Abstract

**Motivation:** Seed filtering is critical in DNA read mapping, a process where billions of DNA fragments (reads) sampled from a donor are mapped onto a reference genome to identify genomic variants of the donor. Read mappers 1) quickly generate possible mapping locations (i.e., seeds) for each read, 2) extract reference sequences at each of the mapping locations, and then 3) check similarity between each read and its associated reference sequences with a computationally expensive dynamic programming algorithm (alignment) to determine the origin of the read. Location filters come into play before alignment, discarding seed locations that alignment would have deemed a poor match. The ideal location filter would discard all poor matching locations prior to alignment such that there is no wasted computation on poor alignments.

**Results:** We propose a novel filtering algorithm, GRIM-Filter, optimized to exploit emerging 3D-stacked memory systems that integrate computation within a stacked logic layer, enabling processing-in-memory (PIM). GRIM-Filter quickly filters locations by 1) introducing a new representation of coarse-grained segments of the reference genome and 2) using massively-parallel in-memory operations to identify read presence within each coarse-grained segment. Our evaluations show that for 5% error acceptance rates, GRIM-Filter eliminates 5.59x-6.41x more false negatives and exhibits end-to-end speedups of 1.81x-3.65x compared to mappers employing the best previous filtering algorithm.

1 Introduction

Our understanding of human genomes today is affected by modern technology’s ability to quickly and accurately determine an individual’s entire genome. The human genome is comprised of a sequence of approximately 3 billion bases that are grouped into deoxyribonucleic acids (DNA), but today’s machines can only identify DNA in short sequences (reads). Therefore, determining a genome requires 3 stages: 1) cutting the genome into many short fragments, 2) identifying the DNA sequence of the fragment, and then 3) mapping the reads against the reference genome in order to analyze the variations in the sequenced genome. In this paper, we focus on improving stage 3, often referred to as read mapping. Read mapping is performed computationally by read mappers after each read has been resolved into a known series of DNA.

We refer to Figure 1 to briefly explain a class of read mappers, seed-and-extend mappers. Seed-and-extend mappers attempt to find locations in the reference genome that closely match each read sequence with the following procedure. It 1) obtains a query read, 2) selects smaller segments (i.e., seeds) of the read, 3) index a data structure with these seeds to obtain a list of possible locations that would result in a match, 4) obtain the sequence from the reference genome, and 5) align the read sequence to the reference sequence with an expensive dynamic programming algorithm in order to determine similarity.
To improve performance on the runtimes of seed-and-extend mappers, we can utilize seed filters, recently introduced by Xin et al. [1]. Seed filters efficiently determine whether a candidate mapping location will result in an incorrect mapping before performing the computationally-expensive alignment step for that location. As long as the filter can eliminate possible locations faster than the time it takes to execute alignment, the entire read mapping process will be accelerated [1, 2]. As a result, several recent works have focused on optimizing the performance of seed filters [1–6].

The onset of seed filters has resulted in a shift of the performance bottleneck to filtering but filters still require large amounts of memory bandwidth to process and characterize each of the candidate locations. We attempt to reduce the time spent in filtering and present a new algorithm, GRIM-Filter, to efficiently filter locations with high parallelism. We observe that the characteristics of GRIM-Filter reflect an algorithm well-suited for implementation on 3D-stacked memory and evaluate GRIM-Filter on our in-house 3D-stacked memory simulator.

3D-stacked DRAM [7–12] is an available and emerging technology that integrates logic and memory in a 3D stack of dies with a large internal bandwidth. This enables the bulk transfer of data from memory to a logic layer that can perform simple parallel operations on the data.

Whereas conventional computing requires the movement of data on buses between core and memory, processing-in-memory (PIM)-enabled devices such as 3D-stacked memory enable simple arithmetic operations in nearby memory with high bandwidth. With carefully designed algorithms mapped for PIM, applications can often be improved immensely as the relatively small bus between core and memory no longer impedes the progress of computation on the data.

Our goal is to develop a seed filter that exploits the high memory bandwidth and processing-in-memory capabilities of 3D-stacked DRAM to increase the performance of hash table based read mappers without sacrificing their high sensitivity or comprehensiveness.

To our knowledge, this is the first seed filtering algorithm that accelerates read mapping by overcoming the memory bottleneck with PIM using 3D-stacked memory technologies. GRIM-Filter can be used with any read mapper, however, in this work we demonstrate the effectiveness of GRIM-Filter with a hash-table based mapper.
Key Mechanism. GRIM-Filter provides a quick method for determining whether a read will not match at a given location, thus allowing the read mapper to skip the expensive alignment process for that location. GRIM-Filter works by counting the existence of small segments of a read in a genome region. If the count falls under a threshold, GRIM-Filter discards the locations in that region before alignment. The existence of all small segments in a region are stored in a bit vector which can be easily predetermined for each region of a reference genome and retrieved when a read results in a potential location to a given region. We find that this regional approximation technique not only enables a high performance boost via parallelism but also improves filtering accuracy over the state-of-the-art.

Key Results. We evaluate GRIM-Filter qualitatively and quantitatively against the state-of-the-art seed filter FastHASH [1]. Our results show that GRIM-Filter yields a 5.59x–6.41x smaller false negative rate (i.e., proportion of locations that pass the filter, but result in a poor match) than the best previous filter, and runs end-to-end 1.81x–3.65x faster than mrFAST with FastHASH for a set of real genomic reads, when we use a 5% error threshold. We also note that as we increase the error rate, the performance of our filter over the state-of-the-art also increases, thus making our filter more effective and relevant for future generation error-prone sequencing technologies.

2 Motivation and Aim
Mapping the reads against the reference genome enables the analysis of the variations in the sequenced genome, and with a higher throughput in mapping sequences, more large-scale analyses are possible. The ability to deeply characterize and analyze genomes on a large scale could change medicine from reactive to a preventative and further personalized practice. In order to motivate our method of improving the performance of read mappers, we pinpoint the performance bottlenecks of modern-day mappers on which to focus our acceleration efforts. We find that across our dataset, mrFAST with FastHASH [1] still spends 15% of computation time aligning locations that are found to be a match, and 59% of the time aligning locations that are later discarded (i.e., false locations). Our goal is to implement a filter that reduces the wasted computation time spent aligning false locations by quickly determining if a location will not match the read and forgo the alignment altogether. The ideal filter would exhibit no additional overhead and correctly find all false locations and shows the potential to improve average performance of mrFAST on the same machine by 3.2x. We note that this speedup is primarily earned by reducing the number of false location alignments, whereas most prior works gain their speedup by implementing parts or all of the read mapper in hardware. These works are orthogonal solutions, and could be implemented together with location filters for additional performance improvement.

3 GRIM-Filter
We now describe our proposal for a new seed filter, GRIM-Filter. At a high level, GRIM-Filter utilizes meta-data on short segments of the genome in order to quickly determine if a read will not result in a match at that genome segment.

Figure 2 shows a reference genome with its associated meta-data. The reference genome is divided into short contiguous segments, on the order of several hundreds of base pairs, which we refer to as bins. GRIM-Filter runs at the granularity of these bins, operating on the meta-data associated with each bin. This meta-data is stored in a bit vector that stores whether or not a token, or small DNA sequence on the order of 5 base pairs, can be found within the associated bin. We refer to each bit
as an *existence bit*. To account for all possible tokens of length *n*, each bit vector must be $2^n$ bits in length, where each bit denotes the existence of a particular token instance. Figure 2 highlights the bits of two token instances of *bin*’s bit vector showing the existence of token GACAG (green) with a 1 and the lack of token TTTTT (red) with a 0.

Because these bit vectors are associated with the reference genome, the bit vectors must only be generated once per reference and can be reused to map any number of reads from other individuals of the same species. However, in order to generate the bit vectors, the genome must be sequentially scanned for every sequence of *n* length tokens. If *bin* contains the first base pair of a token, the token’s corresponding index of the associated *bitvector* must be set (1), but otherwise unset (0). These bit vectors can then be saved for later reuse when mapping reads to the same reference genome used to generate them.

Before alignment, GRIM-Filter checks a read’s potential mapping location by operating on the bit vector of the bin holding the first base pair of that read. This relies on the entire read being contained within a given bin, requiring bins to overlap (i.e., some base pairs are contained in multiple bins) as shown in Figure 2.

GRIM-Filter uses these bit vectors in order to quickly determine if a match within a given error rate is impossible. This is determined before running alignment, the expensive dynamic programming algorithm in order to reduce the number of unnecessary alignment operations. For each location, we 1) load the bit vector of the bin containing the location, 2) operate on the bit vector (as we will describe shortly) to quickly determine if there will be no match, and 3) discard the location if GRIM-Filter determines a poor match. Otherwise, the sequence at that location must be aligned with the read to determine the match similarity.

Using the circled steps in Figure 3, we explain in detail how GRIM-Filter determines whether to discard a location 2 for a read. 1) GRIM-Filter extracts every token in the read and 2) accumulates their respective existence bits from the bit vector. 3) The sums are compared to a threshold (that we explain below), and set to 1 if it meets the threshold, otherwise set to 0. When the read mapper is ready to align a read to a a segment of the reference sequence, the read mapper must
Figure 3: Flow diagram for our algorithm. GRIM-Filter takes in read sequences and generates filter masks on the 3D-stacked logic die using precomputed bit vectors, while the CPU filters locations, queried from the hash table, using the resulting filter mask. The locations of correct mappings and their edit distances are then returned to the user.

4) determine which bit to check against, and then 5) determine whether it should continue with alignment or not.

We now discuss in detail how to determine the threshold value to compare the sum from step 3. A higher sum would represent a higher probability for the read to match well within that bin, since a higher sum represents a higher number of parts of the read being found in the bin. However, intuitively, this may never confirm whether the read would match well or how well the match would be. On the other hand, if the number of parts found falls below a certain threshold, we can guarantee that the read will result in a poor match.

If reads mapped perfectly to the reference sequence, the threshold would simply be the total number of tokens in a read or \textit{read length} – \(n - 1\). However, due to the need for allowing some differences in an alignment, we must compare the accumulation sum against a lower value taking into account the worst case error rate. This threshold can be calculated using the equation given in Figure 4. As shown in the figure, a token of size \(n\) in a bin overlaps with \(n\) other tokens. Assuming a single substitution error between the read and reference sequence, the error will propagate to the \(n\) previous tokens, meaning that those tokens may not be found in that bin. We determine that the equation in Figure 4 reflects the worst case error distribution and error rate (e.g., an error rate of 5\% or less of the read length is widely used [2, 13–15]) in a good match. In the worst case, where the maximum number of errors occurs and every error affects the \(n\) adjacent tokens, the valid accumulation threshold is at its lowest value.

After comparing the accumulated sum against the threshold calculated using the appropriate values (read size, error rate threshold, and token size), GRIM-Filter returns control to the read mapper to align those locations that pass the filter. This process is repeated for all locations, which significantly reduces the number of alignment operations and ultimately reducing the end-to-end read mapping runtime.
3.1 Candidacy for 3D-stacked Memory Implementations

We identify three characteristics of GRIM-Filter that make it a great candidate implementing in for 3D-stacked memory: 1) only requires very simple operations, 2) highly parallelizable since each bin can be operated on independently, and 3) it is highly memory-bound requiring a single memory access for approximately every three instructions.

4 Mapping to 3D-Stacked Memory

In this section, we first introduce 3D-stacked DRAM and describe how GRIM-Filter can be easily mapped to utilize this emerging technology, which attempts to bridge the disparity between processor speed and memory bandwidth. As this disparity increases, memory becomes more of a bottleneck in the computing stack [16]. Along with 3D-stacked DRAM, which enables much higher bandwidth and lower latency compared to conventional DRAM, the disparity between processor and memory is alleviated by the re-emergence of Processing-in-Memory, which integrates processing units inside or near the memory system to leverage high in-DRAM bandwidth and reduce energy consumption by reducing the amount of data transferred to the processor. In this section, we briefly explain the required background for these two technologies, which we will leverage to accelerate DNA read mapping.

4.1 3D-Stacked Memory

3D-stacked DRAM has a much higher internal bandwidth than conventional DRAM, thanks to the closer integration of logic and memory using through-silicon via (TSV) technology as seen in Figure 5. TSVs are vertical interconnects that can pass through the silicon wafers of a 3D stack of dies [17]. TSVs have a much smaller feature size than a standard interconnect, which enables a 3D-stacked DRAM to integrate hundreds to thousands of these wired connections between stacked layers. Using these wide wired connections, 3D-stacked DRAM can transfer bulk data simultaneously, enabling much higher bandwidth compared to conventional DRAM. Figure 5 shows a 3D-stacked DRAM (High Bandwidth Memory, HBM [7]) based system that consists of a 4-layer stacked DRAM using TSVs, a processor die, and silicon interposer that connects the stacked DRAM and the processor. The vertical connections in the stacked DRAM are very wide and very short which results in high bandwidth and low power consumption, respectively [8]. There exist many different 3D-stacked DRAM architectures available today. High Bandwidth Memory (HBM) is already integrated into the new AMD Radeon™ R9 Series Graphics Cards [9] and NVIDIA also announced that they will use HBM in their future products [10]. Hybrid Memory Cube (HMC) is also being developed by a number of different contributing companies [11, 12]. Other new technologies are also around the corner and...
can enable processing-in-memory, such as Micron’s Automata Processor (AP) [18] and Tibco transactional application servers [19, 20].

Figure 5: 3D-Stacked DRAM example: High Bandwidth Memory consists of stacked memory layers and a logic layer connected by high bandwidth TSVs and microbumps [7]. The 3D-stacked memory is then connected to an SOC with an interposer layer that provides high bandwidth between the logic layer and the processing units on the package substrate.

**Processing-in-Memory.** A key technique to increase the memory system bandwidth and reduce energy consumption in the memory system is placing computation units inside the memory system (e.g., PIM). Today, we see processing capabilities appearing in or near conventional DRAM [8, 21–25]. By enabling computation within or near the memory system and only transferring the results to the CPU, PIM provides significant performance improvements and energy reductions compared to the conventional system architecture that transfers all data to the process and only executes instructions within the CPU [21, 22, 26, 27].

**3D-stacked DRAM with PIM.** Combining these two new technologies, 3D-stacked DRAM and PIM enable great opportunities to build very high performance systems. A popular architecture for proposed 3D-stacked DRAM consists of multiple stacked memory layers and a logic layer that control the stacked memory, as shown in Figure 5. As many prior works show [21, 22, 26–29], the logic layer in 3D-stacked DRAM can be utilized not only for managing the stacked memory layers, but also for integrating application-specific accelerators. Since the logic layer already exists and has enough space to integrate compute units, integrating application-specific accelerators in the logic layer requires very small design and implementation overhead and little to no hardware overhead. 3D-stacked DRAM architecture enables us to fully customize the logic layer for the acceleration of applications [22, 29].

4.2 Mapping GRIM-Filter

We use mrFAST with FastHASH [1] as our baseline for code and performance. Our bit vector based implementation exists as an extension to FastHASH as a simple series of calls to an Application Programming Interface (API). FastHASH has an inflexible set of parameters, so there is not as much system-specific tuning that can be done. However, for shared data structures between FastHASH and GRIM-Filter, all parameters are kept consistent for a fair comparison. For those parameters specific to the bit vectors data structure in GRIM, we run tests to find a set of parameters that result in a highly effective filter for our system (shown in Section 6).
Due to the simplicity of our bit vector algorithm, we claim a low development and area cost for the logic layer in the 3D-stacked memory device. The required hardware for the logic layer as seen in Figure 6 simply depends upon the bandwidth available directly from the memory layers via TSVs.

GRIM-Filter involves reading \( p \) bits (existence bits) in parallel from differing bins representing the bin existence for the same token. We distribute our bit vectors throughout memory such that 1) every bit representing the existence of a given token across all bins is allocated a contiguous region of memory, and 2) all bits describing a given bin \( n \) from bit vectors of different tokens will fall in the same column. We then use these existence bits to increment the accumulator in the corresponding indices and repeat for all tokens in the read. This summation step simply requires a vector of incrementers, where each sum value is represented by \( \lceil \log_2(\text{read size}) \rceil \) bits. The maximum value that the final sum can be is equivalent to the size of the read simply due to the fact that that is the number of tokens that compose each read. The number of required sum values and incrementers is specified by \( p \). After this has been repeated for all tokens in the read, we can reference the accumulators and compare the value to the required threshold to determine whether to discard a location.

In order to simplify referencing the accumulator, we utilize comparators for each of the accumulators after summing across each token. We can reduce the final accumulator values to a Boolean representing whether or not the read could possibly exist in the bin. Depending on the available bandwidth of the memory module in question, we simply require \( p \) incremeneter lookup tables (LUT), \( p \) 7-bit counters (for our particular sets of 100 base pair reads), \( p \) comparators, and a single (\( \text{num_bins} \))-bit vector that holds the final result for the given read at each bin. As future 3D-stacked memory devices are expected to have more parallelism, the hardware overhead increases linearly, but the performance overhead of GRIM-Filter reduces equally. GRIM-Filter requires a very small and simple logic layer which gives it an edge over other filtering algorithms that could be implemented on the logic layer.

5 Experimental Methodology

**Evaluated Read Mapper.** We evaluate our proposal using the state-of-the-art hash table based read mapper mrFAST with FastHASH [1]. We chose this mapper for our evaluations as it provides high accuracy in the presence of large error rates, which is required to detect genomic variants within and across species [1, 30]. However, we note that GRIM-Filter can be used with any other mapper.

**Major Evaluation Metrics.** We evaluate 1) the false negative rate (i.e., proportion of locations that pass the filter, but result in a poor match) of our GRIM-Filter, and 2) the performance improvement of the end-to-end read mapper when using GRIM-Filter. To obtain both results, we first integrate GRIM-Filter into mrFAST with FastHASH [1]. We measure the false negative rate of our filter (and the baseline filter used by the mapper) as the ratio of the number of locations that passed the filter but did not result in a mapping over all locations that passed the filter. We detail how we measure the performance improvement of our mechanism next.

**Performance Evaluation.** We measure the execution time improvement of our mechanism by taking three measurements: 1) execution time of the baseline mapper without GRIM-Filter (obtained by executing the source code of the mapper, which is available as open source [1]), 2) execution time of the baseline mapper with GRIM-Filter’s software implementation, which does not take advantage of emerging memory technologies (obtained by executing the source code of the baseline mapper integrated with our software version of GRIM-Filter, which we will make available
as open source software), 3) execution time of the baseline mapper with GRIM-Filter, which takes advantage of execution on 3D-stacked memory. To obtain the last entity, we measure the execution time of the software GRIM-Filter segments in mrFAST and subtract this from the obtained execution time in 2. Then, using a validated in-house simulator similar to Ramulator [31], we determine the overhead in offloading GRIM-Filter to a 3D-stacked memory system and add the overhead execution time to obtain the final execution time. We chose this methodology to estimate the runtime of GRIM-Filter on 3D-stacked memory technologies as such technologies that perform in-memory computation are unavailable to us at this point in time.

**Evaluation System.** Our evaluation system is an Intel(R) Core(TM) i7-2600 CPU @ 3.40GHz with 16 GB of RAM for all experiments.

**Data Sets.** We used ten real data sets from the 1000 Genome Project Phase 1 1000 Genomes Project Consortium (2012). These were the same data sets used by Xin, et al [1] for a fair comparison. Table 1 lists the read length and size of each data set.

| No. of Reads | ERR240726_1 | ERR240727_1 | ERR240728_1 | ERR240729_1 | ERR240730_1 |
|--------------|--------------|--------------|--------------|--------------|--------------|
| Read Length  | 4031354      | 4082203      | 3894290      | 4013341      | 4082472      |

| No. of Reads | ERR240726_2 | ERR240727_2 | ERR240728_2 | ERR240729_2 | ERR240730_2 |
|--------------|--------------|--------------|--------------|--------------|--------------|
| Read Length  | 4389429      | 401341       | 401341       | 4082472      | 4082472      |

Table 1: Benchmark data, obtained from the 1000 Genomes Project Phase I [32]

6 Sensitivity Analysis and Results

We first profiled the reference human genome in order to determine a range of parameters that were reasonable to use for GRIM-Filter. We were able to determine the points of diminishing returns for several parameter values. This data is presented in Section 6.1. Using this preliminary data, we could reduce the required experiments to a reasonable range of parameters. Our implementation enabled the variation of runtime parameters (number of bins, token size, error threshold, etc.) within the ranges of values that we determined from our preliminary experimentation for the best possible results. We then were able to quantitatively evaluate the improvements in the false negative rate and runtime over mrFAST with FastHASH. Our results for the full mapper with GRIM-Filter are presented in Section 6.2.

6.1 Parameter Evaluation Results

In order to determine a range for the parameters that we used for experimentation, we ran a series of analyses on the fundamental characteristics of the human reference genome. Our initial experiments were designed to determine the **memory footprint** of our algorithm for effective performance improvements. To show how each of the different parameters affect the performance of GRIM-Filter, we study a preliminary sweep on the parameters with a range of values that would not incur excessive amounts of memory. Figure 6 shows how varying a number of different parameters affects the **average read existence** across the bins. We define average read existence to be the ratio of bins that pass the filter to all bins comprising the genome, for a representative set of reads. We want this value to be as low as possible because it reflects the filter’s ability to filter incorrect mappings. The fewer bins that these reads, in the representative set, map result in possible mappings, the more likely it
Figure 6: Token lengths 4-6 Read Existence: We use a representative set of reads to collect this data. We see how as error tolerance increases, the average read existence (the ratio of bins that must be checked with alignment to all bins comprising the genome) increases. We note that this value reflects the filter’s effectiveness, assuming that the filter eliminates all false negatives (a low value is good, but zero would mean that the filter eliminates all candidate mappings). Our error tolerance reflects the threshold value that we use to determine whether we can filter any given bin. From Figure 4, we can see how varying the % error tolerance would affect the threshold that we use for filtering. Because we take the ceil of the read length multiplied with error tolerance (e), we see that partial error tolerances would change the threshold calculations even in the case of 100 bp reads. We can see how the plots marked with different colors show that as we increase the number of bins, the existence ratios decreased. The three plots represent the values found as we varied the token size.

will be that we will not have to align a given location. Across the three plots, we vary the token size from 4 to 6. Within each plot, we vary the number of bins to split the reference genome into, denoted by the different colors. The x-axes varies the error threshold between a match, and the y-axes show average read existence. We plot the average and min/max across our 10 data sets (Table 1) as indicated respectively by the triangle and whiskers. We make three observations. First, we observe, across the three plots, that increasing the token size, from 4 to 5, shows massive drops in the read existence while 5 to 6 exhibits significantly diminishing returns. This is due to the fact that, given a random pool of A,C,T,G’s, the probability of observing a substring of size $q$ is $\left(\frac{1}{4}\right)^q$. However, due to the non-uniform distribution of base pairs across the genome and the bin sizes, we see diminishing returns on the average read existence. Second, we observe that across the plots, each increase in the number of bins results in a decrease in the read existence. This is understandable due to the fact that the bin size decreases as the number of bins increases and for smaller bins, we have a smaller sample size that any given substring could exist within. When sweeping the number of bins, we use multiples of 64k because it is an even multiple of the number of TSVs between the logic and memory layers in today’s 3D-stacked memories. We want to use a multiple of 64k so that we can utilize all TSVs for each access. Third, we observe that for each plot, increasing the error threshold results in an increase in the read existence. This is due to the fact that if we allow errors, a wider variety of sequences map to the same read. We conclude from this figure that using tokens of size 5 gives the best tradeoff between memory consumption and filtering efficiency.

To show how we chose our final bit vector size to use for experimentation, we sweep the number of bins and the error threshold ($e\%$). Figure 7 shows how varying these parameters affects the false negative rates of the filtering algorithm. The x-
Figure 7: Bins Parameter Sweep: When running the actual experiments for a subset of the entire benchmarks, we find our filter’s false negative rate as we vary different parameters. We see that as we increase the error threshold, we see a consistent increase in the false negative rates regardless of the number of bins used. We also note that increasing the number of bins results in diminishing returns around 300x64k bins over all error thresholds.

We ran several experiments to examine the benefits behind GRIM-Filter’s ability to parallelize consecutive bins. We noticed significant benefit in exploiting paral-
lelism when $p$ is 4096 (which is the bandwidth for HBM2) [10]. In approximately 10% of the $k$-mers, we see a significant decrease (98.6%) in required window retrievals. In the remaining $k$-mers, we see approximately 10-20% decrease in required window retrievals. From HBM2 specifications [10], we note that the available bandwidth between memory and logic layer is 4096 bits, therefore our chosen experimental $p$ value was 4096. Given larger $p$ values, we have experimental data showing a continual reduction of required window retrievals.

6.2 Full Mapping Results
We used a popular seed-and-extend mapper, mrFAST [30], to retrieve all candidate mappings from ten real data sets from the 1000 Genome Project Phase I [32]. Table 1 lists the number of reads and size of each read in each benchmark. In our experiments we use a token of length 5 and 450x64k bins as discussed in Section 6.1.

Figure 8 shows the number of false negative locations that pass through GRIM-Filter compared to the baseline. The shared x-axis indicates the ten sets of reads and the y-axis indicates the false negative rate. The light green and dark green respectively mark the baseline and GRIM-Filter, and the graphs descending vary in error thresholds. We make two observations. First, we note a significantly lower false negative rate for all benchmarks in all ranges of error thresholds when compared to the results of FastHASH. Second, we observe a phenomenon where the false negative rates increase when increasing the error threshold from 0% to 2% and then decrease from 3% to 5%. We attribute this to a combination of factors. This includes the fact that increasing the error threshold results in more acceptable mapping locations. However, the number of candidate locations do not change. This naturally results in a smaller false negative rate. There is another underlying factor: as acceptable error threshold increases, our thresholding value decreases and allows for more locations to pass through the filter resulting in an increased false negative rate. We conclude that the interaction of these two factors are the cause for the initial increase and later decrease in the false negative rates. We note that when using this filter for higher error threshold, we observe larger improvements in the false negative rate which can be reflected in the runtime. When comparing our filtering algorithm to FastHASH for an error threshold of 5% [1], we see that our algorithm results in 5.97x less false negative locations on average across the benchmarks. This is reflected directly as a decrease in the end-to-end runtime, since fewer locations must be fully aligned.

Figure 9 compares the execution time of GRIM-Filter against the baseline, mrFAST with FastHASH. This graph follows the same format as the previous, except the y-axis now represents the execution time scaled to 1000 seconds. We make two observations. First, we observe that GRIM-Filter shows performance improvement over all benchmarks regardless of the error threshold. Second, as the error threshold increases, we gain increasingly more performance benefit. This is due to the fact that GRIM-Filter is able to discard many more locations than FastHASH at higher error thresholds, thus saving much more execution time by ignoring unnecessary alignments. Again, because of the importance of high sensitivity for calling structural variations and the direct correlation between runtime and error threshold, we report all numbers only looking at the maximum error threshold of 5%. When we compare the runtime of mrFAST with GRIM-Filter against the previous fastest read mapper, mrFAST with FastHASH, we find a 2.08x (3.65x) performance boost on average (max) across the benchmarks. When we further break down the computation time, we find that our performance gains are from an average decrease.

[1] It is most important to compare to 5% error threshold as it is the accepted worst case error rate for read mappers and provides the highest sensitivity.
across datasets of 83.7% computation time on false negative locations. We conclude that employing GRIM-Filter can significantly enhance the performance of a state-of-the-art mapper.

7 Related Works
To our knowledge, this is the first paper to exploit 3D-stacked DRAM and its processing-in-memory capabilities to overcome the recent bottleneck shift to memory bandwidth in read mapping due to the immense improvement on the prior bottleneck, alignment. In this section, we briefly describe related works that aim to accelerate read mapping with hardware support.

Many prior works used FPGAs to accelerate alignment. These include [33–43] and all accelerate read mapping using customized FPGA implementations of different existing read mapping algorithms. Arram et al. [35] accelerate SOAP3 tool on an FPGA engine and it shows up to 134x speedup compared to BWA. Houtgast et al. [39] present a FPGA-accelerated version of BWA-MEM that is 3x faster compared to its software implementation. Other works use GPUs [44–47] for the same purpose. Liu et al. [45] accelerate BWA and Bowtie by 7.5x and 20x, respectively. However, all these accelerators are still bottlenecked by memory bandwidth. Compared to these accelerators, our approach overcomes the memory bandwidth bottleneck by utilizing the up-and-coming 3D-stacked DRAM with a newly designed algorithm that is specific to this technology.

In the case of other hardware optimized implementations with much higher speedups, they focus on the acceleration of the actual alignment (the dynamic programming step) which is the bulk of the computation in mapping. While many works have managed to attain the maximum possible acceleration in alignment through multiple iterations of implementations ranging from ASIC to FPGA, we
explore a newer area in mapping that requires significantly less computation. We show that we can accelerate the entire mapping pipeline by utilizing the inherent massive parallelism in 3D-DRAM. We note that GRIM-Filter is orthogonal to other filters and mapper steps and can be stacked on top of other existing optimizations for further potential acceleration. We show that when we run mapping with GRIM-Filter on a commodity CPU, we see $1.81x - 3.65x$ performance improvement. We speculate substantial potential in tying together the implementation of this filter with other hardware optimized aligners.

8 Conclusion
We introduced a new algorithm, GRIM-Filter, for accelerating genome read mapping. GRIM-Filter takes advantage of an emerging technology, 3D-stacked memory, which enables the efficient use of processing-in-memory to overcome the memory bottleneck in read mapping today. We utilize the processing-in-memory capability of 3D-stacked technology and exploit its massive internal bandwidth to run GRIM-Filter which efficiently and quickly filters large segments of the genome for later steps of read mapping. With the most relevant alignment error acceptance rate of 5%, we show that GRIM-Filter filters locations with approximately $5.59x - 6.41x$ smaller false negative rate than FastHASH and performs $1.81x - 3.65x$ faster than the fastest read mapper, mrFAST with FastHASH. GRIM-Filter is a universal filter that can be applied to any read mapper.

We believe there is huge potential in adapting DNA read mapping algorithms to state-of-the-art and emerging memory and processing technologies. With our results, we hope that our paper, which introduces the first work in doing so for 3D-stacked memories, which are increasingly common in today’s computing landscape,
provides inspiration for other such works to design new sequence analysis algorithms that take advantage of 3D-stacked memory.

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