Building IaaS infrastructures on the AWS Cloud

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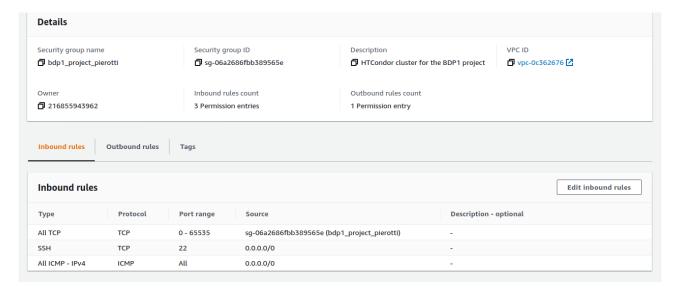
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1 Creation of an HTCondor Cluster for the Alignment of NGS Reads

The demonstrative IaaS infrastructure described in this project consists of an HTCondor cluster of three nodes. One of them acts as Master Node and the remaining two nodes as Worker Nodes. The infrastructure is easily expandable by replicating the Worker Node instances. The Master Node was not used also as a Worker Node since the performance benefits and cost savings would be marginal. Also, this avoids overloading the Master Node, on which the entire cluster depends. Finally, I implemented a shared storage space using the distributed file system NFS (Sun Microsystems, 1984) directly attached to the Master Node but available to all the Worker Nodes.

1.1 Initialization of the Instances on the AWS Cloud

I used the cloud service provider Amazon Web Services (AWS, https://aws.amazon.com/) for this project. Worker Nodes and the Master Node were both built on similar machines. For the Master Node, I chose the t2.medium instance type with a 50 Gb SSD as root storage. For the Worker Nodes, I chose the t2.large instance type with a 50 Gb SSD as root storage. The operating system adopted for both machine types is Ubuntu Server 18.04.4 LTS. The Master Node and the Worker Nodes were all instantiated in the same availability zone (us-east-1a) so that they would be able to communicate through private IPv4 addresses. The security group for the instances was configured as follows:



All the TCP ports were opened to the other members of the same security group since HTCondor daemons use a dynamically assigned port. I opened the ICMP port for accepting incoming ping requests for testing purposes. Since all the TCP ports were open, there was no need for setting up additional ports for NFS.

1.2 Configuration of the Master Node

The PS1 prompt of the Master Node was changed so to make the node easily identifiable from the command line.

```
ubuntu@bdp1-master-node:~$ echo $PS1
\[\e]0;\u@\h: \w\a\]${debian_chroot:+($debian_chroot)}\[\033[01;32m\
]\u@bdp1-master-node\[\033[00m\]:\[\033[01;34m\]\w\[\033[00m\]\$
```

HTCondor (Thain D., Tannenbaum T., and Livny M., 2005) was then installed with the following commands:

```
sudo su
wget -q0 - https://research.cs.wisc.edu/htcondor/ubuntu/HTCondor-Release.gpg.key | apt-key add - #
    import the gpg key of HTCondor
echo "deb http://research.cs.wisc.edu/htcondor/ubuntu/8.8/bionic bionic contrib" >> /etc/apt/sources.
    list # add the repository
echo "deb-src http://research.cs.wisc.edu/htcondor/ubuntu/8.8/bionic bionic contrib" >> /etc/apt/
    sources.list
apt update
apt install htcondor
systemctl start condor # start and enable the condor service
systemctl enable condor
```

The correct proceeding of the installation and the start of the condor service where checked with the following commands:

```
condor.service - Condor Distributed High-Throughput-Computing
  Loaded: loaded (/lib/systemd/system/condor.service; enabled; vendor preset: enabled)
  Active: active (running) since Tue 2020-06-16 10:31:25 UTC; 1min 16s ago
Main PID: 15225 (condor master)
  Status: "All daemons are responding"
  CGroup: /system.slice/condor.service
            -15225 /usr/sbin/condor_master -f
            -15266 condor_procd -A /var/run/condor/procd_pipe -L /var/log/condor/ProcLog -R 1000000 -S 60 -C 111
           Jun 16 10:31:25 ip-172-31-8-109 systemd[1]: Started Condor Distributed High-Throughput-Computing.
<mark>ubuntu@bdp1-master-node:</mark>~$ ps ax | grep condor
                                           master -f
                     0:00 condor_procd -A /var/run/co
                                                        <mark>dor</mark>/procd_pipe -L /var/log/<mark>condor</mark>/ProcLog -R 1000000 -S 60 -C 111
15266 ?
15268 ?
15286 pts/0
                     0:00 grep --color=auto
```

The following lines where appended at the end of the main HTCondor configuration file, located at /etc/condor_config:

```
# Master Node IP
CONDOR_HOST = <Master_Node_private_IP>
# Master Node config
DAEMON_LIST = COLLECTOR, MASTER, NEGOTIATOR, STARTD
```

Finally, the condor service was restarted with the following command:

```
sudo systemctl restart condor
```

I set up the NFS server on the Master Node. A new 100 Gb standard magnetic volume was created from the AWS interface and attached to the machine. A primary partiton was initialized on the volume using fdisk and an Ext4 file system was created onto it using mkfs.ext4. The /etc/fstab file was modified so that the machine would mount the volume automatically at boot under the newly created directory /data. The following line was appended to /etc/fstab:

The following commands were then issued, so to install the appropriate packages:

```
sudo apt install nfs-kernel-server
```

The following line was appended to the NFS configuration file /etc/exports:

```
/data 172.31.0.0/16(rw,sync,no_wdelay)
```

Finally, I set the owner and group of the shared folder to nobody:nogroup and I edited the permissions of the folder so to grant unlimited access to it:

```
sudo chown nobody:nogroup /data
sudo chmod 777 /data
```

The /data folder was so made available to all the Worker Nodes on the address range 172.31.0.0/16. This configuration does not pose a significant security risk since all the machines belong to the same Virtual Private Cloud (VPC). Only machines instantiated on the same VPC could access the exposed volume. Moreover, this configuration grants immediate access to the volume to additional Worker Nodes instantiated in the same VPC. I created a mock file on the /data folder so to be able to recognize the volume when mounted.

```
touch /data/this_is_a_shared_NFS_volume
```

1.3 Configuration of the Worker Nodes

I instantiated on AWS a new t2.large machine with Ubuntu 18.04 LTS. I changed the PS1 prompt so to make the node easily identifiable from the command line.

```
ubuntu@bpd1-worker-node:~$ echo $PS1
\[\e]0;\u@\h: \w\a\]${debian_chroot:+($debian_chroot)}\[\033[01;32m\]\u@bpd1-worker-node\[\033[00m\]:\[\
033[01;34m\]\w\[\033[00m\]\$
```

I installed HTCondor on this system with the same procedure used for the Master Node. Only the /etc/condor/condor_config file was configured differently, by appending the following lines to it:

```
# Master Node IP
CONDOR_HOST = <Master_Node_private_IP>

# Worker Node config
DAEMON_LIST = MASTER, STARTD

HOSTALLOW_READ = *
HOSTALLOW_WRITE = *
HOSTALLOW_ADMINISTRATOR = *
```

I granted to the Worker Node access to the shared NFS volume. The following command was issued to install the required packages and enable the respective services:

```
sudo apt install nfs-common
sudo systemctl start nfs-server
sudo systemctl enable nfs-server
```

A new directory was then created at /data using the mkdir command. The /etc/fstab file was edited by appending the following line, so that the shared volume would be automatically mounted at boot under the directory /data:

```
<Master_Node_private_IP>:/data /data nfs defaults 0 0
```

I verified that the shared volume was accessible from the Worker Node.

```
ubuntu@bpd1-worker-node:~$ ll /data
total 24
drwxrwxrwx 3 nobody nogroup 4096 Jun 17 07:16  /
drwxr-xr-x 24 root root 4096 Jun 17 06:46 ../
drwx----- 2 root root 16384 Jun 16 17:38 lost+found/
-rw-rw-r-- 1 ubuntu ubuntu 0 Jun 17 07:16 this_is_a_shared_NFS_volume
```

I installed the application BWA on the Worker Node:

```
sudo apt install -y bwa
```

I took a snapshot of the Worker Node virtual machine (AMI) through the AWS web interface. In this way, the Worker Nodes could be easily replicable when more computational power would be needed. It would be possible to deploy new Worker Nodes by simply instantiating new virtual machines from the AMI, without the need for manual configuration.

1.4 Submission of a Test Job to the HTCondor Cluster

I instantiated a new Worker Node from the relative AMI. Subsequently, I created a new volume through the AWS interface from a snapshot containing test data used during the BDP1 course (snap-09ee52d8038fb8094, BDP1_2020). This snapshot contained NGS reads from 3 different patients. Each patient had a folder with around 500 fasta files, with 1000 reads each. The new volume was mounted on the Master Node under the directory /data, replacing the empty volume used before. The /etc/fstab file was updated accordingly and the nfs-server service restarted. Finally, I tested that the new volume was accessible from the Worker Nodes.

```
ubuntu@bpd1-worker-node:~$ ll /data
total 28
drwxrwxrwx 4 root root 4096 Apr 26 13:38 //
drwxr-xr-x 24 root root 4096 Jun 17 06:46 ../
drwxr-xr-x 5 root root 4096 Apr 19 14:39 BDP1_2020/
drwx----- 2 root root 16384 Apr 26 09:37 lost+found/
```

The test job consisted in aligning ten fasta files (read_1.fa to read_10.fa from patient 1) to the human genome build hg19, also stored on the shared volume. I used the BWA alignment tool (Li H. and Durbin R. 2009) for the scope. This tool takes advantage of indexing the genome for speeding up the alignment of low-divergent reads. The index for the hg19 build was already in the volume snapshot, so there was no need to compute it from scratch. I copied the test fasta files from the shared volume to the home folder of the Master Node to simulate a real workflow. I created test job file alignment_test.job, with the following content:

```
######## The program that will be executed ######
Executable = alignment_test.py
readnum = $(Process)+1
arguments = read_$INT(readnum).fa
Input
      = read_$INT(readnum).fa
transfer_input_files = read_$INT(readnum).fa
= read_$INT(readnum).log
# will contain condor log
Output
      = read_$INT(readnum).out
# will contain the standard output
      = read_$INT(readnum).error
# will contain the standard error
########### condor control variables ############
should_transfer_files = YES
when_to_transfer_output = ON_EXIT
```

The script alignment_test.py called as executable in alignment_test.job was the following:

```
#!/usr/bin/python
import sys,os
from timeit import default_timer as timer
start = timer()
dbpath = "/data/BDP1_2020/hg19/"
dbname = "hg19bwaidx"
queryname = sys.argv[1]
out_name = queryname[:-3]
fafile = queryname
samfile = out_name + ".sam"
gzipfile = out_name + ".sam.gz"
saifile = out_name + ".sai"
md5file = out_name + ".md5"
print "Input: ", queryname
command = "bwa aln -t 1 " + dbpath + dbname + " " + fafile + " > " + saifile
print "launching command: " , command
os.system(command)
command = "bwa samse -n 10 " + dbpath + dbname + " " + saifile + " " + fafile + " > " + samfile
print "launching command: " , command
os.system(command)
# Checksums
print "Creating md5sums"
os.system("md5sum " + samfile + " > " + md5file)
print "gzipping out text file"
command = "gzip " + samfile
print "launching command: " , command
os.system(command)
# Transfer files to shared volume and clean the Output Sandbox
print "Moving files and clearing the Output Sandbox"
os.system("mv "+ gzipfile + " /data/outputs/"+ gzipfile)
os.system("mv "+ md5file + " /data/outputs/"+ md5file)
os.system("rm "+ saifile)
execution_time = timer() - start
print "Total execution time: " + str(execution_time)
print "exiting"
exit(0)
```

Ten instances of this test job were run on the cluster. The following outputs of condor_q and condor_status were recorded after submission:

```
ubuntu@bdp1-master-node:~$ condor_q
-- Schedd: ip-172-31-8-109.ec2.internal : <172.31.8.109:9618?... @ 06/18/20 08:03:52
OWNER BATCH NAME
                   SUBMITTED
                               DONE
                                             IDLE TOTAL JOB_IDS
                                      RUN
                   6/18 08:03
ubuntu ID: 24
                                                      10 24.0-9
Total for query: 10 jobs; 0 completed, 0 removed, 10 idle, 0 running, 0 held, 0 suspended
Total for ubuntu: 10 jobs; 0 completed, 0 removed, 10 idle, 0 running, 0 held, 0 suspended
Total for all users: 10 jobs; 0 completed, 0 removed, 10 idle, 0 running, 0 held, 0 suspended
ubuntu@bdp1-master-node:~$ condor_status
Name
                                                        State
                                                                   Activity LoadAv Mem
                                                 Arch
                                                 X86_64 Claimed
slot1@ip-172-31-8-22.ec2.internal
                                     LINUX
                                                                   Busy
                                                                              0.000 3979
slot2@ip-172-31-8-22.ec2.internal LINUX
                                                 X86_64 Claimed
                                                                   Busy
                                                                              0.000 3979
slot1@ip-172-31-14-66.ec2.internal LINUX
                                                 X86_64 Claimed
                                                                   Busy
                                                                              0.000 3979
slot2@ip-172-31-14-66.ec2.internal LINUX
                                                 X86_64 Claimed
                                                                   Busy
                                                                              0.000 3979
                Total Owner Claimed Unclaimed Matched Preempting Backfill Drain
  X86_64/LINUX
                                                      0
                                                                            0
                                                                                   0
         Total
                                                      0
                                                                                   Θ
```

The cluster was able to successfully complete the task. The test job produced the following output files:

```
ubuntu@bdp1-master-node:/data/outputs$ ll
total 408
drwxrwxrwx 2 nobody nogroup
                             4096 Jun 18 09:12
drwxrwxrwx 5 root
                             4096 Jun 17 15:11
                    root
-rw-r--r-- 1 nobody nogroup
                               45 Jun 18 08:57 read_1.md5
-rw-r--r-- 1 nobody nogroup
                               31 Jun 18 08:56
-rw-r--r-- 1 nobody nogroup
                               46 Jun 18 09:07
                                                read_10.md5
rw-r--r-- 1 nobody nogroup 55074 Jun 18 09:07
rw-r--r-- 1 nobody nogroup
                               45 Jun 18 08:57
                                                read_2.md5
-rw-r--r-- 1 nobody nogroup 41129 Jun 18 08:57
rw-r--r-- 1 nobody nogroup
                               45 Jun 18 08:57
                                                read_3.md5
rw-r--r-- 1 nobody nogroup
                               31 Jun 18 08:56
rw-r--r-- 1 nobody nogroup
                                                read_4.md5
                               45 Jun 18 08:57
-rw-r--r-- 1 nobody nogroup 54914 Jun 18 08:57
rw-r--r-- 1 nobody nogroup
                               45 Jun 18 09:03
                                                read_5.md5
rw-r--r-- 1 nobody nogroup 77299 Jun 18 09:03
rw-r--r-- 1 nobody nogroup
                               45 Jun 18 09:03
                                                read_6.md5
rw-r--r-- 1 nobody nogroup 55883 Jun 18 09:03
rw-r--r-- 1 nobody nogroup
                               45 Jun 18 09:00 read_7.md5
rw-r--r-- 1 nobody nogroup
                               31 Jun 18 08:58
rw-r--r-- 1 nobody nogroup
                               45 Jun 18 09:00 read_8.md5
rw-r--r-- 1 nobody nogroup
                               31 Jun 18 08:58
rw-r--r-- 1 nobody nogroup
                               45 Jun 18 09:07 read_9.md5
 rw-r--r-- 1 nobody nogroup 53760 Jun 18 09:07
```

The time required to complete the task on a single fasta file ranged from 62.77 to 422.54 seconds, with an average of 227.7 seconds.

```
ubuntu@bdp1-master-node:~$ cat read_*.out |grep "Total execution ti
me:"
Total execution time: 62.765912056
Total execution time: 417.533436775
Total execution time: 116.913583994
Total execution time: 66.0304908752
Total execution time: 115.42266202
Total execution time: 383.357795
Total execution time: 377.316680908
Total execution time: 158.487968922
Total execution time: 161.080944061
Total execution time: 422.54254508
```

1.5 Data Management Model

The general data management model followed was that of transferring the executables and the input fasta files using the HTCondor Input Sandbox. Those files are generally small and their transfer is not likely to overload the Master Node. Moreover, input data are likely to be uploaded dynamically to the cluster by users when new sequencing experiments are performed. This approach makes the upload of new input files to the cluster more straightforward. On the contrary, the large hg19 genome file and genome index files would be made available to the Worker Nodes through the shared NFS volume. The Output Sandbox will contain the condor log, the standard output, and the standard error. These files are really small and need to be immediately available to the submitter for inspecting the proceeding of the job. The aligned reads will instead be compressed and put in the shared volume, to avoid moving large data on the Output Sandbox.

2 Creation of a Container Image for the Alignment of Next-Generation Sequencing reads

I built a containerized version of the BWA application using Docker (https://www.docker.com/). A container image for the BWA application was already available on DockerHub (biocontainers/bwa), but for educational purposes, a new image was built from scratch. The Ubuntu Docker image was used as a base. The local Docker image bwa was built from the following Dockerfile:

```
FROM ubuntu
RUN apt update
RUN apt install -y bwa
RUN apt install -y python
COPY ./alignment_test_docker.py alignment_test_docker.py
```

I run the container using a bind-mount for the /data volume and starting an interactive shell.

```
docker run -v /data:/data -ti bwa /bin/bash
```

I modified the script alignment_test.py to omit the final data movement to the shared volume, and renamed it alignment_test_docker.py. Inside the container, I run the following command to align a sample fasta file:

```
./alignment_test_docker.py read_1.fa
```

The application ran successfully, producing the following output in 213.33 seconds (the container was run on a Ubuntu Server 18.04.4 LTS t2.large AWS virtual machine):

```
oot@871e3f6d9c26:/# cp /data/BDP1_2020/hg19/Patients/patient1/read_1.fa read_1.fa
root@871e3f6d9c26:/# ./alignment_test_docker.py read_1.fa
Input: read_1.fa
launching command: bwa aln -t 1 /data/BDP1_2020/hg19/hg19bwaidx read_1.fa > read_1.sai
[bwa_aln] 17bp reads: max_diff = 2
[bwa_aln] 38bp reads: max_diff = 3
[bwa_aln] 64bp reads: max_diff = 4
[bwa_aln] 93bp reads: max_diff
[bwa_aln] 124bp reads: max_diff = 6
[bwa_aln] 157bp reads: max_diff = 7
[bwa_aln] 190bp reads: max_diff = 8
[bwa_aln] 225bp reads: max_diff = 9
[bwa_aln_core] calculate SA coordinate... 0.21 sec
[bwa_aln_core] write to the disk... 0.00 sec
[bwa_aln_core] 1000 sequences have been processed.
[main] Version: 0.7.17-r1188
[main] CMD: bwa aln -t 1 /data/BDP1_2020/hg19/hg19bwaidx read_1.fa
[main] Real time: 121.035 sec; CPU: 4.582 sec
launching command:  bwa samse -n 10 /data/BDP1_2020/hg19/hg19bwaidx read_1.sai read_1.fa > read_1.sam
[bwa_aln_core] convert to sequence coordinate... 4.28 sec
[bwa_aln_core] refine gapped alignments... 1.13 sec
[bwa_aln_core] print alignments... 0.00 sec
[bwa_aln_core] 1000 sequences have been processed.
[main] Version: 0.7.17-r1188
[main] CMD: bwa samse -n 10 /data/BDP1_2020/hg19/hg19bwaidx read_1.sai read_1.fa
[main] Real time: 92.240 sec; CPU: 5.416 sec
Creating md5sums
gzipping out text file
launching command: gzip read_1.sam
Total execution time: 213.335064888
exiting
```

3 Evaluation of the Resources Needed for Solving a Real Use-Case

A plausible non-trivial use-case that can be addressed using the HTCondor cluster developed in Section 1 is the alignment of a large number of fasta files deriving from a Next-Generation Sequencing (NGS) run to the human reference genome assembly hg19.

The sequencing platform manufacturer Illumina recommends aiming for a coverage of at least 30x in a human Whole-Genome Sequencing (WGS) experiment (https://www.illumina.com/science/technology/next-generation-sequencing/plan-experiments/coverage.html). Given that the human genome has a size of about 3.3 billion base pairs, aiming for a 30x coverage would result in a raw output from the sequencer of at least 99 billion base pairs. To be on the safe side, I considered a raw output of 100 billion base pairs per patient in the following cost estimate. A single NGS read of an Illumina MySeq sequencer can have a length of up to 300 base pairs (https://www.illumina.com/systems/sequencing-platforms/miseq.html). Here I considered a read length of 150 base pairs, which is recommended by the manufacturer for a WGS experiment (https://www.illumina.com/science/technology/next-generation-sequencing/plan-experiments/read-length.html). Under these assumptions, almost 667 million reads would need to be aligned for a single patient. This amounts to about 667000 fasta files of 1000 reads each.

I roughly determined the time needed for aligning a fasta file containing 1000 reads of 150 base pairs each to the hg19 genome assembly in Section 1. This corresponds to 227.3 seconds on a single core of the AWS t2.large machine. Completing the alignment of the data produced in a single WGS experiment would thus require 151609100 seconds of CPU time.

The cluster described in this project consists of one Master Node and two Worker Nodes. The Worker Nodes have two cores each, so the cluster can employ a total of four cores. In this scenario, completing the task would require 37902275 seconds, which corresponds to 1 year 2 months, and 11 days. Of course, this running time is not acceptable for a real-world application.

A more feasible approach would involve replicating the Worker Nodes to have more computational power. This is possible since the alignment of a read is independent of the alignment of other reads, and so the task can be parallelized effectively. For instance, the task could be completed in less than nine days using a cluster of 1 Master Node and 100 Worker Nodes. This will result in a cluster with a capacity of 3 patients per month.

4 Expected Costs

The scenario considered in this costs breakdown consists of aligning the output of 3 WGS experiments per month using the AWS EC2 system with On-Demand pricing on the US East N. Virginia availability zone, on a Linux system (https://aws.amazon.com/pricing). To date (May 2020) the t2.large machine costs \$ 0.0928 per hour, and the cluster will require 100 of them for the Worker Nodes. The t2.medium machine costs \$ 0.0464 per hour, and the cluster will require just 1 of them for the Master Node. With an expected time needed for the task of 9 days, the costs of computation for one patient will amount to \$ 1963. Storage on general-purpose SSD EBS devices costs \$ 0.1 per Gb per month. A 1 Tb disk can be used for storing the hg19 genome and index, as well as the reads of the patients. Therefore, storage will have a cost of \$ 100 per month. The total monthly cost will amount to \$ 5991. Note that costs for data movements in and out of the AWS system have been omitted. Moreover, in a real use-case scenario, a strict security policy for dealing with medical data should be also enforced, according to local regulations. This will likely increase the costs and the overhead required.

5 Application of Concepts from the BDP2 Course to the Task

In light of the topics covered in the BDP2 course, some improvements to the architecture described in this project seem possible. For starters, it would seem reasonable to implement autoscaling of the number of worker nodes in the HTCondor cluster. Another approach could be that of using a containerized system like a Kubernetes cluster (EKS or self-provisioned) or a Docker Swarm for running the application. Finally, an additional possible solution is to use a serverless computing system like AWS Lambda or OpenFaaS (possibly on a self-scaling Kubernetes cluster).

Instead of using a shared NFS volume mounted on the Master Node, it could be more logical to store data on an AWS S3 bucket. This would reduce the strain on the vital Master Node and make the data more easily accessible from outside of the cluster.

6 References

Li H. and Durbin R. (2009) Fast and accurate short read alignment with Burrows-Wheeler Transform. Bioinformatics, 25:1754-60. [PMID: 19451168]

Douglas Thain, Todd Tannenbaum, and Miron Livny, "Distributed Computing in Practice: The Condor Experience" Concurrency and Computation: Practice and Experience, Vol. 17, No. 2-4, pages 323-356, February-April, 2005.

Docker:

https://www.docker.com/

Recommended coverage for a WGS experiment:

https://www.illumina.com/science/technology/next-generation-sequencing/plan-experiments/coverage.html

Read length for a WGS experiment:

https://www.illumina.com/science/technology/next-generation-sequencing/plan-experiments/read-

length.html

https://www.illumina.com/systems/sequencing-platforms/miseq.html

AWS pricing:

https://aws.amazon.com/pricing