Modeling interactions between cationic facial amphiphilic polymers and lipid membranes using Monte Carlo Simulations

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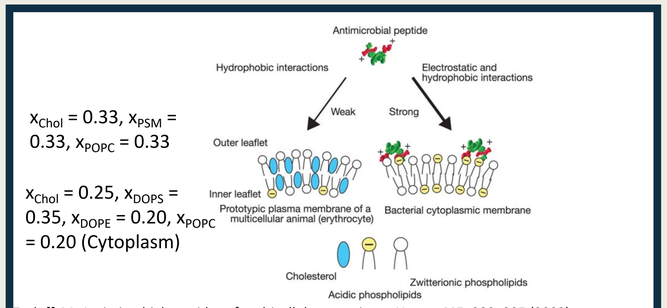
Introduction

Bacterial infections caused by gram negative bacteria are particularly pernicious and difficult to treat because of increasing multi-drug resistance and shortage of industry research devoted to developing new antibiotics. Gram-negative bacteria have a reinforced cell wall composed of an outer membrane, peptidoglycan layer, and periplasm. These layers create challenges for developing an effective antimicrobial. The low financial returns have pushed most pharmaceutical companies away from this area of research leaving only universities to find novel solutions.

Antimicrobial peptides (AMPs) are a natural defense mechanism of the body that have broad spectrum activity. Their cationic charges and hydrophobic components are essential to their mechanism of action. These features allow them to insert into pores on the bacterial membrane causing cytoplasmic leakage and ultimately cell death.

Polymers inspired by AMPs show promise as an effective solution especially because bacteria show low propensity for developing resistance to these polymers.



$x_{Chol} = 0.33$, $x_{PSM} = 0.33$, $x_{POPC} = 0.33$

$x_{Chol} = 0.25$, $x_{DOPS} = 0.35$, $x_{DOPE} = 0.20$, $x_{POPC} = 0.20$ (Cytoplasm)

Zasloff, M. Antimicrobial peptides of multicellular organisms. *Nature* **415,** 389–395 (2002). https://doi.org/10.1038/415389a

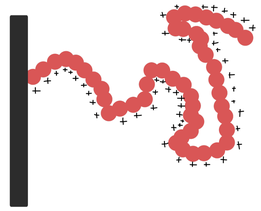
Materials and Methods

Monte Carlo Simulations

- Used to sample multiple times from a probability distribution
- Process
  1. Random moves for the monomer subunits
  2. Energy values calculated for each configurations
  3. The move is accepted if the move leads to a decrease in energy, if the energy increases we check the Boltzmann factor to a random number to see if the move is accepted
  4. Steps 1-3 are repeated
- Configurations that extended into the negative z axis were discarded
- Configurations that were not self-avoidant were also discarded

Script for Polymer Model and Lipid Bilayer Model

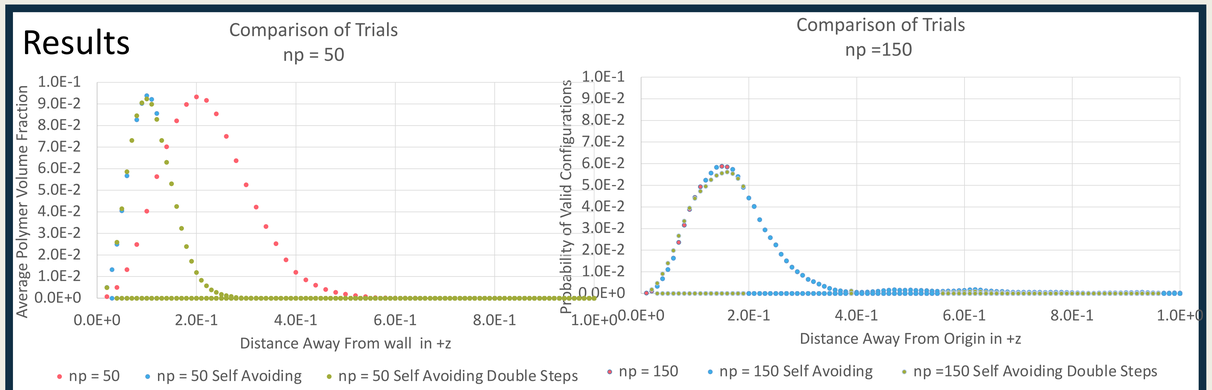
- written in Fortran and executed on the terminal
- Data was compiled on Microsoft Excel
- Models accounted for a single polymer interacting with the lipid bilayer



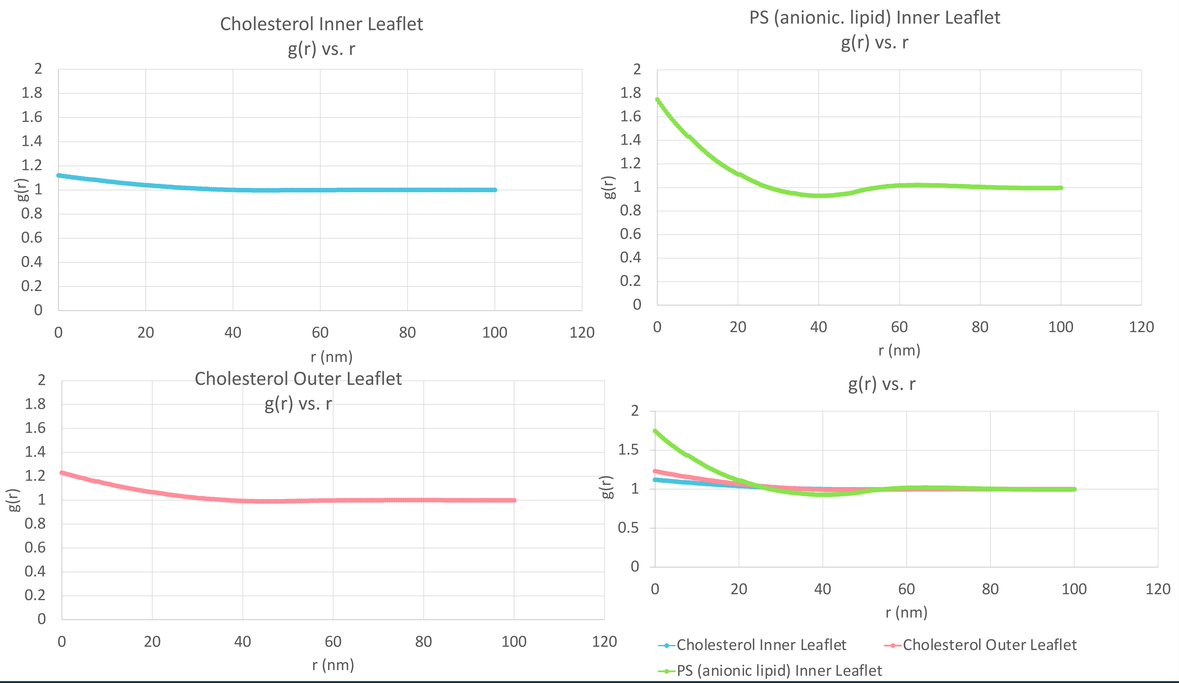
Polymer Facts

- 50 monomer units
- Chi = 5k_BT
  - Same hydrophobicity as lipid bilayer
- +1 charge on each unit

Results



Including self-avoiding interactions stretches the chains. The smaller the chain, the greater the stretching it experiences.



Results

- R is the average distance away from each monomer unit
- G(r) correlates the average distance of membrane molecules (lipids, cholesterol) from the average position of the monomer units
- G(r)=1 represents the state of the lipid membrane when there is no polymer.
- As r increases, the curve approaches 1 because the distance from the polymer is large enough that the lipid bilayer is relatively unimpacted by its presence.
- We only consider the monomer units in the leaflet of interest.
- Cholesterol in the inner and outer leaflet had around a 20% increase over the bulk density while phosphatidylserine (PS) molecules had around a 75% increase over the bulk density.

Conclusion

We used a Monte Carlo Simulation with Self-Consistent Field Theory to model a cationic polymer and a lipid bilayer. We see that there is a uptake of cholesterol in the inner and outer leaflet due to the presence of the polymer. However, the PS groups experience the strongest repulsion to the polymer because their negative charges interact strongly with the positively charged groups on the polymer.

The current theory for the polymer's mechanism of action is that the cationic polymer is attracted to the anionic cell membrane and disrupts membrane function eventually leading to cell death.

Our current lipid membrane model is for a eukaryotic cell with a negatively charged inner leaflet. A prokaryotic cell has a negatively charged inner and outer leaflet.

The results are promising because PS (anionic lipid) had the highest levels of uptake (membrane disruption).
This indicates that a more negatively charged membrane (prokaryotic) would experience more significant disruption than a mammalian (eukaryotic) membrane.

Future of Project

- Model a prokaryotic cell membrane that represents a gram-negative bacterial cell membrane well
- Model a polymer with facial amphiphilicity rather than an 'average' hydrophobicity
- The experimental portion of this project is interested in testing monomers in addition to polymers so computational modeling for monomers will also be necessary.
- We also hope to compare the continuous worm-like chain model to the discretized work-like chain model.

Materials and Methods

Gaussian Model Equations

$$\frac{\partial}{\partial s}q(\mathbf{r},\mathbf{r}_0,s) = \left[\frac{a^2N}{6}\nabla^2 - w(\mathbf{r})\right] q(\mathbf{r},\mathbf{r}_0,s)$$

$$\frac{\partial}{\partial s}q^\dagger(\mathbf{r},\mathbf{r}_0,s) = -\left[\frac{a^2N}{6}\nabla^2 - w(\mathbf{r})\right] q^\dagger(\mathbf{r},\mathbf{r}_0,s)$$

Discrete Stretchable Shearable Worm-Like Chain Equations

$$E\left(\left\{\vec{R}_i\right\}\right) = \sum_{i=1}^{N}\frac{\varepsilon_b}{2\Delta}\left|\vec{u}_i - \vec{u}_{i-1}\right|^2 + \frac{\varepsilon_\parallel}{2\Delta}\left(\left|\vec{R}_i\right| - \Delta\gamma\right)^2, \qquad (4)$$

$$S_{\mathrm{dssWLC}}(k) = \frac{2}{N^2}\sum_{n_1=0}^{N}\sum_{n_2=0}^{n_1}\left\langle \exp\left[ik\left(\vec{r}_{n_2} - \vec{r}_{n_1}\right)\cdot\hat{z}\right]\right\rangle$$

$$= \frac{2}{N^2}\sum_{n_1=0}^{N}\sum_{n_2=0}^{n_1}\left[\boldsymbol{g}^{(n_2-n_1)}\right]_{0,0}$$

$$= \left[\left\{N\boldsymbol{I} + \boldsymbol{g}^{(N+1)} - (N+1)\boldsymbol{g}\right\}\cdot(\boldsymbol{g}-\boldsymbol{I})^{-2}\right]_{0,0} \qquad (11)$$

Gaussian	Discretized Worm-Like Chain
continuous	Discrete subunits
Integral of configurations	Sum of configurations

"Self-Consistent Field Theory and Its Applications." *Soft Matter /*, Wiley-VCH,, 2005, doi:10.1002/9783527617050.
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Acknowledgements

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Citations

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