NEXTMOVE SOFTWARE

NAMING ALGORITHMS FOR DERIVATIVES OF PEPTIDE-LIKE NATURAL PRODUCTS

ROGER SAYLE & NOEL O'BOYLE
NEXTMOVE SOFTWARE, CAMBRIDGE, UK
CHRISTOPHER SOUTHAN,
IUPHAR/BPS GUIDE TO PHARMACOLOGY

250th ACS National Meeting, Boston, MA. Sunday 16th August 2015

30 SECOND OVERVIEW

- This talk describes the development of software for both naming peptides and reading peptide names matching the de facto standard practices currently followed by biochemists.
- Unlike computer representations, like Pisotoia HELM or InChI keys, these names and identifiers match those typically found in the scientific literature and vendor catalogues.
- A significant application of this technology is to check and correct peptide representations in databases.

PROBLEM MOTIVATION

- Maintaining a database of biological activities of mature proteins and peptides presents a significant technical challenge.
- IUPHAR/BPS' "Guide to Pharmacology" and EBI's ChEMBL represent current state-of-the-art efforts to capture/represent peptide-like ligands.
- The ligands require more than (FASTA) bioinformatics including disulfide bridging architecture, non-standard amino acids, post-translational modifications, N- and C- terminal modifications etc.

IUPHAR/BPS GTOP PEPTIDES

- The “Guide to Pharmacology” database contains:
  - The common name “oxytocin”
  - The species, e.g. “human”
  - The UniProt ID “P001178”
  - The 1-letter Sequence “CYIQNCPLG”
  - The 3-letter sequence “Cys-Tyr-Ile-…-Leu-Gly-NH2”
  - A text description “Post-translation modification”, e.g. “A disulfide bond is formed between cysteine residues at positions 1 and 5 and the C-terminal glycine is amidated”.
  - Often SMILES and standard InChIKey.

PROBLEM 1: CONSISTENCY

- The challenge with these advanced formats are that the names, three-letter codes and modification descriptions are text-locked, unreadable by software.

Examples of errors and inconsistency:

Ligand #4463: “PheGlnThrSerGluAlaIleLeuPro…”

Ligand #1335: “…Leu-Arg-AlaPro-Leu-Lys...”

Ligand #8263: “val-leu-gln-glu-leu-asn-val-thr-val”

Ligand #5873: “…Pr-oGl-yGl-ySe-rMe-tLy-sLe-u…”

Ligand #3591: “PHQLLRVPro-His-Ala-Gln-Leu…”

PROBLEM 2: AMBIGUITY

- Ligand #3630 (neuropeptide B29) “(Br)Trp” with note “The n-terminal tryptophan is brominated”.
  - Suggested replacement Trp(6-Br)
- In Ligand #1036, “(Ac)Ala” means N2-acetyl but “(Ac)Lys” means N6-acetyl, in #1188 “Ac-” appears without parenthesis, in Ligand #3853, “AcPhe-” appears without a hyphen…
  - Suggest Ac- at N-term, -N(Ac)Phe infix, Lys(Ac) sidechain
  - This even allows Ac-N(Ac)Lys(Ac)-OH, aka. N(Ac2)Lys(Ac).

PROBLEM 3: DISULFIDE BRIDGING

- Capturing the disulfide bridging architecture in the three-letter (condensed) representation allows it to be read/checked for errors.
- This is done in some places but not in others.
- Disulfide bridges are particularly tricky even for the folks at UNIPROT: Annexin I (ligand #1031, P04083) isn't annotated as disulfide bridged, despite the 3D structure in PDB 1HM6, and the experimental evidence of an intramolecular disulfide described in PubMed 7663390.

TYPES OF PEPTIDE NAME/IDENTIFIER

- **Sequence:** CYIQDCPLG
- **Peptide Name:** [Asp5]oxytocin or [5-L-aspartic acid]oxytocin
- **Chemical IUPAC Name:**

  2-[(4R,7S,10S,13S,16S,19R)-19-amino-4-[(2S)-2-[[(1S)-1-[(2-amino-2-oxo-ethyl)carbamoyl]-3-methyl-butyl]carbamoyl]pyrrolidine-1-carbonyl]-10-(3-amino-3-oxo-propyl)-16-[(4-hydroxyphenyl)methyl]-13-[(1S)-1-methylpropyl]-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentazacycloicos-7-yl]acetic acid

- **Biological IUPAC Name**

  L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-alpha-aspartyl-L-cysteinyl-L-prolyl-L-leucyl-glycinamide (1->6)-disulfide

- **Condensed:** Cys(1)-Tyr-Ile-Gln-Asp-Cys(1)-Pro-Leu-Gly-NH2
- **Pistoia HELM:**

  PEPTIDE1{C.Y.I.Q.N.C.P.L.G.[am]}$PEPTIDE1,PEPTIDE1,1:R3-6:R3$$$

HELM TEETHING PROBLEMS

- Pistoia's HELM notation marks a significant advance over the limitations of one-letter bioinformatics.
- Alas, its original goals didn't include data exchange, which has only recently been addressed by the extensions of inlineHELM and XHELM [and fixes from NextMove Software for improved interoperability].
- Alas, this still doesn't address some core limitations:
  - Pistoia Monomer Library: PEPTIDE1{[fmoc].A}$$$$
  - EBI ChEMBL Monomers: PEPTIDE1{[Fmoc_A]}$$$$

IUPAC CONDENSED NAMES (CHEMBL)

- The following names are machine generated

H-Cys-Pro-Trp-His-Leu-Leu-Pro-Phe-Cys-OH	CHEMBL501567
H-Tyr-Pro-Phe-Phe-OtBu	CHEMBL500195
cyclo[Ala-Tyr-Val-Orn-Leu-D-Phe-Pro-Phe-D-Phe-Asn]	CHEMBL438006
H-Nle(Et)-Tyr-Pro-Trp-Phe-NH2	CHEMBL500704
H-DL-hPhe-Val-Met-Tyr(PO3H2)-Asn-Leu-Gly-Glu-OH	CHEMBL439086
cyclo[Phe-D-Trp-Tyr(Me)-D-Pro]	CHEMBL507127
H-D-Pyr-D-Leu-pyrrolidide	CHEMBL1181307
Ac-DL-Phe-aThr-Leu-Asp-Ala-Asp-DL-Phe(4-Cl)-OH	CHEMBL1791047
H-D-Cys(1)-D-Asp-Gly-Tyr(3-NO2)-Gly-Hyp-Asp-D-Cys(1)-NH2	CHEMBL583516
Boc-Tyr-Tyr(3-Br)-OMe	CHEMBL1976073

PEPTIDE NAMES (CHEMBL)

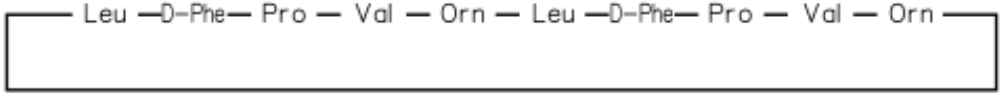
- The following names are machine generated

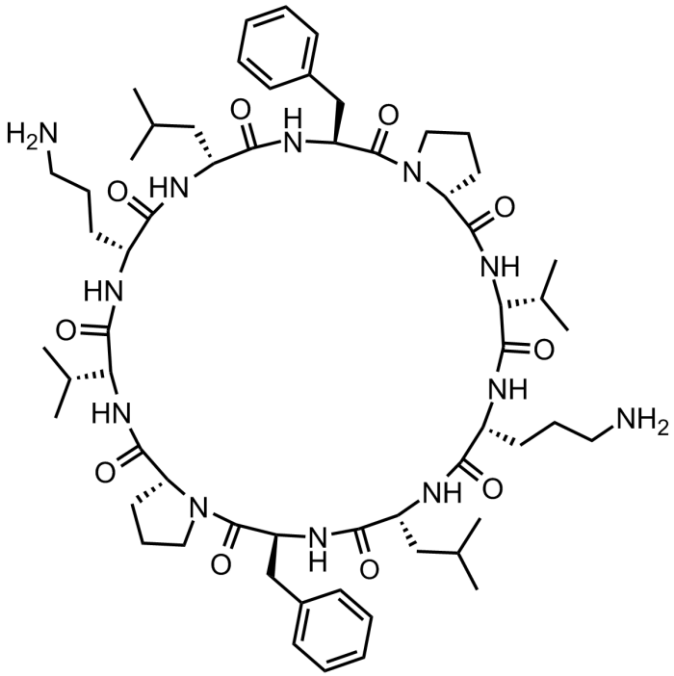
[15-L-arginine]nociceptin	CHEMBL526333
[2-4-chloro-L-phenylalanine]neuropeptide S [human]	CHEMBL441576
[1-L-threonine]cyclosporin A	CHEMBL2370014
[6-L-tryptophan]sermorelin free acid	CHEMBL440438
angiotensin II (3-8)	CHEMBL261120
nociceptin amide	CHEMBL389521
acetyl-alpha-MSH (4-10) amide	CHEMBL410411
[2-L-cysteine,13-L-cysteine]neurotensin disulfide	CHEMBL3278512
myristoyl-[1-L-lysine,4-L-tryptophan]tetrapandin 2 amide	CHEMBL3288219
[2-(4RS)-thiazolidine-4-carboxylic acid,4-L-proline]endomorphin-2	CHEMBL126611
[22-L-serine]kalata B1	CHEMBL1801140

ADVANCED PEPTIDE NAMES

- Named peptides imply not only sequence but also N-terminal acetylation, C-terminal amidation and disulfide bridge topology.
- Example derivative naming operations:
  - gastrin (14-17)
  - motilin amide
  - oxytocin free-acid
  - acetyl-oxytocin
  - deacetyl-abarelix
  - oxytocin reduced
  - endothelin-1 (1→3),(11 → 15)-bis(disulfide)

HOMODETIC CYCLES #1

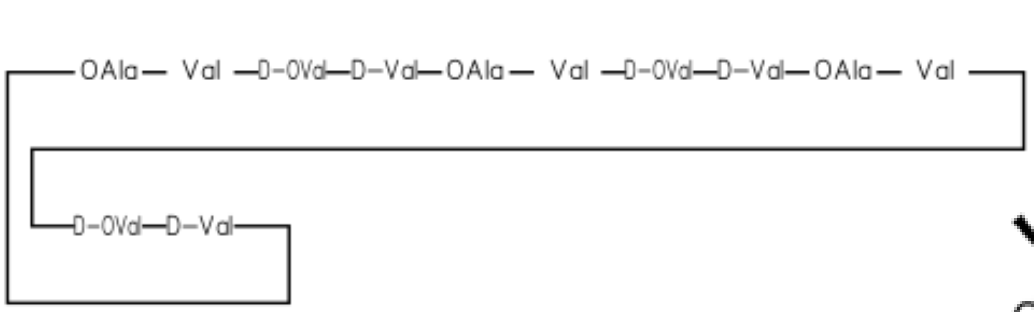


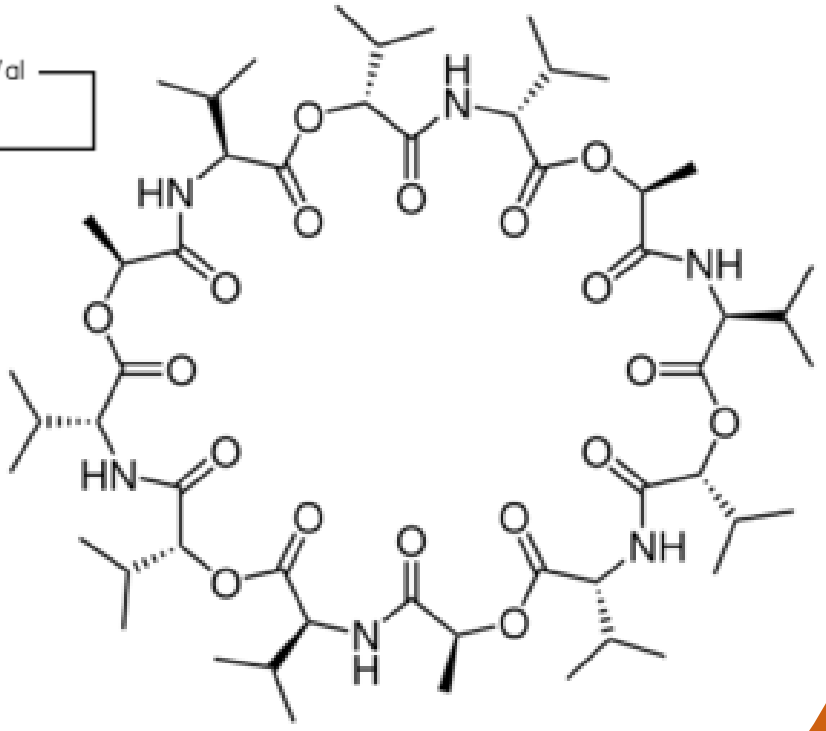


cyclo[Leu-D-Phe-Pro-Val-Orn-Leu-D-Phe-Pro-Val-Orn]

gramicidin S

HOMODETIC CYCLES #2





cyclo[OAla-Val-D-OVal-D-Val-OAla-Val-D-OVal-D-Val-OAla-Val-D-OVal-D-Val]

valinomycin

AMBIGUOUS/PREFERRED FORMS

- [3-L-isoleucine]lypressin vs. [8-L-lysine]vasotocin
- [2-L-phenylalanine]lypressin vs. [8-L-lysine]phenypresin
- [2-L-phenylalanine]ornipressin vs. [8-L-ornithine]phenypressin
- [3-L-isoleucine]ornipressin vs. [8-L-ornithine]vasotocin
- [4-L-methionine]afamelanotide vs. [7-D-phenylalanine]α-MSH

- [Thr1,Lys2]endomorphin-1 vs. [Trp3,Phe4]tuftsin amide
- [Gln3]thyrotropin-releasing hormone vs. [Pro3]eisenin amide
- [Trp1,Val2]endomorphin-2 vs. [Val2,Phe3]gastrin tetrapeptide

NAMED CYCLIC PEPTIDE DERIVATIVES

- Mutants of named cyclic peptides are identified by comparing against all “rotational” permutations.

Example line notation query (CHEMBL478596)

cyclo[Ala-Gly-Thr-Phe-Val-Tyr]

Reference database line notations:

cyclo[Gly-Thr-Phe-Leu-Tyr-Thr] dichotomin B

cyclo[Ala-Gly-Thr-Phe-Leu-Tyr] dichotomin C

Resulting Sugar & Splice peptide name:

[5-L-valine]dichotomin C

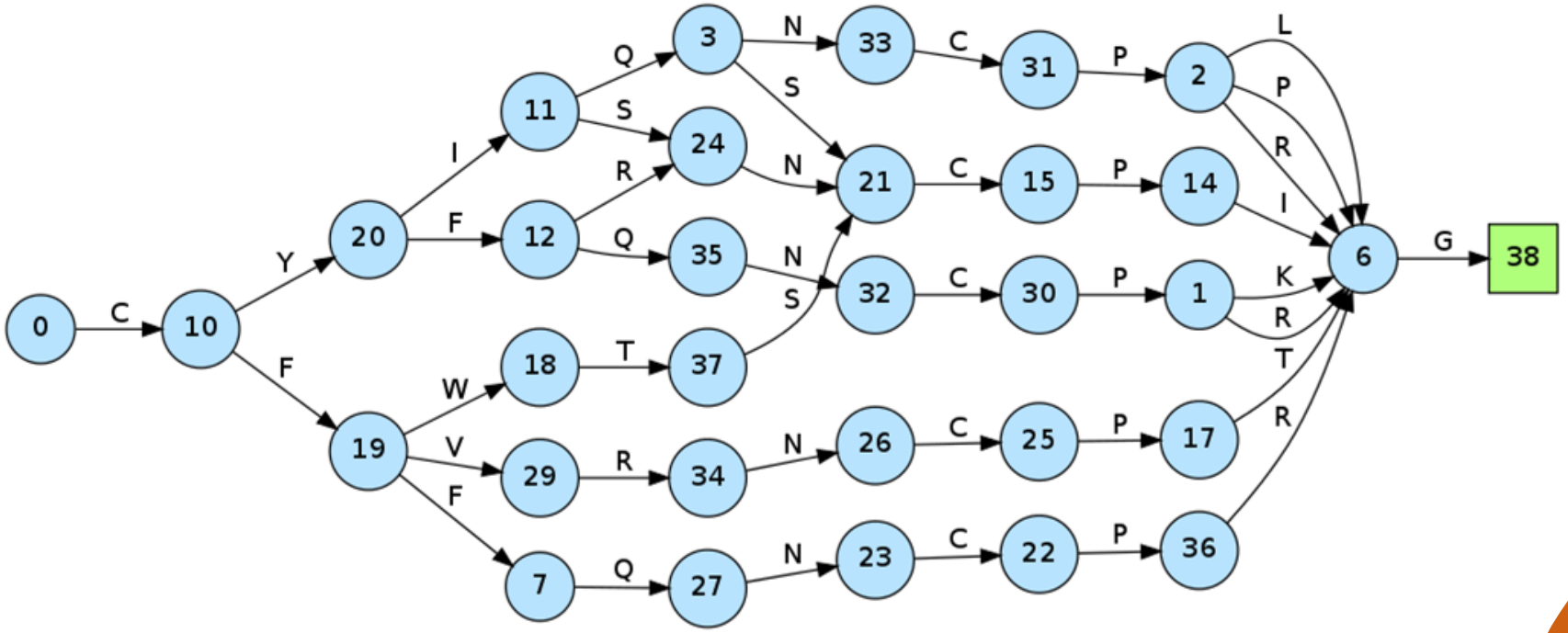
LOWER LOCANTS IN CYCLIC PEPTIDES

- Symmetric cyclic peptides provide an interesting challenge, where substitions are different locants can potentially be synonymous.
- CHEMBL1934531
  - [3-(4S)-4-amino-L-proline]gramicidin S preferred
  - [8-(4S)-4-amino-L-proline]gramicidin S acceptable
- CHEMBL1934536
  - [3-(4R)-4-amino-L-proline]gramicidin S preferred
  - [8-(4R)-4-amino-L-proline]gramicidin S acceptable

SCALING-UP PROTEIN VARIANT NAMING

- The algorithm described for naming peptides can also be applied to naming arbitary protein variants.
- Consider the a database of the following 11 peptides:
  - CFFQNCPRG phenylpressin
  - CFVRNCPTG annetocin
  - CFWTSCPIG octopressin
  - CYFQNCPRG argipressin
  - CYFQNCPKG lypressin
  - CYFRNCPIG cephalotocin
  - CYIQNCPLG oxytocin
  - CYIQNCPPG prol-oxytocin
  - CYIQNCPRG vasotocin
  - CYIQSCPIG seritocin
  - CYISNCPIG isotocin

DAG REPRESENTATION OF SEQUENCES



These 11 peptides may be efficiently represented and search as a “directed acyclic graph” [38 vs. 99 states]

ENTIRETY OF UNIPROT/SWISSPROT

- Using this representation, all 540546 protein sequences in uniprot_sprot, which contains over 192M amino acids, requires 142M states (1.4Gb).
- This data structure allows close analogues to be identified much faster than using NCBI blastp.
- For example, all 540546 sequences can be queried against this database (i.e. all-against-all) in ~9m30s on a single core on a laptop.
- The sequence from PDB 1CRN (crambin 46AA) is canonically named as [L25I]P01542 in 0.002s.

APPLICATION TO PRECISION MEDICINE

- A more realistic example is that sequence of the gene “spastic paraplegia4” with six mutations from OMIM:604277 can be canonically named as [I344K,S362C,N386S,D441G,C448Y,R499C]Q9UBP0
- Run-time for this query is 0.2s.
- By comparison, blastp 2.2.29+ takes about 6s.
  - With default arguments, NCBI blastp run time is 7s.
  - Only 6s with –num_descriptions 1 –num_alignments 1.

30 SECOND SUMMARY

- This talk describes the development of software for both naming peptides and reading peptide names matching the de facto standard practices currently followed by biochemists.
- Unlike computer representations, like Pisotoia HELM or InChI keys, these names and identifiers match those typically found in the scientific literature and vendor catalogues.
- A significant application of this technology is to check and correct peptide representations in databases.

ACKNOWLEDGEMENTS

- Joanna Sharman, IUPhar, Edinburgh University, UK.
- Lisa Sach-Peltason, Hoffmann-La Roche, Basel.
- Joann Prescott-Roy, Novartis, Boston, MA.
- Greg Landrum, Novatis, Basel, Switzerland.
- Evan Bolton, NCBI PubChem project, Bethesda, MD.
- Daniel Lowe, NextMove Software, Cambridge, UK.
- John May, NextMove Software, Cambridge, UK.