Designs for accelerating Bioinformatic problem solving using FPGAs based HPC system

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Abstract

The Human Genome project was marked as completed in the year 2003 which opened vast avenues for research towards developing and enhancing Genomic analysis techniques. With such vast sequence database available, the Genomic research greatly depends on bioinformatics capabilities and improvements to the computational speed would help in analysis the data to discover causes and treatments for various diseases. This has been a major driving factor to develop techniques to increase the processing capabilities of the existing algorithms, tools and techniques by utilizing advancements in computing power. FPGA based acceleration for existing algorithms presents very promising advantages, reducing processing times by huge factor compared to other CPU and GPU based techniques. Similarly, the introduction of high performance clusters to distribute the processing has already been used and shown to be effective for large sequence analysis.

Combining these technologies together possess great benefits for even speeding up the analysis of the huge databases. This paper will present some of the techniques and heterogenous system which have been developed and utilized to speed the the genome analysis from years to days. Initially we look at bioinformatics application areas where FPGA and HPC system are beneficial. Then the paper describes some of the tools and algorthmic accelerators using FPGA and HPC in a heterogenous system. The last part presents some systems and evaluation results in terms of speedup compared to existing systems and tools.

1 Introduction

Humans quest to understand the basic biological processes lead to development of research areas such as biochemistry and biotechnology. Multiple decades of research in the biological molecules helped us in understanding the existence DNA and genome which defines how a living organism behaves and exist. On the other hand the advancement in computer technologies and increased use of them in healthcare, biomedical and computational biological research has helped find cure and medical treatments for many complex health issues and save many lives over the years.

In efforts to increase the knowledge of genomes, the field of Bioinformatic was created. Bioinformatic majorly involves the study of biological molecules (biomolecules) which build up the cells of the living organisms. As with the other biological fields, bioinformatic aims at utilizing the capabilities of the computer science to build and analyse molecular sequences (genes) of genomes. In this direction, The *Human Genome Project*[1] was started in late 1990 and was completed in 2003 successfully. "A 2.91-billion base pair (bp) consensus sequence of the euchromatic portion of the human genome was generated by the whole-genome shotgun sequencing method"[1]. This was a huge step but also presented the problem of huge processing times for analysis of such a large database of genome for extracting any useful information. The existing algorithms for database searches such as Smith-Waterman [2] based on dynamic programming for local similarity estimation and heuristics based BLAST [3] were limited by high computation times. The main limiting factors at this point were the processing capabilities of the computing units on which the algorithms were running.

Various methods in the past decades have evolved to provide higher computing and data processing capabilities for various application domain. The earliest method being hardware acceleration provided by symmetric multiprocessing which allows distribution of computing to different processor sharing a common memory. The next major acceleration achieved has been the development of high performance computing clusters (HPC). HPC system work by splitting and distributing the problem over multiple similar processing units popularly known as nodes. Each of the node, consists of a high performance processor with multiple cores and sharing the same common memory. The nodes in the clusters are connected to each other with high speed Ethernet connections for exchange of data and control information as shown in fig<>. Each node can be used to process a subset of the data parallely decreasing the overall computing time for the problem. Due to such benefits, these techniques have being used to speed up the Bioinformatic algorithms by modification to work on these HPC clusters and utilize the benefits. Implementation of the famous Smith-Waterman algorithm on HPC systems is presented in [4], [5]. A various number of parallel implementation for BLAST such as mpiBLAST [6] are available as well which prove to be more time efficient. Schmidt, Schröder, and Schimmler [7] showed how such improvements can be used to create a parallel system which helps to speed up the molecular sequence analyse.

Add pic of cluster

Another step in increasing the processing capabilities of the clusters is use of GPU. GPUs allow offloading the vector based arithmetic operations for large datasets. The GPUs prove to be excellent accelerators for reducing the processing time of complex calculation on large amount of data which are common in many of the application domain utilizing the clusters. Liu, Schmidt, and Muller-Wittig [8] have presented such a system which is capable of performing 10 times faster compared to serial versions.

Though the parallel implementation with CPU and GPU help in achieving faster processing time, its heavily dependant on the size of the cluster. Also the speedup is de-

[1] `http://https://www.genome.gov/`

pendant on the size of the problem as well. These reasons made researchers to look for areas for improving the execution times of the algorithm by using hardware based accelerators for the algorithms to reduce processing time for each operation. This is where the FPGA has helped a lot by providing opportunities to implement the algorithms directly in the hardware. The flexibility of FPGA based accelerators makes them very useful to design application specific acceleration hardware and also re-use them for different kinds of problems. Currently a lot of accelerators are available which the bioinformatic community is benefiting from. This paper would discuss some of these implementation and give an overview of how such accelerators are integrated with the HPC clusters to build heterogenous systems which are used to achieve very high processing speeds to reduce the time from days to hours required for some bioinformatic application.

The rest of the paper is divided into 3 sections. Section 2 introduces the bioinformatic application domain giving details of algorithms and tools popularly used. Section 3 will present the optimization techniques for genome comparison by FPGA and heterogenous systems and the last section presents results achieved by such optimization for some of the current systems.

2 Bioinformatic and its applications

Bioinformatic can be considered as an amalgamation of molecular biology and computer science. As described by Gokhale and Graham [9, chapter 8], it mainly focuses on analysis and management of biomolecular data and can be important to support research works towards identification of causes of diseases and specialized drug discovery. As mentioned in the introduction one of the most prominent success in the field of Bioinformatics was completing sequencing the human genome. Apart from genome assembly and analysis, bioinformatic also concentrates on protein classification and structure prediction, gene prediction and phylogenetic prediction.

Genomic data is mainly build up from DNA or protein sequences. DNAs make up from a sequence of nucleotide base pairs(bp). The four nucleotide molecules adenine (A), thymine (T), cytosine (C), and guanine (G) form the base pairs and are always arranged such that adenine (A) pairs with thymine (T) and cytosine (C) pairs with guanine (G). These bp can arrange in different ways and different lengths to build up the DNA sequences. The DNA sequences form the gene, the entity known to be responsible for some specific functionality, or the complete genome of the organism. The sequence of DNA are stored on computers as string containing only the the alphabets A, T, C and G representing the respective nucleotide molecules. Similarly the protein molecules are also represented by 20 {A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y} alphabets assigned based on the ammino acids composition.

Mount [10, chapter 2] describes the complex DNA sequencing process which involves extraction of the DNA fragments by using polymerase chain reaction (PCR) and tagging them for identification. Genome sequencing involves a laborious process of generating smaller subclones of the original sequence and then identifying overlaps to assemble the

sequences. Small sequence are easy and cost effective to identify and record but identification of the complete genome with similar techniques can be very costly. To reduce the cost the small sequences are are fed into the computer to create sequence databases using the string representation of the bp and then computer programs are used to assemble them by identifying overlaps. Genome databases collect such new sequences and provide them to researchers for analysis. The main focus of the analysis is identification of similarity between genomes of different organisms and mapping functions to the gene. Such similarities help to identify and build the divergence tree of species through years of evolution. The gene mapping is important to understand how the body behaves and can be used to study effects of different chemicals during drug trials.

All of these studies require some form of string matching to compare or identify subsection from the huge databases. As string comparison involved in the algorithms mostly can be achieved by simple mathematical operations over long operands. they can be easily mapped on simple circuits on the FPGA. As these operations does not involve any complex floating point operations FPGA are suitable to parallelize the computation and speed up the processing with dedicated hardware.

The rest of this section will explain the Bioinformatic application areas where FPGAs based accelerators can be used to speed up the processing. Some of the algorithm will also be presented to understand there functionality and usage in the bioinformatic domain.

2.1 Application areas

As highlighted earlier, the FPGAs can be a suitable target to accelerate the simple processing requirements of the bioinformatic domain and speed up the processing by huge factor. In this subsection, some of the application areas where FPGAs are suitable will be explained.

2.1.1 Genome Assembly/sequencing

Identification of the complete DNA sequence or the Genome of an organism has been one of the most common application of bioinformatic from the early 1990. The identification of complete DNA sequence involves forming small fragments of subclones of the large sequences and then re-arrange the fragments by comparing the ends to find overlaps between the fragments[10, Chapter 2, Genome sequencing]. This method is know as the shotgun sequencing and has been used to create the complete genomes of many organism including human genome as shown in fig. 1.

The main idea involved is comparison of overlap regions in the fragments to arrange them in the sequence. This is mostly achieved in computers by using pairwise comparisons of the strings for the fragments and identifying the similarities towards the end. Such comparison which mostly involve simple comparison operation of some fixed number values can be easily implemented in FPGA with high accuracy.

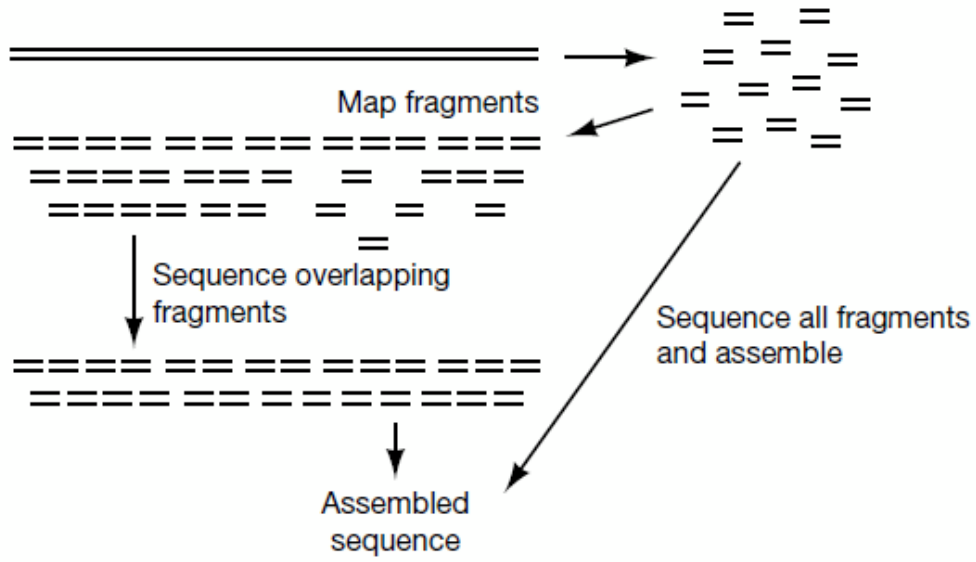


Figure 1: Sequencing process [10, Figure 2.4]

2.1.2 Gene prediction

One of the important aspect of DNA sequencing to identify the sequences which perform a specific functionality within the organism. Such sequences are called genes and an organisms genome can be divided into 100 of gene segment, each of which can be mapped to some specific functionality. The functionality of the gene are identified by predicting the sequences which encode some proteins molecule. Such sequences are identified by looking for open reading frames (ORF) which are sequences of bp which contains a codon encoding one of the ammino acid.

Gene prediction algorithm use the known databases of ammino acid sequences to identify similar patterns in the in the genome and tag them with the identified ammino acid. The ammino acid sequences are used to identify the resulting protein structure and predict it by searching for similar ones on know organism genome. The searches for gene prediction involve multiple databases and can be time consuming if whole database is required to be searched element by element for accuracy. Accurate algorithm based on dynamic programming are available which can perform the exhaustive search but to reduce the complexity of the search, heuristics based algorithms such as BLAST [3] are often used. Such algorithm can't guarantee mathematical accuracy but are known to be good in the predictive search and reducing the search time.

FPGAs can be used for both types of algorithms. The exhaustive searches can be parallelized over multiple systems to reduce the overall time. Similarly the heuristics algorithm can benefits from custom FPGA based hardware for reducing the processing time.

2.1.3 Pylogentic tree

The phylogeny of the organism is used to identify the relationship between them by analysing the differnces in the functionality of the gene location and gene functionality of similar genes. The gene location based analysis try to identify the distance between the similar gene on different organism to estimate the generation differnce among the species. Similarly the functionality based analysis identifies the differnce or similarity in the functionality of similar or different gene sequence by analysing the similarities in the families of proteins they encode. Tree based representation is used for both to present and evolutionary path of organism. Gene with smaller distance would have close common ancestor branches compared to larger distances which will seen by generations gaps. The differences in the protein families are Similarly represented. Two sequences which produce proteins producing similar functionality would lie on neighboring branches.

The analysis in the Pylogentic is similar to sequencing and requires a lot of string comparison algorithm and can also benefit from FPGA acceleration in similar manner.

2.1.4 Genome comparison

Another important bioinformatic application is comparison of genomes of different organism to identify similarities in gene content, gene location and gene number. As the number of fully identified genomes is increasing at rapid pace, the researchers focus a lot to identify these similarities which help to understand the evolution trend of the organisms. If the number of identified gene and there functionality in different genomes are similar to a large extent, this can be easily used to conclude that organism have common evolution history. Similar genes are often map to different functionality which is important indication of divergence during the evolution of the organisms.

The genomic comparison also involve comparison of strings to identify similar pieces but on a longer lengths of the whole genome which can be in 100 thousands bp. This is also an interesting application where FPGAs can be used for acceleration. As genome comparison are much larger problem then the gene comparison which can be easily completed on single processor, FPGA based acceleration can be very profitable to reduce the time of the comparison and produce results much faster.

2.1.5 Protein domain databases

As the protein identification is the most common approach for predicting similarities in the sequence, capabilities to perform quick search on the databases are important. The proteins differ based on the functionality they perform in the cell called as domain. It is important to categorize the proteins in to specific domain based on their functionalities and create some models which helps to fetch the target protiens from databases faster. There are vaious methods and models which accomplish this such as HMMER based on HMM models.

The algorithms basically involve multiple sequence alignment and require iterations to train the models to enhance the protein identification. Such systems can be targeted

```
T T G A A A T G C G – A G T
| |   |   | |   | |   | | |
T T C A T A T – C G T A G T
```

Figure 2: Global alignment of two DNA strings with 10 matches, two mismatches G/C and A/T, and two gaps G/– and –/T [9, Figure 8.2]

Figure 3: Distinction between local and global alignment [10, Figure 3.1]

on FPGA which provide the capability for dynamic remapping which can be used during training.

2.2 Algorithms

This section will describe some of the popular algorithms which are used frequently by researchers in the bioinformatic domain for genome analysis.

2.2.1 Dynamic Programming

The string comparison algorithm form the basis for the most of the studies which are carried out for genome understanding and analysis. This section will describe the dynamic programming algorithm used for local alignment and global alignment. The global alignment was first described by Needleman and Wunsch [11] in there paper in 1970. Later in year 1981 Smith and Waterman [2] proposed the local alignment algorithm for string comparison.

As Mount [10, Chapter 3] describes alignment is a procedure of comparing bp of two of more DNA sequence to identify the individual and sequence of bp which match in each of the strings. The alignment can also be extended to identify and estimate the cost of transformation of individual strings. [9] states the three condition which can occur while estimation the alignment at a given position which are shown in fig. 2:

1. a match occurs when the same character 'x' is present in both strings
2. a mismatch, also called a substitution, when there are two different characters 'x' and 'y'
3. a gap, when there is an insertion of one character in only one string, or symmetrically a deletion in the other string

The global alignment is stretched over the entire sequence whereas the local alignment limits to strong matches within the sequence as shown in **??**.

Formally considering two string $X = \{x_1, x_2, ..., x_n\}$ and $Y = \{y_1, y_2, ...y_n\}$ and H(i,j) maximum similarity score at position i, j, then the global alignment of the strings H(i,j) given by the Needleman-Wunsch equation [11] is

$\forall i : H(i,0) = g_{penalty} \times i \qquad \forall j : H(0,j) = g_{penalty} \times j$

$\forall i, j, ij \neq 0 :$

$$H(i,j) = max \begin{cases} H(i-1, j-1) + d(x_i, y_j) & \text{(match or substitution)} \\ H(i-1, j) - g_{penalty} & \text{(insertion)} \\ H(i, j-1) - g_{penalty} & \text{(deletion)} \end{cases}$$

The local similarity which is defined for the most similar pair of sub-sequences ending at x_i and y_i is given by Smitth-Waterman [2] equation as follows:

$\forall i, j : H(i,0) = H(0,j) = 0$

$\forall i, j, ij \neq 0 :$

$$H(i,j) = max \begin{cases} 0 & \text{(local align. starts here)} \\ H(i-1, j-1) + d(x_i, y_j) & \text{(match or substitution)} \\ H(i-1, j) - g_{penalty} & \text{(insertion)} \\ H(i, j-1) - g_{penalty} & \text{(deletion)} \end{cases}$$

An example of both global and local alignment calculation is shown in fig. 4

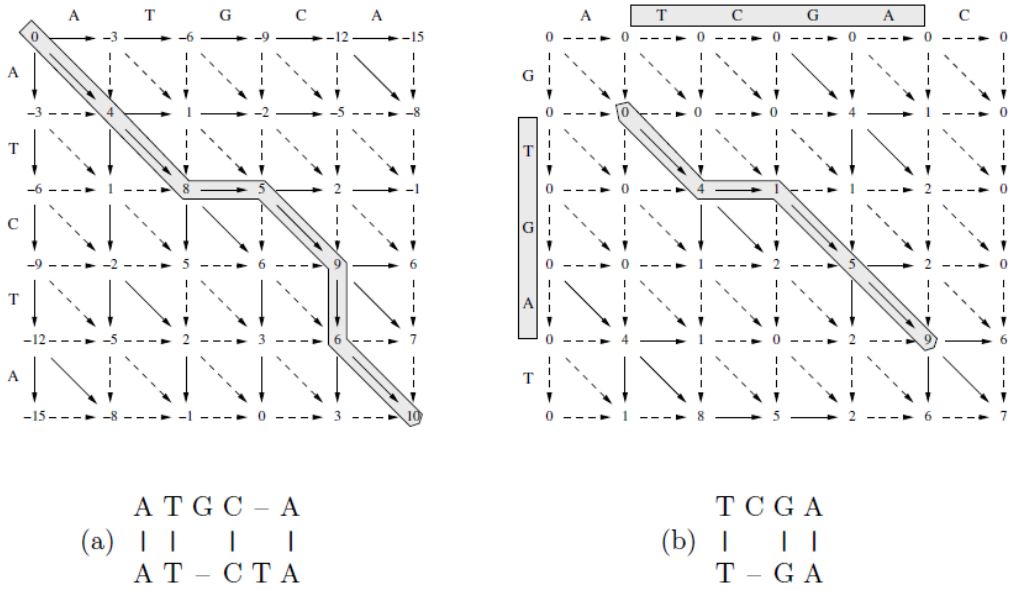
2.2.2 Seed-based Heuristics

As higlighted in the previous sections dynamic programming algorithm are capable of performing mathematically accurate searches but are time consuming. This led researchers build faster algorithns which were based on some heuristics to decrease the time of search and maintaining similar accuracy. FAST [12] and BLAST [3] were initial algorithm proposed based on heuristics which performed very well.

The main idea of heuristics based algorithm is the assumption that important similarities which are small (seeds) are conserved in the same way. This allows the algorithm to perform the dynamic programming calculations only around these seeds. BLAST like algorithm basically execute in three stages as presented in [9]:

1. Look for the exact seeds that apear in both strings.
2. Extend each seed with a limited number of substitution. At this point no insertions or deletion is allowed. The seeds whose score is greater than a defined threshold are retained.
3. Perform full dynamic programming computation on the extended seeds.

The stages are depicted in the fig. 5. The accuracy of the such algortithm depend higly on the seed size. Various extension of the algorithm has been proposed which modify the seed selection criteria to improve the performance.



(a)
A T G C – A
| | | |
A T – C T A

(b)
T C G A
| | |
T – G A

Figure 4: Example of global alignment computation with the NW equation (a) and local alignment computation with the SW equation (b). Scores are +4 for a match, -2 for a mismatch, and -3 for a gap. The solid arrows are the dependencies that lead to the maximum of each (i, j) cell and reveal the best alignment [9, Figure 8.4]

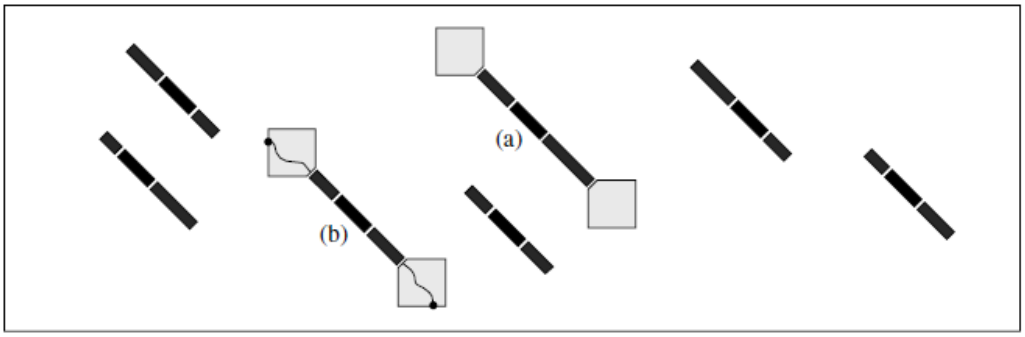


Figure 5: Schematic view of the BLAST 3-stages algorithm. Stage 1: localizes exact seeds (black). Stage 2: extends of the seeds with a few error tolerance (dark gray). The majority of detected seeds doesn't extend at this stage. Stage 3: performs full DP calculations (light gray) on extremely few sequences. Here only the seed (b) leads to a positive sequence [9, Figure 8.11]

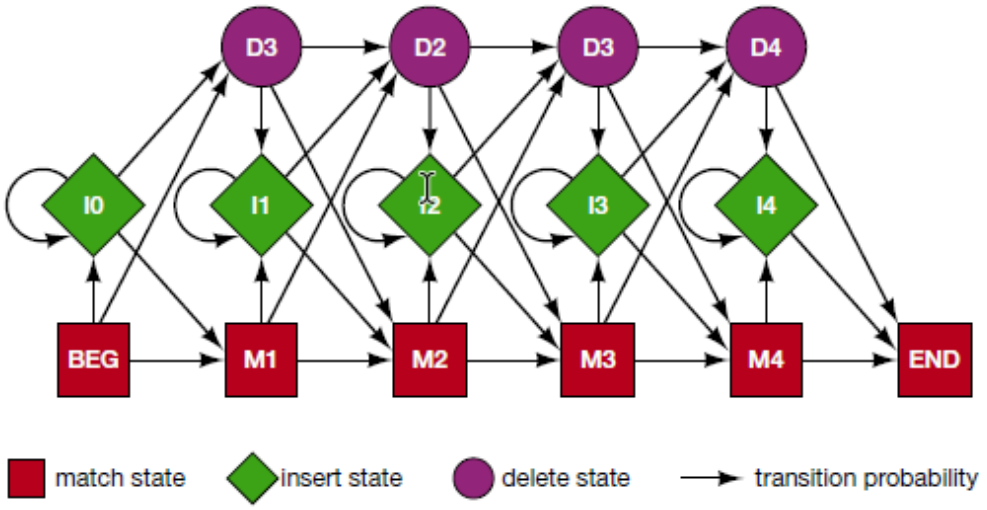


Figure 6: Hidden Markov model for sequence alignment [10, Figure 4.16]

2.2.3 Languages Models and Profiles

Once the a vast range of genomic strings are identified by experiments or by genome sequencing algorithms, building a model to represent the common features among the strings is useful. As noted in previous sections, models can help to decrease the search time of a string in databases by categorizing them based on domains. It often more helpful to develop a generic profile which can be inferred over all the sequences.

Hidden Markov Models (HMM)

Markovian process are processes whose future states are only dependant on current state and has no effect by past states. "HMM [13] is an statistical model which considers all the possible combination of matches, mis-matches and gaps to generate an alignment of a set of sequences" [10]. HMM needs to be trained with some initial data of known sequences. The initial data is selected based on the family of the amino acids required to be identified. The trained HMM can then be used to identify sequences of the same family. fig. 6 shows a HMM states which can be used for multiple sequence alignment.

3 Optimization of Genome comparison algorithms

The previous sections introduces the application areas and highlights the possibilities for using FPGA to optimize some of the application area. This section would present a FPGA based accelerator design for the popular dynamic programming Smith-Waterman algorithm along with the use of this accelerator in the heterogenous system to achieve faster database search.

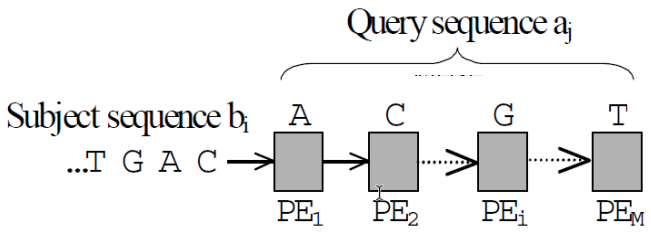


Figure 7: Systolic comparator on a linear processor array [15, Figure 2]

3.1 FPGA accelerators for Smith-Waterman

The string alignment achieved by Smith-Waterman (SW) is highly dependant on the size of the search string and size of the databases. As the size of the databases as been increasing rapidly with identification of new sequences, the processing time for the algorithm increases similarly. As SW is very accurate and important for the bioinformatic community, various acceleration have been developed in order to use it efficiently. Most of the acceleration achieved are done by using parallel processing. The parallelization can be achieved by either splitting and distributing the search over multiple processors [4], [5], [7], [14] or by passing the database string via a systolic comparator array. The FPGA based system are used to accelerate the processing by building hardware systolic cells which can perform very fast comparison. In this section we look at the FPGA based systolic accelerator designed by Oliver, Schmidt, and Maskell [15].

3.1.1 Systollic cells on the FPGA platform

Calculation presented in section 2.2.1 can easily be mapped to an array of Processing Elements (PE) of an FPGA creating systolic cells. Each PE can be initialized by the single character of the search string and then shift the sequence of string from the database systolically through the array as shown in fig. 7. Considering the query string size of M and K be the size of the sequence string to be searched, the PEs are able to complete the comparison in $M + K - 1$ steps with M PEs instead of $M \times K$ required for a sequential processor.

The design presented by Oliver, Schmidt, and Maskell [15] also utilize the reconfigurable nature of the FPGA by providing capabilities to modify the individual PEs to different gap penalty functions, variation of the data width, substitution width and lookup address width.

3.1.2 Operation of the cells

Assuming a sequence query A of length M $A = a_1a_2..a_M$ and B database sequence of length K $B = b_1b_2..b_K$ is to be mapped on a linear array of M PEs with affine gap penalities, then during initialization PEi would be initialized with character a_i along with corresponding gap penalities. After this the sequence B can pass through the array in

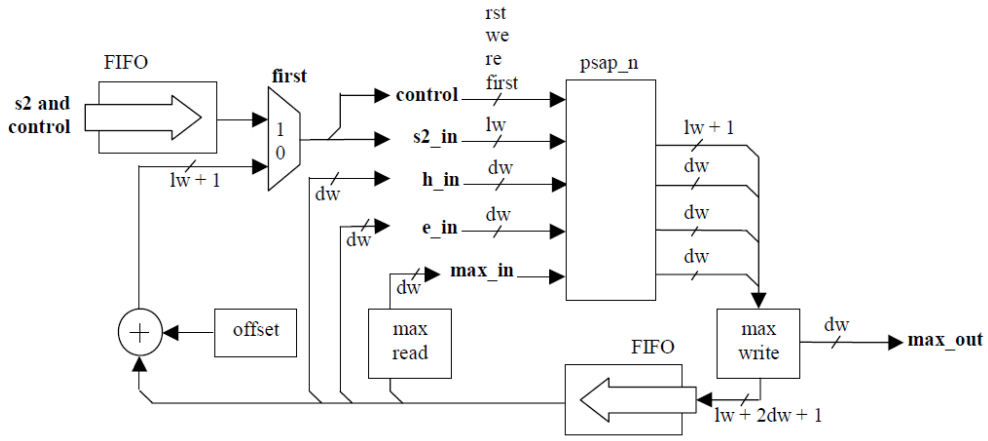


Figure 8: System design of the accelerator [15, Figure 4]

$M + K - 1$ steps. In each iteration k, the values H(i,j) is calculated by each PE parallely in single clock cycle.

The above operation assume that query string size and the number of PEs are equal (M) which is not often the case. The string size will vary and can be greater than PE array size. In this case the computation is partitioned. Considering a query string of size M and PEs having N elements, the query string is partitioned into M/N sequences. Initially the PEs are assigned with i^{th} partition along with gap penalities and then the processor array goes over the database sequence iteratively. After completion of iteration the PEs are updated to next partition values. As it is apparent, loading of the new values can be time consuming and to solve this problem the PEs are extended to store k columns of the strings along with gap penalities to avoid memory operation. The complete system design is shown in fig. 8

3.2 Heterogenous system designs

Using the FPGA accelerator described in the section 3.1

4 Evaluation and comparison

This section should highlight the possible acceleration which is possible with the FPGA based system using the Evaluation data of different techniques and present a comparative study of how this techniques vary to each other and to traditional HPC and serial computing.

This should be able to highlight the advantages of using FPGAs for certain problem to reduce cost and time for for the problems.

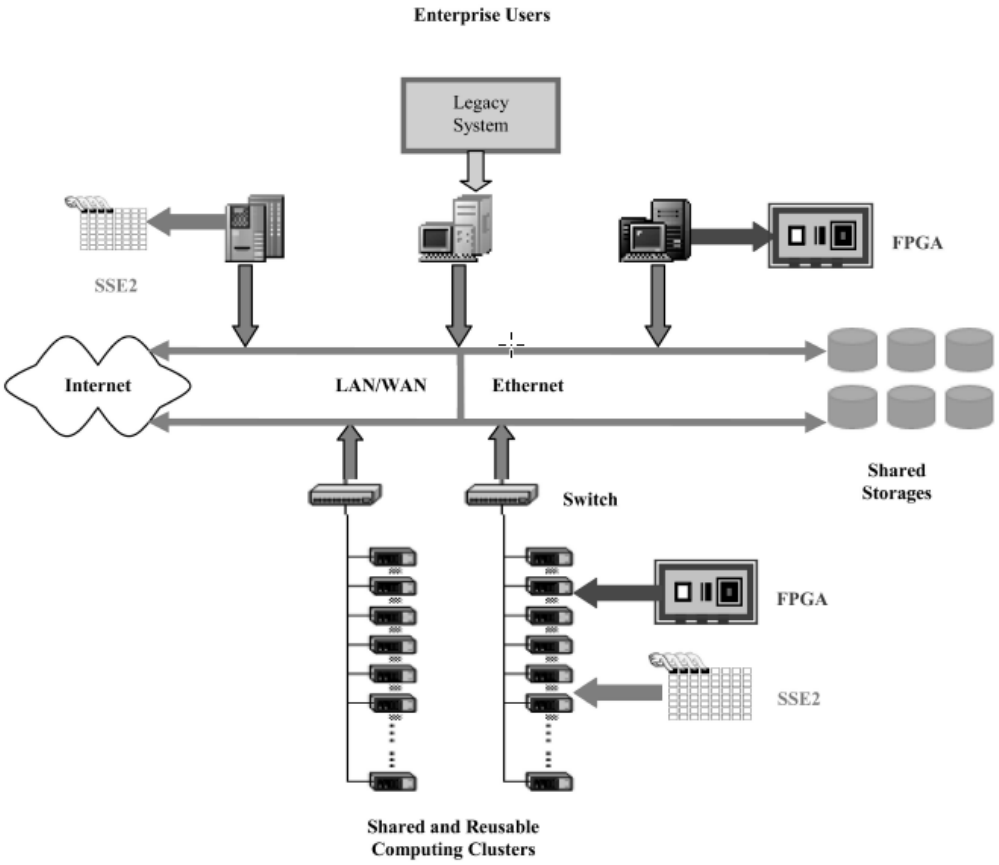


Figure 9: Heterogeneous computing system arc [16, Figure 1]

5 Conclusion

Timelogic accelerators

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