Synchronized iteration for genomic data processing

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Abstract

\textbf{Motivation:} Processing of large data files is unavoidable in genomic pipelines. Many tools that do this are either stand-alone languages or command-line tools. There is an impedance mismatch when these tools are used with a host programming language to support more complex analysis.

\textbf{Results:} A novel concept, Synchrony iterator, is introduced. It allows efficient algorithms underlying such tools to be easily expressed. As a demonstration, the powerful GenoMetric Query Language (GMQL) is emulated using Synchrony iterators in Scala/Python, and the resulting equivalents of these queries are very efficient. Notably, a user can freely intermix GMQL-like queries with other features of Scala/Python, thereby overcoming the impedance mismatch problem.

\textbf{Availability:} Implementations of Synchrony iterator and Synchrony GMQL, in both Scala and Python 3, are available at \url{https://www.comp.nus.edu.sg/~wongls/projects/synchrony}.

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Introduction

Some tools have emerged that exploit the intrinsic structures in genomic datasets to achieve efficiency in processing these large datasets. E.g., the GenoMetric Query Language (GMQL) \cite{5} is a declarative language for processing large quantities of genomic regions, and BEDOPS \cite{6} is a popular command-line toolkit for extracting and manipulating genomic regions.

A challenge, from the perspective of a programmer implementing these tools, is the impedance mismatch between the programming language used for the implementation and the kind of algorithms needed in these bioinformatics tools. Modern programming languages provide good support which makes programs manipulating large collections more readable. Yet it is still difficult to implement efficient algorithms (e.g. intersect collections of genomic regions under non-trivial matching conditions \cite{9}) in an easy-to-understand way.

There are two further challenges, this time from a user-programmer’s perspective. One is that, as these tools provide a rich set of operators on genomic data, the user-programmer has to familiarize himself with their thick manuals to use them effectively, even if he is a competent programmer. The other is that an impedance mismatch \cite{2} often arises when using these stand-alone tools in conjunction with a host programming language, to perform more complex analysis on genomic data.

This paper addresses these three challenges. Firstly, we describe \textit{Synchrony iterator}, a novel class of iterators enabling efficient synchronized iterations over multiple collections to be expressed in simple-to-understand comprehension syntax \cite{1}. Synchrony iterator is efficient and can succinctly implement those efficient algorithms alluded to in the first challenge above.

Secondly, this implies that a user who has mastered Synchrony iterator, which is a single programming construct, as opposed to a thick manual of many genomic operators, is already able to implement typical genomic queries in a simple and efficient way. So, it also addresses the second challenge.

Thirdly, we use Synchrony iterator to emulate GMQL. This emulation results in a Scala/Python library, \textit{Synchrony GMQL}. This library naturally embeds GMQL into Scala/Python. One can thus freely intermix GMQL-like operators into Scala and Python programs, addressing the third challenge. Remarkably, Synchrony GMQL is implemented in about 4,000/1,500 lines of Scala/Python codes, as counted by cloc. Despite the
simplicity of its implementation, Synchrony GMQL outperforms a local installation of GMQL [5]. This is a testimonial to Synchrony iterator as an elegant idea for expressing efficient synchronized iterations on multiple collections in a succinct and easy-to-understand way.

Methods
Basics of Synchrony iterator
We describe Synchrony iterator using our Python implementation, as Python is likely more familiar to the reader. For convenience, we refer to a Synchrony iterator as “eiterator”, as it is an enhanced iterator. An eiterator $ys = \text{EIterator}(Y, cl)$ can be constructed from any iterable object $Y$ (e.g. a list); where $cl$ is an optional argument which is a function for releasing resources held for $Y$ when the iterator is no longer needed. Although the eiterator $ys$ can be used as an iterator of the elements of $Y$ in the usual manner, it is endowed with several additional methods, including $\text{syncWith}$ which characterizes its conceptual novelty. The pertinent method $\text{syncWith}$ is described below, along with some supporting methods.

- $ys.\text{syncWith}(x, bf, cs)$ returns a list $vs$ equivalent to $\text{list}(\text{filter}(cs, \text{takeWhile}(\lambda x, y : bf(y, x) \text{ or } cs(y, x), y, x)))$ and also updates $ys$ to an eiterator equivalent to $\text{dropWhile}(\lambda y, x : bf(y, x) \text{ or } cs(y, x)).\text{prepend}(vs)$. $ys.\text{prepend}(vs)$ updates $ys$ by prepending elements in the list $vs$ to the front of $ys$.
- $ys.\text{peekAhead}(n)$ returns $[]$ if there are fewer than $n$ elements left in $ys$; otherwise, it returns $[y]$ where $y$ is the $n$th element in $ys$, without removing $y$ or any other elements from $ys$.
- $ys.\text{close}()$ releases resources held for $ys$. It is automatically invoked when accessing the last element in $ys$, but it can be invoked earlier to terminate the iteration on $ys$ midway.

Synchrony iterator is an efficient mechanism for “synchronizing” iterations on two or more collections. To appreciate this aspect, let $X$ and $Y$ be two lists. Let $(x << x' \mid X)$ mean $x$ appears before $x'$ in $X$, and $(y << y' \mid Y)$ mean $y$ appears before $y'$ in $Y$. A predicate $bf(y, x)$ is said to be “monotonic” wrt $(X, Y)$ if (i) for each $y$ in $Y$, $bf(y, x)$ implies $bf(y, x')$ whenever $(x << x' \mid X)$; and (ii) for each $x$ in $X$, $bf(y, x)$ implies $bf(y, x')$ whenever $(y << y' \mid Y)$. A predicate $cs(y, x)$ is said to be “antimonotonic” wrt a monotonic predicate $bf(y, x)$ if (i) for each $y$ in $Y$, $bf(y, x)$ and $\neg cs(y, x)$ implies $\neg cs(y, x')$ whenever $(x << x' \mid X)$; and (ii) for each $x$ in $X$, $\neg bf(y, x)$ and $\neg cs(y, x)$ implies $\neg (y', x)$ whenever $(y << y' \mid Y)$. From part 1 of the theorem, $\text{syncmap}(X, Y, bf, cs, f)$ produces a list same as that produced by $[f(x, [y \text{ for } y \text{ in } Y \text{ if } cs(y, x)]) \text{ for } x \text{ in } X]$. Suppose for each $y$ in $Y$, there are at most $k$ elements $x$ in $X$ satisfying $cs(y, x)$. Then $\text{syncmap}(X, Y, bf, cs, f)$ has time complexity $O(|X| + k|Y|)$. In contrast, by part 2 of the theorem, $\text{syncmap}(X, Y, bf, cs, f)$ has linear complexity, $O(|X| + k|Y|)$.

This tremendous gain in efficiency illustrates the powerful synchronized iteration mechanism affected by the seamless interaction between Synchrony iterator and comprehension syntax. For each $x$ in $X$, $vs = ys.\text{syncWith}(x, bf, cs)$ is computed. By definition of $\text{syncWith}$, $vs$ is same as $\text{list}(\text{filter}(cs, \text{takeWhile}(\lambda x, y : bf(y, x) \text{ or } cs(y, x), y, x)))$. The function $\text{takeWhile}$ stops the iteration on $ys$ as soon as it encounters an element $y$ such that both $bf(y, x)$ and $cs(y, x)$ are false. This is due to part (ii) of the antimonotonicity of $cs$, $bf(y, x)$ and $\neg cs(y, x)$ implies $\neg cs(y', x')$ for all subsequent elements $y'$ in $Y$. So, the iteration on $Y$ for this $x$ is safely stopped early, avoiding a full iteration on $Y$. Recall also from the definition of $\text{syncWith}$ that $ys$ is updated to an eiterator equivalent to $\text{dropWhile}(\lambda y, x : bf(y, x) \text{ or } cs(y, x)).\text{prepend}(vs)$ on the next iteration on $Y$ does not start from the beginning of $Y$. Rather it starts from the elements of $vs$ prepended previously, and continues on to where the iteration for the previous $x$ stops. This is due to part(i) of the antimonotonicity of $cs$, $bf(y, x)$ and $\neg cs(y, x)$ implies $\neg cs(y', x')$ for all $x'$ coming after $x$. So, provided $bf$ is monotonic wrt $(X, Y)$, the antimonotonicity of $cs$ implies that each $x$ in $X$ is “seen” by a different segment of $Y$, with overlaps $|vs| \leq k$ on average, resulting in $O(|X| + k|Y|)$ complexity.

Synchrony iterators on large files
Our Synchrony iterator implementation provides the class $\text{EFile}$ for representing large data files. Let $f$ be a file containing a list of entries. Let $df$ be an incremental deserializer function for reading entries in $f$; i.e. $df$ sequentially fetches a few entries at a time, on demand. Let $sf$ be a serializer function for writing entries in $f$. Then $\text{OnDiskEFile}(f, sf, df)$ constructs an $\text{EFile}$ representing the file $f$. While $\text{TransientEFile}(vs, sf, df)$ constructs an $\text{EFile}$ representing an iterable or eiterator $vs$ that can be serialized to and deserialized from disk using $sf$ and $df$. An $\text{EFile}$ $vs$ provides a number of methods, including:

- $vf.\text{iterator}()$, which produces a new Synchrony iterator on $vf$. If $vf$ represents a file on disk, this iterator uses the incremental deserializer associated with $vf$ to read a few sequential entries in $vf$ at a time as needed. So, a Synchrony iterator keeps only a small segment of a large file in memory.
- $vf.\text{serialized}()$, which serializes $vf$ to disk.
- $vf.\text{sorted}()$, which sorts $vf$ on disk using the canonical ordering defined on $vf$. The sorting is done by chopping $vf$ into $m$ chunks, sorting each chunk in memory and writing to a temporary file, then merging the $m$ files. The in-memory sorting has linearithmic complexity, while the final merging has linear complexity. However, due to disk access, the former is dominated by the latter; thus, near-linear performance is observed when $vf$ has many items.
- $vf.\text{mergedWith}(f_1, \ldots, f_n)$, which merges $vf, f_1, \ldots, f_n$, assuming all these $\text{EFile}$ objects are already pre-sorted using their respective canonical ordering.

Theorem 1 (cf. [9]) Let $\text{syncmap}$ be the program below.

```python
def syncmap(X, Y, bf, cs, f):
    ys = EIterator(Y)
    return [f(x, ys.\text{syncWith}(x, bf, cs)) for x in X]
```

Let $X$ and $Y$ be two lists, $bf(y, x)$ be monotonic wrt $(X, Y)$, $cs(y, x)$ be antimonotonic wrt $bf(y, x)$, and $f(x, vs)$ has time complexity $O(|vs|)$. Then,

1. $\text{syncmap}(X, Y, bf, cs, f)$ produces the same list as $[f(x, [y \text{ for } y \text{ in } Y \text{ if } cs(y, x)]) \text{ for } x \text{ in } X]$.
2. $\text{syncmap}(X, Y, bf, cs, f)$ has time complexity $O(|X| + k|Y|)$, provided there is some $k$ such that for each $y$ in $Y$, there are at most $k$ elements $x$ in $X$ satisfying $cs(y, x)$. 


BED files and sample files

We use Synchrony iterator on genomic data files, in particular, BED files compatible with the popular BEDOPS [6] toolkit. A BED file is an on-disk list of BED entries. A BED entry is a region on a chromosome and has some annotations associated with it. It is represented in our implementation as an object in the class `Bed`. A region on chromosome `ch`, starting at position `st`, ending at position `en`, on strand `sn`, that has annotations `{name = nm, score = sc, ...}` is represented as a `Bed` object `x = Bed(ch, st, en, nm, sc, ...)`. Any annotation `ell` on the BED entry represented by a `Bed` object `x` can be accessed as `x.ell`, e.g. `x.chrom` is the chromosome of the BED entry.

We often want to compare BED entries based on their chromosomal positions or loci. So, a predicate object `p = BedPred(y, x)` provides predicates on the loci of `Bed` objects `y` and `x`, including the followings:

- `p.isBefore()`, which is `True` iff the locus of `y` is before the locus of `x` in the “canonical ordering” of loci. Loci are canonically ordered by `(chrom, chromStart, chromEnd, strand)`.  
- `p.overlap(n)`, which is `True` iff the locus of `y` overlaps the locus of `x` by at least `n` bases.  
- `p.d1(n)`, which is `True` iff the locus of `y` does not overlap that of `x` and the distance between them is less than `n` bases.

It is a simple exercise to prove the proposition below. Thus these predicates (and others which we have omitted here) can be used in conjunction with Synchrony iterator.

**Proposition 2** Let `X` and `Y` be two BED files sorted based on the canonical ordering on loci; and `p = BedPred(y, x)` is a predicate object on `y` and `x`, which are respectively `Bed` objects representing some BED entries in `X` and `Y`. Then `p.isBefore()` is monotonic wrt `(X, Y)`, and `p.overlap(n)` and `p.d1(n)` are both antimonotonic wrt `p.isBefore()`.

BED files are represented by the class `BedEFile`, a subclass of `EFile`. This class has two main constructors: `OnDiskBedEFile(f)` for constructing a `BedEFile` object representing the BED file `f`, and `TransientBedEFile(vs)` for constructing a `BedEFile` object representing an iterable or iterator `vs` of `Bed` objects.

Some metadata can also be associated with an entire BED file. A BED file and its associated metadata is called a “sample.” Our Synchrony iterator implementation provides a class `Sample` for representing samples. Its constructor `Sample(f, d)` constructs a sample object representing the `BedFile` object `f` and its metadata `d` (which is a dictionary.) Let `s` be a `Sample` object. Then `s.bedFile` returns its `BedFile` object; `s.ell` returns the value of its metadata labelled as `ell` in the dictionary; `s.bedFileUpdated(ell)` constructs a new sample object with `BedFile` object `f` and the same metadata as `s`; and `s.metaUpdated(d)` constructs a new sample object with metadata `d` and the same `BedFile` object as `s`.

A sample file is an on-disk list of samples. Sample files are represented by the class `SampleEFile`, a subclass of `EFile`. This class also has two main constructors: `OnDiskSampleEFile(f)` for constructing a `SampleEFile` object representing the sample file `f`, and `TransientSampleEFile(vs)` for constructing a `SampleEFile` object representing an iterable or iterator `vs` of `Sample` objects.

**Overview of GMQL**

GMQL [5] features a list of operators to create, store, and process datasets defined in common genomic data formats. Some GMQL operators mirror relational algebra operators, e.g. SELECT, PROJECT and GROUP. Some GMQL operators are genomic-specific, e.g. MAP, JOIN, and COVER.

GMQL is optimized for sample files containing many samples, with each sample having a large BED file. A GMQL query is decomposed into metadata and region operations. Metadata operations are evaluated before region operations. Usually, the effect of a metadata operation is to filter or remove samples from the input. Thus, only samples contributing to the result are passed to data loaders. For region operations, GMQL achieves high performance by binning the genome into chunks and comparing different bins concurrently [4].

For benchmarking, we deploy GMQL on a local installation of Apache Spark, which simulates a small cluster on a single multicore machine. We refer to this as the GMQL command-line interface, or CLI. The machine is a laptop with 2.6 GHz 6-Core i7, 16 GB 2667 MHz DDR4, 500 GB SSD.

**Synchrony emulation of GMQL**

Many queries have common idiomatic structures, which can be abstracted as re-usable query operators. GMQL operators are examples of these. We use Synchrony iterator to implement a Scala/Python library, Synchrony GMQL, that replicates all GMQL operators; i.e. Synchrony iterator is used instead of GMQL’s binning strategy. Two examples (MAP and COVER) are provided below, to illustrate the ease and succinctness of the emulation. Full details of the emulation of all GMQL operators are at [www.comp.nus.edu.sg/~wongls/projects/synchrony](http://www.comp.nus.edu.sg/~wongls/projects/synchrony).

**Emulation of MAP**

Consider the GMQL MAP query, `MAP() U V`, where `U` and `V` are `SampleEFile` objects. For each `Sample` `s` in `U`, each `Sample` `t` in `V`, and each `Bed` entry `x` in `s.bedFile`, this query counts the number of `Bed` entry `y` in `t.bedFile` whose locus overlaps with the locus of `x`. If naively executed, the time complexity of this query is $O(|U| \cdot |V| \cdot m^2)$, assuming each BED file has `m` entries. It has a very succinct and far more efficient implementation below as `maps(U, V)`, which forms every pair of samples and processes the BED files of the pair by `map(X, Y)` to count overlaps using Synchrony iterator; see the four lines of codes delineated as the function `synchronized(xs, ys)`. By Theorem 1, despite its simplicity, this implementation has complexity $O(|U| \cdot |V| \cdot (4 + 1)m)$, when no region overlaps more than $k << m$ other regions. Notably, the linear part $(k + 1)m$ is achieved without using any specialized interval indices (e.g. [3, 4]).

```python
def bf(y, x): return BedPred(y, x).isBefore()  
def cs(y, x): return BedPred(y, x).overlap(1)  
def mapr(X, Y):
    def synchronized(xs, ys):
        for x in xs:
            ss = lambda y: BedPred(y, x).sameStrand()  
            vs = filter(ss, ys syncedWith(x, bf, cs))  
            yield Bed(**x.dict(),'count': len(vs))  
            xs, ys = (X.iterator(), Y.iterator())  
            tr = synchro(xs, ys)  
            cl = lambda : (xs.close(), ys.close())  
            return TransientBedEFile(EIterator(tr, cl))
```
Consider the GMQL query \( COVER(n, m, U) \), where \( n, m > 0 \) and \( U \) is a SampleEFile. Conceptually, it produces "maximal" regions in the underlying genome that each overlaps \( n \) to \( m \) number of regions in the BED files of the samples in \( U \).

It is implemented below as \( \text{covers}(\text{minmax}, \text{U}) \), where \( \text{covers}(\text{beta}(n, m), \text{U}) \) realizes the query \( COVER(n, m, U) \), while \( \text{covers}(\text{atleast}(n), \text{U}) \) realizes \( \text{COVER}(n, \text{ANY}) \).

```python
def covers(minmax, U):
    def aux(S, T):
        for s in S:
            for t in T:
                b = mapr(s.bedFile, t.bedFile)
                yield s.bedFileUpdated(b)
    S, T = (U.serialized(), V.serialized())
    return TransientSampleEFile(EIterator(aux(S, T), cl = lambda(): histo.close()))
def atleast(n):
    return lambda i: n <= i
def betv(n, m):
    return lambda i: n <= i <= m

def covers(minmax, XS):
    mm = first.mergedWith(*rest).serialized()
    rf = mm.mergedWith(ee.sorted())
    ss = mp(mm, lambda r: r.start)()
    ee = mp(mm, lambda r: r.end)()
    rf = ss.mergedWith(ee.sorted()).distinct().serialized()
    return TransientBedEFile(EIterator(rf, cl = lambda(): histo.close()))

def mapr(s, t):
    return TransientSampleEFile(EIterator(it, cl = lambda(): histo.close()))
```

Here, \( \text{covers} \) first extracts \( XS = \{s.bedFile for s in U\} \), which are the BED files associated with the samples in \( U \). Then all the regions in these BED files are extracted in a new BED file \( mm \) and all the start and end positions of these regions are extracted into another new BED file \( rf \). A Synchrony iterator is then used in the function \( \text{syncro}(\text{minmax}, \text{rf}, \text{mm}) \) to generate for each \( x \) in \( rf \)—where \( x \) is overlapped by \( i \) number of regions in \( mm \) and \( i \) satisfies the constraint \( \text{minmax} \)—a new region with the same start position as \( x \) but with its end position set to the nearest end position among the regions in \( mm \) that overlap \( x \). This list of new regions is denoted as \( \text{histo} \) in the program. Finally, the function \( \text{concat}(\text{histo}) \) merges regions in \( \text{histo} \) that overlap each other, to produce the maximal regions desired.

All the steps above are linear in the total number of regions in all the samples, except for a substep needed in producing \( rf \): the substep is the sorting of end positions \( (\text{ee}) \), which has the usual linearithmic time complexity of sorting. However, this linearithmic component is masked by disk access when processing large BED files. I.e., the overall time performance observed in practice is very close to linear. Again, this is achieved without using any specialized genomic interval indices (e.g. [3].)

Performance comparisons

To show that Synchrony GMQL, which is based on Synchrony iterator, has similar or better performance than GMQL CLI, we have chosen four representative operators: MAP, COVER, JOIN, and SELECT. The first three showcase the power of Synchrony iterator when processing large genomic data files, while the last shows that the emulation is also efficient for GMQL operators which do not need Synchrony iterator.

For MAP, the GMQL query chosen is \( \text{MAP}() \ u \ V \), which we saw earlier. The equivalent Synchrony GMQL query is \( \text{mapS}(\text{mapR})(U, V) \). Note that, in contrast to the \( \text{maps} \) and \( \text{mapR} \) functions shown earlier, \( \text{mapS} \) and \( \text{mapR} \) are Synchrony GMQL functions that fully emulate MAP in all its parameters.

For COVER, the chosen query is \( \text{COVER}(1, \text{ANY}) \ u \ V \). Its Synchrony GMQL equivalent is \( \text{covers}(\text{coverR}(\text{atleast}(1)))(U, V) \). Different from the \( \text{covers} \) and \( \text{coverR} \) functions shown earlier, \( \text{covers} \) and \( \text{coverR} \) are Synchrony GMQL functions that fully emulate COVER in all its parameters.

For JOIN, the GMQL query chosen is \( \text{JOIN}(\text{DL}(0)); \text{output: int} \ u \ V \). For each Sample \( s \) in \( U \), each Sample \( t \) in \( V \), this query searches for all regions in \( t.\text{bedFile} \) which have distance less than 0 to any region in \( s.\text{bedFile} \). i.e. it looks for regions in \( s.\text{bedFile} \) that overlap with regions in \( s.\text{bedFile} \). This query outputs the intersection (viz. overlapping area) of each pair of matching regions. The equivalent in Synchrony GMQL is \( \text{joinS}(\text{joinR}(\text{overlap}(1), \text{output} = \text{intersect}))(U, V) \). Here, \( \text{joinS}(f)(U, V) \) forms all possible pairs of \( \text{Sample} \) objects in \( (U, V) \), and applies \( f \) to each of these...
pairs; \texttt{joinR(Overlap(1), output = intersect)} is the Synchrony iterator-based function for joining two BED files, where the \texttt{Overlap(1)} predicate makes the semantic intention more clear.

For \textbf{SELECT}, the GMQL query chosen is \texttt{SELECT(region: (chr1==chr1 OR chr1==chr2)) \textit{U}}. For every \texttt{Sample} \textit{s} in \textit{U}, this query selects all regions found on the first or second chromosome of \texttt{s.bedFile}. The equivalent in Synchrony GMQL is \texttt{onRegion(\texttt{selectR(lambda r: r.chrom == "chr1" or r.chrom == "chr2")}(\textit{U})}. Here, \texttt{onRegion(f)(\textit{U})} applies \textit{f} to \texttt{s.bedFile} for each \textit{s} in \texttt{U}, and \texttt{selectR(lambda r: r.chrom == "chr1" or r.chrom == "chr2")} selects regions on \texttt{chr1} or \texttt{chr2}.

Performance is compared based on the criteria below.

1. \textbf{Execution time}. The queries are run on 9 datasets, cf. the Datasets section, spanning the two dimensions of number of samples and number of lines (i.e. regions) per sample. Execution time includes writing query results to disk.

2. \textbf{Time complexity}. Each query is also run on a second group of datasets. These alternative test cases are meant to show how the time complexity (viz., execution time) increases with respect to either the number of samples, or the number of regions per sample, when the other measure is fixed.

3. \textbf{Memory usage}. Scala executes on top of the Java Virtual Machine (JVM). To verify that Synchrony GMQL maintains its performance even when a low amount of memory is allocated to the JVM, the queries are run two times; once by allocating 2GB of memory to the JVM, and another time by allocating 128MB of memory.

As GMQL CLI is based on Scala, we compare our Synchrony GMQL implementation in Scala with it. Our Scala implementation can be run in strictly sequential mode and also in sample-parallel mode (In this mode, each BED file is processed sequentially, but the BED files of different samples are processed in parallel on all 6 cores of the test machine.) We also show the performance of our Synchrony GMQL implementation in Python for information purpose; it is expected to be an order or two of magnitude slower as it is interpreter-based.

\section*{Datasets}

Table 1. describes all datasets used in the above comparisons. There are 9 reference datasets, named SS through BB, that provide examples of different type of input data, viz., either with large amount of samples, many regions per samples, or a combination of both. All regions come from transcription factor (TF), and a set of genes of interest, all of which are located on the positive strand of human DNA, identify all TFBS that are found in the promoters of said genes. For simplicity, assume that both the TFBS and the genes sample regions, TL and GL, are already sorted according to chromosome, start, end, and strand. Assume also that for each gene, the promoter is located between 2,000 bp upstream and 1,000 bp downstream of its transcription start site (TSS), and the TSS is located at the very first base of the gene.

In GMQL, this query is written below using a combination of \texttt{PROJECT}, \texttt{MAP}, and \texttt{SELECT}; \texttt{PROJECT} takes care of resizing each gene to locate the promoter area; \texttt{MAP} counts how many promoters intersect each TFBS; and \texttt{SELECT} filters out all TFBS that do not match any promoters.

\begin{verbatim}
PLS = SELECT(region: strand == +) GL;
PRM = PROJECT(region_update: start as start - 2000, stop as start + 1000) PLS;
MAT = MAP() TL PRM;
RES = SELECT(region: count >0) MAT;

The same query is expressed below in Python via Synchrony GMQL functions mirroring the GMQL operators.
\end{verbatim}

\begin{verbatim}
pl = selectR(lambda r: r.strand == "+")
prm = projectR(
    'chrStart': lambda r: r.chromStart - 2000, 
    'chrEnd': lambda r: r.chromStart + 1000)

Table 1. Datasets used in Synchrony GMQL performance testing.

<table>
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<th>Sample</th>
<th>Regions</th>
<th>Size [MB]</th>
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<td>10000</td>
<td>10.20</td>
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<td>314364</td>
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\end{verbatim}
We test the two queries using MCF-7 as the TFBS list \(TL\) and ncbiRefSeqGenes10X as the gene list \(GL\); cf. Datasets section. Sequential Synchrony GMQL produces its results in 2.75 seconds (average of 10 runs, stdev = 0.09), while parallel Synchrony GMQL does this in 1.94 seconds (average of 10 runs, stdev = 0.07.) GMQL CLI finishes in 56.14 seconds (average of 10 runs, stdev = 2.26.) Python Synchrony GMQL completes in 35.44 seconds (average of 10 runs, stdev = 0.88.) So, Scala Synchrony GMQL is 20 to 30 times faster than GMQL CLI on this example, while the Python version is 1.58 times faster.

<table>
<thead>
<tr>
<th>Query</th>
<th>Scala Synchrony GMQL</th>
<th>GMQL CLI</th>
<th>Python Synchrony GMQL</th>
</tr>
</thead>
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<tr>
<td>MAP</td>
<td>35.44 seconds</td>
<td>56.14 seconds</td>
<td>35.44 seconds</td>
</tr>
<tr>
<td>JOIN</td>
<td>2.75 seconds</td>
<td>2.75 seconds</td>
<td>2.75 seconds</td>
</tr>
<tr>
<td>COVER</td>
<td>23.14 seconds</td>
<td>23.14 seconds</td>
<td>23.14 seconds</td>
</tr>
<tr>
<td>SELECT</td>
<td>60.00 seconds</td>
<td>56.14 seconds</td>
<td>60.00 seconds</td>
</tr>
</tbody>
</table>

In this program, which also implements the “TFBS found in promoters” query, \(PRM\) and \(TL\) are as defined earlier and evaluate to \(SampleEFile\); and \(mapr\) is as defined earlier (in the section on emulating MAP) and evaluates to \(BedEFile\). The output is a list of triples \((p, tf, s)\), where \(p\) is a \(Sample\) from \(PRM\), \(tf\) is a \(Sample\) from \(TL\), and \(s\) is a \(BedEFile\) containing those regions in \(tf.bedFile\) that overlap some regions in \(p.bedFile\). The twist here is that the output is no longer a \(SampleEFile\), but is the triple \((p, tf, s)\). In a situation where \(GL\) (and thus \(PRM\)) contains multiple samples (each being a separate list of gene promoters), outputting such a triple is natural for keeping track of the provenance of \(s\) (i.e. it is derived from which \(p\) and \(tf\)). This illustrates the free mixing of Synchrony GMQL operations and results with any other features in the host programming language. This natural embedding of efficient genomic querying capability into a host programming language brings great convenience in more complex data processing and analysis pipelines.

**Execution time comparisons**

Figure 1 shows the results of running the MAP, JOIN, COVER, and SELECT queries on 9 reference datasets SS, ..., BB. Time in seconds. Each average is done over 30 runs, except for BM and BB, which are done up to 5 runs due to time constraints. Purple: GMQL CLI. Blue: Sequential Synchrony GMQL. Green: Parallel Synchrony GMQL. Yellow: Python Synchrony GMQL.
Synchronized iteration for genomic data processing

with the observation in the charts for COVER in Figure 2 where, modulo some fluctuations at very low amounts of data and at systems start-up, linearity is observed. The query \( \text{mapS}(\text{mapR})(U, V) \) also has theoretical time complexity \( O(|U||V|(k + 1)m) \), with scaling behaviours similar to JOIN. The query \( \text{onRegion}(\text{selectR}(\lambda r : r.chrom == "chr1" or r.chrom == "chr2")(U)) \) has theoretical time complexity linear in the total number of regions in \( U \) as well. Both their scaling charts are omitted as these add no further insight.

Execution times in constrained memory situation

Figure 3 shows that the execution time of JOIN and COVER in Synchrony GMQL do not differ much when a lot (2GB) or little (128MB) memory is given to the JVM. Similar memory efficiency is observed for MAP, and SELECT in Synchrony GMQL; charts omitted. So, Synchrony iterator does not consume much memory even when there are large amounts of input data.

Conclusion

Synchrony iterator is a paradigm for expressing, in easy-to-understand comprehension syntax, efficient genomic data processing algorithms that require synchronized iterations on two or more streams of ordered genomic regions. We have demonstrated how Synchrony iterators can be used to emulate the powerful genomic query language GMQL in a succinct and efficient way. We have shown that the resulting emulation, Synchrony GMQL, is more efficient than a local installation of GMQL. Thus, Synchrony iterator is an elegant solution to impedance mismatch issues that often arise when designing and implementing genomic data processing pipelines.

Synchrony iterator is designed to keep the technicalities of synchronized iterations from the user, needing only simple definitions of the “is before” (denoted as \( \beta \) in the text) and the “can see” (\( \alpha \)) predicates to function correctly and efficiently. While Synchrony iterator is not specifically designed for bioinformaticians, its use is natural in genomic dataset processing. This is because genomic regions are naturally ordered based on their loci, and because it is often the case that researchers are interested in questions of proximity between loci.

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References