Bioinformatics (MVE360)

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Content

The course covers basic methods used in sequence analysis such as pairwise and multiple alignment, searching databases for sequence similarity, profiles, pattern matching, hidden Markov models, RNA bioinformatics, gene prediction methods and principles for molecular phylogeny.
The course includes modern high-throughput sequencing techniques and their applications, as well as molecular biology databases and different systems to query such databases.
The course considers theoretical principles as well as how existing programs are being used by bioinformaticians.

Learning outcomes (1)

After completing this course, you should be able to:

- implement solutions to basic bioinformatics problems
- discuss the use of bioinformatics in addressing a range of biological questions
- describe how bioinformatics methods can be used to relate sequence, structure and function
- discuss the technologies for modern high-throughput DNA sequencing and their applications
- use and describe some central bioinformatics data and information resources

Learning outcomes (2)

- describe principles and algorithms of pairwise and multiple alignments, and sequence database searching
- perform pattern matching in biomolecular sequences
- describe how evolutionary relationships can be inferred from sequences (phylogenetics)
- describe the most important principles in gene prediction methods
- describe basic principles of hidden Markov models and their application in sequence analysis

Assessment

Grades will be determined by a written exam at the end of the course.
But in order to pass the course you must also submit solutions to specified exercises:

- one small programming task will be set each week;
- an essay on next generation sequencing and metagenomics.

Course home page

http://www.cse.chalmers.se/edu/year/2015/course/MVE360/

What is bioinformatics?

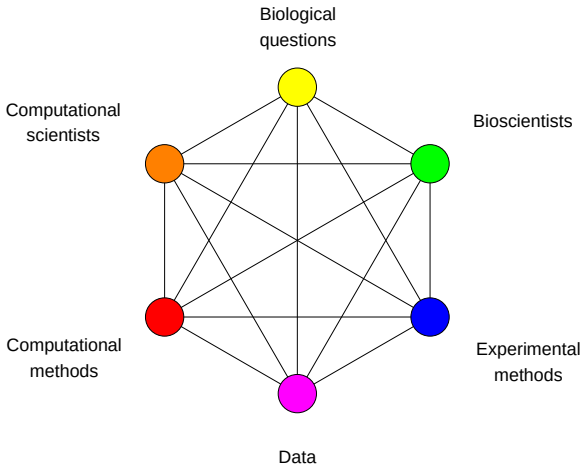
> *"Research, development, or application of computational tools and approaches for expanding the use of biological, medical, behavioral or health data, including those to acquire, store, organize, archive, analyze, or visualize such data."*
>
> *"Bioinformatics applies principles of information sciences and technologies to make the vast, diverse, and complex life sciences data more understandable and useful."*

Working definition by the NIH Biomedical Information Science and Technology Initiative Consortium, 2000
http://www.bisti.nih.gov/docs/CompuBioDef.pdf

What is biology?

Ecosystem	Rain forest, desert, fresh water lake, digestive tract of an animal
Community	All species in an ecosystem
Population	All individuals of a single species
Organism	One single individual
Organ System	A specialised functional system of an organism, e.g. nervous system or immune system
Organ	A specialised structural system of an organism, e.g. brain or kidney
Tissue	A specialised substructure of an organ, e.g. nervous tissue, smooth muscle
Cell	A single cell, e.g. neuron, skin cell, stem cell, bacteria
Molecule	e.g. protein, DNA, RNA, sugar, fatty acid, metabolites, pharmaceutical drugs

Addressing biological questions



Sequences, structures and systems

Sequences

- Nucleic acids (DNA and RNA) and proteins are (unbranched) polymers. Their composition can be described by the sequence of units (nucleotides or amino acid residues) in a chain.

Structures

- Three-dimensional structures can give insights into the molecular basis of biological functions.

Systems

- Biological processes consist of the coordinated actions of molecules.

Biological sequences: some experimental methods

- DNA sequencing
- Protein sequencing
- Next-generation sequencing (NGS)

Biological sequences: some questions

- How similar are a pair of sequences?
- Identify the corresponding units in a pair of homologous molecules that have undergone substitutions and insertions/deletions during their evolutionary history (*pairwise sequence alignment*).
- Given a new sequence, has anything similar (in whole or part) been seen before?
- Reconstruct a phylogenetic tree from the sequences of a set of homologous molecules.
- Given the sequences of many overlapping DNA fragments from a single organism, assemble them to reconstruct a full genome.
- Given the sequences of many DNA fragments from a mixture of organisms, identify the species present in the mixture.

Biological structures: some experimental methods

Find the atomic structure of a macromolecule or complex

- X-ray crystallography
- Nuclear magnetic resonance (NMR) spectroscopy

Identify a low-resolution "envelope" enclosing a large macromolecular complex

- Cryo-electron microscopy
- Small-angle x-ray scattering

Biological structures: some questions

- Can differences in the functions of two similar proteins be explained by differences in their structures?
- Can a drug be designed to fit into the active site of a target protein?
- Can the safety and efficacy of a potential therapeutic protein be predicted from its structure?
- Can the function of a protein be altered by changing its composition, and hence its structure?
- Can a protein's structure be predicted from its sequence?
  - the protein folding problem
- Given the structures of two proteins, will they associate with one another? If so, how will they fit together?
  - the protein docking problem

Biological systems: some experimental methods

Which mRNA molecules are being expressed?

- Microarray gene expression
- RNA-Seq

Which proteins are being expressed?

- (2-D) gel electrophoresis
- Mass spectrometry

In which tissue(s) are particular genes expressed?

- *in situ* hybridization

Biological systems: some questions

- Which genes/proteins are co-expressed (i.e. have similar expression profiles)?
- Which genes are expressed in tumour cells but not in healthy cells?
- If a gene is "knocked out", will an organism survive, and how will the expression of other genes be affected?
- Can protein expression profiles identify proteins that could be targets for drug development?
- Can an individual's expression profile indicate whether they are likely to respond to a particular therapeutic treatment?
- How do biological networks respond to injury or to treatment with a therapeutic drug?

“Scripting: Higher Level Programming for the 21st Century” (John Ousterhout)

http://www.tcl.tk/doc/scripting.html

For the last fifteen years a fundamental change has been occurring in the way people write computer programs. The change is a transition from system programming languages such as C or C++ to scripting languages such as Perl or Tcl. Although many people are participating in the change, few people realize that it is occurring and even fewer people know why it is happening. This article is an opinion piece that explains why scripting languages will handle many of the programming tasks of the next century better than system programming languages.

Scripting languages are designed for different tasks than system programming languages, and this leads to fundamental differences in the languages.

“Scripting: Higher Level Programming for the 21st Century” (John Ousterhout)

In deciding whether to use a scripting language or a system programming language for a particular task, consider the following questions:

- Is the application’s main task to connect together pre-existing components?
- Will the application manipulate a variety of different kinds of things?
- Does the application include a graphical user interface?
- Does the application do a lot of string manipulation?
- Will the application’s functions evolve rapidly over time?
- Does the application need to be extensible?

"Yes" answers to these questions suggest that a scripting language will work well for the application.

“Scripting: Higher Level Programming for the 21st Century” (John Ousterhout)

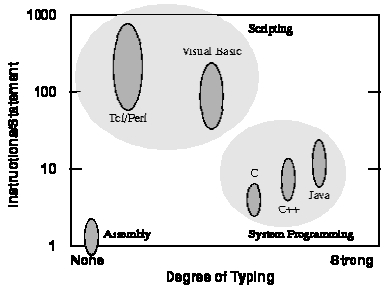


Figure 1. A comparison of various programming languages based on their level (higher level languages execute more machine instructions for each language statement) and their degree of typing. System programming languages like C tend to be strongly typed and medium level (5-10 instructions/statement). Scripting languages like Tcl tend to be weakly typed and very high level (100-1000 instructions/statement).

“Scripting: Higher Level Programming for the 21st Century” (John Ousterhout)

"Yes" answers to the following questions suggest that an application is better suited to a system programming language:

- Does the application implement complex algorithms or data structures?
- Does the application manipulate large datasets (e.g. all the pixels in an image) so that execution speed is critical?
- Are the application’s functions well-defined and changing slowly?

Scripting and system programming are symbiotic. Used together, they produce programming environments of exceptional power: system programming languages are used to create exciting components which can then be assembled using scripting languages.

Perl

Practical Extraction and Report Language

scalar1.pl

```
#!/usr/bin/perl -w

$a = 3;
$b = 5;

$rem1 = $a % $b;            # 3
$rem2 = $b % $a;            # 2

$a++;                       # 4
$b--;                       # 4

$n1 = $a + $b * 2;          # 12
$n2 = ($a + $b) * 2;        # 16
$n3 = 12 / $a / 2;          # 1.5
$n4 = 12 / ($a / 2);        # 6
$n5 = (2*2)**($b-2)**2;     # 256
```


hello.pl

```
#!/usr/bin/perl

print "Hello world\n";
```

simple.pl

```
#!/usr/bin/perl

$a = 2;
$b = 3;
$result = $a + $b;
print "Result is: $result\n";
```


Loops in Perl

```
$i = 1;
while ( $i <= 4 ) {
    print "$i\n";
    $i++;
}

$i = 1;
until ( $i > 4 ) {
    print "$i\n";
    $i++;
}

for ( $i = 1 ; $i <= 4 ; $i++ ) {
    print "$i\n";
}

foreach $i ( (1,2,3,4) ) {
    print "$i\n";
}
```

countdown.pl

```
#!/usr/bin/perl

#
# file:         countdown.pl
# purpose:      a 10 second countdown
#

$countdown = 10;
while ( $countdown != 0 ) {
        print "$countdown...\n";
        sleep 1;
        --$countdown;
}
print "BOOM!\n";
```


string1.pl

```
#!/usr/bin/perl

$empty = "";
$a = "Bioinformatics";
$b = "\"Perl Programming\"\n";
$me = "Graham\tChalmers\t6475\n";

print "$a $empty $b";
print $me;
print "\n";
```

```
Bioinformatics  "Perl Programming"
Graham  Chalmers        6475
```


scalar2.pl

```
#!/usr/bin/perl

$str1 = "Merry";
$str2 = "_Christmas! ";
$a = $str1 . "_Christmas!_";  # Merry_Christmas!_
$b = $str1 . $str2;           # Merry_Christmas!_
$c = "$str1$str2";            # Merry_Christmas!_
$b .= $b;                     # Merry_Christmas!_Merry_Christmas!_
$d = $c x 2;                  # Merry_Christmas!_Merry_Christmas!_
$e = chop($str1);             # y
$f = length($str1);           # 4
$g = lc($str1);               # merr
$h = uc($str1);               # MERR
$i = substr($a,0,3);          # Mer
$j = substr($a,-4,2);         # as
$k = index($a,"m");           # 12
```


string2.pl

```
#!/usr/bin/perl

#
# demonstrate single-quoted strings
#

$empty = '';
$a = 'Bioinformatics';
$b = '\"Perl Programming\"\n';
$me = 'Graham\tChalmers\t6475\n';

print "$a $empty $b";
print $me;
print "\n";
```

```
Bioinformatics  \"Perl Programming\"\nGraham\tChalmers\t6475\n
```

circle.pl

```
#!/usr/bin/perl -w

$pi = 3.1415925;

print "Please type in the radius: ";
$radius = <STDIN>;
chomp($radius);

$area = $pi * $radius * $radius;
$circ = 2 * $pi * $radius;

print "A circle of radius $radius has area $area\n",
      "and circumference $circ\n";
```

```
Please type in the radius: 4
A circle of radius 4 has area 50.26548
and circumference 25.13274
```


copyfile.pl

```
#!/usr/bin/perl -w

open(SOURCE, "file_A")  || die "cannot open file_A: $!";
open(TARGET, ">file_B") || die "cannot open file_B: $!";
while ( $line = <SOURCE> ) {
       print TARGET $line;
}
close(SOURCE);
close(TARGET);
```

```
#!/usr/bin/perl -w

open(SOURCE, "file_A")  || die "cannot open file_A: $!";
open(TARGET, ">file_B") || die "cannot open file_B: $!";
while ( <SOURCE> ) {
       print TARGET; }
close(SOURCE);
close(TARGET);
```


Opening files

```
open(SOURCE1, "file1");       # reading

open(SOURCE1, "<file2");      # reading

open(RESULT1, ">output1");    # writing (create or overwrite)

open(RESULT2, ">>output2");   # writing (create or append)

open(RESULT3, "+<inoutfile"); # reading/writing

open(SOURCE1, "file1") or die "Unable to open file: $!";
open(SOURCE1, "file1") || die "Unable to open file: $!";

close(SOURCE1);
```


Command line arguments

```
#!/usr/bin/perl

#
# file:         arguments.pl
# purpose:      prints the command line arguments
#

print "Command line arguments are: @ARGV\n";
print "The first argument is: $ARGV[0]\n";
```

Variables beginning with an @ symbol are array variables.
(Scalar) element at position i within an array @a is accessed by $a[i-1]

mycat.pl

```
#!/usr/bin/perl
while ( $_ = <ARGV> ) {
        print $_;
}
```

```
#!/usr/bin/perl
while ( <ARGV> ) {
        print;
}
```

```
#!/usr/bin/perl
while ( <> ) {
        print;
}
```


Comparison operators

Operation	Numeric	String
equal	==	eq
not equal	!=	ne
less than	<	lt
greater than	>	gt
less than or equal	<=	le
greater than or equal	>=	ge

What is true?

- anything except "" and "0"
- any number except 0
- any non-empty array

Conditional statements

```
if ( expression ) {
    # do if true
}

if ( expression ) {
    # do if true
} else {
    # do if flase
}

if  ( expression1 ) {
    # do if expression1 is true
} elsif ( expression2 ) {
    # do if expression1 is false and expression2 is true
} else {
    # do if expression1 is false and expression2 is false
}
```


Executing Perl programs

You can invoke the Perl interpreter directly, e.g.

```
perl program.pl
```

Or, if the first line of the program contains "#!" followed by the path of the Perl interpreter, and the program file is executable, you can just type the name of the program file on the command line, e.g.

```
./program.pl
```

To make a program file executable, use the chmod command, e.g.

```
chmod u+x program.pl
```