Assessing the predictive capacity of the Nussinov model

Warm-up

A secondary structure can be given as a list of base-pairs l over a sequence of length n. This first assignment consists in printing the structure back as a well-parenthesized expression.

Implement a function `displaySecStr`, which takes as input a pair (l, n), and returns the well-parenthesized expression. **Remark:** Bases will be numbered starting from 0.

Example:

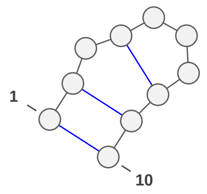
Input		Output
`displaySS([(2,8),(3,7)],10)`	$\longrightarrow$	`"..((...))."`

Parsing secondary structures

We wish to extract a list of base-pairs from the well-parenthesized notation used in the Vienna package. In this notation, two positions are involved in a base-pair if and only if they correspond to matched opening `(` and closing `)` parentheses. Unpaired positions are denoted by dots `.`

Implement a `parseSS(struct)` function, which takes a string `struct` as input, and returns a pair (l, n), where l is the list of base-pairs and n is the length of the string.
Example:

Input		Output
`parseSS("((.(...)))")`	$\longrightarrow$	`([(0,9),(1,8),(3,7)],10)`



The corection of this function will be verified using its *inverse* function `parseSS`, defined above. Namely, for any well-parenthesized sequence `seq`, one should have:

```
displaySS(parseSS(seq),len(seq)) == seq
```

Counting compatible structures

Implement a counting variant of the Nussinov algorithm (setting $\theta = 1$ for the sake of simplicity[1]), into a function `countSS`, which will return the number of secondary structures compatible with a given sequence. To that purpose, it is sufficient to replace any occurrences of `min` and `+` in the dynamic programming equation, seen in the first lecture, with `+` and `*` respectively.

[1] Remind that θ denotes the minimal distance of paired positions.

The function takes as input an RNA sequence `r` and a boolean `debug`. In the normal mode `debug==False`, the function returns the number of secondary structures which only induces base-pairs of the type GC, AU or GU on `r`. When `debug==True`, it relaxes the base-pairing condition, and returns the total number of secondary structures of length `len(r)`.

Example:

Input		Output
`countSS("A")`	⟶	1
`countSS("CAG")`	⟶	2
`countSS("CAGU")`	⟶	3
`countSS("AAAA",True)`	⟶	4
`countSS("AAAAAAAA",True)`	⟶	82

You may use the number of secondary structures for sequence lengths up to 12:

len(r)	1	2	3	4	5	6	7	8	9	10	11	12
S	1	1	2	4	8	17	37	82	185	423	978	2283

to check your implementation.

Nussinov

Now, we move on to the implementation of our variant of the Nussinov algorithm. To that purpose, one must duplicate the code of the `countSS` function, and adapt it into a function `fillMatrix`, which precomputes the energy of the minimal free-energy structure with respect to a Nussinov energy model ($\Delta G(AU) = \Delta G(GC) = \Delta G(GU) = -1$. Additionally, the code will be modified to account for general minimal distances θ between matching positions.

The `fillMatrix` function takes a sequence `r` and a `theta` integer value as input, and return a filled dynamic programming matrix `tab` such that `tab[i][j]` is the MFE for any structure compatible with the interval `[i,j]`.

Example:

```
Entree : fillMatrix(CCCCUUUUGGGGG,3)
Sortie :
tab = [[ 0.  0.  0.  0.  0.  0.  0.  0. -1. -2. -3. -4. -5.]
       [ 0.  0.  0.  0.  0.  0.  0.  0. -1. -2. -3. -4. -4.]
       [ 0.  0.  0.  0.  0.  0.  0.  0. -1. -2. -3. -3. -4.]
       [ 0.  0.  0.  0.  0.  0.  0.  0. -1. -2. -2. -3. -3.]
       [ 0.  0.  0.  0.  0.  0.  0.  0. -1. -1. -2. -2. -3.]
       [ 0.  0.  0.  0.  0.  0.  0.  0.  0. -1. -1. -2. -2.]
       [ 0.  0.  0.  0.  0.  0.  0.  0.  0.  0. -1. -1. -2.]
       [ 0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0. -1. -1.]
       [ 0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0.]
       [ 0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0.]
[ 0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0.]
[ 0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0.]
[ 0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0.  0.]]
```

Once tested, the matrix-filling function will be supplemented by a `traceback` (possibly recursive) function, which builds (one of) the MFE structure(s). This function takes a DP matrix `tab` produced by `fillMatrix` as input, and returns a set of non-crossing base-pairs associated with the minimal free-energy.

Example:

Input		Output
`traceback(tab)`	⟶	`[(0,12),(1,11),(2,10),(3,9),(4,8)]`
`displaySS(traceback(tab))`	⟶	`"(((((...)))))"`

Finally, combine these two functions into a `nussinov` function which takes an RNA sequence as input, and returns a minimal free-energy structure in the Nussinov model.

Half-time summary

The time has now come to compare the predictive capacities of our – minimally simple – RNA folding software with state-of-the-art tools. To that end, we will use the Vienna package, a suite of tools maintained by Ronny Lorenz at the Theoretical Biochemistry Institute of Vienna. The package includes `RNAEval`, which computes the free-energy of a given secondary structure, and `RNAFold` which uses dynamic programming to compute the MFE structure for a given RNA sequence, both with respect to the latest version of the Turner energy model.

We implemented two `Python` *wrappers* for the `runRNAEval` and `runRNAFold` tools through the following functions:

- `runRNAFold(seq)` takes a sequence `seq`, and return a pair `(mfe,E)`, where `mfe` is the MFE secondary structure for `seq`, given as a base-pair list, and `E` is its energy.

You should start by downloading the wrappers (+ data) at:

http://www.lix.polytechnique.fr/~ponty/enseignement/ViennaWrapperCheat.py
http://www.lix.polytechnique.fr/~ponty/enseignement/RNAfoldMathews.dat

Model discrepancies

Firstly, implement a function `compareSS` which takes as input two structures S et S' (represented as base-pair lists), and returns the number of common base-pairs $|S \cap S'|$. We recommend using `Python` sets for a single-line implementation.

Predictive performances

Use the `compareSS` function to implement a `benchmark` function, which takes an RNA sequence ω as input, along with its (assumed known) native structure S, and returns the proportion of base-pairs correctly predicted by the algorithms `nussinov` and `RNAFold` on a reference set of sequence/structures. The dataset was gathered by D. H. Mathews, and can be downloaded from:

```
http://www.lix.polytechnique.fr/~ponty/enseignement/MathewsRNASorted.faa
```