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Extending BioSeq in Julia: Contributions to an open source project

Kristopher Micinski [1,*], James Parker [2] and Matthew Louis Mauriello [2*]
[1]Department of Computer Science, University of Maryland, College Park
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ABSTRACT

Typically, R is the programming language of choice to perform biological computations. While the dynamic nature of the language allows rapid programming, R suffers from poor performance and is conducive to programming errors. One solution to this problem is the newly developed programming language, Julia. Julia boasts many attractive features such as a JIT compiler and a strong type system, which address many of the shortcomings of R. Specifically, the language produces programs with more guarantees about correctness and runs at speeds approaching that of C. In an effort to improve computational biology and research, we implement **?** parsing of BAM files, representation of genomic ranges, and efficient overlap detection **?** in Julia to take advantage of this new language.

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Contact: name@bio.com

1 INTRODUCTION

R is currently the preferred tool of the bioinformatics community. While R works well for rapid programming, it is also conducive to programmer error. The language is weakly typed and coercions are implicit, which often leads to runtime errors or (worse) code that tacitly breaks. For instance, consider the following code that attempts to convert a data frame that is read from a file into a matrix.

```
raw <- read.csv(``genotypes.csv'')
genotypes <- data.matrix(raw)
```

At first glance, this appears innocuous, however consider the case when *raw* contains null data (which R represents as `NA`). The `NA` s are implicitly coerced to `1` in the matrix. If the researcher is unaware of this behavior, this coercion can lead to incorrect analyses and results. This is a very troubling situation, as good scientific practice emphasizes testing and validating *all* methods for correctness. As software is used more and more frequently within scientific research: we need a way to ensure the correctness of software, without adding an undue amount of burden on the programmer.

Another issue with R is that it has poor performance. Because of R's highly dynamic semantics, code is executed within an interpreter (rather than compiled, ala Fortran). Running in an interpreter is much slower than native code executed directly by a machine's hardware. One reason for this is that an interpreter must read a line of code, decode it, and evaluate it. On the other hand, native code is compiled and executed in real time by the processor.

Compiling R is sometimes possible **?**, but made harder because of its dynamic type system. The reason for this lies in the ability of the compiler to compile an expression based on its type (which in many languages dictates memory layout). Consider what must happen when the interpreter parses the expression `A * B`. The operator $*$ is overloaded so that it can work on a multitude of combinations of objects (integers and vectors, matrices, etc...). The interpreter must first deduce the *type* of the object (difficult to do without control flow analysis **?**), and then choose the appropriate implementation of $*$ to use. Instead, if the compiler knows the *type* of the objects, it can simply create a control flow sequence which simply multiplies the operands, or calls a matrix operation:

```
imul %l0 %l1
ccall multiply_matrices %p0 %p1
```

To address the shortcomings of R, we investigate the new programming language Julia and implement select functionality from R fs `BioConductor` package. Julia is a language aimed at scientific computing and a minimal syntax, designed to be approachable by scientists. It actively supports users with writing better code by providing a rich type system, native parallel computation, simple unit testing primitives, a module system, and other features lacking within R. Types allow us to syntactically specify which programs are well formed. Additionally, performance problems commonly found in R are addressed by the Just In Time (JIT) compiler built on top of the LLVM compiler toolkit The JIT compiler allows the compiler to use machine specific opportunities to highly optimize the codebase. Because the system uses LLVM as the underlying compiler, compilation is as efficient as LLVM (which has a very active user community and supports efficient compilation to many architectures).

*to whom correspondence should be addressed

Table 1. Benchmark times relative to C (smaller is better) **?**.

This is apparent in Table 1 from **?**, which compares the performance of Julia to many different languages. To highlight the differences in speed between R and Julia, the table shows that Julia is 517.34 times faster than R at performing quicksort.

A strong type system also allows the programmer to make some guarantees about the parameters of program. more stuff here..

Julia has a library for manipulating biological data called BioSeq (Zea, 2013) , however this library does not provide the functionality we are looking for. Currently it handles DNA sequences at the single nucleotide level, but it does not contain data structures for looking at regions of genes. We expand BioSeq and add additional functionality for working with genomic range data. **?** This rest of this paper is laid out as follows. Section 2 discusses specifically the functionality being added to BioSeq and discusses our hypothesis surrounding performance measures we anticipate being provided by Julia over R. Section 3 discuss the particular algorithms used in the countOverlaps() operation as well as discusses the SAMtools API. Section 4 briefly discusses the level of current implementation. Section 5 explores the benchmarking: procedure, data, results, and makes some basic conclusions. Section 6 explains immediate needs before public release. **?**

2 SYSTEM AND METHODS

This project seeks to replicate a portion of BioConductor package that is currently available in R for the Julia language. Several key elements of this package have been selected, which includes: basic support for **?** genomic data classes (i.e. IRanges, GRanges, etc.), support to perform union and intersection operations over genes, the ability to import large BAM files containing genomic data, and support for running overlap queries **?**. With respect to loading BAM files, we have taken advantage of a Foreign Function Interface (FFI) to take advantage of the SAMtools library.

In order to demonstrate that Julia offers performance benefits over R, we will collect system times on the diverse set of tasks that have been replicated in Julia. In particular, this study will look at the total elapse time of the countOverlaps() pipeline as well as the elapse time of each individual set of tasks. Based on the interpreted vs compiled nature of making code comparisons between Julia and R, we make the following hypothesis:

H1. BAM files processing tasks and currently implement data structure operations will show no significant differences in performance times. The use of FFI to call SAMtools is common across both languages and data structure operations are implemented in a naive fashion. Therefore, it is anticipated that the Julia implementation will be faster than R; however, this difference will not be significant.

H2. Performing the countOverlaps() operation on the GRanges interval object will demonstrate significant performance improvements in Julia that result in improvement in the total elapse time of the pipeline. The countOverlaps() operation has been implemented and optimized for running in Julia and is expected to demonstrate performance improvements over R implementation of the same operation.

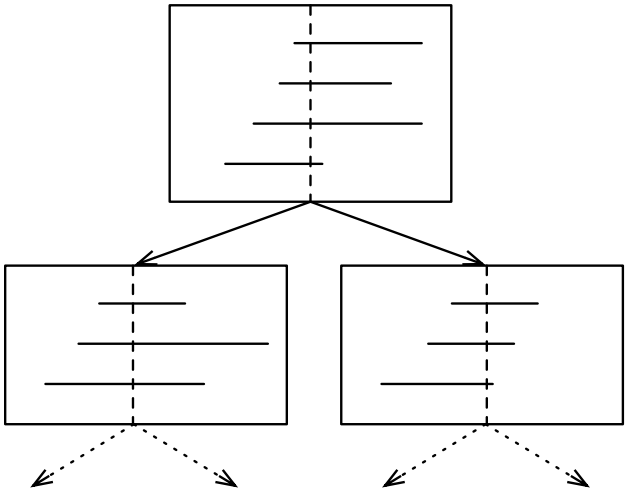

Fig. 1. An interval tree where the intervals in each node are shown as sorted by the start endpoint. The dashed vertical line indicates the center point of the node.

The purpose of this study is to demonstrate the performance benefits over R that are offered by Julia. These demonstrated benefits will provide support for the continued deve lopment of the bioinformatics package gBioSeqh.

3 ALGORITHMS

There are no novel algorithms in our implementation, however we do use specific data structures and algorithms to make certain operations efficient. The main example of this is the use of an interval tree. An interval tree can be constructed out of an array of genomic ranges. Then this data structure can be used to efficiently perform queries to find which intervals overlap.

Interval trees are binary trees that contain intervals **?**. Each node of the tree contains a center point, an array of intervals that overlap the center point sorted by the start endpoint, and another array of the same intervals sorted by the finish endpoint. The node also stores a pointer to a left node which is a parent of all intervals that are left of the center point. The same is true for a right node and intervals to the right of the center point. A diagram illustrating interval trees can be seen in Figure 1 where the shown intervals are sorted by the start endpoint.

Intervals trees can be constructed by taking the mean of the given intervals as the center point. Then intervals that overlap the center point are stored in the current node. Intervals to the left or right of the center point are then recursively split off to construct the left and right nodes until no intervals remain. This how process of construction takes $O(n \log n)$ time.

Interval trees are used to find the intervals that overlap a query interval. This is accomplished by checking if the query interval overlaps with a nodefs center point. If this is true then all the intervals in that node are found to overlap. If the query interval is left of the center point, the nodefs forward sorted array of interval is checked if they overlap with the query. Once one of the intervals is

found to not overlap the query, the algorithm stops checking more intervals because the intervals are sorted. The same approach is applied to the case when the query interval is right of the center point. After a node is finished, it recursively runs the query against its left or right child nodes as necessary. Performing queries on interval trees takes $O(\log n)$ time as long as the tree is sufficiently balanced.

4 IMPLEMENTATION

We implement our codebase to mirror the implementation of the relevant aspects of the `BioConductor` package. When appropriate, our types (classes in R) share the same names and functions, and our implementation uses similar data strctures.

4.1 `IRanges`

4.2 `GRanges`

4.3 Parsing BAM Files

The SAM and BAM file formats represent alignments from RNA-seq data in a standard way. **?** A BAM file lists a large set (hundreds of megabytes or more) of alignments given as a set of read data and metadata (read position, forward or backward, a string indicating status for each position, etc...). We have implemented machinery which allows reading of BAM files within Julia.

Our implementation relies on the SAMtools library : written in C. Julia allows interfacing with C using a simple FFI (foreign function interface) . Procedures from C can be called, and the data can be manipulated (although not all values in C can be represented, many map onto Julia types, which are represented via LLVM). The `ccall` function allows calling C functions by specifying their argument types and arguments (as Julia values). The code is then properly wrapped according to the platform's ABI and the results are transferred back to Julia.

Representing values from C within Julia is possible when the values in C map to a Julia type. Julia includes various types for holding C values, including the native C types such as `Uint8`, but also pointer types such as `Ptr{Void}`. The Julia FFI is still evolving but looks to become a simple way to integrate scientific libraries (written in C) to be called from Julia code. Throughout the development of the BAM parsing library, an author found a bug in Julia which caused a pointer (returned from a C function) to be mishandled by Julia's garbage collector: the bug was reported and will be fixed.

The SAMtools library allows reading extremely large alignment files and holding the results in memory. Because the alignment data could be quite large, it is generally a bad idea to hold all alignments in memory at any one time. Instead, the file supports callback based querying: a user queries alignments from the place in the genome in which they are interested, and the library returns the reads. The reads are returned using a callback function, which is called every time new overlapping reads (from within the region) are found.

Our implementation harnesses the power of SAMtools, but also uses a helper C library to create a simple wrapper which can be called from Julia. The reason for this library is that not all C types in SAMtools can be easily represented in Julia: the library provides stubs which perform operations and map them back to simple Julia types.

Julia FFI also places the requirement that the library be dynamically loaded (rather than statically linked). This requires that the SAMtools library be compiled in a position independent way: to do so we modified the `Makefile` of the SAMtools library to compile a position independent dynamic library (along with our helper stubs) to call the code from Julia.

5 DISCUSSION

these sections/subsections seem a bit weird to me Feel free to change them... the format is loosely based on the guide; hector suggested doing our best with it, but modify as necessary

5.1 Data

Our data was collected using the system timing routines provided by the standard libraries of Julia and R. Table X shows the average time it takes to read in a test data file and map it to memory, run several GRange functions, and complete multiple queries to countOverlaps() routine.

5.2Results

With respect to H1 we found...

With respect to H2 we found...

5.2 Limitations

This implementation developed for this study is very preliminary. The pipeline necessary for performing the countOverlaps() operation has been implemented, but rigorous testing is still required to verify the apparent deterministic behaviour beyond the limited testing that has been performed. Additionally, the data that was used to test has been both randomly generated or provided as sample data for a previous project. The purpose of using randomly generated data was to verify the correctness of the data using simple examples and then testing the performance on various sized data sets. Using past data was done to verify correctness of the FFI interface and SAMtools. Correctness and performance is yet to be verified on large greal datasets. Finally, considerable time was invested into all three components that were constructed for the countOverlaps() pipeline; however, most are not optimized in the same way that countOverlaps() was and therefore are sources of potential performance bottlenecks for future users.

5.3 Conclusions

R might not be the best tool for Bioinformatics. Extending the BioSeq package for Julia will allow researchers to utilize an environment that supports the reduction of programming errors through a typing hierarchy, which provides improved performance over R when combined with the JIT compiler provided by Julia. By implementing a portion of BioSeq, we hope to encourage more development of this package by the Bioinformatics community.

TODO: We propose that the bioinformatics community take advantage of, and begin developing packages for, the Julia Language (http://julialang.org). Julia provides a strong typing architecture that reduces some of the ambiguity in verifying the correctness of a program. Additionally, this information can be provided to a compiler to make some assurances about the code. The JIT compiler of Julia provides performances benefits over R; however, packages for this language are limited making R superior

in terms of ease of use in - especially for the bioinformatics community. Without support from developers and researchers, this actively developing language will continue to be overlooked by researchers despite its many benefits.

6Future Work

This study has demonstrated the preliminary development of expansions to the current BioSeq (Zea, 2013) package being developed for Julia. This study showcases that Julia outperforms R in terms of performance during our selected benchmarking operation. This expansion includes the basic data structures, operations, and interfaces associated with genomic ranges and intervals in R and Bioconductor. However, further work on these objects needs to be performed. Specifically, the genomic ranges are not fully implemented as defined by the R specifications found in the genomic ranges vignette (Carlson et al., 2013) and should be. We aim to complete the functions that perform union and intersection operations across genomic ranges and perhaps a few others as necessary..

We have also demonstrated that a simplified API wrapper for accessing SAMtools, and BAM files, through an FFI can be replicated. The API is very minimal, designed produce GRanges of the data specifically to assist in performing the countOverlaps() operation. This API should also be further developed before release **TODO**: expand on this. Finally, general documentation and clean up tasks still need to be performed before a large release of the project can be considered.

ACKNOWLEDGEMENT

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