J Med Syst (2016) 40: 43
DOI 10.1007/s10916-015-0376-2

MOBILE SYSTEMS

A Systematic Literature Review of Agents Applied in Healthcare

David Isern [1] · Antonio Moreno [1]

Received: 31 January 2015 / Accepted: 9 October 2015 / Published online: 21 November 2015

Abstract Intelligent agents and healthcare have been intimately linked in the last years. The intrinsic complexity and diversity of care can be tackled with the flexibility, dynamics and reliability of multi-agent systems. The purpose of this review is to show the feasibility of applying intelligent agents in the healthcare domain and use the findings to provide a discussion of current trends and devise future research directions. A review of the most recent literature (2009–2014) of applications of agents in healthcare is discussed, and two classifications considering the main goal of the health systems as well as the main actors involved have been investigated. This review shows that the number of published works exhibits a growing interest of researchers in this field in a wide range of applications.

Keywords Intelligent agents · Healthcare · Review

Introduction

Healthcare is a complex environment, subject to a continuous pressure to find increasingly more complex solutions to problems, and at the same time, improve the efficiency of current solutions in terms of costs and resources. In this scenario there are a lot of participants with different roles, such as health institutions, governments, and health professionals and patients paying a more active role daily. Nowadays, current trends go towards the use of distributed solutions such as intelligent agents, cloud environments and application-dependent systems. This paper is focused on the study of agents in the healthcare domain.

The use of health information technology has been shown to improve many aspects of care such as efficiency, cost-effectiveness, quality, safety of medical care delivery, access to the information and healthcare equity [1, 2]. Currently, information systems offer a wide range of functionalities to managers, health practitioners and patients [3, 4]. Just to name a few, they allow automating labour-intensive and inefficient processes, dealing with administrative and financial transactions, managing multi-functional electronic health records and computerised physician order entries, assisting practitioners in hard tasks such as diagnosis, prognosis and guideline enactment, monitoring in real time the state of patients, and supporting medical students in their learning process.

Agents are described as autonomous entities that can sense the world and act (proactively or reactively) on it in order to achieve specific goals [5]. Autonomy, reactivity and proactivity are three features that permit agents to operate in dynamic and uncertain environments. *Cognitive agents*, which are the focus of this work, maintain an explicit model of the environment, have one or more goals to be accomplished, perceive external events, make plans to change the world taking into account their goals, and finally implement them by acting upon the environment [6]. These basic characteristics of agents can be extended. For instance, *intelligent agents* learn about their observations to improve their performances over time. *Socially intelligent reasoning agents* are collections of agents capable of cooperating with other (similar) entities in a rational way [7]. The social ability of agents is supported by communication acts, which permit

This article is part of the Topical Collection on *Mobile Systems*

✉ David Isern
david.isern@urv.cat

Antonio Moreno
antonio.moreno@urv.cat

1 Department of Computer Science and Mathematics, ITAKA Research Group, Universitat Rovira i Virgili, Avda. Països Catalans, 26, 43007 Tarragona, Catalonia (Spain)

agents to coordinate their activities, negotiate about a particular issue, or simply share a particular fact among a set of agents.

On the other side, drawing on [8], *health systems* exhibit the following characteristics: 1) they are loosely coupled and composed by heterogeneous components, 2) they require fault-tolerance, reliability, security and privacy awareness, 3) data (e.g. patient's health record, medical processes) are generated and used by a wide range of devices, and 4) nowadays, unobtrusive networks of sensors enable to gather physiological information from patients. Taking into account the similarity between the properties of agents and the characteristics of healthcare problems, several researchers have proposed agents as a solution to implement pervasive and ubiquitous e-health systems.

One of the key factors of this success is the smart use of computation and communication tools to support healthcare organizations, and agents are one of the technologies that can be adopted to achieve this challenging task [9]. In this setting agents can support healthcare organizations, patients and caregivers, but one of the most important changes is how the assistance is provided through these entities.

One of the features of agents is the natural integration of different entities with different roles. Daily care consists in a distributed endeavour carried out by multidisciplinary teams that plan, schedule and execute complex tasks [10]. There is a wide variety of sources of information (data from electronic medical records, data from medical devices, notes taken daily) that should be taken into account to deliver care to the patient, and artificial agents may cooperate with humans to facilitate the development and enactment of a care plan. From this cooperation, future applications should mitigate the errors in care (human, organizational, ergonomics), be more efficient (in terms of data available, use of up-to-date evidences), and be more equitable (implementing similar processes based on their success).

A previous survey on this area [11] showed the advantages of this paradigm in several areas such as the management of medical data, the implementation of decision support systems, planning, and remote care. However, new works in the last years have increased these areas of application. Thus, the main goal of this systematic survey is to collect all these works and classify them according to the current trends, providing a new up-to-date view of the field.

The rest of the paper is organised as follows. First of all, Section 2 explains the methodology followed to find the papers included in this review. The following section explains the conceptual framework for the classification of articles dealing with the applications of agents in healthcare. Section 4 uses the conceptual framework to classify and summarize all the relevant papers. Section 5 discusses the main features shared by the analysed works. Finally, the last section gives some conclusions and proposes some lines of future research.

Methodology

The main goals of this paper are to perform a systematic analysis of the literature on the application of agents in the healthcare domain, and then to suggest a classification framework of the collected papers. The methodology followed in this paper is similar to the ones used in previous works like [12], which analyses the adoption of RFID in the health domain, and also [10], which analyses the implementation of smart strategies in daily care to improve the care given to patients.

This paper is an extension of a previous well-known survey in this field [11], which covered the works from 2005 to 2008. For this reason we only consider the papers published between 2009 and 2014 (some papers of 2015 were also included because they are already available). Then, taking into account both reviews, the reader can observe the evolution of the field during the last decade and the research lines that can be followed in the future.

Several selection criteria were established in this study. First of all, we have only considered papers written in English. Second, after reading the title, the abstract and, in some cases, the whole content, only articles that deal with *intelligent agents* applied in any field related with *healthcare* have been considered. Finally, papers published in journals have been preferred to other publication venues (such as workshops, PhD dissertations or Master thesis). Regarding the inclusion or not of papers published in conferences, we have also included some conference papers when there are not any other papers published on the same topic by the authors in journals, and the conference is relevant enough (CORE rating A or B). When some papers are related to the same application, the most recent one has been used.

The search was performed in December 2014 across the following databases: ProQuest, ACM Digital Library, SCOPUS (Elsevier), IEEE Xplore, and Science@Direct. We also considered some papers cited in the retrieved articles in order to complete the search. The expressivity of the search procedure depends on the database, but in all the cases we considered the words "intelligent", "agent", and "health" in the search. Additionally, other combinations such as "agent-based", "MAS", "medical education" were also used to help disambiguation.

From each database, we found the following number of relevant papers:

- ProQuest: from a potential set of 161 articles, we selected 17 to review.

- ACM Digital Library: from a potential set of 72 articles, we only considered 4 to review later.
- SCOPUS (Elsevier): from a potential set of 132 articles, 55 were selected for the review.
- IEEE Xplore: 7 of the 10 potentially interesting articles were chosen.
- Science@Direct: 56 more papers were added from this source, from a potential set of 83.

After eliminating the duplicates and reading carefully all the selected articles, 97 works were finally included in this study. The disparity of percentages accomplished in each database depends on several circumstances. For instance, some databases search the keywords in the entire document, not only in the abstract and title, and references can include papers which are not completely related with the scope of the search. In other cases, some documents are not related to computer science. For instance, the word 'agent' is widely used in medicine and all collected documents had to be carefully revised.

Classification framework

The adoption of agents in healthcare has increased in the last 10 years and this technology has been widely used in different care domains. Early studies on agents applied in healthcare such as Nealon and Moreno [13], Družovec et al. [14], and Fox et al. [15] are focused on demonstrating the feasibility of the adoption of intelligent agents in some domains of healthcare and on identifying some benefits that agents can provide in the resolution of some distributed and complex problems. The most well-known initial applications were developed in patient scheduling, organ and tissue transplant management, community care, health information access, decision support systems, and internal hospital management tasks.

Drawing on Villar et al. [9] and Vieira-Marques [16], the classification framework used in this review identifies three broad categories of applications, depending on the intended audience of the application: tools designed for healthcare organizations, tools centred in professionals and tools centred in patients. Furthermore, we identified seven groups of key goals addressed in the analysed applications: data management, monitoring systems and alarms, security and privacy mechanisms, decision support systems, task planning and scheduling, simulation environments, and general care management platforms.

One of the difficulties of this study was to classify the papers taking into account both classifications because in both frameworks, some papers exhibit an overlap among different possibilities. In the case of users, all papers have been classified in only one category (the most prominent in each case), and in the case of types of application, some papers have been classified in more than one category, allowing an overlap (with a maximum of four possibilities). One of the goals of this paper is to detect and analyse the works published in this field of research, and also to detect tendencies or areas of research where agents paid the attention of researchers. For this reason, we tried to identify the main targeted users in all papers, and the main areas of application in order to provide general statistics of usage.

Classification of works based on the intended users

The target user of the application determines several features. We can distinguish among applications that provide services to patients, applications that offer services to health staff (e.g. practitioners, nurses), and applications designed to support healthcare organizations in the implementation or adoption of some rules or guidelines in patient care:

- *Patient-centred applications* are applications in which the main objective is to provide a particular service to patients. This group includes applications that personalize the care given to patients, for instance, adapting general care treatments according to the particular circumstances of the patient [17–21]. Another kind of applications applies Ambient Intelligent concepts in healthcare, relying on a network of sensors that observe a subject and learn/predict his/her behaviour. A good example of these applications is the supervision of elder people, in which these systems can send alerts to a supervisor if an abnormal situation is detected [22–24], or recommend the patient some tasks to perform during the day to improve his/her lifestyle and well-being [25–28]. Nowadays, some of these applications use the mobile device of the patients to give advices or to collect their data [24, 29, 30]. Additionally, this field includes innovative human-computer interaction elements, such as virtual agents designed to dialog with the user about some domain [25, 31, 32] or by integrating other devices as wheelchairs [33].
- *Staff-centred applications* are designed to support medical practitioners (basically doctors and nurses) in daily care. Most of these applications are designed as *personal assistants*, whose aim is to collect and provide the most appropriate medical data to the appropriate point of care [34–37]. These systems are usually composed by two main parts, one that collects the data in a distributed manner, and a second one that filters them before providing them to the medical practitioner. Other applications are designed as decision support systems [38–43]. Usually they analyse medical images or check the patient's health record and recommend the next step to follow in his/her treatment. Finally, another group of applications are designed to manage teams of practitioners taking into account some criteria [44].

- *Healthcare organizations-centred* applications, along with care simulations, are the most common ones. They include a (usually ontological) representation of medical staff and patients, and the internal dependencies among them in a healthcare organization. These systems mimic real relationships in medical organizations in order to follow a treatment (managing the current state of the patient, delivering care, managing outcomes) [45–51], learn about the internal behaviour of the organization and detect weaknesses [52–54], improve the exchange of information among heterogeneous sources (results of tests, results of medical visits, reminders) [29, 55–57], simulate the behaviour of a complex diseases [58–67], or implement some tele-assistance platforms [68, 69]. In this classification, all works related with the management of medical records are also included [70–76].

Classification of works based on the types of applications

The previous classification was made taking into account the main user of the system: a patient, a medical practitioner, or a healthcare organization as a whole. It is also interesting to know the main domains of application of these applications. The seven main types of applications found in the 2009–2014 period are the following:

- *Data-management systems*. These types of systems focus on the efficient retrieval and processing of medical data. These medical data include the patients' data, contained in their electronic health record, and also medical data about treatments collected from the most recent evidences available on repositories. Most of the works in this area go towards the implementation of an electronic health record by maintaining the data scattered physically and providing a virtual view, or by trying to concentrate the data from distributed sources to a central node inside a healthcare organization. Other works propose models that include the integration of agents with existing information systems [55, 56].
- *Implementation of secure platforms*. As mentioned previously, security is a mandatory feature that any distributed system in healthcare should provide but, unfortunately, in some cases security measures must be added a posteriori due to constraints of the programming languages [77, 78]. Some platforms such as JADE provide external libraries that can be added easily to the implemented MAS in order to protect their communications but, in other cases, researchers must implement these features from scratch in a particular system. This area includes general-purpose mechanisms to protect agent-based systems against security threats. It is necessary to guarantee key security properties like confidentiality, integrity, availability, accountability and non-repudiation through different mechanisms such as authentication, authorization, trust management, etc. Additionally, agent-based systems have particular vulnerabilities such as control of the origin of information, access control, unsecure communications among agents, presence of malicious agents or hosts, or the provision of access to the resources and the internal status of other agents [79]. Moreover, in the healthcare area there are particular security threats that should be treated such as preserving privacy and confidentiality in shared access, maintenance of privileges to permit the access to the whole data or to a subset of them, and also anonymisation of the data in order to reuse existing knowledge [80].
- *Decision support systems* (DSSs). A DSS acquires patient data as the input and provides back patient-specific assessments and recommendations by using healthcare processes or knowledge-based models, such as diagnostics or treatments. From the analysed works, two different types of DSSs are identified. The first one uses a knowledge base of examples in order to give an answer to the manager (e.g. by using a decision maker in a distributed way) [81]. Other works model a medical workflow (e.g. a treatment) and locate the patient inside this procedure, taking into account his/her current circumstances [47].
- *Planning*. Systems centred on the coordination and scheduling of human and material resources taking into account preferences, constraints and goals. Planning and distributed coordination of resources are fields where agent technology researchers have paid special attention, exploiting inherent features of agents such as autonomy, social ability and pro-activity [31, 82, 83]. A particular case in point is the deployment of mid- and long-term treatments over patients, which requires the execution of standardized clinical guidelines taking into account the actions and decisions embedded into them [47].
- *Simulation*. Agent-based platforms have been traditionally used to make rule-based simulations of the behaviour of complex systems (e.g. economy [84], agriculture [85], biology [86]). Agent-based simulations in healthcare are one of the current trends with more published papers. According to Koelling and Schwandt [87], in this area the following classification may be considered: health systems, patient-related systems, care delivery, prevention and epidemiology. For instance, simulations are used to compare the assignment of human resources to departments [43], or to evaluate the impact of particular treatment taking into account the evolution of a disease [53, 60, 66, 88, 89]. Another important area in which simulation is used is medical education, in which we may find systems that permit to understand the behaviour of a

complex disease such as diabetes or to use a corpus of patient's scenarios to simulate the effects of mid- and long-treatments [27].

- *Care platforms*. These applications are designed to emulate real health delivery systems using an agent-based approach. In this case, healthcare-based platforms permit to simulate departments such as intensive care units, or a whole healthcare organization [45]. Usually, agents are used to integrate existing information systems through wrappers. Additionally, some platforms are designed to integrate remote care in the daily attention to patients. Remote care includes different levels of interaction between patients and practitioners. A first type of systems just collects and analyses data from sensors connected to the patients at home [68]. A second one permits remote medical visits through video meetings between patients and practitioners [69, 90]. A final kind of systems permits to advise or recommend actions to be performed by the patient [22].
- *Monitoring and alarms.* This category includes agent-based platforms that monitor the current state of a subject (patient) and, taking into account general non-desirable patterns, warn the patient (or a supervisor) about problematic situations [25]. These applications include those designed in Ambient Intelligence, and they are usually applied in hospitals with elder people that should be continuously monitored. These systems are complex because they should include information about sensors (e.g. positioning a patient through RFID mechanisms, vital signs of patients) and information about the domain of application (e.g. map of a building) in order to detect abnormal situations [18, 22, 91].

This classification is intended to identify the main tendencies in the use of agents in the healthcare domain. However, there is a correlation between these areas and also an overlapping among them. All papers have been classified attending to their main goal avoiding overlapping as more as possible.

A previous work by our group ([11]) surveyed the period 2002–2008, which found five main lines of research and explained in detail some relevant works in each area. The paper identified the following areas of interest: management of medical data, decision support systems, planning and resource allocation, a group of applications that include remote care, telemedicine and pervasive care, and finally, composite systems that integrate several of the previous aspects. In this review, we refined this classification adding more areas such as simulations, secure platforms, and monitoring and alarm systems.

Results

This section presents the results of the review of articles dealing with agents applied in the healthcare domain. First of all, we highlight the distribution of articles per year, per journal, per actors and finally, per types of application.

Distribution of articles by year of publication

Based on the literature reviewed, Fig. 1 shows the number of articles considered in this review per year (period 2009–2014). Since 2009 the number of published papers has increased each year. Additionally, after the first month of the year 2015 it has already 4 papers. Clearly, this field of research has been paid more attention in the last years with more results, more published papers and more specialised conferences, workshops and special issues of journals.

The years 2012, 2013 and 2014 supposed important milestones due to the number of published articles (17, 17 and 28 respectively). It should be mentioned a special issue dedicated to this field published in 2014 [92] that has given a boost to the interest in the area. Additionally, since 2003 different workshops and conferences include agents applied in healthcare as part of their topics (see Table 1 for a list of related conferences and workshops in the period of study).

As mentioned before, our work ([11]) surveyed the period 2002–2008. Despite the fact that this work was not a systematic literature review and the goals were not the same, it is possible to analyse also the frequency of appearance of papers in this period. In 2002, there are no referenced papers; 2003, 6 papers; 2004, 5 papers; 2005, 6 papers; 2006, 6 papers; 2007, 5 papers; 2008, 7 papers; and 2009, 3 papers. These figures show a clear growing tendency since 2003, but most of these works are papers published in conferences and workshops due to the low maturity of the field. The present work confirms two assumptions: the increase of interest in this field, and also the increase of quality, because most of the papers referenced in the present work are journal papers instead of conferences and workshops.

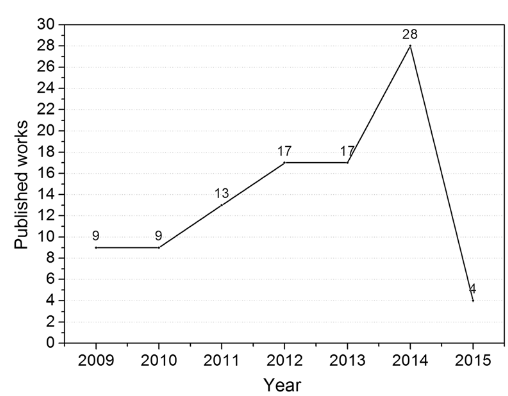

Fig. 1 Distribution of articles by year of publication

Distribution of articles per journal

Table 2 lists the journals containing two or more of the selected articles. This selection contains 46 articles out of 97 articles (49.48 %). The most popular journal publishing articles related to agents applied in healthcare is the "Journal of Medical Systems" with 12 articles (12.37 %), followed by the "International Journal on Artificial Intelligence Tools" with 6 papers (6.19 %), and "Expert Systems with Applications", "Artificial Intelligence in Medicine" and "IEEE Transactions on Information Technology in Biomedicine", each of which has 4 articles (4.12 %). Most of the journals are present in the last list of the JCR and belong to the "Medical Informatics" and "Artificial Intelligence" fields but the list also includes more general journals about information systems such as "Information Sciences" and "Journal of Ambient Intelligence and Smart Environments".

Distribution of articles by actors

Table 3 shows the distribution of articles by actors, where it can be seen that more than half of the articles focus on the organizational level (54 articles, 55.67 %). After that we can find the applications that have the patient as the main actor (26 articles, 26.80 %), finally followed by staff-centred applications (17 articles, 17.53 %).

Distribution of articles by topics

Table 4 shows the distribution of articles by topics. The topics to which researchers have paid more attention in the period of study are agent-based care platforms and simulation (both 29 articles, 21.80 %), and monitoring and alarms applications (24 articles, 18.05 %). After that, we found applications dealing with clinical data (16 articles, 12.03 %), decision support systems (15 articles, 11.28 %), planning (11 articles, 8.27 %) and finally, security issues (9 articles, 6.77 %).

Some works analysed in this review show overlapping between topics. One between "management of data" and "platform", and another one between "management of data" and "decision support system".

Discussion

The previous section showed the classification of the selected works using different criteria. The number of works and applications which apply agents in the healthcare domain has increased in the last five years, as shown in Fig. 1. In Table 3 it can be seen that the platforms that enable healthcare organizations to provide some distributed services concentrate the major contributions in this field. This result is not very surprising due to the nature of the e-health environment. Usually, these applications exploit the physical distribution of resources, services and data in order to achieve a goal. Some researchers proposed whole technological applications applied to one or more departments, sometimes even including resources from different healthcare institutions with different information systems [55]. However, the previous section has shown that there are other types of applications and actors that have captured the attention of the researchers in which agent technology has been instrumental in the design and development of distributed systems that improve the performance with respect to centralized ones in terms of reliability, scalability and, more importantly, enable dynamic, flexible and evolving systems.

Table 1 Conferences and workshops about agents applied in healthcare (2009–2015)

Name of the event	Year	URL
2015 Agent-Directed Simulation (ADS'15) Symposium	2015	http://www.scs.org/springsim
A-Health. Agents and multi-agent Systems for AAL and e-HEALTH held at PAAMS 2015	2015	http://www.paams.net/ahealth15
IX Workshop on Agents Applied in Health Care, A2HC 2015 to be held at AAMAS 2015	2015	http://www.fe.up.pt/A2HC15
Agents and multi-agent Systems for Ambient Assisted Living and e-HEALTH held at PAAMS 2014	2014	http://www.paams.net/a-health14/
Multi-Agent Systems for Healthcare 2014 held at AAMAS 2014	2014	http://paginas.fe.up.pt/~mash14/index.html
Agent Based Simulation held at WIS 2014	2014	http://www.wintersim.org/2014/agentbasedsim.html
Agents and Multi-Agent Systems for Ambient Assisted Living and e-HEALTH held at PAAMS 2013	2013	http://www.paams.net/a-health13/
VIII workshop on agents applied in health care held at AIME 2013	2013	http://deim.urv.cat/~itaka/workshops/aime2013/
Agents for Ambient Assisted Living held at PAAMS 2012	2012	http://www.paams.net/AAAL12/
VII workshop on agents applied in health care held at AAMAS 2012	2012	http://deim.urv.cat/~itaka/workshops/aamas2012/
Agents for Ambient Assisted Living held at PAAMS 2011	2011	http://www.paams.net/~dcai2011/home/anto/webs/aaal2011/
VI workshop on agents applied in health care held at e-HEALTH 2010	2010	http://deim.urv.cat/~itaka/workshops/ehealth2010/

Table 2 Classification of the articles per journal (with a minimum of two publications)

Journal	No.	Percentage	Impact factor (2013)	5-year impact factor	Quartile (area)
Journal of Medical Systems	12	12.37	1.372	1.482	Q3 (Medical informatics; Health Care Sciences & Services)
International Journal on Artificial Intelligence Tools	6	6.19	0.321	0.478	Q4 (Computer Science, Artificial Intelligence)
Artificial Intelligence in Medicine	4	4.12	1.356	1.632	Q2 (Computer Science, Artificial Intelligence); Q3 (Medical Informatics)
Expert Systems with Applications	4	4.12	1.965	2.254	Q1 (Computer Science, Artificial Intelligence)
Computers in Biology and Medicine	3	3.09	1.475	1.547	Q2 (Biology); Q3 (Computer Science, Interdisciplinary Applications)
IEEE Transactions on Information Technology in Biomedicine	3	3.09	2.072	2.584	Q1 (Computer Science, Information Systems); Q2 (Medical Informatics)
International Journal of Environmental Research and Public Health	3	3.09	1.993	(**)	Q2 (Environmental Sciences)
Procedia Computer Science	3	3.09	(*)	(**)	
Applied Intelligence	2	2.06	(*)	(**)	
Applied Soft Computing	2	2.06	2.679	2.970	Q1 (Computer Science, Interdisciplinary Applications; Computer Science, Artificial Intelligence)
IEEE Intelligent Systems	2	2.06	1.920	2.344	Q2 (Computer Science, Artificial Intelligence; Engineering, Electrical & Electronic)
Information Sciences	2	2.06	3.893	3.969	Q1 (Computer Science, Information Systems)
Journal of Ambient Intelligence and Smart Environments	2	2.06	1.082	1.252	Q2 (Computer Science, Information Systems)
Total	*48*	*49.48*			

(*) Journal not included in the last JCR list; (**) Value not available.

Current types of applications

Taking into account the classification of the applications considering the targeted user, as summarised in Table 3, the most common agent-based systems are general healthcare-systems, followed by patient-based ones and, finally, systems designed to support health staff.

General agent-based healthcare systems are designed to be used for health managers and researchers of healthcare organizations. In many cases they include simulations to evaluate and compare different policies to tackle a healthcare problem [93]. For instance, an agent-based simulation may discover those interventions that increase population wellness and quality of care, while simultaneously decreasing costs, or evaluate the dynamic evolution of an infectious disease [43].

Another field of research is the implementation of generic platforms that enable distributed health entities to interact. These platforms model different roles and patterns as well as internal relationships within departments in order to create a complex system. In those platforms humans and resources interact, usually creating and maintaining a shared data structure containing the medical records of patients [94–96]. Most of these care applications, such as decision support systems and monitoring and alarm systems are used to manage and facilitate the daily work of practitioners.

Patient-centred applications put the focus on patients. Personalization of daily care is one of the main goals of these applications, giving special emphasis to the implementation of standardised clinical processes based on the general evidence but taking into account the circumstances of the patient and the human and material resources available in a medical centre. The main aim of these systems is to increase the satisfaction of the patient while, at the same time, making an efficient use of resources and saving costs. Patient-based systems also pursue the enhancement of home-based self-care by using networks of sensors and remote assistance [97]. These systems are centred in two main aspects: preventive care to guide the patient in daily activities [98–100] and monitoring systems able to detect abnormal situations [101, 102].

Table 3 Classification of the articles based on the distribution by users

Dimension	Number of articles	Percentage
Healthcare organization-centred	54	55.67
Patient-centred	26	26.80
Staff-centred	17	17.53
Total	*97*	*100*

Table 4 Classification of the articles based on the distribution by issues

Dimension	Number of articles	Percentage
Platform	29	21.80
Simulation	29	21.80
Monitoring/alarms	24	18.05
Management of data	16	12.03
Decision support system	15	11.28
Planning	11	8.27
Security	9	6.77
Total	*133*	*100*

Some articles are counted more than once because they cover more than one issue

Finally, staff-centred systems are designed to be used by healthcare professionals in daily care. They include the management of complex processes (usually through the adoption of clinical guidelines) [103] and the facilitation of the monitoring of current health states and medical results of the patients [104, 105]. Most of these applications fall into the categories of decision support systems and monitoring and alarm systems [106]. This group of applications permits the adoption and evaluation of workflow processes with the inclusion of the latest clinical practice evidences [107].

The inclusion of security mechanisms is a key feature common in all applications, independently of the intended audience [108].

Current domains of application

Taking into account the domain-based classification of the applications, it has been noticed that care platforms, Ambient Intelligence and management of medical data cover most of the agent-based proposals in e-health.

Agent-based platforms were the first contributions in e-health on the 00's. These systems create distributed complex models that improve the performance, flexibility and reliability of current centralized approaches and permit to understand in more detail the current management of (medical) processes. In some cases, these platforms are designed as open frameworks that can be customized under particular circumstances. Additionally, some works propose to check the validity of those processes and evaluate their temporal and economic impact in all involved actors (general population, medical staff).

Nowadays, one of the most active areas of research is the creation of health monitoring systems, which are sometimes categorised under the Ambient Intelligence (AmI) label [109]. In these systems a network of different kinds of sensors (from mobile devices, RFID, cameras, wearables) provide data about a constantly observed subject (location, vital signs), which are usually stored on a central repository (directly or after a first local analysis that transform raw data into qualitative information on which high-level reasoning processes may be applied). Intelligent agents analyse all these data and they may raise alarms if abnormal or unusual situations are detected, they may provide pro-active advice and reminders about relevant facts (such as medications), and they may understand the behaviour of a patient [23, 29, 110]. Current AmI applications include smart homes, assisted living, health monitoring and also assistance in the community, hospitals, emergency services and homecare of the elderly, among others [22, 25].

Agents act socially by exchanging information among them. Thus, a critical element on their efficiency is how medical and procedural data are shared. Representation of knowledge in healthcare is a traditional field of research due to its application in numerous and different domains [111–113]. Agent-based systems normally use ontologies shared among all entities, which can be created ad hoc for a particular application or adopted from existing ones [17, 47]. Researchers commonly use OWL as ontological representation language, in conjunction with standard large corpuses of medical terms such as SNOMED and MeSH that ease the integration with legacy applications. Additionally, some agent-based systems use information provided by existing health information systems (HIS). This integration is made through existing web services or following the protocols defined in HL7.

Agents permit the creation of distributed electronic health records, transmitting its information in a secure way. In this scenario, data can remain physically scattered among nodes (healthcare institutions, departments, or services that generate some data), and agents are in charge of collecting them when it is necessary or providing a virtual unified view. Other approaches propose the creation of a central repository of patient's related data, and in this case agents are in charge of accessing the appropriate data when it is required or created. Both approaches can be deployed using traditional agents and also mobile agents.

There are two domains where agents have been widely applied in the last years: decision support systems and planning and coordination activities and services. The first field pursues the implementation of distributed decision-making tools using the best evidence-based practices (e.g. fetal monitoring). In the second case, systems create plans of actions that require the coordination of different partners (human and/or resources), which usually act and plan together and share resources, activities and goals (e.g. emergencies, clinical guidelines).

From a developer's perspective, there are currently some programming languages that may be used to deploy agent-based systems. The most referenced ones are two Java-based APIs called Java Agent Development Environment (JADE, [114]) and NetLogo [115]. Both are freeware and they have been widely adopted by researchers. JADE is used practically in all types of applications, whereas NetLogo concentrates on agent-based simulations.

Another field that has been paid increasing attention in the last years is the adoption of security measures in these distributed systems [78–80, 116, 117]. Health records are very sensitive data and systems that manipulate them must ensure a high level of confidentiality. Security mechanisms in Multi-Agent Systems should be applied from the lowest level of communication to ensure reliable transactions between agents. In this sense, frameworks such as JADE provide several mechanisms that can be adopted in any agent-based application. However, some works of this review have been directly designed as secure platforms in the healthcare domain; for instance, to manage the communication of health medical records across agents enabling different types of roles and permissions [73, 75, 118]. Other works have considered security mechanisms just as an added value of their proposal [47, 81].

Finally, agent-based simulations provide a fine-grained framework for describing complex human behaviour. They formally describe each individual agent's behaviour and let the crowd's global one emerge as a result of the local interactions. Simulations try to model realistic agent behaviour while at the same time trying to keep the computational complexity to an acceptable upper limit. Most of these works are designed for medical education purposes [119–122]. In those systems, the most important requirement is to define the internal rules of behaviour of each agent and the relationships between the agents. Agent-based simulations in healthcare deal with epidemiology (e.g., simulation of hepatitis-C [58]), clinical treatments (e.g. evaluate long-term treatments [123]), health systems (e.g. management of emergencies [88], simulation of large structures of sensors [124, 125]), prevention and delivery of care [38].

Conclusions and future lines of research

The rise of agent-based applications in the healthcare domain permits to foresee a promising future to this area. Their flexibility and modularity permits to create complex distributed systems with a good trade-off between development time, cost and performance of the final product.

Agents are autonomous software entities which can perceive the dynamic character of the surrounding environment and decide in a proactive way the most suitable actions to achieve a given goal, taking into account the preferences of a user. Some agents act on behalf of their users and by being socially active they can communicate with the user, with other agents and with the environment through message exchange or auxiliary devices. The complexity of some healthcare problems and their relatedness to the usual characteristics of agents lead to think that this technology is indeed suitable to design, implement deploy and maintain medical applications.

The activities performed by these agents and their sources of information require to address the issue of the legal implications of the performed actions. Although there are several parties who might be potential perpetrators of a wrongful act (such as the programmer, a third party, the supplier, etc.), most analyses of the responsibility for the use of such software systems (as well as the consequences of such use) focus on the human users or the legal entities on behalf of which these systems are operated, and adopt the legal fiction that anything issuing from these systems is considered to be really issued by the natural or legal persons who use them [126]. In these terms, inappropriate transmission of sensitive data, damages or errors in forecasts of results should be considered as risks and mitigated as much as possible and should be explicited in the contracts before designing, developing and delivering implemented systems.

This survey has analysed a set of papers, mainly published in indexed journals and conferences, which have reported recent applications of agents in the healthcare domain (see Tables 5 and 6). It has to be noticed that only a small subset of these works show a real implementation in healthcare organizations of the presented works, so there is still a long way ahead before agent-based systems are routinely used in medical settings. It must also be remarked that, being a purely academic survey, this study has not analysed agent-based commercial products that may be already in use in medical centres. The enhancement of this survey with the analysis of these solutions is one of our lines of future work.

Table 5 Agent-based applications in healthcare based on intended users

Dimension	References
Healthcare organization-centred	[8, 29, 31, 45–76, 82, 83, 88–90, 93–96, 108, 110, 118–122, 124, 127, 129]
Patient-centred	[17–28, 30, 32, 33, 64, 91, 97–102, 123, 125, 130, 131]
Staff-centred	[34–44, 81, 103, 105–107, 132]

Table 6 Agent-based applications based on type of applications

Dimension	References
Platform	[17, 19, 22, 28, 33–35, 37, 38, 44, 45, 47, 48, 55–57, 62, 63, 66, 68, 69, 73, 75, 76, 90, 102, 106, 108, 118]
Simulation	[26, 27, 29, 30, 38, 40, 43, 49, 52–54, 58–61, 64–67, 70, 88, 89, 110, 119–124]
Monitoring/alarms	[18, 21–25, 29, 32, 36, 42, 44, 57, 91, 97–102, 110, 125, 130–132]
Management of data	[20, 34, 35, 50, 51, 55, 56, 74, 76, 94, 96, 103, 105, 107, 108, 129]
Decision support system	[17, 32, 36, 38–40, 47, 67, 72, 81, 82, 107, 108, 127, 132]
Planning	[8, 19, 31, 41, 46–48, 82, 83, 93, 95]
Security	[35, 71, 73–75, 81, 108, 118, 129]

One of the current lines of research in agent-based applications, which is shared with other disciplines in Computer Science and Artificial Intelligence, is the adoption of Semantic Web data and technologies [127, 128]. Future developments in this field will require the creation of large and structured repositories of ontologies, terminologies, and information models that represent general healthcare processes as well as medical knowledge, services and specialized workflows in order to ease the integration or the re-use of agent-based solutions in more general health systems.

The use of networks of sensors, which monitor the current circumstances of patients, eases the implementation of home-based care and, at the same time, reduces the amount of hospitalizations and its high associated cost. In a near future, these living-at-home systems could add more and more intelligent services in order to proactively prevent abnormal situations that affect the current status and the predicted evolution of the patient. Every day there are news about novel wearable devices that offer more advanced functionalities and collect more physiological signs. These devices can be used by patients but also by the general public, and they can employ unsupervised Machine Learning techniques to build predictive models that can foresee the future health problems the user may suffer. In this sense, the management of these data is crucial in preventive care. Additionally, agents can also change their behaviour dynamically according to the current circumstances of the patient, creating systems that can adapt to a wide range of scenarios. Agents acting autonomously and remotely can be a useful solution to tackle these challenging goals.

Finally, agent-based simulations are a good example of reusing knowledge. Agents enable reusing knowledge easily by defining basic behaviours in a group of collaborative agents. The complexity of agent-based simulations in healthcare is continuously increasing, allowing the study of complex diseases such as diabetes or hepatitis C and even some kinds of cancers. In this context, new studies reuse previous ones and improve their accuracy, precision and coverage. Simulations permit to define and compare current healthcare policies, evaluate new alternatives, and consequently, improve near and future workflow procedures. Thus, this kind of systems may be instrumental in the provision of more efficient and effective care procedures.

References

1. Yen, P.-Y., and Bakken, S., Review of health information technology usability study methodologies. *J Am Med Inform Assoc*. 19: 413–422, 2012.
2. Payne, T.H., Bates, D.W., Berner, E.S., Bernstam, E.V., Covvey, H.D., Frisse, M.E., Graf, T., Greenes, R.A., Hoffer, E.P., Kuperman, G., Lehmann, H.P., Liang, L., Middleton, B., Omenn, G.S., and Ozbolt, J., Healthcare information technology and economics. *J Am Med Inform Assoc*. 20(2):212–217, 2013.
3. Campana, F., Moreno, A., Riaño, D., and Varga, L., K4Care: knowledge-based homecare e-services for an ageing europe. In: Annicchiarico, R., Cortés, U., and Urdiales, C. (Eds.), *Agent technology and e-health software agent technologies and autonomic computing*. Birkhäuser Basel, Basel, Switzerland, pp. 95–115, 2008.
4. Chaudhry, B., Wang, J., Wu, S., Maglione, M., Mojica, W., Roth, E., Morton, S.C., and Shekelle, P.G., Systematic review: impact of health information technology on quality, efficiency, and costs of medical care. *Ann Intern Med*. 144(10):E-12–E-22, 2006.
5. Jennings, N., and Wooldridge, M., Software agents. *IEE Review:*. 17-20, 1996.
6. Wooldridge, M., and Jennings, N. *Intelligent Agents: Theory and Practice Know Eng Rev.* 10(2):115–152, 1995.
7. Hogg, L.M.I., and Jennings, N.R., Socially intelligent reasoning for autonomous agents. *IEEE Transactions on Systems, Man and Cybernetics, Part A: Systems and Humans*. 31(5): 381–393, 2001.
8. Bergenti, F., and Poggi, A., Developing smart emergency applications with multi-agent systems. *International Journal of E-Health and Medical Communications*. 1(4):1–13, 2010.
9. Villar, A., Federici, A., and Annicchiarico, R., Agents and healthcare: a glance to the future. In: Annicchiarico, R., Cortés, U., and Urdiales, C. (Eds.), *Agent technology and e-health*. Whitestein Series in Software Agent Technologies and Autonomic Computing. Birkhäuser Verlag, Basel, Switzerland, pp. 141–148, 2008.
10. Pickering, B.W., Litell, J.M., Herasevich, V., and Gajic, O., Clinical review: the hospital of the future - building intelligent environments to facilitate safe and effective acute care delivery. *Crit Care*. 16(2), 2012.
11. Isern, D., Sánchez, D., and Moreno, A., Agents applied in health care: a review. *Int J Med Inf.* 75(3):145–166, 2010.
12. Fosso Wamba, S., Anand, A., and Carter, L., A literature review of RFID-enabled healthcare applications and issues. *Int J Inf Manag*. 33(5):875–891, 2013.
13. Nealon, J.L., and Moreno, A., Agent-based applications in health care. In: Nealon, J.L., and Moreno, A. (Eds.), *Applications of*

software agent technology in the health care domain. Whitestein Series in Software Agent Technologies and Autonomic Computing. Birkhäuser Verlag, Basel, Switzerland, pp. 3–18, 2003.

14. Družovec, M., Welzer, T., and Brumen, B., Agent oriented approach to handling medical data. *J Med Syst*. 29(1):45–57, 2005.
15. Fox, J., Glasspool, D., and Modgil, S., A canonical agent model for healthcare applications. *IEEE Intell Syst*. 21(6): 21–28, 2006.
16. Vieira-Marques, P.M., *Agent based virtual electronic patient record*. Universitat Autónoma de Barcelona, Bellaterra, 2014.
17. Isern, D., Moreno, A., Sánchez, D., Hajnal, A., Pedone, G., and Varga, L.Z., Agent-based execution of personalised home care treatments. *Appl Intell*. 34(2):155–180, 2011.
18. Kafalı, Ö., Bromuri, S., Sindlar, M., van der Weide, T., Aguilar Pelaez, E., Schaechtle, U., Alves, B., Zufferey, D., Rodriguez-Villegas, E., Schumacher, M.I., and Stathis, K., COMMODITY12: a smart e-health environment for diabetes management. *Journal of Ambient Intelligence and Smart Environments*. 5(5):479–502, 2013.
19. Su, C.-J., and Chiang, C.-Y., IAServ: an intelligent home care web services platform in a cloud for aging-in-place. *Int J Environ Res Public Health*. 10(11):6106–6130, 2013.
20. De Meo, P., Quattrone, G., and Ursino, D., Integration of the HL7 standard in a multiagent system to support personalized access to e-health services. *IEEE Trans Know Data Eng*. 23(8):1244–1260, 2011.
21. Wang, M.H., Lee, C.S., Hsieh, K.L., Hsu, C.Y., Acampora, G., and Chang, C.C., Ontology-based multi-agents for intelligent healthcare applications. *J Ambient Intell Humaniz Comput*. 1(2): 111–131, 2010.
22. Kaluža, B., Cvetković, B., Dovgan, E., Gjoreski, H., Gams, M., Luštrek, M., and Mirchevska, V., A multi-agent care system to support independent living. *Int J Artif Intell Tools*. 23(01): 1440001, 2014.
23. Sahli, N., Jabeura, N., and Badra, M., Agent-based framework for sensor-to-sensor personalization. *Journal of Computer and System Sciences*. 81(3):487–495, 2015.
24. Castro Garrido, P., Luque Ruiz, I., and Gómez-Nieto, M., OBCAS: an agent-based system and ontology for mobile context aware interactions. *J Intell Inf Syst*. 43(1):33–57, 2014.
25. Villarrubia, G., Bajo, J., Paz, J.F.D., and Corchado, J.M., Monitoring and detection platform to prevent anomalous situations in home care. *Sensors (Switzerland)*. 14(6):9900–9921, 2014.
26. Vettier, B., and Garbay, C., Abductive agents for human activity monitoring. *Int J Artif Intell Tools*. 23(01):1440002, 2014.
27. Wang, Z., and Paranjape, R., The self-aware diabetic patient software agent model. *Comput Biol Med*. 43(11):1900–1909, 2013.
28. Tapia, D.I., Fraile, J.A., Rodríguez, S., Alonso, R.S., and Corchado, J.M., Integrating hardware agents into an enhanced multi-agent architecture for ambient intelligence systems. *Inf Sci*. 222(0):47–65, 2013.
29. Rodríguez, S., De Paz, J.F., Villarrubia, G., Zato, C., Bajo, J., and Corchado, J.M., Multi-agent information fusion system to manage data from a WSN in a residential home. *Information Fusion*. 23: 43–57, 2015.
30. Vaidehi, V., Vardhini, M., Yogeshwaran, H., Inbasagar, G., Bhargavi, R., and Hemalatha, C.S., Agent based health monitoring of elderly people in indoor environments using wireless sensor networks. *Procedia Computer Science*. 19(0):64–71, 2013.
31. Nieves, J.C., Lindgren, H., and Cortés, U., Agent-based reasoning in medical planning and diagnosis combining multiple strategies. *Int J Artif Intell Tools*. 23(01):1440004, 2014.
32. Lisetti, C., Amini, R., Yasavur, U., and Rishe, N., I can help you change! An empathic virtual agent delivers behavior change health interventions. *ACM Trans Manag Inf Syst*. 4(4):1–28, 2013.
33. Bielskis, A.A., Denisovas, V., Drungilas, D., Gricius, G., and Dzemydiene, D., Multi-agent-based human computer interaction of E-health care system for people withmovement disabilities. *Elektronika ir Elektrotechnika*. 7:77–82, 2010.
34. Bouzguenda, L., and Turki, M., Designing an architectural style for dynamic medical cross-organizational workflow management system: an approach based on agents and web services. *J Med Syst*. 38(4):1–32, 2014.
35. Liu, C.-H., Chung, Y.-F., Chiang, T.-W., Chen, T.-S., and Wang, S.-D., A mobile agent approach for secure integrated medical information systems. *J Med Syst*. 36(5):2731–2741, 2012.
36. Chen, J.-J., Wang, P.-W., Huang, Y.-C., and Yen, H.-C., Applying ontology techniques to develop a medication history search and alert system in department of nuclear medicine. *J Med Syst*. 36(2): 737–746, 2012.
37. Moghaddam, M.K., Shojafar, M., Nami, M.R., and Rashidi, H., An efficient multi-agent system for E-health functionalities. *International Journal of Software Engineering and its Applications*. 7(3):23–34, 2013.
38. Sokolova, M.V., and Fernández-Caballero, A., Evaluation of environmental impact upon human health with DeciMaS framework. *Exp Syst Appl*. 39(3):3469–3483, 2012.
39. Sayyad Shirabad, J., Wilk, S., Michalowski, W., and Farion, K., Implementing an integrative multi-agent clinical decision support system with open source software. *J Med Syst*. 36(1):123–137, 2012.
40. Taboada, M., Cabrera, E., Iglesias, M.L., Epelde, F., and Luque, E., An agent-based decision support system for hospitals emergency departments. *Procedia Computer Science*. 4:1870–1879, 2011.
41. Sokolova, M.V., and Fernández-Caballero, A., Hybrid models in agent-based environmental decision support. *Applied Soft Computing*. 11(8):5243–5258, 2011.
42. Ji, Y., Ying, H., Farber, M.S., Yen, J., Dews, P., Miller, R.E., and Massanari, R.M., A distributed, collaborative intelligent agent system approach for proactive postmarketing drug safety surveillance. *IEEE Trans Inf Technol Biomed*. 14(3):826–837, 2010.
43. Grimaldo, F., Orduña, J.M., Lozano, M., and Ródenas, F., Towards a simulator of integrated long-term care systems for elderly people. *Int J Artif Intell Tools*. 23(01):1440005, 2014.
44. Grando, M.A., Peleg, M., Cuggia, M., and Glasspool, D., Patterns for collaborative work in health care teams. *Artif Intell Med*. 53(3): 139–160, 2011.
45. Jain P Architectural design of a multi agent enterprise knowledge management system (MAEKMS) for e-health. In: International Conference on Information Systems and Computer Networks (ISCON), 2014 Mathura, India, March 01–02 2014. pp 93–98
46. Pajares Ferrando, S., and Onaindia, E., Context-aware multi-agent planning in intelligent environments. *Inf Sci*. 227:22–42, 2013.
47. Isern, D., Sánchez, D., and Moreno, A., Ontology-driven execution of clinical guidelines. *Comput Meth Prog Biomed*. 107(2): 122–139, 2012.
48. Bhat S, Sidnal NS, Manvi SS Agent based approach in accessing distributed health care services. In: 2nd International Conference on the Emerging Areas of Security-Enriched Urban Computing and Smart Grids, SUComS 2011, Hualien, Taiwan, 2011. Communications in computer and information science. Springer Berlin Heidelberg, pp 212-221
49. Xuyan, X., and Lefei, L., An artificial urban healthcare system and applications. *IEEE Intell Syst*. 25(3):63–73, 2010.

50. Nguyen, M.T., Fuhrer, P., and Pasquier-Rocha, J., Enhancing E-health information systems with agent technology. *International Journal of Telemedicine and Applications*. 2009:1–14, 2009.
51. Bouchoul, F., and Mostefai, M., Agent-services and mobile agents for an integrated HCIS. *International Journal of Computer Integrated Manufacturing*. 22(5):458–471, 2009.
52. Silverman, B.G., Hanrahan, N., Bharathy, G., Gordon, K., and Johnson, D., A systems approach to healthcare: agent-based modeling, community mental health, and population well-being. *Artif Intell Med*. 63(2):61–71, 2015.
53. Taboada, M., Cabrera, E., Epelde, F., Iglesias, M.L., and Luque, E., Using an agent-based simulation for predicting the effects of patients derivation policies in emergency departments. *Procedia Computer Science*. 18:641–650, 2013.
54. Dunn, A.G., Ong, M.-S., Westbrook, J.I., Magrabi, F., Coiera, E., and Wobcke, W., A simulation framework for mapping risks in clinical processes: the case of in-patient transfers. *J Am Med Inform Assoc*. 18(3):259–266, 2011.
55. Cardoso, L., Marins, F., Portela, F., Santos, M., Abelha, A., and Machado, J., The next generation of interoperability agents in healthcare. *Int J Environ Res Public Health*. 11(5):5349–5371, 2014.
56. Cardoso, L., Marins, F., Portela, F., Abelha, A., and Machado, J., Healthcare interoperability through intelligent agent technology. *Procedia Technology*. 16(0):1334–1341, 2014.
57. Corchado, J.M., Tapia, D.I., and Bajo, J., A multi-agent architecture for distributed services and applications. *Int J Innovative Comput Inf Contr*. 8(4):2453–2476, 2012.
58. Wasik, S., Jackowiak, P., Figlerowicz, M., and Blazewicz, J., Multi-agent model of hepatitis C virus infection. *Artif Intell Med*. 60(2):123–131, 2014.
59. Pollmächer, J., and Figge, M.T., Agent-based model of human alveoli predicts chemotactic signaling by epithelial cells during early Aspergillus fumigatus infection. *PLoS ONE*. 9(10), 2014.
60. Mao, L., Modeling triple-diffusions of infectious diseases, information, and preventive behaviors through a metropolitan social network—an agent-based simulation. *Applied Geography*. 50(0): 31–39, 2014.
61. Kasaie, P., Andrews, J.R., Kelton, W.D., and Dowdy, D.W., Timing of tuberculosis transmission and the impact of household contact tracing: an agent-based simulation model. *Am J Respir Crit Care Med*. 189(7):845–852, 2014.
62. Cuadros, D.F., Abu-Raddad, L.J., Awad, S.F., and García-Ramos, G., Use of agent-based simulations to design and interpret HIV clinical trials. *Comput Biol Med*. 50(0):1–8, 2014.
63. Crooks, A.T., and Hailegiorgis, A.B., An agent-based modeling approach applied to the spread of cholera. *Environmental Modelling & Software*. 62(0):164–177, 2014.
64. Laskowski, M., Duvvuri, V.R., Buckeridge, D.L., Wu, G., Wu, J., and Moghadas, S.M., Influenza H3N2 variant viruses with pandemic potential: preventing catastrophe in remote and isolated Canadian communities. *Prev Med*. 57(6):910–913, 2013.
65. Murphy, J.T., Walshe, R., and Devocelle, M., A theoretical analysis of the prodrug delivery system for treating antibiotic-resistant bacteria. *IEEE/ACM Trans Comput Biol Bioinform*. 8(3):650–658, 2011.
66. Laskowski, M., Demianyk, B.C.P., Witt, J., Mukhi, S.N., Friesen, M.R., and McLeod, R.D., Agent-based modeling of the spread of influenza-like illness in an emergency department: a simulation study. *IEEE Trans Inf Technol Biomed*. 15(6):877–889, 2011.
67. Sokolova, M.V., and Fernández-Caballero, A., Modeling and implementing an agent-based environmental health impact decision support system. *Exp Syst Appl*. 36(2, Part 2):2603–2614, 2009.
68. Salman, O.H., Rasid, M.F., Saripan, M.I., and Subramaniam, S.K., Multi-sources data fusion framework for remote triage prioritization in telehealth. *J Med Syst*. 38(9):1–103, 2014.
69. Jørgensen D, Hallenborg K, Demazeau Y (2014) Assessment of Agent Architectures for Telehealth. In: Corchado J, Bajo J, Kozlak J et al. (eds) Highlights of Practical Applications of Heterogeneous Multi-Agent Systems. The PAAMS Collection, vol 430. Communications in Computer and Information Science. Springer International Publishing, pp 79–88
70. Tracey, J.A., Bevins, S.N., Vandewoude, S., and Crooks, K.R., An agent-based movement model to assess the impact of landscape fragmentation on disease transmission. *Ecosphere*. 5(9), 2014.
71. Järvinen, H., Garcia-Gasulla, D., and Cortés, U., A push-based agent communication model empowering assistive technologies. *Int J Artif Intell Tools*. 23(01):1440003, 2014.
72. Wu, C.S., Khoury, I., and Shah, H., Optimizing medical data quality based on multiagent web service framework. *IEEE Trans Inf Technol Biomed*. 16(4):745–757, 2012.
73. Nikooghadam, M., and Zakerolhosseini, A., Secure communication of medical information using mobile agents. *J Med Syst*. 36(6):3839–3850, 2012.
74. Liu, C.-H., Chung, Y.-F., Chen, T.-S., and Wang, S.-D., Mobile agent application and integration in electronic anamnesis system. *J Med Syst*. 36(3):1009–1020, 2012.
75. Chen, T.-L., Chung, Y.-F., and Lin, F.S., Deployment of secure mobile agents for medical information systems. *J Med Syst*. 36(4): 2493–2503, 2012.
76. Yang, X., and Miao, Y., Distributed agent based interoperable virtual EMR system for healthcare system integration. *J Med Syst*. 35(3):309–319, 2011.
77. Moreno, A., Isern, D., and Sánchez, D., Provision of agent-based health care services. *AI Commun*. 16(3):167–178, 2003.
78. Rashvand, H.F., Salah, K., Calero, J.M.A., and Harn, L., Distributed security for multi-agent systems – review and applications. *IET Information Security*. 4(4):188–201, 2010.
79. Jung, Y., Kim, M., Masoumzadeh, A., and Joshi, J.B.D., A survey of security issue in multi-agent systems. *Artif Intell Rev*. 37(3): 239–260, 2012.
80. van Deursen, N., Buchanan, W.J., and Duff, A., Monitoring information security risks within health care. *Computers & Security*. 37(0):31–45, 2013.
81. González-Vélez, H., Mier, M., Julià-Sapé, M., Arvanitis, T.N., García-Gómez, J.M., Robles, M., Lewis, P.H., Dasmahapatra, S., Dupplaw, D., Peet, A., Arús, C., Celda, B., Huffe, S.V., and Lluch-Ariet, M., HealthAgents: distributed multi-agent brain tumor diagnosis and prognosis. *Appl Intell*. 30(3):191–202, 2009.
82. Chennaoui, A., and Paquet, M., Multi-agent decision-making support model for the management of Pre-hospital emergency services. *Journal of Machine Learning and Computing*. 4(2):198–203, 2014.
83. Braubach L, Pokahr A, Lamersdorf W (2014) Negotiation-based Patient Scheduling in Hospitals - Reengineering Message-based Interactions with Services. In: Iantovics B, Kountchev R (eds) Advanced Intelligent Computational Technologies and Decision Support Systems, vol 486. Studies in Computational Intelligence. Springer Verlag, pp 107–121
84. Kardas, G., Challenger, M., Yildirim, S., and Yamuc, A., Design and implementation of a multiagent stock trading system. *Software - Practice and Experience*. 42(10):1247–1273, 2012.
85. Isern, D., Abelló, S., and Moreno, A., Development of a multi-agent system simulation platform for irrigation scheduling with case studies for garden irrigation. *Comput Elect Agric*. 87:1–13, 2012.
86. Gorochowski, T.E., Matyjaszkiewicz, A., Todd, T., Oak, N., Kowalska, K., Reid, S., Tsaneva-Atanasova, K.T., Savery, N.J., Grierson, C.S., and di Bernardo, M., BSim: an agent-based tool

for modeling bacterial populations in systems and synthetic biology. *PLoS ONE*. 7(8), 2012.

87. Koelling P, Schwandt MJ Health Systems: A Dynamic System—Benefits From System Dynamics. In: Kuhl ME, Steiger NM, Armstrong FB, Joines JA (eds) Winter Simulation Conference, Orlando, FL, USA, December 4–7 2005. IEEE Press, pp 1321–1327
88. Ramsey, G.W., Evaluating policies using agent-based simulations: investigating policies for continuity of care. *International Journal of Simulation and Process Modelling*. 9(4):255–269, 2014.
89. Lukens, S., DePasse, J., Rosenfeld, R., Ghedin, E., Mochan, E., Brown, S., Grefenstette, J., Burke, D., Swigon, D., and Clermont, G., A large-scale immuno-epidemiological simulation of influenza a epidemics. *BMC Public Health*. 14(1):1019, 2014.
90. Doumbouya, M.B., Kamsu-Foguem, B., Kenfack, H., and Foguem, C., Telemedicine using mobile telecommunication: towards syntactic interoperability in teleexpertise. *Telematics and Informatics*. 31(4):648–659, 2014.
91. Ayala, I., Amor, M., and Fuentes, L., Self-configuring agents for ambient assisted living applications. *Personal Ubiquitous Comput*. 17(6):1159–1169, 2013.
92. Moreno A (2014) Special Issue on New Perspectives on the Use of Agents in Health Care; Guest Editor: A. Moreno. Int J Artif Intell Tools 23 (01):1402001
93. Domnori E, Cabri G, Leonardi L Designing and implementing intelligent agents for e-health. In: 2nd International Conference on Emerging Intelligent Data and Web Technologies, EIDWT 2011, Tirana, 2011. pp 78–85
94. Silva-Ferreira PR, Patriarca-Almeida JH, Vieira-Marques PM, Cruz-Correia RJ Improving expressiveness of agents using openEHR to retrieve multi-institutional health data: Feeding local repositories through HL7 based providers. In: Information Systems and Technologies (CISTI), 2012 7th Iberian Conference on, 20–23 June 2012. pp 1–5
95. Qi, J., Zhang, S., Li, L., and Sun, Y., Cognitive networks available resource health assessment model based on intelligent agent. *Advances in Information Sciences and Service Sciences*. 4(5): 226–234, 2012.
96. Chen, T.-L., Chung, Y.-F., and Lin, F.S., A study on agent-based secure scheme for electronic medical record system. *J Med Syst*. 36(3):1345–1357, 2012.
97. Su, C.J., and Shih, S.C., Building distributed E-healthcare for elderly using RFID and multi-agent. *International Journal of Engineering Business Management*. 3(1):16–26, 2011.
98. Lo, C.-Y., Construction of real-time weight control intelligent recommendation system using multi-agent mechanism. *Advanced Science Letters*. 9(1):30–37, 2012.
99. Aziz, A.A., Klein, M.C.A., and Treur, J., An integrative ambient agent model for unipolar depression relapse prevention. *Journal of Ambient Intelligence and Smart Environments*. 2(1):5–20, 2010.
100. Wang M-H, Lee C-S, Hsieh K-L, Hsu C-Y, Chang C-C Intelligent Ontological Multi-Agent for Healthy Diet Planning. In: Jeon HT, Min KC, Oh K-W (eds) 18th IEEE International Conference on Fuzzy Systems, FUZZ-IEEE 2009, ICC jeju, jeju island, Korea, 2009. IEEE Computer Society, pp 751–756
101. Fuketa, M., Morita, K., and Aoe, J.I., Agent-based communication systems for elders using a reminiscence therapy. *International Journal of Intelligent Systems Technologies and Applications*. 12(3–4):254–267, 2013.
102. Su, C.-J., and Wu, C.-Y., JADE implemented mobile multi-agent based, distributed information platform for pervasive health care monitoring. *Applied Soft Computing*. 11(1):315–325, 2011.
103. Su, C.-J., and Peng, C.W., Multi-agent ontology-based web 2.0 platform for medical rehabilitation. *Exp Syst Appl*. 39(12):10311–10323, 2012.
104. Su, C.J., Chiang, C.Y., and Chih, M.C., Ontological knowledge engine and health screening data enabled ubiquitous personalized physical fitness (UFIT). *Sensors (Switzerland)*. 14(3):4560–4584, 2014.
105. Bovenkamp, E.G.P., Dijkstra, J., Bosch, J.G., and Reiber, J.H.C., User-agent cooperation in multiagent IVUS image segmentation. *IEEE Trans Med Imaging*. 28(1):94–105, 2009.
106. McShane, M., Beale, S., Nirenburg, S., Jarrell, B., and Fantry, G., Inconsistency as a diagnostic tool in a society of intelligent agents. *Artif Intell Med*. 55(3):137–148, 2012.
107. Fox, J., Gutenstein, M., Khan, O., South, M., and Thomson, R., OpenClinical.net: a platform for creating and sharing knowledge and promoting best practice in healthcare. *Computers in Industry*. 66:63–72, 2015.
108. Xiao, L., Hu, B., Croitoru, M., Lewis, P., and Dasmahapatra, S., A knowledgeable security model for distributed health information systems. *Computers & Security*. 29(3):331–349, 2010.
109. Landau, R., Ambient intelligence for the elderly: hope to age respectfully? *Aging Health*. 9(6):593–600, 2013.
110. Chen, B., Agent-based artificial immune system approach for adaptive damage detection in monitoring networks. *Journal of Network and Computer Applications*. 33(6):633–645, 2010.
111. Blobel, B., Goossen, W., and Brochhausen, M., Clinical modeling—a critical analysis. *Int J Med Inf*. 83(1):57–69, 2014.
112. Valls, A., Gibert, K., Sánchez, D., and Batet, M., Using ontologies for structuring organizational knowledge in home care assistance. *Int J Med Inf*. 79(5):370–387, 2010.
113. Pisanelli, D.M. (Ed.), *Ontologies in medicine, vol 102*. Studies in Health Technology and Informatics. IOS Press, Amsterdam, The Netherlands, 2004.
114. Bellifemine, F., Caire, G., and Greenwood, D., *Developing multi-agent systems with JADE. Wiley series in agent technology*. John Wiley and Sons, Chichester, England, 2007.
115. Sklar, E., Software review: NetLogo, a multi-agent simulation environment. *Artif Life*. 13(3):303–311, 2007.
116. Fernández-Alemán, J.L., Señor, I.C., Lozoya, P.Á.O., and Toval, A., Security and privacy in electronic health records: a systematic literature review. *J Biomed Inf*. 46(3):541–562, 2013.
117. Cavalcante, R.C., Bittencourt, I.I., da Silva, A.P., Silva, M., Costa, E., and Santos, R., A survey of security in multi-agent systems. *Exp Syst Appl*. 39(5):4835–4846, 2012.
118. Hsu, W.S., and Pan, J.I., Secure mobile agent for telemedicine based on P2P networks. *J Med Syst*. 37(3), 2013.
119. Wei, D., Xiaogang, Q., Zhidong, C., Xiaolong, Z., and Kainan, C., Heterogeneous and stochastic agent-based models for analyzing infectious diseases' super spreaders. *IEEE Intell Syst*. 28(4):18–25, 2013.
120. Sarpe, V., and Jacob, C., Simulating the decentralized processes of the human immune system in a virtual anatomy model. *BMC Bioinf*. 14(SUPPL6), 2013.
121. Wang KL, Reed NE, Vincent DS (2009) A Multi-Agent Simulation of Kidney Function for Medical Education. In: Paranjape R, Sadanand A (eds) Multi-Agent Systems for Healthcare Simulation and Modeling: Applications for System Improvement. pp 178–194
122. Peng Q, Niu Q, Xie Y, ElMekkawy T (2009) Operating Room Simulation and Agent-Based Optimization. In: Paranjape R, Sadanand A (eds) Multi-Agent Systems for Healthcare Simulation and Modeling: Applications for System Improvement. pp 69–89
123. Hoogendoorn, M., Klein, M.C.A., Memon, Z.A., and Treur, J., Formal specification and analysis of intelligent agents for model-based medicine usage management. *Comput Biol Med*. 43(5): 444–457, 2013.

124. Zhao X, Yuan S, Zhou H, Sun H, Qiu L (2009) An evaluation on the multi-agent system based structural health monitoring for large scale structures. *Exp Syst Appl* 36 (3, Part 1):4900–4914
125. Costa, A., Novais, P., and Simoes, R., A caregiver support platform within the scope of an ambient assisted living ecosystem. *Sensors (Switzerland)*. 14(3):5654–5676, 2014.
126. Dahiyat, E.A.R., Intelligent agents and liability: is it a doctrinal problem or merely a problem of explanation? *Artif Intell Law*. 18(1):103–121, 2010.
127. Sanchez, E., Toro, C., Artetxe, A., Graña, M., Sanin, C., Szczerbicki, E., Carrasco, E., and Guijarro, F., Bridging challenges of clinical decision support systems with a semantic approach. A case study on breast cancer. *Pattern Recognit Lett*. 34(14):1758–1768, 2013.
128. Eccher, C., Scipioni, A., Miller, A.A., Ferro, A., and Pisanelli, D.M., An ontology of cancer therapies supporting interoperability and data consistency in EPRs. *Comput Biol Med*. 43(7):822–832, 2013.
129. Urovi V, Olivieri AC, Torre ABdl, Bromuri S, Fornara N, Schumacher M (2014) Secure P2P cross-community health record exchange in IHE compatible systems. *Int J Artif Intell Tools* 23 (01):1440006
130. Nouira, K., and Trabelsi, A., Intelligent monitoring system for intensive care units. *J Med Syst*. 36(4):2309–2318, 2012.
131. García-Vázquez, J.P., Rodríguez, M.D., Tentori, M.E., Saldaña, D., Andrade, Á.G., and Espinoza, A.N., An agent-based architecture for developing activity-aware systems for assisting elderly. *J Univers Comput Sci*. 16(12): 1500–1520, 2010.
132. Su, C.-J., and Chu, T.-W., A mobile multi-agent information system for ubiquitous fetal monitoring. *Int J Environ Res Public Health*. 11(1):600–625, 2014.