers, where each bag is mapped to a single feature vector which contains relevant information about the whole bag.

MIL basic concepts

Formally a bag is a set $X = \{\overrightarrow{x_1}, \overrightarrow{x_2}, \dots, \overrightarrow{x_N}\}$ of feature vectors called instances, describing an example (e.g. an image or a document). The cardinality of the bags can vary. All instances $\overrightarrow{x_i} \in \mathbb{R}^d$ belong to a d-dimensional space, called instance space. The objective of the MIL problem is to train a model that can predict class label of an unseen bag. In other words, our task is to estimate a classification function $F(X) \in [0,1]$ that provides the likelihood that X is positive. In order to estimate F we are given a training set of M bags and their corresponding labels: $\mathcal{T} = \{(X_1, y_1), (X_2, y_2), \dots, (X_M, y_M)\}$. When required, (such as in the case of instance space classifiers), it is assumed that all instances of a given bag inherit the label of the corresponding bag.

In the MIL framework the label of each bag, as described earlier, is known but the individual labels of each instance of a bag are unknown. From the introduction of MIL in [23] a strong assumption was made regarding the labels of the instances of a bag and the label of the corresponding bag, referred to as *standard MI assumption*. Under this assumption each instance of a bag has a hidden positive or negative class label characterising the instance as positive or negative. The bag is considered to be positive if and only if contains at least one positive instance. Although this assumption is believed to be suitable for many MIL datasets (e.g. the MUSK drug activity prediction problem), alternative MI assumptions are proposed [25] making MIL appropriate for diverse datasets and problems. For example *the collective assumption* proposed in [26] assumes that all instances in a bag contribute equally to the bag's label. Under this assumption instances are assumed to have class labels according to some unknown probability distribution and the bag label is determined by the expected class value of the instances of the corresponding bag.

4.1.2 Problem formulation of frailty prediction

Before formulating properly the problem of frailty status prediction in the context of MIL we will give some intuitions in our context. In the daily life recordings, the tracked activities are neither discrete and predefined (as in controlled experiments), nor the duration of the recordings is the same across subjects. Using the sliding windows technique, we can split the recordings of each individual in (overlapping) time windows (of constant length for all subjects) that describe a local (in time) aspect, and thus we can capture the diverse unknown activities of each subject. On the other hand, the frailty status is a characteristic of the person, which means there is no label information for each "activity" (i.e. each time window). The term "activity" here should not be considered identical with the *Activities of Daily Living* (ADL) defined and automatically classified in the deliverable D4.2. These included characterizations of the subject's motion, such as walking, sitting, laying down etc. Here we generalise the notion of the term "activity" to include additionally to motion (captured by the accelerometer) also other physical conditions (captured by ECG and breathing sensors). However, our goal here is not to segment the biosignals into predefined discrete activities, but to use the activity patterns (no matter what they represent) as clusters of data with reduced intra-cluster variability. This latent space allows to summarize the data and facilitates inference. As activities of each individual are unknown, and not every activity is related to the frailty status of the individual (e.g. recordings while resting are not expected to provide discriminative measurements (i.e. features) for frailty classification) the problem of frailty prediction cannot be formulated as MIL problem using the standard MI assumption (where the bag is considered to be positive if and only if contains at least one positive instance), since we do not really know which activities are related to frailty status. We can assume, furthermore, that there must be patterns of activity that are not discriminating regarding the frailty status and patterns of activity that can be associated to frailty.

In order to formulate the problem of frailty prediction in the MIL framework we represent each subject as a *bag* and the time windows of the recordings as the instances of each bag. We represent the data as tensors $\mathcal{X}^{(i)}$, i = 1,2,...,nrOfSub which

are considered to be the bags, while the slices $\mathcal{X}_{r,:,:}^{(i)} \in \mathbb{R}^{J\times K}$ are considered to be the instances of Bag *i*. Labels are only provided for bags, so $Y_i \in \{0,1,2\}$ are the labels corresponding to non-frail, pre-frail and frail group. Initially instances inherit class labels from the corresponding bag and subsequently class probabilities are updated based on the assumptions that not all instances of a bag are informative in terms for frailty status prediction. The calculated probabilities provide a measure of discrimination and allow us to detect the most informative patterns. Next, we explain the method in more details and assess it based on the currently available recordings.

4.2 Development of MIL framework and application to FrailSafe data

4.2.1 Constructing the training set

In the context of FrailSafe, data are collected from individuals in different sessions, using the two different developed products of Smartex for the measurement of the physiological signals: the WWS (Wearable Wellness System)[1], which was used in the first phase of the project and which we will also call "strap", and the WWBS (Wearable WBan System) which is the new wearable solution, referred to as "vest" here. The WWBS takes its origin from the WWS (Wearable Wellness System)[2], with a further integration of some Inertial Measurement Units (IMUs) in order to have information of higher quality with regards to movement analysis. Together with data on movement, posture and physical activity it records also data from the heart (a full ECG lead, similar to standard Einthoven DI lead) and respiration.

Signals from 7 different channels are monitored during the sessions:

1. Respiratory raw signal (by the piezoresistive sensor)
2. Acceleration
3. Breathing amplitude
4. Breathing rate
5. ECG Heart Rate
6. ECG Heart Rate variability
7. ECG RR interval

First time synchronization of the channels is performed by interpolating all recordings at 25 Hz, then signal segments of low quality are discarded and frames (e.g. of 1 minute duration) are extracted using the sliding windows technique. The multiple frames of each subject are concatenated in a 3 dimensional tensor$\mathcal{X}^{(i)}$ of dimensionality $I_i \times J \times K$*i=1, 2,..., nrOfSub*, where I_i is the *number of time windows* available for each subject*, J* is the number of time points corresponding to each time window and *K* is the number of channels monitored. The number of time windows varies across subjects, but *J* and *K are fixed for all subjects.*

[1] http://smartex.it/index.php/en/products/wearable-wellness-system
[2] http://smartex.it/index.php/en/products/wearable-wellness-system

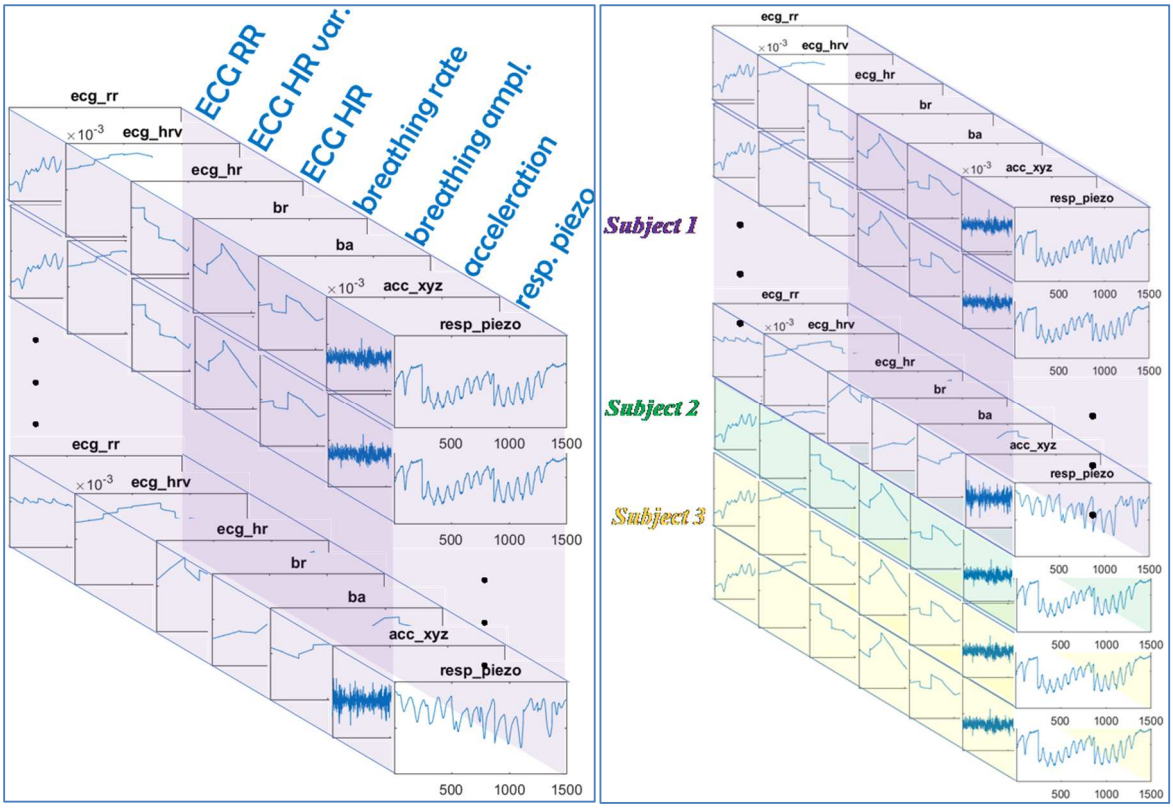

Figure 5. 3d-tensor for one subject (left) and 3d-tensor of all subjects (right).

In order to construct our training set we concatenate all tensors $\mathcal{X}_i$ along the first dimension to produce a new 3D-tensor $\boldsymbol{\mathcal{X}}$ containing all the time windows of all the subjects as is shown in Figure 5. Labels $y_i \in \{0,1,2\}$, (where 0 corresponds to *non-frail*, 1 to *pre*-frail and 2 to frail group) are also provided for each subject.

4.2.2 Data cleaning and representation

Besides the preliminary cleaning of the data, based on the quality of the recordings, we performed a series of more elaborate cleaning procedures since we discovered outliers in some measurements that are probably due to bad recordings. These procedures are summarized below.

1. For the channel measuring the breathing rate we consider only recordings with values in the range $[8, 50]$ that are accepted values of breathing rate, and discard all other recordings.
2. For the channel measuring the heart rate we consider only recordings with values in the range $[40, 200]$ as they are accepted values of heart rate.
3. For all other channels we discard values that belong up to the 5% quantile (i.e. the lower 5% of the values) as well as the values belonging to >95% quantile (i.e. the highest 5% of the values)
4. We keep only these time windows, which have in each channel more than 10% non-outlier values.
5. We construct for each instance (i.e. time window) per channel histograms using as bin centres the 30-quantiles.

The output of this procedure is a tensor of dimensions $10503 \times 30 \times 7$ containing at eachslice the histograms per channel of each instance. Thus, we have 10505 time windows, 30 bins per instance's histogram and 7 channels.

Since two different devices are employed for acquiring measurements we briefly summarize the number of instances (i.e. time windows), the number of bags (i.e. subjects) per class and per device in Table 2. Some subjects have more than one session and possibly not both with the same device, thus the total number of subjects is smaller than the sum of data with strap and vest.

Table 2 Summary of the data

Data Summary per class			
	Strap Data	**Vest Data**	**Total**
Time windows	7003	3500	10503
Number of subjects	89	27	104
Non-Frail	38	9	43
Pre-Frail	42	13	49
Frail	9	5	12

4.2.3 Feature extraction by tensor decomposition

In order to extract features from the multidimensional data described earlier, we employ the well-known tensor decomposition method PARAFAC. We will briefly resume the PARAFAC method and we will explain how we can extract features for MIL problems.

PARAFAC decomposition is a powerful tool in tensor analysis. In PARAFAC decomposition the aim is to approximate the $I \times J \times K$ tensor $\mathcal{X}$ by a sum of rank-one tensors, referred to as latent factors. Formally

$$\mathcal{X} \approx \sum_{r=1}^{R} \boldsymbol{a_r} \circ \boldsymbol{b_r} \circ \boldsymbol{c_r} \quad (1)$$

where $\boldsymbol{a_r} \in \mathbb{R}^I, \boldsymbol{b_r} \in \mathbb{R}^J, \boldsymbol{c_r} \in \mathbb{R}^K$ are the columns of the factor matrices $\boldsymbol{A} \in \mathbb{R}^{I \times R}, \boldsymbol{B} \in \mathbb{R}^{I \times R}, \boldsymbol{C} \in \mathbb{R}^{I \times R}$ respectively, "$\circ$" denotes the outer product and R is the rank of the tensor. Element-wise the PARAFAC decomposition can be written as $x_{i,j,k} \approx \sum_{r=1}^{R} a_{ir} b_{jr} c_{kr}$, $i = 1,2, \dots, I, j = 1,2, \dots J, k = 1,2, \dots, K$.

Sometimes PARAFAC decomposition can be written as

$$\mathcal{X} \approx \sum_{r=1}^{R} \lambda_r \boldsymbol{a_r} \circ \boldsymbol{b_r} \circ \boldsymbol{c_r} \quad (2)$$

where λ_r illustrates the significance of each latent factor. Figure 6 depicts in a graphical way the PARAFAC decomposition.

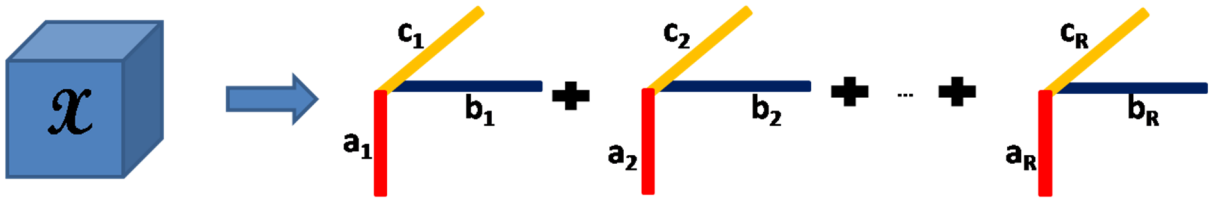

Figure 6 The PARAFAC decomposition

Our goal is to extract features for each instance (i.e. time window) $x_{i,:,:} \in \mathbb{R}^{J \times K}$, where $x_{i,:,:}$ is the i-th slice of tensor $\mathcal{X}$. Each instance can be written as $x_{i,:,:} \approx \sum_{r=1}^{R} a_{ir}(b_r \circ c_r)$, meaning that each instance is a linear combination of $\boldsymbol{b_r} \circ \boldsymbol{c_r}, r = 1,2,\dots,R$, with coefficients $a_{ir}, r = 1,2,\dots,R$. Thus, we can choose as features, for describing an instance, the coefficients$a_{ir}, r = 1,2,\dots,R$, that is the i-th row of factor matrix **A**. Furthermore, we can normalize the columns of **A** and choose as features the matrix $\widetilde{\boldsymbol{A}}$, where $\boldsymbol{A} = \widetilde{\boldsymbol{A}}\, diag(\lambda_r)$, and $\lambda_r, r = 1,2,\dots,R$ are the scaling factors of each column.

4.2.4 One class-SVM for frailty status prediction

Here we will describe our MIL approach for training a model to predict the frailty status based on the data collected from FrailSafe. Firstly, we will give the concept and some intuitions that led us to formulate this approach and subsequently we will describe our methodology.

As aforementioned, in the setting of FrailSafe, subjects wear devices and perform tasks in their daily life that not all of them associated with their frailty status. As a consequence, we need to be able to distinguish instances that are more informative for discriminating the frailty status of the subjects and relying only on them to predict the subject-wise labels.

Figure 7 depicts the class boundaries of the three classes (Non-Frail in green, Pre-Frail in blue and Frail in red) using the three significant features, extracted as described in the previous section. We can observe that only a part of the instances can be informative in terms of predicting the frailty labels and these are the instances that lay in the region of each class that does not overlap with other classes. As this figure is a 3-dimensional projection of our 30-dimensional features it is only indicative and obviously does not provide any proof.

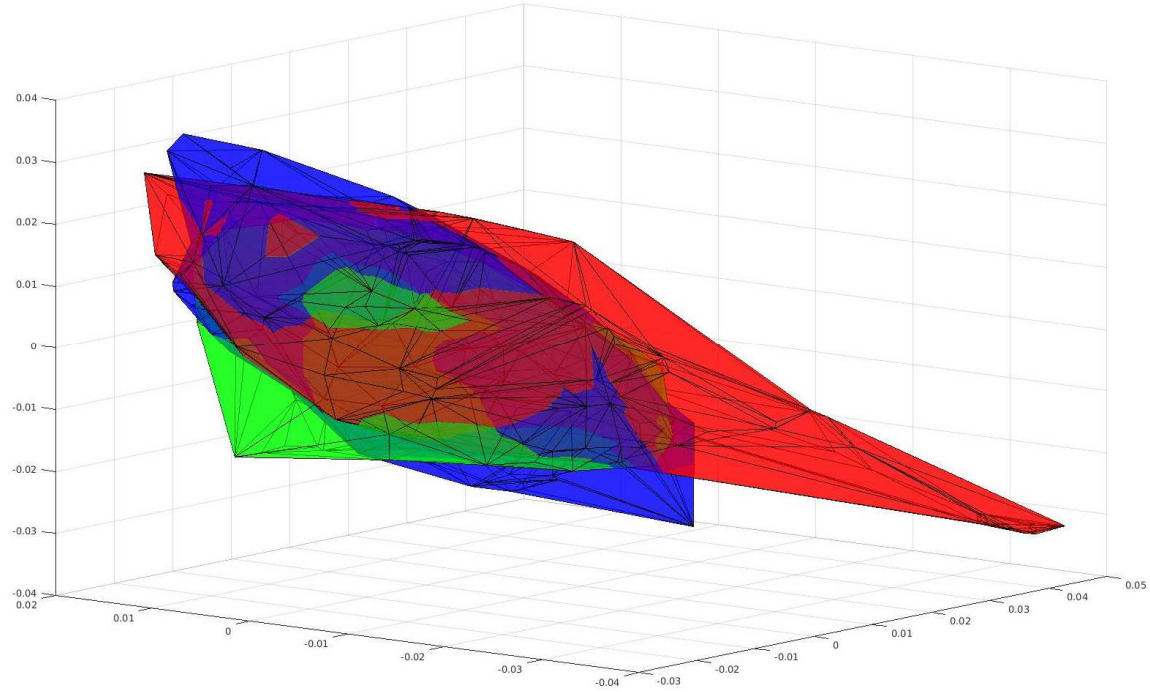

Figure 7 The class boundaries of instances for the 3 significant features: Non-Frail in green, Pre-Frail in blue and Frail in red.

In order to deal with the problem of searching the informative instances and rely on them for predicting bag labels we train 3 distinct classifiers that for each class separately to learn class probability distributions and then we annotate as informative instances only these that have a clear classification based on all the three estimated probabilities. With the term clear (i.e. not ambiguous) classification we mean that there are not conflicts in the prediction, i.e. only one classifier recognizes the instance as positive for its class, with the other two classifiers labeling the same instance as negative for their class.

One-class SVM

In our approach features are extracted using the PARAFAC decomposition method discussed in a previous section. In order to maintain consistency of our model and factor matrices **B** and **C**(both for training and test set), we concatenate along the first dimension the training and test tensors ($\mathcal{X}_{train}$, $\mathcal{X}_{test}$) to a model tensor $\mathcal{X}$ and perform PARAFAC decomposition to $\mathcal{X}$. The training features are the rows of factor matrix **A** that correspond to $\mathcal{X}_{train}$ while the test features are the rows of **A** corresponding to $\mathcal{X}_{test}$.

Subsequently we train three one-class SVM classifiers each one on instances of each of the classes, using Gaussian kernels. In that way, each classifier is trained to discriminate one of the three classes. We then use each of the above classifiers to predict instance-level labels on the test set. In this stage we have 3 distinct predictions for each instance, one from each classifier.

In the next step we want to discover the informative instances. An informative instance can be defined as an instance that has been classified from exactly one

classifier to belong to the class, which the classifier is trained to recognize, and classified by the other two classifiers as not belonging to their corresponding classes. Using these extracted informative instances, we will predict the bag-level labels.

For predicting subject-wise (i.e. bag-wise) labels we rely on the informative instances that we found in the previous step. The label decision is made by counting by a majority voting scheme, i.e. the class assigned to each subject is the one with the most votes. If no informative instance is found, a label of -1 is assigned to the subject meaning no decision could be made. The full algorithm is shown in Table 2.

Table 3 Fusion of one class SVM models in MIL setting

Algorithm: 3 one class_SVM for frailty prediction

Input: training instances' feature X_{tr}, training labels Y_{tr}, test instances' feature matrix X_{ts}, test subject ID's $SubID_{test}$,
Output: predicted subject level labels Y_{ts}

1. Extract positive training examples of each class P_0, P_1, P_2
2. Train 3 one-class SVM models SVM_0, SVM_1, SVM_2, for recognizing classes 0, 1 and 2, using X_{tr} and P_0, P_1, and P2 respectively.
3. **for** i=0 to 2
   using SVM_i and X_{ts} predict the labels $Y_{ts}^i \in \{-1,1\}$of the test set
   end **for**
4. **for each** subject i
   a. find the instances of each subject ***Inf_Inst_i*** that satisfy the equation $\sum_{i=0}^{2} Y_{ts}^i = -1$ (i.e. the informative instances)
   b. assign to each subject the class label of the most predicted class out of ***Inf_Inst_i***.
   c. **if** ***Inf_Inst_i*== *empty***
      do not assign any label to this subject
      end if

end for

4.2.5 Results

We evaluated this method separately on data collected by the FrailSafe devices. In the next section we will use the term vest for the "Wearable WBan System (WWBS)" and the term strap

straps and data collected by vests. We conducted 5-fold cross validation and we report the average testing accuracy over all folds. The features were extracted as reported using the PARAFAC decomposition; the rank of the decomposition was chosen to be 30. We assess performance on normalized features (matrix **A** as presented in equation (2)) as well as in original features (matrix **A** as presented in equation (1)). In the first case the λ parameter (the parameter that denotes the significance of each feature) is not taken into account. In contrast in the second case (i.e. not normalized features) the λ parameter is incorporated into the feature matrix **A** so the features are scaled by their significance value as calculated via the PARAFAC decomposition (see section 4.2.3).

In Table 4 we can see the obtained average accuracy across 5 folds based on cross validation for classification of the frailty status into 3 classes. It can be observed that the accuracy is 48.7% for the vest data when features are not normalized and 46.14% for the strap data, while for normalized features the accuracy is 40.7% for the vest data and 40.6% for the strap data. We observed that when using not normalized features better performance in acquired for both the strap and vest recordings. The data from strap (WWS) were acquired in the first phase of the project when the vest was not available yet and their collection will not continue. Therefore, the accuracy of the method on the data from WWBS is more important. Although the classification accuracy (48.7%) seems low, it is slightly increased in comparison to random guess (33.3%) and also it is expected that the availability of more data samples and more variables (from the rest of the FrailSafe devices and clinical scores) will help to improve prediction.

Table 4 Average 5-fold Cross Validation accuracy

	Data from strap (WWS)	**Data from vest (WWBS)**
Normalized Features (matrix A from eq. (2))	40.6%	40.7%
Not Normalized Features (matrix A from eq. (1))	46.14%	48.7%

4.3 Convolutional Neural Networks for prediction of frailty status

Our previous methods for classification or modelling, presented in previous deliverables of WP4 generally relied on the usage of domain specific features normally selected based on literature or by clinical experts. Finding the best features was the subject of a lot of research and the performance of the classifier was heavily dependent on their quality. The advantage of deep neural networks and especially convolutional neural networks (CNNs) is that they can learn such features by themselves, reducing the need for human experts. A recent review on deep learning techniques for time series analysis can be found in [27].

Building upon our previous work on deep CNNs [28], we aim to implement a deep architecture that employs convolution and pooling operations to capture the salient patterns of the multi-channel time series data at different time scales. The architecture will be similar to the one proposed by Yang et al. [29], which showed very competitive performance. In this architecture, the convolution and pooling filters in the CNN are applied along the temporal dimension for each sensor, and all the feature maps for different sensors are unified as a common input for the neural network classifier.

4.3.1 CNN architecture

The architecture we implemented is shown in Figure 8.

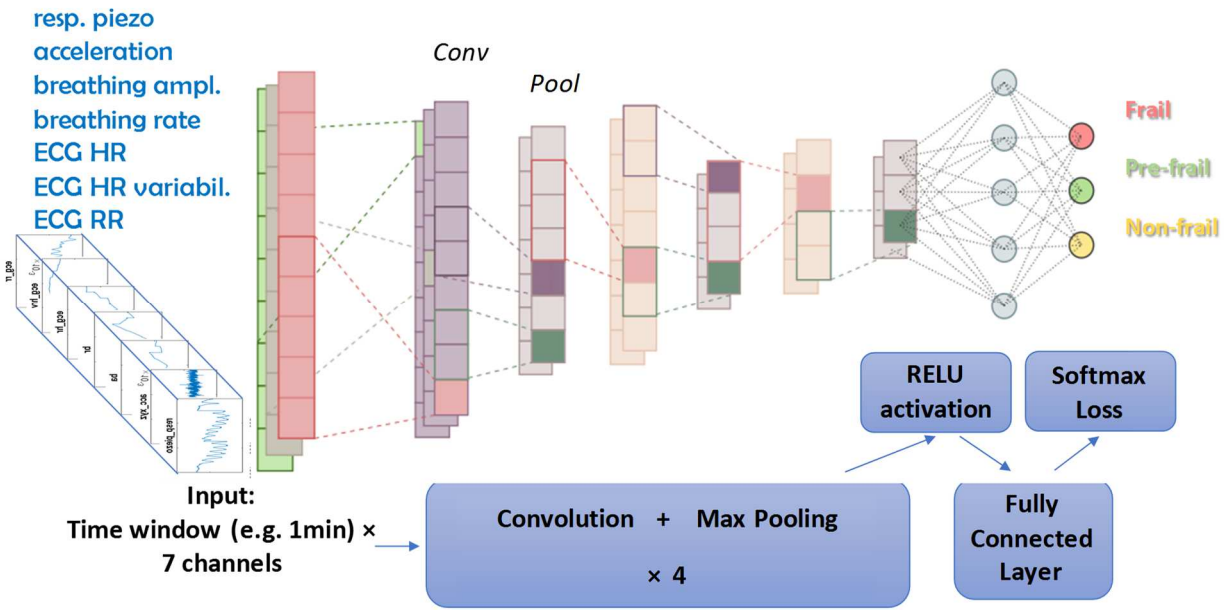

Figure 8: Recognition of frailty using recordings from strap/vest by a deep convolutional neural network (CNN).

The method has been implemented using the MatConvNet functions. The specific parameters of the several layers are included in the Figure 9.

layer	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
type	input	conv	mpool	relu	conv	mpool	relu	conv	mpool	relu	conv	mpool	relu	conv	softmxl
name	n/a	layer1	layer2	layer3	layer4	layer5	layer6	layer7	layer8	layer9	layer10	layer11	layer12	layer13	layer14
support	n/a	100x7	2	1	100x1	2x1	1	100x1	2x1	1	100x1	2x1	1	1	1
filt dim	n/a	1	n/a	n/a	20	n/a	n/a	20	n/a	n/a	50	n/a	n/a	500	n/a
filt dilat	n/a	1	n/a	n/a	1	n/a	n/a	1	n/a	n/a	1	n/a	n/a	1	n/a
num filts	n/a	20	n/a	n/a	20	n/a	n/a	50	n/a	n/a	500	n/a	n/a	3	n/a
stride	n/a	1	2	1	1	2	1	1	2	1	1	2	1	1	1
pad	n/a	2	0	0	0	0	0	0	0	0	0	0	0	0	0
rf size	n/a	100x7	101x8	101x8	299x8	301x8	301x8	697x8	701x8	701x8	1493x8	1501x8	1501x8	1501x8	1501x8
rf offset	n/a	48.5x2	49x2.5	49x2.5	148x2.5	149x2.5	149x2.5	347x2.5	349x2.5	349x2.5	745x2.5	749x2.5	749x2.5	749x2.5	749x2.5
rf stride	n/a	1	2	2	2	4	4	4	8	8	8	16	16	16	16
data size	1500x7	1405x5	702x2	702x2	603x2	301x1	301x1	202x1	101x1	101x1	2x1	1	1	1	1
data depth	1	20	20	20	20	20	20	50	50	50	500	500	500	3	1
data num	256	256	256	256	256	256	256	256	256	256	256	256	256	256	1
data mem	10MB	137MB	27MB	27MB	24MB	6MB	6MB	10MB	5MB	5MB	1000KB	500KB	500KB	3KB	4B
param mem	n/a	55KB	0B	0B	156KB	0B	0B	391KB	0B	0B	10MB	0B	0B	6KB	0B

Figure 9: CNN architecture and parameters of individual layers

4.3.2 Fusion of predictions for inter-subject analysis

A main difference in published works using CNNs for time series classification problems is that in the former the classification (e.g. for activity) is performed for each temporal window, whereas in our case a single decision score (prediction of frailty) has to be made for the whole recording (subject). As described in the previous section this is a Multiple Instance Learning problem. Thus, a fusion operation is required to assign a class label on each subject based on the decision scores of the time windows that constitute the recordings of the subject. We have examined several fusion approaches for prediction of the frailty status of each subject:

1. Maximum likelihood and majority voting across time windows:

   The class label is predicted for each time window based on maximum probability and then the most frequent class was assigned to the subject

2. Maximum similarity of the probability profile:

   A feature vector is extracted to summarize the distribution of probability values of being frail for all time windows. Multi-variate regression is subsequently performed to learn a linear model that predicts the class labels of the training set based on this feature vector. The model is then applied on the test set for prediction.

3. The MIL algorithm MILES [30] is implemented and tested in an iterative scheme where

   MILES algorithm extends ideas from the diverse density framework [31] and the wrapper model in feature selection [32]. The diverse density framework is based on the assumption that there exists a single target concept, which can be used to label individual instances correctly. The target concept that is most likely to agree with the data is then determined by maximizing this probability. MILES identifies instances that are relevant to the observed classification by embedding bags into an instance-based feature space and selecting the most important features. A subset of mapped features that is most relevant to the classification problem of interest are selected by defining a similarity measure between a bag and an instance. Although any feature selection approaches could be applied for this purpose, in MILES a joint approach is selected that constructs classifiers and chooses important features simultaneously. Classification is performed using the 1-norm SVM method because of its excellent performance in many applications. The 1-norm SVM is also referred to as sparse SVM can be formulated as a linear program, which, in general, can be solved efficiently from an optimization point of view.

   Our method iterates between CNN and MILES. The deep network extracts class probabilities for every time window which are used as features in

MILES to select the most relevant instances (i.e. time windows). Once the time windows are selected, these are introduced into the pretrained in the previous iteration CNN to get updated results (learn new parameters for the network). This iterative process resembles the Expectation-Maximization (EM) algorithm.

Results

Results have been produced by all fusion schemes. The obtained accuracy for all fusion schemes is similar or slightly less than the MIL framework with tensors described in section 4.2. Improvement is required; thus results are not analytically reported yet. This is possibly attributed to the small number of samples (subjects), large dimensionality, uncertainty in labelling, and high variability of data that are collected from daily living and not in a controlled environment or an experimental setting. All these issues make the problem very ill-posed. This is the reason why we try to tackle this problem using several state-of-the-art methodologies hoping that with one of them we will obtain adequate accuracy. In the final version of this deliverable we will refine the models using more data thus expect to reach better accuracies.

4.4 Aggregation of temporal parameters towards assessment of frailty transition (future work)

Most of the methods we have developed until now in WP4 focus on the extraction of relevant variables and the calculation of regression or classification models for prediction of the frailty status or for prediction of intermediate clinical metrics (defined in D2.1 as proxy outcomes). Although this was the main goal of the project, i.e. to extract new, more sensitive, frailty indices that cover all clinical domains, part of the clinical prediction engine includes the very ambitious goal of prediction of frailty transition which will facilitate early intervention. A first attempt to study the temporal transition and identify relevant variables has been performed in D4.2 where we calculated the distribution of transition values of the extracted frailty indices built from variables from the clinical evaluation, games, and wearable garments, while in D4.13 we analysed variables from the social domain. Our future work for the final version of this deliverable (D4.17) includes the dynamic prediction based on all (identified as relevant) combined FrailSafe variables or individual prediction scores. The availability of measurements over multiple time points will allow us to track the evolution of the clinical state of the elderly and therefore model frailty transition. This will be performed following the strategy described next and illustrated in **Error! Reference source not found.**.

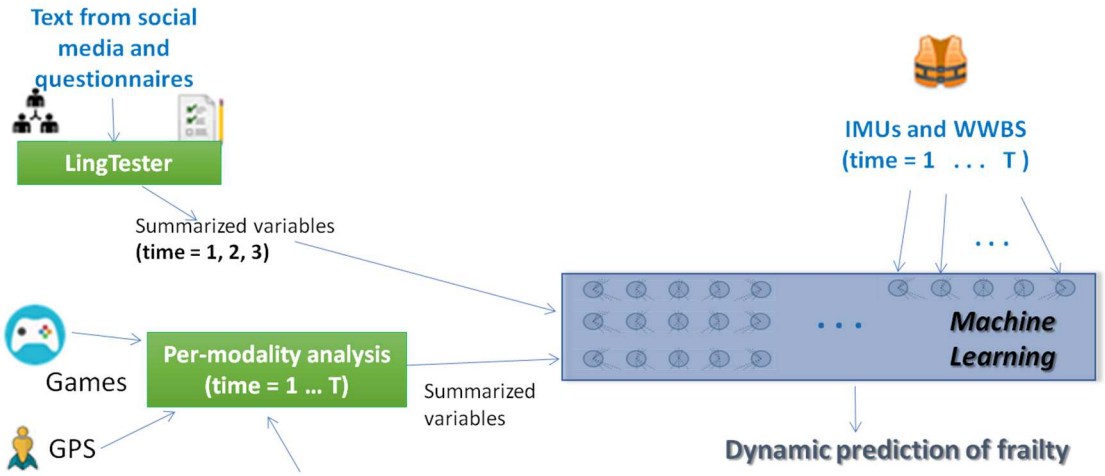

Figure 10: Prediction of frailty transition using multiparametric data by advanced machine learning techniques.

Variables from different domains will be collected together into a data tensor X_{PxTxM}, where P is the number of different statistical properties, such as mean and standard deviation, *T* is the number of time points and *M* the number of modalities, which include different devices or different channels within the same device (e.g. from WWBS). The first step in this aggregation procedure is the synchronization of variables in time. Variables that are collected in sparse intervals, such as during clinical evaluation, will be propagated to the reference time points either by interpolation (for quantitative variables) or by nearest neighbour classification (for ordinal variables). All samples will be concatenated and used within a machine learning algorithm to predict possible adverse events (falls, not planned hospitalization, death). If we denote with the binary variable Y the incidence of an adverse outcome (1 if it happened and 0 if it didn't happen), the aim is to predict Y given $X=\{X^i\}$, where *X* is the set of available samples. We will investigate several classification algorithms for this goal. As a note, the calculation of differences (change in feature values) is a special case of this approach, since the mathematical difference is just a linear mapping of the feature space.

A question that remains is the definition of time reference. In most clinical studies that examine the prognosis of a disease or a treatment define as reference point (baseline) the date of diagnosis of the disease, or the date before the first operation and count the elapsed time until death (survival time). In this study every participant starts from a different frailty level. Therefore, we are considering investigating a temporal alignment of the data based on the date of the adverse event as end time point, and not based on the first clinical evaluation. This will help us to extract early indicators of deterioration in the participants' health condition.

5 Conclusions

In this deliverable, the Decision Support System has been described along with the role of inflammation in the pathogenesis of frailty. The DSS includes the clinical state prediction engine that aims to simulate the behaviour of an existing patient model and a risk assessment module which is responsible for the generation of alerts.

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