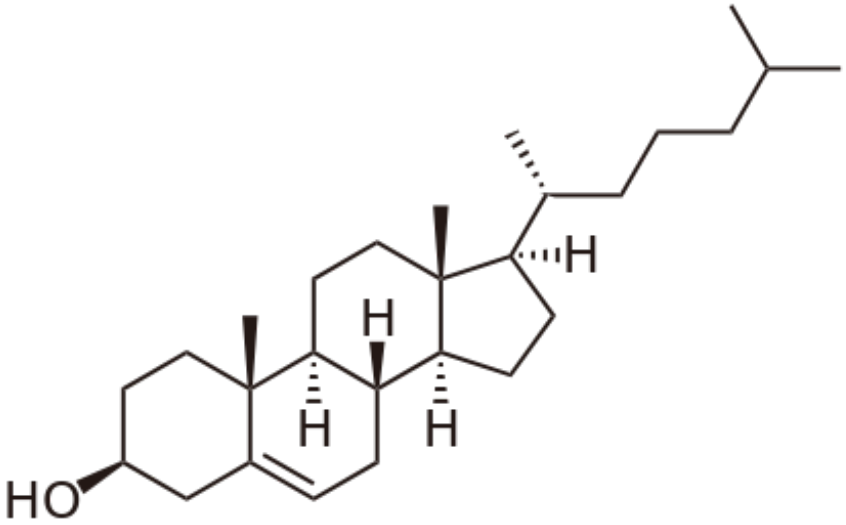
Cholesterol and related molecules

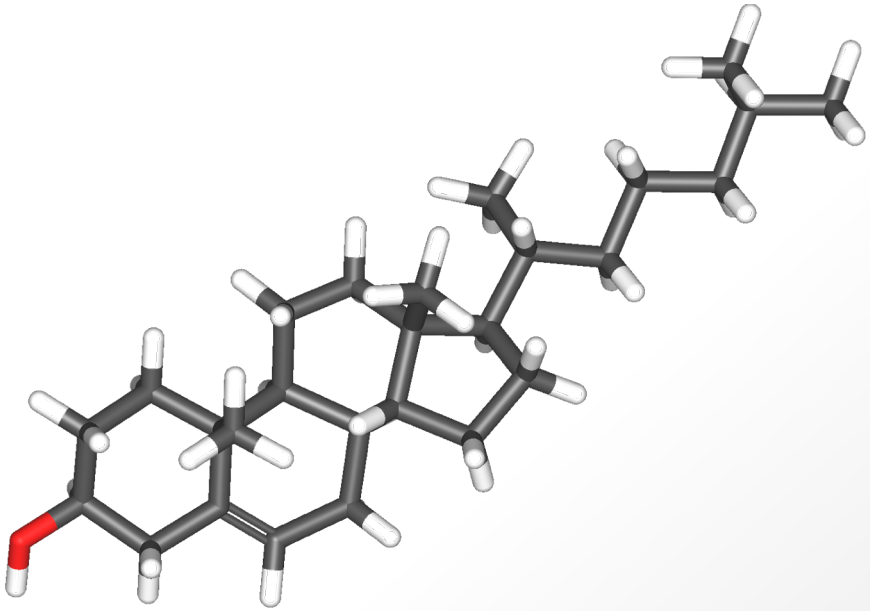
Parameterization challenges, nifty solutions, and new challenges because of the nifty solutions

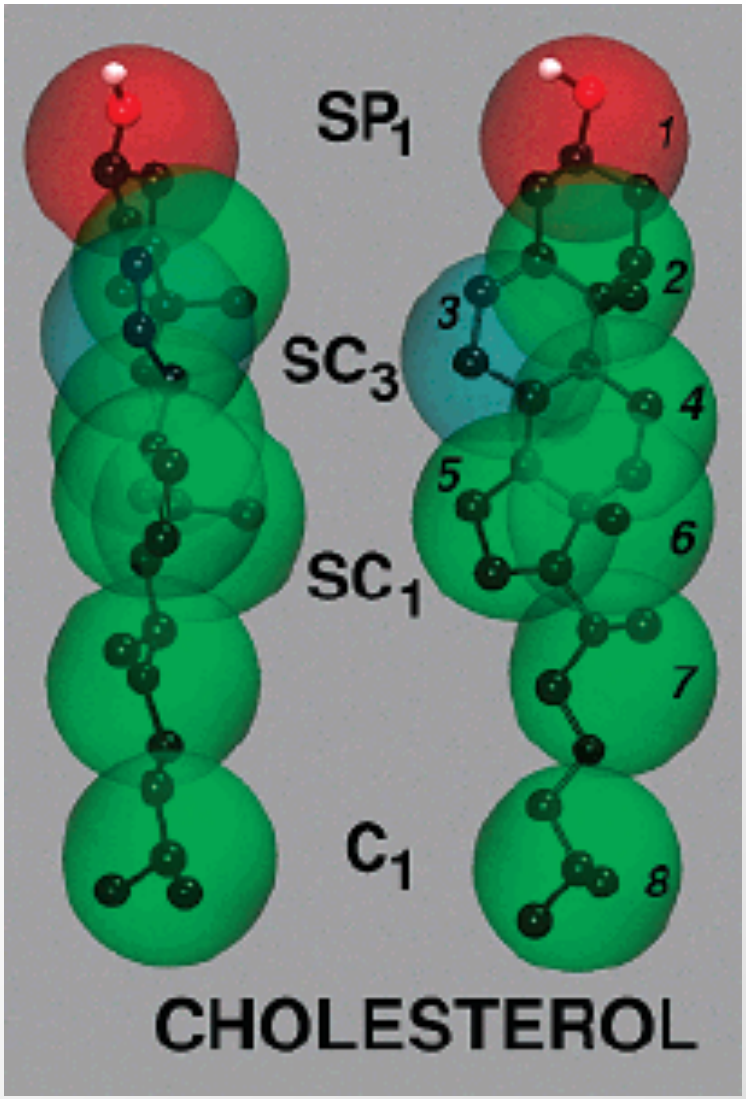
Manuel N. Melo

Multiscale Modeling Lab

Chapter I
Cholesterol

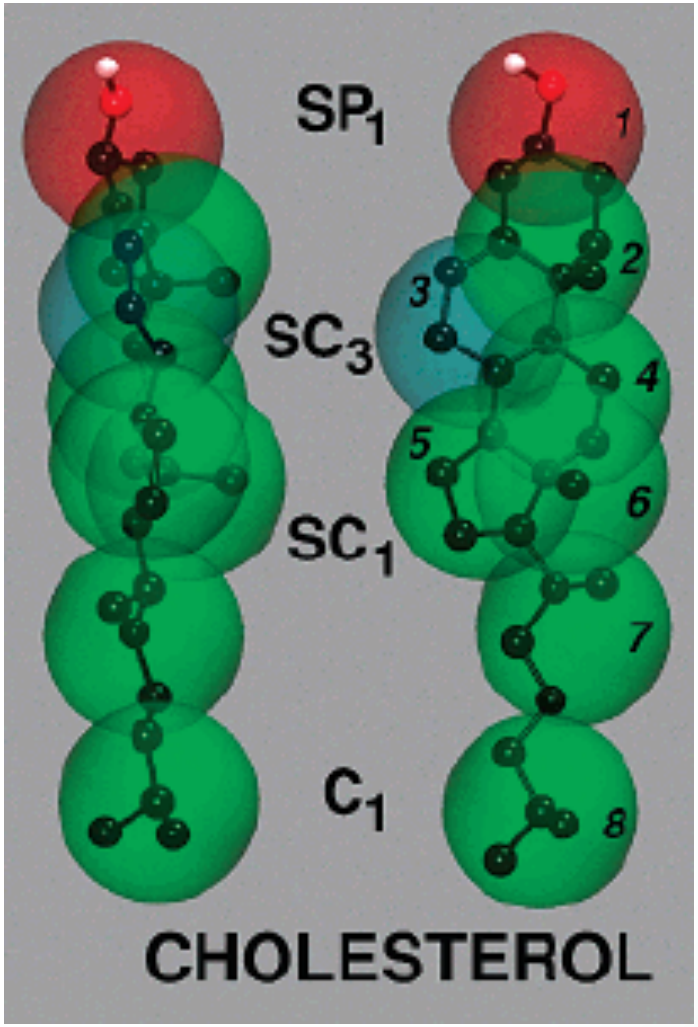






Marrink, S. J., Risselada, H. J., Yefimov, S., Tieleman, D. P., & De Vries, A. H. (2007). The MARTINI Force Field: Coarse grained model for biomolecular simulations. The Journal of Physical Chemistry B, 111(27), 7812–7824. https://doi.org/10.1021/jp071097f

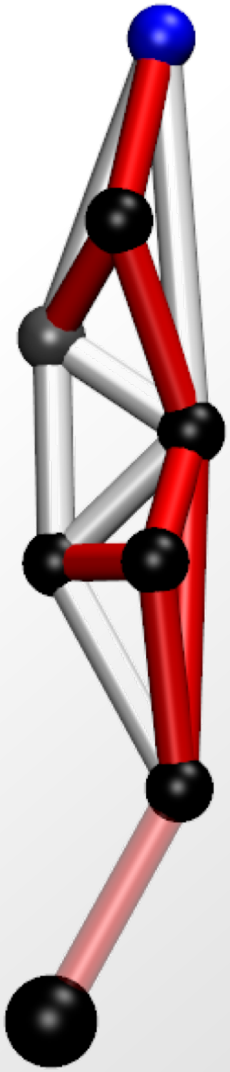

```
bonds that rotated more than 30 degrees:
 atom 1 atom 2  angle  previous, current, constraint length
      3      5   33.9    0.4466   0.3470      0.3460
      5
      4

Step 807
relative
rms 0.505
bonds tha
 atom 1 a
      3
      3
      5
      4
Wrote pdb

Step 807
relative
rms 1662.
bonds tha
 atom 1 a
      3
      3
      5
      4
      1
      1
Wrote pdb files with previous and current coordinates
Segmentation fault      (core dumped)
```



Constraints

Stiff bonds

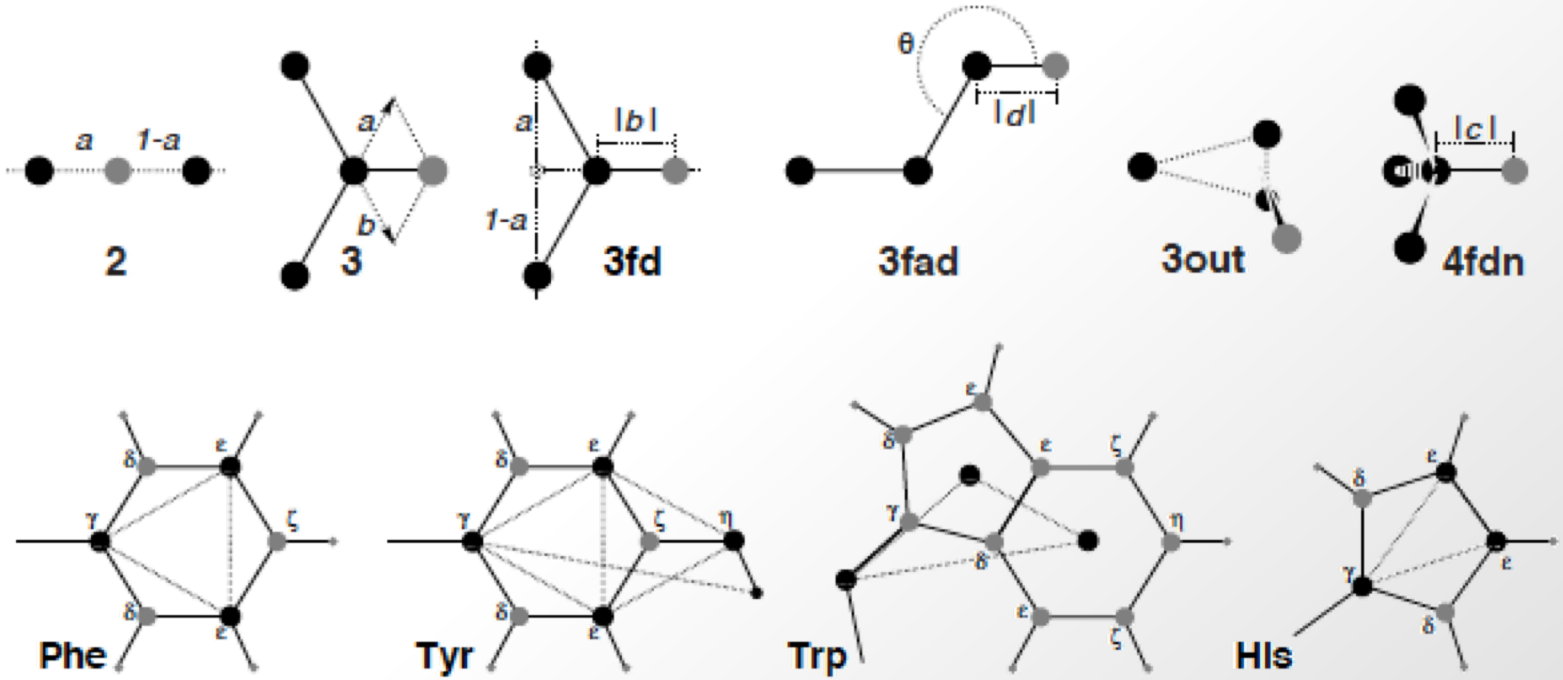
Weak bonds



Virtual interaction sites?

(poor man's rigid-body simulations)

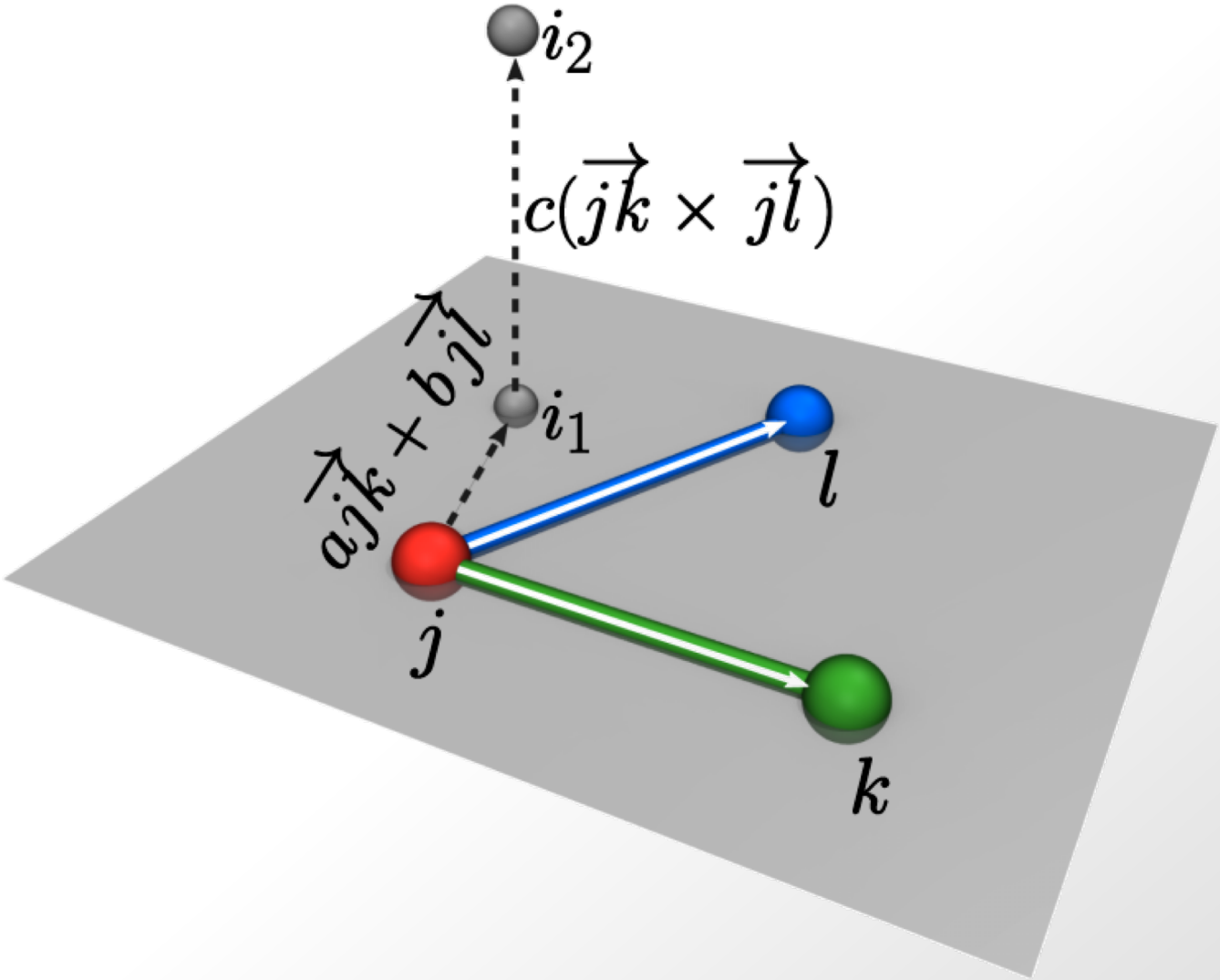
Because we don't need to reproduce cholesterol's high-frequency, low-amplitude vibrations



(Sadly, in GROMACS not yet compatible with updates on the GPU)

Virtual interaction sites?

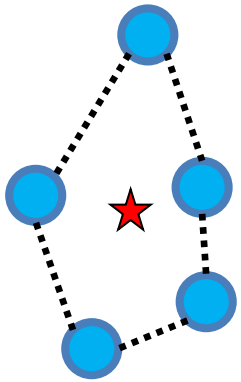
(poor man's rigid-body simulations)



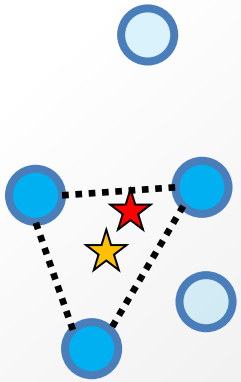
Virtual interaction sites?

(poor man's rigid-body simulations)

It's what's available in GROMACS…



Real rigid body



Virtual-sites
(only the frame particles have mass)

Center-of-mass is off

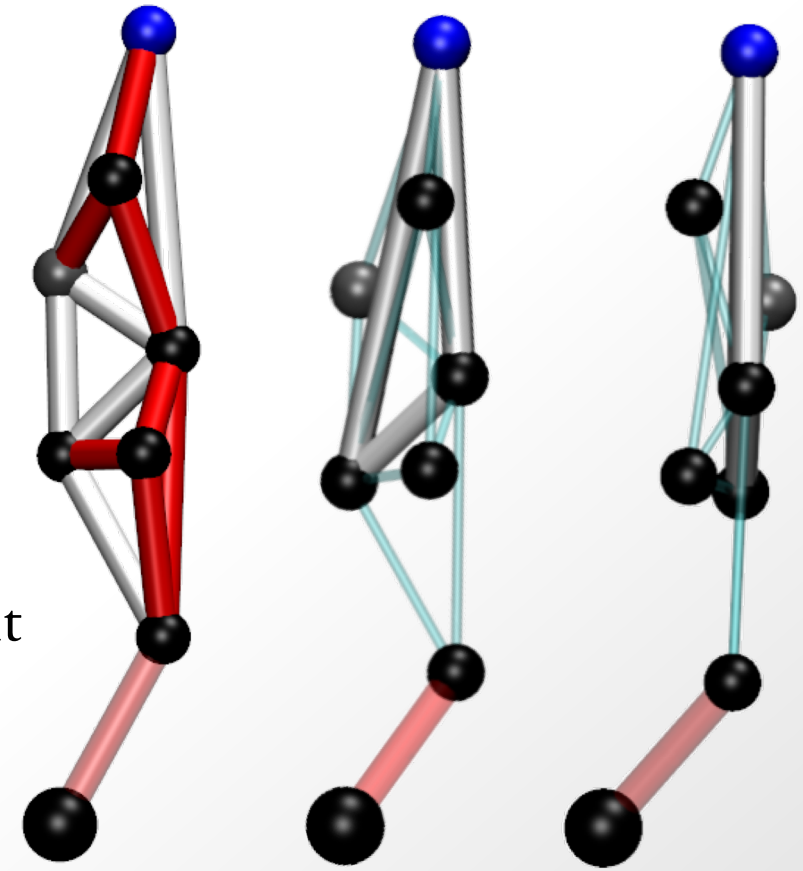
Moment-of-inertia is off (typically lower)

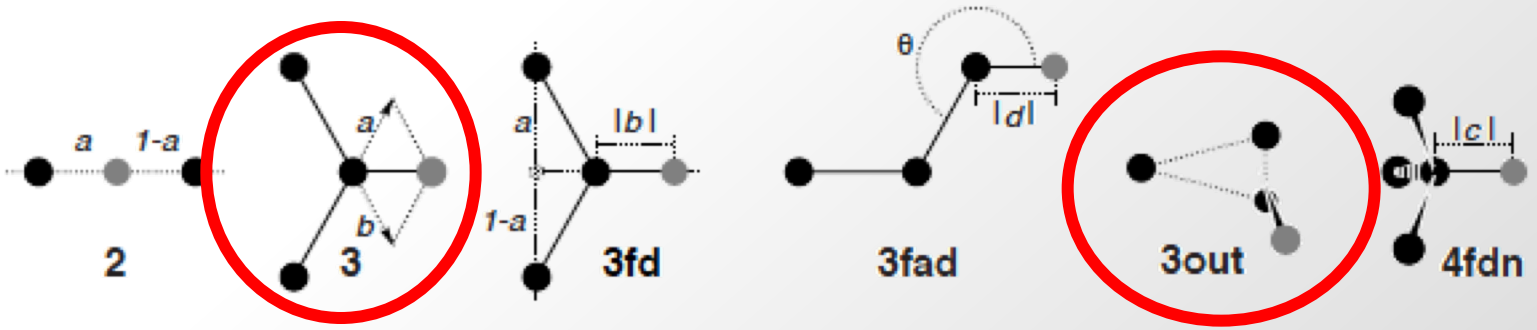
What was done

Three beads for a frame

Average positions of the remaining four beads relative to the frame

Defined those four beads as different virtual sites

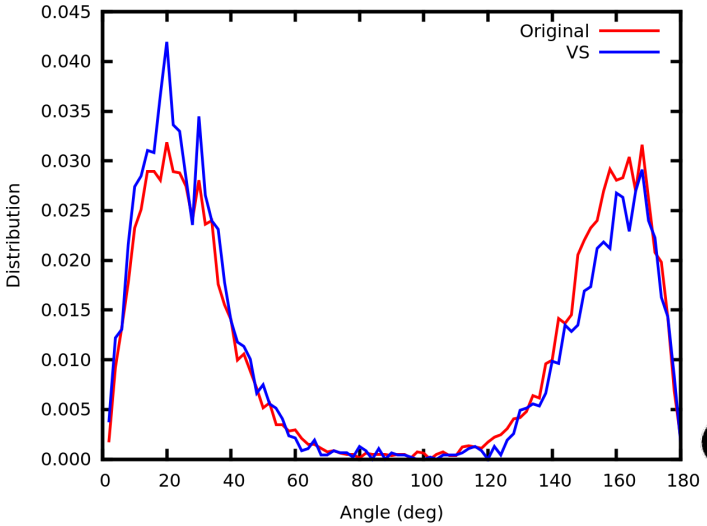


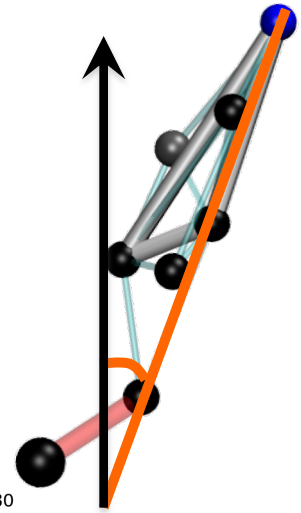


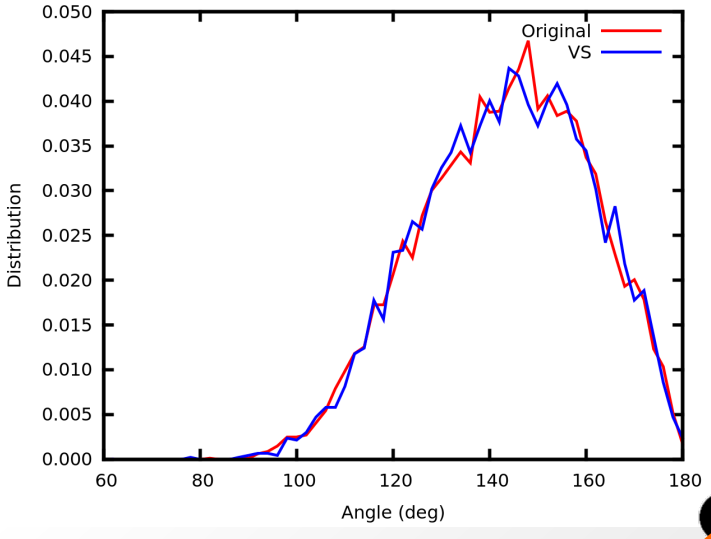
And it worked!

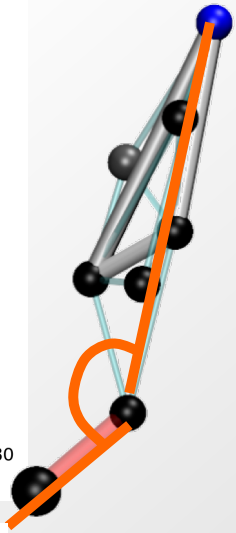
Virtual site version ran stable at 40fs

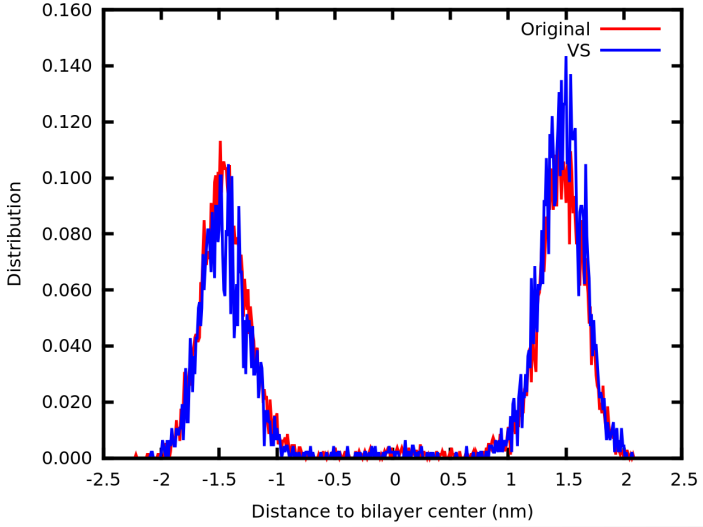
Comparing to a simulation with the original topology ran at 20fs

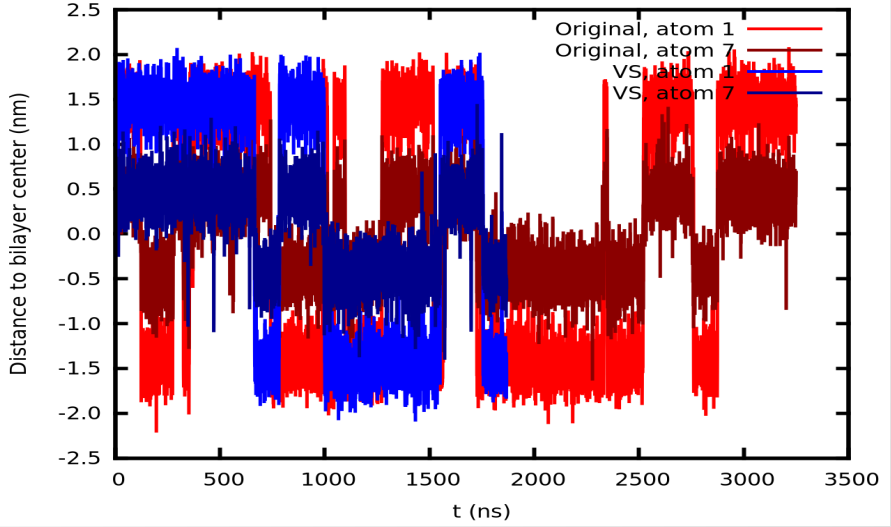












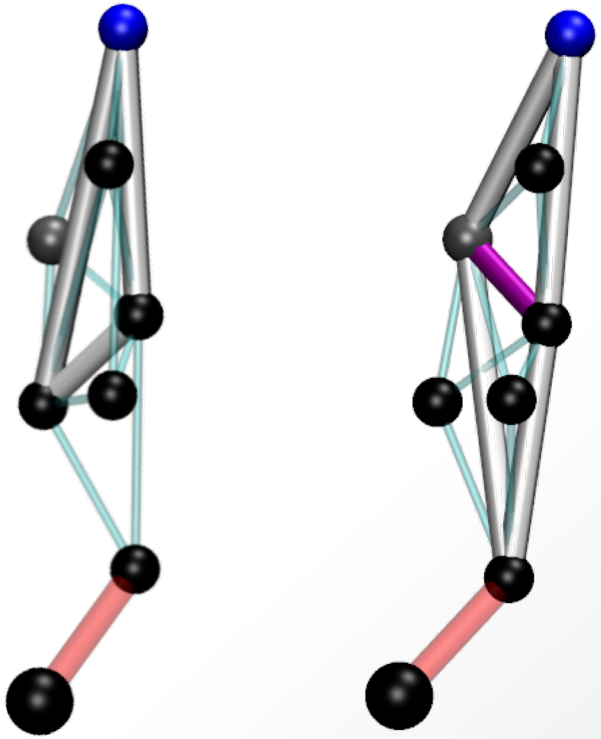
But then the French…

Clément Arnarez

YEAH, COOL. BUT MY HUGE BILAYER SYSTEM WITH MANY CHOLESTEROL MOLECULES STILL CRASHES AT 4OFS.

Is the bonded structure too rigid?

(shock-absorbing hinge solution)

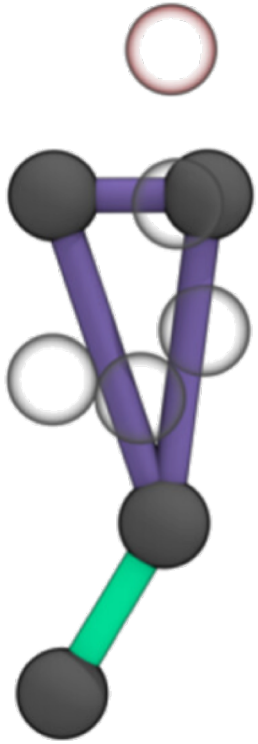


Martini 2

Parameters for Martini sterols and hopanoids based on a virtual-site description. The Journal of Chemical Physics, 143(24). https://doi.org/10.1063/1.4937783


EIGHT YEARS LATER ...

Turns out we just needed less acute frames!



(Also known internally as the ‘codfish model’)

Martini 3

Martini 3 Coarse-Grained force field for cholesterol. Journal of Chemical Theory and Computation, 19(20), 7387–7404. https://doi.org/10.1021/acs.jctc.3c00547

Why this worked

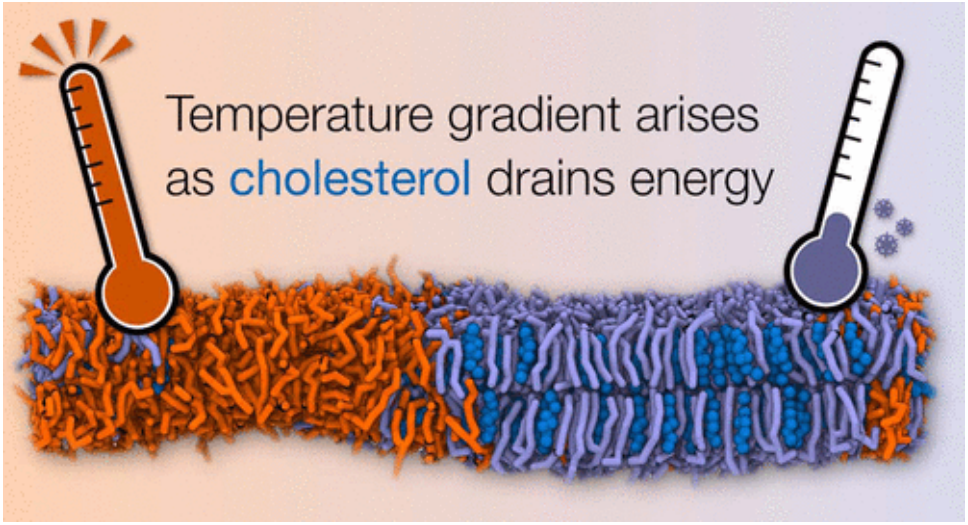
In Martini 3 SASA matching places beads further outward

No longer tried to match moment of inertia (now we match the c.o.m.)

c.o.m. is further away from the frame’s edges

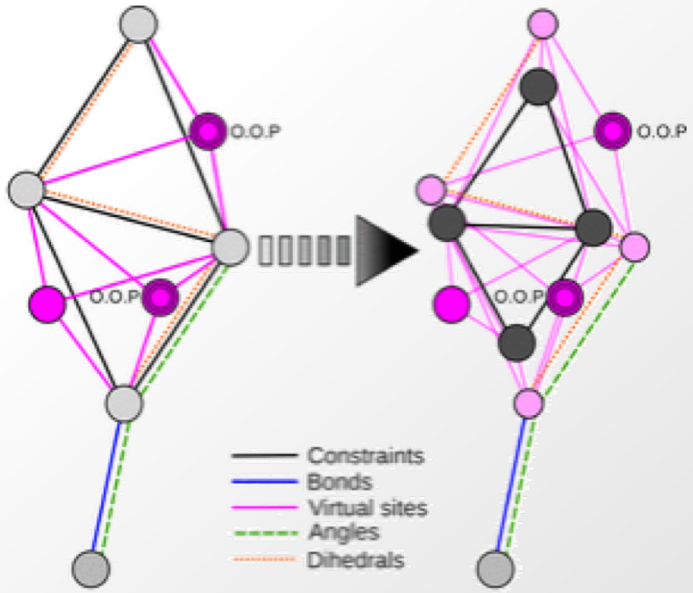
Are virtual sites a poisoned solution?

(probably not, but be careful with coupled construction frames)



Nonconverged constraints cause artificial temperature gradients in lipid bilayer simulations. *The Journal of Physical Chemistry B*, *125*(33), 9537–9546. https://doi.org/10.1021/acs.jpcb.1c03665

The dual frames were the problem



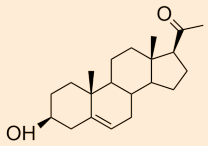
Fábián, B., Thallmair, S., & Hummer, G. (2023). Optimal bond constraint topology for molecular dynamics simulations of cholesterol. Journal of Chemical Theory and Computation, 19(5), 1592–1601. https://doi.org/10.1021/acs.jctc.2c01032

Very subtle artifact introduction with Martini 2 cholesterol

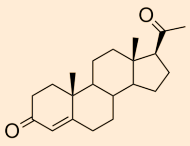
(This time LINCS actually was the culprit, but no `LINCS WARNINGS` were generated!)

Chapter II
Steroid hormones

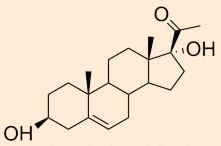
Progestogens



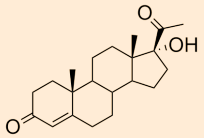
Pregnenolone



Progesterone

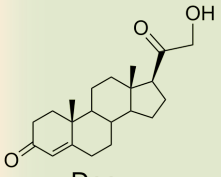


17alpha-Hydroxy pregnenolone

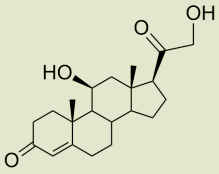


17alpha-Hydroxy progesterone

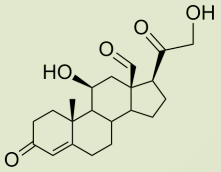
Mineralocorticoids



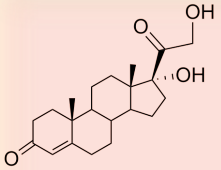
Deoxy-Corticosterone



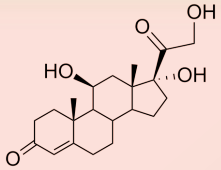
Corticosterone



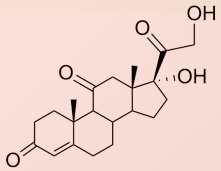
Aldosterone



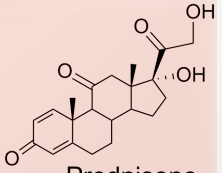
11-Deoxycortisol



Cortisol

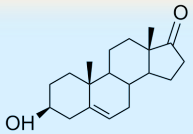


Cortisone

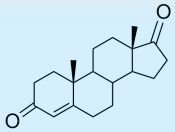


Prednisone

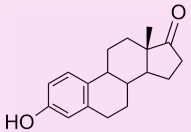
Glucocorticoids



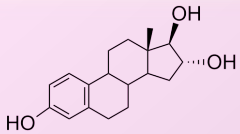
Dehydroepi-Androsterone



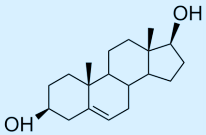
Androstenedione



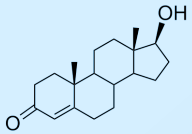
Estrone



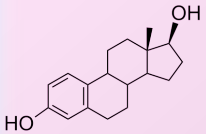
Estriol



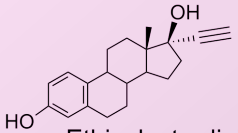
Androstenediol



Testosterone



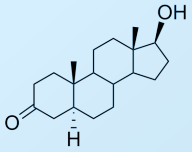
Estradiol



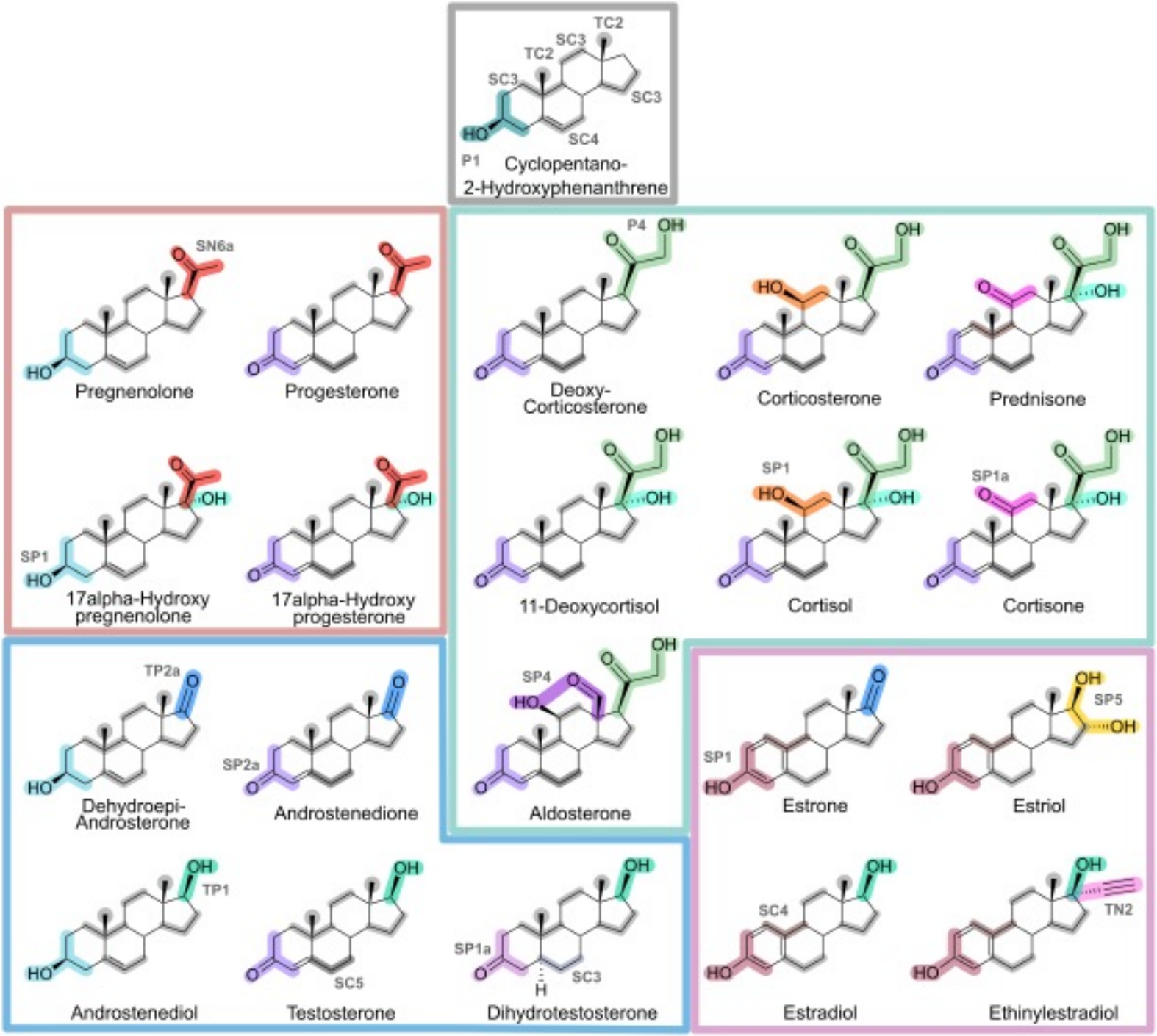
Ethinylestradiol

Androgens

Estrogens



Dihydrotestosterone


TC2
SC3
TC2
SC3
SC3
HO
SC4
P1
Cyclopentano-
2-Hydroxyphenanthrene
SN6a
HO
Pregnenolone
Progesterone
SP1
HO
OH
17alpha-Hydroxy
pregnenolone
17alpha-Hydroxy
progesterone
P4
OH
Deoxy-
Corticosterone
HO
OH
Corticosterone
OH
OH
Prednisone
OH
11-Deoxycortisol
SP1
HO
OH
Cortisol
SP1a
OH
Cortisone
TP2a
HO
Dehydroepi-
Androsterone
SP2a
Androstenedione
SP4
HO
OH
Aldosterone
OH
TP1
HO
Androstenediol
OH
SC5
Testosterone
SP1a
SC3
H
OH
Dihydrotestosterone
SP1
HO
Estrone
OH
SP5
OH
HO
Estriol
SC4
OH
HO
Estradiol
OH
TN2
HO
Ethinylestradiol

Strategy

Obtain atomistic simulations for each

(Are there even atomistic parameters for them? Should we instead model at the QM level?)

Map to CG

Refine virtual-sites / bonded parameters

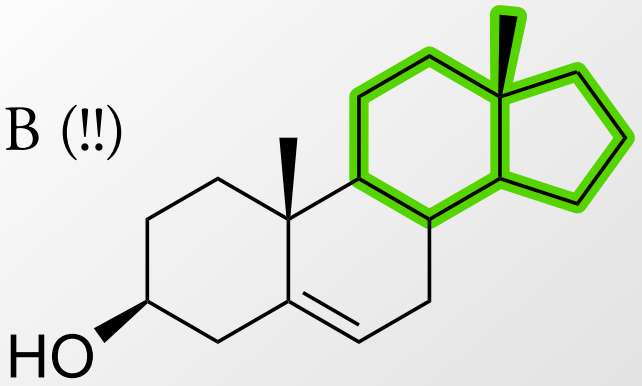
Strategy

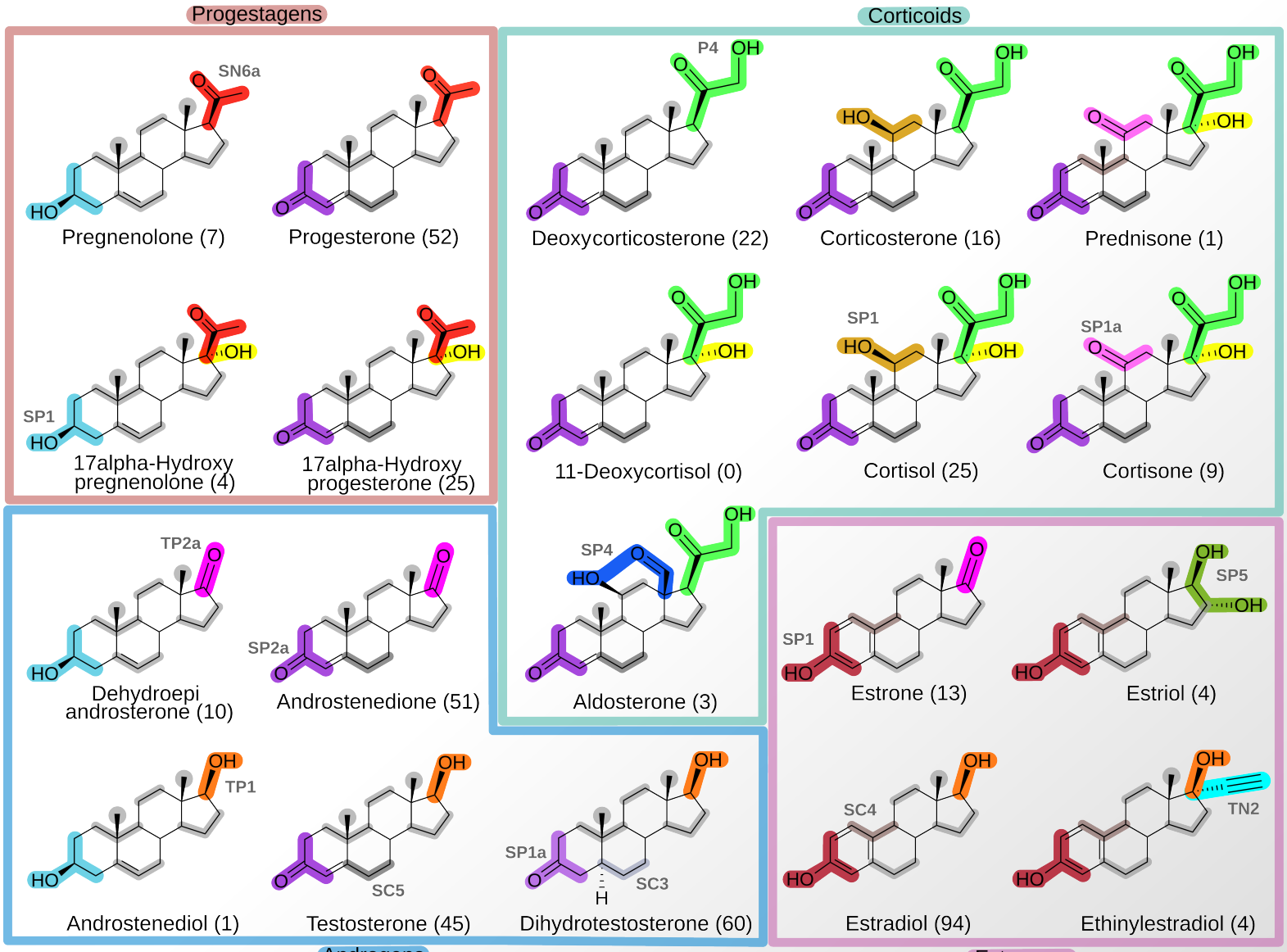
Obtain atomistic structures from the PDB (!!)

Align all to common skeleton

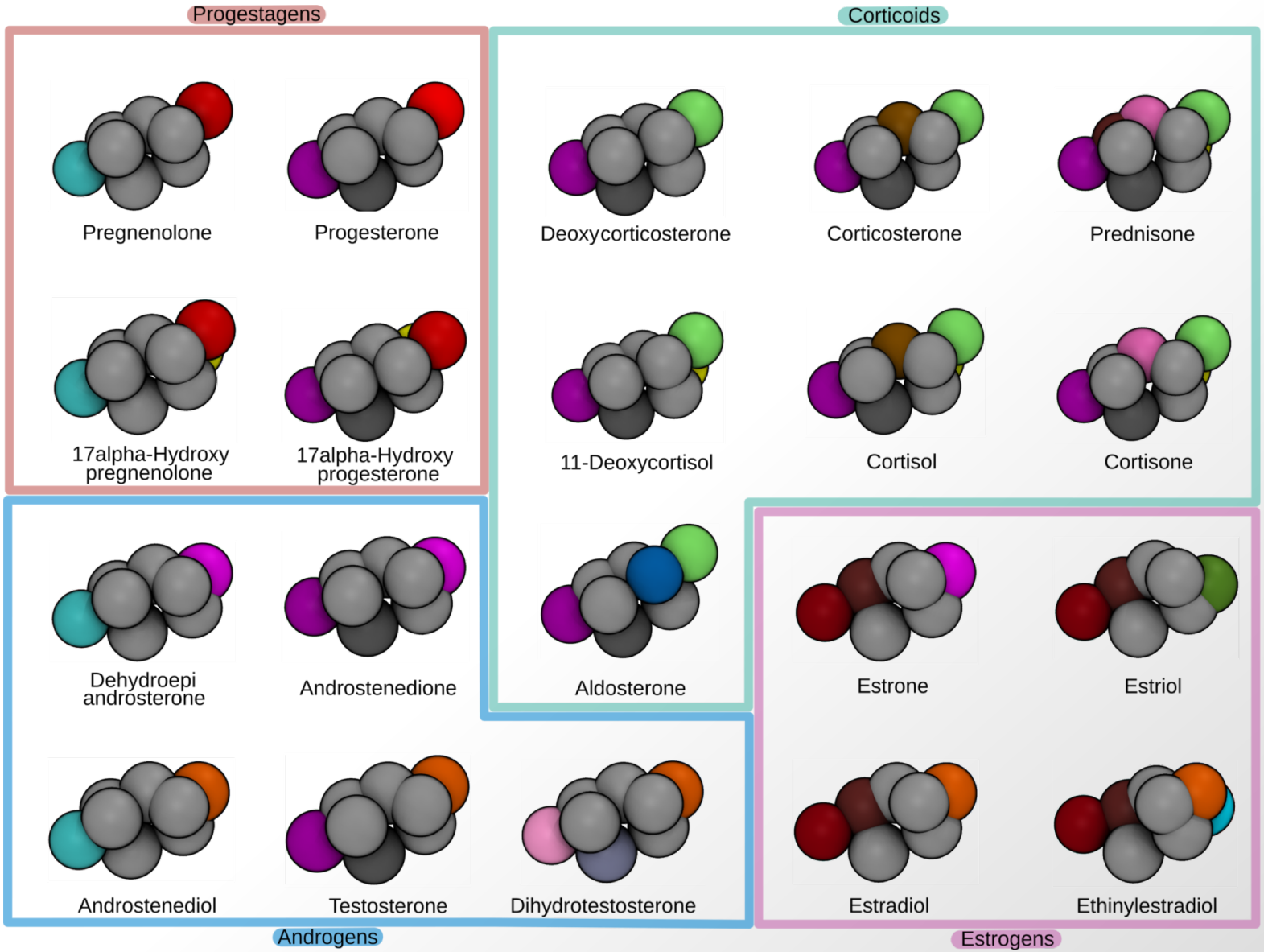
Map to CG

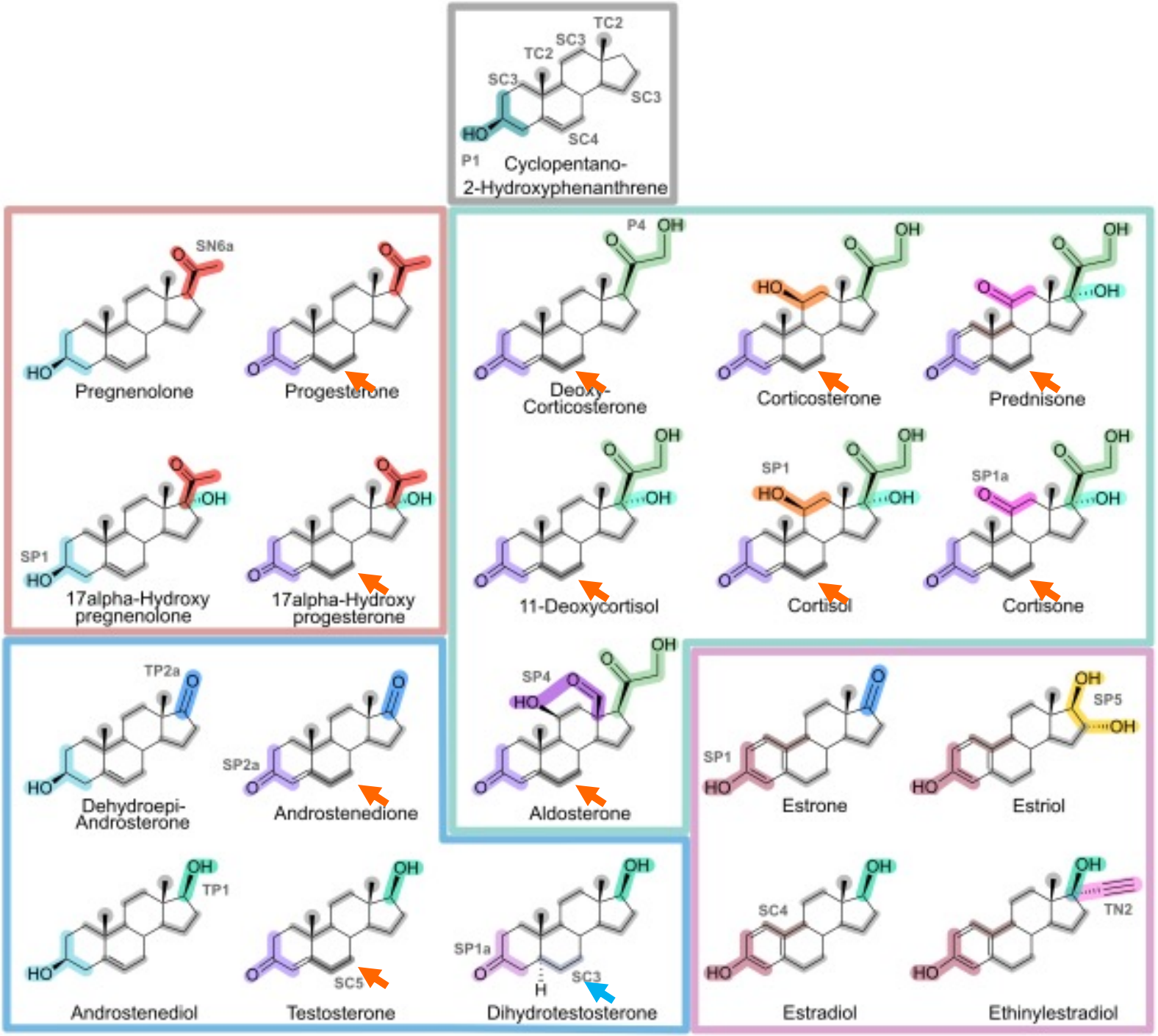
Refine specific virtual-sites / bonded parameters

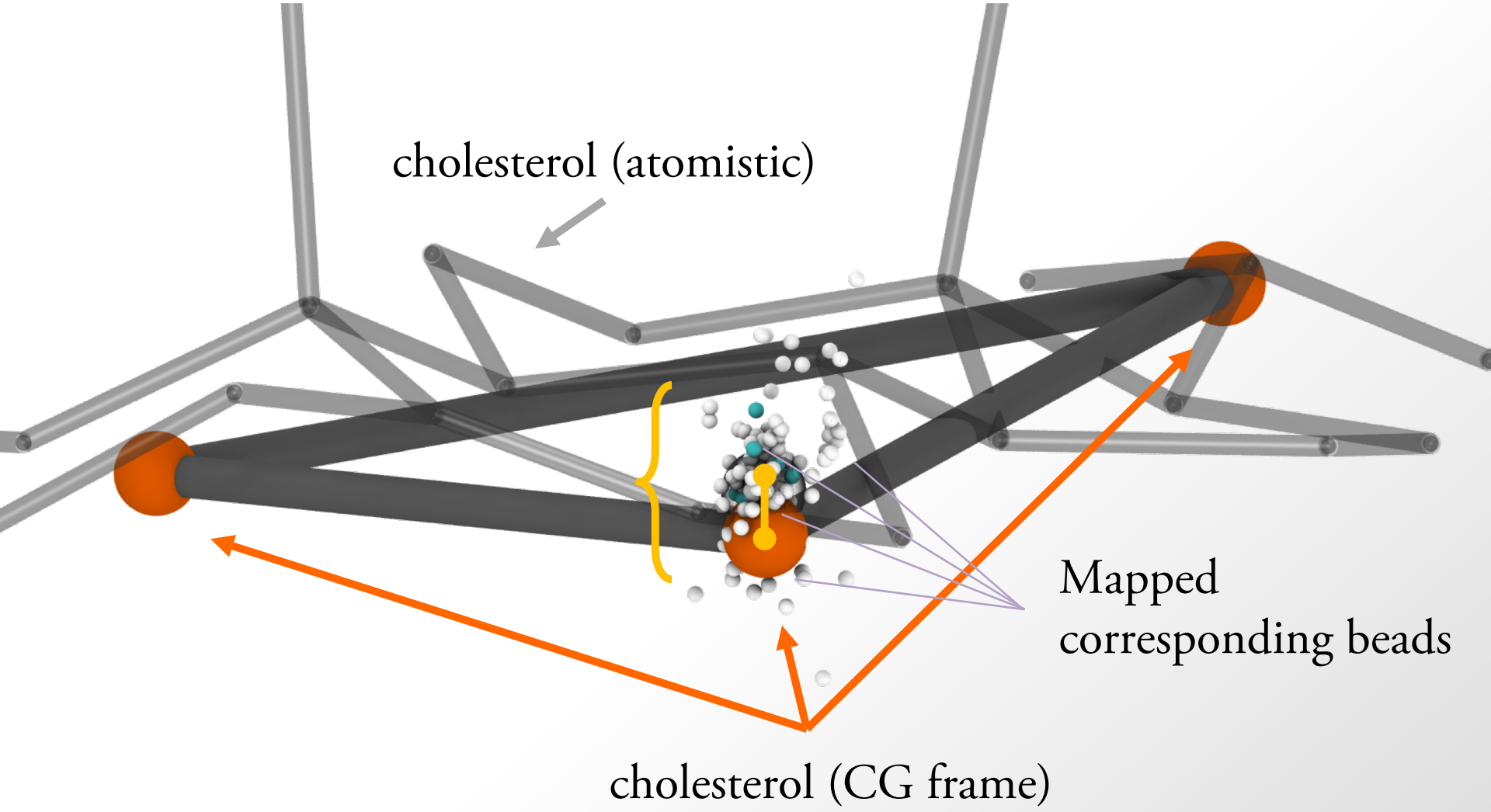



Progestagens
SN6a
HO
Pregnenolone (7)
Progesterone (52)
SP1
17alpha-Hydroxy pregnenolone (4)
17alpha-Hydroxy progesterone (25)
Corticoids
P4
OH
Deoxycorticosterone (22)
Corticosterone (16)
Prednisone (1)
11-Deoxycortisol (0)
SP1
Cortisol (25)
SP1a
Cortisone (9)
SP4
Aldosterone (3)
Androgens
TP2a
Dehydroepi androsterone (10)
SP2a
Androstenedione (51)
TP1
Androstenediol (1)
SC5
Testosterone (45)
SP1a
SC3
H
Dihydrotestosterone (60)
Estrogens
SP1
Estrone (13)
SP5
Estriol (4)
SC4
Estradiol (94)
TN2
Ethinylestradiol (4)

Which of these can use the same parameters as cholesterol?




TC2
SC3
TC2
SC3
SC3
HO
SC4
P1
Cyclopentano-
2-Hydroxyphenanthrene
SN6a
HO
Pregnenolone
Progesterone
SP1
HO
OH
17alpha-Hydroxy
pregnenolone
17alpha-Hydroxy
progesterone
P4
OH
Deoxy-
Corticosterone
HO
OH
Corticosterone
OH
Prednisone
11-Deoxycortisol
SP1
HO
Cortisol
SP1a
Cortisone
TP2a
HO
Dehydroepi-
Androsterone
SP2a
Androstenedione
SP4
HO
Aldosterone
SP1
HO
Estrone
OH
SP5
Estriol
TP1
Androstenediol
SC5
Testosterone
SP1a
H
SC3
Dihydrotestosterone
SC4
Estradiol
TN2
Ethinylestradiol


cholesterol (atomistic)
Mapped
corresponding beads
cholesterol (CG frame)

Strategy

Obtain atomistic structures from the PDB (!!)

Align all to common skeleton

Map to CG

Refine specific virtual-sites / bonded parameters

If low dispersion and small (<0.3 Å) distance to same cholesterol bead:
- use the same virtual-site parameters as in cholesterol

If low dispersion but larger distance to same cholesterol bead:
- use different virtual-site parameters as in cholesterol

If high dispersion:
- replace virtual site approach with bonded restraints

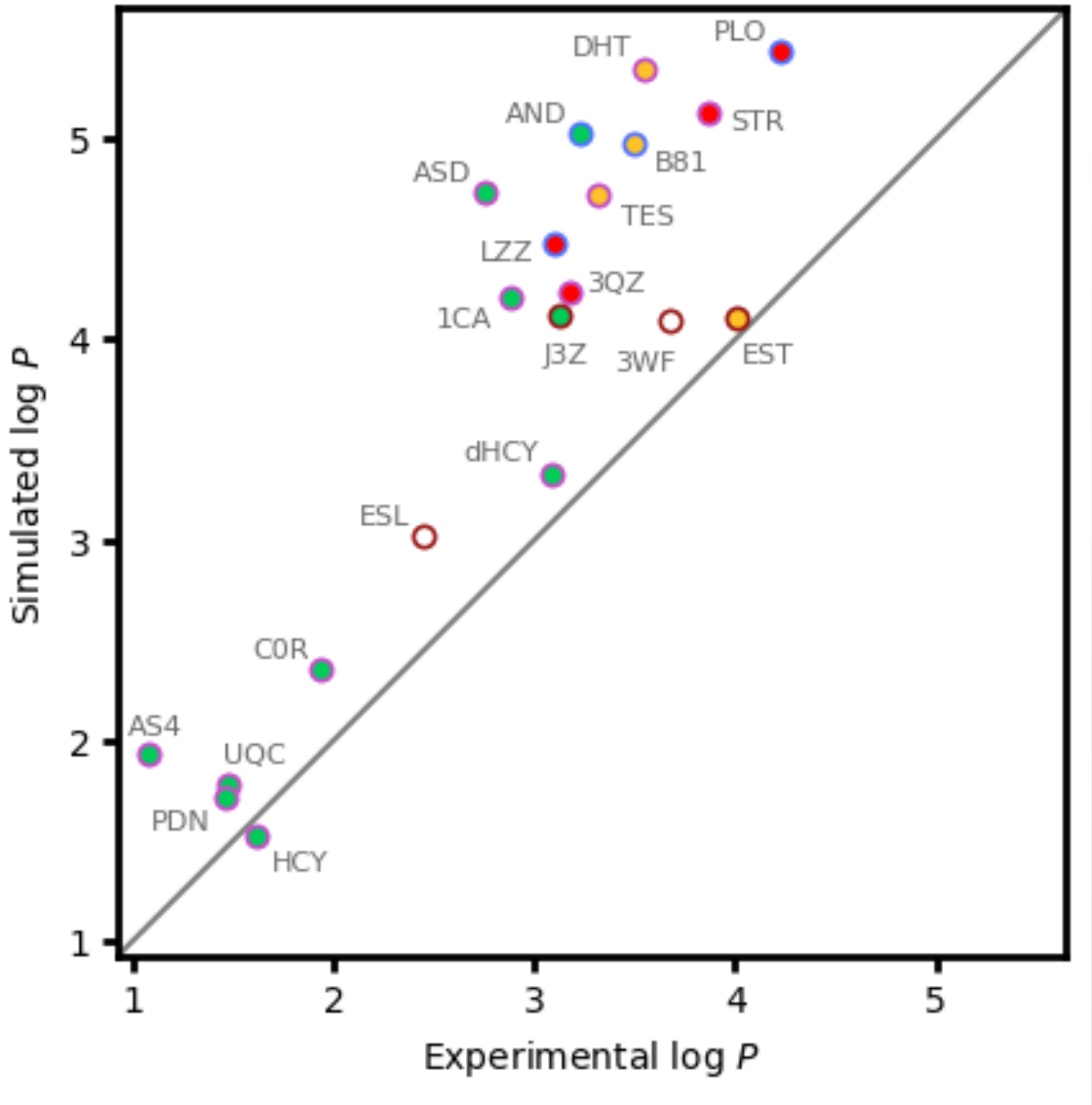
What if we modify the position of one of the frame beads?

We don't

We keep it as a non-interactive, massive particle and add a virtual (interacting) site at the desired position

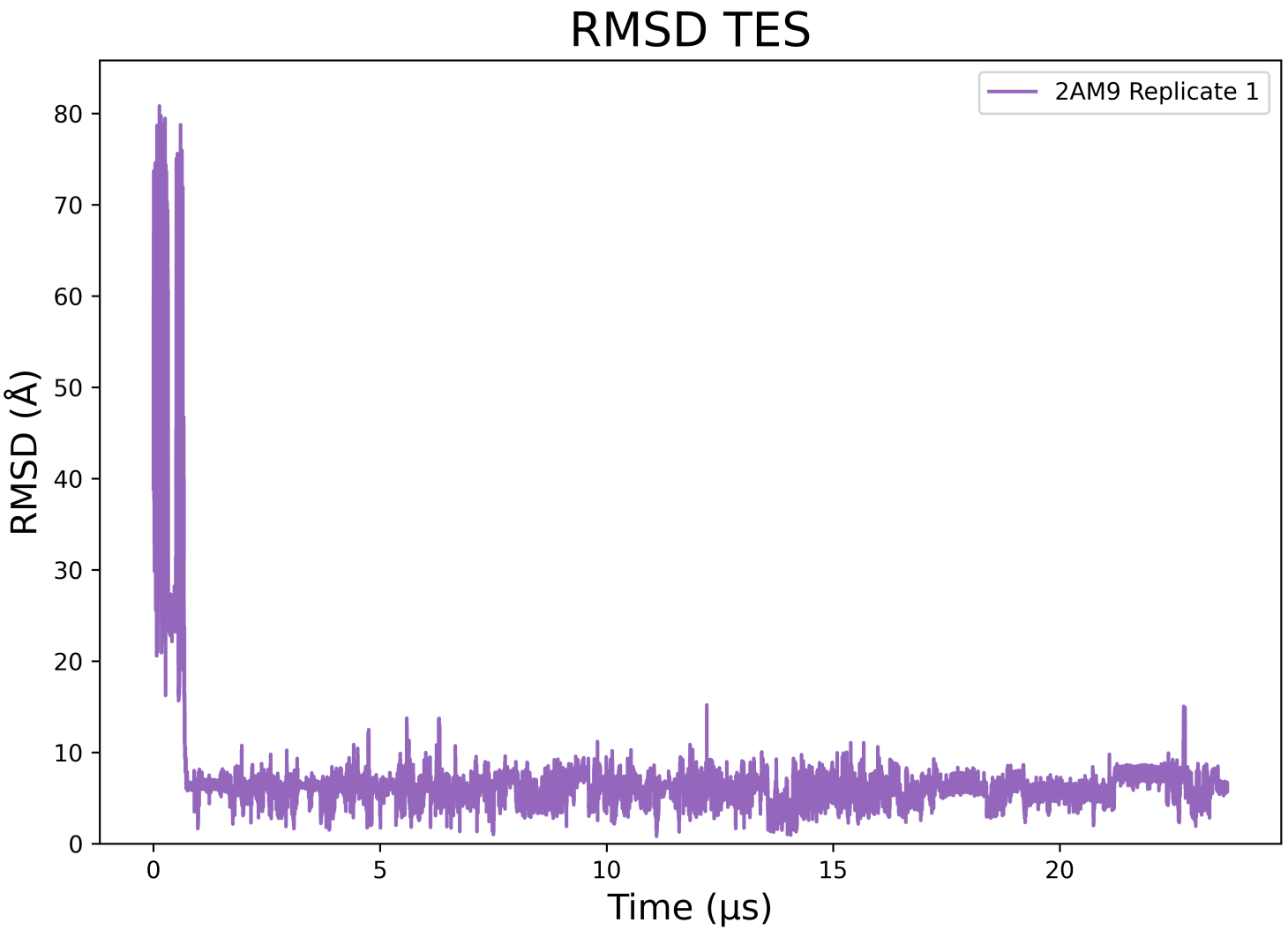
Validation

Validation: logP

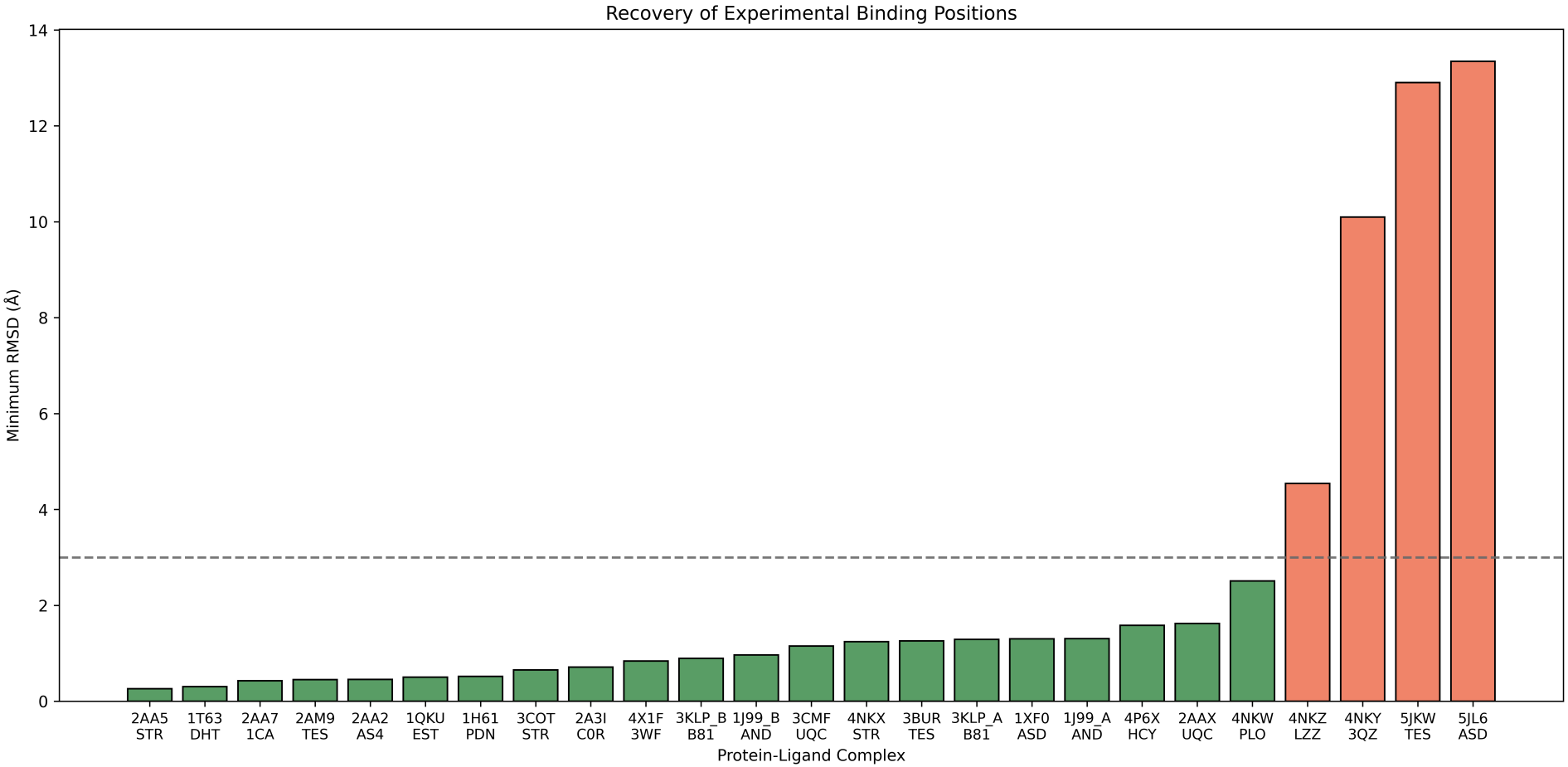


Validation: protein binding

Testosterone + androgen receptor



Validation: protein binding



Conclusions I

Virtual sites aren't perfect, but help a lot in the case of cholesterol

We now have a better grasp on their pitfalls

Still, they incur a performance penalty
(looking at you, GROMACS devs…)

Conclusions II

Who needs finer resolution models when you have the PDB!

Still some excessive hydrophobicity

Good overall recovery of binding sites (heme might need more work)

Some degree of protein model dependence

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