CONSTRUCTION, MOLECULAR DYNAMICS AND STRUCTURAL ANALYSIS OF THE BACTERIAL CELL WALL PEPTIDOGLYCAN LAYER MODELS

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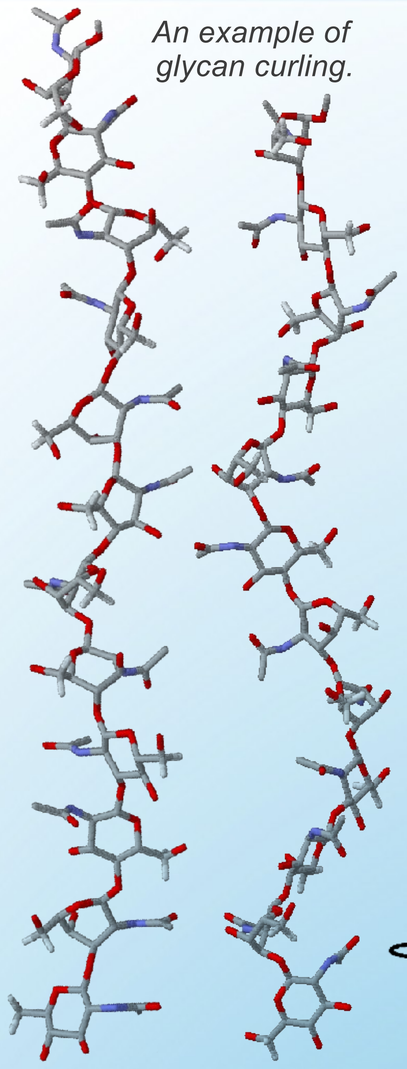
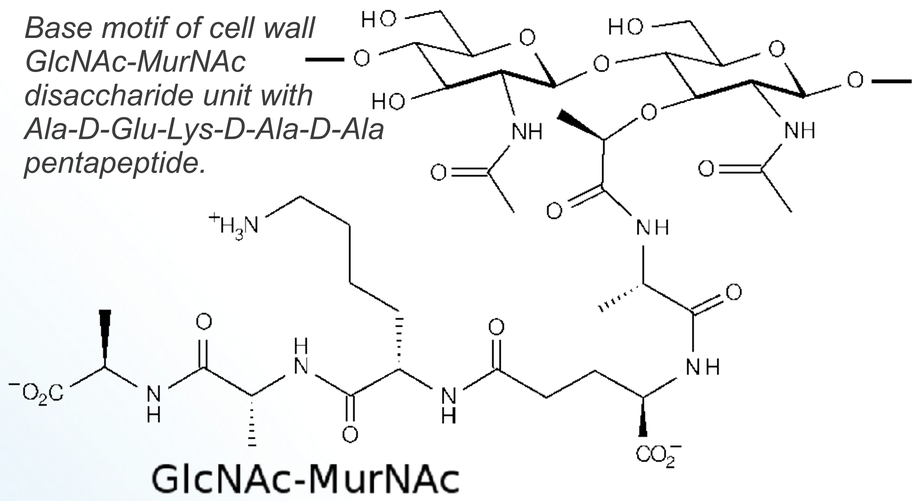


An example of glycan curling.

Introduction:

The peptidoglycan (PG) and teichoic acids (TA) are a key target for antibacterial treatment in the infections caused by some Gram-positive bacteria. Proper understanding of the mechanisms of binding to the bacterial cell wall seems to be crucial for proper development of new drug candidates effective against these bacteria.
The exact three-dimensional structure of the bacterial cell wall PG layer is still unverified because of its complexity and the lack of pure and separate samples, suitable for structural studies. In this work we constructed two different models of Gram-positive bacteria PG layer: the layered model in which the glycan strands run parallel to the cytoplasmic membrane and the scaffold model in which the glycan strands run perpendicular to the membrane. We focused on PG structure and its arrangement in both models. PG conformational changes during geometry optimization, models relaxation and molecular dynamics of fully hydrated PG layer models were discussed.

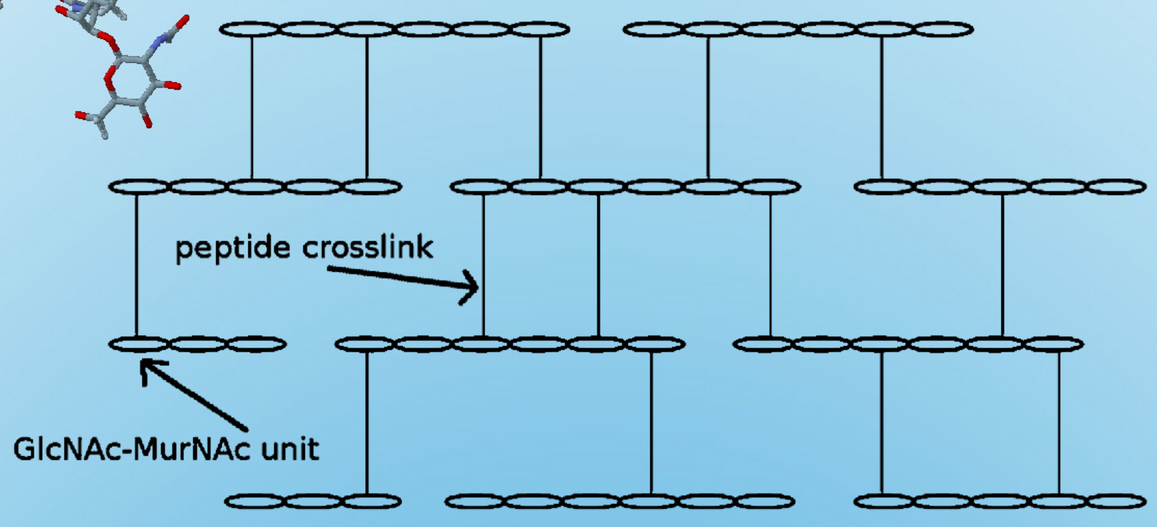


Base motif of cell wall GlcNAc-MurNAc disaccharide unit with Ala-D-Glu-Lys-D-Ala-D-Ala pentapeptide.

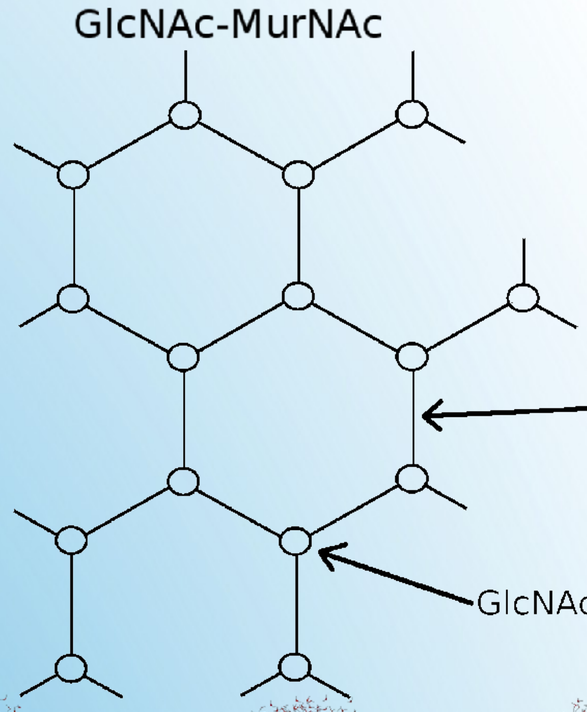
Crosslinking between pentapeptides in the S. aureus peptidoglycan.

Methods:

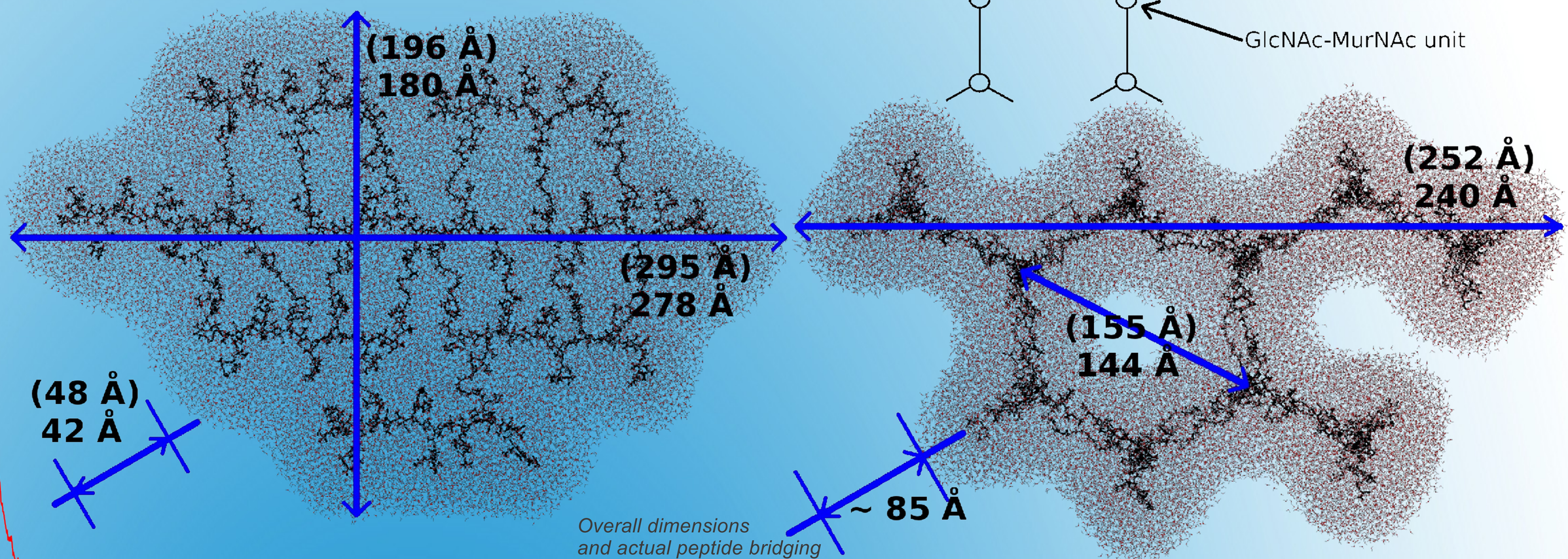
The MD was conducted in constant pressure and temperature (300 K) with free adaptation of the volume and density of the solvating water shell. It was carried out for 1.4 ns (the layered model) and 1.0 ns (the scaffold model) to achieve observable stabilization of changes in sizes of the peptidoglycan layers fragments.
Sizes of the systems: ~180 000 atoms, ~50 000 water molecules and 20 Å water cap.



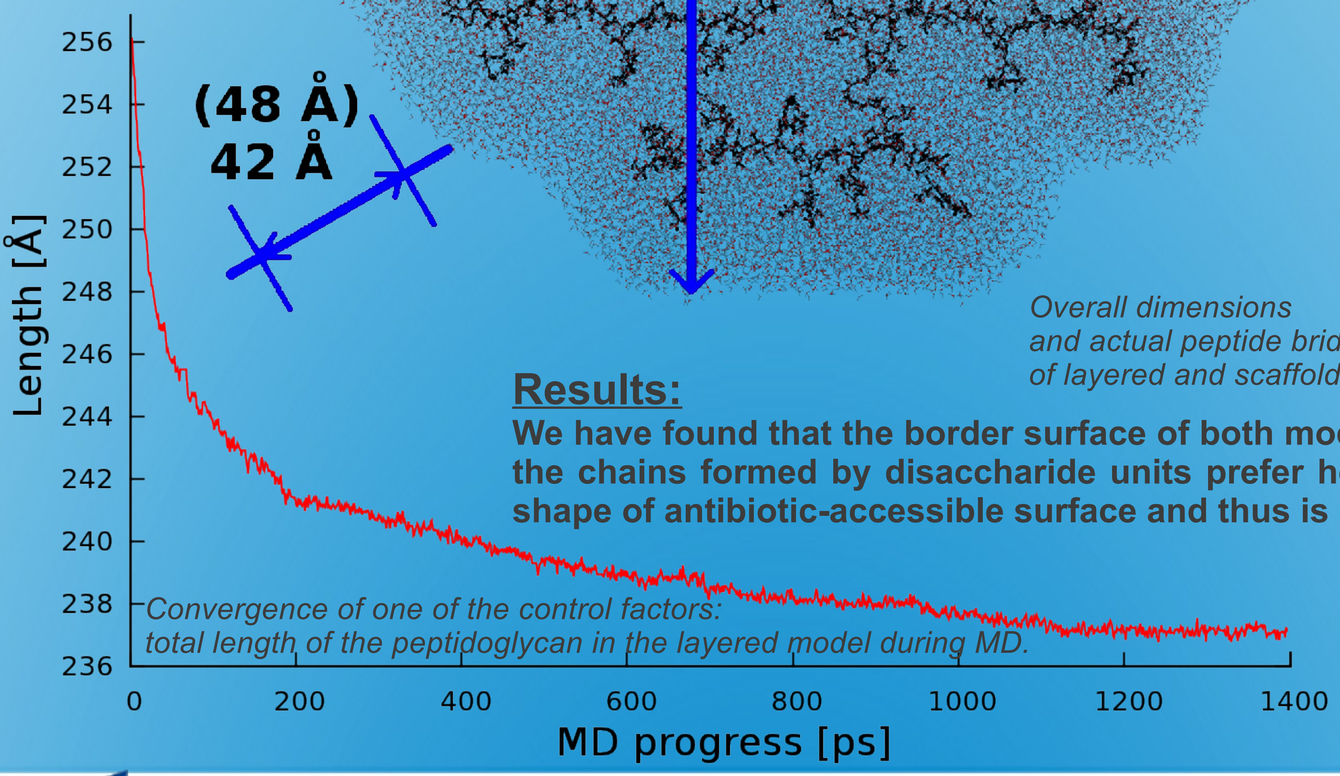
Organization of the peptidoglycan crosslinks in the layered (on the left) and scaffold (on the right) models. The peptide bridges do not present the actual models.



Cross-linking data:
In the actual peptidoglycan layers there are 75% to 90% peptide cross linked. Our models are simplified and consist of only one peptidoglycan layer. We have assumed that 35-65% of the pentapeptides should be involved in binding to the neighboring peptidoglycan layer. The other 25% or 40% in the layered and scaffold model, respectively, is involved in the forming of the actual modeled layer. The glycan strands were constructed with 6 disaccharide units each in the scaffold model and with 8 disaccharide units in the layered model.



Overall dimensions and actual peptide bridging of layered and scaffold models of the peptidoglycan layer during the simulations.



Convergence of one of the control factors: total length of the peptidoglycan in the layered model during MD.

Results:

We have found that the border surface of both models differ from the surface located away from the edge of models and the chains formed by disaccharide units prefer helix-like conformation. This curling of PG chains strongly affects the shape of antibiotic-accessible surface and thus is crucial for new drug development.

The structure of obtained peptidoglycan layer is good basis for a template or the base structure of the bacterial cell wall polymer. It will be used for vancomycin and its analogues docking at the edge of the model as well as in the center of it. Both models, layered and scaffold, are well equilibrated and prepared for further simulations.

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