Full Length Research Paper

Design of an HIV drug resistant patient management system in a digitally connected world

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Accepted 17 June, 2013

It is inevitable that drug resistance will become of concern in the treatment of HIV/AIDS infected patients due to the fact that the virus mutates at a high speed, selective pressure and patients that default from treatment. Not only is the management of HIV drug resistant patients difficult, but so too is the management of the patients’ data. The use of information systems and technology in the e-health context is of paramount importance for more complete and effective management of HIV drug resistant patients and their data. The aim of this paper is to describe an ontological-based software agent solution for the integrated management of HIV drug resistant patients using the connectivity of the World Wide Web. Ontologies and Software agents were used to develop the design of the HIV drug resistant patient management system. The system design developed comprises of seven distinct independent and autonomous modules working together to form the virtual backbone of the system. These are the web interface, directory facilitator, service agent broker, service agents, security facilitator, electronic medical record and a Master presenter. Due to the nature of software agents, other modules may easily be added to the system to improve and widen its functionality.

Key words: HIV, Interpretation algorithms, artificial intelligence, software agents, HIV drug resistance, resistance prediction

INTRODUCTION

The Human immunodeficiency virus (HIV), tuberculosis (TB) and malaria together form a triple burden of disease for resource poor countries like those in Africa. There are currently almost 5.6 million people infected with HIV in South Africa, which is approximately 11% of the South African population (AIDS Committee of Actuarial Society of South Africa, 2011). It is also estimated that there are almost 500 000 patients with AIDS defining conditions (Health Systems Trust, 2011). The management of HIV is further complicated when patients become resistant to antiretroviral drugs, which is defined as the inability of the antiretroviral (ARV) drugs to adequately suppress viral load. It is inevitable that drug resistance will become of concern in treatment of HIV/AIDS infected patients due to the fact that the virus mutates at a high speed, selective pressure and patients that default from treatment. Without effective ARV treatment, patients are susceptible to opportunistic infections which may be fatal, for example, pneumonia and TB. AIDS related conditions, including those attributed to ARV drug resistance, causes 43.6% of deaths in the HIV positive population in South Africa (Health Systems Trust, 2011).

Not only is the management of HIV drug resistant patients difficult, but so too is the management of the patients’ data. Currently in most South African hospitals, HIV drug resistant patient’s data are managed using paper-based records. Intrinsically, paper-based solutions have many disadvantages with respect to complete and effective management of HIV drug resistant patients. These disadvantages may be divided into the following

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categories: organizational, logistical, research and the passive nature of paper. Organizational disadvantages deal with the poor manner in which patient data are stored, slow retrieval of data required, and problems with understanding clinicians handwriting. Logistical disadvantages deal with the difficulties in making paper backups in a clinical environment, security, inability for simultaneous use of patient data, cost factors, redundancy, fragility of paper, and medical errors due to poor record keeping. Research is also rendered less efficient due to the intrinsic disadvantages associated with paper records. Paper-based records do not have any mechanism to bring errors to the attention of the clinician, and importantly does not offer suggestions for more effective medications, possible outcomes of treatment paths, changes in outcomes if treatment plans change, etc. The use of paper alone will inhibit the implementation of South Africa’s national health insurance due to problems associated with paper-based records communication.

The use of information systems and technology in the e-health context is of paramount importance for more complete and effective management of HIV drug resistant patients and their data. In most resource poor countries, there is limited availability of clinical staff specifically trained to deal with HIV drug resistance. Thus clinical decision support systems and telemedicine may provide some support in these resource poor settings. It has also been suggested that electronic medical records be used to support the management of patient data. Although there have been successful implementations of e-health solutions, one disadvantage is that these systems provide disparate support. Different HIV drug resistant e-health clinical decision support systems are not integrated and to the users of such systems, they seem to work independently from each other.

The aim of this paper is to describe an ontological-based software agent solution for the integrated management of HIV drug resistant patients using the connectivity of the World Wide Web. This system aims to provide a simple portal for HIV drug resistance management that will support doctors in a developing country. Such a system should have functionality to predict various measures of HIV drug resistance, integration with electronic medical records, security and user interface operations, interoperability functions and integration with telemedicine.

**HIV drug resistance**

Highly active antiretroviral therapy (HAART) comprises a regimen of three drugs from at least two of the five commercially available antiretroviral drug classes, and is used to manage HIV infection. HIV infection management is however also influenced by: poor treatment regimen prescribed by the physician; WHO stage of the disease which is related to the progression of the disease; drug concentrations achieved; how strictly the patient adheres to the regimen; toxic effects of the drug; and arguably the most important factor, drug resistance (Richman and Staszewski, 2000). Three common reasons that lead to the development of HIV antiretroviral drug resistance are high replication rates, selective pressure due to the innate adaptability of the HIV virus, and initial infection by resistant strains of HIV. Thus it is inevitable that drug resistance will become a reality in many patients’ treatment in the developing world (Frenkel and Tobin, 2004; Cane, 2005; Vercauteren and Vandamme, 2006).

The World Health Organization surveyed 41 countries in Africa, Asia and Mexico. Eighty-three per cent of the countries showed an prevalence of HIV drug resistance of 5%, and 17% had an ARV drug resistance prevalence of between 5% and 15% (http://www.who.int/hiv/facts/drug_resistance/en/). A randomized cohort of HIV positive patients revealed a 6% prevalence of antiretroviral drug (ARV) resistance in the UK (Booth et al., 2007) and a study of 40 USA cities reported a prevalence of 8% (Ross et al., 2007). With an increase in the use of ARVs and initial infection with resistant strains, the prevalence will increase around the world. Thus management of HIV drug resistance and the data associated with HIV drug resistance becomes important.

The process of digitizing patient records will improve the management of the data associated with ARV drug resistant patients. Electronic medical records will allow for better retrieval of patient information, better visualization of important physiological indicators used during the management of ARV drug resistance, autonomous backups, and better communication of patient data.

Currently, phenotypic laboratory tests are used to determine if a patient is resistant to ARVs. Phenotypic tests consist of culturing the HIV from a patient’s blood sample in a laboratory setting. This culture is then exposed to various concentrations of a specific ARV until the rate at which the HIV replicates is reduced by 50%. A similar concentration is then found with the wild type HIV virus; that is, the original HIV without any mutations. The ratio of these two concentrations of the specific ARV is called the IC50 (inhibiting concentration at 50%). If the IC50 is higher than cutoff values described in scientific literature, the virus is regarded as resistant to that specific ARV. This method is however expensive, time consuming, prone to error, requires skilled staff, and can only measure resistance to one ARV drug at a time.

Due to the disadvantages of phenotype testing, especially in resource poor countries, electronic computerized algorithms are being employed to determine ARV drug resistance. Computer based genotype interpretation algorithms usually determine mutations in the patient’s pol gene region, and uses this information to determine the ARV drugs to which patients are resistant. These computer based tests are quicker...
and cheaper than phenotypic tests. Computer based algorithms are usually based on an experts' understanding of the domain, available datasets that are used for machine learning and understanding of published literature. This has led to the creation of several resistance interpretation algorithms, which produce different resistance measures even if applied to the same resistance profile. In order to better manage ARV resistance, clinicians should be provided with a single resistance profile. In order to better manage ARV resistance measures even if applied to the same several interpretation algorithms, which produce different interpretation that combines the outcomes of the different individual interpretation algorithms. There is also a trend in the use of computer algorithms that provide other vital information in order to determine the best antiretroviral therapy for drug resistant patients, for example, prediction of CD4 cell counts, total lymphocyte counts, and the evolution of the HIV virus. One should also consider the fact that developing countries may not even have recourses to perform genotyping. Thus these expert systems should be extended to incorporate standard of care data as the basis of its perfections.

Although models that may be used to choose treatment regimens have been developed, very few are available in the public domain and/or easily accessed through a graphical human (user) interface. The digitally connected world may also help with the management of ARV drug resistant patients, and has been used to create ARV drug resistant portals. Currently there are web-portals that allow one to determine some aspects of HIV drug resistance management. These information portals allow one to determine the current HIV resistance profile of a patient, graph trends in viral and CD4 counts with basic alerts or store basic patient information. BioAfrica.net is an African based bioinformatics resource. BioAfrica.net contains bioinformatics resources that can perform sequence alignments, epitope analysis, tools for proteomics, subtyping and virus genotyping, an RNA virus database, and HIV drug resistance database and tools. The HIV drug resistance database and tools section is made up of the RegaDB collaborative mode and the calibrated population resistance tool (CPT). RegaDB is a drug resistance database developed by the Rega Institute, MyBioData Biomedical IT Solutions and the KatholiekeUniversiteit Leuven. It contains interpretation algorithms and stores some clinical data related to HIV treatment. CPT determines the prevalence of HIV drug resistance in a population and was developed at Stanford University.

Some international web portals for managing HIV treatment information include:

1. Stanford HIV database (http://hivdb.edu): This portal determines the interpretation results of the Rega Institute rules, AgenceNationale de Recherchessur le SIDA (ANRS) rules and the Stanford HIVdb rules. It also allows the use of specific user-defined rules using the algorithm specification interface (ASI) and also allows one the opportunity to create a graphical record of a patient’s ARV history, viral loads, CD4 counts, and sequence data.
2. HIVResistanceWeb (http://www.hivresistanceweb.com/index.shtm): This information portal allows information sharing on ARV resistance and clinical virology. It has a store and forward email based systems that allow one to interact with experts.
3. Los Alamos HIV database (http://www.hiv.lanl.gov/content/index): This information portal contains data on genomes, epitopes, drug resistance mutations, and vaccine trials. It is funded by the Division of AIDS of the National Institute of Allergy and Infectious Diseases (NIAID).

These individual information portals are however limited by the fact that most portals use their own ARV drug resistant treatment algorithms and few collaborate. They also do not have any means of a real-time expert consultation, they are not integrated into a full electronic medical record, and no individual portal has a large variety of tools that may be used to manage HIV therapy.

Software agents may be used to design a system in such a manner as to overcome the associated problems of few skilled professional in resource poor countries, poor integration of different types of electronic tools that will help the management of ARV drug resistant patients, and access to data stored in electronic medical records.

Software agents

Common computational paradigms are not adequate when trying to model the complex processes, interactions (Isern and Sánchez, 2010) and changing needs of the healthcare industry. Agents are programmed software entities that can perceive its environment and act accordingly, facilitate more complete architectures that better model the heterogeneous and distributed systems associated with healthcare. Software agents usually have characteristics of reactivity (the ability to respond to its environment), autonomy (perform tasks without the direct intervention of a human), social ability (the means to interact with other agents) and pro-activeness (programmed to take independent steps that will help solve problems). Software agent architecture typically consists of:

1. Interface agents, which interact with users, receive user input, and display results.
2. Task agents which help users perform tasks, formulate problem-solving plans and carry out these plans by coordinating and exchanging information with other software agents and
3. Directory facilitators that help match agents that request services with agents that provide services.

Software agents have been used previously in the healthcare domain, and range from national electronic
libraries for health (Kostkova et al., 2003), context aware hospital information systems (Rodriguez et al., 2005), pattern recognition for magnetic resonance spectroscopy (Gonzalez-Velez et al., 2009; Lluch-Ariet et al., 2007), health care services (Isern and Sánchez, 2010), to distribution of organs and tissues for transplant (Cortez et al., 2004).

MATERIALS AND METHODS

A literature review was performed in order to determine the agent and ontology technologies that should be included in the design. ScienceDirect, Google Scholar, PubMed and Scopus were searched using the IEEE Computer Society terms: software design concept, design strategy, design methodology, and architectural style. Other information technology terms searched for were agents, software agents, portals and ontology. The following MeSH terms were also included in the search: HIV-1 resistance factor, human; HIV-1; Antigens, CD4; Antiretroviral Therapy, Highly Active; and Artificial Intelligence. The results of these searches were used to design the system.

RESULTS AND DISCUSSION

The design of the ontological-based software agent system for an HIV drug resistant management system is shown in Figure 1. A modular heterogeneous designed approach facilitated by the nature of the software agents was taken. The systems may benefit from advantages associated with modular design, especially those associated with its repetitive and the hierarchical nature. This is supported by Pitterà and D’Errico (2011), who states that the complexity of designing a system may be eased by dividing the system into smaller independent modules, that interact with one another. This has major advantages in terms of management of the system, portability, logic clarity (Baca et al., 2012) and with respect to development time.
This approach resulted in a system comprising of seven distinct independent and autonomous modules working together to form the virtual backbone of the system. These are the web interface, directory facilitator, service agent broker, service agents, security facilitator, electronic medical record and a Master presenter. Due to the nature of software agents, other modules may easily be added to the system to improve and widen its functionality. It is important however, to ensure that all agents have an interface that allows for communication between the backbone system and the software agent itself. Purposeful design is required to ensure semantic interoperability in a modular environment (Yahia et al., 2012).

**Web interface**

The web interface acts as the point of entry for the user. The user should log into the system via the web interface and be given various options depending on his access rights. The web interface is important in terms of ensuring that the system appears to work seamlessly from the user’s point of view. The web interface will direct the user to the various possible tasks that may be performed and directs attention to the outputs of each task requested.

**Directory facilitator**

The directory facilitator normally is the virtual central access point of all service agents that interact with the system and provide some type of service. Thus the directory facilitator acts like a “virtual yellow pages” that has a directory listing of the service agents that may perform the task the user requests. In this way, it is the directory facilitator that has the ability to control the communication and interaction with all the service agents. In this design however, the directory facilitator coordinates the different types of services provided by the system and not the actual service itself. It keeps a list of all possible services types that the system supports and the user may request. For each type of service requested, the directory facilitator requests support from a service agent broker that manages and organizes the individual service agents that may provide the service. This has the advantage of not overburdening the directory facilitator with the tasks of organizing individual service agents. In the lucrative health care domain, one can conceive that there would be a large number of service agents that will provide similar services. Since the system will provide a number of services, there will be a large number of service agents that need to be coordinated. If all these service agents are coordinated by directory facilitator alone, there are chances of poor (slower) performance of the system, and increased chance of error.

In the proposed system, it is envisioned that the directory facilitator will have agents that will predict: current CD₄ cell count, future CD₄ cell count, ARV drugs the patient is currently resistant to, predict ARV drugs the patient may become resistant to, predict changes to CD₄ cell count associated with changes in ARV drugs, and provide a security and telemedicine service associated with the system (Singh and Mars, 2010, 2012a, b). Other agents may easily be incorporated into the system via service agent brokers.

**Service agent broker**

The service agent broker acts like an intermediary agent between the directory facilitator and the actual service agents that can perform actual services. The service agent broker has a listing of all the service agents that may perform tasks associated with the service type provided by the service agent broker. When a call is received from the directory facilitator for a particular service, the service agent broker will analyze the instruction and find the best agent/s to perform the task. The data required by the agents to complete their tasks are passed through the service agent broker to the agent itself.

In order to facilitate the best choice of service agent, the service agent broker needs to semantically understand the roles and capabilities of the individual service agents from the metadata that describes the service agent itself. In order to facilitate this understanding, ontology may be used to describe the domain and the service agent broker will make use of this to determine the best agent for the service required. It is envisioned that the overall system will comprise of various service agents that contain expert algorithms that will facilitate the choice of the best of antiretroviral therapy.

**Security facilitator**

There is a need for strong security protocols due to the private and confidential medical information moving through the system, as well as the autonomous nature of software agents. When agents request registration to the respective service agent brokers, the brokers need to determine if the agents comply with the security protocols. There should be protocols that deal with the technical aspects of security using up-to-date encryption techniques, identification using digital signature infrastructure, agents should ensure confidentiality, privacy and data validity. There should also be protocols that deal with the service the agent provides: is the agent created/endorsed by authoritative organizations; are all techniques that are used to provide the service based on
scientific literature; agents and creators should be easily identified and should be contactable; and does not break any local legislation. Added to this, it is envisioned that various health care certification organizations (like health on the net foundation and the utilization review accreditation commission) will add to the credibility of the agents.

**Electronic medical record**

Electronic medical records need to be incorporated into the design of the system, in order to improve access to information, facilitate expert system interaction, alleviate the problems associated with research, the passive nature of paper, and logistical and organizational issues. The web interface will communicate directly with the various databases that house the patient information. Since there may be many different databases, each with their own database schemas, there need to be an interface written to aid in communication between the web interface and the electronic medical record.

Due to the shortage of doctors and specialists in developing counties, there is a need for a telemedicine service in the system. This will lessen the burden on specialists that the country is on short supply off. It will also importantly facilitate the merging of telemedicine and medical informatics. This design will allow patients electronic medical records to be accessed via agents during a telemedicine consult.

The design allows for the telemedicine consulting doctor to have access to the electronic medical record of the patient via the web portal. Agents may be created that given patient information, security checks and other meta-data, for example, displaying device, patient specific information from the electronic medical record may be obtained.

**Master presenter**

It is necessary to ensure that all responses are appropriately displayed on the screen for the user, in a way that is easily comprehended. It thus follows, that the design of the graphical user interface of the web interface is an important consideration to facilitate the use of the system (Shneiderman and Plaisant, 2010). The interface needs to be user friendly and easy to learn (Molina et al., 2012). The role of culture in the design of the user interface also plays a significant role especially in developing countries, and the Culture-Centred Design (CCD) method should be applied when designing the interface (Alostath et al., 2011). Thus, adaptive user interfaces are required depending on the nature of the information that needs to be communicated, technology used, and the various cultural aspects (Hervás and Bravo, 2011). The autonomous nature of agents also lend to the use of adaptive user interfaces.

A Master presenter agent is therefore required. This agent, with the help of a displaying/interface ontology (Rahmani and Thomson, 2012), will take the information from each service agent and display the results in the most appropriate way in the web interface. Thus, according to modular design principles, the interface design, technology used, and data processing are kept separate. Of particular importance to developing country healthcare, is the adaptive display to mobile devices. It has been documented that in developing countries there is relatively good diffusion of cellular phone devices and coverage (Hodge, 2005; Singh, 2008; Brouwer and Brito, 2012) (Brouwer and Brito, 2012; Hodge, 2005; Singh, 2008), which in turn facilitates the use of mobile health (Lester and Karanja, 2008).

**Conclusion**

Drug resistance will become of concern in treatment of HIV/AIDS infected patients and without effective ARV treatment patients are susceptible to opportunistic infections. This paper describes one possible solution to build an integrated environment in which patients and their data may be better managed.

**REFERENCES**


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