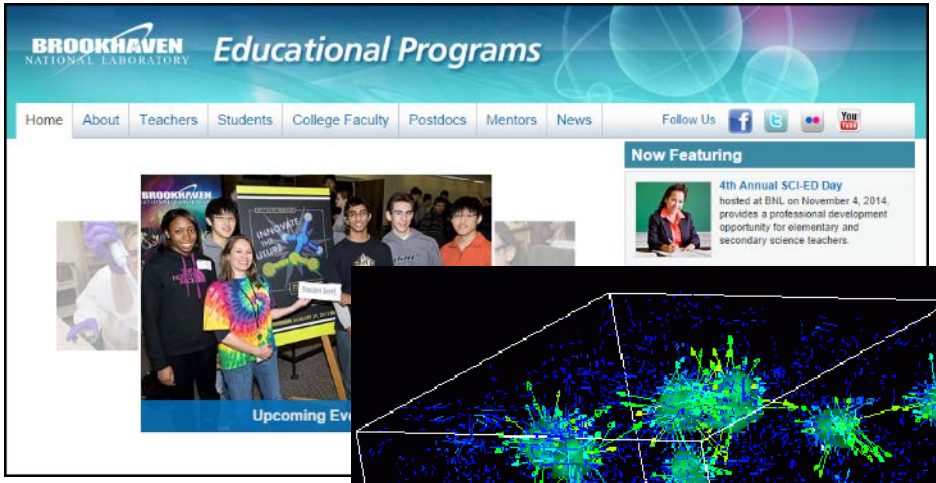

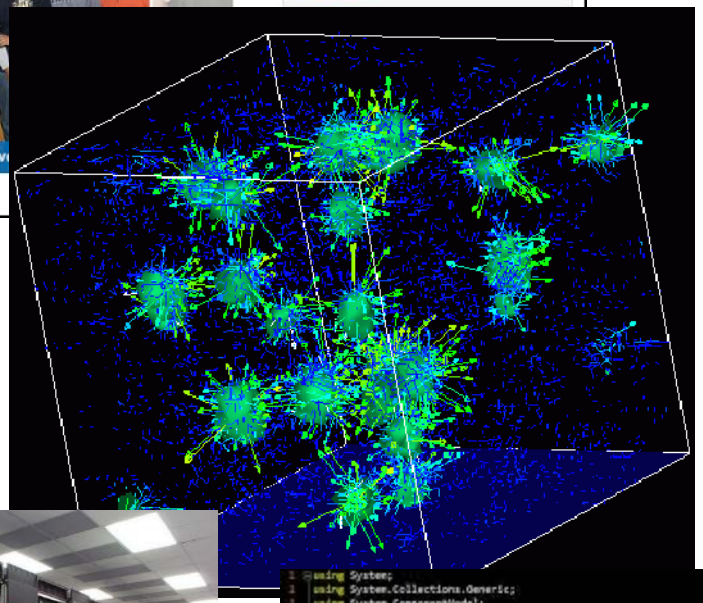

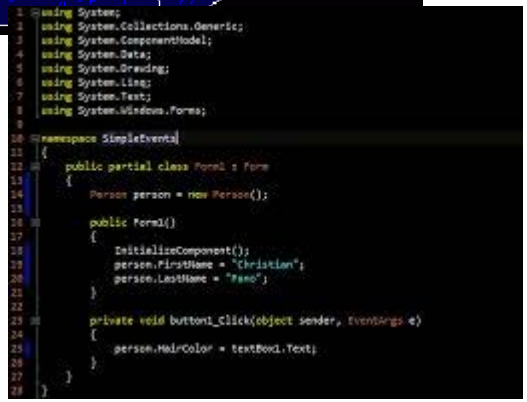

Survey of Scientific Computing (SciComp 301)

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Session 18
Computational Biology, Earth Science

Session Goals

- Gain an appreciation for a **suffix sort** to find the **longest repeated substring** (LRSS) in a sequence
  - Consider the use of this algorithm in the realm of **bioinformatics** and genetic sequence alignment
  - Consider interesting research questions that stem from using the algorithm to **explore DNA**
- Assess the value of considering in DNA, not just the single longest repeated substring, but also the most (and least) ***frequently*** repeated substrings of a given length

What is the Longest Repeated Substring?

input string

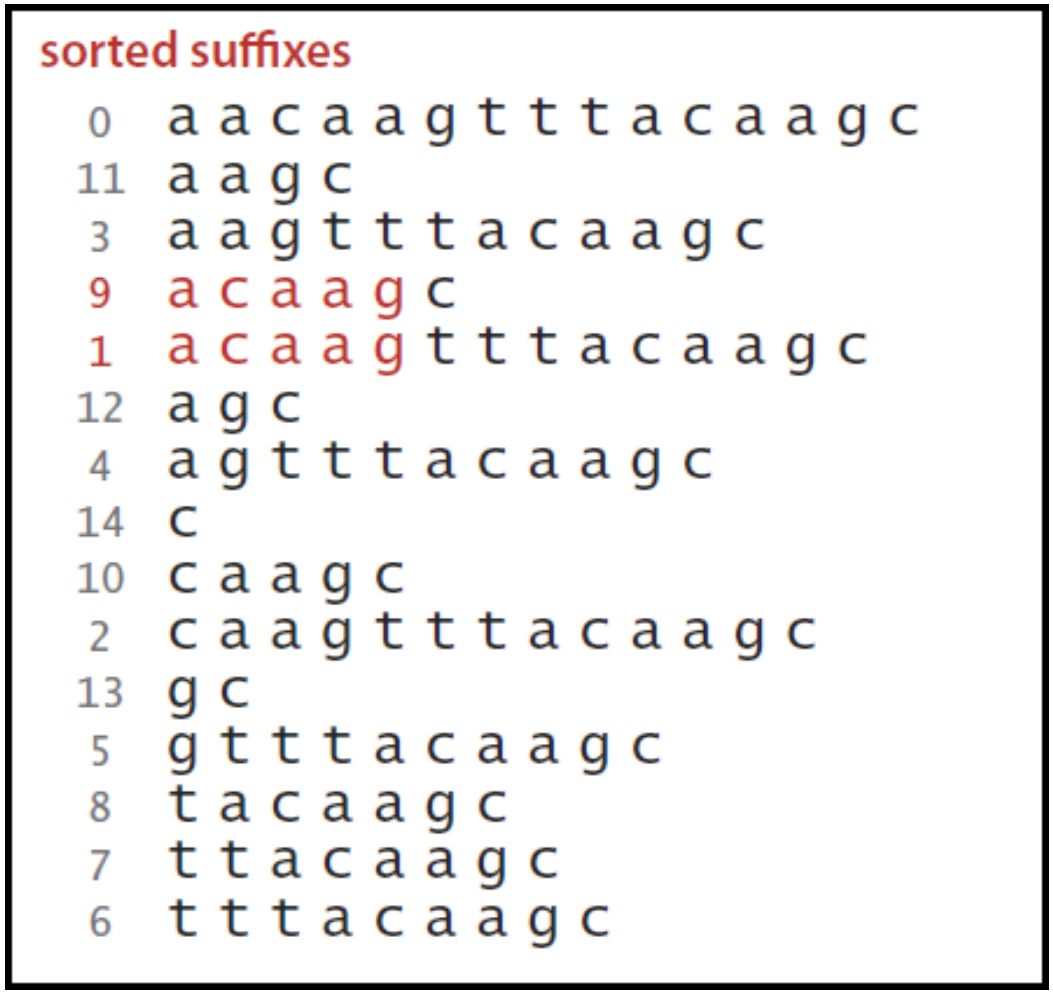
```
  0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
  a a c a a g t t t a c a a g c
```

Step 1 - Form the Suffixes array

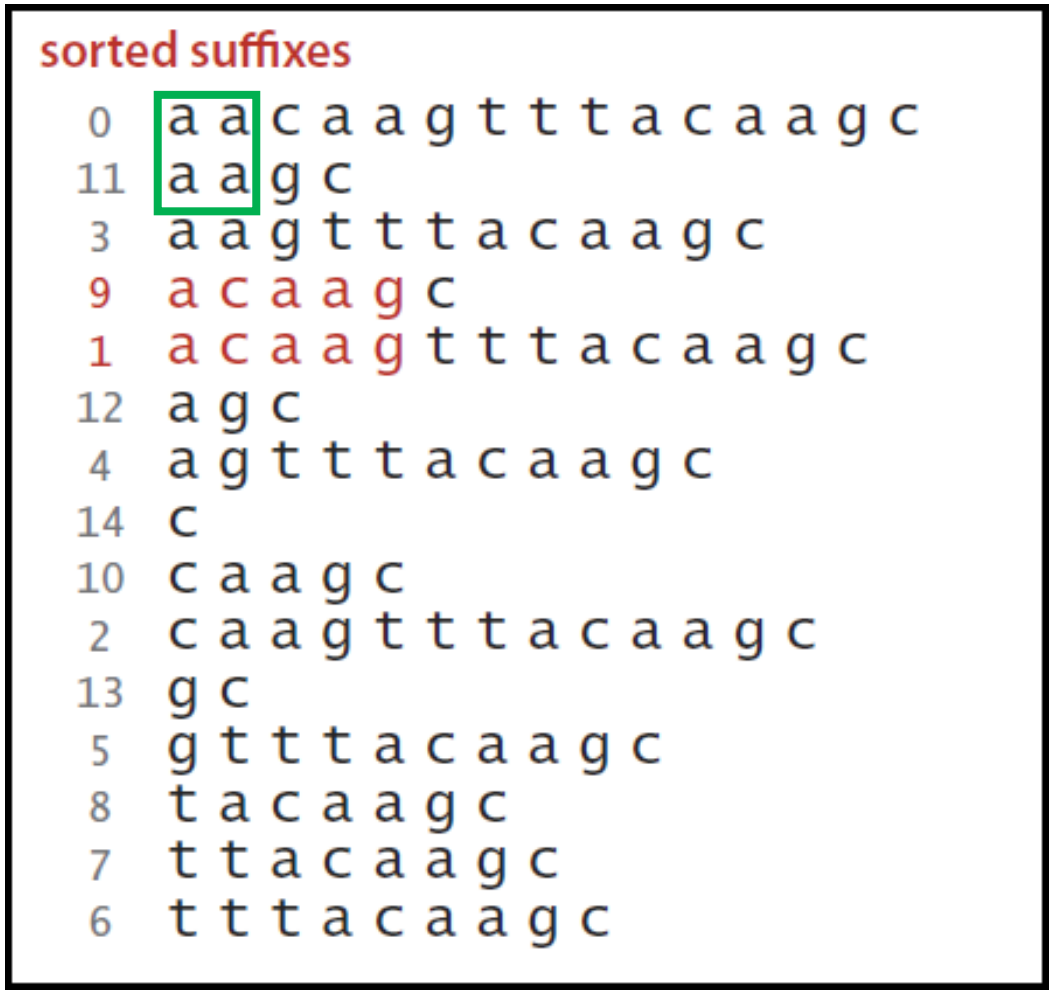
suffixes

```
 0  a a c a a g t t t a c a a g c
 1  a c a a g t t t a c a a g c
 2  c a a g t t t a c a a g c
 3  a a g t t t a c a a g c
 4  a g t t t a c a a g c
 5  g t t t a c a a g c
 6  t t t a c a a g c
 7  t t a c a a g c
 8  t a c a a g c
 9  a c a a g c
10  c a a g c
11  a a g c
12  a g c
13  g c
14  c
```

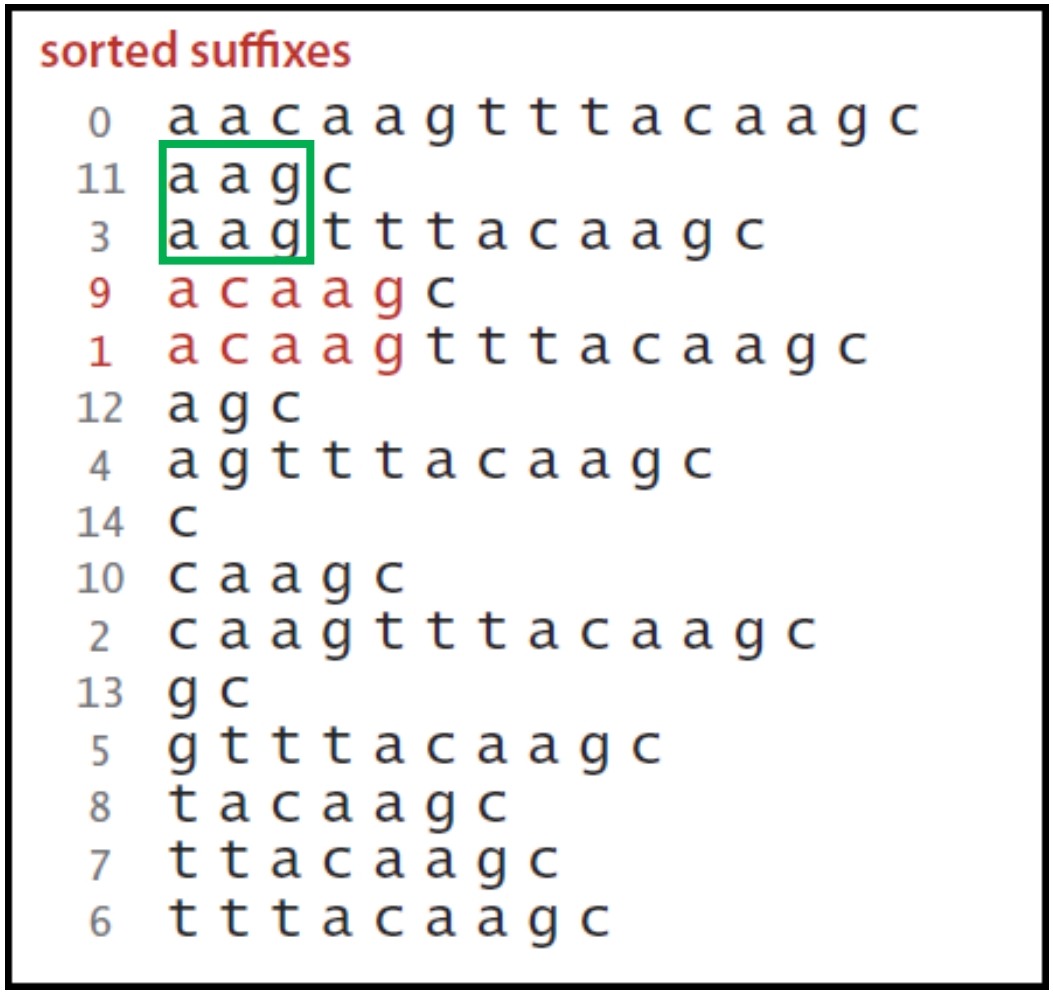
Step 2 – Sort the Suffixes array



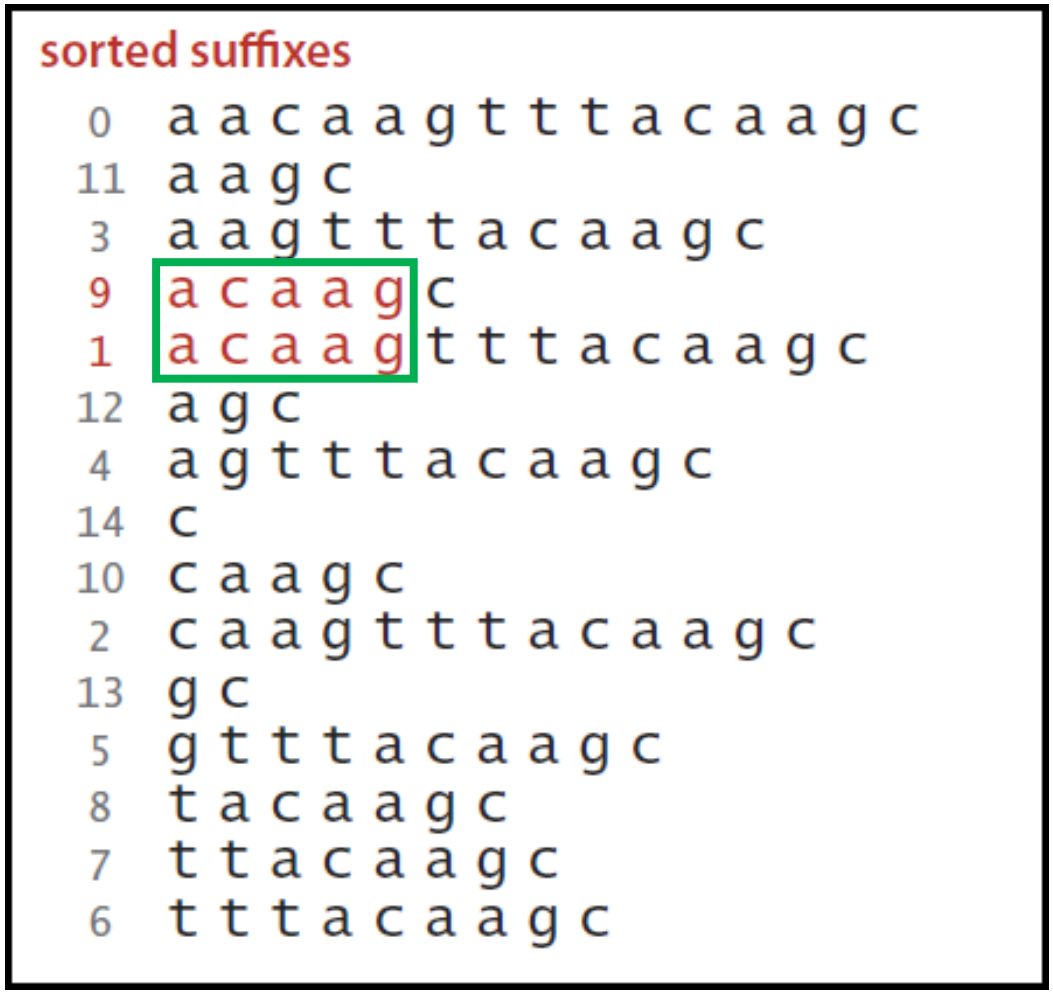
Step 3 – Scan the Suffixes array



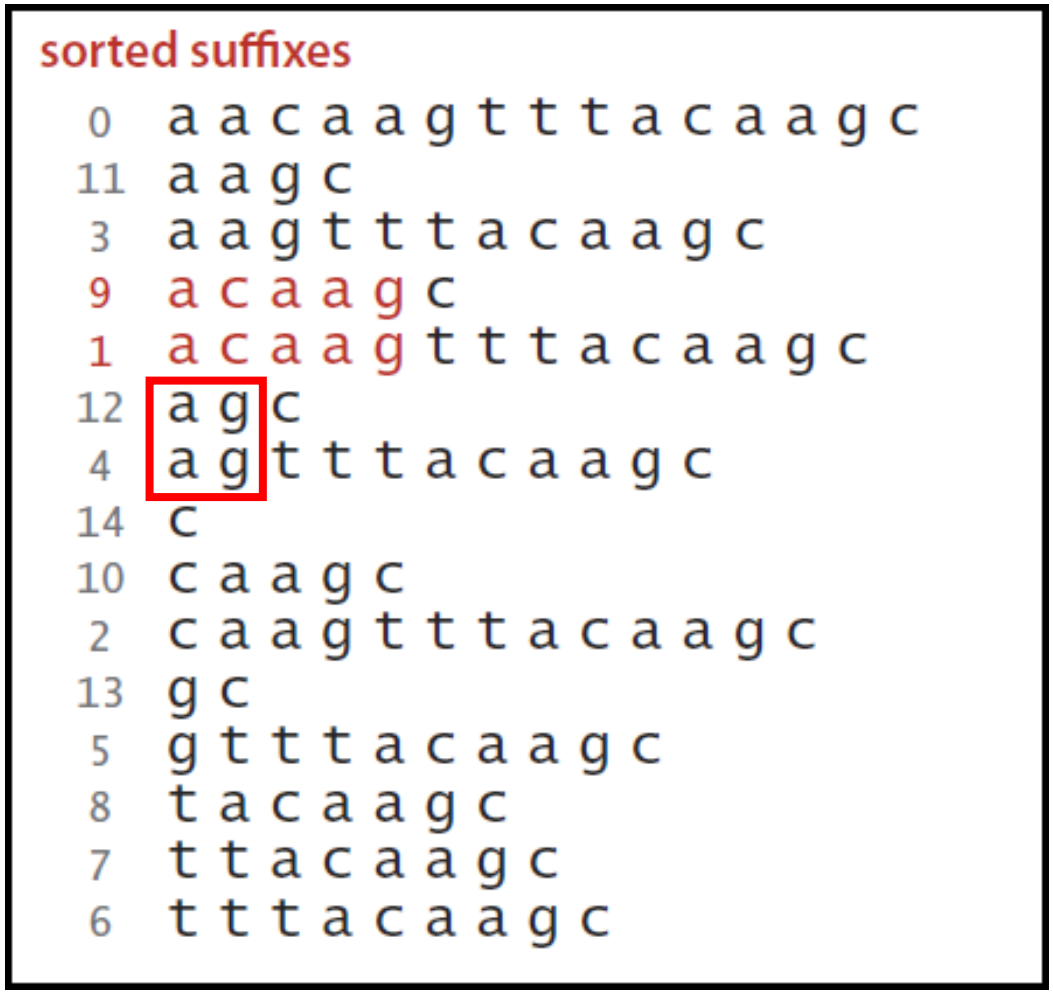
Step 3 – Scan the Suffixes array



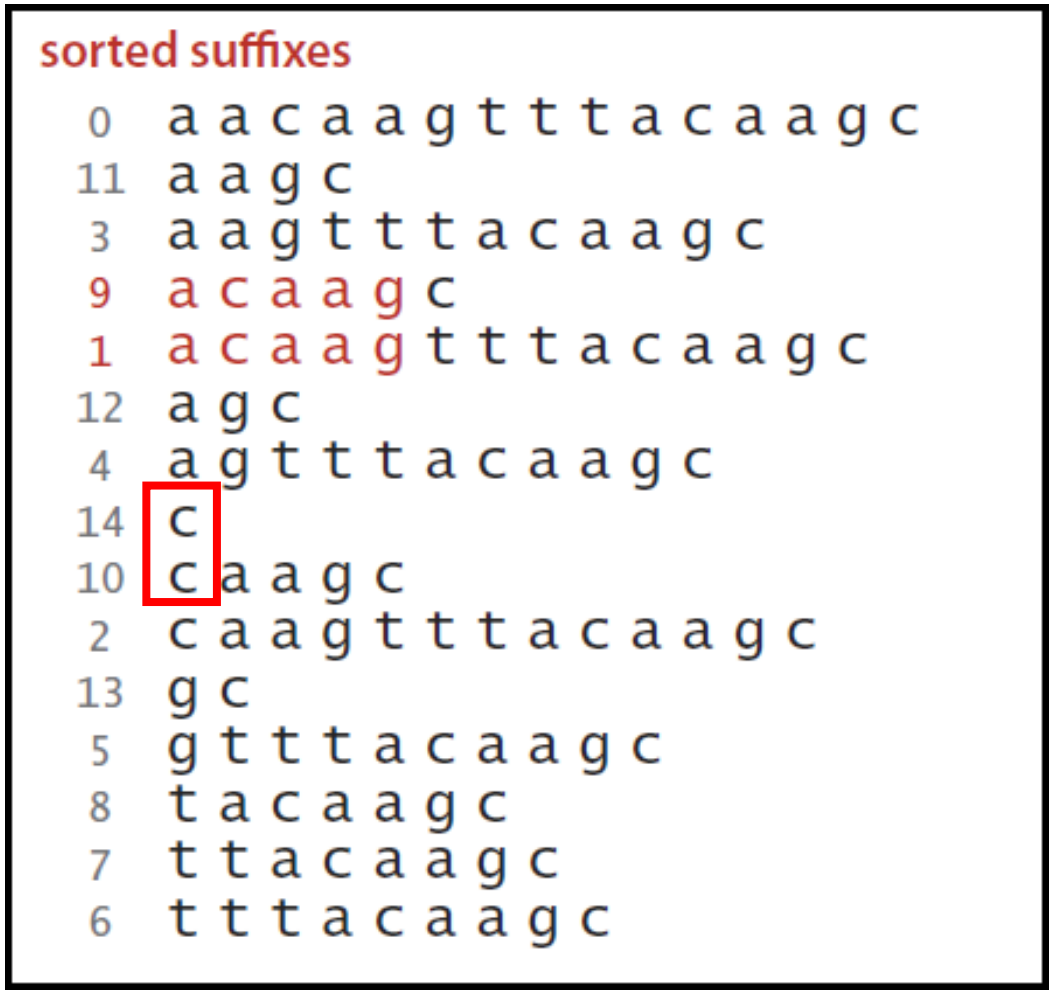
Step 3 – Scan the Suffixes array



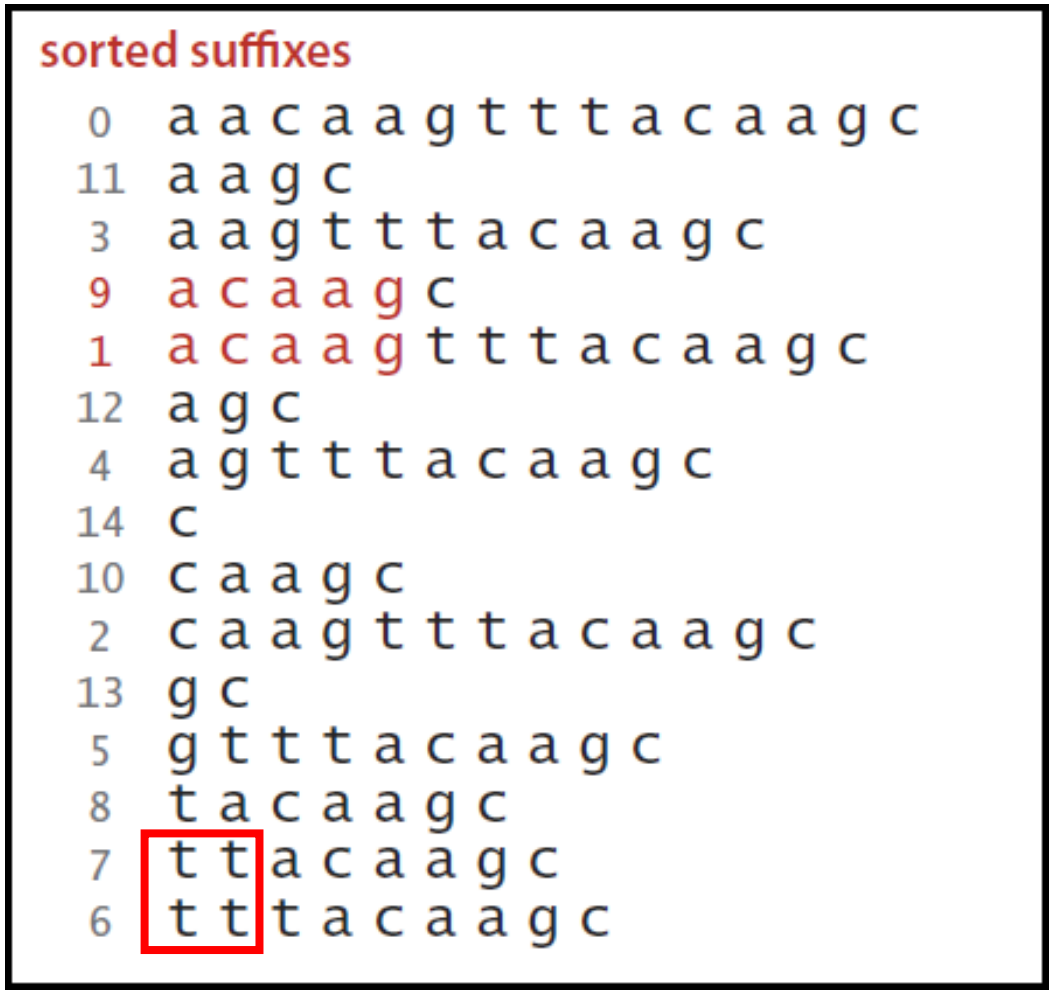
Step 3 – Scan the Suffixes array



Step 3 – Scan the Suffixes array

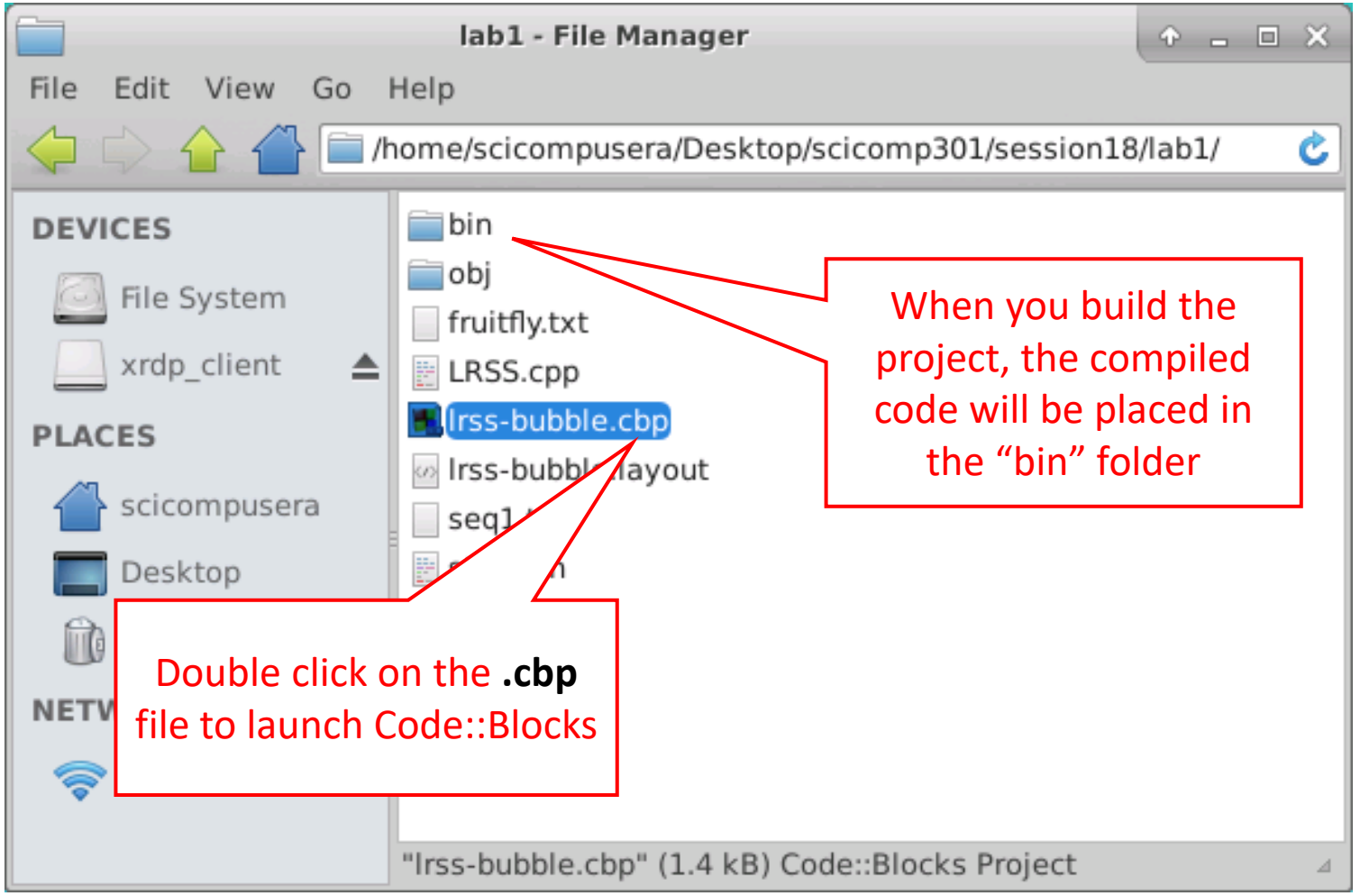


Step 3 – Scan the Suffixes array



Step 3 – Scan the Suffixes array

Open Lab 1 – Longest Repeated Substring



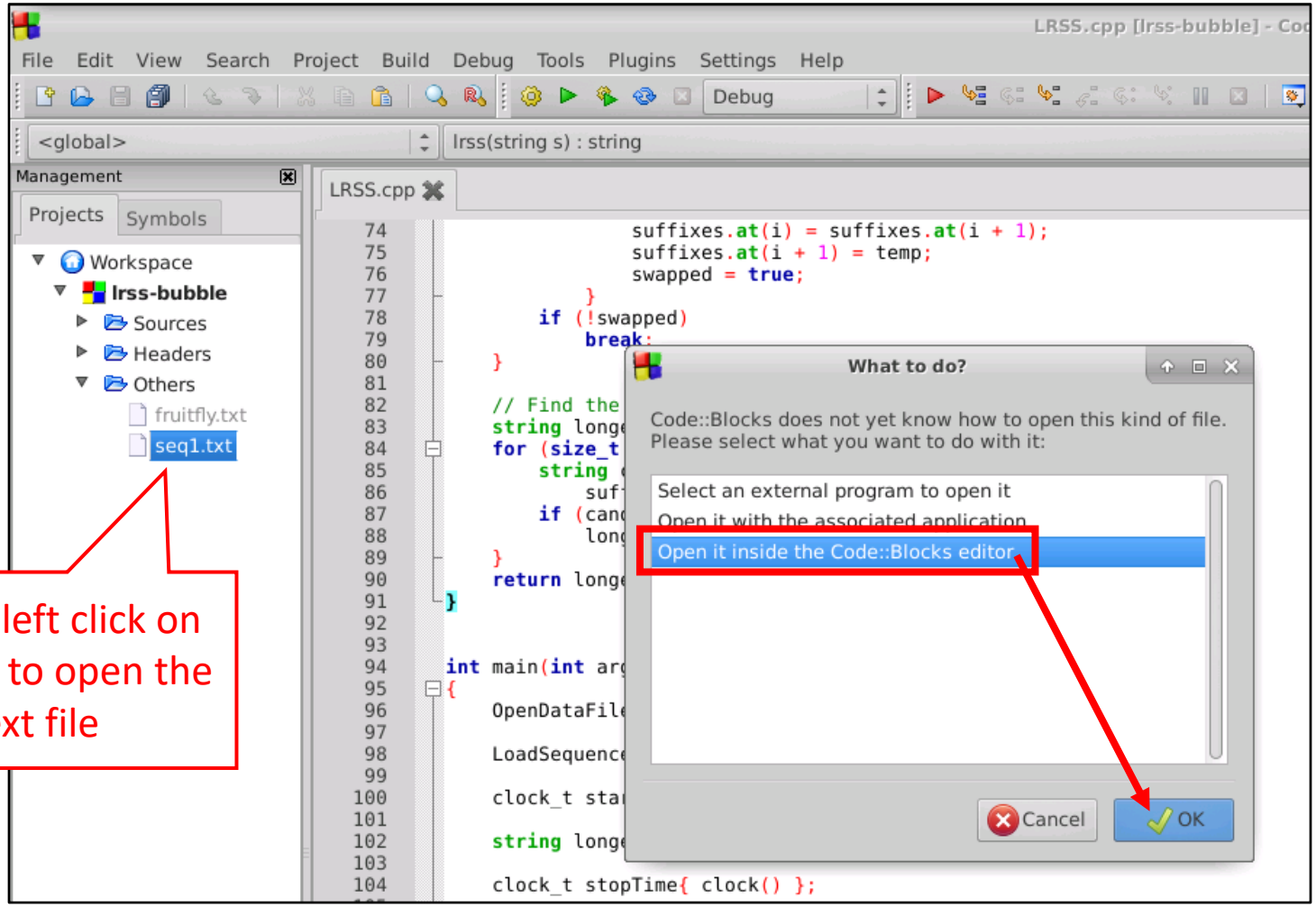
View Lab 1 – Longest Repeated Substring

```
 94  int main(int argc, char *argv[])
 95  {
 96      OpenDataFile(argc, argv);
 97
 98      LoadSequence();
 99
100      clock_t startTime{ clock() };
101
102      string longest = lrss(*seq);
103
104      clock_t stopTime{ clock() };
105
106      cout << "The longest repeated substring in "
107          << "\"" << filename << "\" is: "
108          << longest << endl << endl;
109
110      double totalTime{ ((double)(stopTime - startTime)
111          / CLOCKS_PER_SEC) * 1000 };
112
113      cout.imbue(std::locale(""));
114      cout << "Total run time (ms): "
115          << totalTime << endl;
116
117      CloseDataFile();
118
119      return 0;
120  }
```

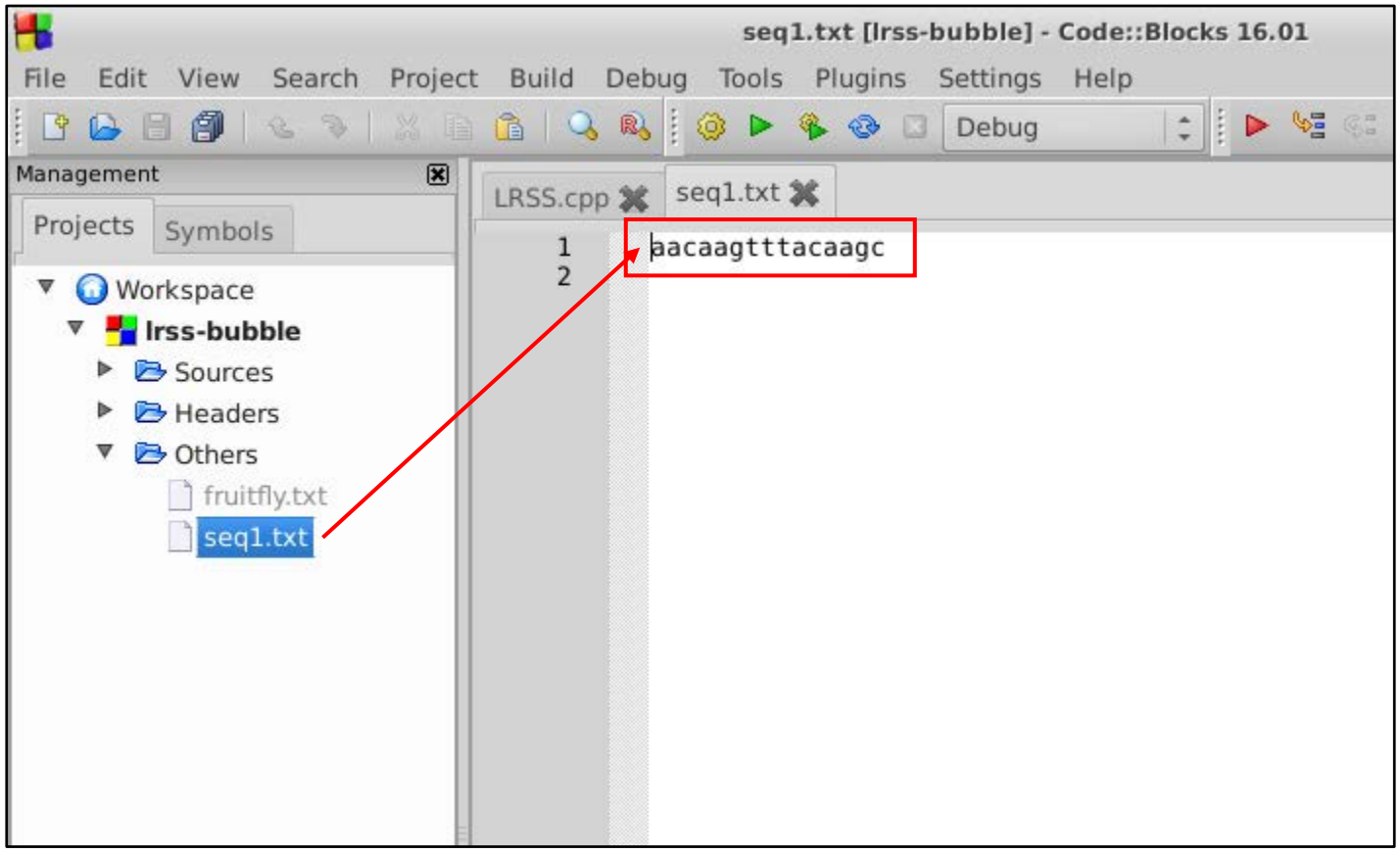
```
string lrss(string s)
{
    // Create the suffix array
    vector<string> suffixes(s.size());
    for (size_t i{}; i < suffixes.size(); ++i)
        suffixes.at(i) = s.substr(i, s.size() - i);

    // Bubble sort the suffix array
    while (true) {
        bool swapped = false;
        for (size_t i{}; i < suffixes.size() - 1;++i)
            if (suffixes.at(i) > suffixes.at(i + 1)) {
                string temp = suffixes.at(i);
                suffixes.at(i) = suffixes.at(i + 1);
                suffixes.at(i + 1) = temp;
                swapped = true;
            }
        if (!swapped)
            break;
    }

    // Find the longest repeated substring (lrss)
    string longest{};
    for (size_t i{}; i < suffixes.size() - 1;++i) {
        string candidate = match(suffixes.at(i),
            suffixes.at(i + 1));
        if (candidate.size() > longest.size())
            longest = candidate;
    }
    return longest;
}
```

Lab 1
Longest Repeated Substring

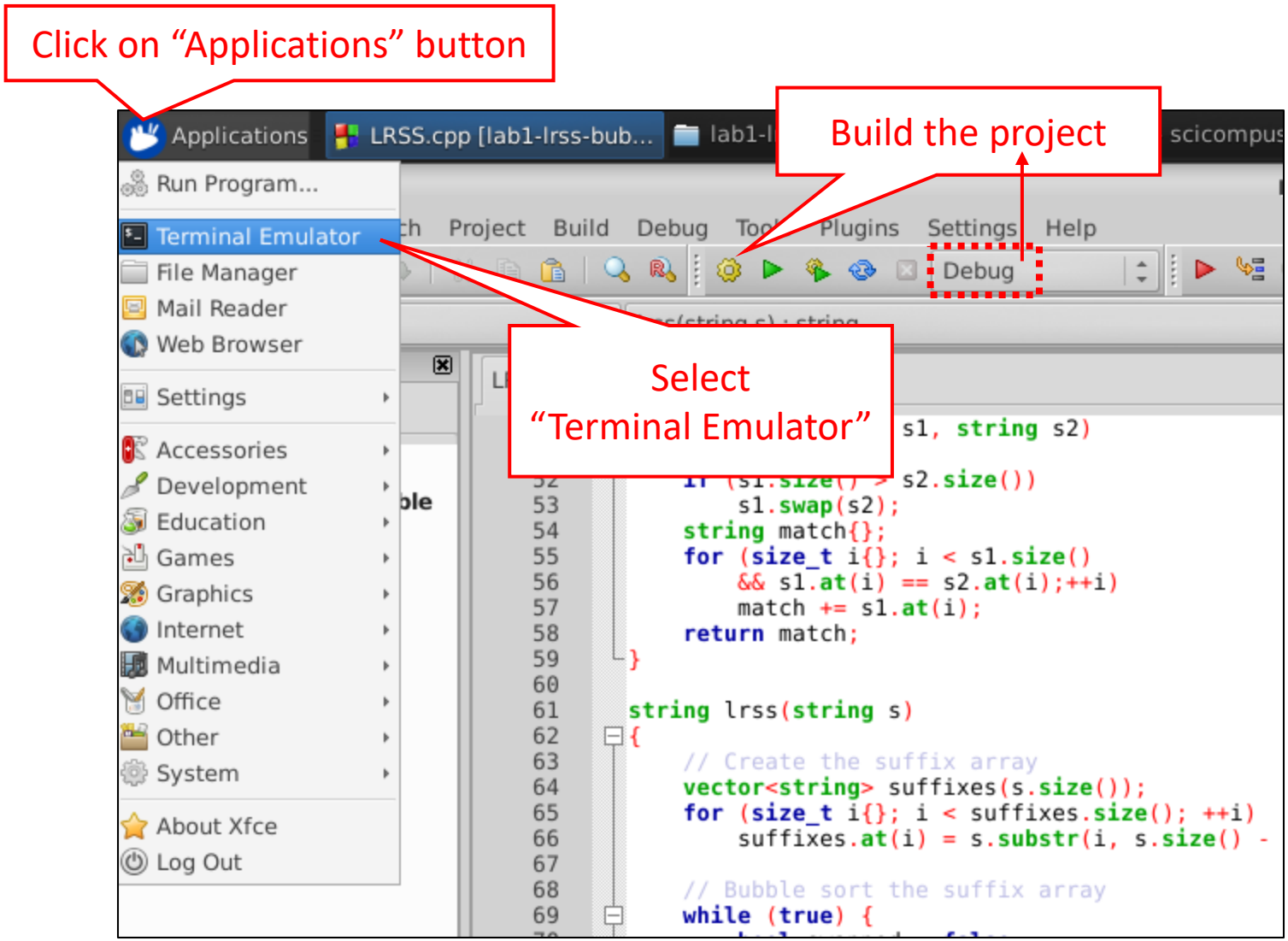
View Lab 1 – Longest Repeated Substring



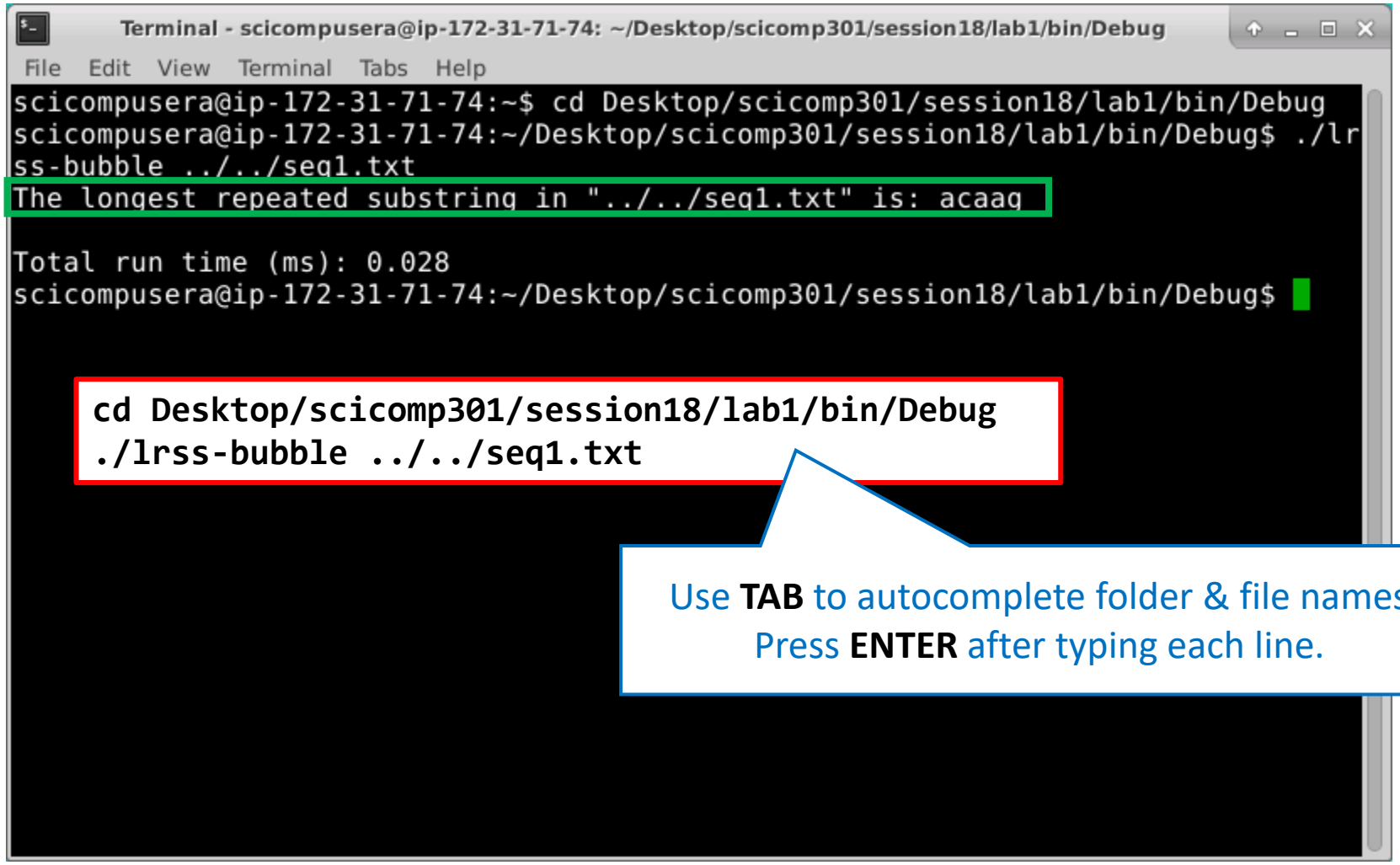
View Lab 1 – Longest Repeated Substring



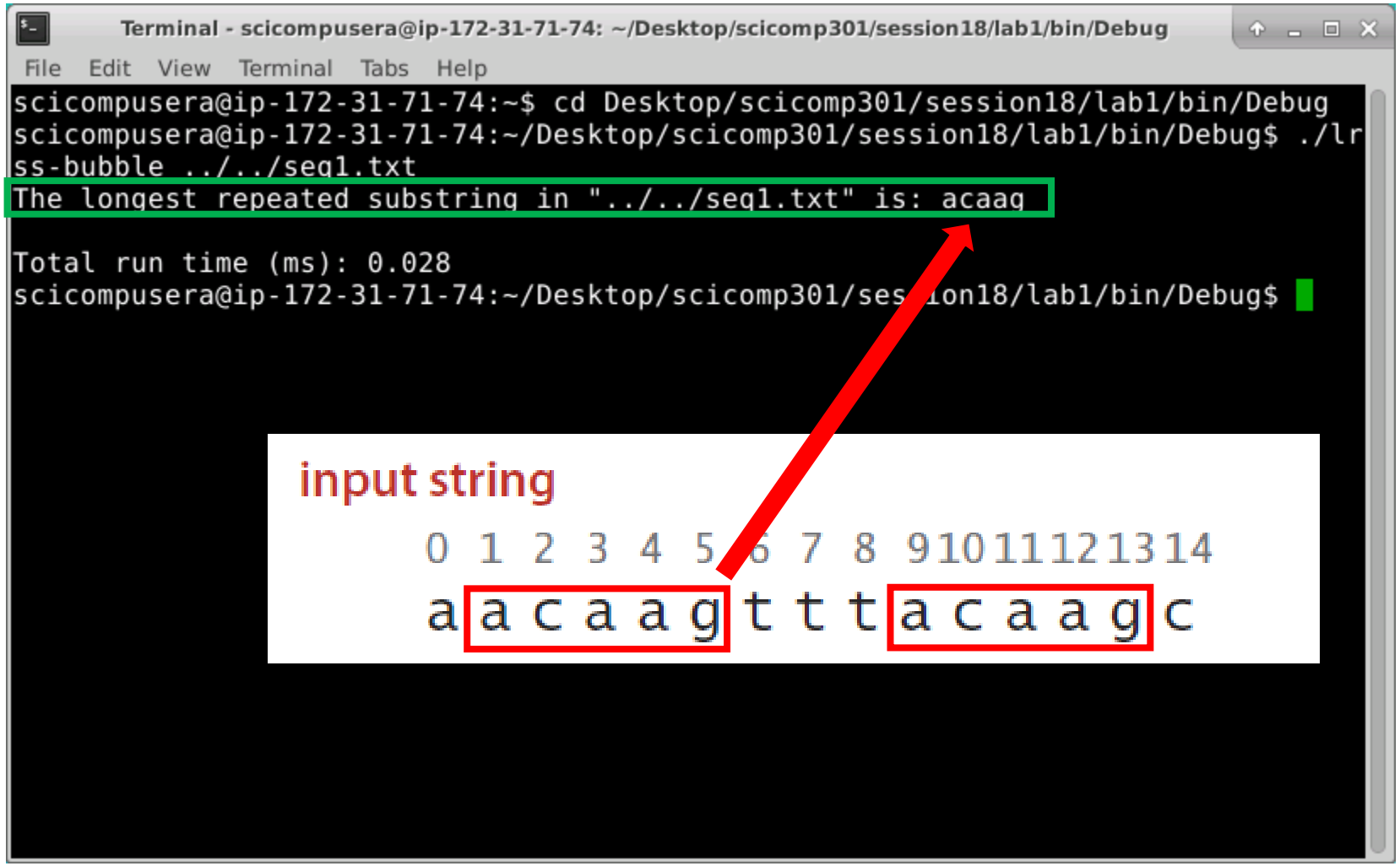
Build Lab 1 – Longest Repeated Substring



Run Lab 1 – Longest Repeated Substring

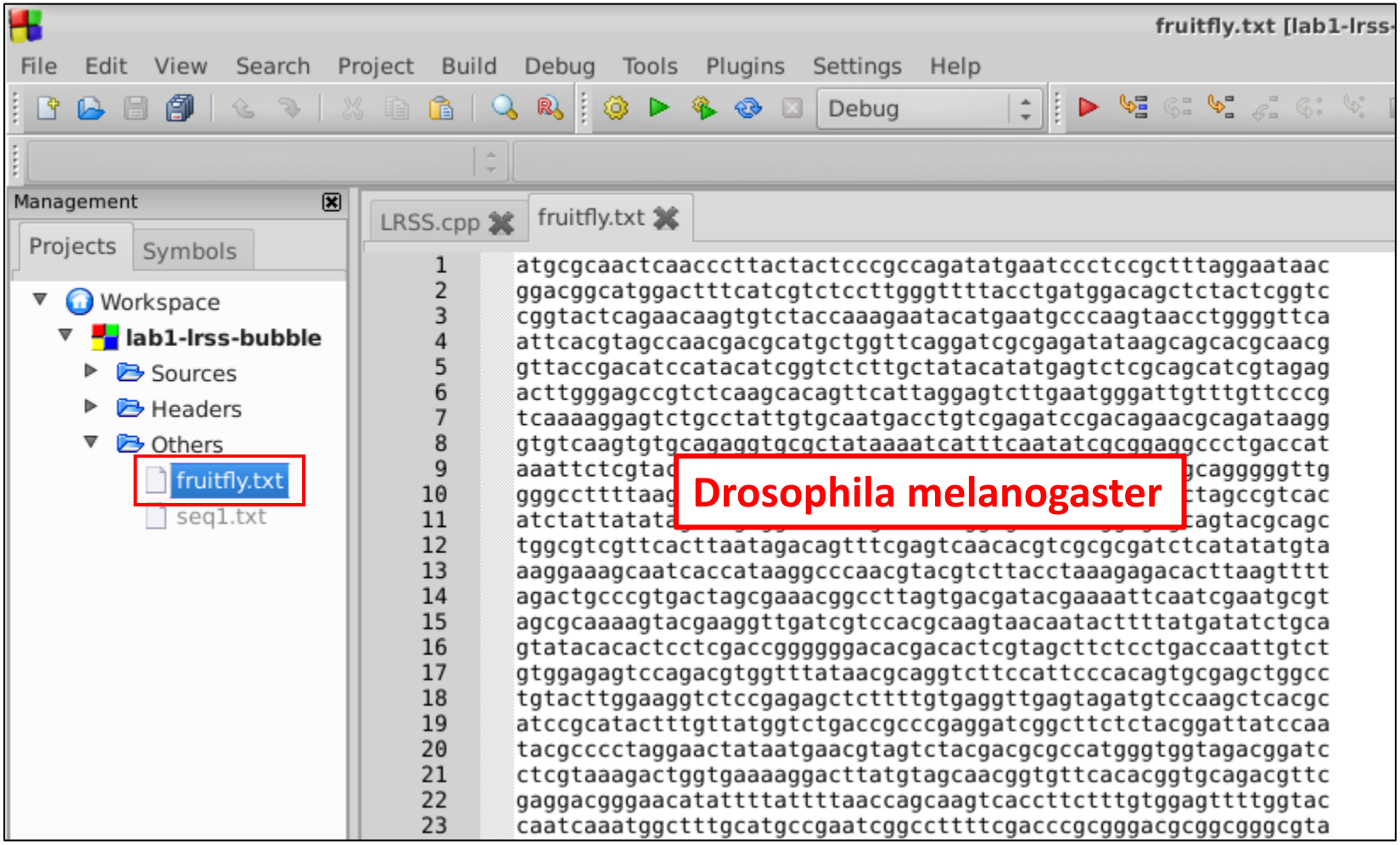


Check Lab 1 – Longest Repeated Substring

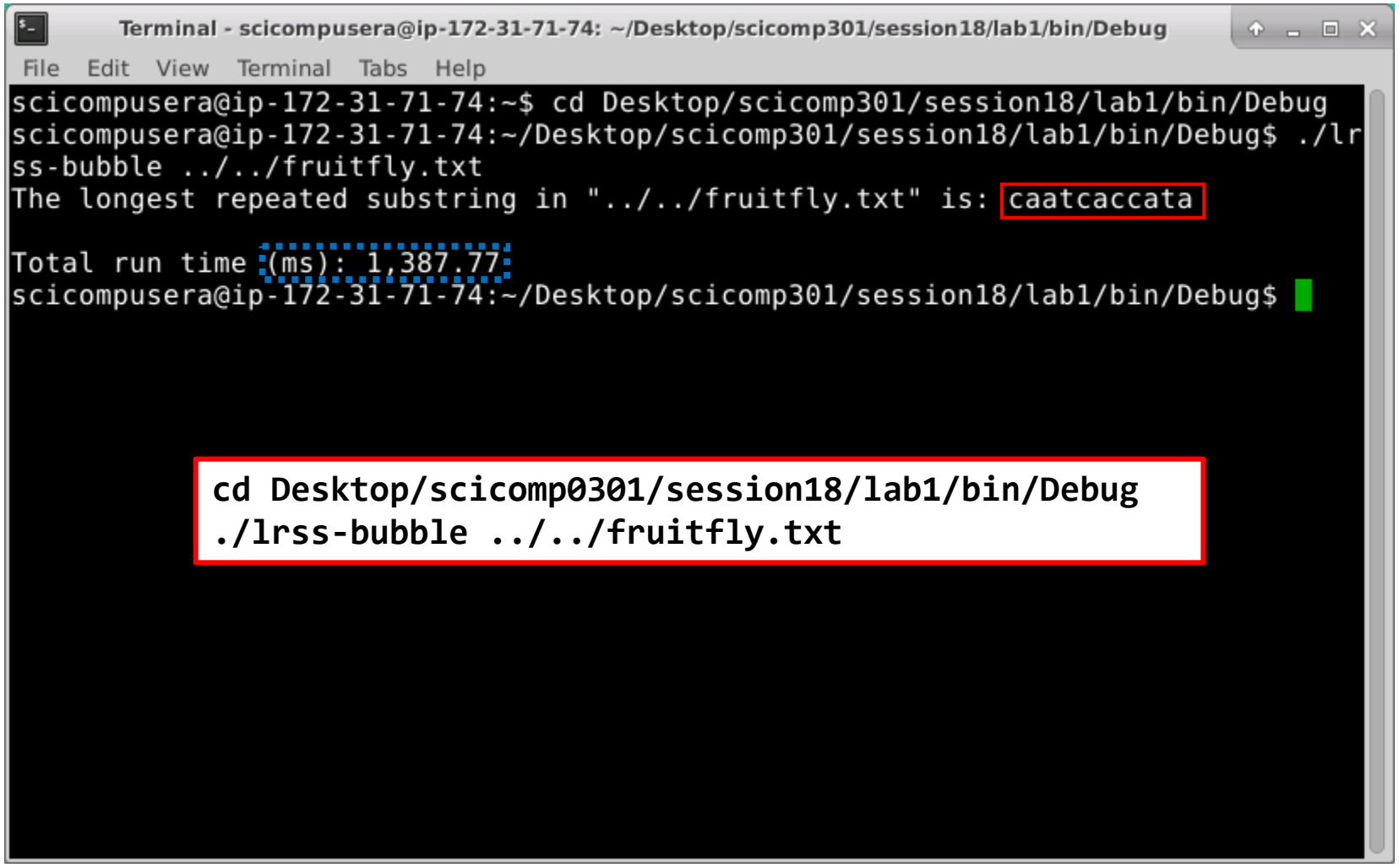


View Lab 1 – Longest Repeated Substring

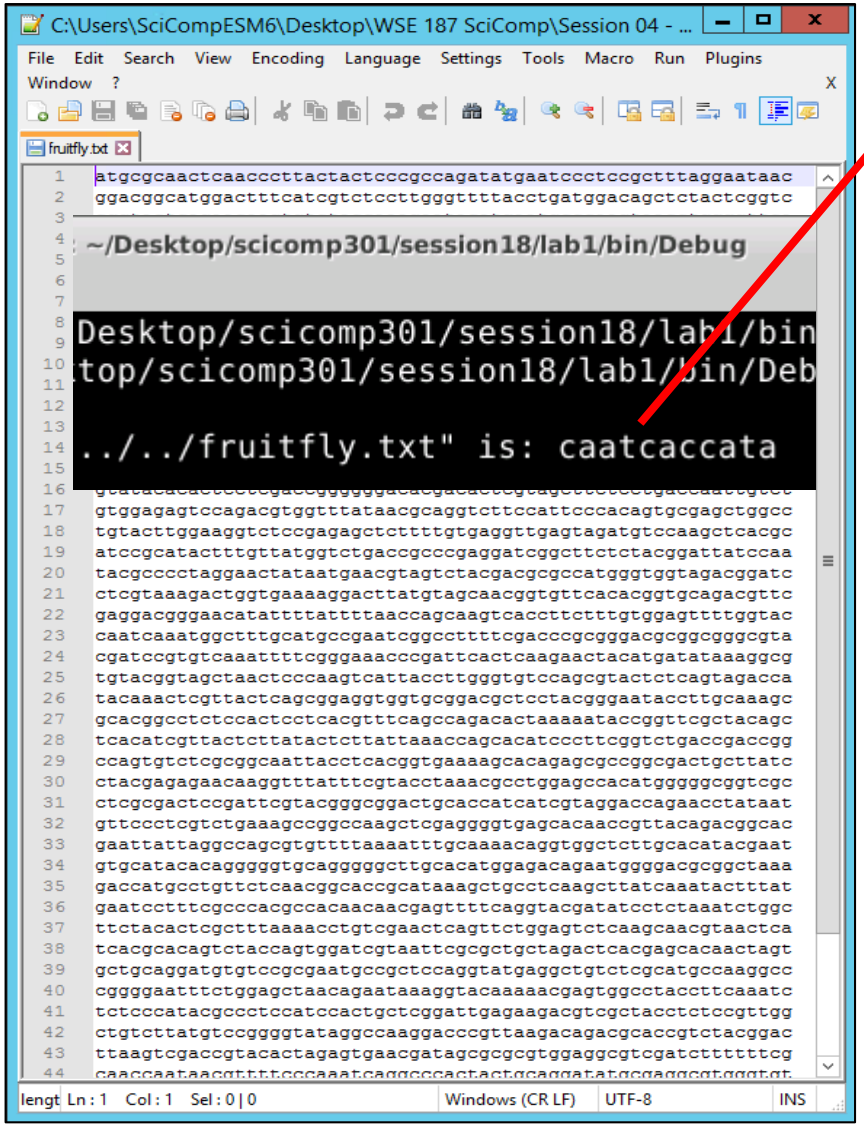
http://www.fruitfly.org/sequence/download.html

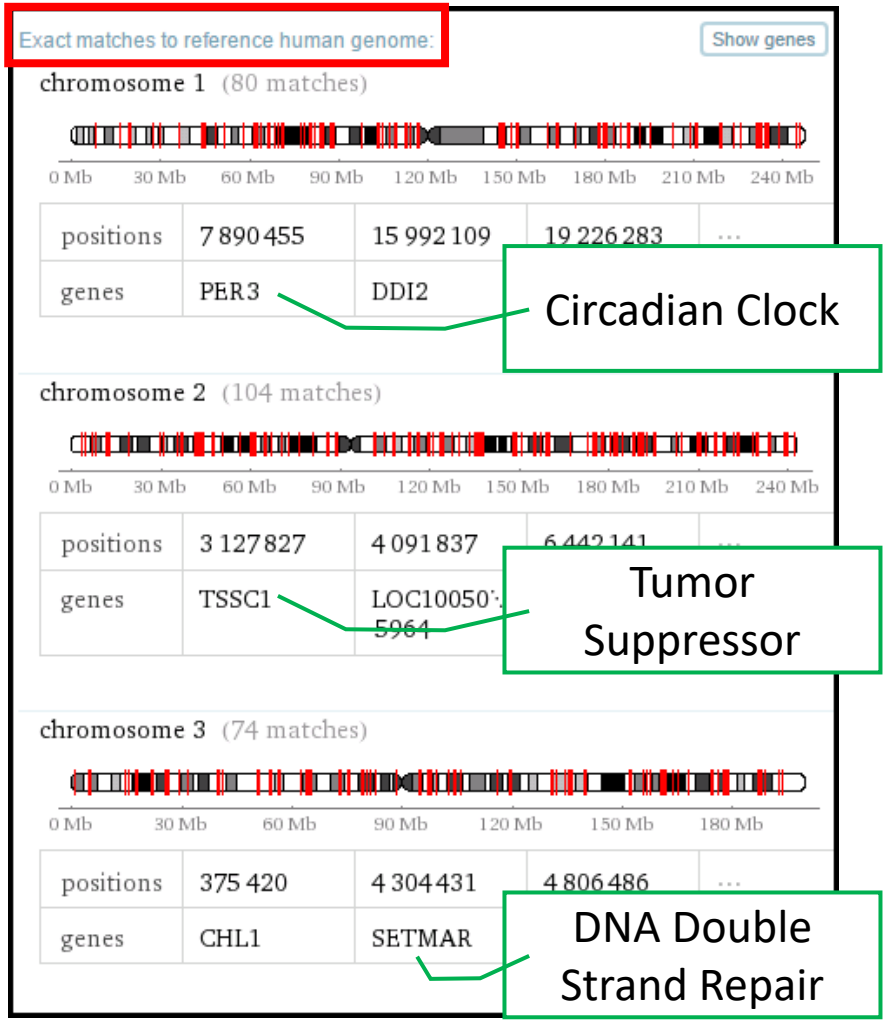


Run Lab 1 – Longest Repeated Substring



http://www.wolframalpha.com/input/?i=CAATCACCATA





The Bubble Sort Algorithm

- The Bubble Sort is not very efficient because it can "move" only **one element** only **one slot** during **one pass**
  - The code spends a lot of time scanning through the array **reconfirming** that no swaps are needed between ***adjacent*** elements, just the same as it likely had confirmed that very fact on the previous pass through the array
  - Therefore it wastes time constantly **rediscovering** that two elements are already in the right order – this is the culprit
- Wouldn't it be better if we could move an item with a ***higher*** value ***farther*** to the **end** of the array in **one big jump**, rather than only a single slot each pass?
  - And can we stop wasting time scanning through groups of elements we have **already proven to be in order**?

The Quicksort Algorithm

- Invented by **Tony Hoare** in 1959, **Quicksort** is an efficient sorting algorithm that uses a **divide & conquer** strategy to overcome the problems of Bubble Sort
  - On each pass, a portion of the vector is **split** according to a **pivot** value – those elements with a value **<=** the **pivot** are swapped with those elements with a value **>** the **pivot**
  - This act of partitioning separates the current section of the vector into a "**left**" portion having **smaller** values than the pivot, and a "**right**" portion having **larger** values than the pivot
- The **left** and **right** portions are then sorted (**conquered**) independently, and each portion is further split (**divided**) into smaller and smaller sized sub-portions, until the whole vector is eventually sorted

Open Lab 2 – LRSS Quicksort

Bubble Sort

```
while (true) {
    bool swapped = false;
    for (size_t i{}; i < suffixes.size() - 1;++i)
        if (suffixes.at(i) > suffixes.at(i + 1)) {
            string temp = suffixes.at(i);
            suffixes.at(i) = suffixes.at(i + 1);
            suffixes.at(i + 1) = temp;
            swapped = true;
        }
    if (!swapped)
        break;
}
```

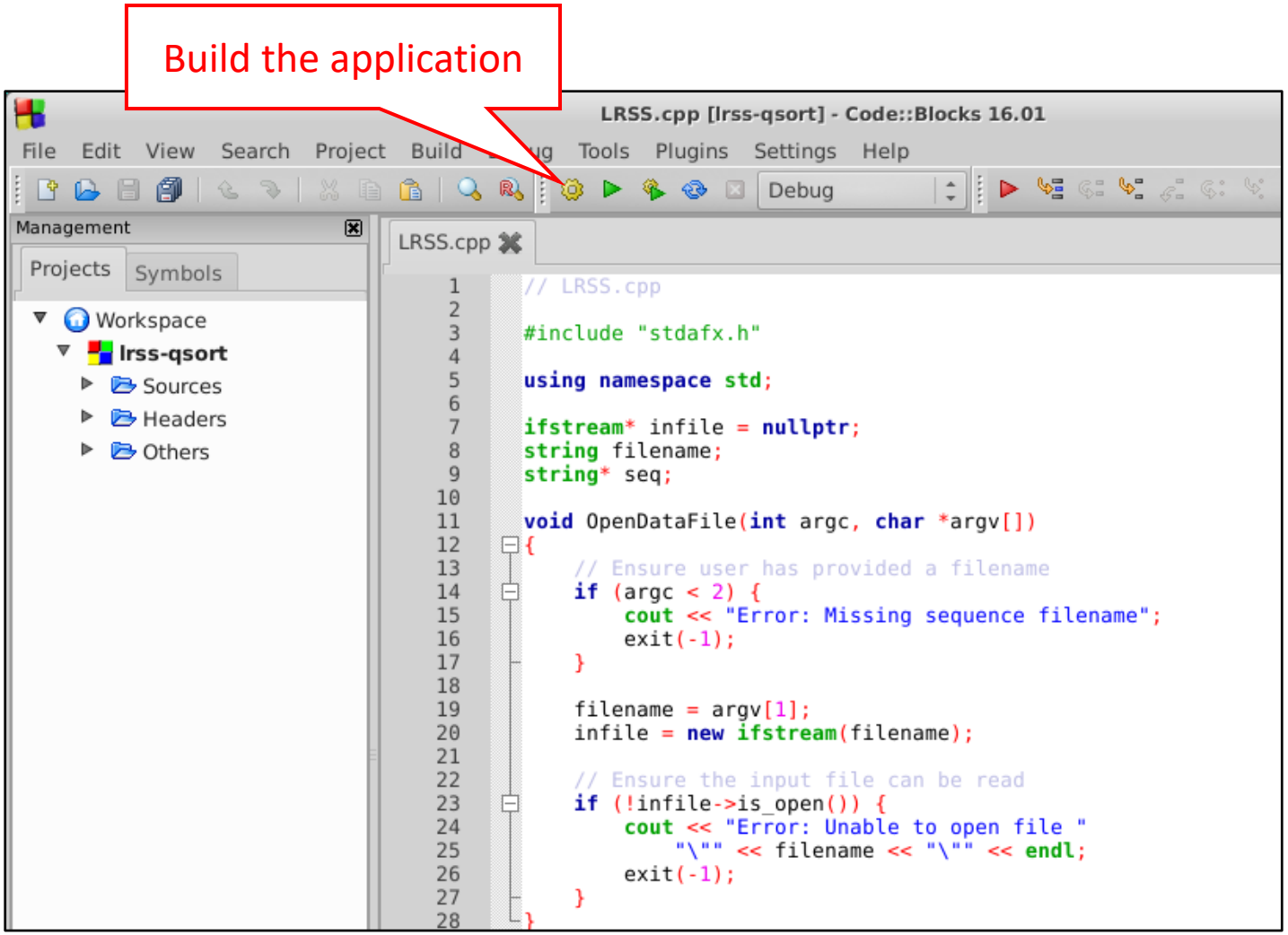
Quicksort requires longer and more complex code than bubble sort.

Is it worth it?

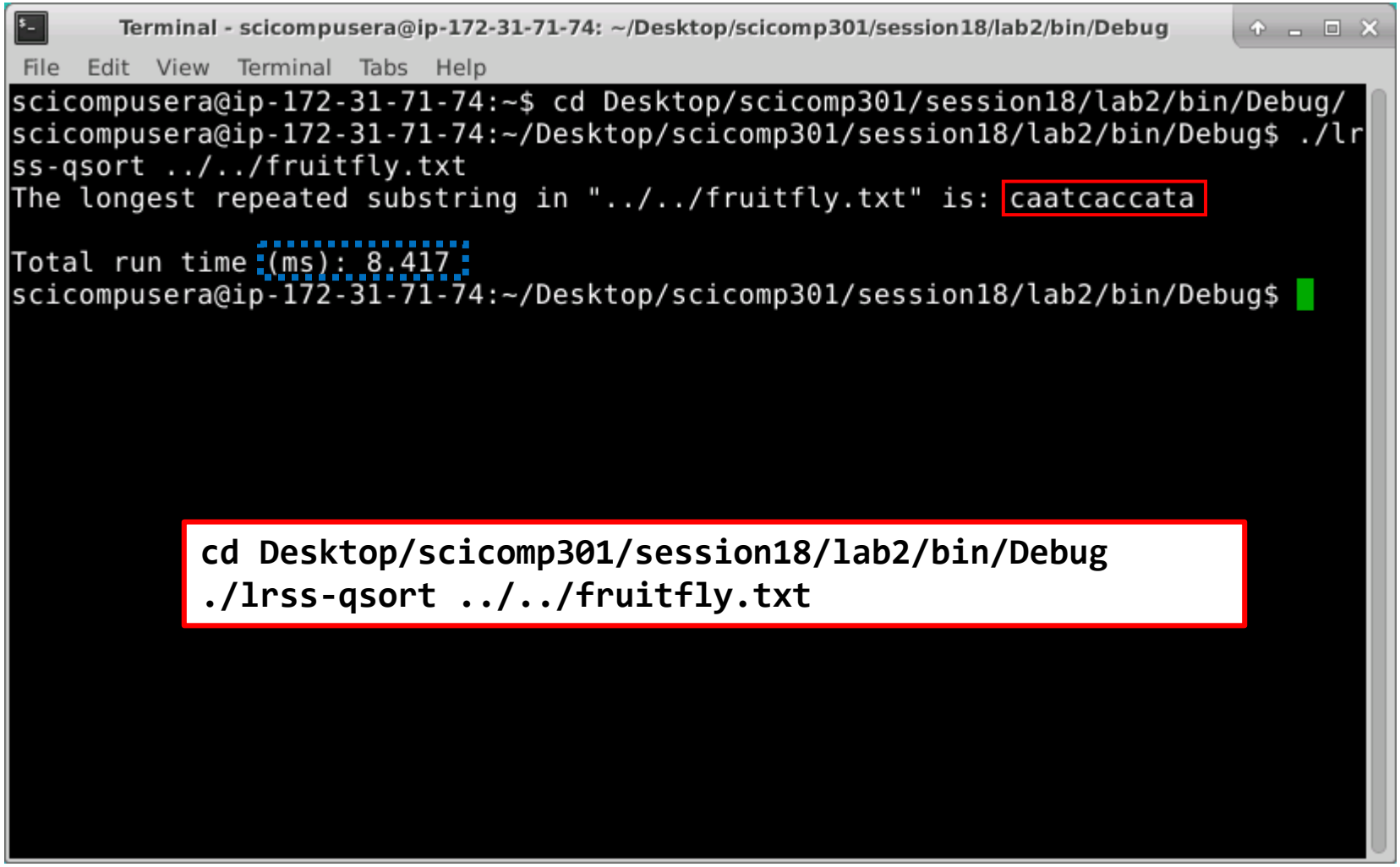
Quicksort

```
template<typename T>
int partition(vector<T>& v, size_t left, size_t right)
{
    T pivot = v.at(right);
    size_t i = left;

    for (size_t j = left; j < right; ++j)
        if (v.at(j) <= pivot){
            v.at(i).swap(v.at(j));
            i++;
        }

    v.at(right) = v.at(i);
    v.at(i) = pivot;

    return i;
}

template<typename T>
void quicksort(vector<T>& v, int left, int right)
{
    if (left < right)
    {
        int q = partition(v, left, right);
        quicksort(v, left, q - 1);
        quicksort(v, q + 1, right);
    }
}
```

Build Lab 2 – LRSS **Quicksort**

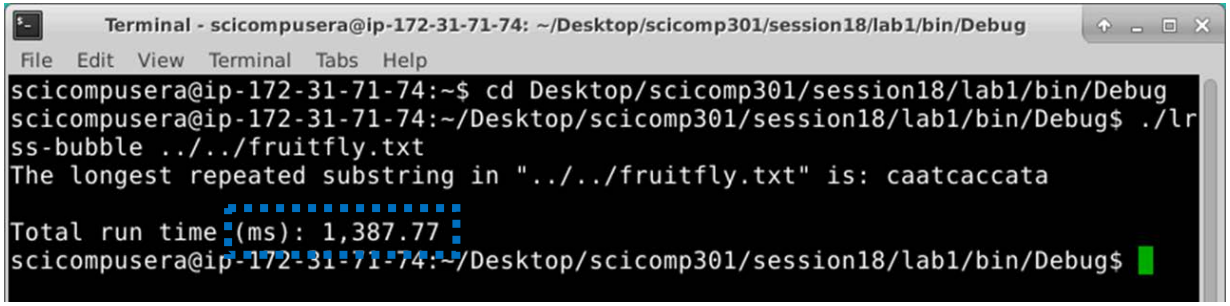


Run Lab 2 – LRSS **Quicksort**

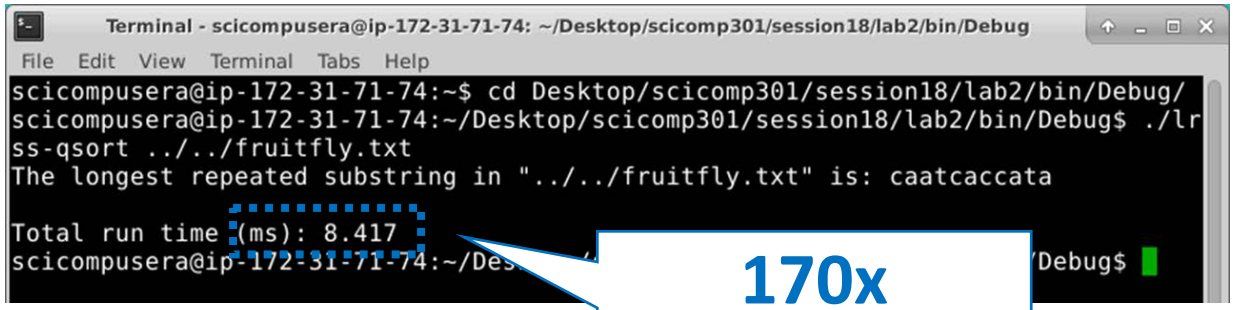


Check Lab 2 – LRSS Quicksort

Bubble Sort



Quicksort



The Role of Lecithin-Retinol Acyl Transferase in Keratinocyte Mechanics

Emily Peterson

Smithtown High School East

Project ID 2250

LRAT and Cancer

- ↓ Cell wall strength ⟹ ↑ cancer
- ↓ Keratin ⟹ ↓ Cell wall strength
- ↓ K5 ⟹ ↓ Keratin
- ↑ RA ⟹ ↓ K5
- ↑ Retinol ⟹ ↑ RA
- ↓ LRAT ⟹ ↑ Retinol
- ↓ LRAT ⟹ ↑ cancer

- Cancer is invasive
- Cytoskeleton filaments
- K5 is a gene
- Retinoic Acid regulates K5
- Retinol is Vitamin A
- LRAT moderates Retinol
- LRAT controls cell stiffness?

LRAT

TCTGCTCCTCGGGCGGCCTTGAGCAGTGCCTAACGTTGAGCGTGAGGCTCGTGCTCCGGGTCTCGCGGGCGGCCGCCTCGGGCGTCGAGTCCCGGAG
ATTGGACAGACACCAGAGCCTGGGGACCGCGGAGTGACCGGGTGGGGCTGGAGGGCGGCGCCGCGCCTTCTGGGGAGACGCGGAGGTATCAGGACCT
GGGCTATGCTCCTGATTTTATACAGACTGCCATGGCTCCAGATATAAAAGACCAAATAAAAAGATAAGAATTGCTGGCAACATATGCACTAAACTTC
GTTTTGAAAAATCCCCTTGATGCCGATCACTGAGAAGTGATCCACAGGATGAAGAACCCCATGCTGGAGGTGGTGTCTTTACTACTGGAGAAGCTGC
TCCTCATCTCCAACTTCACGCTCTTTAGTTCGGGCGCCGCGGGCGAAGACAAAGGGAGGAACAGTTTTTATGAAACCAGCTCTTTCCACCGAGGCGA
CGTGCTGGAGGTGCCCCGGACCCACCTGACCCACTATGGCATCTACCTAGGAGACAACCGTGTTGCCCACATGATGCCCGACATCCTGTTGGCCCTG
ACAGACGACATGGGGCGCACGCAGAAGGTGGTCTCCAACAAGCGTCTCATCCTGGGCGTTATTGTCAAAGTGGCCAGCATCCGCGTGGACACAGTGG
AGGACTTCGCCTACGGAGCTAACATCCTGGTCAATCACCTGGACGAGTCCCTCCAGAAAAAGGCACTGCTCAACGAGGAGGTGGCGCGGAGGGCTGA
AAAGCTGCTGGGCTTTACCCCCTACAGCCTGCTGTGGAACAACTGCGAGCACTTCGTGACCTACTGCAGATATGGCACCCCGATCAGTCCCCAGTCC
GACAAGTTTTGTGAGACTGTGAAGATAATTATTCGTGATCAGAGAAGTGTTCTTGCTTCAGCAGTCTTGGGATTGGCGTCTATAGTCTGTACGGGCT
TGGTATCATACACTACCCTTCCTGCAATTTTTATTCCATTCTTCCTATGGATGGCTGGCTAACTTCATACCCCCATGTCAGTGTGTGTATTCTGTAT
GTAAATATGTTTATATTTATAGAGCATCAATCAATATAAGCATTATTGAGAAAAATGTGACCCGTAACACTGTGTTCTGGATAAAAATGTGATTAGG
AATCACGCAAAGTGCTTACTGTGTAAGCCCAAGAACAAAGGCTTTCTGAATCTTCTCAGGCAGTTCAGATTTAAAGCACCATCCAAACCTTGGAAAT
ACGACAGGGTGTGGTAGAATTCAGCAATATGAGAAAACCAGCCCCTAAAATGATAGCCACAAGAGATTAATTGTGTTTTTTTTTCTCCTGTAATCCT
TGTACTGTTCGGCTGAATTTGAAGATTGGAAGACTTATATTGAGACCAGTAACTTTACTGTAAATTTACTTTGTTTCATTGAAAAAACAAATTGATA
AACATATTAAACTGGAAGAATTTTCTTTATTCAAATGAAAACATGTTTGATGACTGGTCAAAAAATAAGCTCATAATCTATTTTTTTCATGTAGTAT
ATAAGTCAAGAATGTTTTATTGTCATTATGTGAAACCAATATTGGCAAATAGTACTTTAATGATGAAGTAAATGACCAGAAATTATAGAAATCTGTG
TTTTCCTGTAAAAATAGCACTATAGTATCACTTGAACAATTTGATTTGGCTTTACTTACTAGGAAGCCTGGAATTCATTATTTTTTTCCTTTTATGT
GCCACTGTGGCTACTTTAAATCACTCTGAGAGGTAAATGGATATAGGATTGAAGTTATGTGGGTATTTGGCATGTGTGTGTGAAATAAATATGTAGA
TAGTCACATATACACAGACTGAGAGATAAATTGTTCTTGATTGCTTTATTATCATCATACTAGTGTGTTCATTATAGAGTATCTGTAGAGGTGAATG
TAAAAGTAAGTCCAATCTATTTTCTTATGTCATTGAATTTGTAGTGTTAACTTGCATATATGTTATTGGATGGGTTGTCTTTTAAAGCATTTACTAA
TGTACTCTGAAATTTTTAAAAGCCTTCAGATTTGTTTTCTAGTCACTTTTTTCCATATCATTTCTAATTATAGTTTATATCCTTAAAAGAAGGATGC
CACAGTAGTATGTAAAACCCAAACAAGTAGAACCCAAGCAAATAAAATTATTTAAAATAATTTTAAAGTGGCTTAGTACTGCCAGTCATGTAAATTG
ATTCTGCTGAGGGTCTTATAAGAATTGAGATATAACAATGGTAAAACAAGCATTCAAGCACTTTTACAAAATTACCAAATTCTTAAAATGAAGCCAC
AGCTAGACTTGCATTTCAGGTATTAAAATTGCTTTCTTAACTGTCAAGAATCACAAAATAACAAATCATATTATGAGTGAATATGGGGAGGGCGGGG
CCAATCAGTCAATGATAATCTGAACAAATTTTAAGAGCAGATTTTAGATTAATAATGTTTTATCACCACTAATTTGCCCACAACAAACTCAGTATTT
AATTTTTCAAATTAAATATTAAATTATTTAAGTATTTTAAATAATTAAAACATTAAATGGCAACACCATAGAATATAGGTGTTCTCTGGACCTATTC
TAACCACTTAAAATTATCTTAAGTATGCATACATAAAAGCAACCACTATGAGAACTACCGTGTTAGTGGTTTTTCACTTACTGTATATTACCCTTGT
AGGAATAGTTTAAGGAAATTCATTTCTTAAAAATATAGTGTCCTCAAATAATTAATTTTTTTGCAAACTTTAGTTATTACAGGCAGCAAAAACCACT
GTCTGAAACTAAATCTGTGTTCAAAGATGAAGACCCCTCATTAAAAGCCAAGGACGTTCTTAAGATTGGAACTGACATAATTAGTCTTGACTTACTT
CATTAAAGCAAGATTCAATTCCT

Open Lab 3 – Substring Frequency

We sum the # of occurrences each substring of a given length appears

```
void WriteSubstrings()
{
    cout << "Creating file \""
        << filename << "\" ...";

    *outfile << "length,count,freq,seq,proteins"
        << endl;

    map<string, int> table;

    for (int len{ 3 };len < 19;++len)
    {
        table.clear();
        for (size_t pos{};pos <= seq->length() - len;++pos)
        {
            string key = seq->substr(pos, len);
            auto p = table.find(key);
            if (p == table.end())
                table.insert(pair<string, int>(key, 1));
            else
                p->second++;
        }

        // Copy sorted map to an unsorted list
        vector<pair<string, int>> list;
        for (auto& p : table)
            list.push_back(p);

        WriteFreq(list, len, true, 5);
        WriteFreq(list, len, false, 5);
    }

    cout << " done!" << endl;
}
```

View Lab 3 – Substring Frequency

```
void WriteFreq(vector<pair<string, int>>& list, int len,
    bool topmost, size_t limit)
{
    string freqLabel;
    if (topmost) {
        freqLabel = "Most";
        // Sort list by decreasing substring frequency
        sort(list.begin(), list.end(),
            [](const pair<string, int> &a,
                const pair<string, int>& b)
        {
            return a.second > b.second;
        });
    }
    else
    {
        freqLabel = "Least";
        // Sort list by increasing substring frequency
        sort(list.begin(), list.end(),
            [](const pair<string, int> &a,
                const pair<string, int>& b)
        {
            return a.second < b.second;
        });
    }

    size_t range = list.size() > limit ? limit : list.size();
    for (size_t row{};row < limit;++row) {
        *outfile << len << "," << list.at(row).second
            << "," << freqLabel << "," << list.at(row).first
            << "," << GetCodons(list.at(row).first) << endl;
    }
}
```

Instead of targeting **cout**, we can insert into a file stream to create a CSV file

DNA Codon Table

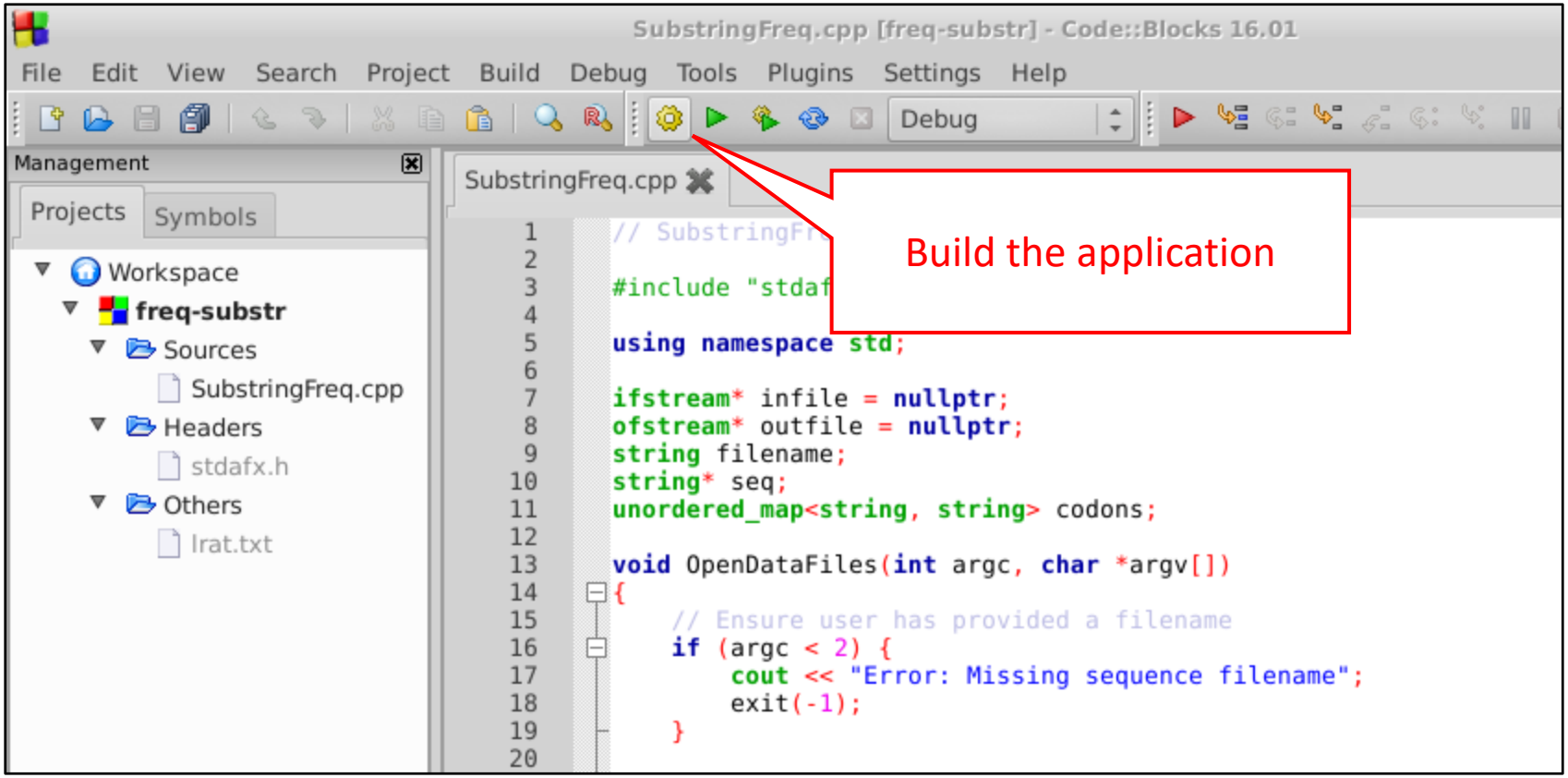
Standard genetic code

1st base	2nd base								3rd base
	T		C		A		G		
T	TTT	(Phe/F) Phenylalanine	TCT	(Ser/S) Serine	TAT	(Tyr/Y) Tyrosine	TGT	(Cys/C) Cysteine	T
	TTC		TCC		TAC		TGC		C
	TTA	(Leu/L) Leucine	TCA		TAA[B]	Stop (*Ochre*)	TGA[B]	Stop (*Opal*)	A
	TTG		TCG		TAG[B]	Stop (*Amber*)	TGG	(Trp/W) Tryptophan	G
C	CTT		CCT	(Pro/P) Proline	CAT	(His/H) Histidine	CGT	(Arg/R) Arginine	T
	CTC		CCC		CAC		CGC		C
	CTA		CCA		CAA	(Gln/Q) Glutamine	CGA		A
	CTG		CCG		CAG		CGG		G
A	ATT	(Ile/I) Isoleucine	ACT	(Thr/T) Threonine	AAT	(Asn/N) Asparagine	AGT	(Ser/S) Serine	T
	ATC		ACC		AAC		AGC		C
	ATA		ACA		AAA	(Lys/K) Lysine	AGA	(Arg/R) Arginine	A
	ATG[A]	(Met/M) Methionine	ACG		AAG		AGG		G
G	GTT	(Val/V) Valine	GCT	(Ala/A) Alanine	GAT	(Asp/D) Aspartic acid	GGT	(Gly/G) Glycine	T
	GTC		GCC		GAC		GGC		C
	GTA		GCA		GAA	(Glu/E) Glutamic acid	GGA		A
	GTG		GCG		GAG		GGG		G

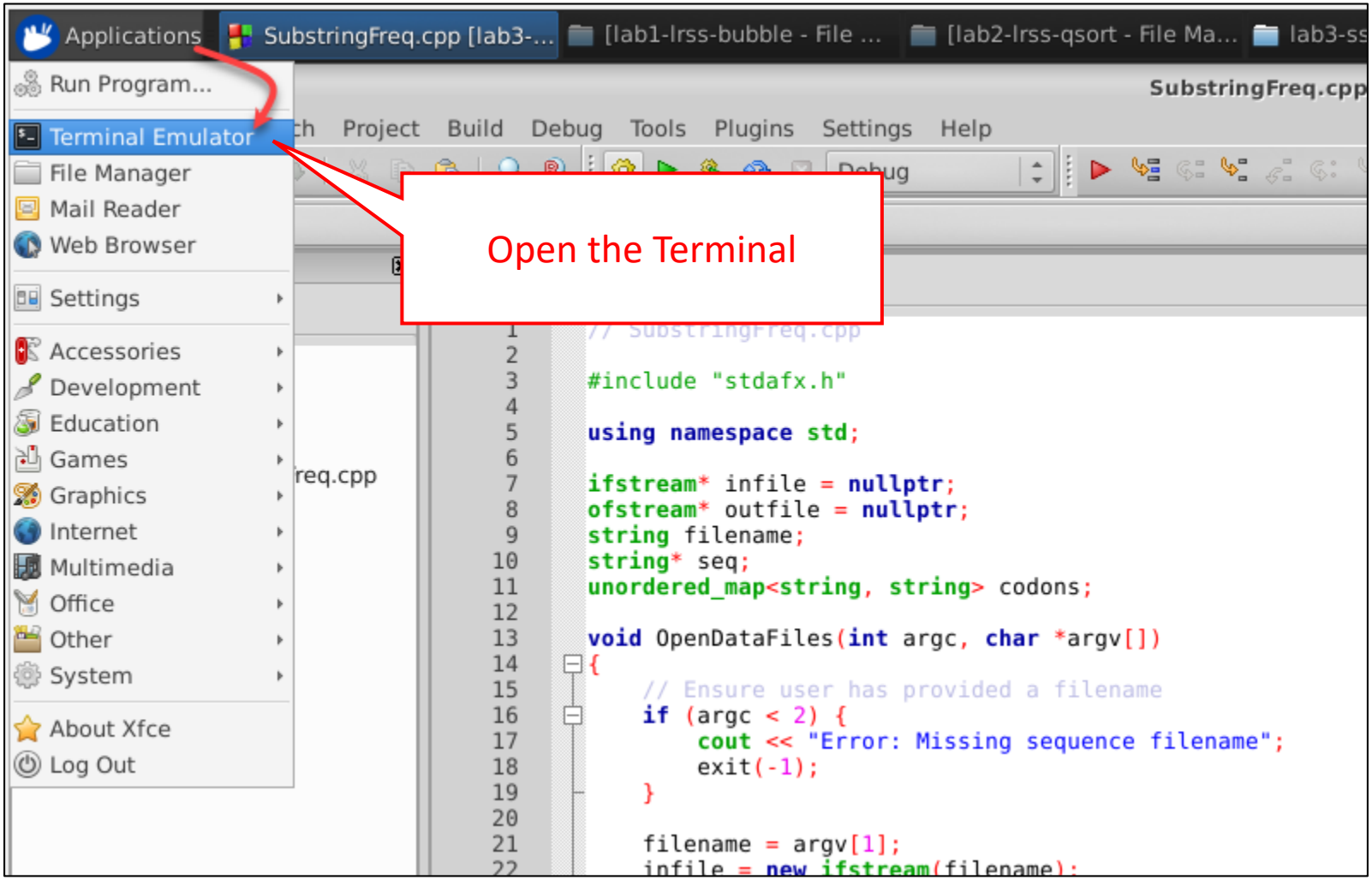
View Lab 3 – Substring Frequency

```
void AddCodon(string label, vector<string> seqs)
{
    for (auto& s : seqs)
        codons.insert(pair<string, string>(s, label));
}

void InitCodons()
{
    AddCodon("Ala", { "GCT","GCA","GCC","GCG" });                // Alanine (Ala/A)
    AddCodon("Arg", { "CGT","CGC","CGA","CGG","AGA","AGG" });    // Arginine (Arg/R)
    AddCodon("Asn", { "AAT", "AAC" });                           // Asparagine (Asn/N)
    AddCodon("Asp", { "GAT", "GAC" });                           // Aspartic Acid (Asp/D)
    AddCodon("Cys", { "TGT", "TGC" });                           // Cysteine (Cys/C)
    AddCodon("Gln", { "CAA", "CAG" });                           // Glutamine (Gln/Q)
    AddCodon("Glu", { "GAA", "GAG" });                           // Glutamic Acid (Glu/E)
    AddCodon("Gly", { "GGT", "GGC","GGA","GGG" });               // Glycine (Gly/G)
    AddCodon("His", { "CAT", "CAC" });                           // Histidine (His/H)
    AddCodon("Ile", { "ATT", "ATC","ATA" });                     // Isoleucine (Ile/I)
    AddCodon("Leu", { "TTA","TTG","CTT","CTC","CTA","CTG" });    // Leucine (Leu/L)
    AddCodon("Lys", { "AAA", "AAG" });                           // Lysine (Lys/K)
    AddCodon("Met/Start", { "ATG" });                            // Methionine (Met / M) & Start
    AddCodon("Phe", { "TTT", "TTC" });                           // Phenylalanine (Phe/F)
    AddCodon("Pro", { "CCT","CCC","CCA","CCG" });                // Proline (Pro/P)
    AddCodon("Ser", { "TCT","TCC","TCA","TCG","AGT","AGC" });    // Serine (Ser/S)
    AddCodon("Thr", { "ACT","ACC","ACA","ACG" });                // Threonine (Thr / T)
    AddCodon("Trp", { "TGG" });                                  // Tryptophan (Trp/W)
    AddCodon("Tyr", { "TAT", "TAC" });                           // Tyrosine (Tyr/Y)
    AddCodon("Val", { "GTT", "GTC","GTA","GTG" });               // Valine (Val/V)
    AddCodon("Stop", { "TAA", "TGA","TAG" });                    // Stop
}
```

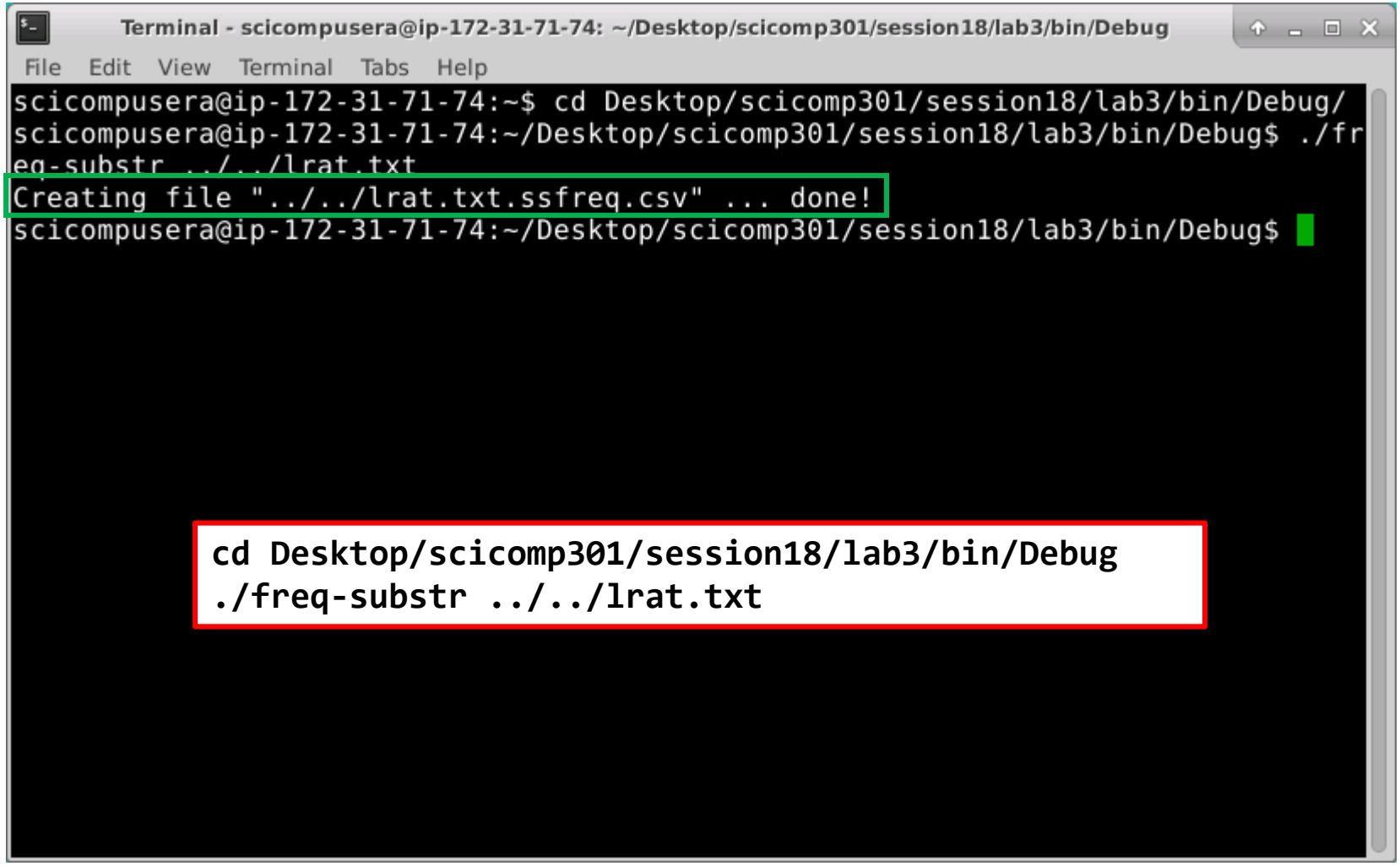
Build Lab 3 – Substring Frequency



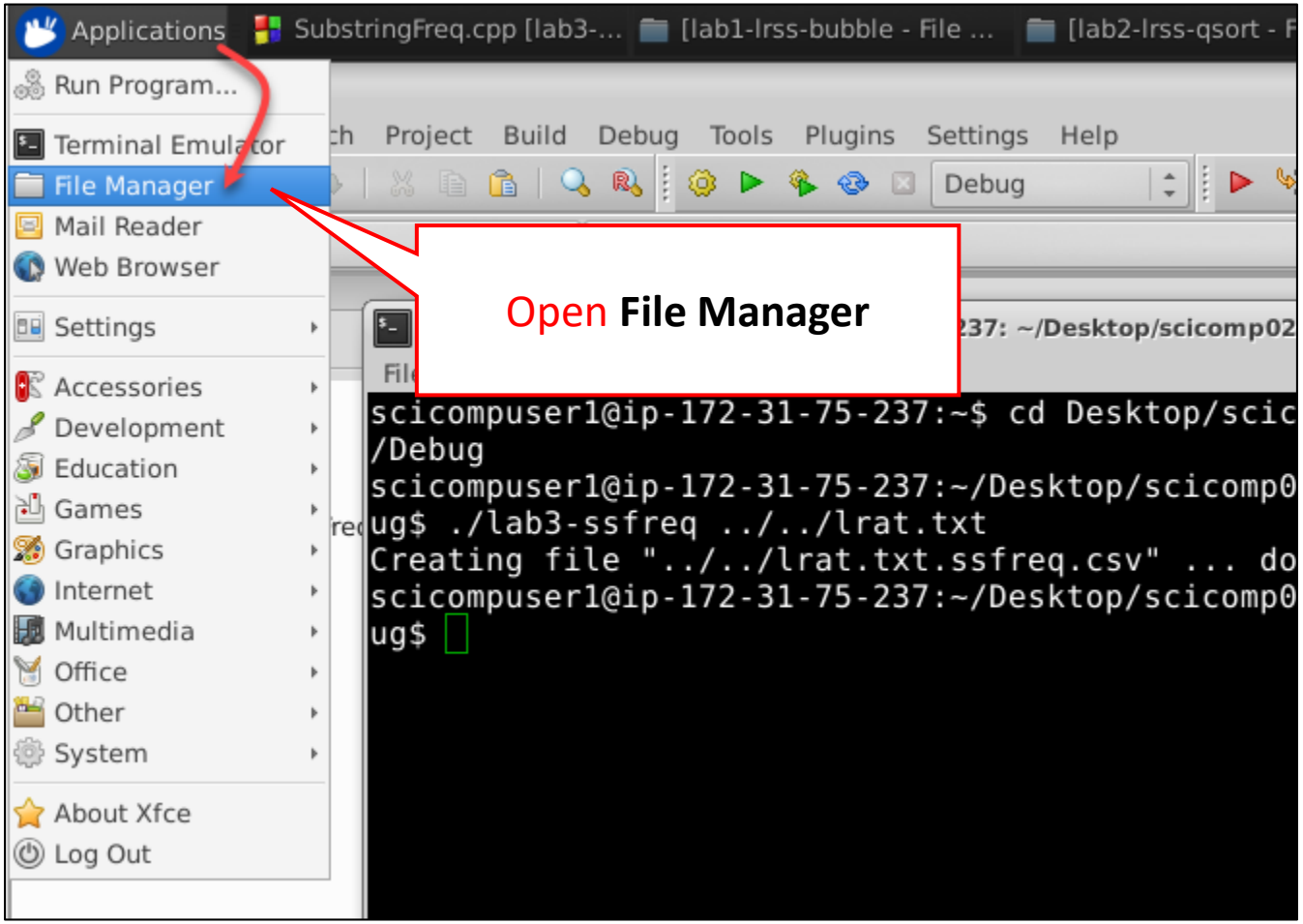
Run Lab 3 – Substring Frequency



Check Lab 3 – Substring Frequency



Check Lab 3 – Substring Frequency



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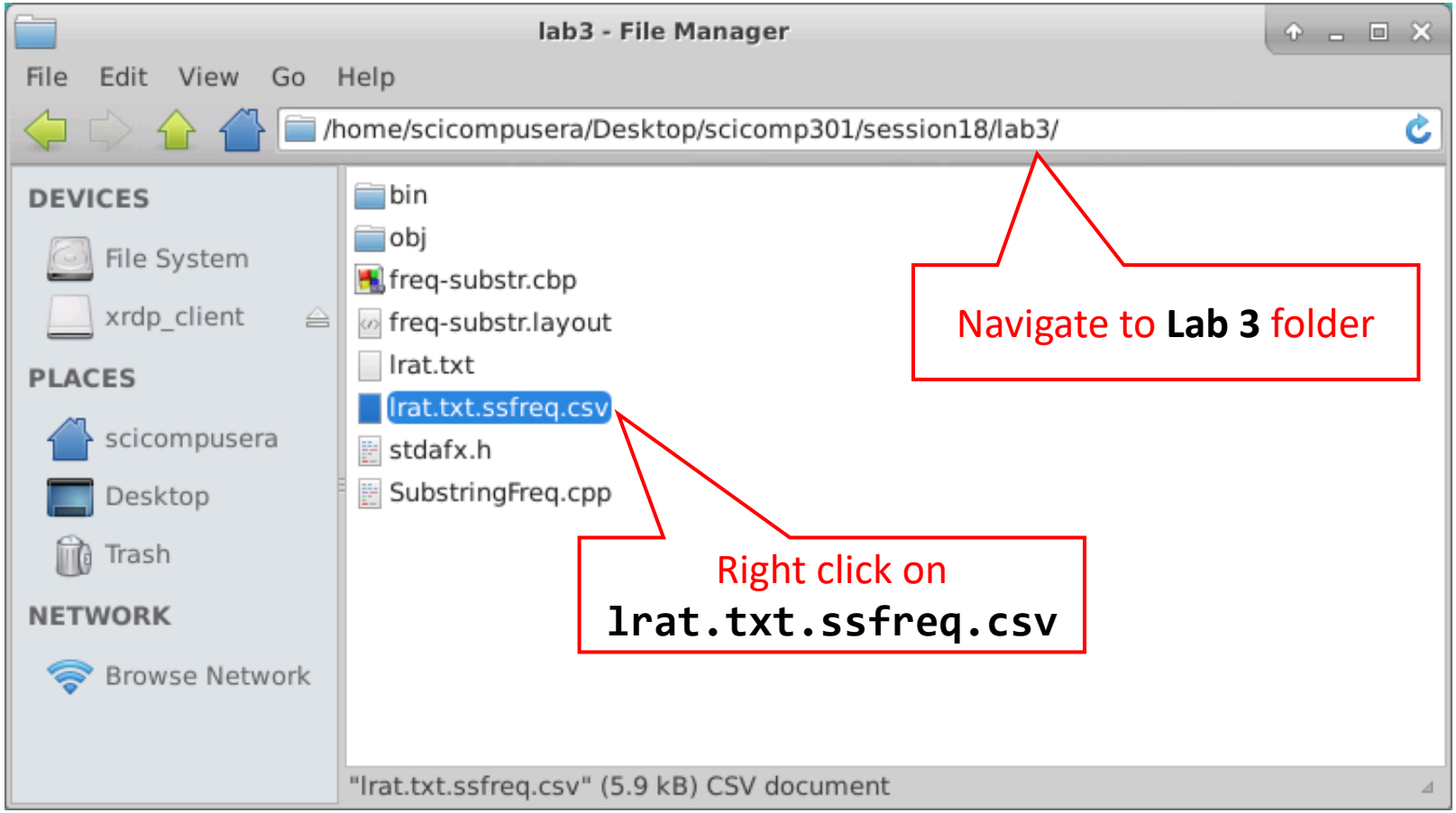
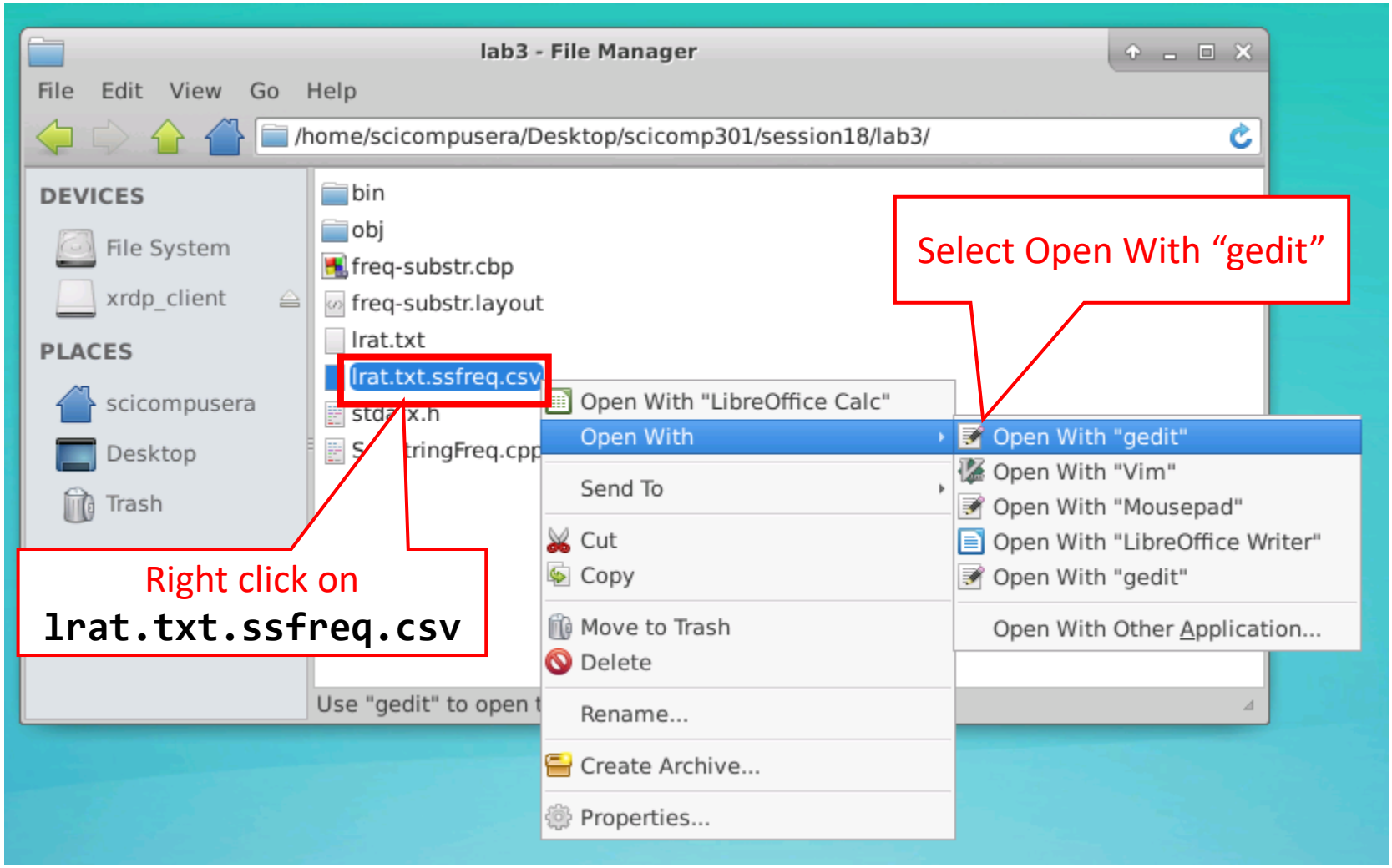
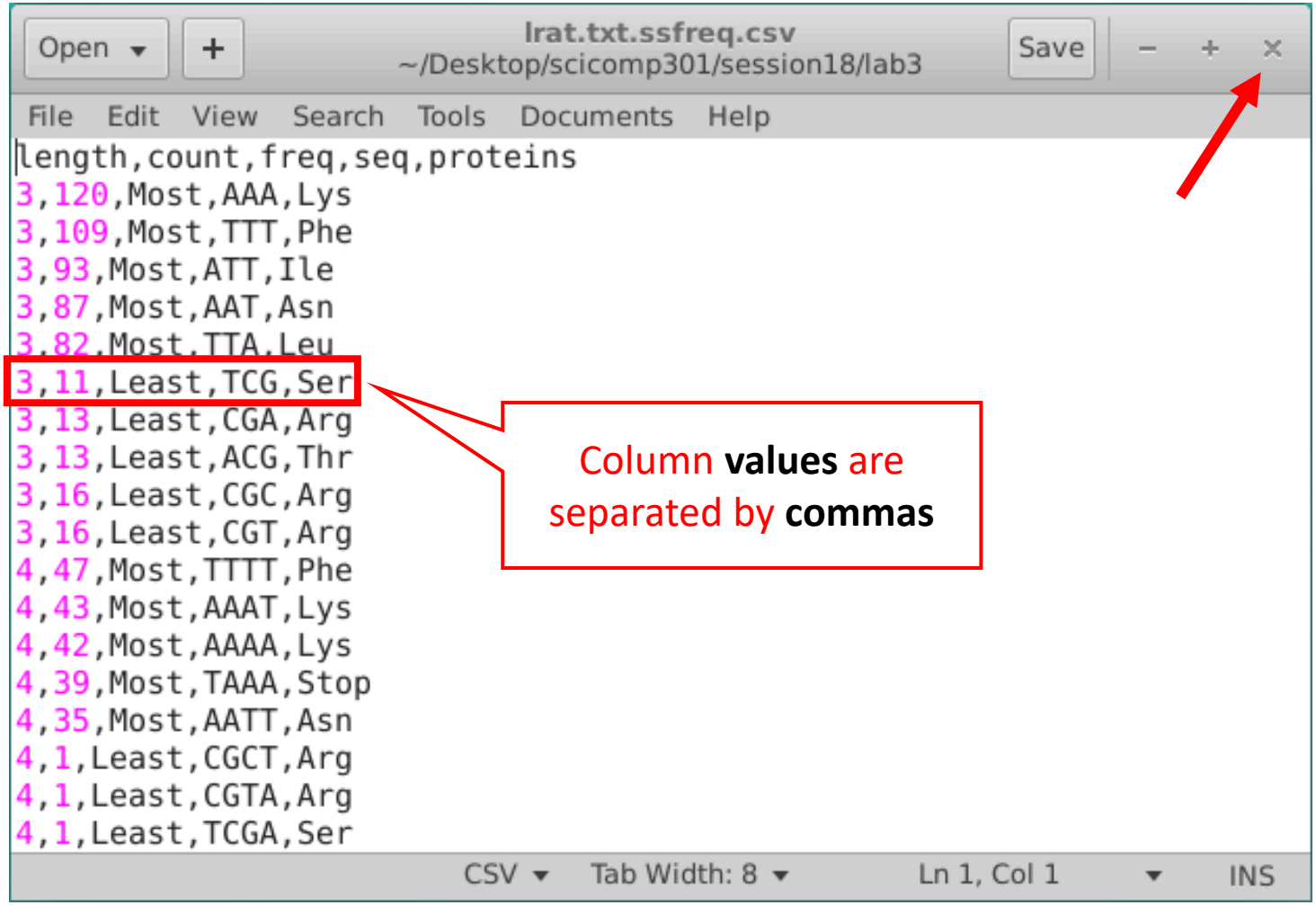


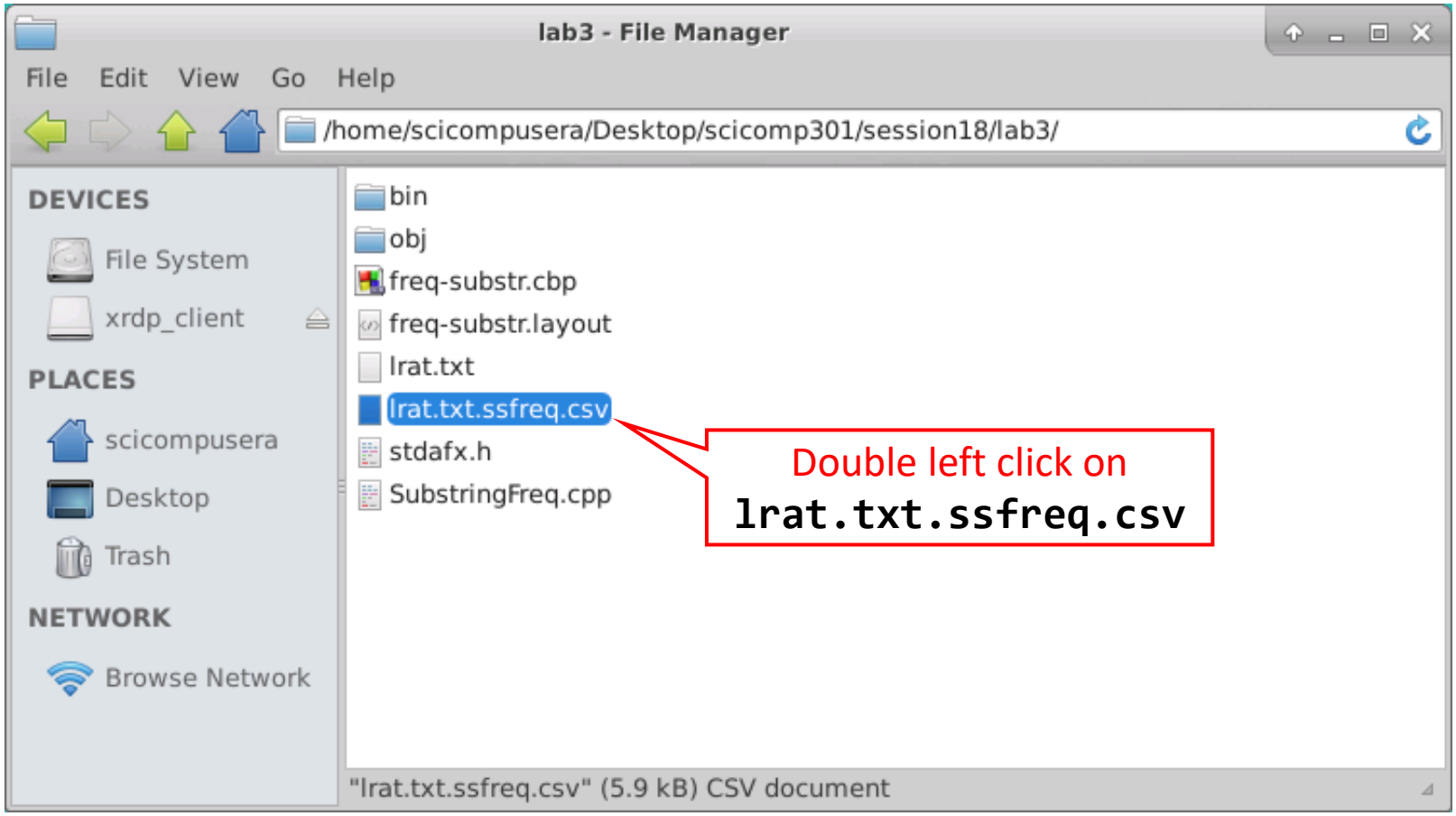
Check Lab 3 – Substring Frequency



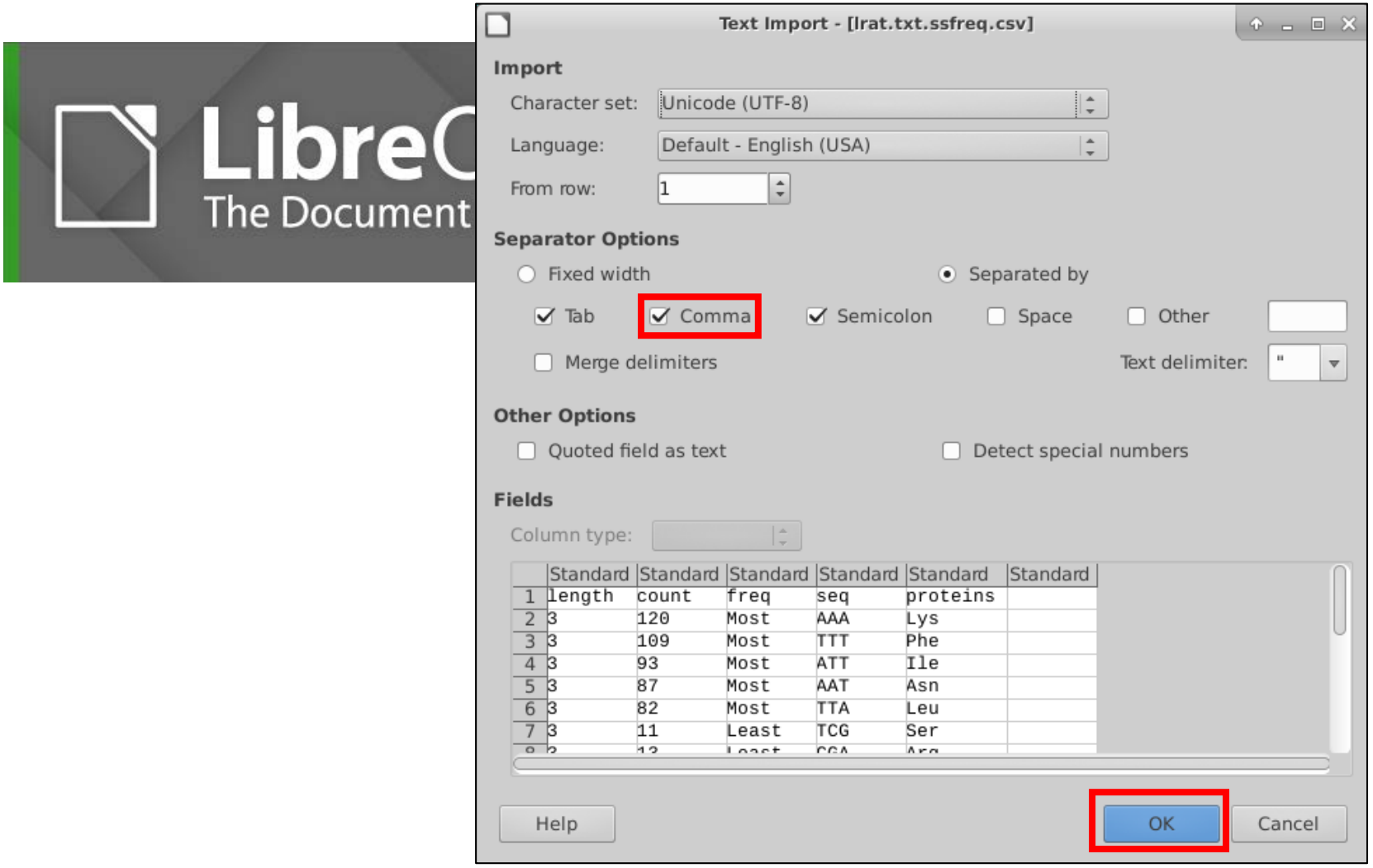
Comma Separated Value Files (.CSV)



Check Lab 3 – Substring Frequency



LibreOffice Calc ≈ Microsoft Excel



Lab 3
Substring Frequency

	A	B	C	D	E	F	G	H	I
1	length	count	freq	seq	proteins				
2	3	120	Most	AAA	Lys				
3	3	109	Most	TTT	Phe				
4	3	93	Most	ATT	Ile				
5	3	87	Most	AAT	Asn				
6	3	82	Most	TTA	Leu				
7	3	11	Least	TCG	Ser				
8	3	13	Least	ACG	Thr				
9	3	13	Least	CGA	Arg				
10	3	16	Least	CGC					
11	3	16	Least	CGT	Arg				
12	4	47	Most	TTTT	Phe				
13	4	43	Most	AAAT	Lys				
14	4	42	Most	AAAA	Lys				
15	4	39	Most	TAAA	Stop				
16	4	35	Most	AATT	Asn				
17	4	1	Least	TCGA	Ser				
18	4	1	Least	CGAA	Arg				
19	4	1	Least	CGTA	Arg				
20	4	1	Least	CGCT	Arg				
21	4	1	Least	TGCG	Cys				
22	5	21	Most	TTTTT	Phe				
23	5	19	Most	TTAAA	Leu				
24	5	19	Most	TAAAA	Stop				
25	5	15	Most	AAATA	Lys				
26	5	15	Most	AAATT	Lys				
27	5	1	Least	CGGCG	Arg				
28	5	1	Least	TGCGA	Cys				
29	5	1	Least	TGCCT	Cys				
30	5	1	Least	TGCCG	Cys				
31	5	1	Least	GTTGC	Val				
32	6	11	Most	TTTTTT	Phe	Phe			
33	6	9	Most	TTAAAA	Leu	Lys			
34	6	8	Most	ATTAAA	Ile	Lys			
35	6	8	Most	AAATAA	Lys	Stop			
36	6	7	Most	TTTAAA	Phe	Lys			
37	6	1	Least	AATCAG	Asn	Gln			

Lists the 5 most frequent and 5 most infrequent substrings of a given length

Codons are mapped where possible

Check Lab 3 – Substring Frequency

17	1	Least	AGCAAGATTCAATTCCT	Ser, Lys, Ile, Gln, Phe			
18	1	Most	TCTGCTCCTCGGGCGGCC	Ser, Ala, Pro, Arg, Ala, Ala	FGG		
18	1	Most	CTGCTCCTCGGGCGGCCT	Leu, Leu, Leu, Gly, Arg, Pro	FGG		
18	1	Most	TGCTCCTCGGGCGGCCTT	Cys, Ser, Ser, Gly, Gly, Leu	FGG		
18	1	Most	GCTCCTCGGGCGGCCTTG	Ala, Pro, Arg, Ala, Ala, Leu	FGG		
18	1	Most	CTCCTCGGGCGGCCTTGA	Leu, Leu, Gly, Arg, Pro, Stop	FGG		
18	1	Least	ATTAAAGCAAGATTCAAT	Ile, Lys, Ala, Arg, Phe, Asn	LRAT		
18	1	Least	TTAAAGCAAGATTCAATT	Leu, Lys, Gln, Asp, Ser, Ile	LRAT		
18	1	Least	TAAAGCAAGATTCAATTC	Stop, Ser, Lys, Ile, Gln, Phe	LRAT		
18	1	Least	AAAGCAAGATTCAATTCC	Lys, Ala, Arg, Phe, Asn, Ser	LRAT	MME	
18	1	Least	AAGCAAGATTCAATTCCT	Lys, Gln, Asp, Ser, Ile, Pro	LRAT		
19	1	Most	TCTGCTCCTCGGGCGGCCT	Ser, Ala, Pro, Arg, Ala, Ala			
19	1	Most	CTGCTCCTCGGGCGGCCTT	Leu, Leu, Leu, Gly, Arg, Pro			
19	1	Most	TGCTCCTCGGGCGGCCTTG	Cys, Ser, Ser, Gly, Gly, Leu			

Dave Biersach:
This protein is important for blood clot formation (coagulation), which is needed to stop excessive bleeding after injury

Dave Biersach:
A common acute lymphocytic leukemia antigen

LRAT Genetic Homologs

FGG

From Wikipedia, the free encyclopedia

Fibrinogen gamma chain, also known as **FGG**, is a human gene found on Chromosome 4.

The protein encoded by this gene is the gamma component of fibrinogen, a blood-borne glycoprotein composed of three pairs of nonidentical polypeptide chains. Following vascular injury, fibrinogen is cleaved by thrombin to form fibrin which is the most abundant component of blood clots. In addition, various cleavage products of fibrinogen and fibrin regulate cell adhesion and spreading, display vasoconstrictor and chemotactic activities, and are mitogens for several cell types. Mutations in this gene lead to several disorders, including dysfibrinogenemia, hypofibrinogenemia and thrombophilia.[1] Alternative splicing of the mRNA chain results in two transcript variants; the common γA chain and the alternatively spliced γ' chain. Approximately 10% of the total plasma fibrinogen consists of γA/γ' fibrinogen, with <1% consisting of γ'/γ' fibrinogen. Increased and decreased levels of γA/γ' fibrinogen have been associated with CAD and DVT respectively.

FGG

GTCGACCTCCATCACGGCCTATAAGAGTGAGGGGGAGTCAGCGGAGTTCTCCTTCCCACTCAACCTTGGAGAGGAAAGCCTGCAGGGAGAGTTGAGATGGAAGGCAGAGAAGGCTCCTTCTTCCCAGTCCTGGATCACCTTCTCCCTAAAGAACCAAA
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Trail of Discovery

Resistance of cancer cells to immune recognition and killing.

Lipinski B[1], Egyud LG.

Author information

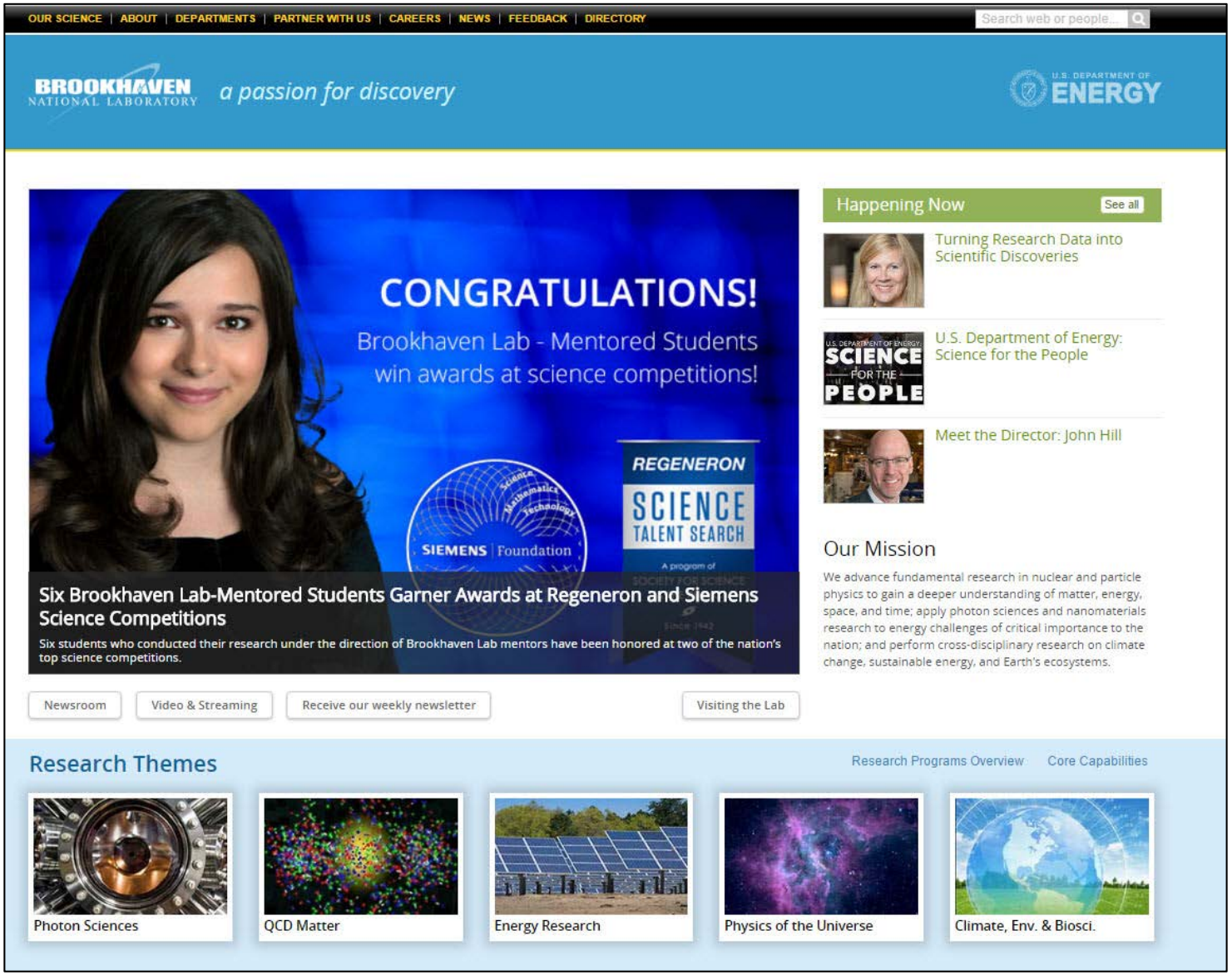
Abstract

It is well recognized that, in order for a wound to heal, the fibrin clot must be eliminated by fibrinolytic enzymes. In certain instances, however, fibrin is ineffectively degraded or even not degraded. For example, in pregnancy, the placenta contains a layer of fibrin (Nitabuck's layer) which presents as 'self' to the immune system. Similar situations have been observed in many solid tumors. A hypothesis is presented according to which tumor cells can escape detection and attack by the immune system in most cancer patients. The tumor dons a 'coat' of the host's own protein on its cell surface. The coat is composed of fibrin and of a polymeric form of human serum albumin (HSA) which, by contrast to pure fibrin, is resistant to fibrinolytic degradation. Such a coated tumor appears as 'self' to the immune system, and thus is not detected as a tumor by the immune system (i.e. natural killer cells). When tumors are prepared for in vitro assays against drugs, they are routinely treated with proteolytic enzymes (e.g. pepsin, or chymotrypsin, etc.) which dissolve the protein coat, exposing the tumor cell surface to the drug. Thus, the in vivo existence of a coat on the tumor surface may explain why some drugs have little or no effect in vivo, while the same drugs are active in vitro.

Prior thought: Cancer evades phagocytosis

New thought: Cancer evades **fibrinolysis**

Applied Scientific Computing



Applied Scientific Computing

Meet the Regeneron Scholars:

Finalist Emily Peterson: Smithtown High School East
Mentor: David Biersach, Information Technology Division
Title of Project: "Lecithin-Retinol Acyltransferase in Squamous Cell Carcinoma: The Relationship Between Oncology and Wound Repair"

Finalist Emily Peterson +ENLARGE

Emily Peterson met Brookhaven Lab mentor David Biersach at a scientific computing seminar he was giving at her high school, where he learned of her research on skin cancer. Emily's research, conducted as a Simons Fellow under the guidance of Stony Brook University Professor Marcia Simon, focused on the possibility that a gene expression problem might inhibit the production of an enzyme responsible for strengthening cell walls. As cancer is invasive, skin cells with weak walls are more susceptible to becoming tumorous. Biersach showed Emily how a classic computer algorithm that looks for repeated substrings can be used in a novel way to determine if DNA sequences are likely to have important biological functions. This is accomplished by searching the human genome for other occurrences of these repeated sequences. They discovered that this enzyme's sequence also occurs in an enzyme involved in blood clotting. When blood clots form to heal a wound, the human body knows to leave the clot alone until the wound is fully repaired. After healing, a chemical signal triggers the body to break down the clot. The similarity in gene sequences that Peterson discovered suggests that cancer cells potentially use the same "don't bother me" signaling mechanism as blood clots, thus allowing the tumor to continue to grow in stealth mode. This collaboration is an excellent example of how students can apply skills in scientific computing directly to their research projects. Peterson hopes to continue her research by studying the enzyme's 3D atomic structure.

Applied Scientific Computing

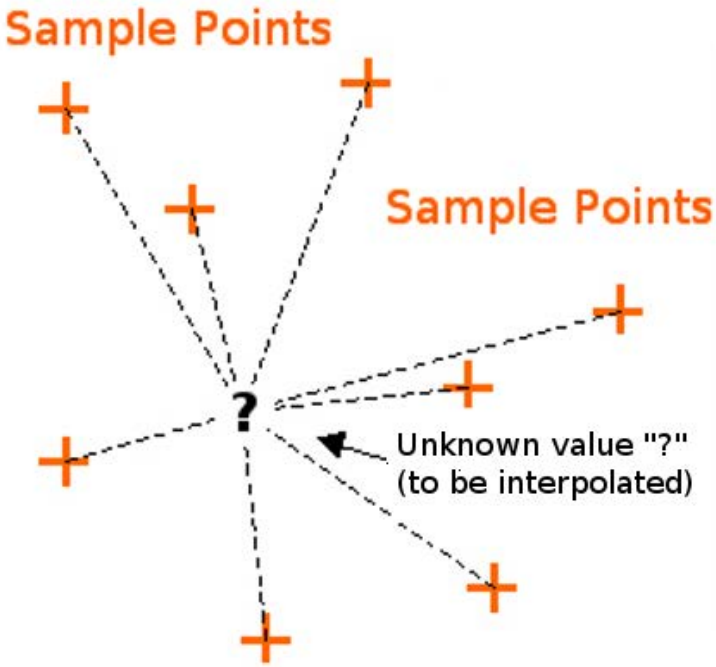
Trail of Discovery

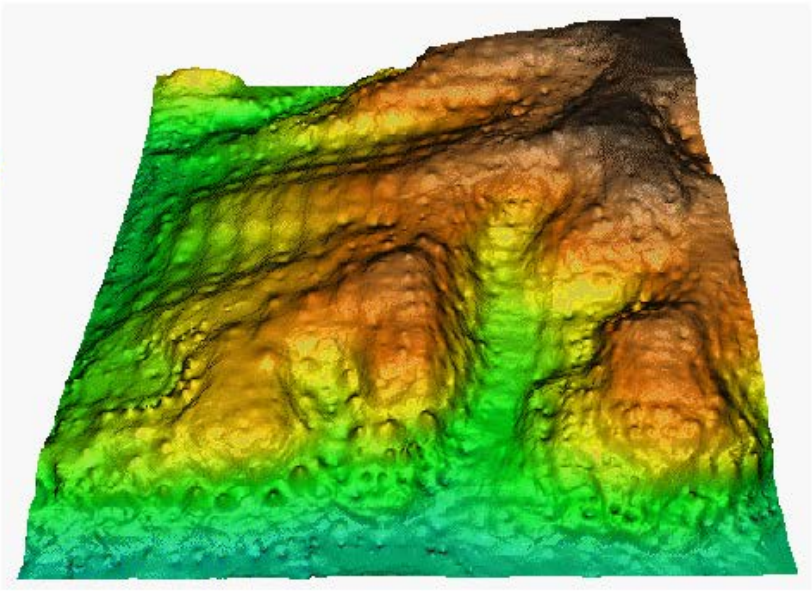
- By considering not just the longest repeated substring, but also the five most (and five **least**) frequent substrings, Emily determined LRAT and FGG share common encodings
- FGG signals your body to **remove blood clots** after any damage is healed – it disposes healthy cells that are no longer needed
- Perhaps **cancer tricks your immune system** into thinking the cancerous cells are healthy and should not be disposed
- It may not be that the lack of LRAT results in a reduction in cell wall stiffness (hence a greater chance of cancer spreading) – but there could be a link between something in LRAT and enabling cancer cell **"stealth mode"**

Session Goals

- Understand methods for **interpolating multi-dimensional data** taken from random sample locations
- Analyze the mathematics of the **Inverse Distance Weighting** (**IDW**) method
- Convert non-uniformly measured spatial data to a **regular conforming mesh**
- Develop approaches for estimating "**goodness of fit**" for predicted interpolated data points
- Use the **Root Mean Square Deviation** (**RMSD**) statistic as a measure of model accuracy

Interpolating Spatial Data





Interpolating Spatial Data

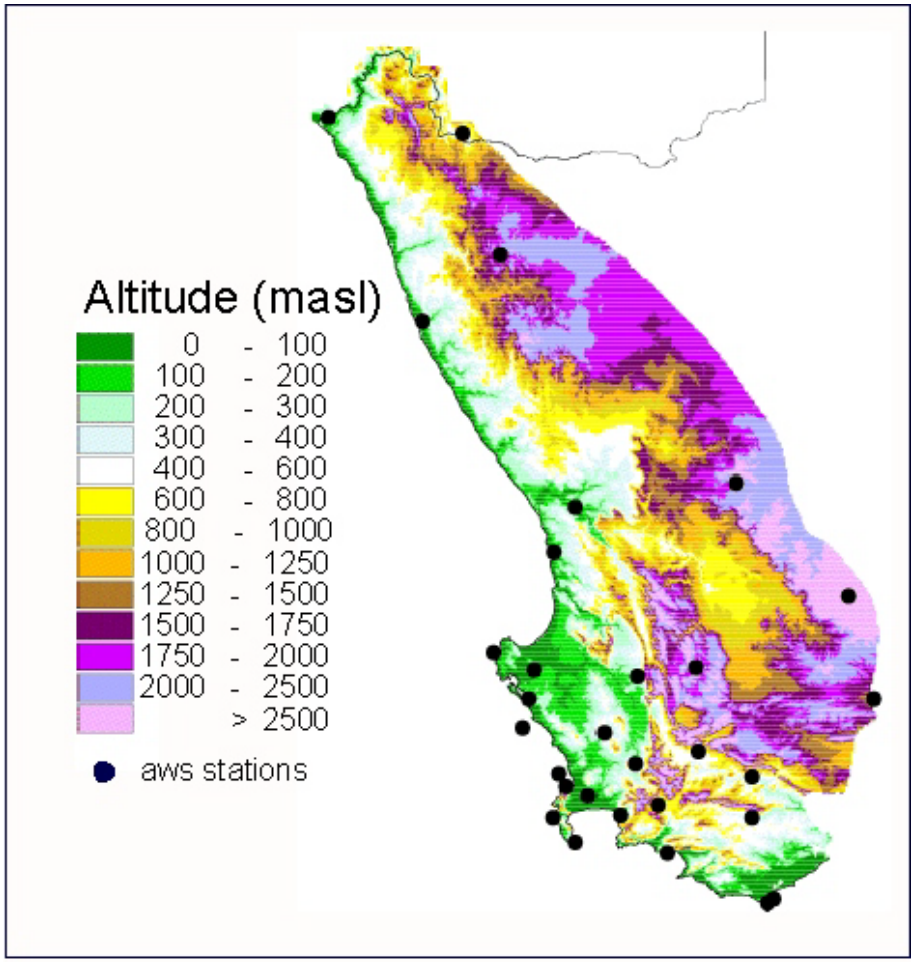
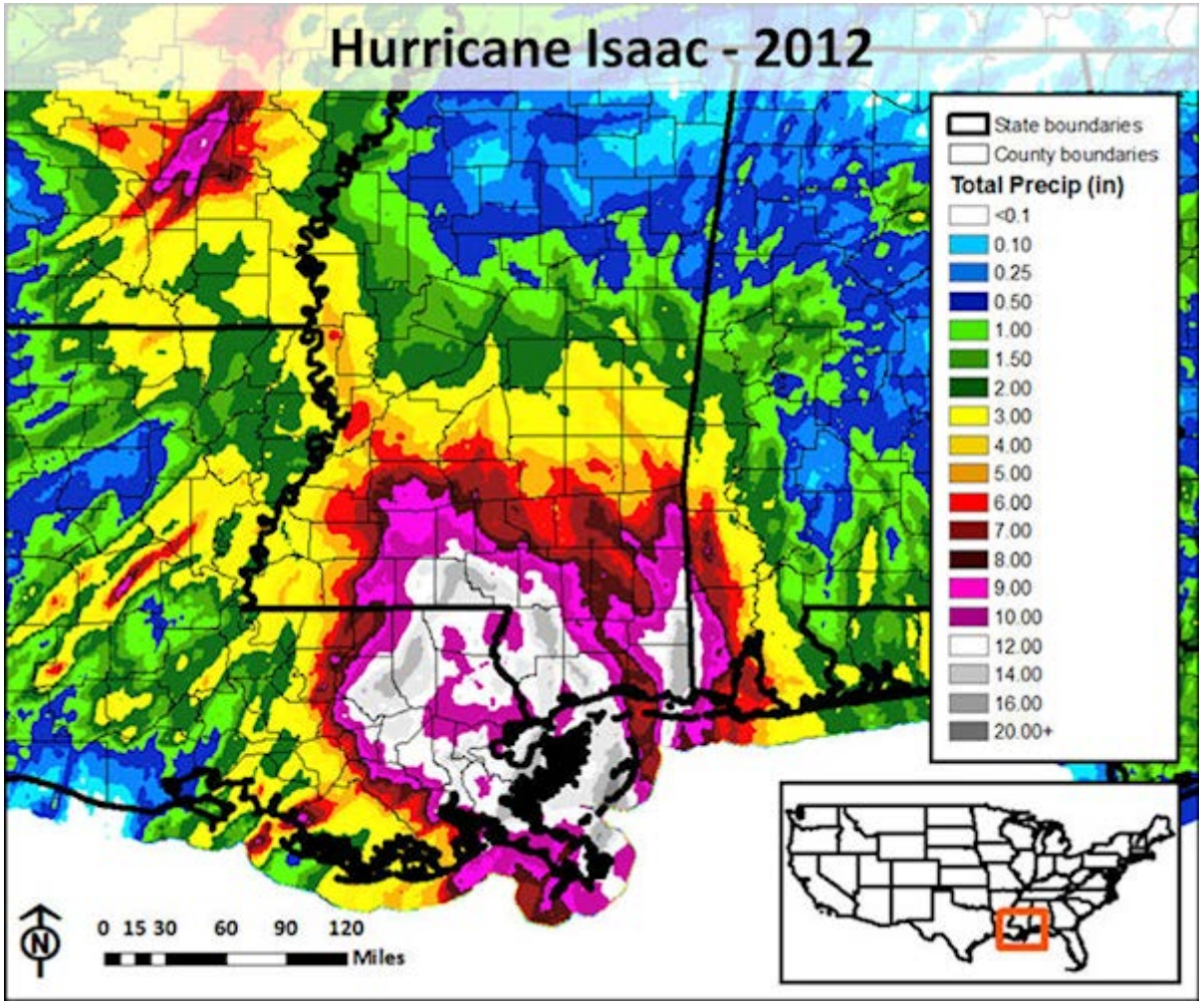
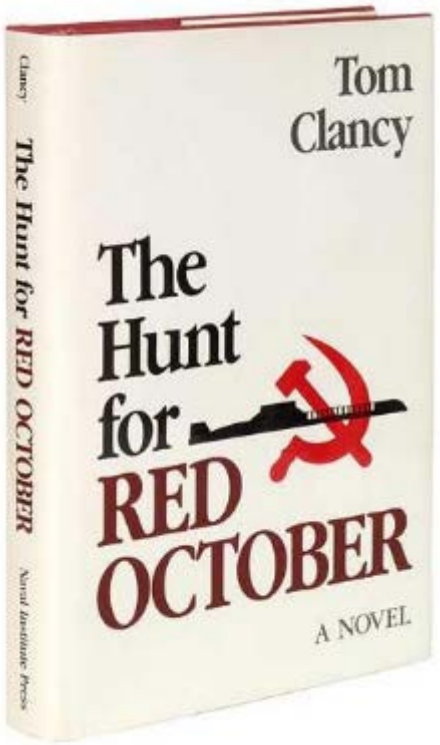


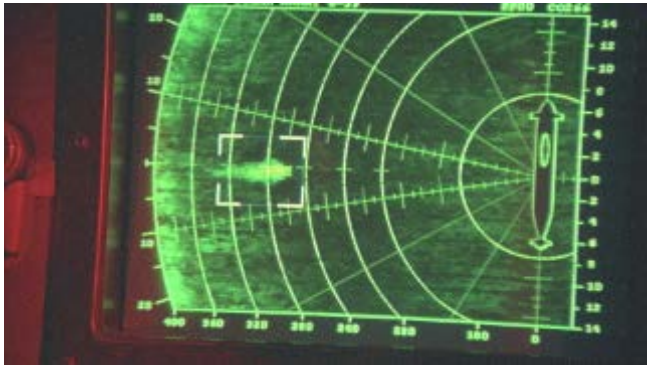
Figure 6 Altitude (200x200m) over the winter rainfall region of South Africa (after Directorate of Land Surveys and Information, 1996)

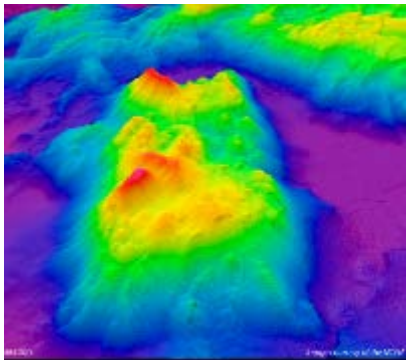
Interpolating Spatial Data



Interpolating Spatial Data

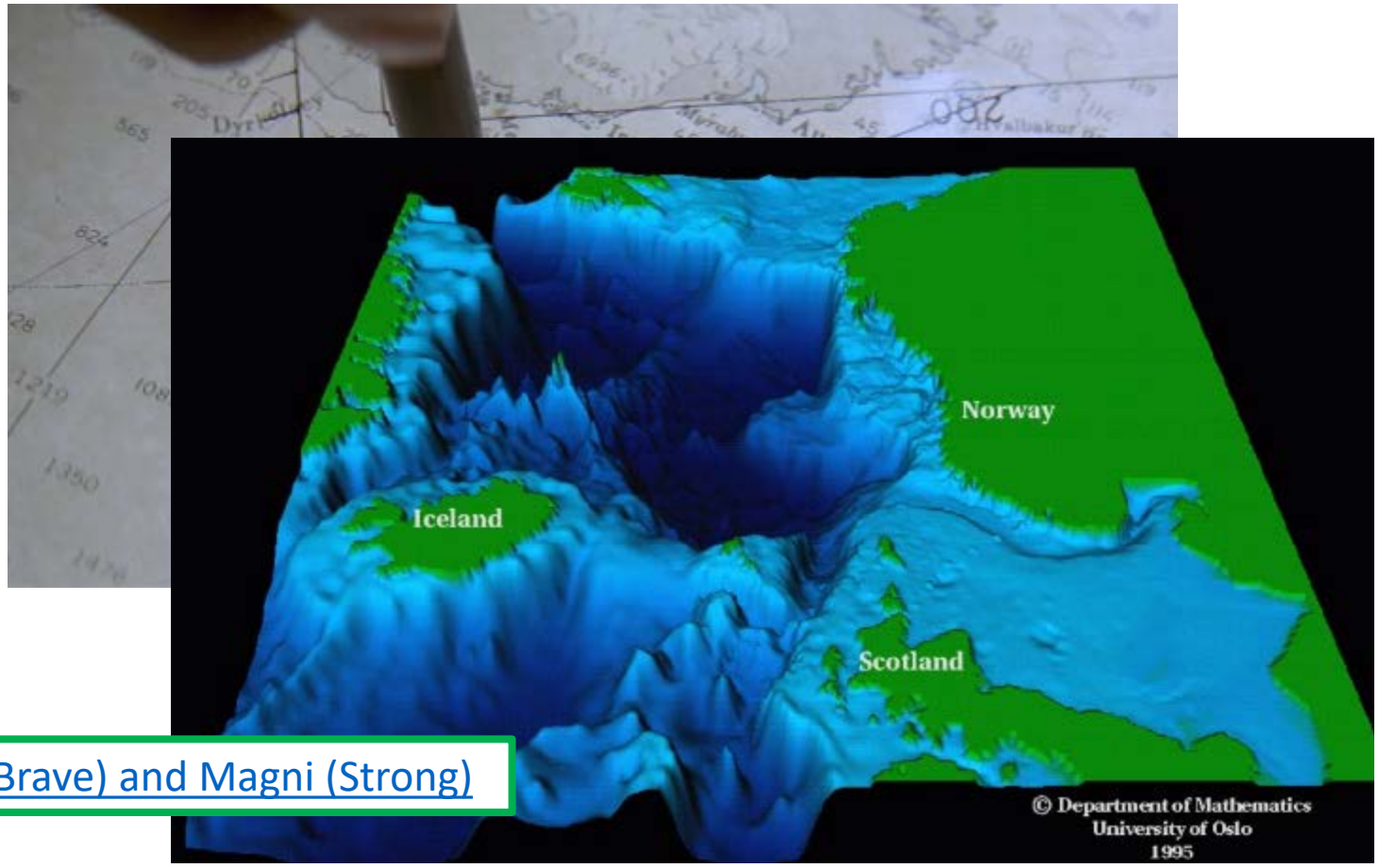






[Jonsey Reports]

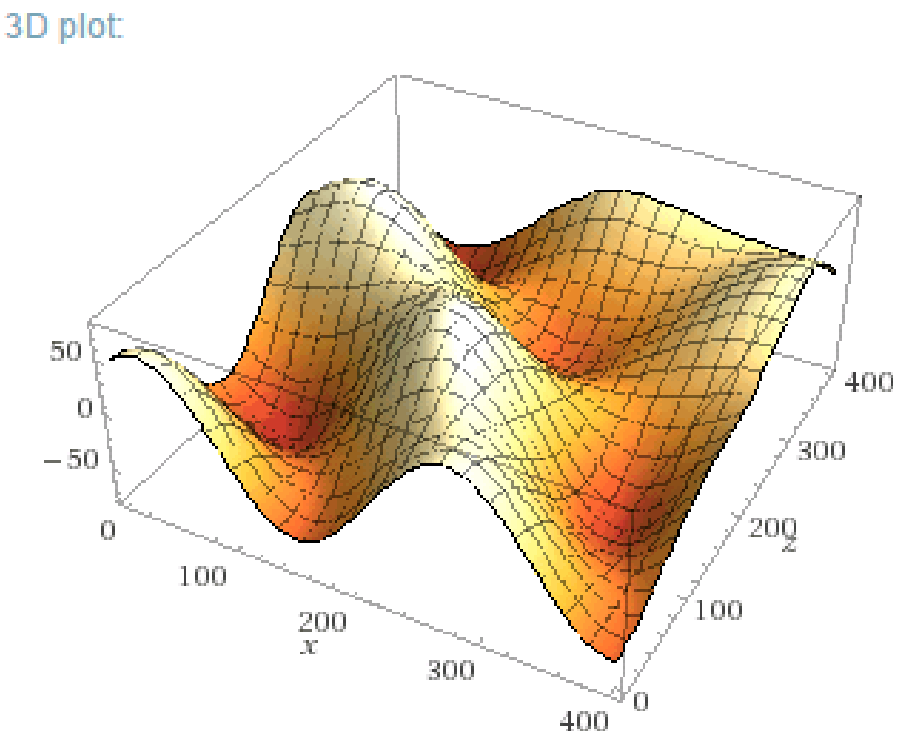
Interpolating Spatial Data



Modi (Brave) and Magni (Strong)

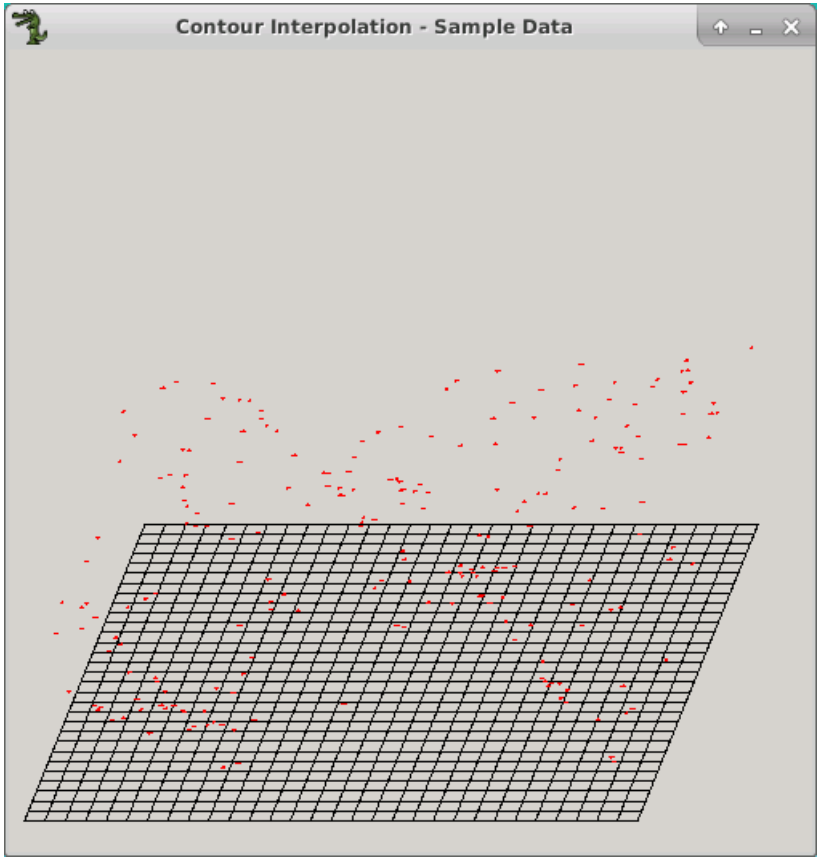
An “Actual” Ocean Floor

$$y = 30 \sin\left(\frac{x}{4}\right) \cos\left(\frac{z}{4}\right) + 50 \cos\left(\frac{\sqrt{x^2 + z^2}}{4}\right)$$



Sample Ocean Depth Soundings

- Ocean area is **400** units square, partitioned into grid of **30 x 30** intervals
- Depth samples were taken from **220 random** locations
- Floor reference grid has height y = **-80**
- Oblique projection



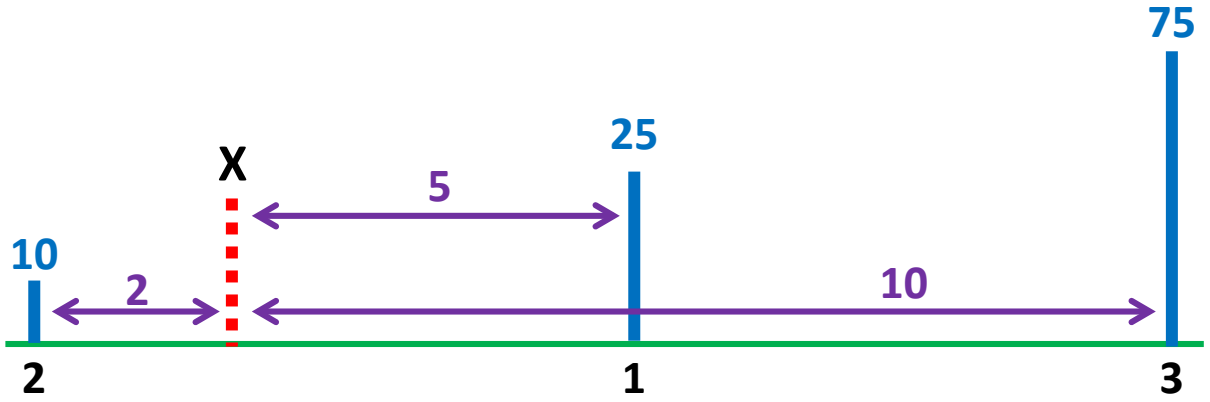
Sample Ocean Depth Soundings

```
void InitSamples()
{
    seed_seq seed{ 2017 };
    default_random_engine prng{ seed };
    uniform_int_distribution<int> dist{ 0, oceanSize };

    // Generate random sample points
    for (size_t i{};i < numSamples;++i) {
        samples[i].x = dist(prng);
        samples[i].z = -dist(prng);
        samples[i].y = GetActHeight(samples[i].x, samples[i].z);
    }

    // Create a small marker at each sample point (a horizontal facet)
    for (size_t i{};i < numSamples;++i)
    {
        size_t v0 = vSamples.add(samples[i].x, samples[i].y, samples[i].z + 2);
        size_t v1 = vSamples.add(samples[i].x + 2, samples[i].y, samples[i].z);
        size_t v2 = vSamples.add(samples[i].x, samples[i].y, samples[i].z - 2);
        size_t v3 = vSamples.add(samples[i].x - 2, samples[i].y, samples[i].z);
        fSamples.add(&vSamples, { v0,v1,v2,v3 });
    }
}
```

The Inverse Distance Weighting (IDW) Method

- IDW is a type of deterministic method for **multivariate interpolation** of a set of *scattered* points
- The value assigned to *unknown* points are calculated from a **weighted average** of the values at the *known* points
- The theory is the farther away a known point is from the unknown point, the **less** that known distant point can contribute to the unknown height
- *Closer* known points contribute *more* to the unknown height than known points that are farther away
- Your contribution **is inverse** to your distance

The Inverse Distance Weighting (IDW) Method



Sample Index	1	2	3
Distance (d) from Sample to **X**	5	2	10
Sample Known Height	25	10	75

				Totals
Weight = 1/d^p (set p = 1)	0.2	0.5	0.1	0.8
Sample Height • Weight	5	5	7.5	17.5

$\left(\frac{17.5}{0.8}\right)\rightarrow$ **Height at X = 21.875**

The Inverse Distance Weighting (IDW) Method

A general form of finding an interpolated value u at a given point x based on samples $u_i = u(x_i)$ for $i = 1, 2, ..., N$ using IDW is an interpolating function:

$$u(\mathbf{x}) = \begin{cases} \dfrac{\sum_{i=1}^{N} w_i(\mathbf{x}) u_i}{\sum_{i=1}^{N} w_i(\mathbf{x})}, & \text{if } d(\mathbf{x}, \mathbf{x}_i) \neq 0 \text{ for all } i \\ u_i, & \text{if } d(\mathbf{x}, \mathbf{x}_i) = 0 \text{ for some } i \end{cases}$$

where

$$w_i(\mathbf{x}) = \frac{1}{d(\mathbf{x}, \mathbf{x}_i)^p}$$

The p value indicates the "power" of the distance penalty

The Inverse Distance Weighting (IDW) Method

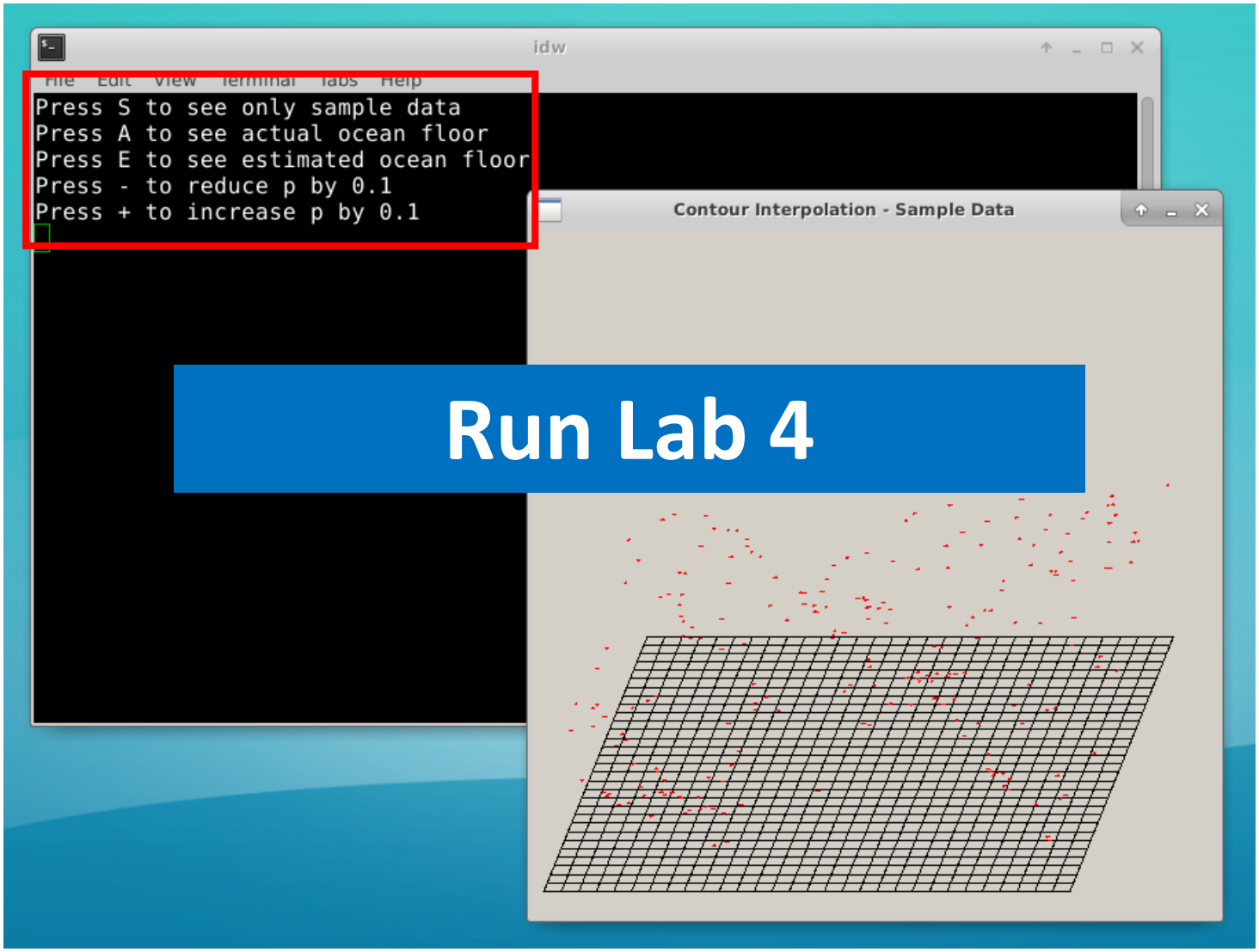
$$u(\mathbf{x}) = \begin{cases} \dfrac{\sum_{i=1}^{N} w_i(\mathbf{x}) u_i}{\sum_{i=1}^{N} w_i(\mathbf{x})}, & \text{if } d(\mathbf{x}, \mathbf{x}_i) \neq 0 \text{ for all } i \\ u_i, & \text{if } d(\mathbf{x}, \mathbf{x}_i) = 0 \text{ for some } i \end{cases}$$

where

$$w_i(\mathbf{x}) = \frac{1}{d(\mathbf{x}, \mathbf{x}_i)^p}$$

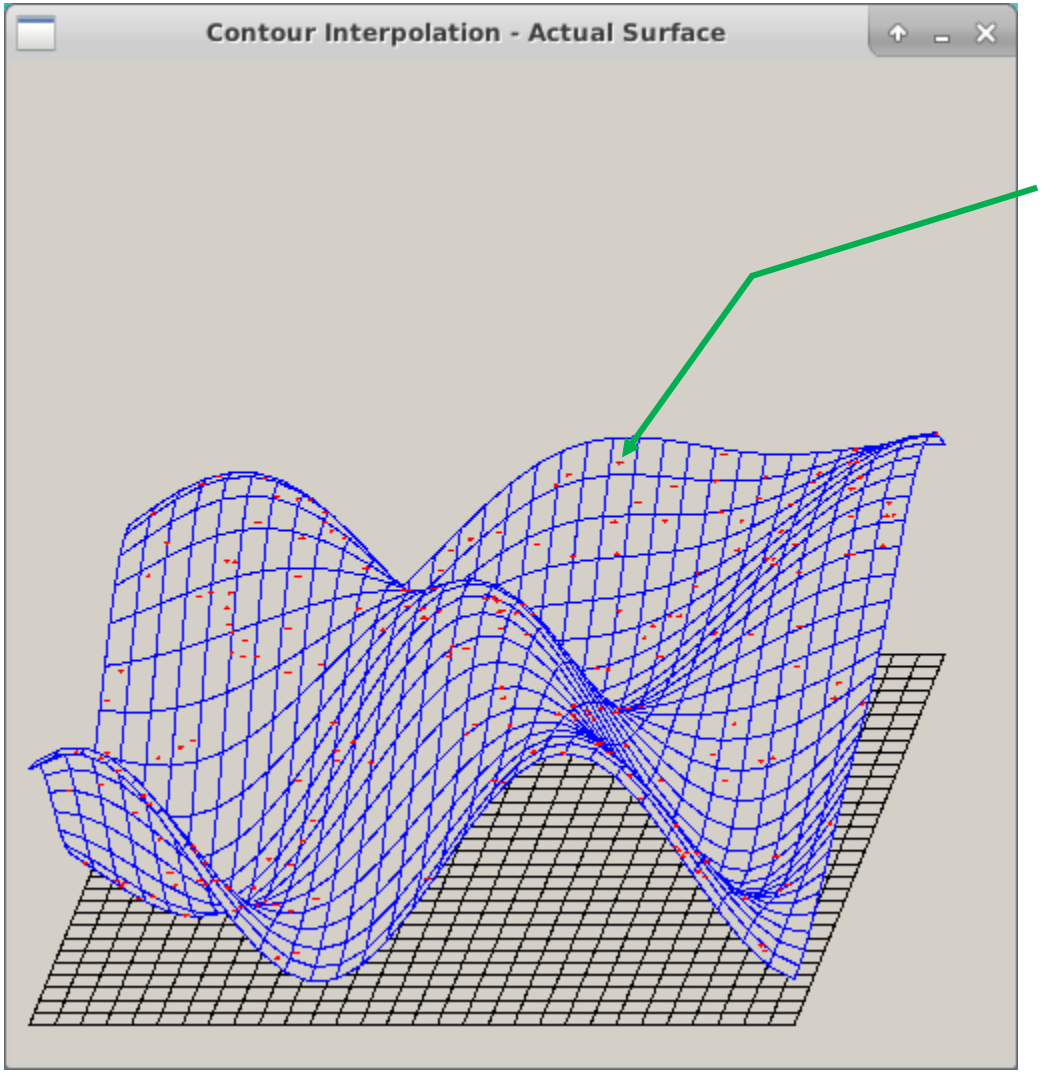
```
double GetEstHeight(double x, double z)
{
    double sumWeight = 0;
    double sumHeightWeight = 0;

    for (size_t n{}; n < numSamples; ++n) {
        double distance = sqrt(pow(x - samples[n].x, 2)
            + pow(z - samples[n].z, 2));

        if (distance == 0) return samples[n].y;

        double weight = 1 / pow(distance, p);

        sumWeight += weight;
        sumHeightWeight += samples[n].y * weight;
    }

    double height = sumHeightWeight / sumWeight;

    return height;
}
```

Inverse Distance Weighting



Actual Ocean Floor

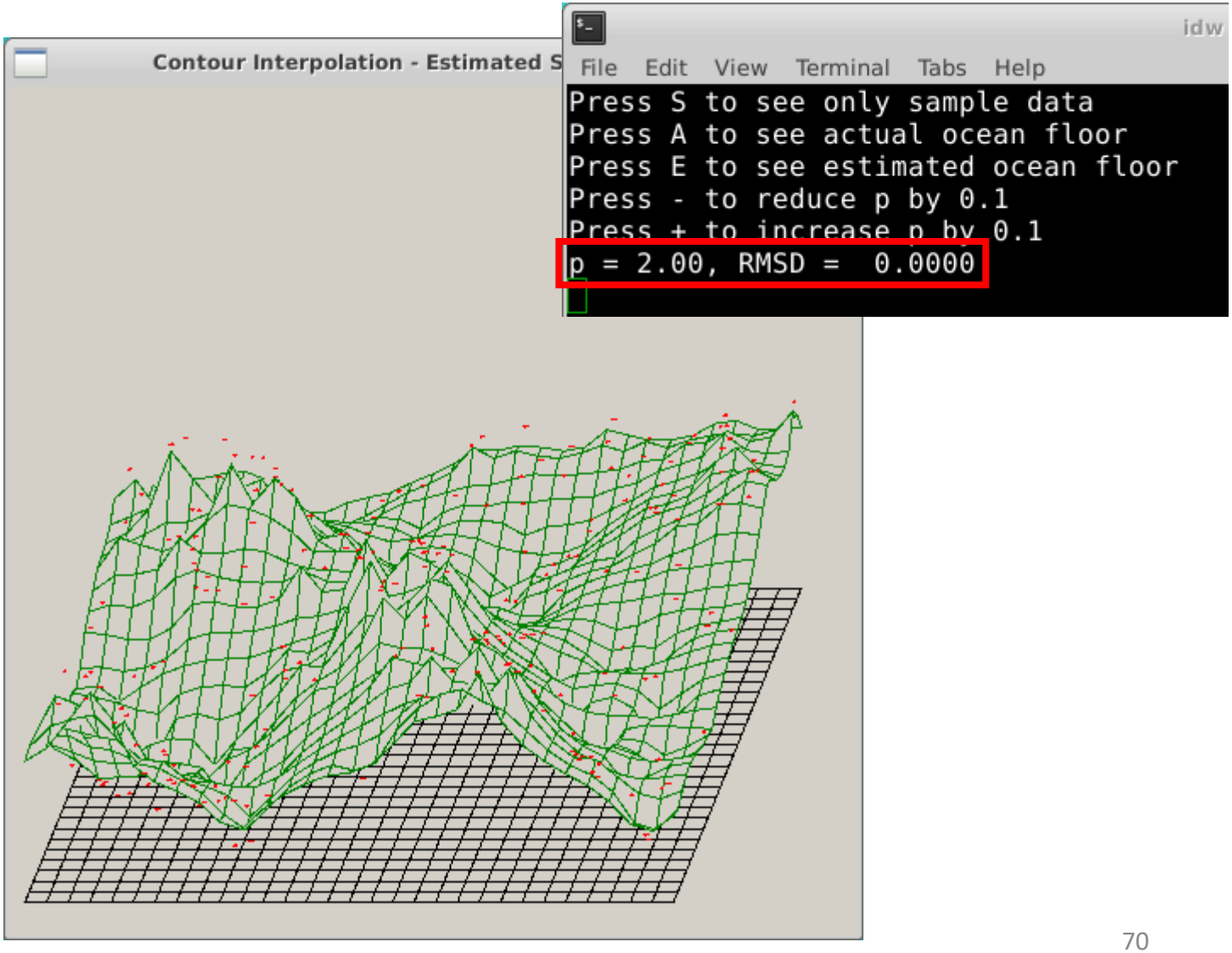
Press the **A** key to see the actual ocean floor



The **red** "dots" are the sample data points

Estimated Ocean Floor

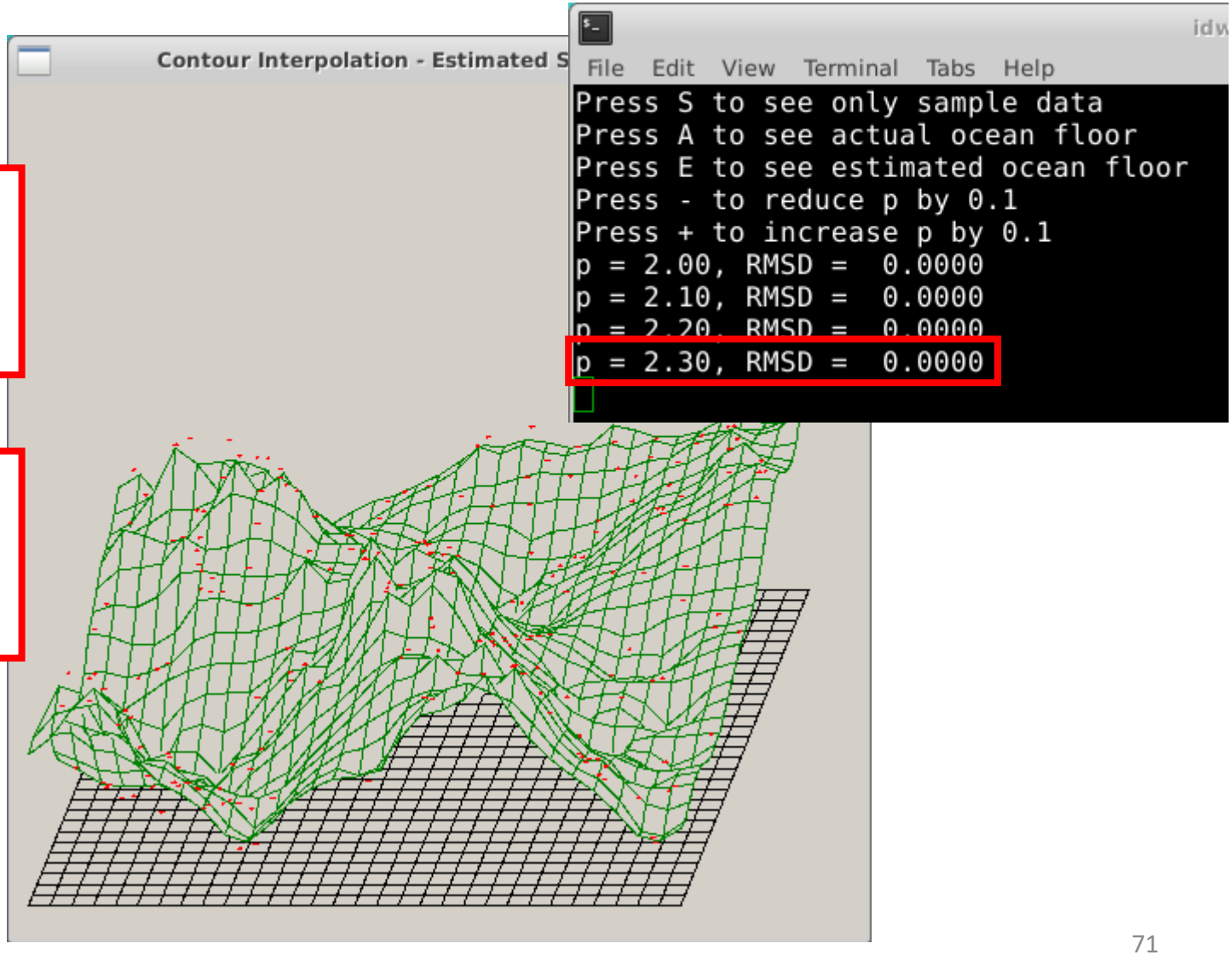
Press the **E** key to see the estimated ocean floor



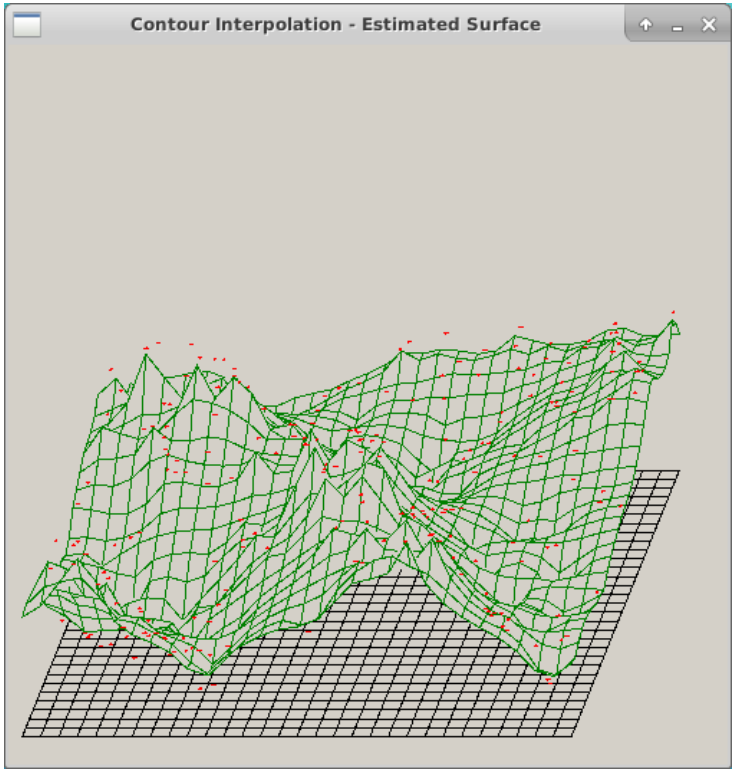
Estimated Ocean Floor

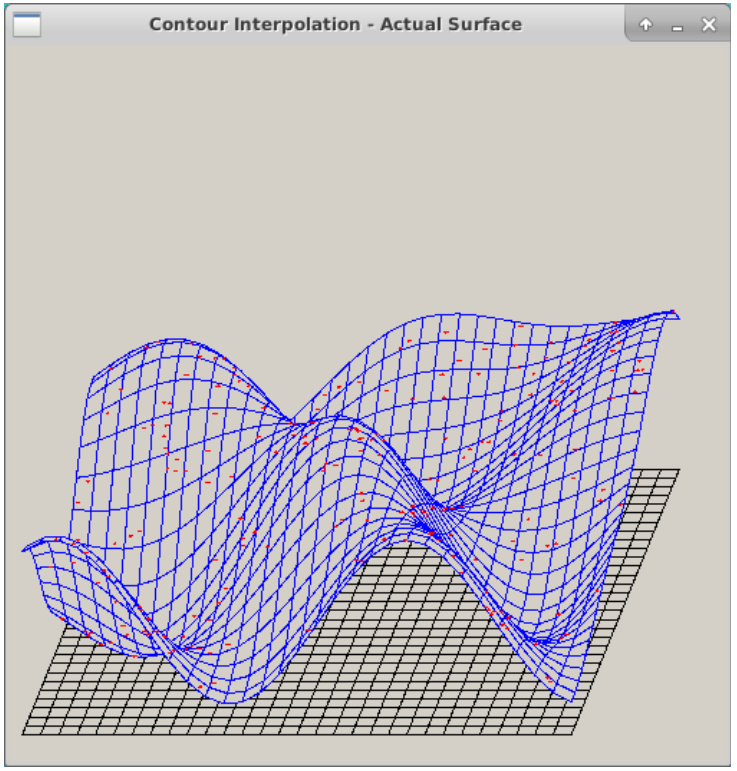
Press the + key to increase p (power) by 0.1

Press the - key to decrease p (power) by 0.1



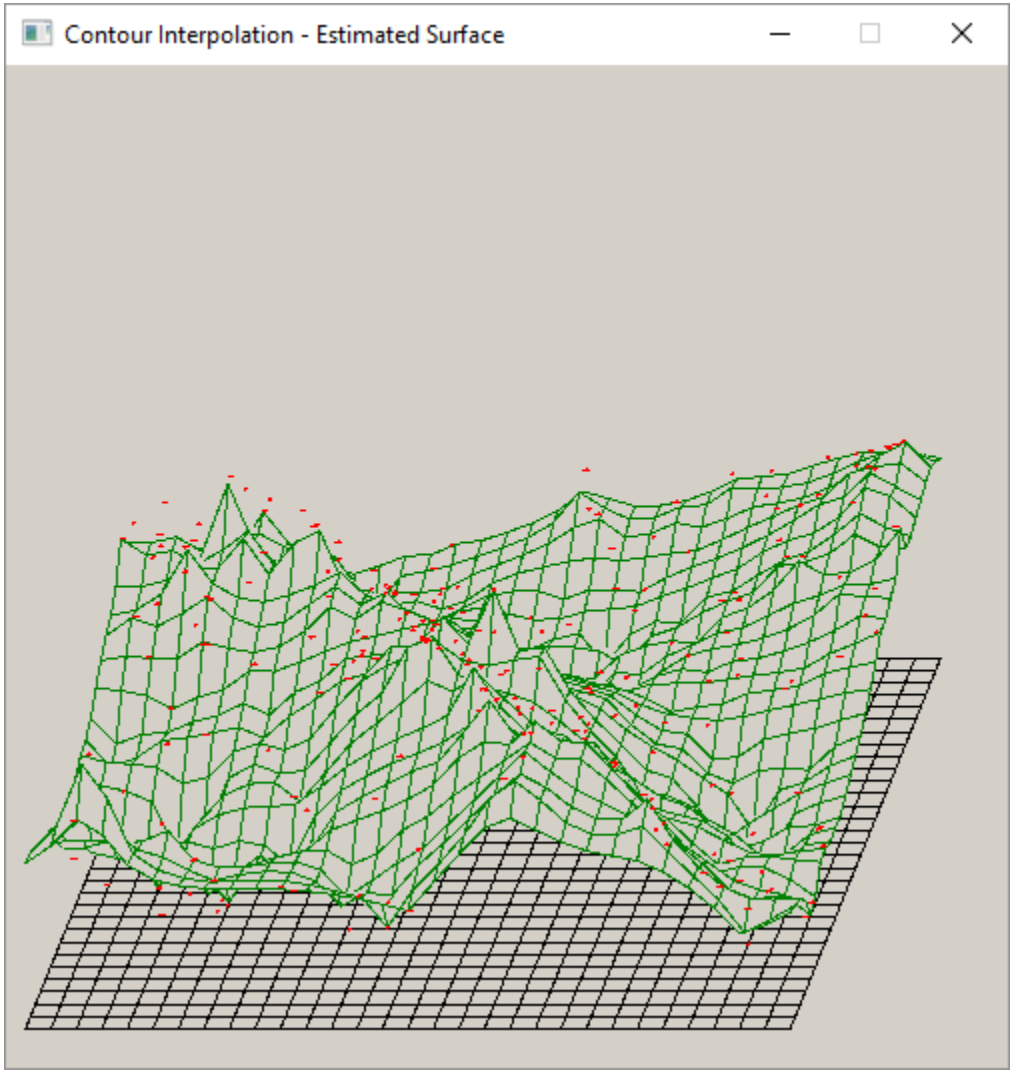
Estimated vs Actual (p = 2.0)



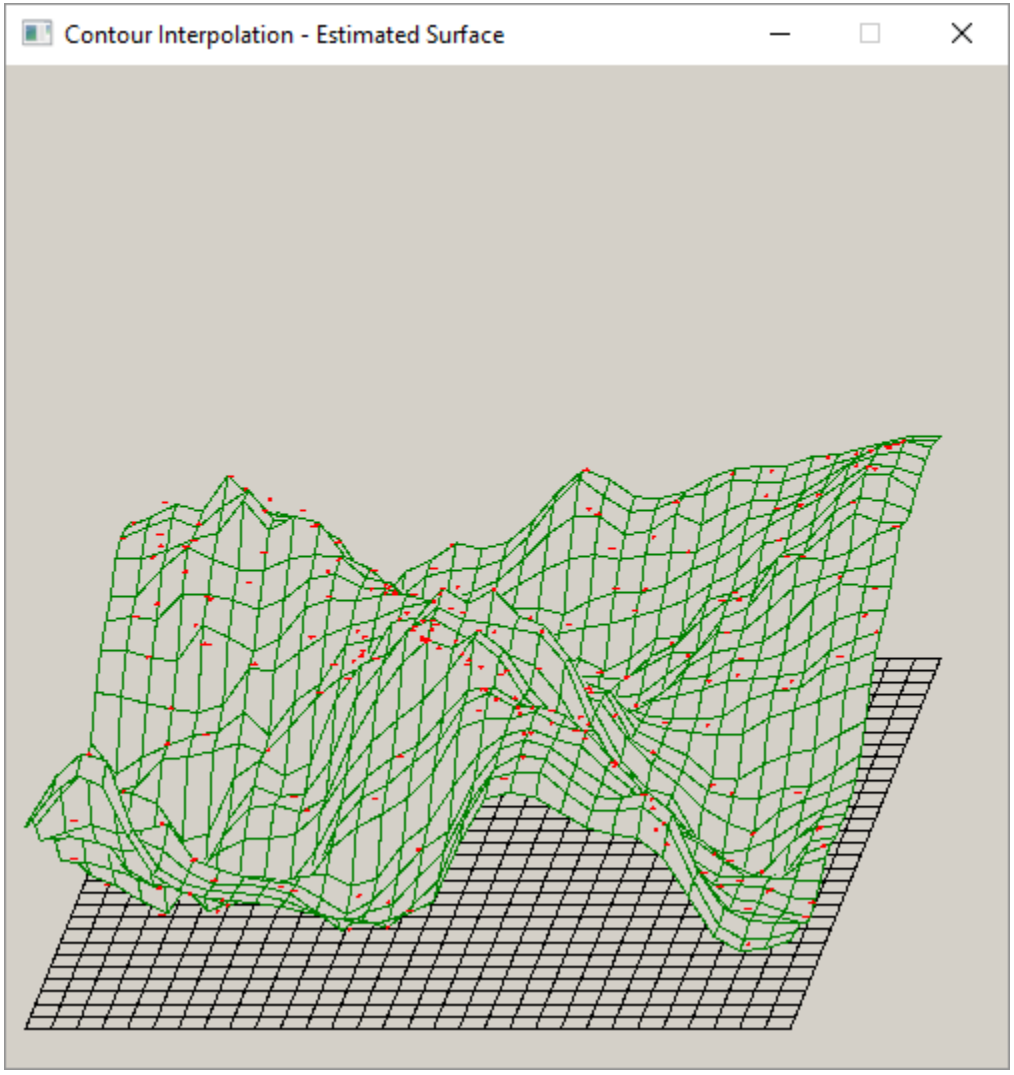


A first order approximation having only 24%
of the world sampled (220 of 900 actual points)

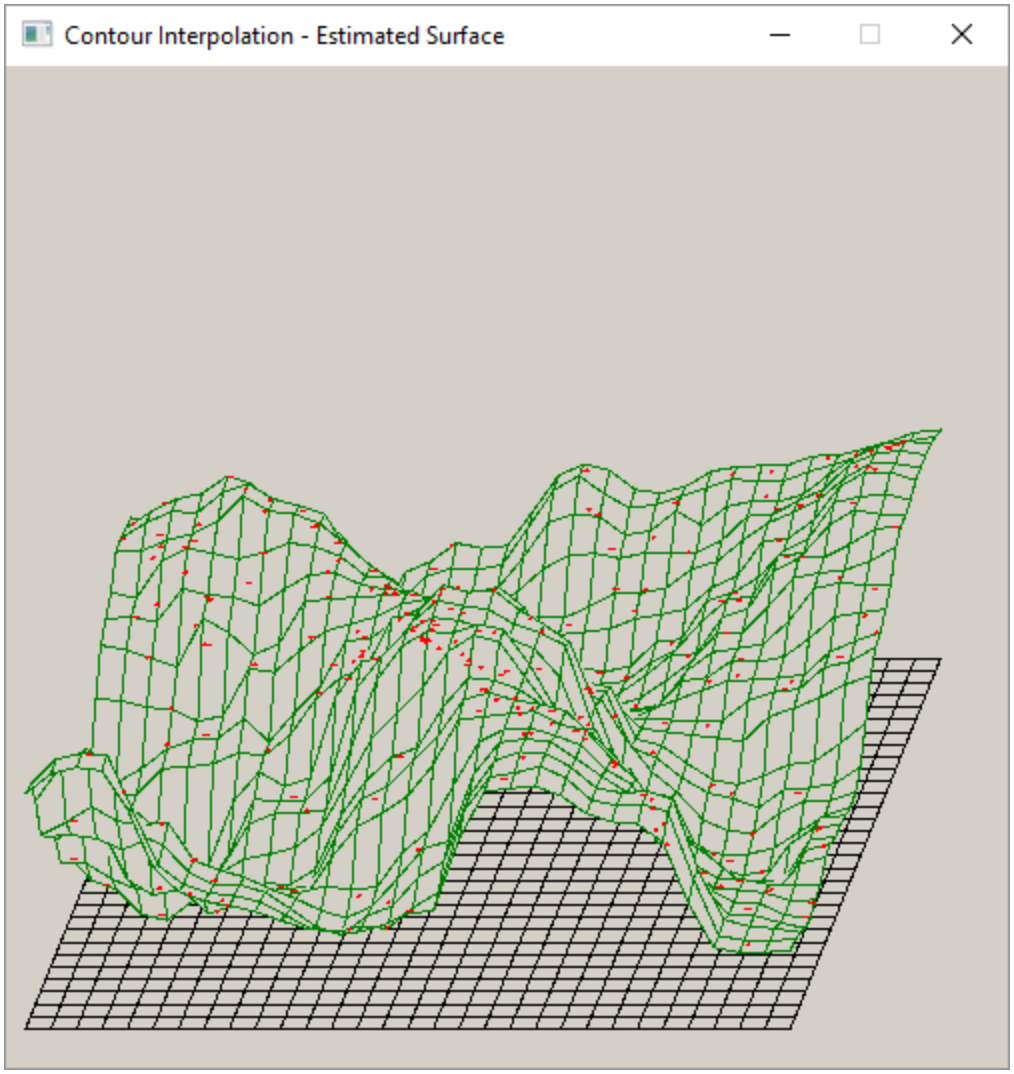
Estimate (p = 2.0)



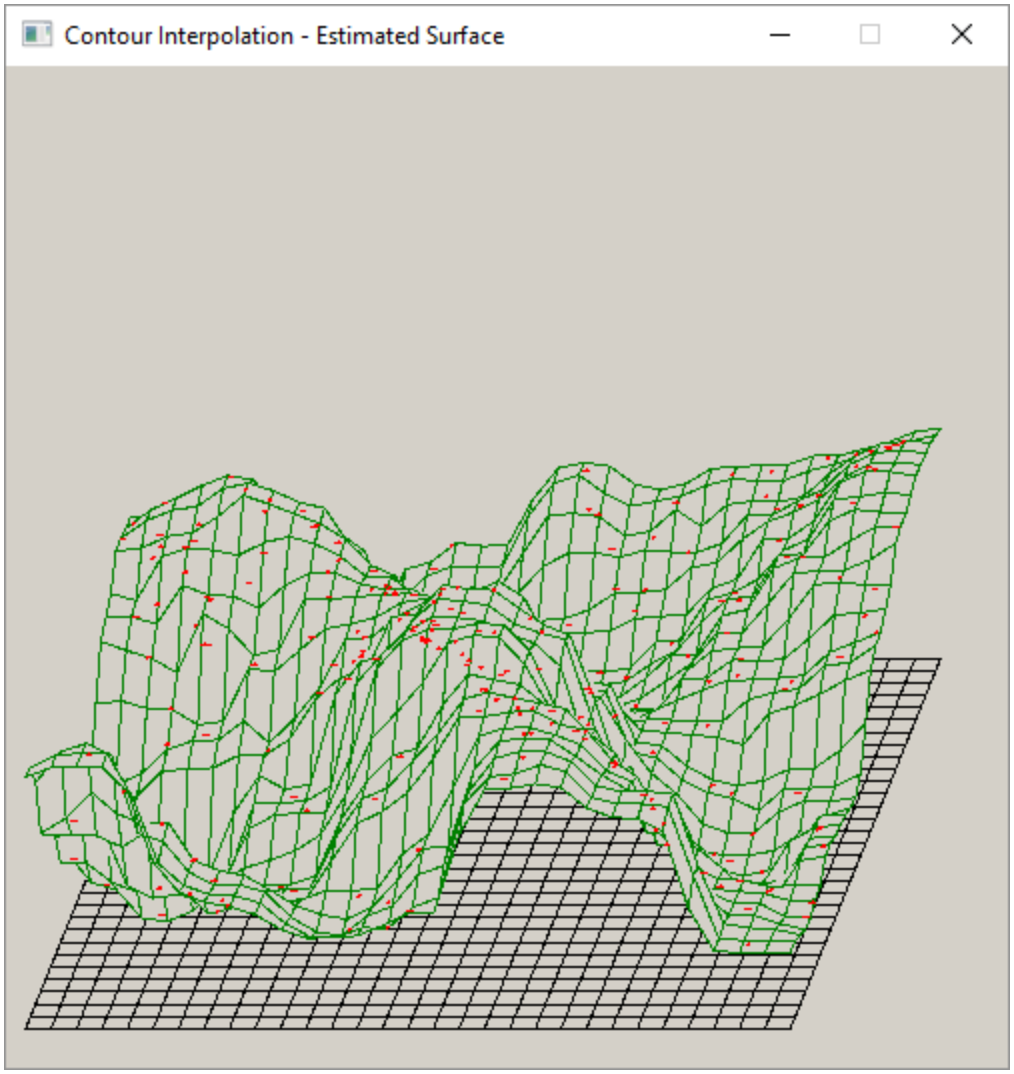
Estimate (p = 3.0)



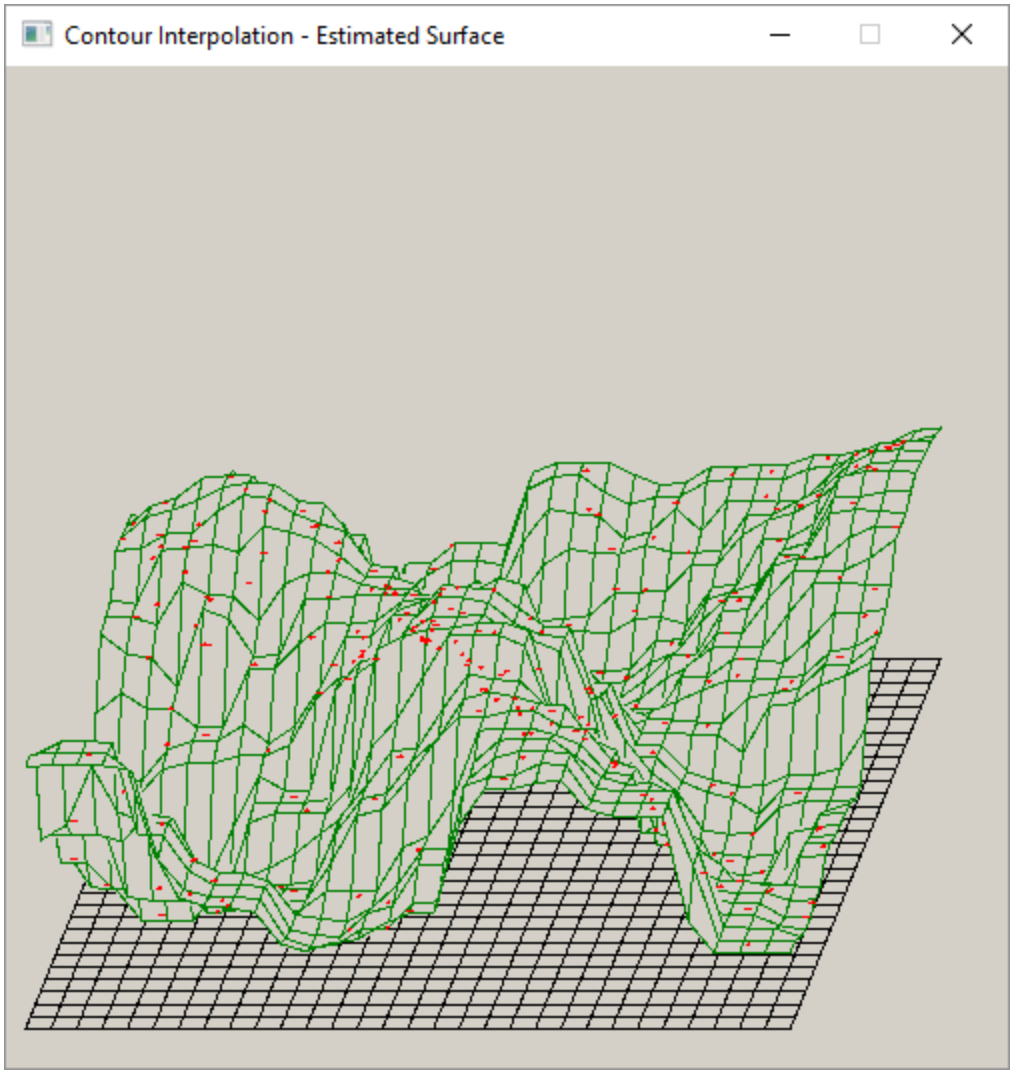
Estimate (p = 4.0)



Estimate (p = 5.0)



Estimate (p = 9.0)



Root Mean Square Deviation

- As we increase the **power** term **p**, is our model getting *better* or *worse* at predicting reality?
- The root-mean-square deviation (**RMSD**) is a statistic to measure the differences between values **predicted** by a model and the values actually **observed**

$$\mathrm{RMSD} = \sqrt{\frac{\sum_{t=1}^{n} (\hat{y}_t - y)^2}{n}}.$$

- By averaging **the errors** $(actual - estimated)^2$ across **all sample points**, we calculate a comparative statistic that can help empirically determine the optimal **p** value because it will minimize the overall error of the model

Edit Lab 4 - Calculate the RMSD

```
77  double CalcRMSD()
78  {
79      double rmsd = 0;
80      double sumErrors = 0;
81      for (int iz{ intervals - 1 };iz >= 0;--iz) {
82          for (int ix{}; ix < intervals;++ix) {
83              double x = ix * delta;
84              double z = -iz * delta;
85              double act = GetActHeight(x, z);
86              double est = GetEstHeight(x, z);
87              sumErrors += 0;
88          }
89      }
90      rmsd = 0;
91      return rmsd;
92  }
```

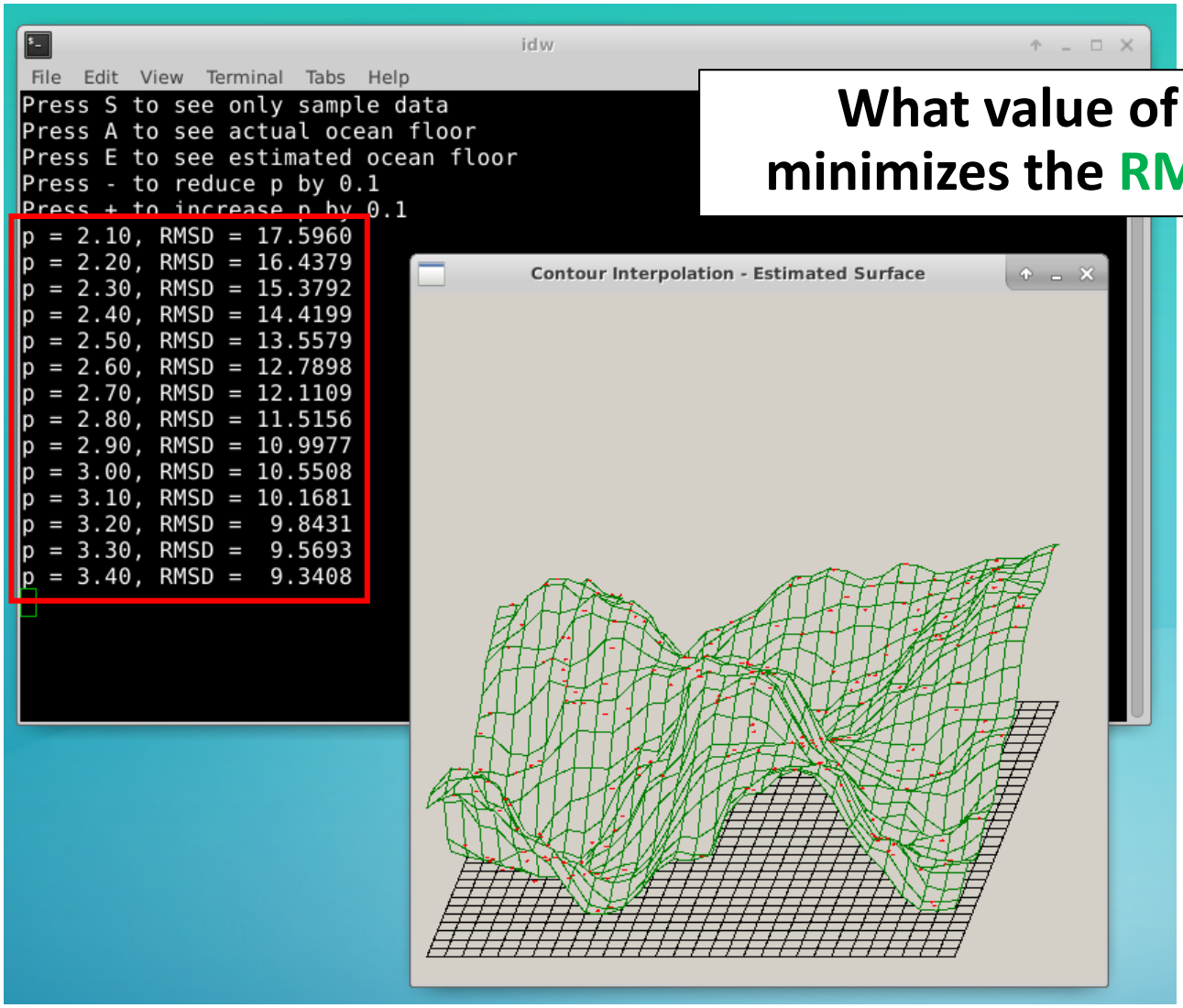
Fix the code to calculate sumErrors and rmsd

Edit Lab 4 - Calculate the RMSD

```
77  double CalcRMSD()
78  {
79      double rmsd = 0;
80      double sumErrors = 0;
81      for (int iz{ intervals - 1 };iz >= 0;--iz) {
82          for (int ix{}; ix < intervals;++ix) {
83              double x = ix * delta;
84              double z = -iz * delta;
85              double act = GetActHeight(x, z);
86              double est = GetEstHeight(x, z);
87              sumErrors += pow(act - est, 2);
88          }
89      }
90      rmsd = sqrt(sumErrors / (intervals * intervals));
91      return rmsd;
92  }
```

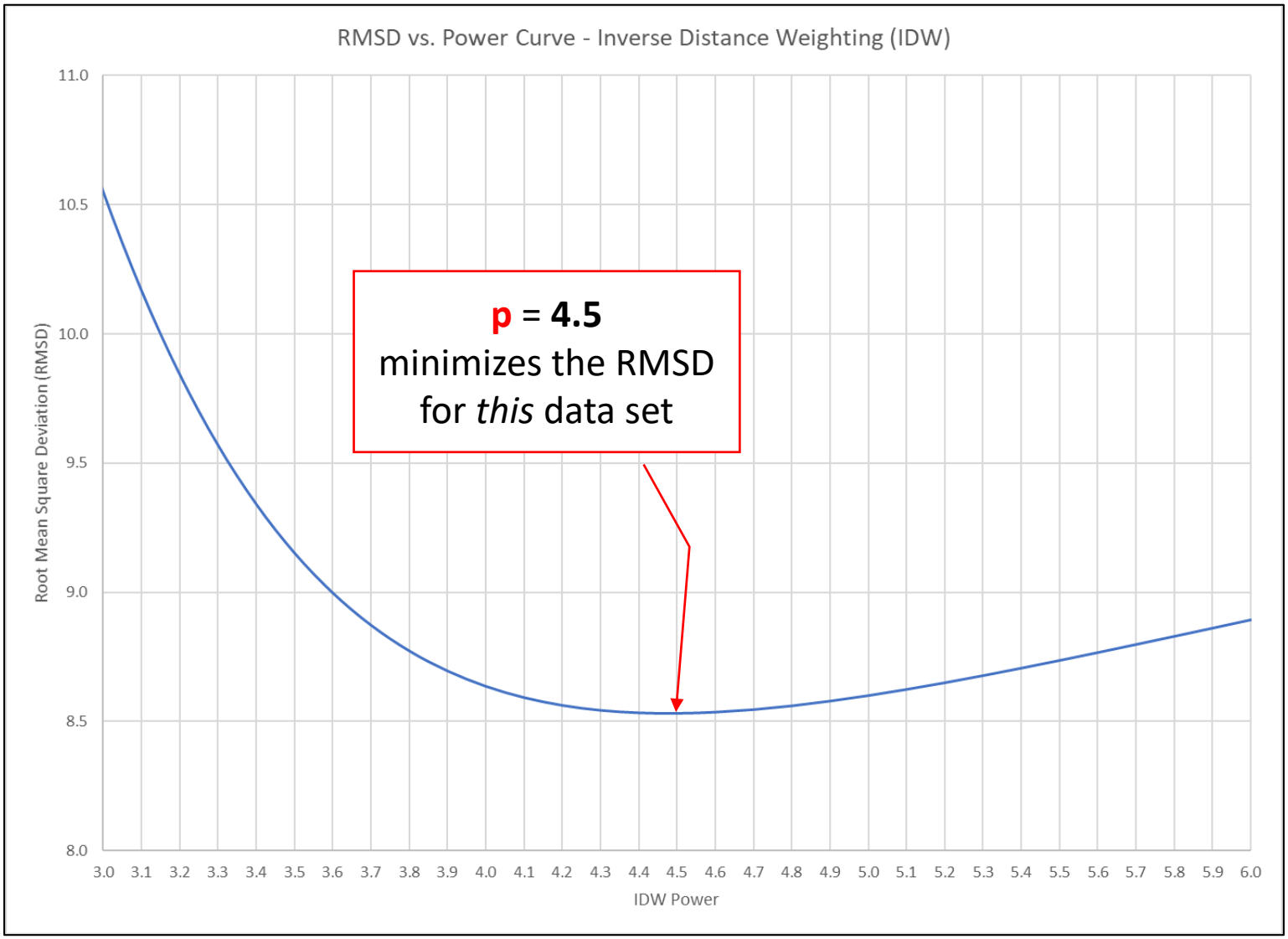
What value of p minimizes the RMSD?

Check Lab 4 - Calculate the RMSD



What value of p minimizes the RMSD?

Graphing the **RMSD**



Now you know…

- Identifying repeated sequences in DNA can lead to new understandings of genetic structure and purpose
  - **Suffix sort** is a very clever way to find the **longest repeating substring (LRSS)**
  - Sequence alignment tools (BLAST, etc.) look for which two sequences share a similar subsequence
  - Alternatively, LRSS looks inside a single sequence, to see what patterns might repeat ***within it***
- There could be biological significance of **a very long substring** that appears **only a *few* times** within the entire sequence

Now you know…

- The **Inverse Distance Weighting** (**IDW**) method can interpolate multi-dimensional data taken from random sample locations
  - How to convert non-uniformly measured spatial data into a **regular conforming mesh**
  - How to use **RMSD** as one metric to characterize the "goodness of fit" for predicted interpolated data points
- Scientists ***rarely*** enjoy the luxury of having too many data samples – we must often interpolate to fill in the missing gaps