

A background image showing a male scientist on the left wearing glasses and looking through a microscope, and a female scientist on the right in a white lab coat looking down at something in her hands. The image is overlaid with large, semi-transparent blue and orange circles.

An efficient algorithm to find matched pairs of a peptide

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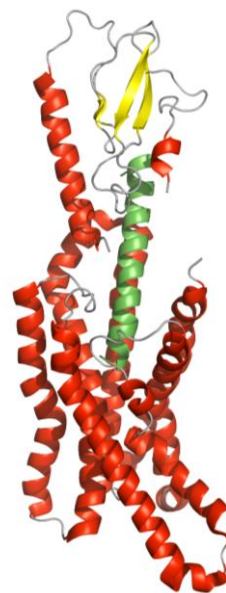
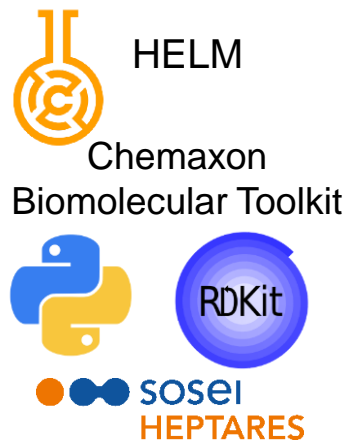
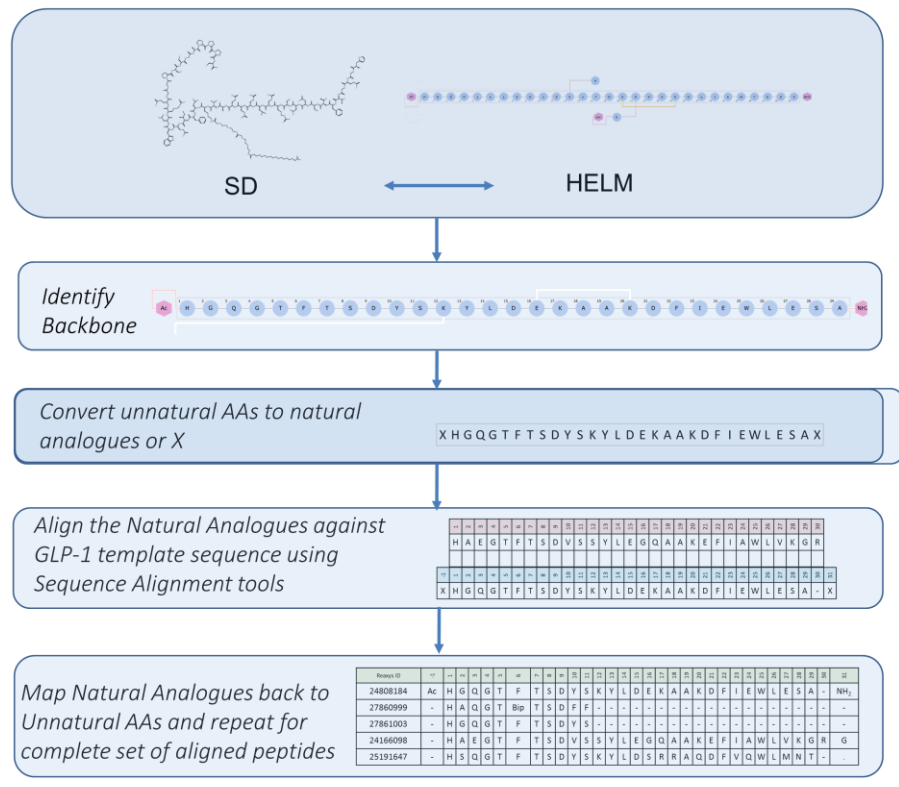
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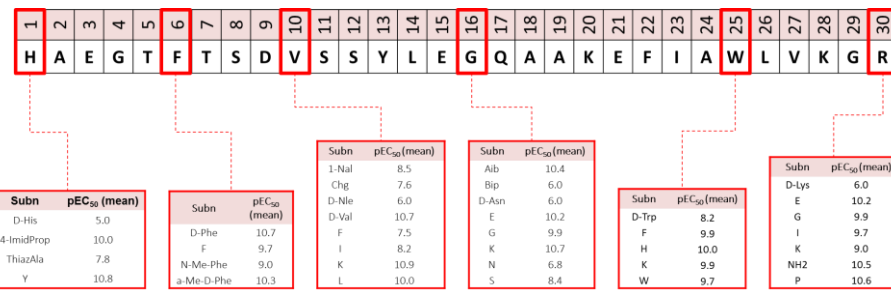
Structural Cheminformatics based GPCR Peptide Ligand Design

Sequence Alignment and Annotation workflow



Structure-Based Peptide Ligand design

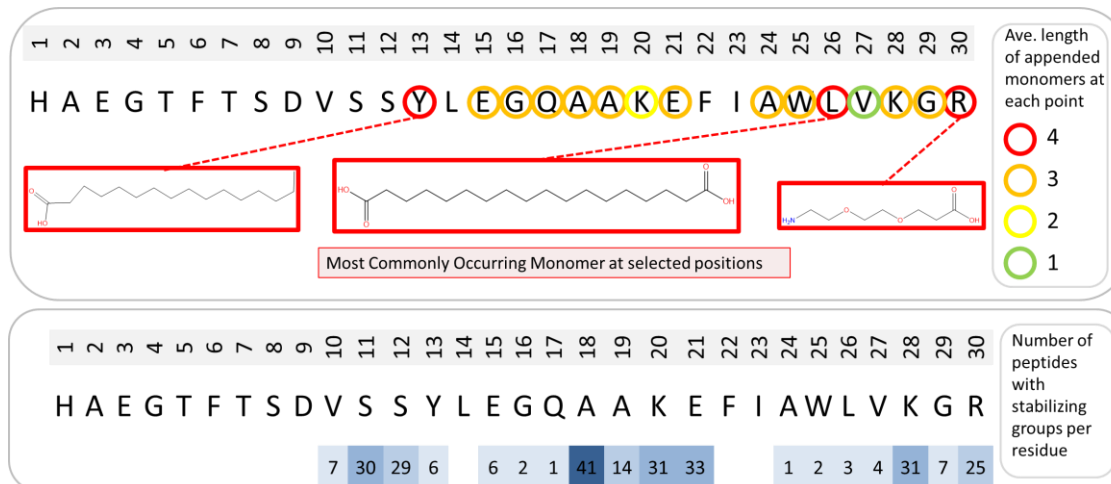
Residue level analysis of Peptide properties



Property Modulation within Matched Peptide Pairs



Property Modulation within Matched Peptide Pairs



Introduction

- “Making a hash of it: The advantage of selectively leaving out structural information”
 - <https://www.nextmovesoftware.com/talks.html> - 258th ACS National Meeting, Aug 2019
- Describes ‘molhash’
 - Generate molecular hashes useful for finding pairs of tautomers, mesomers, regioisomers, etc.
 - <https://nextmovesoftware.github.io/molhash/introduction.html>
 - Using hashes can be an efficient alternative to brute-force algorithms
- Incorporated into RDKit (since 2019.09)
 - Example of use by Takayuki Serizawa: <https://iwatobipen.wordpress.com/2019/10/27/a-new-function-of-rdkit201909-rdkit-chemoinformatics/>
- The problem: finding all matched pairs (in terms of sequence) within a dataset of peptides
 - Singly-substituted peptides
 - Shout-out to related work: “Matched Peptides: Tuning Matched Molecular Pair Analysis for Biopharmaceutical Applications”
 - Julian Fuchs, Bernd Wellenzohn, Nils Weskamp, Klaus Liedl – *JCIM*. **2015**, 55, 2315.

Find words that differ by a single letter – brute force

- For each word in a list of English words, convert each letter to each of the other letters of the alphabet in turn
 - Check whether there is a match in the list
- “isotropic”: 225 substitutions tested
 - **asotropic**
 - **bsotropic**
 - **csotropic**
 - **dsotropic**
 - **esotropic** ←
 - **fsotropic**
 - ...
 - **iaotropic**
 - **ibotropic**
 - **icotropic**
- Not an efficient approach
 - Consider the extension to two letters changed – 22500
- Does not handle letters or other characters not initially considered
 - diacritics (naïve, piñata, ångström), Greek characters, capital letters, hyphens

Find words that differ by a single letter – using a hash

- For each word in a list of English words, create hashes where each letter in turn is replaced by an asterisk

- Collate words using the hashes: `collate = defaultdict(list); collate[myhash].append(word)`

- “isotropic”:

- ***sotropic**
- **i*otropic**
- **is*tropic**
- **iso*ropic**
- **isot*opic**
- **isotr*pic**
- **isotro*ic**
- **isotrop*c**
- **isotropi***

- “inotropic”:

- ***notropic**
- **i*otropic**
- **in*tropic**
- **ino*ropic**
- **inot*opic**
- **inotr*pic**
- **inotro*ic**
- **inotrop*c**
- **inotropi***

- “esotropic”:

- ***sotropic**
- **e*otropic**
- **es*tropic**
- **eso*ropic**
- **esot*opic**
- **esotr*pic**
- **esotro*ic**
- **esotrop*c**
- **esotropi***

- Collated by hash:

- ***sotropic**: [isotropic, esotropic]
- **i*otropic**: [isotropic, inotropic]
- **is*tropic**: [isotropic]
- **iso*ropic**: [isotropic]
- ...30 other hashes with a single entry

- For each word in a list of length ≥ 2 , use that word to collate other words in the same list:

- isotropic: [inotropic, esotropic]
- inotropic: [isotropic]
- esotropic: [isotropic]

Find sequences that differ by a single residue – using a hash

- For each sequence in a list of peptides, create hashes where each residue in turn is replaced by an asterisk

- Collate sequences using the hashes: `collate = defaultdict(list); collate[myhash].append(seq)`

- “isotropic”:

- ***sotropic**
- **i*otropic**
- **is*tropic**
- **iso*ropic**
- **isot*opic**
- **isotr*pic**
- **isotro*ic**
- **isotrop*c**
- **isotropi***

- “inotropic”:

- ***notropic**
- **i*otropic**
- **in*tropic**
- **ino*ropic**
- **inot*opic**
- **inotr*pic**
- **inotro*ic**
- **inotrop*c**
- **inotropi***

- “esotropic”:

- ***sotropic**
- **e*otropic**
- **es*tropic**
- **eso*ropic**
- **esot*opic**
- **esotr*pic**
- **esotro*ic**
- **esotrop*c**
- **esotropi***

- Collated by hash:

- ***sotropic**: [isotropic, esotropic]
- **i*otropic**: [isotropic, inotropic]
- **is*tropic**: [isotropic]
- **iso*ropic**: [isotropic]
- ...30 other hashes with a single entry

- For each sequence in a list of length ≥ 2 , use that sequence to collate other sequences in the same list:

- isotropic: [inotropic, esotropic]
- inotropic: [isotropic]
- esotropic: [isotropic]

Some tweaks

- Support doubly-substituted matched pairs
 - “isotropic”: ****otropic**, ***s*tropic**, etc.
- Consider one-residue extension/deletion as a matched pair:
 - As well as the nine “isotropic” hashes shown earlier, also include ***isotropic** and **isotropic*** (no other changes needed)
- Use a list, instead of representing the peptide sequence as a string
 - Residues can be represented by arbitrary strings, such as three-letter codes, modified residues, or internal names: e.g. [“Ile”, “N(Me)Ser(O-Ac)”, ...]
 - Generate a hash by replacing one of the entries with a “*” (copy the list first), and convert to a string with “-”.join(mylist).