# Simulation-guided *de novo* design of antimicrobial peptides

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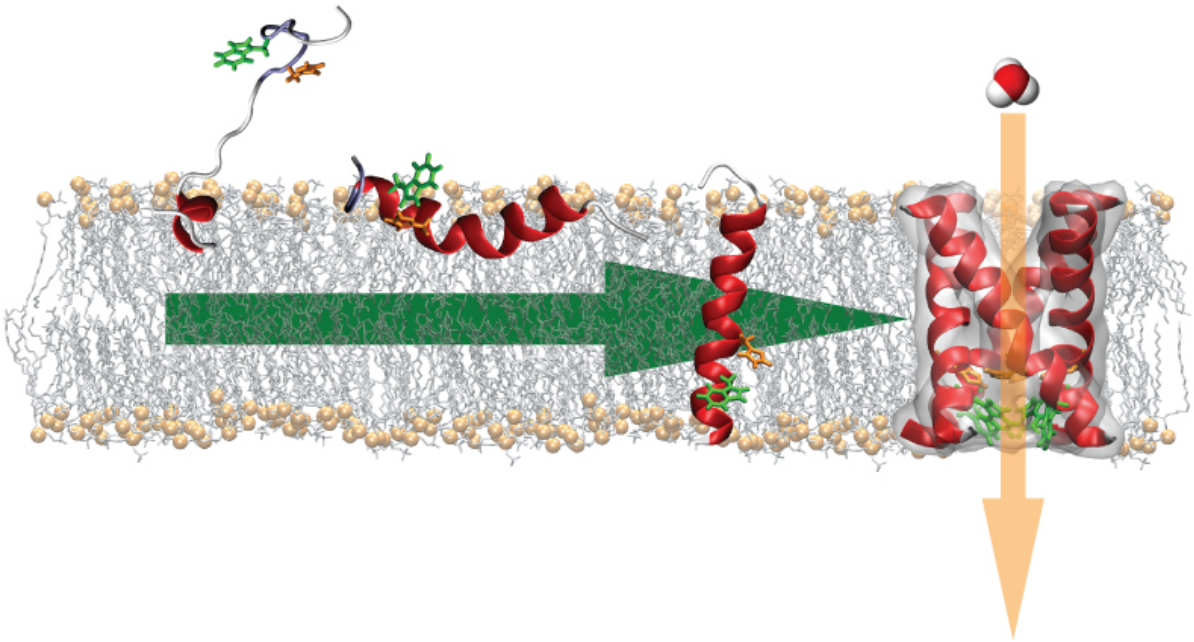

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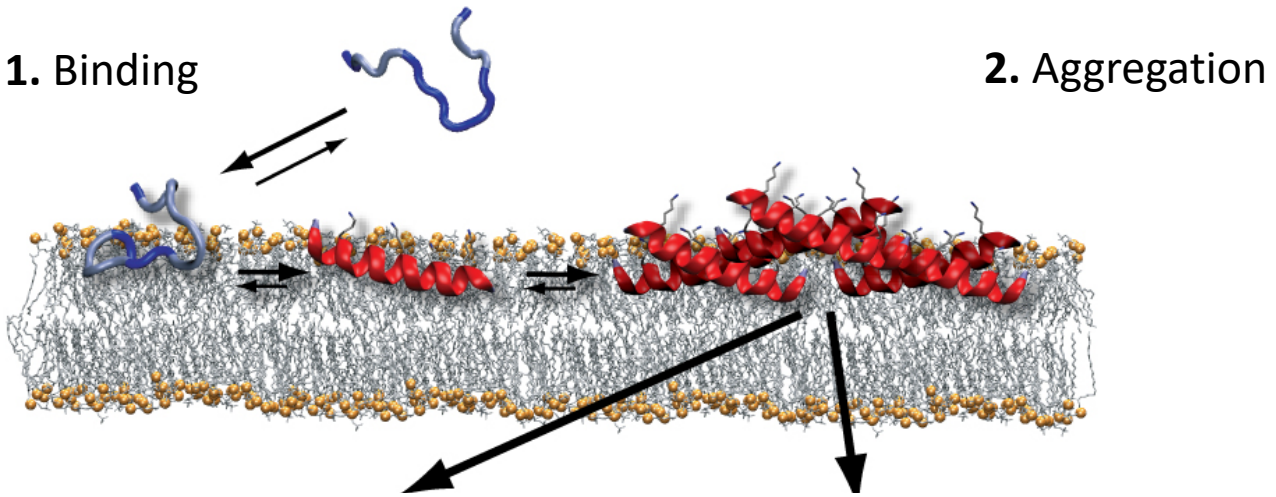
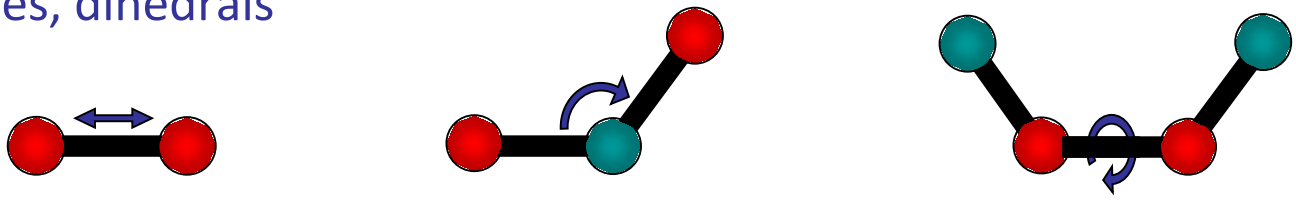
# Membrane-active antimicrobial peptides (AMPs)




**Without structural information mechanisms and design remain elusive**

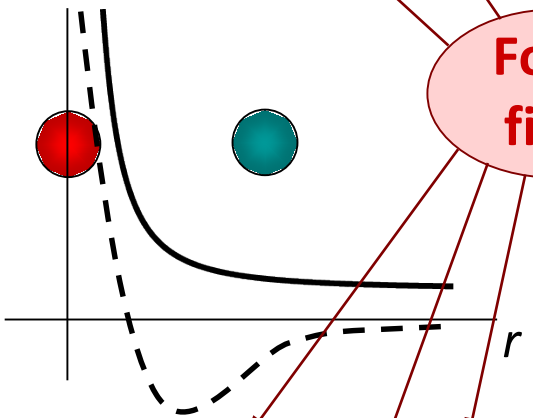
# Molecular dynamics simulations

## Bonds, angles, dihedrals



$$V_{bon} = \sum_{bonds} k_{bond}(r - r_{equilib})^2 + \sum_{angles} k_{angle}(q - q_{equilib})^2 + \sum_{dihedrals}\sum_{n} \tfrac{1}{2}V_n(1 + \cos(nf - g))$$

## Coulomb, Van der Waals




**Force field**

$$V_{nb} = \sum_{i}^{n}\sum_{j}^{n}\left(\frac{q_i q_j}{r_{ij}} + 4e_{ij}\left(\frac{s_{ij}^{12}}{r_{ij}^{12}} - \frac{s_{ij}^{6}}{r_{ij}^{6}}\right)\right)$$

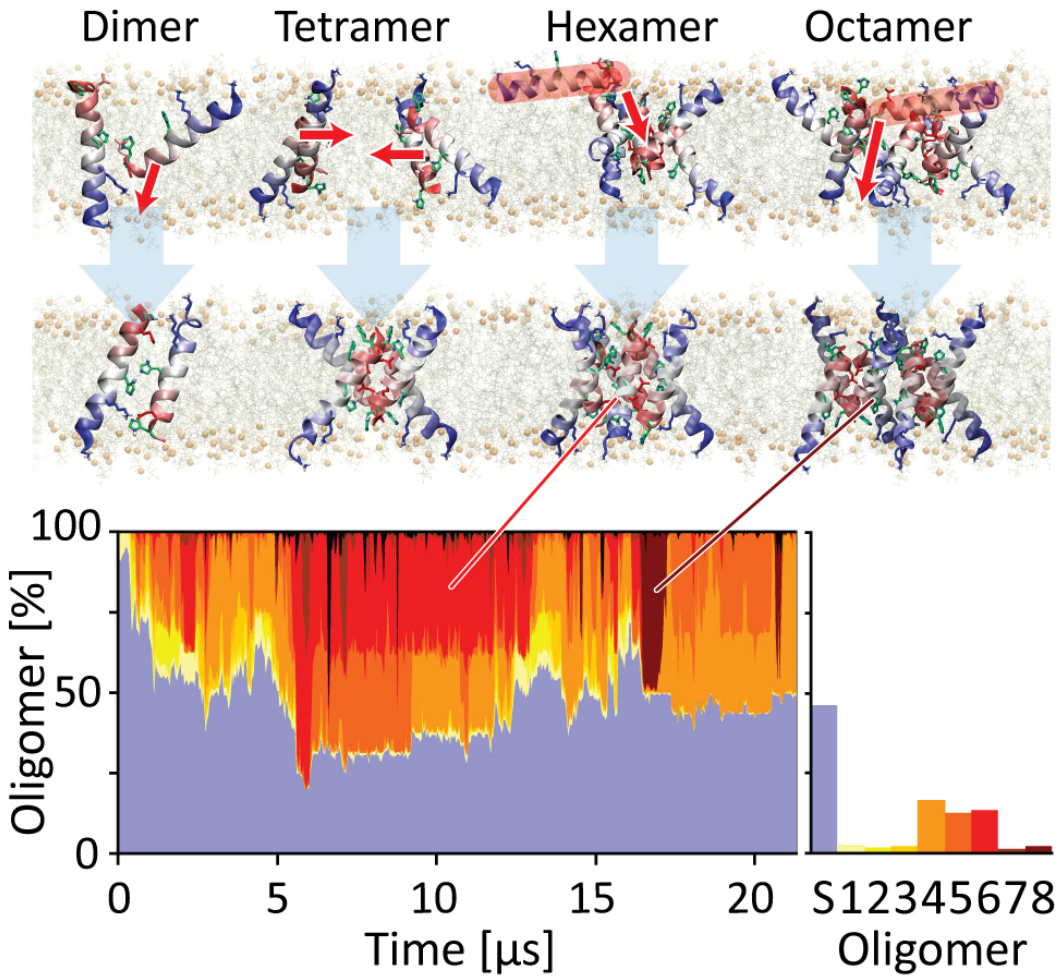
# The functional structures of the Australian tree frog AMP maculatin

Assembly simulation

**Assembly**

**Pores**

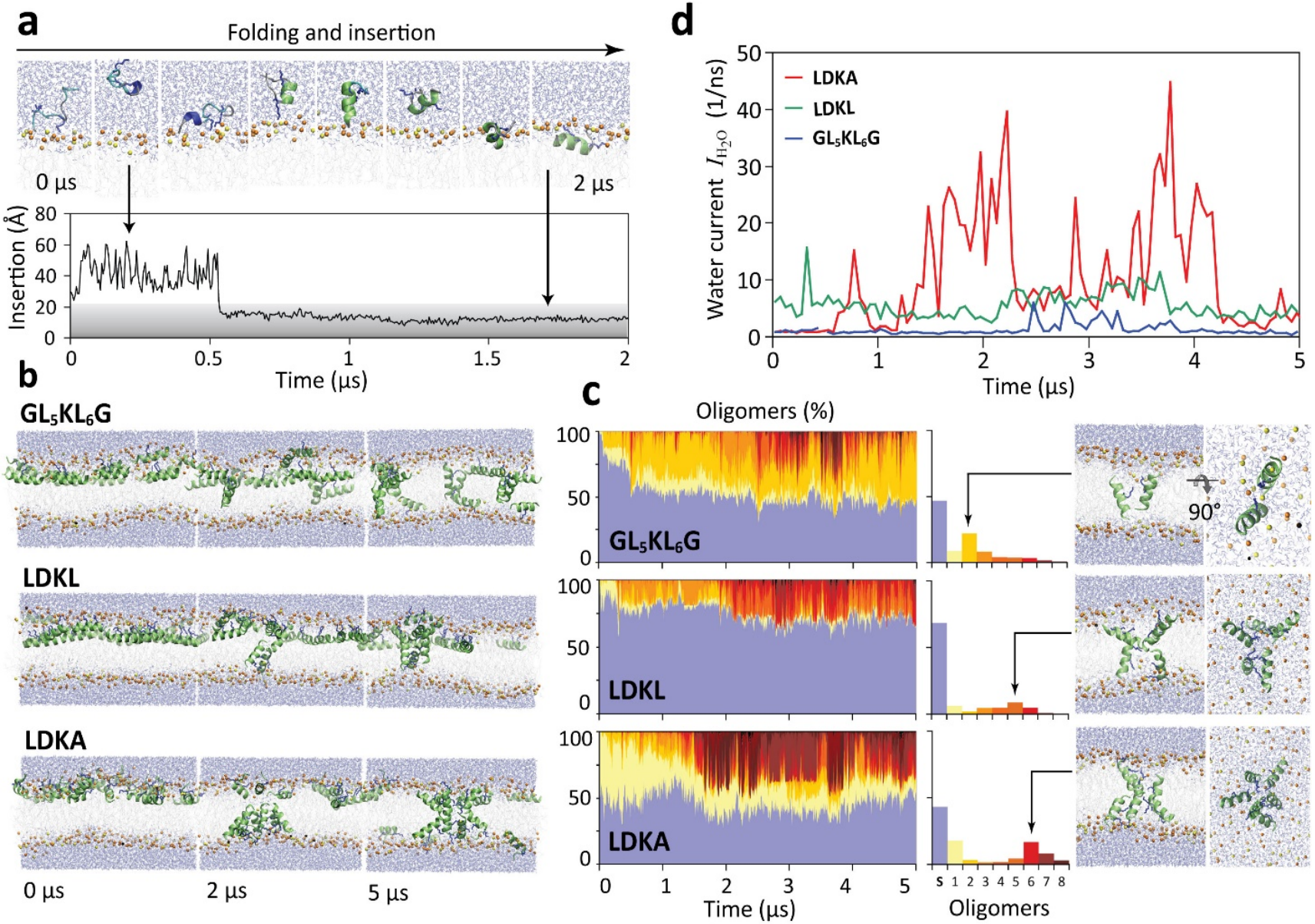
**Lifetimes**




**Simulations can predict the ensemble of the transient functional pores**

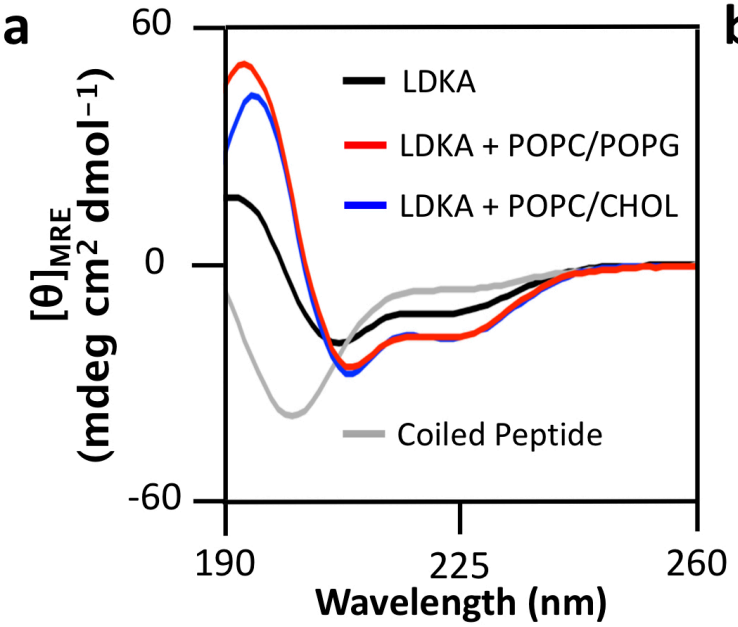
Wang et al., *Nature Comm.* (2016)

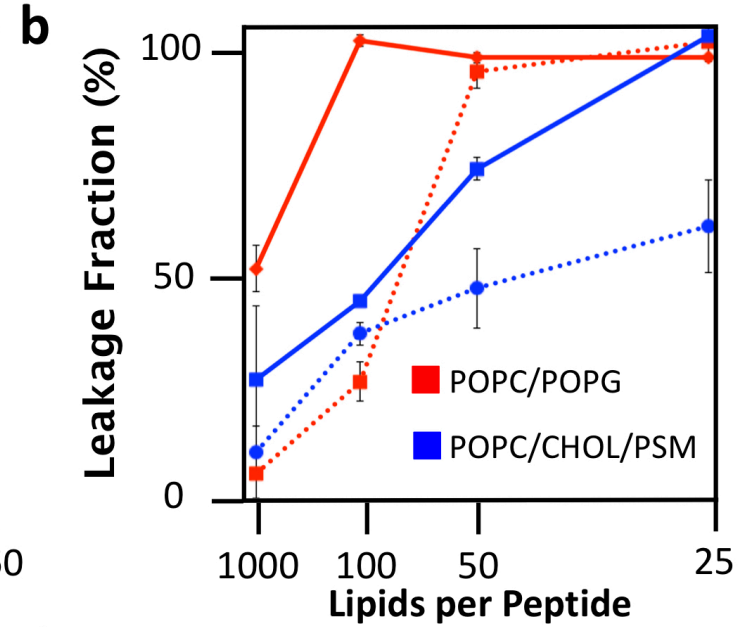
# Simulation-guided design of novel antimicrobial peptides




Chen et al., *JACS* (2019)

# The designed peptides form pores and are active against bacteria

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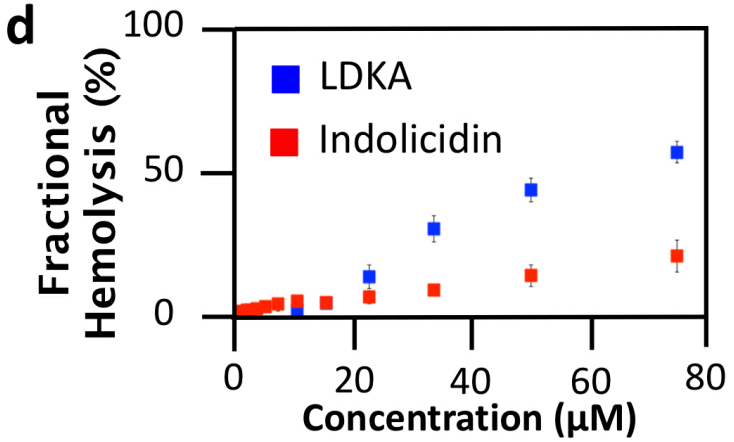
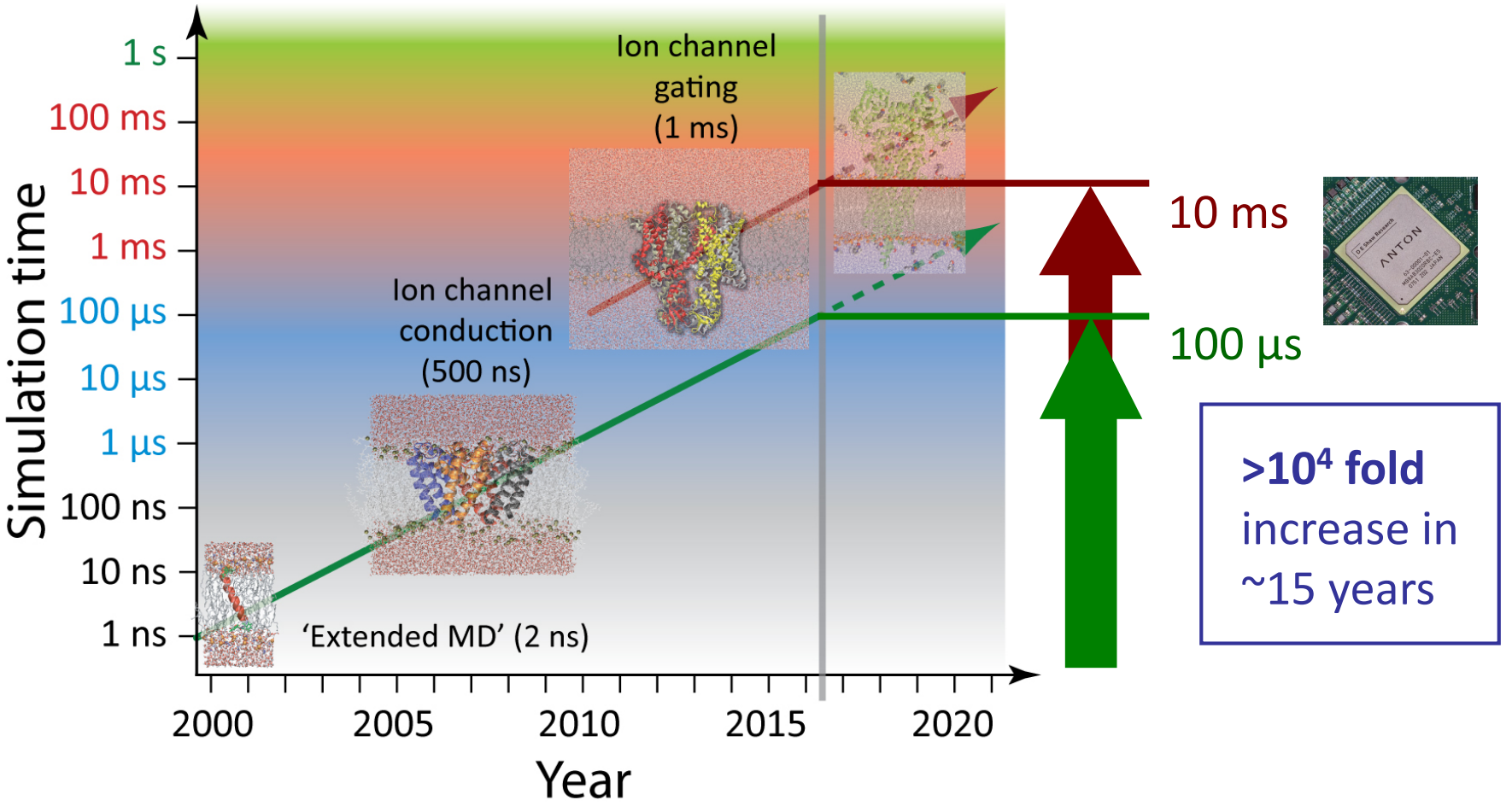
| Minimum Inhibitory Concentration (MIC) | | |
|---|---|---|
| *E. coli* ATCC 25922 | *S. aureus* ATCC 27853 | *P. aeruginosa* PAO1 |
| 35±9 µM | 10±0 µM | 66±14 µM |



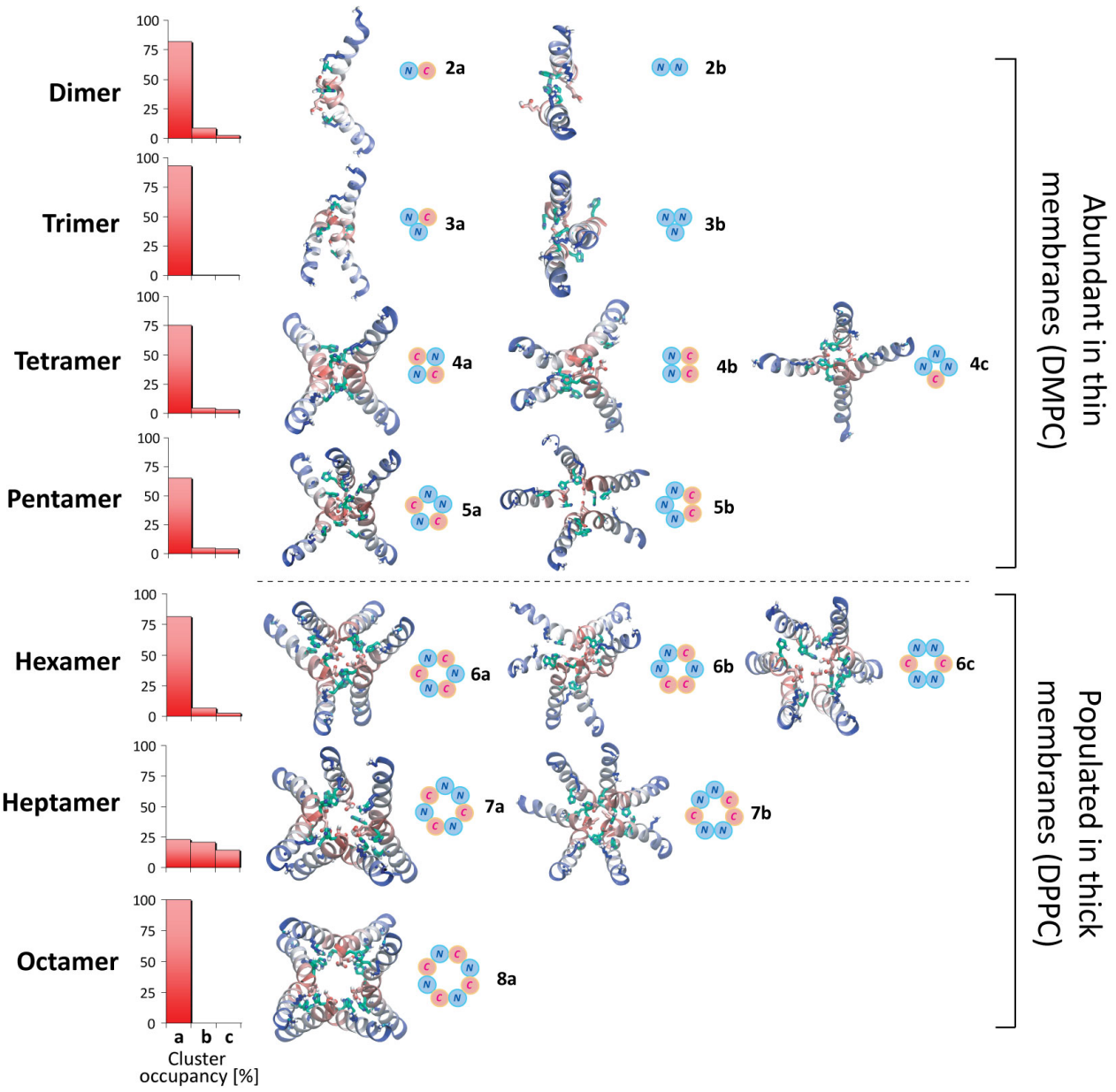

**Bottlenecks: the lack of realistic models of bacterial membranes**

# The molecular dynamics ‘revolution’




Atomistic simulations of millisecond processes in **< 10 years**

# Broad ensemble of structures: relevance of bacterial resistance?




Wang et al., *Nature Comm.*, (2016)