# Informatics and Computer Simulations: Experience of SPARC

23rd May 2019, Budapest

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# Computational Simulations of Pharmaceutical Formulations: A Case study

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# Topics

1. Components
2. Parameters for analysis
3. Evolution from packing to nanoparticle formation
4. Snapshots of nanoparticle formation
5. Analysis
6. Summary

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# System input

Total number of atoms 327376
Ensemble: NPT
Total simulation time: 200ns

Formulation components (considering one half of original system):

| | |
|---|---|
| Drug molecule | 30 |
| Fatty acid | 15 |
| PEG | 456 |
| Cholesterol | 4 |
| PVP | 6 |
| Ethanol | 543 |
| Water | 99270 |
| Sodium ions for neutral pH | 4 |
| **TOTAL** | **100,327** |

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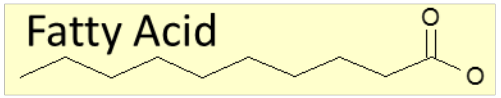
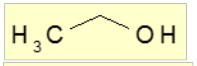
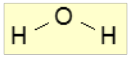
# Molecular Structures

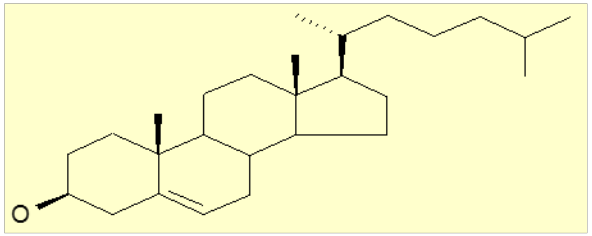



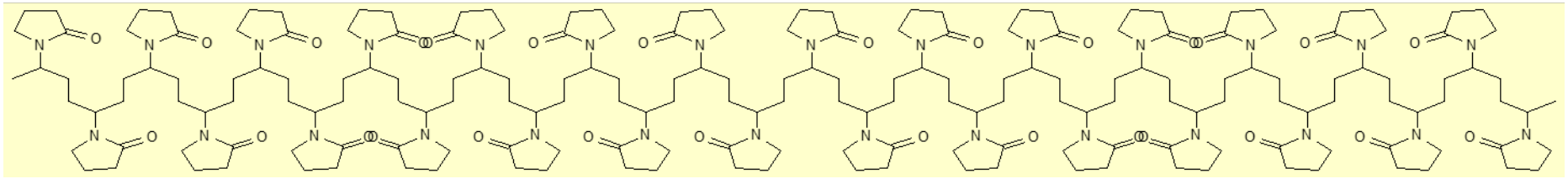

Ethanol

Drug Molecule




Water



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# Computational Pharmaceutics

Parameters considered for analysis are:

H-bond analysis

RMSD

Potential energy

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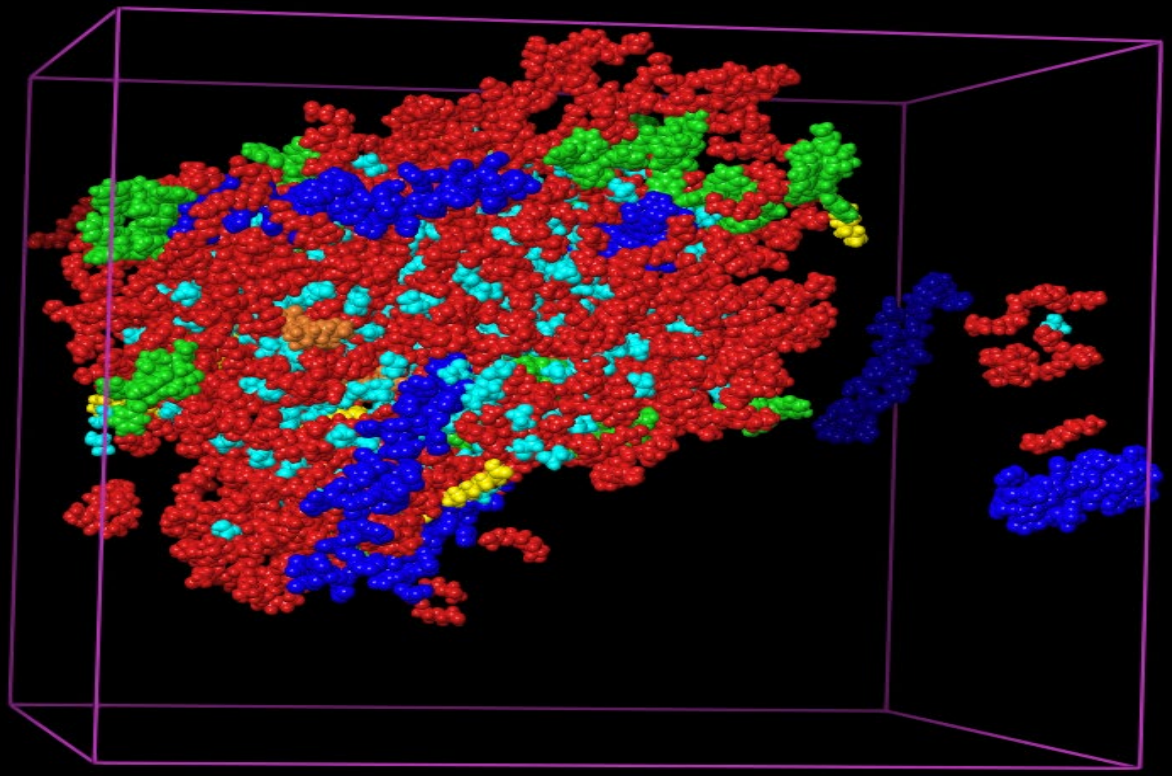
# Simulating Drug Molecule…

Green = Drug
Blue = PVP
Red = PEG
Yellow = FA
Brown = CHO
Cyan=EtOH



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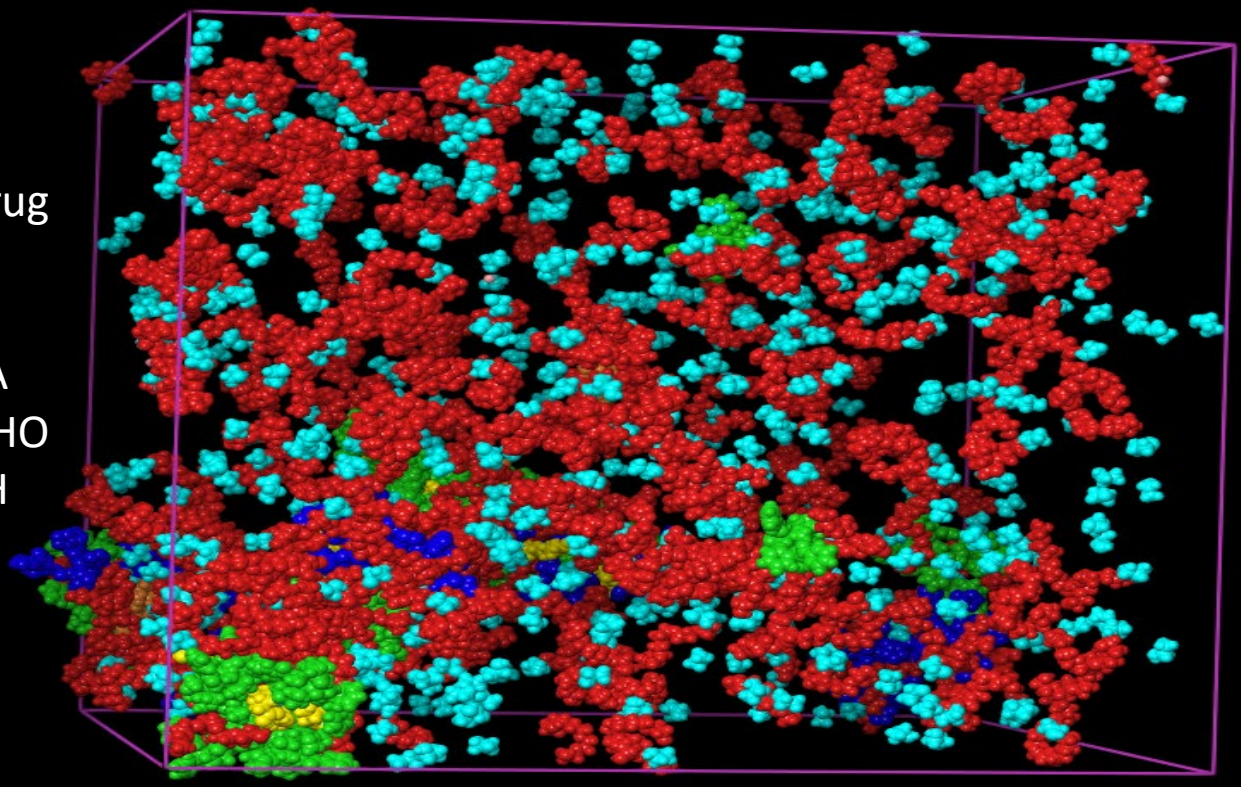
# MD simulation

Green = Drug
Blue = PVP
Red = PEG
Yellow = FA
Brown = CHO
Cyan=EtOH



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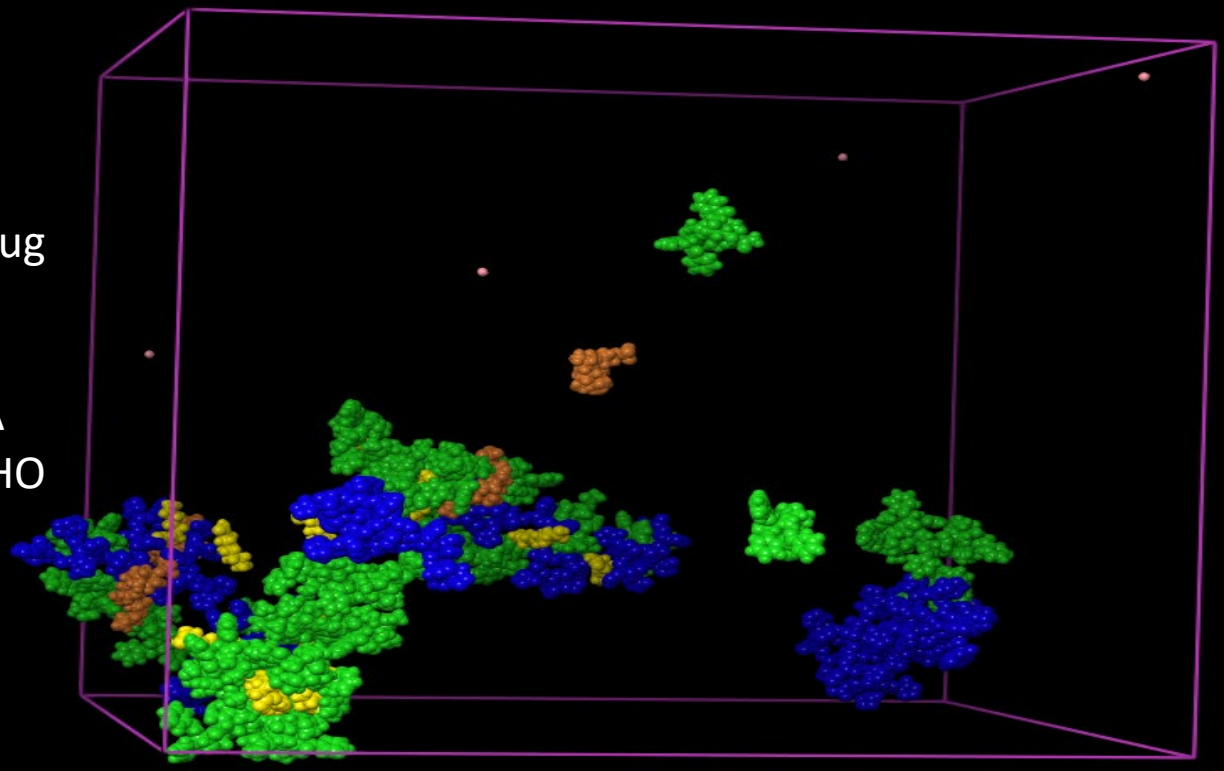
# T=20 ns

Green = Drug
Blue = PVP
Red = PEG
Yellow = FA
Brown = CHO



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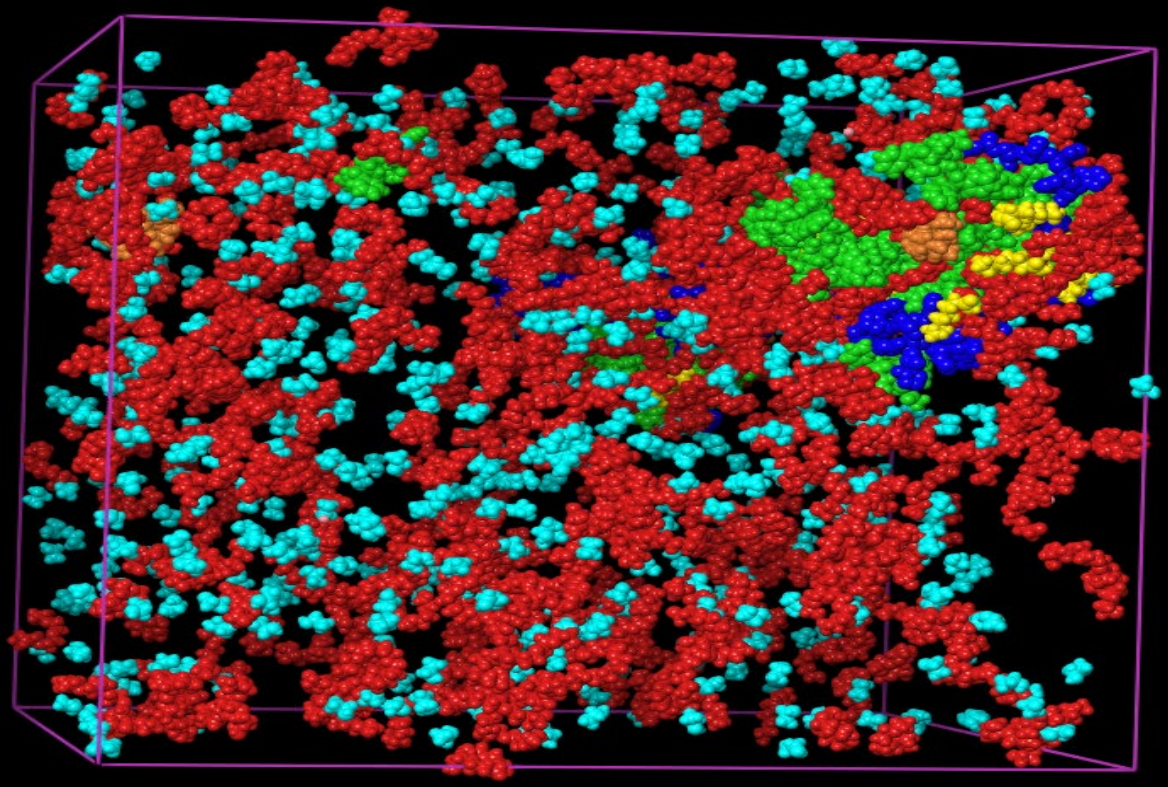
# T=40 ns

Green = Drug
Blue = PVP
Red = PEG
Yellow = FA
Brown = CHO
Cyan=EtOH



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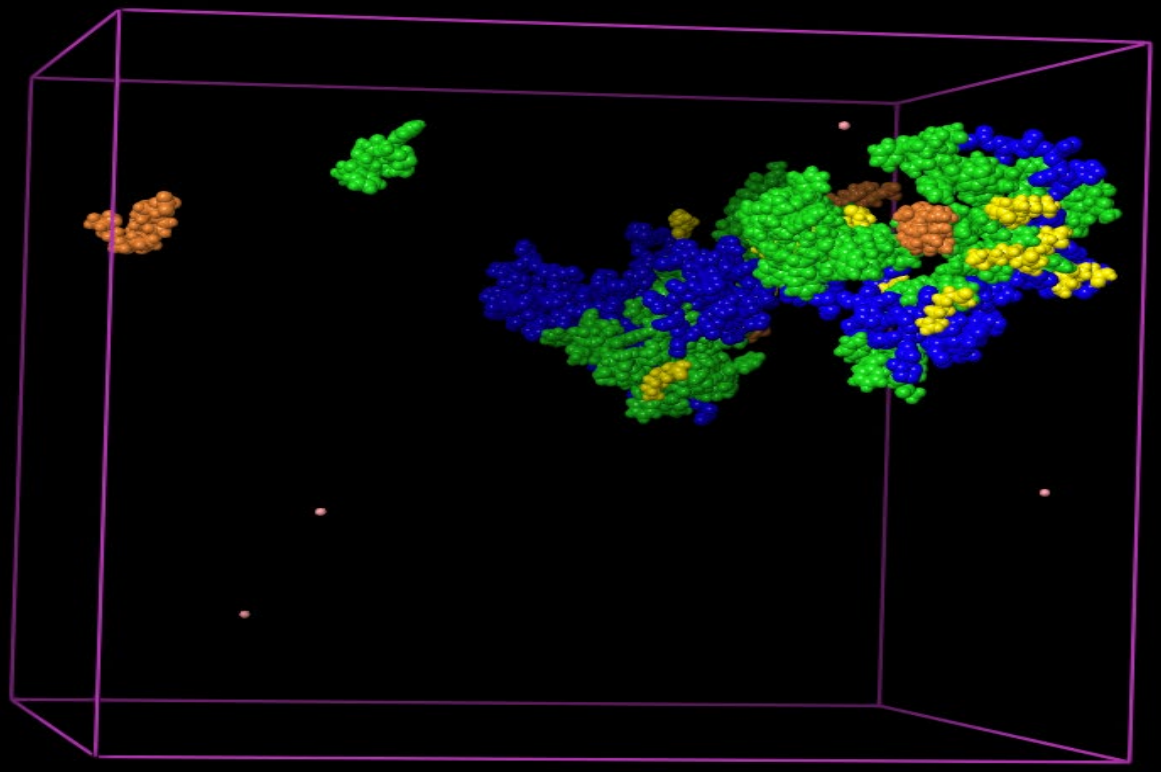
# T=40 ns

Green = Drug
Blue = PVP
Red = PEG
Yellow = FA
Brown = CHO
Cyan=EtOH



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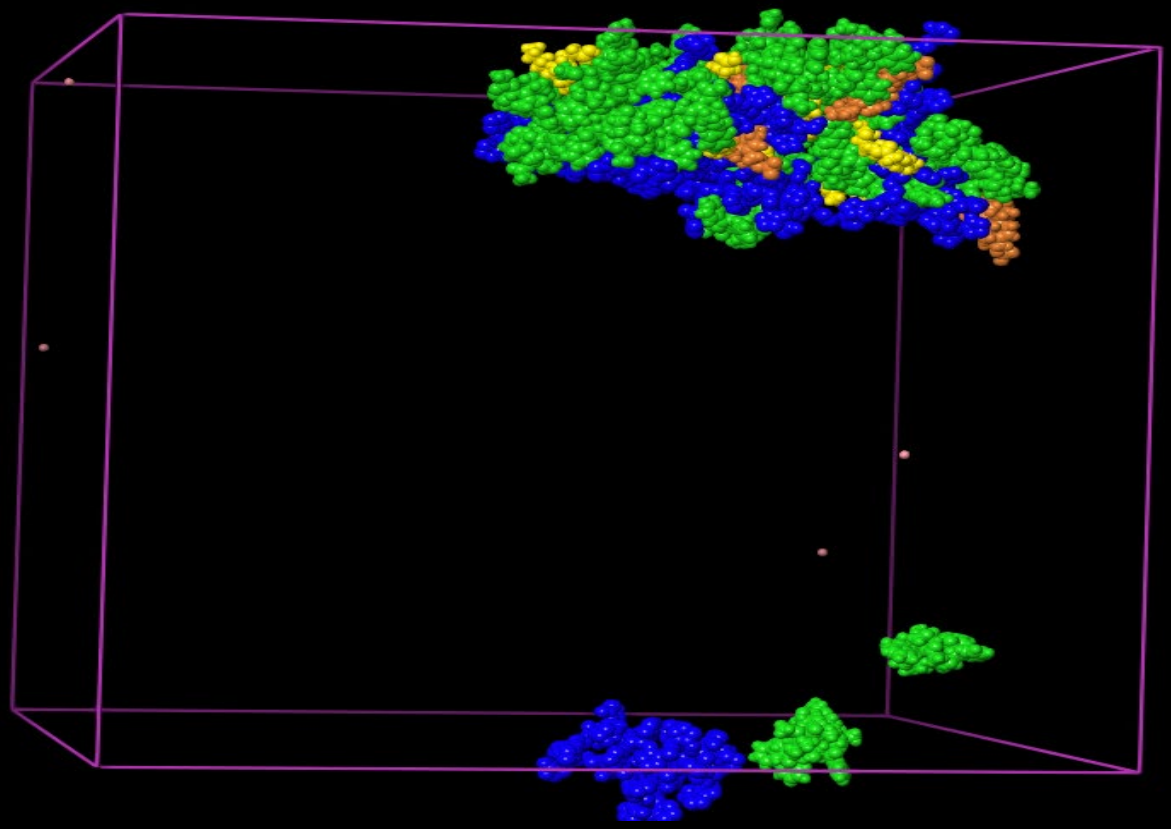
# T=60 ns

Green = Drug
Blue = PVP
Red = PEG
Yellow = FA
Brown = CHO
Cyan=EtOH



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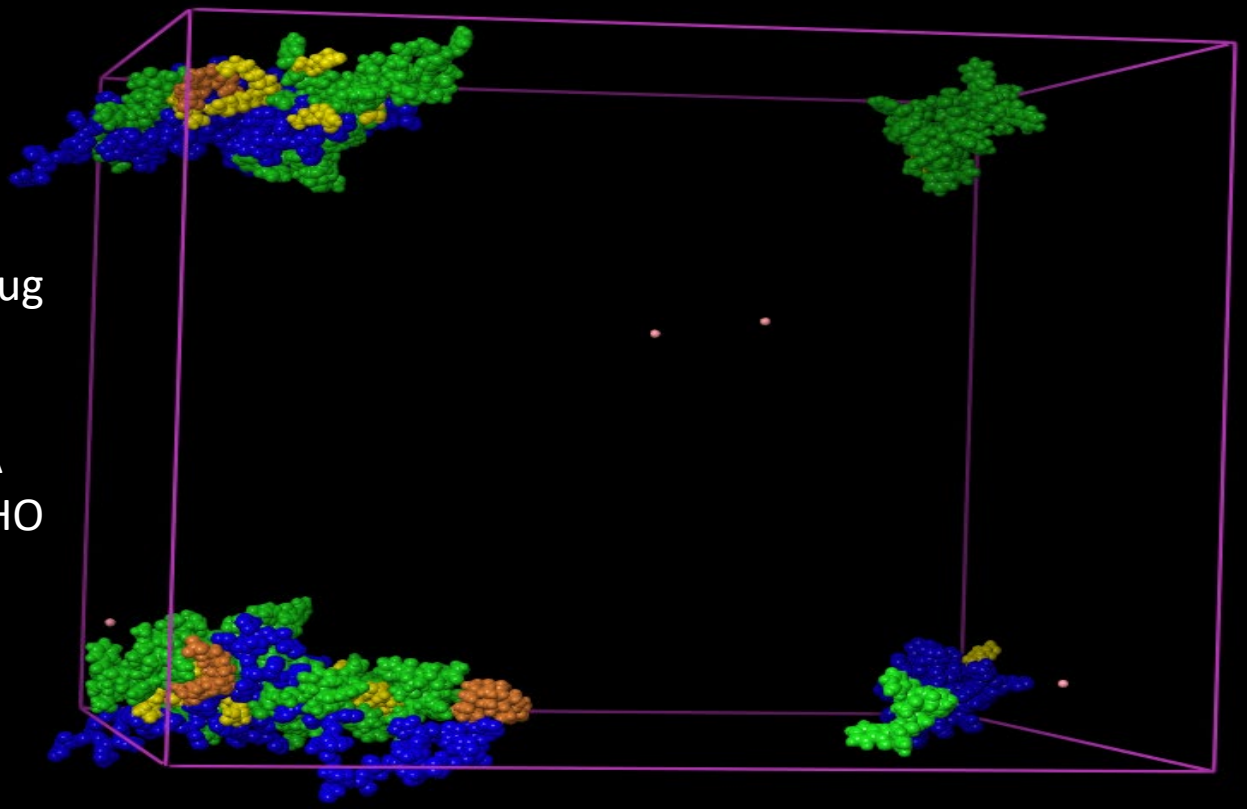
# T=80 ns



Green = Drug
Blue = PVP
Red = PEG
Yellow = FA
Brown = CHO
Cyan=EtOH

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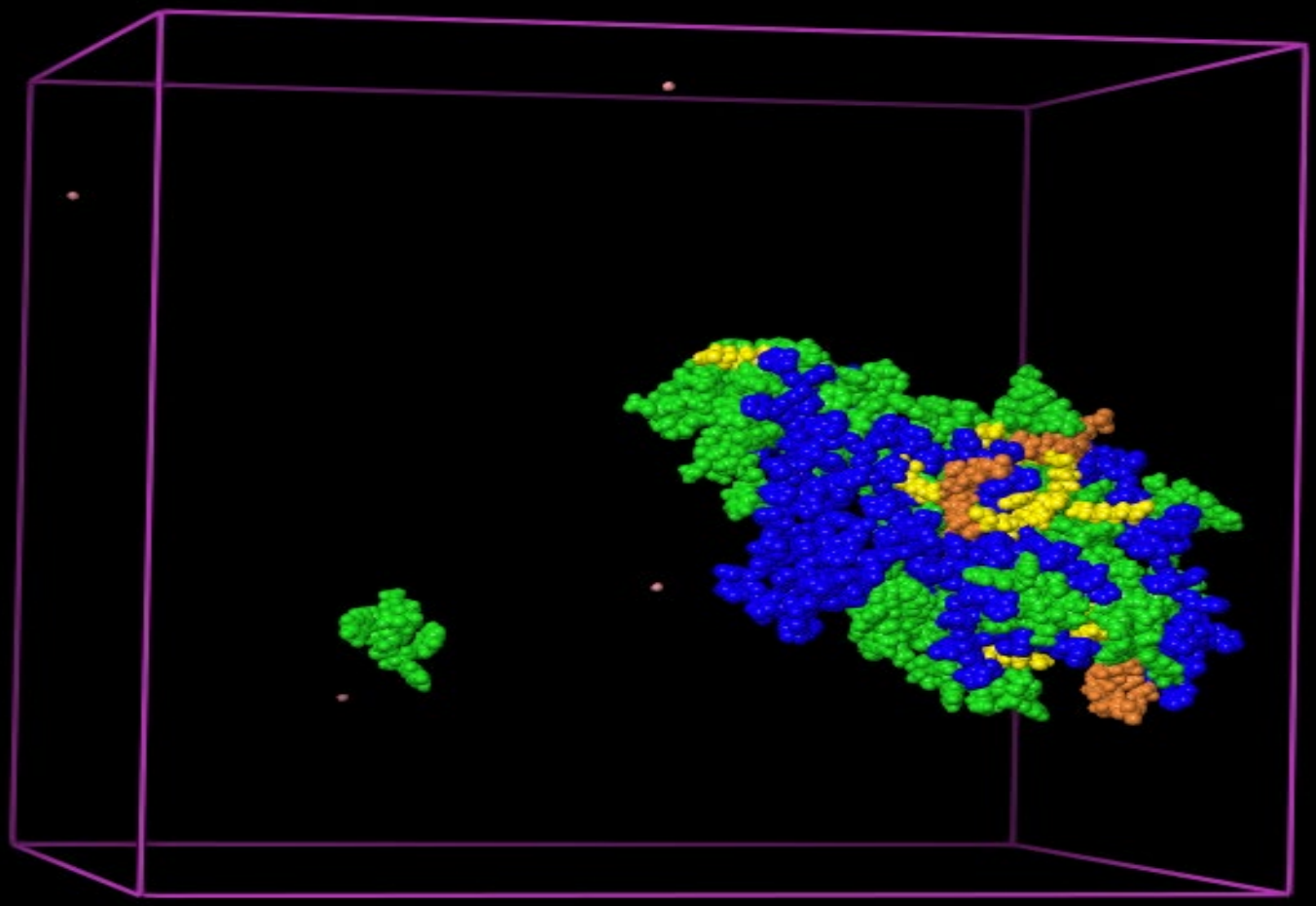
# T=100 ns

Green = Drug
Blue = PVP
Red = PEG
Yellow = FA
Brown = CHO
Cyan=EtOH



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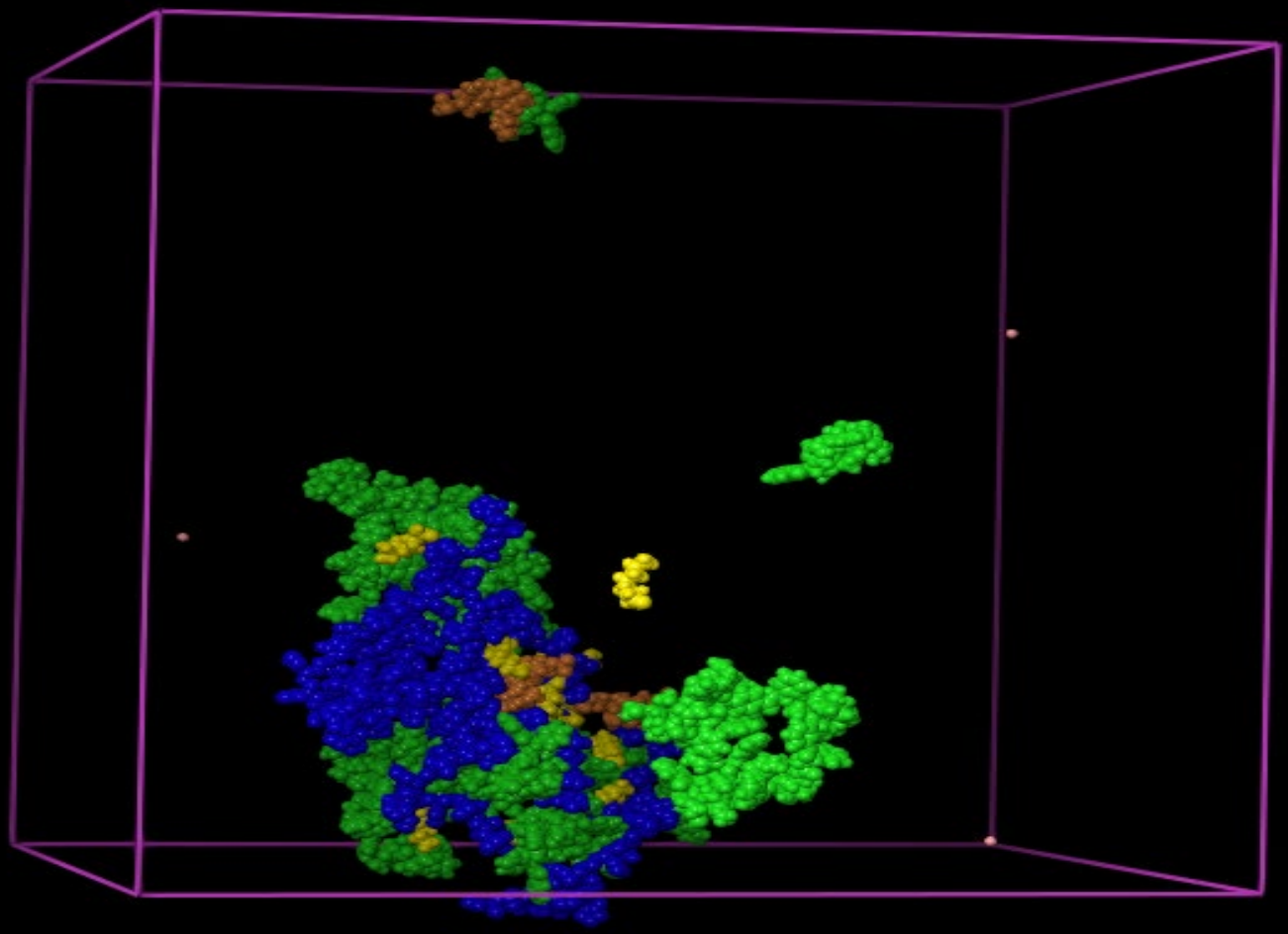
# T=120 ns

Green = Drug
Blue = PVP
Red = PEG
Yellow = FA
Brown = CHO
Cyan=EtOH



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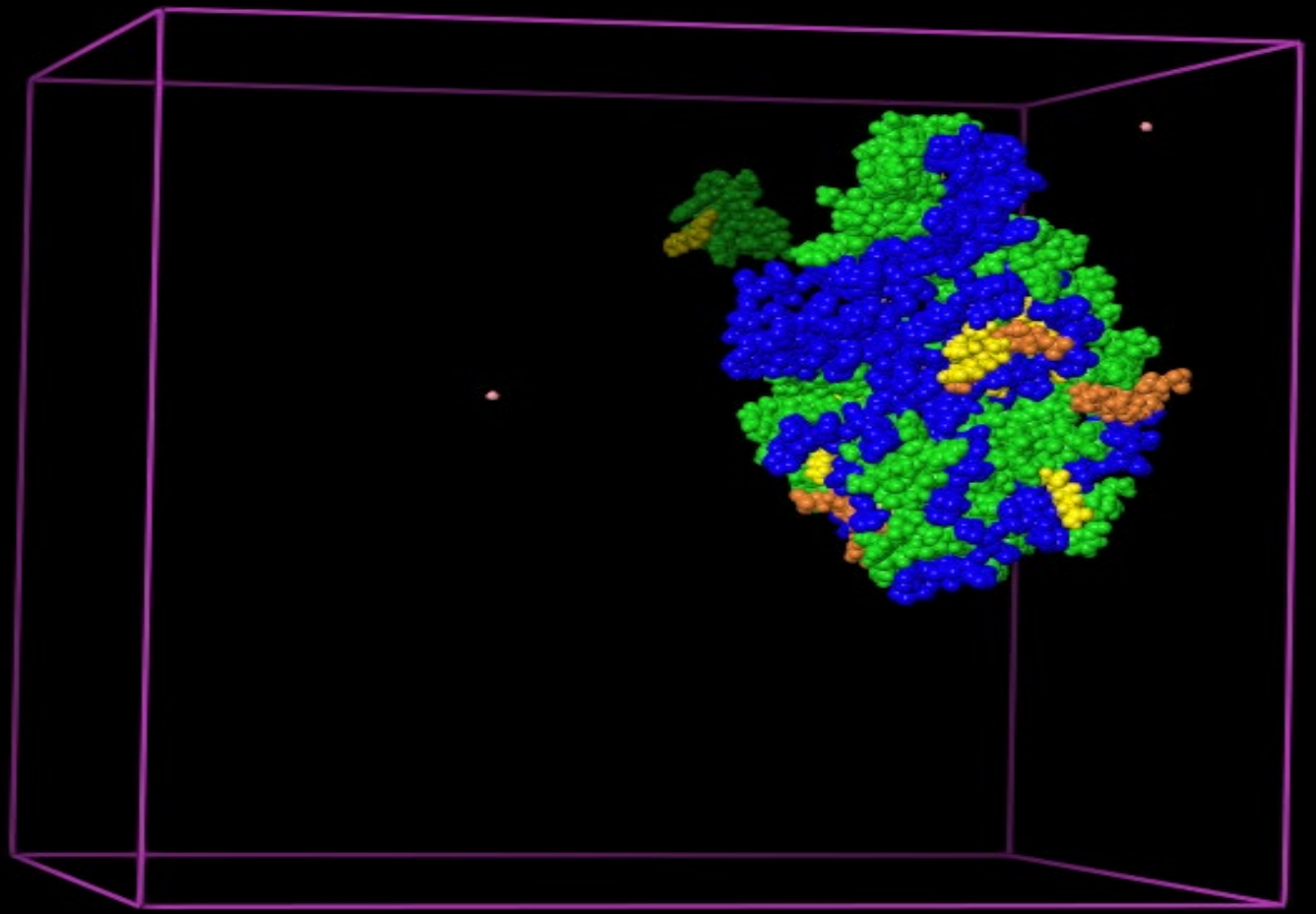
# T=140 ns

Green = Drug
Blue = PVP
Red = PEG
Yellow = FA
Brown = CHO
Cyan=EtOH



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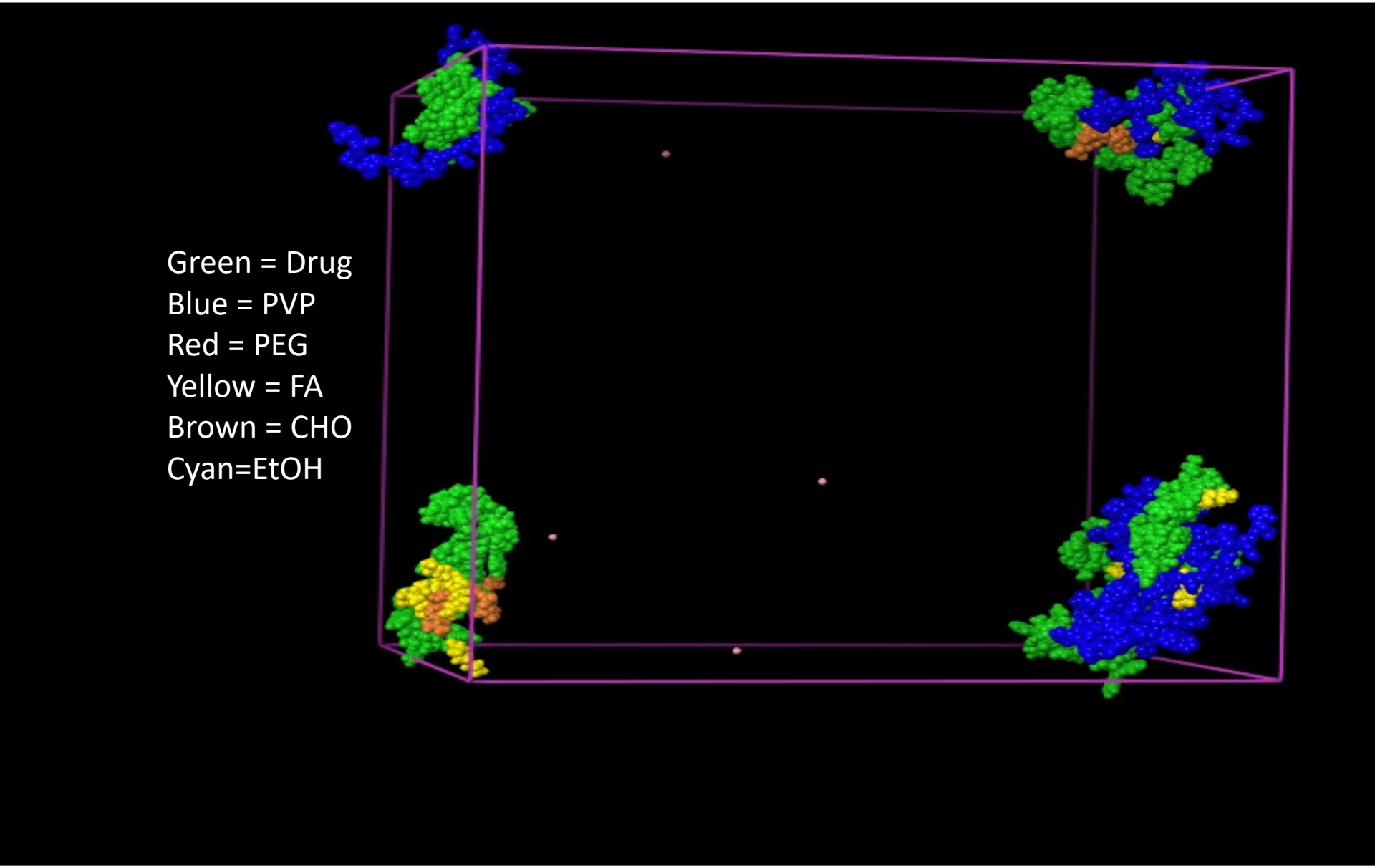
# T=160 ns

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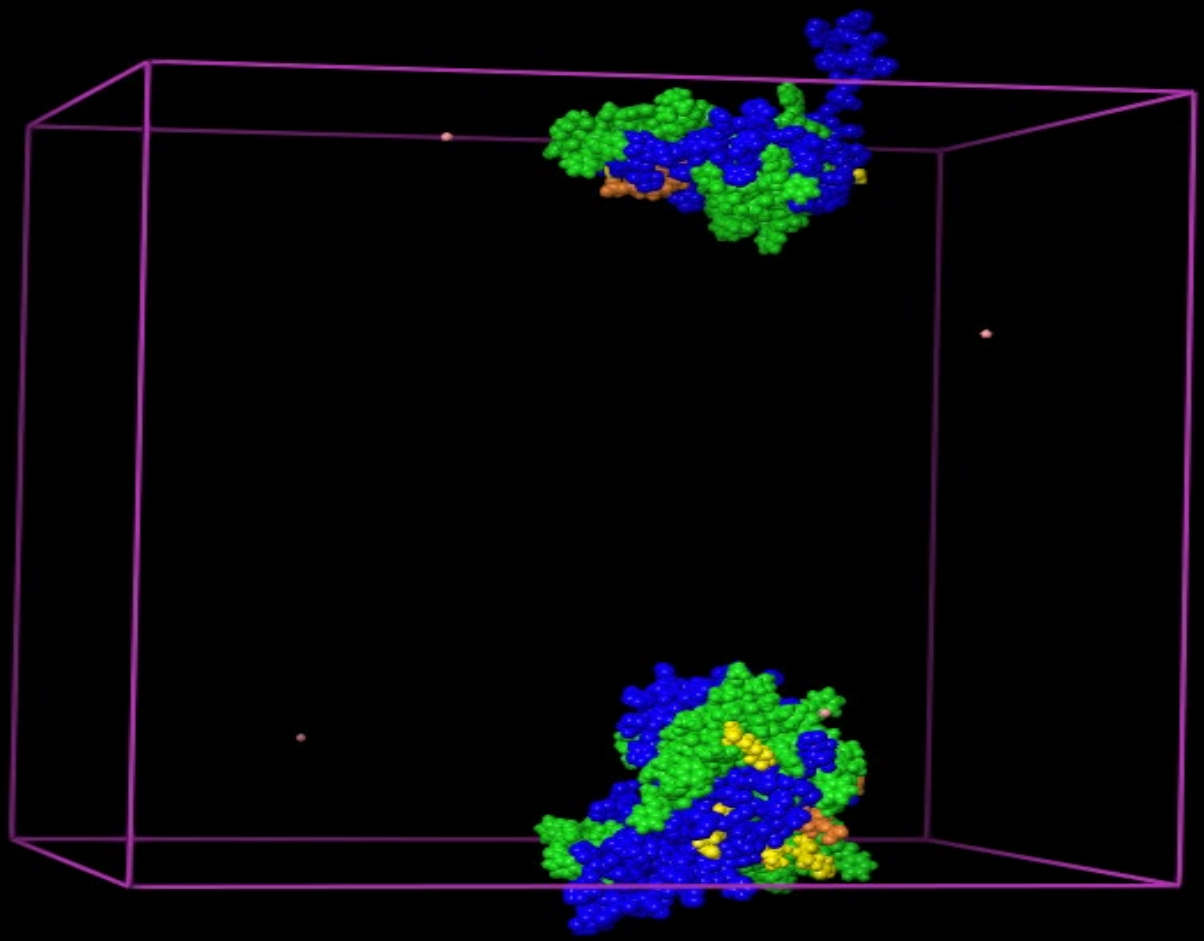
# T=180 ns

Green = Drug
Blue = PVP
Red = PEG
Yellow = FA
Brown = CHO
Cyan=EtOH



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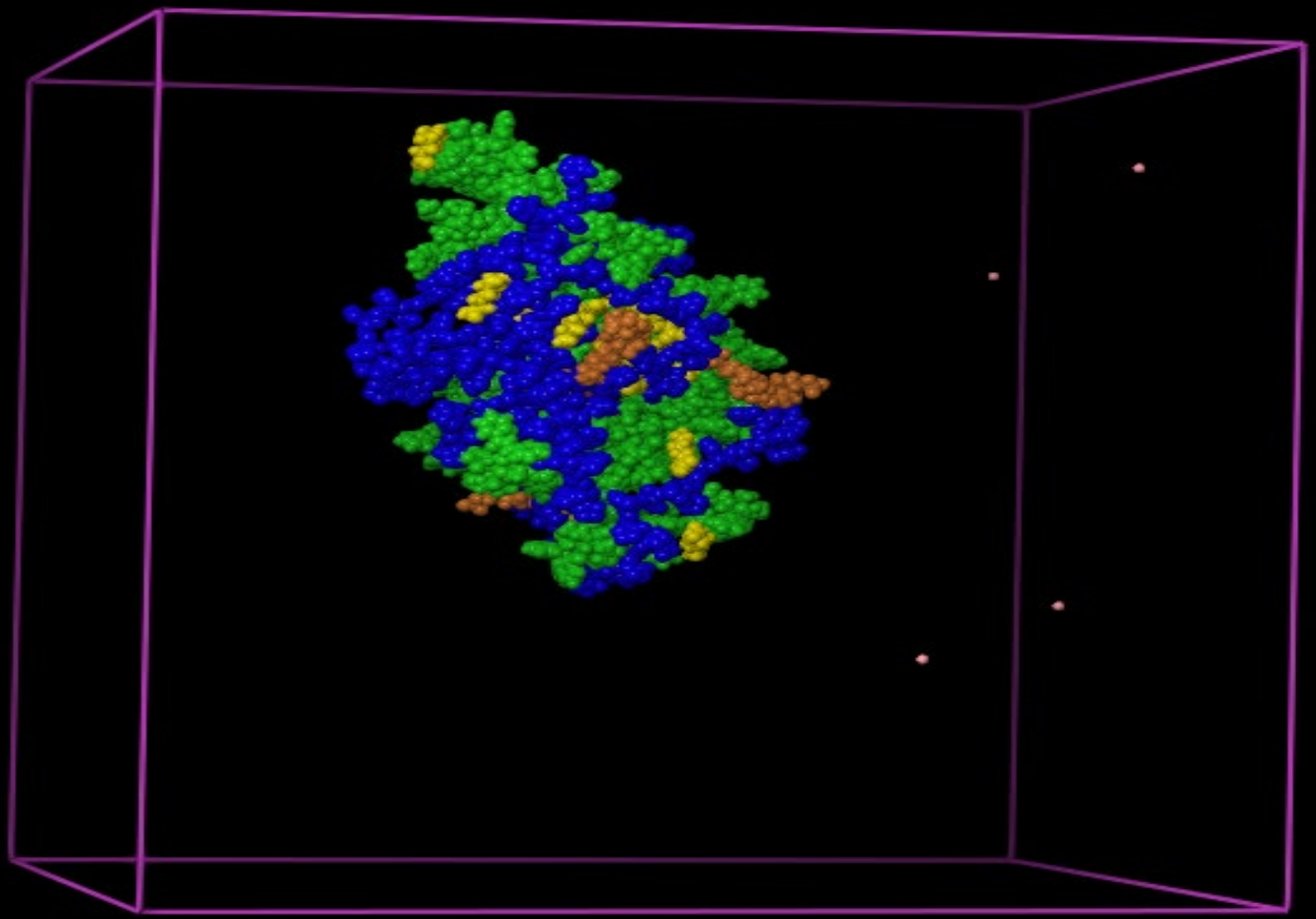
# T=200 ns

Green = Drug
Blue = PVP
Red = PEG
Yellow = FA
Brown = CHO
Cyan=EtOH



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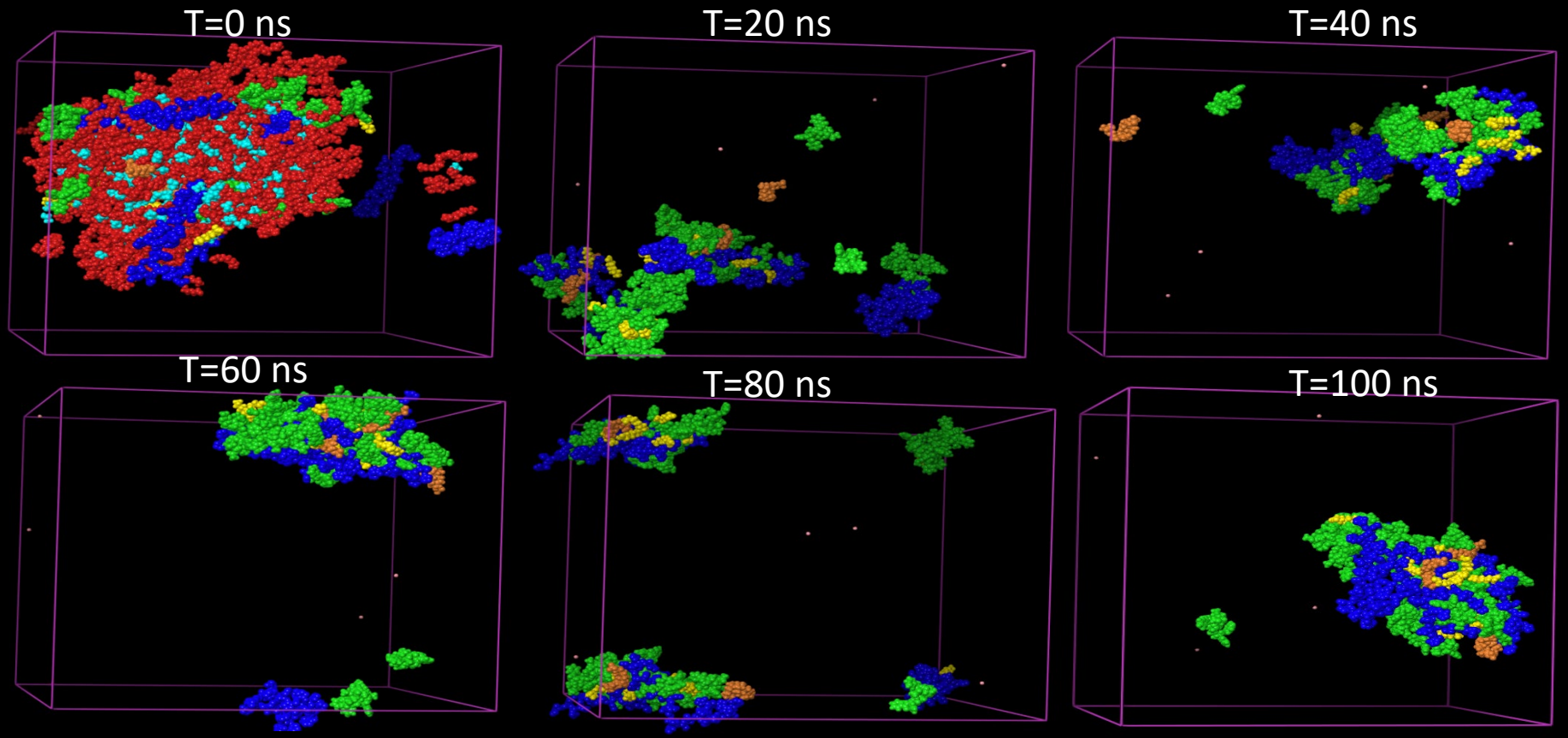
# Nanoparticle simulation snapshots…

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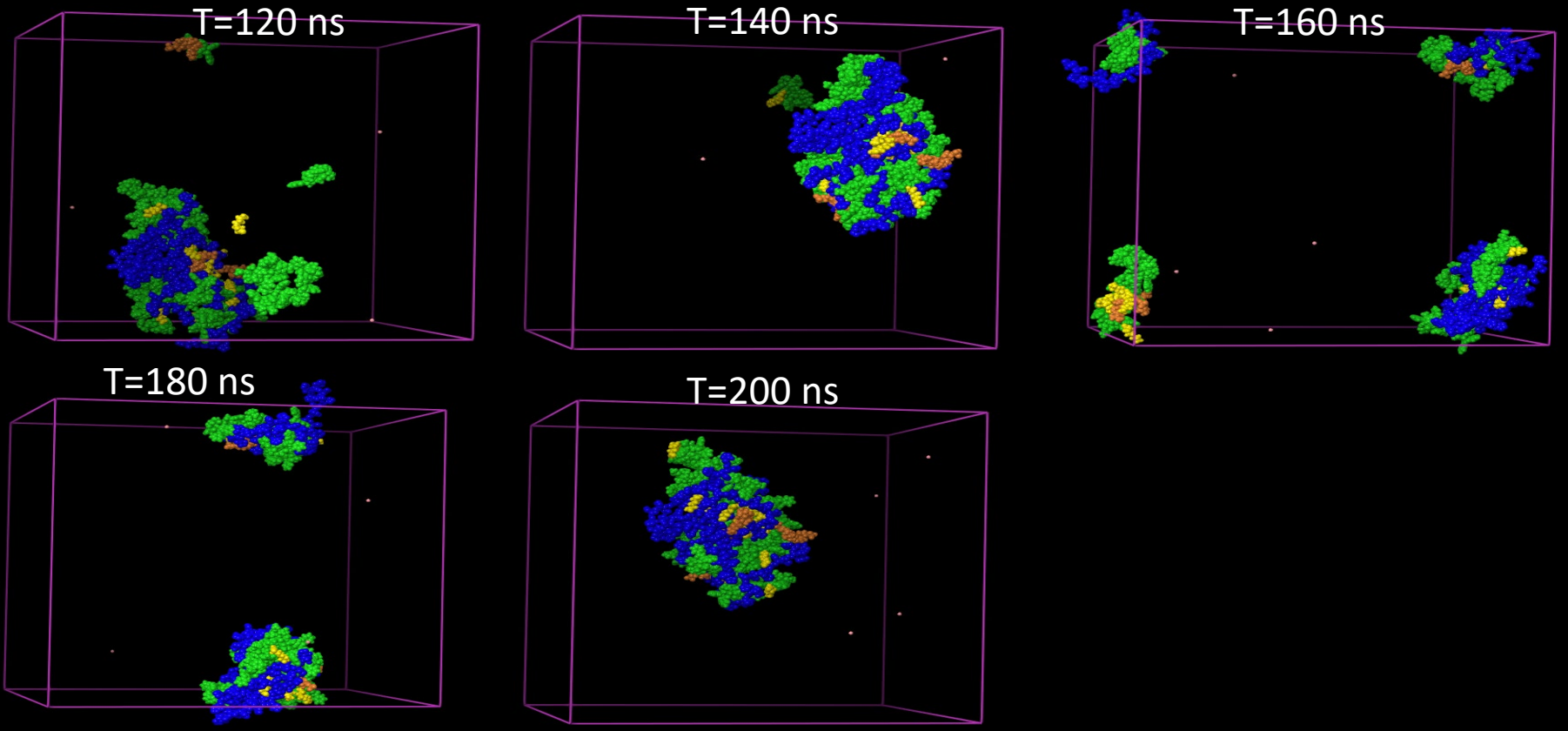
# Nanoparticle simulation snapshots…

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# Analysis…

H-bond analysis

RMSD

Potential energy

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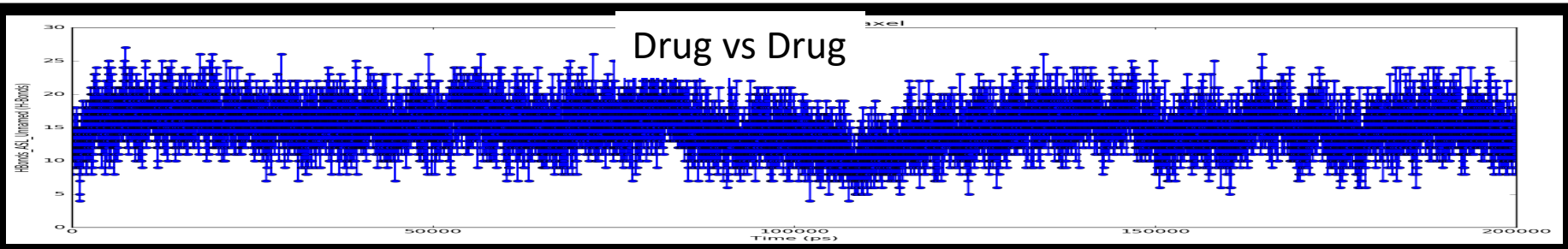
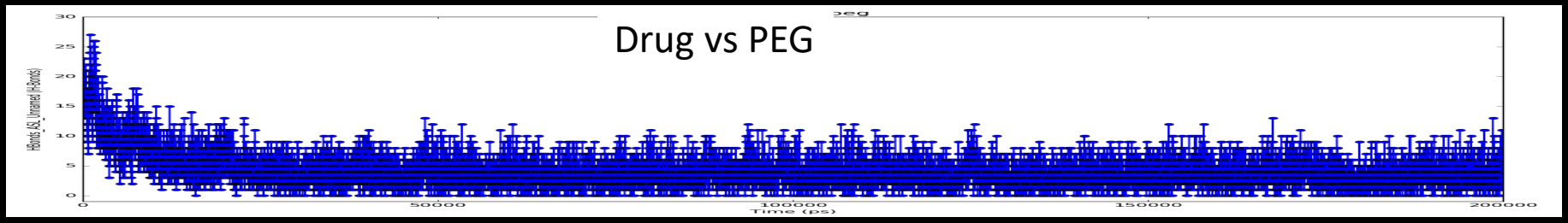
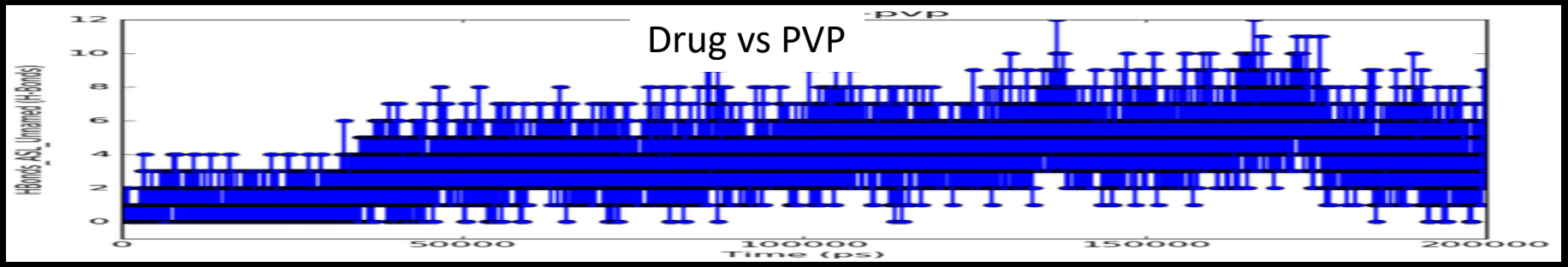
# H-bond analysis

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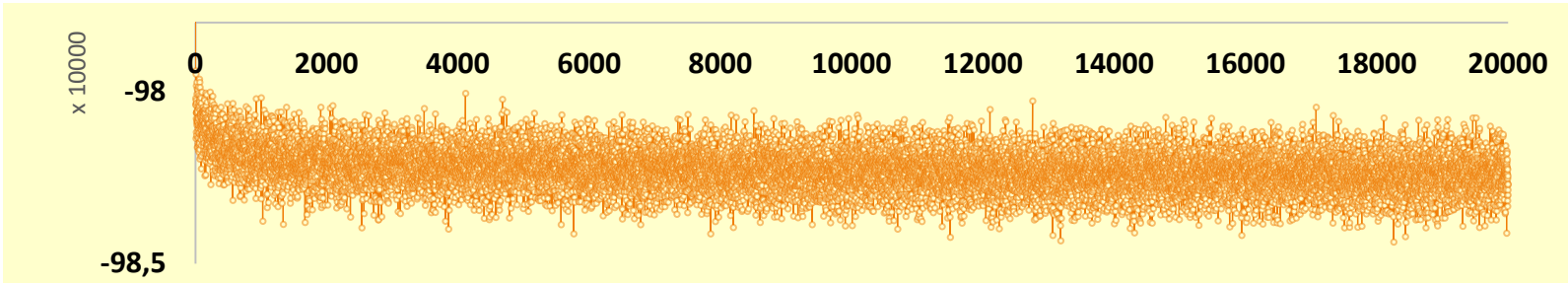
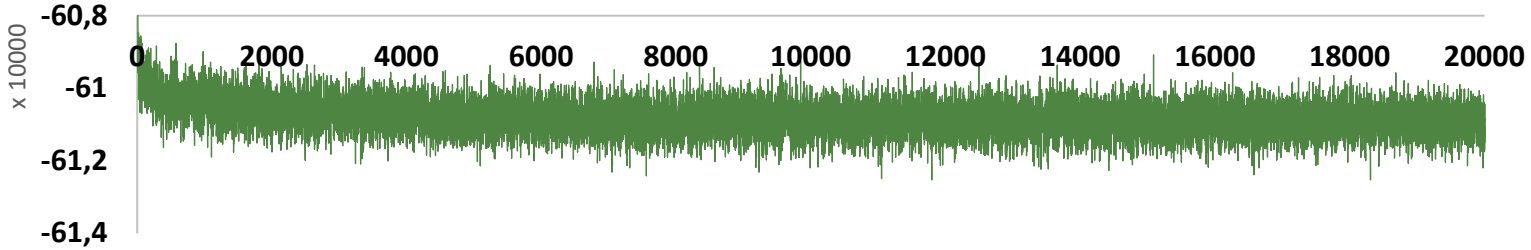
# Potential Energy vs Time



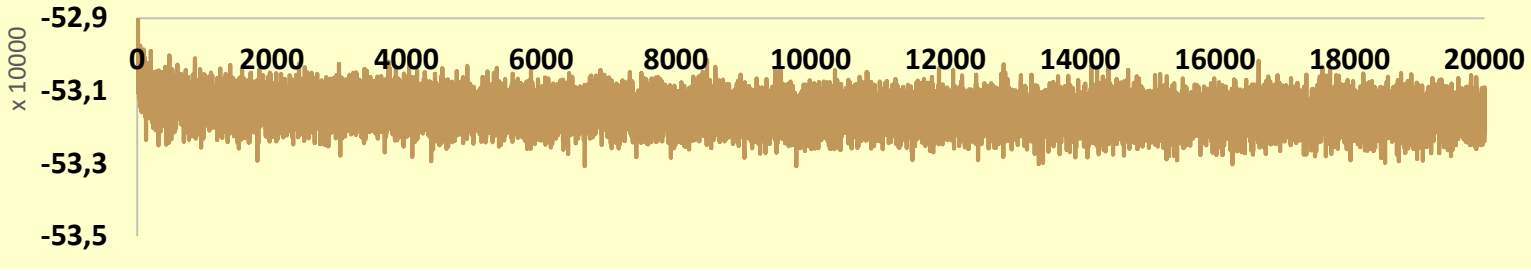

Avg. PE: -98 x$10^4$
**ΔPE** -10018

Full system




Avg. PE: -61 x$10^4$
**ΔPE** -8222

System -PVP




Avg. PE: -53 x$10^4$
**ΔPE**-3979

System -PEG

Run Time: **200ns** Ensemble: **NPT** **Energies: Kcal/mol**

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# Other systems studied…

| System | Drug | NoPVP | NoPEG | NoFA | NoCHO |
|---|---|---|---|---|---|
| Average_Drug-Drug | 15.14 | 31.28 | 32.80 | 23.57 | 29.58 |
| Average_Drug-PVP | 3.45 | - | 7.93 | 9.24 | 8.18 |
| Average_Drug-PEG | 4.04 | 15.23 | - | 16.10 | 14.91 |
| Average_Drug-FA | 0.48 | 4.28 | 5.84 | - | 2.85 |
| Average_Drug-CHO | 0.053 | 0.75 | 1.36 | 0.086 | - |

Removal of PVP, PEG, FA and CHO increases Drug-Drug H-bonds

Role of PEG seems increasing as soon as any of the excipients are removed – which means that in the absence of any of the components Drug can still form aggregates in the presence of PEG

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# Summary

- Composition is as per the experimental stoichiometry
- Simulation carried for 200 ns – parameters studies are stable
- Studies conducted also without PVP, PEG, CHO, FA. PVP and PEG has a larger role in NP stabilization in comparison with CHO and FA
- Length of the nanoparticle ~10nm (exclusion – PEG, water, EtOH)
- Width is ~7nm
- This study can help us understand the role of each excipient in such formulations and help in optimizing formulations
- Computational optimization can be leveraged for difficult to formulate drugs

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# Acknowledgments

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Head Drug Discovery

Dr. Ajay Khopade
VP, FDD

My colleagues

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And

Sun Pharma Advanced Research Company Limited
Vadodara, Gujarat, India

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# Thank You

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