REVIEWING PROTEIN-SUBSTRATE INTERACTIONS USING NAMD

PROJECT PRESENTATION BY-

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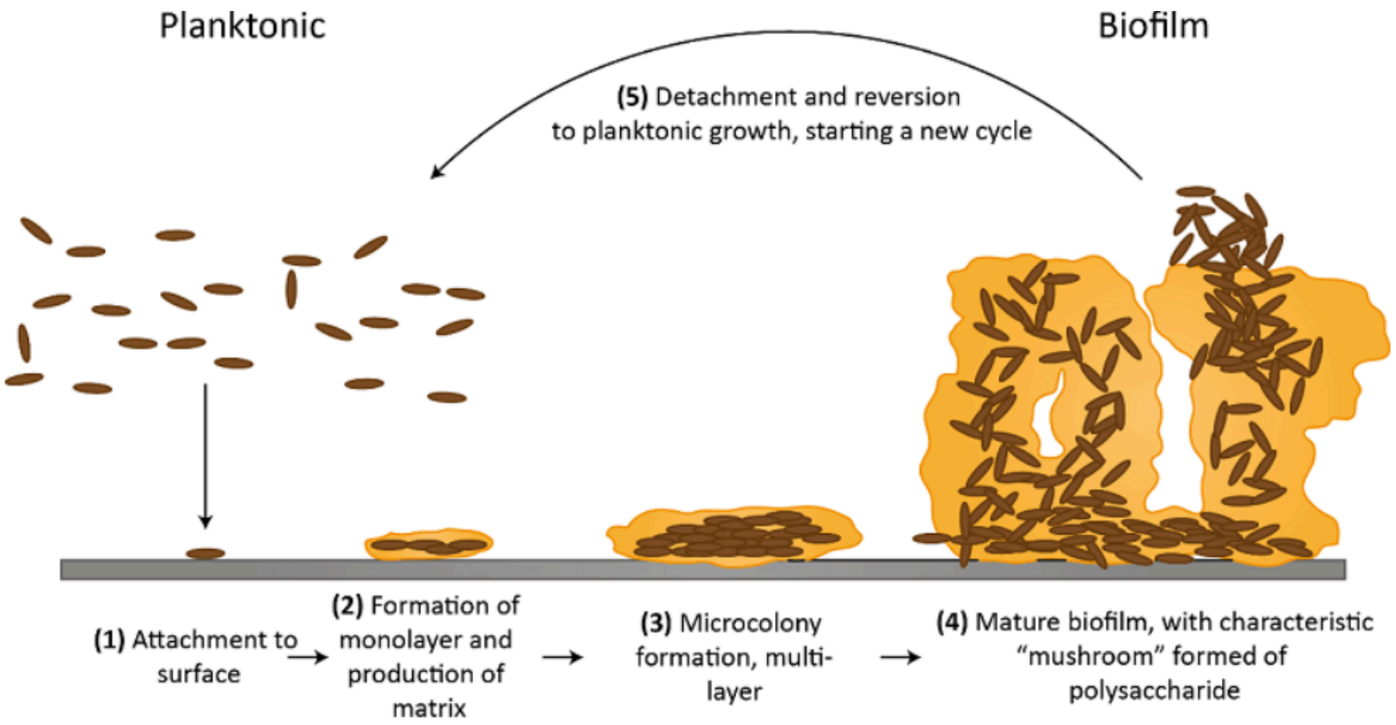
CURRENT PROBLEMS

- Occurrence of postoperative infections after implantation procedures is primarily due to **adhesion of bacterial cells on the implant surface**.

- A film of proteins from the host's body gets deposited on the implant surface - **BIOFILM FORMATION**

- This happens in three steps primarily:

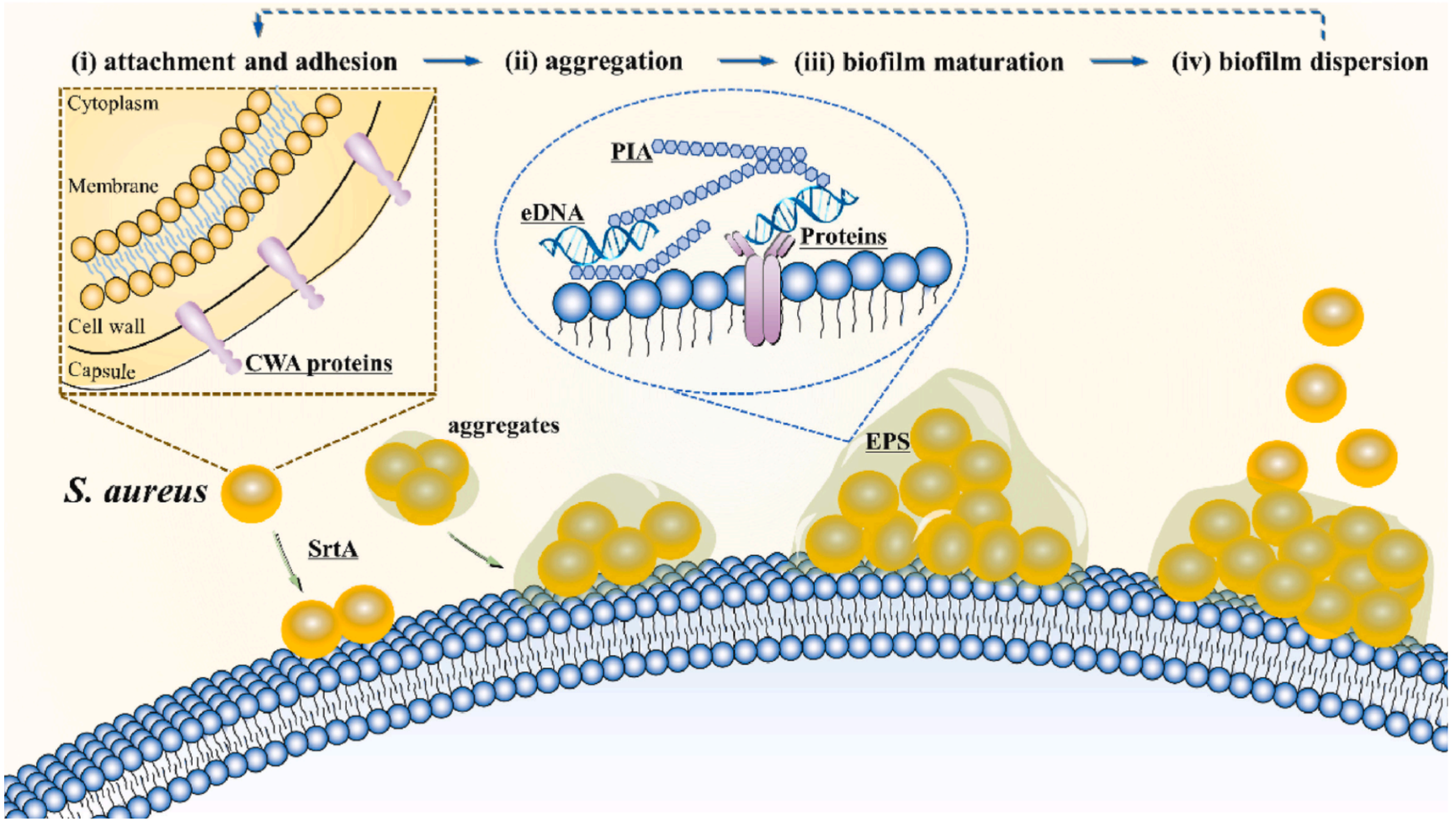
1. Rapid surface attachment
2. Multilayered bacterial cell proliferation
3. Intercellular adhesion in an extracellular polysaccharide matrix



Schematic representation of a biofilm formation
British Society for Immunology. "Biofilms and Their Role in Pathogenesis."

Raj, Arindam, Neeraj Dhandia, and Kantesh Balani. "Adhesin Protein Interaction of Staphylococcus aureus Bacteria with Various Biomaterial Surfaces." ACS Biomaterials Science & Engineering, vol. 6, no. 11, 2020, pp. 6161–6172.

BIOFILM FORMATION



S. aureus biofilm formation process: (i) initial attachment and adhesion, (ii) aggregation, with cell division and proliferation as well as EPS production; (iii) biofilm structuring and maturation, and (iv) biofilm dispersion, with cell detachment from the aggregate biofilm to planktonic state.

Xiying Wu et al. 2024. "Staphylococcus aureus biofilm: Formulation, regulatory, and emerging natural products-derived therapeutics."

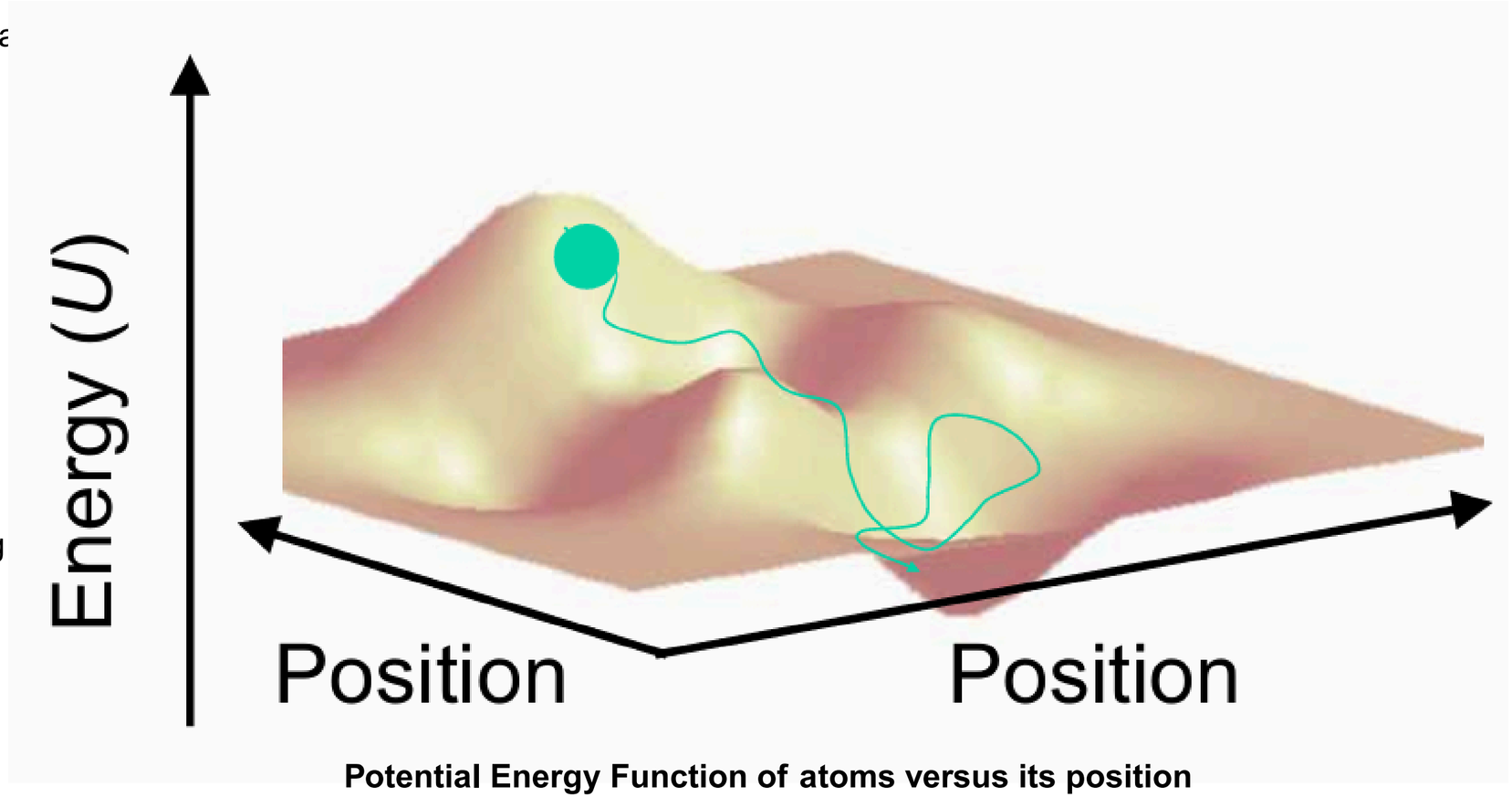
WHAT IS NAMD ?

- **Molecular dynamics** is a computer simulation method for analysing the trajectories of atoms a molecules.

So, to observe the protein-substrate (implant surface) interactions better, we use the software:

- NAMD(Nanoscale Molecular Dynamics) for computing atomic trajectories by solving equations of motion by using empirical force fields (like CHARMM).

- VMD(Visual Molecular Dynamics) for viewing molecules.



Potential Energy Function of atoms versus its position

Lesk, A. M. (n.d.). Lecture 4: Sequence alignment algorithms. Stanford University.

Phillips, J. C., et al. (2022). NAMD User's Guide: Running NAMD. Theoretical and Computational Biophysics Group, University of Illinois at Urbana-Champaign.

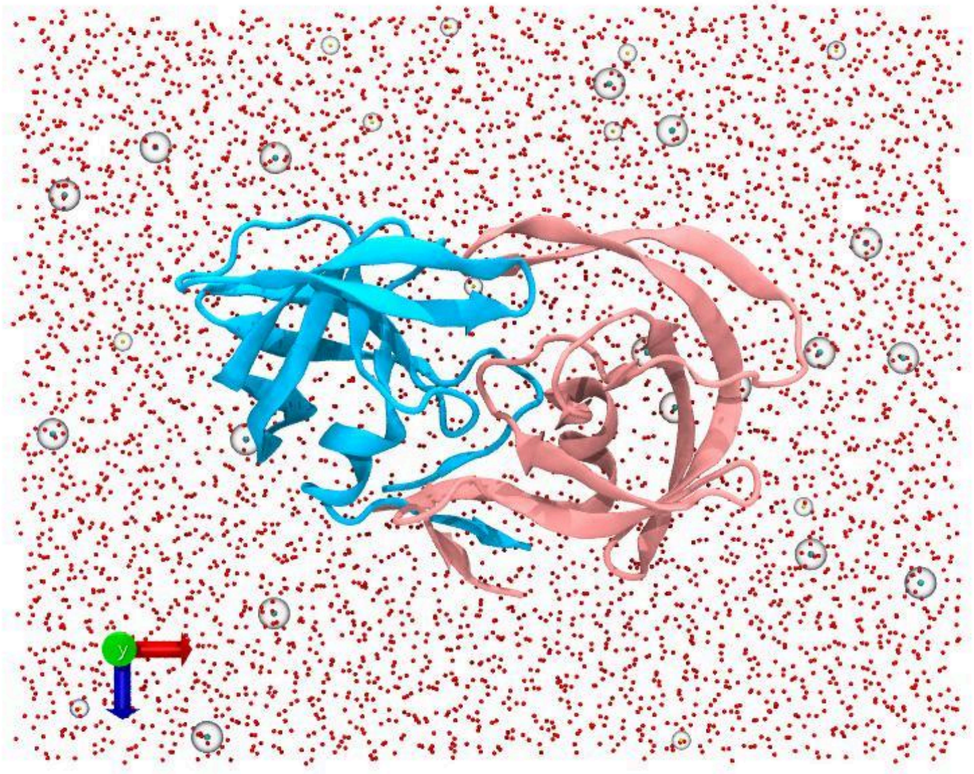
WHY DO WE NEED TO USE NAMD?

- The input and output file formats used by NAMD are identical to those used by CHARMM and X-PLOR, which assures that the MD trajectories from NAMD can be read by CHARMM or X-PLOR.

- NAMD performs **Steered Molecular Dynamics (SMD)**, which helps us explore the elastic properties and unfolding pathways of the proteins.

- Analysis of various parameters is possible like protein unfolding, ligand binding, ion channel function and membrane dynamics.

- It is designed to handle very large biomolecular systems and is optimized for parallel computing, so it runs efficiently on supercomputers and clusters.



HIV Protease Model

Melbourne Bioinformatics. "Molecular Dynamics 201: Building Input Files, Visualising the Trajectory."

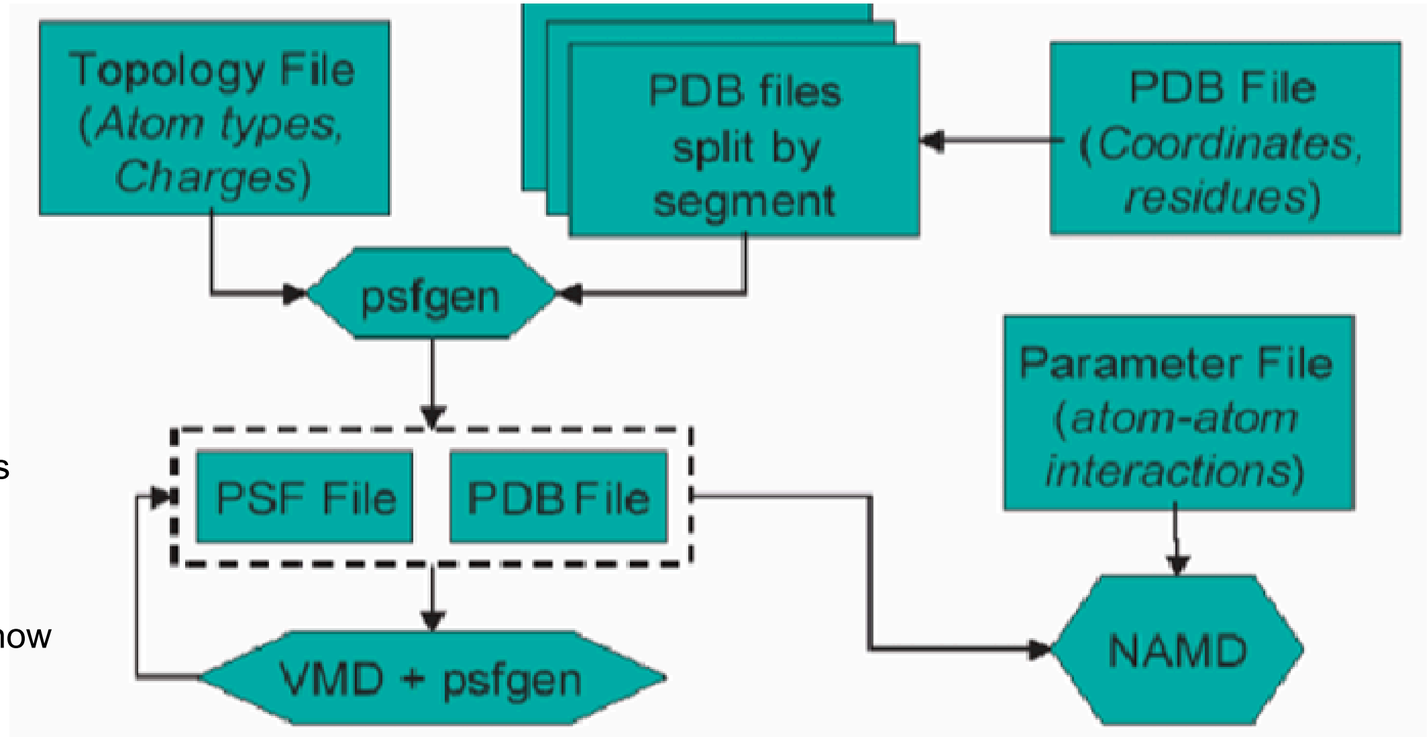
Phillips, J. C., et al. (2022). NAMD User's Guide: Running NAMD. Theoretical and Computational Biophysics Group, University of Illinois at Urbana-Champaign.

Lesk, A. M. (n.d.). Lecture 4: Sequence alignment algorithms. Stanford University.

REQUIREMENTS FOR NAMD

In order to run any MD simulation, NAMD requires at least four things:

- **Protein Data Bank (PDB)** file: It stores atomic coordinates and velocities for the system.
- **Protein Structure File (PSF)**: It stores structural information of the protein, such as various types of bonding interactions.
- **Force field parameter file**: The parameter file defines bond strengths, equilibrium lengths, etc.
- **Configuration file**: The configuration file tells NAMD how the simulation is to be run.



Flow Chart for preparing the PSF, for NAMD simulations

Lesk, A. M. (n.d.). Lecture 4: Sequence alignment algorithms. Stanford University.

PSF contains all of the molecule specific information needed to apply a particular force field to a molecular system.

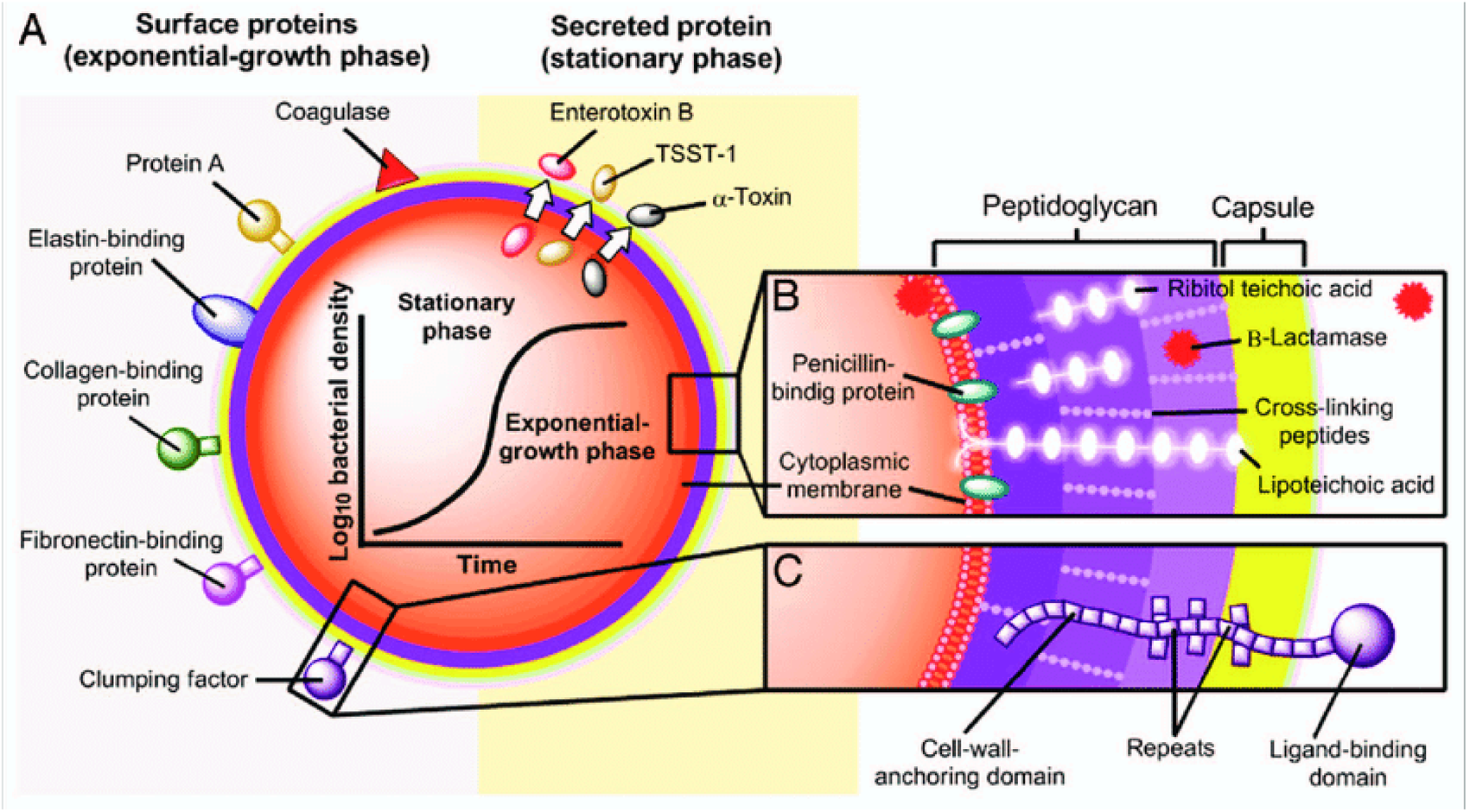
Phillips, J. C., Braun, R., Wang, W., Gumbart, J., Tajkhorshid, E., Villa, E., ... & Schulten, K. (2022). NAMD User's Guide: Version 3.0.1 – Chapter 1: Basics of NAMD. Theoretical and Computational Biophysics Group, University of Illinois at Urbana-Champaign.

HOW DO WE PLAN TO PROCEED?

The very first step would be to analyze and develop the PSF of the bacteria. Taking *S. Aureus* as our first example, the cell wall surface protein on this bacteria are-

1. Serine-Aspartic Acid Dipeptide repeats
2. A leucine-proline-unknown-threonine-glycine amino acid chain motif
3. Hydrophobic, membrane-spanning domain
4. Positively charged residues embedded on the cell wall

We would need to generate a psf with the above mentioned substances.



Pathogenic factors of *S. Aureus* showing both the structural and secreted products

Vatansever, F., Ferraresi, C., de Sousa, M. V., Yin, R., Rineh, A., Tegos, G. P., & Hamblin, M. R. (2013). "Can biowarfare agents be defeated with light?" Virulence, 4(8), 796–825

Raj, Arindam, Neeraj Dhandia, and Kantesh Balani. "Adhesin Protein Interaction of Staphylococcus aureus Bacteria with Various Biomaterial Surfaces." ACS Biomaterials Science & Engineering, vol. 6, no. 11, 2020, pp. 6161–6172.

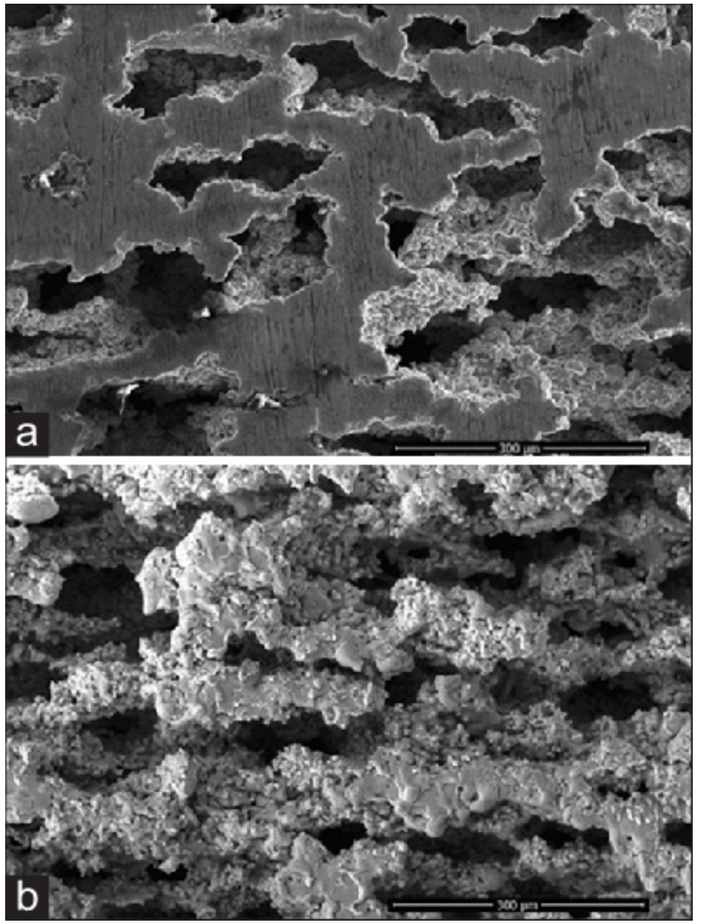
PARAMETERS FOR CONSIDERATION

As mentioned before, there are certain **“PARAMETERS”** when it comes to studying substrate-bacteria interactions. These are changes that take place when the implant enters the body.

THE VARIOUS **PARAMETERS** FOR **SUBSTRATE SURFACE + BACTERIAL ADHESION** ARE AS FOLLOWS-

1. Difference in chemical nature
2. Roughness
3. Porosity
4. Hydrophobicity
5. Surface Energy
6. Fluid Shear Rate
7. Force field for inorganic systems
8. Secondary interactions (Van der Waals force, hydrogen bond) apart from the ligand-receptor ones
9. Minimum energy configuration of the protein structure in different environments
10. Constant velocity of pulling of dummy atom linked to SMD with spring
11. Constant Temperature (~310 K)
12. Constant Pressure (1 atm).

Raj, Arindam, Neeraj Dhandia, and Kantesh Balani. "Adhesin Protein Interaction of Staphylococcus aureus Bacteria with Various Biomaterial Surfaces." ACS Biomaterials Science & Engineering, vol. 6, no. 11, 2020, pp. 6161–6172.



The microstructure of the implants: (a) Without nanosized hydroxyapatite coating, an average pore size is 62 ± 6 μm; (b) With NHAP coating, an average pore size is 45 ± 5 μm

Nadezhdin, S., Kolobov, Y. R., Rogachev, A. S., & Pogrebnyak, T. A. (2018). Osteogenic properties of new porous composite materials based on titanium with bioactive covering

THANK YOU!