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discovery services

make the molecules that matter

ACS 2018 New Orleans

Using molecular fields to understand molecular determinants of the olfaction process

Dr Martin Slater

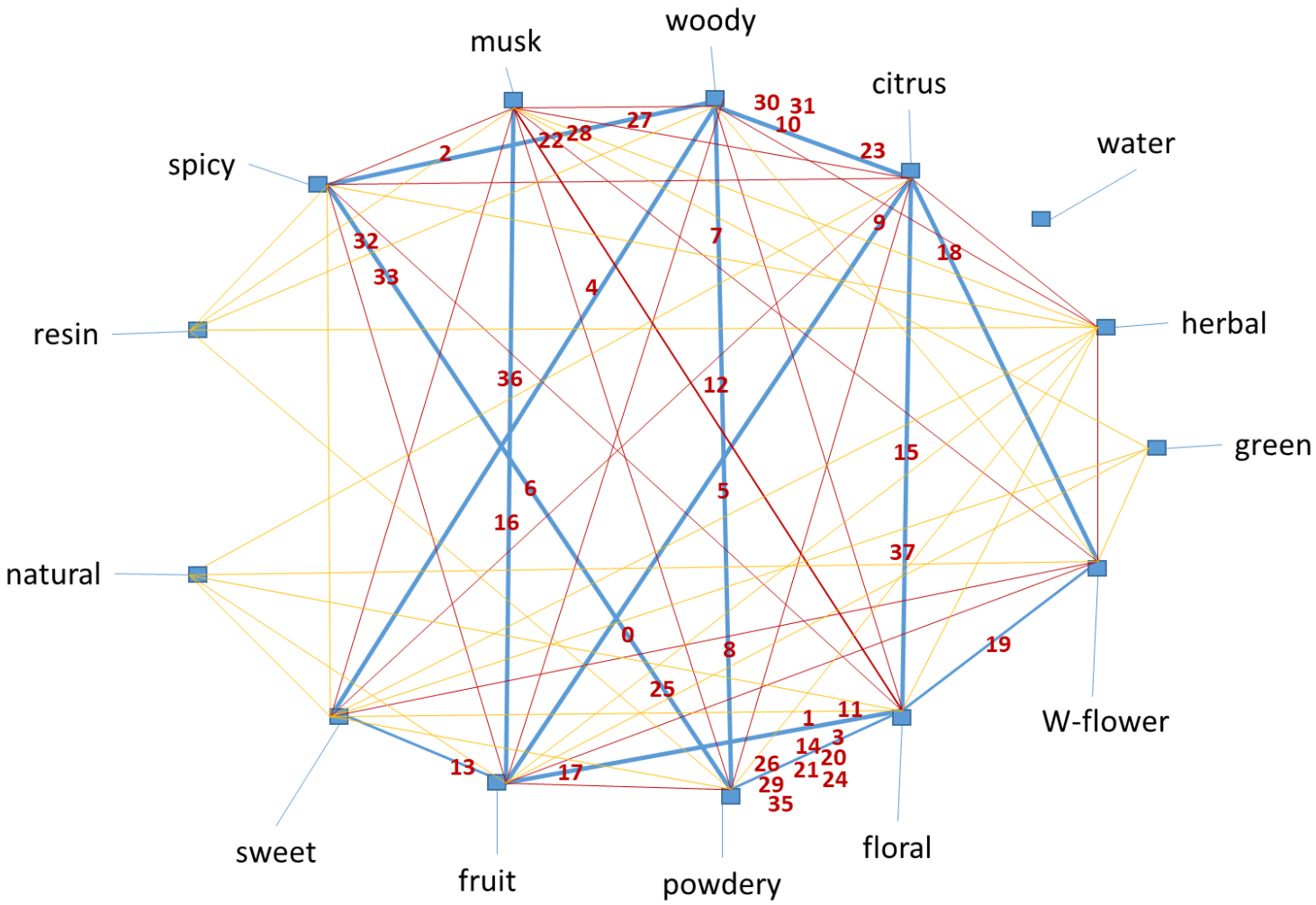
What is in a fragrance?

Perfumes

- Approximately 36,000 commercially available perfumes
- Complex mixtures of odorant ingredients
- Often classified using a musical analogy
  - ‘notes’ and ‘chords’
  - multiple levels of description

Other ‘less agreeable’ fragrances

- Faeces, urine, bacon, sweat, fish, guano, sulfur
- Eau de fromage ?



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Olfaction process

- A matter of faith?
  - Classical molecular recognition of odorants at olfactory receptors?
  - Vibrational theory; tunnelling infra red spectroscopy (Innovative thinking from Luca Turin)

- A matter of fact…!
  - Fragrance molecules are relatively small and volatile –
    - need to reach olfactory neurones in the nasal cavity

  - Single, ‘pure’ odorant molecules have multiple perceived odour properties
    - Eg. Molecule Number One
    - Odorant to receptor relationship is: **‘one-to-many’** (ie combinatorial, poly-pharmacological)

  - Genetic variation affects perception in individuals – fuzzy definitions for odour perception
  - Over 400 olfactory GPCR receptors expressed; 1 type per neurone
  - A neurological rather than a purely biophysical phenomenon (phantosmia)

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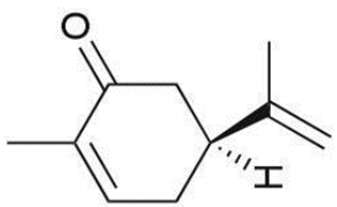
Can molecular similarity describe the olfaction process

> Does 2D molecular similarity relate to odour perception?

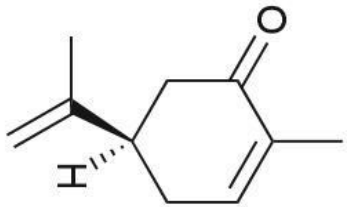
Chemical Functionality	Odour property	Odour property
Acids	sour	cheesy
Alcohols	fresh	sweet, alpine
Aldehydes	fresh	flowery,
Alkanes	woody	musky
Amines	fishy	rotting food
Esters	fruity	musky
Thiols	beefy	pungent

So yes…sort of…?

Tanimoto similarity = 1



(S) Carvone-(+)
Caraway



(R) Carvone-(-)
Spearmint

…but…no not really!

> Can we do better with 3D?

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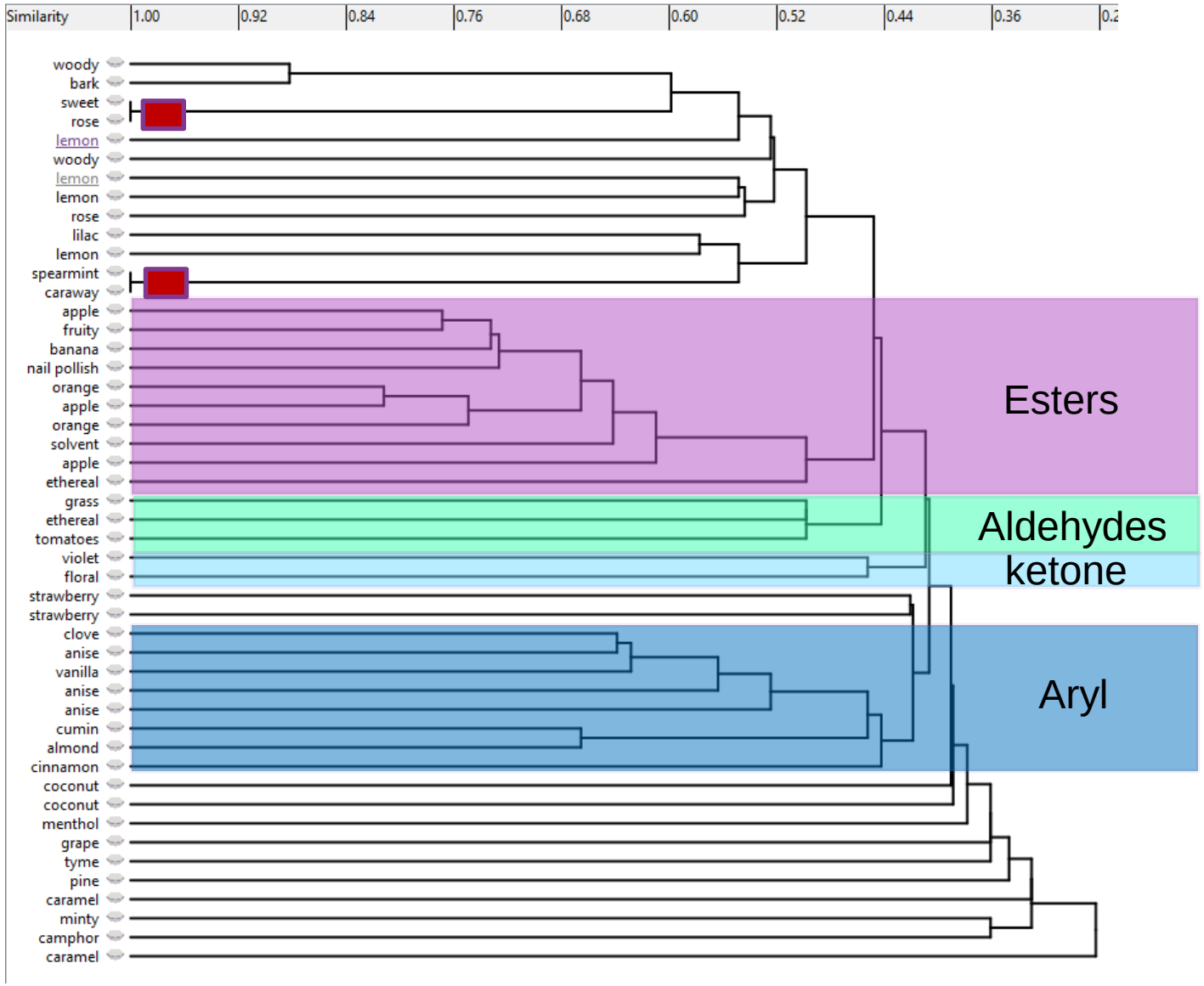
Results: FCFP4 2D Clusters



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Similarity Matrices

2D FCFP4 sim

Title	apple	orange	orange	apple	fruity	banana	solvent	apple	nail pollish	strawberry	floral	rose	sweet	lemon	rose	bark	woody	woody	lemon	lemon	strawberry	lemon	lilac	caraway	spearmint	coconut	grass	tomatoes	grape	anise	anise	anise	clove	vanilla	almond	cinnamon	cumin	coconut
apple	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
orange	1	0	0	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
orange	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
apple	0	1	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
fruity	0	0	0	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
banana	0	0	0	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
solvent	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
apple	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
nail pollish	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
strawberry	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
floral	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
rose	0	0	0	0	0	0	0	0	0	0	0	0	1	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
sweet	0	0	0	0	0	0	0	0	0	0	0	1	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
lemon	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
rose	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
bark	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
woody	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
woody	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
lemon	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
lemon	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
strawberry	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
lemon	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
lilac	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
caraway	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
spearmint	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
coconut	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
grass	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
tomatoes	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
grape	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
anise	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
anise	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
anise	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
clove	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
vanilla	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
almond	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
cinnamon	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
cumin	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
coconut	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
caramel	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

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3D odorant molecular analysis

> Can 3D molecular information tell us anything useful about olfaction?

If so:

> How do we determine odour-active conformations

> How do we superimpose molecules to compare them

> How do we actually compare them?

> One possible solution is it to assume that there is a consensus binding site for odorant molecules at their receptors?

> Take trans retinal as a model ligand system for hOR GPCR activation?

> Numerous odorant molecules have been de-orphanized can we build models?

Odorant	hOR
allyl phenylacetate	OR51L1
eugenol methyl ether	OR2J2
(+)-carvone	OR1A1
1-octanethiol	OR2C1
3-phenyl propyl propionate	OR10A6 L287P
eugenol	OR10G7
eugenol methyl ether	OR5K1
geranyl acetate	OR2A25
TMT	OR5K1
undecanal	OR56A4

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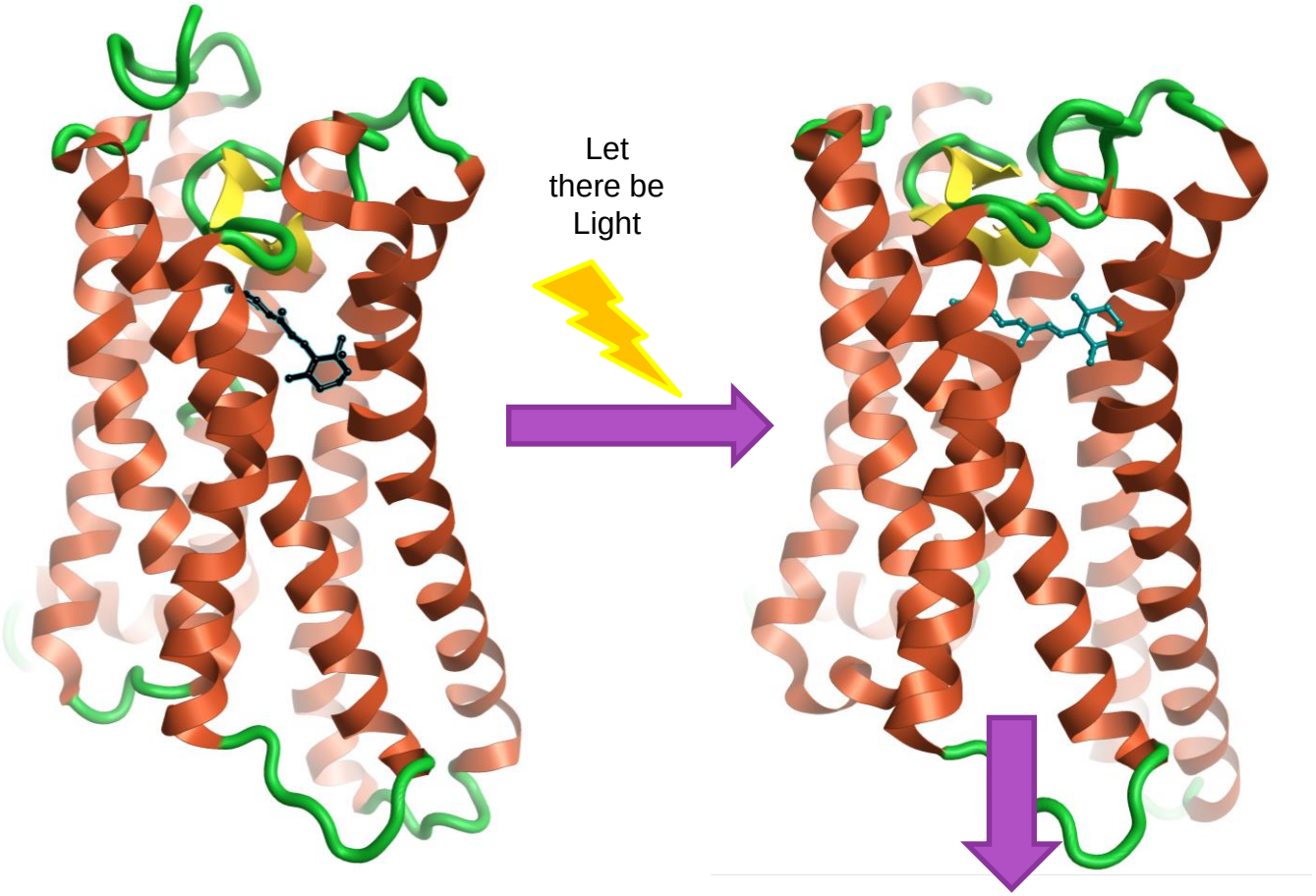
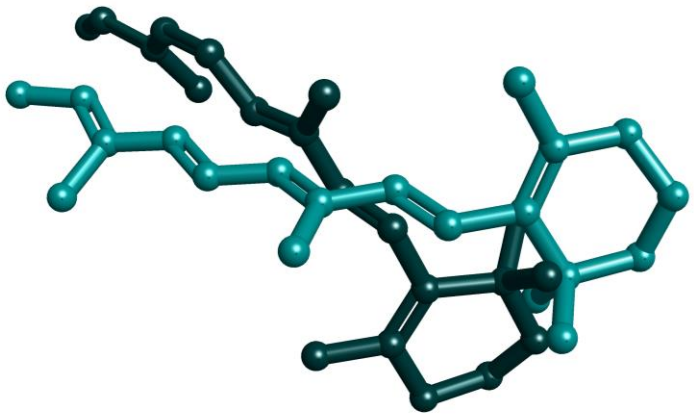
Protein molecular target – olfactory GPCRs

> Olfactory receptors are related to the light sensory GPCR ‘Rhodopsin’



Cis to trans retinal



ligand conformation change stimulates protein conformational change - leading to activation

G-protein / transducin mediated - signalling

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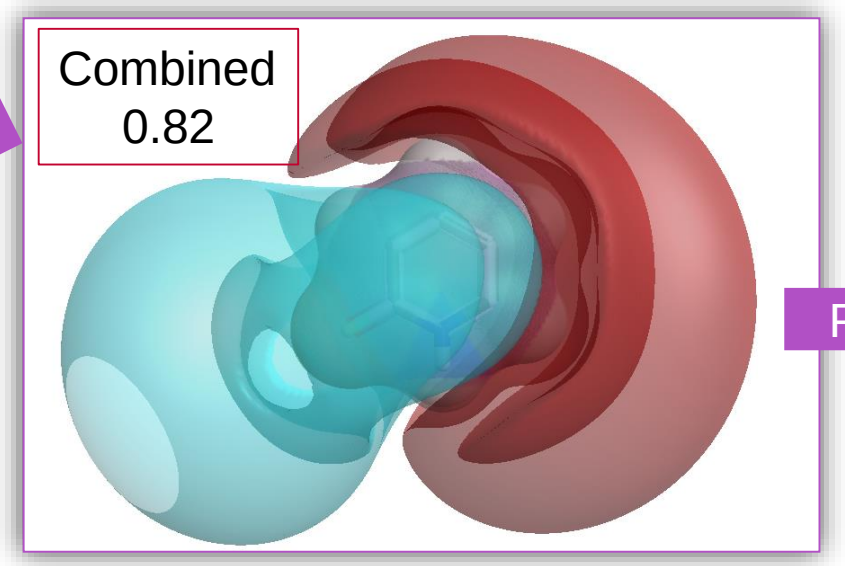
Compare odorants using 3D Electrostatic and shape similarity



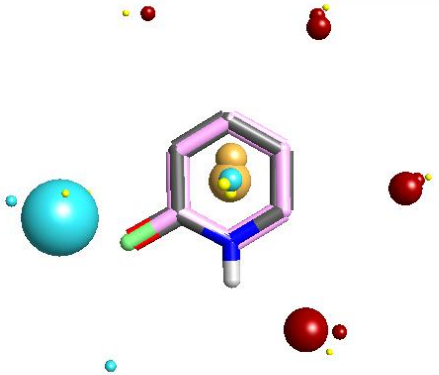
Score

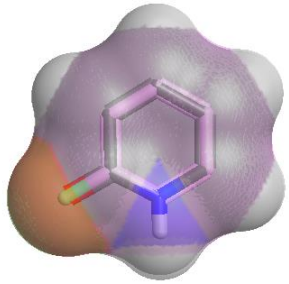
Virtual screening
Scaffold hopping

Pose

Bioactive conformation hypothesis
SAR interpretation
Molecule Design

Fields
0.66





Shape
0.98

Cheeseright et al,
J. Chem Inf. Mod., 2006, 665

Grant, Gallardo, Pickup,
J. Comp. Chem., 1996, 1653

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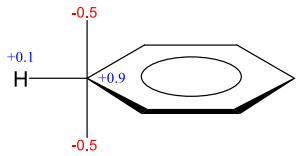
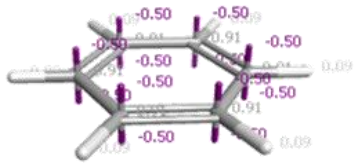
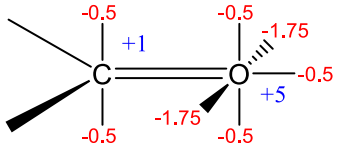
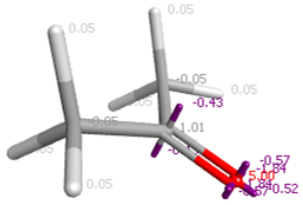
The Cresset difference - the XED force field

- XED force field – eXtended Electron Distribution
  - Multipoles via additional monopoles

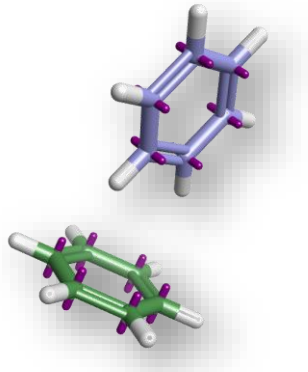








  - Huckel
    - separation of π and σ charges
      - π charges added to ‘xed’ atoms
      - σ charges added to nuclei
      - Excellent modeling of substituent effects
    - find bond orders and assign hybridization
      - Analogue N(sp^3) atoms – pyramidal to planar



  - Full molecular mechanics force field with excellent coverage of organic chemistry, water and proteins
    - Minimization, conformations etc.
    - Not a dynamics force field

Vinter, *J. Comput.-Aided Mol. Des.*, **1994**, 8, 653-668

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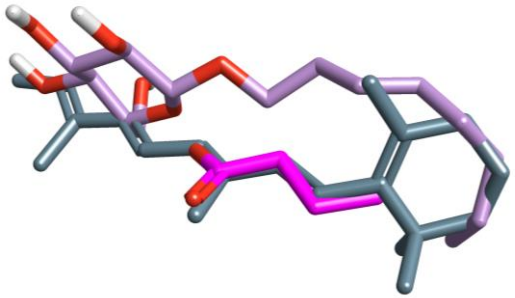
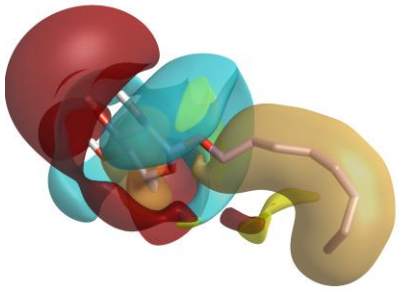
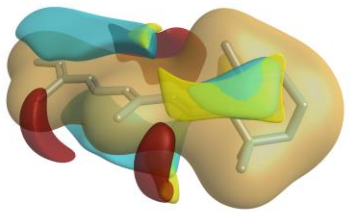
Work-flow in Cresset's ligand modeling suite: Forge

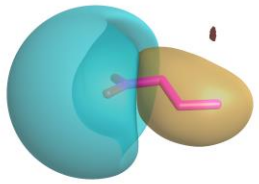
> Extract trans retinal from PDB:3PQR
> Extract BOG from PDB: 4J4Q
> Model proprionate / beta ionone into OR O51E2 model



> Use as templates for the molecular alignment based on shape and electrostatic match
> Conformationally search 48 diverse odorants
> Align them and score them for similarity
> Construct an all-by-all similarity matrix and cluster







Cresset's XEDFF3 molecular fields:

Cyan	negative
Red	positive
yellow	neutral
gold	hydrophobic

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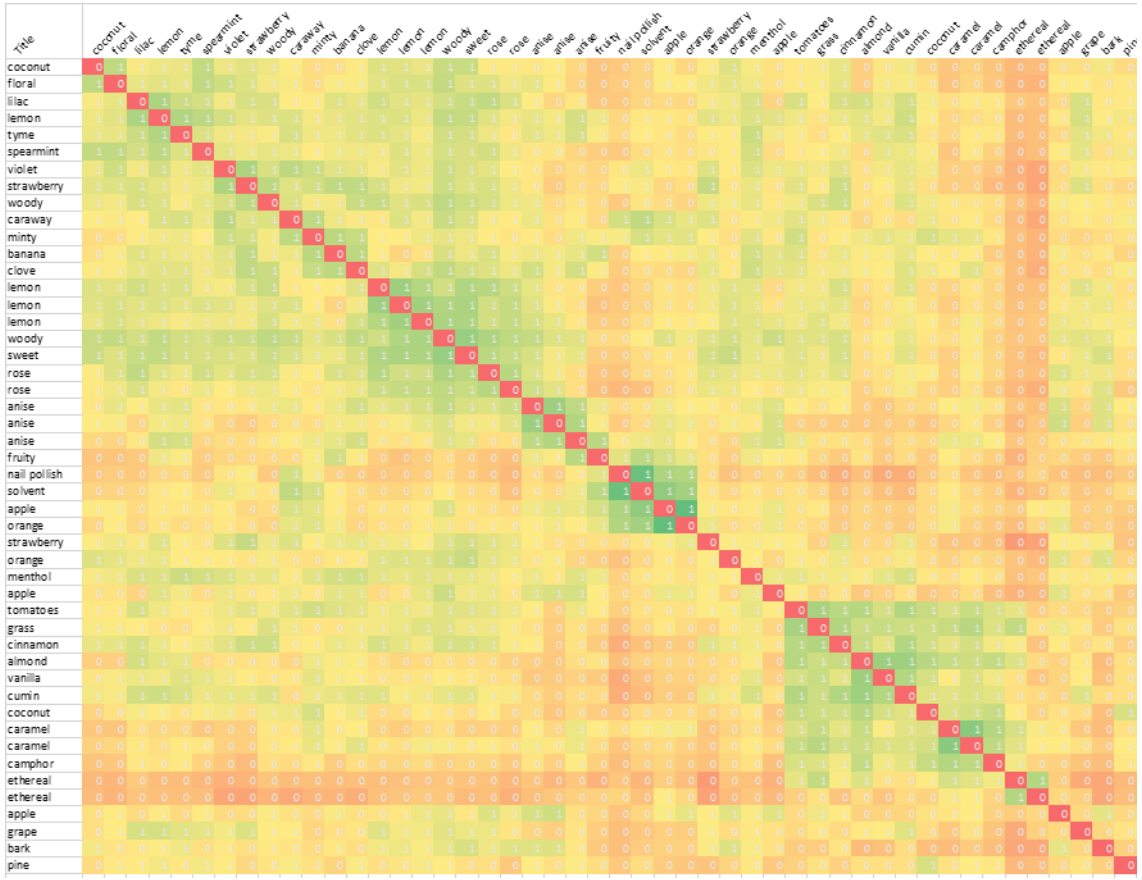
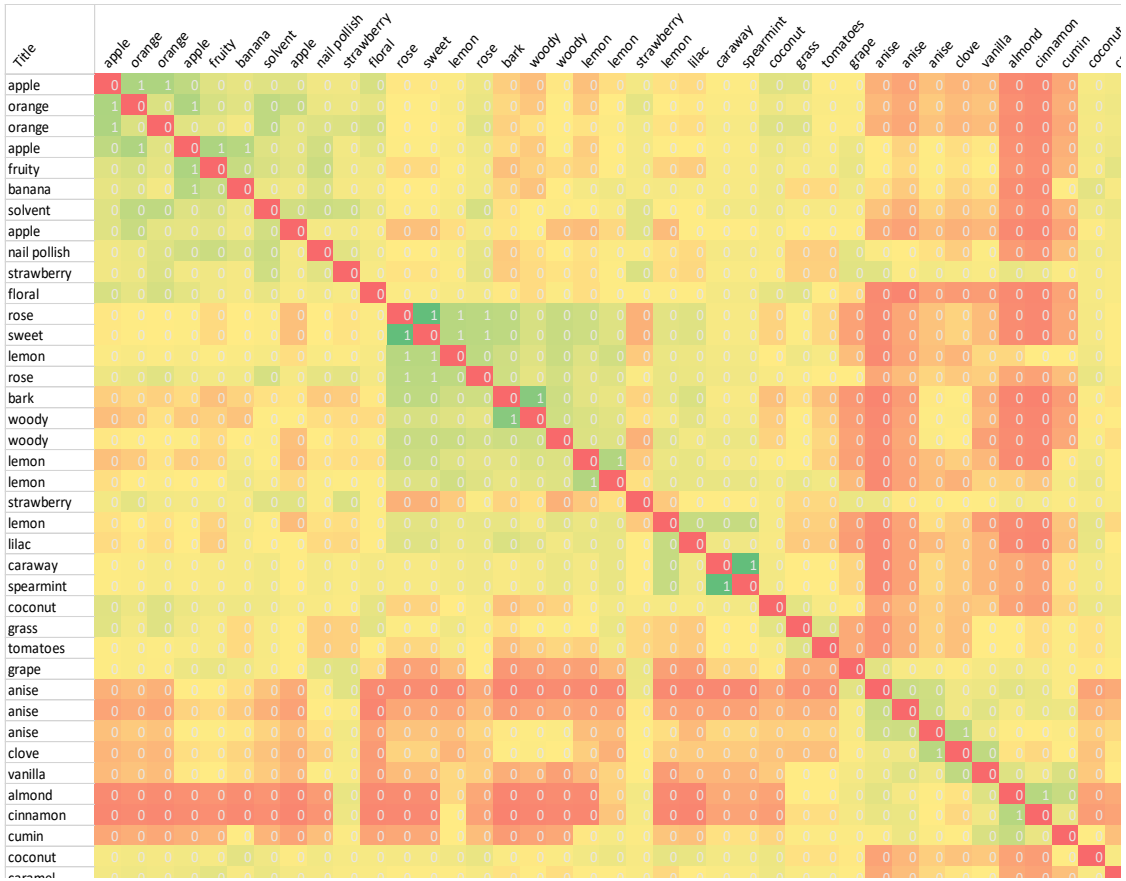
Similarity Matrices

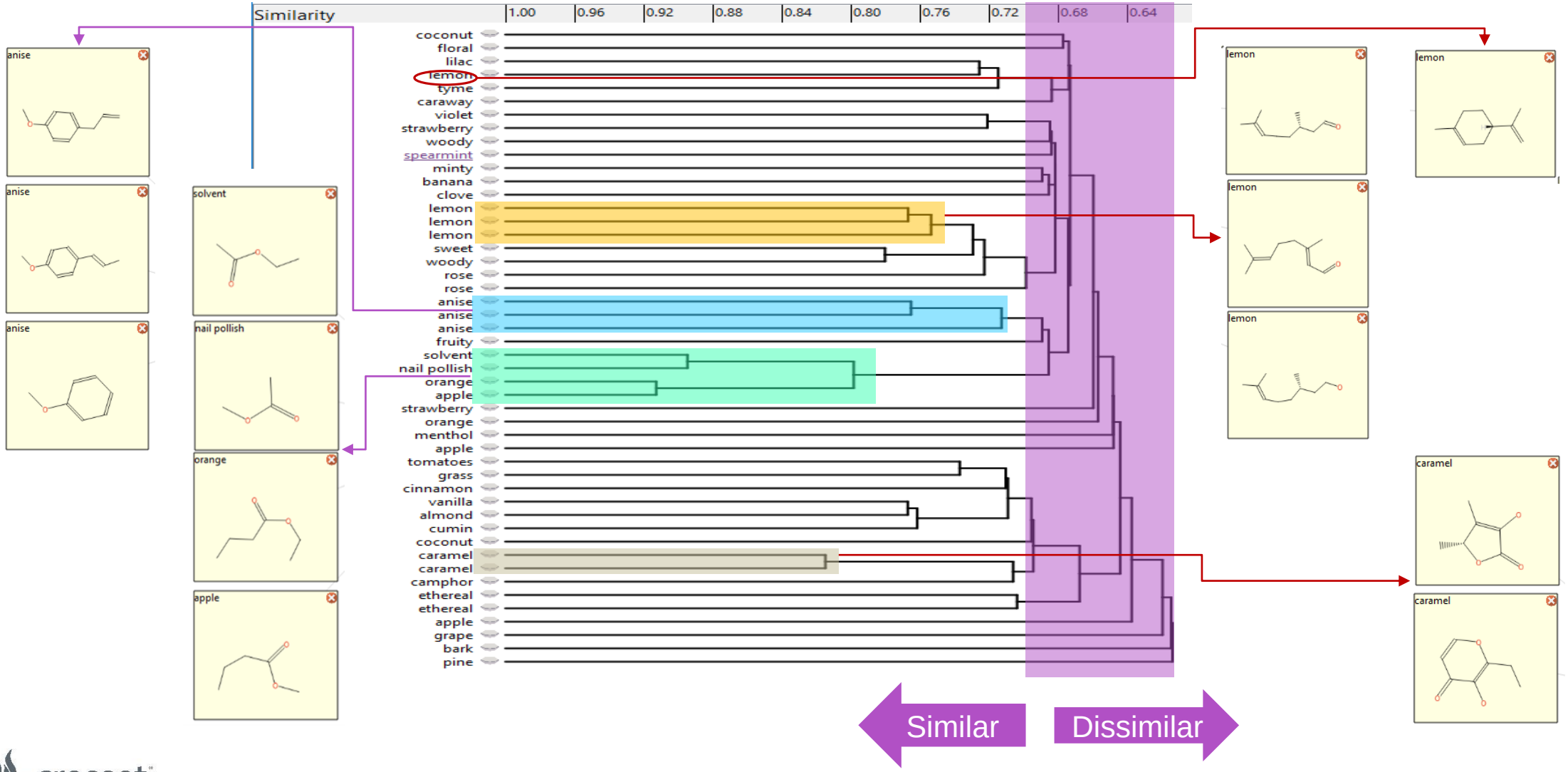


3D Field sim



2D FCFP4 sim

Results: 3D field and shape hierarchical clustering



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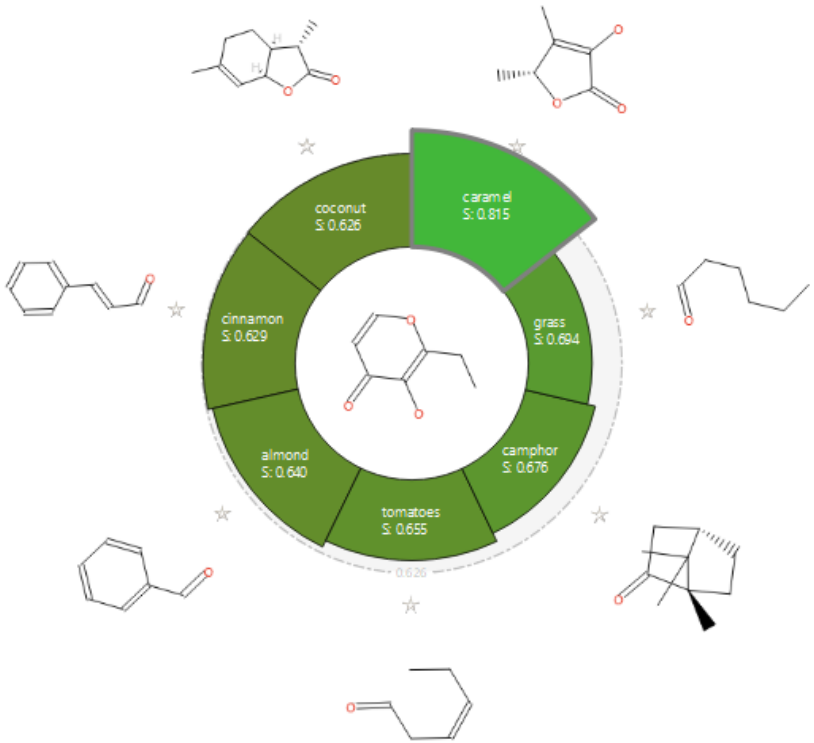
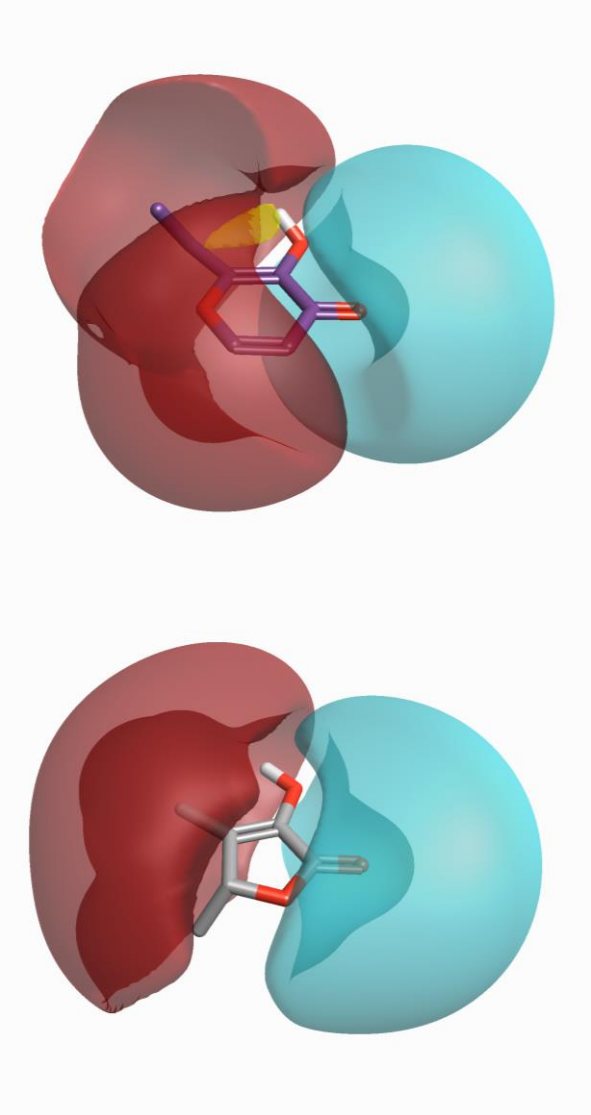
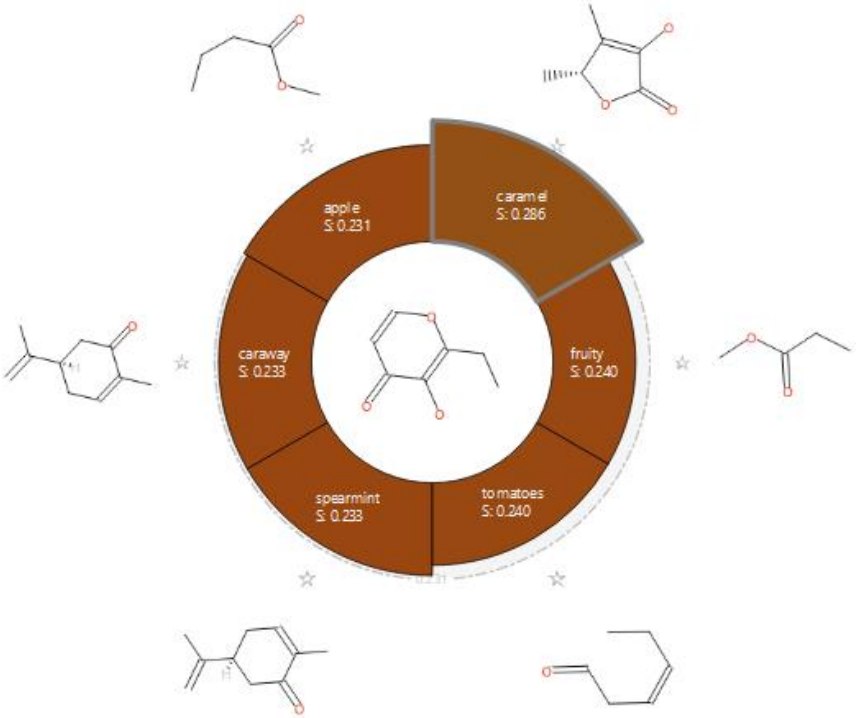
3D visualisation – caramel 3D similars

3D field sim = 0.82





2D FCFP4 sim = 0.29



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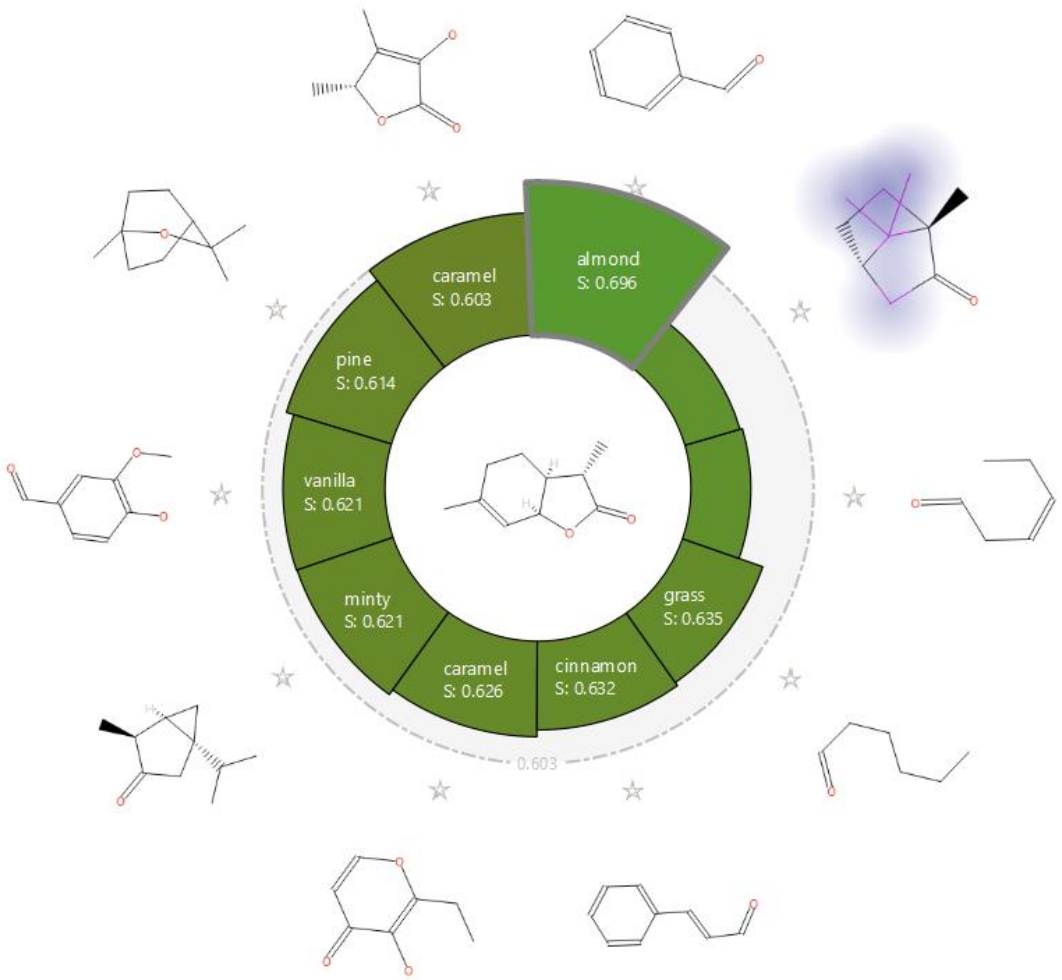
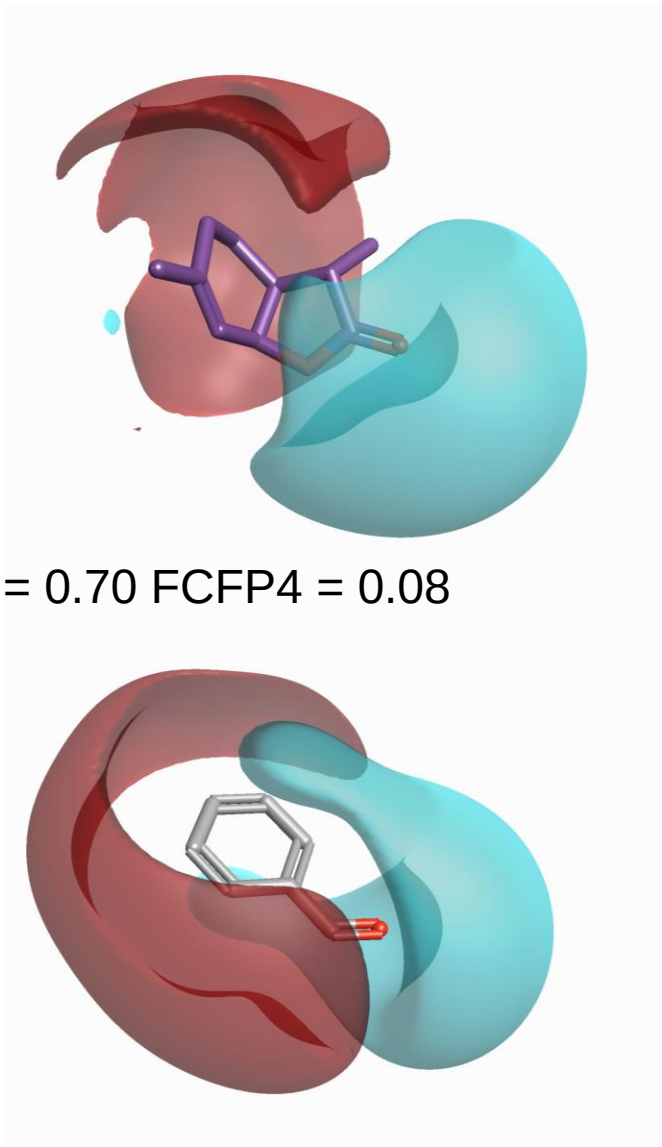
Diverse nutty pharmacophore





Fsim = 0.70 FCFP4 = 0.08

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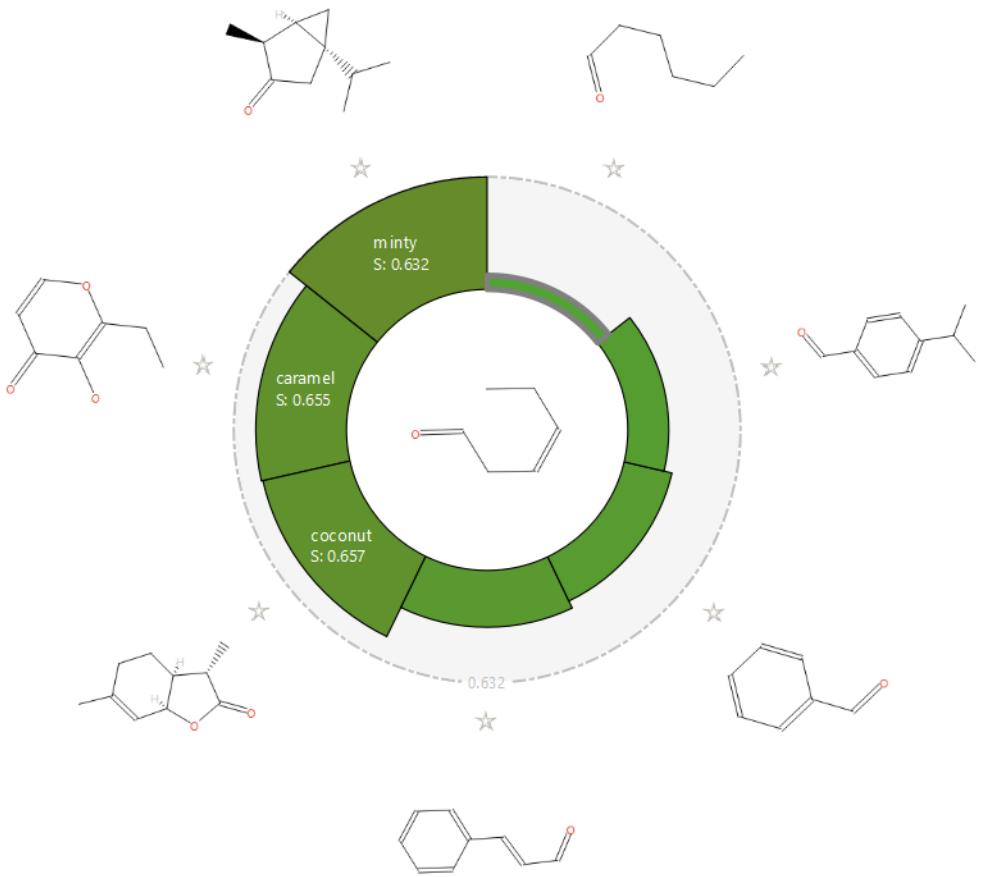
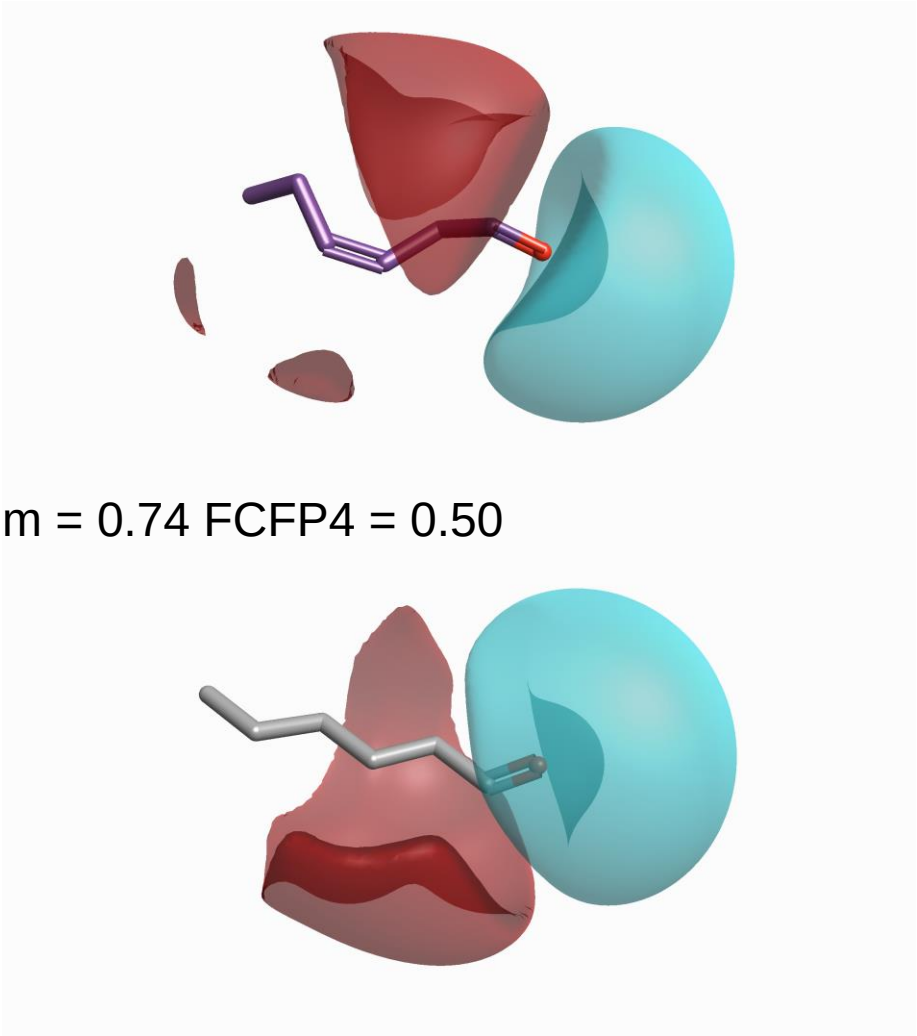
Green – grass and tomato





Fsim = 0.74 FCFP4 = 0.50

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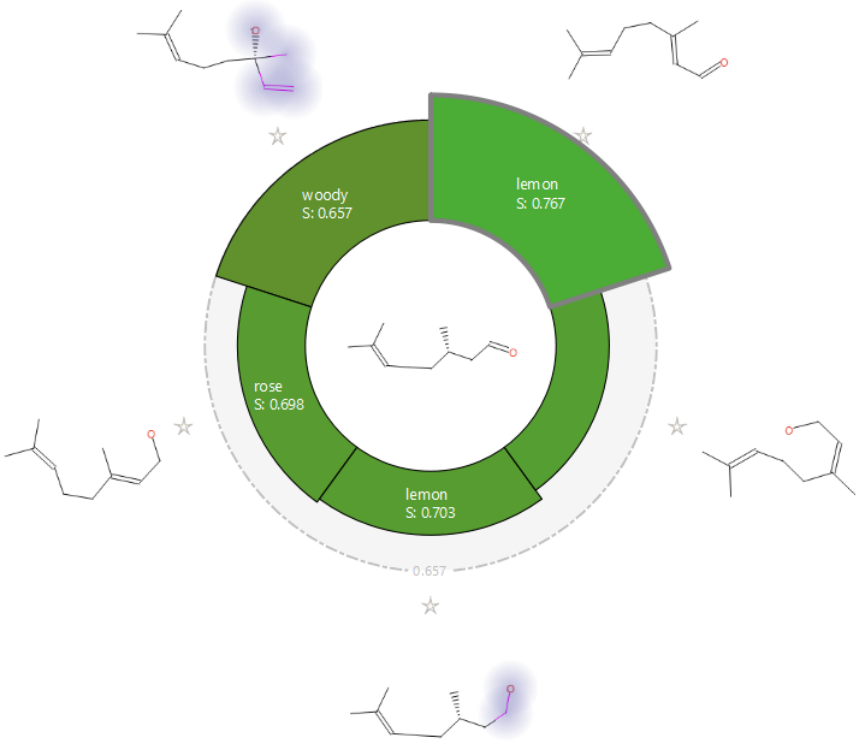
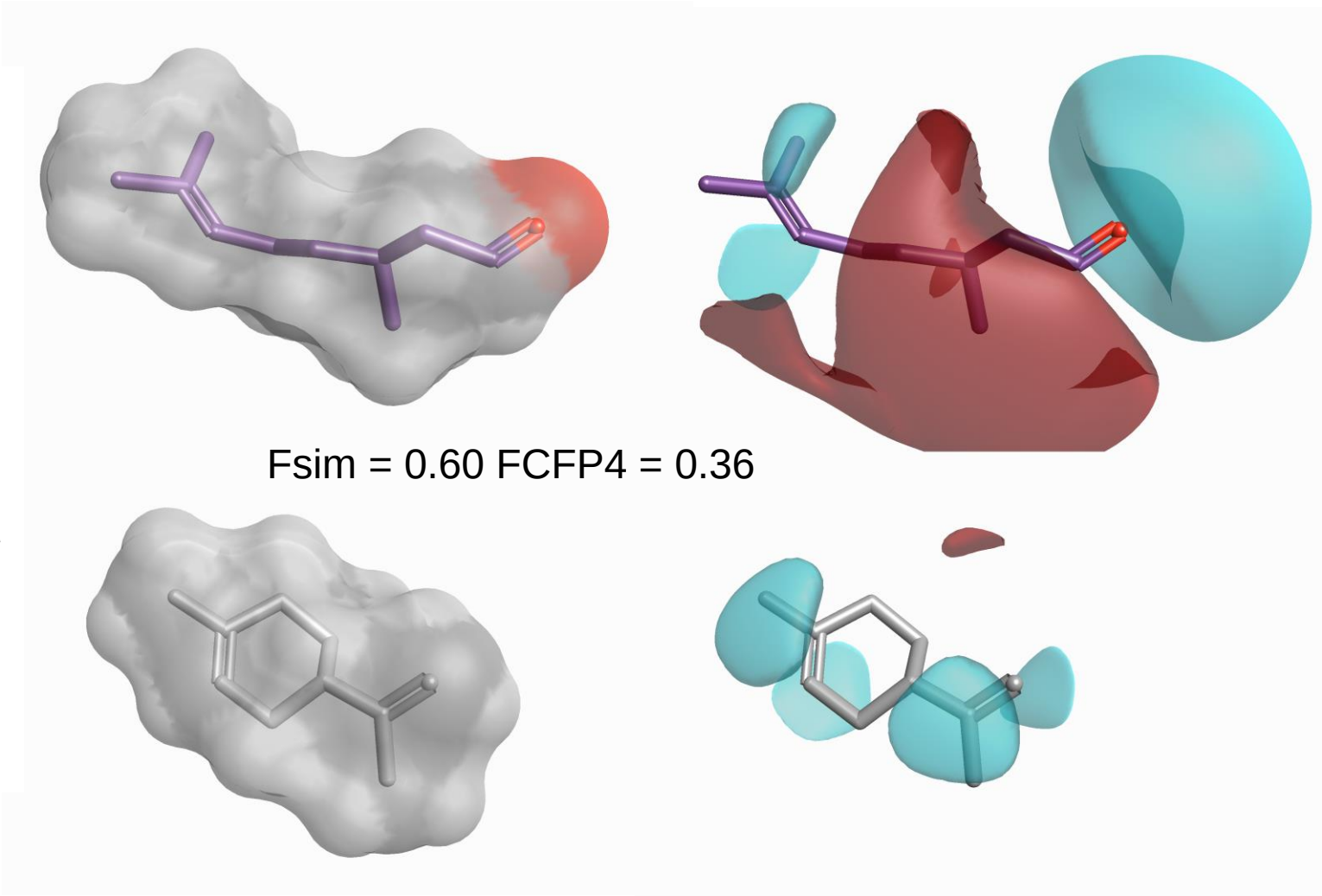
Discrete lemon pharmacophores?





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Conclusion

- Very small sample of odorant space but, never-the-less, interesting outcomes
  - Proof of concept
- 3D field-based similarities give a different view on odorant molecules
- Potential for unravelling less intuitive relationships between diverse molecules and their odour perception
- Possibility for identifying divergent / convergent relationships in odorant SAR

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Additional material

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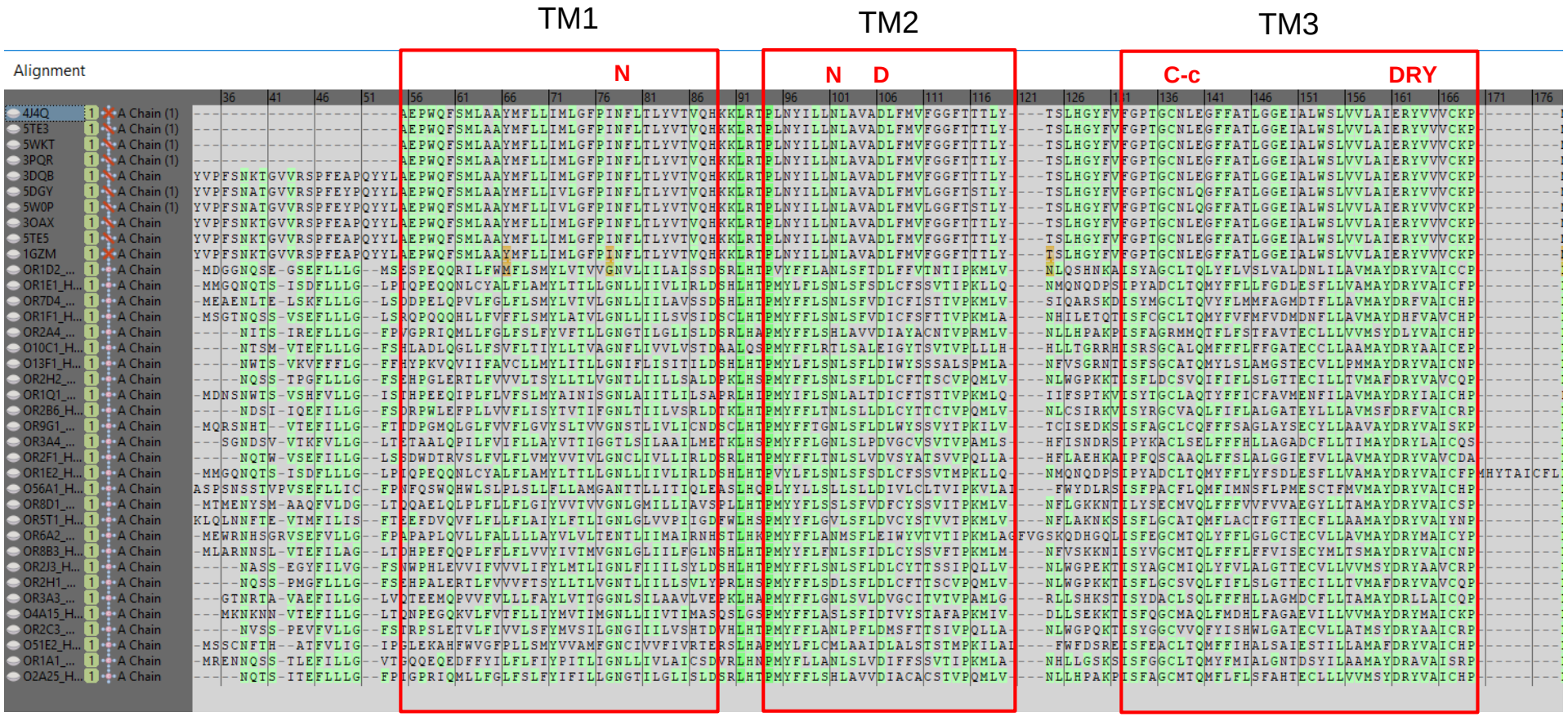
Similarity to rhodopsin & conservation across olfactory receptors

> Sequences of the OR's are highly conserved with each other

Rhodopsin X-ray structure sequences

20 X hOR sequences



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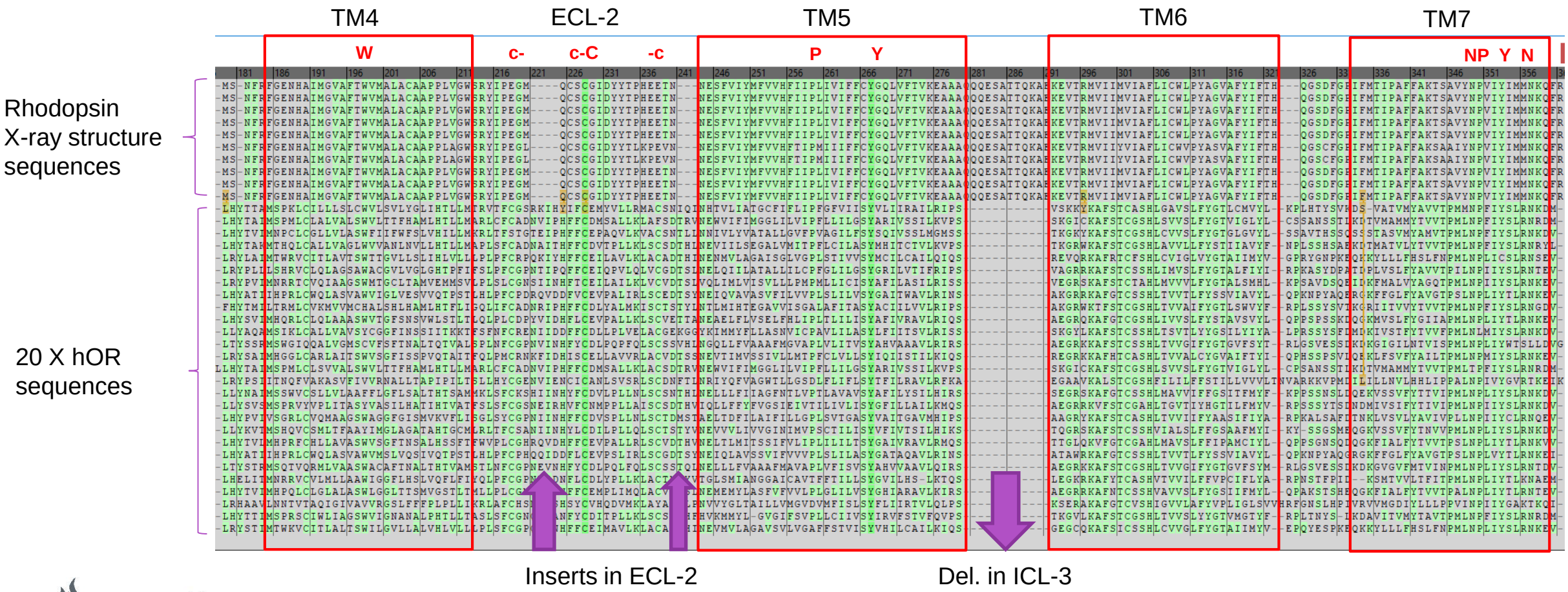
Conservation across olfactory receptors

> Different from class A GPCRs where there is much diversity in loop structures

  > very different recognition patterns – ranging from small molecules to proteins in contrast to OR's



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