A Survey on Agents Applications in Healthcare: Opportunities, Challenges and Trends

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Abstract

Background and Objective: The *agent* abstraction is a powerful one, developed decades ago to represent crucial aspects of artificial intelligence research. The meaning has transformed over the years and now there are different nuances across research communities. At its core, an agent is an autonomous computational entity capable of sensing, acting, and capturing interactions with other agents and its environment. This review examines how agent-based techniques have been implemented and evaluated in a specific and very important domain, i.e. healthcare research.

Methods: We survey key areas of agent-based research in healthcare, e.g. individual and collective behaviours, communicable and non-communicable diseases, and social epidemiology. We propose a systematic search and critical review of relevant recent works, introduced by an exploratory network analysis.

Results: Network analysis enables to devise out 5 main research clusters, the most active authors, and 4 main research topics.

Conclusions: Our findings support discussion of some future directions for increasing the value of agent-based approaches in healthcare.

Keywords: Healthcare, agent-based research, literature survey, network analysis

1. Introduction

In computer science research, the concept of *agent* is one of the most relevant and significant, particularly in the field of Artificial Intelligence (AI) [1]. The term is multifaceted to be declined in many practical uses and several possible applications. Moreover, over the years, agent-oriented methodologies have been adapted to multiple domains, such as engineering, technological development, or organisational studies. Disciplines of interest expand beyond computer science to economics, sociology, humanities, healthcare. This last topic is of particular interest because of the relevance in itself, and also because of the organisational difficulties due to the unpredictability of the specific domain, the continuous scientific and technological progress, and the interdependence of the different factors (and actors) involved. Moreover, recent years have seen major advances in technology that have impacted healthcare, such as parallel computing or neural networks (e.g., medical imaging), new mobile and cellular technologies in cyber-physical systems, Internet of Medical Things (IoMT), as well as cloud environments for hospital information systems. These areas are very complex, and the need for interaction between different actors is important as emerged in the recent

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pandemic emergency. All are increasingly interdisciplinary areas in which the concept of agent and the agent-oriented paradigm can play a relevant role in improving the analysis and understanding of complex systems, the engineering of distributed systems, and the design of human-computer interactions.

In this paper, we propose a literature review of the agent concept in healthcare studies by considering a broad concept of health. In fact, we focus on both studies concerning particular diseases of the individual and concrete applications for management in the health sector. In addition, we deal with both research on agent-based systems in the traditional sense, but also the most recent research on modelling the processes of virus spread, as well as on device systems aimed at preventing and treating health conditions, such as IoMT or assistive technologies that include the adoption of conversational interfaces (such as chatbots or voice assistants). Our survey covers the years 2015 - mid 2022, a period not covered by previous relevant literature reviews. We introduce our study by performing a semantic network analysis based on relevant terms of a large selection of scientific papers in the subject. Social network analysis (SNA) provides meaningful insights in an automated way while also facilitating the qualitative analysis [2]. In particular, we built networks of citations (i), co-authors (ii), and co-occurrences of terms from the abstracts (iii). In (i), we detect most influential research works cited by selected recent papers. By (ii) we identify the most prolific and strongest research groups, while with (iii) we automatically identify the main research terms, topics, and subjects of research. After this exploratory analysis, we deepen the survey by focusing on a selection of about 150 papers with a manual inspection and categorisation of each. We emphasise that the foremost goal of this survey is to overview the state of the art in utilisation of agent technologies and models in the healthcare domain, by carefully and thoroughly analysing the most mature research contributions available. In doing so, we give up exhaustiveness of our research to keep the collected papers to a manageable number allowing for manual analysis.

1.1. The concept of agent and multi-agent system

The concept of *agent* was originally proposed as a synonym for automaton, i.e. a computational entity endowed with a certain degree of operational *autonomy* [3]. The concept then evolved into a cornerstone of AI research, denoting a software entity capable of three fundamental activities [1]:

(i) perceiving stimuli from outside (e.g. a computational or physical environment) to understand what the current situation is,

(ii) deciding what goals to pursue given such stimuli and how to achieve such goals, and

(iii) acting as needed to progress towards goal achievement, e.g. by operating in the environment or by communicating with other co-existing agents.

The possibility of communicating and, more generally, of interacting with other agents gave birth to the whole research area of *multi-agent systems*, concerned with the models and technologies required to let a collective of cooperating or competing agents achieve some system goals in effective and efficient ways, as a form of distributed AI [4].

Finally, with the resurgence of machine learning approaches under the deep learning paradigm, the agent concept expanded to include entities capable of learning how to act in a given environment, especially through techniques belonging to or stemming from the research area of reinforcement learning and multi-agent reinforcement learning [5, 6].

In the computer science research literature, the most traditional studies concern systems of autonomous decision-making entities that need to communicate or coordinate with each other, in the perspective of *Multi-agent systems* (MAS) composed of intelligent and situated agents [3]. Another typical research area involves computational frameworks to address the construction of the software, i.e. *Agent-oriented programming* [7]. A software engineering approach is also defined *Agent-oriented modeling* [8] as well as *Agent-Oriented Software Engineering* (AOSE) [9].

A more recent perspective focused on the interactions among individual autonomous entities to understand macro phenomena emerging from micro-scale behaviour is called *Agent-based modeling* (ABM) [10]. It is usually adopted as a prominent approach to model complex systems dynamics, according to the vision of *the whole is more than the sum of its parts*, being particularly effective in modelling internal behaviours of involved entities as well as mechanisms of interactions and mutual interplay.

Finally, another recent perspective involves *Conversational agents*, i.e. the adoption of software entities exploiting unconstrained natural language input and output capabilities.

1.2. Challenges of healthcare informatics

Agents and multi-agent systems can be an effective solution for many challenges that emerged in the process of digitalisation of healthcare services.

In this Section, we report some of the main healthcare contexts, and their properties, that literature demonstrates can be improved if an agent approach is adopted, as we are reviewing in this paper.

Distributed Systems. Patients during the diagnosis process typically go through a various set of examinations, as well as during care and treatments typically exploit a set of services, that are delivered in an intrinsically distributed way. This is even more prominent if we think at the advance of telemedicine and telecare, that is long since envisioned as one of the way to revolutionise the management of a wide spectrum of medical conditions [11], but bootstrapped by the recent pandemic global situation. Both the physical infrastructure, *i.e.* medical devices of any type, and human expertise, are distributed across care-facilities and home environments, and must be integrated and coordinated to guarantee a better care. In particular, data acquired from different sources must be available everywhere and at any time to enable fast diagnosis and treatment.

Given that medical systems and infrastructures are intrinsically distributed, agents and multi-agent systems are demonstrated to provide a suitable and effective modelling method and programming paradigm for distributed systems, since they are software entities that can live and autonomously act across different devices and nodes of a network [12].

Intelligent Systems. Another interesting thread of novel applications concerns the design of systems that can support *(i)* domain experts in the diagnosis and treatment processes, and *(ii)* patients in the adherence to the therapy, in maintaining a healthy life style, and generally in self-managing their condition.

Clinical decision support systems, recommender systems, chatbots, all fall in this context. They are usually based on AI technologies to automatise recognition and reasoning processes. Among the others, also agents are adopted since they can be programmed to manifest intelligent behaviour by autonomously observing external facts on top of which they reason and provide suggestions and alerts.

Conversational agents are an example in this context: they provide an interface between digital and human by answering questions, suggesting or reminding therapies and healthy life styles, acquiring data and accordingly providing support to decision making [13].

Simulation. Mainly in biomedical research, but also in industrial contexts, modelling and simulation techniques play an important role in the design of novel devices and equipment. Through simulation, prediction, explanation and forecasting are performed, as well as what-if analysis to evaluate in-silico and prior production if the designed system works as expected and how it behaves in different scenarios, such as external situations or internal failures.

Several works adopted ABM in health topics, as described in similar general surveys [14] and special surveys, e.g. ABM of chronic diseases [15] or noncommunicable diseases [16]. Moreover, simulation is adopted in the analysis of organisational processes, for instance with the goal to optimise care paths, or in biomedical research to model diseases, or to identify drugs and their interaction with human organs.

The remainder of the paper is organised as follows: we first introduce the methodology of the proposed literature review in Section 2. Section 3 describes the exploratory network analysis. Section 4 anticipates the upcoming detailed analysis of the surveyed papers with a bird-eye view of the trends, prospects, and challenges arising. Section 5 thoroughly comments on the literature review results. Section 6 provides a discussion to conclude the paper.

2. Methods

For the sake of reproducibility, we here fully describe the research method adopted to select relevant papers in the domain of interest, and the social network metrics adopted to perform an exploratory analysis of the corresponding research landscape.

2.1. Search parameters

We searched for papers by using keywords related to the agent abstraction and technology, as well as to the healthcare domain. Such keywords were composed in a search string of two parts[1] as follows:

- “agent based”, “multi agent”, “agent oriented”, “agent technology”, “conversational agent”, “agent language”, “agent programming” formed the first part of the search string. Common variations of such terms and compositions have also been considered, such as “agent-based” instead of “agent based”, and “agent technologies” instead of the singular form.
- “health”, “healthcare”, “health care”, or “medicine” formed the second part of the search string, connected with a logical AND to the first part

We limited the temporal extension of the considered papers to the window between January 1st, 2015 to July 1st, 2022, to avoid overlap with previous surveys on the same subject [17, 18].

The search was conducted on three popular bibliographic databases, ACM Digital Library, IEEE eXplore and Scopus, and limited to journal and conference publications. Although we believe that Scopus satisfactorily covers the relevant scientific landscape, we noticed some missing articles that were present in the other datasets (e.g. those very close to the closing date of the period we considered).

This resulted in 2,941 distinct papers, that have been collected in a PostgreSQL database (available in the code repository), with the following data and meta-data: title, authors, abstract, keywords (when available), and publication venue.

The whole pipeline, whose remainder is described in the next Subsections, is depicted in Figure 1.

2.2. Network Analysis

Based on the whole pool of 2,941 papers, we performed an automated exploratory analysis with the goal of detecting the most relevant research topics and communities. For the purpose, we exploited Social Network Analysis (SNA) techniques, that are described in this Section. Network analysis typically helps to explore

[1] The code repository: https://github.com/sulemil/ag4he

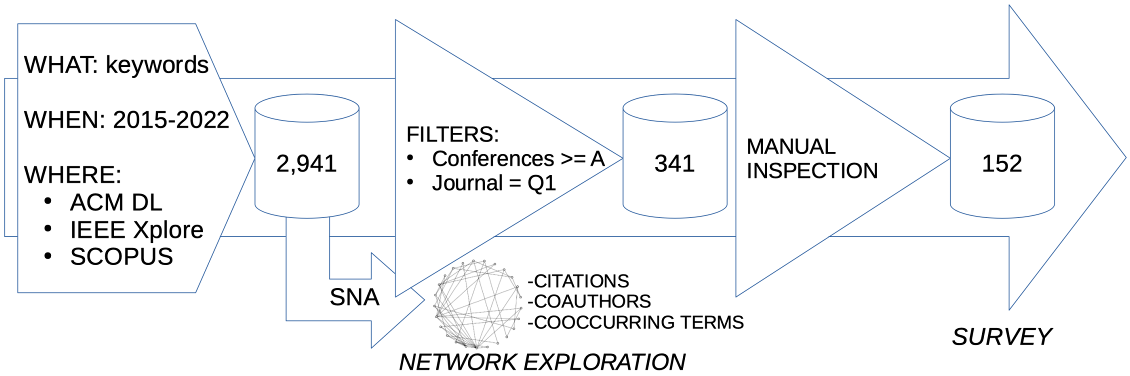

Figure 1: Search, analysis, and selection pipeline.

the links (edges) that exist between entities (vertices or nodes) in a graph [19]. If there is a meaning in the direction of the edges, the graph is oriented (directed network), otherwise it is an undirected network. Results of such analysis are delivered in Section 3.

Metrics. The metrics that can be computed on the graph give an idea of what the *structure* of the overall network looks like, or of the *importance* of a particular node or edge with respect to the others. As described below, the main network metrics indicate some basic features (i), the position/role of a node in a graph (ii), as well as the existence of cohesive *groups* (iii).

1. Basic network metrics. In this work we consider the following basic metrics to define the shape of the network: *diameter* (the longest path between any two nodes in the network), *density* (the ratio of observed edges to the number of possible edges), as well as the *average clustering coefficient*, which indicates the average probability that two neighbours of a vertex are themselves neighbours.
2. Degree and Centrality. A common metric to identify the most relevant vertices is the number of links or edges connected to the vertex (*degree*) that can be further separated into *in-degree* (incoming edges) and *out-degree* (outgoing edges) in oriented graphs. To further investigate the topology of the network, we compute centrality metrics which are able to capture the vertex's position in the network, for example, relative to other cohesive groups of vertices. Centrality metrics may for instance detect *bridges*, that is, vertices that are closer to vertices in other groups [20].
3. Communities. Moreover, to verify if the network has communities or clusters, i.e. more connected parts, we consider a *community detection* method, i.e. Louvain's *modularity*, to identify cohesive groups of vertices [21]. We applied the method combined with an algorithm to improve the visualization of communities, e.g. Fruchterman-Reingold [22].

Citations network. The first context, within which we used the above described metrics, is to analyse the *citations network*, that is, considering each article as a vertex and each citation as an edge from one citing article to the cited article. In a directed graph of this type, the input edges of a node, i.e. its in-degree metrics (In-D), represent the relevance of the article (indeed high citations indicate, usually, high relevance). In the overall network, we are also interested in finding cohesive groups of articles belonging to some research communities. On purpose, we applied modularity to automatically identify the densest groups of citations, likely to correspond to research communities. In such a network, we can also consider centrality measures, e.g., *betweenness* centrality (Betw), in order to identify the articles working as bridges through different communities.

Co-authors. The second context of application of our SNA is that of co-authorship of papers. The presence of articles with shared co-authors allows to unveil key collaborations among researchers. Groups of co-authors indicate the existence of research focused on specific areas, within the survey themes. In addition, we are especially interested in capturing groups of influential authors, i.e., authors having a high centrality with respect to others.

Terms co-occurrences. We also performed a textual analysis based on co-occurrence network, i.e. a network of terms co-occurring in the same sentence of abstracts. Pre-processing has been applied to the abstract of all the papers. We filtered part-of-speech of interest, i.e. nous, adjectives, and verbs, then we removed stopwords, numbers, and punctuation marks. Moreover, we unified terms composed of multiple words (e.g., "social network", "artificial intelligence"). Finally, we computed the stemming of the terms to use their root form, thus allowing the creation of more links between terms, ultimately having a more meaningful network. On the obtained graph, where the extracted terms are the vertices, and their co-occurrences are the edges, we applied SNA to identify the main clusters of research topics.

2.3. Further filtering

To reduce the number of papers actually surveyed to a more relevant selection and manageable size, we further filtered the 2,941 results collected so far by looking at the quality of the publication venue as assessed by notable independent organisations, in particular Scimago[2] for journals and the CORE ranking system[3] for conferences. We understand that the venue of the article may not be directly related to the quality of the work, and that some papers published in venues considered to be of lower quality according to the indices may be of good quality instead. However, we preferred an objective criterion for achieving a good quantity of papers, rather than making a discretionary selection based on subjective and non-replicable criteria. We noted that considering journal papers with core of the second quartile and type B conferences, we would have a set of about 600 articles. First, it means that there is probably a considerable amount of high quality works. Moreover, we decided to further refine the selection since our literature review considers in-depth reading of the articles. In particular, we excluded from the subsequent manual inspection publications that *are not* in journals ranked Q1 and in conferences ranked A. We considered the most recent rankings from the year 2021, which provide a good approximation of the immediately preceding years as well. This reduced the batch of papers for analysis to a much more manageable pool of 341 items. In summary, relying on the CORE rankings makes it possible to maintain, on the one hand, a focus on contributions from the literature in which computer science plays a prominent role, as demanded by the nature of this survey, and, on the other hand, keep the number of paper collected manageable so as to be manually analysed.

This has been further restricted to the final size of 152 papers, after that manual inspection revealed either alternate versions of essentially the same paper (conference vs. journal extension), papers in which the core contribution is not exactly about application of agent techniques to healthcare, but rather healthcare is merely used as the application domain to conceptually assess a proof-of-concept (e.g. a scalable multi-agent architecture whose property are conceptually evaluated by imagining it application in an healthcare domain). In very few cases the key terms were used with alternate meaning (e.g. agent in the context of chemical reactants). The surviving papers are the one considered in Section 5 of the present manuscript.

[2] `https://www.scimagojr.com/`
[3] `http://portal.core.edu.au/conf-ranks/`

3. Exploratory Analysis

First of all, in order to provide for an exhaustive overview of the research landscape of agent-based healthcare research, we here report on the exploratory analysis we carried out through the usage of the SNA metrics and techniques reported in previous Section. In particular, the citations network allows to roughly detect research communities, their cohesion, relationships; the co-authoring network enables to spot research collaboration more specifically, and could highlight long lasting, cross-disciplinary research groups; the keywords network allows to detect research topics, and is used to conveniently partition this survey, as detailed in Section 5.

3.1. Citations network

The whole network (N-All) includes 96,833 vertices (articles) and 124,580 edges (citations), and is very sparse with a density of 0.01, a diameter of 26, and an average path length of 7.5. In an effort to improve readability of results, we filtered vertices with direct connections higher than 10, that is, we focus on the most relevant papers according to their number of citations. The reduced network (N-10D) includes 367 vertices and 852 edges, its diameter is 9, and the average path length is 4.

Figure 2 adopts the Force-Atlas algorithm [23] for improving the layout, and we resized vertices and labels according to the corresponding *In-D* or *Betw* measures. On this network, the modularity algorithm automatically identified 5 distinct groups: a first one (on the left) includes studies on conversational agents, chatbots, and relational agents in healthcare, with reference shown to the most active authors; a second one (top right) is about classic MAS literature, indeed here can be found reference works on the agent paradigm by Wooldridge and Jennings [3, 24]; the third and fourth groups (middle right, next to each other) both cover the research area of ABM, heavily influenced by Bonabeau [25], but the former mostly deals with complex networks and social simulation, whereas the latter admission scheduling, hospital organisation, emergency department management; the fifth group is about COVID-19 and epidemics. As a summary, Table 1 reports the articles with an highest In-D (i.e., the most cited ones) and highest Betweenness centrality (i.e., the most influencial authors) in the mentioned citation network.

		Ranking						
Network	Metric	I	II	III	IV	V	VI	VII
N-All	In-D	[26]	[27]	[28]	[29]	[30]	[31]	[32]
	Betw	[3]	[33]	[34]	[35]	[36]	[24]	[37]
N-10D	In-D	[25]	[38]	[39]	[40]	[41]	[42]	[43]
	Betw	[44]	[45]	[1]	[46]	[47]	[48]	[49]

Table 1: Ranking of the seven most relevant articles in term of number of citations (In-D) and centrality (Betw)

3.2. Co-authors network

The network of researchers who have published together, from 2015 to mid-2022, is interesting as it shows small research communities, sparingly interacting with one another. The graph in Figure 3 identifies the pairs of most frequents coauthors, having an edge degree higher than 5 (indicating they have collaborated on more than 5 papers on the subjects of agents and healthcare). The graph demonstrates how the modularity algorithm identifies several distinct communities in the whole network of coauthors. In this graph we also

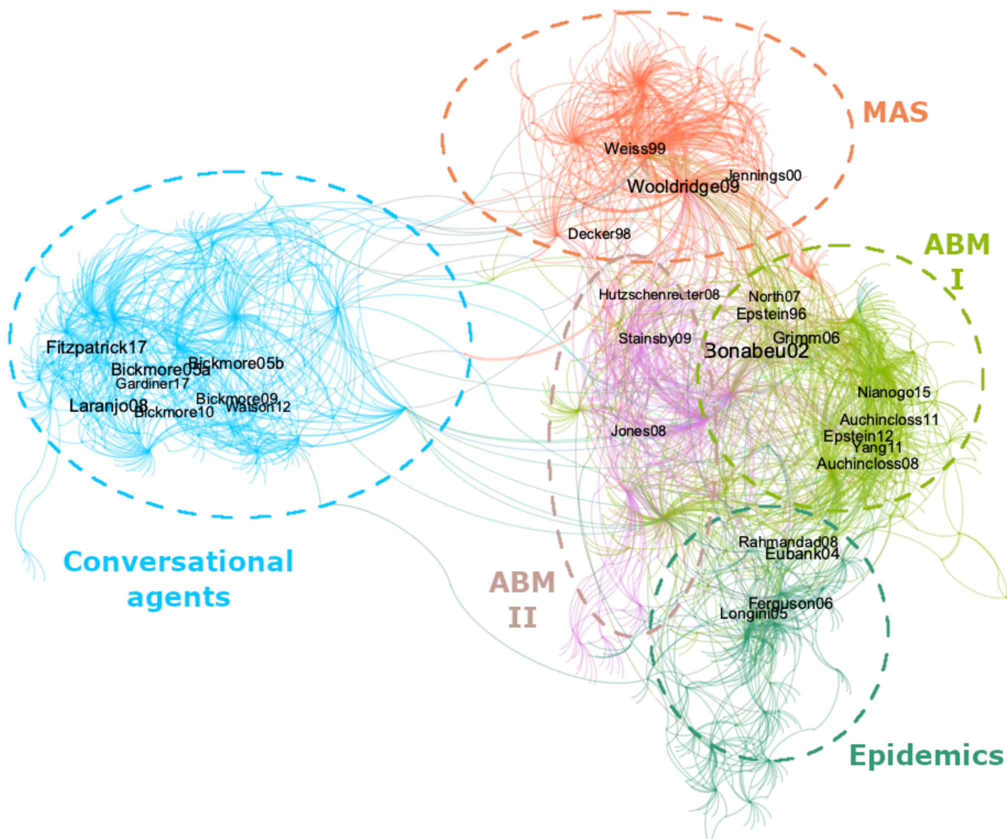

Figure 2: Citation network of the 2,941 references, with in-degree equals to or greater than 10. Vertices labels' size refer to In-D. The modularity algorithm automatically identifies 5 groups, i.e. references to papers concerning MAS, conversational agents, epidemics, and two groups of ABM references

emphasized (adding their label) the authors acting in the middle of different clusters, as bridges between different communities, i.e. the authors with the highest betweenness centrality measure.

The graph in Figure 4 shows the most frequent relationships between co-authors in the period of the survey, as evidenced by the weight of the arcs (thickness, in the image). The size of the nodes is proportional to the degree measure. We distinguish some strong research collaborations among which we clearly recognize the one of the research groups of Calvaresi and Schumacher [50] (they work on MAS in ambient assisted living and blockchain). They are the most frequent co-authors with 15 collaborations in the considered period. We notice also the groups of Tracy, Cerda, and Keynes (coauthors in several works on ABM in public health) [14] as well as Cotfas-Delcea-Milne [51]. Other relevant collaborations are Bickmore-Zhang on conversational agents [52], as well as Moghadas-Galvani, working on agent-based simulation of COVID-19 [53].

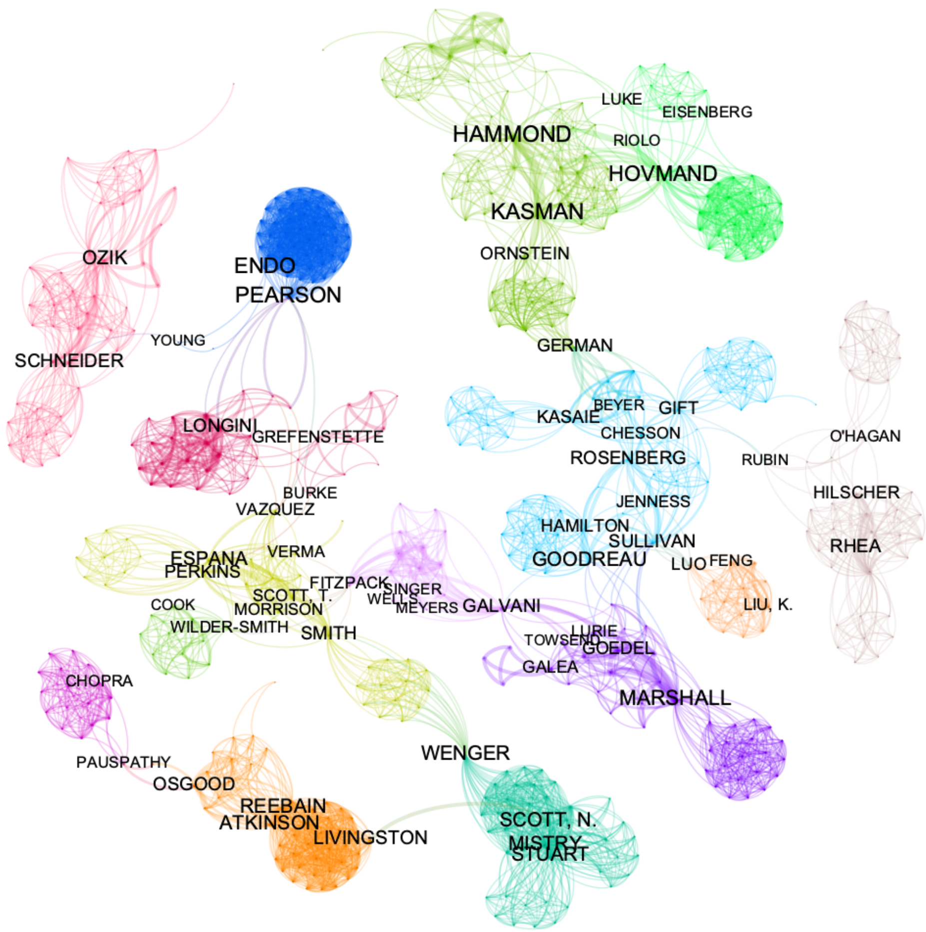

Figure 3: Coauthors network from paper 2015 to mid-2022. Vertices are authors with higher centrality (betweenneess and closeness) acting as a bridge on communities.

3.3. *Terms co-occurrence network*

The network of co-occurrent terms appearing in papers' abstracts is very large, with 3,430 vertices (stems of terms) and 58,344 edges (co-occurrences). The diameter is relatively small (7), as well as the average path

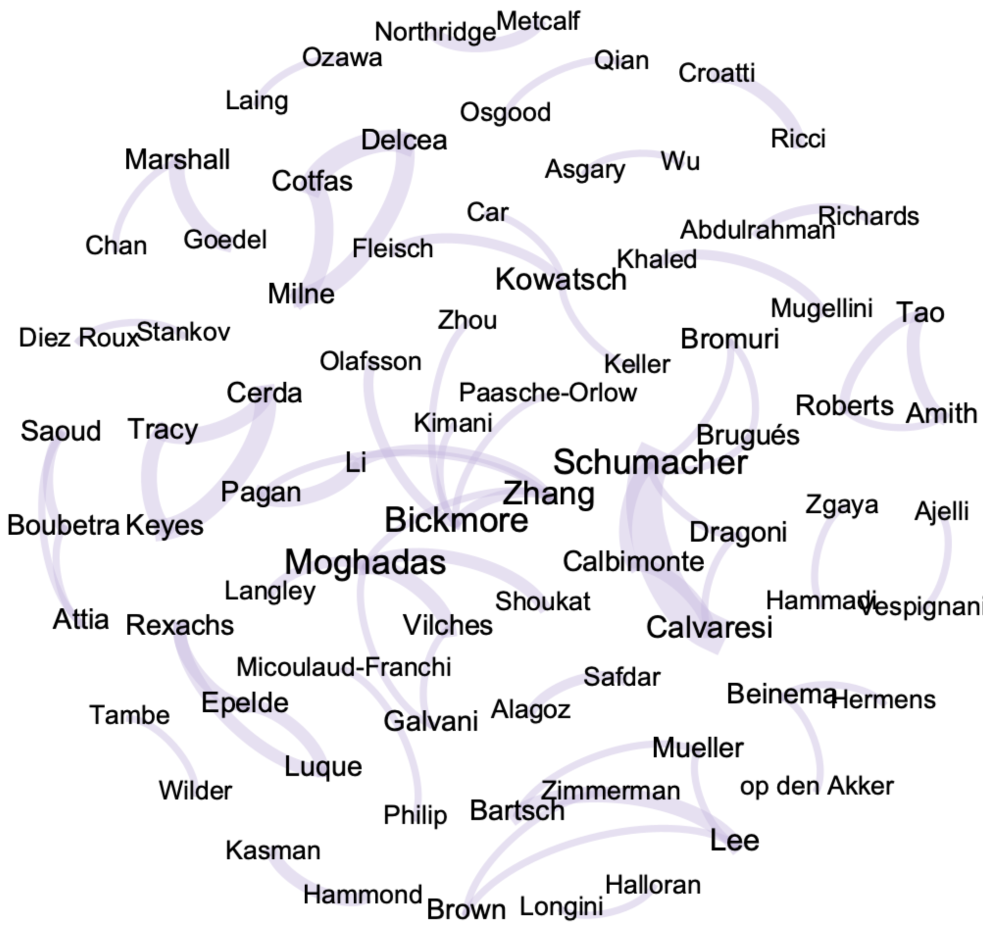

Figure 4: Coauthors network from paper 2015 to mid-2022. Vertices are the authors with most frequent coauthors, according to higher edges' weight (over 5).

length (2.7), while the average clustering coefficient is relatively high (0.75). This means it is a small-world network, similarly to other word co-occurrence networks [54].

In addition, the average degree of vertices is 34, which means that every term is linked to each others on average 34 times. Nevertheless, the degree distribution indicates that few nodes are largely connected, while the vast majority has a relatively low degree.

In order to reveal the more relevant keywords, we filtered the graph by eliminating the less significant terms (vertices with a degree lower than 100), as well as the general stems present in most groups (degree higher than 600). Figure 5 depicts the resulting network of 275 terms, whereas a modularity algorithm detects the following research topics, well aligned with the research communities also detected by the previous network analysis:

- *MAS platforms.* This research topic concerns the agent paradigm used to build distributed computing systems. It includes 62 stems referring to technology and software architectures (technolog, platform, architectur), practical applications (applic, implement, task, solut, practic), need for intelligent decision making (smart, effici, intellig, knowledg, manag, problem, decis), need for communication amongst

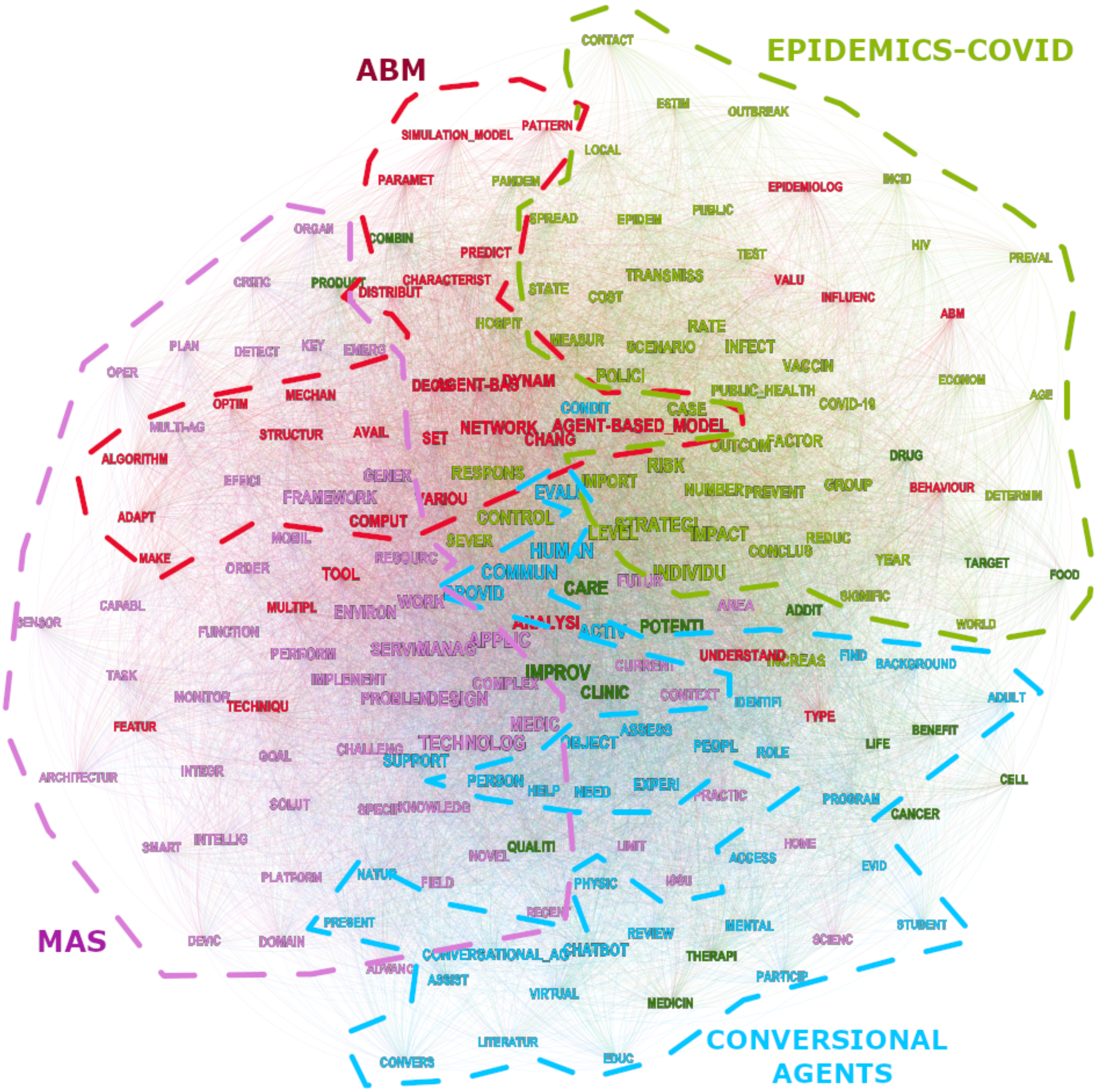

Figure 5: Co-occurrence network of stems from the abstracts of the 2,941 papers. The map underlines the main distinctive groups of related terms, i.e. MAS, ABM, Conversational agents, Epidemics-Covid. A fifth group includes stems related to healthcare and clinical issues, which are transversal to the others.

agents/sub-systems (commun, inform, support, assist).

- *ABM*. A second group of 65 stems hints at research focused on the agent paradigm used for modelling complex systems. Typical works in the area includes simulation of dynamic networks, as well as the adoption of optimisation algorithms (network, dynam, simul, optim, algorithm). Several methodological terms can be identified in this group, involving the modeling and evaluation perspective (evalu, framework, comput, assess, distribut, predict, paramet).

- *Conversational agents*. A group of 32 stems can be referred to human-machine interfaces, i.e. chatbots (human, convers, chatbot). This kind of researches focuses on the interaction of people with software entities (behavior, virtual, interact, adapt, understand).

- *Epidemics.* A large group of stems constitutes a fourth group, where the focus is on diseases affecting the overall population, as in the cases of epidemics or vaccination (spread, covid-19, diseas, vaccin, pandem, epidem, popul, immun, peopl, infect, transmiss, hiv, contact). These studies typically aim at measruing the impact of the disease or halthcare delivery from the management perspective (risk, strategi, cost, scenario, impact, respons, outcom) and public policies (polici, economic, public, intervent, prevent, reduct, program, control).

- *Healthcare and clinical issues.* Finally, a smaller group of 15 stems refers to various clinical aspects that cannot be directly mapped to a specific research topic and community, such as clinic, treatment, care, cancer, medicin, drug, therapi, food, trial.

The next Section recall these categorisation while placing the surveyed literature within such areas.

4. Trends, Prospects, and Challenges

As this survey is contributing to clarify, agents and multi-agent systems have been widely and effectively applied to the healthcare domain, besides the many others [55], not only for conceptual features but also for their technical properties, such as encapsulation of decision making, decoupling of control, interoperability, and execution distribution. The main research areas emerged from the above-mentioned exploratory network analysis are multi-agent systems, agent-based modelling and simulation, there including an extensive batch of works specifically target at epidemiology (e.g. COVID-19 onset), and conversational agents.

In this Section, we provide an overview of the main features of the agent approach that makes its application an opportunity in different fields of healthcare. Moreover, we provide a critical analysis of the main challenges of the aforementioned nuances and applications of agent-based techniques to this domain, and the main trends observed in literature. Table 4 outlines and summarises the principal facts.

Multi-agent Systems. Multi-agent systems are already used for many different purposes in healthcare research and development: modelling and simulation of phenomena of interest for multiple stakeholders (e.g., patients, staff, hospital administration) and across a spectrum of competing goals (e.g., improve delivery of care, optimise resources usage), encode intelligent behaviours to provide decision support to both patients, clinical staff, and administrators, and as a software engineering tool (models, languages, platforms, and methodologies) for the design, development, and execution of complex distributed computing systems.

However, despite this success, there are still issues to deal with to bring MAS towards full realisation of their potential with respect to healthcare practice. First of all, in recent years there has been an outstanding surge in machine learning approaches applied to healthcare practice (especially decision support systems), so that machine learning almost became synonym with AI. The role of MAS with respect to machine learning research and practice is yet to be fully assessed, but there already exist proposals for principled integration of the two complementary approaches, either complementing each other in delivering the same functionality, or leveraging separation of concerns to deliver different functionalities depending on the problem at hand. Another trend with an impact on MAS is the rise of the IoMT, that increasingly works as a backbone of personalised and telemedicine solutions. In this field, although agent-based solutions would perfectly fit the distributed nature of deployments and the need for decentralised intelligence, MAS platforms are not so well suited to execution on constrained devices.

	Distributed MAS	Agent-based Modelling	Conversational Agents
Opportunities	high-level modelling, large-scale simulation, inter-organisational co-operation, seamless distribution, software encapsulation & modularity	Ease of understanding for stakeholders, parallelisation techniques, high-performance computing	human in the loop, patient empowerment and engagement, personal assistant
Challenges	MAS engineering expertise, stakeholders' & users' trust, adjustable autonomy tradeoff, symbolic vs. sub-symbolic, computational requirements	The calibration and validation of model results, comorbidity and joint influences, transparency and explainability	Natural Language Processing, emphatic behaviour, explainable, reliable and trustworthy
Trends	encapsulation of ML components, orchestration of sub-systems, interfacing to humans	Hybrid simulation, automatic construction of simulation models based on real data	the release of autoregressive transformer language models substantially increases the literature in this field and potentially improves the adoption of CAs in healthcare [56]

Table 2: Overview of the opportunities, challenges, and trends presented by MAS while applied to healthcare scenarios, as stemming from the surveyed literature.

Other challenges with respect to application of MAS to healthcare exist, but we argue these two have the strongest potential impact on agent technologies adoption, as both machine learning and IoMT already contributed to advance the state of art in healthcare delivery through technology.

Agent-based modelling. A first point of attention on the ABM side focuses on model validation. This kind of models are often very complex, expensive to run, and this implies that the approach is more complex to be validated than other causal modelling procedures. A challenge in using ABM to analyse interventions or perform computational experiments concerns the calibration of model results against empirical observations. In fact, the construction of validated models requires a robust characterisation of parameter spaces, which is often difficult to achieve in practice. For models that have large parameter spaces, the brute-force approach is often not feasible. Some efforts aim to reduce the computational costs associated with complex model analysis, including parallelisation techniques and frameworks that allow exploration of models on high-performance computing resources [57]. Another relevant issue concerns the expansion of the models to consider comorbidity and joint influences more systematically, which can improve the exploitability of agent-oriented approaches to inform public health research, practice, and policy. The inclusion of key stakeholders (e.g., medical staff) in the construction process may also be a desirable solution to counter the difficulty of reading the results, moving toward greater transparency and explainability of the models themselves. Finally, an interesting future challenge concerns the possibility of building ABMs from real data (more or less) directly, whereas real data are currently used mainly for parameter construction and model validation. Starting from real logs (e.g., recorded in the information systems of healthcare organisations) to automatically construct the main characteristics of the agents and the rules of interaction, can be the basis for models and simulations that are more closely aligned with reality, similar to the process mining techniques that are now the norm for discrete-event simulations [58].

Conversational Agent. The main challenge once designing an agent to be part of a chatbot is to make it totally reliable and trustworthy, as well as emphatic. While making the agent to kindly and friendly interact with humans is relatively simple, and literature reports different effort in this direction by providing a set of sentences and words that can be adopted, making the agent trustworthy implies that the agent internal architecture, and the system which enables data acquisition and processing, is properly modelled and designed. However, most of the work available in literature and cited in Section 5.3 is mostly focused in discussing the peculiarities and needs of the application domain, but fails in providing architectural details, models and approaches adopted from an agent perspective. We thus miss how CAs are really implemented, on top of which technologies and adopting which kind of agent model. This paves the way towards new research directions devoted at the definition of a general model and architecture that can be adopted regardless the application domain.

Although this survey will bring us to the conclusion that the approach owns a set of features that perfectly suite healthcare system requirements, we still can not demonstrate that their adoption has moved from research to real systems design and implementation. We explain the scepticism of health professionals, towards a more pervasive application of agents and MAS, and AI in general, by noting that the common sense is still concerned by possible errors of algorithms, by the lack of transparency, by the the fear that an automatic system may be equal or better than man, by the need of proper regulation of doubtful cases.

5. Survey

In this Section we describe the relevant works gathered in each of the three areas, after the filtering steps (Section 2.3), and comment on cross-cutting aspects such as the goal pursued by the system, the specific application domain within the healthcare sector, the actors targeted by deployment. Each Section includes a mind-map that organises the material according to the features that best categorise the work developed in the three areas.

5.1. Multi-agent systems

We broadly called the first research area emerged from our survey as “multi-agent systems”, as all works described in the following first and foremost propose to adopt a MAS for achieving some goals. The specific tasks carried out, functionalities delivered, and goals achieved obviously vary, but a few core ways to exploit MAS can be devised out: *distribute computations* across different system components, both conceptually, in the sense of “separation of concerns”, and practically, with distributed computing nodes; *encapsulate decision making* and functional responsibilities in different system components (the different agents); and support *technological interoperability* amongst distributed and heterogeneous legacy software components as well as healthcare organisations/stakeholders.

Figure 6 summarises the main drivers of MAS technology adoption in the healthcare domain, and the main application domains of MAS therein. The drivers are represented as the direct children of the grey circle in the middle of the mind map, while the grandchildren of the middle circle visually attribute application domains to the features they require.

The following paragraphs follow this rough distinction in commenting the articles surveyed, provided that such a categorisation is only proposed to conveniently group together the research works, but some of them may easily belong to more categories as the usage of the agent abstraction may pursue multiple goals at once.

5.1.1. Conceptual/infrastructural distribution

The first batch of research works we briefly comment are all concerned with *conceptually* distributing responsibilities for carrying out tasks or goal achievement to distinct, autonomous and pro-active computational entities: the agents, indeed.

For instance, a MAS is combined with deep learning and augmented reality for medical imaging segmentation [59]. There, the MAS is used for conceptually distributing the segmentation process across portions of the image, thus partitioning the learning task and improving accuracy by exchanging segmentation information. Deep learning is then used for the automated construction of segmentation models from the partitioned medical imaging data, while augmented reality is incorporated to visualize the results of the segmentation. In reference [60], instead, an agent-based platform is proposed to optimise orchestration of an hospital Emergency Department, with a special attention on staff utilisation with respect to key performance metrics regarding quality and efficiency of care delivery. There, agents are used to conceptually

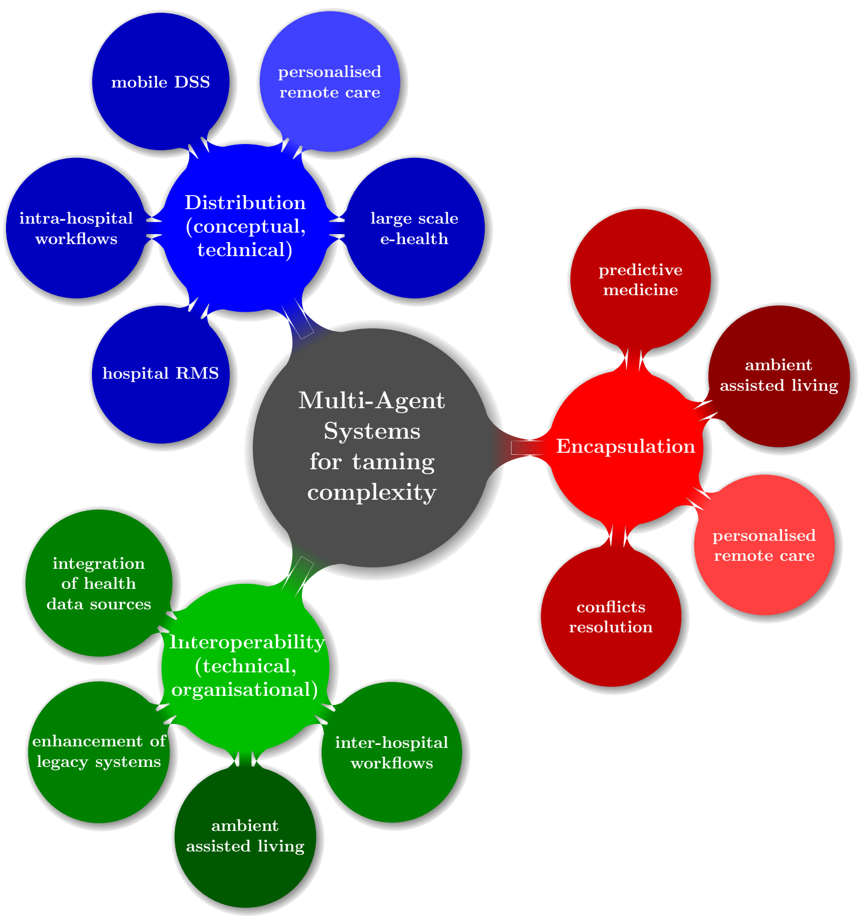

Figure 6: Application domains for MAS technology adoption in healthcare. Same application domains are similarly shaded (e.g. ambient assisted living is darker).

distribute (and encapsulate) responsibilities of different tasks to different entities (the agents, indeed), each able to undergo autonomous decision making. Another similar effort [61] utilises an agent-based platform for optimised management of hospital resources. Every entity of interest for the goal is modelled as an agent – personnel, medical equipment, patients – as it is an autonomous entity with its own decision making criteria. The agent-based platform then is in charge of monitoring resources consumption and of their re-scheduling if bottlenecks are found. In this work, thus, agents are used as a way to encapsulate autonomous decision making and distribute decision making criteria. Finally, the work in [62] proposes a model-driven development methodology for implementing ambient assisted living solutions for Parkinson patients. The target implementation abstraction for the model driven development workflow is a MAS. The choice is due to the agent abstraction being perfectly suited to encapsulate autonomy of patients and wrap access to environment devices.

Another batch of works, instead, is about practical distribution of computations across devices or architectural layers. Some authors, for instance, propose agent oriented programming and mobile computing to design a programmable, distributed Personal Health System called MAGPIE, aimed at monitoring patients affected by chronic diseases [63]. As agents are autonomous software entities that pursue a set of goals in an intelligent way and act proactively, they effectively work as smart monitoring tools that are capable of reasoning in a complex and proactive way on the current patients' physiological parameters. Agents are hence exploited to support a twofold goal: distribution of computations across patients' devices rather than on a centralised server, and encapsulation of intelligent reasoning techniques (as per the category defined by next paragraph), complemented by doctors' expert knowledge encoded in rules. Others propose a telemedicine system featuring virtual agents as part of Post-Traumatic Stress Disorder (PTSD) therapy, but pursue the same objective of computational distribution, by executing agents at patients' homes [64]. Virtual agents are in fact meant to help patients recollect their memories in a digital diary, by asking appropriate questions guided by specific ontologies as well as by a 3D reconstruction of PTSD-related scenes made by patients themselves. In [65], instead, it is proposed a MAS-based cognitive assistant platform delivering ambient assisted living for elderly people. In particular, authors focus on adding to an existing platform an agent for emotional recognition to be executed in patients proximity: while elderly people are engaged in planned activities, their emotional response is monitored, so that in the future only enjoyable activities are proposed again. Their proposed agent is also evaluated in a multiagent-based simulation framework.

Other works take distribution to greater scale by proposing agent-oriented platforms to support execution of collaborative processes specifications, that is, collaboration agreements between different hospital organisations [66]. The agreement negotiation stage is also supported by agents. Hence, agents are used to encapsulate the collaboration responsibilities of the distributed organisations participating in the agreement, as well as to orchestrate execution of the collaboration processes specifications, therein included carrying out the communication protocols to exchange data. Further increasing the scale of the system, agents can be used to distribute computations across a geographical area within a system aimed at biological threats detection [67], or to perform intrusion detection for Internet of Medical Things deployments [68]. In the former case, the system is layered in three slices: personal monitoring agents that are installed in citizens personal devices (e.g. smartphones) with the duty of monitoring their vital signs; agents deployed at the Edge to collect data and localize the threat; a Cloud-based processing engine to further process data. In the latter, the network is partitioned and each partition assigned to a cluster-head that releases mobile agents roaming the nodes in their partition to try to detect either network attacks or anomalies in sensor readings.

Finally, in [69] a mobile agents system is proposed to assist doctors in following best practices while prescribing drugs. A three layer architecture is deployed, exploiting agents to distribute computations (and responsibilities) across these layers: doctor agents run in doctors' smartphones and provide contextual suggestions on drugs prescription, patient agents run in every department to provide personalised recommendations, and drug agents run in hospital servers to encapsulate the prescriptions best practices. Also authors of [70] distributed agents across a layered architecture aimed at early detection of severe COVID-19 cases. The system comprises three layers: Edge, where data is gathered and severity prediction models are deployed; Fog, where a MAS carries out a scheduling process meant to prioritise the most severe patients for hospital admission; Cloud, where data is stored for further processing (e.g. training, auditing). Thus, agents are used to implement a distributed otpimisation algorithm.

5.1.2. Encapsulation of intelligence/responsibilities

All the works in this category use agents for a similar reason: encapsulating intelligence, autonomy, proactive behaviour, or responsibilities, to endow the system with modularity, hence flexibility of deployment and adaptation to change.

For instance, in [71] the main research question tackled is about the integration of Digital Twins (DTs) with agents and MAS technologies in healthcare. In particular, the paper argues, while DTs can be used to digitise medical devices, processes, and organisations, for the purpose of predictive analytics, simulation of what-if scenarios, and strategical decision making, agents can be used to model and engineer the medical applications acting upon DTs. Agents, in fact, are widely recognised as the most rich abstraction for modelling intelligent systems and applications. The authors demonstrate their claims by analysing a use case of intelligent trauma management, where agents are used to *model intelligence* and *engineer the distributed* software components in charge of autonomous decision making (e.g. assisting medical personnel, handling hospital resources). Another work by the same authors [72] proposes an agent-based personal medical assistant to aid trauma team members of an Italian hospital to facilitate documentation of the whole trauma handling process and assist medical staff with context-aware alarms and suggestions while operating. The paper describes in due detail the architecture of the system, that features a BDI agent in charge of assisting the trauma team: the Trauma Assistant Agent. The Belief Desire Intention architecture – a sort of standard *de facto* to encapsulate intelligence within rational agents – is exploited to encode trauma resuscitation best practices into the agent plans library, so that the Trauma Assistant Agent can properly react to the contextual conditions of the patients, that are dynamically changing in time. The JaCaMo platform is used for its development and execution. Also in the work in [73] agents are used as the means to encapsulate intelligent behaviour: an agent-oriented methodology for developing ambient assisted living systems is proposed, and the main motivation for adopting the agent abstraction is said to be encapsulation of autonomous decision making and intelligence, besides distribution of control. Likewise, the authors of [74] utilise agents to encapsulate predictive models and distribute computations in a system meant to predict hypertension risk. Finally, in [75] a Cloude-Edge platform is proposed to remotely monitor EEG signals of patients. Such a platform features agents whose responsibility is, on the one hand, to control distribution of computations across the Edge-to-Cloud spectrum, on the other hand to encapsulate the prediction capabilities delivered by a neural network model, to anticipate patients needs before an emergency event happen.

Other works are not concerned specifically with re-using or modularising some intelligent functionality, but with encapsulating responsibilities to different sub-systems, each represented by an autonomous agent.

In [76], for instance, the authors exploit multi-agent planning to perform reconciliation of clinical guidelines in the case of comorbid patients and while accounting for their treatment preferences. The challenge in doing so is that conflicts arise both regarding specific guidelines for different diseases, and patients preferences. The multi-agent paradigm is useful as each agent encapsulates the knowledge to deal with each guidelines, hence the problem of deciding the best course of action turns to a multi-agent planning problem, and can exploit readily available coordination and conflicts-resolution strategies. Similarly, authors of [77] adopts agents deployed on the Cloud to bear different responsibilities, in the spirit of separation of concerns, within a system meant to provide emotional support and pneumonia-related predictions to caregivers of patients suffering of dementia or Alzheimer disease, personalised to each patient. Finally, the MET4 MAS platform [78] is proposed to support interdisciplinary healthcare teams operations according to established clinical workflows. In particular, the WADE agent platform is used to perform team formation and resource/task allocations, besides general workflow execution support, two activities where agents and MAS have a long history of successful application.

5.1.3. Technological interoperability

The last "category" for MAS applications to healthcare has interoperability as its main driver, either towards legacy systems and devices or amongst different systems and organisation.

Of the former kind is the system described in [79]: an m-health application for the continuous self-management in chronic disease patients. Agents are used to ensure interoperability of various Personal Health Devices (PHDs) and Electronic Medical Records (EMRs) by wrapping and mediating access to such assets while implementing standard healthcare protocols. Accordingly, there are agents to manage the application database, the PHDs, protocol translation, the control logic of the Android application exposed to patients. Thus, agents are used for a specific task matching well their characteristics, that is, supporting interoperability amongst distributed software components.

Authors of [80], instead, propose a MAS-based decision support system as a tool helping hospital administrators to optimise organisation and usage of the Pediatric Emergency Department (PED). Each agent in the MAS represents an actor of the PED, and the collective of actors tries to achieve optimal behaviour through negotiation with others. In particular, agents try to optimise both patients' waiting times and allocation of hospital resources to incoming tasks. The agent abstraction is used in this paper to wrap access to legacy hospital systems, organise the distributed architecture of the system, and interface with people (e.g. medical staff users). As the technological platform where to implement the system, JADE has been used [45]. In [81] agents are used with a two-fold goal: on the one hand, they mediate access to and data collection from vital signs monitoring devices, hence enabling interoperability, on the other hand they distributed computations amongst patient devices and the system infrastructure. Authors of [82] exploit agents to encapsulate devices and functions of an ambient assisted living installation for assisting patients with Acquired Brain Injury. There, agents mediate access to devices and encapsulate ambient intelligence functions supporting patient daily activities.

For the latter kind of interoperability support, instead, authors of [83] described a project whose long-term aim is to improve medication adherence of elderly people and Parkinsons patients. Such a system is actually constituted by three distinct subsystems, each featuring its own components, in turn, in a Systems of Systems perspective. Agents are the software entities in charge of encapsulating each subsystem within suitable API, and of mediating interactions between such systems. In [84], instead, a MAS is used to support semantic interoperability between different healthcare organisations, and is specifically chosen as a development paradigm for the capability of agent to encapsulate autonomy and pro-active behaviours.

5.2. Agent-based modelling

A second kind of research includes ABM in different healthcare application areas. ABM models constitute a family of models that are based on some common features: firstly, individual units are modelled for the execution of relatively simple operations, as in the case of elementary (dichotomous) decisions or stochastic behavior. They do not use sophisticated architectures or very complex behavioral rules. Second, agent interaction takes place in a virtual environment (e.g., a lattice or multidimensional space) in which they can act. Therefore, it is possible to visualize agent behaviors as a physical system, e.g., simulating evacuations, traffic, biological systems, infections, etc. Thirdly, simple behaviors of agents generate complex global patterns as consequences produced by interactions.

Within this commonality of goals, we can identify a high-level distinction of the literature on ABM into two macro categories (as well as multiple subtopics). A first macro category of simulations focuses more on characterising agents in the most realistic way possible by adopting variables, defining rules of behavior, and interaction with the environment. A second macro-category concerns models in which the modelling effort is mainly through the use of mathematical equations to define the behavior of agents as individual entities. This category mainly concerns work in the area of computational biology, as we will see later in detail. We will label this group of ABMs as *functional ABM*.

Impact of ABM on the real world. In ABM, the variables and rules underlying the construction of models are usually generated from secondary data analysis and time series. Each individual model is able to generate synthetic data from simulations, which can then be compared with real-world data. Typically, this effort involves the validation and calibration of the models.

In terms of topics, although the scope of agent-based simulations is vast, we can outline five main areas of applications: healthcare processes/hospital management (e.g., ED); epidemiology, influence-like virus spread; social aspects (dependency, home care, elderly facilities); spatial impact (spatial perspective, closed environment); Covid-19. These labels are not strict and homogeneous, but there are overlaps and they only serve to return a picture of the variety of applications within the main macro categories. Figure 7 summarise the main application contexts of ABM.

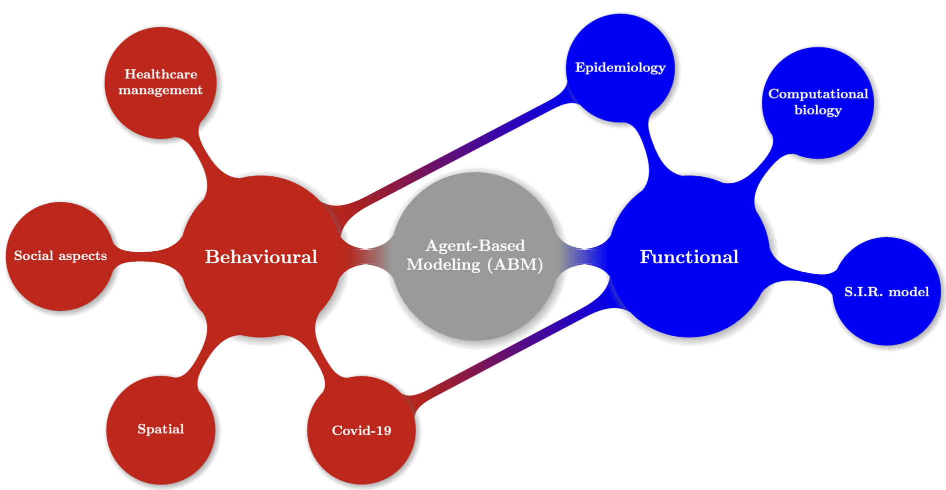

Figure 7: Application domains for ABM techniques adoption in healthcare.

5.2.1. Healthcare management

A first group of research work investigates organisational aspects in a healthcare management perspective, e.g. hospital departments. On this topic, a certain interest concerns the modeling of emergency services and emergency department (ED). This is a complex and unpredictable hospital department where agent modeling can play a significant role.

Several works have focused on simulation to examine performance parameters, e.g. waiting and throughput time, as in the case of EDs in Spain to explore prediction [85] or optimization [86]. In this context, [87] provides a prediction of future performance and demand on ED through ABM integrated with statistical learning and clinical data. The simulation takes into account both regular patients and patients with Non-Communicable Diseases (NCDs) based on clinical data. The study investigates the impacts of changes in population and age distribution of patients with NCDs on ED performance through estimations of Length-of-Stay (LoS) between years 2019 and 2039. In [88], authors propose the adoption of an agent-oriented decision support system by introducing ABM of a hospital ED for performing scenario analysis. There, a genetic algorithm application suggests the criteria for the patients' selection. Other recent works on ABM applications in healthcare management investigate the role of telemedicine on ED [89], smart beds with internet-of-things solutions [90], as well as the intrahospital movements [91]. Several agent-based business process simulations concerning healthcare management have been presented recently in [92]. From a territorial management perspective, agent-based simulation of the process of vascular access creation in hemodialysis patients investigate suitable solutions for system improvement to find more effective factors according to the characteristics and conditions of each center or medical system [93]. An agent-based model of collective behavior of routine dental check-ups in a social network allows to investigate patterns in the amount of demand for dental visit at society level [94].

Finally, [95] is a research article of *functional ABM* describing an hybrid simulation on emergency coordination center in Germany where the agent concept was used to model independent entities (call-takers, ambulances, emergency doctors, and helicopters) accomplishing complex tasks following specific protocols.

5.2.2. Epidemiology

A relevant ABM line of research concerns the phenomena of virus spread, as in the case of infectious diseases or the influenza virus. A recent work performed scenario analysis for preventing *chikungunya* virus infection [96]. The work has been performed in the GAMA platform [97] with the integration of geographic information (GIS). The research adopted census data to account for the spatial movement of infections, including also climate data to capture the temporal nature of an epidemic.

Most part of epidemiological approaches involve *functional ABM* researches. In [98] authors elaborate an agent-based model of the innate immune response system for sepsis illness to investigate the nonlinear optimization problem of potential control strategies, by applying genetic algorithms to suggest complex treatment. [99] presents an agent-based framework, a stochastic model that simulates, on a sub-hourly timescale, the different daily activities of all individuals in a population. The contact patterns of individuals are accurately modeled. With the use of agent-based epidemic and mobility models, individual-level transmission of influenza, and its subsequent spread, are accurately modeled. In [100] authors compare five ABM of close-contact disease transmission models consisting of household, school, workplace and district clusters. People in a cluster can have social contacts and transmit an influenza-like disease, with a transmission probability assumed to be age dependent. [101] describes a method for computing the risk of infection of any individual in the community, as a result of their spatiotemporal interactions. The work introduces a stochastic agent-based epidemic model (and optimizations) to better capture the dynamic disease spreading in a community.

In [102], authors develop an agent-based model for dengue virus transmission and uses it to assess the extent of uncertainty in dengue vaccination impact projections attributable to uncertainty about breakthrough infections. The analysis provides an assessment of the extent to which a potentially important source of uncertainty about (dengue) vaccine profile might affect vaccination impact projections. Another research work proposes an interaction-oriented approach to model and simulate the individual's daily behavior and all the dynamics affecting patients with NCDs [103]. The model describes individuals living within a social network daily engaged in activities of the physical environment, also discussed in [104].

Finally, a wide range of agent-based approaches adopt compartmental models, labeling the population according to baseline categories S, I, or R (Susceptible, Infectious, or Recovered) and other subsequent variants. In fact, some work consider a Susceptible-Exposed-Infectious-Removed (SEIR) model to describe the spread of the virus. In particular, influence models are reproduced in [105] to investigate the generality of critical slowing down (a dynamical feature of systems approaching phase transitions) by implementing five transmission models with very varied structures undergoing the same epidemic transition: the loss of herd immunity in a population due to declining vaccine uptake. They were assigned identical epidemiological and demographic parameters to provide a meaningful comparison. The results provided some discussion about health disparities with respect to age and income attributes. Similarly, [106] performs a high-performance agent-based simulation model with a SEIR disease model to simulate the spread of influenza in the corresponding synthetic contact network. Other work on diffusion concerns the simulation of the transmission of antibiotic resistance between human pathogens [107]. Finally, a bunch of ABM work involves Covid-19 diffusion, as described in the following section.

5.2.3. Covid-19 diffusion

Agent-based models have proven functional in modeling Covid-19 diffusion, as evidenced by the large body of work on the subject. Most studies belong to type *functional ABM*, whereas transitions between states and mathematical modeling merge with agent-based simulations. For instance, [108] proposed a tool to inform real-world policy decisions for a variety of national and subnational settings, while [109] analyze the spread processes by considering the existence of different regions in the environment (e.g. home, work, commerce site, school) and some specific characteristics in the current scenario (e.g. social distancing, awareness). The attention to spatial diffusion is typical in ABM, as better detailed also in the next paragraph. This is also the case of Covid-19 researches on the diffusion in localized environment [110], at school [111], as well as in facilities [112], where the interactions between agents (individuals) and the environment is at the core of ABM to assess the impact over social considerations.

Some researches proposes ABM also to explore the spread of Covid-19 in a wider region, as well as to describe vaccination strategies from a decision support system perspective [113]. In [114], the authors investigate the genetic algorithm methodology to address best vaccination criteria, i.e., to define vaccination rates for population types over time. A decision support system is also addressed by [115].

A recent model investigates contact-tracing interventions for early transmission dynamics of Covid-19 in South Korea [116]. An agent-based simulation of the epidemic including detailed age-stratification and realistic social networks parameterised in UK is presented to investigate non-pharmaceutical interventions (NPI) in [117].

On the same topic, some researches exploit the typical ABM tool NetLogo to investigate the impact of the adoption of NPI [118] as well as social distancing and mask usage [119]. A similar approach is explored in [120] illustrating a descriptive model of the COVID-19 epidemic, calibrated to the UK situation, based on different types of knowledge, starting from official statistics, observed clinical characteristics, theoretical understanding of the ways in which interventions interfere with transmission, and expert assessment of responses to interventions. A similar work concerns Germany, where [121] focuses on agents created from empirical data to incorporate factors like age, gender, wealth, and attitudes towards public health institutions. Their model aims to explore the empirical trends of fear and protective behaviour in Germany but struggles to simulate the accurate scale of disease spread. Hybrid approaches involve different modeling perspectives, as the effort in [121] to investigate the transmission across a heterogenous network mediated by bank/agency staff. Their model combines modules describing the network of the staff (ABM), and intra-facility (system dynamics).

5.2.4. Social aspects

Modeling social interactions between individuals, such as groups, are a specificity of ABMs. In fact, this type of modeling has been widely used in the social sciences to investigate social relations, interdependencies between individuals and institutions, or socio-cultural and economic aspects, also with respect to healthcare issues. For instance, [122] focuses on individual and collective behaviour in epidemic. Authors proposed an ABM to study the dynamics of an epidemic, including a decision-making model based on cultural orientation where the theory of planned behavior is used to simulate the dynamics of an epidemic and observe the effects of individuals' preferences to comply with or ignore the established epidemiological intervention measures. Another research investigates the relationship between individual behaviour and their socio-cultural environment. A relevant research work focused on diabetes care by modeling agents as "affecting patients with generally autonomous units that make decisions based on their inherent behaviors and by observing changes in the environment". In particular, their model describes the dissemination of a Type 2 diabetes guideline that recommends individualizing glycemic goals. The proposed framework demonstrates how to incorporate various socio-cultural factors to better predict guideline dissemination behaviors, by using existing cross-sectional surveys from physicians across the United States [123]. Another work investigates the role of trust, in a pharmaceutical supply chain ABM [124].

Some researches concern simulations of health and social aspects related to mental health, addiction, or problematic behaviors. For instance, [125] investigates suicide prevention. Their model demonstrates the impact of disqualification (for anyone receiving psychiatric treatment) on population rates of suicide by firearms. In [126], authors investigates a treatment-as-prevention strategy on HIV by adopting a time-evolving adaptive network. The model is a stochastic, agent-based HIV epidemic model that accounts for a broad set of virological, immunological, behavioral, and epidemiological phenomena. In [127] the simulation addresses the diffusion of obesity as a contagious disease by including socio-environmental influences. On decision-making perspective, [128] investigates the planning strategies of welfare facilities, home care centers and day care centers with ABM, addressing the demographic aging process of a human population and agent-based behaviors. In [129], authors modeled caregiver routing problem in home health care to provide organizational suggestions to home health care (HHC) service providers.

Some research investigates alcohol addiction problem. A NetLogo model simulates a population of 18-25 year old heavy alcohol drinkers on a night out in Melbourne to provide a means for conducting policy experiments to inform policy decisions [130]. Another model [131] examines whether taxation can reduce income inequalities in alcohol-related violence, by simulating the heterogeneous effects of alcohol price by income, level of consumption and beverage preferences.

5.2.5. Spatial perspective

One of the peculiarities of agent-based models concerns the possibility of describing phenomena involving individuals (agents) occurring in a space, be it a geographic location or a circumscribed environment. In fact, ABM were useful for simulating health issues in enclosed places. For instance, models have been adopted to mimic influenza transmission risks in a shopping mall environment [132], to support infection control strategies at school [133], in a smart home environment [134], or to address boarding and social distancing problems to avoid infection in buses [135].

On a large scale, agent-based spatial simulation involved geographical concerns with respect to health risks [136], whereas the impact of socioeconomic segregation on infectious diseases was considered in [137]. In [138], the model investigates the case of refugee and internally displaced person settlements. Based on the JUNE open-source framework, the model includes data on geography, demographics, comorbidities, physical infrastructure, obtained from real-world observations of a refugee settlement in Bangladesh. A similar work focused on vaccination and pastoralism in East Africa [139]. Finally, an high performance ABM environment investigates an influenza-like illness spreading over Delhi, where population networks are based on surveyed data [140]. The authors provide a detailed overview of an Agent-Based Computational Epidemiological Modeling perspective in [141].

5.3. Conversational agents

Conversational agents (CAs) are software agents that can hold natural language conversations with users. They are known in the literature also under the wider name of cognitive assistants, or personal assistant agents [142]. They are able to emulate an interpersonal communication between a computer and the user and, accordingly, they are designed to speak and behave as a real human. They can be or not equipped also with a human-like physical form, including facial expressions and body movements: in the first case they are defined as embodied CAs (ECAs), otherwise we can simply speak about chatbots, text-only displays which however are considered in literature less effective than ECAs in engaging patients and improving their commitment and motivation. Moreover they are typically designed to provide assistance to users by augmenting their cognitive capabilities. Literature can be classified based on different metrics. However, since they are meant to support the human-in-the-loop model, we choose here to split the work based on the intended users, meaning patients or healthcare providers as outlined in Figure 8. Moreover, the figure shows those main tasks, that each of the two categories has to daily manage, that literature evidences demonstrate can feasibly be supported by CAs adoption.

5.3.1. Care recipient-oriented applications

The first class, which comprises the majority of developed work, reports applications to a wide range of health conditions. Most of the work available applies CA to chronic health conditions, mainly not life threatening but such that they significantly reduce the quality of life for the patient. We've categorised the support they are meant to provide as services for:

1. training, such as coaching home care, initial education, searching for online health information
2. facilitating engagement, by improving and encouraging adherence, promoting behaviour change, motivating the users
3. providing tailored treatment advice, according to the view of personalised medicine
4. supporting diagnosis
5. detecting unusual behaviour and generating alert

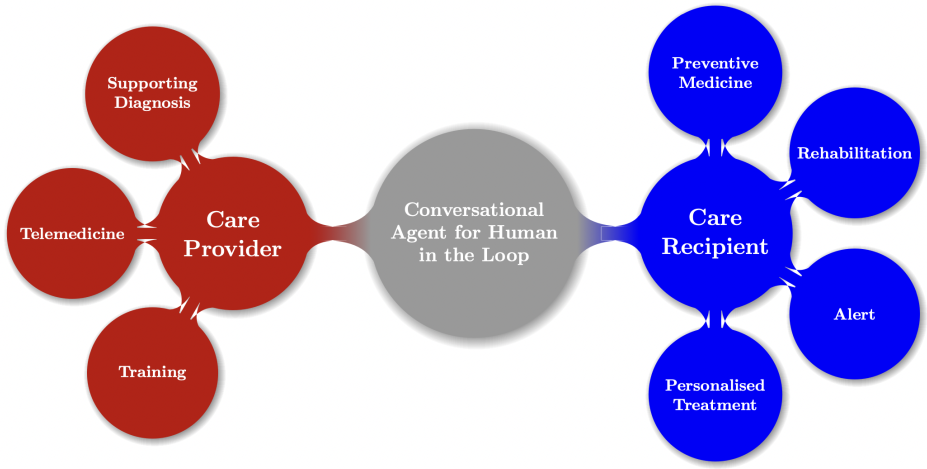

Figure 8: Application domains for CAs technology adoption in healthcare, i.e. which human actors are involved and to which extent they are supported by software agents.

with the overall goal to approach health services to a significant population that currently cannot or does not get as much access, to support the principle: *care anywhere, at anytime and to anyone*. To be effective and truly supporting, literature identifies some main characteristics of CAs: the software must demonstrate three essential components, *trust*, *empathy* and *expertise*.

In the context of chronic disease pathology, the basic idea is that CAs can support the disease self-management and improve patient engagement, with the goal of preventing or delaying the onset or progression of complications associated with the chronic disease. As a prominent example, [143] discusses this issue by presenting Laura, an ECA delivering daily support for self-management and education of people affected by diabetes (Type 2). Laura provides education, feedback and motivational support for blood glucose level monitoring, taking medication, physical activity, healthy eating, and foot care. Unfortunately, beyond the description of functionalities and results, the paper fails in providing architectural elements and technical contents discussing how Laura has been implemented and maintained.

Moving away from applications to chronic diseases, in [144, 145, 146, 147, 148] CAs are adopted as part of mental health-related services. As a specific example, [145] prevents fatal consequence of some mental health disorders, by detecting and alerting about risks associated with suicidal behaviours. For psychotherapeutic purposes, CA should be able to generate empathic responses implementing an emotional model based on the cognitive theory of emotions, and it should be represented physically to ease and make more comfortable the interaction with the user.

In [149] a CA has been applied to paediatric urinary incontinence that, even though not life threatening, affects the psychosocial well-being and quality of life of patients. The paper presents Dr Evie (eVirtual agent for Incontinence and Enuresis), a culturally neutral female character, following literature evidences that female physicians are associated with empathic communication and positive relationship building.

[150] identifies an other challenging field that can benefit from the adoption of chatbot as a means to interact with patients: cancer patients who suffer from the lack of reliable information about their disease, treatments or symptoms. Other examples are given by [151], where a CA is adopted to support users in monitoring their biological values, in performing self-diagnosis and possibly in suggesting doctors, or by [152] where the goal is to provide pharmaceutical care.

5.3.2. Care provider-oriented applications

Generally speaking, agents are applied as cognitive assistants to support care providers in different tasks, mostly in the training and daily activities such as diagnosis, remote monitoring and treatment. For instance, [153] introduces CAs in the context of healthcare education, as a tool for training healthcare students and, more generally, for pedagogical reasons. They simulate a patient-doctor interview by creating virtual patient social agents of different etiologies, gender, race, age and background so as to reproduce diversification among individuals. The paper focuses on the creation of virtual patients more than the ECA itself. [72] introduces a BDI-agent for supporting human operators during the trauma resuscitation process, by autonomously tracking the most relevant events and generating alerts for a set of adverse conditions.

5.4. Summary

This detailed review developed in the three areas categorises literature works according to different criteria, such as the intended users, the functionalities and the applications, and enables the identification of relevant existing research that we summarise in the following.

The first area identified concerns the MAS adoption for designing and developing distributed systems, that is is mostly driven by (i) the need to *distribute* not only actual computations, but also the system functionalities and the responsibilities of software components in a conceptual way; (ii) the desire to *encapsulate* some "intelligent" behaviour or decision making in a reusable software components that can pro-actively pursue the application goals; and (iii) the need to increase the abstraction level of legacy software components for better integration or *interoperability* with other systems.

These features, that is distribution, encapsulation, and interoperability, are directly stemming from many healthcare applications, that *require* them to deliver their functionalities. For instance, practical distribution of computational efforts is a requirement for any mobile health applications or ambient assisted living deployments. Or, encapsulation is a requirement for any personalised care approach, that aims at customising and contextualising treatments to the specific conditions of each patient.

In summary, looking at the surveyed literature, MAS models and technologies are a go to choice for dealing with some peculiar challenges posed by the healthcare domain, such as distribution of responsibilities (and computations), personalisation and contextualisation of decision making, and organisation interoperability. The driving features and applications just presented are pervasively mentioned in the surveyed literature, hence the mind map in Figure 6 is an accurate depiction of the research landscape of agents applied to healthcare in the specific category of MAS based approaches.

The second area identified concerns the adoption of agents for modelling complex healthcare systems. The main facts to be emphasised here are that agent-based modelling techniques in healthcare have multiple applications, both as harbingers of simulations to improve knowledge of a given phenomenon and as decision support systems. A common characteristic of these models is that they are easy to understand for people not skilled in computer science. Studies in healthcare, even theoretical ones, benefit from a robust and explainable technique that can track the albeit complex interactions among agents and account for the existence of emergent phenomena. Figure 7 summarises the principal kind of models and their healthcare applications.

The last area discusses the role of conversational agents in healthcare for supporting human activities. As shown in Figure 8, the most proper categorisation is according to the intended user, whether they are patients – for improving engagement, self-management and home care – or care-givers—for supporting diagnosis, training, and remote monitoring. Since they are meant to direct interact with human users, the main challenge once designing CAs is to make them reliable, emphatic and trustworthy. Recent advances in large-scale language models open the way for a new generation of CAs, whose ability to understand and interact with humans holds the premise for a possible massive application in healthcare.

6. Conclusions and Outlook

Previous prominent broad surveys on the topic of agent in healthcare are mostly related to researches published in the period 2010-2014 [17], or in the years 2005-2009 [18].

In this paper, we updated the literature overview to the following period 2015 - mid 2022, since in recent years a number of new researches have been developed that exploit the concept of agent with different nuances of meaning. Therefore, we investigated recent trends and the role of the agent approach, as well as agent-related methodologies and technologies, in the healthcare domain. We organised the survey according to the three main different topics that emerged from an initial exploratory network analysis, i.e. distributed systems and MAS, complex systems and ABM, conversational agents. For each of the three areas, we provided a discussion of the opportunities, challenges and trends.

Given the opportunities that the agents and multi-agent systems bring, by definition and construction, we conclude that they are playing a significant role in designing effective healthcare systems. However, their adoption is still not mainstream since a number of issues and challenges revealed some critical research questions and application gaps, as this survey pointed out. Accordingly, recent trends demonstrate that their adoption can be improved if new technologies will be exploited on a large scale: for instance, large AI models can be integrated in conversational agents for improving their capacity to be reliable and trustworthy.

Disclosures

The authors declare that there are no conflicts of interest related to this article.

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