Cross-tier Web Programming for Curated Databases: a Case Study

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Abstract

Curated databases have become important sources of information across several scientific disciplines, and as the result of manual work of experts, often become important reference works. Features such as provenance tracking, archiving, and data citation are widely regarded as important features for the curated databases, but implementing such features is challenging, and small database projects often lack the resources to do so.

A scientific database application is not just the relational database itself, but also an ecosystem of web applications to display the data, and applications which allow data curation. Supporting advanced curation features requires changing all of these components, and there is currently no way to provide such capabilities in a reusable way.

Cross-tier programming languages allow developers to write a web application in a single, uniform language. Consequently, database queries and updates can be written in the same language as the rest of the program, and it should be possible to provide curation features via program transformations. As a step towards this goal, it is important to establish that realistic curated databases can be implemented in a cross-tier programming language.

In this article, we describe such a case study: reimplementing the web frontend of a real-world scientific database, the IUPHAR/BPS Guide to PHARMACOLOGY (GtoPdb), in the Links cross-tier programming language. We show how programming language features such as language-integrated query simplify the development process, and rule out common errors. Through an automated functional correctness evaluation, we show that the Links implementation correctly implements the functionality of the official version. Through a comparative performance evaluation, we show that the Links implementation performs fewer database queries, while the time needed to handle the queries is comparable to the official Java version. Furthermore, while there is some overhead to using Links because of its comparative immaturity compared to Java, the Links version is usable as a proof-of-concept case study of cross-tier programming for curated databases.
Introduction

Curated databases have become important data resources across several scientific disciplines. Such databases collect the current state of knowledge about a topic and many have become important reference works. They are constructed through the manual effort of experts, often over a long timespan, and it is widely appreciated that versioning and provenance-tracking are important for assessing the validity and freshness of the data, or tracing the origin of errors or discrepancies (Buneman et al., 2008). Unfortunately, implementing support for fine-grained provenance-tracking or versioning is a challenging task, usually performed on a system-by-system basis. Many such database projects, particularly smaller or shorter-term ones, lack the resources and expertise to do this.

A curated database is not just an isolated relational database, but also has surrounding infrastructure such as a web application for viewing or searching the data, and an editing interface used by the database curators to add or modify data. Each of these components are nontrivial to develop. A typical web application is really a distributed program involving code running on several “tiers”: Java or Python running on the server, JavaScript and HTML on the web browser, and SQL on a database. Curation interfaces can be either web applications or traditional client-server database applications; in either case, modifying such a system is a nontrivial task, especially when the added functionality spans two or all three tiers.

Thus, augmenting an existing curated database web application (or designing a new system from scratch) to provide features such as versioning, provenance-tracking, or citation requires taking these requirements into account across two or more system layers, adding complexity beyond that of the basic functionality of the system. General-purpose techniques have been explored for supporting such features (Buneman et al., 2008, 2004), but there is currently no way to provide them in a reusable way.

Cross-tier web programming

Cross-tier programming languages (Chlipala, 2015; Cooper et al., 2006; Radanne et al., 2016; Serrano et al., 2006) have been proposed to simplify web and database application programming. The vision is that the programmer should only need to write a single program in a single language; the language implementation then takes care of the details of partitioning the program into client, server and database components, distributing the code, and coordinating their communication in the running program. A major benefit is the fact that database queries and updates can be written and checked for consistency in the same language as the rest of the program. In principle, advanced features such as provenance and versioning could be provided for such programs by program transformation: that is, by rewriting the program (possibly with some lightweight annotations) so that new functionality is implemented according to a high-level pattern. Indeed, Fehrenbach and Cheney (2018) have already shown how provenance tracking can be added as a programming language feature: a user must simply change a keyword in a query in order to obtain provenance metadata, rather than hand-crafting provenance tracking per application.

We argue that cross-tier programming is well-suited for curated databases: by using a single cross-tier language rather than a conventional multi-language approach, curated database developers should be able to focus on their application logic, and could (in the future) use pre-packaged techniques for provenance-tracking and archiving provided by the language implementation (or even a library).

However, to date, cross-tier programming languages have not been widely used for curated databases. Before investigating the use of cross-tier programming languages to provide language-integrated curatorial support, we must first ask:

Are cross-tier programming languages capable of implementing realistic curated databases?
Contributions

In this article, we answer the above question in the affirmative. We provide the first case study of cross-tier web programming for scientific databases by using Links, a functional, cross-tier web programming language (Cooper et al., 2006), to implement a workalike web front-end for the IUPHAR/BPS Guide to PHARMACOLOGY Database (GtoPdb); an important curated pharmacological database (Armstrong et al., 2019). Links is a research project that has been developed in Edinburgh over many years, and is not a widely-used mainstream programming language; however, by using it to develop case studies such as this one, we plan to demonstrate the value of cross-tier programming for scientific databases, and evidence the viability of language-based support for curation.

In the remainder of the article, we describe the background of GtoPdb and why it is an interesting database to use as a case study, and describe some aspects of the Links implementation. We then report on the evaluation of the case study, showing broad functional equivalence via an automated functional correctness analysis, and report on the results of a performance evaluation. The performance evaluation shows that the Links implementation performs comparably with the official Java implementation, as well as providing lower overall query counts and more predictable performance results for database queries. We conclude with a summary of lessons learned so far and directions for future work.

Background

The International Union of Basic and Clinical Pharmacology (IUPHAR) / British Pharmacological Society (BPS) Guide to PHARMACOLOGY (GtoPdb) is an expert-curated database that captures interactions between human proteins (“targets”) and ligand molecules from the pharmacological and medicinal chemistry literature. The resource is open-access and intended as a “one-stop shop” portal to pharmacological information. It provides a searchable database with quantitative information on 3,000 drug targets and related proteins, organised into families, and 9,700 approved and investigational drugs, antibodies, and natural hormones, metabolites, and neurotransmitters that act on them. GtoPdb provides succinct overviews, key references and recommended experimental ligands for each target. It is a useful resource for researchers and students in pharmacology and drug discovery and provides the general public with accurate information on the basic science underlying drug action.

Figure 1. Screenshots of official GtoPdb application and Links reimplementation
GtoPdb has its origin in IUPHAR-DB which was first compiled in 2003 (Harmar et al., 2009; Sharman et al., 2013, 2011). Its scope was expanded between 2012 and 2015 to define the data-supported druggable genome, and was renamed GtoPdb (Armstrong et al., 2019; Pawson et al., 2014; Southan et al., 2016). GtoPdb is distinguished by a unique model of data collection and curation, with the guidance and support of the Nomenclature model of data collection and curation, with the guidance and support of the Nomenclature Committee of IUPHAR (NC-IUPHAR) and its 96 target class subcommittees. These subcommittees comprise over 500 pharmacology experts who provide regular updates and contributions to GtoPdb.

The GtoPdb web application communicates with two underlying databases: a main, PostgreSQL, database which contains the bulk of the data and a second, Oracle, database which contains ligand structure information. The main application layer is written in Java, with static pages written in JavaServer Pages (JSP), JavaScript and HTML. The curation interface (i.e., the interface used by curators to create and edit the database) is a custom-built, standalone Java application with a GUI.

GtoPdb is a substantial curated database: the 2019 release comprises 89 megabytes of data contained in 181 tables. As a measure of scope, the Java codebase for the web interface (which includes some pages out of the scope of our reimplementation) stands at 17935 lines of code for data transformation code; 28819 lines of JSP rendering code; and a data access layer (which also contains query code used for the curation interface) consisting of 43129 lines of code, written over a period of 16 years.

Reimplementing GtoPdb in Links

We now turn our attention to our reimplementation of the GtoPdb frontend in Links. Our reimplementation uses an unaltered copy of the PostgreSQL database release. Figure 1 shows an example page, displaying a view of the ligand information for beclometasone dipropionate extracted from the database. Figure 1a shows the official version of the page, and Figure 1b shows our reimplementation in Links. The same underlying information is displayed on each page. The Links version has some minor differences such as different rounding used for floating-point numbers, as well as a banner to differentiate it from the official version.

GtoPdb Structure

The GtoPdb interface consists of nine main data pages:

**Target List** GtoPdb groups pharmacological targets into different categories including G protein-coupled receptors, ion channels, nuclear hormone receptors, kinases, catalytic receptors, transporters, enzymes, and other protein targets. This page links to the family list for each type of target.

**Family List** A family is a group of related pharmacological targets. The family list page displays a hierarchically ordered tree of families.

**Family Data** The family data page provides summaries of each target in the family, and links to the more in-depth object data pages.

**Object Data** In GtoPdb, an object is a pharmacological target such as a receptor. The object data page displays all information associated with a target, and is the most complex page. The page can render 52 individual properties about each object (for example, associated interactions and 3D structures).

**Disease List** A list of all diseases in the system.

**Ligand Families** A list of ligands, classified into families.

**Ligand List** A list of all ligands in the system, with the ability to filter by category.
**Ligand Data** Displays data associated with ligands, such as relevant interactions, structural information, and a summary of clinical use.

**Disease Data** Displays information about a disease, including references to external databases, related pharmacological targets, and ligands known to affect the disease.

The official implementation contains additional smaller auxiliary data pages and searching functionality, but the nine pages above are the most prominent and involved, so we concentrate on these pages for our Links reimplementation.

**Language-Integrated Query**

In the Java implementation of GtoPdb, all database queries are carried out using SQL prepared statements. Our first major departure from the previous implementation is the use of Links’s support for language-integrated query. While language-integrated query is best known in Microsoft .NET languages such as C# and F# (Meijer et al., 2006; Syme, 2006), it is also available as part of Links (Cooper, 2009; Lindley and Cheney, 2012), based on techniques developed originally in the Kleisli system (Wong, 2000).

Instead of constructing SQL statements directly, language-integrated query allows database queries to be written as a standard expression in a programming language. In particular, we use a flavour of language-integrated query pioneered by Trinder (1991), who adapts the notion of a list comprehension (similar to a mathematical set comprehension) to the setting of relational queries. As an example, consider an SQL expression which retrieves the names of all ligands which have been approved for use in humans. In SQL, we might write:

```sql
SELECT name FROM ligand WHERE approved
```

Given an appropriate Links declaration of the ligand table, we can write the above query as:

```java
query { for [l <-- ligand] where (l.approved) [l.name] }
```

The query is written as a list comprehension, with elements generated by the ligand table, where the where clause filters each element to only consider those which are approved. Unlike embedded SQL, the query is also typechecked to ensure the table field names and query results are used consistently in the program.

Differently from most implementations of language-integrated query, Links supports efficient nested queries. A nested query is a query whose result type contains collections nested inside other collections. (In contrast, an SQL query always returns a flat table: a collection of records of values of primitive types such as integers and strings.) To illustrate, the following nested query returns records including the ligand name and its set of synonyms:

```java
query { for [l <-- ligand]
    [(name = l.name, synonyms = for [l2s <-- ligand2synonym] where
        (l2s.ligand_id == l.ligand_id) [l2s.synonym]]) ] }
```

This query will return a list of records (name,synonyms), in which name is a string and synonyms is a list of strings. A natural, but inefficient, way to execute such a query is to first retrieve the set of all ligands (with their names and IDs), and then run one query per ligand to find its synonyms. In Links, the above nested query is instead transformed to two equivalent SQL queries. It is important to note that the shredding technique to implement nested queries proposed by Cheney et al. (2014) gives a guaranteed upper bound on the number of SQL queries needed to run a nested query: the upper bound is the number of occurrences of collections in the query result type, and this is independent of the number of records returned by a query.

A second useful feature of language-integrated query in Links is that certain user-defined functions can be used within queries for convenience, and such functions will be inlined to simplify the query expression to a form that can be translated to SQL. This relies on query normalisation (Cooper, 2009) to generate efficient SQL code directly from query expressions. As a simple
example demonstrating both nested queries and user-defined functions at once, the nested query above can also be written as:

```java
fun getSynonyms(id) {
    for ([l2s <-- ligand2synonym] where [l2s.ligand_id == id]
        [l2s.synonym])
} query { for [l <-- ligand]
    [([name = l.name, synonyms = getSynonyms(l.name)])]
}
```

In this example, this capability makes the query expression longer (but arguably a bit more readable due to the extra documentation provided by the function name); however, such functions can also be reused across many query expressions, potentially saving a great deal of code repetition, and aiding maintenance.

**Example: Listing Ligands**

GtoPdb provides functionality for listing all ligands in the database, filtered by category: example categories include approved drugs, or ligands relevant to either immunopharmacology or malaria pharmacology. Let us consider this page as an extended example.

Each row in the displayed table shows the ligand’s name, unique GtoPdb ID, synonyms or trademark names, and icons displaying whether the ligand is an approved drug; contains a radioactive or chemical (e.g. fluorescent) label; is relevant to immunopharmacology; is relevant to malaria pharmacology; or has an entry in the protein 3D structure database (PDB). We can gather this information through the use of a single query expression:

```java
query {
    for [l <-- ligand]
        where [ligandFilter(l, filterType)]
            [id = l.ligand_id, name = l.name, approved = l.approved, radioactive = l.radioactive,
             labelled = l.labelled, immuno = l.in_gtip, malaria = l.in_gtmp, synonyms =
             for ([l2s <-- ligand2synonym] where [l2s.ligand_id == l.ligand_id && l2s.display]
                 [l2s.synonym], hasPDB =
                 not(empty(
                 for [p <-- pdb_structure]
                     where [p.ligand_id == l.ligand_id]
                     [p])))]
}
```

We begin by querying the ligand table. If the ligand matches a given predicate based on the filter type, then the query produces a record with the required information. Of particular interest are the synonyms and hasPDB fields of the output record, which are not fields in the ligand table but instead refer to other tables.

The synonyms field is a one-to-many relation from ligands to synonyms. As an example, the common painkiller paracetamol is also known by the trade names Panadol and Tylenol. The Java implementation gathers the relevant synonyms using a PostgreSQL view. To express this nested relation in Links, we use its support for nested queries (Cheney et al., 2014), as explained above, to populate the synonyms field with a collection of all relevant synonyms.

The hasPDB field should be true if the pdb_structure table in the database contains an entry with the same ligand ID as the current ligand. Note that we can use the native Links functions not and empty in Links query code; these are translated to SQL EXISTS constraints.
**Functional Predicates**

Let us revisit how we filter the ligands to display. Some filters are based on boolean flags in the ligand table (for example, approved), or on the type field, and others perform more complicated tests. In the Java implementation, such filtering is implemented by building a query using string concatenation and Java conditional expressions. For example, to filter all approved drugs, the implementation uses code like the following:

```java
if (type.equalsIgnoreCase("Approved")) {
    query += " WHERE approved IS TRUE " ;
} else if (type.equalsIgnoreCase("Synthetic organic")) {
    query += " WHERE type = 'Synthetic organic' " ;
}
```

Each ligand type has a case which adds the correct type into the query, chained as `else if` clauses. Query strings generated in this way could be ill-formed, leading to failure at runtime (for example, if spaces between concatenated strings are omitted). Instead, we can take advantage of the fact that Links is a functional programming language, and define a function that tests whether a ligand matches a filter. We begin by defining a variant type (similar to an enum in Java) describing each filter:

```capital
typedef Filter = [
    Approved | SyntheticOrganic | EndogenousPeptide | Immuno | ... ];
```

We then define a function called `ligandFilter` that given an entry in the ligand table, and a filter type, returns whether the ligand matches the filter:

```capital
fun ligandFilter(ligand, filterType) {
    switch (filterType) {
        case Approved -> ligand.approved
        case SyntheticOrganic -> ligand.type == "Synthetic organic"
        case EndogenousPeptide ->
            ligand.type == "Peptide" 
            && isEndogenous(ligand)
        case Immuno -> ligand.in_gtip
    ...
    }
}
```

Note that the EndogenousPeptide case calls another function `isEndogenous`, illustrating that we can use functions to break the query logic down into smaller parts. The `ligandFilter` function can be used directly in the query, and Links correctly inlines it (and `isEndogenous`) so that the eventual SQL query is similar to the one generated by the Java code. Using the number of lines of code as a rough measure of complexity, the Java version needs 145 lines of code to filter the list of ligands, whereas the Links version requires only 54, with the additional advantage that Links will always generate type-correct queries.

### Displaying a Data Page

We have now seen an example of how Links can be used to implement a GtoPdb data page. More generally, in both the Java and Links implementations, the process for displaying each data page is as follows:

1. Parse any input arguments to the page request (for example, ligand or object ID)
2. Perform database queries to populate a data model
3. Parse all text fields in order to obtain a list of any referenced scientific literature and relevant ligands
4. Render the web page content and deliver the response
In the Java implementation, there is a single Java data model used for both the web interface and the curation tool, and sometimes this means that additional information is retrieved but not displayed. In the Links implementation, each page has its own data model based on what is to be displayed to the user, but the queries and processing code can be reused over different files. The Java implementation makes use of a data access layer which contains many methods to populate the model, whereas each Links page begins with a large nested query followed by a processing phase.

Text fields in GtoPdb may contain references to supporting scientific papers and crossreferences to ligands. As an example, consider the following excerpt, detailing comments about the agonist interactions targeting the D1 dopamine receptor:

Some substituted benzazepines such as SKF-83959 are G-protein biased agonists of the dopamine D<sub>1</sub> receptor and fail to activate β-arrestin recruitment <Reference id=28036/>; their ability to signal through G<sub>q</sub>-mediated pathways has been controversial <Reference id=33435/>.<br><br><Ligand id=6077/>, <Ligand id=9637/> and related compounds exhibit slow dissociation rates from the D<sub>1</sub> receptor.

References to scientific papers are introduced using Reference tags, and references to ligands are introduced using the Ligand tag. The text also includes standard HTML tags. The above text would be rendered as shown below:

Some substituted benzazepines such as SKF-83959 are G-protein biased agonists of the dopamine D<sub>1</sub> receptor and fail to activate β-arrestin recruitment [17]; their ability to signal through G<sub>q</sub>-mediated pathways has been controversial [32].

A68930, A77636 and related compounds exhibit slow dissociation rates from the D<sub>2</sub> receptor.

In order to display the text, we need to parse the Reference and Ligand tags, so that the required data about the corresponding references and ligands can be fetched in a subsequent query. This separate pass allows us to build a sorted, numbered, reference list, rather than storing references per data page in the database in a more fragile way.

**Evaluation**

In this section, we evaluate our Links reimplementation of GtoPdb against the original. Firstly, we show a functional correctness analysis, which gives a good degree of confidence that the Links reimplement provides an equivalent level of functionality to the original version. Secondly, we show a comparative performance analysis, which in particular shows that Links generates fewer queries, but shows that the relative immaturity of Links compared to the Java compiler results in longer page build times.

The data generated by our experiments, as well as the code used to generate the charts, is publicly available on Figshare (Fowler, 2019).

**Functional correctness**

The first evaluation criterion is functional correctness: does the Links reimplementation provide broadly the same functionality as the original?

To this end, we have undertaken an automated functional correctness evaluation, using a 1300-line Python script. Our approach is to use Selenium (Holmes and Kellogg, 2006) to load each page and interact with the page to ensure all details are shown, and then use BeautifulSoup (Richardson, 2020) to parse the results into a JSON object. The JSON
objects for the Links and Java pages can then be compared directly. For some less involved pages, such as the family and disease lists, the results can be compared directly. For larger pages, such as the object and ligand display pages, parsing the data directly is intractable due to the large number of different display formats, and subtle differences in rendering across the two implementations.

However, since GtoPdb only displays a data box if relevant data is present for a particular entity, and references are contained within the text of each piece of displayed data, a good approximation is to compare the data headers and reference list of each page. Although an approximation, this approach was sufficient for us to identify and fix many omissions and errors, and even helped identify a minor bug in the official implementation. As an example, consider the JSON object for *Guanylyl cyclase, 21*:

```json
{
    'basic_info': {'family': 'Nitric oxide (NO)-sensitive '}
        ('soluble) guanylyl cyclase',
    'id': 2897,
    'nomenclature': 'Guanylyl cyclase, 21'},
    'data_headers': ['Activators', 'Database Links',
        'Endogenous ligand(s)', 'Enzyme Reaction',
        'Inhibitors', 'Previous and Unofficial Names',
        'Quaternary Structure: Subunits'],
    'references': [7527671, 9742221, 11242081, 12086987,
                 19089334, 28557445, 29859918]}
```

The JSON object contains the basic information for the target, the data headers, and the Pubmed IDs for each reference in the references list.

We exhaustively verified all main summary pages, namely the family list, disease list, ligand list, and ligand families pages. (The target list page is static, so is not of interest for the evaluation). For each data page, we performed the check on 150 randomly chosen entity identifiers.

Overall, we managed to validate the vast majority of pages. The one shortcoming of the Links implementation with respect to functional correctness is that its parser cannot handle malformed data: in particular, malformed HTML (such as text including `< or > literals instead of the escaped HTML &lt; and &gt;) is unsupported. This leads to some pages failing the references check, since parsing for some fields fails. However, the number of affected pages is small: the validation showed errors on two disease data pages, five family data pages, two object data pages, and no ligand pages. We manually checked each error to ensure that it was due to malformed HTML.

**Performance**

The second evaluation criterion is performance. Although we have shown that Links is capable of reimplementing the main functionality of GtoPdb, and that our reimplementation displays the same data, it is important to ensure that our cross-tier methodology is not unacceptably detrimental to performance. We therefore evaluate our approach on four of the main data pages: the object data page; the disease data page; and the lists of all diseases and ligands.

We evaluate each page with respect to three dimensions:

- **Query Count**: the number of queries executed when generating a given page. As the nested language-integrated query approach used by Links ensures that query count is bounded by the number of collection types in the result (Cheney et al., 2014), we would
hope that the Links implementation would generate substantially fewer queries than constructing queries by hand.

- **Query Handling Time**: the amount of time spent processing database queries. In the Links implementation, this also includes the time spent normalising the query into SQL and parsing the results into Links data structures, in addition to query execution itself.

- **Page Build Time**: the amount of time spent building a page on the server, measured from the point at which the request is received until the point before the response is sent to the client. As Links is an interpreted language (as opposed to Java, which runs on a virtual machine incorporating a Just-In-Time (JIT) compiler), we would expect page build time to be slower on Links. We show results both including and excluding query handling time.

We collect the metrics by adding instrumentation code to the Links interpreter itself, and by implementing an instrumented version of the PreparedStatement class in the Java code. Measurements were performed on both the Links and Java versions of the code running locally on a laptop with an Intel Xeon E-2176M 2.7GHz CPU, and 8GB of RAM. We used the Python pandas library (McKinney, 2010) for data processing, and matplotlib (Hunter, 2007) to generate charts.

**Object Data**

Figure 2 shows box plots detailing the number of queries, total query handling time, and page build time when displaying the object data page for 150 randomly selected object IDs. The data represents the arithmetic mean of 20 requests for each page.

**Query count**

Figure 2a shows the results for the number of queries generated to display the page. As expected, due to the use of nested queries the Links implementation generates a lower number of queries (median: 117) compared to the Java version (median: 229). Notably, the query count of the Links implementation is much more predictable, with a standard deviation of 43.38 in the Links implementation, in contrast to 275.15 in the Java implementation. A smaller standard deviation, and consequently greater predictability of the query count, is a good indicator that the number of queries is less dependent on the contents of the data and more uniform across different data pages.

The maximum query count in the Links implementation is 413, and the maximum query count in the Java implementation is 2549. The outlier in the Java implementation is due to object 262 (the Histamine H\(_1\) receptor) being associated with an unusually large number of drug interactions: each interaction requires 9 database queries, along with additional queries to fetch information about the ligands associated with the interaction.

**Query time**

Figure 2b shows the query handling time for both implementations. The original Java implementation has a better median query time of 56.72ms compared to 121.31ms in the Links implementation: this disparity is likely due to a combination of query normalisation and marshalling the returned values into Links data structures. Nevertheless, again, performance of the Links implementation is more predictable with a standard deviation of 8.43 compared to 70.83 in the Java implementation.
Figures 2c and 2d show the page build time for both implementations, excluding and including query handling time respectively.

As expected, the Java version performs substantially better than the Links version due to the maturity of the Java Virtual Machine and associated Java ecosystem. Concretely, the median page build time for the Links version is 465.24ms and the median page build time for the Java version is 85.65ms. Additionally, the performance of the Java version is more predictable, with a standard deviation of 76.39 compared to 223.34 in the Links implementation.

An additional bottleneck in the Links implementation is the implementation of a parser which is run on each text field in order to extract inline reference and ligand IDs contained
within text fields. It is likely that improvements in this part of the code could lead to substantial performance improvements.

Figure 3. Experimental evaluation of implementations (Disease and Ligand Lists)

**Disease and Ligand Lists**

Figure 3 shows the experimental results for the pages listing all diseases and ligands: the data displayed is again the mean over 20 iterations. There are two filters for diseases (all diseases, and immuno-relevant diseases), and twelve filters for ligands, as opposed to thousands of rows of objects and ligands. Thus, it is possible and instructive to plot the data in a non-aggregated form.

**Query count**

The Links implementation substantially outperforms that of the Java implementations: the Links implementations use only two queries to gather the information required to display the lists, whereas the Java implementation of the disease list (showing all diseases) requires 8995 queries and the ligand list (showing approved ligands) requires 30479. The additional number of queries is because the Java implementation populates a model which contains more information than is necessary for the page: as an example, the disease list page generates many queries retrieving links to external databases, but these are never displayed.

**Query time**

The number of additional queries required in the Java implementations is reflected in the time spent performing queries. Concretely, the median query time in the Links implementation was 56.48ms for the disease list and 955.69ms for the ligand list, compared to 735.97ms for the disease list and 3246.87ms for the ligand list in the Java implementation.

**Page build time**

As with the object data page, the Links implementation does not perform as well as the Java implementation when generating the disease list page, due to the maturity of the underlying technologies. In fact, in spite of the large number of queries required, the Java implementation outperforms the Links implementation on the disease list.
However, in spite of the slower page generation time, the much lower query time in the Links implementation of the ligand list actually allows the Links implementation to perform better than the Java version on all categories but one.

**Disease Data**

Figure 4 shows the results for the disease data page. Again, the results represent the arithmetic mean over 20 iterations for 150 randomly selected disease IDs.

The findings are consistent with the previously reported results, with Links performing substantially better on query count (Figure 4a) and comparably on query handling time (Figure 4b), but worse on page build time (Figure 4c). The outlier for query count and execution time in the Java implementation is Crohn’s disease, which contains substantially more ligand interactions than the other disease pages considered. The same disease accounts for the outlier in the Links page build time, which is due to the necessity of parsing more description fields.
<table>
<thead>
<tr>
<th>Page</th>
<th>Links</th>
<th></th>
<th>Java</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Std. dev.</td>
<td>Min</td>
<td>Max</td>
</tr>
<tr>
<td>Disease Data</td>
<td>12</td>
<td>3.31</td>
<td>11</td>
<td>43</td>
</tr>
<tr>
<td>Disease List (n= 2)</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Family Data</td>
<td>82</td>
<td>126.32</td>
<td>49</td>
<td>963</td>
</tr>
<tr>
<td>Family List (n= 7)</td>
<td>14</td>
<td>24.07</td>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>Ligand Data</td>
<td>78</td>
<td>6.51</td>
<td>73</td>
<td>115</td>
</tr>
<tr>
<td>Ligand Families (n= 1)</td>
<td>2</td>
<td>–</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ligand List (n= 12)</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Object Data</td>
<td>117</td>
<td>43.38</td>
<td>104</td>
<td>413</td>
</tr>
</tbody>
</table>

**Figure 5.** Summary of query counts

**Summarised Results**

We have looked at two of the list pages and two of the main data display pages. For completeness, we include summary results of all pages below.

As with the data displayed in previous sections, we repeated all measurements 20 times; the data displayed represents the arithmetic mean of the 20 iterations. The summary data for data pages represents the median, standard deviation, minimum, and maximum values for the same 150 randomly chosen objects as used in the functional correctness evaluation.

The values for the list data pages represent the same summary statistics but for the different filters that can be applied to the list (for example, the disease list allows a user to view all diseases, or just those diseases which are relevant to immunopharmacology). The number of possible filters is explicitly noted in the table.

**Query counts**

Figure 5 shows the summary of query counts. As per our hypothesis, the Links query counts are almost uniformly lower and with smaller standard deviations.

The one exception is the ligand data page, although this is due to the pages being architected differently. The ligand data page (see Figure 1) consists of multiple subpages, accessible via different data tabs. In the Links implementation, data for all tabs is retrieved on the first page load, and users can navigate the different tabs without reloading the page. In the Java implementation, only data for the relevant tab is loaded, with each subpage requiring a new page load.

**Query times**

The picture is similarly good with query handling times, shown in Figure 6; the median query times are generally lower in the Links reimplementation (with the exceptions of the ligand data and object data pages), and the standard deviations are generally far lower, indicating greater predictability.

**Page build times**

As discussed previously, the Links page build times (Figure 7) are generally worse than the Java page build times (with the exception of the ligand list page), however the median page build times are generally still well under a second, so we would argue that the performance detriment is not prohibitive, especially given the greater query safety guarantees and performance.
<table>
<thead>
<tr>
<th>Page</th>
<th>Query Time (ms)</th>
<th>Links</th>
<th>Java</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Media n</td>
<td>Std. dev.</td>
<td>Min</td>
</tr>
<tr>
<td>Disease Data</td>
<td>7.98</td>
<td>1.96</td>
<td>6.70</td>
</tr>
<tr>
<td>Disease List</td>
<td>56.48</td>
<td>25.76</td>
<td>38.27</td>
</tr>
<tr>
<td>Family Data</td>
<td>62.75</td>
<td>28.19</td>
<td>51.23</td>
</tr>
<tr>
<td>Family List</td>
<td>5.05</td>
<td>8.56</td>
<td>1.16</td>
</tr>
<tr>
<td>Ligand Data</td>
<td>121.71</td>
<td>335.79</td>
<td>108.65</td>
</tr>
<tr>
<td>Ligand Families</td>
<td>0.87</td>
<td>–</td>
<td>0.87</td>
</tr>
<tr>
<td>Ligand List</td>
<td>955.69</td>
<td>2282.65</td>
<td>69.94</td>
</tr>
<tr>
<td>Object Data</td>
<td>121.31</td>
<td>8.43</td>
<td>111.02</td>
</tr>
</tbody>
</table>

**Figure 6.** Summary of query handling times

**Related work**

Our case study uses Links. There are other cross-tier languages, including Hop (Serrano et al., 2006), Ur/Web (Chlipala, 2015), and Eliom (Radanne et al., 2016). To the best of our knowledge, none of them has been used to implement curated databases.

Language-integrated query support is now being considered in several languages, for example including the Quill library for Scala1. We mentioned Links’s support for nested queries as an important advantage of using Links for implementing GtoPdb. Similar techniques offering similar guarantees have been proposed by Grust et al. (2010), with the most recent step in this line of work being a language-integrated query library for Haskell called DSH (Giorgidze et al., 2010). It might be interesting to conduct a similar case study implementing GtoPdb in Haskell using DSH, and compare with the Links version; alternatively it may also be worthwhile to develop a Java or Scala implementation of language-integrated query that supports nested queries, that could be used natively with GtoPdb or other Java-based systems.

**Conclusion and Future Work**

In this work, we have produced the first real-world case study of a curated scientific database, the IUPHAR/BPS Guide to Pharmacology, in a cross-tier functional programming language. Our approach leverages language-integrated query, which makes it possible to write type-safe queries instead of manually constructing SQL.

GtoPdb is a substantial curated database, built over a period of 16 years. The current Links implementation runs on an unmodified version of the GtoPdb database release, with the 9 major data pages implemented. The codebase of our Links case study currently stands at 13812 lines of code after around 5 months of effort by the first author, who had previous experience with Links. While it may be tempting to attempt a direct comparison on lines of code for each

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1 Quill, https://getquill.io/
page, such a comparison would be unreliable due to the difference in the structure of the two applications.

<table>
<thead>
<tr>
<th>Page</th>
<th>Links Median</th>
<th>Links Std. dev.</th>
<th>Links Min</th>
<th>Links Max</th>
<th>Java Median</th>
<th>Java Std. dev.</th>
<th>Java Min</th>
<th>Java Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Data</td>
<td>235.70</td>
<td>234.82</td>
<td>197.76</td>
<td>2384.15</td>
<td>13.37</td>
<td>31.38</td>
<td>7.83</td>
<td>354.47</td>
</tr>
<tr>
<td>Disease List (n=2)</td>
<td>1221.12</td>
<td>1218.97</td>
<td>359.18</td>
<td>2083.07</td>
<td>805.94</td>
<td>983.48</td>
<td>110.52</td>
<td>1501.37</td>
</tr>
<tr>
<td>Family Data</td>
<td>431.81</td>
<td>479.93</td>
<td>309.80</td>
<td>4070.39</td>
<td>104.47</td>
<td>299.13</td>
<td>33.08</td>
<td>2002.07</td>
</tr>
<tr>
<td>Family List (n=7)</td>
<td>223.63</td>
<td>23.35</td>
<td>208.44</td>
<td>279.54</td>
<td>119.73</td>
<td>217.22</td>
<td>36.42</td>
<td>669.33</td>
</tr>
<tr>
<td>Ligand Data</td>
<td>439.45</td>
<td>421.70</td>
<td>346.28</td>
<td>3507.80</td>
<td>44.05</td>
<td>6.37</td>
<td>40.91</td>
<td>66.74</td>
</tr>
<tr>
<td>Ligand Families (n=1)</td>
<td>231.35</td>
<td>–</td>
<td>231.35</td>
<td>231.35</td>
<td>36.89</td>
<td>–</td>
<td>36.89</td>
<td>36.89</td>
</tr>
<tr>
<td>Ligand List (n=12)</td>
<td>1483.64</td>
<td>3274.54</td>
<td>314.46</td>
<td>12292.94</td>
<td>3392.51</td>
<td>8610.89</td>
<td>214.41</td>
<td>31170.69</td>
</tr>
<tr>
<td>Object Data</td>
<td>465.24</td>
<td>223.34</td>
<td>380.51</td>
<td>2119.50</td>
<td>85.65</td>
<td>76.39</td>
<td>49.00</td>
<td>712.82</td>
</tr>
</tbody>
</table>

**Figure 7.** Summary of page build times

Finally, we have performed an automated functional correctness check, and conducted a performance evaluation and shown that the use of Links does not impose unacceptable overheads; indeed, the use of language-integrated query and nested queries results in lower query counts and comparable time spent handling queries in general. The evaluation has shown us that cross-tier programming languages have equivalent functionality to traditional tiered systems, however it is also worth noting that writing code in a single language and allowing early static error detection increases the robustness of the technical infrastructure in the long term.

**Future work**

Our experience shows that Links is up to the task of implementing web application front-ends for curated databases, which is prerequisite to our goal of language support for data curation. We have already begun implementing the GtoPdb curation interface in Links, in particular using relational lenses (Bohannon et al., 2006; Horn et al., 2018) to integrate curation activities more tightly with web-based graphical user interfaces (Horn et al., 2020).

Our next step is to design and implement language features which will aid curation, such as archiving, inspired by the work of Buneman et al. (2004).

Our work has concentrated on relational databases; we also plan to investigate language-integrated query for NoSQL databases, allowing us to implement case studies for a wider range of databases. This requires first adapting existing work on language-integrated query from relational to NoSQL data models and query languages.

**Acknowledgements**

We thank the IDCC and IJDC reviewers for their helpful comments. This work was supported by ERC Consolidator Grant Skye (grant no. 682315), and an ISCF Metrology Fellowship grant provided by the UK government’s Department for Business, Energy and Industrial Strategy (BEIS). Fowler was also supported by EPSRC Grant EP/K034413/1 (ABCD).
IUPHAR/BPS Guide to PHARMACOLOGY is supported by the International Union of Basic and Clinical Pharmacology (IUPHAR), and the British Pharmacological Society (BPS).

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