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Binary Interval Search (BITS): An Optimal Algorithm for Interval Intersection Counting

Ryan M. Layer[1], Aaron Quinlan[2]*, Gabriel Robins[1], and Kevin Skadron[1]

[1]Department of Computer Science, University of Virginia, Charlottesville, VA
[2]Department of Public Health Sciences and Center for Public Health Genomics, Univeristy of Virginia, Charlottesville, VA

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ABSTRACT

Motivation: The integration and comparison of diverse genomic datasets is fundamental to understanding the biology of the genome and the genetic basis of human disease. Researchers must explore many large datasets of genome intervals (e.g., genes, polymorphisms, and sequence alignments) in order to place their experiments in a broader context and make new discoveries. Relationships between experimental datasets and genome annotations are typically measured by identifying intervals that intersect: that is, they overlap and thus share a common genome interval. Given the continued advances in DNA sequencing technologies, efficient methods for measuring relationships between many, often large, sets of genomic features is crucial for future discoveries.

Results: Here we introduce the Binary Interval Search (BITS) algorithm, a novel and scalable approach to the interval set intersection problem. Our analyses illustrate that BITS is as efficient as existing approaches on a single CPU and outperforms existing methods for many common applications. Moreover, we demonstrate that the BITS algorithm is well-suited to parallel computing architectures such as Graphics Processing Units (GPUs), yielding substantial speedups (over ??x) over single CPU implementations. We demonstrate the utility of this scalable algorithm for Monte-Carlo measurements of statistical associations between experimental datasets and genomic features. We note that our approach is especially suited to the emerging "hybrid" computing cluster nodes equipped with GPU cards to boost computing throughput.

Availability: http://bedtools.googlecode.com

Contact: arq5x@virginia.edu

1 INTRODUCTION

Searches for intersecting intervals in multiple sets of genomic features are crucial to nearly all genomic analyses. For example, intersection is used to compare ChIP enrichment between experiments and cell types, identify potential regulatory targets, and compare genetic variation among many individuals. Interval intersection is the central operation in a broader class of "genome arithmetic" techniques, and, as such, intersection underlies the functionality found in genome browsers (Kent *et al.*, 2002; Robinson *et al.*, 2011) and popular analysis software such as SAMTOOLS (Li *et al.*, 2009), BEDTOOLS (Quinlan and Hall, 2011), GATK (McKenna *et al.*, 2010), and GALAXY (Giardine *et al.*, 2005).

Given the importance of interval set intersection to genomic discovery, many sequential algorithms have been developed based on trees, NCLists (Alekseyenko and Lee, 2007), or linear sweeps of pre-sorted intervals (Richardson, 2006). For example, the UCSC genome browser introduced a clever scheme based on R-trees that places intervals from one dataset into hierarchical "bins" (Kent *et al.*, 2002). Intervals from a second dataset are then compared to matching bins in order to narrow the search for intersections to a focused portion of the genome. While this popular approach is used by the Kent tools software, BEDTools (Quinlan and Hall, 2011), SAMTOOLS, and TABIX, the underlying tree structure demands substantial memory for large datasets and is often difficult to parallelize. As an alternative, memory-efficient approach, recent versions of BEDTools and other software conduct a linear "sweep" through pre-sorted datasets while maintaining a priority heap to track intersections as they are encountered. While the complexity of such sequential sweep algorithms can be shown to be theoretically optimal, they are nonetheless difficult to scale to parallel architectures.

As the throughput of massively parallel DNA sequencing continues to increase, the limitations of these traditional approaches to interval intersection become increasingly acute. Traditional techniques for measuring gene expression (e.g., microarrays) and chromatin states (e.g., ChIP-chip) are being supplanted by sequencing-based techniques (RNA-seq and ChIP-seq, respectively), and whole-exome and whole-genome experiments are now routine. Consequently, typical genomics labs now conduct analyses including datasets with millions, if not billions of intervals. Experiments of this size require substantial computation time per pair-wise comparison, and a typical analysis requires comparisons to many large sets of genomic features. As extant sequential solutions scale poorly and are already reaching their theoretical performance limits, it is clear that parallel approaches must be developed to allow discovery to keep pace with the scale and complexity of modern datasets.

The current generation of Graphics Processing Units (GPUs), such as NVIDA's CUDA, can improve performance for the subset of problems that map well to the massively parallel single instruction,

*to whom correspondence should be addressed multiple data (SIMD) architecture. These architectures deploy hundreds of basic parallel processing units, and can support thousands of concurrently executing threads. In order to fully utilize the hardware, a problem must be decomposed into many small subtasks. Problems that do not fit this model are less likely to dramatically benefit from GPU hardware.

Neither the linear sweep algorithm nor the existing search algorithms are good candidates for the GPU architecture. Parallel sweep algorithms have been proposed (Goodrich *et al.*, 1993; Kriegel *et al.*, 1992; McKenney and McGuire, 2009) for segment intersection (a generalization of interval intersection), but they depend on a partitioned input space scheme that can exploit only limited parallelism. Search algorithms, where one set is a list of interval queries and the other set is an interval database, can leverage a higher degree of parallelism by performing searches concurrently. However, the database generation can be even slower than the searching itself, and may be difficult to parallelize. **TODO: this feels a bit weak**

In this manuscript we introduce the Binary Interval Search (BITS) algorithm as a new and scalable solution to the fundamental problem of interval set intersection. Our algorithm is optimal in the sequential case, avoids slow linear sweeps, does not require *ad hoc* data structures, and maps well to parallel architectures. The BITS algorithm is based on the novel observation that the size of the intersection between two sets can be directly computed without the need to enumerate each intersection. For each interval in the query list, two binary searches are performed to determine the number of intervals in the database that intersect the query interval. Each pair of searches is independent, and thus all the searches can be performed in parallel. This type of algorithm is perfectly suited to GPU-type architectures that are optimized for large numbers of threads.

Our analysis shows that the parallel BITS algorithm, when applied to a GPU architecture, can provide substantial (over 75X) speedups over other widely-used sequential interval intersection approaches. These results are particularly promising for applications that require large numbers of intersection operations, such as database searches and Monte Carlo simulations.

1.1 The Interval Set Intersection problem

Before we describe our parallel set intersection algorithm, we review some basic definitions. A genomic interval is a single continuous stretch of a genome with a start and end location (e.g., a gene), and a genomic interval set is a collection of genomic intervals (e.g., all known genes). More generally, an interval is the set of all numbers between a start value and an end value, that can be represented as the pair $(a.start, a.end)$. Two intervals a and b *intersect* when $(a.start \leq b.end)$ and $(a.end \geq b.start)$. The intersection of two interval sets $A = \{a_1, a_2, \ldots, a_N\}$ and $B = \{b_1, b_2, \ldots, b_M\}$ is the set of interval pairs:

$$\begin{aligned}\mathcal{I}(A,B) = &\{< a, b > | a \in A, b \in B, \\ &a.start \leq b.end \wedge a.end \geq b.start\}\end{aligned}$$

Intervals within a set can intersect, but *self-intersections* are not included in $\mathcal{I}(A, B)$. The interval set intersection problem is a special case of the segment intersection problem where all points are located on the same line, and each segment belongs to one of two sets.

There are four natural sub-problems for interval set intersection, listed here in order of increasing generality and complexity.

1. The *decision problem* $\mathcal{I}_{\mathcal{D}}(A, B)$: given interval sets A an B, does there exist and interval in A that intersects and interval in B?
2. The *counting problem* $\mathcal{I}_{\mathcal{C}}(A, B)$: how many pair-wise intersections exist between the intervals A and B?
3. The *per-interval counting problem* $\mathcal{I}_{\mathcal{P}}(A, B)$: how many intervals in B intersect each interval in A?
4. The *enumeration problem* $\mathcal{I}(A, B)$: what is the total set of pair-wise intersection between A an B?

1.2 Related Work

Most interval set intersection algorithms use either a linear sweep to scan the intervals in both sets, or search for intersections using a pre-computed data structure.

1.2.1 Linear Sweep Algorithms **TODO: cite Richardson, BEDTOOLs, BEDOPS**

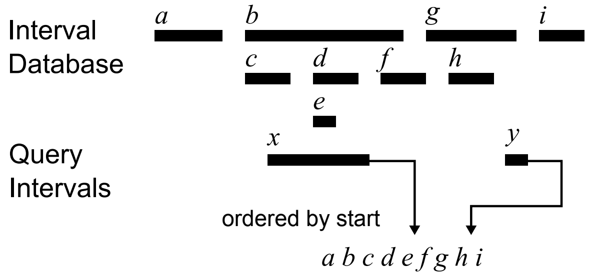
In general, the linear sweep algorithm combines intervals from A and B into a single set S, and the elements in S are then processed in order. An *active structure* tracks intervals as they enter and exit the "context", and two intervals intersect if and only if they are in context at the same time.

To correctly track the intervals that are in context, all segment starts, ends, and intersections behind the sweep must be known. McKenny and McGuire (McKenney and McGuire, 2009) proposed that segments be broken at the partition boundaries, which effectively resets the sweep invariant between partitions. The broken segments are re-joined in the final result. Although partitioning allows for some amount of parallel execution, the level of parallelism that is possible in linear sweep algorithms is limited to the number of partitions that can be created, which is a function of how the segments are distributed, not the size of the segment set.

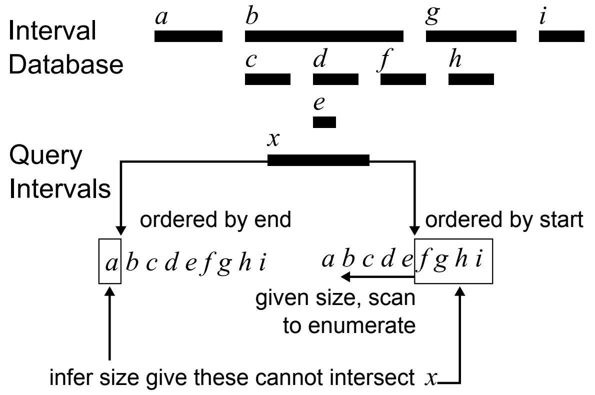
1.2.2 Searching algorithms **TODO: cite Richardson, BEDTOOLs, BEDOPS**

An alternative to the linear sweep involves searching for intersections. Given two interval sets A and B, B is treated as a database of intervals, and A is utilized as set of query intervals. For each interval $a_i \in A$, the search returns the set of intervals in B that intersect a_i.

The correctness of the searching algorithm is complicated by a subtle detail. If the intervals in B are sorted by their starting positions, then a binary search of B for the query interval end position $a_i.end$ will return the interval $b_j \in B$, where b_j is the last interval in B that starts before interval a_i ends. This would seem to imply that if b_j does not intersect a_i, then no intervals in B intersect a_i, and if b_j does intersect a_i, then other intersecting intervals in B could be found by scanning the intervals starting before b_j in decreasing order, stopping at the first interval that does not intersect a_i. However, as shown in Figure 1(a) this technique is complicated by the possibility of intervals wholly *contained* inside other intervals.



(a) The search for y in the database returns interval h, which does not intersect y. All preceding intervals must be scanned to ensure correctness.



(b) Two lists, one sorted by start and the other by end, can be used to find the size of the intersecting set without enumerating the intersecting intervals.

Fig. 1. Contained intervals complicate intersection searches. A single list (a) does not allow for efficient searching because all prior intervals must be scanned for correctness. Two lists (b) can be used to find the intersecting set size.

An interval $b_j \in B$ is “contained” if there exists an interval $b_k \in B$ where $b_k.start \leq b_j.start$ and $b_j.end \leq b_k.end$. Considering such intervals, if the interval found in the previous binary search b_j does not intersect the query interval a_i, we cannot conclude that no interval in B intersects a_i, because there may exist an interval $b_{j-x} \in B$ where $b_{j-x}.end > a_i.start$. Furthermore, if b_j does intersect a_i, then the subsequent scan for other intersecting intervals cannot stop at the first interval that does not intersect a_i; it is possible that some earlier containing interval intersects a_i. Therefore, the scan is forced to continue until it reaches the beginning of the list.

Search algorithms can expose a higher degree of parallelism by allowing each thread to handle one interval query, making it possible for the parallelism to be proportional to input size, rather than to the distribution of intervals within the input space. This level of parallelism may not be possible using existing sequential search algorithms, due to their reliance on methods and secondary structures that do not map well onto massively parallel architectures.

2 METHODS

2.1 Binary Interval Search (BITS) Algorithm

We now introduce our new Binary Interval Search (BITS) algorithm for solving the interval set intersection problem. The key observation underlying the BITS algorithm is that the size of the intersection between two sets can be determined without *enumerating* each intersection. For each interval in the query set, two binary searches are performed to determine the *number* of intervals in the database that intersect the query interval. Each pair of searches is independent of any others, and thus all searches can be performed in parallel.

Our algorithm uses a different, but equivalent, definition of interval intersection. Previously, the intersecting set was defined as the set of intervals in the interval database B that end after the query interval a_i begins, and which begin before a_i ends. However, contained intervals make it difficult to find this set directly. The search for the intersecting intervals can start at the interval in B closest to a_i, but must continue to the beginning of B because there is no condition indicating that all intersecting intervals have been found. By restating the intersection definition, we are able to determine the size of the intersecting set, which provides a terminating condition for the search, so that it may stop once the last interval in the intersecting set has been found.

We define the set of intervals $\mathcal{I}(B, a_i) \in B$ that intersect query interval $a_i \in A$ to be the intervals in B that are not in either the set of intervals that end before a_i begins, or in the set of intervals that start after a_i ends. That is:

$$\begin{aligned}\mathcal{L}(B, a_i) =& \{b \in B | b.end < a_i.start\}\\ \mathcal{G}(B, a_i) =& \{b \in B | b.start > a_i.end\}\\ \mathcal{I}(B, a_i) =& B/(\mathcal{L}(B, a_i) \cup \mathcal{G}(B, a_i))\end{aligned}$$

Finding the intervals in $\mathcal{I}(a_i, B)$ for each $a_i \in A$ by taking the difference of B and the union of $\mathcal{L}(B, a_i)$ and $\mathcal{G}(B, a_i)$ is not efficient. However, we can quickly find the size of $\mathcal{L}(B, a_i)$ and the size $\mathcal{G}(B, a_i)$, then infer the size of $\mathcal{I}(B, a_i)$. With the size of $\mathcal{I}(B, a_i)$, we can directly answer the decision problem, the counting problem, and the per-interval counting problems. Moreover, the size can also serve as the previously missing terminating condition in the enumeration problem.

Algorithm 1: Single interval intersection counter

Input: Sorted interval starts and ends B_S and B_E, query interval a
Output: Number of intervals c intersecting a

Function ICOUNT(B_S, B_E, a) **begin**
  $first \leftarrow$ BSEARCH$(B_S, a.end)$
  $last \leftarrow$ BSEARCH$(B_E, a.start)$
  $c \leftarrow first - last$
  return c

The core function in our algorithm ICOUNT$(B_S, B_E, a_i) = |\mathcal{I}(B, a_i)|$ determines the number of intervals in the database B that intersect query interval a_i. As shown in Figure 1(b), B is split into two integer lists $B_S = [b_1.start, b_2.start, \ldots, b_M.start]$ and $B_E = [b_1.end, b_2.end, \ldots, b_M.end]$, then B_S and B_E are sorted numerically. Next, two binary searches are performed, $first =$

Algorithm 2: Interval intersection counter

Input: Database intervals array B and query interval array A
Output: Number of intersections c betweeen A and B

Function $\textsc{Counter}(A, B)$ **begin**
  $B_S \leftarrow [b_1.start, \ldots, b_M.start]$ where $|B| = M$
  $B_E \leftarrow [b_1.end, \ldots, b_M.start]$ where $|B| = M$
  $\textsc{Sort}(B_S)$
  $\textsc{Sort}(B_E)$
  $c \leftarrow 0$
  for $i \leftarrow 1$ **to** $|A|$ **do**
    $c \leftarrow c + \textsc{ICount}(B_S, B_E, A[i])$
  return c

Algorithm 3: Per interval intersection counter

Input: Database intervals array B and query intervals array A
Output: Array of intersections counts C where $|C| = |A|$

Function $\textsc{PerIntervalCounter}(A, B)$ **begin**
  $B_S \leftarrow [b_1.start, \ldots, b_M.start]$ where $|B| = M$
  $B_E \leftarrow [b_1.end, \ldots, b_M.start]$ where $|B| = M$
  $\textsc{Sort}(B_S)$
  $\textsc{Sort}(B_E)$
  $C \leftarrow [0, \ldots, 0]$
  for $i \leftarrow 1$ **to** $|A|$ **do**
    $C[i] \leftarrow \textsc{ICount}(B_S, B_E, A[i])$
  return C

Algorithm 4: Intersection enumerator

Input: Database intervals array B and query intervals array A
Output: Array of pair-wise intersections E

Function $\textsc{Enumerator}(A, B)$ **begin**
  $B_S \leftarrow [b_1.start, \ldots, b_M.start]$ where $|B| = M$
  $B_E \leftarrow [b_1.end, \ldots, b_M.start]$ where $|B| = M$
  $\textsc{Sort}(B_S)$
  $\textsc{Sort}(B_E)$
  $C \leftarrow \textsc{PerIntervalCounter}(A, B)$
  $R \leftarrow \textsc{PrefixSum}(C)$
  $E \leftarrow [< 0, 0 >, \ldots, < 0, 0 >]$
  $start \leftarrow 0$
  for $i \leftarrow 1$ **to** $|A|$ **do**
    $end \leftarrow R[i]$
    $from \leftarrow \textsc{BSearch}(B_S, A[i].end)$
    while $end - start > 0$ **do**
      if $A[i]$ *intersects* $B[from]$ **then**
        $E[start] =< A[i], B[from] >$
        $start \leftarrow start + 1$
      $from \leftarrow from - 1$
  return E

$\textsc{BSearch}(B_S, a_i.end)$ and $last = \textsc{BSearch}(B_E, a_i.start)$. Since B_S is a sorted list of each interval start coordinate in B, the elements greater than or equal to $first$ in B_S correspond to the set of intervals in B that start after a_i ends. Similarly, the elements less than or equal to $last$ in B_E correspond to the set of intervals in B that end before a_i starts. From these two values, we can infer the size of the set $\mathcal{I}(B, a_i)$:

$$|B| - first = |\mathcal{G}(B, a_i)|$$
$$last = |\mathcal{L}(B, a_i)|$$
$$|B| - (last + (|B| - first)) = |\mathcal{I}(B, a_i)|$$

This problem cannot be solved with a single sorted list because contained intervals prevent the total ordering of B. If B is sorted by interval start coordinates, then the interval end coordinates may be unordered and $last$ can not be found efficiently. Similarly, if B is sorted by interval end, $first$ can not be found efficiently. With the subroutine $\textsc{ICount}(B_S, B_E, a_i)$ thus defined, the four interval set intersection problem variants can now be solved:

1. *Decision problem:* Let c be an accumulator variable that is initialized to zero; then for each $a_i \in A$, accumulate $c = c + \textsc{ICount}(B_S, B_E, a_i)$. If $c \neq 0$ then return *yes*, otherwise return *no*.
2. *Counting problem:* Let c be an accumulator variable that is initialized to zero; then for each $a_i \in A$, accumulate $c = c + \textsc{ICount}(B_S, B_E, a_i)$. The total accumulated count c is returned.
3. *Per-interval counting problem:* Let C be an accumulator array where element $C[i]$ corresponds to the number of intersection for each element in $a_i \in A$. Fore each $a_i \in A$, set $C[i] = \textsc{ICount}(B_S, B_E, a_i)$. The total list of counts C is then returned.
4. *Enumeration problem:* First find the per-interval counting array $C = \textsc{PerIntervalCounter}(A, B)$ then the let R be the prefix sum of C. The array R is used to track the number of intervals that must be found in each of the subsequent scans. Let $start = 0$ track the number of enumerated intersections. For $i = 1 \ldots |A|$, let $end = R[i]$ where $end - start$ is the nubmer intervals in B that intersect a_i. Let $from = \textsc{BSearch}(B_S, a_i.end)$ be the initial position of the scan. While $end - start > 0$ some number of intervals in B must be scanned for an intersection with a_i. If a_i intersections b_from then let $E[start] =< a_i, b_from >$ and $start = start + 1$. Then let $from = from + 1$. Finallty the total set of intrsecting intervals E is returned.

2.2 Time Complexity Analysis

To compute $\textsc{ICount}(B_S, B_E, a_i)$ for each a_i in A, the interval set B is first split into two sorted integer lists B_S and B_E, which requires $O(|B| \log |B|)$ time. Next, each instance of $\textsc{ICount}(B_S, B_E, a_i)$ searches both B_S and B_E, which consumes $O(|A| \log |B|)$ time. For the counting problems, combining the results of all $\textsc{ICount}(B_S, B_E, a_i)$ instances into a final result can be accomplished in $O(N)$ time. The total complexity of the counting problems is therefore $O((|A| + |B|) \log |B|)$.

The enumeration problem requires additional steps to scan the intervals in B_S. In the best case scenario, each scan requires $\textsc{ICount}(B_S, B_E, a_i)$ extra steps, to a total of $O(|B| \log |B| + C)$ time, where is C is the number of intersections. However, contained intervals can cause the scan to process more than C elements. If there exists some a_i that intersects b_j and b_{j-2}, but not b_{j-1} (i.e., b_{j-2} contains b_{j-1}), then the enumeration scan will consider one extra element, namely b_{j-1}. In the pathological case, b_0 contains intervals $\{b_1, \ldots, b_N\} \in B$, a_i intersects b_0, and a_i starts after interval b_N ends. This scenario would cause the enumeration scan to consider all the elements in B. If all a_i in A are pathological, then each scan would required $|B|$ extra steps, to a total of $O(|B| \log |B| + |A||B|)$ time.

2.3 Parallelization

Performing a single operation independently on many different inputs is a classic parallelization scenario. When based on the subroutine $\text{ICOUNT}(B_S, B_E, a_i)$, which is independent of all $\text{ICOUNT}(B_S, B_E, a_j)$ for $a_j \in A$ where $i \neq j$, interval set intersection can be a *pleasingly parallelizable* problem that easily maps to a number of parallel architectures.

2.3.1 OpenMP A popular option for parallelizing applications is the OpenMP standard. Converting a sequential program into a parallel program can be as simple as adding a single compiler directive. We report performance benchmarks using OpenMP as a comparison reference when considering alternative parallel architectures.

2.3.2 CUDA NVIDIA's Compute Unified Device Architecture (CUDA) is a single instruction multiple data (SIMD) architecture that provides programmers a general interface to a large number of parallel graphics processing units (GPUs).

The BITS algorithm is especially well suited for the NVIDIA CUDA architecture for a number of reasons. First, CUDA is optimized to handle large numbers of threads. By assigning each thread one instance of $\text{ICOUNT}(B_S, B_E, a_i)$ for all $a_i \in A$, the number of threads will be proportional to the file size. CUDA threads also execute in lock-step and any divergence between threads will cause reduced thread utilization. While there is some divergence in the depth of each binary search performed by $\text{ICOUNT}(B_S, B_E, a_i)$, it has an upper bound of $O(log|B|)$. Outside of this divergence $\text{ICOUNT}(B_S, B_E, a_i)$ is a classic SIMD operation. And finally, the only data structure required for this algorithm is a sorted list. Sorting on GPU has been an active area of research for many years, and current GPU sorting algorithms can sort billions of integers within seconds (Merrill and Grimshaw, 2011).

3 RESULTS

We compared the performance of the counting, per interval counting, and enumeration algorithms (the three most widely used interval intersection sub-problems) in BITS to two other popular interval intersection software packages, BEDTools (Quinlan and Hall, 2011) and Kent tools (Kent *et al.*, 2002). While BITS maps well to multiple parallel architectures (multi-core CPU using OpenMP, and NVIDIA GPU using CUDA), a fair comparison cannot be made between parallel BITS and Kent tools or BEDTools because parallel version of these packages are not available. Therefore, we demonstrate the value of our algorithm by comparing sequential versions. We then show the added benefit provided by BITS using parallel architectures.

The performance of a particular solution may depend on the distribution of intervals within the sets. For example, a solution that places intervals in bins may perform poorly when intervals are unevenly distributed across the bins. Therefore, each algorithm was evaluated considering three different representative interval intersection scenarios, the components of each scenario are given in Figure 2:

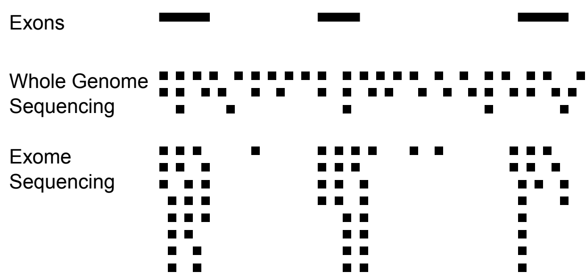


Fig. 2. Representative interval intersection scenarios.

1. *Uniform interval distribution*: the intersection between human exons and human genome-wide sequencing data. Despite representing roughly 1 percent the human genome, exons are evenly distributed throughout the genome. Genome-wide sequencing experiments typically produce short sequence intervals that are approximately uniformly distributed across the genome. Thus, each exon will intersect roughly the same number of sequencing intervals, and a large number of sequencing intervals will not intersect an exon.
2. *Biased interval distribution*: the intersection between human exons and human exome sequencing data. By design, exome sequencing experiments intentionally focus DNA sequences to the coding exons. Thus, the vast majority of sequence intervals will "pile up" in only a few regions (i.e., the exons) across the genome. In contrast to the previous scenario, nearly every exon interval will have a large number of sequence interval intersections, and nearly all sequencing intervals will intersect an exon.
3. *Many short intervals*: the intersection between human exome sequencing data and human genome-wide sequencing data. Since both sequencing data sets have a large number of short intervals and they are from different distributions, there will be a small number of intersections.

Both the genome-wide and exome intervals are from the 1000 Genomes Project NA12878 individual. To test scalability, we varied the number of intervals in both the exome and genome-wide sets by randomly sampling between 10^4 and 10^7 intervals. The human exon data set includes the exons from all RefSeq genes, obtained from the UCSC Genome Browser.

All run-times were measured on a 2.66 GHz quad-core Intel Xeon X555 CPU with 8 MB of cache running Ubuntu Linux version 4.4.3 (kernel version 2.6.32-34). Run-times for CUDA were measured on an NVIDIA Tesla C2050 GPU with 448 1.15 GHz cores, 3 GB of global memory, CUDA driver version 4246739, and CUDA runtime version 4.0. The source code was compiled using gcc version 4.4.3, and NVIDIA CUDA compilation tools release 4.0, V0.2.1221. In each case, run-times measure the performance of the intersection algorithm and thus do not include disk reading, writing, or the time required to initialize the GPU.

The results of our tests are given in Figure **??**, Figure **??**, and Figure **??**.

TODO: this sections is incorrect. Refocus on general equivalence and superiority for very large datasets and for biased data.

In nearly every case, the sequential version of BITS outperformed both Kent tools and BEDTools. The most striking improvement was in the interval counting operation, where —in the largest operation (10M many short intervals, a total of $2e^7$ intervals)— sequential BITS achieved a speedup of 7.7x over Kent tools and 27.4x over BEDTools. In this same case the speedup over Kent tools and BEDTools by OpenMP BITS was 13.1x and 46.6x, and the speedup by CUDA BITS was 143.7x and 508.8x, respectively.

While BITS did have some improvement in enumeration operation, the speedup was an order of magnitude lower than in the counting operations, and Kent tools performed better than sequential bits in one scenario. This result is expected given that BITS is optimized for counting intersections, which is generally more a useful operation in large-scale comparisons.

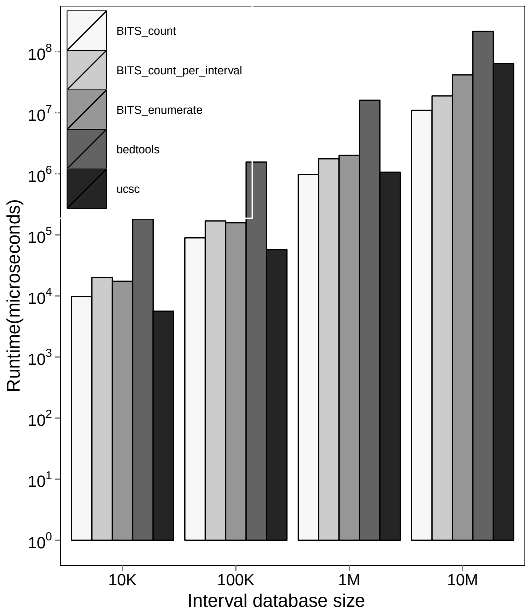


Fig. 3. Run times for each algorithm using exome and whole-genome datasets (FIX: caption and need error bars).

The performance profiles of counting (Figure **??**) and per interval counting (Figure **??**) were similar for all algorithms. In these two scenarios, excluding the smallest data sets, all versions of BITS performed faster than both Kent tools and BEDTools. For the 10K database, Kent tools performed faster than the sequential and OpenMP version of BITS by up to a factor of three. The following table gives the average speedups of the three versions of BITS over Kent tools and BEDTools for the 10 million interval database.

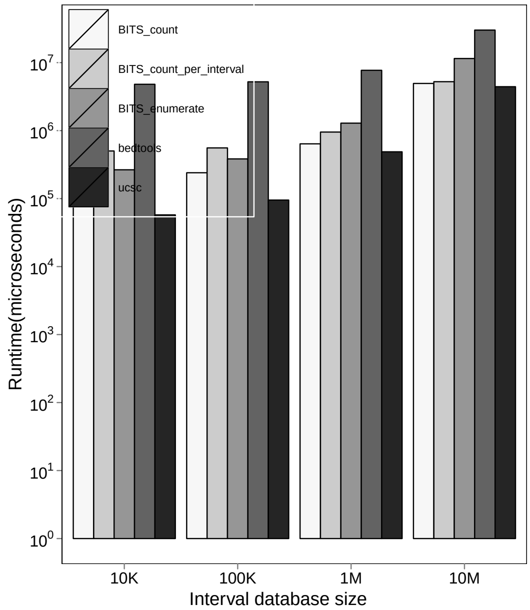


Fig. 4. Run times for each algorithm using exons and whole-genome datasets (FIX: caption and need error bars).

	Kent tools	BEDTools
Sequential	4.5x	17.7x
OpenMP	11.1x	43.1x
CUDA	75.8x	285.4x

For enumeration, the performance improvements of the sequential and OpenMP versions of BITS were an order of magnitude lower against BEDTools, and non-existent against Kent tools. In fact, Kent tools performed better than sequential BITS by a factor of nearly three for the smallest database (Figure **??**), and the run times of the two where nearly equivalent for the largest database. The CUDA version of BITS did provide a modest improvement over both Kent tools and BEDTools, but at a level lower than in counting and per interval counting. The following table gives the average speedups of the three versions of BITS over Kent tools and BEDTools for the 10 million interval database.

	Kent tools	BEDTools
Sequential	1.5x	7.3x
OpenMP	1.3x	6.4x
CUDA	3.8x	24.9x

The fact that BITS performed better in counting than in enumeration is to be expected given BITS is based on the observation that counting can be performed without enumerating each intersection, and that enumeration in BITS first counts the number of intersections then makes a second pass to enumerate. While this is a limitation of the BITS algorithm, counting and per interval counting are the primary functions used to analyze large

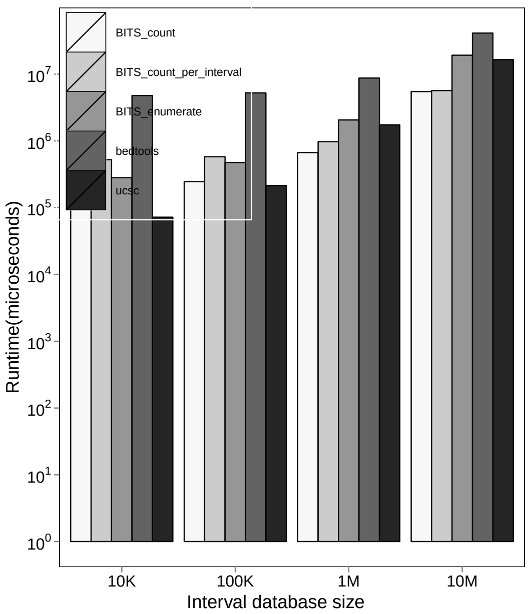


Fig. 5. Run times for each algorithm using exons and whole-exome datasets (FIX: caption and need error bars).

data sets. For example, the utility of the full list of 9,148,823 intersection between human exon and the exome sequencing of the NA12878 individual (the biased distribution scenario) is limited, while the number of intersections per exon can provide insight into deletions, duplications, and other properties of NA12878's genome.

4 CONCLUSION

We have developed a highly scalable approach to interval intersection that exploits the speed and simplicity of the binary search. Our binary interval search (BITS) algorithm is founded upon the novel observation that the count of overlapping intervals between two sets can be obtained without the computational burden of enumerating each individual intersection. We illustrate that the two binary searches conducted against the database for each query interval are independent, and thus, the BITS algorithm is well suited for GPU architectures that are optimized for large numbers of concurrent threads. Our results with the CUDA architecture demonstrate speed increases of up to 143x and 508x relative to existing approaches to genome interval intersection. Using a single CPU, we still observe improvements of 17.7x and 49.5x, illustrating the our new approach will benefit existing tools that are incapable of exploiting GPU architectures. This substantial performance increase is especially relevant to modern genomic analyses given the staggering scale and complexity of current and future datasets. Indeed, given that the BITS algorithm excels at *counting* overlaps, it is perfectly suited to address many fundamental yet computationally intensive genomic analyses including RNA-seq transcript quantification, ChIP-seq peak detection, and searches for copy-number and structural variation.

We also note that the performance gains that BITS offers increase as the number of interval comparisons increases. Therefore, we anticipate that our approach will enable previously intractable large-scale comparisons of experimental datasets with comprehensive genome annotation databases that contain thousands of distinct genome annotation sets. Moreover, this approach is directly amenable to Monte Carlo measurements of associations between interval sets, as such simulations require thousands of iterations in order to demonstrate significance. Given the performance and simplicity of the algorithm, we anticipate that it will benefit a wide range of existing tools ranging from visualization tools to widely-used genomic analysis software.

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