Application of Formal Method in Drug Allergy Process Framework Specification

Zacchaeus Oni Omogbadegun
Department of Computer & Information Sciences, College of Science & Technology, Covenant University, Ota, Ogun State, Nigeria
Email: zacchaeus.omogbadegun@covenantuniversity.edu.ng

ABSTRACT
Healthcare delivery is a collaborative process with many healthcare practitioners from multiple healthcare organizations participating in patients’ treatment. Allergies affect nearly one-fourth of the world population and cause or contribute to significant chronic illness. Consequently, high prevalence of allergic disease, its rising trend over time and the appearance of new allergens to which patients react, there is a demonstrated need to formalize the specification of detecting and resolving various drug allergies. We used Z-specification language notations and Business Process Management tools to generate a formal specification of drug allergy business processes framework that fulfills structural soundness property as an integral part of an enhanced collaborative virtual healthcare system. This provides the much-awaited means of unifying design methods so as to better understand usability phenomena supporting enhanced virtual collaboration that would have high level of success assurances possible in healthcare. In improving clinical quality, safety and access to health care in the remotest areas of the developing world, health care systems have to be reorganized to systems that function in a cross-border fashion. A significant redesign of healthcare business processes with formal methods to prevent adverse outcomes in medication administration is desirable.

Keywords: chronic diseases, collaborative, drug allergy, formal methods, healthcare business process

1. Introduction
Health care is primarily about people-to-people interactions, understanding, diagnosis, physical contact, communication, and ultimately, providing care. Healthcare delivery is a collaborative process with many physicians, healthcare specialists, nursing staff and healthcare technicians from multiple healthcare organizations participating in the treatment of patients[1]. Clinical work in modern hospitals is characterized by a high degree of mobility, frequent interruptions, and much ad hoc collaboration between colleagues with different expertise. Pharmacies permeate and interconnect various actions developed in different sectors within the complex process of the use of drugs in a hospital. The health care systems have to be reorganized to systems that function in a cross-border fashion. This demands a significant redesign of business processes, which is only possible if a change from the enterprise-centric view to a system-wide perspective with the patient/citizen at the centre is to be achieved [2].

2. Drugs and Allergy
Drugs are one of the main tools of medical therapy and are a significant part of hospital budgets. Different health systems provide services to allergy patients through both the primary and secondary care sectors, with large variations between countries.

Among the factors that influence the likelihood of allergic drug reactions are the dose of the drug, how the drug is metabolized and the degree to which the drug and metabolites bind to human proteins, the route of exposure, and the sensitivity of the individual as determined by age, genetics, and environmental factors. Drug allergies appear to develop with equal frequency in atopic and nonatopic individuals. In addition, patients with a history of drug allergy appear to be at increased risk of adverse reactions to other pharmacologic agents. Age seems to be related to the risk of allergic reactions because they occur less frequently in children. This may be related to immaturity of the immune system or decreased exposure. The presence of some concurrent diseases predisposes to drug reactions [3].
When a provider administers a medication, the collaborative virtual healthcare system will support matching each medication and the patient’s ID bracelet and alert the provider in real-time of potential administration errors such as: wrong drug, wrong dose, wrong route, wrong time and patient. In addition, other clinical checks, such as allergies, drug-lab and drug-drug interactions can be performed at the time of administration. After a drug reaction has been characterized, specific treatment can be instituted. The investigation and management of patients with a potential history of an allergic reaction to drugs are one of the most challenging tasks an allergologist encounters in his or her practice. The first and probably the most important step is to obtain a good clinical history and all the available information regarding the details of the drug(s) implicated in the allergic reaction, particularly dosage, route of administration, exact interval between administration of the drug and the onset of the reaction, and all clinical details regarding the reaction. For most drugs there is a paucity of information regarding the underlying mechanisms contributing to acute allergic reactions. Therefore, in cases where there is limited literature or where the drug is known to mediate allergic reactions by more than one pathway, screening for drug allergies by skin prick testing (SPT), intradermal tests or radioallergosorbent testing (RAST)) will not be sufficient to rule out drug allergy. This method poses serious dangers in precipitating life-threatening allergic reactions [4]. Fig. 1 presents a clinical approach to a patient with suspected allergic drug.

2.1. A general approach to a case of drug allergy

<table>
<thead>
<tr>
<th>Clinical history of allergic reaction to drug/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the suspected drug known to mediate the reaction via IgE?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Is RAST available?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Perform RAST</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Is it important the patient receives this drug?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Challenge test</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Consider desensitization</td>
</tr>
<tr>
<td>Drug allergy confirmed</td>
</tr>
<tr>
<td>Drug allergy excluded*</td>
</tr>
<tr>
<td>Drug allergy excluded</td>
</tr>
</tbody>
</table>

Fig. 1 The clinical approach to a patient with suspected allergic drug [4]
2.2 Epidemiology

Allergic diseases affect nearly one-fourth of the population and cause or contribute to significant chronic illness. Adverse drug reactions (ADRs) are any noxious, unintended, or undesired reactions to or effects of a drug that occur at doses used in humans for prophylaxis, diagnosis, or treatment representing an increasing problem in clinical medicine. Adverse drug reactions constitute a common medical problem in all countries. It has been reported that allergic reactions to drugs account for 5–10% of ADRs and probability of allergic reaction for most drugs is 1–2% [4]. Adverse drug reactions are a major cause of morbidity and mortality worldwide. It has been estimated that 5–15% of patients develop adverse reactions to medications during treatment. This number increases to 30% for hospitalized patients. Of all hospital admissions, approximately 0.3% are due to adverse medication reactions. ADRs account for 2–6% of all hospital admissions [5]. Approximately 3–5% of hospitalizations are due to drug reactions, and 10–15% of hospitalized patients suffer from adverse drug reactions during their hospital stay. Drug allergies are a serious problem: 0.32% of hospital patients die from adverse drug reactions in the United States, corresponding to 106,000 estimated fatalities in 1994 (the fourth commonest cause of death in the United States) [6].

Drug intolerance is defined as an undesired effect produced at therapeutic or subtherapeutic dosages, whereas idiosyncratic reactions are uncharacteristic reactions that cannot be explained by the known pharmacologic reactions of the drug. Diseases exacerbated by allergy, as well as primary allergic disorders, are among the most common disorders seen by primary care physicians. Allergic-influenced diseases include allergic rhinitis, ophthalmic allergies, asthma, urticaria and angioedema, atopic dermatitis, drug allergies, food allergies, anaphylaxis, and stinging insect allergies [7].

3. Methods

The entire project adopted the state-based notations Z/Object-Z, event-based notation for the specification, Communicating Sequential Processes (CSP)/Timed-CSP using graphical modeling notations (StateChart and Unified Modeling Language (UML) complemented by Coloured Petri Nets); Formal verification by Model-Checking with SPIN and PROMELA; Implementation of the prototype with JAVA; and Experts’ (Healthcare professionals and Patients) collaboration and evaluation of the system to determine effectiveness performance.

This paper extracts use of Z-specification language and Business Process Management (BPM) tools from the enumerated set.

3.1. Formalization

The main building block of a Z-specification language is a two-dimensional graphical structure called a schema. A schema is analogous to a subroutine or procedure of a programming language. It represents the static aspects (the states) and the dynamics aspects (the operations on the states) of a system. Schemas can also be expressed in terms of other schemas. Fig. 2 shows the basic structure of a schema.

![Fig. 2 A Z Schema](image)

The schema name should be meaningful. This name can be used by another schema for reference. The signature declares the names and types of the entities (the state variables) that define the system state. The predicate defines relationships among the state variables by means of expressions which must always be true (data invariant). Predicates can specify initial values of variables, constraints on variables, or other invariant relationships among the variables. When there are more than one predicate, they are either written on the same line separated by the and operator or written on separate lines (as if separated by an implicit ). Predicates may also be specifications of operations that change the values of state variables. Operations define the relationship between the old values of the variables and the operation parameters to result in the changed values of the variables. Operations are specified by specifying pre-conditions and post-conditions. Pre-conditions are conditions that must be satisfied for the operation to be initiated. Post-conditions are the results that accrue after the operation is complete [8].
3.1.1 DefineAllergy

By following established steps in developing Z-language specifications i.e. present the given, user-defined, and global definitions; define an abstract state; define the initial state; and present the state transition operations, we demonstrated these in the immediate section:

Doctors write prescriptions [9] after interacting with a patient. Such prescriptions consist of drugs, patients name, doctor name, and the drugs administration. A patient could be allergic to one or more drugs. (Generally a patient could be allergic to a drug or elements such as pollen, nuts, etc. The function Allergy relates Patient to Drug. These are captured under the same name of drugs).

\[
\text{DefineAllergy} \\
\text{Allergy : Patient } \rightarrow \text{ Drug}
\]

Fig. 1 Formal DefineAllergy Function

Initially, the Allergy list is empty. This fact is captured in the schema AllergyInit, depicted in Fig. 4.

\[
\Delta \text{DefineAllergy} \\
\text{allergy'} = \{\}
\]

Fig. 2 Formalized Allergy Function Initialized

3.2.2 AddAllergy Schema

When a doctor diagnoses a patient to be allergic to a drug, the doctor adds this fact to the allergy list using AddAllergy operation. This is represented in Fig. 5.

\[
\text{AddAllergy} \\
\text{DefineAllergy} \\
\text{drug? : Drug} \\
\text{patient? : Patient} \\
\text{(patient?, drug?) } \not\in \text{ allergy} \\
\text{allergy} = \text{allergy} \cup \{(\text{patient? } \mapsto \text{Drug?)}\}
\]

Fig. 3 AddAllergy Schema

3.2.3 Prescription

Now, the system should not allow a doctor to prescribe drugs to which the patient is allergic. The schema Prescription captures this requirement and the process of a doctor prescribing medicine, and this is represented in Fig. 6.
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Prescription

\[ \text{DefineAllergy} \]

\[ \text{Doc?} : \text{Doctor} \]

\[ \text{Pat?} : \text{Patient} \]

\[ \text{drug?} : \text{Drug} \]

\[ \text{PrescriptionList, PrescriptionList}^\prime : \text{P Drug} \]

\[ (\text{Pat? drug?}) \notin \text{allergy} \]

\[ \text{PrescriptionList}^\prime = \text{PrescriptionList} \cup \{\text{drug?}\} \]

Fig. 4 Prescription Schema

The \( \text{E} \) operator is used in the signature section of this schema to indicate that the schema \text{DefineAllergy} is used here but its variable values will remain unaltered after the operation.

4. Discussion

A graph \( G \) consists of a set of nodes, \( V \), and a set of edges, \( E \). Each edge \( e_i \) is defined by a pair of nodes \( (v_i, v_j) \). A graph can be directed, meaning \( (v_i, v_j) \neq (v_j, v_i) \), or undirected, meaning \( (v_i, v_j) = (v_j, v_i) \). It can also be weighted, meaning each edge \( e_i \) has an associated numerical weight \( w(e_i) \). In some cases, it is convenient to treat the weight function as a function from \( V = V \) to real numbers (denoted \( w : V \times V \rightarrow R \)).

An \textit{activity} is a piece of work to be done. An activity might be, for instance, a manual activity like drug administration, patient diagnosis, drug prescription, or an automated activity, like invoking a script or e-prescription. An activity can also be a decision, e.g., between two further activities, or another situation like waiting for previous activities to finish, e.g., patient diagnosis before drug prescription. An \textit{activity instance} is a concrete realization of an activity. Examples of an activity instance are actually diagnosing a patient, actually prescribing a particular drug, or an actual administration of intra-venous fluid (IV). A \textit{control flow} defines temporal execution dependencies between activities. An example is patient diagnosis and thereafter prescribe drugs. Control relations are written as pairs of activities, e.g., (Diagnose Patient, Prescribe Drugs). We assume transitivity of control flow relations, but not symmetry and reflexivity for doing so leads to medical errors. A \textit{process} is a set of activities related by control flow.

4.1 Process Graph

A \textit{process graph} \( G = (N, E, T) \) is a triple representing a business process:

- \( N \) is a nonempty set of nodes,
- \( E \subseteq (N \times N) \) is a set of directed edges between nodes, and
- \( T : N \rightarrow \{\text{ACT, XOR, AND, DISC, OR, RIM}\} \) is a total function assigning a type to each node.

A process graph resembles the graph structure of business process notations that is applied in this paper. The structure of a simple patient diagnosis process is captured in a process graph as exemplified in Fig. 7.

Our running example might consist of activities: (P) \text{Prescribe drug}, (A) \text{Administer drug}, and (O) \text{Observe drug allergy}. The dependencies are straightforward: P has to happen before A and A has to be finished before O, accordingly, the control flow relations are given as (P, A), (A, O). A \textit{process instance} is the concrete realization of a business process. An example of a process instance in healthcare services delivery is actual monitoring the drug allergy. Interaction flow defines temporal dependencies between two activities of different processes. An example is patient diagnosis and drug prescription as to diagnosis. Interaction flow relations are written as pairs of activities from different processes (Diagnose Patient, Prescribe Drug). An interaction is given by a set of processes related by interaction flow. An example of interaction is given by Patient Registration, Diagnosis, Prescription, Drug Administration, Drug Allergy Check/Monitoring.

Formally, the patient diagnosis business process starts at the left-hand side with a \textit{start event}, denoted as a circle (N1). Afterward, the control flow is split into two parallel branches using a parallel split gateway (the
interpretation of the “+” sign, here (N2), is quite different compared to its interpretation in process algebra. A patient is registered and diagnosed concurrently, represented by N3 and N5.

Afterward, the control flow is joined with a synchronizing merge gateway, denoted with an “O” inside, (N6). This kind of merge waits for all activated, preceding branches to finish before continuing the control flow further downstream. If that happens, the diagnosis is (quality) checked (N7). If the quality check fails, the patient is diagnosed again (N8, N4), while otherwise the business process terminates with an end event (N9). The condition is evaluated using an exclusive choice gateway denoted with an “X” inside. If a patient is diagnosed again, the synchronizing merge gateway pays for its considerable implementation cost, since in the second iteration it only waits for the diagnose patient activity (N5) to finish before continuing the control flow.

Formally, a process graph is defined as a triple. In our Simple Patient Diagnosis Process diagram above (Fig. 7),

- \( N = \{N_1, ..., N_9\} \)
- \( E = \{(N_1, N_2), (N_2, N_3), (N_2, N_4), ..., (N_8, N_9)\} \)
- \( T = \{(N_1, ACT), (N_2, AND), (N_3, ACT), (N_4, XOR), (N_5, ACT), (N_6, OR), (N_7, ACT), (N_8, XOR), (N_9, ACT)\} \)

4.2 Structural Soundness

In addition to the function \( T \) in our definition of process graph, we would introduce some notation to relate nodes with their connecting edges. Let \( N \in N \). Then \( \bullet N = \{(X, N) \in E\} \) denotes the set of incoming edges for node \( N \), whereas \( N\bullet = \{(N, X) \in E\} \) denotes the set of outgoing edges of node \( N \). Moreover, \( R(E) \) denotes the transitive closure of \( E \). For presentational convenience, we restrict the types of process graphs considered to a subset known as structurally sound process graphs. This restriction is taken over from workflow theory and simplifies the theory without restricting its expressive power.

Let \( G = (N, E, T) \) be a process graph. \( G \) is structurally sound, if the following properties hold:

- There is exactly one node \( \text{init}_G \in N \) with no incoming edges, i.e., \( \bullet \text{init}_G = \emptyset \) and \( \forall N \in N \setminus \text{init}_G: \bullet N \neq \emptyset \); \( \text{init}_G \) is called the initial node of \( G \).
- There is exactly one node \( \text{final}_G \in N \) with no outgoing edges, i.e., \( \bullet \text{final}_G = \emptyset \) and \( \forall N \in N \setminus \text{final}_G: \bullet N \neq \emptyset \); \( \text{final}_G \) is called the final node of \( G \).
- Every node \( N \in N \setminus \{\text{init}_G, \text{final}_G\} \) is located on a path from the initial to the final node of \( G \), i.e., \( (\text{init}_G, N) \in R(E) \) and \( (N, \text{final}_G) \in R(E) \).

Furthermore, we require that the type of the initial and the final node is always \( ACT: T(\text{init}_G) = ACT \) and \( T(\text{final}_G) = ACT \). The example of Fig. 7 fulfills the structural soundness property.
5. Conclusion

Medicine is an ever-changing science. Allergy, in which the immune system over-reacts to everyday stimuli, is a growing problem. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. Adverse drug reactions have been established as a major cause of morbidity and mortality worldwide. Continuity of care requires a cooperative environment among autonomous complementary medical departments in terms of data and functions. Despite the difficulties inherent in evaluating drug allergy, appropriate clinical data should be obtained to evaluate a drug reaction. Key points that should be addressed include complete review of all the presenting signs and symptoms; identification of any other causes (underlying illness) of the signs and symptoms; list of all medications, with starting time, stopping time, route of administration, and dose changes; temporal relation between the administration of the drug and the drug reaction; complete history of previous drug reactions; and knowledge about whether the medications used have been associated with similar drug reactions. This aspect of the project has formalized the specifications of drug allergy business processes that fulfill structural soundness property as an integral part of the targeted enhanced collaborative virtual healthcare system.

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References

Biographies and Photographs


![Zacchaeus Oni Omogbadegun](image)