MOLECULAR MODELING OF *STREPTOCOCCUS PNEUMONIAE* CAPSULAR POLYSACCHARIDE ANTIGENS.

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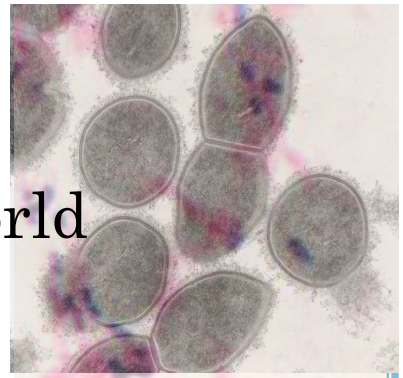
Streptococcus pneumoniae



- leading cause of disease esp. in developing world
  - meningitis, pneumonia, otitis media, sinusitis, bronchitis …
  - annual global mortality ≈1 000 000 for children < 5 years

- more than 90 serotypes
- conjugate vaccines
  - better immune responses in young children than polysaccharide-only vaccines

- Pneumococcal Vaccine Project
  - development of affordable and effective pneumococcal vaccines for the developing world

PATH

PNEUMOCOCCAL VACCINES

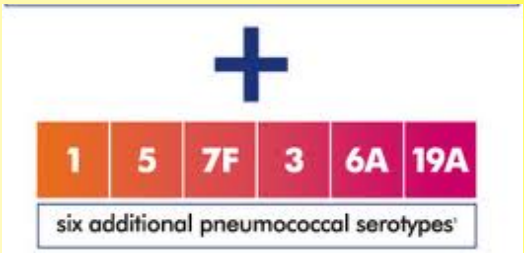
PCV7 (2000) very successful

subsequent rise in non-vaccine serotypes led to the recent licensure of:

- **GSK's PCV10**

- coupling chemistry employed for serotype **19F** may provide better cross protection against **19A***

- **Pfizer's PCV13**



Serotypes **6A** and **19A** :

- many cases of disease
- antibiotic resistance
- otitis media.

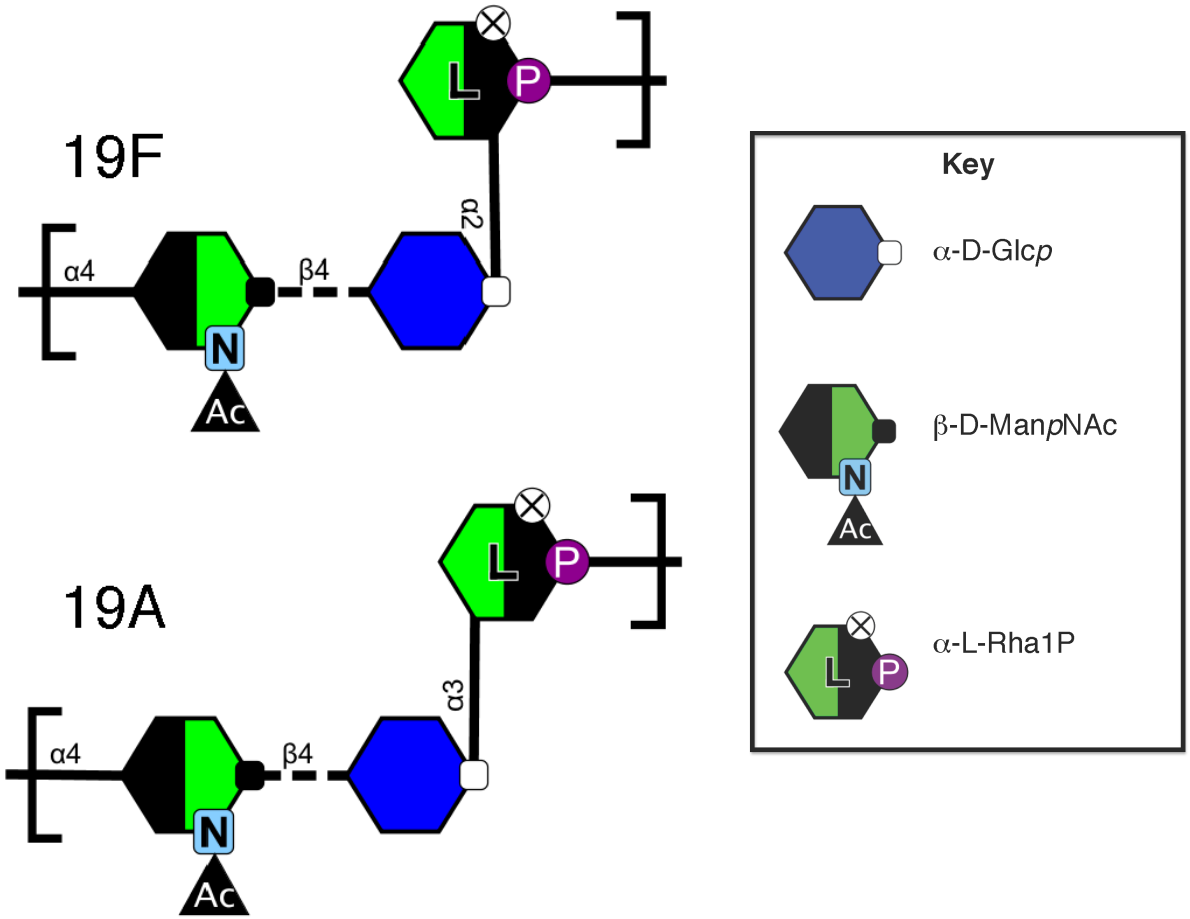
Efficacy in children yet to be established.

* Poolman et al., Clin. Vaccine Immunol. 2011, 18, 327–336

Streptococcus pneumoniae: Serogroup 19

Serotypes 19A and 19F now cause most pneumococcal disease.

Null hypothesis:
change in configuration
***->** change in conformation*
***->** no cross protection of serotype 19F vaccination against 19A*



19F: [->4)-β-D-ManpNAc-(1->4)-α-D-Glcp-**(1->2)**-α-L-Rhap-(1-P-]

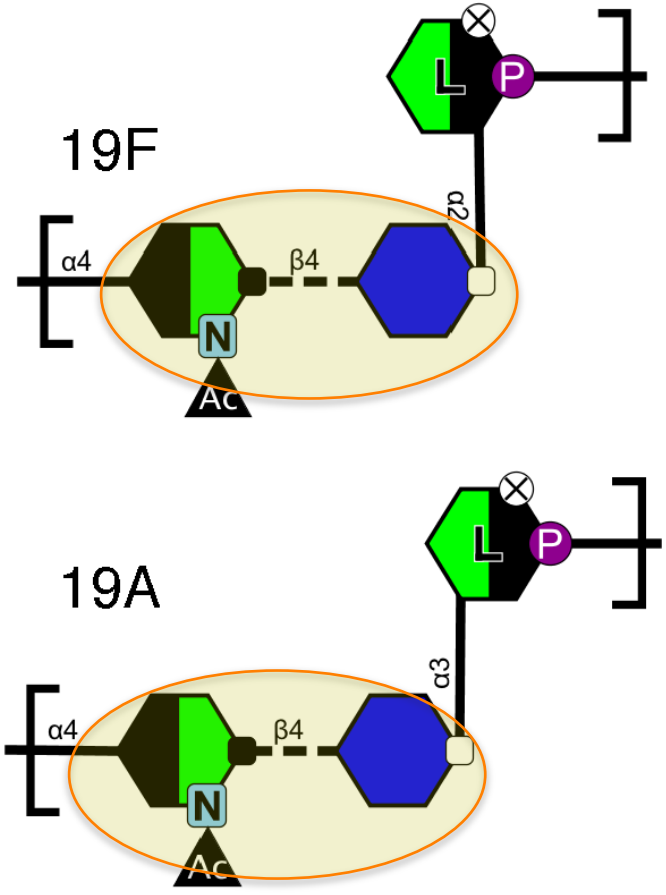
19A: [->4)-β-D-ManpNAc-(1->4)-α-D-Glcp-**(1->3)**-α-L-Rhap-(1-P-]

Systematic procedure for Modelling

- Step 1: **common linkage**

M14G (ManNAc β (1->4)Glc)

vacuum Φ, Ψ PMF
with CHARMM
and GLYCAM



comparisons of modelling predictions with different force fields important for validation

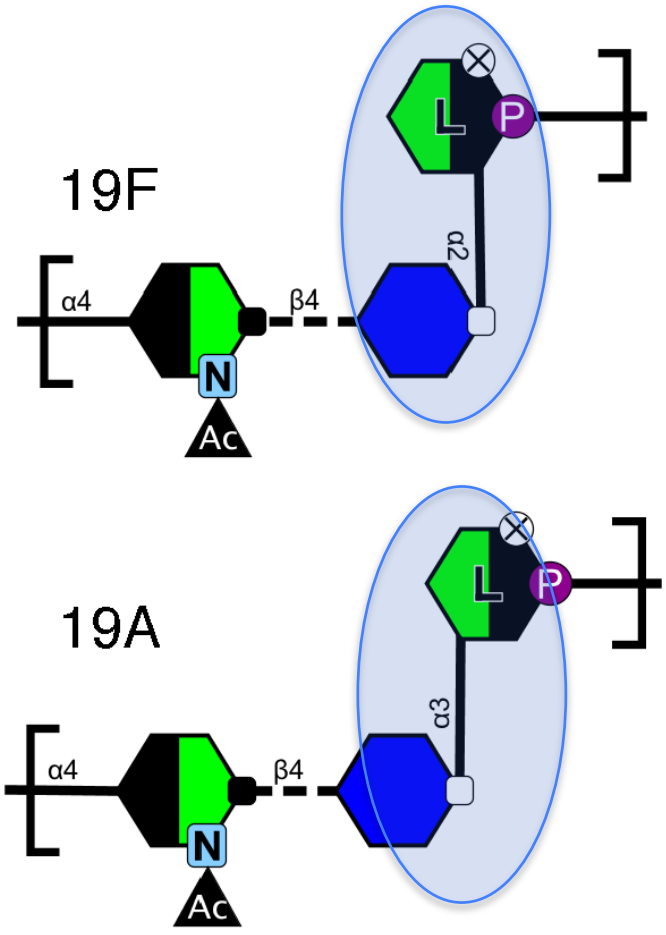
Systematic procedure for Modelling

Step 2:

G12R

and

G13R



vacuum Φ, Ψ PMFs
and solution simulations
with CHARMM
and GLYCAM

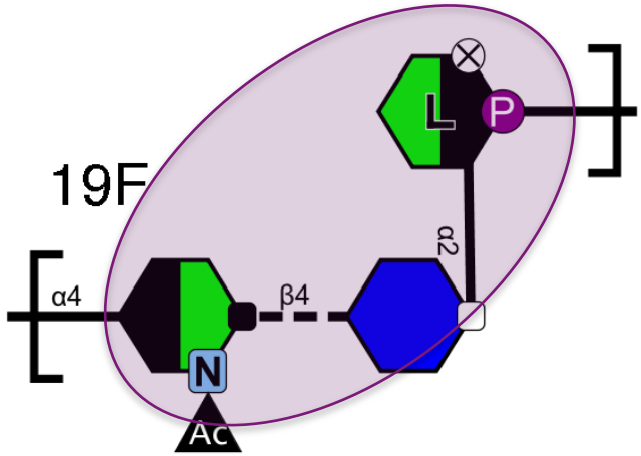
prior work showed no difference in linkages

Ciuffreda et al., Carbohyd. Res. 1992, 232, 327–339.

Systematic procedure for Modelling

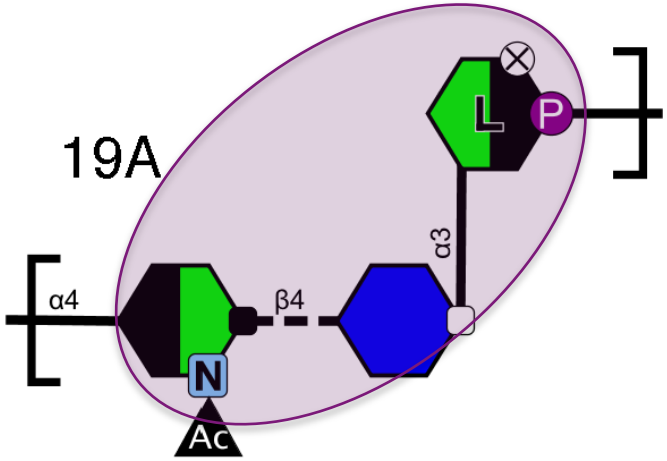
- Step 3: trisaccharides

M14G12R



and

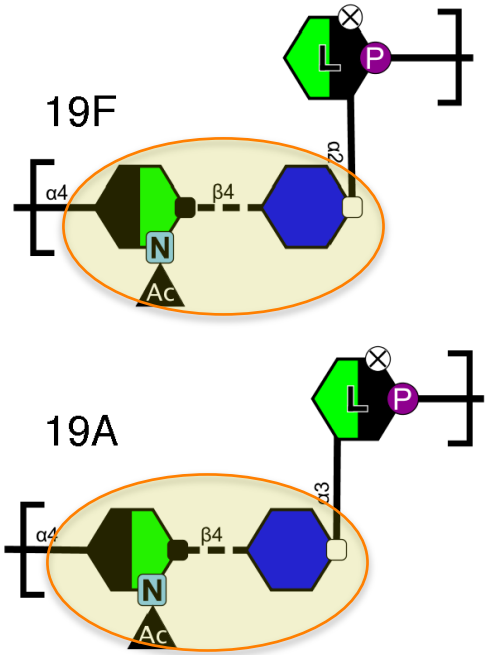
M14G13R

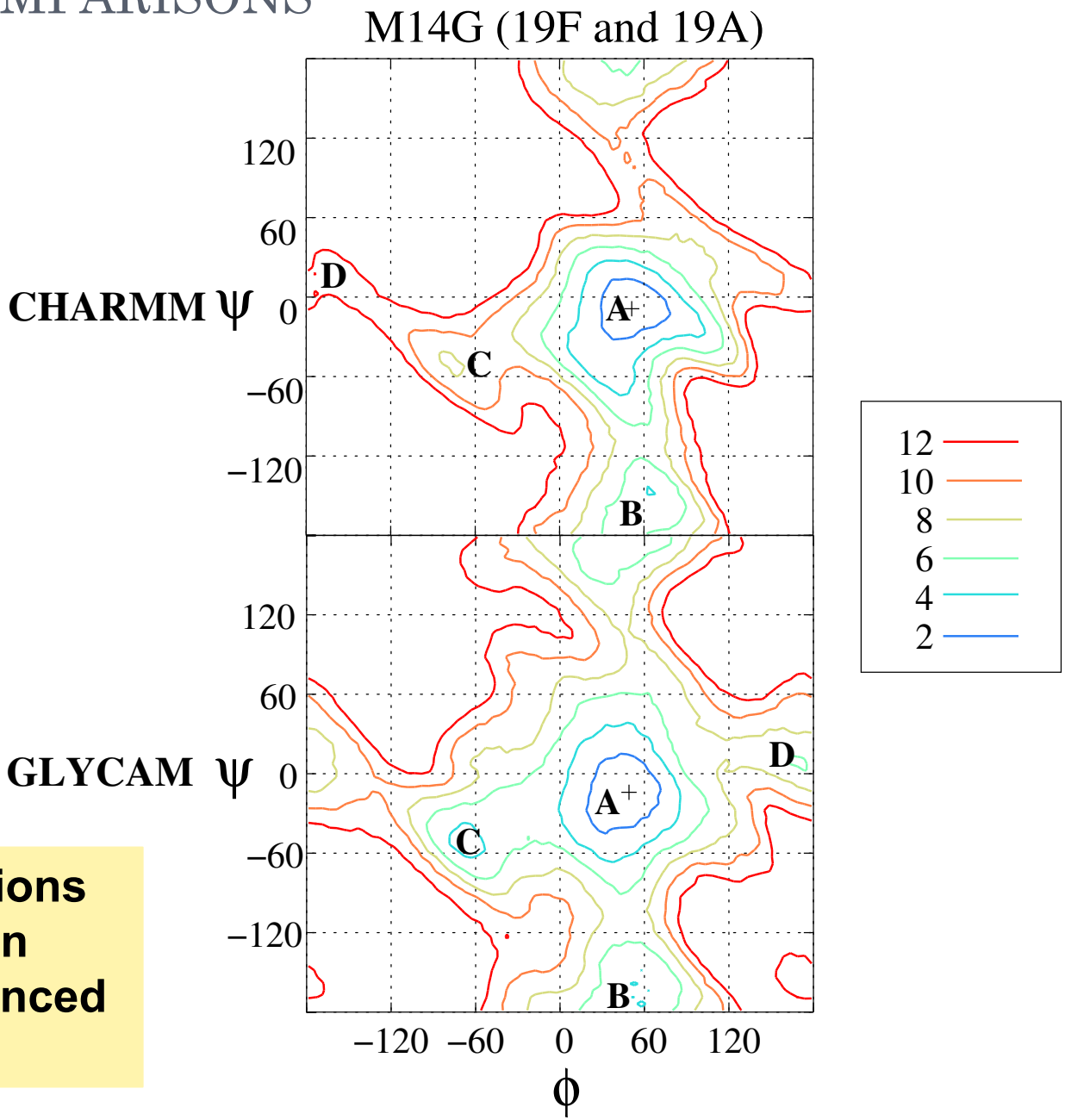


solution simulations
with CHARMM
and GLYCAM

currently no parameters for phosphodiester linkage -> polysaccharide

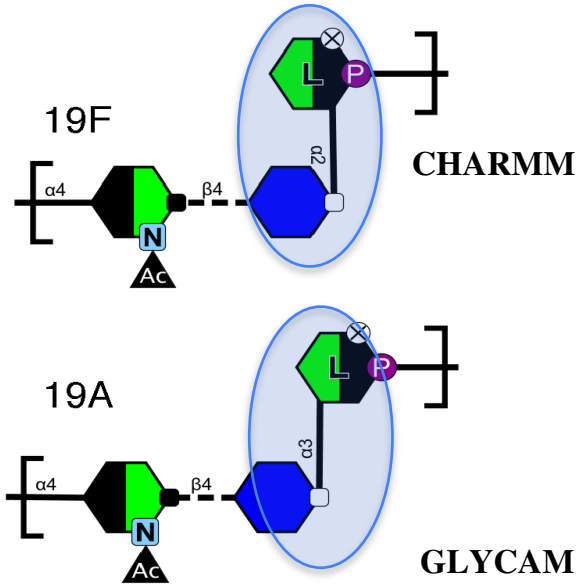
Force Field Comparisons

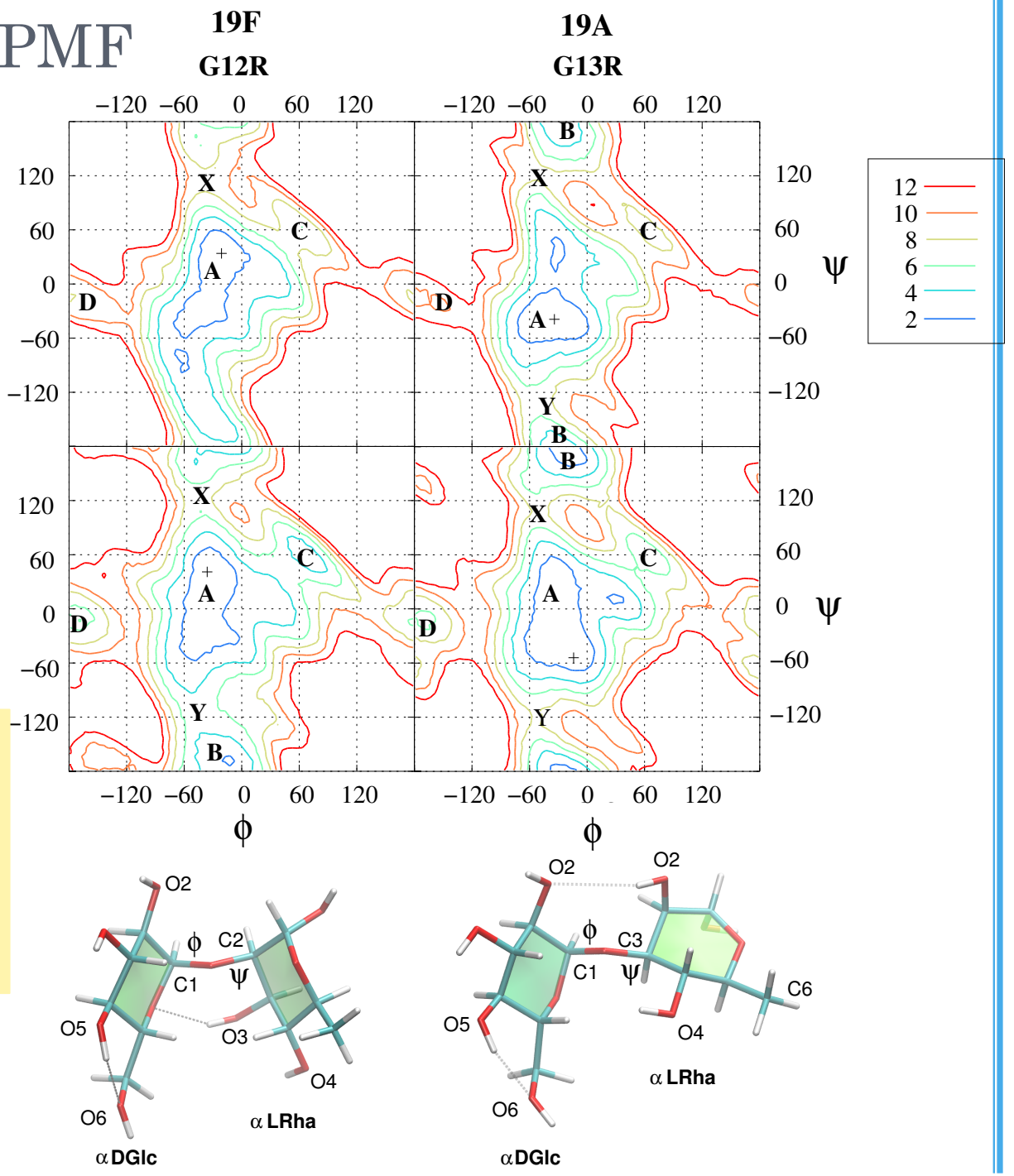




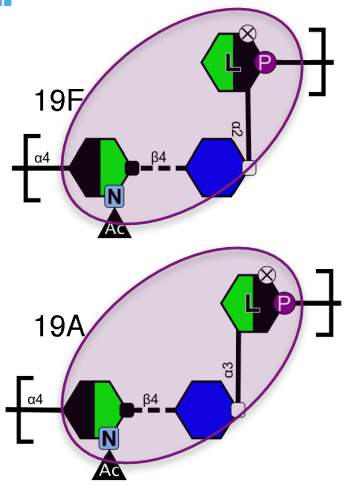
- **minima same locations**
- **relative difference in energy more pronounced in CHARMM**

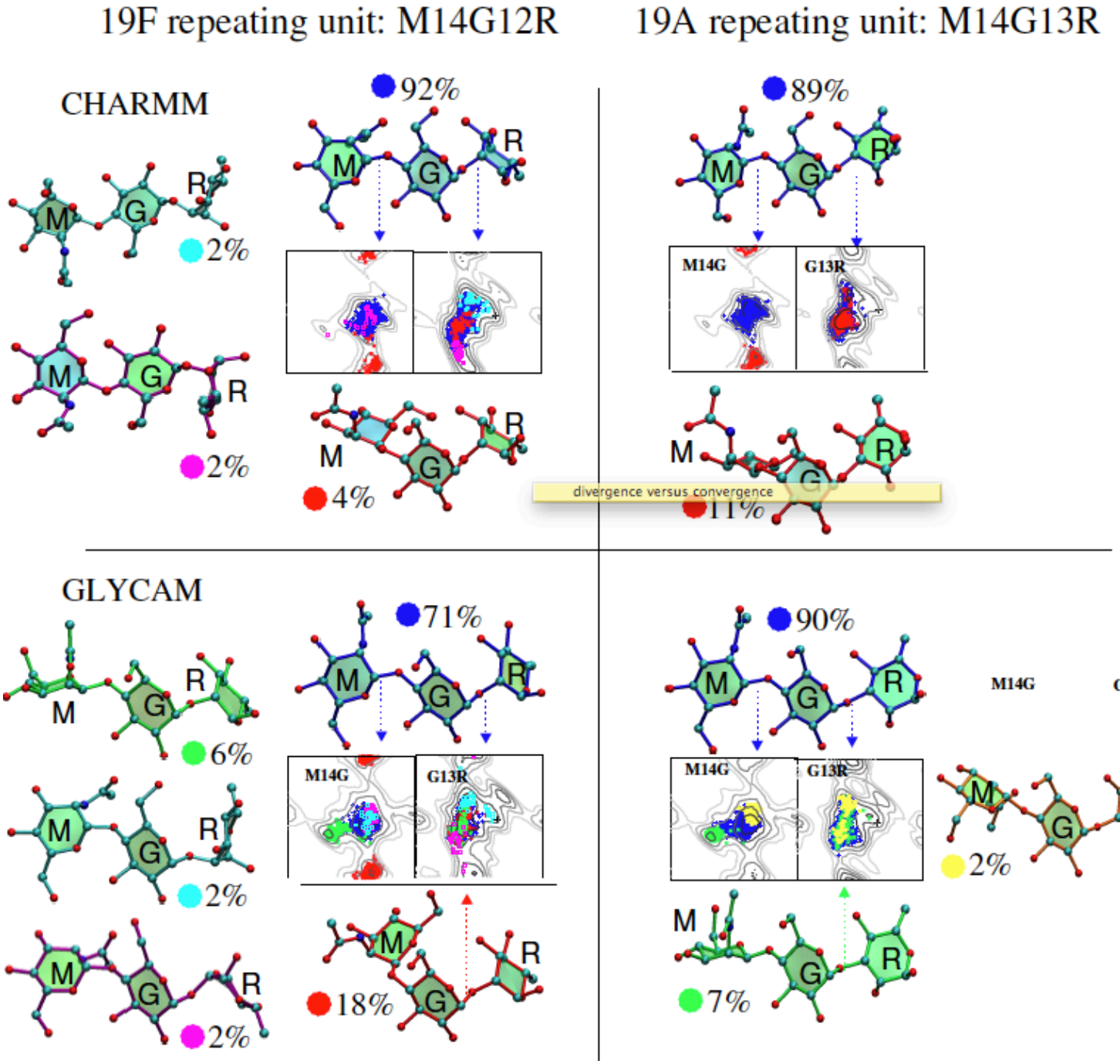
G12R AND G13R: PMF





- **G12R and G13R PMF's show key differences**
- **greatest for CHARMM force field**





•different confs predicted for 19F versus 19A in both FF's.

Conclusions

- both CHARMM and GLYCAM predict different conformations for 19A and 19F trisaccharide repeating units.
  - “bent" conformations G12R linkage

- CHARMM and GLYCAM in broad agreement
  - GLYCAM has broader minimum wells and secondary minima lower in energy in relative to the global minimum.
    - more flexible linkages
    - Small charges on the aliphatic hydrogens in CHARMM can account for some of the differences

support for Null hypothesis: change in conformation in polysaccharide which could affect binding

- Future work: phosphodiester linkage and NMR

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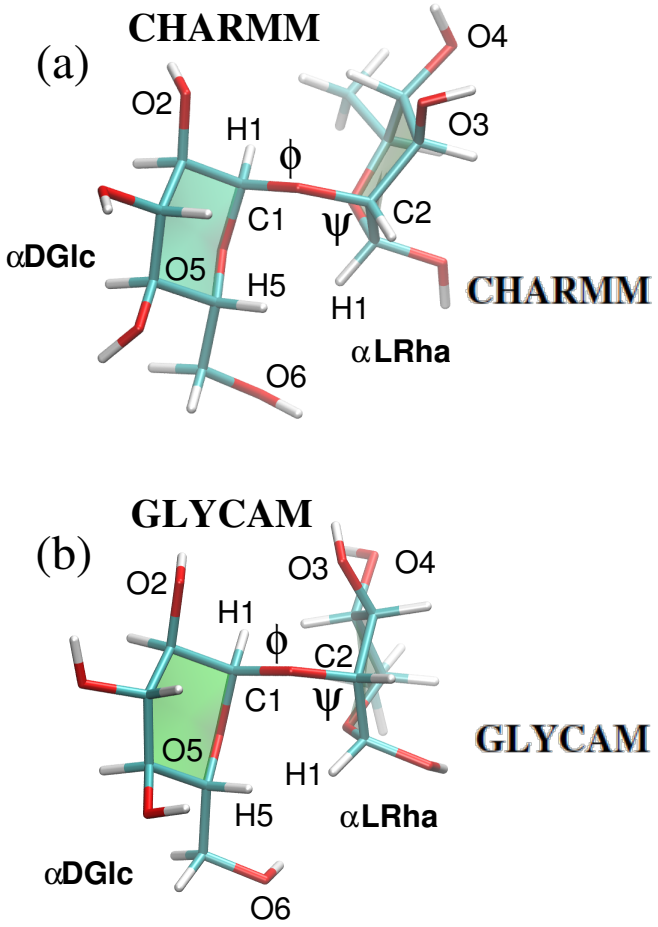
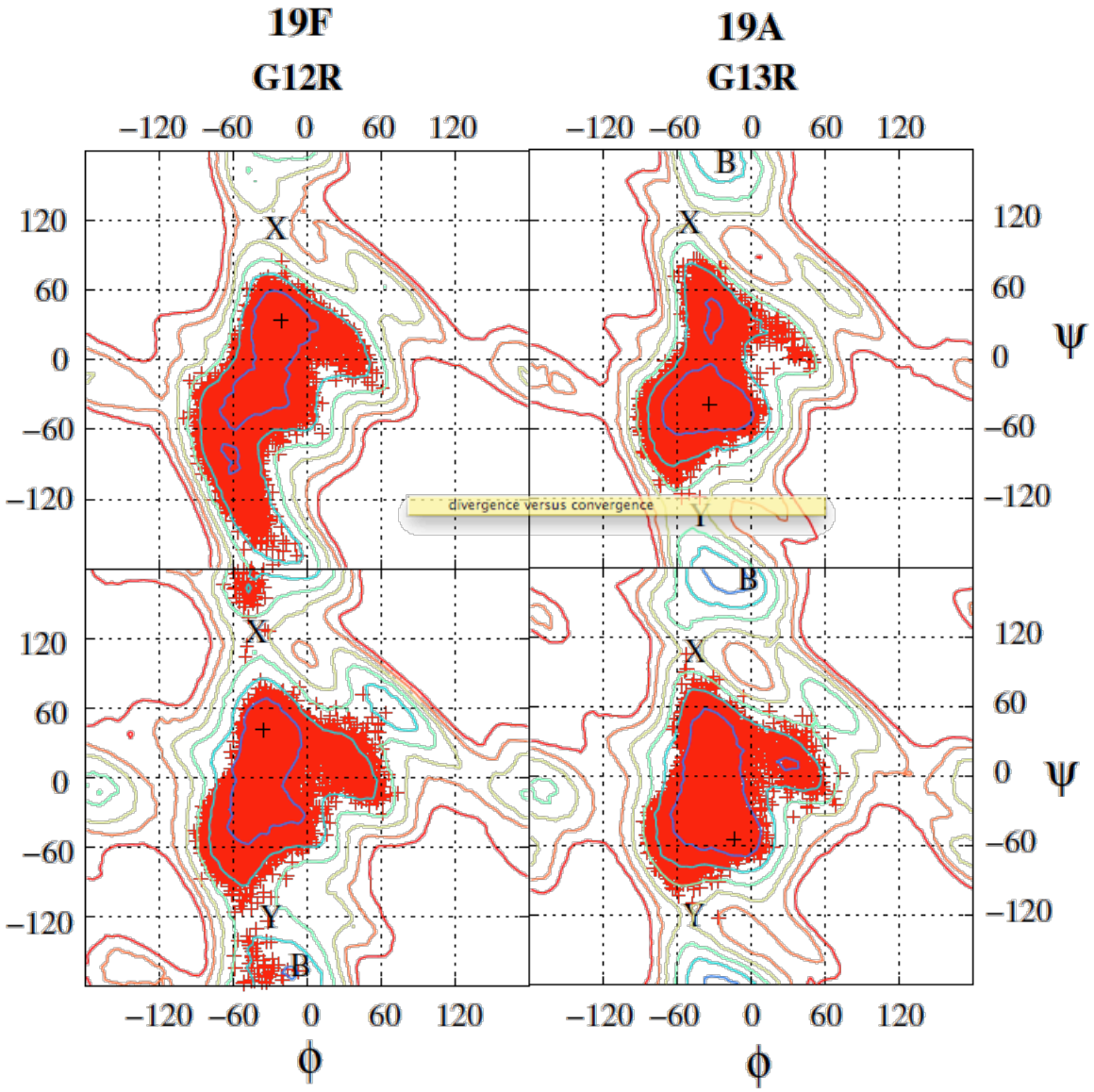
G12R AND G13R: SOLUTION DYNAMICS

19F:G12R B–well conformations





TRISACCHARIDES: SOLUTION DYNAMICS