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myAirCoach - Analysis, modelling and sensing of both physiological and environmental factors for the customized and predictive self-management of Asthma"

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Executive Summary

The main objective of WP1 “User needs, system requirements, architecture” of the MyAirCoach project is the definition of the overall user needs, the architecture and the system specifications of the myAirCoach infrastructure, in order to define and deliver a number of representative use cases and user scenarios, exemplifying the novelties of the myAirCoach framework. The first deliverable of WP1 provides the baseline definition for commencing the work of the project, by reporting on the latest developments in the specific areas that myAirCoach will address. The presented work is divided into three parts that cover the current advances in the areas of : i) inhaler devices and sensors for asthma’s disease, ii) computational modelling of lung behaviour and iii) self-management, decision support and personal guidance systems for patients with asthma disease.

Initially, we provide a short technical summary of the available asthma related devices and more specifically of the products that could offer crucial insights for the development of the sensing capabilities of the myAirCoach system. This summary is then complemented, by describing other critical parameters that could be monitored, (e.g., physiological, environmental) along with the corresponding hardware components that need to be integrated to the proposed system. Special attention is given to the role of fractional exhaled nitric oxide (FeNO), that is capable of providing additional information regarding the level of bronchial inflammation.

The second part of this deliverable is devoted on the review of the methods for developing computational models that simulate the behaviour of the pulmonary system including structure, mechanical representation, computational fluid dynamics and biological/chemical properties of the lung. Different methods for linking those models with the different environmental and physiological sensing parameters, is also described in order to provide all necessary means for integrating the Computational Model results with the measurements of the different sensors and self-reports, providing predictions that could be used to alarm patient on potential upcoming dangerous events, like asthma exacerbations. This information could also supplement the input to the personal guidance system that will be the main topic of discussion in the last part of this document.

Finally, we focus on providing a review of personal guidance applications and virtual community platforms that could be essential for producing the final myAirCoach integrated system, explicitly taking into account security and privacy issues. A short description of different interactive information visualization techniques that allow the representation of medical information and the end user (e.g., patients, caregivers) interaction with the system is presented. This deliverable is concluded by summarizing different cloud-based software modules responsible for the customization and co-design of both the myAirCoach application and the Virtual Community Platform ensuring the effective communication and collaboration between patients and their caregivers.

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List of abbreviations and acronyms

(*in alphabetic order*)

FEV1	Forced Expiratory Volume in one second
WBAN	Wireless Body Area Network
BAN	Body Area Network
ICT	Information and Communication Technology
mHelath	Mobile Health
DSS	Decision Support System
MDL	Model Description Language
PDA	Personal Digital Assistant
BNC	Body Node Coordinator
TFE	Time Frequency Representation
SE	Shannon Entropy

1 Introduction

The major objective of myAirCoach is to provide **mHealth personalised asthma monitoring services** empowering and guiding patients with Asthma to better manage their own health. The proposed mhealth management system will be based on a wireless body area network that will be composed by an ergonomic, compact and sensor based inhaler device that is capable of recording several physiological, behavioural and environmental parameters. The recorded data will be then transmitted to a nearby body node coordinator (BNC) (e.g., smart phone) via low-power short-haul radios (e.g., ZigBee, Bluetooth LE), and then to a remote cloud based server via the Internet.

A pipeline of advanced algorithms and data fusion techniques starting from raw measurements processing, feature extraction, indicators quantification, personal profile data, computational and statistical modelling approaches, will ensure **clinical state awareness** and a **timely optimal treatment**. Besides, a "**personal mHealth guidance system**" will empower patients to optimize their treatment towards personalised pre-set goals and guidelines (healthy lifestyle, exercise, dietary habits), either automatically or driven by a healthcare professional. The mobile device will run an optimized lightweight guidance and support platform that will be interconnected with a cloud platform where rigorous analysis of all patient data will be carried out in order to increase relative and care givers' awareness of Asthma and the factors that affect its progression. Therefore, myAirCoach system is expected to provide clinicians with timely and adequate indications of increasing symptoms or exacerbations, while at the same time it will make an important contribution in helping people in managing successfully their asthma disease.

From a high-level architectural point of view, the target system will consist of three layers (tiers), as shown in Figure 1:

A. The myAirCoach Wireless Body Area Network (WBAN) including all the integrated sensors for data collection of the individuals' health status and behavioural/environmental activities
B. The myAirCoach Application Layer: it contains i) the Mobile Device which runs an optimised, lightweight service platform (mobile guidance and support platform) ii) the other part of the PMHS running at cloud-based server (e.g. being accessed by healthcare professionals, primary/secondary care organisations) where apart from remote monitoring and educational support, rigorous analysis of all patients' data is carried out to further the understanding of asthma control and monitoring (Clinical modelling and prediction engine).

The myAirCoach Knowledge Layer depicts both the internal and external sources of unprocessed ('raw') data, models, and other information from the myAirCoach application domains, including also metadata, user profiles and stored resource data. This layer will provide support for storing annotated semantic descriptions of content and appropriate correlated patterns (user models/profiles, action plans andtreatments, etc.) and other information sources that are needed for the myAirCoach platform. Thus, the 'raw' data are transformed into information and patterns (knowledge and information) by means of a combination of data information mining and retrieval services and tools located in the Application Layer.

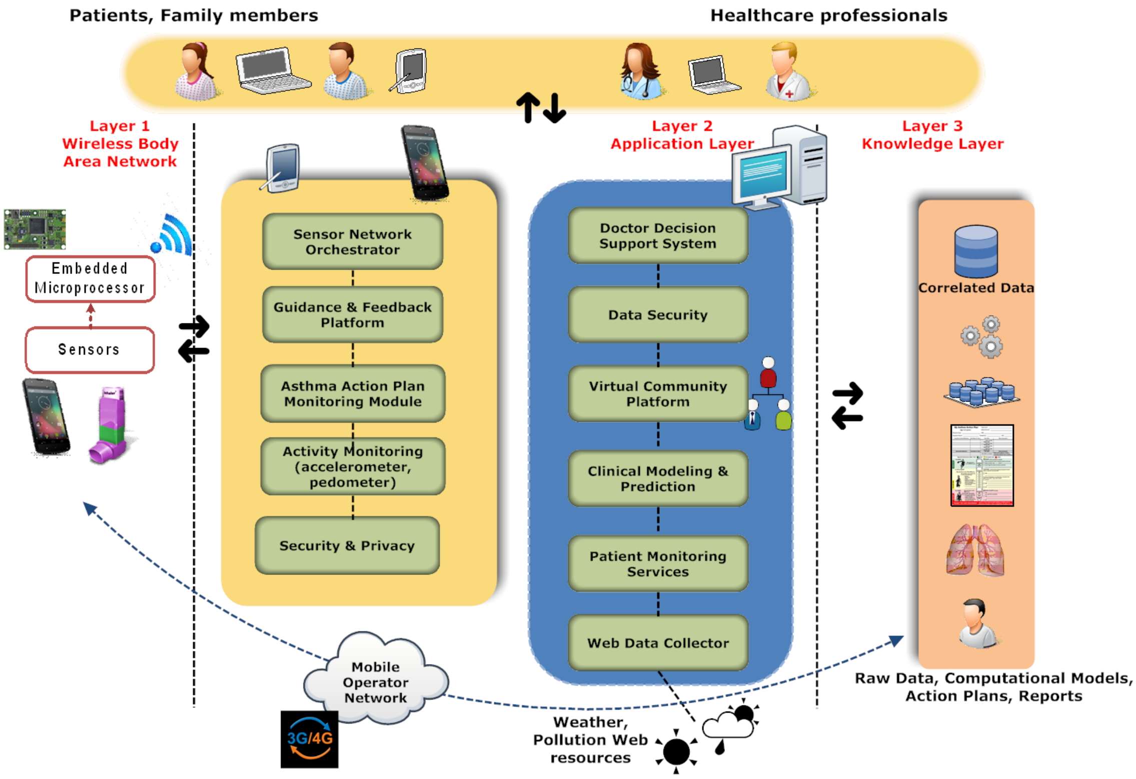


Figure 1: MyAirCoach Architecture

The aim of this deliverable is to provide the baseline definition for commencing the work in each of the aforementioned layers, by reporting on the current advances and by benchmarking all latest developments in the specific areas that myAirCoach will address, including: i) inhaler devices and sensors for asthma's disease, ii) computational modelling and prediction of lung behaviour and iii) self-support management and personal guidance systems for patients with asthma disease. The main body of the deliverable is divided into the three sections described below.

Section 2 presents the technical characteristics of several available asthma related devices, offering crucial insights for the development of the WBAN. Other critical parameters that could be monitored, (e.g., physiological, environmental) along with the corresponding hardware components that need to be integrated into the proposed system are also described, while special attention is given to the role of fractional exhaled nitric oxide (FeNO), that is capable of providing additional information regarding the level of bronchial inflammation.

Section 3 is focused on the state of the art methods for developing the Knowledge layer, including computational models that simulate the behaviour of the pulmonary system including structure, mechanical representation, computational fluid dynamics and biological/chemical properties of the lung. Different methods for integrating the Computational Model results with the measurements of the different sensors and self-reports, providing predictions that could be used to advice patients on potential upcoming dangerous events, like asthma exacerbations, are also described.

Finally Section 4 is devoted to the core parts of the application layer, including the personal guidance system and the myAirCoach community platform. It initially presents a number of different interactive information visualization techniques that allow the representation of medical information and the end user (e.g., patients, caregivers) interaction with the system. Different cloud-based software modules responsible for the customization and co-design of both the myAirCoach application and the Virtual Community Platform are also described.

2 Sensing Systems for monitoring asthma patients critical parameters

The foreseen myAirCoach Wireless Body Area Network (WBAN) will consist of a) a smart mobile device enhanced with sensing capabilities such as accelerometer and GPS tracker, which are integrated in the vast majority of modern smartphones , b) the sensor-based inhaler device which will contain both physiological and environmental sensors and will be developed in the framework of the myAirCoach project and finally, c) the Aerocrine NIOX VERO (FENO measurements) that will be extended and integrated in the myAirCoach system. In this section we provide a short technical summary of the available asthma related devices and more specifically of the products that could offer crucial insights for the development of the WBAN layer of the myAirCoach system. Several critical parameters that could be monitored, (e.g., physiological, environmental) along with the corresponding hardware components that need to be integrated to the proposed system is also provided, while special attention is given to the role of fractional exhaled nitric oxide (FeNO), which is capable of providing additional information regarding the level of bronchial inflammation and will be the basic component of the indoors sensing framework of myAirCoach.

2.1 Mobile Health Devices for Asthma

Modern mobile health devices of asthma concentrate and are based mainly upon the accurate monitoring of inhaled medication use as a means for the improvement of adherence and the overall optimization of treatment approaches. Recent reviews have focused on this area and presented modern approaches of adherence monitoring based on inhaler devices enhanced with sensing capabilities[1,2].

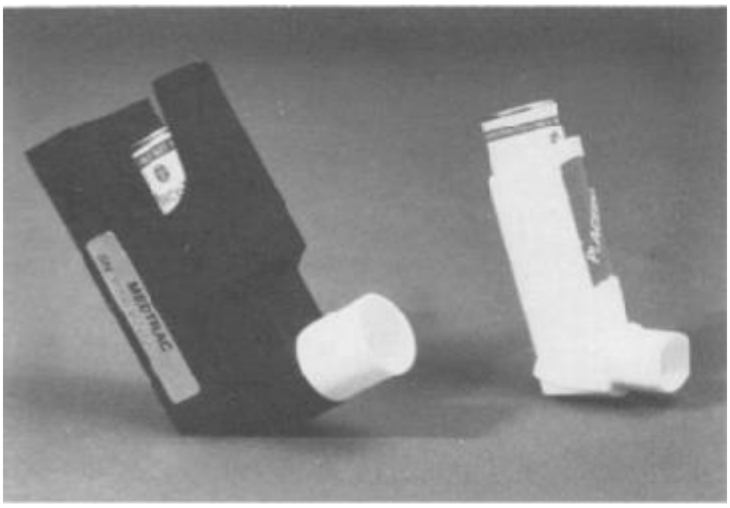
The current section is intended towards this direction but aims to provide a wider view that includes not only commercially available devices but also novel approaches currently in their development phase and research products published in scientific literature. In addition, the current review includes devices that did not much attention and could not manage to transform into commercially viable products. This approach is aiming to outline the crucial difficulties and risks so as to be avoided in the course of the myAirCoach project and also gain valuable insights for the development of an easy to use device that will hold commercial value in addition to the scientific, technological and research outcomes that myAirCoach is aiming to produce

Furthermore, and in order to extend beyond the devices that are designed to extend the capabilities of inhalers, alternative approaches are presented such as asthma patches and mobile digital stethoscopes. Even though the development of such sensing approaches is outside the scope of the current project it is important to review the most important sensing alternatives so as to integrate any of their components that can benefit the myAirCoach system and hopefully be the basis for possible synergies with other commercial and research institutions.

Overall the following subsections provide a short technical summary of asthma related devices and products that could offer helpful insights for the design of the myAirCoach system with special focus on the development of the hardware components and the selection of the system's sensing capabilities. A concise comparison table is presented at the end based on the information available on the related online resources.

2.1.1 Nebulizer Chronolog

Technical Summary
Types of inhalers supported
Pressurized metered dose inhaler (pMDI)
Sensing Capabilities
Pressing sensor (plain tactile button switch)
Monitoring Capabilities (Based on the measurements of sensors)
Time of inhaler use
Connectivity
Data can be uploaded to a PC

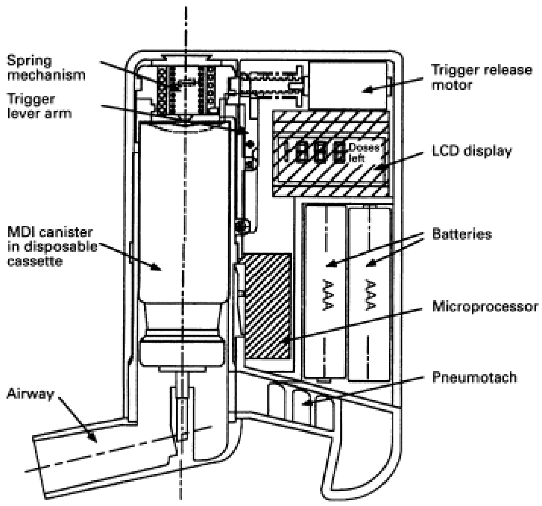


The Nebulizer Chronolog was the first device to gain FDA (United States Food and Drug Administration) approval as a monitoring device for asthma[3]. The Nebulizer Chronolog was designed as an electronically enhanced plastic casing surrounding the inhaler canister that allowed the time recording of actuations of the inhaler through a micro-switch1. The date and time of each actuation are stored in the device and were then uploaded to a Personal Computer (PC) for analysis.

The experience of the Nebulizer Chronolog outlines the importance of creating an add-on component that fits onto the commonly used and safety approved inhaler devices. Following this strategy the safety and regulation approval of the myAirCoach inhaler device could be significantly simplified, and lead to faster commercialisation of the components. Furthermore, one of the main difficulties for the commercial success of the Nubuliser Chronolog was it difficult use in terms of the requirement of manually uploading the collected data on a PC and studying them for the extraction of useful conclusions. Modern wireless technologies in addition with the wide spread of mobile smart devices forms the basis for the solution of this issue of usability and shows how the maturity and popularity of modern technologies leverages the objectives of the myAirCoach project.

2.1.2 SmartMist

Technical Summary
Types of inhalers supported
Pressurized metered dose inhaler (pMDI)
Sensing Capabilities
Pressing sensor (plain tactile button switch)
Monitoring Capabilities (Based on the measurements of sensors)
Time of inhaler use Pneumotach
Output Capabilities
Small LCD Screen for the presentation of medication use indicators
Functional Capabilities
Automated inhaler activation based on inspiratory flow



The SmartMist device integrated a microprocessor and solid-state memory for recording the date and time of inhaler actuations, in addition to the inhalation flow before, during and after every use. Furthermore the device included all electromechanical components that allowed the actuation of the inhaler through inhalation. A plunger within the device was designed to push downward on the inhaler canister once a specific inspiratory flow rate (25 to 60 L/min) and volume (250 to 500mL) have been reached1’[4]. Finally the device was able to provide instant feedback on inhalation technique whilst a dose is being administered by displaying a flashing red light when inhalation is too rapid, a solid green light when inhalation is good and no light when inhalation is too weak.

SmartMist is one of the very few examples where electromechanical components are used in order to simplify and optimise the actual inhalation process by providing accurate timing of canister activation. The crucial disadvantage of this approach is that the intervention in the mechanism of medication delivery complicates the safety regulation processes. The design of SmartMist is indicative of the crucial trade-off between the high number of functionalities and the small size of the resulting device. As already mentioned before, modern smartphone technologies are promising to shift this trade-off since the presentation of results and the control of some basic functionalities can be done through the screen of the patient's smartphone.

2.1.3 MDILog

Technical Summary
Types of inhalers supported
Pressurized metered dose inhaler (pMDI)
Sensing Capabilities
Strain Gauge Accelerometer Thermistor
Monitoring Capabilities (Based on the measurements of sensors)
Time of inhaler use Proper inhaler use Patient breath temperature
Output Capabilities
Small LCD screen for the presentation of medication use indicators
Connectivity
Infrared port communication

The MDILog was developed as an attachment for the casing of a standard pMDI inhalers1. The device is capable of recording actuations through a mechanical beam with a strain gauge, shaking of the inhaler with a movable magnet, and actual inhaling through a heated thermistor. For each of these three sources of data, the date and time are recorded. The MDILog device has the storage capability of 1300 data logs which can be transferred to a PC using an infrared port.

The MDILog device offers an interesting and novel suggestion for monitoring the use of the inhale. The device is fitted with a small mechanical beam that is connected with the plastic frame of the inhaler. In this way, and through the use of a strain gauge measuring the mechanical load on the beam, the system is able to determine when the inhaler is being used. On the one hand, the main advantages of this method is that it is not affected by ambient noise such as the sound based approaches described below, but on the other hand the disadvantages of the device include costly implementation of such sensing approach and the difficulty of correctly fitting the device onto the inhaler. The incorporation of an accelerometer and a thermistor are two main similarities of this project with the foreseen myAirCoach system, but for the case of the current project it will be considered to combine the thermistor and any other breath sensor with a buffer chamber which will allow the accurate measurements that will not be significantly affected by outside conditions or the flow rate of the users breath.

2.1.4 Smart Inhaler Tracker

Technical Summary
Types of inhalers supported
Pressurized metered dose inhaler (pMDI)
Sensing Capabilities
Pressing sensor
Monitoring Capabilities (Based on the measurements of sensors)
Time of inhaler use
Connectivity

Data can be uploaded to a PC through a USB connection Centralized database for the collection of all measurements from all users.

The Smart Inhaler Tracker device consists of a plastic casing, similar to the most modern inhalers, but with an additional compartment for the housing of electronics1. When a patient presses downwards and applies pressure to their inhaler, the canister connects with a switch within the device, resulting in the recording of a time and date stamp for the actuation. Furthermore the device has the capability to store the information of 1600 inhalations. The recordings can be transferred to a PC through a USB cable, where specialized software can upload all the data to an online database where it is kept in password protected storage, to be viewed by the patient, clinician or researcher or other person with granted access.

The Smart Inhaler Tracker device is one of the fist devices that were designed on the basis of a centralised database collecting all the data and providing specialised interfaces for their presentation. In this way the project's experience can provide important information for the development of the myAirCoach system in terms of patient satisfaction and also protection of the patient's privacy. Furthermore, the Smart Inhaler Tracker device follows a very interesting approach that is not interfering with the medication delivery, but cannot be considered an attachment device either, since the placing of the switch under the canister cannot be detached from the inhaler. This characteristic seems unappealing since it will introduce difficult issues in the safety validation of the device without offering functionalities that cannot be moved to a detachable component.

2.1.5 Propeller Health

Technical Summary
Types of inhalers supported
Pressurized metered dose inhaler (pMDI)
Sensing Capabilities

Pressing sensor (plain tactile button switch)
Monitoring Capabilities (Based on the measurements of sensors)
Time of inhaler use (using the smartphone clock) Location of patient when inhaler is used (using the smartphone GPS tracker)
Connectivity
Synchronization with smartphone through Bluetooth Synchronization with the central server via the smartphone
Smartphone application functionalities
Gather and present the monitored parameters Data sharing with family and doctor Monitoring of patients from the side of doctor

The Propeller sensor keeps track of asthma medication, with a record of the time and place of each inhaler use[5] based on a sensor that attaches to the top of the traditional pMDI inhalers. The Propeller sensor wirelessly syncs with modern smart phone devices using Bluetooth technology. The sensor is combined with a mobile app that allows the user to view the captured data and the personalized feedback and advices on how to improve asthma control or COPD status. In addition patients have the option to share their Propeller data with their doctor or family members and provide them with an accurate picture of their disease that can allow a more objective assessment of the current level of asthma control and whether or not a change in therapy may be needed. Finally, propeller community trends provide also the possibility to see areas where symptoms are occurring most often as an indicator of exacerbation triggers in the area

Figure 2: The evolution of asthmapolis sensor to the propeller system

Propeller Health is one of the most complete commercial solutions for effective asthma management. The combination of hardware sensing elements and modern software approaches forms the main connection between Propeller Health and the goals of myAirCoach project. First of all the experience of development of the hardware components can offer crucial help for the design of the myAirCoach sensing elements. Figure 2 is an indicative depiction of this process for the propeller system, starting with the prototype of the device, followed by two versions of the final product as it is offered nowadays. The myAirCoach project is aiming to build upon this design and sensing functionalities and extend them with highly useful parameters that will differentiate the produced system from Propeller Health. As far as it regards the software tools for the support of patients, myAirCoach will try to study the advantages and disadvantages of the propeller tools and community platform and build upon them by using innovative Decision Support Tools and Modelling approaches that promise to create further enhanced functionalities for the myAirCoach system.

2.1.6 SmartInhaler

Technical Summary
Types of inhalers supported
Pressurized metered dose inhaler (pMDI) Dry powder inhaler (DPI)
Sensing Capabilities
Track inhaler use (No information is provided regarding the sensors used. Based on the fact that there are alternative versions for both pMDI and DPI the sensors are probably microphone)

Basic menu selection using tactile buttons
Output Capabilities
Plain button/LED interface on the device LED and sound reminders
Monitoring Capabilities (Based on the measurements of sensors)
Time of inhaler use (using the clock of the smart device used)
Connectivity
Synchronization with smart device through patented technology Synchronization with a cloud service via the smart devices or PCs
Smartphone application
Medication usage information Device battery level Scheduling of medication Medication reminders Data sharing with family and doctor Monitoring of patients from the side of doctor

SmartInhaler is offering a series of devices for modern types of inhaler and with different sets of capabilities[6]. In general SmartInhaler devices offer the possibility to track the inhaler is used and send this information through Bluetooth connection to a cloud based personal health record. Based on the device there is also the possibility of basic reminder options by using audio-visual interactions such as beeping sound and LED indicators. Finally, the majority of the offered devices offer input capabilities such as small touch screens or basic tactile buttons. In order to better describe the offered functionalities two indicative devices are presented in the following table covering both pMDI and DPI inhalers.

SmartTouch AV™ Dulera®	**Additional capabilities**
	• Customizable ring tones for medication reminders • TouchScreen display to view medication use and enable changes in preferences, such as reminder times • Bluetooth® and USB Communications • Available in Rechargeable version

SmartDisk®	Additional capabilities
	• Audio and Visual Reminders • Bluetooth and USB Communications • Available in Rechargeable version

The SmartInhaler platform is also supported by an online environment and specialised applications for smart devices that allow the easy, effective and privacy preserving use by the patients regardless of their level of clinical knowledge related to asthma disease. Among the offered tools, patients can monitor their medication usage and check SmartInhaler device information such as battery levels.

Smartinhaler App™	SmartinhalerLive ™
	

2.1.7 CareTRx: solution for inhalers

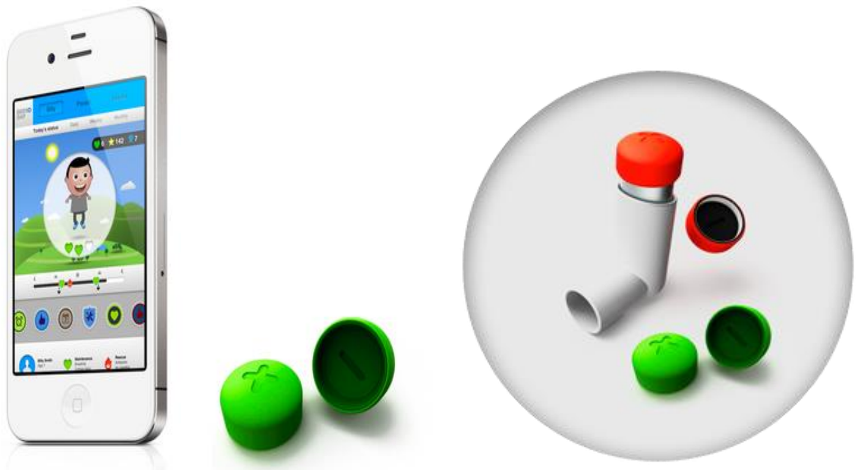
Technical Summary
Types of inhalers supported
Pressurized metered dose inhaler (pMDI) combined with spacer
Sensing Capabilities
Pressing sensor (plain tactile button switch)
Output Capabilities

Glowing reminder on the gecko cap device
Monitoring Capabilities (Based on the measurements of sensors)
Time of inhaler use (using the smartphone clock) Location of patient when inhaler is used (using the smartphone GPS tracker)
Connectivity
Synchronization with smartphone through patented technology Synchronization with a cloud service via the smartphone
Smartphone application
Medication usage information (time and location) Collect input by the user (symptoms, triggers, peak flow measurements, exacerbation events) Gamification approaches and motivational mechanisms for the achievement of asthma related goals Data sharing with family and doctor.

The CareTRx system provides scheduled dose reminders through the use of an attachment sensor that fits on top of the canister of metered-dose inhalers (MDIs) and visual feedback based on light emitting diodes[7]. The device is also supported by a specialised application for smart device platforms that allows the tracking of asthma and COPD medications, symptoms, triggers, peak flow measurements, and flare-ups. Based on individual medication use and other events, the app provides timely notifications to better understand the level of control, displays trends and patterns, and offers motivational badges for achieving goals. Patients can allow their caregiver to have access to their data or print and share summary reports.

2.1.8 GeckoCap

Technical Summary
Types of inhalers supported
Pressurized metered dose inhaler (pMDI) combined with spacer
Sensing Capabilities
Pressing sensor (plain tactile button switch)
Output Capabilities
Glowing reminder on the gecko cap device
Monitoring Capabilities (Based on the measurements of sensors)
Time of inhaler use (using the smartphone clock) Location of patient when inhaler is used (using the smartphone GPS tracker)
Connectivity
Synchronization with smartphone through patented technology Synchronization with a cloud service via the smartphone
Smartphone application
Medication usage information (time and location) Collect input by the user (symptoms, triggers, patient comfort, exacerbation events) Gamification approaches and motivational mechanisms for the achievement of asthma related goals Data sharing with family and doctor



Following the approach of previously described approaches, GeckoCap is formed by an interconnected device in the form of an inhaler attachment and simple software that empower patients as well as their caregivers to better manage asthma[8]. GeckoCap platform uses modern smartphone technologies, data analytics, social reinforcement, and gamification so as to improve asthma medication adherence. Inhaler use is recorded and transmitted to a secured cloud service where the data can be further analysed. Patients are encouraged to self-manage their asthma through goals and rewards that are geared toward their specific challenges. Parents for children with asthma gain peace of mind through a smart notification system on their mobile phones with access to discrete and longitudinal data.

The main differentiator of the GeckoCap system is the use of modern gamification approaches so as to increase the adherence of asthma treatment especially among patient of younger age. Social reinforcement is another valuable component of the system that further supports asthma treatment through the incorporation of important components of the modern technological environment. The foreseen visual community platform of the myAirCoach project is also heading in this direction with the additional benefit of bringing together the community of asthma patients and stimulating their anonymous interaction for the exchange of experiences and solutions to everyday problems related to their disease. Furthermore, the myAirCoach project is aiming to develop innovative visualization approaches that are expected to further support the adherence of treatments based on the increased knowledge of patients about their condition. Finally, and even if child oriented gamification is not one of the main priorities of the project, the intuitive interfaces of the system are expected to increase the attractiveness of the system by younger patients.

2.1.9 Sensohaler + Verihaler

Technical Summary
Types of inhalers supported
Pressurized metered dose inhaler (pMDI) Dry powder inhaler (DPI)
Sensing Capabilities
Sound (microphone)
Monitoring Capabilities (Based on the measurements of sensors)
Flowrate Inhaled volume Peak inspiratory flowrate Firing of a breath actuation mechanism (BAM) Delivery of formulation through the air path of the inhaler
Connectivity
Synchronization with smartphone through Bluetooth low energy Synchronization with the cloud via the smartphone

Smartphone application
Gather and present the monitored parameters Collect input by the user (corrections or additions to the above described parameters)

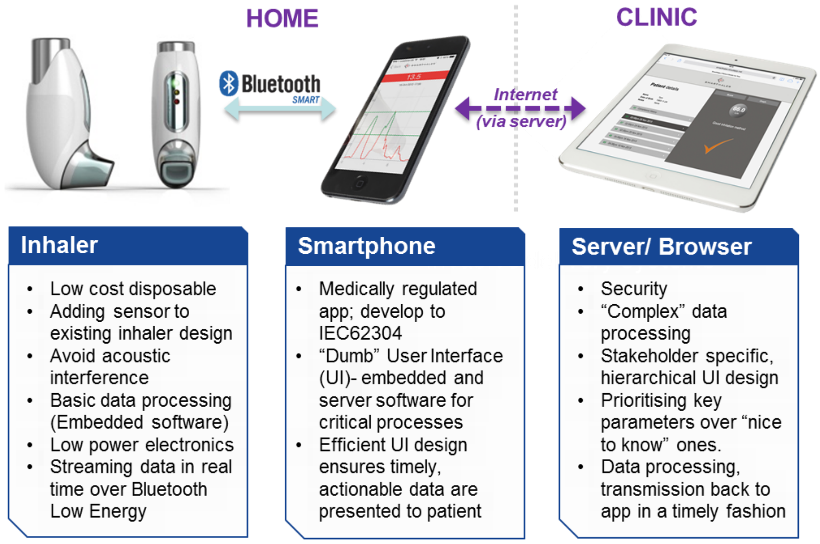


Figure 3: Sensohalerdevice and Verihaler software platform

Sensohaler is a new technology that is aiming to monitor key performance characteristics of inhaler use[9].The core sensor technology incorporates a small, inexpensive microphone attached to the device casing which can be retrofitted to an existing inhaler platform and works with both metered dose (pMDI) and dry powder (DPI) inhalers. A proprietary algorithm removes unwanted background noise from the acoustic signal and extracts key information about the use of the device. For example, parameters related to peak inspiratory flow rate, inhaled volume, timing of breath-actuated firing mechanisms and the delivery of the drug formulation itself have all been successfully extracted. It also records time and date of usage. VeriHaler is a connected health software system designed for monitoring adherence in asthma or COPD patients on the basis of the sensing capabilities of the Sensohaler device.

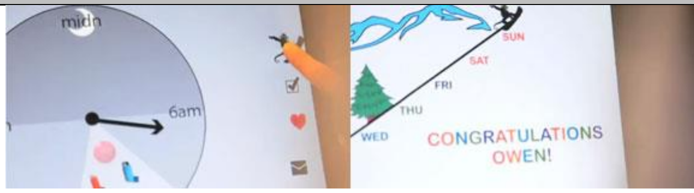
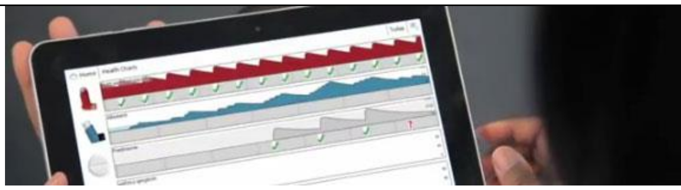
The above figure summarizes the main challenges and advantages of the Sensohaler and Verihaler system and also outlines its crucial differences when compared with the myAirCoach approach both in terms of the foreseen Body Area Network and the increased capabilities of the Decision Support Tools and Personalized Patient Modelling approaches and also based on the fact the myAirCoach system is aiming to create a home sensing module on the basis of the NIOX device as described in the following section 2.2

2.1.10 Chameleon: Wireless Asthma Inhaler

Technical Summary
Types of inhalers supported

Pressurized metered dose inhaler (pMDI) combined with spacer
Sensing Capabilities
Peak flow meter
Output Capabilities
LED line indicating the level of Peak Exhaled Flow
Monitoring Capabilities (Based on the measurements of sensors)
Peak Inhaled Flow Location of patient when inhaler is used (using the smartphone GPS tracker)
Connectivity
Synchronization with smartphone through Bluetooth Synchronization with a central server via the smartphone
Smartphone application
Gather and present the monitored parameters Collect input by the user (triggers, symptoms) Gamification approaches and motivational mechanisms for the achievement of asthma related goals Alerts when patient enters a highly polluted area Data sharing with family and doctor Monitoring of patients from the side of doctor

The Chameleon is a web enabled inhaler targeted at helping children to better manage their Asthma, based on a device with combined functionalities of spacer and inhaler enhanced with Bluetooth communication capabilities that allow its interaction with modern smartdevices[10]. The Chammeleon application is mainly oriented towards child patients of asthma and was designed to allow children to track their medication usage and their lung function via a game based app developed to motivate them to achieve optimal outcomes. The device has also the capability to send alerts to the user when in areas of high pollen count or when they are entering other high risk areas that have triggered asthma attacks in similar patients. Finally, the systems odder to parents and doctors the ability to track and manage medication usage and attacks over time

Chameleon Device	Software Interfaces
	  

2.1.11 T-Haler: Training inhaler

Technical Summary
Types of inhalers supported
Pressurized metered dose inhaler (pMDI) combined with spacer
Sensing Capabilities
No information is given regarding the sensors. Based on the described functionalities and the size of the device the sensors used are probably an accelerometer and an acoustic sensor
Output Capabilities
Visual indications
Monitoring Capabilities (Based on the measurements of sensors)
Shaking of the inhaler prior to use Inhalation flow Timing of the inhaler actuation
Connectivity
Synchronization with a PC
Smartphone application
Gather and present the monitored parameters Gamification approaches and motivational mechanisms for teaching how to use the inhalers in a proper way

The T-haler device is one of the latest approaches for the monitoring of inhaler use based on three main factors of inhaler use, namely: shaking the inhaler prior to breathing in, inhalation flow and timing of actuation[11]. The sensing approach of T-Haler goes beyond the traditional monitoring of the instances when the patient utilizes the inhaler, and tries to formulate a monitoring framework that determines how well the patient is using the inhaler and therefore how effective is the application of medication into the lungs. The device also supports wireless communication and basic visual outputs and is supported by interactive software components.

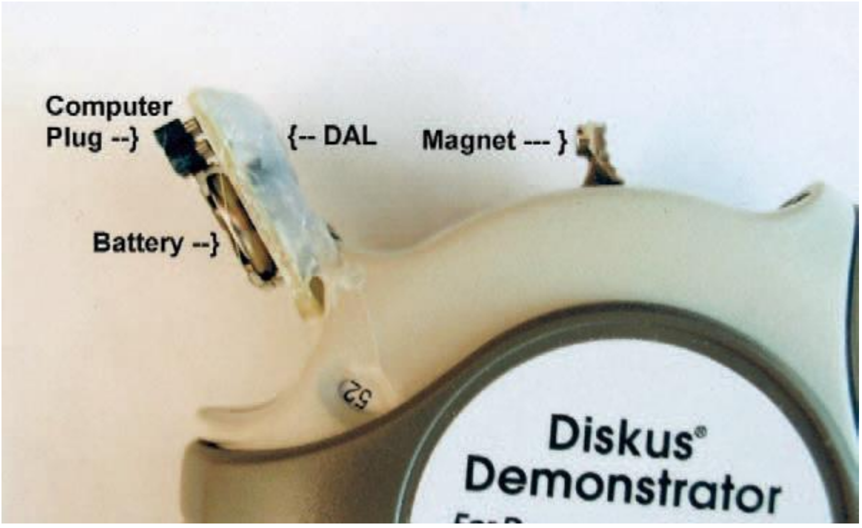
2.1.12 INCA

Technical Summary
Types of inhalers supported
Dry powder inhaler (DPI)
Sensing Capabilities
Sound based analysis of inhaler use
Output Capabilities and Control
LED indications Deliver medication automatically and at the right time during the breath in cycle

The INCA (Inhaler Compliance Assessment) device primarily consists of a microphone, microcontroller and battery. The INCA device can be used in conjunction with the common Diskus inhaler[12]. The INCA starts recording the acoustic signal once the Diskus is opened and switches off when the inhaler is closed. The audio recording of the microphone are stored on the device from where they can subsequently be uploaded to a computer via USB connection. Finally novel processing approaches are used in order to address the proper use of the inhaler in terms of timing of breathing in the medication.

2.1.13 Diskus Adherence Logger

Technical Summary
Types of inhalers supported
Dry powder inhaler (DPI)
Sensing Capabilities
Sound based analysis of inhaler use
Output Capabilities and Control
LED indications Deliver medication automatically and at the right time during the breath in cycle



The Diskus adherence logger consists of a small magnetic sensor that is mounted on the discus device and is used to assess the proper use of the inhaler in terms of the correct position before its actuation[13]. USB port connection is the only available connectivity of the device with a computer, where and with the use of specialised software all the data can be used by the patient or the responsible doctor.

2.1.14 Inspiromatic inhaler device

Technical Summary
Types of inhalers supported
Dry powder inhaler (DPI)
Sensing Capabilities
No information is given regarding the sensors. Based on the described functionalities and the size of the device an acoustic sensor is probably used. Another possibility is a miniaturized air flow sensor.
Output Capabilities and Control
LED indications Deliver medication automatically and at the right time during the breath in cycle

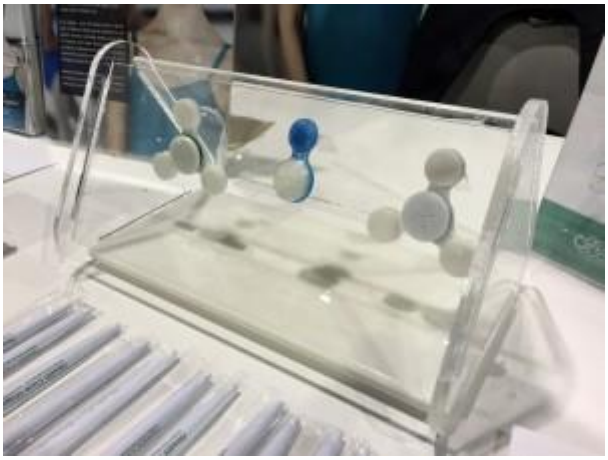
Inspiromatic inhaler is a “smart” dry powder inhaler designed to have some important key advantages over existing inhaler models. Its internal microcontroller and flow sensor detect the right time to deliver the medication and automatically disperse the drug particles in the right size without need for forceful inhalation. Furthermore, the device provides instant feedback in the form of a green light or red light to indicate if the patient is inhaling correctly, and a beeper when the whole dose has been delivered.

Inspiromatic is one of the very few examples of DPI oriented technologies towards the accurate assessment of treatment adherence and the support of proper inhaler use, extending beyond the simple monitoring of time of use.

2.1.15 ADAMM

Technical Summary
Types of inhalers supported
Not attached to an inhaler. Smart patch attached to the patient’s chest
Sensing Capabilities
No information is provided regarding the sensor used. Based on the size of the device and the described capabilities the device is probably measuring the only sound.
Monitoring Capabilities (Based on the measurements of sensors)
Cough counting Respiration Wheeze Heart Rate Inhaler detection Voice journal
Connectivity
Synchronization with smartphone (No info on the used communication technology, most probably Bluetooth Low-Energy)

Synchronization with a cloud service via the smartphone
Smartphone application
Journaling of monitored parameters Medication reminders Treatment plans



ADAMM (Automated Device for Asthma Monitoring and Management) is an upcoming wearable that holds the promise to identify asthma attacks based on the measurements of heart rate, respiration, coughing, and breathing sounds[14]. In addition the device will use this information to predict and detect if an asthma attack may be imminent. ADAMM system also has wireless communication capabilities in order to connect with as specialised smartphone app that will remind the users to take their medication, alert them of a possible asthma attack. ADAMM is seeking FDA approved and targeting for a launch sometime in the second quarter of the year.

The experience of the ADAMM project supports the objective of the myAirCoach project to extend the Body Area Network of asthma patients not only by using the novel inhaler of the system but also include modern clinical and activity assessment devices such as smart bracelets in order to assess parameters such as heart rate. In this way the project aims not only to support the modelling of patients but also to identify possible indicators of asthma disease based on the detailed analysis of the collected data.

2.1.16 AirSonea

Technical Summary
Types of inhalers supported
Not attached to an inhaler. Digital stethoscope capabilities
Sensing Capabilities

Sound measurements
Monitoring Capabilities (Based on the measurements of sensors)
Wheeze detection and monitoring
Connectivity
Synchronization with smartphone
Smartphone application
Instructions for proper use of the device Wheeze result calculation and presentation

AirSonea digital stethoscope is designed to be easily used and operate with modern smartphone devices in order to provide a service to record WheezeRATE™ results, track medication plan and share objective data the responsible caregivers. AirSonea accurately records breathing sounds and detects wheeze, one of the primary signs of asthma[15].

2.1.17 Asthma wellness kit

Technical Summary
Types of inhalers supported
Not attached to an inhaler. Breath Sensor and Controller
Sensing Capabilities
Peak flow meter
Output Capabilities - Control
Heat exchanger (Technologically improbable mainly due to power limitations)
Monitoring Capabilities (Based on the measurements of sensors)
Exhaled peak flow
Connectivity
Synchronization with smartphone (No info on the used communication technology, most probably Bluetooth low-energy)

Synchronization with a cloud service via the smartphone
Smartphone application
Interactive presentation of monitored parameters Medical guidance Motivational stories Interactive monitoring Weather information database

The 'Asthma Wellness Kit' is an innovative idea for an asthma management system that includes a mouth-worn product which contains a built-in heat exchanger and peak-flow meter[16]. The heat exchanger humidifies and levels the temperature of the inhaled air, while the peak-flow meter is providing the ability to monitor airway contractions providing an indicator for a possible asthma attack.

Even though the 'Asthma Wellness Kit' is still at a concept stage with no plans for production at the moment, its approach and design can be helpful for the development of the myAirCoach system. The integration of a heat exchanger and peak flow meter in a device of this size seem highly challenging in addition to the reduced evidence on the study of all the above parameters for the prediction of asthma attacks, especially in the uncontrolled conditions of the patients daily living environment and irrespective of her/his activity levels.

2.1.18 Comparison of mobile health devices for asthma

Table 1: Comparison Table of mobile health devices for asthma

Name of Device	Nebulizer Chronolog	SmartMist	MDILog	SmartInhaler Tracker	Propeller Health	SmartInhaler	CareTRx	GeckoCap	Sensohaler + Verihaler	Chameleon	T-haler	Inspiromatic Inhaler	INCA	Discus Adherence Log	ADAMM	AirSonea	Asthma Wellness Kit
Inhaler / Non Inhaler																	
Inhaler Type Compatibility																	
pMDI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						
DPI						✓			✓			✓	✓	✓			
Sensors on the device																	
Pressing Sensor (Button)	✓		✓	✓	✓	✓	✓	✓									
Sound Sensor (Microphone)						✓			✓		✓	✓	✓		✓	✓	
Peak Flow Meter		✓								✓							✓
Accelerometer			✓								✓						
Thermometer			✓														
Magnetic Sensor													✓	✓			
Monitored parameters (in combination with smartphone																	

Name of Device	Nebulizer Chronolog	SmartMist	MDILog	SmartInhaler Tracker	Propeller Health	SmartInhaler	CareTRx	GeckoCap	Sensohaler + Verihaler	Chameleon	T-haler	Inspiromatic Inhaler	INCA	Discus Adherence Log	ADAMM	AirSonea	Asthma Wellness Kit
when connectivity is available)																	
Time of inhaler use	✓		✓	✓	✓	✓	✓	✓	✓	✓			✓	✓			
Location of inhaler use					✓		✓	✓	✓	✓							
Flowrate									✓								
Inhaled volume		✓							✓								
Peak inhaled flow									✓	✓	✓						
Peak exhaled flow																	✓
Firing of breath actuation mechanism (DPI)									✓								
Proper delivery of medication (DPI)									✓				✓	✓			
Shaking of the inhaler (Proper use)			✓								✓						
Timing of inhaler actuation (Proper use)		✓									✓						
Cough counting															✓		
Respiration Assessment															✓		
Wheeze Detection															✓		

Name of Device	Nebulizer Chronolog	SmartMist	MDILog	SmartInhaler Tracker	Propeller Health	SmartInhaler	CareTRx	GeckoCap	Sensohaler + Verihaler	Chameleon	T-haler	Inspiromatic Inhaler	INCA	Discus Adherence Log	ADAMM	AirSonea	Asthma Wellness Kit
Heart Rate Monitoring															✓		
Voice journal															✓		
Inhaler detection															✓		
Output Capabilities of the device																	
Light reminders						✓	✓										
Sound reminders						✓											
Light indication of peak flow level										✓							
Light indications for guidance during use												✓					
LCD Screen		✓	✓	✓													
Control capabilities																	
Automatic selection of the amount of medication												✓					
Automatic delivery of medication		✓										✓					
Smartphone application functionalities																	
Presentation of all monitored parameters					✓	✓	✓	✓	✓	✓	✓				✓	✓	

Name of Device	Nebulizer Chronolog	SmartMist	MDILog	SmartInhaler Tracker	Propeller Health	SmartInhaler	CareTRx	GeckoCap	Sensohaler + Verihaler	Chameleon	T-haler	Inspiromatic Inhaler	INCA	Discus Adherence Log	ADAMM	AirSonea	Asthma Wellness Kit
Medication usage time					✓	✓	✓	✓									
Medication usage location					✓		✓	✓									
Scheduling of medication						✓	✓	✓							✓		✓
Medication reminders						✓	✓	✓	✓	✓		✓			✓		
Data sharing with family and doctor					✓	✓	✓	✓		✓							
Monitoring of patient groups by the doctor					✓	✓				✓							
Battery life						✓											
Gamification approaches							✓	✓		✓	✓						✓
Alerts for polluted environment										✓							
Instructions for proper use / Educational capabilities											✓					✓	
Input from users																	
Symptoms							✓	✓		✓							
Triggers							✓	✓		✓							
Peak Flow Measurements							✓	✓									

Name of Device	Nebulizer Chronolog	SmartMist	MDILog	SmartInhaler Tracker	Propeller Health	SmartInhaler	CareTRx	GeckoCap	Sensohaler + Verihaler	Chameleon	T-haler	Inspiromatic Inhaler	INCA	Discus Adherence Log	ADAMM	AirSonea	Asthma Wellness Kit
Exacerbation events							✓	✓									
Corrections and additions to the measurements									✓								
Wheather information database									✓								✓

2.1.19 Conclusion

The above sections outlined the main solutions and research approaches for the mobile monitoring of asthma disease aiming to the increased adherence of treatment and the long term optimisation of the patient's condition. A wide spectrum of devices and technologies was identified covering different patient age groups and using different inhalers. Based on this review and as summarised in the above table a variety of disadvantages have been identified where the myAirCoach system can contribute and present a novel approach that not only improves the available solutions but also differentiates significantly in its both the hardware and software components.

2.2 Importance of NO as critical factor for asthma and Available Nitric Oxide sensors

Nitric oxide, which is produced in the lungs and is present in exhaled breath, has been implicated in the pathophysiology of lung diseases, including asthma. It has been shown to act as a vasodilator, bronchodilator, neurotransmitter and inflammatory mediator in the lungs and airways. Over the years, fractional exhaled nitric oxide (FeNO) has been proposed as a non-invasive marker of airway inflammation in asthma. FeNO levels are raised in people with asthma and can be lowered by effective treatment with corticosteroids.

Nitric oxide (NO), molecule of the year in 1992[17], has recently excited much interest in the scientific community. Ten years ago this simple molecule, one of the smallest biologically active substances, was known primarily for its nuisance value. It was one of the noxious gases produced by car exhausts, destroying the ozone layer, and was implicated in acid rain. Only a short time later, NO was recognized as a key signalling molecule in a wide variety of biological functions, and NO research affects all branches of medicine[18]. In the lung, NO acts as a vasodilator, bronchodilator and nonadrenergic non-cholinergic (NANC) neurotransmitter and is an important mediator of the inflammatory response. Nitric oxide is formed in the lungs and the presence of NO has been detected in the exhaled air of several animal species, including humans[19]. Although NO is an evanescent gas, it can be measured directly and rapidly by chemiluminescence in vivo. Since such measurements were first reported in 1991 by Gustafsson and colleagues[20], many studies have confirmed the ease and reproducibility of such readings. Levels of exhaled NO are increased in untreated asthma, and decrease with appropriate anti-inflammatory treatment[21]. Because exhaled NO is reproducible and totally non-invasive, and levels of NO correlate with some measures of airway inflammation, exhaled NO has been suggested as a simple way of assessing asthma[22]. Since the initial studies, exhaled nitric oxide has been reported to be altered in many lung diseases other than asthma, and it has become apparent that other exhaled markers may also be detected[23].

2.2.1 Efficacy of FeNO-guided asthma management in adults

Four studies (based in the UK, New Zealand, Sweden and the USA) were included in the NICE UK review. The quality of the four studies was assessed according to the Cochrane Library and Centre for Reviews and Dissemination (CRD) handbook.

The 4 studies were Smith et al. 2005[24]; Shaw et al. 2007[25]; Syk et al. 2013[26]; Calhoun et al. 2013[27] and a high degree of heterogeneity in all aspects of study design were present across the 4 studies. The number of patients in the trials ranged from 94 to 229, and they were recruited from primary care in 3 studies.

Exacerbations were reported in all 4 studies, although definitions varied and results were not always consistent across the studies. However, all 4 studies reported a fall in exacerbation rates per person year, although it appeared that this was mostly driven by mild and moderate exacerbations.

For severe exacerbations, the Syk et al. (2013)[26] study reported higher rates of oral corticosteroid use in the intervention arm (although the difference was not statistically significant), while the composite outcome of moderate or severe exacerbations favoured the intervention arm. In the other studies, the difference in direction of effect between the outcome for oral corticosteroid use and the composite outcomes that included less severe exacerbations was not evident. Oral corticosteroid use and the composite outcomes of severe and less severe exacerbations decreased in intervention arms, although there was still an apparently greater effect in the composite outcomes. Rate ratios calculated by the NICE UK External Assessment Group for major/severe exacerbations ranged from 0.79 (95% confidence interval [CI] 0.44 to 1.41) to 1.29 (95% CI 0.51 to 3.30), while rate ratios calculated by the External Assessment Group for composite outcomes of all severity of exacerbation ranged from 0.52 (95% CI 0.30 to 0.91) to 0.63 (95% CI 0.40 to 0.98).

Despite the high level of between-study heterogeneity, an exploratory meta-analysis of the rates of major and severe exacerbations using fixed effects methods was conducted. The result showed no heterogeneity, with an I^2 statistic of 0%. The pooled estimate was 0.87 (95% CI 0.64 to 1.19, p=0.38). This indicates that there were fewer major exacerbations in the intervention arm, but the difference did not reach statistical significance.

A sensitivity analysis was done by the NICE UK External Assessment Group using the results of studies that reported the number of exacerbations resulting in oral corticosteroid use. The pooled risk ratio was 0.90 (95% CI 0.56 to 1.45), indicating a statistically non-significant difference for asthma management with FeNO measurement. However, the NICE UK External Assessment Group noted that there were only 2 studies in this analysis. Both studies reported non-significant differences, but with risk ratios on opposite sides of the line of no effect. This could suggest that differences in study design, step-up and step-down protocols, and patient characteristics may account for differences in direction of effect.

When considering the composite outcome of all exacerbations and failure rates, 3 studies reported composite outcomes that the NICE UK External Assessment Group considered to be broadly similar and to represent 'treatment failure'. In 2 studies, FeNO-guided management groups showed numerically, but not statistically significant, lower rates of failure. In the Syk et al. (2013) [26] study, the improvement was statistically significant, with a rate of 0.22 in the intervention arm compared with 0.41 in the control arm (p=0.024). The rate ratio calculated by the NICE UK External Assessment Group was 0.52 (95% CI 0.30 to 0.91). A meta-analysis of these rates was conducted despite the high level of heterogeneity between study characteristics. The result showed a statistically significant effect, with a rate ratio of 0.58 (95% CI 0.43 to 0.77). This represents a statistically significant effect in favour of using FeNO-guided management in people with asthma for the composite outcome of all exacerbations and treatment failure rates.

An additional study (Honkoop et al. 2013)[28] was identified by the NICE UK External Assessment Group. The study was a randomised controlled trial with a 12-month follow-up period and dose titration at baseline and every 3 months thereafter. The number of people in the study was larger than in the other 4 studies and they were recruited from primary care. Outcome data were limited because this study was only reported in a conference abstract; however, a non-significant trend towards a reduction in courses of oral prednisolone was reported for the FeNO measurement group compared with the comparator arms. The NICE UK External Assessment Group performed an additional meta-analysis that included the Honkoop et al. study, calculating the rate ratio for exacerbation as 0.69. Errors could not be calculated for this meta-analysis because the exact numbers of people and events were not reported. Results of the meta-analysis ranged from significant to non-significant in favour of FeNO measurement, depending on the error rate imputed.

All studies reported some data on inhaled corticosteroid use. Two studies reported inhaled corticosteroid use as a mean per day at the end of the study, with mean differences of −270 micrograms per day (95% CI −112 to −430, p=0.003) and −338 micrograms per day (95% CI −640 to −37 micrograms, p=0.028) respectively, in favour of FeNO-guided management. The Syk et al. (2013) study showed a small (non-significant) increase in inhaled corticosteroid use in the intervention arm (586 micrograms, standard error [SE] 454; compared with 540 micrograms, SE 317, in the control arm). One study reported means per month, although it is unclear if this was an average over the whole course of the study, or the means for the final month of the study. The means were very similar at 1617 micrograms per month in the intervention arm and 1610 micrograms per month in the control arm.

A meta-analysis used standardised mean difference analysis because outcomes were not reported in a standardised way. This showed an overall effect of −0.24 standard deviations in favour of FeNO-guided management, although this narrowly missed significance (95% CI −0.56 to 0.07, p=0.13).

Two studies used versions of the Asthma Quality of Life Questionnaire (AQLQ) to measure quality of life. Both showed no effect in the global score, but 1 investigated domains and found a statistically significant difference in the symptoms score. A meta-analysis of the overall scores showed no effect on quality of life, with a standardised mean of 0.00 (95% CI −0.20 to 0.20).

All 4 original studies (excluding Honkoop et al. 2013)[28] reported data for asthma control. In 3 studies, asthma control did not change but in the Syk et al. (2013)[26] study there was a statistically significant increase in asthma control between the 2 trial arms. Two studies (Smith et al. 2005[24] and Calhoun et al. 2012[27]) reported no significant difference between groups for bronchodilator use. Syk et al. did not report the significance of the difference between the 2 arms, reporting a median of 1.56 (interquartile range [IQR] 0.06 to 5.18) uses per week in the intervention arm, and a median of 0.94 (IQR 0.03 to 2.81) in the control arm. No asthma-related adverse events or deaths were reported.

Fractional exhaled nitric oxide (FeNO) testing is recommended as an option to help diagnose asthma:

• In adults and children who, after initial clinical examination, are considered to have an intermediate probability of having asthma (as defined

In the British guideline on the management of asthma 2012) and

• When FeNO testing is intended to be done in combination with other diagnostic options according to the British guideline

On the management of asthma .

Further investigation is recommended for people whose FeNO test result is negative because a negative result does not exclude asthma.

FeNO measurement is recommended as an option to support asthma management (in conjunction with the British guideline on the management of asthma 2012) in people who are symptomatic despite using inhaled corticosteroids.

2.2.2 Available Nitric Oxide sensors

Available sensors for exhaled NItric Oxide monitoring are based on 2 principles today, electrochemical and chemiluminescence. An overview of these principles can be found in the following references, Cao et.al. (Electroanalysis 4 (1992) 253-266) and Robinson et. al.(*Anal. Chem.*, **1999**, 71 (22), 5131-5136) respectively.
The method to analyze Fractional exhaled Nitric Oxide (FeNO) is based on published recommendations by the European Respiratory Society (ERS) and the American Thoracic Society (ATS), This Joint Statement was adopted by the ATS Board of Directors, December 2004, and by the ERS Executive Committee, June 2004 (American Journal of Respiratory and 'Critical Care Medicine vol 171 2005) and Reddel et.al. (American Journal of Respiratory and 'Critical Care Medicine vol 180 2009).

Based on this methodology only two analytical principles have been developed into a product, cleared for clinical practices.

The following tables give an overview of the product available for FeNO analysis in clinical practices

Table 2: Products available for FeNO analysis.

Product	Manufacturer	Detection principle	Approved in
NIOX MINO	Aerocrine	Electrochemical	EU, US, Japan, China
NIOX VERO	Aerocrine	Electrochemical	EU, US, Japan
NOBreath	Bedfont	Electrochemical	EU
Hypair	Medisoft	Electrochemical	EU
CLD 88sp NO analyzer	Ecomedics	Chemiluminescence	EU

There are a number of technologies suggested in the research but none have been developed into clinical practice.

FeNO Clinical utilization

Since more than 10 years FeNO have been part of the clinical practice for Asthma management. The method is endorsed by health care specialist associations in Europe, Japan and US. An overview is given in table 2 below.

Table 3:Current acceptance of FeNO use by Guidelines and society consensus publications

Europe	China & Japan	USA
UK NICE Guidelines for FeNO Use (2014)	Matsunaga et al 2010, Japanese consensus publication	American Thoracic Society Guidelines (2011)
UK NICE Guidelines for Asthma diagnosis (coming July 2015)		
French speaking respiratory society position paper (2014)		
Bjermer et al consensus publication (2013) – 11 European experts, 7 countries		

Current utilization of FeNO testing worldwide

There have been conducted worldwide to date >10 million FeNO tests.FeNO testing in clinical practice is growing annually. More than 30 countries worldwide are using FeNO testing in asthma clinical practice. Some of these are:
Switzerland, Denmark, Spain, Germany, Austria, Sweden, UK and Ireland, Italy, Holland, Czech, Turkey, Finland, Norway, Israel, UAE, India, China, Japan, Korea, Australia, New Zealand, USA.

2.3 Other Potential parameters that are critical for Asthma

This section reflects a first investigation into the potential parameters that are of interest for monitoring the asthma status and patients compliance with the care plan in the concept of myAirCoach. Therefore the following paragraphs list the potential measurements to be investigated for the sensing infrastructure in the project. An initial classification and priority ranking of these measurements considering their clinical relevance and therapy sub-goals is given (selected by the project's physicians of ICL, UMAN and LUMC), but however there is no assessment of technical feasibility or how to integrate it in the myAirCoach sensing settings. Such detailed investigation is given in deliverable D3.1 – Definition of sensor components and communication strategy.The list of sensing parameters is merely classified by *therapygoals* and *relevance*.

Therapy goals specify the category of information where appropriate input of data will have effect on, i.e. the objectives of sensing certain parameters. This is classified as follows:

- Improvement of medication adherence by monitoring medication intake (e.g. dose and time) and correct/incorrect inhaler use.
- Provision of clinical state awareness as feedback to patient and physicians e.g. by assessing collected data against behaviour of the patient and biomarkers of asthma.
- Increasing awareness of environmental risks by monitoring environmental parameters continuously and on demand, e.g. during medication intake/inhaler use, to analyse interference of these parameters with actual asthma status.
- To minimize patient's efforts that are needed to collect appropriate data about the asthma status by automated processes instead of manual collection as well as convenient use the myAirCoach system.

Relevance of measurement: From the clinical perspective there are a lot of potential parameters that are of interest and clinical relevance. However, some of these parameters can only be gathered in a laboratory environment or are not appropriately measureable for daily use/collection. Hence, data is primarily ranked by its needs to be included in myAirCoach in the following way:

- High – Inclusion of measure into the sensing infrastructure is of high clinical interest and will be given priority in the selection of sensors.
- Medium – Inclusion of measure is considered and will be done if straightforward and convenient use for the patient can be assured.
- Low – Inclusion of parameter should not be investigated to minimize patient's efforts and save development time.

2.3.1 General status

The general health status is the starting point for any therapy or medication (not only in asthma) as it might indicate other/additional diseases and/or contradictions for therapy interventions. Therefore the myAirCoach system must not merely collect asthma related data. To provide a clear and useful clinical view of the patient under surveillance the parameters listed in the following table should be included in the monitoring application.

Table 4 : Relevant parameters for monitoring the general health status of asthma patients

Type of parameter: **Pulse**	Relevance: **High**

Description: Pulse represents the tactile arterial palpation of the heartbeat. The pulse rate may signify many things as for example also poor asthma control. However in myAirCoach this is more related to give some insight into the general health status of the patient.	Therapy goals: • Clinical state awareness • Minimal patient effort
Type of parameter: **Activity**	Relevance: **High**
Description: Activity as the collection of any reference measure indication the level of physical stress on daily routine. This also relates to the general health and fitness state of the patient and can therefore indicate worsening of asthma or bad health conditions.	Therapy goals: • Clinical state awareness • Minimal patient effort
Type of parameter: **Location**	Relevance: **High**
Description: Location is given by pairing of latitude and longitude of the spherical coordinate system. This parameter is linked to all other parameters gathered as it might indicate locations of exacerbations or medication intake. This information might then be further fused with other data sources (e.g. weather data base) to enhance data collection.	Therapy goals: • Awareness of environmental risks • Minimal patient effort
Type of parameter: Oxygen saturation	Relevance: **Medium**
Description: Oxygen saturation measures the percentage of haemoglobin binding sites in the bloodstream occupied by oxygen. Decreased oxygen saturation might reflect exacerbation phases.	Therapy goals: • Clinical state awareness • Minimal patient effort
Type of parameter: Body temperature	Relevance: **Medium**
Description: Refers to the normal human body temperature. It can indicate respiratory tract infections – particularly infections affecting the upper airways, such as the flu.	Therapy goals: • Clinical state awareness • Minimal patient effort
Type of parameter: Blood pressure	Relevance: Low
Description: Blood pressure refers to the arterial pressure in the systemic circulation. It is directly interrelated to the general health status.	Therapy goals: • Clinical state awareness • Minimal patient effort
Type of parameter: Hormone change	Relevance: Low
Description: In this context in particular, it refers to the menstrual cycle of female humans as this	Therapy goals: • Clinical state awareness

might affect asthma conditions and asthma clinical state.	

2.3.2 Clinical/Physiological asthma status

A key target of the myAirCoach system is providing mobile and convenient means to monitor the physiological status of asthma patient. Respective parameters of interest are listed below table.

Table 5: Relevant biomarkers for asthma control.

Type of parameter: **Breathing rate/ Respiratory cycle**	Relevance: **High**
Description: Normal breathing (tidal) is the ratio of time of inspiration to expiration (breaths inhaled and exhaled per minute). An increased Respiratory Rate is associated with poor asthma control.	Therapy goals: • Clinical state awareness
Type of parameter: **Medication usage**	Relevance: **High**
Description: the parameter assesses medication use and patient compliance with treatment, e.g. by counting the number of medication intakes.	Therapy goals: • Medication adherence • Minimal patient effort
Type of parameter: **Inhalation technique**	Relevance: **High**
Description: This parameter measures effectiveness of medication intake and thereby reflects the "real" dose of medicine that has been taken.	Therapy goals: • Medication adherence • Minimal patient effort
Type of parameter: **Air flow rate**	Relevance: **Medium**
Description: This parameter signals the amount of air that flows in/out during inspiration and expiration respectively.	Therapy goals: • Medication adherence • Minimal patient effort
Type of parameter: **Lung functions**	Relevance: **Medium**
Description: this parameter requires measuring the peak expiratory flow and forced expiratory volume in one second. Both are measures of airway narrowing and require a full inspiration and then a forced / fast full expiration.	Therapy goals: • Medication adherence • Clinical state awareness • Minimal patient effort
Type of parameter: **Breath sounds / Wheeze rate / Stridor**	Relevance: **Low**
Description: it monitors normal and abnormal conditions during normal breathing.	Therapy goals: • Medication adherence • Clinical state awareness

Table 6: Relevant parameters for monitoring the clinical/physiological status of asthma patients.

2.3.3 Biomarkers of Asthma

There exist several biomarkers for determining the actual asthma status. Table 5 lists the most important ones that shall be collected in the myAirCoach project. Type of parameter: **Nitric oxide (NO or FeNO)**	Relevance: **High**
Description: it measures amount of NO in one exhalation breath as this is one of the most used biomarkers for asthma today.	Therapy goals: • Medication adherence • Clinical state awareness
Type of parameter: **Breath temperature**	Relevance: **High**
Description: An increase in breath temperature may signify increased airways inflammation. This should also correlate with the FeNO measurements and could be related to asthma control.	Therapy goals: • Medication adherence • Clinical state awareness
Type of parameter: **Hydrogen (H+)**	Relevance: **Medium**
Description: Changes in hydrogen content in exhaled breath is another known biomarker for asthma.	Therapy goals: • Medication adherence • Clinical state awareness

2.3.4 Environmental factors

There has been a lot of research providing evidence that environmental factors directly influence the asthma status and trigger exacerbation phases. Therefore a main target in myAirCoach is collecting environmental data in particular in parallel to inhaler use or medicine intake to correlate and assess these effects. The list of respective parameters is given in the following Table:

Table 7: Relevant environmental parameters to be correlated to asthma control

Type of parameter: **Ambient temperature**	Relevance: **High**
Description: it refers to the air temperature in certain place.	Therapy goals: • Awareness of environmental risks • Minimal patient effort
Type of parameter: **Ambient humidity**	Relevance: **High**
Description: it Refers to the relative air humidity in certain place.	Therapy goals: • Awareness of environmental risks • Minimal patient effort
Type of parameter: **Nitrogen dioxide (NO_2)**	Relevance: **High**
Description: it Refers to the ambient concentration of nitrogen dioxide in certain place.	Therapy goals: • Awareness of environmental

	risks • Minimal patient effort
Type of parameter: **Sulphur dioxide (SO_2)**	Relevance: **High**
Description: it Refers to the ambient concentration of sulphur dioxide in certain place.	Therapy goals: • Awareness of environmental risks • Minimal patient effort
Type of parameter: **Particulates (PM10, PM2.5)**	Relevance: **High**
Description: it Refers to the ambient concentration of particulate matter (PM) or particulates, which is microscopic solid or liquid matter suspended in the Earth's atmosphere. Subtypes of atmospheric particle matter include Respirable Suspended Particle (RSP; particles with diameter of 10 micrometres or less (PM10)) and fine particles (diameter of 2.5 micrometres or less (PM2.5)).	Therapy goals: • Awareness of environmental risks • Minimal patient effort
Type of parameter: **Carbon black**	Relevance: **Medium**
Description: Carbon black is a material produced by the incomplete combustion of heavy petroleum products. Short-term exposure to high concentrations of carbon black dust may produce discomfort to the upper respiratory tract through mechanical irritation.	Therapy goals: • Awareness of environmental risks • Minimal patient effort
Type of parameter: **Ozone (O_3)**	Relevance: **Medium**
Description: Ozone (or tri-oxygen) is an inorganic molecule with the chemical formula O_3. Ozone is a potential respiratory hazard and pollutant.	Therapy goals: • Awareness of environmental risks • Minimal patient effort
Type of parameter: **Relevant pollen counts**	Relevance: **Medium**
Description: Pollen count is the measurement of the number of grains of pollen in a cubic meter of air. It is especially relevant for allergic persons.	Therapy goals: • Awareness of environmental risks • Minimal patient effort
Type of parameter: **Volatile Organic Compounds (VOCs)**	Relevance: **Medium**
Description: VOCs are organic chemicals that have a high vapour pressure at ordinary room temperature. Some VOCs are dangerous to human health, in particular for asthma patients.	Therapy goals: • Awareness of environmental risks • Minimal patient effort

Type of parameter: **Pollution**	Relevance: **Medium**
Description: Pollution in myAirCoach refers to air pollution as the release of chemicals and particulates into the atmosphere. It's a general term of a set of individual pollutants that have also been mentioned above.	Therapy goals: • Awareness of environmental risks • Minimal patient effort
Type of parameter: **Smoke**	Relevance: **Medium**
Description: Smoke is a collection of airborne solid and liquid particulates and gases emitted when a material undergoes combustion or pyrolysis. It is commonly an unwanted by-product of fires and caused by smoking cigarettes of course. Asthma patients have indicated smoke as a trigger for exacerbations.	Therapy goals: • Awareness of environmental risks • Minimal patient effort
Type of parameter: **Thunderstorms**	Relevance: **Low**
Description: A thunderstorm, also known as a lightning storm, is a type of storm characterized by the presence of lightning and its acoustic effect on the Earth's atmosphere known as thunder. Evidence has been provided showing thunderstorms are linked to increased asthma symptoms and attacks[29].	Therapy goals: • Awareness of environmental risks • Minimal patient effort
Type of parameter: **House Dust Mite (HDM)**	Relevance: **Low**
Description: The house dust mite (HDM) is a cosmopolitan pyroglyphid that lives in human habitation. House dust mites are a common cause of asthma and allergic symptoms worldwide[30].	Therapy goals: • Awareness of environmental risks • Minimal patient effort
Type of parameter: **Animal allergens**	Relevance: **Low**
Description: An allergen is a type of antigen that produces an abnormally vigorous immune response. Animal allergens are called dander, which is an informal term for a material shed (composed of skin cells) from the body of various animals.	Therapy goals: • Awareness of environmental risks • Minimal patient effort
Type of parameter: **Fungal allergens**	Relevance: **Low**
Description: Basidiospores were described as being possible airborne allergens and are linked to asthma. Basidiospores are the dominant airborne fungal allergens. Fungal allergies are associated with seasonal asthma.	Therapy goals: • Awareness of environmental risks • Minimal patient effort

Type of parameter: **Fragrance or airborne allergens**	Relevance: **Low**
Description: Allergic reaction due to fragrances or other airborne allergens, e.g. related to paint fumes.	Therapy goals: • Awareness of environmental risks • Minimal patient effort

2.4 Signal processing algorithms for the real time monitoring of sensor based parameters

Several experts in the fields of information and communication technologies (sensing, signal processing, wireless communication, HW/SW design), respiratory medicine, inhaler devices focus on building novel mhealth systems that facilitate the early diagnosis and management of such diseases through a personalized approach. Although medical devices that detect these sounds are already commercially available[31], they operate on-demand in hand held form and cannot be used for continuous tracking the intensity of symptoms. To that end, the authors in[32] proposed a low-cost wearable sensing system consisting of low power miniaturized wearable sensor, recording breath signals, and transmitting them to a body node coordinator (BNC) e.g., a smartphone, that serves as a gateway and facilitates the continuous monitoring of breath sounds.

The concept of an mhealth sensing system that facilitates the continuous monitoring of asthmatic wheezes is shown in Figure 4. This system requires new schemes and algorithms to be implemented in order to optimize the energy consumption and the total hardware cost at the transmitter. Low energy consumption significantly increases the battery lifetime of the breath sensor, while the hardware cost reduction makes the mhealth system economically viable and more easily accepted by the individual customers. Both requirements motivate the design of compression/reconstruction schemes, with high compression ratio capabilities and reduced computational requirements. The vast majority of audio compression schemes available in the literature[33] charge the transmitter with most of the processing, thus not coping effectively with the above requirements.

Compressed Sensing (CS) approaches for signal compression/reconstruction offers an affordable solution for audio compression in wireless sensor networks [34], by allowing the reconstructing of audio signals from a small number of random linear observations. In this report we demonstrate the benefits of CS based compression/reconstruction schemes for the efficient tele-monitoring of breath sounds in wireless body area networks (WBANs). More specifically, we enhance the benefits of the conventional CS schemes proposed in[34], by taking into account specific characteristics (e.g., block sparsity, sample correlation) of the breath sounds in the eigen spectrum domain. The presented novel recovery algorithm, named PCA based Group LASSO, increases the mhealth system energy efficiency by a factor of 1.8 as compared to traditional CS recovery approaches.

The rest of the section focuses on the transmission and analysis of breath sounds. However, it should be noted that the presented compression and de compression techniques could be useful for the transmission of any raw data recorder in the WBAN. The rest of this section is outlined as follows: Section 2.4.1, presents the system model. Section 2.4.2 describes the operations that can be carried out at the BNC including the proposed recovery algorithm. Finally, Section 2.4.3. describes different methods for extracting asthma related indicators, such as: the existence of wheezes and/or the instantaneous respiratory rate.

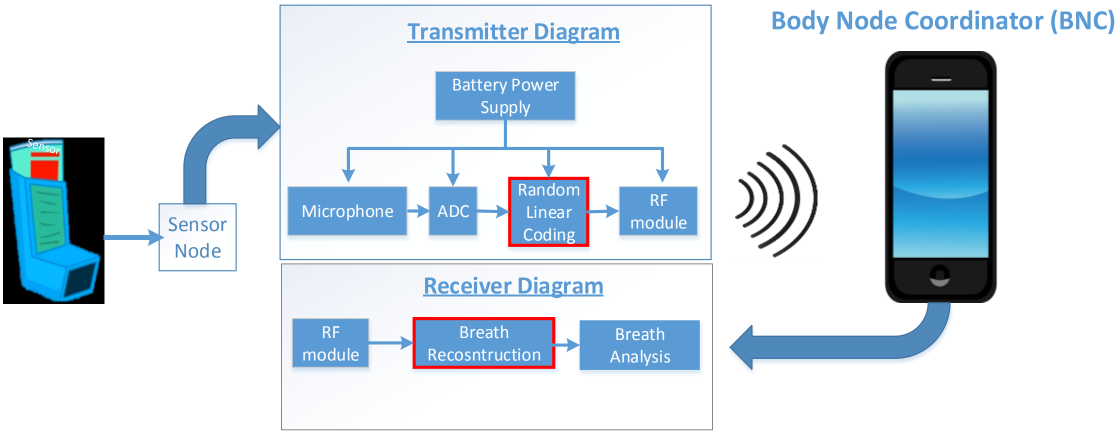


Figure 4: mHealth system for wheeze telemonitoring.

2.4.1 Breath Telemonitoring Model

Figure 4 illustrates the tele-monitoring system model under study. In particular, we consider a WBAN formed by an acoustic sensor (source node) that records a real time breath sound and transmits it to a BNC (e.g., smartphone). We assume that the sensor can be attached to the body or even on the inhaler of the patient.

The breath signal is recorded by the microphone, digitized and divided into segments of N samples. Each segment is represented as a vector $\boldsymbol{x} = [x_1, \dots, x_N]^T$, where $x_i \in \mathbb{R}$. We assume that the recorded signal to be transmitted contains noise itself and, as a result, it may be written as $\boldsymbol{u} = \boldsymbol{x} + \boldsymbol{w}_s$, where $\boldsymbol{u} = [u_1, \dots, u_N]^T$ are samples of the noisy signal and $\boldsymbol{w}_s = [w_1, \dots, w_N]^T$ is the random noise. For each segment, the source generates M random linear combinations by using a random matrix $\boldsymbol{A}$ of dimension $M \times N$ (Random Linear Coding - RLC) and performs quantization as follows:

$$\boldsymbol{y}_q = Q(\boldsymbol{A}\boldsymbol{u}) = \boldsymbol{A}\boldsymbol{x} + \boldsymbol{w}_q, \qquad (1)$$

where$Q: \Re \rightarrow Y_i$ is a scalar quantization function[1] that discretizes its input, by performing a mapping of each real element of $\boldsymbol{y}$ to a finite set of codewords Y_i and $\boldsymbol{w}_q$ represents the combination of the sensing and quantization error. The encoded samples are then transmitted to the BNC where the reconstruction of the original signal and breath reconstruction and analysis is taking place. At this point it should be mentioned that the overhead introduced by the transmission of the random encoding coefficients, can be significantly reduced by: i) adopting the policy that was used in [35],

[1] Typical quantizers are usually optimized by selecting decision boundaries and output levels in order to minimize the distortion (e.g., mean square error) between the input real number and its quantized representation.

that is, instead of transmitting a full encoding matrix, the authors propose the transmission of the coefficient in the first row and then the generation of the $M-1$ rows at the destination by performing predefined shifts of the received row, and ii) considering that the same encoding coefficients remain fixed for a number of L segments, where $L >> N^2$

2.4.2 Efficient Reconstruction of Breath Sounds

Several sparse representation methods, such as the discrete cosine/wavelet transform (DCT,DWT)[36], have been used in the past for sparsifying audio signals. Their sparse representation efficiency is based on the fact that they tend to decor-relate (e.g., DCT, DWT) a given signal and redistribute the energy contained in the signal, so that most of energy is contained in a small number of components. In this case, $\boldsymbol{x}$ can be expressed as $\boldsymbol{x} = \Psi \boldsymbol{s}$, where $\Psi \in \mathbb{R}^{N \times N}$ is an orthonormal basis matrix of an appropriate transform domainand $\boldsymbol{s}$ is a sparse representation vector. The reconstruction of breath sound at the BNC can be performed by exploiting the sparsity of the breath signal in some transform domain (e.g., DCT, DWT) through the use of the classical CS theory.

2.4.2.1 Conventional CS approach

According to the classical CS approach, vector $\boldsymbol{s}$ may be recovered from $\boldsymbol{y}$ by solving the problem:

$$min_s\{\| \boldsymbol{s} \|_0 : \| \boldsymbol{y}_q - \boldsymbol{A}\Psi\boldsymbol{s} \|_2^2 \leq \epsilon\}, \quad (2)$$

where the parameter ϵ corresponds to the predefined error tolerance and $\|\cdot\|_2$ is the ℓ_2 - norm of the input vector, respectively. The above optimization problem is computationally intractable and it cannot be used for practical applications. CS suggests replacing the ℓ_0 quasi-norm by the convex ℓ_1-norm and solving the following problem: $min_s\{\| \boldsymbol{s} \|_1 : \| \boldsymbol{y}_q - \boldsymbol{A}\Psi\boldsymbol{s} \|_2^2 \leq lon\}$, where $\| \boldsymbol{s} \|_1 = \sum_{i=1}^{N} | s_i |$. Lagrange relaxation allows us to efficiently approximate the solution of the aforementioned problem by solving the problem:

$$\hat{\boldsymbol{s}}_L := \arg\min_{\boldsymbol{s}} \| \boldsymbol{y}_q - \boldsymbol{A}\Psi\boldsymbol{s} \|_2^2 + \lambda \| \boldsymbol{s} \|_1, \quad (3)$$

whereλ is a penalty parameter that can be tuned, to trade off the value of the ordinary least square error $\| \boldsymbol{y} - \boldsymbol{A}\Psi\boldsymbol{s} \|_2^2$ for the number of the non-zero entries (degree of sparsity) in $\boldsymbol{s}$. Algorithmically, the aforementioned convex optimization problem in eq. (3), known as LASSO problem, can be tackled by any generic second-order cone program (SOCP) solver. The original signal in the time domain can be reconstructed by computing$\hat{\boldsymbol{x}}_L = \Psi \hat{\boldsymbol{s}}_L$.

2.4.2.2 Exploitation of the Group Sparsity in a transform domain

Many wheezing sounds are represented in the frequency domain, as a cluster of one main peak in parallel with several lower amplitude peaks. Thus, vector $\boldsymbol{s}$ can be viewed as a concatenation of K blocks of length d:

[2] Experimental results have shown that the aforementioned strategies do not affect the performance of the decoding algorithms presented in Section 3. Thus, it is reasonable to neglect the communication overhead that is introduced by the transmission of the encoding coefficients to the BNC and assume that matrix $\boldsymbol{A}$ is considered to be known at the receiver.

$$\boldsymbol{s} = [\quad \boldsymbol{s}^T[1], \boldsymbol{s}^T[2], \dots, \boldsymbol{s}^T[K] \quad]^T, \tag{4}$$

where$\boldsymbol{s}[i] = \left[s_{(i-1)d+1}, \dots, s_{id}\right]^T$ denotes the i^{th} block and $N = Kd$. Note that only few clusters, including those that correspond to wheezes, consist of large amplitudes and can be considered as non zero blocks. The aforementioned structureis known as block sparse structure and enables the signal recovery from a reduced number of samples [37], compared to sparse structures. By simply using the ℓ_1 relaxation for reconstructing $\boldsymbol{s}$, we ignore the fact that the signal is block-sparse, i.e., the non-zero entries occur in consecutive positions. To exploit block sparsity, we reconstruct vector $\boldsymbol{s}$ by solving:

$$\hat{\boldsymbol{s}}_{GL} := \arg\min_{\boldsymbol{s}} \| \boldsymbol{y}_q - \boldsymbol{A}\Psi\boldsymbol{s} \|_2^2 + \lambda \sum_{i=1}^{R} \| \boldsymbol{s}[i] \|_2, \tag{5}$$

which is also known as group LASSO problem. Similarly to the LASSO algorithm, in the group LASSO approach, the following function $\sum_{i=1}^{R} I\,(\| \boldsymbol{s}[i] \|_2 \neq 0)$[3], equals to the number of non-zeroblocks $\boldsymbol{s}[i]$ invector $\boldsymbol{s}$ for a given block size $d = N/R$ and is replaced by$\sum_{i=1}^{R} \| \boldsymbol{s}[i] \|_2$. In other words, the non-smooth indicator function $I(\| \boldsymbol{s}[i] \|_2 \neq 0)$, that shows whether the i-th block is zero or non-zero, is replaced by the convex function $\| \boldsymbol{s}[i] \|_2$. Then, the breath signal in the native domain $\boldsymbol{x}$ can be reconstructed as in the LASSO case, by computing $\hat{\boldsymbol{x}}_{GL} = \Psi\hat{\boldsymbol{s}}_{GL}$

2.4.2.3 PCA based group LASSO

Orthogonal transforms such as discrete cosine transform, and wavelet transform construct effective dictionaries for sparse modelling of several kind of signals such as audio, biosignals[34,35]. Their ability to sparsify the signal, is based on the fact that they i) tend to decorrelate the components of a given signal ii) tend to redistribute the energy contained in the signal so that most of energy is contained in a small number of components[36]. The principal component analysis(PCA) transform, is a linear transform that completely decorrelates the signal components and concentrates the signal energy to a small number of coefficients. This is achieved by fitting a low-dimensional subspace to the data in a way that minimizes the l_2 approximation error[36]. Suppose that $\boldsymbol{R}$ corresponds to the covariance matrix of the signal:

$$\boldsymbol{R} = \mathbb{E}[\boldsymbol{x}\boldsymbol{x}^T]. \tag{6}$$

Now, let $\boldsymbol{R} = \boldsymbol{E}\Lambda\boldsymbol{E}^T$ be the eigenvalue decomposition of matrix$\boldsymbol{R}$. Matrix $\boldsymbol{E}$ is an orthogonal matrix with the eigenvectors of $\boldsymbol{R}$ and Λ is a diagonal matrix consisting of the eigenvalues of $\boldsymbol{R}$ in decreasing order. Then the exploitation of sparsity or block sparsity of the breath signal in the PCA domain occurs by eqs. (3) and (5) after setting $\Psi = \boldsymbol{E}$.

The breath signal in the native domain $\boldsymbol{x}$ canbe then reconstructed as in the previous sections, by multiplying the resulted vectors $\hat{\boldsymbol{s}}_L$ and $\hat{\boldsymbol{s}}_{GL}$ with$\boldsymbol{E}$.

2.4.3 Breath Analysis

To evaluate the efficiency of the proposed compression/reconstruction schemes, we need to examine whether important indicators, such as the respiratory rate and the

[3] $I(\cdot)$ is the non smooth indicator function

existence of wheezes, can be reconstructed by the decompressed audio samples.In the rest part of this section we describe different techniques that can be used for estimating the instantaneous respiratory rate and for detecting the presence of wheezes.

2.4.3.1 Instantaneous Respiratory Rate

The instantaneous respiratory rate (IRR) can be estimated directly from the reconstructed audio samples after using the Shannon entropy approach. The Shannon entropy of a random signal with probability density function p is defined as:

$$SE(p) = -\sum_{i=1}^{N} p_i \cdot log(p_i)$$

where N is the number of outcomes for the random variable p. More specifically, the received audio raw data are sequestered into 25 ms windows with 50% overlap. For each window the Shannon entropy was computed. The pdf p can be estimated either by using the histogram or by using the Parzen - Window density estimation method with a Gaussian Kernel[38,39] .The SE estimated from each window is assigned to the middle point of the window and is interpolated using the cubic spline in order to recover the original duration audio signal. Figure 5 shows and example of the computed SE signal using the described approach.

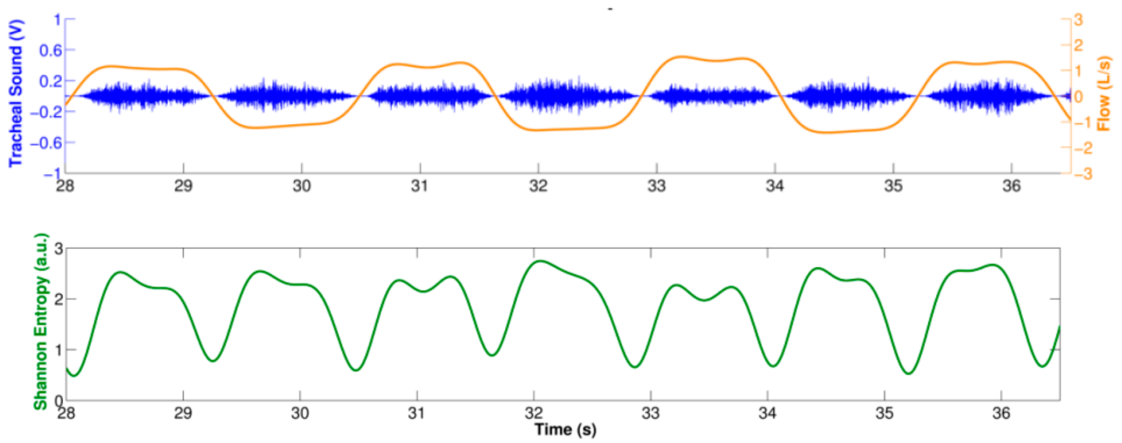
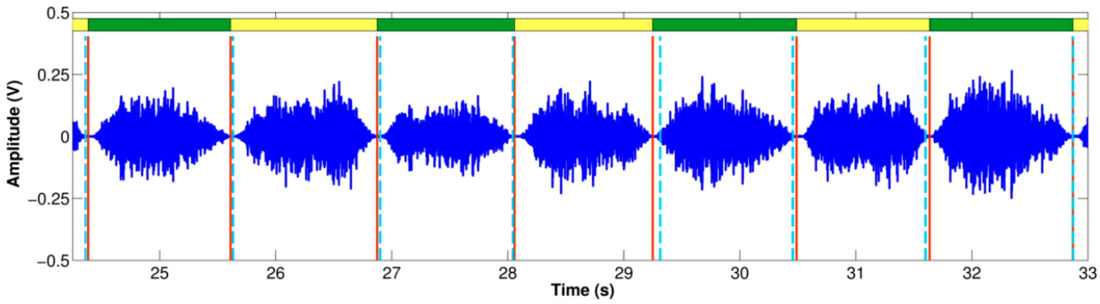


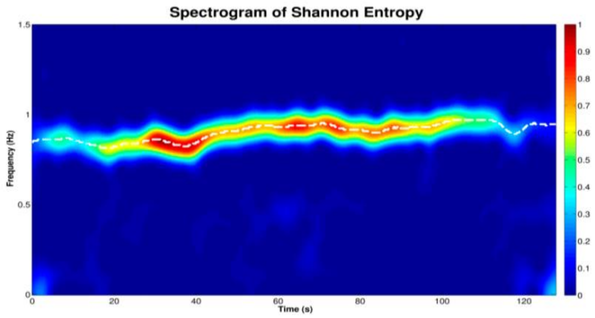
Figure 5: Segment of an breathing sound. The yellow positive lobes correspond to inspirations while the negative lobes correspond to expirations. The bottom subfigure shows the estimated shannon entropy occured from the recorded breath signal.

In order to estimate the IRR from the calculated SE signal, two different approaches may be applied: i) execution of a phase onset algorithm in the time domain ii) use of a time frequency representation (TFR).In order to estimate the breath phase onset, the SE signal is inverted and the corresponding local maxima are automatically detected. However, the TFR can lead to more accurate results and allows to determine which frequencies of a signal under study are present at a certain time. This characteristic is useful when analysing signals whose frequency content varies with time, as is the case for the respiratory rate. Figure 6 (a) shows an example of breath-phase onset detection using the breath sounds acquired using a smartphone. Solid red lines indicate the breath-phase onsets detected using the SE signal. Dashed blue lines indicate the breath-phase onsets detected using only the information from the acquired breath sounds.

The most widely-used TFR in the respiratory sounds field is the spectrogram (SP) given by the magnitude of the short time Fourier transform (STFT)[40,41]. Figure 6 (b)shows the spectrogram of the SE signal, where the main frequency content is located at twice the value of the breathing frequency, since SE has two lobes for each breathing cycle.



(a)



(b)

Figure 6: Example of: (a) A phase onset execution algorithm (b) a TFR by estimating the spectogram of the audio signal

2.4.3.2 Detection of Wheezes

The proposed tele-monitoring schemes are studied also by using wheezing sounds from a database of pre-recorded respiratory sounds. The database consisted of 18 sounds that contained more than one uninterrupted interval of wheezing. These sounds were recorded using 11 kHZ sampling rate and 8-bit depth. Due to the lack of a single standard respiratory sound database, the recordings used in our study were drawn from multiple commonly referenced Internet sources[42,43,44].

Many wheeze detection schemes[45] are based on the time frequency analysis of breath sounds. To be more specific, they make use of the short time Fourier Transform (STFT) and a set of rules related to the duration, the temporal continuity and the spectral continuity of peaks in expected frequency bands. As a result in order to evaluate the diagnostic quality of the compressed breath recordings and evaluate the accuracy of the system, we make use of whether the wheezes can be identified in the spectrogram of the breath signal. Figure 7, shows the spectrogram of the reconstructed breath sounds at the BNC, assuming that a different number of encoded samples are transmitted. It should be noted that the Wheezes can be identified in the reconstructed spectrogram when NMSE< -10 dB.

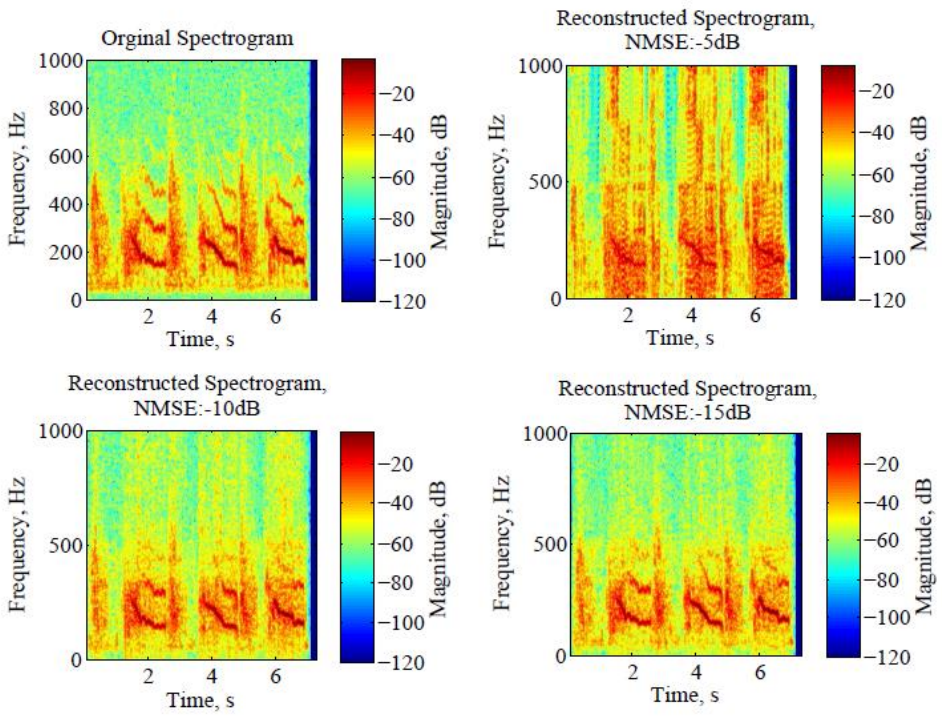


Figure 7: Spectrogram of reconstructed Breaths at the BNC

3 Clinical Modelling and Prediction

This section focus on providing a detailed review of different methods that can be used for implementing multi-scale computational model of the pulmonary system, including structure and mechanical representation, computational fluid dynamics and biological/chemical properties of the lungs. The proposed methods will be the core element of the clinical modelling and prediction block of the myAirCoach system. Furthermore , an overview of different probabilistic and data mining techniques that will be applied to the available environmental and clinical measurements for predicting the clinical state of patients will be also presented. Finally, this section presents different patient models that will be essential for representing the respiratory system in finer detail, emphasizing on the monitored parameters and the results of the clinical modelling and prediction engine.

3.1 Multi-scale computational models of the pulmonary system

3.1.1 Introduction

The study of the behaviour of any biological system (e.g., pulmonary system) must allow the analysis of all the individual components and the way they interact. Attempting to model a biological system as a whole, one misses the understanding of how the behaviour of system components at one level produces different behaviour at other levels.

The essence of multi-scale modelling does not refer to the inclusion of every biological detail, but rather in the selection of features appropriate to the level of scale being modelled. Multiscale modelling has proven crucial to our current understanding of how certain events that originate at the molecular level lead to partial or total loss of the mechanical function of the lung.

Multi-scale models of the pulmonary circulation have led to a deep understanding of the overall physiology of the lung. At each scale, it is always the question of which biological details have to be included in the model and which can be left out.

The answers to the aforementioned questions can provide useful information related to the airway hyper-responsiveness (AHR) and as a result of inflammatory factors related to asthma [AHR is a complex mechanism that reflect multiple process that manifest over multiple scales and can be used for determining several symptoms related to asthma such us: airway narrowing and mechanical impedance of the asthma[46]. This can be achieved by parameterizing these models using several techniques like spirometry, measurement of the exhaled nitric oxide, in vitro data, etc and then use them in the clinical state prediction engine, that aims to simulate their behaviour for a specific patient, taking into account, up to date measurement of environmental and physiological factors.

The main goal of section 3.1 is to provide a description of the recent advances in the development of multi-scale computational models of the pulmonary system, including structure mechanical representation and computational fluid dynamics. The remainder of this deliverable is organized as follows: In section 3.1.1, we briefly provide a definition and a description of the features of multi-scale computational lung modelling. In section 3.1.2, we present the lung structure along with different methods that have been used for structural representation of the human airways. In section 3.1.3, we describe the mechanical representation of the lung along with forward and inverse modelling methods. In section 3.1.4, we present computational fluid dynamics (CFD) as a mean to predict the fluid flow. We also present the justification of use, the benefits of their application along with the presentation of CFD methodology. Finally, the final section concludes this deliverable and presents the relation to the myAirCoach Project.

3.1.2 Multiscale Computational Model

In this section, a multiscale lung approach is introduced. A lung consists of multiple tissues. Tissues are composed of cells, cells of organelles, and organelles of macromolecules, with each step having different characteristics. Each level of integration (molecular level, cell level, tissue level, organ level) is referred to as “a scale”. An example of a multiscale model of the lung is provided in Figure 7.

Lung multi-scale modelling refers to the process of modelling all scales and the way that they interact. Thus, a key goal of multi-scale modelling is to understand how changes at one scale affect the others. To be more specific, molecular scale modelling deals with interactions between molecules and molecular compounds that play a significant role in the generation of forces and movements. The cellular scale refers to the cellular response to molecular interaction. The tissue scale deals with the sum of forces generated at the cellular level that play a significant role in the form and shape of the airways. Finally, the organ scale refers to the structural and mechanical characteristics of the whole lung along with the fluid dynamics that develop inside the airways[47].

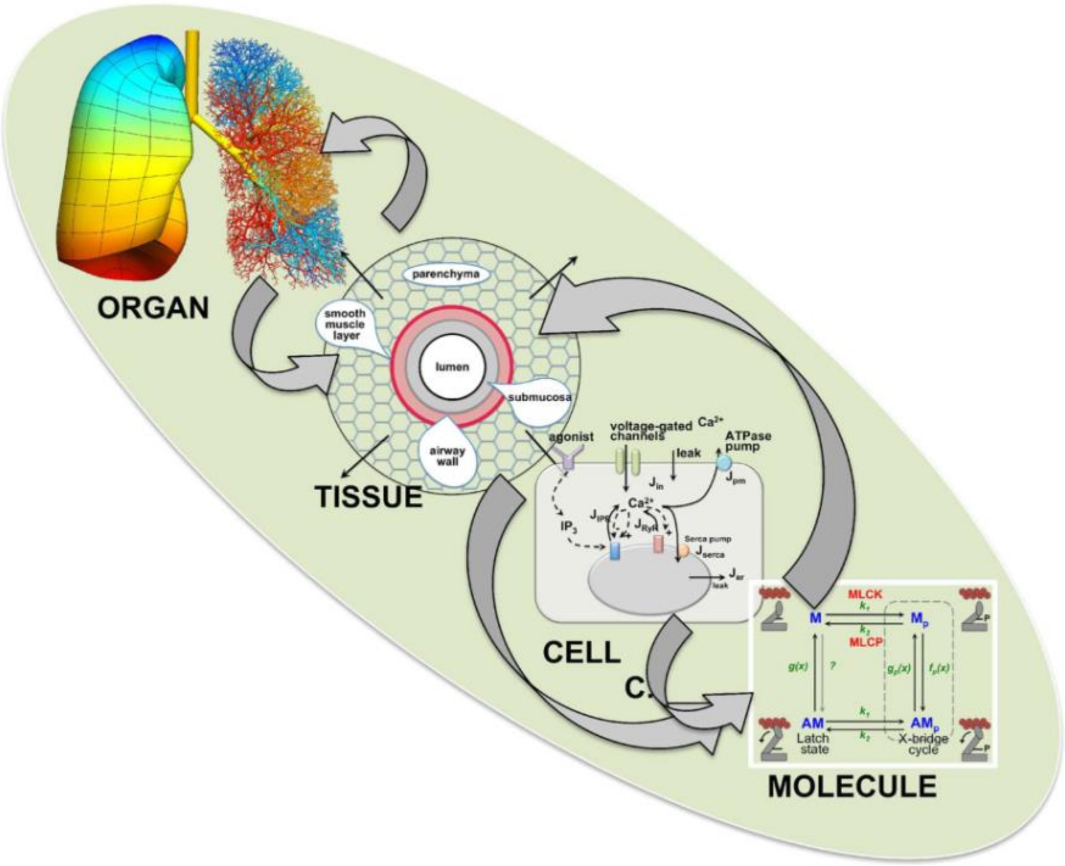


Figure 8: The four spatial scales of a multi scale lung model

3.1.3 Structural representation

In the following section the structure of the lung is analyzed, methods for representing the lung structure are described, along with methods for reconstructing the airway tree.

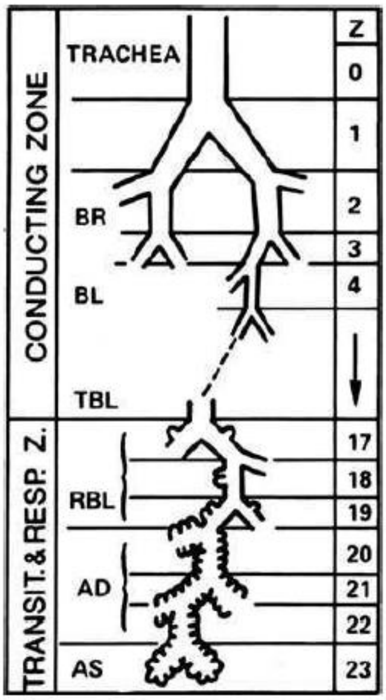


Figure 9:Lung Structure (Vbronchus(BR), bronchiole(BL), terminal bronchiole (TBL) , respiratory bronchiole(RBL), alveolar duct(AD),alveolar sac(AS).)

3.1.3.1 Lung structure

Figure 98 provides the structure of a Lung. By inspection, it can be seen that the lung is divided anatomically into two zones: i) the conductive and ii) the respiratory zones. The conducting includes the trachea and a series of branching ducts, including the main bronchi, lobar bronchi, segmental bronchi, and the terminal bronchioles. The conducting airways drive inspired air to the respiratory zone that consists of respiratory bronchioles. These contain a few budding alveoli and finally lead to the alveoli-lined acini. The conducting zone consists of the first 16 generations while transitional/respiratory zone consists of generations 17-23.

3.1.3.2 Structural representation

Early models of the lung use symmetrically branching networks to represent airways and vessels, providing generic representations of the structure. To overcome this limitation, 3D structural models are currently used. Those models are fully patient-specific and are represented by high-resolution 3D meshes of the central airways, typically including 7-9 generations of branching. Smaller airways (corresponding to lower generations) are not currently represented in these models due to the increased storage and processing requirements, determined by the size of the meshes.

1D simplified centerline model

Alternatively, simplified 1D centerline approaches can be used to represent the structure of the full airway. Tawhai et al.[48] developed a volume filling branching (VFB) algorithm, which has provided a morphometrically-realistic method to generate patient-specific airway models, used in several modelling studies. Note that the 1D branches provide only an estimation of the structure of the airway tree. In the rest of the section, we focus on techniques for the construction airways 3d model from CT images because the 3d models are used as input for computational fluid dynamic procedures.

Human airways 3D model reconstruction

The process of generating 3D models of the human airway from CT images can be divided into three stages, so called as i) image acquisition stage, ii) segmentation stage and iii) surface/volume reconstruction stage. In the image acquisition stage, the medical images (also known as 2D cross sections) are obtained from various sources (e.g., Single Photon Emission Computed Tomography (SPECT) , Positron Emission Tomography (PET) , Computed Tomography (CT) , Magnetic Resonance Imaging (MRI)).

In the segmentation stage, each 2d cross-sections that was produced by computed tomography is partitioned into a number of homogeneous segments in such way that the boundaries between homogeneous areas are revealed. The above is achieved by common algorithms based on threshold, edge detection, and region characteristics.

Finally, in the surface reconstruction phase a 3D matrix is constructed by a series of 2D cross-sections, separated by an interval distance. This matrix contains information about tissues and structures that are distinguished from one another by differences in brightness or greyscale level. The surface is then reconstructed by the concatenation of successive segmented CT-images[49].

The structural representation of the lung is used as input for the mechanical representation that is shortly described in the following subsection.

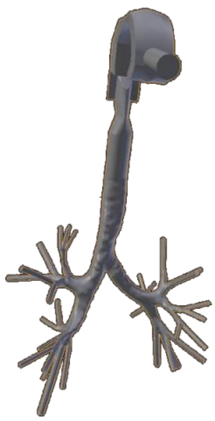


Figure 10 : A reconstructed 3d model, occurred from computational tomography images.

3.1.4 Mechanical Representation

The following section analyses the mechanical modelling of the lung and describes the forward and inverse modelling methods. Lung mechanics refers to the description of lung mechanical properties with relation to the structure of the lung. There are two types of models used for representing the mechanical function of the lung known as i) computational forward models and ii) mathematical inverse models. Computational forward models are constructed from prior knowledge about lung structure while mathematical inverse models are identified directly from experimental data. Both models provide a complementary description of the lung mechanical function as described in Figure 11.

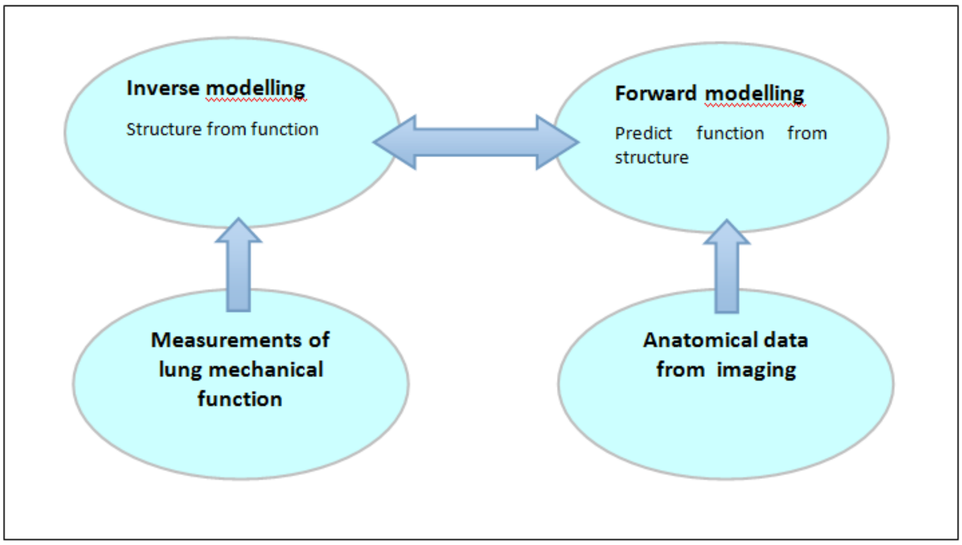


Figure 11: Synergy between forward and inverse modelling

3.1.4.1 Forward modelling

Forward modelling is used for predicting the mechanical behaviour in response to alterations in various functional and structural relationships. Typically, forward models depend on anatomy and thus involve large computational structures. These include individual airway segment lengths and diameters, as well as fluid dynamics properties, all of which can be used to simulate various physiological or pathological conditions.

There are two approaches regarding forward modelling of the lung: i) The symmetric forward model of Weibel and Gomez[50],[51] and ii) the forward model of Horsfield and coworkers[52] that accounted for branching and dimensional asymmetry. Weibel and Gomez[50,51] were the first to use a comprehensive morphologic approach to develop a forward model of the human lung. The lung model they used was divided into the conductive zone that was composed of larger airways and blood vessels, and the respiratory zone that contained respiratory bronchioles, alveolar ducts, alveoli, and the capillary network. They came to the estimation that the human lung contains approximately 300 million alveoli and that they are ventilated by an airway tree composed of an average 23 dichotomous branching generations. Weibel's symmetric model has been used extensively for computational studies of lung function. But since each airway in a given generation possesses identical dimensions, these simulations need only to take into account 23 airway generations, with 16 of them referring to the conducting zone of the bronchial tree. Weibel's model, although it provides provide a very convenient description of an average pathway in the human airway tree, it does not account for realistic asymmetry in airway branching or dimensions.

To overcome the limitation mentioned above, Horsfield and co-workers[52] proposed a model that takes into account realistic asymmetries. They counted and ordered all the airway segments based on lengths and diameters, allowing efficient calculations of mechanical properties by employing serial and parallel addition of the impedances of each airway.

3.1.4.2 Inverse modelling

Besides the forward modelling, inverse model analysis can be also used so as to provide additional interpretations of the respiratory system. The main goal of inverse modelling is to provide mechanical analogs of the respiratory system that may adequately characterize its dynamic behaviour. The inverse models typically consist of a limited number of lumped physical elements (usually varying from 4 to 6), which should ideally correspond to precise physiologic quantities such as airway resistance or tissue elastance. These parameters are then estimated by fitting the model to impedance data using various linear or nonlinear techniques, yielding functional insight into global respiratory mechanics. In recent studies, the model most frequently used for characterizing the impedance of the lungs and the respiratory system as a whole is the so-called constant phase model[53].

3.1.5 Computational Fluid Dynamics

In the following section, the definition of computational fluid dynamics (CFD) is given, and the benefits of this method are described. Computational fluid dynamics is a branch of fluid mechanics that uses numerical methods and algorithms to solve and analyse problems that involve fluid flows. Several researchers and application developers are currently working on providing software that improves the accuracy and speed of simulation scenarios such as transonic or turbulent flows.

Recently, CFD has gained significant interest in both the engineering and medical community because of its non-invasive nature. It should be noted that they have been also utilized to characterize the fluid flow in human airway models, enabling the prediction of the fluid flow characteristics when one or multiple input flow variables (such as mean inspiratory/expiratory flow rate, breathing rate, input flow turbulence, and lung pressure) are varied. Furthermore, they allow the investigation of different flow variables and fluid forces to a certain level of detail. Based on patient-specified 3D structural models, CFD enables the revealing of the nature of airflow in the trachea and bronchial tree under both physiological and pathology conditions.

3.1.5.1 Methodology

CFD Methodology includes: i) the construction of a 3d model, ii) the definition of governing equations based on the generated model iii) the process of discretizing the governing equation and the iv) numerical solution of the discretized equations.

The generation of a detailed mesh is very important for obtaining reliable computational solutions. A good quality mesh improves numerical stability and increases the likelihood of attaining a reliable solution. In the CFD community, mesh generation is also known as grid generation. Three type of meshes is typically used for representing the human airway, which are presented below:

- Regular or Body-fitted Meshes
- Structured, Block Structured, or Unstructured Meshes
- Conformal and Non-Conformal Meshes

After generating a highly detailed 3D mesh, CFD requires the definition of equations that govern the motion of a fluid. This equation is derived from the laws of the conservation of mass, momentum, and energy. The fluid motion is governed by the time-dependent three-dimensional either compressible or incompressible Navier-Stokes system of equations. However, in the case of modelling the air flow inside the airways of the lung, it is assumed that the flow is incompressible.

By inspecting Figure 12 we can see that the governing laws and transport equation for the flow variables that describe the fluid flow need to be stated and converted into a set of algebraic equations that are then numerically solved. Initially, the algebraic equations are applied to the flow domain that has been divided into smaller cells during the mesh generation. This process is known as discretization. Applying a discretization of the governing equations means that the obtained solutions correspond to discrete points in the spatial domain, which are also known as mesh points. The discretization can be achieved by applying any of the following approaches:

- Finite Difference Method
- Finite Volume Method
- Finite Element Method

These methods define the set of algebraic equation that have to be solved so as to provide details related to the fluid flow characteristics. Both direct and iterative numerical solutions methods are available in the open literature. These methods estimate the velocity field based on a coupling between the pressure and velocity. The data provided by a numerical simulation in raw form is simply representative numbers stored at locations within the spatial domain. The ability to analyse and create meaningful results from this vast array of data is a significant and important part of any CFD solution.

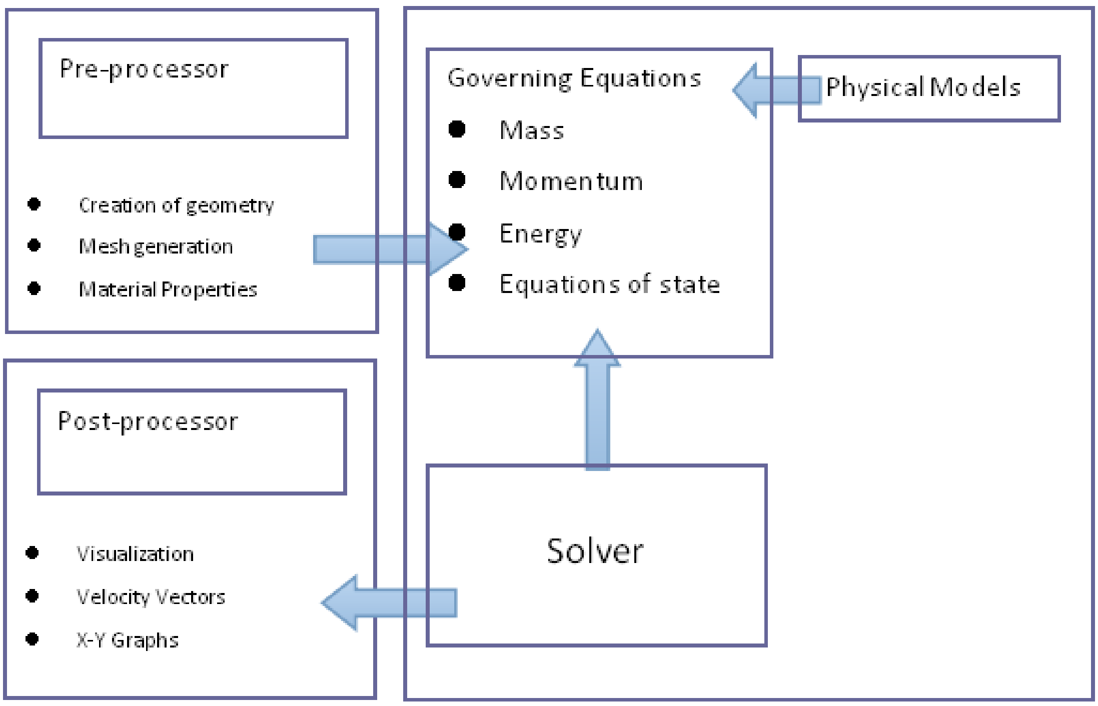


Figure 12 : Solution workflow

3.1.5.1.1 Finite Difference Method

In the finite difference method, the partial derivatives are approximated by finite difference equations at each grid nodal point. These derivatives, replaced by finite difference approximations, yield an algebraic equation for the flow solution at each grid point[49]. In principle, finite difference method can be applied to any grid. However, the method is more commonly applied to structured grids since it requires a high degree of regularity. The spacing between the grid points does not need to be uniform, but there are limits on the amount of stretching or distortion that can be imposed, to maintain accuracy.

3.1.5.1.1.1 Finite Volume Method

The first step of the FV method is to divide the computational domain into a finite number of discrete control volumes. Within each control volume, there is a centroid where the variable values are calculated and stored. Interpolation is used to determine the variable values at the finite volume surfaces in terms of the values at the finite volume centre. Suitable quadrature formulation is used to approximate the surface and volume integrals. In a control volume, the bounding surface areas of the element are the faces through which the flux moves across[49].

3.1.5.1.1.2 Finite Element Method

The solution domain is divided into a finite number of elements. The governing equation is solved for each element. The overall solution is obtained by “assembly”. Equations are multiplied by a weight function before integrated over the entire domain.

3.1.5.1.2 Numerical Solution

A system of linear or nonlinear algebraic equations is generated in the discretization process. It can be solved by several numerical methods. The complexity and size of the set of equations depend on the dimensionality and geometry of the physical problem. In this section, we present essentially two types of numerical methods: direct methods and iterative methods.

3.1.5.1.2.1 Direct Solution Methods

One of the most basic methods for solving linear systems of algebraic equations is the Gaussian elimination. The algorithm derives from the basis of the systematic reduction of large systems of equations to smaller ones.

3.1.5.1.2.2 Iterative Methods

Direct methods for example Gaussian elimination can be employed to solve any system of equations. Unfortunately most CFD problems usually result in a large system of non-linear equations. As a result, the cost of using this method is quite high as it requires a lot pre-conditioning of the matrix to prepare it for the direct method process. This fact leaves the option of employing iterative methods. In an iterative method, one guesses the solution and uses the equation to improve the solution systematically until it reaches a specified level of convergence. If the number of iterations is small in achieving convergence, an iterative solver may cost less to use than a direct method.

3.1.6 Relation to the myAirCoach Project

At the myAirCoach project, a parameterized patient-specific multi-scale computational model will be used. Both inverse and forward modelling methods will be applied. The model above will be used for computational fluid dynamics modelling and simulation so as to predict the lung behaviour and response to environmental factors that play a significant role in asthma.

3.2 Probabilistic & Data mining techniques on Sensors Signals

3.2.1 Introduction

This section refers to the design and implementation of machine learning algorithms that can be used for identifying a set of physiological related indicators from the measurements captured by the different types of sensors. A machine learning algorithm can take advantage of examples (data) to capture characteristics of interest of their unknown underlying probability distribution. Data can be seen as examples that illustrate relations between observed variables. Every instance in any dataset used by machine learning algorithms is represented using the same set of features. The features may be continuous, categorical or binary. If instances are given with known labels (the corresponding correct outputs) then the learning is called *supervised*, in contrast to *unsupervised learning,* where instances are unlabelled.

Supervised learning is one of the tasks most frequently carried out by so called Intelligent Systems. Thus, a large number of techniques have been developed based on Artificial Intelligence (Logic-based techniques, Perceptron-based techniques) and Statistics (Bayesian Networks, Instance-based techniques). Supervised machine learning is the process of learning a set of rules from instances (examples in a training set), or more generally speaking, creating a classifier that can be used to generalize from new instances. The resulting classifier is then used to assign class labels to the testing instances where the values of the predictor features are known, but the value of the class label is unknown.

The process of applying supervised ML to a real-world problem is described in Figure 12. The first step is collecting the dataset. If a requisite expert is available, then s/he could suggest which fields (attributes, features) are the most informative. If not, then the simplest method is that of “brute-force,” which means measuring everything available in the hope that the right (informative, relevant) features can be isolated. However, a dataset collected by the “brute-force” method is not directly suitable for induction. It contains in most cases noise and missing feature values, and therefore requires significant pre-processing. The second step is the data pre-processing. Depending on the circumstances, researchers have a number of methods to choose from to handle missing data[54]. The authors in [55] have recently introduced a survey of contemporary techniques for outlier (noise) detection. These researchers have identified several strengths and weaknesses of the presented schemes.

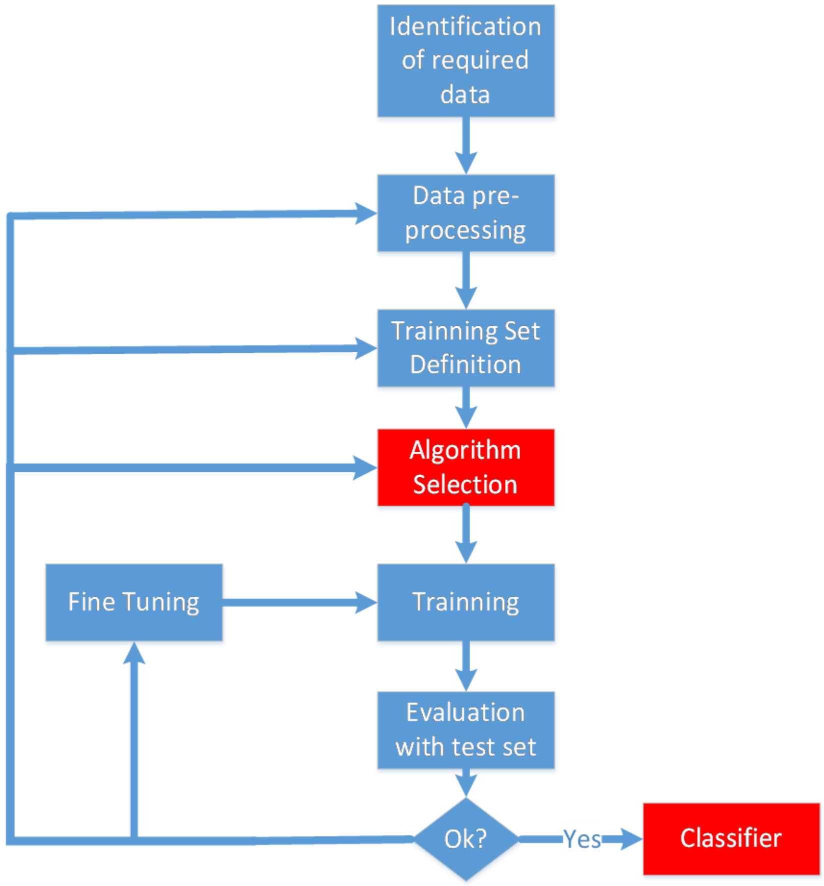


Figure 13: Supervised ML Process

Instance selection is not only used to handle noise but to cope with the infeasibility of learning from very large datasets. Therefore, instance selection in these datasets is an optimization problem that attempts to maintain the mining quality while minimizing the sample size[56]. It reduces data and enables a data mining algorithm to work effectively with very large datasets. A review of different procedures for sampling instances from a large dataset is presented in[57]. Feature subset selection is the process of identifying and removing as many irrelevant and redundant features as possible. This reduces the dimensionality of the data and enables data mining algorithms to operate faster and more effectively. The correlation between different features, in many cases influences the accuracy of supervised ML classification models. This problem can be addressed by constructing new features from the basic feature set. This technique is called feature construction/transformation. These newly generated features may lead to the creation of more concise and accurate classifiers. In addition, the discovery of meaningful features contributes to better comprehensibility of the produced classifier, and a better understanding of the learned concept.

The choice of which specific learning algorithm we should use is the more critical step of the procedure. The classifier's evaluation is most often based on prediction accuracy (the percentage of correct prediction divided by the total number of predictions).In order to evaluate the classifier's accuracy, the two-thirds of the training set is used for training and the other third for estimating performance. Alternatively, the training set can be divided into mutually exclusive and equal-sized subsets and for each subset the classifier is trained on the union of all the other subsets. The error rate for the classifier is then estimated by the average of the error rate of each subset. The rest of this report describes various classification algorithms and the recent attempt for improving classification. The advantages and disadvantages of the presented methods are summarized in Table 8.

Algorithm	Predictive Accuracy	Fitting Speed	Prediction Speed	Memory Usage	Easy to Interpret	Handles Categorical Predictors
Decision Trees	Medium	Fast	Fast	Low	Yes	Yes
SVM	High	Medium	*	*	*	No
Naïve Bayes	Medium	**	**	**	Yes	Yes
Nearest Neighbor	***	Fast***	Medium	High	No	Yes***
Discriminant Analysis	****	Fast	Fast	Low	Yes	No

Table 8: Advantages and disadvantages of ML algorithms

* SVM prediction speed and memory usage are good if there are few support vectors, but can be poor if there are many support vectors. When you use a kernel function, it can be difficult to interpret how SVM classifies data, though the default linear scheme is easy to interpret.

** Naive Bayes speed and memory usage are good for simple distributions, but can be poor for kernel distributions and large data sets.

*** Nearest Neighbor usually has good predictions in low dimensions, but can have poor predictions in high dimensions. For linear search, Nearest Neighbor does not perform any fitting. For *k*d-trees, Nearest Neighbor does perform fitting. Nearest Neighbor can have either continuous or categorical predictors, but not both.

**** — Discriminant Analysis is accurate when the modelling assumptions are satisfied (multivariate normal by class). Otherwise, the predictive accuracy varies.

3.2.2 Logic Based Algorithms

In this section we will concentrate on two groups of logical (symbolic) learning methods: decision trees and rule-based classifiers.

3.2.2.1 Decision trees

Decision trees are trees that classify instances by sorting them based on feature values. Each node in a decision tree represents a feature in an instance to be classified, and each branch represents a value that the node can assume. Instances are classified starting at the root node and sorted based on their feature values. The problem of constructing optimal binary decision trees is an NP-complete problem and thus theoreticians have searched for efficient *heuristics* for constructing near-optimal decision trees. The feature that best divides the training data would be the root node of the tree. The same procedure is then repeated on each partition of the divided data, creating sub-trees until the training data is divided into subsets of the same class. There are numerous methods for finding the feature that best divides the training data but a majority of studies have concluded that there is no single best method[58]. Comparison of individual methods may still be important when deciding which metric should be used in a particular dataset.

One of the most useful characteristics of decision trees is their comprehensibility. People can easily understand why a decision tree classifies an instance as belonging to a specific class. Since a decision tree constitutes a hierarchy of tests, an unknown feature value during classification is usually dealt with by passing the example down all branches of the node where the unknown feature value was detected, and each branch outputs a class distribution. The output is a combination of the different class distributions that sum to 1. The assumption made in the decision trees is that instances belonging to different classes have different values in at least one of their features.

3.2.2.2 Rule-based classifiers

The authors in[59], stated that decision trees can be translated into a set of rules by creating a separate rule for each path from the root to a leaf in the tree. However, rules can also be directly induced from training data using a variety of rule-based algorithms. An overview of existing works in rule-based methods can be found in [60]. The goal is to construct the smallest rule-set that is consistent with the training data. A large number of learned rules is usually a sign that the learning algorithm is attempting to "remember" the training set, instead of discovering the assumptions that govern it. A separate-and-conquer algorithm search for a rule that explains a part of its training instances separates these instances and recursively conquers the remaining instances by learning more rules, until no instances remain.

The most useful characteristic of rule-based classifiers is their comprehensibility. In addition, even though some rule-based classifiers can deal with numerical features, some experts propose these features should be discretized before induction, so as to reduce training time and increase classification accuracy[60]. Classification accuracy of rule learning algorithms can be improved by combining features (such as in decision trees) using the background knowledge of the user[61] or automatic feature construction algorithms[62].

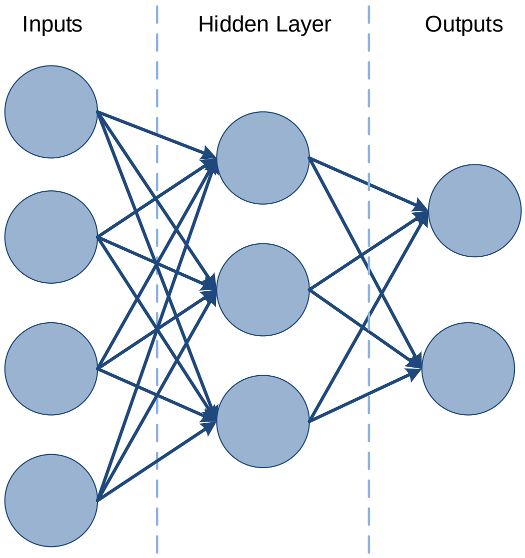


Figure 14: Feed forward ANN

3.2.3 Perceptron-based techniques

Other well-known classification algorithms are based on the notion of perceptron. Perceptron can be briefly described as: If $x1$ through xn are input feature values and w1 through wn are connection weights/prediction vector (typically real numbers in the interval [−1, 1]), then perceptron computes the sum of weighted inputs and the output goes through an adjustable threshold: if the sum is above threshold, output is 1; else it is 0. The most common way the perceptron algorithm is used for learning from a batch of training instances is to run the algorithm repeatedly through the training set until it finds a prediction vector which is correct on all of the training set. This prediction rule is then used for predicting the labels on the test set Perceptrons can only classify linearly separable sets of instances. If a straight line or plane an be drawn to separate the input instances into their correct categories, input instances are linearly separable and the perceptron will find the solution. If the instances are not linearly separable learning will never reach a point where all instances are classified properly. Artificial Neural Networks have been created to try to solve this problem.

The authors in[63], provided an overview of existing work in Artificial Neural Networks (ANNs). A multi-layer neural network consists of large number of units (neurons) joined together in a pattern of connections. Units in a net are usually segregated into three classes: input units, which receive information to be processed; output units, where the results of the processing are found; and units in between known as hidden units. Feed-forward ANNs (Figure 14) allow signals to travel one way only, from input to output. Generally, properly determining the size of the hidden layer is a problem, because an underestimate of the number of neurons can lead to poor approximation and generalization capabilities, while excessive nodes can result in over fitting and eventually make the search for the global optimum more difficult[64]. The authors in[65] also studied the minimum amount of neurons and the number of instances necessary to program a given task into feed-forward neural networks.

ANNs have been applied to many real-world problems but still, their most striking is advantage is their lack of ability to reason about their output in a way that can be effectively communicated. For this reason many researchers have tried to address the issue of improving the comprehensibility of neural networks, where the most attractive solution is to extract symbolic rules from trained neural networks. Setiono and Loew [66] divided the activation values of relevant hidden units into two subintervals and then found the set of relevant connections of those relevant units to construct rules. More references can be found in[67], an excellent survey. However, it is also worth mentioning that Roy[68] identified the conflict between the idea of rule extraction and traditional connectionism. In detail, the idea of rule extraction from a neural network involves certain procedures, specifically the reading of parameters from a network, which is not allowed by the traditional connectionist framework that these neural networks are based on.

3.2.4 Statistical learning algorithms

Conversely to ANNs, statistical approaches are characterized by having an explicit underlying probability model, which provides a probability that an instance belongs in each class, rather than simply a classification. Under this category of classification algorithms, one can find Bayesian networks and instance-based methods. A Bayesian

Network (BN) is a graphical model for probability relationships among a set of variables (features). The Bayesian network structure *S* is a directed acyclic graph (DAG) and the nodes in *S* are in one-to-one correspondence with the features *X*. The arcs represent casual influences among the features while the *lack* of possible arcs in *S* encodes conditional independencies. Moreover, a feature (node) is conditionally independent from its non-descendants given its parents.

Typically, the task of learning a Bayesian network can be divided into two subtasks: initially, the learning of the DAG structure of the network, and then the determination of its parameters. Probabilistic parameters are encoded into a set of tables, one for each variable, in the form of local conditional distributions of a variable given its parents. Given the independences encoded into the network, the joint distribution can be reconstructed by simply multiplying these tables. Within the general framework of inducing Bayesian networks, there are two scenarios: known structure and unknown structure.

In spite of the remarkable power of Bayesian Networks, they have an inherent limitation. This is the computational difficulty of exploring a previously unknown network. Given a problem described by *n* features, the number of possible structure hypotheses is more than exponential in *n*. If the structure is unknown, one approach is to introduce a scoring function (or a score) that evaluates the “fitness” of networks with respect to the training data, and then to search for the best network according to this score. Several researchers have shown experimentally that the selection of a single good hypothesis using greedy search often yields accurate predictions [68].

3.2.5 Support Vector Machines

Support Vector Machines (SVMs) are the newest supervised machine learning technique. An excellent survey of SVMs can be found in[69]. SVMs revolve around the notion of a “margin”—either side of a hyperplane that separates two data classes. Maximizing the margin and thereby creating the largest possible distance between the separating hyperplane and the instances on either side of it has been proven to reduce an upper bound on the expected generalisation error. In the case of linearly separable data, once the optimum separating hyperplane is found, data points that lie on its margin are known as support vector points and the solution is represented as a linear combination of only these points. Other data points are ignored. Therefore, the model complexity of an SVM is unaffected by the number of features encountered in the training data (the number of support vectors selected by the SVM learning algorithm is usually small). For this reason, SVMs are well suited to deal with learning tasks where the number of features is large with respect to the number of training instances. Even though the maximum margin allows the SVM to select among multiple candidate hyperplanes, for many datasets, the SVM may not be able to find any separating hyperplane at all because the data contains misclassified instances. The problem can be addressed by using a soft margin that accepts some misclassifications of the training instances (Veropoulos et al.[70]). Nevertheless, most real-world problems involve non-separable data for which no hyperplane exists that successfully separates the positive from negative instances in the training set. One solution to the inseparability problem is to map the data onto a higher-dimensional space and define a separating hyperplane there. This higher-dimensional space is called the feature space, as opposed to the input space occupied by the training instances.

Training the SVM is done by solving *N*th dimensional QP problem, where *N* is the number of samples in the training dataset. Solving this problem in standard QP methods involves large matrix operations, as well as time-consuming numerical computations, and is mostly very slow and impractical for large problems. Sequential Minimal Optimization (SMO) is a simple algorithm that can, relatively quickly, solve the SVM QP problem without any extra matrix storage and without using numerical QP optimization steps at all. SMO decomposes the overall QP problem into QP sub-problems. Keerthi and Gilbert[71] suggested two modified versions of SMO that are significantly faster than the original SMO in most situations.
Finally, the training optimization problem of the SVM necessarily reaches a global minimum, and avoids ending in a local minimum, which may happen in other search algorithms such as neural networks. However, the SVM methods are binary, thus in the case of multiclass problem one must reduce the problem to a set of multiple binary classification problems. Discrete data presents another problem; although with suitable rescaling good results can be obtained.

3.2.6 Utilization of Data Mining Techniques in Medical Diagnosis of Asthma

Data mining has been widely used in healthcare systems and has been proved to be a very important field of computer science with application in diagnosis and in deeper understanding of medical data. Various healthcare systems are attempting to use available data mining techniques in order to discover hidden relationships in huge data available within clinical databases. They are focusing on exploiting and converting these relationships to valuable information that can be used by physicians and other clinical decision markers for identifying risks associated with diseases and predicting accurately potential upcoming dangerous events (e.g., asthma exacerbations). The general idea of several data mining techniques is to learn from what was happened in past examples and model oftentimes nonlinear relationships between independent and dependent variables. The resulting model provides formalized knowledge and allows the prediction of an outcome.
The authors in[71] focus on providing a medical system for asthma diagnosis. They investigated the performance of several efficient machine learning algorithms, such as: k – nearest neighbours, random forest, and support vector machine. The study was conducted on a dataset consisting of 169 asthmatics and 85 non - asthmatics visiting the Imam Khomeini and Masseeh Daneshvari Hospitals of Tehran. The proposed method that achieved the highest accuracy is based on the k- nearest algorithm together with pre-processing based on the Relief – F strategy and the Cross Fold data sampling.

A similar study was carried out by the authors in[72]. The study dataset was based on daily self-reports submitted by 26 adult asthma patients during home tele-monitoring consisting of 7001 records. Two classification algorithms were employed for building predictive models: naïve Bayesian classifier and support vector machines. Using a 7-day window, a support vector machine was able to predict asthma exacerbation to occur on the day 8 with the accuracy of 0.80, sensitivity of 0.84 and specificity of 0.80. Their study showed that data mining methods have significant potential in developing individualized decision support for chronic disease tele-monitoring systems

In order to diagnose the disease asthma with the use of probabilistic and data mining techniques, the authors in [73] proposed the use of auto-associative memory neural networks and Bayesian networks. They presented a comparative study of these algorithms by gathering the clinical signs and symptoms of asthma patients from various resources. Based on the analysis of such data, they concluded that the Auto-associative memory neural networks are more efficient and accurate for identifying the disease.

Similarly, to the previous studies, common machine learning techniques with an expert-built Bayesian Network have been applied in[74,75] , to determine eligibility for asthma guidelines in paediatric emergency department patients. The authors, created an artificial neural network, a support vector machine, a Gaussian process, and a learned Bayesian network to compare each method's ability to detect patients eligible for asthma guidelines. The study was performed at the Vanderbilt Children's Hospital ED, including 4,023 patient of age 2-18 years old, were only 9.6% of them were diagnosed with asthma. The data were randomly split into a training set (n=3017) and test set (n=1006) for analysis. All four evaluated machine learning methods achieved high accuracy, while the automatically created Bayesian network performed similarly to the expert-built network.

3.2.7 Relation to MyAirCoach

The design and implementation of signal processing algorithms that compute the value of a set of physiological related indicators on the basis of measurements captured by the different types of sensors requires the specification of informative indicators that will be specified based on state of the art analysis and the experience of participating experts. A combination of supervised learning and knowledge based approaches as those described above, will be used to fuse the information collected by the different types of sensors and the computational models in order to assess the risk factors defined in WP2. The use of Support Vector Machines and Spectral Clustering approaches that are seen to be efficient in similar cases will be investigated. Moreover, a data fusion model will be designed to allow for automatic detection, aggregation and combination of data from multiple sources (subjective/self-reported data, physiological data, behavioural activity data). The presented methods will be extended to ensure robustness, reliability, extended coverage in space and time, great data space dimension, low ambiguity and resiliency to information explosion.

3.3 Digital Representation of Patient Models and Electronic Health Records

A patient model is an explicit representation of the properties of an individual patient in regards to her/his health condition and how all this information can be used to reason about the needs, preferences or future behaviour of this patient and the evolution of her/his health condition. As the medical systems are continuously enhanced with modern information technologies patient models are becoming a crucial component of healthcare and they are holding the promise to encapsulate the majority of health factors in order to be used for the personalization of healthcare and therefore for the optimization of its results and efficiency. Electronic Health Records can be considered a specific case of patient models where the contained medical parameters are primary used by healthcare personnel in their raw format without any consideration for processing and automated analytics.

In order to clearly describe the overlaps and differentiating characteristics of patients' models and electronic health records a simple example from respiratory medicine can be considered. Assume an electronic health record containing the peak exhales air flow measurements of patients as they are measured by patients themselves of their responsible doctors. These measurements can be used by both doctors and patients for the selection of the appropriate medication. Patient models on the other hand should include a much wider spectrum of patient information which should be utilised for the personalised annotation of the raw measurements and the automated extraction of valuable conclusions related to the health condition of the patient. Furthermore, personalised patient models can form the basis of prediction capabilities that may indicate a foreseen risk and be used for the prevention of future situations that may jeopardise the health of the specific patient.

There can be a wide variety of model types which are discriminated along the following four dimensions:

- What is modelled: Average patient (generalised systems designed to cover the majority of users with the maximum accuracy) or Individual patient (tailored to the specific user)
- Source of modelling information: Model constructed explicitly by the user (in this case the doctor or medical researcher) or Model abstracted by the system on the basis of the user's behaviour and collected data
- Time sensitivity of the model: Short-term (highly specific information) or Longer-term (more general information)
- Update methods: Static model or Dynamic model adapting to the continuous changes of the patient's characteristics.

The existing standards related to User Modelling provide guidance to ICT and non-ICT product and service designers on issues and design practices related to Human Factors. They aim to help designers and developers to maximize the level of usability of products and services by providing a comprehensive set of Human Factors design guidelines and meta-models in machine-readable formats.

Based on the following review of available standards and approaches, the model representation within the myAirCoach system will be based on the EN13606, and more specifically on the openEHR standard. Furthermore, all the following described representation approaches can offer fundamental insights for the adaptation and extension of openEHR towards the goals and functional requirements of the myAirCoach system. This standard is a reference model for building Clinical- and User

Models using archetypes, and it is supported by an open source community and a variety of tools. The standard describes the two level modelling approaches to separate (clinical) knowledge by using archetypes, from software. These archetypes are shared and open source model.

Figure 15 presents an indicative example of the archetype for Pulmonary Function Testing presented as a mind map. Specific use for eternal vocabularies like Snomed, ICD (9 or 10) and Loinc are well covered by this reference architecture.

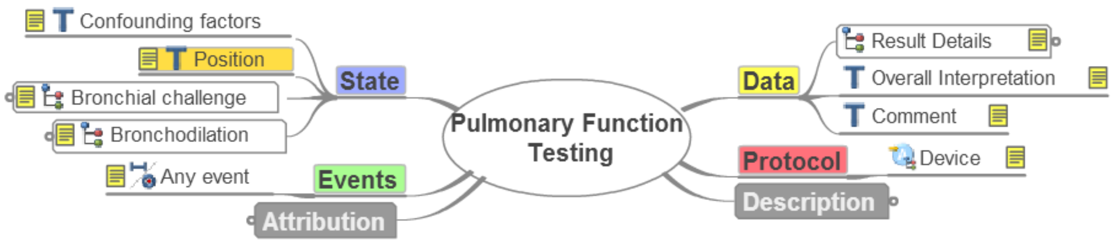


Figure 15: Archetype of the clinical model for Pulmonary Function Testing

3.3.1 CEN/ISO EN13606: Electronic Health Record Communication

The CEN/ISO EN13606[76] is a European norm from the European Committee for Standardization (CEN) also approved as an international ISO standard. It is designed to achieve semantic interoperability in the electronic health record communication.

The overall goal of the CEN/ISO 13606 standard is to define a rigorous and stable information architecture for communicating part or all of the electronic health record (EHR) of a single subject of care (patient) between EHR systems, or between EHR systems and a centralized EHR data repository. It may also be used for EHR communication between an EHR system or repository and clinical applications or middleware components (such as decision support components) that need to access or provide EHR data, or as the representation of EHR data within a distributed (federated) record system.

To achieve this objective, CEN/ISO 13606 follows an innovative Dual Model architecture. The Dual Model architecture defines a clear separation between information and knowledge. The former is structured through a Reference Model that contains the basic entities for representing any information of the EHR. The latter is based on archetypes, which are formal definitions of clinical concepts, such as discharge report, clinical measurements or family history, in the form of structured and constrained combinations of the entities of a Reference Model. It provides a semantic meaning to a Reference Model structure.

The interaction of the Reference Model (to store data) and the Archetype Model (to semantically describe those data structures) provides an unseen capability of evolution to the information systems. Knowledge (archetypes) will change in the future, but data will remain untouched.

Potential relevance to Patient Modelling of MyAirCoach:
• It is selected as the basic representation of the myAirCoach models and EHR • It specifies a healthcare classification system including a set of classes that define the building blocks of EHRs. • It is structured around archetypes that represent particular clinical concepts.

3.3.2 OpenEHR : Specification Program

The main work of the openEHR Foundation[77] is performed by four 'programs' which respectively focus on specifications, clinical modelling, software, and localisation. The Specifications Program defines the formal models and languages defining openEHR data, openEHR content models (archetypes and templates) and openEHR services and APIs. These specifications are published and used in their own right and also underpin the Clinical Modelling Program (for which they provide the language of archetypes) and the Software Program (for which they provide schemas and interface definitions for software).

The goals of the Specification Program include:

- quality in health information: to enable data quality, validity, reliability, consistency and currency of clinical data across the data lifecycle from creation to archival, and across enterprises and sectors;
- support current technology: to actively support widely used ICT technologies e.g. major programming languages and frameworks;
- standards connections: to provide means for the specifications to be useful to users of related de jure standards, e.g. by providing additional transformation or mapping specifications and/or implementation guides;
- manage impact of change: to ensure the preservation of validity of clinical data created according to previous releases of the openEHR specifications.

Potential relevance to Patient Modelling of MyAirCoach:
• The open source approach of the OpenEHR framework promises a fast and easy integration within the myAirCoach system. • The work done in all the programs of the foundation (specifications, clinical modelling, software, and localisation) can provide insights and useful tools for the development of the myAirCoach system.

3.3.3 ISO 13120:2013: Context representation in healthcare classification systems

The main purpose of ISO 13120:2013[78] is to formally represent the content and hierarchical structure of healthcare classification systems in a markup language for the safe exchange and distribution of data and structure between organizations and dissimilar software products.

The scope of healthcare classifications systems covered in ISO 13120:2013 encompasses terminologies, and is constrained to traditional paper-based systems (like ICD-10) and systems built according to categorical structures and a cross thesaurus (like ICNP). ISO 13120:2013 is intended for representation of healthcare classification systems in which classes have textual definitions, hierarchical ordering, named hierarchical levels (such as "chapter", "section"), inclusion- and exclusion criteria, and codes. It is not intended to cover any formal representation, either for definition or composition, of concepts, or for specification of classification rules. Systems with such formal specifications can at best be partially represented using ISO 13120:2013, and are hence out of scope.

Potential relevance to Patient Modelling of MyAirCoach:
• It specifies a healthcare classification system that among others, it covers asthma related medical terminologies.

3.3.4 ClaML: Classification Markup Language for Health Informatics

The Classification Mark-up Language (ClaML)[79] is an XML based format designed specifically for classifications. It was accepted in 2007 as European norm (CEN/TS 14463). Additional details on the specification and use can be found in the respective CEN document (www.cen.eu), it is indicative the WHO decided to use this format to share its classifications such as the ICD.

This format allows the capture of information on the classification hierarchy (i.e. parent child relations). The level of the current representation's granularity allows the identification of different rubrics within the classification categories.

The main XML elements used in this format are the following:

- The main element (root element) is **"ClaML"** for the definition of the classification as such.
- The element **"Class"** is used for the definition and structuring of the chapters, groups and categories. The classes define their parent and children classes by using **"SuperClass"** and **"SubClass"** elements so that the hierarchical representation is captured.
- Each **"Class"** may have one or more **"Rubric**s**"** which are used to define different aspects of that class. For example, title, inclusions, exclusions are separate Rubrics under a "Class" element.
- A "**Reference"** tag can be used to identify the cross references within the classification.
- The element **"ModifierClass"** and **"Modifier"** are used for the definition and integration of sub-classifications (Modifiers), in the ICD-10 as list of codes for the fourth and possible fifth character of the codes.

Potential relevance to Patient Modelling of MyAirCoach:
• It specifies an XML data format specification for the classification and description of medical diagnosis and procedures that can contribute significantly for the representation of both the asthma condition of patients and the suggested treatment approaches.

3.3.5 ICD: International Classification of Diseases

Following the successful and wide use of ICD-9, ICD-10[80] was endorsed by the Forty-third World Health Assembly in May 1990 and came into use in WHO Member States as from 1994. The classification is the latest in a series which has its origins in the 1850s. The first edition, known as the International List of Causes of Death, was adopted by the International Statistical Institute in 1893. WHO took over the responsibility for the ICD at its creation in 1948 when the Sixth Revision, which included causes of morbidity for the first time, was published. The World Health Assembly adopted in 1967 the WHO Nomenclature Regulations that stipulate use of ICD in its most current revision for mortality and morbidity statistics by all Member States.

The ICD is the international standard diagnostic classification for all general epidemiological, many health management purposes and clinical use. These include the analysis of the general health situation of population groups and monitoring of the incidence and prevalence of diseases and other health problems in relation to other variables such as the characteristics and circumstances of the individuals affected, reimbursement, resource allocation, quality and guidelines.

It is used to classify diseases and other health problems recorded on many types of health and vital records including death certificates and health records. In addition to enabling the storage and retrieval of diagnostic information for clinical, epidemiological and quality purposes, these records also provide the basis for the compilation of national mortality and morbidity statistics by WHO Member States.

Potential relevance to Patient Modelling of MyAirCoach:
• It provides classifications of diseases and other health problems, providing the framework for the accurate representation of asthma patients in terms of comorbidities and related diseases.

3.3.6 ICF: International Classification of Functioning, Disability and Health

The International Classification of Functioning, Disability and Health, known more commonly as ICF[81], is a classification of health and health-related domains. These domains are classified from body, individual and societal perspectives by means of two lists: a list of body functions and structure, and a list of domains of activity and participation. Since an individual’s functioning and disability occurs in a context, the ICF also includes a list of environmental factors.

The ICF puts the notions of 'health' and 'disability' in a new light. It acknowledges that every human being can experience a decrement in health and thereby experience some degree of disability. Disability is not something that only happens to a minority of humanity. The ICF thus 'mainstreams' the experience of disability and recognises it as a universal human experience. By shifting the focus from cause to impact it places all health conditions on an equal footing allowing them to be compared using a common metric – the ruler of health and disability. Furthermore ICF takes into account the social aspects of disability and does not see disability only as a 'medical' or 'biological' dysfunction. By including Contextual Factors, in which environmental factors are listed ICF allows to records the impact of the environment on the person's functioning.

Potential relevance to Patient Modelling of MyAirCoach:
• Provides a list of domains of activities that can be used for the more accurate representation of patient activity levels. • Includes a list of environmental factors as they will be assessed and studied in the myAirCoach project

3.3.7 EMMA: Extensible MultiModal Annotation Markup Language

EMMA is part of a set of specifications for multimodal systems endorsed by the W3C through their recommendation in 2009[82]; and proposed for the W3C Multimodal Interaction Framework[83].

An XML markup language is provided by EMMA in order to contain and annotate the semantic interpretation of user input gained from various input channels. Annotations and interpretations of user input are supported by a set of elements and attributes.

This standard data interchange format is primarily to be used between the components of a multimodal system, especially those responsible for interpretation and integration of user's input.

Generally, an EMMA document comprises

- instance data: application specific input information
- data model: usually defined by the application including content of an instance and constraints on the structure
- meta-data: annotations linked to the instance data; values are added at runtime

Potential relevance to Patient Modelling of MyAirCoach:
• It can be used to represent information automatically extracted from a user's input or automated measurements by an interpretation component.

4 Personal Guidance System and the MyAirCoach Virtual Community Platform

This section is devoted to the description of the a selection of methods that help for the design and implementation of the myAirCoach Personal Guidance System. In the first part special focus on the information visualization schemes that will be utilised to present the information efficiently and effectively to all the user groups and for all the platform interfaces foreseen by the project. The following sections focus on the mobile and cloud based interfaces that allow patients to control their health status. The existing cross-platform sensing infrastructures are then presented outlining the basic architecture for the collection of measurements and finally a review of digital tele-monitoring self-management programs for people with chronic diseases is presented.

4.1 Visualization Tools for Asthma Related Personalized Systems

As technological innovation reaches most areas of modern health care, medical institutions are faced with the challenge to manage far greater volumes of information, that provide a more accurate assessment of both the status of patients and of the healthcare system as a whole[84,85]. This highly accurate information environment promises to accelerate clinical research and generate new clinical knowledge despite the significant difficulties that it introduces. However, and despite the substantial evidence showing the benefits of modern digital patient technologies, healthcare providers often report modest improvements in their ability to make better decisions by using more comprehensive clinical information[86],[87].

The large volume and high complexity of clinical data now being captured for each patient poses many challenges and is the main reason behind the inefficiency in the application of novel medical approaches[88], underlining the ineffectiveness of traditional approaches to deal with the exploding increase of Big Data and present the extracted knowledge in a comprehensive manner. Big Data have been defined as large datasets from a variety of sources and data types that cannot be managed or processed using standard software tools within a reasonable time[89]. The computational difficulties of high volume, variety and velocity of these data sets are at the same time their great advantage as they can allow the discovery of new insights or new forms of value which could not be found in smaller datasets[90],[91].

Big data analytics and visual analytics are the two main tools for the understanding of large amounts of clinical data, with a number of interactive interfaces being developed so as to unlock the value of large-scale clinical databases for a wide variety of different tasks. The discipline of Visual Analytics approaches focuses on this issue by developing innovative approaches for the support of human cognition by combining and enhancing data analysis and visualization approaches[92],[93]. Visual analytics is an emerging discipline that has shown significant promise in addressing many of these information overload challenges[94].

Both Big Data and Visual Analytics can contribute significantly to improving the quality of health care and stimulating clinical research by using de-identified health data and pragmatic clinical trials[95] reducing in this way the need for highly expensive Randomized Controlled Trials (RCTs)[96]. Furthermore, Big Data combined with Visual

Analytics holds the promise to improving the delivery of health services and change the position of patients in the healthcare environment by increasing their knowledge and understanding and promote self-care approaches on the basis of accurate and continuous measurements in the daily living environment.

The following paragraphs present some of the most recent approaches for health visualization approaches and tools as found in available software tools and scientific bibliography together with a preliminary analysis of their relation to the myAirCoach project and how they can be used and adapted for the purposes of the current project.

4.1.1 AsthmaMD visualisation tools and interfaces

AsthmaMD is a modern mobile application targeting the disease of asthma and it is highly based on the informative visualisation of asthma related parameters and the creation of intuitive interfaces that can help patients replace the paper based approaches of the past[97]. The following figure summarises some indicative functionalities of AsthmaMD including Visualisation of disease severity (a) and adherence. Furthermore the application provides high intuitive interfaces for the creation of reminders(c), the logging in personalised asthma journals (d) and action plans (e). Obviously AsthmaMD is highly relevant to the goals and objectives of the MyAirCoach mobile platform, and especially with the foreseen user interface components. Even if the foreseen system of MyAirCoach will be enhanced with modelling and prediction capabilities and will be also support the interactions of a wider community of patients and healthcare professionals, the visualisation approaches of AsthmaMD can offer significant help for the initial design of the system, and important conclusions can be drawn by the experience of AsthmaMD. Furthermore, the public comments and feedback of the AsthmaMD application will be a valuable asset for the development of MyAirCoach.

Figure 16: Visualization approaches of the AsthmaMD application.

4.1.2 AsthmaHealth visualisation tools and interfaces

Powered by Apple's new ResearchKit, this mobile application offers a variety of functionalities and intuitive visualisation approaches aiming to help asthma patients understand their health condition and follow their treatment through the optimal and most efficient manner[98]. AsthmaHealth is another application that can offer important insights for the development of the MyAirCoach user interfaces, towards the increased usability of the final system and the effective and efficient management of the disease by patients themselves. Similarly to the previously presented mobile application, AsthmaHealth overlaps with only a portion of the MyAirCoach capabilities but the experience of this app, as it is expressed in the finally selected interfaces and also in the public user comments , can offer valuable insights for the future development of MyAirCoach and the study of it visualisation methodologies.

Figure 17: Visualization approaches of the AsthmaHealth application.

4.1.3 Understanding variations in paediatric asthma care

In this research paper a novel visualisation approach is presented aiming to the understanding of asthma in children and on the basis of 5784 paediatric asthma emergency department patients[99]. The system prototype was implemented with Gephi for rapid iterations, feedback, and refinement[100] and by using a data-driven document (D3) approach[101] On the backend, a python-based web server was used to support a portable database containing patient visits and care histories.

Even though the propose system is implemented as a browser based visual analytic tool its interactive nature and the design organisation are going to offer significant insights towards the functionalities of the myAirCoach system especially for the support of researches and healthcare professionals. The above adopted presentation of correlations through the connection of nodes can be also used for the understanding of asthma symptoms and their informative correlation with physiological measurements. It is important to underline that the myAirCoach system is aiming enhance and extend the medical record of patients with important environmental and lifestyle parameters allowing in this way the understanding of asthma risk factors and how they affect the patient condition. Finally, the filtering bars of the above system can be also used in the case of myAirCoach in order to allow researchers to focus on a specific group of patients and doctors to focus on previous incidents that resemble the characteristics of their patient.

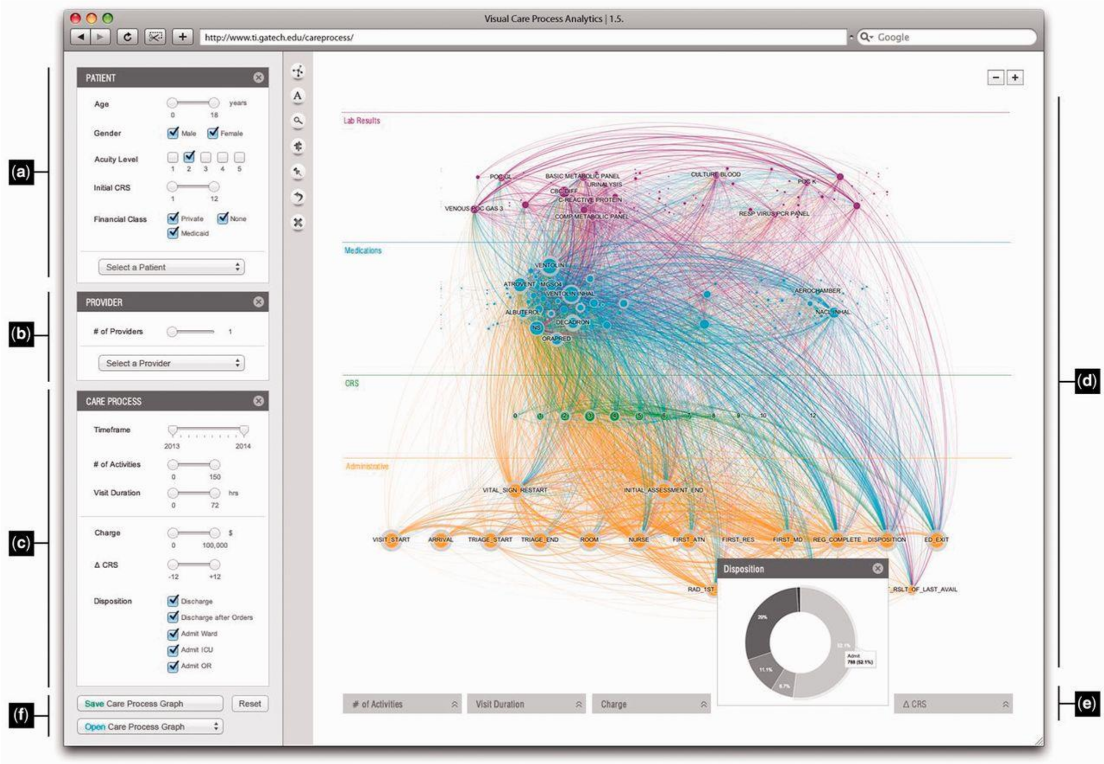


Figure 18: User Interface and Visualization Approach for the study of paediatric asthma care

The proposed tool is composed bya filter pane, consisting of (A) patient (e.g., age, sex, race), (B) provider, and (C) care process filter characteristics (e.g., visit duration, charge, disposition), and (D) a main visualization pane containing a time-ordered semantic substrate representation with zoom + pan, search, label on/off, and edge on/off controls. A collection of analytical tools including care process outcome summary charts (disposition distribution shown here) are also provided in (E). Care of patients with an ESI of 2 is coloured, while other patients' care activities and processes are greyed out.

4.1.4 Big data and visual analytics in anaesthesia and health care

This paper presents the visualisation approaches used in the health care environment and takes the first steps toward the formulation of a universal methodology for the design of such environments[102]. Even though the current study focuses on the visualisation approaches that support healthcare personnel in general and specifically medical researchers, the visualisation approaches presented can be used for the design of the Electronic Health Records and its presentation to both doctors and patients themselves. The time oriented visualization approach of Figure 19 can be adopted for the presentation of not only the patient's medical history but also for the presentation of the measurements of the sensors that will be integrated with the MyAirCoach system. The statistically oriented view of Figure 20 is also a useful starting point for the development of analytics tools that will be implemented by the final system, aiming to support scientific researchers to understand and use the collected data, doctors to use the patients history and optimise the suggested treatment, hospital administrator to understand the inefficiencies in their organisation structures and more importantly patients to improve their health through the understanding of the current state of their condition and the effects of their treatments for its improvements.

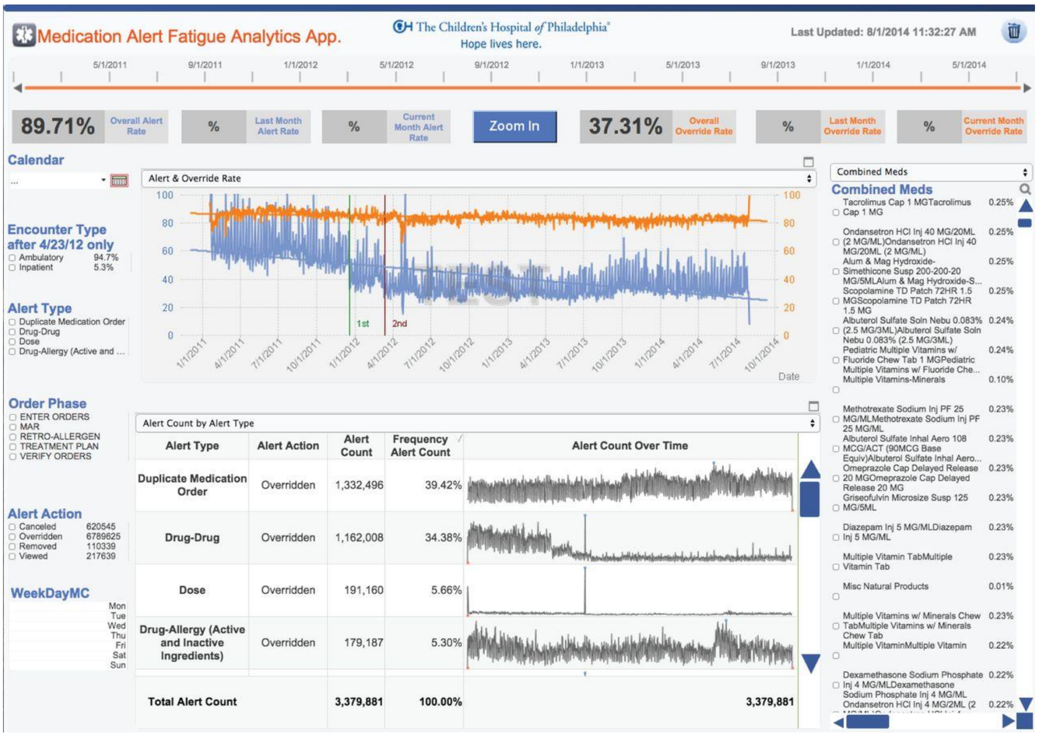


Figure 19: Screen shot of The Children's Hospital of Philadelphia Perioperative Blood Transfusion visual analytics dashboard(Tools used to enable the user to explore historic blood transfusion data).

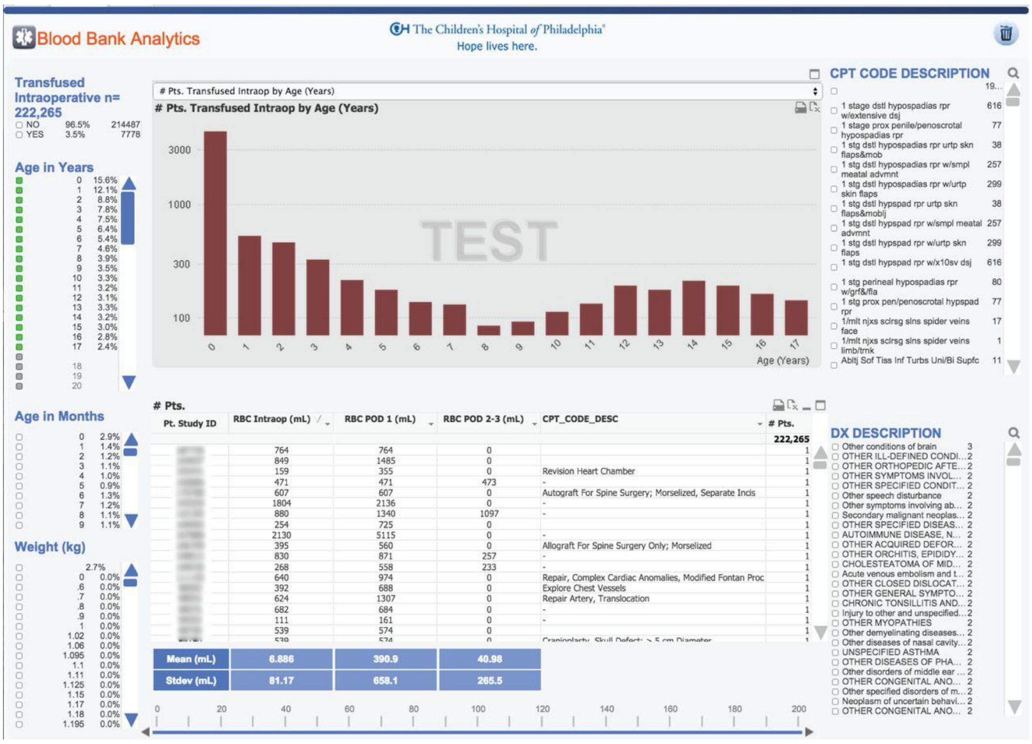


Figure 20: Screen shot of The Children's Hospital of Philadelphia Medication Alert Fatigue visual analytics dashboard (Tools used to enable the user to explore electronic health record medication alert data)

4.1.5 Visualization of Medicine Prescription Behaviour

The current environment for the visualisation of medicine prescription behaviour has been thoroughly described in recent bibliography[103,104], outlining the importance of such approaches for the efficient management of healthcare towards cost effectiveness, but also as a means for the protection of patients and the optimisation of their treatment. The treatment of asthma is significantly connected with the timely intake of medications which is also dependent of the proper use of the inhaler devices. Therefore the visualisation of electronic health records of asthma patients should always involve the presentation of medications used as a function of time and also in relation to the effects on the patient's condition. Even though the above approach focuses mainly on the supervision of medication prescriptions from a management and administration point of view, can offer useful ideas for the supervision of treatment adherence by patients and also allow patients to understand their treatment approach and schedule their visits to their doctor and pharmacy based on the use of their inhalers.

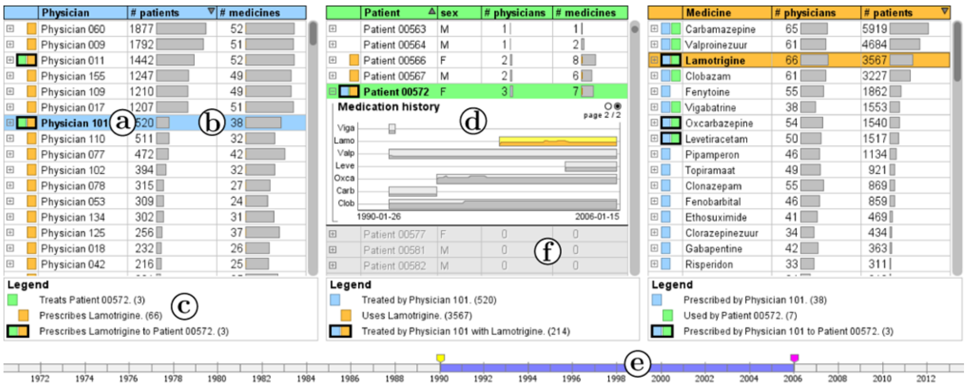


Figure 21 Screenshot of the 3TV describing physicians, patients, and medicines.

(a) A selected physician is highlighted with a blue color; (b) Additional columns show distribution characteristics such as the number of patients treated by a physician; (c) A legend explains in natural language how the RRGs have to be interpreted, and shows between brackets how many of these exist in the corresponding table; (d) Row extensions can be used to obtain detailed information about a specific item, in this case the patient's medication history; (e) The selection on the timeline indicates the interval from which the data is taken; (f) Grayed out rows show physicians, patient, or medicines that have no prescriptions in the selected time window.

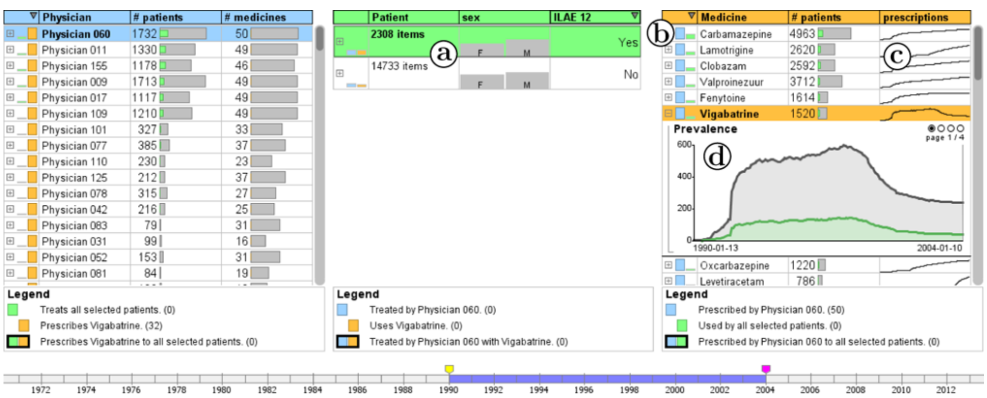


Figure 22: Screenshot of the 3TV with a different configuration.

(a) Patients are grouped by the column that indicates whether they have a symptomatic localization-related syndrome (classified as ILAE 12), this results in two groups; (b) By sorting on the RRG column, we find out that Carbamazepine is the most commonly prescribed medicine for patients with this syndrome; (c) Sparklines give a global indication of how the number of prescriptions associated with each row develops over time; (d) An extension showing a medicine's prevalence (the number of patients using it) over time, the green graph represents the selected patients. In case of Vigabatrin we spot a sudden decrease of patients just before the year 2000, due to a discovery that this medicine can cause blindness. Other views on medicines can be selected by pressing the buttons in the top right corner of the extension.

4.1.6 Visual Analytics to Enhance Personalized Healthcare Delivery

The current visualisation approach aims to aggregate the complex environment of healthcare parameters and electronic health records in a common framework that will allow the fast and efficient supervision by doctors[105,106,107]. It is therefore no surprise that the visualization approaches included in this platform can provide a very useful perspective in the presentation of asthma related information and in the framework of the myAirCoach project. First and foremost, the time line of the patient's condition is enhanced with the continuous presentation of the predicted values which are separated using different colours and an adapted time scale. Furthermore, the current approach includes the visualization of the different therapies as a function of time, underlining in this way any issues of polypharmacy, and helping practitioners understand the relation of therapies with the measured health outcomes for the specific patient. Furthermore, the recommendation pane including very useful information such as the percentage of patients that saw an improvement when following this approach is a very useful tool for both doctors but can also help patients understand their condition and be more engaged when following their doctor's suggestions.

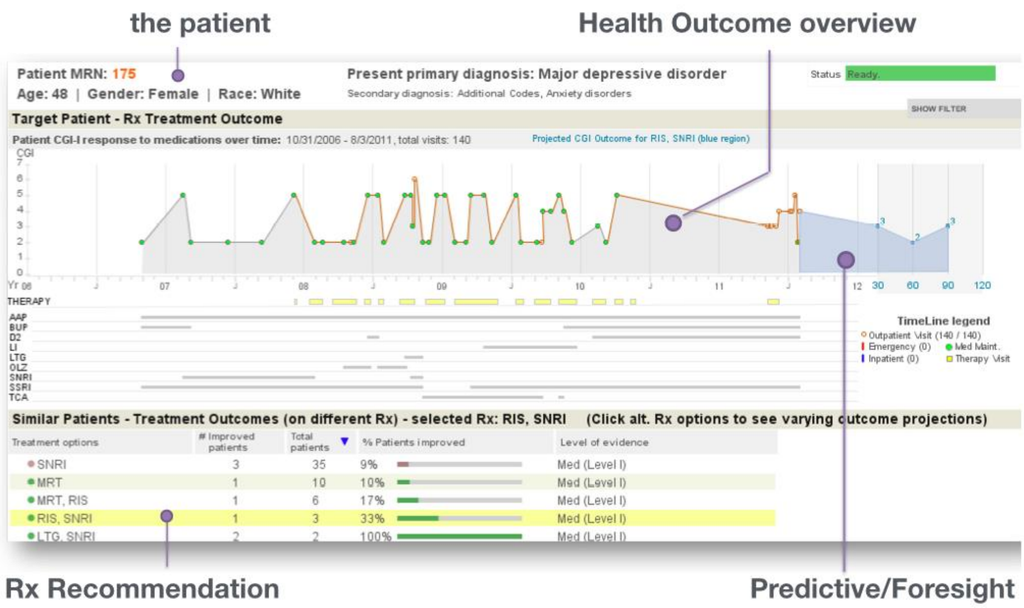


Figure 23: Dashboard-style visual User Interface with integrated and interactive data views to impact health delivery

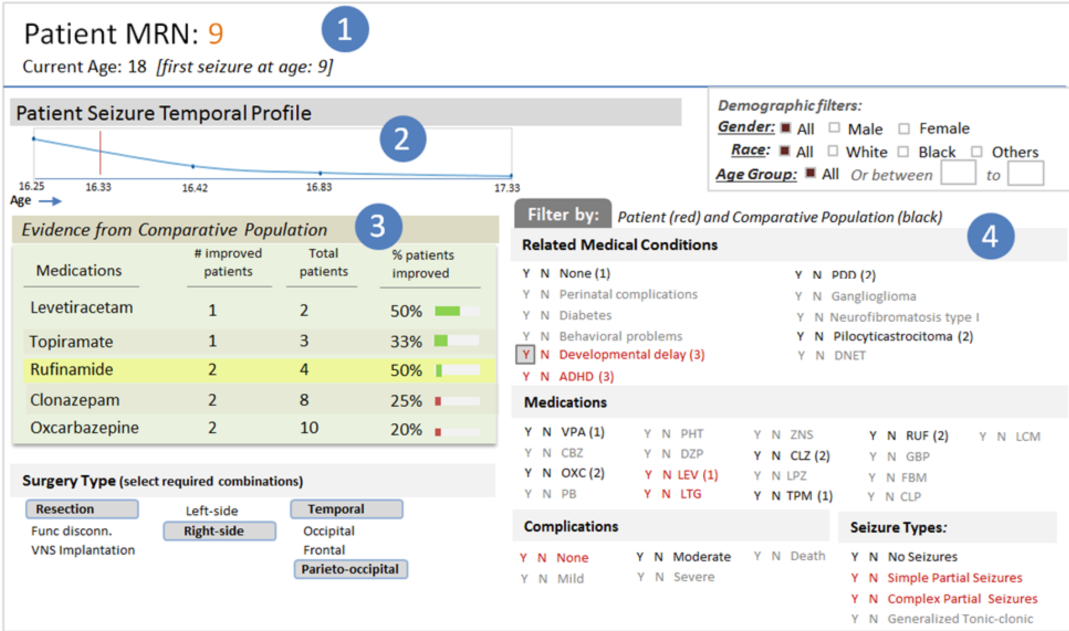


Figure 24: View showing comparative population data for use in decision support for an individual patient.

Different data views are labeled. 1: Demographics for an individual patient; 2: Seizure history for an individual patient; label 3: Treatment evidence aggregated from the comparative population; 4: Data attribute level filters with yes/no (Y/N) toggles for variable selection.

4.1.7 Visual Analytics in Asthma Phenotyping And Biomarker Discovery

The current study presents some fundamental visualisation approaches for the study of asthma and especially for the understanding of the relations between biomarkers and molecular-based phenotyping[108]. Even though the myAirCoach project is not aiming to study the cytokine expression of asthma patients, the clustering and visualization approaches are expected to prove highly valuable for the clustering of patients on the basis of the sensing capabilities and the clinical assessment methodologies of the MyAirCoach project. Both the node-connection graphs and the heat maps will allow researchers to identify trends within their test subjects and help them cluster correlate the health status of asthma patients with physiological, environmental and behavioural parameters as they will be assessed by the MyAirCoach system.

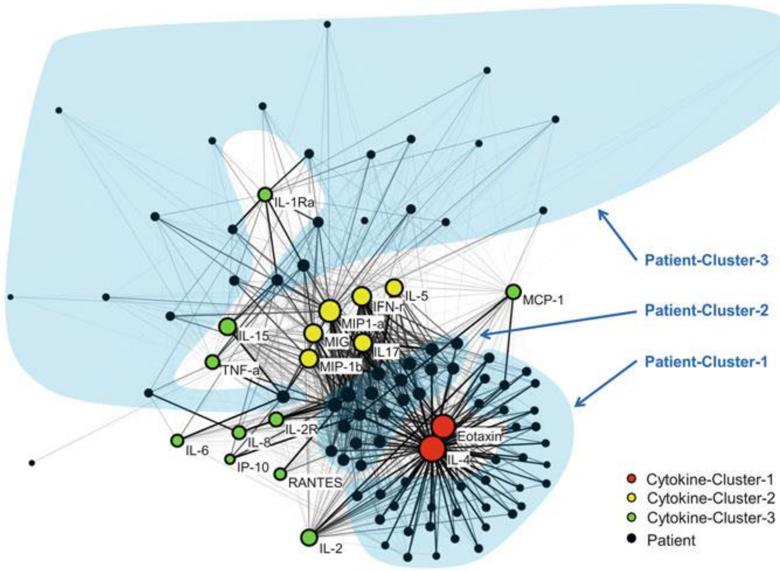


Figure 25: Clustering of patients with similar cytokine expression using node connection graph

Application of Kamada–Kawai, a force-directed algorithm, to the circular layout. The algorithm pulls nodes with similar cytokine expression patterns closer together, while pushing apart those with dissimilar expression patterns. The layout of the network suggested the existence of disjoint patient and cytokine clusters, and revealed inter-cluster relationships such as how the patient clusters express particular cytokine clusters. However, quantitative methods must be used to identify cluster boundaries

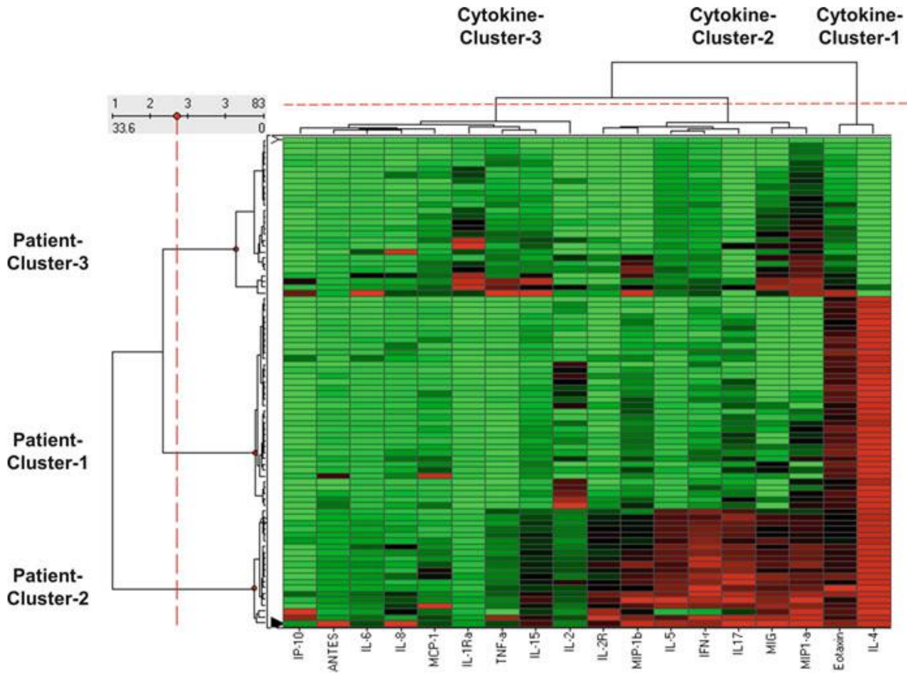


Figure 26: Clustering of patients with similar cytokine expression using a heat map

A heat map where the *rows* represent patients, the *columns* represent cytokines, and the *colors* represent normalized cytokine values (*green* = 0, *red* = 1). The *rows* and *columns* are ordered based on the results of agglomerative hierarchical clustering. The patient and cytokine dendrograms are shown on the *vertical* and *horizontal axes* , respectively. Each dendrogram shows a natural break at three clusters indicated by the *red lines*

4.1.8 Big Data and Health Analytics: Interactive Visualization

Two recent publications[109],[110] have provided a comprehensive review of some alternative interactive visualisation approaches with special focus on EventFlow as it is presented in Figure 27. Despite the fact that asthma is not the targeted application of EventFlow its visualisation structure can be very useful for the definition of respective myAirCoach tools in order to support doctors to supervise efficiently their patients and medical researchers to manage clinical trials and also study their results.

Among the visualisation platforms reviewed in this book chapter it is important to mention the case of PatientsLikeMe (Figure 28). This platform can provide with valuable information for the design of the Virtual Community Platform as it will be developed under the MyAirCoach project. The polling bars as used by the PatientsLikeMe platform are a useful tool for the engagement of patients and can also help them understand their disease, find people with similar difficulties and discuss their treatments.

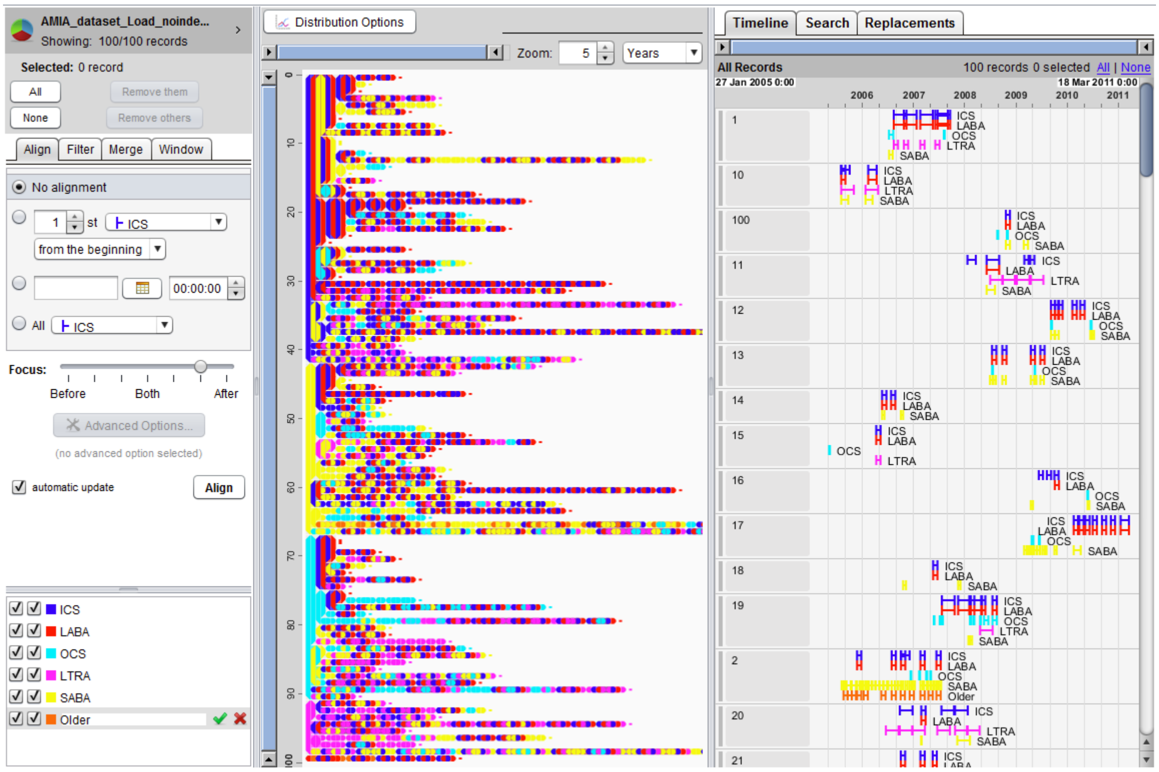


Figure 27: EventFlow overview of 100 patients' prescription records. (Different prescriptions are indicated with different colours)

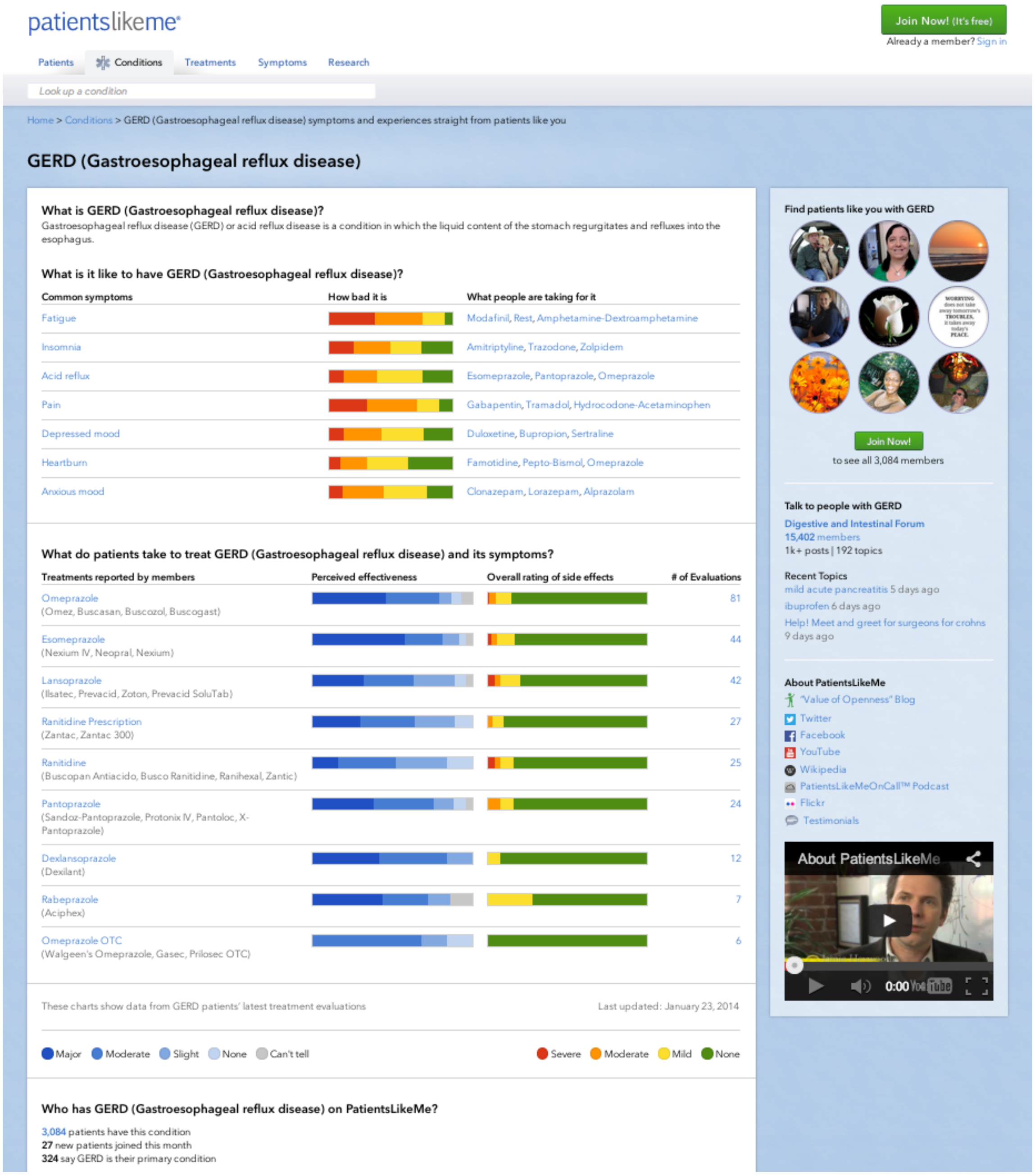


Figure 28: A PatientsLikeMe example visualization interface

4.1.9 Optimizing the Utility of Claims Data through Visual Analysis

The current research focuses on the optimisation of the cost efficiency of a healthcare system based on the geographical visualisation of for the promotion of transparency in terms of the supervision of medication claims[111]. Even though the goals of the MyAirCoach project do not include the study of healthcare costs, the geographic presentation of asthma related parameters is a crucial component towards the understanding of environmental factors that affect asthma, and the support of patients and doctors with alerts for areas of high pollution that my cause asthma exacerbations or worsen the patient's asthma condition. The above examples offer some indicative approaches towards this direction and can be used to define the initial design of the related system components.

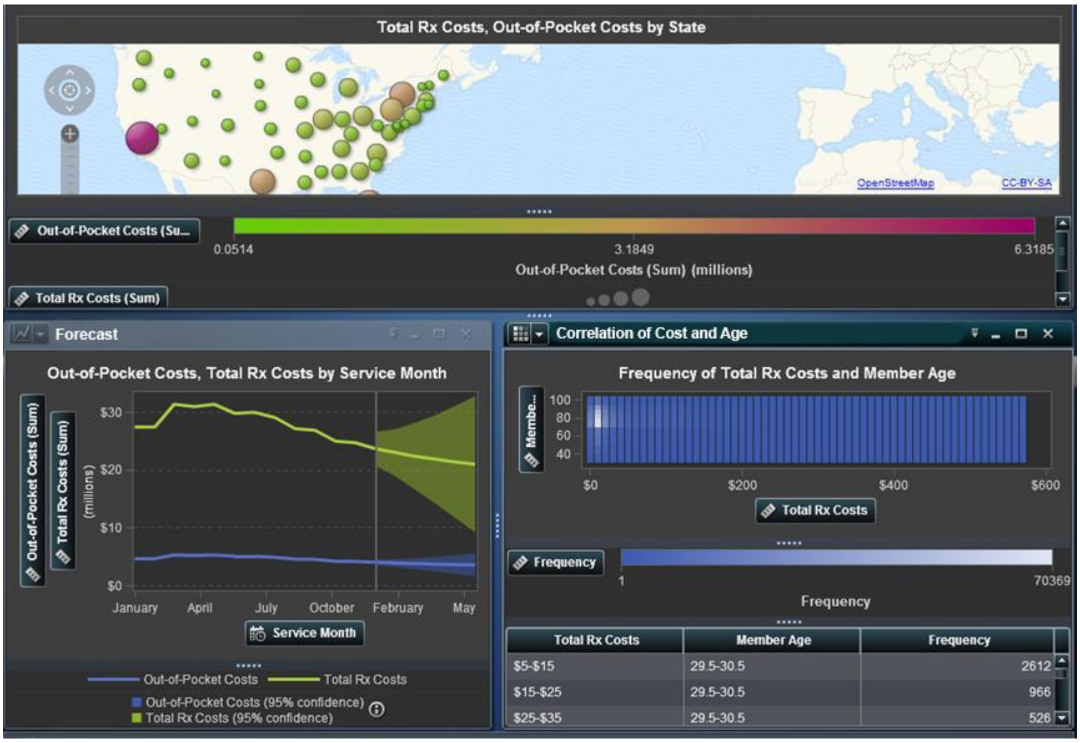


Figure 29: SAS Visual analytics showing dispersion of Medicare costs by multiple variables

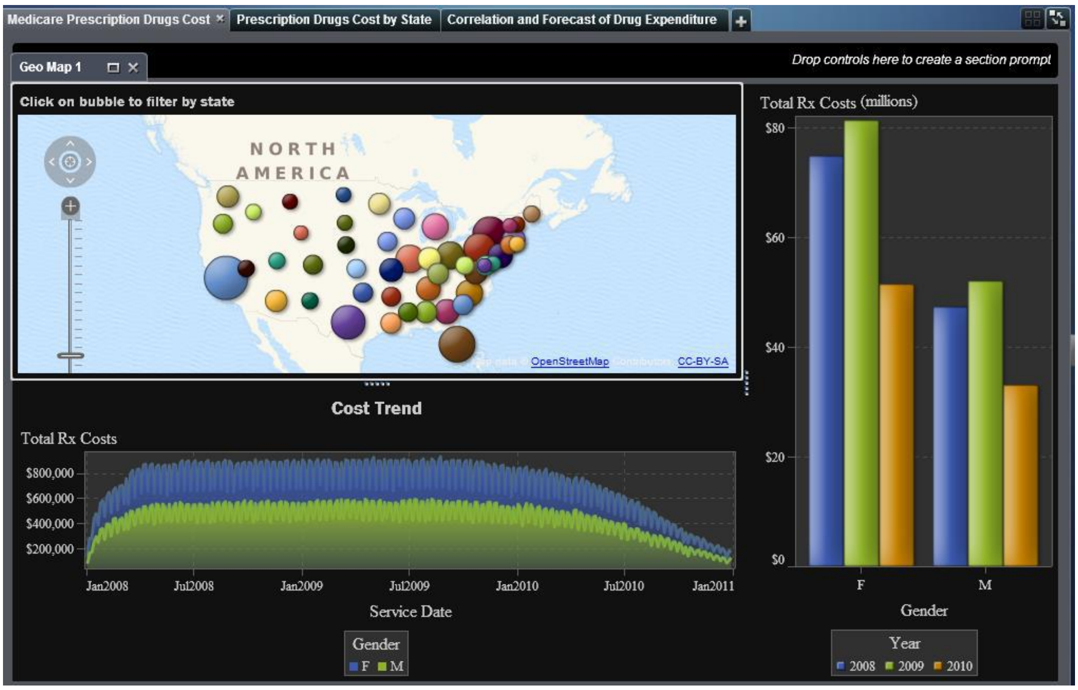


Figure 30: SAS Visual Analytics shows Medicare cost trends by multiple variables.

4.1.10 Information Visualisation for Healthcare Informatics

The current research studies introduces the concept of the Five Ws in the area of medical information visualisation, namely who, when, what, where, and why. The proposed system seeks to improve the usability of information captured in the electronic medical record (EMR) and show via multiple examples the time and effort needed to access and analyse the medical patient information can be lowered on the basis of the above described framework of Five Ws[112],[113].

Both the visualisation approaches of the following figures, namely the radial and sequential views, may prove very useful for the representation of asthma condition. Firstly the radial view can be used in order to visualise the relations between measured parameters and identified risk factors, whereas the sequential presentation holds the promise to further simplify the presentation of the evolution of the disease as a function of time. Even though the above system is developed to the holistic presentation of the patients' health status, it can offer valuable ideas for the multi-parametric depiction of asthma condition and especially the combination of physiological, environmental and behavioural parameters as they will be assessed and studies under the framework of MyAirCoach.

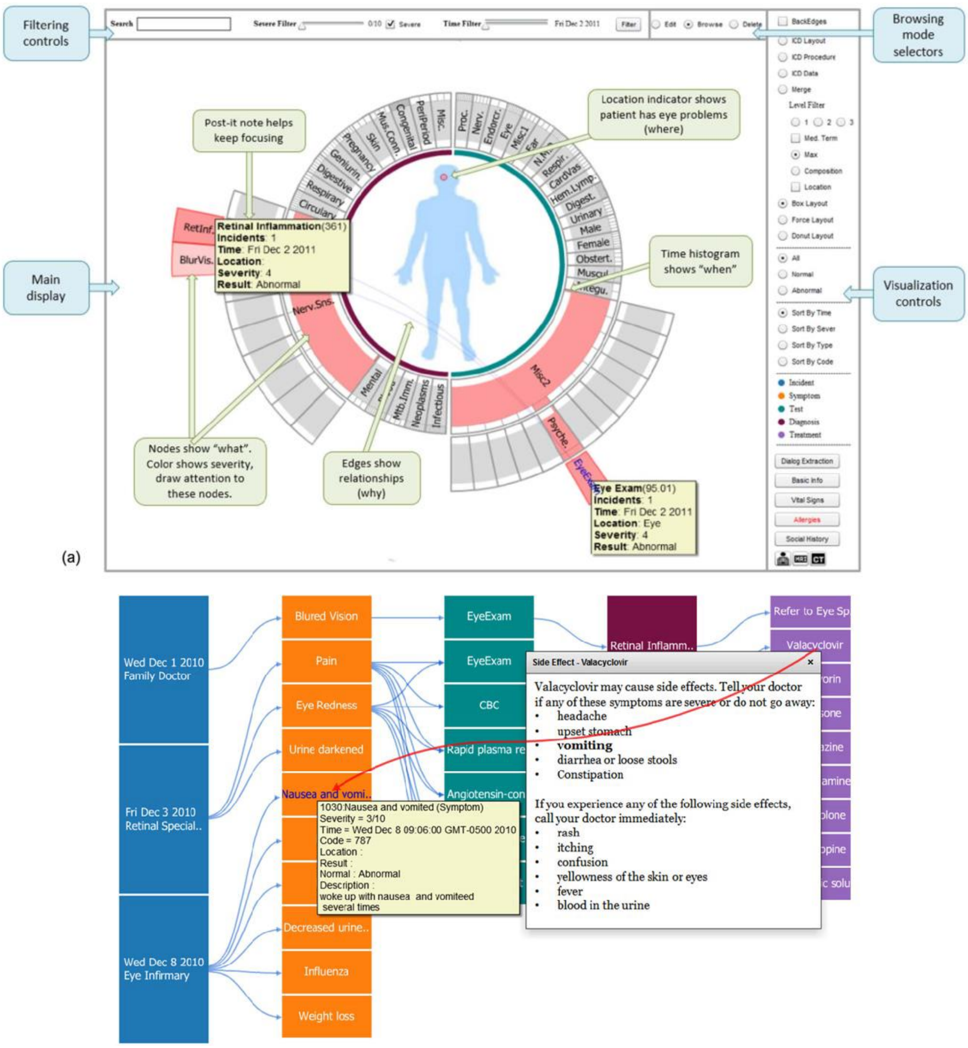


Figure 31: The radial and sequential views of the proposed system of health informatics visualisation

4.1.11 Mutlifacet visual Analytics for Healthcare

The current study presents three visualisation approaches of health related data oriented towards the clustering of patients data[114]. In addition to the commonly used visualisation approach of clustering with node-connection diagrams (Figure 32), the SolarMap and DICON displays are presented which are two innovative enhancements for the presentation of clustering results based on their separation parameters. In the first case (Figure 33) the parameters of clustering are presented in a circle around the clustering diagram together with their connections with each node. Furthermore, the DICON approach visualises these parameters chromatically for every clustered node and helps the user to understand easily the fundamental basis of the clustering in terms of the differentiating parameters. All the above approaches can provide significant help for the design of similar functionalities for the myAirCoach system.

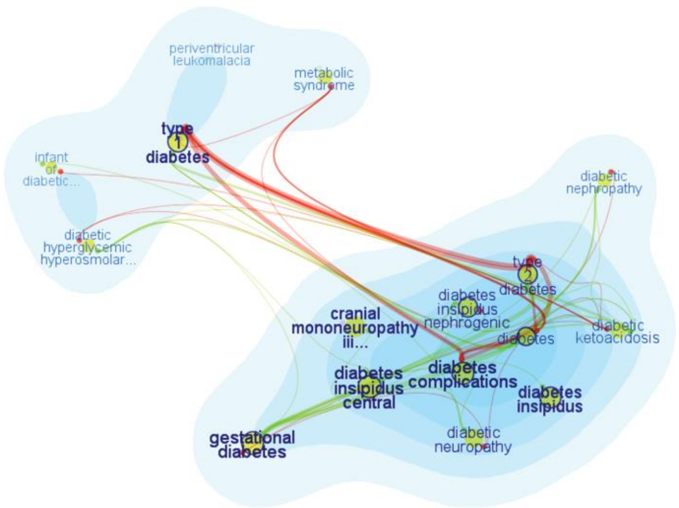


Figure 32: FacetAtlas visualization showing two clusters corresponding to type 1 and type 2 diabetes.

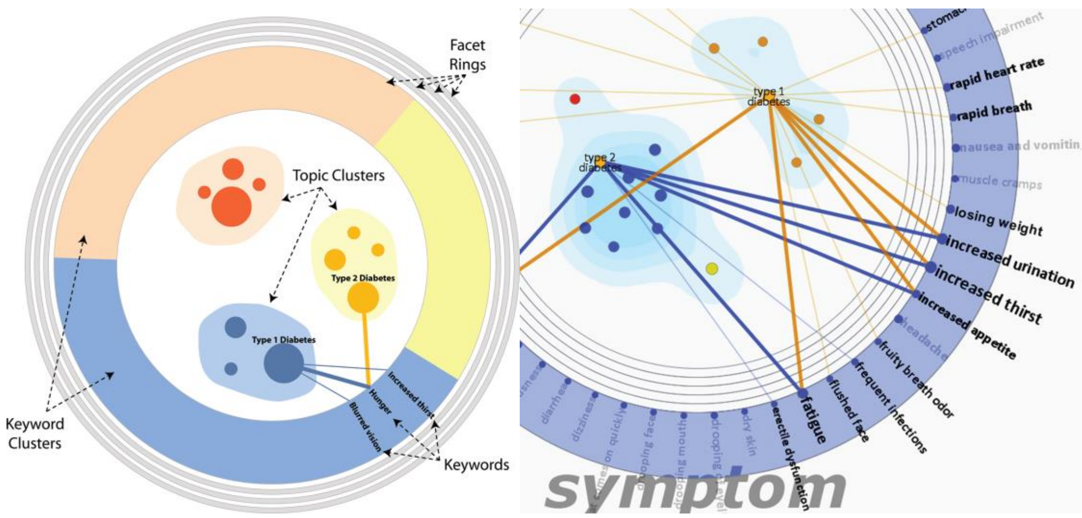


Figure 33: Visual Encoding of SolarMap.

Figure 34: DICON displaying 50 distinct five-dimensional patient clusters.

The visual design of the icons makes it easy to determine which cohorts of patients are similar to one anotherVisual encoding for the DICON visualization technique. (a) Each individual entity is described by a feature vector. (b) The individual features are encoded using color-coded cells, which are packed together to form an icon for the entity. (c) Multiple icons can be grouped to form a cluster icon, which is shown in (d).

4.2 Mobile and cloud based interfaces, allowing the follow up of patients clinical status in real life conditions

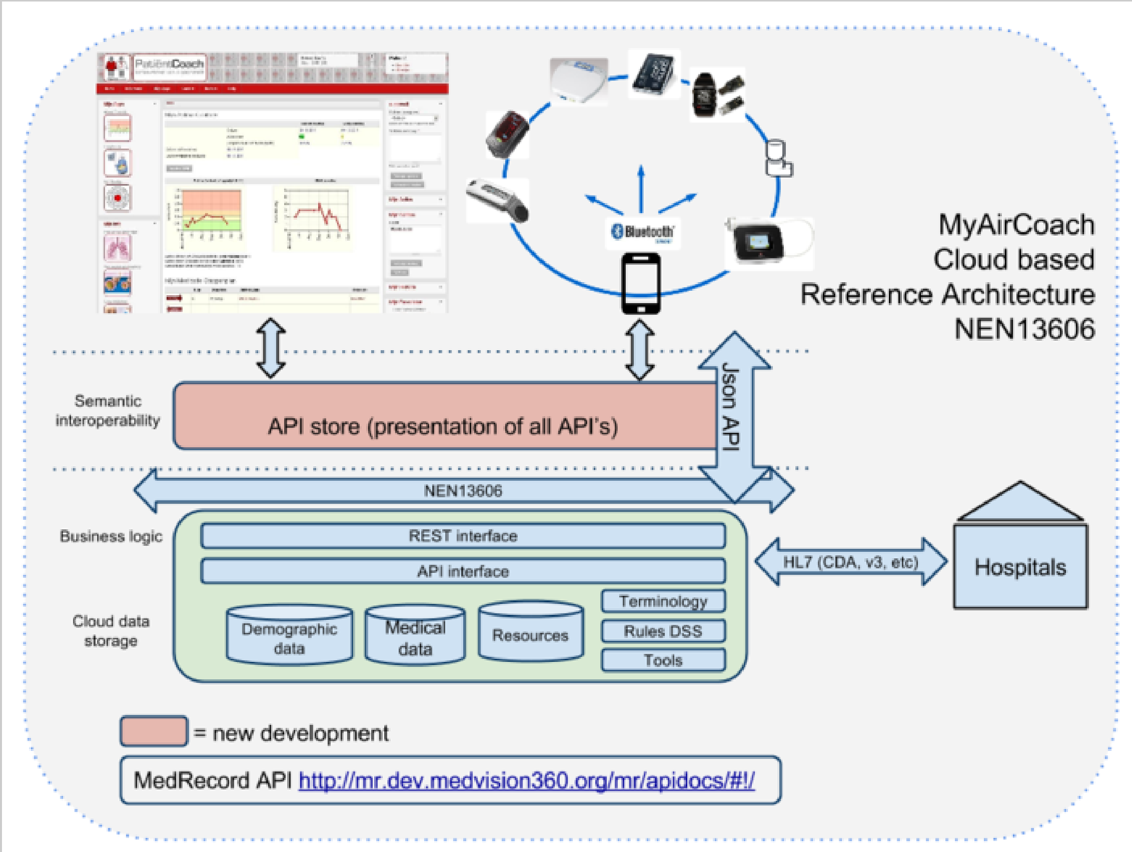


Figure 35: Cloud Based Reference Architecture

At this moment few Cloud based interfaces serving both mobile as well as HTML5 interfaces are present in the clinical domain. The HL7 v3 standard is based on XML and therefore not the best suited for using on a mobile device since the addition of tags and attributes lands extra weight to data payload.

4.2.1 HL7 FHIR interface

Source[115]: FHIR is a more granular way to exchange data without the rigid workflow of traditional HL7 (version 2 or 3). No overhead of SOAP and other complicated approaches is adopted by using a straightforward RESTful style approach, which gives high emphasis on conformance and reference implementations, connections etc. as part of the core process. It focuses on hitting 80% of the common use cases rather than the 20% of exceptions (80/20 rule).

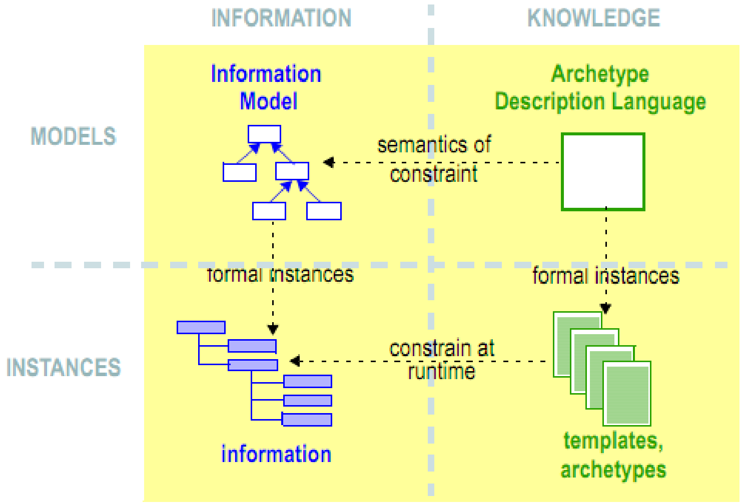
4.2.2 openEHR and EN13606

A more generic and powerful approach is using the EN13606 or openEHR. Actually within this architecture the use of FHIR resources is no problem, see also the joint development of an archetype[116] based on FHIR resources.

4.2.2.1 Archetypes

An archetype is a re-usable, formal model of a domain concept. The formal concept was originally described in detail in a paper by Thomas Beale, current specifications are here[117].Extracting the following schema from that document it's easy to illustrate the relationship between archetypes and data:

For example an archetype for "Breast cancer identification" is a model of what information should be captured for this kind of identification - usually primary tumour, lymphatic nodes and presence of metastasis and instrument or other protocol information. In general, they are defined for wide re-use, however, they can be specialized to include local particularities.

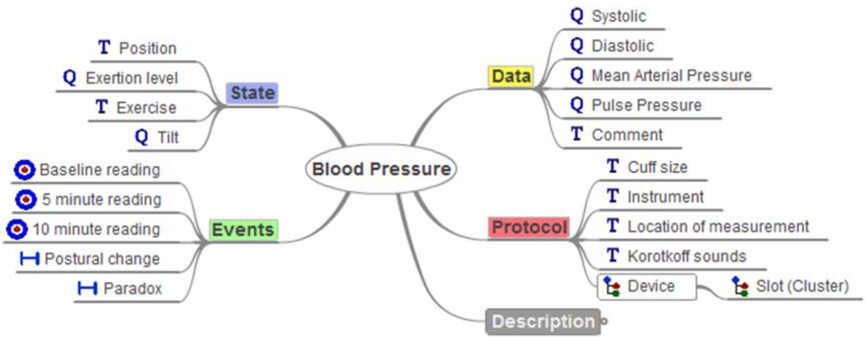


The key benefits of archetypes include: Knowledge-enabled systems: the separation of information and knowledge concerns in software systems, allowing cheap, future-proof software to be built; Knowledge-level interoperability: the ability of systems to reliably communicate with each other at the level of knowledge concepts; Domain empowerment: the empowerment of domain specialists to define the informational concepts they work with, and have direct control over their information systems.

OpenEHR archetypes are used as the main basis to build OWL classes, subclasses and properties. Once these clinical archetypes are translated into OWL objects we combine them to set up one Medical Ontology which becomes the starting point of the inference process.

In the field of Electronic health records there are a number of existing information models with overlaps in their scope which are difficult to manage, such as between HL7 V3 and SNOMED CT. The openEHR approach faces harmonisation challenges unless used in isolation.

While individual health records may be vastly different in content, the core information in openEHR data instances always complies to archetypes. The way this works is by creating archetypes which express clinical information in a way that is highly reusable, even universal in some cases. To get to the point where information is suitably presented for clinical care it always involves a number of archetypes.



The openEHR approach uses the CEN- and ISO-standardised "archetype definition language" (expressed in ADL syntax or its XML/Json equivalent) to build archetypes; these are reusable, formal models of domain concepts. Archetypes are used in openEHR to model clinical concepts such as "blood pressure" or "medical prescription".

4.2.2.2 Terminologies (vocabularies)

Terminologies arranged in hierarchies, such as SNOMED-CT, contain ontological components in that they use relationships between concepts to define other concepts.

The Archetypes and terminologies can be related directly in two ways:

1. A node in an archetype which has a meaning represented in a terminology may be bound to that terminology and the relevant concept; and
2. A node in an archetype may constrain the values of a DV_CODED_TEXT to be a specified set of terms from a particular terminology.

In fact, the archetype itself maintains a link to the specified set of terms.

4.2.3 Relevance to the MyAirCoach project

To provide a common interface for both HTML5 (web apps) as well as native mobile apps, for MyAirCoach we propose an even more advanced Rest API. This API should be able to provide Json, but also Java for native development or Php libraries for GUI side.

4.3 Existing cross-platform infrastructures with sensors that measure physiological and environmental parameters

Healthcare management requires inter-disciplinary principles management of lifestyle, psychological and social health managements for individual needs in different level of health care process such as case management, feedback and learning, clinical decision making based on clinical guidelines and standards. Through Information, technology communication and intelligent platforms can this sensing infrastructure be realistic and feasible due to provide a huge automated data based on computational modelling techniques and monitoring with combination of mobile health technologies and sensors via a stable and secure network.

For this reason, an embedded services framework has potential to offer a smart solution towards different level of interoperability in different layer and categories and meets the standards not only for personal health record systems level but also for other level of communications between applications and systems. This type of health ecosystems enables also increasing scalability and utility of IT- infrastructure as an appropriate solution to ensure quality of systems as well as clinical outcomes.

However, increasing of mobile health applications and the lack of interoperability between them has always been major problems in mobile health in EU[118].

As initial requirement of the foreseen myAirCoach platform and in order to deal with interoperability issues through comprehensive approaches, we introduce set of tools and platforms as well as related methodological guidelines. For this reason we include a brief overview over existing technologies based on appropriate standards in healthcare domain.

4.3.1 The common standards in e-health

IEEE[119]**:** These standards are for industry standards in a broad range of industries. This is the best-known ICT standards, which are relevant for number of activities to eHealth that (formerly known as IEEE 1073 or informally as MIB) is stablished by the Engineering in Medicine ad Biology Society (EMBS) and is concerned with medical and personal health device communications. In addition, the formation of ISO TC215, the IEEE 11073 cover the global work on point-of-care medical device communication has been harmonised by merging CEN and IEEE work , mostly within developing and owned published jointly by three bodies under the lead of IEEE.

ISO/IEEE 11073-10418[120]**:** Standards to healthcare application interfaces. A normative definition of communication between personal tele health international Normalized Ratio (INR) devices (agents) and manager as cell phones , personal computers, personal health appliances and set top boxes in manner that enable plug and play interoperability. This standard also includes terminology, information profiles, application profile standards and transport standards. It also establishes the use of specific term codes, formats and behaviours in Tele- health environments restricting optionally in base framework in favour of interoperability. It specifies also a common core of INR monitoring.

HL7(Health Level 7)[121]**:** HL7 standard framework is for the exchange, integration, sharing and retrieval of electronic health information. These standards describe how information is packed and communicated from one party to another, setting the language, structure and data types required for seamless integration between systems. This standard supports also clinical practice and the management, delivery and evaluation of health services. Unlike the representational structures of CEN and ISO and their national counterparts, HL7 is based on individual or corporate membership. HL7 is ANSI accredited and an open dialogue platform (Joint initiative council-JIC) with ISO and CEN that has established. HL7 includes other standard rather than point to point messaging standard, today. Clinical Document Architecture (CDA) is for storing and retrieving persistent information, such as Medical Records, which it integrates with the HL7 V3 Reference Information Model (RIM). This standard is also for developing decision support services (DSS) based on Service Oriented Architecture.

HL7 Version 3[HL7V3]: HL7 support also other applications such as GELLO : A common Expression language , Arden syntax for Medical Logic system or Module , Management Health Records. Developed based on object-oriented data, XML implementation technology specifications, Continuity of Care Document (CCD) and Functional Profile for

Personal and Medical the Clinical Object Workgroup (CCOW) ContextSpecification for V3 structures *1.1,R1, DTR1.1,3XML ITS* Structure. This standard concerns also domain analysis model, emergency medical services. It supports also clinical decision support; Virtual Medical Record (vMR), Knowledge Artefact Specification, release 1.2.

CEN: The intention of CEN standards broadly cover by default the technical specification (CEN TS) as normative document produced in Technical Committees with national delegations and approved by them but not undergoing the formal national enquiry process. Another area is Technical Report (CEN TR) as informative documents produced in Technical Committees with national delegations and approved by them and informative publications. Further, it supports CEN Workshop Agreement (CWA), which is normative documents produced in open workshops and agreed consensus of those participating. However, CEN standards are developed and agreed by the three officially recognized European Standardization such as European Telecommunications Standards Institute (ETSI) and Electro technical Standardization (CENELEC). These standards provide platform for the development of European standards and other technical specifications across range of segments. In addition, CEN and CENELEC standards integrate with International Organisation for Standardization (ISO) standards too.

CEN/TC 251 Health informatics[122]**:** This standard is committed to delivering consensus-based interoperability standards for health within Europe and provides the opportunity for all member states to engage through the standardization life cycle, knowing that this will provide

Continua Health Alliance[123]**:** These standards categories support Healthcare Informatics data standards with consumer electronic technologies through guidelines and specifications necessary to enable connectivity devices and services. These standards support Bluetooth SIG for wireless connectivity, USB Personal Health Device Specification from ISO/IEEE for protocol definitions. Continua Health Alliance V1 standards are for integration with standards –based electronic health records (EHRs) consist of the CDA-based Personal Health Monitoring (PHM) specification from HL7 and the XDR Profile Specification from IHE.

Continua uses Use case driven process where all members have input to decision on which integration capabilities are developed. Continua goal is not to create new standards but to identify the best possible class existing standards that suite to the Use Case requirements and provide profiling to ensure tight interoperability. Continua Standards enable coordination of range changes in existing standards to enable a set of personal tele-health use cases.

IHE[124]**:** Integrating the HealthCare Enterprise (IHE) is based on integrates existing Base Standard to enable fulfilment of identified tasks. IHE promotes the coordinated use of Base Standards such as DICOM, HL7, ISO, OASIS, W3C and further more standards in order to address specific clinical needs in support of optimal patient care.

IHTSDO[125]**:**The International Health Terminology Development Organisation acquires own and administers to the right to SNOMED CT and other health terminologies.

SNOMED CT: This standards establish and implement clinical terminologies to support safe and accurate, effective change of related health information. The focus is on semantically accurate health records that are interoperable. It supports directly patient care and clinical terms in Version 3.

ISO[126]**:** International Organization for Standardization (ISO) developing international standards that are fully compliant with the requirements set by the Agreement on Technical Barriers to Trade of WorldTrade Organization (WTO). ISO standards convers international software quality and sub-characteristics detail aspects and criteria such as flexibility (ISO/IEC 2510), usability, and interoperability, and environmental management (ISO 14000). ISO Standards supports eHealth architecture roadmap and Health Informatics-IHE global standards adaption related to analyses interoperability requirements in support of a use case(ISO/TR 28380:2014). ISO 22000 highlights the major steps in the implementation process in order to understand task with practical advices related to management of systems to meet the requirements.

ISO/TC 215: ISO has established range of eHealth standards through its Technical Committee 215,"Health Informatics". These standards promote interoperability between independent systems to enable compatibility and consistency for health information and data as well as to reduce duplication of effort and redundancies. Furthermore, ISO's 93 standards in "Health Informatics" address healthcare delivery, clinical research, public health, prevention and wellness. However pat of ISO's activity in eHealth involves the rebranding of specifications developed in other standards such as Hl7 or DICOM (e.g ISO 12052:2006 is "Digital Imaging and Communication in Medicine (DICOM)).

Of Course as Multimedia diagnostic grows more and more; there are series of Standards effort on mobile health applications or multimedia diagnostic area based and dependent upon core telecommunications services and infrastructures. Few selected cases are:

ITU–T[127]:

(x)DSL- Digital Subscriber Line: It enables standards for broadband internet access over traditional twisted pair telephone networks. For example remote diagnostic applications.

Digital Video Compression Standards: ITU-T and ISO/IEC JTC1 have jointly developed I compression specifications such as ITU-T T.81, also known as JPEG, or ITU-T.800 JPEG-2000. These standards are necessary for imaging, including digital cameras and other imaging devices used for medical applications such as DICOM.

Quality of Service Standards: ITU-T Recommendations for standardizing performance and reliability of information transmission on a variety of networks such as ITU Recommendation G.9960 and Recommendation G.9961 as needs for quality medical information transmitted to and from home environments.

Information Security Standards: ITUT-telecommunications security standards such as X.800-X.849 Recommendations , the X.1000-X.1099 information and network security standards which includes tele biometrics , the X.1120-X.1139 mobile security standards, and also personal health information over mobile networks and other transmission systems.

Voice over the internet: ITU-T offers Recommendation H.323, a signalling protocol for transmitting audio and visual information over the internet.

ITU-T Focus Group on M2M:

These standards support requirements for Machine-to-machine communication over a telecommunication network and so medical providers can observe the patients' health status remotely.

In addition, interoperability is always associated with data formats in order to transfer the messages through communication protocols, which needs to be well-defined syntax and encoding, even if they are only in the form of bit-tables. The presented data is common to use high-level syntaxes as HTMl, XML, or ASN1.

4.3.2 Existing cross platforms and solutions

Service Oriented architecture (SOA) as a semantic architectural style

In orchestrating a SoA solution, services that are (internally) implemented with different languages, architectural styles and on platforms from different vendors, can be used together transparently. SoA can thereby use Web Service technologies as the way of publishing, discovering and accessing a service. Web Service technologies include SOAP (Simple Object Access Protocol) and XML (eXtendible Mark-up Language) for exchanging messages containing structured and typed information to access services, to publish and describe a service and UDDI (Universal Description Discovery and Integration) for dynamically finding and invoking web services. On top of these now well-established protocols, a host of new protocols have been developed to support the orchestration of services and describe the semantics of services (e.g. OWL-S builds on OWL to define a core set of mark-up language constructs for describing the properties and capabilities of Web services and WS-Coordination provides a method of defining, coordinating the actions of individual web services in distributed applications and supporting workflows and business processes (defined in BPEL)). WSRF (Web Services Resource Framework) defines an open framework for modelling and accessing stateful resources using Web services (a web service is by itself stateless as it retains no data between invocations and needs therefore any WSRF operation implementation).

A basic web service architecture has besides the SOAP protocol, also components such as a language for service description named WSDL (Web Service Description Language) and a registry for looking up available web services called UDDI (Universal Description, Discovery and Integration).

Semantic technologies and Middleware for internet of things /M2M

The recent years´ developments in the Internet of Things domain have resulted in a large body of knowledge of technology and methodology for applying IoT to different domains, of which *eHealth/mHealth* is one. Parts of this knowledge has been generalized and compiled into the EU reference architecture for IoT systems, The IoT

Architectural Reference Model[128]. All development efforts and projects can benefit from relating to this model, by applying its concepts, and possibly also by contributing to its further refinement, which eventually may lead to further standardization.

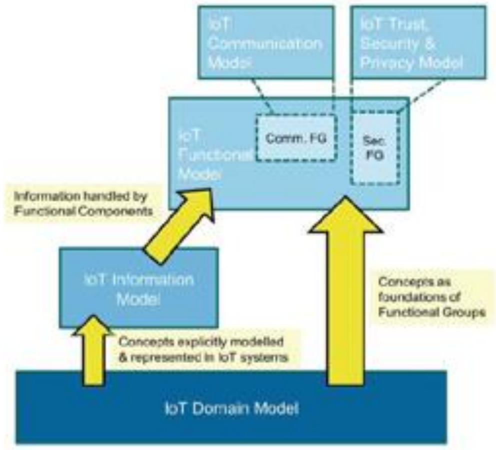


Figure 36: Sub-models of the IoT Reference Model[128]

One of the first IoT projects to leverage the IoT-ARM is the FI-WARE[129], one of the projects in the FI-PPP[130] European programme for Internet-enabled innovation. The project developed a set of re-usable general purpose building blocks (i.e., SW components) for the implementation of IoT system platforms, so called Generic Enablers (GEs). The GE components have been developed by a number of different organizations and are available from the FI-Ware repositories and sites. The components implement a variety of generic IoT platform functions, such as communications, storage and addressing services.

Application projects then deploy the GEs in order to implement domains specific functionality, e.g., in eHealth. One such eHealth application of FI-Ware is the FI-Star project[131], which has conducted a number of European field trials such as tele-health network for diabetes patients (NO), virtualization of operating theatres (DE), remote monitoring and consultation (PL, IT).

Another current project in the domain of public services, is the FP7-project ALMANAC, whichdevelops a Smart City platform that integrates Internet of Things edge networks (also called capillary networks) with telecommunication metro access networks, targeting Smart City applications. The project seeks synergies among city services, infrastructures and resources by creating innovative cost-effective Smart City applications and services, while also involving the citizens. To this purpose, ALMANAC focuses on seamless interconnection among all kind of devices, existing urban services, and external service providers while establishing a very strong interconnection between the ALMANAC platform, its users/citizens and the outside world. The ALMANAC platform builds on the LinkSmart middleware[132].

Linksmart Open Souce Middelware

The LinkSmart middleware was initially developed by the European project Hydra. This was a 4-year integrated project in FP6.The LinkSmart middleware allows developers to incorporate heterogeneous devices and services into their applications by offering easy-to-use web service interfaces for controlling any type of physical device irrespective of its network technology such as Bluetooth, ZigBee, RFID, Wi-Fi, Ant+ etc. Developer tools with device/resource catalogues and REST APIs are supported. LinkSmart incorporates means for secure peer-to-peer (P2P) communication, device and service discovery, event processing and service orchestration. The service-oriented architecture (SOA) applies to both the implementation of the middleware managers themselves and for the higher-level device interfaces in the form of software proxies. The system behind LinkSmart was implemented on the main IDEs, .NET and Eclipse.

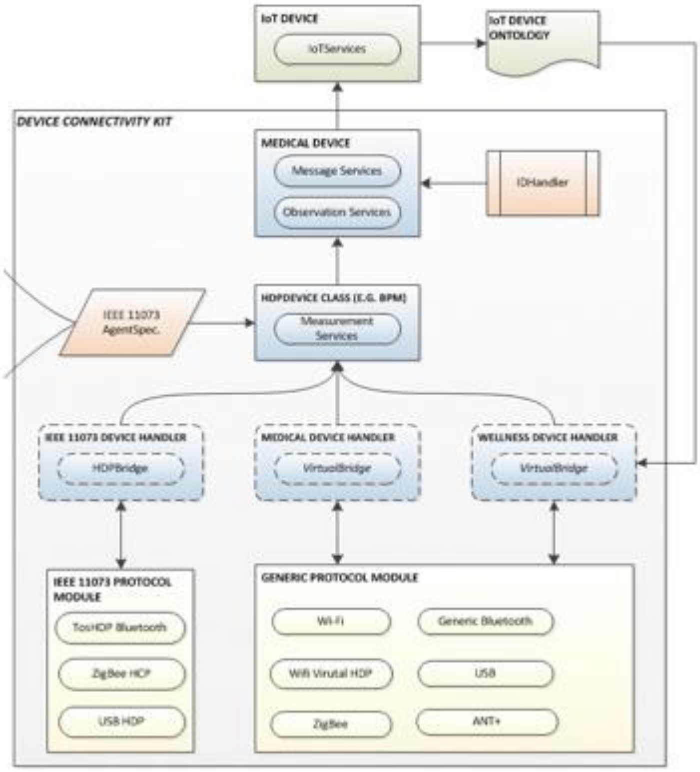


Figure 37: Medical device connectivity interface based on LinkSmart

Since the close of the Hydra project, the LinkSmart middleware has been adapted and extended by several RTD projects and used in commercial applications. Among these, the ebbits[133] project with applications in food traceability and car manufacturing, and as referenced elsewhere in this proposal, the REACTION and InCasa projects addressing (1) remote monitoring with decision support for diabetes patients, and (2), domotic support for the frail and the elderly respectively.

REACTION[134]

REACTION platform is developed as an integrated ICT platform to provide integrated care plan to diabetes patients in different healthcare regions across Europe. The platform offers both loge-term and short-term management of diabetes episode through professional decision support for both in-hospital and primary care. The platform enable diabetes patients to have a better overview over their physiological values as well as lifestyle changes (diet + physical activity). Hydra middleware incorporates support for self-discovery of devices such as BAN or PAN.

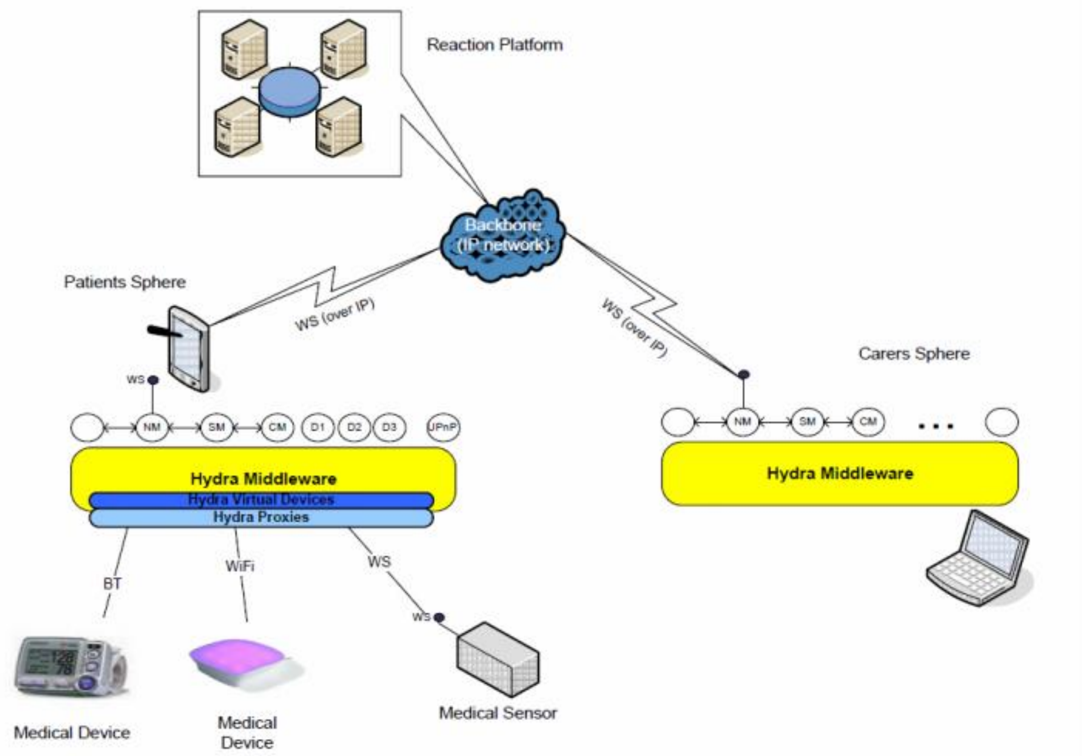


Figure 38: Incorporation of devices, sensors by Hydra middleware

REACTION platform supports data semantic interoperability based on e-health standards such as ISO/IEEE 11073 for personal health device data , CEN , IEEE 11073-10417:2009) for blood glucose meter and IEEE P11073-10419 for insulin pump. The table below is a short summary of different medical devices that communicate to REACTION platform as continues device.

Specialisation	Standard	Status
Basic ECG (1 to 3 lead)	IEEE P11073-10406	In development
Blood pressure	IEEE 11073-10407:2008	Standard
Body composition analyser	IEEE P11073-10420	In development
Glucose meter	IEEE 11073-10415:2009	Standard
Independent living activity hub	IEEE 11073-10471:2008	Standard
INR	IEEE P11073-10418	In development
Insulin pump	IEEE P11073-10419	In development
Medication monitor	IEEE 11073-10472:2010	Standard
Peak flow	IEEE P11073-10421	In development
Pulse Oximeter	IEEE 11073-10404:2008	Standard
Thermometer	IEEE 11073-10408:2008	Standard
Weighing scales	IEEE 11073-10415:2008	Standard

Table 9: IEEE11073 Personal Health Device Standards

In addition, the platform is designed to support the management of multiple diseases and co-morbidities.This intelligent platform enables monitoring through medical devices and sensors such as e-patch to monitor ECG and providing feedback through closed loop as well as alarm for emergency management to acute diabetes episodes.

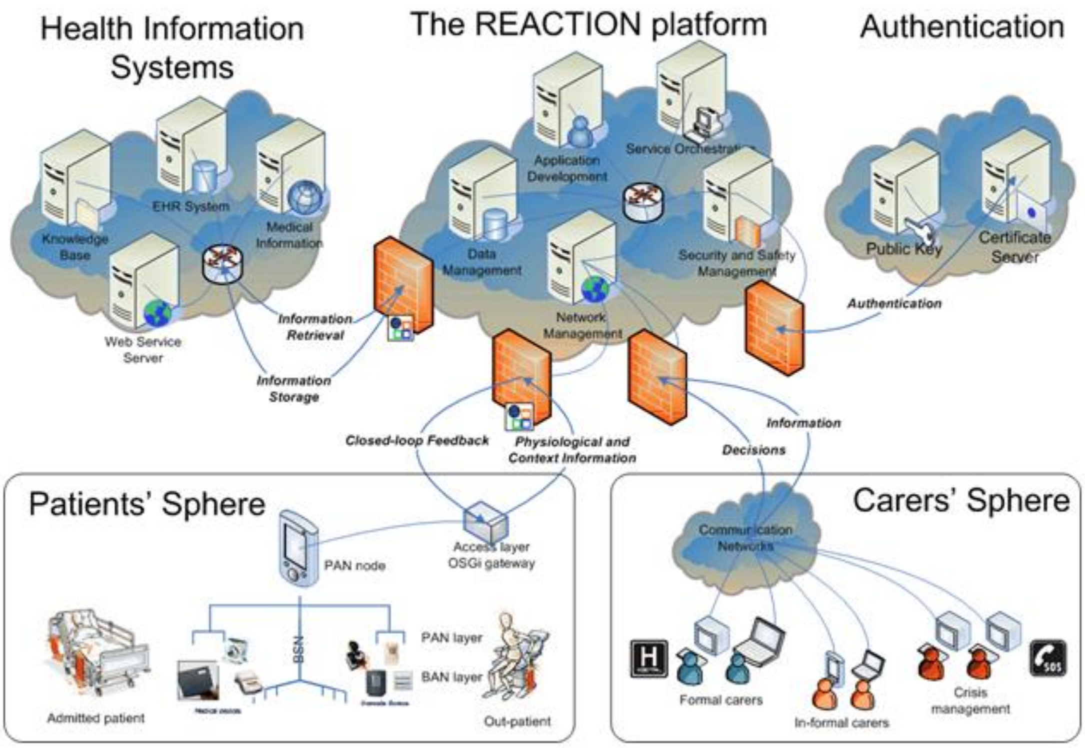
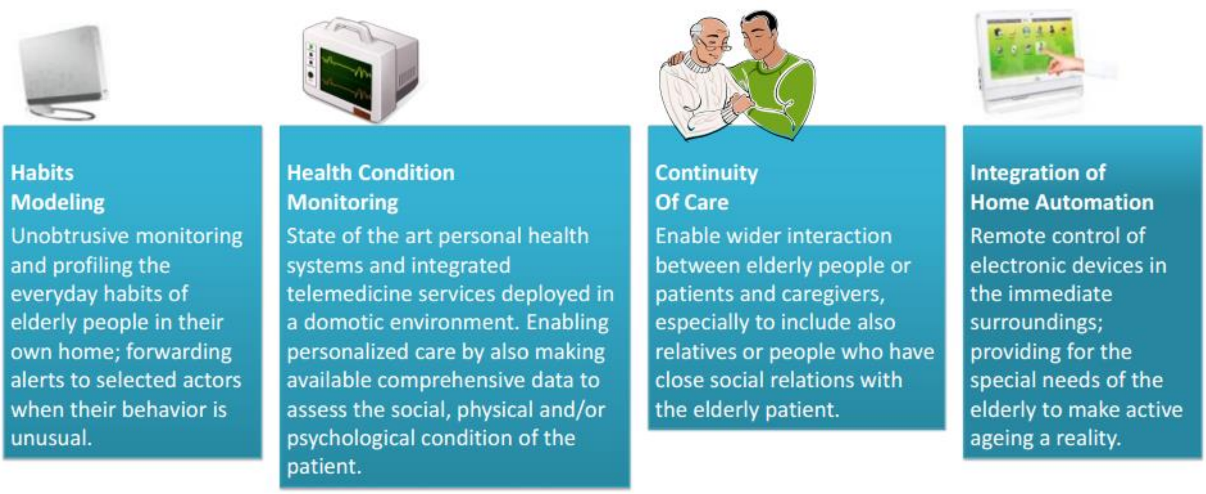


Figure 39: the REACTION platform with adjacent spheres

inCASA[135]

Thissolution aimed at helping elderly people at home through monitoring of their chronic condition health. This platform is built by using state of the art information and communication technologies (ICT). It includes integrating solution/services for e-health/environment monitoring to collect data and analyse data in order to profile user behaviour, implement customised intelligent multilevel alerts/communication services. These services had focus on European elderly people to extend the time people can live in their preferred environment by increasing their autonomy, self-confidence and mobility as well as improving the quality of life. The senior citizen in Europe is encouraged to promote a better and healthier lifestyle to minimize the risk of co-morbidity by using a stable and secure network with their care organisations or families. This framework offers common approaches.



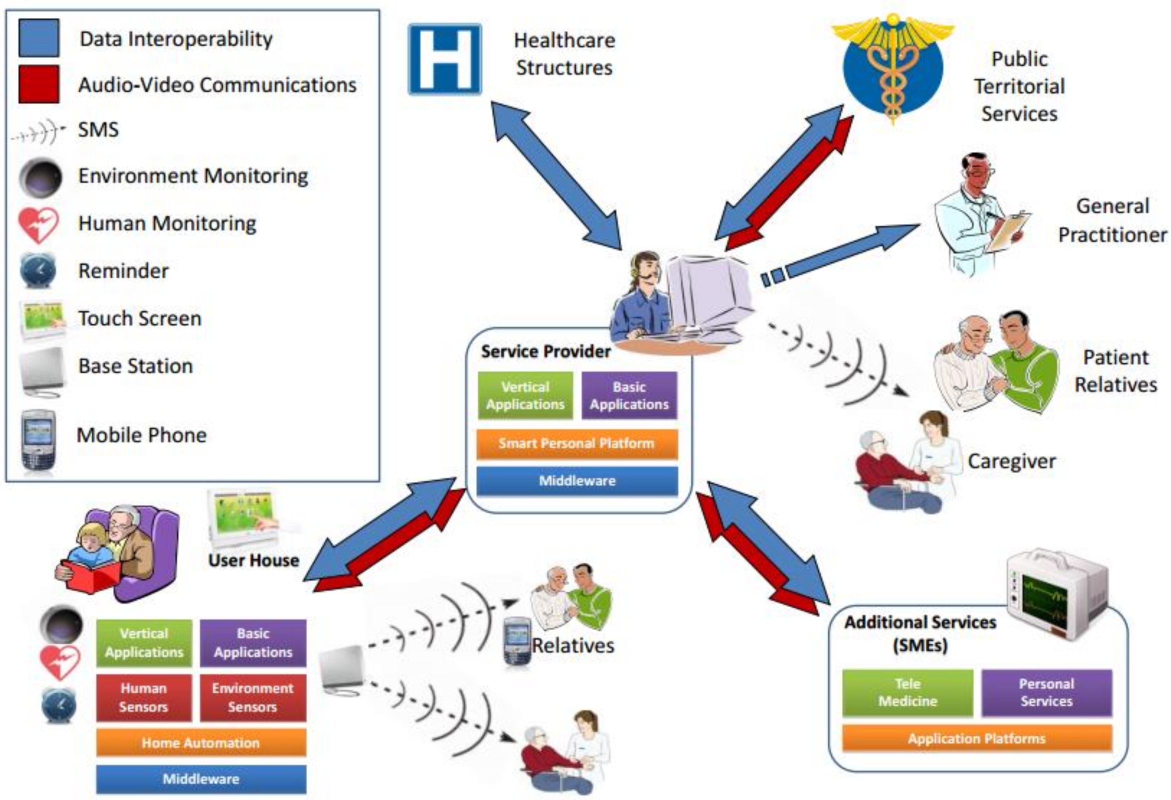


Figure 40: inCasa platform & combination of Telehealth + Telecare for quality of life to EU elderly people

4.3.3 Personal Health Record

Over the past several years, there has been a remarkable upsurge in activity surrounding the definition of personal health record (PHR) by the American Medical Informatics Association's College of Medical Informatics.Personal health records include applications to assist patients to be involved actively in their own care or wellbeing[136]. However, personal health record systems include decision-support capabilities that help patients to manage chronic condition[128]. In addition, the importance of integrated PHRs with electronic health record systems (EHR), for fully support improvements in patient health outcomes, has also emphasized in several studies[137,138,139,140].

The Apple HealthKit

As the number and variety of mHealth apps and devices (see e.g., Ant+, Whithings[141]) increase, more commercial solutions for their integration become available These play a similar role as the generic middleware platform approaches do, although they are mostly based on proprietary solutions.

The Apple HealthKit[142] is an integration tool that enable apps to share and present health data by presenting an integrated view on the phone. IPhones with iOS 8 or newer have this new health app pre-installed, which is responsible for presenting and managing a variety of health data sources. Graphical presentations such as graphs and lists are already built into the health app, resulting in shorter development cycles for apps that provide health and fitness services to iOS. The developer can then focus solely on the integration between the devices and the phone while letting development kit take care of presentation and sharing.

Figure 41: Integration of health app data (from www.apple.com)

Besides presentation, apps can also share data through the HealthKit. Thus, an app designed for running (s.a. Runkeeper) can then access data from other sensor/well-being devices e.g., smart scales (c.f. Withings), making it possible to calculate burned calories. This is a simple example, health data can be combined in much more complex ways. Requirements for HealthKit is an iPhone with iOS 8 or newer, iPad is not compatible. Data must be synchronized locally though health data is currently stored on the phone.

HealthVault[143]

HealthVault has a framework based on personal health record that allows each person to store its own health information online everywhere at any time. These services allows connection of patients and doctors, hospitals, pharmacies, insurance providers. The application allows connectivity to medical devices such as blood pressure, pedometer, weight scale, peak flow meter and pulse oximeter.

The platform allows uploading of health data both manually or paper based medical records, which can convert to electronic records by a nurse or trainer and then imported to into the HealthVault. These possibilities enable sharing of information between allowed actors who have access to data in a secure network. The user as owner of data can determine which applications get access to his/her data and what kind of access these applications are allowed to have.For example, a diabetes patient can give READ and WRITE access to his/her diabetes clinical team. The platform also provides authentication services. These services include account management by the users and sharing account with family members. This platform also enables connecting to other mobile applications that includes important health information’s such as Microsoft Health,mPHR2,CareCoach, HealthWallet, HoMedics, In Touch EMRand iTriage.

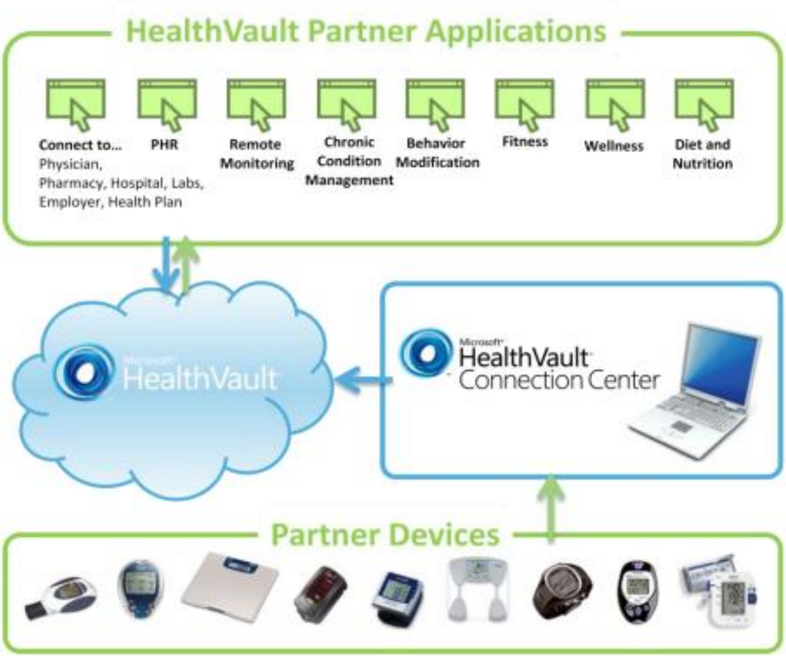


Figure 42: Health Vault Ecosystem and IT-infrastructure

HealthVault software development kit (SDK) has developed for .NET, windows 8, Android and ios (iphone + ipad). HealthVault can integrate to other wellbeing applications and sensor based devices such as FitBit or MyfitnessPal and runkeeper too. The platform supports DICOM application for medical imaging and it allows uploading and download medical imaging DVD through.

The Table below has shown a summary of connections model for HealthVault.

Table 10: Summary of Health Vault application connection Model

Model	Description	Pluses	Minuses
Native HealthVault	The application uses HealthVault user authentication, data types and storage.	User signs up and signs in only once per session. Data integration with HealthVault is seamless. Application doesn't have to maintain its own data store.	Application is dependent on HealthVault for several essential services and functionality.
Linking	The user authorizes an application to link to their HealthVault record so that the application can read data from or write data to HealthVault with or without user intervention. Applications should provide functionality for user to cancel or update the link at any time from within the application.	After setting up the link between HealthVault and the application once, data can flow between them (in batch mode) without further user involvement.	There is extra intricacy in design and development as user's PersonID and RecordID are required to be retrieved from HealthVault and stored locally for offline data access.
Patient Connect	The user authorizes an application to read or write data to their HealthVault record via an experience on HealthVault.com.	The application doesn't need to build a patient-facing web experience; only a one-time setup on HealthVault.com is necessary. The application can then read or write data in the user's HealthVault record as necessary.	
Drop-off/ Pick-up	The application "drops off" data to HealthVault and the user "picks it up" and adds it to their record by entering a numerical code and answering a secret question.	The user initiates the actual data exchange with HealthVault and therefore does not need to give the application any access to their HealthVault record. This is good for situations where the patient and the application do not need a persistent connection.	Since a persistent connection is not made between the patient and the application, every time the patient wants to pick up data from the application, they have to enter a code and answer a secret question as though they were doing it for the first time.
Software on Device Authentication (SODA)	Software on Device Authentication (SODA) applications are client applications whereby each install of the application has a unique identity in HealthVault.	Supports distributed desktop and mobile device applications. This is appropriate when your application is distributed and not hosted in a secure environment, such as a data center.	User must make at least one trip to the web in order to authorize their installation of the application. The user experience must be carefully crafted to ensure the user is guided smoothly from the application to HealthVault and then back to the application.

MyCare Pathways (My Care flows)

The objective of MyCare flows is to facilitate Swedish citizens to follow their own care in the healthcare flow to manage especially lung cancer, stroke and heart disease as well as hip surgeries and health disease.

The platform is developed based on business models that meets needs for exchanging of various information strategic alliances among several of caregiver's organisations, companies and similar residential services.

The platform includes an API gateway that enables Health 2.0 companies can build application that interact with electronic health records (EHR) in a national level. This is an open platform offers a information infrastructure that covers and define different aspects of security such as form of services, resource statute services and integration of services.

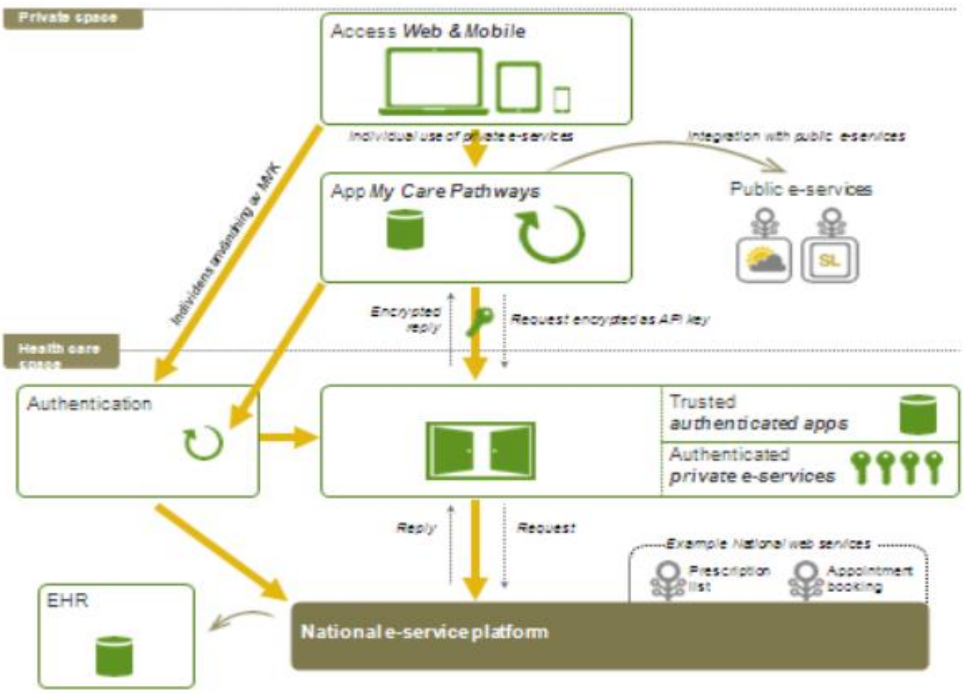


Figure 43: MyCare flow infrastructure

The services are also compatible with standards of information integrations such as HL7 v3 Green CDA 2 that agrees to all patients to have a better overview over their own information's such as referrals, lab, radiology images, scheduling of care visits, prescribed medication and preferred care provider[144].

As My Care flow is developed based on different aspects of patients' needs through performing needs of patients and requirements analyses with distinct patient's groups and also patients engagement framework aspects (inform me , engage me, empower me and partner with me) , the solution has meet successfully patient centric design too[140].

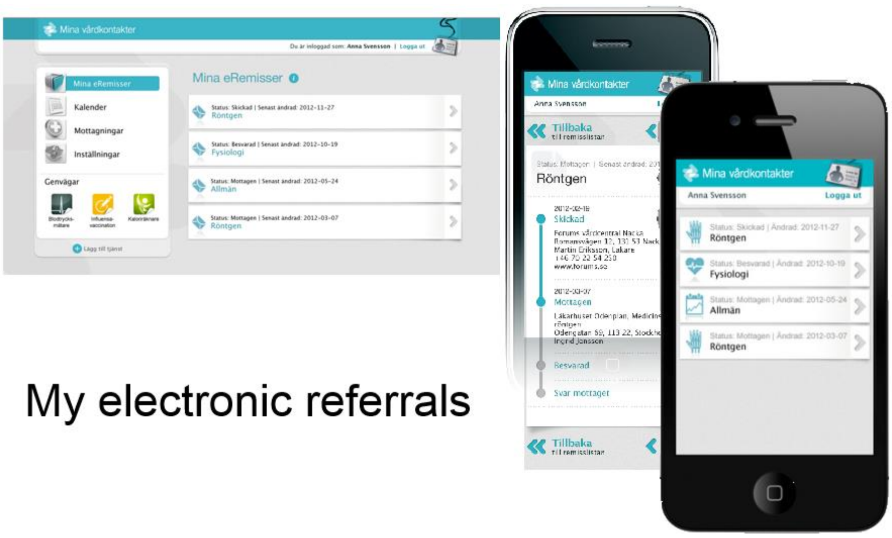


Figure 44:GUI of e-services in MyCare flows

Table 11: Summary of e-services of My Care flows

e-Service	Description
My Calendar	A service to keep track of care-related or personal appointments and get reminders about appointments and encounters
My Medicine	A service to keep an overview of the list of earlier and current drug prescriptions, to get information about drugs (e.g. contraindications) and prescriptions (e.g. retrieval date, reminders about renewal) as well as instructions for administration
My Diary	A service to enter personal notes, keep track of the personal health condition (e.g. problems, self-rehab activities, self-monitoring of medical data and life style factors), and to share that data with care givers
My Care Providers	A service to manage contact data about physicians, institutions involved in the care process (e.g. hospital department, rehabilitation clinic), the stroke team, and nurses. Additionally, the service contains dates of stays at different institutions and other measures to compare and choose between different health care providers.
My Health Information	A service providing an overview of the patient's diagnoses, treatments, patient history, and laboratory results in an understandable way.
My Information flows	This service represents an excerpt of the patient record concerning the flow of documents and information between different care givers (e.g. discharge summery).
My Referrals	Sub-service within My Information flows that enables the patient to keep track of referrals between different health care providers
My Aids	A service containing information about the available and technical and cognitive aids
My Rights	A service helping to clarify the patient's rights in terms of care choice and guarantees

LinkWatch[145]

LinkWatch is an intelligent platform for medical data collection as well as monitoring of patients at their home. The platform enables monitoring of vital signs as well as weight and physical activities. The data can be collected via touch PC, tablet or hidden data receiver based on individual interest of technologies and needs.

Figure 45: LinkWatch medical device and Touch Screen

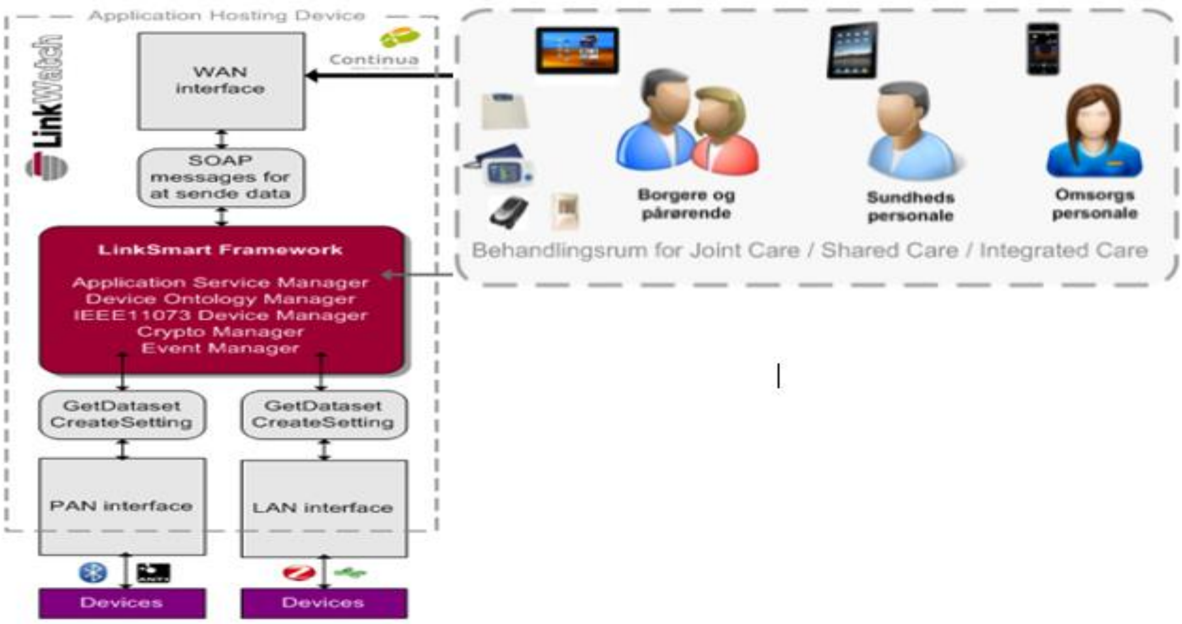


Figure 46: LinkWatch based on LinkSmart Framework

The platform enables data acquisition equipment through an engine that consists of LinkWatch TeleMonitoring for using of long-term user-driven design process. The physical measurements of patients and activities will be transmitted automatically into the platform. The patient can measure or reject them as confirmations. Once the patient approves the measured data, it will be send to the server while the patient receives a feedback clearly for transaction that is completed. LinkWatch also supports peak flow meter, blood glucose meter, Heart Rare, ECG. Those communications are via Bluetooth, NFC, ZigBee, ANT + and USB.

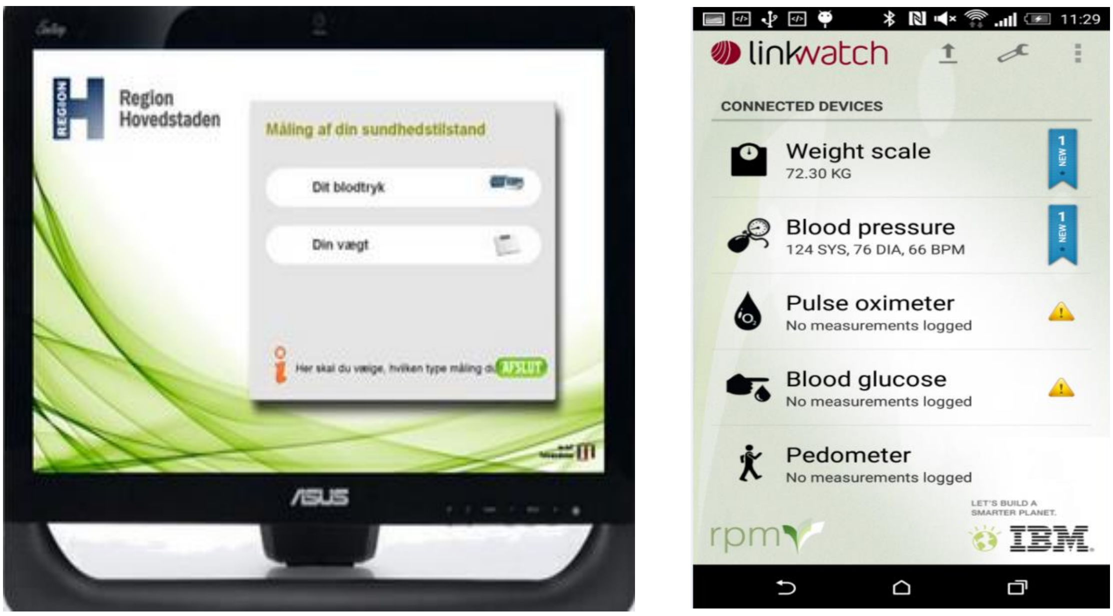


Figure 47: GUI of LinkWatch on Android & Touch PC

The user interface has achieved huge acknowledgements by the patients as user-friendly and easy tools to use at their home. The figure 12 exposed some screen shuts.

4.3.4 Relation to MyairCoach

In developed countries, the chronic diseases indicates high percentages of death and more than 75% of health expenditure[146]. The importance of self-management strategies for chronic illness to deliver healthcare outcomes has been highlighted over twenty years[147].

As asthma is the most serious global health problem among chronic condition health, the importance of self-management is emphasized by global recommendation for asthma population [30].

In addition, it is highly recommended by the global asthma recommendations, a written plan to asthma people is critical to assess different level of asthma control[148]. Therefore, all patient with asthma should be skilled and trained in their own self-management program by using of a written action plan to enhance the understanding of the disease and involving them to their own care while receiving appropriate respond to worsening their asthma conditions[146].

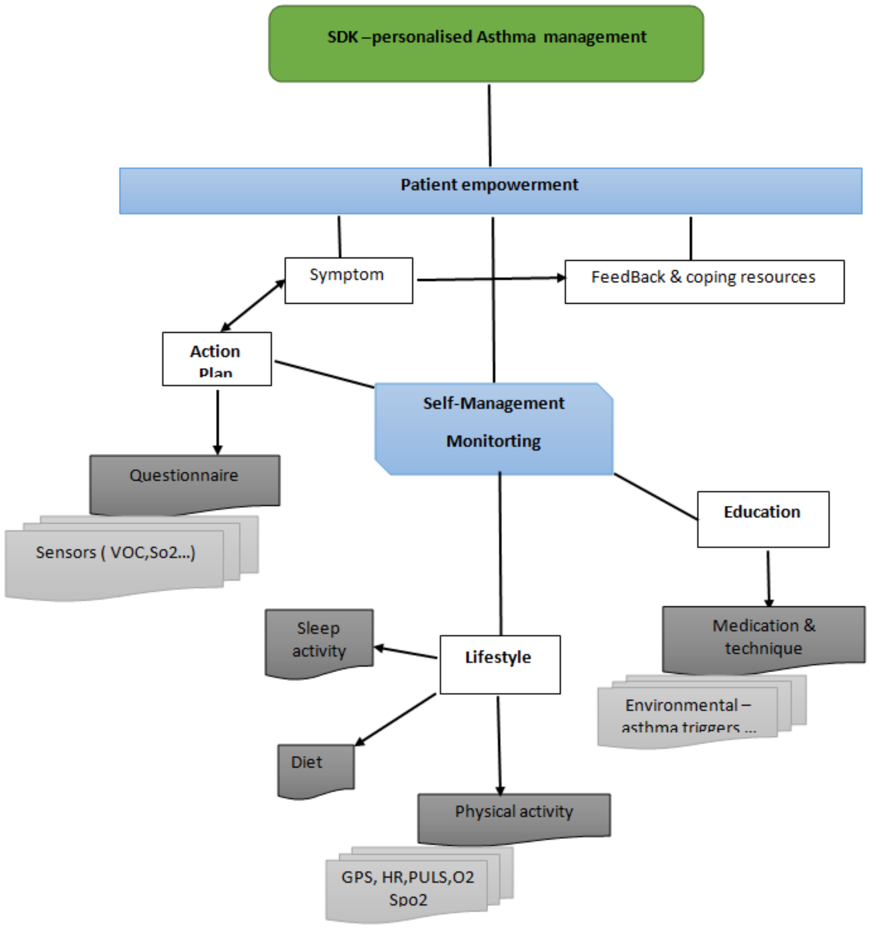


Figure 48: SDK –asthma for patient's empowerment

The optimal treatment of Asthma patients is a big challenge as it depends on managing dynamic circadian parameters such as behavioural factors, physiological state, environmental parameters and treatment compliance (DOW).

When developing many mobile applications in healthcare chain in EU countries, the interoperability is recognized as major issues for information's exchanging among different actors in healthcare [1].

Due to meet challenges regarding diverse dimensions such as interoperability and standards in all categories and layer of myAirCoach platform, and user centric design based on users' needs through engaging patients, improving and developing appropriate software development kit (SDK)and open API based on Asthma needs will be beneficial in into asthma patients daily life.

4.4 Digital Tele-monitoring self-management programs for people with chronic diseases

Information and Communication Technology (ICT) plays an essential role in supporting daily life in today's digital society[149],[150]. In health care, ICT has the potential to enhance the quality of care in the management of patients with chronic diseases, to improve adherence with therapy and allowing early detection of exacerbations by continuously monitoring and providing feedback to the patient[151] . Internet-based strategies have been shown to be beneficial in the management of a variety of chronic diseases such as hypertension[152], HIV[153] and chronic heart failure[154] by enabling patient empowerment and behavioural change[155],[156]. Moreover, there is an increasing demand from patients for using internet applications in the management of their diseases[157].

According to the current asthma guidelines, treatment strategies should target minimization of symptoms, optimization of lung function and prevention of exacerbations with few medication related side-effects[158]. However, despite wide availability of effective therapies for asthma, a considerable number of patients do not manage to achieve these proposed targets and experience a profound burden of disease[159,160] with a significant impact on their quality of life and on society as a whole[160]. ICT support might play an important role in order to improve the management of patients with a chronic disorder, including asthma.

4.4.1 Self-management

Self-management refers to the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent in living with a chronic condition. Efficacious self-management encompasses ability to monitor one's condition and to affect the cognitive, behavioural, and emotional responses necessary to maintain a satisfactory quality of life[161]. To effectively self-manage, the patient needs to:

- Accept the diagnosis and understand the condition
- Understand the purpose of the medications and be able to use medication and devices correctly

- Appreciate the importance of environmental influences, including lifestyle
- Recognise factors that make the condition worse
- Understand the value of self-monitoring
- Be able to recognise and treat worsening symptoms or function
- Know when to seek urgent medical attention
- Appreciate the need for regular structured review [162].

For most patients with asthma, much of this information may be summarised in a written action plan, developed in collaboration with the patient. The action plan also provides a structure for sharing information with patients about the following topics:

- information about what represents good disease control,
- their usual therapy and its purpose,
- signs that suggest that their condition is worsening,
- when to increase existing treatment,
- when to start reserve treatments, and
- when to seek urgent medical advice[162].

Many patients find it difficult to manage their health on a day-to-day basis. Self-management support is the help given to people with chronic conditions that enables them to manage their health. Self-management support goes beyond simply supplying patients with information. It includes a commitment to patient-centred care, providing clear and useful information to patients, helping patients set goals and make plans to live an active and healthier life.

The use of ICT in the management of patients with asthma could potentially help to overcome some of the barriers at the patient, professional and organizational level which hamper the effectiveness of conventional asthma therapies. Firstly, ICT might empower patients with the tools and skills to become adequate self-managers and thereby gain control over their disease. For patients with asthma this includes self-monitoring (for example lung function), being able to detect and respond to symptom worsening, possibilities to tailor medication to their individual needs, and the ability to easily contact a professional. Secondly, health professionals may find ICT useful in order to interactively support patients' self-management, establishing a patient-professional partnership. Thirdly, at the organizational level of healthcare, ICT might enable proactive care, for example by providing easy to use and personalized asthma action plans[163], and by identifying patients who are at risk of symptom worsening[164].

Although many variants of ICT applications have been developed for management of individual patients in the respiratory field[150,165,166], there are only sparse data on their effectiveness and, therefore, the role of these applications in asthma (self)-management is still unclear.

4.4.2 Tele-management: definition

In the medical scientific literature there is a wide variability in terms to describe the usage of ICT applications in support of self-management of chronic diseases. Some of the commonly used terms are eHealth, telemedicine, telehealth, tele-monitoring and tele-management. Whereas, eHealth refers to the complete field of health services which are delivered or enhanced by ICT[167],[168], the definition of telemedicine and telehealth refers to the delivery of healthcare services to remote areas by using ICT for information transmission from the patient to a healthcare professional, and back to the patient in order to save consultations and avoid journeys[169],[170]. From a patient care perspective, also tele-monitoring is inherently reactive, patient problems can be detected which are then responded to by a remote clinician.

The term tele-management is more focused on the ongoing management of the individual patient by employing ICT applications[171]. In this review tele-management will be defined as an interactive and proactive management approach, consisting of an ongoing partnership of patients and professionals supported by ICT and focused on clinical outcomes and patient goals in the individual. The cornerstone of tele-management is supporting patient self-management and tailoring treatment to the individual patient needs. Tele-management may be useful for several reasons. First, disease activity is typically monitored by subjective physician assessment in the office and via validated clinical measurements. Tele-management may improve disease monitoring through more frequent assessment of symptoms, signs and patient goals and may reveal worsening of the condition for patients and professionals. Second, tele-management may be an effective mechanism to provide tailored education to patients and support self-management decisions. Third, tele-management has the potential to assess adherence to medical therapy and to monitor for side effects from medications. Therefore, a tele-management approach consists of the following components: an individualized treatment plan including self-monitoring and goal setting, medication management including alerts and reminders, case-specific education and a written action plan, and integration with the electronic medical record of the health care provider[172,173].

4.4.3 Tele-management: reminders and medication adherence

Adherence with medical advice and treatment has been one of the major challenges for today's health-care systems worldwide. Mobile phone-based interventions have gathered interest and are considered promising in this area of health systems[174].

It has been shown that SMS and telephone reminders are effective in increasing the rate of attendance in clinics in diverse settings. Wide penetration of mobile phones in addition to directness, convenience, immediacy, confidentiality, and low-cost characteristic of SMS makes it an appealing way of increasing medication adherence[174].

Free *et al.* conducted a systematic review to assess the effectiveness of mHealth interventions on health behaviours of consumers in the United Kingdom. One of their aims in reviewing 26 trials was to assess if SMS was effective in increasing adherence to ART [175]. They showed that communicating with SMS decreased the viral load with a relative risk of 0.85 (95% CI, 0.72-0.99). However, they concluded that although this intervention was effective, it should be tested in other contexts and also its cost-effectiveness should be investigated[175]. Kannisto *et al.* performed a narrative literature review of 60 studies and concluded that although SMS reminders are used with different patient groups in health care, SMS is less systematically studied with randomized controlled trial study design[176]. Although the amount of evidence for SMS application recommendations is still limited, having 77% (46/60) of the studies showing improved outcomes may indicate its use in health care settings. However, more well-conducted SMS studies are still needed[176].

Tao *et al.* conducted a meta-analysis of randomized controlled trials (RCTs) up to January 2014 which evaluated the effects of electronic reminders on patient adherence to medication in chronic disease care[176]. A random-effects model was used to pool the outcome data. Subgroup analyses were performed to examine a set of moderators. Data from 20 studies, representing 22 RCTs, were synthesized. Thirteen trials utilized short message service (SMS) reminders, three used pager reminders and six employed electronic alarm device-triggered reminders. The meta-analysis showed that the use of electronic reminders was associated with a significant, yet small, improvement in patient adherence to medication (pooled Cohen's d=0.29, 95% confidence interval 0.18, 0.41). The effect was sensitive to sample size, type of disease and intervention duration. The frequency and type of electronic reminders appeared to have no moderating effect on medication adherence. Therefore, the use of electronic reminders seems to be a simple and potentially effective way of improving patient adherence to chronic medication.

A recent study in primary care patients with asthma compared inhaler reminders and feedback and/or personalized adherence discussions with active usual care alone[177]. GPs received action plan and inhaler technique training. GPs enrolled patients prescribed combination controller inhalers, with suboptimal asthma control. Inhaler monitors recorded fluticasone propionate/salmeterol adherence and provided twice-daily reminders for missed doses, and adherence feedback. The authors concluded that inhaler reminders offer an effective strategy for improving adherence in primary care compared with a behavioural intervention or usual care, although this may not be reflected in differences in day-to-day asthma control.

4.4.4 Tele-management: self-management of asthma and other chronic disorders

Tele-management projects and programs have been designed to help in tertiary prevention and management of different diseases such as diabetes, cardiovascular diseases, asthma, mental and psychiatric conditions, chronic obstructive pulmonary disease, and others[178]. de Jongh et al. conducted a systematic review to assess the effects of SMS and MMS in helping people self-manage their long-term illnesses. They also aimed to assess the users' opinion about the interventions, utilization and costs of health-care services, and also safety of interventions. After reviewing four randomized controlled trials (all classified as of moderate quality), synthesis of the evidence showed no significant effects for SMS or MMS in controlling glycosylated hemoglobin (HbA1c) (an index of diabetes control over prolonged period of time), complications, and body weight in diabetic patients in comparison to usual care or e-mail reminders; no significant effect in hypertensive patients for mean blood pressure or frequency of achieving controlled blood pressure; but significant improvement in asthma patients in peak expiratory flow variability and symptoms score. Self-management capacity scores were improved in diabetic patients. The authors concluded that messaging interventions might be beneficial in self-management of long-term illnesses. But long-term effects, acceptability, costs, and risks of these interventions should be assessed accordingly[174,178].

A meta-analysis conducted by McLean et al. included 21 randomized controlled clinical trials on tele-healthcare interventions in both children and adults with asthma[179]. These studies embodied a broad range of different interventions varying from follow-up of medication adherence by telephone to internet-based self-monitoring and feedback. The authors conclude that tele-healthcare was not associated with a clinical relevant improvement in asthma related quality of life or risk of visits to the emergency department. However, in this meta-analysis there were only few examples of a comprehensive tele-management approach in asthma. Furthermore, patients in the control strategies often received an enhanced form of usual care, which makes it difficult to draw final conclusions on the effectiveness of tele-management in asthma. In the study by Van der Meer *et al.* in patients with mild to moderate persistent asthma it was demonstrated that a comprehensive tele-management approach consisting of a treatment plan, self-monitoring of lung function by FEV1 and asthma control with feedback, and e-communication with a professional to support the patients' self-management can lead to significant improvements in quality of life, symptom-free days, asthma control and lung function as compared to usual care[180]. More recently, a post-hoc analysis of the study demonstrated that patients with partly controlled or uncontrolled asthma benefited the most from the tele-management strategy[181]. In addition, this study showed that about 60% of the patients were still using the tele-management service on their individual indication, after one year. There was a wide variability in the intensity of the usage of the tele-management service, based on patient preferences, which was the most intensive during the first three months. This illustrates that tele-management does not seem to make patients too dependent on technological support but rather supports informed and educated patient autonomy.

In addition the benefits shown in patients with mild to moderate asthma, tele-management might be particularly advantageous for children and adults with severe persistent asthma who are at higher risk of hospital admission due to asthma exacerbations or patients who have prednisone-dependent asthma[182,183]. In a study performed in Taiwan[184] it was demonstrated that patients with severe asthma who were managed via a mobile telephone based interactive system had a significant improvement in lung function and reduced number of exacerbations as compared with patients included in the usual care strategy (paper self-management tools only). The patients in the mobile phone group received a software package for their mobile phone, which consisted of an electronic diary (peak expiratory flow rate, daily asthma symptom score, need for reliever use) and a treatment decision support tool which gave feedback based on the level of asthma control from the previous seven days.

Another study focused on tapering of oral corticosteroid dose in patients with prednisone-dependent asthma[185]. In this randomized controlled trial a strategy combining an internet-based tool and daily monitoring of symptoms, lung function and Fraction of exhaled nitric oxide (FeNO) was superior to usual care in tapering the dose of oral corticosteroid in patients with prednisone dependent asthma, without decreasing lung function or asthma related quality of life. Patients in the internet-group had access to a web-page consisting of an electronic diary (lung function, FENO, daily asthma symptom score and assessment of asthma control), on which patients received direct treatment advice.

Summarizing, studies in adults show that tele-management applications, whether involving mobile telephone-based interactive systems or internet-based systems, are promising tools for supporting the management of patients with asthma. There is increasing evidence that a comprehensive tele-management approach leads to an important and sustained gain in quality of life and clinical outcomes, especially in adult patients with moderate to severe asthma and supports informed and educated patient autonomy. Novel sensor -based intelligent technologies have high potential to further improve clinical outcomes and quality of life.

4.4.5 Quality of life technologies

Technologies to maintain or enhance the physical, social, or emotional functioning that can be applied in a tele-management approach in order to achieve or maintain a satisfactory quality of life have been named quality of life (QoL) technologies[186]. These authors have identified four relatively orthogonal QoL attributes that can be used to characterize QoL systems[186]:

1. *Functional domain targeted*: Technologies typically address a specified need, which may be narrow (e.g., monitoring glucose levels) or broad (e.g., enhancing mobility). Identifying the need being addressed is critical for at least two reasons: (1) it helps define the significance or potential value of the technology and (2) it helps identify appropriate outcome measures for assessing its effectiveness.
2. *Compensatory, preventive and maintaining, or enhancing*: Technologies can be viewed as existing along a continuum where they compensate for diminished functioning at one end and enhance normative functioning at the other. In between, they may prevent decline or maintain functioning, or serve to alert the individual or an observer to an impending threat to functional ability. Highly adaptive or intelligent technologies will have the ability to address the needs of individuals throughout this continuum.
3. *Passive or interactive*: This dimension characterizes the extent of user involvement in operating the technology. One of the trade-offs between passive and interactive systems is that passive systems generally require more intelligence to achieve the same goal.
4. *System intelligence*: Technologies vary in the extent to which they perceive, reason, learn, and act in the service of addressing individual needs and desires regarding their QoL. Most existing technologies have limited capacity to adapt to user abilities, needs, preferences, and environments. The development of

intelligent systems is a fundamental goal of the next generation of QoL technologies.

myAirCoach will concentrate on technologies that provide direct functional benefit to the user and that are of particular value to individuals with existing or emerging functional impairments due to asthma. These next generation of QoL technologies will need to have the ability to monitor individuals in their natural environments, intelligently adapt to the capacity and needs of the individual, and provide appropriate levels of assistance that significantly improve functioning while maintaining high levels of individual autonomy.

Current QoL technologies cover a variety of services for management of patients with chronic conditions[174,178]. Many mHealth devices are available under the Health & Fitness category of iTunes and android app stores. Although not specifically developed for patients, these devices allow people to track performance, similar to monitoring clinical conditions, and to plan workout, similar to management of chronic conditions and might therefore play a role in patients with a chronic condition like asthma. Many patients with obesity or asthma overestimate their health status as excellent or very good. Mobile health devices may help them to monitor their clinical condition. Patients after an exacerbation are more likely to be motivated to manage their condition well to prevent the next exacerbation based on their own experience. People without this experience fight a potential attack that might or might not come in the near future. For those, it is quite rational to choose immediate benefits from a lifestyle for sure over only potential hazards in the far future. When providing mHealth and fitness applications, the willingness to engage in health behaviours needs to be addressed for the respective group of users.

Both mHealth applications for the management of chronic conditions and mobile sports applications track users' performance and physiological states with diagrams plotting variables over a period of time[178]. With increasing numbers of sensors, we would expect increasing difficulties to decide which readings are important and which are not. Most users will not be able to understand this huge amount of available information, and professionals will not have the capacity for processing that much information for that many patients[178].Even if users would understand the data, it is unlikely that they can apply the implications for their behaviour and health. Research on health behaviour has investigated for decades the motivation-action gap within the field of preventive medicine: many people know that they should change their lifestyle, but only a few succeed. One result from that research is that people need metacognitive support for translating their goals into specific behaviours[178]. For example, people often start with general goals, like losing 4% body weight in 4 weeks (DietBet, version 1.2, DietBet, Inc.). For reaching that goal, they need to plan actions that are expected to result in that outcome. Not knowing which action will result in how much weight loss contributes to the motivation-action gap. The second hurdle for reaching health aims is the difficulty to backtrack success or failure to causing actions. Most of these reports plot one variable at the time. They do not explain relationships and they do not conclude advice based on the data despite having the technological potential to do so[178].

To summarize, given an increase in sensor data for mobile health and fitness applications as implementation of a tele-management approach, there are issues to address concerning users' motivation, needs, and preferences. It is unlikely that increasing the amount of potentially available data will increase users' understanding or progress toward their personal health goals. First, they have difficulties with reading, understanding, and integrating the data. Second, they will encounter problems when concluding implications of data for their behaviour.

4.4.6 Intelligent coaching solutions

For solving the challenges concerning users' characteristics and understanding data for deriving implications for users' behaviour, Adibi *et al.* proposed a modular approach of architecture, modelling, and tutoring as successfully practiced in cognitive modelling of human cognition and behaviour[187].

Health behaviour theories provide *Cognitive architectures* that mirror our current understanding of the human mind[187] and provide the theoretical background for interventions by defining parameters of attention, memory, reasoning, problem solving, learning, and skill acquisition. Health behaviours are defined as aiming for good health by preventing illness when healthy or restoring health when ill [178,188]. Theories agree that there exist several factors impacting behaviour change and/or that change happens along different states. The health action process approach (HAPA[189],) integrates concepts from most health behaviour theories and describes behaviour change as a process along several states, from motivation through planning to action. Physiological theories complement health behaviour theories by contributing physiological parameters for behaviour change. Most QoLT evaluation dimensions focus on physical decline of functioning and technical support, neglecting patients' cognitive coping strategies. Adjusting to a patient's current physical functioning level displays global system intelligence. Taking into consideration day-to-day performance adds a layer of local system intelligence of adjusting support to current needs.

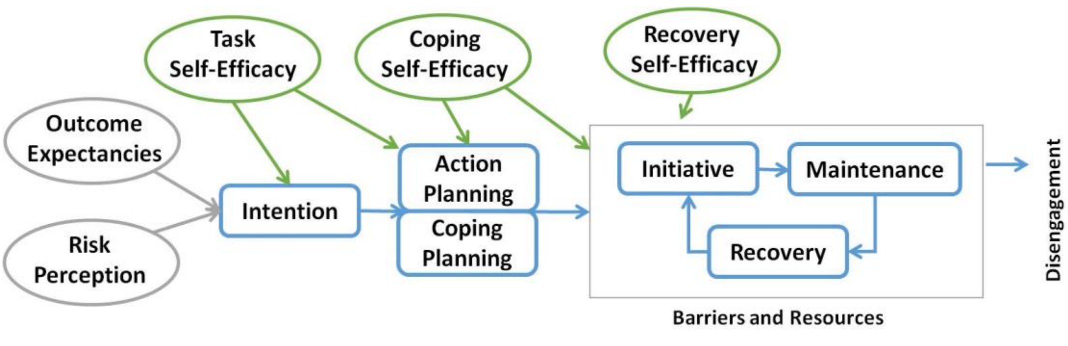


Figure - Schematic representation of the Health Action Process Approach (HAPA).

Cognitive models for specific tasks complement the theory with task-specific knowledge and skills while adhering to the structural constraints of the cognitive architecture for a variety of task domains. Great advantage of cognitive models is that they simulate an individual user performing a specific task and produce exactly the same data as human participants do[178]. Cognitive models produce the same simulated sensor data as users would base on model states. Finally, cognitive tutoring systems build instruction for a domain on the cognitive architecture, on knowledge about the task domain, and on educational principles.

Cognitive tutoring systems[178] are able to provide in-time, personalized support because they have an internal model of the user integrated that mirrors a user's current understanding and updates constantly while the user learns. For behaviour change, mobile applications supported by remote servers would do the job of cognitive tutoring systems for guiding users toward their health goals.

The modular approach of architecture, modelling, and tutoring permits channelling of knowledge as it accumulates in the field for behaviour change in general, for specific behaviours, and for guiding instruction. It allows to split general parameters from task- or situation-specific parameters. It supports discriminating between theory and implementation via modelling or simulation. Updating one conceptual level can be done without modifying all other levels as well but impacting those downward from theory through model to tutoring system.

4.4.7 Relation to myAirCoach

myAirCoach will support patients in performing self-management tasks including using medication and devices correctly, recognising factors that make the condition worse and treating worsening symptoms or function or seeking urgent medical attention as part of a tele-management approach. The myAirCoach system will be grounded on models of physiological, environmental and behavioural factors that influence asthma control and the occurrence of asthma exacerbations. However, effectively using this information for self-management will depend on patients’ characteristics and understanding of these data and requires subsequent health behaviour changes. Therefore, in order to support patients’ self-manage effectively, the design of the final intelligent myAirCoach application needs to be based on a modular approach of cognitive architecture, modelling, and tutoring.

5 Conclusion

Asthma is a life-long chronic inflammatory disease of the airways, which is very common worldwide, affecting people of all age, race and gender. The knowledge and understanding on what triggers an asthma attack and how these triggers can be avoided are critical features for maintaining a good quality of life. The major objective of myAirCoach is to provide novel mHealth personalized asthma monitoring services empowering and guiding patients with asthma to manage their own health. To this end, a novel architecture consisting of an ergonomic, compact and efficient sensor-based inhaler device, which communicates with a mobile device, is proposed. This personal mHealth guidance system can empower patients with asthma to optimize their treatment towards personalized pre-set goals and guidelines (healthy lifestyle, exercise, dietary habits).

WP1 focuses on the “User needs, system requirements, architecture” of the MyAirCoach project and provides the definition of the overall user needs, the architecture and the system specifications of the myAirCoach infrastructure, in order to define and deliver a number of representative use cases and user scenarios, exemplifying the novelties of the myAirCoach framework. The first deliverable of WP1 provided the baseline definition for commencing the work of the project, by reporting on the latest developments in the specific areas that myAirCoach will address. More specifically, this document was divided into three parts that cover the current advances in the areas of : i) inhaler devices and sensors for asthma’s disease, ii) computational modelling of lung behaviour and iii) self-management, decision support and personal guidance systems for patients with asthma disease.

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