Working with DNA strings and ranges

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Introduction

Genomic Intervals with Data

Coverage and Other Piecewise Constant Measures

Long Biological Strings

Developer's Notes

Resources

Outline

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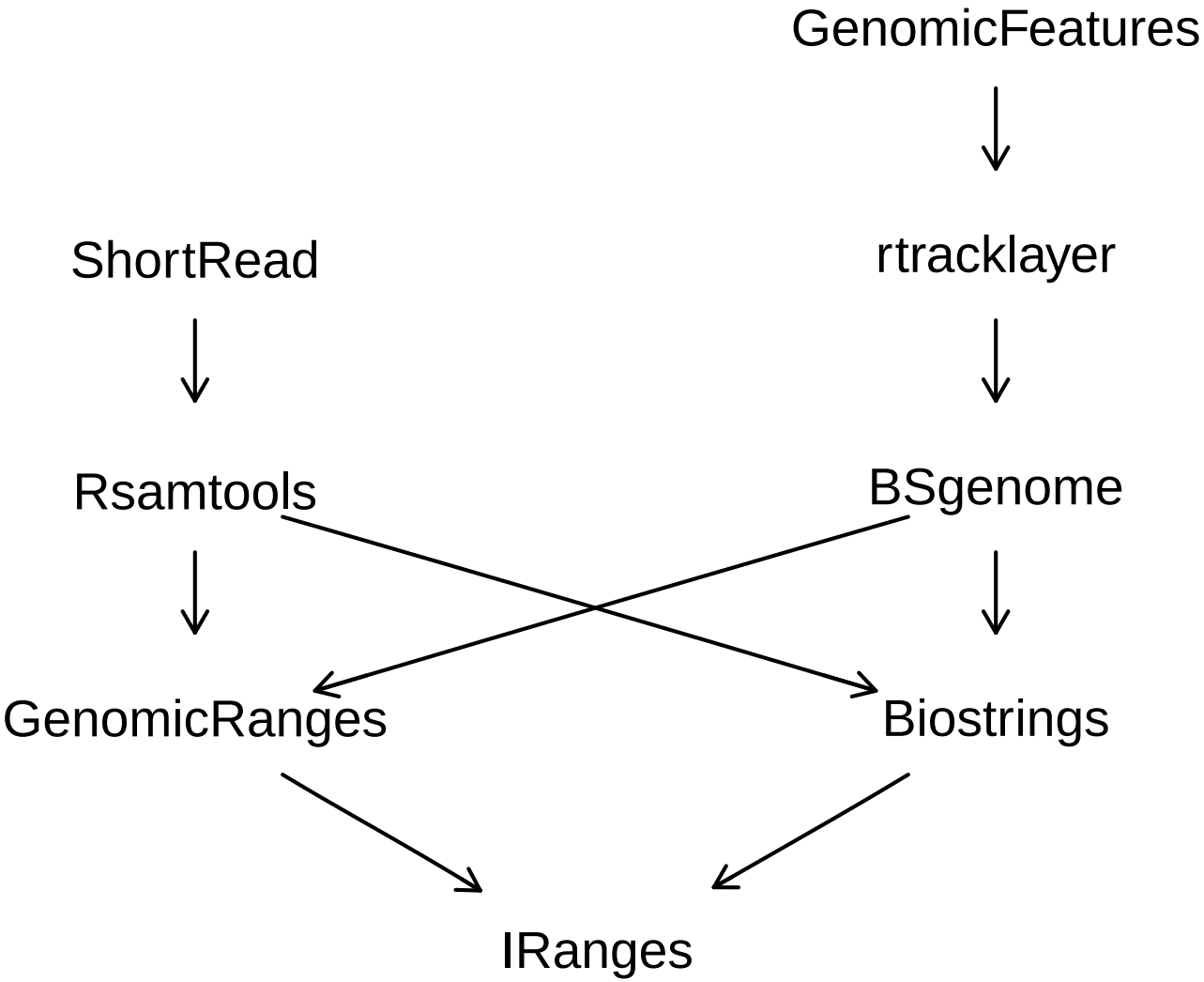
Bioconductor Sequence Packages



Bioconductor Sequence Infrastructure Packages

IRanges

- Long sequences (compressed & pointer referenced)
- Views on long sequences
- Integer interval tools (e.g. interval overlap)

GenomicRanges

- Genomic intervals (*GRanges*)
- Discontiguous genomic interval sets (*GRangesList*)

Biostrings

- Long DNA/RNA/amino acids sequences
- Sequence & PWM matching and pairwise alignment tools

Bioconductor Sequence Infrastructure Classes

Long piecewise constant sequences

Rle, *RleList*

Ranges (as sequences & intervals)

IRanges

Genomic intervals with data

GRanges

Genomic interval sets (e.g. spliced transcripts)

GRangesList

Long DNA sequences

DNAString, *DNAStringSet*, ...

Views on long sequences

RleViews, *RleListViews*, *XStringViews*, ...

Concept I: Run-Length Encoding (RLE)

Issue

- Chromosomes can be hundreds of million of base pairs long, making them hard to manage in computer memory.
- Fortunately, coverage vectors tend to follow an integer step function.

Solution

- Run-length encoding (RLE) is a common compression technique for storing long sequences with lengthy repeats.
- An RLE couples values with run lengths, e.g. the vector 0, 0, 0, 1, 1, 2 would be represented as (3) 0's, (2) 1's, and (1) 2.
- The *IRanges* package uses the *Rle* and *RleList* classes to house coverage vectors.

Concept II: Sequence Views

Issue

- Chromosomes can be hundreds of million of base pairs long, making subsequence selection inefficient.

Solution

- Store the original sequence using a pass-by-reference semantic.
- Associate ranges with the sequence to select subsequence.
- Example:
  - 7007-letter sequence: `<<SNIP-3000>>AGATTCA<<SNIP-4000>>`
  - View range: `[3001, 3007]`
  - => 7-letter subsequence: `AGATTCA`

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Naive representation for intervals with data

Data characteristics

- Genomic coordinates consist of chromosome, position, and potentially strand information
- May have additional values, such as GC content or alignment coverage

data.frame approach

```
> chr <- c("chr1", "chr2", "chr1")
> strand <- c("+", "+", "-")
> start <- c(3L, 4L, 1L)
> end <- c(7L, 5L, 3L)
> naive <- data.frame(chr = chr, strand = strand,
+                     start = start, end = end)
```

Genomic intervals with data

GRanges

- Used by *GenomicFeatures*, a transcript annotation generator
- Intervals not required to be grouped by chromosome/contig
- Methods strand aware
- *GRangesList* class can hold exons within spliced transcripts

GRanges construction

GRanges constructor

- Instances are created using the `GRanges` constructor.
- Starts and ends are wrapped in an *IRanges* constructor.
- Chromosome/contig supplied to `seqnames` argument.
- Underlying sequence lengths can be suppled to `seqlengths` argument.

GRanges example

```
> bioc <- GRanges(seqnames = chr,
+                 ranges = IRanges(start = start, end = end),
+                 strand = strand,
+                 seqlengths = c("chr1" = 24, "chr2" = 18))
```

GRanges display

GRanges `show` method

```
> bioc
```

```
GRanges with 3 ranges and 0 elementMetadata values
    seqnames    ranges strand |
       <Rle> <IRanges>  <Rle> |
[1]     chr1    [3, 7]      + |
[2]     chr2    [4, 5]      + |
[3]     chr1    [1, 3]      - |

seqlengths
 chr1 chr2
   24   18
```

Note

- Optional interval data would appear to the right of `|` divider.

GRanges class decomposition

GRanges slots

```
> getSlots("GRanges")

       seqnames          ranges          strand         seqinfo
          "Rle"       "IRanges"           "Rle"       "Seqinfo"
elementMetadata     elementType        metadata
          "ANY"     "character"          "list"
```

Notes

- If (mostly) sorted, *Rle* vectors reduce memory usage and provide faster group selection
- `elementMetadata` holds optional interval data
- `metadata` holds optional whole object info

Interval operations

Intra-interval

`flank`, `resize`, `shift`

Inter-interval I

`disjoin`, `gaps`, `reduce`, `range`

Inter-interval II

`coverage`

Between two interval sets I

`union`, `intersect`, `setdiff`

Between two interval sets II

`punion`, `pintersect`, `psetdiff`

Between two interval sets III

`findOverlaps`, `countOverlaps`, `%in%`, `match`

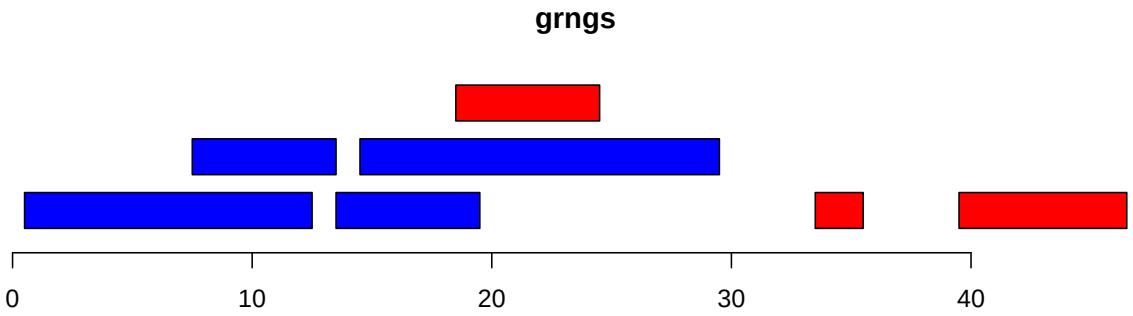
Low level

`start`, `end`, `width`

Creating a new *GRanges* object

New object to use in interval operations

```
> ir <- IRanges(c(1, 8, 14, 15, 19, 34, 40),
+               width=c(12, 6,  6, 15, 6, 2, 7))
> strand <- rep(c("+", "-"), c(4,3))
> grngs <- GRanges(seqnames = "chr1", ranges = ir,
+                  strand = strand,
+                  seqlengths = c("chr1" = 50))
```



blue = positive strand, red = negative strand

GRanges subsetting

seqselect

```
> seqselect(grngs, strand(grngs) == "-")
```

```
GRanges with 3 ranges and 0 elementMetadata values
    seqnames    ranges strand |
       <Rle> <IRanges>  <Rle> |
[1]     chr1  [19, 24]      - |
[2]     chr1  [34, 35]      - |
[3]     chr1  [40, 46]      - |

seqlengths
 chr1
   50
```

Other functions

`[`, `head`, `tail`, `window`, `subset`, `subsetByOverlaps`

Intra-interval (1/2)

Shifting intervals

If your interval bounds are off by 1, you can shift them.

```
> shift(grngs, 1)

GRanges with 7 ranges and 0 elementMetadata values
    seqnames    ranges strand |
       <Rle> <IRanges>  <Rle> |
[1]     chr1  [ 2, 13]      + |
[2]     chr1  [ 9, 14]      + |
[3]     chr1  [15, 20]      + |
[4]     chr1  [16, 30]      + |
[5]     chr1  [20, 25]      - |
[6]     chr1  [35, 36]      - |
[7]     chr1  [41, 47]      - |

seqlengths
 chr1
   50
```

Intra-interval (2/2)

Resizing intervals

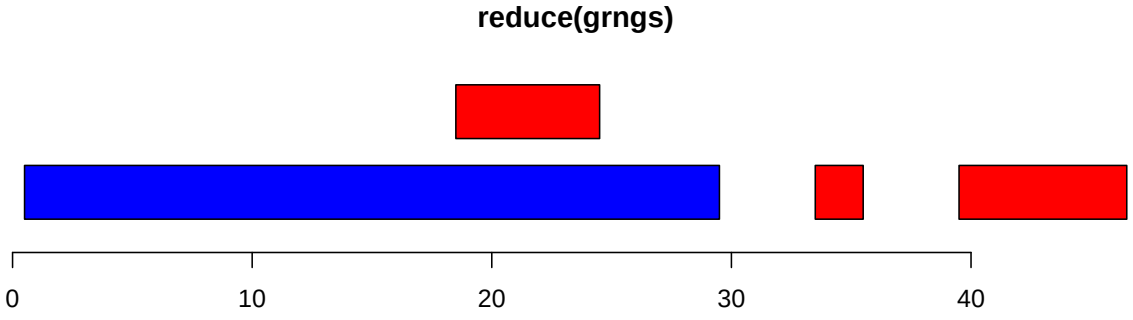
"Growing" alignment intervals to an estimated fragment length.

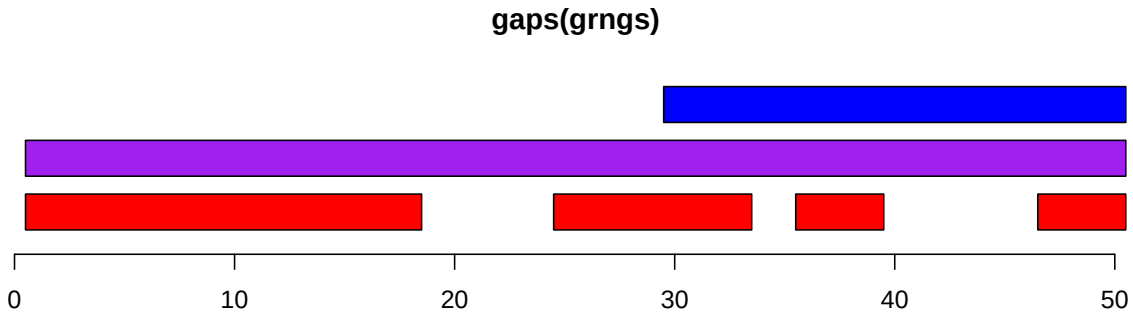
```
> resize(grngs, 10)
```

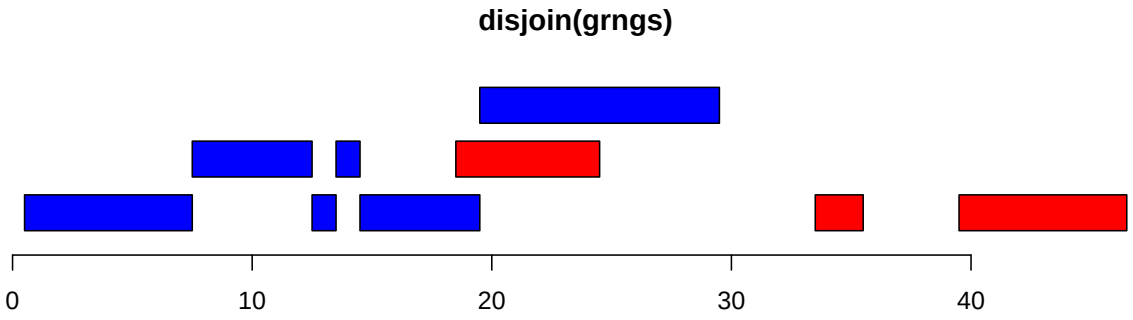
```
GRanges with 7 ranges and 0 elementMetadata values
    seqnames    ranges strand |
       <Rle> <IRanges>  <Rle> |
[1]     chr1  [ 1, 10]      + |
[2]     chr1  [ 8, 17]      + |
[3]     chr1  [14, 23]      + |
[4]     chr1  [15, 24]      + |
[5]     chr1  [15, 24]      - |
[6]     chr1  [26, 35]      - |
[7]     chr1  [37, 46]      - |

seqlengths
 chr1
   50
```

Inter-interval I







Overlap detection

Finding interval overlaps

`findOverlap` and `countOverlaps` produce a mapping and a tabulation of interval overlaps, respectively

```
> ol <- findOverlaps(grngs, reduce(grngs))
> as.matrix(ol)
```

```
     query subject
[1,]     1       1
[2,]     2       1
[3,]     3       1
[4,]     4       1
[5,]     5       2
[6,]     6       3
[7,]     7       4
```

```
> countOverlaps(reduce(grngs), grngs)
```

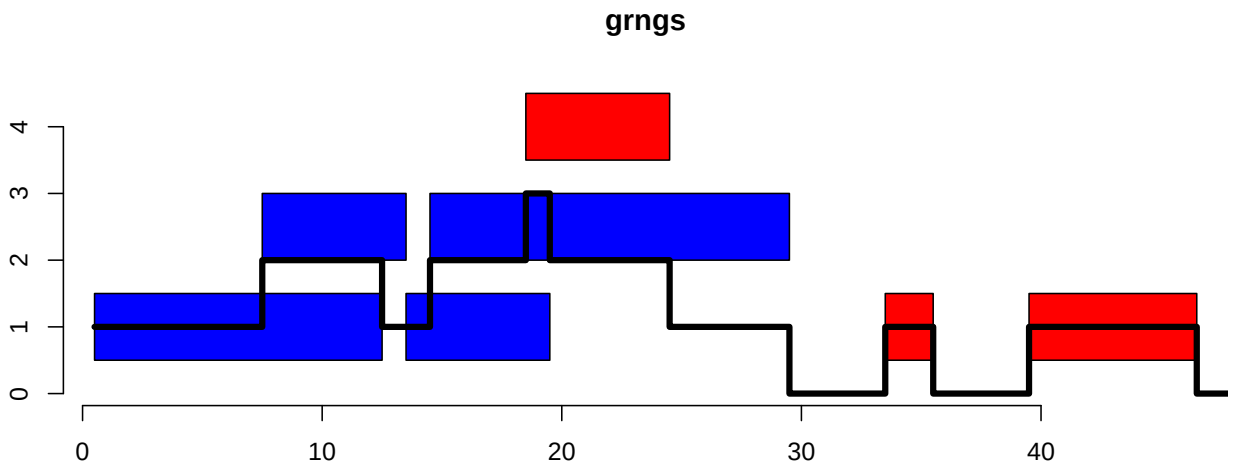
```
[1] 4 1 1 1
```

Elementwise counts of overlapping intervals

Coverage

- `coverage` counts number of ranges over each position
- Subset by strand to get stranded coverage

```
> cover <- coverage(grngs)
```



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Piecewise constant measures

Issue restated

- The number of genomic positions in a genome is often in the billions for higher organisms, making it challenging to represent in memory.
- Some data across a genome tend to be sparse (i.e. large stretches of "no information")

Rle and *RleList* classes

- Solve the set of problems for positional measures that tend to have consecutively repeating values.
- *Do not* address the more general problem of positional measures that constantly fluxuate, such as conservation scores.

Numerous *Rle* methods (1/2)

```
 [1] "!"             "["             "[<-"           "%in%"
 [5] "aggregate"     "as.character"  "as.complex"    "as.data.frame"
 [9] "as.factor"     "as.integer"    "as.logical"    "as.numeric"
[13] "as.raw"        "as.vector"     "c"             "chartr"
[17] "coerce"        "Complex"       "cor"           "cov"
[21] "diff"          "end"           "findRange"     "findRun"
[25] "gsub"          "IQR"           "is.na"         "is.unsorted"
[29] "length"        "levels"        "levels<-"      "mad"
[33] "match"         "Math"          "Math2"         "mean"
[37] "median"        "nchar"         "nrun"          "Ops"
[41] "paste"         "pmax"          "pmax.int"      "pmin"
[45] "pmin.int"      "quantile"      "rep"           "rep.int"
[49] "rev"           "runLength"     "runLength<-"   "runmean"
[53] "runmed"        "runq"          "runsum"        "runValue"
[57] "runValue<-"    "runwtsum"      "sd"            "seqselect"
[61] "seqselect<-"   "shiftApply"    "show"          "slice"
[65] "smoothEnds"    "sort"          "split"         "splitRanges"
[69] "start"         "sub"           "substr"        "substring"
[73] "summary"       "Summary"       "table"         "tolower"
[77] "toupper"       "unique"        "var"           "Views"
[81] "which"         "width"         "window"
```

Numerous *Rle* methods (2/2)

Arith

`+`, `-`, `*`, `^`, `%%`, `%/%`, `/`

Compare

`==`, `>`, `<`, `!=`, `<=`, `>=`

Logic

`&`, `|`

Math

`abs`, `sign`, `sqrt`, `ceiling`, `floor`, `trunc`, `cummax`, `cummin`, `cumprod`, `cumsum`, `log`, `log10`, `log2`, `log1p`, `acos`, `acosh`, `asin`, `asinh`, ...

Math2

`round`, `signif`

Summary

`max`, `min`, `range`, `prod`, `sum`, `any`, `all`

Complex

`Arg`, `Conj`, `Im`, `Mod`, `Re`

Coverage example

Coverage from a *Saccharomyces cerevisiae* (Yeast) RNA-seq experiment contained in two objects `SRR002051.pluscvg` & `SRR002051.minuscvg`

```
> c(class(SRR002051.pluscvg), class(SRR002051.minuscvg))

[1] "SimpleRleList" "SimpleRleList"

> SRR002051.pluscvg[["chrI"]]

'integer' Rle of length 230208 with 10746 runs
  Lengths: 1061   33  271   33 2937 ...   33  237   33  679
  Values :    0    1    0    1    0 ...    2    0    1    0

> SRR002051.minuscvg[["chrI"]]

'integer' Rle of length 230208 with 10966 runs
  Lengths:   10   33 1070   33 4050 ...   29  104   33  808
  Values :    0    1    0    1    0 ...    2    0    1    0

> SRR002051.pluscvg[["chrI"]] + SRR002051.minuscvg[["chrI"]]

'integer' Rle of length 230208 with 18155 runs
  Lengths:   10   33 1018   33   19 ...   33   96   33  679
  Values :    0    1    0    1    0 ...    1    0    1    0
```

Plotting coverage

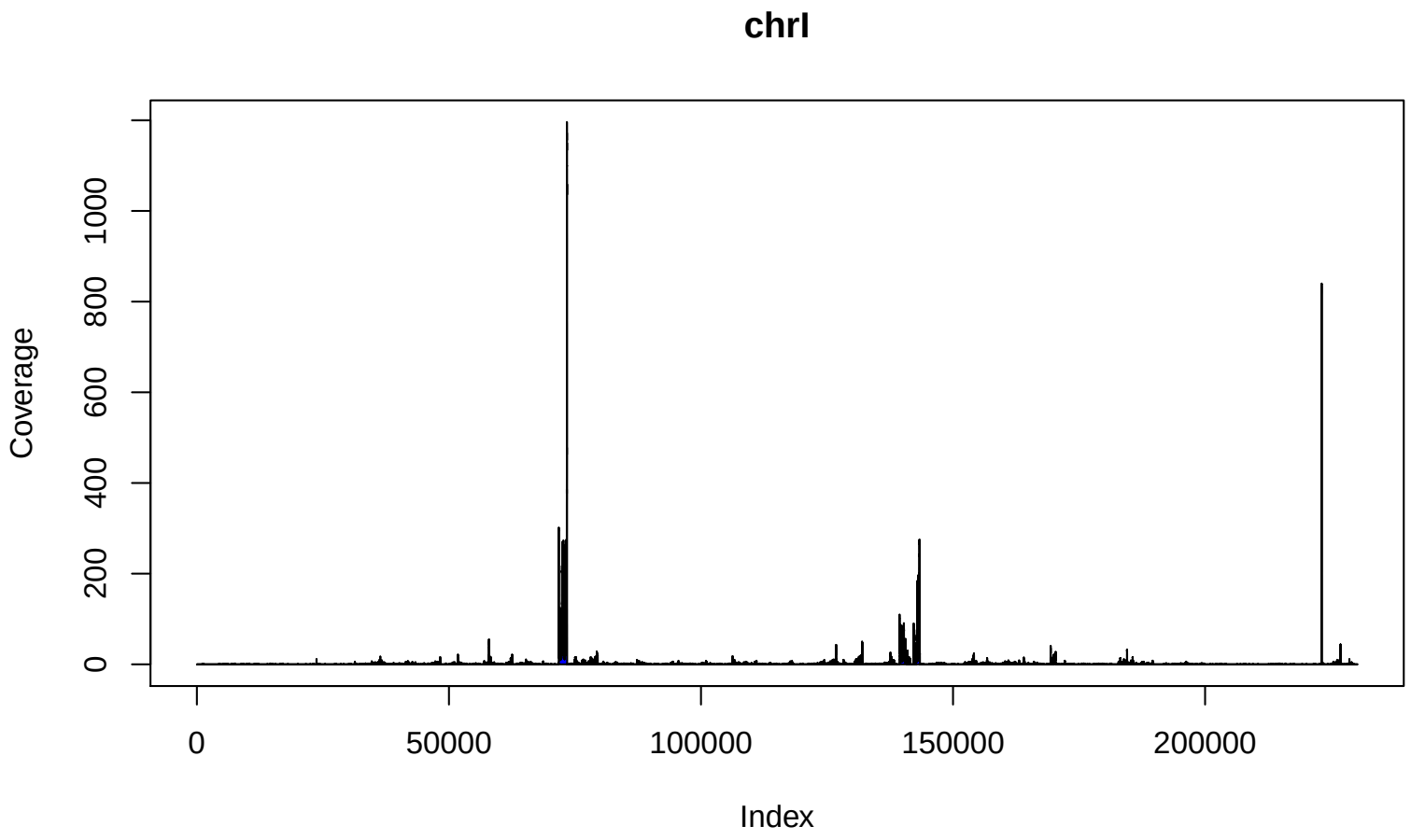
Custom function

```
> plotCoverage <-
+ function(x, chrom, start=1, end=length(x[[chrom]]), col="blue",
+          xlab="Index", ylab="Coverage", main=chrom)
+ {
+     xWindow <- as.vector(window(x[[chrom]], start, end))
+     x <- start:end
+     xlim <- c(start, end)
+     ylim <- c(0, max(xWindow))
+     plot(x = start, y = 0, xlim = xlim, ylim = ylim,
+          xlab = xlab, ylab = ylab, main = main, type = "n")
+     polygon(c(start, x, end), c(0, xWindow, 0), col = col)
+ }
```

Plotting coverage on one strand

Plotting chr1+ coverage

```
> plotCoverage(SRR002051.pluscvg, "chrI")
```



Plotting stranded coverage

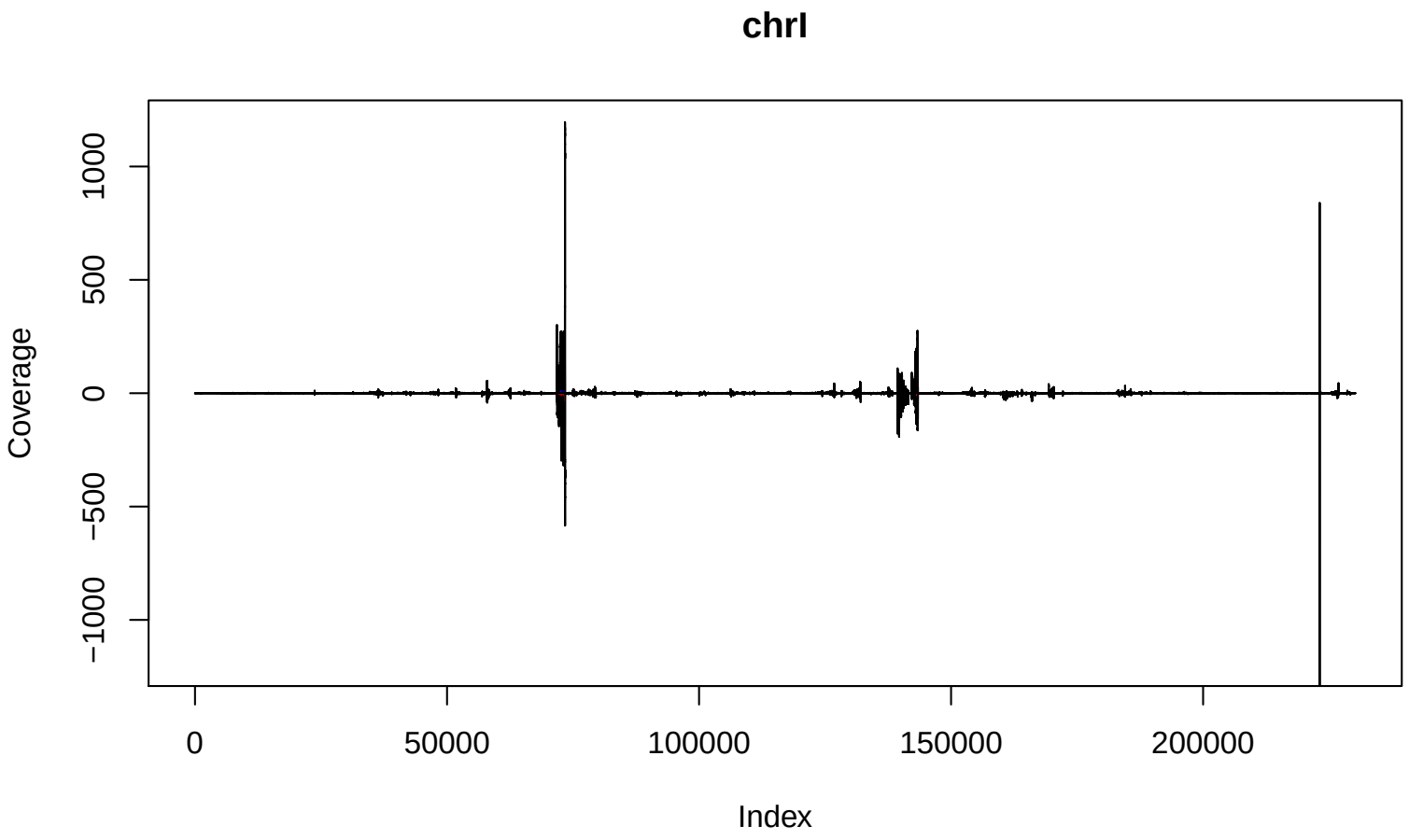
Custom function

```
> plotCoverageStrands <-
+ function(pos, neg, chrom, start=1,
+          end=max(length(pos[[chrom]]), length(neg[[chrom]])),
+          pos.col="blue", neg.col="red", xlab="Index",
+          ylab="Coverage", main=chrom)
+ {
+     pos1 <- pos[[chrom]]
+     neg1 <- neg[[chrom]]
+     if (length(pos1) < end)
+         pos1 <- c(pos1, Rle(0L, end - length(pos1)))
+     if (length(neg1) < end)
+         neg1 <- c(neg1, Rle(0L, end - length(neg1)))
+     posWindow <- as.vector(window(pos1, start, end))
+     negWindow <- as.vector(window(neg1, start, end))
+     x <- start:end
+     xlim <- c(start, end)
+     ylim <- c(-1, 1) * min(max(posWindow), max(negWindow))
+     plot(x = start, y = 0, xlim = xlim, ylim = ylim,
+          xlab = xlab, ylab = ylab, main = main, type = "n")
+     polygon(c(start, x, end), c(0, posWindow, 0), col = pos.col)
+     polygon(c(start, x, end), c(0, - negWindow, 0), col = neg.col)
+ }
```

Plotting coverage on both strands

Plotting chr1 coverage, both strands

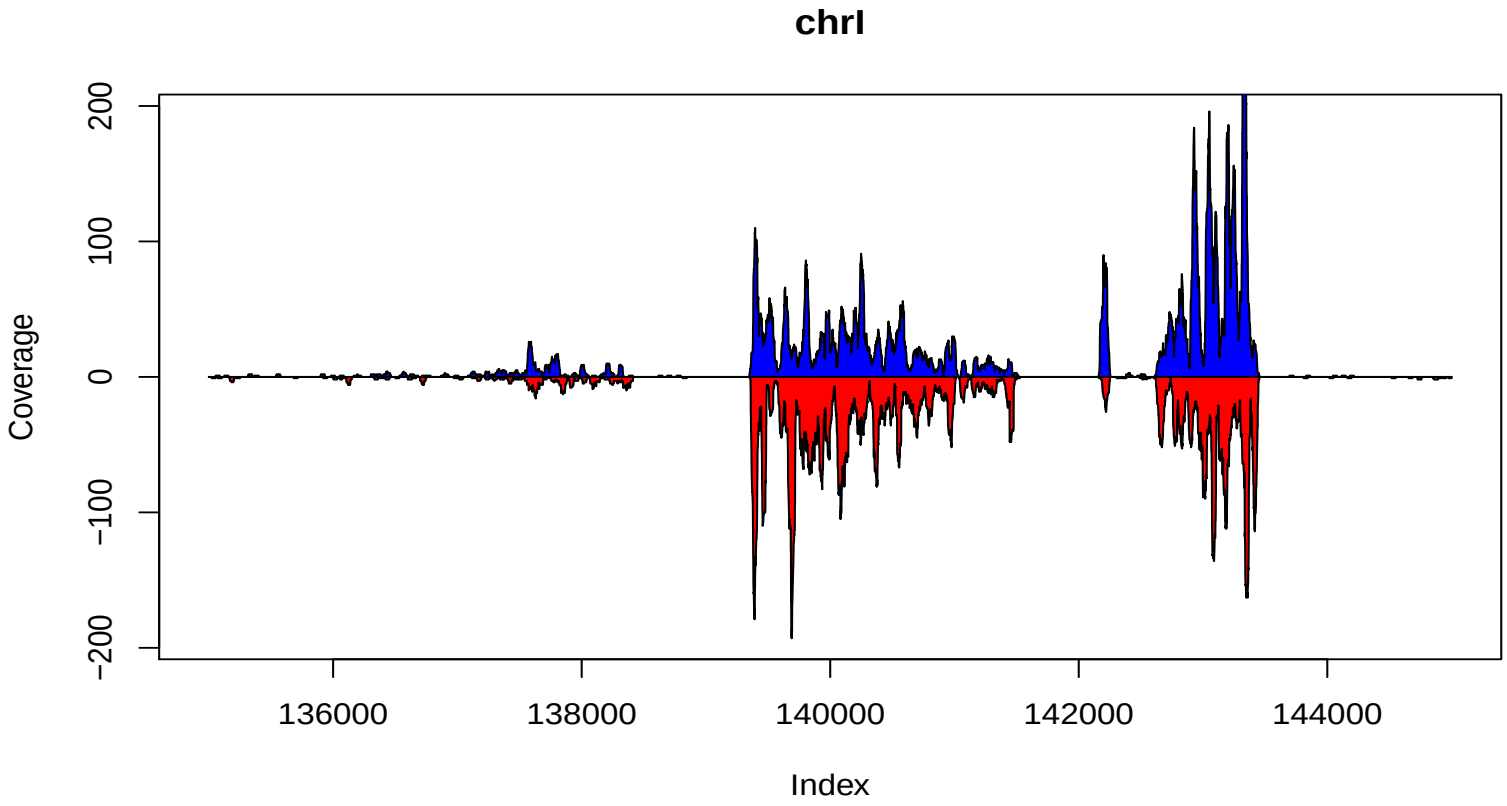
```
> plotCoverageStrands(SRR002051.pluscvg, SRR002051.minuscvg, "chrI")
```



Plotting Coverage on both strands

Plotting chr1 coverage, both strands

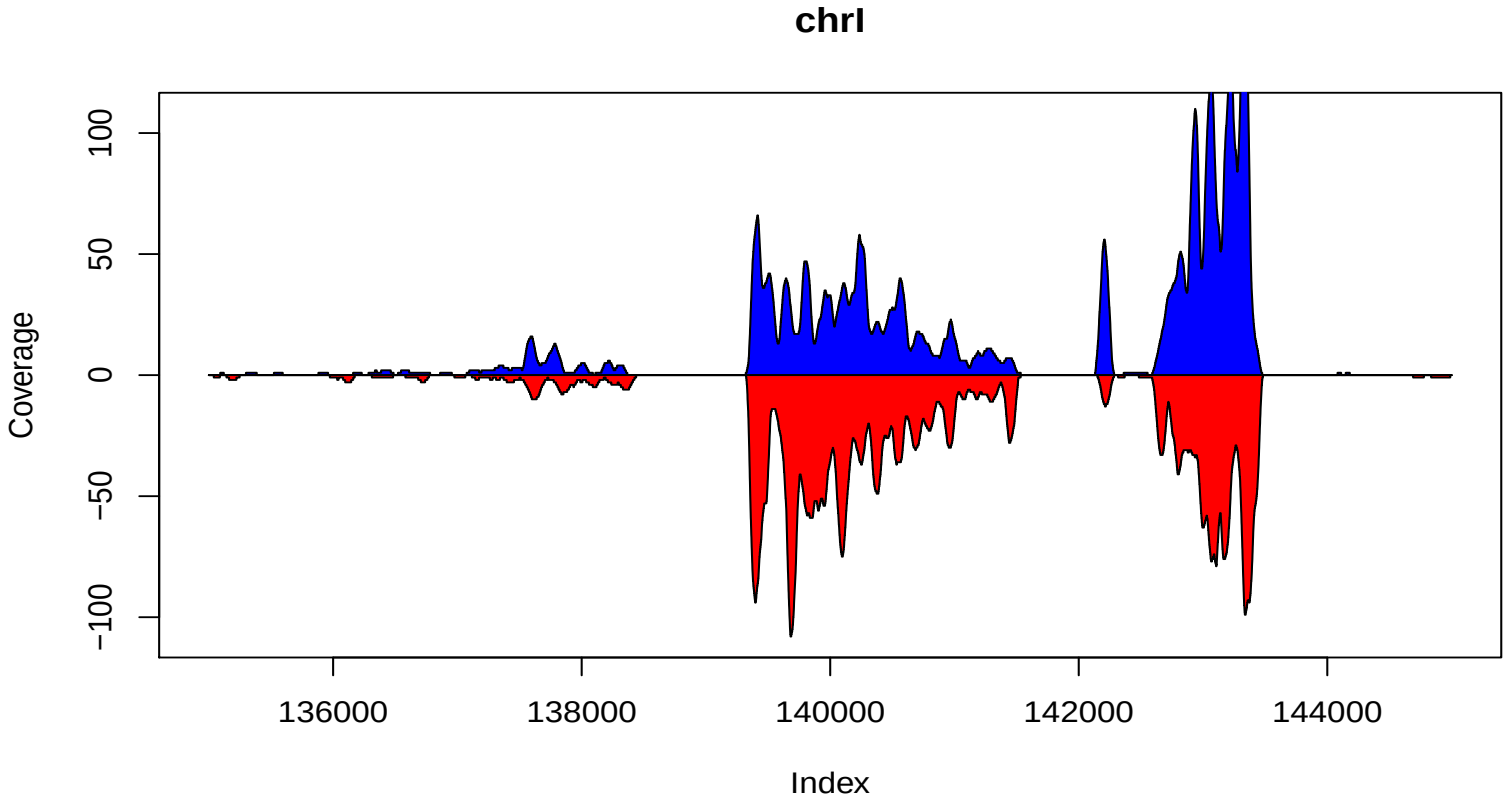
```
> plotCoverageStrands(SRR002051.pluscvg, SRR002051.minuscvg, "chrI", 135000, 145000)
```



Smoothing coverage

Running window mean

```
> posSmoothCover <- round(runmean(SRR002051.pluscvg, 75, endrule = "constant"))
> negSmoothCover <- round(runmean(SRR002051.minuscvg, 75, endrule = "constant"))
> plotCoverageStrands(posSmoothCover,negSmoothCover,"chrI",135000,145000)
```



Combining coverage

Combining coverage using "parallel" minimums

```
> combSmoothCover <- mendoapply(pmin,
+                               posSmoothCover,
+                               negSmoothCover)
> identical(class(posSmoothCover), class(combSmoothCover))
```

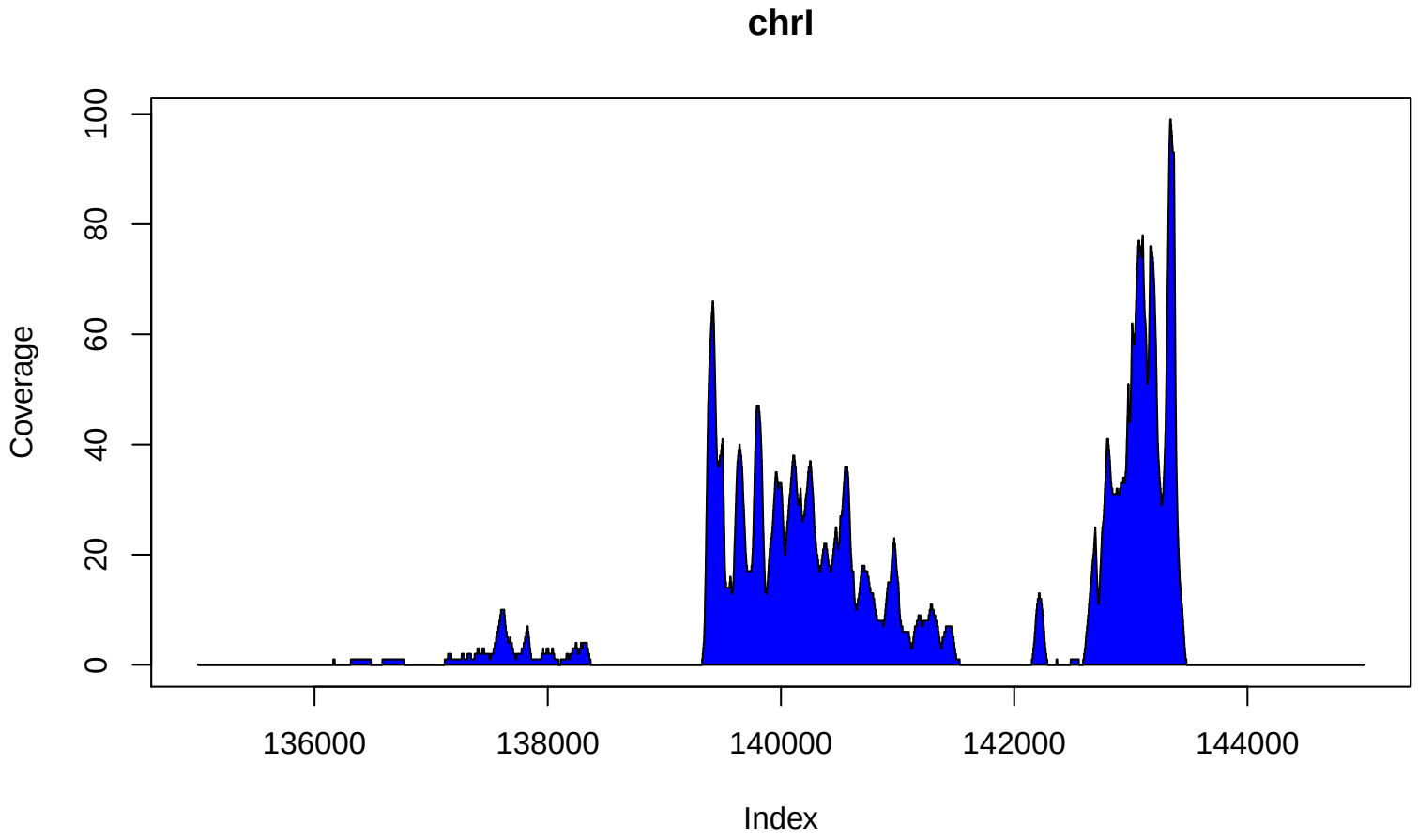
```
[1] TRUE
```

- The `mendoapply` function defined in *IRanges* packages as a member of the `apply` family.
  - Performs elementwise operations across multiple inputs of the same type.
  - Returns an object of the same type as the inputs.
- The minimum coverage value on either strand can be computed using `pmin`.

Plotting combined coverage

Plotting chr1, combined strands

```
> plotCoverage(combSmoothCover, "chrI", 135000, 145000)
```



Island selection

```
> islands <- slice(combSmoothCover, lower=1)
> islandsWithWidePeaks <- islands[viewMaxs(islands) >= 8L &
+                                 width(islands) >= 500L]
> islandsWithWidePeaks

SimpleRleViewsList of length 18
$chrI
Views on a 230208-length Rle subject

views:
      start    end width
 [1]  35842  36437   596 [1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 ...]
 [2]  51702  52348   647 [1 1 1 1 1 1 1 1 1 1 1 1 1 2 2 2 ...]
 [3]  57739  58468   730 [1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 ...]
 [4]  71710  73489  1780 [1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 ...]
 [5]  78565  79577  1013 [1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 ...]
 [6] 125982 126891   910 [1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 ...]
 [7] 131073 132113  1041 [1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 ...]
 [8] 137117 138090   974 [1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 ...]
 [9] 139324 141532  2209 [ 1  1  1  1  1  2  2  2  2  3 ...]
[10] 142591 143476   886 [1 1 1 1 1 1 1 1 2 2 2 2 2 2 3 3 ...]
[11] 169320 170437  1118 [1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 ...]
[12] 225804 226924  1121 [1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 ...]

...
<17 more elements>
```

Common methods for *Views* objects

- Subset via `[`, `[[`, etc.
- Manage edge cases via `trim` & `restrict`
- *Ranges* operations such as `start`, `end`, `width`, etc.
- Perform within view calculations via `viewSums`, `viewMins`, `viewMaxs`, `viewWhichMins`, `viewWhichMaxs`, `viewApply`

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Long biological string framework

Biostrings string types

```
> library(Biostrings)
> names(completeSubclasses(getClass("XString")))
```

```
[1] "BString"   "DNAString" "RNAString" "AAString"
```

DNA

```
> data(yeastSEQCHR1)
> c(class(yeastSEQCHR1), nchar(yeastSEQCHR1))
```

```
[1] "character" "230208"
```

```
> yeast1 <- DNAString(yeastSEQCHR1)
> yeast1
```

```
  230208-letter "DNAString" instance
seq: CCACACCACACCCACACACCCACACACC...GGTGTGGTGTGGGTGTGGTGTGTGTGGG
```

```
> IUPAC_CODE_MAP
```

```
     A      C      G      T      M      R      W      S      Y
   "A"    "C"    "G"    "T"   "AC"   "AG"   "AT"   "CG"   "CT"
     K      V      H      D      B      N
  "GT"  "ACG"  "ACT"  "AGT"  "CGT" "ACGT"
```

List of strings

Biostrings string list types

```
> head(names(completeSubclasses(getClass("XStringSet"))), 4)
```

```
[1] "BStringSet"   "DNAStringSet" "RNAStringSet" "AAStringSet"
```

DNA strings

```
> data(srPhiX174)
> length(srPhiX174)
```

```
[1] 1113
```

```
> head(srPhiX174, 3)
```

```
  A DNAStringSet instance of length 3
    width seq
[1]    35 GTTATTATACCGTCAAGGACTGTGTGACTATTGAC
[2]    35 GGTGGTTATTATACCGTCAAGGACTGTGTGACTAT
[3]    35 TACCGTCAAGGACTGTGTGACTATTGACGTCCTTC
```

XString class decomposition

XString slots

```
> getSlots("XString")

         shared          offset          length elementMetadata
    "SharedRaw"       "integer"       "integer"           "ANY"
    elementType        metadata
    "character"          "list"

> getSlots("XStringSet")

            pool           ranges  elementMetadata
"SharedRaw_Pool" "GroupedIRanges"            "ANY"
     elementType         metadata
     "character"           "list"
```

Notes

- `shared`, `offset`, `length`, `pool`, and `ranges` slots regulate pass-by-reference semantic.
- `metadata` slot can be used to hold annotation information.

Basic string utilities

Subsequence selection

`subseq`, `Views`

Letter frequencies

`alphabetFrequency`, `dinucleotideFrequency`, `trinucleotideFrequency`, `oligonucleotideFrequency`, `letterFrequencyInSlidingView`, `uniqueLetters`

Letter consensus

`consensusMatrix`, `consensusString`

Letter transformation

`reverse`, `complement`, `reverseComplement`, `translate`, `chartr`

I/O

`read.DNAStringSet`, `read.RNAStringSet`, `read.AAStringSet`, `read.BStringSet`, `write.XStringSet`, `save.XStringSet`

String matching/alignment utilities

matchPDict

matchPDict, countPDict, whichPDict, vmatchPDict, vcountPDict, vwhichPDict

vmatchPattern

matchPattern, countPattern, vmatchPattern, vcountPattern, neditStartingAt, neditEndingAt, isMatchingStartingAt, isMatchingEndingAt, which.isMatchingStartingAt, which.isMatchingEndingAt

pairwiseAlignment

pairwiseAlignment, stringDist

matchPWM

matchPWM, countPWM

OTHER

matchLRPatterns, trimLRPatterns, matchProbePair, findPalindromes, findComplementedPalindromes

Letter frequencies

Single-letter frequencies

```
> alphabetFrequency(yeast1, baseOnly=TRUE)
```

```
    A     C     G     T other
69830 44643 45765 69970     0
```

Multi-letter frequencies

```
> dinucleotideFrequency(yeast1)
```

```
   AA    AC    AG    AT    CA    CC    CG    CT    GA    GC
23947 12493 13621 19769 15224  9218  7089 13112 14478  8910
   GG    GT    TA    TC    TG    TT
 9438 12938 16181 14021 15617 24151
```

```
> head(trinucleotideFrequency(yeast1), 12)
```

```
 AAA  AAC  AAG  AAT  ACA  ACC  ACG  ACT  AGA  AGC  AGG  AGT
8576 4105 4960 6306 3924 2849 2186 3534 4537 2680 2707 3697
```

Basic transformations

Standard transformations

```
> x
  21-letter "DNAString" instance
seq: TCAACGTTGAATAGCGTACCG
> reverseComplement(x)
  21-letter "DNAString" instance
seq: CGGTACGCTATTCAACGTTGA
> translate(x)
  7-letter "AAString" instance
seq: STLNSVP
```

Bisulfite transformation

```
> library(BSgenome.Celegans.UCSC.ce2)
> alphabetFrequency(Celegans$chrII, baseOnly=TRUE)
      A       C       G       T   other
4878194 2769208 2762193 4869710       3
> chrIIbis <- chartr("C", "T", Celegans$chrII)
> alphabetFrequency(chrIIbis, baseOnly=TRUE)
      A       C       G       T   other
4878194       0 2762193 7638918       3
```

Letter consensus

Consensus matrix

```
> snippet <- subseq(head(sort(srPhiX174), 5), 1, 10)
> consensusMatrix(snippet, baseOnly=TRUE)
```

```
      [,1] [,2] [,3] [,4] [,5] [,6] [,7] [,8] [,9] [,10]
A        5    5    1    0    4    2    1    0    1     0
C        0    0    1    0    0    2    0    0    0     0
G        0    0    3    4    0    0    0    4    0     3
T        0    0    0    1    1    1    4    1    4     2
other    0    0    0    0    0    0    0    0    0     0
```

Consensus string

```
> consensusString(snippet)
```

```
[1] "AAGGAMTGTK"
```

```
> consensusString(snippet, ambiguityMap = "N", threshold = 0.5)
```

```
[1] "AAGGANTGTG"
```

String matching

Match counting

```
> data(phiX174Phage)
> genome <- phiX174Phage[["NEB03"]]
> negPhiX174 <- reverseComplement(srPhiX174)
> posCounts <- countPDict(PDict(srPhiX174), genome)
> negCounts <- countPDict(PDict(negPhiX174), genome)
> table(posCounts, negCounts)
```

```
         negCounts
posCounts    0
        0 1030
        1   83
```

Match locations

```
> matchPDict(PDict(srPhiX174[posCounts > 0]), genome)
```

```
MIndex object of length 83
```

Pairwise alignments

Alignment scores

```
> data(phiX174Phage)
> posScore <- pairwiseAlignment(srPhiX174, genome,
+                               type = "global-local", scoreOnly = TRUE)
> negScore <- pairwiseAlignment(negPhiX174, genome,
+                               type = "global-local", scoreOnly = TRUE)
> cutoff <- max(pmin.int(posScore, negScore))
```

Alignments

```
> pairwiseAlignment(srPhiX174[posScore > cutoff], genome,
+                   type = "global-local")
```

```
Global-Local PairwiseAlignedFixedSubject (1 of 1112)
pattern:    [1] GTTATTATACCGTCAAGGACTGTGTGACTATTGAC
subject: [2750] GTTATTATACCGTCAAGGACTGTGTGACTATTGAC
score: 69.36144
```

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Long compressed sequence classes (*IRanges*)

Rle

- Compressed atomic vectors
- Methods for standard *R atomic vector* functions
- Concrete class with sub-typing at the slot level

CompressedList

- Compressed list of S4 objects
- Methods for standard *R list* functions
- Virtual class with sub-typing at the subclass level

IRanges (as Sequences)

- `as.integer` coercion
- Subscripting via `seqselect`, `window`, and `[`

Pointer referenced sequence classes

XVector (*IRanges*)

- External pointer-based atomic vectors
- Virtual class
- Concrete subclasses:
  - *XRaw* – Underlies *Biostrings* infrastructure
  - *XInteger* – Experimental integer vector class
  - *XDouble* – Experimental real number vector class

XString (*Biostrings*)

- Virtual class
- Concrete subclasses:
  - *BString* – Any "biological" sequence
  - *DNAString* – DNA sequence
  - *RNAString* – RNA sequence
  - *AAString* – Amino acid sequence

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Bioconductor Web site

- '*IRanges*', '*GenomicRanges*', and '*Biostrings*' links.
- `http://bioconductor.org`
- 'Installation', 'Software', and 'Mailing lists' links.

Help in *R*

- `help.start()` to view a help browser.
- `help(package = "Biostrings")`
- `?findOverlaps`
- `browseVignettes("GenomicRanges")`