

Model Driven Engineering for Large-Scale Clinical Research

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Abstract—Scientific progress in medicine is increasingly dependent upon the large-scale integration of data from a range of sources. This data is acquired in different contexts, held in different systems, and subject to different processes and constraints. The value of the integrated data relies upon common data points having a consistent interpretation in each case; to achieve this at scale requires appropriate informatics support. This paper explains how a model-driven approach to software engineering and data management, in which software artefacts are generated automatically from data models, can be used to achieve this. It introduces a simple data modelling language, consistent with standard object modelling notations, together with a set of tools for model creation, maintenance, and deployment. It reports upon the application of this approach in the provision of informatics support for two large-scale clinical research initiatives.

I. INTRODUCTION

Scientific progress in medicine consists principally in the introduction of new diagnostics and new therapeutics: new ways of figuring out what is wrong, and new ways of doing something about it. The causes of disease, the expression of symptoms, and the response to treatment, can be extremely complex, involving many levels of biology—genomics, proteomics, metabolomics—and a wide variety of lifestyle and environmental factors.

To obtain the evidence to support the introduction of a new diagnostic or therapeutic, while taking account of the variations in biology and environment, we need to make detailed, comparable observations of a suitably large number of individuals. These observations will be made by different people, under different circumstances, and stored and processed in different information systems. A significant degree of coordination is required to achieve an adequate combination of detail and comparability.

One means of achieving this involves prior agreement upon a prescribed dataset: a precise specification of the observations needed to answer a particular question. An information system is then implemented or configured to match this dataset, and staff are trained to acquire data to match the prescribed interpretation. This can be time-consuming and expensive. Furthermore, the data acquired is unlikely to be re-used: not only is the dataset as a whole tailored towards a particular question, but the same may be true of the individual observations.

It should be clear that this is unnecessary. A dataset can be composed by drawing upon, and adding to, a library of existing data definitions. As a precise specification, it can be

used as the basis for the automatic generation or configuration of an information system for data capture, reducing costs while enhancing the value of the data obtained. The enhanced value comes in part from the fact that some of the data has been recorded against existing definitions, but also from the fact that definitions are readily available—in a re-usable, computable form—for all of the data collected.

Costs can be further reduced, and scientific progress accelerated, by re-using data already collected: in other scientific studies; in the course of care delivery; or from other sources, including new sensor technologies. Precise data definitions are important here also: we need to know whether the data already collected is fit for purpose, whether its interpretation is consistent with the analysis that we intend to perform. In most cases, these definitions will be created retrospectively, by progressively adding information about the context of collection, and any subsequent processing, until the interpretation of the data is clear.

Having created precise definitions for existing data, we can enhance the value of the data, and reduce the costs of research, by making these definitions available in a standardised, computable form. In designing and proposing a new clinical study, researchers can take account not only of what questions have been asked before, but also of what data already exists, in other research databases or in clinical information systems. In this way, we can eliminate unhelpful variation in study design and unnecessary duplication of effort in data collection.

Furthermore, if we have both precise definitions of existing data, and precise definitions of data requirements for a study, then we can provide automatic support for aspects of study design and delivery: definitions can be compared, queries can be generated for data extraction, and—if summary metadata on the contents of existing databases is available—the feasibility of a particular study can be assessed in advance.

Scientific progress in medicine is increasingly dependent upon this kind of automatic support for data management and integration. Without it, we will be unable to assemble the evidence needed—detailed, comparable data on thousands or millions of individuals—to produce new insights, to validate new discoveries, and to support the introduction of new diagnostics and therapeutics into clinical practice.

This paper explains how a model-driven approach to software and data engineering can provide the support required for large-scale clinical research. It introduces a simple data

modelling language, consistent with standard object modelling notations, together with a set of tools for model creation, maintenance, and deployment. It then reports upon the experience of applying these tools within two large-scale clinical research initiatives.

One of these initiatives involves the re-use of data captured in existing clinical information systems. In the area of translational research, in which new innovations are developed and evaluated in the context of clinical practice ('from bench to bedside'), the data needed to support the science is often the same as that needed to support high-quality care delivery and service improvement. In existing clinical systems, however, the same observation may be recorded in many different ways, and there are significant challenges.

The other involves the development of new information systems for data acquisition and management, as well as the customisation and re-use of existing systems wherever possible. Here, the emphasis is upon defining new, generic datasets, in specific therapeutic areas, with the aim of supporting a wide range of studies using the data collected. A particular challenge for informatics development and data re-use stems from the constant updating of these datasets to take account of new knowledge, new constraints, and new objectives.

Together, these initiatives provide an initial validation of the approach. The software tools are in use by clinical researchers, rather than the software engineers responsible for their design. Data is being collected to the definitions that they have produced, using software that they have generated. It is too early to undertake any quantitative, comparative evaluation; however, it is our hope that a report of the approach taken, and the experience gained thus far, will be useful to those working in the field of automated software engineering.

II. DATA MODELS AND METADATA

A. Data models

A dataset definition for clinical research will consist of a number of different parts, each of which declares a set of related data items. Typically, this will be a set of data items that would be collected together: in the completion of a 'case report form' in a study, or in the report of a clinical event. These parts may be 'repeating', in that there may be more than one form of that type completed, or more than one event of that type reported upon.

A data item declaration should explain not only the name under which values are to be stored, but also the type of those values. If the type is numeric, then the unit of measurement should be given. If the type is an enumeration, then the intended interpretation of each value should be explained. Finally, the parts of the dataset may be connected or related to one another, and these relationships may have constrained multiplicities.

It should be clear that a dataset definition can be represented as a class diagram or object model. Data items can be introduced as attributes, parts of the model as classes, and relationships between classes as associations—complete with multiplicities. Data types and enumerations can be used to

support attribute declarations, and hence data item definitions; constraints can be used to express range restrictions and intended relationships between data items.

Class diagrams can be used also to provide precise definitions for data sources: existing clinical systems or research databases. These systems may be implemented using a combination of technologies but, assuming that the value of the data justifies the effort required, precise object models can be created to describe the interfaces that they might present for data re-use.

B. Models as metadata

Having constructed precise object models to describe datasets and data sources, we can use them as a basis for automated software and data engineering. This involves the use of models as metadata in three respects: for software artefacts that are generated or configured; for data that these artefacts store or process; and for other models, capturing relationships between data points declared in different models, and hence the data stored or processed against them.

For the first of these, we need only maintain the relationship between the implementation and the model that was used to generate or configure it. If the model is stored in a repository or *model catalogue* and published, then we have only to create a link between the implementation and this published instance. This link may be created automatically in the case where the model is generated, partially or completely, from an existing implementation: for example, from the schema of a relational database.

For the second, a link must be created between each data point, or collection of data points, and the corresponding declaration in the data model. The model catalogue then requires some support for the language in which the data model is expressed, sufficient to support the creation and manipulation of links to specific components: in particular, to specific classes and attributes. If the data is acquired or processed using a software implementation for which a data model has already been registered, then that model may provide a basis for the automatic creation of a link to the corresponding declaration.

For the third, we need the same ability to create and manipulate links between components of different models. Instead of links between model and implementation, however, we have links representing different kinds of relationships: provenance and re-use of model components; versioning of models; and, most importantly, *semantic relationships* between attributes or classes—assertions that one attribute or class has the same meaning or interpretation as another. This is precisely the information needed to support automation in data discovery, integration, and re-use.

C. Data Model Language

The core features of our modelling language are familiar: classes, associations, attributes, constraints, enumerations, data types. However, our interpretation of these features is narrower than that set out in, for example, the specifications of the

Unified Modeling Language (UML) [1] or Ecore [2]. For this reason, and because of the need to refer explicitly to models and capture semantic relationships between models, classes, and attributes, we define a domain specific language for data models.

We extend this language to include additional modelling features pertaining to certain kinds of implementation artefacts, such as forms, messages, databases, and documentation. This is necessary only when the feature in question may have a bearing upon the data semantics, and may thus serve as a source or target for a link describing a property or relationship.

For example, a section of a form, corresponding to one or more classes of data, might comprise information about allergies. We may wish to link this section to a term in an ontology recording this fact. This makes it easier for someone interested in models of allergy information to locate and possibly re-use the definitions; it also adds context to any semantic links to data classes and attributes associated with that section.

The generated or configured part of an implementation may include features not described by the data model. This will be the case wherever a model-driven or generative approach has been adopted in the development of an application. In this case, the artefact generated from or represented by the data model is itself a model, in a different modelling language. The use of a data model, in our domain specific language, as metadata for this other model should come as no surprise: it is no different from the use of a model as metadata for program source code.

III. IMPLEMENTATION

A. Data Model Language

The data model language was implemented using the Eclipse Modeling Framework (EMF) [3], with the class and association entities being based upon Ecore [2] classes. Additional metaclasses were included to represent attributes as *data elements*, and the range of values permitted as *value domains*. A value domain has an associated *datatype*, specifying representation, with an optional notion of *units*.

Language extensions for specific implementation types were implemented in the same framework. As an example, consider the metamodel for forms shown in Figure 1, which includes an additional class *Section* alongside the core classes *DataClass*, *DataElement*, *DataConstraint*, and *DataAssociation*. This class may contain any *DataConcept*, including *Section* itself. As a subclass of *DataConcept*, it can be linked to data concepts in other models. Other metaclasses, including *ValueDomain* are not shown.

B. Model Catalogue

The model catalogue stores classes, data elements, constraints, and associations only as components of data models. It stores also administrative links between models—recording, for example, the fact that one model is a new version of another—and semantic links between data concepts: classes and elements.

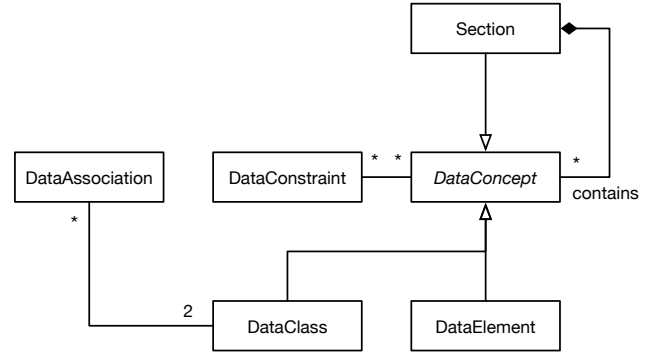


Fig. 1. Extending the data model language

In the current version of the catalogue, associations are not considered as concepts for semantic linking. The instantiation of an association as a reference type is a platform-specific concern, and thus associations are quite different from ordinary data elements or attributes, in having only an abstract notion of a value domain.

At present, if we wish to reason about an association as a concept, we need to introduce an explicit reference or identifier type into our model. This is analogous to the use of foreign keys in a relational database. It would, however, be a relatively straightforward matter to allow linking of associations as abstract data concepts.

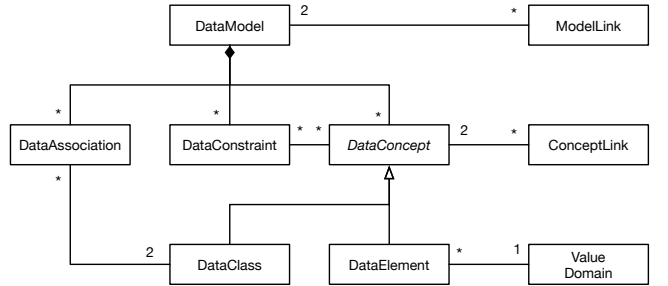


Fig. 2. Model catalogue contents

Figure 2 is a simplified representation of the information stored. The actual implementation includes also the notion of a *ValueConcept*, which may be used to support semantic linking of value domains and—in the case of an enumerated value domain—the value elements they contain.

C. Metadata registration

In designing the language, we gave due consideration to the ISO/IEC 11179 international standard for metadata registration. This standard sets out a metamodel for data definitions, together with a set of processes for their registration and publication: the core set of metaclasses is shown in Figure 3.

In the ISO/IEC 11179 standard, data elements correspond to individual data points and may be grouped or classified into ‘data element concepts’. Each concept represents a set

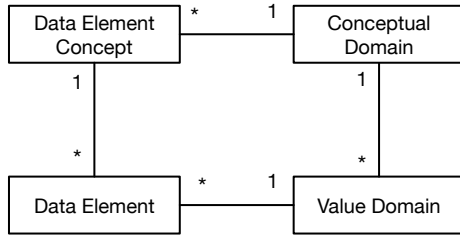


Fig. 3. ISO/IEC 11179 core metaclasses

of data elements that are capturing ‘conceptually’ the same information: for example, different ways of measuring blood pressure. Value domains are classified into ‘conceptual domains’, representing different ways of recording the same kind of observations.

The only other form of semantic link supported by the standard is the classification of data element concepts according to a single property-based hierarchy. A single classification scheme is unlikely to capture semantic information in a way that suits the purposes of different users, and represents a problem for registration: who is to decide quite where a new data element fits within the existing hierarchy?

The approach taken in our implementation of the model catalogue is more general: the use of semantic links supports multiple classification schemes, and allows the representation of relationships other than simple taxonomies. However, it should be clear that our catalogue could be used, under suitable constraints, as an effective implementation of the ISO/IEC 11179 standard.

This applies also to the processes of registration, versioning, and publication. Every object stored in the catalogue is managed as an *administered item*, in the language of the standard. The richer notion of linking in the catalogue implementation allows us to exploit this administrative information in the automatic creation and maintenance of semantic links, and the administrative processes are generalised to provide support for collaborative development, but the option of a constrained form of implementation remains.

D. Technology platform

The existing model catalogue is built using the Groovy/-Grails framework, which takes a model-view-controller approach to data management and presentation. The key advantage of this platform has been the ability to revisit the underlying data representation—the domain model—without needing to re-implement the presentation layer, and vice versa. As the software was developed in the course of application, this was particularly important.

The plug-in architecture of the framework allowed us to add in cross-cutting features—such as global search, access control, and a collaboration environment—without re-engineering the data representation and presentation aspects. This architecture, and the built-in support for domain-specific

languages, was particularly helpful in the development of model import and export pipelines: facilitating the generation and configuration of software artefacts from models, as well as the generation of models for existing artefacts.

The web interface was developed using the AngularJS JavaScript library, which worked well in support of the continuing iteration of the design through interaction and collaboration with users. Although the users were highly-skilled clinical scientists, they had little or no intuition or experience in data modelling. Concepts such as inheritance, reference, composition, and instantiation were unfamiliar and confusing to them. Only through close collaboration were we able to develop a presentation of these concepts that they found accessible.

The persistence layer was implemented using the Grails Object Relational Mapping (GORM), enhancing portability but creating some concerns with regard to scalability: no performance issues have been encountered to date, but the potential exponential increase in complexity, as further linked models are added, and further relationships are inferred, means that an alternative platform may need to be considered.

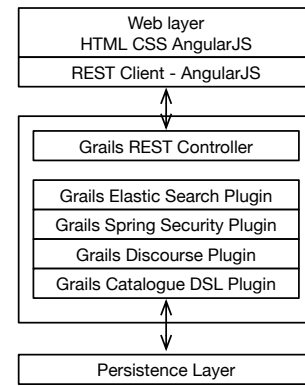


Fig. 4. Implementation architecture

The current technology stack is shown in Figure 4. The discourse plugin provides support for collaborative development of models and data definitions, with users able to contribute to a comment history for each administered item, prompting responses from other users as necessary. This proved particularly important given that many of the clinical scientists were contributing to the dataset development in their spare time.

E. Generation pipelines

The existing implementation has been used to generate several different types of artefact, including:

a) *Case report form models for consumption by the OpenClinica clinical trials management system*: These take the form of Excel spreadsheets with columns specifying form structure, question text, response types, logical constraints (including skip logic), and presentation controls. These models are generated from form models in the data modelling language by way of a complex transformation: the hierarchical

structure of the data model is flattened to produce lists of sections, repeating groups, and questions. Default values and implementations are included as part of the transformation: for example, we provide custom validation for textual fields that are tagged with constraints in the form of regular expressions.

b) Database triggers: To support the automatic processing of data received from the clinical trials system, we require a collection of triggers for the underlying database. These ensure that the combination of existing and newly-received data is properly normalised. This is particularly important where data is being collected against different versions of the same form.

c) XML schemas for electronic document submission: This is a more straightforward transformation, as the structure of the XML schemas is closer to that of the data models. However, additional processing is required to produce normalised, readable schemas. For example, if there are several data elements sharing the same value domain, we would wish to include that value domain only once within the schema.

d) Tools for creating and validating .csv files: For some of the systems that we are working with, the easiest way to import or export information is in comma-separated value format. In this case, we are not generating a specification of the data format in some implementation language; we are instead generating tools that will ensure that the values presented in a file comply with the model constraints.

e) Data manuals: Datasets and data standards in health informatics are communicated through documents in which each data point is listed along with its intended interpretation. By generating these manuals automatically, we are able to ensure consistency between the information that they present and the tools used for data acquisition and processing. The models used to generate the manual are semantically linked to those used for XML schema and case report form generation.

IV. EXPERIENCE

A. Re-use of data from clinical information systems

The UK National Institute of Health Research (NIHR) is funding an £11m programme of work across five large university-hospital partnerships: at Oxford, Cambridge, Imperial College London, University College London, and Guy's and St. Thomas'. The aim of the programme is to create the infrastructure needed to support data re-use and translational research across these five institutions.

The programme, the NIHR Health Informatics Collaborative (HIC), was initiated in 2013, with a focus upon five therapeutic areas: acute coronary syndromes, renal transplantation, ovarian cancer, hepatitis, and intensive care. The scope was increased in 2015 to include other cancers—breast, colorectal, lung, and prostate—and other infectious diseases, including tuberculosis.

The key component of the infrastructure consists in repositories of patient data within each of the five institutions. The intention is that these repositories should hold a core set of data for each therapeutic area, populated automatically from clinical systems, together with detailed documentation on the provenance and interpretation of each data point.

Researchers can use the documentation to determine the availability and suitability of data for a particular study. They can use it also to determine comparability across institutions: whether there are any local differences in processes or equipment that would have a bearing upon the combination and re-use of the corresponding data. Once a study is approved, the repositories act as a single source of data, avoiding the need for data flows from individual clinical systems.

The development of the infrastructure required the development of a 'candidate data set' for each therapeutic area, as a core list of data points collected in the course of routine care that would have value also in translational research. Each institution then set out to determine which information systems, within their organisation, could be used to populate each of the candidate data sets: this was termed the 'data exploration exercise'.

The results of the exercise informed further development of the data sets, and data flows were established. To demonstrate and evaluate the new capability, 'exemplar research studies' were initiated in each therapeutic area, using data from all five institutions.

Each institution had a different combination of existing systems, a different approach to data integration, and a different strategy for informatics development. It was not feasible or appropriate to develop a common 'data repository' product for installation. Instead, a set of data models were distributed, and each institution worked to implement these using their own messaging, business intelligence, or data warehousing technologies.

None of the institutions had the capability to provide documentation on the provenance and interpretation of their data in any standard, computable format; the model or metadata aspect of the infrastructure was entirely new. It was this that drove—and continues to drive—the development of a comprehensive model catalogue application.

At the start of the project, teams of clinical researchers and leading scientists were given the responsibility of creating the candidate data sets for each therapeutic area. They did this by exchanging spreadsheets of data definitions in email. This proved to be a slow process, and face to face meetings were needed before any real progress could be made.

It proved difficult to properly represent repeating sections of the dataset—corresponding to investigations or interventions that may happen more than once for the same patient. Researchers resorted to Visio diagrams to try to explain how observations fitted into clinical pathways or workflows—and discovered that there were significant differences between pathways for the same disease at different institutions.

In one therapeutic area, these differences had a profound effect upon the interpretation of certain observations, and the candidate dataset was extended to include additional information on the pathway. Due to the complexity of the pathways involved, this was a time-consuming and error-prone process. Furthermore, the spreadsheets quickly became inconsistent with the Visio diagrams.

The candidate datasets were distributed to the informatics teams at the five institutions in the form of XML schemas. At first, these were created from scratch, rather than being generated. There were many requests for changes to the schemas; these proved difficult to track and coordinate.

The exploration exercise was reported by adding columns to the distributed versions of the candidate dataset spreadsheets, listing the information systems containing the data points in question, or suggested alternatives where there were significant differences due to local systems and processes.

This was despite the availability of an initial version of the model catalogue. Researchers and local informatics teams preferred to work with spreadsheets, having little or no knowledge of modelling languages such as UML and no automatic support for model creation and maintenance. It fell to the software engineering team at the coordinating centre to record the datasets and variations in the catalogue.

While it was disappointing to have the researchers still working in spreadsheets, the ability to generate XML schemas from models, and to manage relationships between data items in different models and different versions, proved invaluable. In the second phase of the project, with more therapeutic areas being added, researchers are starting to abandon the spreadsheet mode of working, and are instead maintaining the datasets as data models, in the catalogue.

B. Coordination of clinical data acquisition

The UK Department of Health, through the NIHR and the National Health Service (NHS), is providing funding for the whole genome sequencing of blood and tissue samples from patients with cancer, rare disorders, and infectious disease. A network of regional centres is being established to collect samples and data, and to provide access to genomic medicine across the whole of the country. The funding committed to date is approximately £300m.

The results of the whole genome sequencing will be linked to detailed information on each participant: clinical and laboratory information drawn from health records, ontological statements regarding abnormal features or conditions, and additional information obtained from the participant or their representatives. The information required will depend upon the nature of the disease that the patient is suffering from. For example, information on breast density is required in the case of breast cancer, but not for other diseases.

131 different diseases have been included in the sequencing programme thus far. Each disease corresponds to a different combination of clinical and laboratory data points, a different set of ontological statements, and a different set of questions for the participant. There are, however, significant overlaps between diseases: for example, many different rare diseases will require the same information on kidney or heart function.

The modelling task is at least an order of magnitude greater than that required for the NIHR HIC, and yet candidate datasets have already been created for more than half of the diseases included. This is due partly to the availability of the model catalogue application from the start of the project,

and partly to the availability, within the catalogue, of the full complement of HIC-defined data models and related data sets—including the national NHS data dictionary and the national cancer reporting datasets.

The informatics infrastructure required for the genomic medicine programme needs to support frequent extensions or revisions to the models proposed. As the analysis of the genomic data proceeds, new questions will be asked, and new information will be required from the health records.

Two routes are available for the provision of data from the network of contributing centres: direct data entry into electronic case report forms, in a on-line clinical trials management system; and electronic submission of data in XML format. The intended interpretation of the data required is explained in a regularly-updated set of data manuals.

It is important that the forms used for direct data entry, the schemas used for XML submission, and the data manuals are properly synchronised. An initial approach to this, in which a single model was used as the basis for the generation of all three kinds of artefact, proved inconvenient in practice. Although the same data points were to be collected in each case, the distribution of these data points across classes and sections was different.

Accordingly, the model catalogue is used to store three different models for each dataset: one for the generation of the forms, another for the generation of the XML schemas, and one for the generation of the data manual. These models are semantically-linked. If one is updated, then the fact that the others may now be inconsistent will be flagged to the user.

The same linkage is made with regard to existing reporting datasets and clinical audits. To avoid duplication of effort, the reporting datasets for the genomic medicine programme have been aligned with these activities. The existing datasets have been modelled, and updates to them will be tracked in the catalogue: again, potential inconsistencies can be flagged.

The degree of data definition re-use facilitated by the model is promising. Table I shows the percentage of data definitions in the core cancer models developed for the genomic medicine programme that could be drawn from the two main, national cancer reporting datasets—the Cancer Outcomes and Services Dataset (COSD) and the Systemic Anti-Cancer Therapy dataset (SACT)—or from the standard NHS data dictionary.

TABLE I
DATA DEFINITION RE-USE FOR CANCER MODELS

Source	Data Elements	%
Cancer Outcomes and Services Reporting	60	28.45 %
Systemic Anti-Cancer Therapy Reporting	2	0.95 %
NHS Data Dictionary	12	5.7 %
New Definitions	137	64.9 %
TOTAL	211	

The degree of data definition re-use for rare disease is slightly lower than this, although still promising. There is no existing national reporting or registry activity for many of the rare disease areas, and the datasets used by individual research programmes are not readily available.

V. RELATED WORK

A. ISO/IEC 11179

The work described in this paper has evolved from the CancerGrid project [4], where an ISO11179-compliant metadata registry was developed for curation of semantic metadata and model-driven generation of trial-specific software [5], [6]. The approach to generating forms in the CancerGrid project has been generalised significantly with the introduction of a data modeling language and a broader notion of semantic linking.

Another effort to develop an implementation of ISO11179 is found in the US caBIG initiative [7]; however, their caCORE software development kit [8] applies model-driven development only to generate web service stubs, requiring developers to create application logic by hand, whereas our technique integrates with existing clinical Electronic Data Capture tools and workflows, such as OpenClinica [9].

B. Ontology modelling

Several efforts have addressed ontological representations of ISO11179 for enabling data integration across metadata registries (MDRs). Sinaci and Erturkmen [10] describe a federated semantic metadata registry framework where Common Data Elements (CDEs) are exposed as Linked Open Data resources. CDEs are described in the Resource Description Framework (RDF), and can be queried and interlinked with CDEs in other registries using the W3C Simple Knowledge Organization System (SKOS). An ISO11179 ontology has been defined as part of the framework, and the Semantic MDR has been implemented using the Jena framework. Jeong *et al.* [11] present the Clinical Data Element Ontology (CDEO) for unified indexing and retrieval of elements across MDRs; they organise and represent CDEO concepts using SKOS. Tao *et al.* [12] present case studies in representing HL7 Detailed Clinical Models (DCMs) and the ISO11179 model in the Web Ontology Language (OWL); a combination of UML diagrams and Excel spreadsheets were used to extract the metamodels for fourteen HL7 DCM constructs. A critical limitation of this approach is that the transformation from metamodels to their ontological representation in OWL is based on a manual encoding. Leroux *et al.* [13] use existing ontologies to enrich OpenClinica forms; our Model Catalogue technique can integrate these ontologies to capture compliant data in a similar fashion, but does so by using an ISO11179 meta data registry and model driven methodology.

Ontology repositories can be considered closely analogous to model catalogues, they provide the infrastructure for storing, interlinking, querying, versioning and visualising ontologies. Relationships capturing the alignments and mappings between ontologies are also captured, allowing easy navigability. Linked Open Vocabularies [14] provides a service for discovering vocabularies and ontologies published following the principles of linked data. Besides the above features, it provides documentation about ontologies automatically harvested from their structure and identifies dependencies. Apache Stanbol [15] provides a set of reusable components for semantic

content management. The Apache Stanbol Ontology Manager provides a controlled environment for managing ontologies and ontology networks.

C. Data warehousing

In data warehousing [16], metadata is modelled in order to copy information from business systems into a centralised ‘data warehouse’, for decision support and to analyse business performance. Data warehouse models can be arranged in normalised form, following the relational approach [17], or ‘dimensional’ form [16] as quantifiable *facts* and *dimensions* which denote the context of facts. The Common Warehouse Metamodel (CWM) [18] from the Object Management Group is a UML-based framework to enable data warehousing in practice. Data warehousing is focused on write-once models, and for working with rigidly structured data; this is in contrast to the more general approach taken in ISO11179, where models are expected to evolve and change over time. The core metamodel of the CWM standard overlaps with the *concept* and *value* elements of the ISO11179 meta model.

D. Model-driven engineering for e-Health

Several examples of model-driven engineering for e-Health software are reported in the literature [19], [20], [21], [22], [23]. Payne [24] formalises the typical pattern followed in these methods: a multi-phase approach, where data modelling is a separate phase from stakeholder engagement and data integration. This approach is taken Khambati *et al.* [22], where an Eclipse-based tool is used to develop domain-specific languages to model and generate tools for mobile health-tracking applications. The advantage of the approach is the ability it provides for clinicians to modify the model of the study, which is specified in the DSL, and automatically regenerate the application from the model. A similar approach is taken in the *True Colours* system [19], using the Booster model-driven toolkit to derive a patient self-monitoring application for mental health. The Booster approach demonstrates the lesson that data tends to be managed better within a model-driven process, leading to higher quality and more reusable assets. Schlieter *et al.* [23] record their experience gained from using model-driven engineering to implement an application for path-based stroke care; amongst the lessons learned, they recommend using existing ontological models where possible, and being prepared to reconcile a heterogeneity of models from the various stakeholders under a common metamodel. In contrast to these systems, our metadata-oriented approach supports the creation of applications that can interoperate with existing data, standards and systems. Rather than simply using MDE to develop stand-alone systems, MDE processes are used in the management of clinical trials metadata from which software is derived.

In the Model Driven Health Tools (MDHT) [25] project, the HL7 Clinical Document Architecture (CDA) standard [26] for managing patient records is implemented using Eclipse UML tools [27]. The benefits of applying MDE are clear: modelling tools are used to model the CDA standards, and

interoperable implementations of the standard are automatically derived from the models. In principle, this is similar to our Model Catalogue approach, where the CDA metadata can be represented and implementations derived. However, MDHT supports only the CDA standard, whereas the Model Catalogue can interoperate with any metadata standard. The CDA standards are large and complex: Scott and Worden [28] advocate a model-driven approach to simplify the HL7 CDA, supported by three case studies: the NHS England ‘Interoperability Toolkit’, simplification of US CDA documents, and the Common Assessment Framework project for health and care providers in England. The Model Catalogue supports similar simplifications, where large and complex metadata schemes are simplified by mapping only relevant metadata in the generated artefacts.

E. Electronic data capture

A range of tools are available for clinical Electronic Data Capture (EDC), including Catalyst Web Tools [29], OpenClinica [9], REDCap [30], LabKey [31] and Caisis [32]. Franklin *et al.* [33] present a two-year case-study comparing EDC tools, and Leroux *et al.* [34] report on a further study comparing Clinical Trials Management Systems. We use the Model Catalogue tool to generate case report forms for OpenClinica, but in principle any EDC tool could be supported.

The state of the art in EDC is represented by the Research Electronic Data Capture (REDCap) [30] web-based application, which supports metadata capture for research studies, providing an online interface for data entry, audit trails, export to common statistical packages and data import from external sources. Like the Model Catalogue, the REDCap system focuses on the clinical metadata. However, REDCap and similar EDC tools are typically insular systems, importing any data into a centralised data silo; in contrast, the Model Catalogue aims to provide a platform to support and integrate existing data stores and systems within the clinical environment.

There is also a distinction in the level of expertise expected to operate the tools. The metadata management — creation, revision, sharing — in EDC is typically considered a IT-specialist task [30], [33], requiring experts to initialise the metadata separately for each study. With the Model Catalogue, clinical domain specialists have the ability to adapt and modify metadata as needed, and treat models as the central artefacts. Effectively, the Model Catalogue follows the same metadata workflow as REDCap, but without the need for modelling experts to develop, adapt or share the metadata models.

VI. CONCLUSION

A. Lessons learned

The experience of applying the data model language, the model catalogue, and the associated generation tools in the context of clinical research informatics has led to the following suggestions.

A data dictionary is not enough. A simple, flat list of data definitions does not support re-use at scale: it requires the user to place all of the contextual information into the definition

of each data item, and mitigates against the automatic generation and application of definitions. Instead, a compositional approach is required, in which data elements are defined in explicit context.

A catalogue is not enough. The models in the catalogue must be linked to implementations, and to each other, with a considerable degree of automatic support. If the models are out of sync with the implementations, and with the data, then their value is sharply diminished. If you are going to manage data at scale, you need a data model-driven approach.

The tools must be usable by domain experts. To have the processes of model creation and maintenance mediated by software engineers is problematic: there may be misunderstandings regarding interpretation, but—more importantly—there are not enough software engineers to go around. An appropriate user interface, that closely matches the intuition and expectations of domain experts, is essential.

There will be more models than you think. Different models will be required for different types of implementation, and—in any research domain, at least—data models will be constantly evolving, with data being collected against different versions.

Intelligent, automatic support is essential. The information content of precise data models is considerable, and there may be complex dependencies between data concepts and constraints. A considerable degree of automation is required if users are to cope with this complexity.

The model catalogue and the associated toolset should, as far as possible, automatically: create or propose links, including classifications; manage model versioning, and the consequences for linked data concepts; manage dependencies, including those between different models for same dataset, targeted at different implementation platforms.

This should come as no surprise. If, as Warmer and Kleppe [35] suggest, the model-driven approach is about “using modelling languages as programming languages rather than merely as design languages” then we should aim to provide modellers with the same kind of support that programmers have come to expect from modern integrated development environments.

B. Future development

The development of the language, the catalogue, and the associated toolset continues apace. The existing interface, shown in Figure 5 is being refined and extended in collaboration with experts from a wider range of application domains. The degree of automatic support for model management is increasing: for example, Figure 6 shows how the toolset is able to automatically detect and present variations between related models.

Furthermore, as well as models to support the acquisition and integration of data, we require data models for the processes of analysis, in terms of: the datasets used, the workflows enacted, and thus the provenance and reproducibility of the results obtained. Here, again, a considerable degree of automation is required if we are to meet the needs and expectations of those engaged in large-scale clinical research.

Catalogue

Data Architect

★ Favorites

Search

Draft Models

COSD

GEL

GEL Rare Diseases

Disease List

Essential Sample Metadata

Participant Information

Registration

Contact

Consent

Inheritance

Clinical

Family

13

1

4

14

3

6

1

Consent

DRAFT

Properties

Attachments

Children

Data Elements 6

History 1

Is Base For

Is Based On

Is Favourite Of

Is Synonym For

Metadata

Parents 1

Related To

Name	Description	Value Domain	Metadata
Date of Consent	Date on which consent form signed	Date	
Name and Version of Consent Form	name and version of form used	String	
Name and Version of Participant Information Sheet		String	
Consent Details	yes/no answers to optional questions	yesNoUnk	
Consent Form	scanned copy of paper consent form, signed by the participant	xs:base64Binary	
Person Taking Consent	the name of the person taking consent	String	

All Classifications

Fig. 5. web interface to the model catalogue

Catalogue

Data Architect

★ Favorites

Search

Contains	13 item(s)	13 item(s) 6 item(s)
Affected Disease Status (Genomics England, Rare Diseases)	Affected Disease Status (Genomics England, Rare Diseases)	Affected Disease Status (Genomics England, Rare Diseases)
Affected Disease Status (Other) (Genomics England, Rare Diseases)	Affected Disease Status (Other) (Genomics England, Rare Diseases)	Affected Disease Status (Other) (Genomics England, Rare Diseases)
Biological Relationship to Proband (Genomics England, Rare Diseases)	Biological Relationship to Proband (Genomics England, Rare Diseases)	Biological Relationship to Proband (Genomics England, Rare Diseases)
Biological Relationship to Proband (Other): (Genomics England, Rare Diseases)	Biological Relationship to Proband (Other): (Genomics England, Rare Diseases)	Biological Relationship to Proband (Other): (Genomics England, Rare Diseases)
Consanguinity (Genomics England, Rare Diseases)	Consanguinity (Genomics England, Rare Diseases)	Consanguinity (Genomics England, Rare Diseases)
Father Affected (Genomics England, Rare Diseases)	Father Affected (Genomics England, Rare Diseases)	Father Affected (Genomics England, Rare Diseases)
Mother Affected (Genomics England, Rare Diseases)	Mother Affected (Genomics England, Rare Diseases)	Mother Affected (Genomics England, Rare Diseases)
Number of full brothers (Genomics England, Rare Diseases)	Number of full brothers (Genomics England, Rare Diseases)	Number of full brothers (Genomics England, Rare Diseases)
Number of full brothers affected (Genomics England, Rare Diseases)	Number of full brothers affected (Genomics England, Rare Diseases)	Number of full brothers affected (Genomics England, Rare Diseases)
Number of full sisters (Genomics England, Rare Diseases)	Number of full sisters (Genomics England, Rare Diseases)	Number of full sisters (Genomics England, Rare Diseases)
Number of full sisters affected (Genomics England, Rare Diseases)	Number of full sisters affected (Genomics England, Rare Diseases)	Number of full sisters affected (Genomics England, Rare Diseases)
Number of Participants Expected	Number of Participants Expected	Number of Participants Expected
Participant Type	Participant Type	Participant Type
Probable Inheritance (Genomics England, Rare Diseases)	Probable Inheritance (Genomics England, Rare Diseases)	Probable Inheritance (Genomics England, Rare Diseases)
	Consent Details (Genomics England, Rare Diseases)	Consent Details (Genomics England, Rare Diseases)
	Consent Form (Genomics England, Rare Diseases)	Consent Form (Genomics England, Rare Diseases)
	Date of Consent (Cancer Outcomes and Services Dataset, Genomics England, Rare Diseases)	Date of Consent (Cancer Outcomes and Services Dataset, Genomics England, Rare Diseases)
	Name and Version of Consent Form (Genomics England, Rare Diseases)	Name and Version of Consent Form (Genomics England, Rare Diseases)
	Name and Version of Participant Information Sheet (Genomics England, Rare Diseases)	Name and Version of Participant Information Sheet (Genomics England, Rare Diseases)
	Person Taking Consent (Genomics England, Rare Diseases)	Person Taking Consent (Genomics England, Rare Diseases)
Parent Of	0 item(s)	0 item(s)

Fig. 6. automatic detection of model variation

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