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Towards Using Rule-Based Multi-Agent System for the Early Detection of Adverse Drug Reactions

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Abstract

Adverse Drug Reactions (ADRs) represent troublesome and potentially fatal side effects of medication treatment. To address the burden induced by ADRs, a preventive approach is necessary whereby clinicians are provided with new data-driven decision-support systems to foresee the factors leading to ADRs and plan precautionary activities effectively.

We develop a multi-agent system which monitors the factors leading to the onset of ADRs using information found in the patient records in a hospital setting. The system uses a fuzzy rule-based reasoning engine utilising decision rules developed by clinicians. We evaluate the ability of the framework to identify the cause of ADRs from patient records in a case study involving records of mental health patients. Our work is the first preventive agent-based aid tool.

Introduction

An adverse drug reaction (abbreviated ADR) describes any harm associated with the use of medication at a normal prescribed dosage (Nebeker, Barach, and Samore 2004). The onset of an ADR indicates a hazardous event which warrants the cessation of treatment or changing the dosage given to a patient (Edwards and Aronson 2000). The types of and risk associated with ADRs can range from a mild headache to a cardiac arrest, which can seriously effect the patient’s well being. Moreover, ADRs present a financial burden on health care providers. A report published in 2004 presented a projected analysis of 18,820 patients and showed that the annual costs for ADRs that led to hospital admissions in the U.K. would total at £466m (Laws 2004).

The problem with preventing ADRs is the manifold nature of the factors contributing to their onset. ADRs are drug-specific but their occurrence can be be influenced by the patient’s habits (e.g. compliance), comorbidities, interactions with other drugs the patient is taking, etc. Usually in a hospital setting, being aware of all the factors that may lead to undesired drug reactions for every patient is difficult due to the decentralized nature of the data and large influx of information. This can easily lead to missing vital facts which could contribute to the undesired reactions. For example, an audit performed in the South London and Maudsley NHS Foundation Trust (SLAM) for Mental Health uncovered cases where patients were given medications to which they are recorded to be allergic, which has led to death in two cases in 2011 (Taylor, Paton, and Kapur 2012).

Because the ability of multi-agent systems (MAS) to decompose complex problems and deal with decentralisation, there have been several proposals for their use in detecting ADRs (Mansour et al. 2012; Ji et al. 2005; 2007). (Ji et al. 2005; 2007) develop a collaborative multi-agent system for actively monitoring ADR signal pairs obtained from electronic patient data stored in different health care systems. The system monitors patient health records for ADR instances and uses fuzzy reasoning to attribute them to single causes. (Mansour et al. 2012) takes a learning approach and builds a team-based system to isolate the causes. In essence, all previous work aims to discover unknown ADRs for licensed drugs, especially newly-released drugs.

In this paper, we examine the different problem of ADR prevention by actively monitoring the factors clinically known to lead to them. We present the first phase of a rule-based multi-agent aid tool to be used in a hospital setting. The proposed system (1) anticipates the occurrence of ADRs based on the clinical history, symptoms, medication history, habits and personal traits of the patients using the information found in their hospital records (2) enforces testing guidelines by creating a personalized test schedule for each patient specific to their conditions and drugs and oversees its execution by health care professionals (3) monitors changes in the patients data pertinent to their symptoms, physical traits (e.g. rapid weight gain or loss) and personal habits (e.g. smoking habit changes) and abnormal test results, identifying warning signals as well as possibilities for clinician error. We demonstrate the effectiveness of the system in retrospectively identifying the cause of ADRs from patient records in a case study involving three drugs and records of patients with bipolar disorder.

Key Elements to ADR Prevention and Discovery

Discussions with health care providers in the South London and Maudsley NHS Foundation Trust (SLAM) revealed the following key elements which have contributed to the occur-
Additional monitoring for patients prescribed specific Antipsychotics

<table>
<thead>
<tr>
<th>Test</th>
<th>Initial check</th>
<th>Annual checkup</th>
<th>Lithium</th>
<th>Valproate</th>
<th>Carbamazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal function</td>
<td>Yes</td>
<td>Yes</td>
<td>At start and every 6 months; more often if evidence of deterioration or patient starts taking interacting drugs</td>
<td>Urea and electrolytes every 6 months</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>If indicated by history or clinical picture</td>
<td>At start and if there are risk factors or existing cardiovascular disease</td>
<td>At start if risk factors for, or existing cardiovascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma levels of drug</td>
<td>At least 3-4 days after initiation and 3-4 days after every dose change until levels stable, then every 3 months</td>
<td>titrate by effect and tolerability. Use plasma. levels to ensure adequate dosing and/or compliance</td>
<td>2 weeks after initiation and 2 weeks after dose change.</td>
<td>Then every 6 months</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: A subset of the physical monitoring guidelines for people with bipolar disorder (based on NICE (National Institute of Health and Clinical Excellence 2006) Guidelines and NPSA advice (National Patient Safety Agency 2009))

ence of ADRs:

1. **Monitoring Tests**: Many drugs affect the liver, renal, thyroid, cardiac and other functions, requiring guidelines for continuous monitoring of the patients taking these drugs. These guidelines are specific to the drug, condition and patient characteristics. In the UK, they are recommended by the National Institute of Clinical Excellence (NICE). Table 1 shows the intricacies involved in organising such schedules. A system which actively enforces these guidelines may help avoid drastic consequences. For instance, a recent audit for Lithium (an anti-psychotic) showed that 30% of the recommended routine tests have not been performed, potentially due to the lack of organisation, leading to consequences as severe as renal failure (Prescribing Observatory for Mental Health-UK for South London and Maudsley NHS Foundation Trust 2012).

2. **Allergies**: prohibit the prescription of a drug, the replacement with an alternative treatment or the administration of lower dosages. Allergies may not be immediately visible within the patient’s notes and maybe overlooked if the clinician does not take maximum care. An audit performed at SLAM uncovered cases where patients were given medications to which they were recorded to be allergic, which has led to death in two cases in 2011 (Taylor, Paton, and Kapur 2012).

3. **Patient Habits**: such as smoking or the degree of compliance with a drug regime. For instance, the necessary dosages for some anti-psychotic drugs maybe higher for smokers. If smoking cessation or considerable reduction in the number of cigarettes smoked occur, a dosage decrease is usually required. Therefore, active monitoring of smoker patients is necessary to prevent relapse or unwarranted ADRs (Koon 2007).

4. **Drug-drug interactions**: It is well-documented that certain groups of drugs will interact with others. In many cases, if the interaction is known to be high-risk, co-prescribing of these drugs will be avoided unless the benefits outweigh the risks. In other cases, dosage alteration is sufficient to avoid undesired event.

5. **Comorbidity**: is either the presence of one or more disorders in addition to a primary disease, or the effect of such additional disorders. In patients with comorbidities, drug and dosage monitoring or different testing schedules are recommended depending on the case.

**A Multi-Agent System for Preventing ADRs**

Based on the key elements defined in the previous section, we formulate the following objectives:

**Objectives**

1. Minimise erroneous actions by the clinicians which could lead to an ADR, e.g prescriptions overlooking (1) allergies (2) drug-drug interactions (3) possible comorbidities.
2. Enforce adherence to guidelines with respect to routine tests according to the patient’s case. Analyse the results of abnormal tests, finding their links to (1) patient habits (2) comorbidities (3) allergies (4) drug-drug interactions.
3. Monitor changes in the patient records which require further examination by clinicians and possible drug or dosage changes, e.g. smoking habit change.

**The MAS Architecture**

The structure proposed here is adaptable to reactive as well as cognitive behaviour. The type of behaviour is task-
dependent and is implemented by a rule-based engine. We define a MAS as:

\[ \text{MAS} = \langle \mathcal{R}, \mathcal{T}, \mathcal{R}, \mathcal{A} \rangle \]  

(1)

Where \( \mathcal{R} \) the set of roles the agents can assume, \( \mathcal{T} \) is the set of tasks it can claim responsibility for, \( \mathcal{R} \) is the rule base and \( \mathcal{A} \) is the set of all agents running in the MAS.

Agent Roles Apart from infrastructure-managing agents (e.g. database, user interface), our system’s agents assume a set of roles defined around the parameters outlined earlier. Table 2 lists the variables associated with each role.

1. **Test Monitor Agent**: creates a personalised test schedule appropriate to the patient’s case and adjusted to the patient’s personal characteristics (e.g. age), comorbidities and medications. This agent monitors adherence to the schedule it creates by sending reminders of different degrees of urgency to the clinicians using the information found in the records. Two variables record this information for the required tests: scheduled records whether a NICE-recommended test has been scheduled or whether a clinician has scheduled an ad-hoc test and performed records whether a scheduled test has been performed.

2. **Allergy Monitor Agent**: examines the patient records for possible allergies which clash with the clinicians prescription proposals and qualifies their level (none, mild, moderate, severe). This agent is also equipped with a reasoning mechanism providing suggestions to clinicians of alternative medications depending on the type and severity of the allergy.

3. **Compliance Monitor Agent**: We restrict the habit monitoring functionality to monitoring compliance as other functionalities (e.g. smoking habit monitoring) are work in progress. This agent analyses the patient dosage charts, test results and any symptoms or relapse episodes for compliance indicators. The agent uses two variables to measure compliance, a nominal variable compliance which distinguishes between patients who have been taking the drug and those who require re-initiation of the drug due to zero compliance and a fuzzy variable degree, describing the level of compliance in patients who are taking the drug. degree is used by clinicians to assess the dosage required for each patient.

4. **Drug-Drug Interactions Monitor Agent**: collaborates with the comorbidity monitor agent to find instances of interacting drugs and analyses the interaction, qualifying it in terms of level (none, high, low) and mechanism (describing how the interacting drugs affect each other, with values increase, decrease, designating the effect of increasing or decreasing each other’s metabolism rates). The agent also suggests alternative drugs in the case of undesired interactions.

5. **Comorbidity Monitor Agent**: examines the patient’s case for possible dosage alterations specific to the comorbidity. This agent type also seeks to find any undesirable drug-drug interactions and by coordinating with the drug-drug interaction agent. A comorbidity is represented using two nominal variable: present denotes the presence of a comorbidity and type lists the diseases it models.

6. **Symptom Monitor Agent**: monitors the patient records for any symptoms which indicate deterioration or are warning signs for possible ADRs (e.g. a cough maybe indicative of pneumonia, which is a common ADR of using clozapine, an anti-psychotic drug). This agent ranks symptoms using a fuzzy variable indicative which qualifies the likelihood of the symptom-ADR relation as unlikely, possibly and likely. The agent also cooperates with the other agents to isolate the causes of the observed symptoms.

Agent Tasks A task is defined by a triggering set of events, the agent observations made from the events, a set of agent possible observations, a set of agent possible decisions and a set of actions. We therefore define a task \( t \in \mathcal{T} \) by a four-element tuple:

\[ \mathcal{T} : \{ t \in \mathcal{T} : t = (\varepsilon, \sigma, \delta, \varsigma) ; \varepsilon \in \mathcal{E}, \sigma \in \mathcal{O}, \delta \in \mathcal{D}, \varsigma \in \mathcal{C} \} \]  

(2)

Where \( \mathcal{E} \) is the set of all possible events, \( \mathcal{O} \) is the set of all possible observations, \( \mathcal{D} \) is the set of possible decisions and \( \mathcal{C} \) the set of all actions respectively. Each agent role has its own set of permissible tasks, which restrict what the agent can observe, decide and actions it can carry out.

The Rule Base The rulebase \( \mathcal{R} \) implements the hybrid reactive and cognitive nature of the agents by distinguishing two types of rules. More specifically, \( \mathcal{R} = \{ \Theta \cup \Delta \} \), where:

- \( \Theta (\mathcal{O}) \) are the reactive rules, which map the set of observations to actions for reactive tasks.

\[ \Theta : \mathcal{O} \rightarrow \mathcal{C} \]  

(3)

- \( \Delta (\mathcal{O}) \) are the decision rules, which map the set of observations to decisions for decision-making tasks.

\[ \Delta : \mathcal{O} \rightarrow \mathcal{D} \]  

(4)

We assume that the rule set \( \mathcal{R} \) is consistent, i.e. \( \forall r_1, r_2 \in \mathcal{R} \), \( r_1 (e_1 \rightarrow a_1) \land r_2 (e_2 \rightarrow a_2) \), \( a_1 \) and \( a_2 \) do not cancel each other.

The Agents We can now define an agent \( \alpha \in \mathcal{A} \) assuming role \( \mathcal{R} \) as follows:

\[ \alpha_{\mathcal{R}} = \langle \mathcal{K}_{\alpha}, \mathcal{W}_{\alpha}, \mathcal{T}_{\alpha}, \mathcal{R}_{\alpha} \rangle \]  

(5)

\( \mathcal{K}_{\alpha} \) is the domain knowledge base, making up what the agent knows about the domain, \( \mathcal{W}_{\alpha} \) is the working knowledge base, containing the current state of the patient information system retrieved from the patient records which are relevant to the agent. \( \mathcal{T}_{\alpha} \) is the task list defined by the role \( \mathcal{R} \) which \( \alpha \) assumes and \( \mathcal{R}_{\alpha} \) is the subset of \( \mathcal{R} \) relevant to \( \alpha \). \( \mathcal{K}_{\alpha} \) and \( \mathcal{W}_{\alpha} \), along with the rule base \( \mathcal{R}_{\alpha} \) make up the agent’s working memory.

The agent execution follows a perception-reaction cycle repeatedly carrying out the steps shown in figure 1. Algorithm 1 details the observe module, which maps the set of triggering events to observations the agent understands. We omit the details of the decide, reason and act modules for due to space constraints.
Agent Communication and Reasoning

Ontology  We defined an ontology specifying the vocabulary used in the knowledge bases $\mathcal{X}_\alpha$ and $\mathcal{W}_\alpha$, and which the agents use for communication and reasoning.

The ontology consists of three schemas. a concept schema for modeling concepts, a predicate schema modeling predicates used for evaluating rule conditions and an action schema defining agent actions. Figure 2 shows the concept and predicate schemas of the ontology. We omit the action schema due to space constraints.

Rule-based Communication A subset of the reactive rules are dedicated for agent communication whereby the rule actions are communicative messages designated to other agents in the system. The rule-driven process governing agent cooperation is shown in Table 3.

In the table, the columns correspond to the different agents and the corresponding parameters being evaluated, and the rows correspond to the different rules. ● designates the destination of the message sent by the action section of the rule. For example, rule CR3 enforces safety precautions against drug-drug interaction by firing if the comorbidity monitor agent discovers the presence of a comorbidity ($\text{present} = \text{yes}$). The agent then proceeds to prompt the drug-drug interaction agent to check if there are any possible drug-drug interactions.

Implementation

We used the JAVA-based JADE 4.3.0 platform (Bellifemine, Caire, and Greenwood 2007) to implement the system. We used JESS (Friedman-Hill 2003) to implement the rule-based engine. JESS is JAVA-based and includes a toolkit for incorporating fuzzy rule-based reasoning with JADE: FuzzyJess (Orchard 2001). With the help of clinicians, we designed 99 rules, 17 drug-drug interaction rules, 12 allergy conflict rules, 7 compliance rules, 38 routine test rules, 9 comorbidity rules and 16 symptom rules. We populated the

<table>
<thead>
<tr>
<th>Factor</th>
<th>Variable</th>
<th>Values</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-drug interactions</td>
<td>interaction level</td>
<td>none, low, high</td>
<td>Fuzzy</td>
</tr>
<tr>
<td></td>
<td>mechanism</td>
<td>increase, decrease</td>
<td>Nominal</td>
</tr>
<tr>
<td>Allergy conflict</td>
<td>allergy level</td>
<td>none, mild, moderate, severe</td>
<td>Fuzzy</td>
</tr>
<tr>
<td>Compliance</td>
<td>compliance degree</td>
<td>yes, no</td>
<td>Nominal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>occasional, regular, punctual</td>
<td>Nominal</td>
</tr>
<tr>
<td>Routine Test</td>
<td>scheduled</td>
<td>yes, no</td>
<td>Nominal</td>
</tr>
<tr>
<td></td>
<td>performed</td>
<td>yes, no</td>
<td>Nominal</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>present</td>
<td>yes, no</td>
<td>Nominal</td>
</tr>
<tr>
<td></td>
<td>type</td>
<td>disease names list</td>
<td>Nominal</td>
</tr>
<tr>
<td>Transient symptom</td>
<td>indicative</td>
<td>unlikely, possibly, likely</td>
<td>Fuzzy</td>
</tr>
</tbody>
</table>

Table 2: The parameters used for ADR Prevention and Management

<table>
<thead>
<tr>
<th>Rule</th>
<th>D level</th>
<th>A mechanisms</th>
<th>T Scheduled</th>
<th>T Performed</th>
<th>Result</th>
<th>C Level</th>
<th>B Present</th>
<th>S Indicative</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1</td>
<td>high, low</td>
<td>increase, decrease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR2</td>
<td></td>
<td></td>
<td>yes</td>
<td>yes</td>
<td>low, high</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR3</td>
<td></td>
<td></td>
<td>yes</td>
<td>yes</td>
<td>low, high</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR4</td>
<td></td>
<td></td>
<td></td>
<td>yes</td>
<td>low, high</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR5</td>
<td></td>
<td></td>
<td>yes</td>
<td>yes</td>
<td>low, high</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR6</td>
<td></td>
<td></td>
<td></td>
<td>yes</td>
<td>low, high</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR7</td>
<td></td>
<td></td>
<td>yes</td>
<td>yes</td>
<td>low, high</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR8</td>
<td></td>
<td></td>
<td>yes</td>
<td>any</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR9</td>
<td></td>
<td></td>
<td></td>
<td>yes</td>
<td></td>
<td></td>
<td></td>
<td>possibly, likely</td>
</tr>
<tr>
<td>CR10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>possibly, likely</td>
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<tr>
<td>CR11</td>
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<td>possibly, likely</td>
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<td>CR12</td>
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<td>possibly, likely</td>
</tr>
<tr>
<td>CR13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>possibly, likely</td>
</tr>
</tbody>
</table>

Algorithm 1 Observe Algorithm

Input: $e \in \mathcal{E}, \kappa \in \mathcal{T}_\alpha$  
Output: $o \in \mathcal{O}_\alpha$

1: for $t : (e, \sigma, \delta, \varsigma) \in \mathcal{T}_\alpha$ do
2: if $e \in \epsilon$ then
3: $\mathcal{P} \leftarrow \{(t, \sigma) : \mathcal{P}\}$
4: if $t \equiv \kappa$ then  
5: $o \leftarrow \sigma$
6: else
7: push($e$, eventQueue)
8: end if
9: end if
10: end for

ontology using:

- For drug-specific information including naming, interactions, allergies and side effect, we used the electronic Medicines Compendium (eMC)\(^1\).
- For ADRs, routine tests, comorbidity, test result thresholds and appropriate dosages, we used the SLAM prescribing guidelines (Taylor, Paton, and Kapur 2012).

**Experimental Results**

We performed a case study built around mental health patients with bipolar disorder in the South London and Maudsley NHS foundation Trust to assess the system’s ability to retrospectively identify the factors contributing to ADRs from patient records. The study involved the three antipsychotic drugs shown in Table 1 (lithium, valproate and carbamazepine). We analysed the records of 253 bipolar patients who developed ADRs and were prescribed at least one of the three drugs. The aim was to assess the platform’s ability to qualify the six different parameters based on the information found in the records. We evaluated the results by consulting with clinicians when necessary or by a thorough examination of the records. The results are given in Figures 3 and 4 and are detailed below.

1. 29 ADR cases in which symptoms were not taken into consideration by clinicians. For example, in 9 cases, carbamazapine-related pneumonia occurred where the records contained indications of a cough or flu in earlier entries in the patient records.
2. 38 cases of allergy-induced ADRs. Again, the patient entries recorded allergy entries but the clinicians failed to spot them. In 10 cases, the patient showed mild symptoms that were not used by the clinicians.
3. Missed routine tests were the leading factors to 28 cases of renal failure, 2 strokes and 9 ADRs associated with thyroid function. Out of these, 7 cases were also due to inappropriate test schedules in the presence of comorbidities (e.g. not performing the necessary tests required for ruling out cardiac effects in high-risk patients) and 14 cases were due to inappropriate test schedules which overlooked drug-drug interactions (for example, not scheduling appropriate renal function tests when additional drugs

\(^1\)http://www.medicines.org.uk/emc/glossary.aspx?view=130
4. A large number of ADRs (78) were due to comorbidity and drug-drug interactions. For example, 38 cases were due to an inappropriate dosage of insulin given to diabetic patients who were prescribed valporate. Valporate increases the concentration of insulin in the plasma and caution should be taken when co-prescribing it with valporate. In most cases, the insulin dosage given was a reduced one, but was not appropriate for the patient’s case.

Discussion, Conclusions and Future Work

In this work, we presented the first phase of a multi-agent system for the management of factors contributing to the onset of adverse drug reactions. There are several key novelties in the system: (1) it builds a general rule-based framework which can be used to implement multi-agent systems for similar problems (2) it uses multi-agent communication to investigate multiple factors contributing to abnormal events due to prescribed medications (3) it manages the scheduling of events for patient care as per medical guidelines and thus reduces the chance of occurrence of ADRs due to negligence. We validated the first phase using real patient information with the help of clinicians and identified cases where the system was able to correctly discover factors that attributed to the onset of ADRs.

As this is the first phase, there are aspects not covered in this work: (1) monitoring factors that map to variables requiring a temporal representation (e.g., smoking habit change, weight gain or loss and quantifying it as rapid or slow) (2) devising a reasoning engine which relates the recommended dosage to personal attributes such as gender, age and ethnic background (3) a reasoning engine for analysing test results and investigating the possible causes of abnormal results, linking them to other elements found in the records. We are also currently working on creating ontology entries for drugs other than the ones considered here and devising additional rules if required.

References


