D5.1 Consolidated Roadmaps Report

Due date of deliverable: November 30th 2008

Actual submission date: January 19th 2009

Amended: February 28th 2009

Deliverable dissemination level: PU

Grant no.:	FP7-IST-2007- 215291
Project acronym:	PHS2020
Project full title:	Roadmapping Personal Health Systems: Scenarios and Research Themes for Framework Programme 7th and beyond
Instrument:	Support Action- SA
Start date of project:	January 1st 2008 Duration: 12 months
Funding Scheme:	Support Action- SA

Organisation name of lead contractor for this deliverable: MIP

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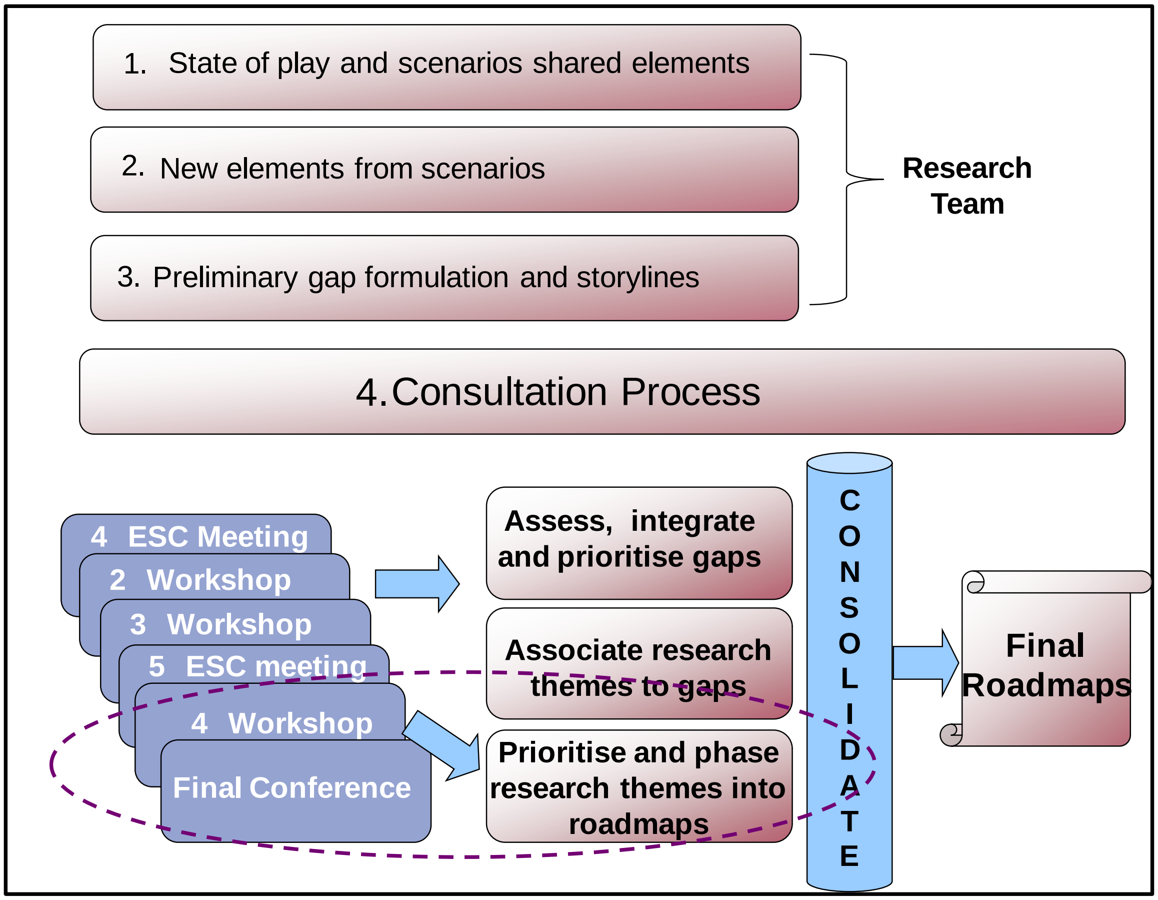
Introduction

This is Deliverable D5.1 “Consolidated Roadmaps report”, produced with the input from the two *ad hoc* roadmapping consultation events highlighted within the figure below (PHS2020 4th Consultation Workshop, Brussels 21 November 2008; PHS2020 Final Conference, Brussels 5 December 2008). The figure has been adapted from the similar version produced in the consolidated gap analysis report[1].

Figure 1: Roadmapping events within the gap analysis and roadmapping process



Source: MIP elaboration

For the reader who may want to start directly from this final deliverable of PHS2020 we provide below a very synthetic account and contextualisation of how these final roadmaps have been produced. In doing this it will be useful to first state that the detailed background can be found in the previous reports all available for download at PHS2020 project website[2]:

- PHS2020 Deliverable D2.1, *State of Play*, which reviewed the major technological innovation dynamics and the key socio-economic barriers and bottleneck;

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[1] PHS2020 Deliverable D4.1, *Gap Analysis Report*, p. 7.

[2] http://www.phs2020.com/index.php?option=com_content&task=category&sectionid=7&id=21&Itemid=27

- PHS2020 Deliverable D3.1, *Consolidated Scenario Report*, which from the trend identified in the state of play extracted four possible future scenarios;
- PHS2020 Deliverable D4.1, *Gap Analysis Report*, which extracted 54 gaps from the systematic comparison between current developments identified in the state of play and the foreseen scenarios.

Following our multi-tier approach, which mixed analysis and consultation events[3], the steps recalled briefly below have led to the production of this report.

The preliminary draft of the State of play was delivered and discussed on April 4 2008 during the 2nd Experts Support Committee (henceforth ESC) meeting and was revised following the input received.

In parallel to the revision of the State of Play, the scenarios cycle of drafting, consultation and revision was launched using PHS2020 scenarios building methodology and related tools[4]. At the 3rd ESC the very first and preliminary version of the scenarios was discussed and the input of the discussion led to the production of a second intermediate draft.

This second draft of the scenarios was presented and discussed on June 20 2008 at PHS2020 1st Consultation Workshop held in Sheffield. As a result of the input of the workshop a third draft was produced.

This third draft was discussed with Gartner’s analysts, whose input have been used by the project team to produce the fourth draft that was discussed during the 4th ESC meeting and the 2nd Consultation workshops both held in Pisa, respectively, on July 14 and July 15 2008. The input of these two consultation events were incorporated in the final version of the scenarios deliverable mentioned earlier (D3.1 Consolidated Scenario Report).

During the two mentioned events in Pisa, we anticipated the discussion and extraction of gaps from the state of play and the scenarios, as well as the preliminary association of research themes to identified gaps.

On the basis of the preliminary insights and input provided by the experts in Pisa, MIP research team proceeded to the systematic comparison of current developments (D2.1 State of Play) and the foreseen scenarios (D3.1 Consolidated Scenarios Report). This produced the first draft of the Gap Analysis Report, which was presented and discussed during PHS2020 3rd Workshop in Barcelona (26 September 2008). During this event the association of research themes to gaps was also contemplated.

Finally, the list of gaps and research themes emerging from the Barcelona workshop and summarised into the second draft of the gap analysis report were further assessed and discussed during the fifth and final meeting of the ESC held in Milan on October 6 2008.

Starting from the wide analysis of the state of play the project has been gradually zooming closer to the final expected outcome of proposing a few roadmaps for research themes to be funded in FP7 and beyond. This has implied a progressive reduction of complexity and selection of key issues and topics. In particular from the first draft of the gap analysis to this final draft, through the input of the Barcelona workshop and the 5th

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[3] See PHS2020 Deliverable D2.1, *State of Play*, pp. 8-11.

[4] See PHS2020 Deliverable D3.1, *Consolidated Scenario Report*, § 2 .

ESC meeting, we have moved from a large list of 54 gaps[5] to a shorter list of about 20 of them[6], which have been further synthesised and grouped into five domains of research already associated with preliminary proposals of research themes. This final synthesis presented in Table 5 of the *Gap Analysis Report* (pp. 39-41).

This summary table, reproduced in the next two pages as Table 1, constituted the starting platform for the discussion during the last two consultation events mentioned earlier at the very start of this introductory section. The rationale and considerations for the re-grouping of gaps and preliminarily identified research themes into the five research domains illustrated in Table 1 are presented in paragraph 4.3 of the *Gap Analysis Report* and are not repeated here. Yet, in Table 1 for each gap we added a cross reference to the synthetic box illustrating it in the *Gap Analysis Report* (with the indication of the page).

Before launching the final consultation events, starting from the final synthesis of Table 1 here (Table 5 of *Gap Analysis Report*) MIP research team performed an additional search on relevant scientific sources[7] and extracted some additional background and insights that went into the preliminary version the five roadmaps proposed for each of the five identified research domains of Table 1.

Accordingly, the final proceedings of the gap analysis consulting process and this further work on scientific sources were incorporated into the first draft of this report on the proposed roadmaps, which was discussed during PHS 4th and final consultation Workshop held in Brussels on November 21 2008.

Re-elaborating the input of this workshop a second draft was elaborated and presented during PHS2020 Final Conference held in Brussels on December 5 2008.

Finally, the input from this conference and from several written comments sent by some experts in its aftermath have been consolidated into this last and final version of the roadmaps report.

The sheer size of the work preceding this final report with the five proposed roadmaps cannot be summarised in any exhaustive way here. Yet, for those reading only this final report we provide at least some background and contextualisation. For each of the five roadmaps we present one section structured along the following three paragraphs:

1. **Contextualisation**. Where we briefly recall the key findings in terms of current development and gaps;
2. **Further insights**. Here the key input from the review of the scientific literature carried out after the closure of the gap consultation cycle are summarised;
3. **Proposed Roadmap**. A visualisation of the proposed roadmap is presented and briefly commented.

Section 6 provides some preliminary conclusions that will be further fleshed out in PHS2020 Final Book (Deliverable D6.2).

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[5] See PHS2020 Deliverable, *Gap Analysis Report*, Table 1, Table 2, Table 3 (pp. 10-15).

[6] See PHS2020 Deliverable, *Gap Analysis Report*, Table 4 (p. 17).

[7] As compared to those gathered and screened for the production of the state of play, these sources: a) have a more forward looking perspective and underline the futuristic potentiality of research and the needs for further advancements; b) include topics earlier not fully considered in the state of play.

Table 1: From gaps to research domain and preliminary themes

Research domains	GAPS	Preliminarily associated research themes
Integration External Knowledge ***(boxes: 1, 3, 5)***	• Lack of integration of updated clinical evidence, biomedical and genetic information to ensure scientific control, risk assessment, and personalisation • Validation of data from uncontrolled conditions (enucleated and moved here from Gap of Box 2)	• Integration of up-to-date medical info from bio-banks, trials; • Integration of genetic and biomedical information • Controlled studies to correlate and compare data obtained in both “clinical settings” and “uncontrolled conditions”(from context aware PHS) to identify normal and abnormal patterns of parameters uses for action/actuation taking into account personal and contextual factors (to be used for correction/rectification)
	• Need of holistic clinical guidelines and pathways to align PHS delivered care to best practices and to capture the multi-facet nature of health status	• software systems integrating and modelling guidelines within PHS
	• Need of innovative and holistic DSS for healthcare professionals to provide an holistic picture of human body complexity through prediction/simulation/visualisation	• Integration of PHS and VPH (supported by modelling and prediction); • Development of VPH-inspired interfacing for PHS DSS;
Data processing ***(boxes: 2, 4, 13)***	• Lack of capacity to process data coming from different sources and to address the issue of data generated under “uncontrolled conditions”;	• Data fusion and multimodality (data processing, interpretation and modelling capable of simultaneously treating vital and physiological signs, genetic, biomedical, and contextual parameters such as individuals activities, location, emotional status, external environment; • Correction/rectification techniques to normalise data gathered under “uncontrolled conditions”
	• Lack of capacity to recursively learn from individuals specific characteristics and context and automatically adapt data processing to personalise monitoring and enabling actuation reducing the need of healthcare professionals intervention	• Auto-adaptive and data fusional algorithms and related prediction and modelling techniques; • Development of automatic calibration
	• Lack of personalised aid decision tools for users	• Development of simulation tools based on holistic data processing (see above) and easy imaging and visualisation (see VPH related themes)
Interfacing & Interaction ***(boxes: 6, 10, 11, 12)***	• Lack of multi-channel delivery and inter-action creating risk of exclusion due to lack of access to, or confidence in, PHS typical interaction channels	• Development of multi-channel delivery and inter-action systems including more commonly used devices (i.e. mobile, Digital TV, etc.)
	• Need of more understandable and easy to interpret input and guidance to users;	• Development optimal and easy-to-use interfacing techniques; • Development of straightforward imaging;
	• Need to better inform and educate PHS users	• Development of PHS related e-Learning and web2.0 tools

Research domains	GAPS	Preliminarily associated research themes
Sensors ***(boxes: 4, 7, 8, 9, 14, 15, 16, 17)***	• Lack of capacity to capture new signs on the environment (both physical and chemical parameters) and on the peculiar situations of individuals (activity, location, emotional status) • Monitoring techniques not able to correctly link physiological signs, with motions, gestures, and environmental data;	• New sensors for context awareness (environment, emotional status, punctual location and situation, etc) and for gathering data in "uncontrolled conditions"; • Investigate out to incorporate data from environmental sensors • Incorporation of advancements in human-computer interfaces and ambient intelligence (in order to "read" emotions though facial expressions and gestures, see later) • Incorporation of on- board processing
	• Need to go beyond the "one sensor- one signal" and "one sensor- one disease" paradigm to optimise energy and bandwidth usage • Need to simplify and reduce the amount of data transfers • Need to increase flexibility and better adapt the sensors to individual characteristics (reduce invasiveness and consider allergies)	• Optimisation of multi-modality to insure multi-disease and multi-signal assessments • Self-calibration of sensors • Optimisation of sensors area networks and modularisation of components (plug & play)
	• Lack of knowledge on the long term effect of sensors contact with, and presence in, the human body; • Lack of closed loop systems moving PHS beyond monitoring and into diagnosis and treatment (i.e. dispensation and reaction): ○ Actuators in general ○ Personalised drug delivery ○ Endoscopy capsules	• Integration of researches on alternative sensors' materials (e.g., biological and molecular sensors) • New smart sensors encompassing multimodality, computational power and actuation functionalities (including alternative energy sources: i.e. body energy) • Incorporation of controlled drug delivery sensors (implantable and minimally invasive)
Lab on Chip ***(boxes: 18, 19, 20)***	• Avoid fragmentation of testing and the need of traditional lab tests to complete Point Of Care (POC) testing	• Investigation on including multiple biomarkers on a single chip • Research on "new" biomarkers more adapted to POC; • Integration of Micro-Opto-Electro-Mechanical-System (MOEMS)
	• Reduce human intervention in sample preparation;	• Development of on-board sample preparation; • Further research on micro-fluidic techniques optimising "sample course control";

Research domains	**GAPS**	**Preliminarily associated research themes**
	• Reduce time to result;	• Optimising of fluidic control and run-time; • Further research on alternative array technologies adapted to POC-solutions

Before entering into each of the five research domains and their roadmaps it is important to stress that the key summary findings reported in Table 1 above were a starting platform that, however, has been integrated and to some extent changed as a result of the additional review of the literature conducted and of the input received from the experts during the two roadmapping consultation events. Accordingly the five proposed roadmaps: ***a) include themes that do not appear in the last column of Table 1; b) include some of the themes of the last column of Table 1 in slightly modified fashion (either rephrased or grouped together with new themes; c) have dropped some of the themes of the last column of Table 1.***

1 Integration of external knowledge

1.1 Contextualisation

Data processing, sensors, interfacing, and Lab on chip, that is the other four proposed roadmaps, derive logically from our state of play and from how PHS projects have been defined and carried out so far with FP5, FP6 and FP7. On the contrary, the idea of having a separated roadmap on a research domain termed “Integration of External Knowledge” was not already inscribed in the standard parameters of how the PHS field is defined and was mainly an input from experts (especially clinicians) during the consultation process. Whereas earlier we had only marginally dealt with this issues as part of the data processing sub-system, the input received in Barcelona and during the 5th ESC meeting led us to consider them as part of research domain in their own right. The domain was termed “Integration of External Knowledge”, to covey the idea of PHS incorporating input from biomedical and genomic research and from clinical practice. It must be noted, however, that ***between the domain “Integration of External Knowledge” and “Data Processing” there are some evident overlaps[8], which could justify collapsing the two domains into one single roadmap***. We opted for keeping them separately for the sake of highlighting the novelty of integrating scientic and clinical knowledge into PHS as compared to the research projects funded so far within FP6, FP6 and FP7 under the PHS label.

It is worth stressing that the input leading to identify this new research domain emerged especially as a result of concerns elicited by the two scenarios of the “Self-Caring Society” and of the “The Caring State”. These two scenarios, although for different reasons and with different focus, envisage a large scale adoption of PHS applications, which triggered concerns especially among healthcare professionals.

First, the “Self-Caring Society” scenario was associated to the need of very strict scientific control, that is integration of PHS with the latest clinical evidence and holistic guidelines (not vertically segmented but addressing the multiple aspects of the diseases) into a closed loop with evaluation of PHS outcomes.

Second, the very large use of PHS in both the “Self-Caring Society” and in the “Caring State” scenarios led experts to questions the economic sustainability and to argue that,

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[8] See on this PHS2020 Deliverable D4.1, *Gap Analysis Report*, pp. 42-43.

without some filter, it would only increase costs and overload of information to have everyone using such applications especially with respect to those potentially suited for healthy individuals (prevention and early detection). This in turn led to identifying the need of users risk profiling to produce a stratification that help define which groups of users shoud be the target by which PHS applications. This in turn evidently called for PHS to integrate, and being informed by, evidence coming from molecular and genetic research and evidence.

Third, the “Self-Caring Society” scenarios with empowered users demanding symmetric and negotiating interaction with the healthcare professionals elicited from them the need of being provided with new and innovative predictions and simulation tools

These topics and especially the issue of molecural and genetic data, then, became part of the gap analysis and the discussion went further in the subsequent consulation events and especially in the 2nd Consultation Workshop in Barcelona (26 September 2008). In that occasion it was futher argued the need for PHS to:

- **Integrate clinical evidence and guidelines holistically**. The argument, made especially by clinicians, is that PHS do not sufficiently embed, and are not steadily fed by, the evolving clinical evidence and related guidelines. This results in healthcare professionals scepticism and fear that the use of PHS applications might have unintended consequences and damage the doctor-patient relation. When they do incorporate some level of clinical evidence and guidelines, currently developed PHS application do so in a mono-dimensional and vertical way (i.e. one disease at the time), whereas in many cases chronic patients present conditions of co-morbidity (2 o 3 more diseases)[9]. Accordingly PHS do not provide a complete picture of the individual health status and may provide inappropriate input, failing to address the needs of patients with co-morbid illnesses. It was added, though, that this lack of multi-dimensional focus characterises also medicine in general, often leading to poor quality of life, physical disability, high healthcare use, multiple medications, and increased risk for adverse drug events and mortality, thus optimising care for the co-morbid population is a very high priority (Boyd et al, 2005). Patients with multiple co-morbidities put the clinicians under tremendous pressures from different angles (Turner, 2006).
- **Integrate molecular and genetic data**. It was argued, especially by researchers working across the boundaries of medicine and informatics, that the current limitations of PHS is that they are capable of capturing only intermediate phenotypes (biochemical and physiological values) at best, while they have little or no capability to incorporate the assessment of environmental factors and of genetic information. As in the timeframe of PHS2020 it will probably be possible to have the personal genome in a few hours and at low cost, genetic and environmental factors should be included into PHS to increase their capacity of producing personalised and individualised early diagnosis, treatment and

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[9] In 1999, 48% of Medicare (USA) beneficiaries aged 65 years or older had at least 3 chronic medical conditions and 21% 5 or more (Boyd et al, 2005).

prevention. How this fits into the three building blocks, is that the models and the algorithms need to be more complete, and incorporate mentioned data. Additionally, also the feedback provided can include the crossing of the risk factors of genomic and dynamic information

On the other hand, it must be stressed that some clinicians raised strong doubts as to the time when the results from the analysis of the human genome will become fully available. We will come back to this issue in the next sub-paragraph in light of the further insight produce through the additional review of the scientific literature conducted before the final consultation leading to roadmap started.

1.2 Further insights

Knowledge into practice: a challenge for medicine as such. The need of scientific control of PHS and of incorporating in them state of the art evidence and knowledge was raised by clinicians and could indeed be seen as tactical way to justify an overall cultural resistance. In fact the problem of putting knowledge into practice is more a general and structural challenge of medicine as such rather than a pitfall specific to PHS applications. Medicine is one of the most knowledge intensive empirical sciences, frequently changed, updated, and re-evaluated, with a steady flow of new risk factors identification, new drugs and diagnostic tests, new evidence from clinical studies (Peleg and Tu, 2006). Naturally this creates a formidable challenge in terms of ensuring that such new knowledge and evidence inform even the traditional practice of medicine[10]. Much still remains to be done to ensure that lessons learned from scientific research and clinical studies and trials inform and improve the quality of health services and the availability of evidence-based medicine (Kerner, 2006). It has been even argued that efforts should go into interpreting existing knowledge more than into producing new one (Choi *et al* 2003)[11]. It is evident the need to constantly inform the practice of medicine with the canonisation of guidelines reflecting the most updated knowledge, carefully adapted on an individual basis (Durso, 2006). This would improve compliance to state of the art knowledge of both physicians and patients (Findley and Baker, 2002; Hayward *et al* 1995; Protheroe *et al* 2003; Shaneyfelt *et al* 1999; Shiffman *et al* 2003). In this respect research on **genomic information** has made a vast progress during the past years and could greatly enhance the goal of personalised treatment (Marcelino and Feingold, 1996). As seen, then, the issue of aligning practice to knowledge it is still a challenge for traditional medicine (Shortell *et al* 2007). Therefore, incorporating the most recent and evidence-based knowledge into Personal Health Systems or, to put it differently, “infusing medicine into technology” is not an easy task**.** Yet, the potential of information technology to support both clinicians and patients in gathering data, making clinical decisions, and managing medical and lifestyle actions more effectively is high and should be leveraged. It is worth noting that, however, this is not a challenge that science and technology can solve alone. It requires the commitment of policymakers, state planners,

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[10] McGlynn (2003), for instance, showed that only 55% of US adults receive care inspired by the most up to date knowledge based recommendations. Actually, it takes approximately five years for new guidelines to be adopted into routine practice (Batel et al, 2003)

[11] Some argue that the best evidence is for what *does not* work (Fixsen et al, 2005).

managers of service provider agencies (e.g., health departments, managed care organizations), and the purveyors of programs and practices (Rosenthal et al, 2005).

Indeed Rosenthal et al (2005) touch upon issues clearly captured by three gaps included in our Full List[12] and deemed correctly as being beyond the focus of technological research, which are:

- Little integration of care delivery processes (# 3 of Full List);
- Knowledge and information segmented (# 4 of Full List);
- Lack of shared platform for data repository and exchange (# 5 of Full List)

In different ways they point to the fragmentation and “Turf Wars” that the experts consulted discussed several times in our consultation and events and figure also prominently in several of the presentations delivered during the “Personal Health Systems Workshop – Market perspectives & innovation dynamics” organised in Brussels by the EC Join-Research Centre IPTS (Institute for Prospective Technological Studies) on February 6 2009[13].

The relevance of Biomedical Informatics. The vision behind the emerging field of Biomedical Informatics (BMI) is precisely that of tackling the challenges described above. BMI is emerging from the integration of Medical Informatics and Bioinformatics (see INFOBIOMED 2003 and SYMBIOmatics 2007). Medical informatics (MI), in its original sense before integration with Bioinformatics, can be broadly defined as the *intersection of information science, computer science, and health care, addressing the resources, devices, and methods required to optimize the acquisition, storage, retrieval, and use of information in health*. Health informatics tools include not only computers but also clinical guidelines, formal medical terminologies, and information and communication systems. Bioinformatics (BI), also known as computational biology, can be defined as *the creation and advancement of databases, algorithms, computational and statistical techniques, and theory to solve formal and practical problems arising from the management and analysis of biological data*[14] MI and BI originated in different context and responded to different drivers that have created a gaps between the two for some time. Indeed they differ as much as medicine differs from biology (INFOBIOMED 2003, p. 6 and pp. 13-14). MI emerged to address the practical short term objectives (rather than long term scientific ones) of delivering care and has been fragmented as a result, not only of the the very disparate needs of different specialists, but also of different administrative and management rules and practices[15]. BI has been much more focussed and oriented to science and basic research as it originated to respond to the need of managing the enormous amount of data that biological research started to produce and particularly to analyse large numbers of protein and nucleic acid sequences. BI focussed on biological sequence analysis, structural biology and molecular information repositories and its

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[12] See PHS2020 D4.1, *Gap Analysis Report*, table 1, p. 11.

[13] http://is.jrc.ec.europa.eu/pages/TFS/sps.html

[14] See for instance Cristianini and Hahn (2006), Srinivas, ed. (2006), and Baldi and Brunak (2001).

[15] This has resulted for a long time in an application-centred perspective and a wide range of different applications mostly local and with limited level of collaboration across expetise and institutional boundaries.

development accellerated also in relation to the well known Human Genome Project (HGP). BMI has emerged as the attempt to bridge these two disciplines and finds its rationale in both a more practical and more fundamental reason. First, at the practical level, MI and BI have used similar tools and methodologies such as, for instance, machine learning, natural language processing, image analysis, data mining of large database. Second, more fundamentally the rationale for merging MI and BI is the same that calls for integration of medicine and biology and reside in the well known genotype-phenotype distinction (Johannsen 1911)[16] and the related need of capturing both in order to understand the causes of diseases and improve treatment, medications and drugs development, as well as early detection and prevention. The complete sequencing of the Human Genome and the related genetic and proteomic data have opened new possibilities to grasp the mechanisms of diseases, especially multigenic ones that are more common than monogenic diseases. On the other hand, many diseases, besides the genetic component, have also an environmental component and this calls for knowing also the phenotype of diseases where classical clinincal and epidemilogical evidence comes into the picture. Naturally there are still uncertainties as to the timing when the results for the analysis of the human genome will become fully available for use. Indeed a World Health Organisation (WHO) report suggests the needs of : a) being cautious on the medical benefits of genomics especially for the timescale required; b) pursuing genomics research not to the detriment of clinical practice and of epidemiological research; and c) integrating genomics into clinical research involving patients and into epidemiological studies in the community (2002, p. 6). These are exactly the grounds on which the BMI vision rests. Results of molecural medicine and biology research can benefit clinical medicine on the one hand, and clinical data will in turn be useful for these research. As a result, many new possibilities could open up in the future. Combining individuals' genotype and behaviour may predict possible emergence (for healthy individuals) or development (for individuals with some initial signs of a disease) of diseases, and accordigly define intermittent diagnostic evaluations plan matched by recommendations regarding changes in lifestyle, a medical regimen or procedures. In order to realise these promises the large amount of data generated in the laboratory by BI must be integrated with the data and techniques of MI, electronic health records, clinical decision systems, image- and signal-processing. BMI is an emergin field aiming precisely at putting the world of BI and MI together and at contributing to the discovery and creation of novel diagnostic and therapeutic methods. So the mission of BMI is *to provide the technical and scientific infrastructure and knowledge to allow evidence-based,* ***individualised*** *healthcare using all relevant sources of information*. Indeed in two calls from the FP6, namely Call 1 and Call 4, the objective for Biomedical Informatics was defined as to *"develop and promote knowledge in the areas of medical informatics that enable disease prevention and therapy, and the development of tools enabling the* ***individualisation*** *of diagnoses and treatment"*[17].

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[16] For an analysis of Johannsen legacy see also Churchil (1974)

[17] European Commission, DG Information Society and Media, (2007), *eHealth portfolio projects – Sixth Research and Development Framework Programme, 2002-2006*, Brussels, available at http://ec.europa.eu/information_society/activities/health/docs/publications/fp6upd2007/fp6ehealth-projects_upd.pdf, (accessed January 2009).

The potential synergies between PHS, BMI and VPH. In the extract from the FP6 Work Programme reported above we added emphasis on the terms '***individualised'*** and '***individualisation'*** as this is the clear link between BMI and the need of making PHS more personalised. In fact, there is probably no other piece of information as unique to each concrete individual as his/her genetic configuration. Accordingly the integration of molecular and genetic data is a way of making PHS more personalised. On the other hand, it must be stressed that BMI is relevant for PHS also for what regards the integration of clinical evidence and clinical guidelines, which responds to the concern expressed by clinicians during our consultation workshop as to ensuring a robust control based on clinical knowledge and evidence. The best way to show how BMI could provide input to, and is in potential synergies with, PHS is to list below the key pillars of current BMI research (INFOBIOMED 2003) and the its future research agenda (SYMBIOmatics, 2007) in BMI.

Key pillars:

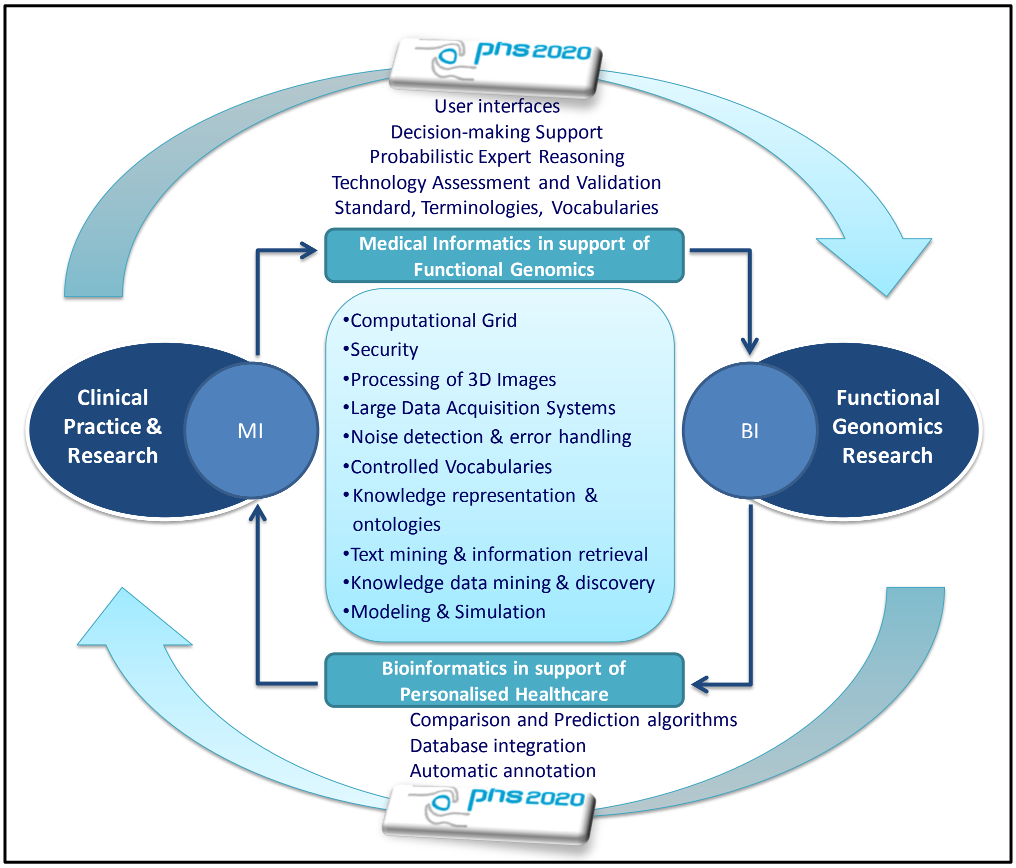
- **Patients data as input to Functional Genomics**. Functional Genomics requires patient data coming from clinical information systems (laboratory tests, annotation of biological samples or familial history). Medical Informatics can and should, therefore, play a role in facilitating this data for post-genomic research.
- **Genomic for individualized Healthcare**. Bioinformatics provide input to practicing clinicians and medical informaticians to understand and use molecular level data to provide personalised services. Acquiring, representing, analysing, and integrating this kind of data is the practice of Bioinformatics that help the real integration of genetic data of the patients in clinical information systems;
- **Holistic Genomic Medicine**. BMI integrates information coming from the different levels (molecular, clinical or environmental) and produces the personalization of clinical solutions;
- **Enabling Technologies**. Innovative information and communication platform interfaced with new analytical devices and virtual learning environments to facilitate the implementation of the integration between different sources of information and knowledge.

Research agenda:

- Integration of data from biosensors and medical devices into clinical information systems;
- Integration of patient molecular data into Electronic Health Records;
- Connecting bio-banks to large scale databases to enable data mining;
- Patient profiling and lifestyle management;
- Modelling and simulation of biological structures and processes/diseases.

It is probably pleonastic to remark how most of the bullet points above resonate many of the issues we have discussed so far in this book with respect to PHS. If we stretch the definition of Medical Informatics to include within it PHS as one of its component, then one could subsume all of our discussion as just one dimension within the emerging BMI domain and related research agenda. It could be argued that PHS are among the various medical devices contributing to clinical information systems. This, however, would be incorrect for three reasons. First, PHS are not mere medical devices but more complex system including devices. Second, they are still not much connected to clinical information systems. Third, and most importantly PHS, if fully deployed, would entail a dynamic and personalisation contributions, yet lacking in clinical information systems. Fourth, the very nature of PHS, which can capture and in the future will better capture different parameters in a mobile fashion, can produce those contextual and environmental data specific to each individual and needed as input to functional genomics, which currently clinical information systems and large scale databases do not contain. Indeed, as we show below with the help of figure 2, we claim that PHS can be an additional and active third pillar in the process of integration between MI and BI. In other word not only PHS would benefit from this integration but they would also contribute to it. The figure overleaf is an adaptation of the graphic visualisation by which the integration of MI and BI into BMI applications has been depicted in the White Paper produced by the Network of Excellence INFOBIOMED. We simply added a symbol for PHS in 2020 to convey the idea that PHS solutions could at the same time be complemented and complement MI and BI applications. PHS would be first strengthened with input from MI and BI, and then once they achieve increased reliability their data would in turn provide additional evidence for both MI and BI applications.

Figure 2: The bi-directional integration between PHS and BMI



Source: Adapted from INFOBIOMED (2003, p. 18, Figure 4)

Evidently a key challenge to cope with for this scenario to occur is that of ***validating and intelligently processing data gathered under "uncontrolled conditions"***, which cuts across this research domain and that on “**Intelligent PHS Data Processing**”. In this respect a clear area of potential synergy between PHS and BMI emerge if we consider the kind of new mobile parameters that context aware next generation sensors may produce. In the traditional medical domain various types of long term data bases can be identified - ranging from registries (only few core data elements) up to research data bases (in-depth data about a defined population subset). Integrating these valuable data sources with ongoing mobile data in a data warehouse system would allow to correlate objective measures with context related health or subjective well-being. However, current medical data bases focus on unhealthy people. Aiming at detecting social and mental status too, additional data bases (e.g. for “stressed” people) are needed. For instance, it has been suggested to create a data base of emotional concepts, in order to be able to categorize emotions and to infer emotional trends over time (Lisetti et al 2003). Finally, it is worth noting that in the transitions towards Framework Programme 7, the field of Bioinformatics has been merged into the reasearch priority “Virtual Physiological Human”, whose ultimate goal is *to let scientists and medical practitioners know as much as possible about the “real physiological human” by tackling all areas of human anatomy and physiology and integrating data from all levels (molecule, cell, tissue, organ, etc)*[18]. This will enable real “personalised” care, thanks to the use of models, simulation and visualisation techniques for predicting the outcome of interventions (surgical and pharmacological) on the individual. Advancements in the field of Virtual Physiological Human (VPH) will also assist the design of targeted implants and artificial organs for the individual, as well as the discovery of innovative personalised drugs. Also in this case we can point out at the potential synergies that would derive from convergence of PHS and VPH within future research projects. As VPH models are both descriptive, predictive and additionally formed taking into consideration pathological, physiological, and anatomical data, they can become the basis for a PHS new DSS primarily for clinicians but eventually possible to share with users. VPH is further important for developing interfacing technologies that give a just picture of personal aspects, both for clinical use, and for patients to give an illustrative picture of how each individual body is formed and affected by different actions and behaviours. In addition there is also a contribution from PHS to VPH that could derive from this integration. Convergence between PHS and VPH further means that PHS provides better measurement and reliable data so that VPH build better models with in turn produce better design of artificial organs to be implanted ad become also part of PHS. Thinking very futuristically, there could be spin-offs from such integration between PHS and VPH, positively over spilling on the users. It could produce a sort of “tamagochi” of oneself, a device that can tell everyday how one has performed, and whether or not one has behaved well towards his/her health. This could be among those tools that could motivate people to behave in sound and preventive fashion (if they are healthy), to refrain from certain specific behaviours (if they have been diagnosed with a potential future risk), to adhere to

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[18] European Commission, DG Information Society and Media, (2007), *eHealth portfolio projects – Sixth Research and Development Framework Programme, 2002-2006*, Brussels, available at http://ec.europa.eu/information_society/activities/health/docs/publications/fp6upd2007/fp6ehealth-projects_upd.pdf, (accessed January 2009).

prescriptions and lifestyle guidelines (if they are already chronic patients and/or are following a rehabilitation programme).

1.3 Proposed roadmap

The table below synthetically provides a snapshot of the preliminary research themes associated to the gaps and of the key input from the further review of the literature. In combination with the comments and changes introduced during the two consultation events focussing on the roadmap they shape the final proposal graphically presented in Figure 3 reported in the next landscape page.

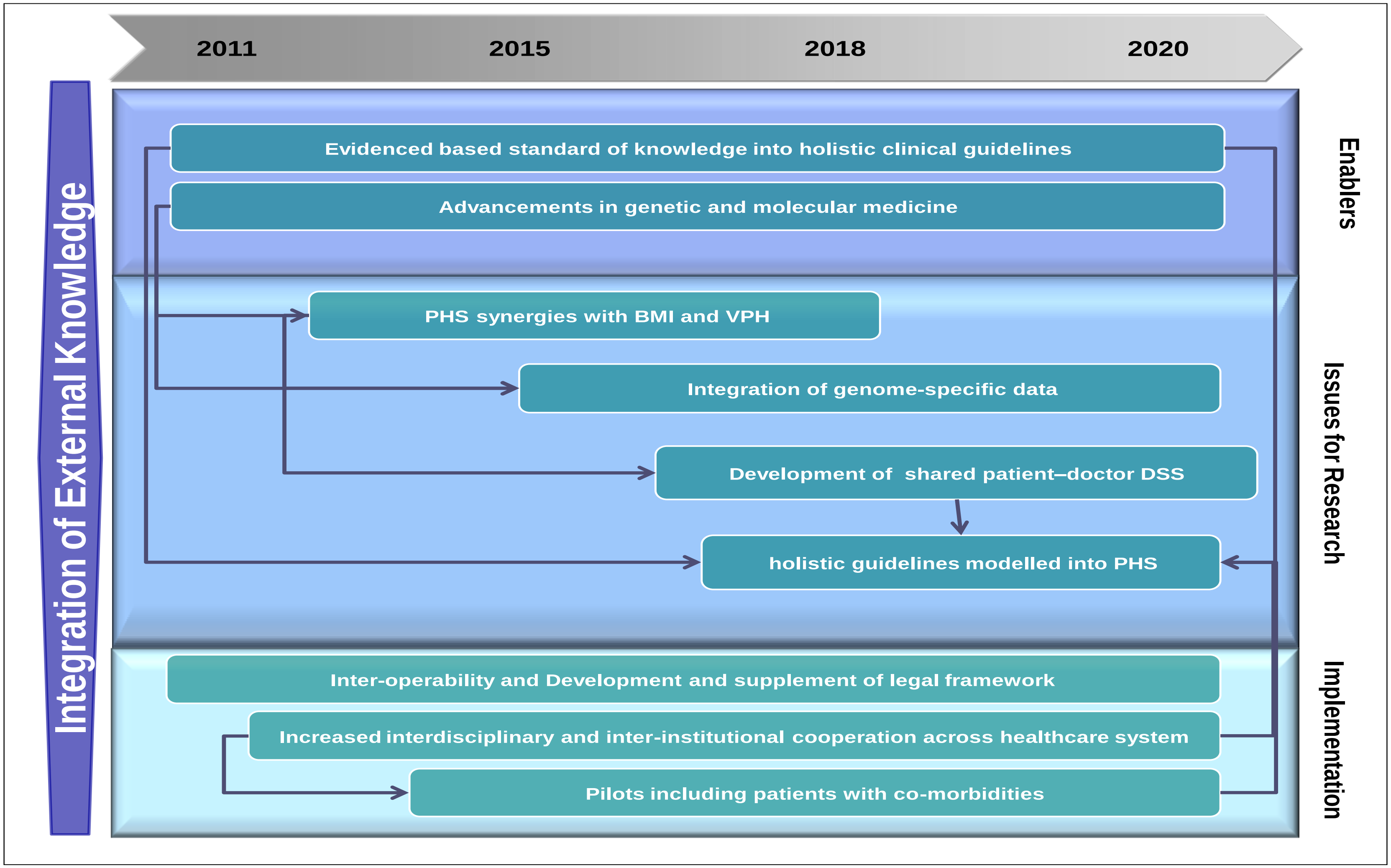
Table 2: Re-compacting information: Integration of External Knowledge

Gaps (Figure 1, p. 4)	Preliminary research themes (Figure 1, p. 4)	Further insights
• Lack of integration of updated clinical evidence, biomedical and genetic information to ensure scientific control, risk assessment, and personalisation • Validation of data from uncontrolled conditions (enucleated and moved here from Gap of Box 2)	• Integration of up-to-date medical info from bio-banks, trials; • Integration of genetic and biomedical information • Controlled studies to correlate and compare data obtained in both “clinical settings” and “uncontrolled conditions”(from context aware PHS) to identify normal and abnormal patterns of parameters uses for action/actuation taking into account personal and contextual factors	• Knowledge into clinical practice a problem for medicine as such (see also about holistic guidelines) • Relevance of Biomedical informatics (BMI) • Potential synergies between PHS and BMI • Need of new databases storing mobile data to correlate with data in other traditional medical databases
• Need of holistic clinical guidelines and pathways to align PHS delivered care to best practices and to capture the multi-facet nature of health status	• software systems integrating and modelling guidelines within PHS	• Holistic nature of guidelines a matter of institutional / cultural change (recalling implementation gaps 3,4,5)
• Need of innovative and holistic DSS for healthcare professionals to provide an holistic picture of human body complexity through prediction/simulation/visualisation	• Integration of PHS and VPH (supported by modelling and prediction); • Development of VPH-inspired interfacing for PHS DSS;	• Further support to idea of VPH/ PHS synergies

It can be safely stated that the elements already captured at the end of the gap analysis (those summarised in Table 1) have been confirmed and further refined by the consultation and the further review of the scientific literature.

The increased ***personalisation of both monitoring, preventing and treating*** and more ***robust clinical and scientific control*** through the integration into PHS of clinical evidence and biomedical and genetic data and information is at the core of the proposed convergence with ***Biomedical Informatics (BMI)*** and with ***Virtual Physiological Human (VPH)***.

Figure 3: Visual Roadmap for "Integration of External Knowledge"



Source: Authors' elaboration

To this convergence toward personalisation PHS brings the additional important input of contextual data, which raised challenged to be addressed by research such studies to address the issue related to the reliability of ***data gathered under "uncontrolled conditions"*** and the need of ***new databases with mobile contextual data***.

Accordingly within the broadly defined theme of PHS convergence with BMI and VPH we can envisage the following topics:

- Controlled studies to ***correlate and compare data obtained in both "clinical settings" and "uncontrolled conditions"*** to identify normal and abnormal patterns of parameters used for action/actuation taking into account personal and contextual factors;
- ***Integrate*** ongoing mobile ***data captured by PHS*** with ***clinical and biomedical and genetics data*** (large scale database, bio-banks, trials, research databases) into ***data warehouse*** system;
- **Data mining** on newly integrated databases to correlate both ***genetics with diseases*** phenotyping and more generally correlate ***objective measures*** (about genotypes and phenotypes) with ***context related parameters***;
- ***Integration*** of data from ***biosensors and medical devices*** into ***clinical information systems***;
- Use of newly combined evidence for ***patient profiling and lifestyle management***;
- Improve ***modelling and simulation*** of biological structures and processes/diseases (***VPH***) with data from ***PHS***

Evidently this research theme present a number of complementarities/overlaps with elements of other roadmaps:

- The integrated interpretation and processing of genetic, biological, and contextual data it is clearly at the cross-road with themes of the roadmap on "**Data Processing**";
- Controlled studies to ***correlate and compare data obtained in both "clinical settings" and "uncontrolled conditions"*** need input from new context aware sensing (as do the creation of integrated database mentioned under second bullet above);
- In turn the result of such controlled studies feed into the for the normalisation of "uncontrolled conditions" data through correction/rectification techniques that are part of the "**Data Processing**" roadmap.

With respect to the first dimension very important is the ***inter-operability*** among devices, databases, and with health records (personal and in general all those included in clinical information systems). In addition the ***appropriate legal framework*** will have to be developed if ***patient profiling***, ***early detection*** and ***related secondary prevention*** treatment are to be put in practice.

With respect to the second dimension the enabler is mainly advancement in genetics and molecular medicine. If that happens it will further advance the PHS/BMI/VPH convergence and would eventually lead to the new research theme "**Integration of Genomic-Specific Data**". As research realising synergies between PHS and VPH progress sit will be possible to launch a the new research theme "**Development of Share**

Patients Doctor Decision Support Systems”. Naturally this theme need input from, and is in overlap with, elements of other roadmap:

- It needs input from advancements in predictions and modelling techniques considered in the “**Data Processing**” roadmap;
- Its results, expected to produce innovative and user friendly tools based on visualisation and simulation, are clearly in overlap with the issue of “Intuitive patient decision aid tools” and included in “**Data Processing**” research domain) and of “imaging and visualisation techniques for intuitive and easy to interpret input” and included as part of “**Interfacing & Interaction**” research domain)

The idea of developing systems that would integrate and model holistic guidelines (addressing ***co-morbidities*** but also many other dimension to ***personalise*** them) has not been rejected, but both the experts during the consultation and the review of the literature have shown that is a tough challenge technological research cannot solve. Turning updated knowledge into standardise and consensual guidelines for clinical practice is a challenge for medicine as such and is not specific to PHS. It depends both on the dynamic of knowledge production itself and on the institutional fragmentation and “turf wars” ridden nature of the Healthcare system. Accordingly the theme of PHS incorporating holistic guidelines is included but further on in the future and it is clearly indicated how it depends on both enabling and implementation issues: further efforts at extract guidelines as a kind of research/analytical activity (enabler) and at putting into practice and improving them through more integration and collaboration between tiers of healthcare and between them and research. In this latter aspect it is worth mentioning that these same two enabling and implementation issue are relevant also for what can be done with new data gathered about context (see later **§ 4.2** text on context awareness challenges). Indeed, once sensors will systematically gather mental and social state data we will still need consolidated and standardized measures against which evaluate in a combined way physical, mental and social parameters. Otherwise we would not know what kind of feed-back should PHS capturing emotional and social state, especially those aiming at life-style management, should provide to improve the well-being of users. Accordingly, multi-disciplinary and inter-institutional cooperation is needed especially for lifestyle management to decide: a) what are the signals required to detect context, social interaction and activity; and b) what is the minimum set of signals to achieve a desired performance lifestyle performance.

2 Data processing

2.1 Contextualisation

Already at the end of our work on the State of Play and before the all consultation process started we concluded that ***PHS today are called 'personal' as the focus is on the person possibly outside of institutional care but they are not necessarily personalized***. if Personal Health System have to develop into Personalised Health Systems, more research development is needed to build auto-adaptive and self-calibrating solutions gradually and constantly adapting to each specific individual history, characteristics, mental state and context. This requires both the advancement in the development of sensors that we treat later (**§ 4**), infusion of clinical evidence and of molecular and genetic data into PHS that we discussed in the previous section, ***and naturally more sophisticated algorithms and data processing solution capable of turning inert data and information into knowledge and knowledge into wisdom (which knowledge for which action)***.

Currently, PHS data analysis focuses on standard measures, commonly accepted in medicine, to detect abnormal physiological conditions or, in the case of aging, abnormal physical state (i.e., early fall detection), without considering context (environmental conditions, location, type of interaction i.e. from voice signalling, emotional state) and person specific parameters (age, social class, education, life history, genetic characteristics). PHS applications still concern a limited number of parameters that can vary within a pre-defined range, without the capabilities to take into account peculiar conditions and characteristics of the individual, and to automatically adapt the expected values of medical parameters. This can lead to false positive early warning: that is a vital signs is above the threshold but this may be due to peculiar characteristics of the individual or of the specific context in which he/she is. In this context healthcare professional intervention is still a major part of current PHS solutions. A corollary of which is that actuation and treatment through PHS is still far away, while monitoring remains the main focus of today's personal health systems. In case of acute episodes, today's PHS is too limited in terms of automatic and in-time intervention. To become truly ***personalised***, requiring less intervention on the side of healthcare professionals and enabling more actuation and treatment, PHS must be powered by ***auto-adaptive and self-calibrating data processing and interpretation/modelling solutions***, on which to build systems that do not only monitor the condition of an individual, but also deliver on-time and evidence-based prediction supporting actuation.

Currently, in some cases, PHS applications may also deliver individual feedback according to patients' status, and additionally offer some educational guidance related to the specific condition. However, the value chain of data management and processing is long and fragmented, in a sense that data is processed with many steps and at several levels (i.e. data elaboration usually involves external devices). Although intelligent systems are being developed (i.e. Decision Support System, DSS), healthcare professional intervention is still a major part of current PHS solutions, mainly due to the lack of intelligent systems encompassing predictive algorithms enabling self-adaptation and self-calibration, as well as automatic and on-time intervention. A key barrier is also represented by lack of context awareness and other individualised data beyond vital and physiological signs, which is evidently more an issue of the kind of sensors used than of data processing. Yet, even if other kind of signs and information were available and could be acquired as raw data, it would still be difficult to turn it into knowledge given the status of intelligent processing currently embedded into PHS. For instance, if we talk about self-adaptation and self-calibration, naturally we lack sensors reliably gathering environmental and context data, but also algorithms accurate enough to process the data in such a way that they can provide truly personalised services.

2.2 Further insights

Intelligence in support of decision and action. From a general perspective the gaps identified for the data processing capabilities of PHS applications fall into the broad discipline of Decision Support Systems. In a way what PHS application currently lack is the capability to produce input for decision and action (especially for automatic actuation of action). In this respect we can take from the DSS discipline the idea that the ***intelligence*** needed for decision and action requires first the identification of a problem, then the design of possible alternative solutions, and finally the criteria for analysing the alternatives and choosing one for implementation (Shim *et al* 2002). If we apply this to the field of PHS we see that the problems are clear and that increasing amount of data and information are gathered about an important part of the problems (vital and physiological signs, but we still need to: a) gather and process data ***on other important dimensions of the problems*** (personal context, environment, clinical evidence, biomedical and genetic information); b) improve the design of alternatives (***information into knowledge***); and c) develop criteria and models for choice (***knowledge into action/ actuation***). Without the capability of turning the gathered data into knowledge and action, PHS run the risk of increasing the information overload and the problem of what to do with data already lamented today by healthcare professional even in their traditional practice. If PHS will generate large amount of data without producing intelligence they will only compound this information overload challenge (Foster *et al* 2005; Kriegel *et al* 2007). It has been argued that, if we did not reach yet more intelligent solutions in the field of PHS and other technology driven applications in the healthcare sector, this is the result of ***too much attention placed on the networking of distributed sensing and too little on tools to manage, analyse, and understand the data*** (Balazinska et al, 2007). In order to proceed into this direction one of the 'grand challenges' is to limit the number of computer-generated recommendations a clinician or a user has to deal with to a manageable number based upon an explicit model, thus ***reducing the ''alert fatigue''*** that is a frequent cause of dissatisfaction both among professionals and users (Sittig *et al* 2007). The goal is to develop decision support systems and automatic actuation in a way that takes into consideration the peculiarities and preferences of users and addresses the concerns of healthcare professionals (Ruland and Bakken 2002). To put these considerations differently, there is a need to move from a fragmented "signal driven design" to a more holistic " personalised and goal-driven design", which would better enable: a) defining what to collect, when, and how to collect it; and also b) processing and visualising its results in view of the sought goal. These broadly defined challenges entail several issues we treat below.

Data validation. Discussing a broader topic than PHS Foster *et al* (2005) affirm that Decision Support Systems in the healthcare sector must incorporate clinical evidence and knowledge as fundamental parameters for ***data validation*** in terms of both ***quality*** and

accuracy. This further reinforces our argument about the need to integrate external knowledge, which we have treated earlier as a separate and new research domain with its own roadmap and especially as an area for convergence between PHS and BMI. As we clearly pointed out in the *Gap Analysis Report*[19] and mentioned briefly in this document (see p. 8), it is evident here how the two research domains and related roadmaps "Integration of External Knowledge" and "Data Processing" overlap. Evidently, the additional clinical and bio-medical /genetic information to be incorporated into PHS would then need to be processed and interpreted. A specific issues overlapping even more clearly these two domains is that related to the use of data gathered under "***uncontrolled conditions***"[20], namely conditions that are clearly different from the traditional "clinical settings" and as such may be the cause of measurement errors (recorded parameters being distorted, for instance, by environmental factors). Data thus produced can be interesting to clinicians but currently cannot be used, for instance, to take decision on treatment or to trigger actuation[21]. This problem has two implications, one more related to clinical trials and the other concerning more the technicalities of data processing. First, controlled studies are needed including measurements on a number of parameters for a given sample of individuals in both clinical settings and in "uncontrolled conditions" as to include personal conditions and environmental factors. These should enable to assess normal and abnormal patterns in light of personal patterns and context. Second, with this input PHS powered by innovative self-adaptive algorithms should recursively process data and identify truly abnormal patterns, as well as rectify/correct parameters that may appear as abnormal only due to very peculiar contextual conditions.

More efficient treatment of data: *multimodal data fusion* **[22]**. Data is gathered through several sensors distributed over the body and in most cases we still have a situation of "one sensor / one signal", which requires data fusion. Moreover, the more we go in the direction of context aware and personalised PHS the more this data will also present different modalities (for instance strings and graphs) that need to be integrate correctly

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[19] PHS2020 Deliverable D4.1, *Gap Analysis Report*, pp. 42-43.

[20] See more on this in PHS2020 Deliverable D4.1, *Gap Analysis Report*, pp. 22-24 where the main gap for data processing (lack of auto-adaptive algorithms, etc) is discussed.

[21] The decision to intervene are usually based on risk thresholds defined using statistical patterns established under clinical settings. Parameters gathered under uncontrolled conditions, if distorted by measurement errors, may trigger unnecessary intervention (i.e. meet the risk threshold due to measurement error) or miss intervention when needed (i.e. do not meet the risk threshold due to measurement error).

[22] The literature on data fusion and on multimodal data integration is vast and span several disciplines and we used selectively to define the two terms (see for instance Mitchell 2007; Qi *et al* 2004; Klein 1993). "Fusion" is a term describing the integration of data from multiple sensors using a combination of mathematical algorithms and data transfer architecture. Fusion Algorithms allow data from various sensors to be combined, painting a more accurate picture of the happenings and allowing to take immediate action if a threat is determined. Two basic architectures are used in theory, Measurement Fusion and Track Fusion. In practice, however, a combination, or hybrid system is often used. In several articles "data fusion" and "multimodal data integration" are used in an alternate manner implying that there is not a substantial distinction among them (see for instance Qi *et al* 2004 or Tripathi *et al* 2008). In this way one may talk about "multimodal data fusion" as a particular case of data fusion, when the data not only come from different sensors but also have different modalities (typically strings and graphs). On the other hand, one could distinguish them as follows: multimodal data integration might be viewed as set combination wherein the larger set is retained, whereas fusion is a set reduction technique with improved confidence. For our purpose here and in the definition of the roadmap we will not distinguish them in a clear cut way and will treat them as one research theme.

for a reliable measurement and data processing. Data fusion is particularly important, at least until multi-signs sensors with on board processing will be developed (see later), for context aware PHS applications capturing emotional, activity and environmental parameters (Tröster 2005; Lukowic *et al* 2002). The heterogeneity of possible contexts demands for fusion and multi-modal integration of data deriving from various sensors. Whereas vision and speech recognition are established tools to mirror the human's perception, context detection using vision and speech creates a high computing load. The use of different, simple sensors capturing these parameters in different ways can reduce the communication and computational effort, yet they increase the data fusion efforts. Currently, however, there is still no established framework for exploiting the benefits of data fusion, which hampers the production of consistent actionable intelligence due to invalid incorporation of redundant information and to information corruption (Luo *et al* 2007). Another challenge is the capacity to fuse the gathered data both collectively and on an individual basis, mirroring the situation of users' activities and environmental conditions[23]. The key need is engineering a framework enabling adaptation to "uncontrolled" chaotic environments such as those which would characterise a PHS services embedded into a "smart home" or provided as the users perform normal daily activity at work (Pallapa and Das, 2008). Moreover, we can envisage PHS applications capable to integrate parameters gathered by external environmental sensors (neither in contact with the users' body nor placed in their homes) or available within the health records of hospitals information systems, or even in the information system of organisations not belonging to the healthcare sector. Futuristically, we may picture a situation where PHS applications, after detecting abnormal conditions for a chronic patients, may: a) automatically access and query the patient health profile; b) access databases about patients suffering similar conditions to correlate the parameters; c) obtain data from airport records on his/her latest travel and identify his/her presence in places where some epidemic were recorded. All of this points into the direction of PHS fully context aware and context embedded, going beyond the "Event-Condition-Action approach" (Choi et al, 2006). Yet, for this to happen through automated query-processing task, data should already be in well-defined inter-operable syntax and semantics (Egenhofer, 2002).

Such inter-operable syntax and semantics, however, are not currently available even only for vital and physiological signs and, thus, the situation is more complicated when we will add context awareness. Therefore, efforts are needed for format and semantic integration of data coming from disparate sources (Halevy, 2003). In this respect the issue of ***multimodal data fusion*** is crucial. Before data analysis starts, the differences between data from different sources have to be even-handed via fusion and integration. Otherwise one risk identifying patterns as a result of errors due to the different origins of the data rather than reflecting some real health conditions. Evidently this points to the overlapping between the technicalities of multimodal data fusion and the substantive issue of studies comparing data gathered in clinical settings with those gathered in "uncontrolled conditions" to define normal and abnormal patterns in the observed parameters. On the

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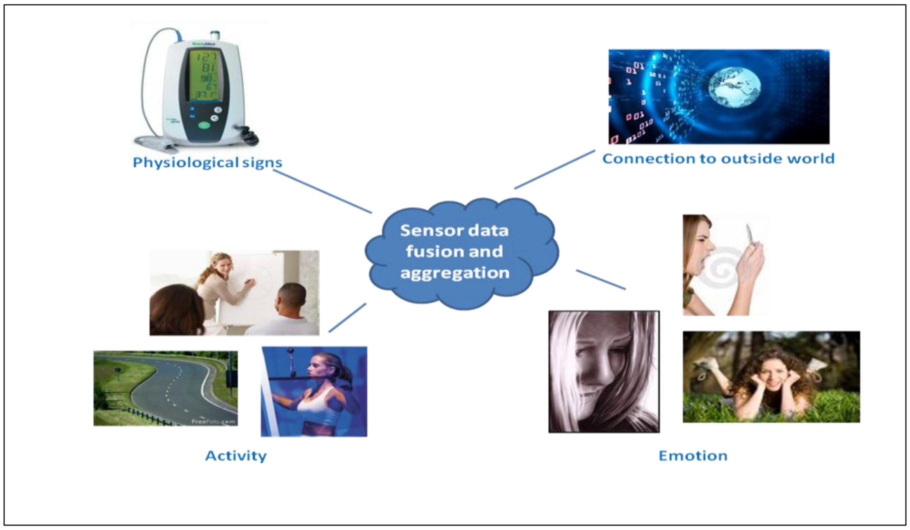
[23] Evidently, it would be more useful to take into account users' behaviour as an entity and deriving work flows from it, rather than considering events as basal units (Shchzad et al, 2005).

side of data processing technicalities we can stress the ***need of well-organized and scalable data pre-processing*** through appropriate statistical examinations and algorithms to integrate data as different as such as, for instance, strings and graphs[24].

Figure 4: Sensor data fusion and aggregation in multiple contexts



Source: Authors' elaboration

Improve extraction of patterns. Assuming the technicalities of data treatment are solved, intelligent data processing in PHS application should advance the extraction of new understandable patterns and also make previously extracted patterns better understandable. For example, currently many data mining algorithms do not distinguish between causality and co-occurrence. There is a great difference between finding the origin of the disease or finding just an additional symptom. A direction of research that should be leveraged within the PHS field is that of ***machine learning and neural nets***. Since acquiring knowledge from experts is complicated, a major part of decision support systems recently developed machine-learning (ML) techniques, which are able to discover knowledge automatically learning by example (Peleg and Tu, 2006). The most common technique being **neural nets** (network of interconnected simple processing elements). Neural nets recognize patterns in the input data and classify the input. Furthermore, many of the developed decision support systems are based on models that support **probabilistic reasoning**. Examples of such models are **Bayesian networks**. Artificial neural networks, decision trees, support vector machines, Bayesian networks, are all examples of methods that are used today to mine data. The challenge to overcome in this field is represented by the difficulty of transforming attributes of different scales into a mathematically feasible and computationally suitable format. This, however, need to be tackled not only to better extract patterns but also to achieve to achieve predictive modelling and exploration.

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[24] Data pre-processing is a useful technique instrumental to improve data fusion. In general, when we obtain a database, it is necessary to select the appropriate variables used as the inputs in order to eliminate the noise contained in the selected variables and to normalize the filtered variable. Achieving this is termed data pre-processing (see for instance Huang *et al* 2002).

Adaptivity and self-calibration. As the complexity increases, there is a need to extract more complex patterns and to recursively process them in order ***to achieve both more personalisation and more modelling and predictive power***. PHS applications that are context aware and dynamically capable of learning and adapting to users very unique characteristics and conditions are a quintessential case of increased complexity. First, currently available algorithms for the most part are dedicated to a limited set of standard patterns and need to be upgraded to treat new parameters such as those capturing context. Second, aiming at providing truly personalized, proactive PHS, adaptivity and personal calibration of algorithms are very important (Roggen *et al* 2006). Personal calibration is crucial to go beyond standard parameters measuring vital and physiological signs and capture for each single user environmental conditions, emotional and social state, as well as individual demographic and social characteristics (age, social class, past history) and should be integrated with adaptive algorithms for context recognition. These two elements would ensure that PHS data processing system deal with information in an intelligent way, in other words in the same way as a human domain expert would: learning from experience but in an automatic and self-recursive way. A clinician might learn by direct experience (though repeated observation) that vital sign X of patient A goes above a risk threshold due to very specific personal characteristics or under certain situations and does not require any treatment. If this information is not fixed and if patient A change doctor, this information is lost. A PHS intelligent system, embedding personal calibration and adaptive algorithms, would learn and fix such information and many others and dynamically continue to do so a self-modify itself. Under an ideal situation such intelligent system would: a) learn fast from a large amount of data and
adapt incrementally in both real time (online), and in an off-line mode (new data is accommodated as it becomes available); b) be open and flexibly incorporate new elements relevant for its task; c) have a memory to keep track of information that has been used in the past and be able to retrieve some of it for the purpose of inner refinement, external visualisation, or for answering queries; d) be self-reflexive and analyse itself in terms of behaviour, global error and success. Currently algorithms learning only in an off-line mode are use to detect physical status only. For full context awareness, however, real time on-line learning is a prerequisite to achieve personal calibration. This new breed of adaptive context recognition algorithms may make use of bio-inspired techniques such as the “Evolving Connectionist Systems” modelled following the brain functioning, which have been shown to provide adaptivity and learning in other fields (Kasabov 2006).

Holistic Modelling and prediction. Adaptivity and personal calibration would reinforce the modelling and predictive capabilities of PHS data processing components. In health science well studied human models are available, which are based mostly on standard objective parameters . Augmenting these models by contextual data, social interactions or activities of daily living, could dramatically increase the predictive power (Roggen *et al* 2006). Thus, PHS could contribute to increase the predictive capabilities of healthcare decision support systems in general. This naturally require copying with several challenges such as modelling data coming from different sources and different devices (pointing again to the issue of inter-operability). Once these different kind of data are available, automatic processing need to be developed to track and assess historical, present and future events and related co-dependencies. Recent progress toward unifying the treatment of probabilistic models (for example, through abstractions such as dynamic Bayesian networks) could also pave the way for building a rich toolbox of statistical models (Balazinska et al, 2007).

Patterns management and visualisation. Having addressed all of the previous issues, then the number of potentially applicable patterns will be too large to be assessed by a human user, without a system organizing the results and providing a user friendly fruition through visualisation. Future systems must provide a platform for pattern discovery where it is possible to browse for interesting information, enabling generation of a large variety of well understandable patterns. Combining modelling and visualisation techniques then we could have those patient decision aids that were identified as one of the gap within the data processing research domain.

Privacy algorithms. Finally, advanced data processing could also address ethical issues through the development and application of privacy- preserving algorithms (Agrawal and Srikant, 2000, Samarati and Sweeney, 1998). These advancements aim to control the released data, either through random perturbations or by hiding recognizable attributes, so that individual privacy is not compromised but useful data mining can still be performed. However, these approaches are still very immature and will not become mainstreamed for some time.

By way of concluding the analysis in this paragraph it is worth pointing out two aspects. First, while considered as an issue falling outside strictly defined PHS research and concerning more broadly defined implementation issues, ***inter-operability emerges from the above considerations as a crucial bottleneck today and pillar in the future if achieved, as it would lessen the data fusion, multimodal integration and data pre-processing efforts***. Second, it is clear how ***tightly entwined are the “Data Processing” and “Sensor” research domains*** and that the ***two partially merge when smart sensors capable of on board processing and self-calibration are developed***.

2.3 Proposed roadmap

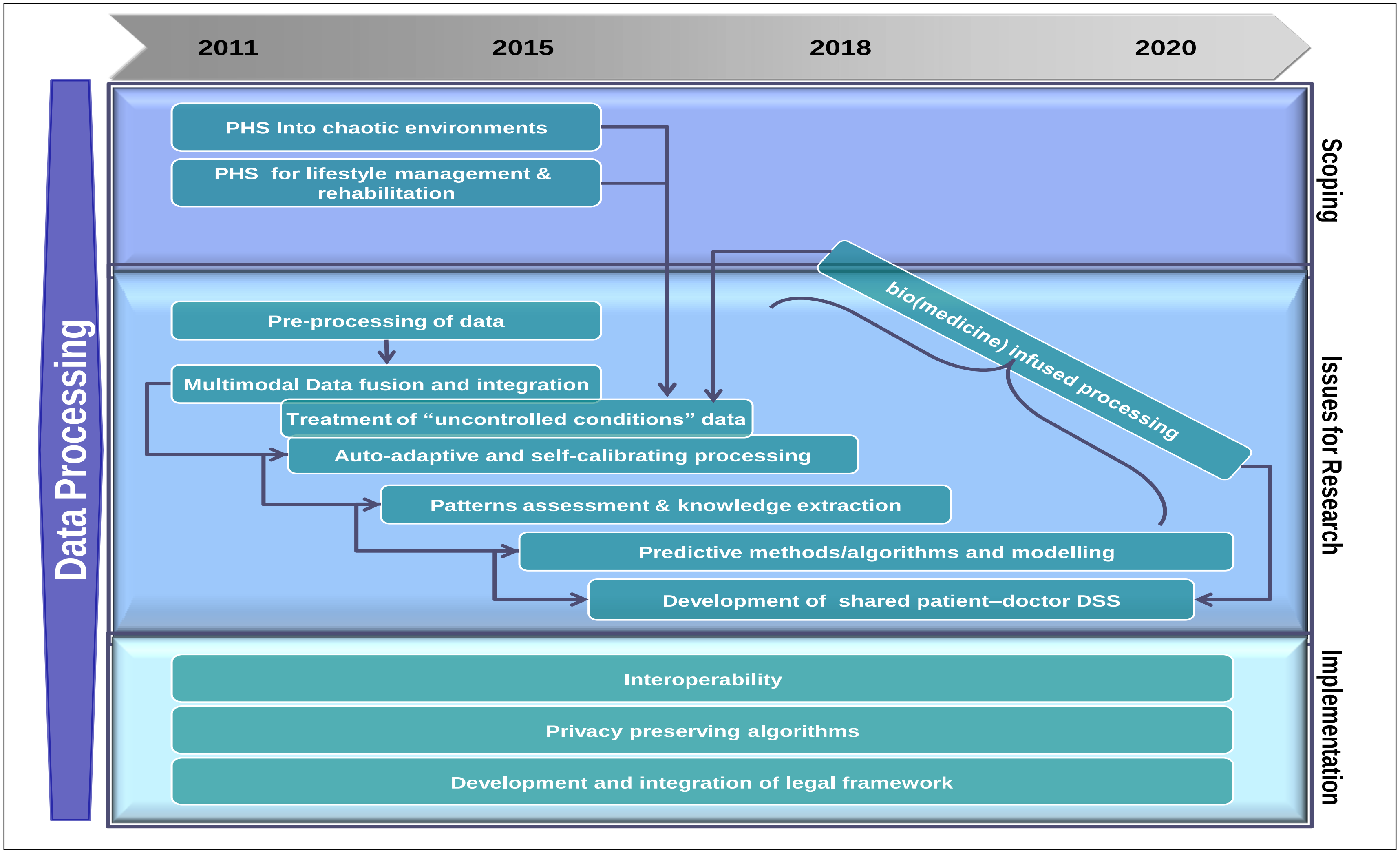
The table below synthetically provides a snapshot of the preliminary research themes associated to the gaps and of the key input from the further review of the literature. In combination with the comments and changes introduced during the two consultation events focussing on roadmapping they shape the final proposal graphically presented in Figure 5 reported in the next landscape page.

Table 3: Re-compacting information: Data Processing

Gaps (Table 1, p. 7)	Preliminary research themes (Table 1, p. 7)	Further insights
• Lack of capacity to process data coming from different sources and to address the issue of data generated under “uncontrolled conditions”;	• Data fusion and multimodality (data processing, interpretation and modelling capable of simultaneously treating vital and physiological signs, genetic, biomedical, and contextual parameters such as individuals activities, location and emotional status, and external environmental data; • Correction/rectification techniques to normalise data gathered under “uncontrolled conditions”	• Main issue becomes multimodal data fusion and integration; • Data pre-processing as instrumental; • Data from chaotic environments interesting test bed for new applications (overlaps with “uncontrolled conditions” data) • Importance of inter-operability (syntax and semantics) • Privacy preserving algorithms
• Lack of capacity to recursively learn from individuals specific characteristics and context and automatically adapt data processing to personalise monitoring and enabling actuation reducing the need of healthcare professionals intervention	• Auto-adaptive and data fusional algorithms and related prediction and modelling techniques; • Development of automatic calibration	• Self-adaptivity and self-calibration one issue, in addition: ○ Patterns extraction (and related data mining) ○ Prediction and modelling
• Lack of personalised aid decision tools for users	• Development of simulation tools based on holistic data processing (see above) and easy imaging and visualisation (see VPH related themes)	• Criteria for user friendly visualisation outputs from prediction and modelling

Ever since the end of the state of play review our initial intuition has been that PHS lacked the sophisticated intelligence to be ***truly personalized*** systems, through ***self-adaptation*** and ***self-calibration*** to the peculiar holistic conditions of each single individual, which as result restrains support to decision making, treatment and automatic actuation through ***prediction and modeling***.

Figure 5: Visual Roadmap for “Data Processing”



Source: Authors’ elaboration

This intuition has been corroborated during the gap analysis consultation process and we can safely state that it has been confirmed by by the consultation and the further review of the scientific literature. On the other hand, the latter have helped providing a more complete picture where ***self-adaptivity*** and ***self-calibration***, ***prediction*** and ***modelling***, figure prominently alongside other elements that were not given enough visibility in the gap analysis such as: the ***importance*** of advancement in ***data processing*** especially for going beyond monitoring and enabling ***lifestyle management*** and ***rehabilitation*** applications, pre-processing and multimodal data fusion and integration, pattern extraction and related data mining, etc. The roadmapping consultation events and the further review of the literature have also provided more context and importance to the issue of how to treat data originating from **"uncontrolled conditions"**, which have surfaced in the previous paragraph on "**Integration of External Knowledge**", in this one on data processing, and will be discussed again in the next one on sensors. So, from being a sub-issue it has become a research theme in its own rights, in relation to which it also emerged the importance of ***chaotic environments*** as a test bed for gathering and processing of data raising higher challenges.

The complementarities/overlaps between this roadmap and the one on "**Integration of External Knowledge**" have been cited several times in previous part of this chapter, so they are simply identified in Figure 5 and not discussed further.

Many of the technologies and the developments later exploited for PHS have sprung from military applications, where users not only under high level of stress but also embedded into chaotic environments. Equally chaotic (though admittedly less stressful) environments in terms of the signs to be gathered would be those characterising a PHS services embedded into a "smart home" or provided as the users perform normal daily activity at work (Pallapa and Das, 2008). As illustrated earlier (see **§ 2.2**), these are situations where ICT can monitor and act on medical needs tenuously and promptly but where data challenges are great (fusion and integration of sign with different modality, normalisation of such parameters as they are typically originating in "uncontrolled conditions"). Accordingly we propose here initial **scoping studies** to define how such environments could be integrated as test bed for technological research focussing on advancing PHS level of sophistication in processing and intelligence. ***Scoping activities*** are also proposed on a topic that is clearly correlated to this one on "chaotic environments". Current PHS applications, we have seen, are far too focused on existing medical conditions, mainly entailing monitoring functionalities for cardiovascular diseases and diabetes. However, they have ***major potential for going beyond these boundaries, enlarging to general health management, lifestyle applications and hence, prevention, rehabilitation, and even treatment***. As there is a current increase of focus on prevention, studies should also consider how PHS can optimally be tailored and adopted for the aim of lifestyle management in mobile and/or chaotic situations/environments. Similarly, it has also been suggested several times during the consultation events to assess the potentiality to integrate PHS with users' homes and domotics, to further personalise the services rendered by personal health system applications. A similar investigation should be made for already available service-based information (night/day, weather, travel, fitness, nutrition etc), giving opportunity to connect health with life-based parameters, and at the same time taking advantage of the "connected society" and the "sensor web".

As long as signs will come from many different sensors (i.e. one sensor/one sign) with little or no on-board processing capabilities and also until ex ante inter-operability with standardise syntax and semantics across many domains (PHS devices, electronic health records of various nature, databases, etc) data processing need to address the challenge of ***treating data with different modalities*** (for instance strings and graphs) that need to be integrated correctly for a reliable measurement and ensuing steps (interpretation, pattern extraction, prediction and modelling). This a more complicated task than simple ***data fusion*.**

The sheer size and diversity of data that truly personalised PHS integrating external knowledge will have to processes raise the data handling challenges and calls for new research into efficient "**Pre-Processing of Data**" preferably in order to, amongst other issues, decrease the size of datasets. While visualised separately, this can be considered as an additional instrumental support for the following theme. In case more sensors improve on-board processing, pre-processing could performed already there at source.

Next and much more important research theme to ensure the high quality of data is what can be broadly defined "**Multimodal Data Fusion and Integration**" of signs with different modalities (for instance strings and graphs). Before data analysis starts, the differences between data from different sources have to be even-handed via fusion and integration. Otherwise one risk identifying patterns as a result of errors due to the different origins of the data rather than reflecting some real health conditions. The goal of this activity should be, first, eliminate data redundancies and distortions and, second, perform ***data fusion at different levels***. In fact, it is possible fuse data at the level of a single network of sensors, at the level of a Lab On Chip, at the level of environmental sensors. Eventually, there is still need of a second level data fusion to merge all that data together. In a similar manner, data fusion can be done for fusion of physiologic data, motion, chemical values, emotional and contextual data, etc, ***finally reaching a real multi-modal data fusion.***

While it could be treated as either part of the previous or of the next research theme, we visualised the separately the "**Treatment of 'Uncontrolled Conditions' Data**", given how prominently has figures as instrumental to achieve true personalisation applying processing, patterns extrapolation, prediction and modelling on a combined set of data also capturing context. In close connection with the results of controlled studies ***correlating and comparing data obtained in both "clinical settings" and "uncontrolled conditions"*** (see previous roadmap), normalisation of such data should be achieved through new and innovative rectification and correction techniques to be developed *ad hoc*.

The theme "**Auto-adaptive and Self-Calibrating Processing**" capture what has been since the beginning the main gaps identified in PHS data-processing sub-system and pursuing this research direction should produce ***auto-adaptive algorithms to be integrated into PHS functioning, capable of gathering and recursively processing data from different sources (including from "uncontrolled conditions"/ "chaotic environments", adapting to individuals' peculiarities and modifying/rectifying the information provided to the rest of the system,*** for it to extract knowledge and take the most appropriate decision in each occasion in relation to action/actuation (treatment in the case of disease monitoring or feedback/assistance in the case of lifestyle management/rehabilitation). Further, under an ideal situation such intelligent system would: a) learn fast from a large amount of data and adapt incrementally in both real time (online), and in an off-line mode (new data is accommodated as it becomes available); b) be open and flexibly incorporate new elements relevant for its task; c) have a memory to keep track of information that has been used in the past and be able to retrieve some of it for the purpose of inner refinement, external visualisation, or for answering queries; d) be self-reflexive and analyse itself in terms of behaviour, global error and success. Achieving such state would bring a key input to enhance ***predictive and modelling power***.

An additional input in this direction would come from research on the theme of "**Pattern Assessment and Knowledge Extraction**", that is systems deriving understandable patterns and making already available patterns understandable, in addition to developing methods to turn discovered trends and patterns into rules. The progress of statistical methods and artificial intelligence discussed earlier in **§ 2.2** could offer interpretation of the complex patterns that are created by the collection of data produced by PHS. These patterns are of special interest, not only to extract knowledge for the specific user, but it can also offer knowledge concerning whole populations. Thus, different clinical and lifestyle conditions can be easily linked to cause-and-effect and also to optimal treatments.

The understanding of mentioned patterns together with innovative auto-adaptive and self-calibrating characteristics will support research aiming at advancing and refining "**Predictive Algorithms/Methods and Modelling**". This would give also the ***opportunity for prediction to foresee events and accordingly, act on them on time.*** This is possibly one of the major outcomes of the entire application. ***By using predictive algorithms, establishing patterns or evolution of patterns, it is possible to predict the evolution of a disease, and therefore pave the way for actuation (***e.g., drug delivery, electrical stimulation, etc.). Predictive algorithms are required also to assess and estimate different possible actions and optimal actuation considering a particular situation.

The previous mentioned developments will then support research to develop "**Shared Patient-Doctor DSS**", which has been already include in the previous roadmap and is included here in place of the "Intuitive Patient Aid Decision Tools" that was one of the gap of this research domain.

Obviously, all of the data integration, fusion, and mining activities require the operation of interoperability, why it is strongly recommended to carry on this field of research in the implementation studies. Correspondingly, this has to be further supported by a strong legal framework, where also the privacy and ethical issues are assured.

3 Interfacing & Interaction

3.1 Contextualisation

Also for this research domain personalisation is the main drivers, although from a different perspective. Other research domains in a way address the 'production' or "back-office" side of PHS personalisation. The themes of this domain address personalisation from the perspective of users' experience, in other words users' fruition of, and interaction with, PHS as services, and also from the perspective of the broader matter of health awareness. The various future scenarios elaborated have played a role in eliciting these issues, and in particular the "Self-Caring Society" one. First, a possible negative effects of this scenario is that it would produce further exclusion of those groups in society less digitally connected and less confident with the use of technology and capable of understanding its input. Second, consumerist attitudes toward health and independent self-caring activities can produce negative results if users access uncontrolled source of health information and/or are not adequately educated in health matters in general and on the various aspect of the PHS applications they will use in particular. From these two risks several gaps emerged directly related to needed actions. First, to counterbalance the risk of PHS being a source of exclusionary processes, PHS need new technological solutions ensuring multi-channel interaction and including also channels more accessible and easy to use (i.e. mobile and/or digital television) for less technology confident individuals. Second, assuming individuals use PHS services through their preferred channel, next PHS must deliver to users input and feed-back that are intuitive and easy to use through state of the art imagining and visualisation techniques. At the end of the gap analysis we also identifies as technological research themes the development of quality controlled Web 2.0 tools on matters related to PHS and of PHS application embedding eLearning modules for users in order educate users and increase correct health awareness and attitudes. During the roadmapping events, however, these two themes we considered more appropriate as object of implementation activities rather than as research themes.

Indeed the issue of ensuring that PHS services are not a new source of exclusionary process and that are users friendly enough to favour acceptance and adoption is very important both from a general policy perspective and from the more practical one of avoiding the risk of PHS remaining a niche market. We pointed out the importance of how the cognitive maps and capabilities of users in interpreting health related information is usually frustrated by the technicality of the information produced by PHS systems. While some of these issues are of broader non technological nature, nonetheless interfacing and interacting aspects were identified as fundamental requirements for the success and take-up of PHS. As a matter of fact, if PHS are to revolutionise in the future the traditional healthcare delivery as we know it, the user perspective has to be put at the centre of research and delivery. This means that PHS personalisation will highly depend on the nature of disease (e.g. chronic care requires different services than preventive one), on the technological level reached by both diagnostic and communication, and last but very importantly on the users' ability to interact with the technology and, on the other hand, on the technological device's potential to adapt to users' needs and context. The goal is to reduce the patient's mobility limitations to a minimum and particular attention is paid to the design of the interface to the patient (Fischer, 2007). Current PHS applications do not include imaging and visualisation functionalities. Yet patients' awareness about their health conditions and understanding of the ongoing of the therapies are key issues, both for ensuring compliance and for optimising treatment. Consequently, and by taking advantage of the latest developments in enabling technologies, PHS solutions should be designed in a perceptive, adaptive, and most importantly reactive way.

3.2 Further insights

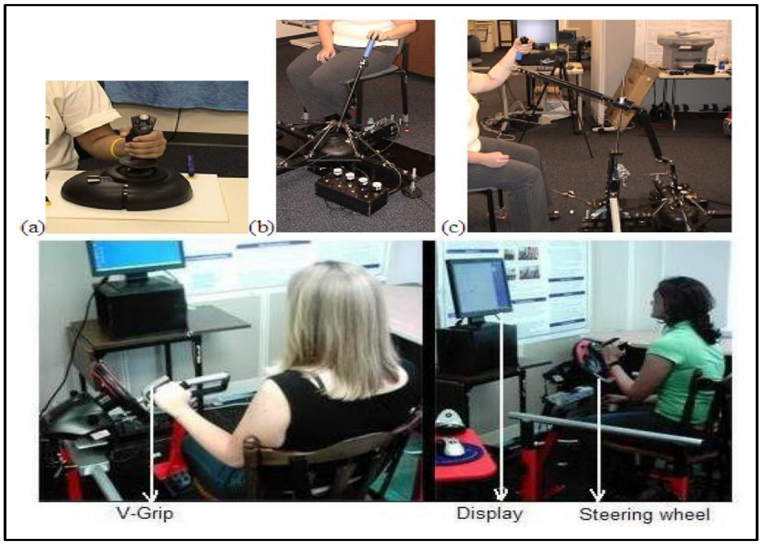
First, when discussing the great promises of PHS we should never forget that in the large majority of cases the typical user of these services would be over the age of 60. Today one out of ten in advanced societies is 60 years or above and in 2050 this proportion will become one in five (Cai and Abascal, 2006). It is unquestionable that with age come reduced functional abilities: from arthritis to decreased learning capabilities, from reduced speech intelligibility to mobility issues; from osteoporosis to reduced organs' sensitivity (may it be vision, hearing, smell, tactile sensation, taste, etc.). Furthermore and as pointed out by Hawthorn in his paper:

> "the effects of age become noticeable from the mid forties onward. So this is not just about design for yet another minority group, the one termed senior citizens. This paper is concerned with design for the second half of our lives and for a group that will shortly be nearly half the workforce and over half of the adult population." (Hawthorn, 2000)

This situation brings in a few levels of complications for the work of PHS-interfacing designers and of engineers who develop the interaction and interfacing functions of PHS: they can no longer concentrate exclusively on developing the latest most-advanced highest-resolution flat portable screen, instead they need to design having in mind average users profile in mind and widen usage to the largest universe of user minorities that deserve further attention from medicine-applied technology. Furthermore, on the route to 2020 the "one size fits all" paradigm will no longer apply for no two people are exactly alike, especially when it comes to medicine. New technology will play a very important role in the quality of life of elderly and disabled people who wish to continue to live autonomously and can be assisted by technology in their daily routines (Edwards and Grinter, 2001) and in this process of decision making and science development consultations can play no marginal role. End users are the key to PHS adoption and effectiveness and they will need to voice their needs both during research and implementation.

Force feedback devices and joystick. Force feedback devices such as joysticks and steering wheels can potentially improve the interaction quality of PHS from the perspective of users. These are widely and successfully used in the market of computer games, where it is estimated that more than 500 games use force feedback today and more than 100 tactile hardware products are available on the gaming market (Chang 2002). For instance, the application of force feedback devices to the robotic therapy field looks particularly promising for providing assistance to hemiplegic patients; the devices' relative low cost and large availability on the market could also allow further applicability in rehabilitation equipments that can be safely used from home in less severe cases (Feng and Winters 2007), such as stroke rehabilitation. Examples of force feedback devices that could be explored and improved in the near future are **SideWinder Joystick** from Microsoft and **Wheel force-reflecting technology by Logitech**, both of which have been experimented on the UniTherapy project, along with two custom-made therapy platforms, TheraJoy (adapted joystick) and TheraDrive (steering wheel). More specifically, the UniTherapy platform was designed to allow the personalization of the therapy via tasks, devices, and tele-support of the relationships between patient, therapy provider and the rehabilitation technology. As a further development of the technology, personalisation of the therapy should also be a target of research: a signalling device could remind the patient about his/her daily exercise schedule, a video could show him/her how to carry out each set of exercises, sensors could be applied to monitor values (such as heart beat) to make sure that the patient is not over-exercising; furthermore, research could make it possible for the rehabilitation machine to detect whether the patient is carrying out her exercises properly (i.e. if she is using the right muscles) and to monitor the patient's improvements (i.e. if ability to raise injured limbs raises over time). Experiments have already proved that different device interfaces (such as wheel and conventional joystick) and device settings (device location in the arm workspace) significantly affect tracking and muscle performance outcomes (Johnson et al., 2007), which is why an effective roadmap cannot but include challenging and promising areas such as this one. Further steps into the enhancement of force feedback devices will entail the use of high-tech sensitive gloves that can capture hands' movements with no need for the user to touch appliances, as well as artificial hands, fingers and a face for impaired users. Needless to say, along with the development of more sophisticated appliances, there is a need to improve the cost-to-benefit ratio of robot-assisted therapy strategies and their effectiveness for rehabilitation therapy in home environments characterised by the low supervision by clinical experts, low extrinsic motivation as well as low cost requirement.

Figure 6: UniTherapy Joystick and Steering Wheel Systems



Source: Johnson *et al* (2007)

Speaking devices and applications for the blind. Another area that has been providing interesting applications and that should, in the near future, produce great utility for users with visual impediments is research on speaking devices. The ageing process leads many people to lose they sight abilities at different levels, sometimes preventing them from reading medicines' prescriptions or any message appearing on technological devices, such as their blood-pressure values on the sphygmomanometer. Similar obstacles are faced by people who have become blind or are blind from birth. It is therefore believed that the use of audio and non-visual interface aspects would allow direct and active interaction with devices that would otherwise be impossible achieve through the visual medium, if not with the help of a third party. Enabling users to interact and improving their level of technology appropriation will free a whole new range of possibilities for technology developments that in the more distant future will be able to have visually-impaired people as their targets. Such advances will provide user empowerment, independence and also alternatives. It is therefore important that these new developments are not perceived as marginalising or stigmatising, but rather as "normalising" tools. It also hoped that by the year 2020 (and possibly even earlier), **Touch&Braille** technologies will make it possible for visually disabled users to read just about anything, were it on their computer screen, on their mobile phone or on their latest PHS device. These technologies will further enable them to convert anything into Braille, whatever the language of the user, thus facilitating the creation of media content for blind users. The road towards this goal is not far in the distance: some basic technologies have already been created as in the case of **RoboBraille**[25], an email-based translation service capable of translating attached documents to and from contracted Braille and to synthetic speech.

Hand-writing recognition. A further but equally important step in the roadmap of PHS development in the field of interfacing, interaction and diffusion will be the integration of handwriting recognition to computers and other technological appliances: keyboards will be a distant memory, a forgotten hindrance to people's adoption of ICT. Thanks to handwriting recognition typing will no longer be required to interact with machines: if we are not speaking to them or using touch screens, steering wheels or wearing high-tech gloves, you will be sure to catch us handwriting directly into the screen. A much more intuitive, natural way of actively interacting with technology will sure favour many in the use of PHS.

Voice activation devices. Next we come to another theme that has emerged as a potential milestone on our roadmap from the literature review, which is integration of voice activation devices to personal health care devices. The use of technology in the home is on the increase but difficulties in operating household appliances as well as performing other daily activities are part of the effects of, in many cases, growing older and losing sensory and cognitive abilities. Voice activated environment controls and other sophisticated control panels are examples of the effort put into making technology for increasingly comfortable, non-cumbersome and efficient home environments. Ifukube (2007) for instance suggests that intelligent tools that are able to recognise both verbal and non-verbal information should be developed – which leads us to the final potential milestone in the roadmap: imaging and visualisation.

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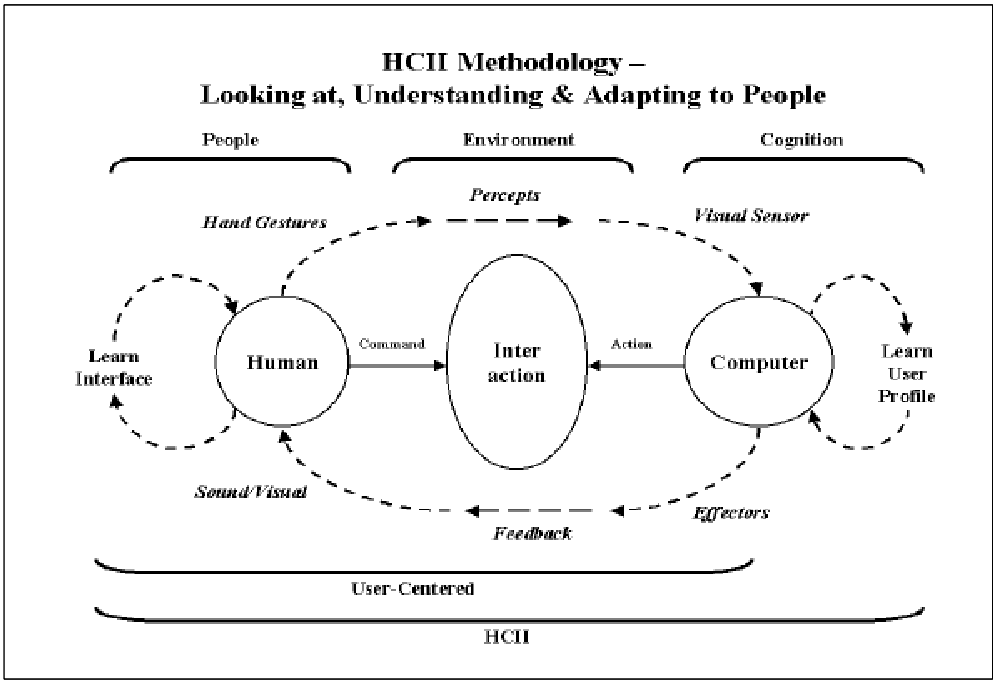
[25] http://www1.robobraille.org/websites/acj/robobraille.nsf

Imaging and visualisation. Nothing could be rendered more personalised in technology than visualisation: users love to customise their computer's desktops, mobile phones or mp3 player' interface by downloading new icons, new wallpapers, changing the font, etc. This is not just because users are increasingly demanding in terms of appearance; rather it has mainly to do with their needs to ease and speed up their use of technology. Personalised imaging and visualisation will help embrace as wide a pool of users as possible in the use of PHS and to make sure they stay connected in the long run. We started off by saying that, whichever the route followed by the roadmap, research will have to focus on the users' profile and on the identified targets of this domain. However, PHS systems do not only aim to support the elderly and people with disabilities; in fact there is an increasingly wide part of the research that focuses on giving people the chance to keep up their healthy living standards, or to improve their eating habits; or to increase their daily exercise and training, just to name a few. This domain, jointly with the rest, calls for parallel research on improving the imaging and visualisation offered on PHS devices. 3D Holograms have largely been researched in the media and information sector (i.e. hologram anchormen to present the news) and they are a good example of the sort of direction research may steer toward: imagine having your trustworthy caregiver or nurse visit you at home every day to remind you about taking the pills you always forget to take, to encourage you to carry out your daily rehabilitation exercises, to get feedback on the progresses you are making on your diet. Yes, because in the future holograms may actively interact with the patient.

Affective computing. Additional promising fields within the interaction and the interfacing field are brain computer interface and affective computing. The most interesting potential of these technologies is the possibility to finally link physical and emotional signals. According to Chen and Wechsler (2007), affective computing is considered to be a methodology with means to recognize **"**emotional intelligence**"**. The authors present a human-computer intelligent interaction methodology (illustrated below), as a way of improving human activity and creativity. With this methodology, the authors have developed an online educational system which provides an interactive mathematical learning environment that is personalized to each student with **intelligent state feedback** to tailor the appropriate mathematics exam data set for the student in order to evolve his/her mathematical skills. In the case that the student replies correctly he/she will be challenged with a more difficult test question set. On the other hand, if the answer is incorrect, an easier question set will be administered at the next round. After conclusion of test, each student is provided with feedback that shows the correct answers of each question, the difficulty level of the questions, the student's final score to each set, and a predicted score along with probability bands that show satisfactory performance ranges. In the PHS field, this may open up major opportunities not only for providing individuals with a learning platform, but also for adaptation of services to each and every unique case. As the link between mental and emotional states and PHS becomes increasingly inevitable for the pursuit of personalised PHS, complementing the brain-computer interface is the affective computing. This technology has enabled building systems that have several affective abilities, especially: recognizing, expressing, modelling, communicating, and responding to emotion (Picard, 2003). The main goal being; enabling ICT to better serve people's needs by adapting to them and not the other way around

Figure 7: Human-computer intelligent interaction



Source: Chen and Wechsler (2007)

Multi-channel interaction systems. Finally, we come to deal with a theme of this research area that ultimately will enable all aforementioned technologies to yield the highest returns, that is multi-channel interaction systems. Some researchers (see for instance Feng, and Winters 2007) claim that a standardized but flexible abstract user interface description for target devices (e.g. intelligent appliance) or services (e.g. web services, software program) will be required, so that any remote control can connect to discover, access and control a remote device or service on top of network communication protocol (e.g. UPnP, Java/Jini, OSGi). With such an abstract user interface description, a remote control with universal interface capabilities (e.g. speech interface, natural language interface, tactile interface) should be able to be supported by various computing devices ranging from desktop computer to handheld PCs. Multimodal approach facilitates users' adaptation to the format of information displaying that suits them best, due to external circumstances or personal preferences. Multimodal interfaces will therefore benefit all users and promote "universal access" (Jacobson, 2002). The richness provided by multimedia and multimodal interactive systems is especially appropriate for older people who often suffer from reduced sensory, motor and intellectual capabilities (Alm *et al* 2001). Particularly important to the group of older people, where cognitive capabilities are diminished, is the fact that the multimodal interface gives people the "feeling of experiencing information instead of acquiring it" (Hoogeveen, M., 1995), due to the increased stimulation of the senses, strong recognition effects and higher emotion arousal. Thus, it is believed that carefully applied multimodality improves user-friendliness, the impact of the message, and the entertaining value of the system and improves learning of the system.

3.3 *Proposed roadmap*

The table below synthetically provides a snapshot of the preliminary research themes associated to the gaps and of the key input from the further review of the literature. In combination with the comments and changes introduced during the two consultation events focussing on roadmapping they shape the final proposal graphically presented in Figure 8 reported in the next landscape page.

Table 4: Re-compacting information: Interfacing and Interaction

Gaps (Table 1, p. 7)	Preliminary research themes (Table 1, p. 7)	Further insights
• Lack of multi-channel delivery and inter-action creating risk of exclusion	• Development of multi-channel delivery and inter-action systems including more commonly used devices (i.e. mobile, Digital TV, etc.)	• Force feed-back applications; • Multi-modal interaction; • Alternative sensing; • Affective computing • Motivational support tools • Multi-channel interactions
• Need of more understandable and easy to interpret input and guidance to users;	• Development optimal and easy-to-use interfacing techniques; • Development of straightforward imaging;	• 3D Holograms

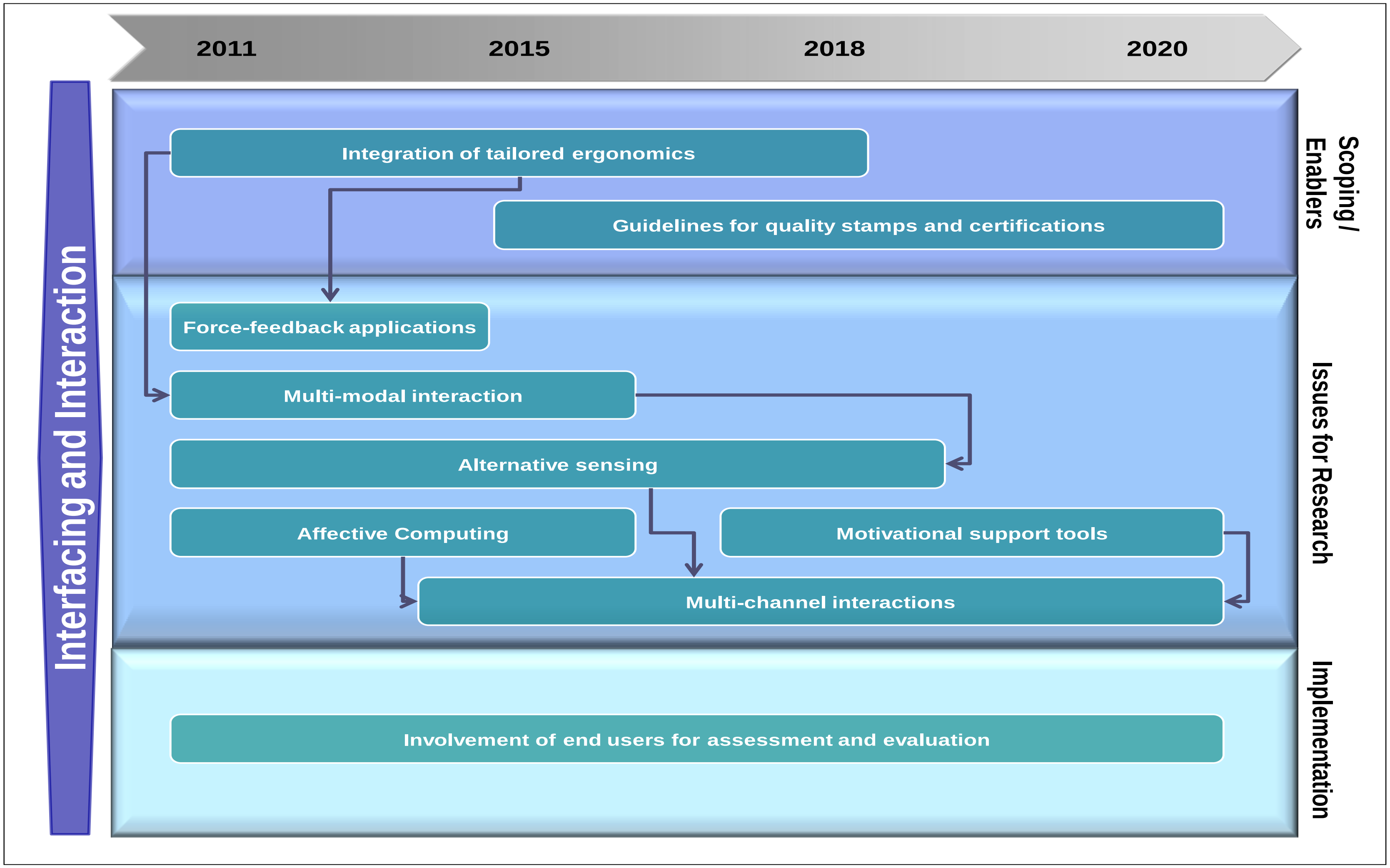
How we interact with our PHS solutions will play a major role in the potential implementation and future take-up. This entails that the main focus of research should be developing user-friendly systems that are adaptable to all individuals and various context of use. Which in turn indicates that services are to be offered through several manners and channels, facilitating not only the adoption but also the preferred interaction. In other words, personalisation of Personal Health Systems entails also the users' experience in the fruition of PHS services, and in interaction with them.

Ease of use plays, as mentioned previously, an important role in the adoption of Personal Health Systems. Consequently, it is recommended to look into how to best tailor different PHS to different applications by the use of ergonomics through scoping studies. It would also be favourable to develop guidelines to further ensure that those PHS that are to be developed in the future follow certain quality measures concerning user-friendliness.

As PHS offers special opportunity for disabled individuals, it would be most advantageous to ***implement "natural languages" and alternative sensing***. This entails that current research should continue developing systems using e.g. Braille translations, and methods for "remote reading" by the use of e.g. RFid. This would make it possible for e.g. visually impaired to know e.g. which bus is approaching and which destination it takes by a communicated voice-activation.

Equally, the ***Force Feedback Devices*** currently used by the gaming and entertainment industry and is beginning to be implemented in the PHS field, ***widens significantly the field of treatment and rehabilitation,*** and thus should be further developed with the most

Figure 8: Visual Roadmap for "Interfacing and Interaction"



Source: Authors' elaboration

recent technological progressions. As also suggested for new research, also affective computing offers many optimistic opportunities in this area.

During the consultation processes, it has also been suggested to carry on in ***enlarging the scope of modes in which PHS is offered, constituting one important step towards multi-channel delivery systems.*** In specific, these are preferred to also be automatic in application transfer i.e. if a user is travelling, the service is offered through the mobile device, when he/she arrives at home the service is automatically transferred and offered through the TV-set. This to enhance mobility and multi-modal interaction possibilities, other than increasing users' comfort in their interaction with machinery

In parallel, new research should focus on implementing ***"natural sensing"*** as far as possible i.e. by developing PHS with voice-activation systems, hand writing recognition systems, speaking functions etc. Static 2D images shall be replaced with 3D visual systems in order to provide more realistic and effective digital information to the user. Creation of dynamic digital content calls for research on more interconnected, highly navigable and intuitively-searchable content.

Furthermore, there is great interest for new research to concentrate efforts on the development of ***avatars and holograms***. These technologies allow for wide opportunities on issues of both interfacing and interaction. In fact, on one hand, representations have incredible potential for creating more-effective and realistic interfaces that will ease the use of technology for many users – both experts and "newbies". On the other hand, provided that humans will be given the possibility to interact among themselves through the graphical interface, impressive opportunities are bound to be created for the healthcare system. It is precisely for these reasons that research will need to pull efforts on this area of technology.

This development area is expected to help overcome the limits of PHS in interaction and transmission of information in a perceptive manner, thus leading to the development of more intuitive and easy to understand tools. It will further allow for the incorporation of self- and environment imaging.

As stated in many ways, both in the literature reviewed and during the consultation process, ***poor adherence to medical prescriptions, and low compliance to treatments are extremely common among patients.*** This can be due to several factors, which often are in combination: complexity of prescriptions (e.g., several medications to be taken at different times during the day), low perception of benefits, mistrust towards the treatment, forgetfulness, etc. In addition, health and lifestyle management often require ***behavioural change*** (e.g., stop smoking, change in diet, start training programmes, etc), which is extremely difficult for patients to pursue for long periods. Therefore, ***it is strongly recommended to develop new systems and tools which meet this challenge, which could help in dramatically increasing effectiveness of medical treatments***. ***This can be done in several ways, depending on treatments' requirements, as well as, and equal important, on individuals' preferences towards the type of interfaces and channels to use.*** Examples can be game/social networks for motivational interaction, applications based on web 2.0 platforms, or as an expert once suggested, simply by developing a personal traffic light (if one complies with recommendations a green light is provided; if not, a red light is switched on), to be delivered through several channels (e.g., telephone, both mobile and fixed, digital TV, Internet, etc), even combined.

In this roadmap, strong accent has been put of research on ***interfaces,*** including avatars and holograms, and affective computing as well; the immediate outcome of this stream of research being ***powerful tools for providing effective support and feedback to users,*** improving thus their compliance to treatment, and healthy behaviour in general. ***Affective computing*** can go further beyond in this field, as its main potential is to finally link physical and emotional signs. This may lead to PHS not only offering users a learning platform, but also adapting services to each unique case. In other terms, ***Personal Health Systems could become personalised in the sense of recognising, expressing, modelling, communicating and responding to users' emotions, thus adapting their services to peoples' needs and not the other way round.*** This could entail, for instance, finding each time the better way to communicate with the user, depending on his/her contextual and emotional state (e.g., stress conditions, etc.)

Naturally, the ease-of-use is best determine by actual users, why it is of major importance to involve end users as early as possible, both in the development and testing process, as suggested for the implementation assessments

4 Sensors

4.1 Contextualisation

In our state of play we considered, among others, the following attributes for sensors in the PHS context:

- Position;
- Invasiveness;
- Level of comfort;
- Type of sensor;
- Interactivity level (lack or presence of actuation);
- Whether it includes on board processing;
- Signs per sensor and disease per sensor;
- Type of data gathering.

At the level of research projects noticeable progress and advancement have been achieved if we look longitudinally at the frontier of innovation of PHS FP5 projects compared to those launched in FP7, although much space remains for substantial improvements. As far as sensors position is concerned, for instance, stationary and portable sensors are being substituted by smart wearable sensors, providing large contact surface with human body (which increases measurement accuracy) and better comfort for users. If we call those developed so far by research projects as “second generation PHS sensors” (distinguishing them from first generation sensors included in product and services currently available in the market), the comparison between the state of play and the scenarios identified various gaps that need to filled in for the development “third generation PHS sensors”. “Second generation PHS sensors” still miss calibration, optimised power supply, capacity of efficient and effective multi-disease and multi-signs context aware data gathering, actuation, on-board processing that already fully perform multimodal data fusion. Sensors still have problems in gathering reliable data under movement. As put it by one expert during consultation, for instance, there are no ECG devices that displays T-wave elevation or sub-elevation under movement and the same applies to respiration. When it comes to wearable sensors, currently there is still the need to calibrate every couple of hours to get them to work properly. There is too rigidity in sensors networks architecture preventing their adaptability to the very peculiar characteristics of each single individual and little space of modularisation and “plug & play” approaches. Capturing signs reflecting the emotional and psychological status of individuals are out of the current possibilities of data gathering by sensors. During the gap identification phase, the main characteristics of sensors were compared to the main features of future PHS applications, as outlined in the scenarios. One of the crucial issues to be solved in order to spread PHS adoption is the comfort of data gathering systems (i.e., the devices where sensors are applied, for gathering patients’ data). A key issue is to overcome the trade-off between accuracy of measurement, which requires frequency of measurement, and large contact surfaces, and comfort, as individuals want to have complete freedom of movement (ideally, they should not even feel the contact with sensors).

4.2 Further insights

The importance of developments in MEMS and NEMS. Microelectromechanical systems (**MEMS**) are devices with tiny moveable parts that respond to control voltages and are mass produced, for instance, by several manufacturers as airbag sensor in cars (Tröster 2004: 132). We briefly treated these technologies in the state of play[26] and then they have repeatedly surfaced in the gap analysis associated to gaps mainly related to sensors but with implications also for data processing[27]. In very brief and simplified terms the micro- and nano- systems: a) interact with their physical environment; b) are minimally invasive (implanted MEMS can be the size of a grain of rice); c) integrate sensing, computation and actuation, possibly capturing several signs; d) can increase energy efficiency and decrease bandwidth requirements (an implanted MEMS requires no batteries, as radio transmitter and receiver held near the body provides the power and interrogates it). It is quite evident, then, how they can contribute to fill many of the gaps discussed about sensors. Indeed the emergence of MEMS is considered as one of the major technological breakthrough in the last 20 years. They are considered as building blocks for complex micro-robots performing a variety of tasks and are used to construct systems which function very close to biological systems existing in nature (Frenz 2008). MEMS-based sensors have several advantages: can be mass-produced lowering average costs of production, have small size, low power consumption, lightweight and small volume. Fabrication of MEMS involves developing smart structures, which communicate via feed-back in closed-loop systems. This requires merging computation with sensing and actuation into integrated micro-level systems that interact with the physical world. Materials commonly used for fabricating MEMS include traditional microelectronic materials (like, for instance, silicon, silicon nitride, polyamide, gold, aluminium), and non-traditional ones (e.g., ferroelectric ceramics, shape memory alloys –SMA, and chemicals sensing materials). These micro-machines systems are designed by integrating different micro-components into one functional unit comprising sensors, actuators, ICs for data processing, etc. In this development, a variety of micromachining technologies, ranging from the conventional silicon bulk and surface micromachining to LIGA and LASER techniques are employed, each one having specific advantage or merit for a specific product. Another process useful for MEMS application is substrate bonding. Silicon, glass, metal and polymeric substrate can be bonded together through several processes like fusion bonding, anodic bonding, eutectic bonding and adhesive bonding. Substrate bonding helps in achieving a structure that is otherwise difficult to form e.g., hermetically sealed large cavities, a complex system of enclosed channels or simply to add mechanical support and protection (Gupta and Ambad, 2007).

MEMS for wearable sensors. Wearable sensors are indeed a very important development where it is safe to state that PHS application have been a driving force. As illustrated by De Rossi and Lymberis (2005) there are three very simple but forceful arguments underscoring the importance of wearable sensors: a) about 90% of the skin

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[26] Deliverable D2.1, *State of play*, pp. 36-37 and p. 47.

[27] PHS2020 Deliverable D4.1, *Gap Analysis Report*: Box 8 (p. 29); Box 14 (pp. 33-34); Box 15 (p. 34); Box 16 (pp. 34-35); Box 17 (p. 35).

surface is into contact with textiles; b) fabrics are flexible and conform well to the human body; c) they are relatively inexpensive and eventually disposable. Yet, there are still a number of challenges and of corresponding innovative solutions emerging (Akita *et al* 2008; Liao *et al* 2008; Roggen *et al* 2006; Bonfiglio *et al* 2005; Tröster 2004)[28]. Not all but many of such challenges can be overcome through the application of MEMS into textile producing **smart wearable sensors** with improved measurement precision and more efficient energy consumption. Tracking of body motions, gestures and positions provide information useful for activity classification, for de-noising of other bio-signals, e.g. ECG, and for interpretation of the physiological status. Miniaturised MEMS based accelerometers, gyroscope, magnetometer, piezoelectric embedded into wearable can improve such tasks. Even before the current rise to prominence of MEMS, micro-systems embedded directly into fabrics, or in clothing components like buttons, were considered a way to improve wearable sensors by decreasing their invasiveness and preserving the quality of the gathered data and by making them energy autonomous through solar cells mechanical (i.e. leg motion) and thermal (i.e. body temperature) energy (Bharatula *et al* 2004; von Büren *et al* 2004; Starner 1996). MEMS greatly enhance these possibilities envisaged earlier for less advance micro-systems. An additional critical issue is that of the material more suitable to be employed and various solutions are being explored(see Liao *et al* 2008; Bonfiglio *et al* 2005)[29]. Even in this case, advancements in MEMS technology embedded into wearable sensor can help improve these aspects.

MEMS, implants, and actuation. MEMS, alongside other bio- and nano-technologies, represent a key factor for the development of new implantable sensors, as explained in the following example (see Figure 9 overleaf). Miniature MEMS sensors, similar to those that trigger airbags in cars, might be implanted in the hearts of people suffering from a heart disease. The sensors would make it easy to measure blood pressure inside the heart, which at present involves repeated operations. The implant, the size of a grain of rice, is one of a new breed of medical devices that requires no batteries. A radio transmitter and receiver held near the body provides the power and interrogates the implant. In the figure below is highlighted the device has been designed for people with congestive heart failure, where fluid builds up in organs and limbs because the heart fails to pump enough blood around the body.

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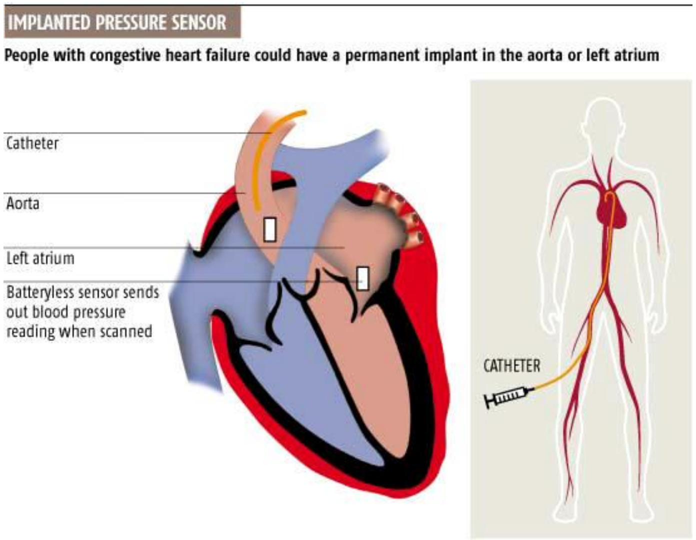
[28] This is only a very selective list of possible references that are sufficient for our purpose here that is mainly illustrative with no claim go into the very details of the various solutions.

[29] The core of the smart wearable is the textile transistors, with respect to which the textile industry has some constraints. For instance, concerning the use of metal yarns, usually the use of a single metal fibre is avoided, because of problems of low flexibility and resistance to stretching and friction. In this respect, some new techniques are being developed: 1) production of a yarn with a core of “normal” textile and with spiralled metal filament; 2) use of pure metal yarns made of several metal fibres, prepared as long filaments or from staples; 3) a yarn made by twisting metal fibres around a filament or a previous spun yarn, thus concealing the core. Applying these techniques, metal yarns can be used with commercial weaving machines, maintaining technical properties comparable with traditional yarns. In addition, more “traditional” material, like optical fibres, can be used to monitor vital signs in a minimally invasive way, having the capability to be modelled like human hair, with similar size and flexibility characteristics. Optical fibres, in fact, are thin, lightweight, chemically stable and generally biocompatible. In addition, fibre communication technology is well established. By the way, in vivo use for monitoring still has some open issues, like the speed and accuracy of measurement over time.

Figure 9: Implanted MEMS Sensor



Moreover , active micro-catheters (see also figure 43) and active guide wires, which incorporate micro-actuators at their tips and are controlled from outside the body, have been developed. These actuators, which incorporate Titanium-Nickel Shape memory alloy (SMA) micro coils, are capable of several motions such as torsional and extending motions, sensibly improving the effectiveness of the catheter for navigating difficult blood vessels branched with highly acute angles, and the selective embolisation of arteries for treatment for treatment of tumours, like myoma of uterus. Modular MEMS-based actuators are being researched to provide **motion systems to capsular endoscope[30],** exploiting the thermal expansion of PDMS (polydimethylsiloxane), and using a bulk micro-machining fabrication technique (Lee et al., 2007). Several other diagnostic and treatment tools for use in the human body are being developed, using the alternatively bonding and micromachining fabrication techniques, as an ultra-miniature fibre-optic pressure sensors, an ultrasonic therapeutic tool for sono-dynamic therapy and sono-poration (Lee et al., 2007). Yet, it must be stressed that the use of metal alloys (including Nickel) in MEMS can limit their potentialities, since it can reduce the adoption of these kind of applications by an increasing part of population due to allergy to nickel, especially when considering that the prevalence of contact dermatitis and atopy is increasing (Dawn et al., 2000).

Molecular Nano Technology and Nanorobotics. Technological developments of relevance for PHS are coming from MNT in general, and from nano-robotics applications in particular. These complex molecular machines, in fact, with embedded nanoscopic features may provide broad advances in the healthcare sector. Current developments in nano-electronics and nano-biotechnology are providing feasible development pathways to

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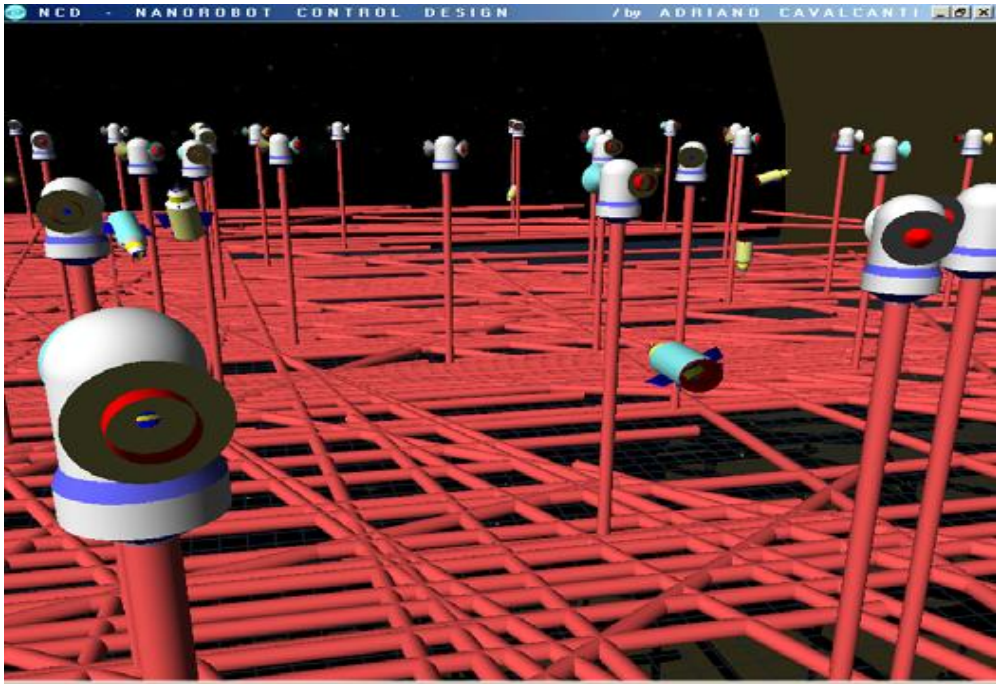
[30] Conventional endoscope is becoming an important medical tool diagnosing human disease, although it has a few drawbacks: a) require sophisticated skills for doctors to use it; b) the endoscope inspection is painful and invasive for the patient; c) it is difficult to inspect the small intestine using the endoscope. New capsular endoscopes, which can move by the motion of the intestine, have been developed to obviate to the three drawback of the conventional endoscope. Yet, this new capsular endoscope still has the limitation of not being able to move by itself. MEMS-based actuators are being developed to produce self-movable capsular endoscope applications.

enable molecular machine manufacturing, including embedded and integrated devices which can comprise the main sensing, actuation, data transmission, remote control uploading, and coupling power supply subsystems addressing the basics for operation of medical nanorobots. Considering the properties of nanorobots to navigate as blood borne devices, they can help important treatment processes of complex diseases in early diagnosis and smart drug delivery. A nano-robot can provide efficient early diagnosis of cancer and help with smart chemotherapy for drug delivery. Nano-robots as drug carriers for timely dosage regimens allows maintaining the chemical compounds for a longer time as necessary into the bloodstream circulation, providing predicted pharmacokinetic parameters for chemotherapy in anti-cancer treatments, avoiding at least some of the side-effects of chemotherapy (Cavalcanti, et al., 2008a and 2008b). Clearly, this kind of applications is far beyond current solutions for ensuring drug intake and compliance with medical prescription of patients (Barnes and Reeves, 2008, Fook et al. 2007). These, in fact, are mainly based on applications inferring actual drug intake monitoring patient’s vital functions and mobility, at occurrence providing reminders and alarm functions for falls detections or common infections (like Urinary Tract Infections). The application of nano-robots with embedded sensor devices for drug delivery and diagnosis is, therefore, undoubtedly an interesting subject, which can enable significant improvements as a high precision device for medical treatments. A nano-robot architecture using embedded CMOS (Complementary Metal Oxide Semiconductor) for sensing, communication and actuation, as the result of many breakthroughs in nanotechnology, with a complete integrated set of nano-bioelectronics, should help in setting directions for the fast development and manufacturing designs of future molecular machines. The nano-robot must be equipped with the necessary devices for monitoring the most important aspects of its operational workspace. For biomedical application the temperature, concentration of chemicals in the blood, and electromagnetic signatures are some of the relevant parameters when monitoring the human body to detect some diseases. The application of new materials has demonstrated a large range of possibilities for use in manufacturing better sensors and actuators with nano-scale sizes. This downscaling will continue, according to the Semiconductor Industry Association’s roadmap (International Technology Roadmap for Semiconductors, 2006). By 2016, high performance ICs will contain more than 8.8 billion transistors in a 280 mm2 area—more than 25 times as many as on today’s chips built with 130 nm (nano-meters) feature sizes. Those developments allied with 3D simulation should facilitate the manufacturing design of nanorobots with integrated embedded nano-electronics and circuits**.**

Nevertheless, even such a promising field presents some problems when looking at practical adoption of nano-robots. Many of them concern possible toxicity of nano-materials, which can lead to increased production of reactive oxygen species (ROS), including free radicals. So far, there are no conclusive studies on toxicity of all nano-particles, nor on long-term effects on human body.

Biosensors and nanobiotechnology. Biosensors and nanobiotechnology, both converging with nanoelectronics, to same extent address the issue of reducing possible undesired effect in that they combine a biological component with a physicochemical detector component for the detection of an analyte. The main potential of these development, however, are not only in the material used, but also in the capacity to identify the target molecule (given the availability of the needed biological recognition element) in a disposable and portable system in alternative to laboratory based techniques. In a biosensor a) the biological component (i.e. tissue, enzymes, nucleic acids, etc) interacts with the target analytes and should produce a signal that b) is transformed into a another signal by a detector element working in various ways (physicochemical way; optical, piezoelectric, electrochemical, etc.), which c) is processed by the associated electronics or signal processors component displaying the results in an intuitive way for the user.

Figure 10: Nanorobots search for organ-inlets demanding protein injection



Source: Cavalcanti *et al* (2008a)

In 2006 in the US an implanted biosensor has been presented in a patent application, for instance, incorporating living components (tissues or cells) that are electrically excitable or are capable of differentiating into electrically excitable cells to be used to monitor the presence or level of a molecule in a physiological fluid[31]. As the author rightly claim, such solutions compared to traditional laboratory test have the advantage that they enable a high frequency of measurement and avoid the discomfort of associated with periodic blood draws. Moreover, if coupled by user friendly and intuitive visualisation, they could also be used in tertiary prevention: if patients diabetes were able to continuously see a display of glucose concentration in blood or tissue, they could better avoid extremes of glycaemia and reduce their risk for long term complications. Finally, it is claimed that implanted biosensor (because of the use of biological material) would overcome the problem related to the fact that ***fibrosis of the foreign body capsule typically develops around the implanted sensors 3-4 weeks after implantation and reduce the influx of substrates such as glucose and oxygen***. A further development comes from the

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[31] United States Patent Application 20060234369 by Sih, Haris, J. (see details at: http://www.freepatentsonline.com/y2006/0234369.html?query=Implantable+biosensor&stemming=on)

convergence between nanoelectronics and nanobiotechnology in the form of ***nanorobots with embedded nanobiosensors and actuators*** (Cavalcanti *et al* 2007; Cavalcanti *et al* 2008b; Liu and Shimoara 2007). This development enables molecular machine manufacturing, including embedded and integrated devices, which can comprise the main sensing, actuation, data transmission, remote control uploading, and coupling power supply subsystems, addressing the basics for operation of medical nanorobots. In 2006 a sensor/actuator with biologically-based components has been patented in the US by Xiong *et al* [32]. This actuator has a mobile member that moves substantially linearly as a result of a biomolecular interaction between biologically-based components within the actuator. Such actuators can be utilized in nanoscale mechanical devices to pump fluids, open and close valves, or to provide translational movement (see Figure 11 in next page).

Contactless sensing and bio-imaging. Whether it applies only to sensing or to both sensing and actuation, the issues of non invasive or minimally invasive sensors/actuators and of the effects that their materials will have on human body have emerged from the consideration so far as of strategic importance, and they apply to both on- (wearable) and in- (implantable) body sensing and actuation, and also to the very new and promising development in MEMS/NEMS and in MNT and nanorobotics. In consideration of this, technologies supporting improvements of non invasive and minimally invasive monitoring and actuation are being given further impetus. Among them, promising technologies supporting development of contactless sensors can be integrated from other areas also in the field of PHS, ***exploiting magnetic field***, for instance, sensors could be developed that integrate also communication capacities through ***nano-antennas***. In the same way, advancements in imaging techniques, exploiting the characteristics of micro- and nano-devices, could lead to interesting applications. Among those, ***bio-photonics*** for non invasive/minimally invasive detection of analytes can be mentioned. This kind of application would allow to measure the analyte in blood without extracting the sample, but simply getting almost in contact with it, (e.g., penetrating into the first layer of skin, near blood vessels), and obtaining results in few seconds.

An even more fascinating application of imaging concerns tongue scanning, a developments joining advanced medicine technology with Traditional Chinese Medicine (TCM). Traditional Chinese Medicine has become fascinating because of its holistic approach to health, including physiological but also environmental and emotional aspects, in which modern medicine is gaining interest. Therefore, joining "traditional" knowledge with "scientific" tools and methods is being considered as a very interesting area. Tongue diagnosis in a standard technique of Chinese Traditional Medicine (Liu, *et al* 2007). The relationship between some diseases and abnormalities in the patient's tongue and tongue coating has been substantiated by clinical evidence. The association, for instance, between the various viscera cancers and the changes of colour, coating, degree of wetness and coarseness, shape and dorsum shape of the tongues, has motivated the development of various tongue visualization techniques. There are several issues to be addressed in computerized tongue image analysis. The methods to capture the tongue

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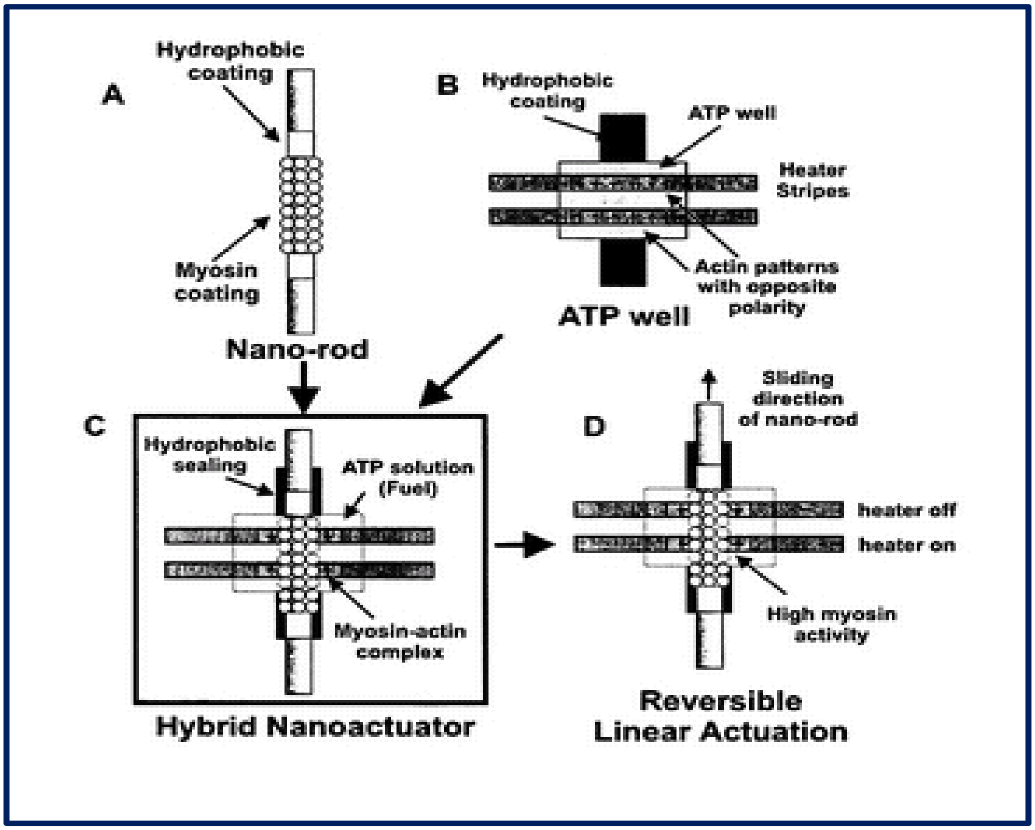
[32] United States Patent 7014823 (see details and name of other inventors at http://www.freepatentsonline.com/7014823.html)

image, followed by effective segmentations of the tongues and calibrations of their colours need to be considered.

Figure 11: Bio-molecular based actuator



Source: Xiong *et al* (2006, see http://www.freepatentsonline.com/7014823.html)

Generally, two kinds of quantitative features, chromatic and textural measures, are extracted from tongue images. Selection and representation of tongue image features are the next issues to be tackled with. In the early studies, charge-coupled device (CCD) cameras were used to capture the tongue images and a red, green, blue (RGB) model was used to represent the colours. The next problem is the fuzzy characteristics of the data itself. Further challenges concern the processing of tongue images: the more recent approaches include fuzzy theory, neural networks, parallel coordinate visualization, Bayesian networks, and integrations of them (Lukman, et al., 2007).

Context awareness: importance and state of the art. The context aware and more holistic data processing going beyond vital and physiological signs discussed earlier must be fed by new sensors capable to capturing the relevant and currently less evident signals. Context awareness is important in two ways. First, the understanding of users context is fundamental for a ***full comprehension of physiological parameters avoiding false positive or the chance of missing a risk situation***. For instance, it is only matching vital parameters with activity and behaviour information that permits a correct assessment of cardiovascular risk and trigger appropriate action. In this first sense, thus, context awareness is instrumental to monitoring and treatment of users with a chronic disease or with an early detected risk that could develop into a full blown disease. Second, in a much broader sense context awareness is important because ***it has been demonstrated that the mental and social state of individuals have an impact on their health*** (Danner *et al* 2001; Diener *et al* 1997; Diener and Lucas 2000; Giles *et al* 2005)[33] and indeed the World Health Organisation defines health a sense of physical, mental and social well-being and not simply as a the absence of disease or infirmity (WHO 1946)[34]. In this second sense, then, ***PHS context awareness is fundamental also for life style management applications*** helping the health savvy users preserve a good health status along three directions (physical, mental, and social state) and prevent the outset of diseases. The issue of context awareness is certainly not a new one in research and already more than a decade ago it was stressed, for instance, that a truly personalised wearable system should automatically recognize the activity and the behavioural status of a user as well as of the situation around him and to use this information to adjust the systems' configuration and the functionalities (Abowd *et al* 1998). Indeed research has achieved noticeable advancements for the dimensions of context recognition listed in the Table 5

Yet these capabilities need to be expanded significantly in order to understand higher level, more complex, contexts than what is currently state of the art (Roggen *et al* 2006). Advancement in this field should lead to have sensors capturing the various dimensions of what we mean by broadly defined context of an individual:

- His/her punctual situation of an individual at any given time:
    - Location (indoor / outdoor);
    - Time of the day
    - Activity (sleeping, walking, performing a particular task)
    - Gesture and position
- His/her environmental surroundings:
    - Weather conditions;
    - Illumination;
    - Noises;
    - Chemical features (i.e. particle in the air)
- His/Her emotional state (i.e. stress, depression, etc)
- His/her social state (i.e. degree of interaction, communication style, etc.)

Table 5: Context detecting sensors

Accelerometer	Motion patterns of the body and limbs
Microphone	Speaker recognition, localization by ambient sounds, activity detection, speech features
Visible light sensor	Localization of light sources
Rotation (gyroscope)	Body movements
Compass	Orientation of the body and the head
Air Pressure	Vertical motion in elevator or staircase

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[33] Cited in Roggen *et al* (2006).

[34] See comments of this definition as moving from health to happiness in Saracci (1997).

IR light sensor	Sunshine, localization of lamps
UV light sensor	Localization of fluorescent light tubes
Environment temperature	Outdoor, indoor
Humidity	Location, weather conditions
WLAN / GSM / CDMA	Location, user environment
Bluetooth, ZigBee	Services and devices nearby

Source: adapted from Roggen et al (2006)

Some of these parameters are detected by the sensors listed in Table 5, although as we will show later even in this case there are challenges for future research. Evidently the area where research is only at an embryonic stage is that concerning emotional and social state. Movements and gait have been analysed deeper than parameters such as facial expressions that could help detect the emotional state, and mainly concern fall detectors and movement patterns in controlled environments using cameras as data gathering devices (Pham *et al.*, 2008), or gyroscopes (Farella *et al*, 2008).

In this respect it is worth stressing that out of the large number of EC funded research projects analysed in out state of play[35], only two FP6 project have addressed the behavioural aspect of health: INTREPID[36] and AUBADE[37]. Some of the emerging direction of research are discussed below.

Context awareness: emotional and social state. The notion of ‘Affective Computing’, introduced more than a decade ago (Picard 1997), is important for achieving context awareness. It designs machines with the skills to recognize their users’ affective expressions (including stress, depression and other emotional states), and to respond intelligently. In two recent review of the state of the art in wearable systems it is claimed that social and mental state may be monitored and evaluated using only ***wearable devices*** (Roggen et al 2006; Tröster 2004). This claim is based on the fact that various emotion classes[38] may be detected from brain signals (Davidson *et al* 1990), or physiological signals such as cardiovascular patterns (Schwartz *et al* 1981). Accordingly accelerometers, microphone, galvanic skin response (GSR), temperature and ECG sensors could be sufficient if integrated combination with local communication devices (e.g. WLAN) to detect the basic mental states like stress, fear, depression, as well as basic social states like interactions or communication styles. Several examples are cited to support this view. Four wearable sensors (EMG, SpO2, skin conductance, respiration sensor) have been applied to detect and to classify eight different motions like anger, grief, joy or hate with a classification accuracy between 60 and 70 percent (Picard et al

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[35] See PHS2020 Deliverable D2.1, *State of Play*, Annex III (pp. 111-131).

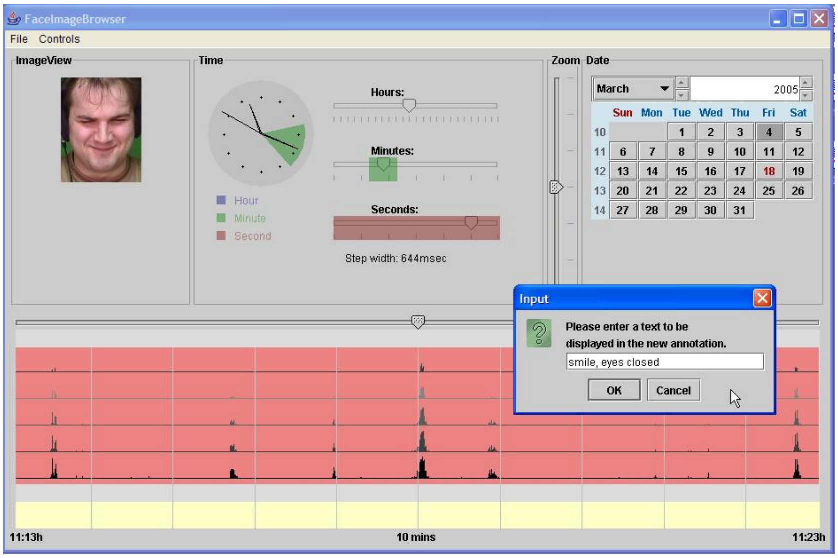
[36] The project developed a multi-sensor context-aware wearable system for the treatment of phobias (see: http://cordis.europa.eu/fetch?CALLER=PROJ_IST&ACTION=D&RCN=71097).

[37] An intelligent, multi-sensorial wearable system that can ubiquitously monitor and classify the emotional state of users in near time using signals mainly obtained from their faces has been developed. (see PHS2020 Deliverable D2.1, *State of Play*, p. 118, p. 146, and p. 198).

[38] See Scherer (2005) for a classification of emotions and how they should be measured.

2001). Acoustical properties of speech which can easily be recorded by a collar microphone, are suited as indicators of depression and suicidal risk, as described in (France et al 2000). Face-to-face interaction between people within a community can be detected with a wearable 'sociometer' consisting of an IR transceiver and a microphone (Choudhury *et al* 2003). Another direction of research , not necessarily connected to wearable devices, is that of ***Human-Computer Interaction***, where machines that are centred on human needs and react to behavioural stimuli are being developed. In order to understand the role of emotional behaviour in human-computer interaction, and to integrate this knowledge into PHS, however, several aspects still need to be researched in a multi-disciplinary perspective including psychology and anthropology, neurology and, naturally, ICT. Appraisal theory has become one of the most active approaches in the domain of emotional psychology. According to the appraisal theory of emotions, the emotional responses results from a dynamic evaluation (appraisal) of needs, beliefs, goals, concerns, environmental demands that might occur consciously or unconsciously. Several theories have been proposed, but all converge in the view that a specific set of properties of antecedent events defines a particular emotional outcome. Applying dimensions proposed by the theories, and relate them to aspects of the interface or interaction, constitutes an interesting basis to anticipate the user emotional experience towards an interactive system. Also, given the user experienced emotion towards some event triggered by the interaction, it might prove feasible to identify the causes, as a combination of the user evaluation of the event along the different appraisal dimensions (Branco, 2003). Facial expressions constitute the most important but even the most difficult aspects to study, for different reasons. Universal facial expressions, though distinct, are not uniformly produced or perceived. Asymmetry, due to neurobiological constraints and the relative spontaneity of facial movement, is one source of variation, but there are many others. In addition to underlying physical variation in the face and in movement, empirically measured facial behaviour varies according to factors such as sex, age, and cultural background. Also important in facial expression are individual factors, such as sociality of situation and the emotion-eliciting nature of visual or other stimuli. Humans vary in their ability and tendency to produce facial expressions, and this variation is presumably elated to underlying muscular, neurobiological, or social differences, or even different success in nonverbal communication and overall expressiveness (Schmidt and Cohn, 2001). Attempts in automatic analysis and recognitions of facial expressions have so far relied on the use of cameras, and on developing algorithms able to analyse expressions from images of face. Problems related to this methodology relates to three aspects: a) detecting face and its permanent features such as eyebrows, eyes, mouth, in an input image; b) detecting the changes in the shape and location of the permanent facial features by making a comparison with an expressionless face of the observed subject; and c) interpreting these changes in terms of some interpretation categories, like the Action Unit in the Facial Action Coding System (FACS) (Pantic and Rothkrantz, 2003). However, no main achievements in this respect have been attained so far, especially for what concerns visual processing and integration into PHS application (i.e., crossing physiological parameters with facial expressions to extract information about patients' status).

Figure 12: An example of a facial expression automatic analysis



Please enter a text to be displayed in the new annotation.

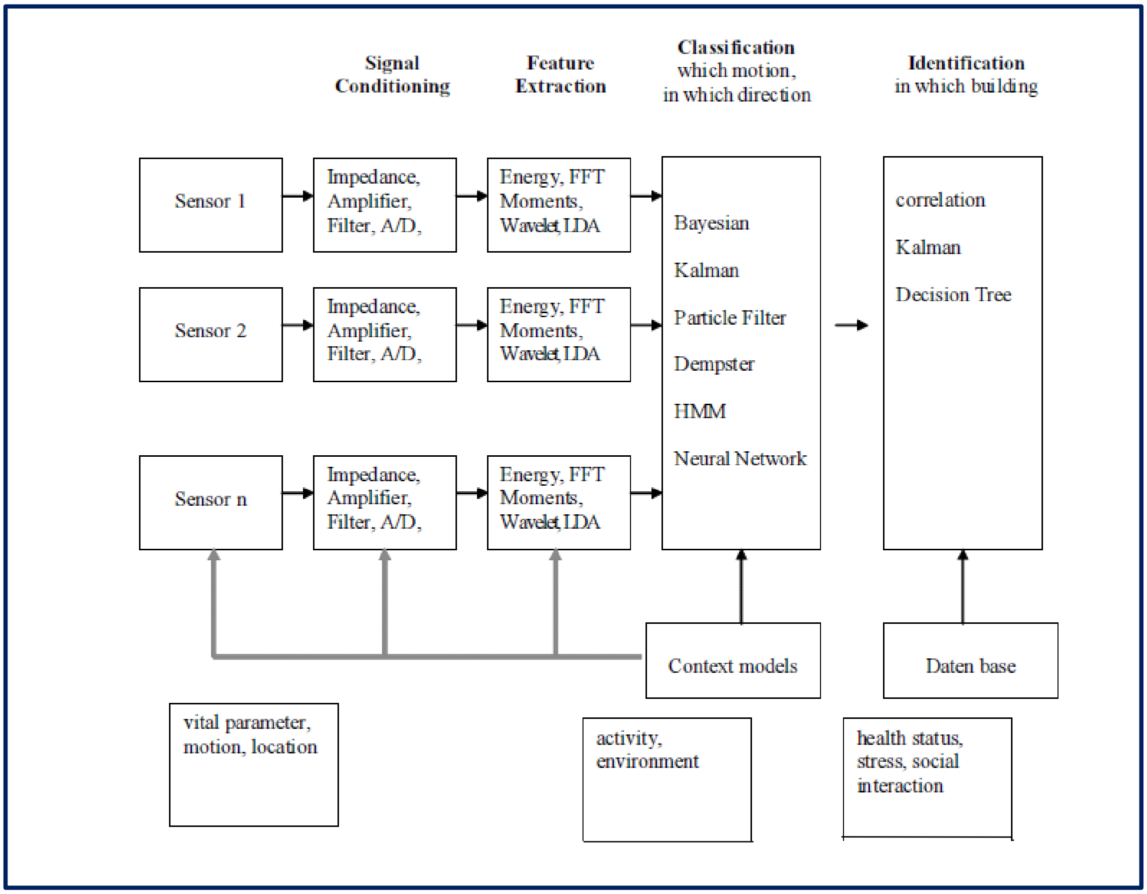
smile, eyes closed

Source: Lyons *et al* (2005)

Before moving to finally list a number of challenges for the achievement of context awareness in PHS, it is worth stressing the potentially many-fold benefits of developing systems capable to intelligently adjusting to users emotional status. In fact, this has positive effects not only for the mere gathering of data through sensing, but can also improve users acceptance and adoption of PHS. First, human-computer dialogue can be crucial those groups in society that, for various reasons (i.e. age, education, etc) have reduced capability of interacting with usual PHS devices (like PDAs), and a low attitude towards learning how to use technology in general. Second, advancements in affecting computing and human-computers interaction could produce the appropriate motivations and ‘prompts’ for individuals adherence to clinical guidelines and lifestyle management, which would apply to both the technology confident and to the technology resistant individuals.

Context awareness: challenges. If we consider the sensors listed in Table 5 capturing some of the context relevant parameters, first they are all based on devices requiring a constant and large area of contact with the skin, which is a barriers for users acceptance, especially by health individuals not suffering from diseases but interested in lifestyle management. Second, they must ensure reliability of measurement in the context of movement. Third, at least for application monitoring life critical situations (so in this case not life style management) in mobile situations , they require ***processing capabilities embedded into on-body sensors, in order to process and transmit all necessary information***. Finally, even in this case we face the issue of “clinical settings” versus “uncontrolled conditions”: the signal performance achieved in a standard medical conditions cannot be guaranteed in a mobile environment. ***Methods have to be provided to correlate the clinical and mobile data***. Moving to the monitoring of emotional and social state the challenges are in general those of an area of research much less mature. First, such states cannot be easily translated to simple physical outcomes gathered by single sensors. Second, there are not yet consolidated and standardized measures against which evaluate in a combined way physical, mental and social parameters. Third, although affecting computing and human-computer interaction may in the future help, it is not yet clear what kind of feed-back should PHS capturing emotional and social state, especially those aiming at life-style management, should provide to improve the well-being of users. Accordingly, to respond to the second and third challenge multi-disciplinary and inter-institutional cooperation is needed especially for lifestyle management to decide: a) what are the signals required to detect context, social interaction and activity; and b)what is the minimum set of signals to achieve a desired performance lifestyle performance. A fourth open issue, which is clearly in overlap with the topics discussed with regard to the "***Integration of External Knowledge***" and already treated there as one of the object of integration between PHS and BMI, is the question of data collection and correlation of emotional parameters with parameters contained in other clinical databases. Finally, after recognition and sensing of context relevant parameters challenges are still open for their processing. Although we have already treated this topic earlier, it is worth reviewing it again here in light of the more technical discussion developed so far with regard to context parameters. We will do this with the help of Figure 13 below taken from an earlier mentioned contribution (Tröster 2004). The figure illustrates several methods and tools have been proved for data fusion, feature extraction and classification. The Bayesian decision theory offers a fundamental approach for pattern classification.

Figure 13 Context recognition data path

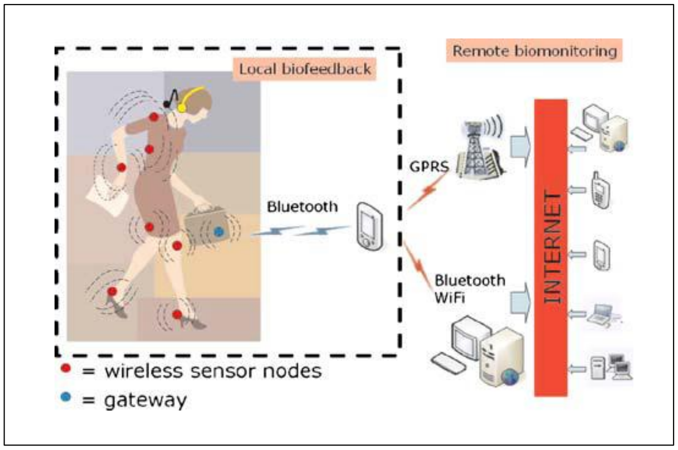


Source: Tröster (2004: p. 131).

Nonparametric techniques like the k-nearest neighbour approach enable the design of decision functions only based on sample patterns. The Kalman filter or the recently proposed particle filter approach are helpful tools for the tracking and monitoring of states, for example, of hand gestures in video sequences. Hidden Markov Models and the Viterbi algorithm are appropriate to estimate a sequence of decisions. The adaptive and learning properties qualify multilayer neural networks for context recognition by the training with repetitive presentations of the target values, e.g. motion patterns. All of these methods, however, are by far not capable of interpreting arbitrary real world situations. ***Progress in multimodal data processing, in cognitive science and artificial intelligence are strongly needed to achieve the vision of context aware, measurement reliable, and intelligent PHS devices***.

Sensors network. While so far we have focussed on the characteristics of sensors, which are clearly crucial for their application in PHS, the issue of sensors network is also worth discussing. Sensors' networks are essential in order to sense, collect, and disseminate information about the observed individual**.** The issue of sensors' network has two dimensions, one related to ***communication*** and one related to their composition and possibly their ***modularisation*** (or ***componentisation***). Both, however, as many other topics discussed throughout our work have to do with the objective of making PHS more personalised. Sensors' networks constitute the backbone for the construction of really personalised PHS. It is evident that wired sensors are incompatible with users' everyday life, especially if we aim at lifestyle management or even at monitoring and treatment of users with mild forms of chronic diseases in such a way that they can remain economically and socially active. Therefore, wireless sensors networks represent the only option for ubiquitous health monitoring. Wireless sensor networks share many of the challenges of traditional wireless networks, such as limitation in energy and bandwidth availability at each node, and error-prone channels. Yet, energy limitation is more constraining is in sensors networks than in other wireless networks because of the nature of the sensing activity and of the difficulty in recharging batteries (Tilak *et al.*, 2002). An important peculiar requirement wireless sensors networks architecture in PHS is openness and reconfigurability of sensors**.** In fact, sensors need to be easily added or removed from the network, since the personalised needs of users may change over time. Adding new sensors in a Body Area Network, then, should be supported by sensors modularisation possibilities, or in other word through a "Plug & Play" mode. Concerning processing capabilities, they are distributed along the network, both in the sensors nodes and in the CPU. Intelligence should also be distributed in all sensor nodes, so as to operate in an overall efficient manner, enabling the nodes to process incoming information and to act accordingly. In this way, the necessary bandwidth required for communication will be sensitively reduced, increasing the overall efficiency of the network. However, the balance of the trade-off between intelligent on-board processing and communication in a condition of limited available energy is influenced by several factors, including the communication technology chosen (Bluetooth, ZigBee, etc), and there are no general rules. On the contrary, the solution is found on a case by case basis. All these issues are not new in the sensor domain, and are being researched on and solved in many fields. However, when considering ubiquitous monitoring for healthcare applications (and PHS in particular), current solutions face the problem of being tightly coupled with the sensor hardware technology involved, resulting in proprietary solutions. Apart from standardisation and interoperability issues, open architecture and standard ways for exchanging information and managing services in the application level are crucial, in order to integrated both sensor platforms and body area networks, towards efficient intra-BAN and extra-BAN communication (Triantafyllidis et al., 2008). These issues assume even greater importance if considering next steps in PHS application, like integration of physiological parameters with contextual and psychological signals, or with Smart Homes.

Figure 14: An example of body sensor network



Source: Farella *et al* (2008)

Sensors self-calibration. Finally, an open issues concerning intelligent sensors with computation capability point to the calibration of sensors, or, even better, self-calibration of sensors (Rivera et al. 2007). This is an issue related to that of reconfigurability of sensors in real time. For instance, the sampling frequency of a physiological parameter monitor may have to change, on the basis of personalised criteria (such as age, for instance). In the same way, personalised thresholds for physiological parameters should also be reconfigurable. Self-calibrating sensors, on the other hand, may obviate these problems. In order to design intelligent sensors for measurement systems with improved features a simple reconfiguration process for the main hardware will be required in order to measure different variables by just replacing the sensor element, building reconfigurable systems. Reconfigurable systems ideally should spend the least possible amount of time in their calibration. An auto-calibration algorithm for intelligent sensors should be able to fix major problems such as offset, variation of gain and lack of linearity, all characteristic of degradation, as accurately as possible. The linearization of output signal sensors and the calibration process are the major items that are involved in defining the features of an intelligent sensor, for example, the capability to be used or applied to different variables, calibration time and accuracy. While these aspects concern better the data processing then the sensor in itself, it clearly affect the performance of the sensor. A sensor extremely sensitive to changes (like movements, for instance, or other conditions) needs continuous calibration, reducing the efficiency of the entire network. While several methods are being researched on to solve this issues (like artificial neural network, piecewise and polynomial linearization methods), none specific solution has been so far envisaged for healthcare applications.

4.3 Proposed roadmap

The table below spreading in the following page synthetically provides a snapshot of the preliminary research themes associated to the gaps and of the key input from the further review of the literature.

Table 6: Re-compacting information: Sensors

Gaps (Table 1, p. 7)	Preliminary research themes (Table 1, p. 7)	Further insights
• Lack of capacity to capture new signs on the environment (both physical and chemical parameters) and on the peculiar situations of individuals (activity, location, emotional status) • Monitoring techniques not able to correctly link physiological signs, with motions, gestures, and environmental data;	• New sensors for context awareness (environment, emotional status, punctual location and situation, etc) and for gathering data in "uncontrolled conditions"; • Investigate how to incorporate data from environmental sensors • Incorporation of advancements in human-computer interfaces and ambient intelligence (in order to "read" emotions though facial expressions and gestures, see later) • Incorporation of on- board processing	• Context awareness strategic for lifestyle management • Importance of capturing emotional and social state • Lack of databases with data on parameters related to context (already treated within the roadmap on "**Integration of External Knowledge**") • Non invasive MEMS enabled and energy autonomous smart wearable for context awareness • Need of new/improved on-board processing capabilities • Self-calibration also in relation to the "uncontrolled conditions" of data gathering • Context aware wearable devices • Affective computing • Human-computer interaction/dialogue (also helping motivation for lifestyle management) • Inter-disciplinary and inter-institutional cooperation needed to establish parameters (already treated within the roadmap on "**Integration of External Knowledge**")
• Need to go beyond the "one sensor- one signal" and "one sensor- one disease" paradigm to optimise energy and bandwidth usage • Need to simplify and reduce the amount of data transfers • Need to increase flexibility and better adapt the sensors to individual characteristics	• Optimisation of multi-modality to insure multi-disease and multi-signal assessments • Self-calibration of sensors • Optimisation of sensors area networks and modularisation of components (plug & play)	• Sensors networks modularity to improve multimodality, optimise energy and bandwidth efficiency, enhance adaptability to personalised needs and characteristics • On board processing important for overall efficiency of Body Area Network • Advanced in BAN design and communication protocol • Inter-operability strategic • Self-calibration and reconfigurability important for smart sensors with on

Gaps (Table 1, p. 7)	Preliminary research themes (Table 1, p. 7)	Further insights
(reduce invasiveness and consider allergies)		board processing
- Lack of knowledge on the long term effect of sensors contact with, and presence in, the human body; - Lack of closed loop systems moving PHS beyond monitoring and into diagnosis and treatment (i.e. dispensation and reaction): ○ Actuators in general ○ Personalised drug delivery ○ Endoscopy capsules	- Integration of researches on alternative sensors' materials (e.g., biological and molecular sensors) - New smart sensors encompassing multimodality, computational power and actuation functionalities (including alternative energy sources: i.e. body energy) - Incorporation of controlled drug delivery sensors (implantable and minimally invasive)	- Further emphasis on risk of sensors effects on the body and on lack of related evidence - Miniaturise MEMS implanted sensors and actuators - Personalised diagnosis and drug delivery through nanorobots - Bio-imaging (Contactless sensing:bio-photonics for non invasive/minimally invasive detection of analytes) - Biosensors and Nanobiotechnology

When we first started the preliminary discussion of gaps at the Pisa Workshop (15 July 2008) one of the leading European experts in the field of PHS sensor formulated the following very general gap: ***"PHS sensors still miss calibration, optimised power supply, multiples signs per sensor, actuation, multi-modal analysis and fusion"*** (included as # 2 in the Full List, see Gap Analysis Report, Table 1 p.10). This key message has been then further elaborated by other experts formulating other gaps related sensors and led to the formulation of gaps and preliminary research themes presented in the first two columns of the table above, which reproduce the simplified sub-grouping illustrated earlier in **§ 4.2** (context awareness, sensors networks, materials and functionalities). In general it can be noticed from the third column of the table that the insights from the additional review of the scientific literature support most of the preliminary identified gaps and provide further context to them and also pointed out new elements. Above all, however, both these further insights and the input obtained during the two roadmapping consultation events underscore how entwined are the various dimensions from which one can look at what is need to produce new third generation PHS sensors filling the identified gaps. It is, thus, a challenging task that of breaking down into separate themes direction of research where there are several complementarities, inter-dependencies and overlaps. For this reason, unlike for other roadmaps, in this case a discussion of these complementarities is in order before presenting the graphic visualisation of the roadmap and commenting it.

Sensing and possibly leading to the activation of an action, accomplished through healthcare professional intervention or direct actuation (an alert, assistance, stimulation, force feedback, neuro feedbacks and treatment and delivery of drug), are in a way the basics of sensors. In practice, however, both sensing and actuation are only two dimensions of a more complex system. To make sense of this complexity in order to present the proposed roadmap it is worth going back to the goal of future PHS as defined earlier in the *Gap Analysis Report* (p. 38 and p. 42).

The overall goal of the research themes proposed in the five roadmaps is to ***make Personal Health Systems truly personalised and efficient, which means that they function*****:** a) capturing the very peculiar characteristics of individuals (vital and physiological signs, but also their genetic outlook, as well as their clinical history, and their socio-demographic and socio-economic conditions); b) ensuring awareness of very punctual contextual conditions (location, activity being performed, emotional and social state, physical and chemical conditions in the environment, etc); c) intelligently processing such information to support traditional action and automatic actuation, thus, bringing new applications and services going beyond monitoring (treatment, drug delivery, feed back of various kinds for lifestyle management, assistance for rehabilitation); d) using devices as minimally invasive and comfortable as possible, and adaptable to the very personal specificities and needs of each single individuals (i.e. avoiding materials to which one may be allergic, or which may negatively interact with individual specific health and contextual parameters, or which may have negative long term effect regardless in general) ; e) providing ‘front-end’ fruition modalities that respond to different attitudes and needs of different typology of users; f) optimising energy and bandwidth consumption and reducing waste.

We can now try to define what we consider now – so in light of the further evidence gathered and analysed after the completion of the state of play (so in a slightly different fashion from the various parameters of the State of Play Model) – the characteristics of sensors

1) **Scope of data gathering;**
2) **Quality of data;**
3) **Non invasiveness and materials;**
4) **Functionalities;**
5) **Sensing sub-system efficiency.**

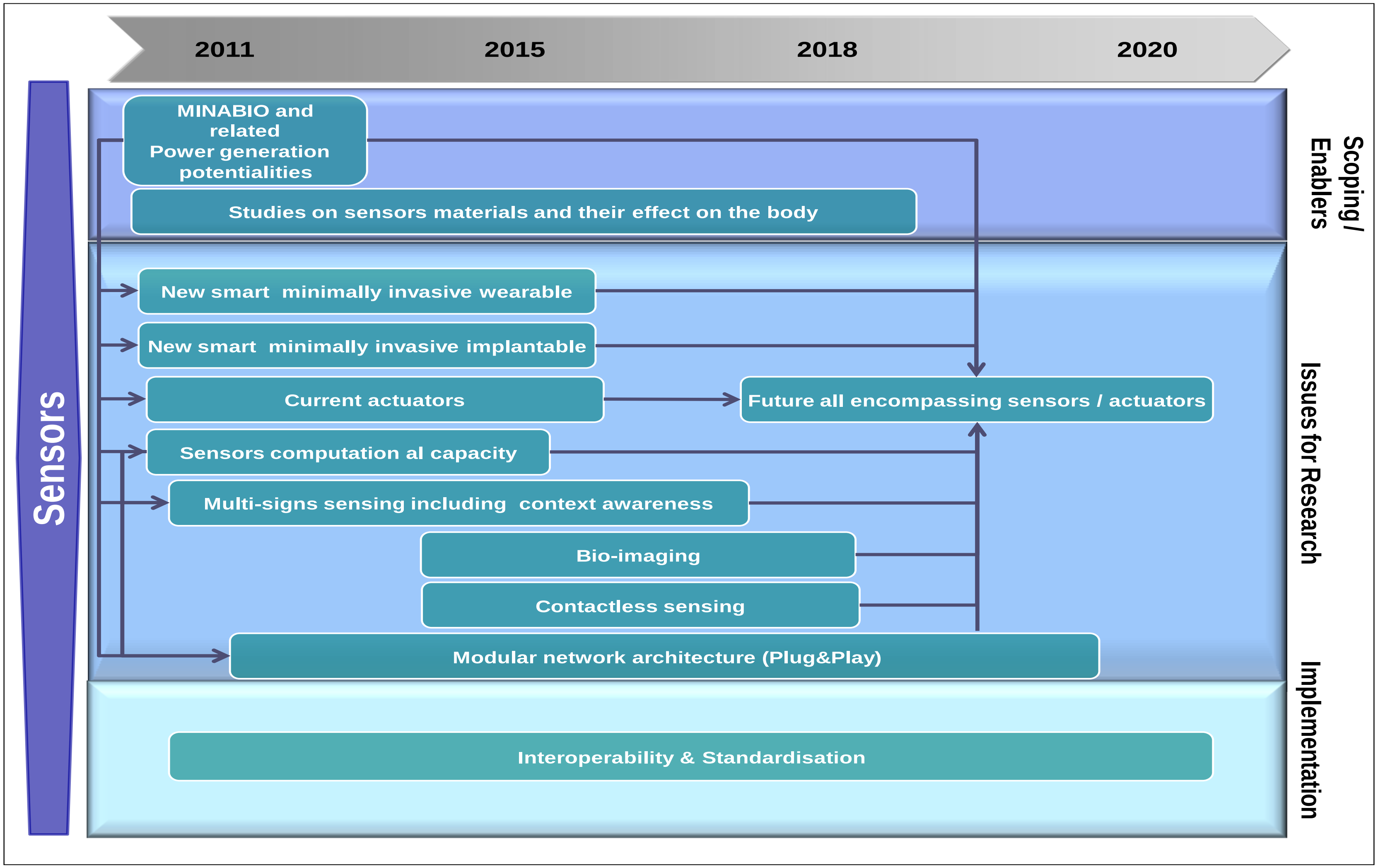
Now we show how these five characteristics, whose definition will emerge from the various elements grouped under each of them, respond to the six PHS requirements listed above and how they are closely entwined and inter-related.

1) **Scope of data gathering**. Addressing requirements a) and b) but also related to **(2)** for treatment of data with different modalities, to **(3)** for non invasiveness and materials, to **(4)** for what concern motivational action, and partially also with **(5)**:
    a. ***New sensors to capture context*** meet requirement b) but need on board processing (for wireless and mobile applications) and raise the issue of correction/rectification of “uncontrolled conditions” data and are, thus, related to, dependent on **(2)**;
        i. ***Affective computing*** as a way of detecting emotional and social state can also help create innovative motivational tool for lifestyle management (thus also related to **(4)**);

        ii. ***MEMS enabled*** miniaturised and energy autonomous ***wearable*** sensors capturing emotional state (requirement b) but also related to **(3)** and **(5)**);
    b. ***Sensors*** capturing ***multiple signs*** addressing a) and also enabling to reach new diseases but naturally related to multimodal treatment and so connected to **(2)** and to **(5)** for reduction of data transfer
2) **Quality of data**. Instrumental to requirement c) and related to sensors ***computational/processing*** capacity but also instrumental to **(4)** and **(5)** below:
    a. ***On board processing*** capabilities for provision of better data to the data processing sub-system or for accomplishing data processing altogether within the sensor (requirement c) , but also in relation with **(4)** for actuation and with **(5)** for optimisation of energy and bandwidth usage by reducing data transfer);
    b. ***Self-calibrating sensors***, same as above plus very important in relation to the challenges raised by new data on context (see **(1)**)
3) **Non invasiveness and materials**. Addressing requirements d) but also converging with **(4)** for what concerns in-body actuation and with **(5)** below (new materials instrumental to alternative power generation):
    a. ***Bio-imaging*** and ***contactless sensors*** fully addressing requirement d) and reducing challenges related to (5);
    b. ***Miniaturised MEMS implantable*** partly address d **(**reduce invasiveness but effect of materials on body still an open issue) and clearly instrumental to (4) (as they embed actuation) plus they may address (5) (MEMS potentiality to harness alternative source of energy);
    c. ***Nanorobots*** same as above;
    d. ***Biosensor, Molecular Nano Technology, Bio Nano Technology***, same as above plus possible improvement due to use of organic / biological components (for effect on body)
4) **Functionalities**. Intended mainly as the capacity of supporting various form of actuation. As seen, this is practically the result of elements already included in the previous three characteristics;
5) **Sensing sub-system efficiency**:
    a. **New sensors networks architecture** optimise energy efficiency and bandwidth usage meeting requirement f) , which is highly related to sensors computational capacities (so **(2)** above);
    b. **Sensors network modularity** also address f) but it is also instrumental to b) and d) in the sense that increase the flexibility to adapt to very personal needs and characteristics and in this sense is related **(1)** (capturing context and flexibly including and correcting sensors) to **(3)** (adapting sensors materials to personal characteristics)

This exhaustive list ensure that the graphic visualisation is contextualised and avoid misleading the readers: the boxes included in the graphic are not and cannot be mutually exclusive given the complex web of complementarities and inter-relation illustrated above. It would probably be possible to present a more clear cut roadmap if we were focussing on sensors for a given specific disease or a given specific task, but not for a general sensors roadmap such as the one we aimed at.

Figure 15: Visual Roadmap for "Sensors"



Source: Authors elaboration

In addition to the long premise above two other considerations are needed before we very briefly review the various elements in the visualised roadmap.

First, precisely as a result of the complex inter-relations discussed above, the time-horizon of this roadmap is very tentative and, we may add, merely illustrative. Indeed the various inter-relations make very difficult defining a time logical sequencing among the various research themes.

Second, many of the new and innovative solutions illustrated in **§ 4.2** (briefly and selectively recalled in the list of the previous page) would result from synergies and fallouts of developments achieved in fields other than those associated to the strictly defined PHS research. These includes: ***MEMS and NEMS, Nanorobots, Biosensors, Bionanorobots and the possibility of alternative power generation (including ways to use energy from the body) that are associated to them***. Sticking to our conceptualisation they would all have to be included as enablers in the “Scoping/Enablers” layer of the roadmap. Instead we propose a scoping study identified in the graphic visualisation with the acronym **MINABIO** on the mentioned **MI**cro-, **NA**no-, **BIO**- technologies. The purpose of the study will be to go deeper than it was possible to do within the scope of PHS2020 in analysing and assessing the applicability of these technologies (including their potentiality to leverage energy from the body) to the field of PHS. We then assume that these technologies will gradually be included into, and further enhance, the various themes included in the layer of the roadmap focussed on research.

Within the “Scoping/Enablers” layer of the roadmap as enablers of most of the research themes we included needed studies on the effects of the sensors materials on human body. Lack of knowledge about this phenomenon is a very crucial gap that is, however, clear beyond the scope of PHS research. Yet, input from other research field will need to be considered in the design of future PHS research projects addressing the themes proposed here.

We now proceed to list and very briefly comment the various other elements in the roadmap following the order in which they appear

Wearable sensors have been deeply investigated in the medical domain, so that they can be considered as key pillar of PHS research. However, despite the notable advancements, several challenges need to be overcome: improve the quality of measurement increasing users’ comfort at the same time, increasing energy efficiency, and improving their embedded processing capacity. New materials can be identified as suitable for building smart wearable sensors, and new fabrication techniques are needed in order to realise the full potential of these sensors. As illustrated earlier, great potentiality may spring by harnessing **MEMS enabled smart and energy autonomous wearable sensors**.

Although a more recent development than in the case of wearable, a similar considerations can be made for **implantable sensors**. Future research should both continues along the lines followed so far to ***reduce invasiveness*** and ***increase reliability*** (avoiding problems like ***fibrosis***, see p. 50) and then incorporate the potentialities of ***MEMS/NEMS*** and possibly merge with ***Nanorobots***, ***Biosensors***, ***Bionanorobots*** and practically turn into the **all encompassing sensors/actuators of the future**.

The exact same consideration applies to **current actuators** where research should continue to move from simple ***alert*** to real actuation such as ***personalised drug delivery*** and eventually evolve into the **all encompassing sensors/actuators of the future.** A different issue regards ***actuation*** related to ***lifestyle management*** where input will come from ***context aware sensing of emotional and social state*** through ***affective computing and human-compute interaction and dialogue***. As we explained, these technique would at the same time capture context and devise new way of motivate people which overlap with the topics and research themes treated in the next roadmaps on interfaces and interaction.

The research themes "***Sensors Computational Capacity***" includes under one heading the issues of ***on-board processing***, ***self-calibration***, and ***multimodality***. This is not a new topic in PHS research. However, it acquires a special relevance in light of the evolution process of Personal Health Systems, and their final goal of providing an holistic and really personalised support to users. In order to do this, an increasing amount of data and information has to be gathered and processed, to extract the correct pattern and take the correct decision for each individual. This ambitious goal entails an increase in the number of data to be gathered, in the number of sensors necessary, and in their computational power. In order for sensors to be capable to perform these complex tasks, an increase in their computation power in necessary. In this way, in fact, sensors themselves will be capable of reducing redundancies and errors in measurement, at the same time decreasing the amount of data to be transferred for processing. This represents a fundamental requisite for the final objective of having sensors capable of multi-modal sensing and actuation. "Second generation" sensors (i.e., those developed so far by research project) still miss calibration, in the sense that they have to be periodically calibrated by users, not to mention the impossibility to detect if a value measured in normal for a certain individual because of his/her peculiar characteristics. ***Self-calibrating sensors would represent a fundamental characteristics for intelligent sensors***, being able to detect which are the "real" thresholds of physiological parameters for each individual, at the same time notably increasing the performance of the sensors itself and of the sensors network in general. While this issue is clearly linked to the domain of data processing, research on sensors cannot ignore it, especially if the futuristic vision of sensors able to detect, actuate (and therefore process the relevant information, and take decision) is adopted. So the various elements comprised under these research theme are instrumental and strategic in various ways. They address the challenges of data treatment raised by context aware sensing. They are a key pillar for future all-encompassing and actuation, and as such they will also benefits from new solutions coming from the various technologies summarised under the acronym ***MINABIO***. Finally, they contribute to the goal of energy and bandwidth use optimisation (reduction of data transfer).

Next we have the goal relate to expanding the ***scope of data gathering with sensors capturing multiple and more signs, including those reflecting context***. These advancements should enable to enlarge the number of disease to be treated and improve treatment and especially lifestyle management application through the holistic sensing of context (including emotional and social state), which is also key to personalised and intelligent data processing. ***Context awareness is a crucial dimensions for PHS***, directly impacting several of the research domains identified as most important for future research: integration of external knowledge, data processing, and sensors. Context awareness is important in order to better comprehend individuals' physiological parameters, thus avoiding false positives or the risk of missing risk situations. In addition to this, context is fundamental to assess the health status of an individual, as social and mental state of an individual have a crucial importance on individuals' health. Therefore, context awareness is important not only for monitoring and treatment of people suffering from chronic diseases or with high risk profiles, but also for lifestyle management applications. While some parameters such as ***movement, and environmental conditions*** (e.g., light, temperature, particles in the air, pressure, etc), ***are easier to monitor***, ***emotional and social state pose major challenges***. First, it is not easy or even possible to translate these states into simple physical outcomes gathered by one single sensor. Second, there are not consolidated methodologies to evaluate physical, mental and social parameters in a combined way. Third, it is not easy to determine which kind of feed-back PHS gathering these information should provide, even though advancements in disciplined such as Affective computing and Human-computer interaction could be of help (it is evident an overlap with the "Interfacing & Interaction" domain).

Bio-imaging and contactless sensors and improve non-invasiveness and comfort of PHS. Integration of bio-sensors would lead to the incorporation of new sensors (made with biological and molecular materials), including to application of ***bio-photonics*** for non invasive/minimally invasive detection of analytes. Contactless sensors, when integrated, would allow to include features like radio frequency-based sensors (with nano-antennas). Bio-imaging sensors will lead to develop PHS imaging sensors for non-invasive monitoring, to be applied for endoscope (smart pills probes not requiring robots nor medical direct intervention), or, more futuristically, tongue imaging and retina scanning. In addition, and not less important, this dramatic reduction of invasiveness and obtrusiveness of sensors could represent a key factor for acceptance of Personal Health Systems.

An aspect needing support is the ***integration and testing of modular sensors networks, enhancing a Plug & Play structure*** (i.e., as final goal it would be possible to combine sensors, in terms of numbers and functions, on the basis of needs and requirements of each individuals, without creating an "ad hoc" network each time). This address at the same time an efficiency (energy and bandwidth optimised use) and effectiveness (flexibility and adaptability to users specificities and needs) goal.

As already hinted at, eventually ***all these characteristics of sensors should be merged into "all-encompassing" sensors, able to detect information, not only for physiological parameters, but also for context (including the environment, and the social and mental state of the users), process them, and decide whether to take an action, and which one (actuation)***. In this view, sensors would incorporate many of the functions of data processing, also embedding the analysis of the external knowledge relevant. This would open the way for personalised drug delivery exploiting the characteristics on nano-fabricated intelligent robots, capable of delivering the appropriate dosage directly to the cells when treatment is needed, notably increasing effectiveness, and reducing side effects, of treatment.

In the field of research support implementation, definition of common standards allowing ***full interoperability*** of sensors emerges as the main issues. It has to be recalled that, also in the case of sensors, full integration with eHRs is a crucial pre-requisite, as it is evidently fundamental that data gathered are needed to feed the profile of each individual, and that, continuous updating is fundamental as well. A further step, allowing for a really comprehensive diagnosis and treatment, would be the link to larger demographic and environmental data (particularly crucial for contextual sensing), in order to have a complete picture of the course of a disease, as well as updated information on health status of the population. As already explained for the “Data processing” domain, this requires interoperability of components and communication protocols, as well as encryption techniques ensuring protection of sensitive data (maybe including also bio-metric security).

5 Lab on Chip

5.1 Contextualisation

The State of Play defines Lab on Chip (hereinafter, LoC) as a device used in the field of Point-of-Care (PoC) medical solutions, normally employed at the component level. LoC allow to integrate multiple laboratory functions on a single unit capable of handling small fluids volumes. The State of Play also identified three main attributed that are generally associated to LoC and that characterise their nature, namely:

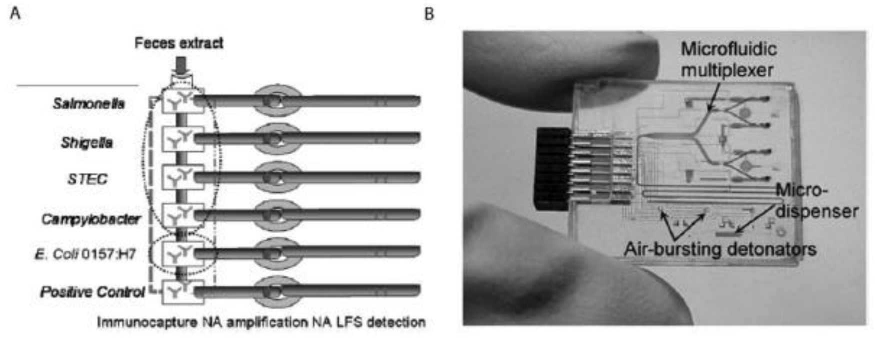
- The **material** the LoC is mostly made of, which could be either glass, plastic, or silicon;
- The **sample preparation**, more specifically whether the sample has to be prepared before applying it onto the chip (non embedded) or if it goes directly from patient onto chip (embedded), thus requiring less effort and time from the healthcare professional;
- The **target detection**, which is the degree of concentration in target sample sequence (e.g., length of DNA snip necessary for performing a certain analysis). On the basis of target detection, LoC can be defined as:
    - Mono-target: if the application is designed to detect only one specific target (i.e., only one specific protein);
    - Multi-target low: if the application is designed to detect a limited number of targets (2 or 3 targets);
    - Multi-target, high: if the application is able to detect a large number of targets simultaneously (about 30 to 50).

First, Point-of-Care systems (PoC) can currently run tests (blood, urine etc) limited to 2-3 biomarkers. This often leads physicians to complete tests through traditional means (i.e. laboratories), for they need to base their diagnosis on several inter-dependent factors, thus defeating time savings achievable through LoC. Hence, it is of major importance to encompass all additional biomarkers needed for a complete diagnosis in one single lab-on-chip. Second, after extracting a sample from the patient (normally, body fluids), most of the times healthcare professionals are required to carry out further preliminary steps before the sample can be applied onto the LoC for final analysis. However, body fluids are very sensitive to environmental factors (e.g. temperature and contamination) and this may defeat the use of LoC. Thus, the steps from sample extraction to sample application onto the chip need be decreased to a minimum, in order to assure a valuable quality of results. Third, current POC solutions require a minimum of 15 minutes of run-time and time to result. In most cases, this does not even include the time of sample extraction and sample preparation, which often add up to several hours. POC is designed to be a decision aid tool to professionals in order to take more in-time and accurate decisions. However, current systems are still too complex and time-consuming, thus forcing both physician and patient to unnecessary waiting. Consequently, in order to accomplish a closed loop circle of testing and diagnoses, time to result needs to be drastically reduced.

5.2 Further insights

General considerations. The rapid development of Lab-on-Chip systems has opened new routes for full integration of sampling, mixing, reaction, separation and detection functions on a single microchip to perform specific analytic tasks. In recent years, online detections of ***DNA, glucose and lactate, oxygen, pH, cells*** in miniaturized analysis systems have been actively pursued with a wide variety of detection schemes, such as electrochemical detection, optical absorbance, fluorescence detection, evanescent-wave coupling and plasmonic resonance, etc (Wu et al, 2006). Despite the impressive achievements that have been made in recent years, ***new devices will undoubtedly be needed*** (see Figure 16) to address future users' needs. The design criteria of these devices are vast, demanding, and context-dependent, and they will need to be considered carefully from the early stages of development (Chin et al, 2006).

Figure 16: Integrated LoC devices



Note: (A) Schematic representation of LOC for detecting enteric diseases. (B) Picture of a plastic LOC device for point-of-care clinical diagnostics

Source: Chin *et al.* (2006)

What will then be the ***main directions*** for designing and deploying LoC devices? Some argue that the top-ranking overall priority is modified molecular technologies for ***affordable, simple diagnosis of infectious diseases*** (Daar et al, 2002). Others have identified as a main priorities the development of technologies for assessment of individuals for multiple conditions or pathogens at point-of-care and enabling quantitative assessment of population health status (Varmus et al, 2003). Also important are ***non-communicable diseases***, such as cardiovascular disease (i.e. ischemic heart disease and stroke), cancer, ***neuro-psychiatric conditions*** (i.e. unipolar depressive disorder), and respiratory diseases (i.e. chronic obstructive pulmonary disorder and asthma). As the standard of living of countries improves and average life span increases, the burden of disease gradually shifts to non-communicable diseases. This shift is exacerbated by changes in diet (towards saturated fats and sugars) and high tobacco use (Beaglehole and Yach 2003). Obesity and diabetes are increasingly becoming a threat to people's wellbeing across the European Union, while asthma, epilepsy, dental caries, diabetes, rheumatic heart disease, and injuries are becoming increasingly prominent contributors to morbidity (Seidell 2002). LoC research holds substantial potential for fulfilling these priorities by ***automating complex diagnostic procedures*** that are normally performed in a centralized laboratory into a hand-held ***micro fluidic chip***. This capability could ***empower*** healthcare professionals and patients with important health-related information in even the most remote settings.

Reducing test fragmentation. Research in this field is expected to fulfil the need to overcome fragmentation of testing, which is usually due to incurring traditional lab tests in order to complete testing procedures. Different classes of diseases usually need to be tested in order to diagnose a patient's health status. In order to do so, several classes of analytes need to be marked, which in turn require different diagnostic technologies to be applied on one single chip. On the other side of the spectrum, multiple classes of assay technologies are needed to produce complete diagnostic information for groups of related diseases, and often even for a single disease - for confirmatory testing, identification of resistant subtypes, and/or staging of a disease. For example, yes/no testing for antibodies, analysis of RNA levels, and counting of CD4+ lymphocytes are all crucial information for diagnosing and staging HIV/AIDS. Chip technologies are being researched that are able to carry out all of the above at the same time in order to provide more sophisticated and reliable information on the patient's health status: detection tests, confirmatory tests, identification of resistant subtypes, staging of a disease, etc. In some cases different types of detection tests for the same disease may also be useful in order to cross information and obtain more accurate results. As similar classes of analytes (e.g. proteins, nucleic acids) serve as useful markers for very different diseases and conditions, then similar designs of diagnostic technologies will be applicable for disparate classes of diseases. (For example, yes/no protein markers are useful for diagnosis of HIV/AIDS as well as indicators of coronary heart disease. This observation calls for carefully considering the integration of ***multiple modular technologies at the earliest design stages of LOC diagnostic devices***. For complex assays, a ***series of different reagents*** need to be delivered into the micro-fluidic chip. In centralized testing facilities, these procedures can be performed manually by a technician, an external liquid handling robot, or on-chip valves that are controlled by an external instrument. For portable automated devices, passive delivery of a series of reagents is an attractive option (Linder et al, 2005). Some assays will require mixing of samples with different reagents. In such cases, ***active micro mixers*** can be used if a power supply is available. ***Passive mixers***, which rely on the geometry and topography of the micro channels, can also be used to mix and dilute samples (Chin et al, 2006). In general, however, heterogeneous assays (which include many immunoassays) do not require mixing since the analyte is captured on the surface. Bio-degradable materials could, not only be environmentally friendly, but also increase reliability of testing.

Rapid, robust, portable, non invasive, testing and optimised sample preparation. Immediate results of testing is desirable for both professionals and users, but there are still constraints to be overcome. The most prevalent example of diagnostic tests, providing yes/no results in minutes in the form of a visible band (this tes typically use gold colloids or latex beads conjugated to antibodies),is the immunochromatographic test (Chin et al, 2006). Moreover, immunochromatographic strips are cheap to produce. These strip tests, however, are not quantitative, and ***are not sufficiently sensitive for the detection of all important markers***. Development to improve strip tests for diseases, such as Chlamydia and trachoma from Lee's group (Lopez et al, 2006) is ongoing because LoC devices are believed to hold great capabilities for high analytical performance, and for multiplexed and parallel analysis of many relevant markers at once. This capability, however, is challenged by the fact that different analytes typically call for different LoC designs. For optimisation of time to result nucleic acid amplification methods emerge as promising. Among these methods currently ***Polymerase Chain Reaction*** (***PCR***) has been the most used due to its simplicity. PCR's speed can be improved by ***increasing the heat transfer rate or decreasing the thermal mass***. The dynamic continuous-flow-based PCR amplification can therefore overcome the issue of lack of speed flexibility by utilizing the '***time-space conversion***' concept. The nucleic acid amplification occurs as the sample is continuously pumped through a micro fluidic channel during each temperature cycle. The attractive features of this approach include (Zhang, C. and Xing, D. 2007):

- The analysis processes of nucleic acids can be performed in a dynamic format on an integrated PCR chip;
- The temperature transition times depend only on the sample flow rate and the time needed for the sample to reach a thermal equilibrium;
- The heat inertia of PCR system is decreased to a minimum because only the sample's thermal mass need to be taken into consideration;
- The reaction volume can range from several microliters to several tens of microliters.

Pursuing high-speed PCR, therefore, appears as one of the major motivations in the development of on-chip PCR. With the advent of ***MEMS*** technology, the development of miniaturized PCR chips will become possible (Lee et al, 2007). The miniaturization of PCR devices offers several advantages such as ***short assay time***, ***low reagent consumption*** and ***rapid heating/cooling rates***, as well as great potential of integrating ***multiple processing*** modules to reduce size and power consumption. In order to meet the current demands for a ***fairly rapid lab-on-chip toxicity detector*** the integration of light-emitting whole-cell sensors with solid-state devices for detection of low-emission levels has been proposed (see for instance Elman et al, 2008). ***Optical spectroscopy*** is also signalled as promising. For instance, ***fluorescence-based imaging*** (both single and multiphoton) is perhaps the research direction that has most influenced the development of fast and sensitive optical detectors. Examples of techniques in this class include ***Forster Resonance Energy Transfer (FRET)***, ***Fluorescence Lifetime Imaging Microscopy (FLIM)***, and ***Fluorescence Correlation Spectroscopy (FCS)***. The success of these techniques, particularly FLIM, derives from the ability to characterize an ***environment based on the time-domain behaviour*** of certain fluorophores with high resolution in space domain. The new developments range from multiphoton microscopy, to voltage sensitive dye (VSD) based imaging, particle image velocimetry (PIV), instantaneous gas imaging, etc. Moreover, ***Bio-photonics use for optical spectroscopy could have interesting applications for localisation of molecules***. In some diseases, in fact, like skin cancer, it is extremely important to be able to exactly localise some analytes or also anti-bodies that can be linked to cancer, at the very beginning of cancer appearance (for very early detection and diagnosis, before having symptoms or even chemically detectable sensors in blood). This kind of applications could be used for biopsy (without surgery) or suspect melanoma. Furthermore, advanced processes are also able to ensure in-pixel and on-chip processing of ***ultra-high-speed signals*** that are typical of single-photon detectors. However in such systems, the remaining obstacle appears to be the illumination device that is currently the object of intensive research (Charbon, 2008). Thanks to the use of cutting-edge ***silicon technology***, the final production chip will be likely to be very small, and hence extremely cheap. That in turn should allow it to be integrated into a low cost, disposable, single-use cartridge that plugs into a larger reusable device. For this usage model, bodily fluids will be passed over the chip and the resulting signal or data will be wirelessly sent to a control system. By simply replacing the cartridge, the users (either the patient himself or the healthcare professional) will be able to repeat for each test subject.

Portable, disposable, non invasive, on- in- body chips. The use of LoC devices to advance the capabilities of Point of Care require the combined optimisation of several ***design*** criteria. For remote point-of-care testing (for instance, in rural areas), the fixed instrument must be ***portable*** and ***cheap***, and the disposable must be extremely cheap. All components of the device (including the instrument and disposable) must be ***robust*** and ***rugged*** under a variety of environmental conditions. Having said that there is a large body of existing research on LoC designs for point-of-care testing for physicians' and home use (Lauks, 1998; Tudos et al, 2001), devices for military applications (Belgrader et al, 2001) and first responders, and extraterrestrial sensors (Akiyama et al, 2001; Cultertson et al, 2005; Skelley et al, 2005) in designing LoC device. In all these settings, ***integration, portability, low power consumption, automation, and ruggedness*** are important qualities. A cheap, disposable Lab On Chip, to be applied directly by the patient on the skin (like patches) could help in having a very wide and low-cost screening, while processing (not low-cost) could be centralised at GPs and/or hospitals. In addition to be small, cheap, and disposable, such chips should also be ***non-invasiveness***. Although whole blood (from venipuncture or finger prick) and its derivatives (plasma and serum) are most common physiological fluids, the use of less invasive samples such as saliva, urine) faeces, sperm, tears and sweat are gaining prominence (Li et al, 2005, Srinivasan et al, 2004). With advancements in markers detection, as well as in miniaturisation, further developments can be envisaged. Such achievements will lead to a progressively easiness of use of Lab On Chip devices, which would progressively become devices suitable for home use, directly by patients. Even more futuristically, on body applications, like disposable "patches" to be applied on moles by patients for early detection of skin cancers (leading to mass screening) could be foreseen. At the same way, in body application, with Lab On Chips applied within the body (with minimally invasive procedures) could be imagined, to be "activated" on demand, or periodically, and providing detailed information when needed.

Optimisation of sample preparation. Future research can also improve sample preparation, currently requiring labelling of the organic sample (e.g., blood), and fluorescence-based detection for imaging and counting. This intermediate labelling step complicates the sample preparation and detection process, the label can alter the molecule's binding properties and therefore decrease the detection reliability. ***Label-free Microfluidic Devices (LFMD)*** are the being researched, and have already had some successful applications in diagnosis of specific diseases as well as on analysis of specific molecules. For instance, a micro fluidic device for whole blood CD4 counting that requires no sample handling or specific labelling for HIV diagnosis (Xuanhong, et al., 2007). Also, detection of proteins linked with certain types of cancer (Wang, 2006), as well as measuring and morphologic analysis of blood components like platelets (Inglis, et al., 2007) have been successfully researched.

Fabrication techniques. Research is also focussing on different fabrication techniques allowing for cheap mass fabrication and integration and easily extendable to a multi-array biosensor with thousands of sensing spots for real Lab On Chip devices, like, among others, Silicon-On-Insulator biosensors based on microring cavities, fabricated with standards Complementary Metal Oxide Semiconductor (CMOS) processing (De Vos et al., 2007).

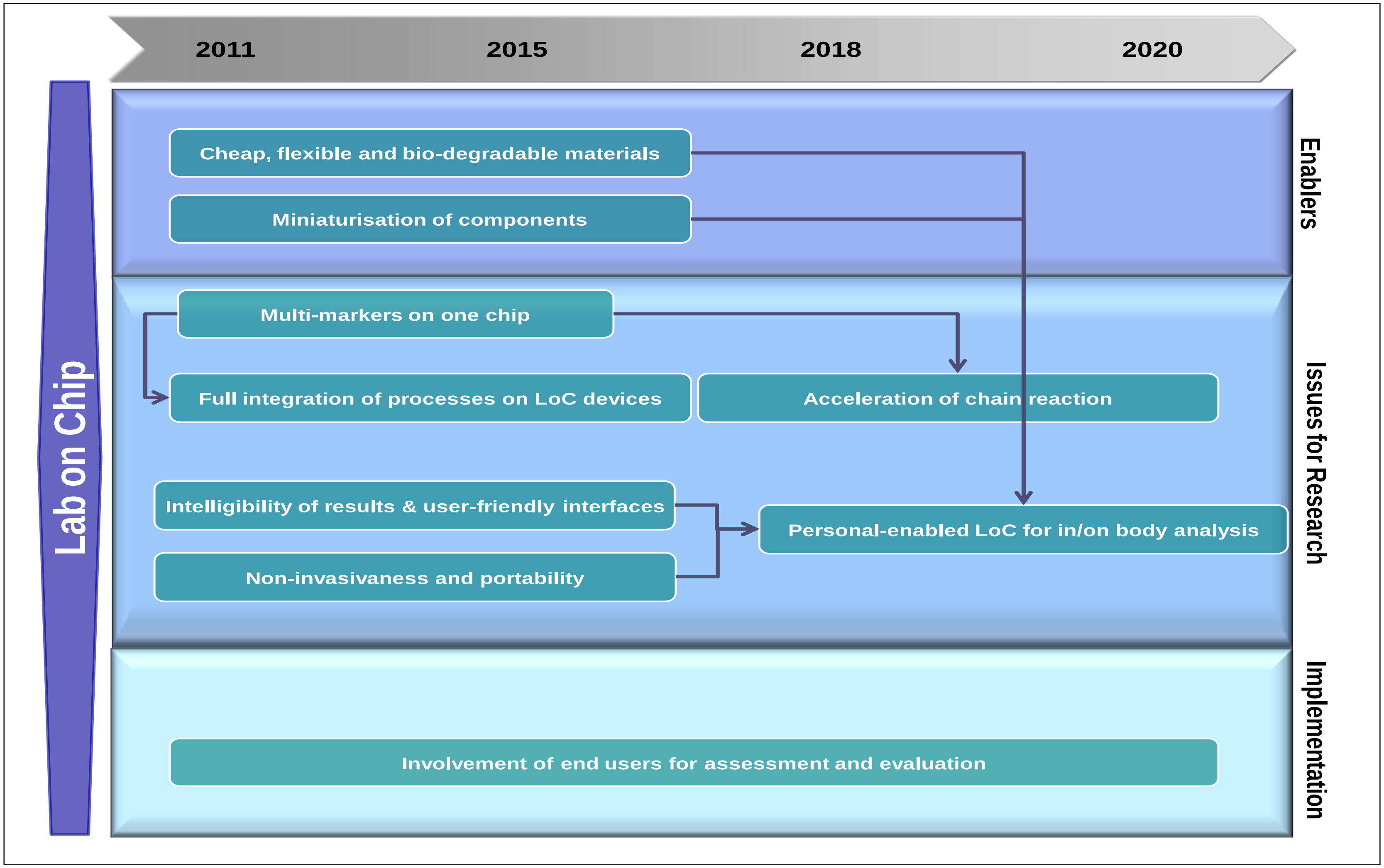
5.3 Proposed roadmap

The table below synthetically provides a snapshot of the preliminary research themes associated to the gaps and of the key input from the further review of the literature. In combination with the comments and changes introduced during the two consultation events focussing on the roadmap they shape the final proposal graphically presented in Figure 17 reported in the next landscape page.

Table 7: Re-compacting information: Lab on Chip

Gaps (Table 1, p. 7)	Preliminary research themes (Table 1, p. 7)	Further insights
• Avoid fragmentation of testing and the need of traditional lab tests to complete Point Of Care (POC) testing	• Investigation on including multiple biomarkers on a single chip; • Research on "new" biomarkers more adapted to POC; • Integration of Micro-Opto-Electro-Mechanical-System (MOEMS)	Further insights • Multiple assays' analysis through multiple chips on the same marker (corollary: multiple modular technologies at the earliest design stages of LOC); • Bio-degradable materials; • Different reagents into Microfluidic chips; • New fabrication techniques for bio-sensor supported Lab on Chip.
• Reduce human intervention in sample preparation;	• Development of on-board sample preparation; • Further research on micro-fluidic techniques optimising "sample course control".	Further insights • Free Label Micro-fluidic Chips; • Widen choice of samples (so to automate sample extraction).
• Reduce time to result (process integration);	• Optimising of fluidic control and run-time; • Further research on alternative array technologies adapted to POC-solutions.	Further insights • Nucleic acid amplification (MEMS-driven miniaturised PCR); • Silicon technology; • Optical spectroscopy and bio-photonics; • Ultra high speed signals.
Not given due importance	Not given due importance	• Improve non-invasiveness at the same time as providing portability • User friendly intuitively readable results • Cost effectiveness

Figure 17: Visual Roadmap for "Lab on Chip"



Source: Authors elaboration

In looking at Lab On Chip, it seems as ***empowering*** patients and healthcare professionals by way of placing in their hands a fully-functional, automated device that can support the provision of information on their health-status is the very bottom line of the calls for improvements and further developments in the field of Lab On Chips. Many challenges faced by current applications are likely to be overcome before 2020 and those achievements will lead to surmount some of the main issues that are slowing down ***mass adoption***. Naturally such achievement will require a number of research aspects to be fulfilled as prerequisites:

- First of all, ***cheap and flexible materials*** will be key for the marketability of the products and, therefore, for their adoption on behalf of the wider community. Improving the compromise between affordability of devices and rapid analysis may become viable thanks to the use of cutting-edge ***silicon technology***, which will also allow for great improvements in terms of ***miniaturisation of components***;
- Investigations concerning the integration of ***bio-degradable materials*** are also envisaged. These activities would in turn help identify what kind of materials would be more suitable for low-cost, disposable, and easy-to-use Lab On Chips. Studies on alternative materials for sensors and Lab On Chips are mainly carried out outside the development of strictly-defined PHS. However, achievements in this field are extremely relevant for PHS, as they influence factors, like costs, decisive for adaption. ***Contamination*** between fields of studies will therefore be key on these aspects of research;
- Furthermore, it will be vital to widen the spectrum of ***different reagents*** than can be employed on the chip as well as the mixers and to improve the compromise between design and applicability of different analytes.

As these advancements become enablers for the new frontiers of research, breakthrough technologies are required to turn application several ***different classes of analytes*** on the same chip into reality. This would in turn help complete the diagnosis process by informing on for confirmatory testing, identification of resistant subtypes, and/or staging of a disease. Research on biomarkers that can be applied to PoC, as well as investigation on including ***multiple biomarkers on a single*** chip, will therefore require particular attention. However this will only feasible if ***multiple modular technologies*** are developed at the earliest design stages of LoC, thus taking into account all the variables affecting their adaptation on chip. The integration of ***Micro-Opto-Electro-Mechanical Systems*** – nano systems capable of high-precision micromachining - is likely to generate positive results in this respect and will have to be taken into account. Similar arguments will apply to investigation on different reagents into ***microfluidic chips***, which deal with precise control and manipulation of fluids that are geometrically constrained to a sub-millimetre scale; these are considered an especially promising technology for PoC applications, featuring a full process integration, reduced consumption of sample and reagents, as well as short turn-around times and ease of handling.

Next on the roadmap, the full ***integration of all functions into one chip*** (namely, sampling, mixing, reaction, separation, and detection) will ***dramatically reduce the time*** and complexity of the technological devices. Accordingly, this will avoid human interaction in the various phases of detection and will boost their adoption even by the uneducated patients at home. In this respect, ***miniaturisation of components*** is indeed granted even higher significance especially for its contribution to advancements in terms of ***portability and mobility*** of LoC devices. Furthermore, biomarkers should have clearly defined cut-off values with high sensitivity and specificity to allow anyone to ***read the results*** and make healthcare professionals' empowerment possible. Employing low-cost materials to allow lab-on-chips to be integrated into low-cost, disposable devices will be a key aspect in the mass distribution of LoC devices, as well as advancements in terms of invasiveness: biomarkers should be easily attainable from ***non-invasive samples*** such as body fluids (saliva, sweat, etc.) and cells.

In particular, this progress will concern mainly ***the reduction of time to results***, making LoC more compatible with the usual visit time of GPs, and the integration of multi-markers into one chip, widening the range of application. Current systems are still too complex and time-consuming, thus forcing both physician and patient to unnecessary waiting. Consequently, in order to accomplish a closed loop circle of testing and diagnoses, time to result needs to be drastically reduced. In this respect, ***optimisation of control and run-time*** of the aforementioned microfluidic chips need be further investigated by researchers, as well as ***optical spectroscopy and bio-photonics***. In addition, improving ***timing for localisation of molecules*** (i.e. through optical spectroscopy) and exploring ***ultra high-speed signals*** or similar areas of study can improve time effectiveness: these could be the sort of initiatives that should find support in the near future. Finally, the development of ***on-board sample preparation*** and the ***investigation of nucleic acid amplification methods*** (MEMS-driven miniaturised ***Polymerase Chain Reaction***, for instance) represent further promising areas of research and ought to be given appropriate attention.

It has been suggested that ***Lab On Chips could be integrated into on-body or even in-body applications*** by integrating ongoing researches on new materials and techniques for identifying, analysing, measuring and counting cells and molecules. Direct identification of molecules (like components of bloods), but also viruses and bacteria, would speed up the analysis process. On/in the body applications, depending on the type of technology and purpose of the analysis, would allow for the gathering of relevant information on-demand, as well as increase individuals empowerment on their health status, as many steps leading to very early diagnosis of diseases would be in their hands. These kind of applications would include the possible integration of several ***optical and non-optical techniques***, like, among others ***Label-free LoC, bio-photonics applications*** allowing for localisation of single molecules (for instance, for really early diagnosis of cancer, before symptoms appear or chemical substances linked to the tumour are detectable into blood), nano high pressure liquid chromatography (nano hplc).

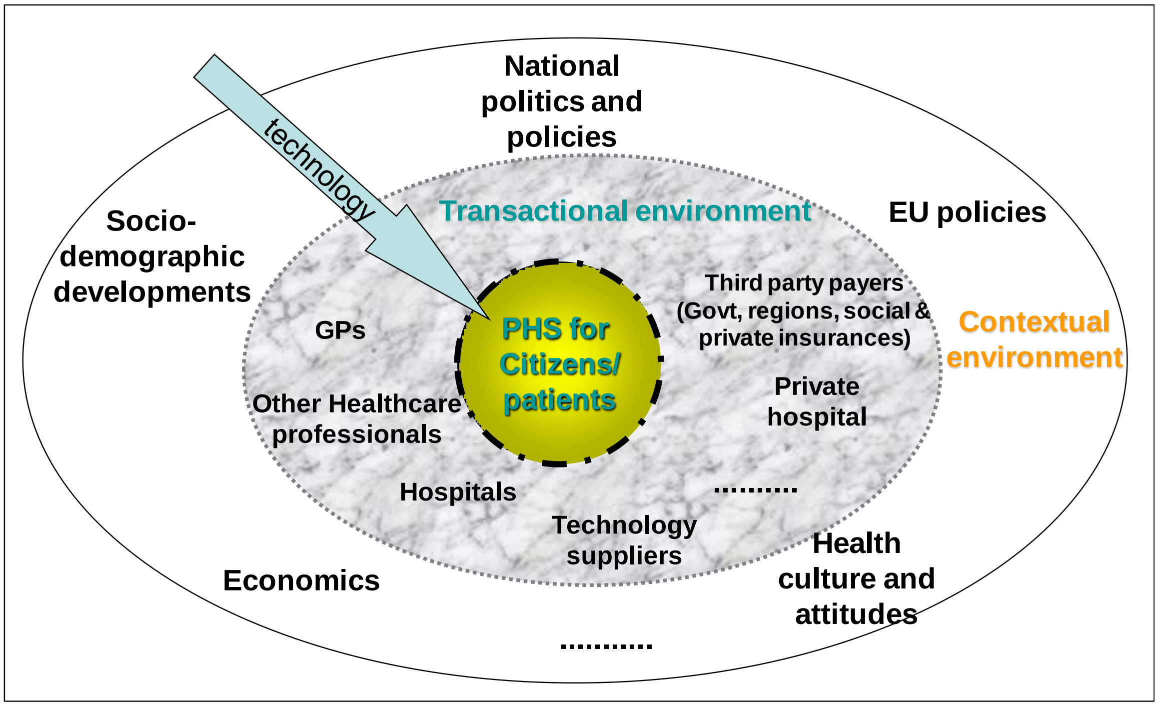
Finally, several important criteria are essential for the development of biomarkers. Biomarkers should be made easily measurable using standardized and ***cost-efficient*** methods, and their ***effectiveness*** ought to be improved to reduce required quantities of sample. Albeit the strong emphasis placed on Lab On Chips in the last ten years, evidence about their benefits (especially in terms of cost-effectiveness) are still questioned by several categories of stakeholders involved in the care process. ***Cost-benefit analysis*** ought to be the main focus of research activities supporting ***implementation***. In order to enhance adoption, as well as to provide evidence supporting efforts in continuing and new research, cost/benefit analysis should therefore receive early support and a strict cooperation between research and ICT industry is required, including at the same time a direct involvement of the healthcare sector (i.e., healthcare research and providing institutions), possibly embracing even a number of GPs.

In conclusion, while not explicitly illustrated in the roadmaps, it is worth recalling that a fundamental pre-requisite for Lab On Chips functioning is their ***direct communication and exchange of data with PHRs.*** A further step, allowing for a comprehensive diagnosis and treatment, would be the link of PHS (and of PHRs) to larger demographic and environmental data, in order to have a complete picture of the course of a disease, as well as updated information on health status of the population. This requires interoperability of components and communication protocols, as well as encryption techniques ensuring ***protection of sensitive data*** (maybe including also bio-metric security).

6 Conclusions: research themes and beyond

Especially in the extensive analysis of the state of play and in the discussion to build the scenarios it emerged clearly how the future of PHS depends on several domains and on vast number of variables and players. It can be safely stated that **PHS represent a complex socio-technical system**[39] **shaped by the different levels and multitude of players and organisations/ institutions as intuitively conveyed in the figure below.**

Figure 18: PHS as a complex socio-technical system



Source: MIP elaboration

In a complex and dynamic socio-technical system

- to some extent the factors within each dimension affect one another, resulting in different directions for development or different areas of emphasis within the larger idea they represent;
- More important, perhaps, each cluster represents a set of trends, developments, actions, preferences, and choices that are at least moderately independent of the other clusters;
- At the same time, however, the main effects of each cluster interact with the other clusters in both predictable and unexpected ways;
- The social elements and the technical aspects are continually evolving on their own while continuously interacting with each other in ways that cannot be overtly controlled.

It is evident then that the future of PHS depends on a large number of dimensions and variable, of which technology is one and probably not the most determining one.

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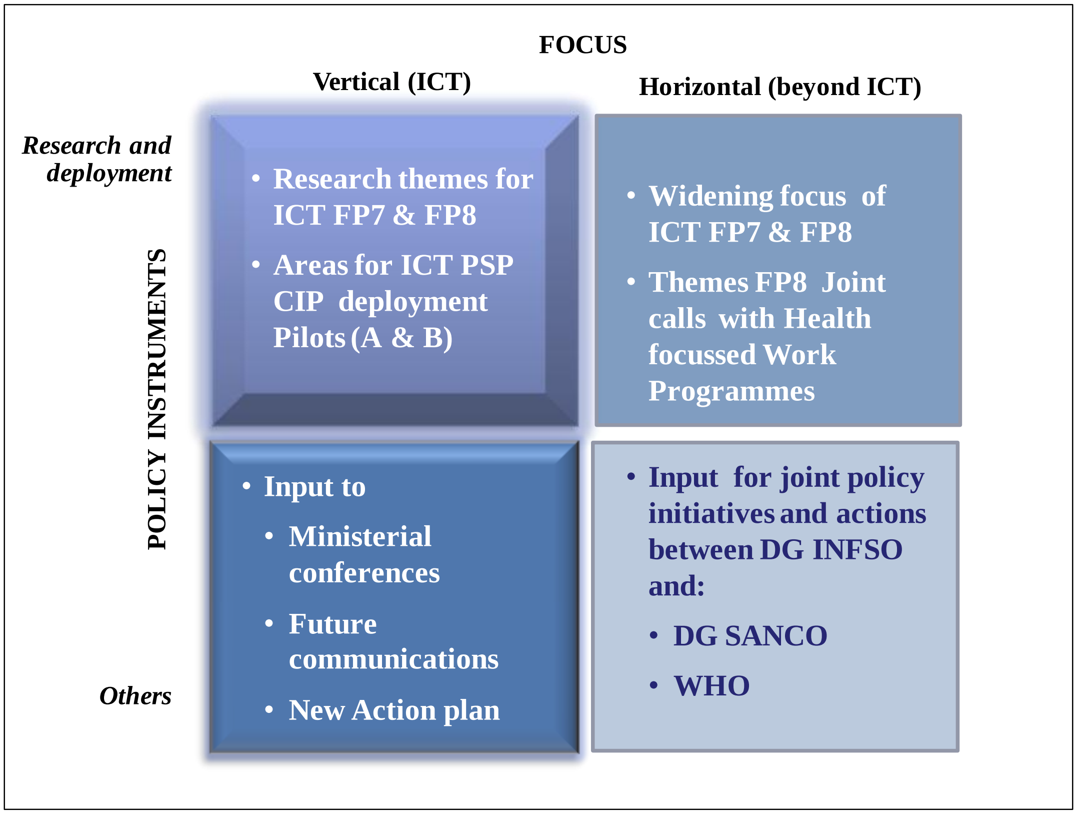
[39] On the concept of socio-technical systems see classical analysis such as Forrester (1961), Thompson, (1967) and Trist, (1981).

Accordingly, the potential proposals for future policy actions that could be derived from the work carried out by PHS2020 span across the full range identified in the matrix below using two dimensions:

- The **policy instrument:**
    - Support to research and deployment activities
    - Other instruments such as communications, action plans, awareness raising activities, etc
- The **focus of the proposals**
    - Vertical and strictly focussed on ICT (defined by DG INFSO mandate)
    - Horizontal and multi-disciplinary beyond an ICT exclusive focus

Figure 19: Potential areas of recommendations



POLICY INSTRUMENTS \ FOCUS	Vertical (ICT)	Horizontal (beyond ICT)
Research and deployment	• Research themes for ICT FP7 & FP8 • Areas for ICT PSP CIP deployment Pilots (A & B)	• Widening focus of ICT FP7 & FP8 • Themes FP8 Joint calls with Health focussed Work Programmes

Others	• Input to
	  • Ministerial conferences
	  • Future communications
	  • New Action plan
		• Input for joint policy initiatives and actions between DG INFSO and:
		  • DG SANCO
		  • WHO

Source: MIP elaboration

Evidently given the core objective of PHS2020 and DG INFSO mandate the top left box clearly evidenced in the figure represented the main outcome expected and has been treated in the previous section.

Potentially, however, the future PHS2020 could concerns not only support to research and deployment but also more strictly defined DG INFSO policies initiatives (the bottom left box), as well as many other domains beyond that of ICT.

We think that the evidence and analysis contained in all of PHS2020 deliverables taken together provide enough food for thought that can be leveraged for future DG INFSO policy initiatives (the bottom left corners in the matrix). It is not our ambition, however, to develop proposals in this area, for this is the prerogative of the Commission.

There is also scope for policy initiatives going beyond the exclusive ICT focus and bridging it with more health related matters where DG INFSO could establish a policy dialogue with DG SANCO and also with other international organisations such as WHO.

We advance instead briefly a few recommendations below for what concerns the object of the top right corners.

PHS is a dynamic and complex socio-technical system resulting from the interactions of different sub-systems with their respective players, practices, expertises. ICT is only one component of this system, and ICT expertise is only one among a vast range of relevant and needed disciplines, including naturally medicine but also other broadly defined socio-economic issues (business models, users needs and cognitive maps, regulation, organisation and institutional re-design and restructuring, etc). So PHS2020 involves a plurality of different players and a plurality of expertises.

While this is rhetorically always acknowledged, the practice EC funded research is different. Especially large RTD projects formally include involvement of stakeholder players, clinical trial and pilots, as well as “socio-economic” work streams and packages but their actual weight tend to remain marginal, if not ‘ritual’, in the overall architecture of research activities.

This fact seriously compromises the likelihood that research products respond to the actual practice of healthcare and embed the expertise and knowledge needed to convince clinicians, consider the nuances of users needs, organisational and institutional functioning. Surely the Framework Programme is for pre-competitive research that will then have to be adapted for deployment. Yet when the product of this research are so misaligned with respect to institutional/organisational realities and users needs it is very likely that it will never be used. We have **two proposals** to address these shortcoming.

First, **a methodological change in the PHS ICT research projects** that might be financed in the last years of FP7 (up to 2013) **and in FP8 to increase their multi-stakeholders and multi-disciplinary nature, and particularly to infuse medicine into ICT.** It is not a proposal to change the focus, as this will remain mainly on RTD, but rather a **meta-proposal** in the sense that it concerns the requirements of the calls and the evaluation criteria. We propose the following four criteria :

1. Proposals should include all non ICT relevant stakeholders, clinical and “socio-economic expertise” with respect to the addressed domain;
2. Clinical and socio-economic expertises should be deployed both upstream (i.e. *ex ante*) and downstream (i.e. *ex post*) to the core technological development activities, whereas currently they are mostly downstream and are often carried out residually simply because they are written in the Description of Work (DoW) and not for their real added value;
3. All large scale project should include real life clinical trials of some reasonable dimensions (not 3000 subject but neither 15 as it is too often the case)
4. At least 30% of the requested funding should be allocated between “clinical” trials, “socio-economic” analysis and activities, and at stakeholder involvement activities

These four criteria are self-evident and we simply add a brief consideration on the second one. This criteria aims at ensuring that also single research projects improve the higher level “governance” in terms of the design and modelling of the expected technological product with respect to the targets addressed and the organisational/institutional context of application.

The **second proposal**, in addition to the previous one or in alternative if that prove not feasible, **is the definition and launch of a joint call on PHS between the ICT Work Programme of DG INFSO and the Health Work Programme of DG Research.** This could achieve two objectives:

a) enable a truly multi-disciplinary approach and real synergies between ICT and Health research;
b) enable cross-fertilisation by groups of applicants that usually do not collaborate: each area of FP create its own silos of organisations presenting proposals that usually do not mix with others, thus foregoing potential important synergies and cross-innovation.

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