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Binary Interval Search (BITS): A Scalable Algorithm for Counting Interval Intersections

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ABSTRACT

Motivation: The comparison of diverse genomic datasets is fundamental to understanding genome biology. Researchers must explore many large datasets of genome intervals (e.g., genes, sequence alignments) to place their experimental results in a broader context and to make new discoveries. Relationships between genomic datasets 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 statistically significant relationships between many sets of genomic features is crucial for future discovery.

Results: We introduce the Binary Interval Search (BITS) algorithm, a novel and scalable approach to interval set intersection. We demonstrate that BITS outperforms existing methods at counting interval intersections. Moreover, we show that BITS is intrinsically suited to parallel computing architectures such as Graphics Processing Units (GPUs) by illustrating its utility for efficient Monte-Carlo simulations measuring the significance of relationships between sets of genomic intervals.

Availability: https://github.com/arq5x/bits

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1 INTRODUCTION

Searching for intersecting intervals in multiple sets of genomic features is crucial to nearly all genomic analyses. For example, interval 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 fundamental operation in a broader class of "genome arithmetic" techniques, and as such, it underlies the functionality found in many genome analysis software packages (Kent *et al.*, 2002; Giardine *et al.*, 2005; Li *et al.*, 2009; Quinlan and Hall, 2011).

As high throughput sequencing technologies have become the *de facto* molecular tool for genome biology, there is an acute need for efficient approaches to interval intersection. Microarray techniques for measuring gene expression and chromatin states have been largely supplanted by sequencing-based techniques, and whole-exome and whole-genome experiments are now routine. Consequently, most genomics labs now conduct analyses including datasets with billions of genome intervals. Experiments of this size require substantial computation time per pair-wise comparison; moreover, typical analyses require comparisons to many large sets of genomic features. Existing approaches scale poorly and are already reaching their performance limits. We therefore argue the need for new scalable algorithms to allow discovery to keep pace with the scale and complexity of modern datasets.

In this manuscript, we introduce the Binary Interval Search (BITS) algorithm as a novel and scalable solution to the fundamental problem of counting the number of intersections between two sets of genomic intervals. BITS uses two binary searches (one each for start and end coordinates) to identify intersecting intervals. As such, our algorithm executes in $\Theta(N \log N)$ time, where N is the number of intervals, which can be shown to be optimal for the interval intersection counting problem by a straight-forward reduction to element uniqueness (known to be $\Theta(N \log N)$ (Mirsa and Gries, 1982)). We illustrate that a sequential version of BITS outperforms existing approaches. We also demonstrate that BITS is intrinsically suited to parallel architectures. The parallel version performs the same amount of work as the sequential version (i.e., there is no overhead) which means the algorithm is work-efficient, and because each parallel thread performs equivalent work, BITS has little thread divergence. While thread divergence degrades performance on any architecture (finished threads must wait for over-burdened threads to complete), the impact is particularity acute for GPUs where threads share a program counter and any divergent instruction must be executed on every thread.

1.1 The Interval Set Intersection problem

We begin by reviewing some basic definitions. A genomic *interval* is a continuous stretch of a genome with a chromosomal start and end location (e.g., a gene), and a genomic *interval set* is a collection of genomic intervals (e.g., all known genes). Two intervals a and b *intersect* when $(a.start \leq b.end)$ and $(a.end \geq b.start)$. The

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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:

$$\mathcal{I}(A,B) = \{\langle a,b\rangle | a \in A, b \in B, \\ a.start \leq b.end \wedge a.end \geq b.start\}$$

Intervals within a set can intersect, but *self-intersections* are not included in $\mathcal{I}(A,B)$. There are four natural sub-problems for interval set intersection: 1) *decision* - does there exist at least one interval in A that intersects an interval in B?; 2) *counting* - how many total intersections exist between sets A and B?; 3) *per-interval counting* - how many intervals in B intersect each interval in A?; 4) *enumeration* - what is the set of each pair-wise interval intersections between A an B? While BITS solves all four sub-problems, it is designed to efficiently *count* the number of intersections between two sets, and as such, it excels at the *decision*, *counting*, and*per-interval counting* problems.

1.2 Limits to parallelization

Interval intersection has many applications in genomics, and as such, several algorithms have been developed that, in general, are either based on trees (Kent *et al.*, 2002; Alekseyenko and Lee, 2007), or linear sweeps of pre-sorted intervals (Richardson, 2006).

The UCSC genome browser introduced a widely-used scheme based on R-trees. This approach partitions intervals from one dataset into hierarchical "bins". Intervals from a second dataset are then compared to matching bins (not the entire dataset) to narrow the search for intersections to a focused portion of the genome. While this approach is used by the UCSC Genome Browser, BEDTools (Quinlan and Hall, 2011), and SAMTOOLS (Li *et al.*, 2009), the algorithm is inefficient for counting intersections since all intervals in each candidate bin must be *enumerated* in order to count the intersections. Since the number of intersections is at most quadratic, any enumeration-based algorithm is $O(N^2)$.

Moreover, these existing approaches are poor candidates for parallelization. Thread divergence can be a significant problem for hierarchical binning methods. If intervals are not uniformly distributed (e.g., exome sequencing or RNA-seq), then a small number of bins will contain many intervals while most other bins are empty. Consequently, threads searching full bins will take substantially longer than threads searching empty bins. In contrast, BITS counts intersections directly without enumerating intersecting intervals and therefore, the underlying interval distribution does not impact the relative workload of each thread.

Recent versions of BEDTools and BEDOPS (Neph *et al.*, 2012) conduct a linear "sweep" through pre-sorted datasets while maintaining an auxiliary data structure to track intersections as they are encountered. While the complexity of such sequential sweep algorithms is theoretically optimal, the amount of parallelism that exists is limited, and some overhead is required to guarantee correctness. Any linear sweep algorithm must maintain the "sweep invariant" (McKenney and McGuire, 2009), which states that all segment starts, ends, and intersections behind the sweep must be known. A parallel sweep algorithm must either partition the input space such that each section can be swept in parallel without violating the invariant, or threads must communicate about intervals that span partitions. In the first case parallelism is limited to the number of partitions that can be created, and threads can diverge when the number of intervals in each partition are unbalanced. In the second case, the communication overhead between threads prevents work efficiency and can have significant performance implications. In BITS, the amount of parallelism depends only on the number of intervals and not the distribution of intervals within the input space, and there is no communication between threads.

2 METHODS

A seemingly facile method for finding the intersection of A and B would be to treat one set, A, as a "query" set, and the other, B, as a "database". If all of the intervals in the database were sorted by their starting coordinates, it would seem that binary searches could be used for each query to identify all intersecting database intervals.

However, this apparently straight-forward searching algorithm is complicated by a subtle, yet vexing 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 (e.g, interval e in Fig. 1A). 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, this technique is complicated by the possibility of intervals that are wholly *contained* inside other intervals (e.g., interval *c* in Fig. 1B).

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. As contained intervals are typical in genomic datasets, a naive binary search solution is inviable.

2.1 Binary Interval Search (BITS) Algorithm

We now introduce our new Binary Interval Search (BITS) algorithm for solving the interval set intersection problem. This algorithm uses binary searches to identify interval intersections while avoiding the complexities caused by contained intervals. The key observation underlying BITS 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 all others, and thus all searches can be performed in parallel.

Existing methods define the intersection set based on *inclusion*: that is, 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, we have seen that contained intervals make it difficult to find this set directly with a single binary search.

Our algorithm uses a different, but equivalent, definition of interval intersection based on *exclusion*: that is, by identifying the set of intervals in B that *cannot* intersect a_i, we can infer how many intervals *must* intersect a_i. Formally, we define the set of intervals

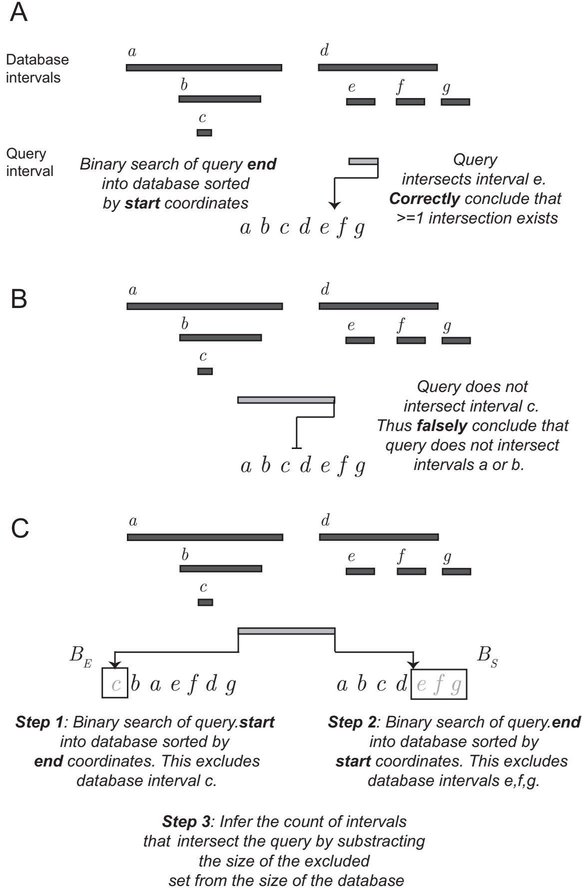

Fig. 1. Comparing a naive binary search for interval intersection to the BITS approach. **A**. Binary searches of intervals sorted by start coordinate will occasionally identify overlapping intervals. However, contained intervals prevent knowing how far one must scan the database to identify all intersections. **B**. Contained intervals also cause single binary searches to falsely conclude that no intersections exist for a given query interval. **C**. To overcome these limitations, BITS uses two binary searches of the database intervals: one into a sorted list of end coordinates and the other into a sorted list of start coordinates. Each search excludes database intervals that *cannot* intersect the query, leaving solely the intervals that *must* intersect the query.

$\mathcal{I}(B, a_i) \in B$ that intersect query interval $a_i \in A$ to be the intervals in B that are neither in the set of intervals ending before ("left of", set $\mathcal{L}$ below) a_i begins, nor in the set of intervals starting after ("right of", set $\mathcal{R}$ below) a_i ends. That is:

$$\mathcal{L}(B, a_i) = \{b \in B | b.end < a_i.start\}$$

$$\mathcal{R}(B, a_i) = \{b \in B | b.start > a_i.end\}$$

$$\mathcal{I}(B, a_i) = B \setminus (\mathcal{L}(B, a_i) \cup \mathcal{R}(B, a_i))$$

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 $\mathcal{R}(B, a_i)$ is not efficient. However, we can quickly find the size of $\mathcal{L}(B, a_i)$ and the size $\mathcal{R}(B, a_i)$, and 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. The size of $\mathcal{I}(B, a_i)$ also serves as the termination condition for enumerating intersections that was missing in the naive binary search solution.

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 ← BSEARCH(B_S, a.end)
    last ← BSEARCH(B_E, a.start)
    c ← first − last      /* = |B| − (last + (|B| − first)) */
    return c
```

The BITS algorithm is based upon one fundamental function, $\text{ICOUNT}(B_S, B_E, a_i) = |\mathcal{I}(B, a_i)|$ (Algorithm 1), which determines the number of intervals in the database B that intersect query interval a_i. As shown in Fig. 1C, the database B is split into two integer lists $B_S = [b_1.start, b_2.start, \ldots, b_M.start]$ and $B_E = [b_1.end, b_2.end, \ldots, b_M.end]$, which are each sorted numerically in ascending order. Next, two binary searches are performed, $last = \text{BSEARCH}(B_E, a_i.start)$ and $first = \text{BSEARCH}(B_S, a_i.end)$. Since B_E is a sorted list of each interval end coordinate in B, the elements with indices less than or equal to $last$ in B_E correspond to the set of intervals in B that end *before* a_i starts (i.e., to the "left" of a_i). Similarly, the elements with indices greater than or equal to $first$ in B_S correspond to the set of intervals in B that start *after* a_i ends (i.e., to the "right" of a_i). From these two values, we can directly infer the size of the intersection set $\mathcal{I}(B, a_i)$ (i.e., the *count* of intersections in B for a_i):

$$|B| - first = |\mathcal{R}(B, a_i)|$$

$$last = |\mathcal{L}(B, a_i)|$$

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

Using the subroutine $\text{ICOUNT}(B_S, B_E, a_i)$, all four interval set intersection problem variants can be solved. Pseudocode for the *decision*, *per-interval counting*, and *enumeration* sub-problems can be found in the Supplemental Materials.

The BITS solution to the counting problem. Since BITS operates on arrays of generic intervals ($\langle start, end \rangle$), and input files are typically chromosomal intervals ($\langle chrom, start, end \rangle$), the intervals in each dataset are first projected down to a one-dimensional generic interval. This is a straight forward process that adds an offset associated with the size of each chromosome to the start and end of each interval. Once the inputs are projected to interval arrays A and B, the COUNTER (Algorithm 2) sets the accumulator variable c to zero; then for each $a_i \in A$, accumulates $c = c + \text{ICOUNT}(B_S, B_E, a_i)$. The total count c is returned.

2.2 Time Complexity Analysis

The time complexity of BITS is $O((|A| + |B|) \log |B|)$, which can be shown to be optimal by a straight-forward reduction to element uniqueness (known to be $\Theta(N \log N)$ (Mirsa and Gries, 1982)). To compute $\text{ICOUNT}(B_S, B_E, a_i)$ 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 $\text{ICOUNT}(B_S, B_E, a_i)$ searches both B_S and B_E, which consumes $O(|A| \log |B|)$ time. For the counting problems, combining the results of all $\text{ICOUNT}(B_S, B_E, a_i)$ instances into a final result can be accomplished in $O(|A|)$ time.

Algorithm 2: Interval intersection counter

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

Function $\text{COUNTER}(A, B)$ **begin**
  $B_S \leftarrow [b_1.start, \ldots, b_{|B|}.start]$
  $B_E \leftarrow [b_1.end, \ldots, b_{|B|}.end]$
  $\text{SORT}(B_S)$
  $\text{SORT}(B_E)$
  $c \leftarrow 0$
  for $i \leftarrow 1$ **to** $|A|$ **do**
    $c \leftarrow c + \text{ICOUNT}(B_S, B_E, A[i])$
  return c

2.3 Parallel BITS

Performing a single operation independently on many different inputs is a classic parallelization scenario. When based on the subroutine $\text{ICOUNT}(B_S, B_E, a)$, which is independent of all $\text{ICOUNT}(B_S, B_E, x)$ for intervals x in the query set where $a \neq x$, counting interval intersections is a *pleasingly parallelizable* problem that easily maps to a number of parallel architectures.

NVIDIA's CUDA is a single instruction multiple data (SIMD) architecture that provides a general interface to a large number of parallel GPUs. The GPU is organized into multiple SIMD processing units, and the processors within a unit operate in lock-step. The BITS algorithm is especially well suited for the this architecture for a number of reasons. First, CUDA is optimized to handle large numbers of threads. By assigning each thread one instance of $\text{ICOUNT}(B_S, B_E, a)$, the number of threads will be proportional to the input 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 $\text{ICOUNT}(B_S, B_E, a)$, it has an upper bound of $O(log|B|)$. Outside of this divergence $\text{ICOUNT}(B_S, B_E, a)$ is a classic SIMD operation (Kirk and Hwu, 2010). Finally, the only data structure required for this algorithm is a sorted array, and thanks to years of research in this area, current GPU sorting algorithms can sort billions of integers within seconds (Merrill and Grimshaw, 2011; Satish *et al.*, 2009).

3 RESULTS

3.1 Comparing BITS to extant sequential approaches

We implemented a sequential version of the BITS algorithm (”BITS-SEQ”) as a stand-alone C++ utility. Here we assess the performance of this implementation relative to BEDTOOLS `intersect` and UCSC Genome Browser's (“UCSC”) (Kent *et al.*, 2002) `bedIntersect` utilities (see Supplemental Materials for details). We compare the performance of each tool for *counting* the total number of observed intersections between sets of intervals of varying sizes (Figure 2). The comparisons presented are based on sequence alignments for the CEU individual NA12878 by the 1000 Genomes Project (The 1000 Genomes Project Consortium, 2010), as well as RefSeq exons. Owing to the different data structures used by each algorithm, the relative performance of each approach may depend on the genomic distribution of intervals within the sets. As discussed previously, tree-based solutions that place intervals into hierarchical bins may perform poorly when intervals are unevenly distributed among the bins. We tested the impact of differing interval distributions on algorithm performance by randomly sampling 1 and 10 million alignment intervals from both whole-genome and exome-capture datasets for NA12878 (see Supplemental Materials). Each algorithm was evaluated considering three different interval intersection scenarios. First, we tested intervals from *different* distributions by comparing the intersection between exome-capture alignments and whole-genome alignments. Since each set has a large number of intervals and a different genomic distribution, we expect a small (relative to the total set size) number of intersections. We also tested a *uniform* distribution by counting intersections between Refseq exons and whole-genome sequencing alignments. Here each interval set is, for the most part, evenly distributed throughout the genome; thus, we expect each exon to intersect roughly the same number of sequencing intervals, and a large number of sequencing intervals will not intersect an exon. Lastly, we assessed a *biased* intersection distribution between exons and exome-capture alignments. By design, exome sequencing experiments intentionally focus collected DNA sequences to the coding exons. Thus, the vast majority of sequence intervals will align in exonic regions. 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.

3.1.1 BITS excels at counting intersections.

In all three interval distribution scenarios, the sequential version of BITS had superior runtime performance for counting intersections. BITS was between 11.2 and 27.9 times faster than BEDTools and between 1.2 and 5.2 times faster than UCSC (Figure 2). This behavior is expected; whereas the BEDTools and UCSC tree-based algorithms must *enumerate* intersections to derive the *count*, BITS *infers* the intersection count by exclusion without enumeration.

3.1.2 BITS excels at large intersections and biased distributions.

The relative performance gains of the BITS approach are enhanced for very large datasets (Figure 2B). Since tree-based methods have a fixed number of bins, and searches require a linear scan of each associated bin, the number of intervals searched grows linearly with respect to the input size. In the worst-case where all intervals are in a single bin, a search would scan the entire input set. In contrast, BITS employs binary searches so the number of operations is proportional to log of the input size, regardless of the input distribution.

Similarly, exome-capture experiments yield biased distributions of intervals among the UCSC bins. Consequently, most bins in tree-based methods will contain no intervals, while a small fraction contain many intervals. When the query intervals have the same bias, the overhead of the UCSC algorithm is more onerous, as a small number of bins are queried and each queried bin contains many intersecting intervals that must be enumerated in order to count overlaps. As the BITS algorithm is agnostic to the interval distributions, it will outperform the UCSC algorithm (Figure 2A, 2B) for common genomic analyses such as ChIP-seq and RNA-seq, especially given the massive size of these datasets.

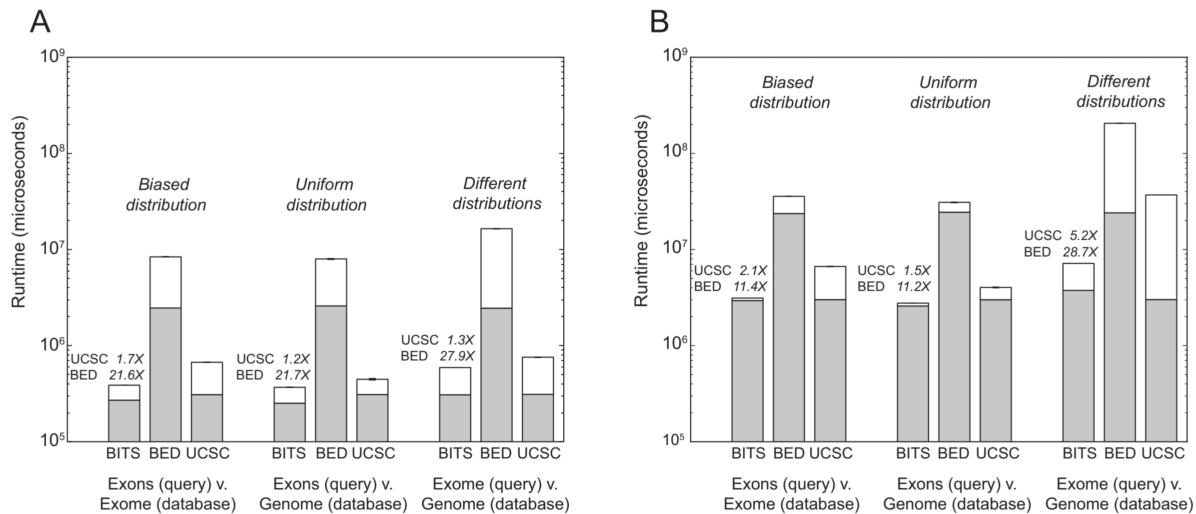

Fig. 2. Run times for counting intersections with BITS, BEDTools, and UCSC "Kent source". **A**. Run times for databases of 1 million alignment intervals from each interval distribution. **B**. Run times for databases of 10 million alignment intervals from each interval distribution. Bars reflect the mean run time from five independent experiments and error bars describe the standard deviation. Gray bars reflect the run time consumed by data structure construction, while white bars are the time spent counting intersections. Above each BITS execution time we note the speed increase relative to BEDTools and "Kent source", respectively. "Exons" represents 400,351 RefSeq exons (autosomal and X, Y) for the human genome (Build 37). BED = BEDTools; UCSC = "Kent source".

3.2 Applications for Monte Carlo Simulations

Identifying statistically significant relationships between sets of genome intervals is fundamental to genomic research. However, owing to our complex evolutionary history, different classes of genomic features have distinct genomic distributions, and as such, testing for significance can be challenging. One widely-used, yet computationally intensive alternative solution is the use of Monte Carlo simulations that compare *observed* interval relationships to an *expectation* based on randomization. All aspects of the BITS algorithm are particularly well suited for Monte Carlo (MC) simulations measuring relationships between interval sets. As described, all intersection algorithms begin detecting intersections between two interval sets by setting up their underlying data structures (e.g., trees or arrays). The BITS setup process involves mapping each interval from the two-dimensional chromosomal interval space (i.e., chromosome and start/end coordinates) to a one dimensional integer interval space (i.e., start/end coordinates ranging from 1 to the total genome size). Once the intervals are mapped, arrays are sorted by either start or end coordinates. In contrast, the UCSC setup places each interval into a hash table. As shown in Figure 2, data structure setup is a significant portion of the total runtime for all approaches.

However, in the case of many MC simulation rounds, where a uniformly distributed random interval set is generated and placed into the associated data structure, the setup step is faster in BITS, whereas the setup time remains constant in each simulation round for UCSC. For BITS, the mapping step is skipped in all but the the first round and in each simulation round only an array of random starts must be generated. The result is a 6x speedup for MC rounds over the cost of the initial intersection setup. For UCSC, both the chromosome and the interval start position must be generated and then placed into the hash table with no change in execution time.

This speedup in BITS is extended on parallel platforms, where the independence of each intersection is combined with efficient parallel random number generation algorithms (Tzeng and Wei, 2008) and parallel sorting algorithms (Merrill and Grimshaw, 2011; Satish *et al.*, 2009). Monte Carlo simulations have obvious task parallelism since each round is independent. BITS running on CUDA ("BITS-CUDA") goes a step further and exposes fine-grain parallelism in both the setup step, with parallel random number generation and parallel sorting, and the intersection step where hundreds of intersections execute in parallel. The improvement is modest for a single intersection (only parallel sorting can be applied to the setup step) where BITS-CUDA is 4x faster than sequential BITS and 40x faster than sequential UCSC. However, as the number of MC rounds grows performance improves dramatically. At 10,000 MC rounds and 1e7 intervals, BITS-CUDA is 267x faster than sequential BITS and 3,414x faster than sequential UCSC. An improvement of this scale allows MC analyses for thousands of experiments (e.g., 25,281 pairwise comparisons in Section 3.3).

We demonstrate the improved performance of BITS over UCSC for Monte Carlo simulations for measuring the significance of the overlaps between interval sets in Table 1. As both the number of MC rounds and the size of the dataset grows, the speedup of both sequential BITS and BITS-CUDA increases over UCSC. For the largest comparison (1e7 intervals and 10,000 iterations), BITS-SEQ is 12x faster that UCSD, and BITS-CUDA is 267x faster than BITS-SEQ and 3,414x faster than sequential UCSC.

3.3 Uncovering novel genomic relationships.

The efficiency of BITS for Monte Carlo applications on GPU architectures provides a scalable platform for identifying novel relationships between large scale genomic datasets. To illustrate BITS-CUDA's potential for large-scale data mining

experiments, we conducted a screen for significant genomic co-localization among 159 genome annotation tracks using Monte Carlo simulation (see Supplemental Materials). This analysis was based upon functional annotations from the ENCODE project (ENCODE Project Consortium, 2007) for the GM12878, H1-hESC, and K562 cell lines, including assays for 24 transcriptions factors (often with replicates), 8 histone modifications, open chromatin, and DNA methylation. We also included diverse genome annotations from the UCSC genome browser (e.g, repeats, genes, and conserved regions).

Using BITS-CUDA, we measured the log2 ratio of the observed and expected number of intersections for each of the 25,281 (i.e., 159*159) pairwise dataset relationships using 1e4 Monte Carlo simulations (Figure 3). As expected, this analysis revealed that 1) the genomic locations for the same functional element are largely consistent across replicates and cell types, 2) methylated and semi-methylated regions are similar across cell types, and 3) most functional assays were anti-correlated with genomic repeats (e.g., microsatellites) owing to sequence alignment strategies that exclude repetitive genomic regions. Perhaps not surprisingly, this unbiased screen also revealed intriguing patterns. First, the strong enrichment among all transcription factors (TF) assays suggests that a subset of TF binding sites are shared among all factors. This observation is consistent with previous descriptions of "hot regions" (Gerstein *et al.*, 2010). In addition, there is a significant, specific, and unexplained enrichment among the Six5 transcription factor and segmental duplications.

Pursuing the biology of these relationships is beyond the scope of the current manuscript; however, we emphasize that the ability to efficiently conduct such large-scale screens facilitates novel insights into genome biology. This analysis presented a tremendous computational burden made feasible by the facility with which the BITS algorithm could be applied to GPU architectures. Indeed, each iteration of our Monte Carlo simulation tested for intersections among 4 billion intervals among the 25 thousand datasets, yielding over 44 trillion comparisons for the entire simulation. Whereas this simulation took just over 6 days (9,069 minutes) on a single computer with one GPU card, we estimate that it would take at least 112 traditional processors to conduct the same analysis using traditional approaches such as the UCSC tools or BEDTools.

Table 1. Runtime (seconds) comparison for Monte Carlo simulations. Timings in italics were extrapolated owing to long run times.

		Number of MC iterations			
Size	Tool	1	100	1000	100000
1e5	BITS-CUDA	0.73	1	4	28
	BITS-SEQ	0.41	7	68	680
	UCSC	0.17	14	138	1,381
1e6	BITS-CUDA	2	3	1	103
	BITS-SEQ	5	120	*1,200*	*12,000*
	UCSC	6	878	*8,780*	*87,800*
1e7	BITS-CUDA	14	22	97	835
	BITS-SEQ	66	2,235	*22,350*	*223,500*
	UCSC	568	28,508	*285,080*	*2,850,800*

4 CONCLUSION

We have developed a novel algorithm for interval intersection that is uniquely suited to scalable computing architectures such as GPUs. Our algorithm takes a new approach to counting intersections: unlike existing methods that must enumerate intersection in order to derive a count, BITS uses two binary searches to directly infer the count by excluding intervals that *cannot* intersect one another.

We have demonstrated that a sequential implementation of BITS outperforms existing tools and illustrate that, because it is based on binary searches (which have predictable complexity), BITS is task efficient and is thus highly parallelizable. As such, we show that a GPU implementation of BITS (BITS-CUDA) is a superior solution for Monte Carlo analyses of statistical relationships between sets of genome intervals, since observed intersections among many sets must be compared to thousands of randomized simulations.

Given the efficiency with which the BITS algorithm counts intersections, it is also perfectly suited to many fundamental genomic analyses including RNA-seq transcript quantification, ChIP-seq peak detection, and searches for copy-number and structural variation. Moreover, the functional and regulatory data produced by projects such as ENCODE have driven the development of new approaches (Favorov *et al.*, 2012) to measuring relationships among genomic features in order to reveal yet undetected insights into genome biology. We recognize the importance of scalable approaches to detecting such relationships and anticipate that our new algorithm will foster new genome mining tools for the genomics community.

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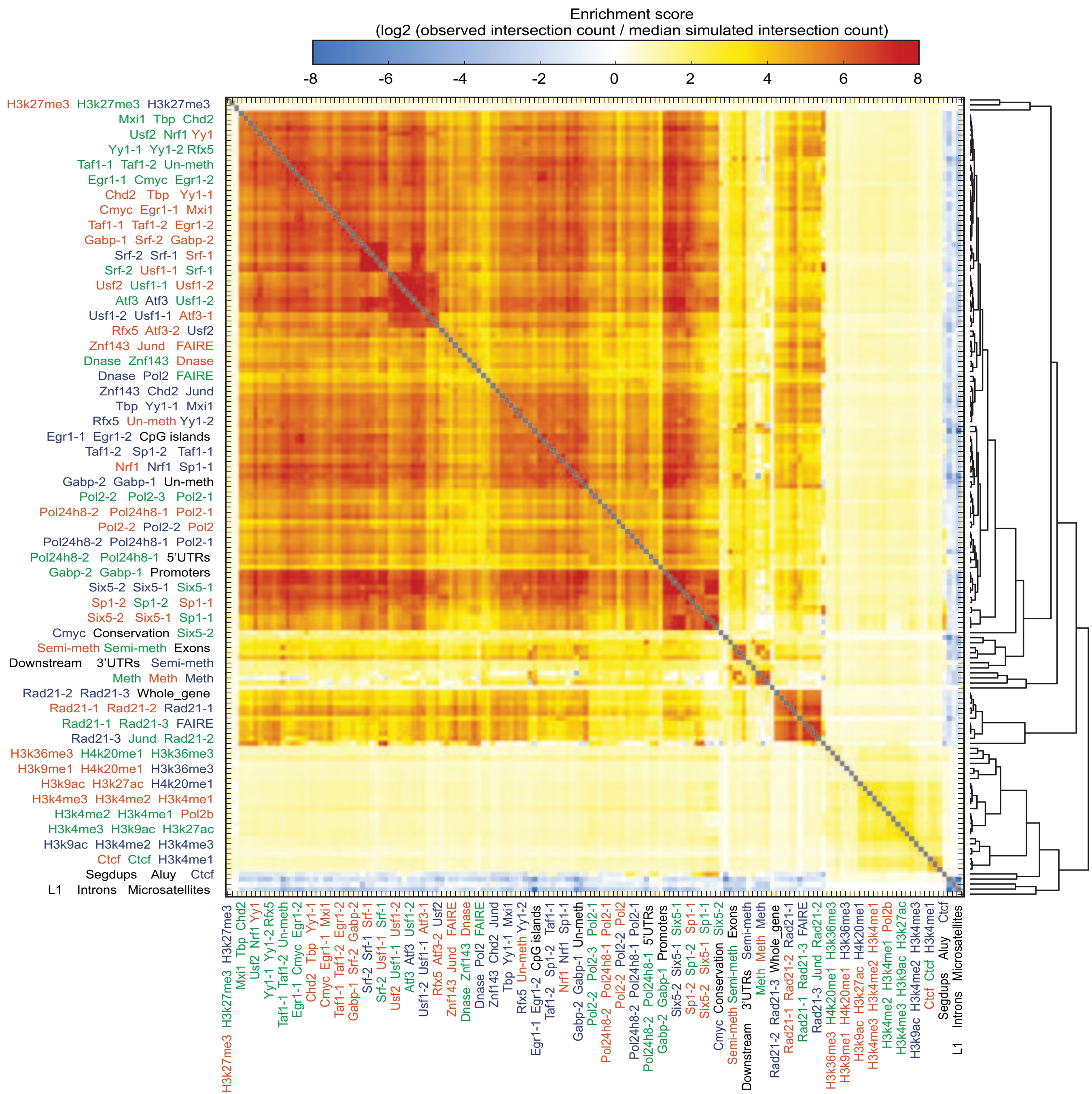

Fig. 3. BITS-CUDA measurements of spatial correlations among 159 genome features from the ENCODE project and from the UCSC Genome Browser. For each comparison, we show an enrichment score reflecting the log2 ratio of the observed count of intersections over the median count of intersections from 10000 MC simulations. Each set of three labels on the X and Y axes correspond to three consecutive rows or columns, respectively. Assays from the GM12878 cell line are in green, H1-hESC in blue, and K562 in red. Annotation tracks from the UCSC Genome Browser are in black.

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