



Schrödinger

Molecular modeling and machine learning for drug formulation

John Shelley, Fellow

David Nicholson, Principal Scientist

July 15, 2025



Agenda

- Introducing Schrödinger
- Nature and value of modeling
- Modeling and simulation for drug formulation
 - Modeling the formation, structure and behavior of mRNA-containing lipid nanoparticles
 - Excipient/polymer selection for small-molecule drug formulation including amorphous solid dispersions
- Customer stories
- How to work with Schrödinger

Introducing Schrödinger

MISSION

To improve human health
and quality of life by
transforming the way **new**
medicines and **materials** are
discovered through advanced
computational methods

Our unique commitment to scientific innovation, software development, and support



30+ years of innovation in molecular modeling scientific research and product development



Over 800 employees worldwide; >40% Ph.D.



More than 50% of the company dedicated to research and development

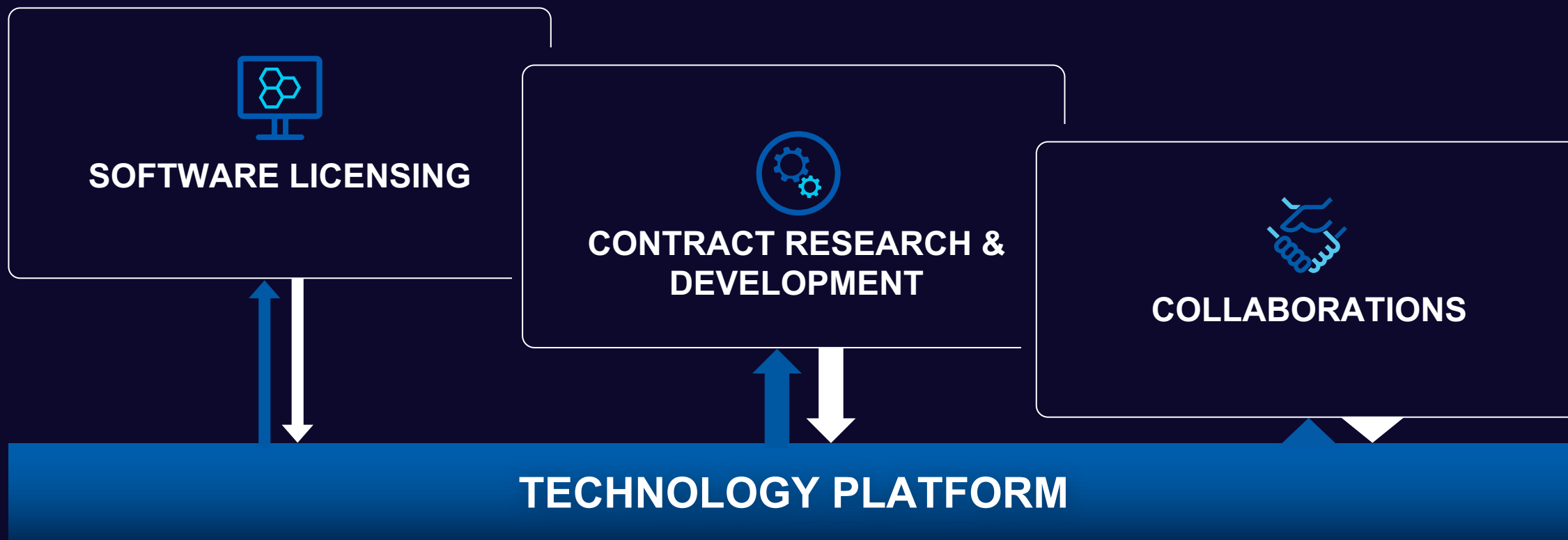


Large scientific support & education teams offer expertise and support in knowledge-transfer



Quarterly software releases with performance and feature improvements

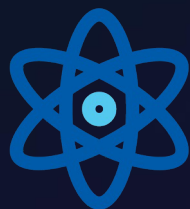
Engagement models



Highly successful collaborations and transfer of know-how improve the applicability of the software platform

Nature and Value of Modeling

Digital chemistry strategy built on three pillars



**Physics-based
modeling**

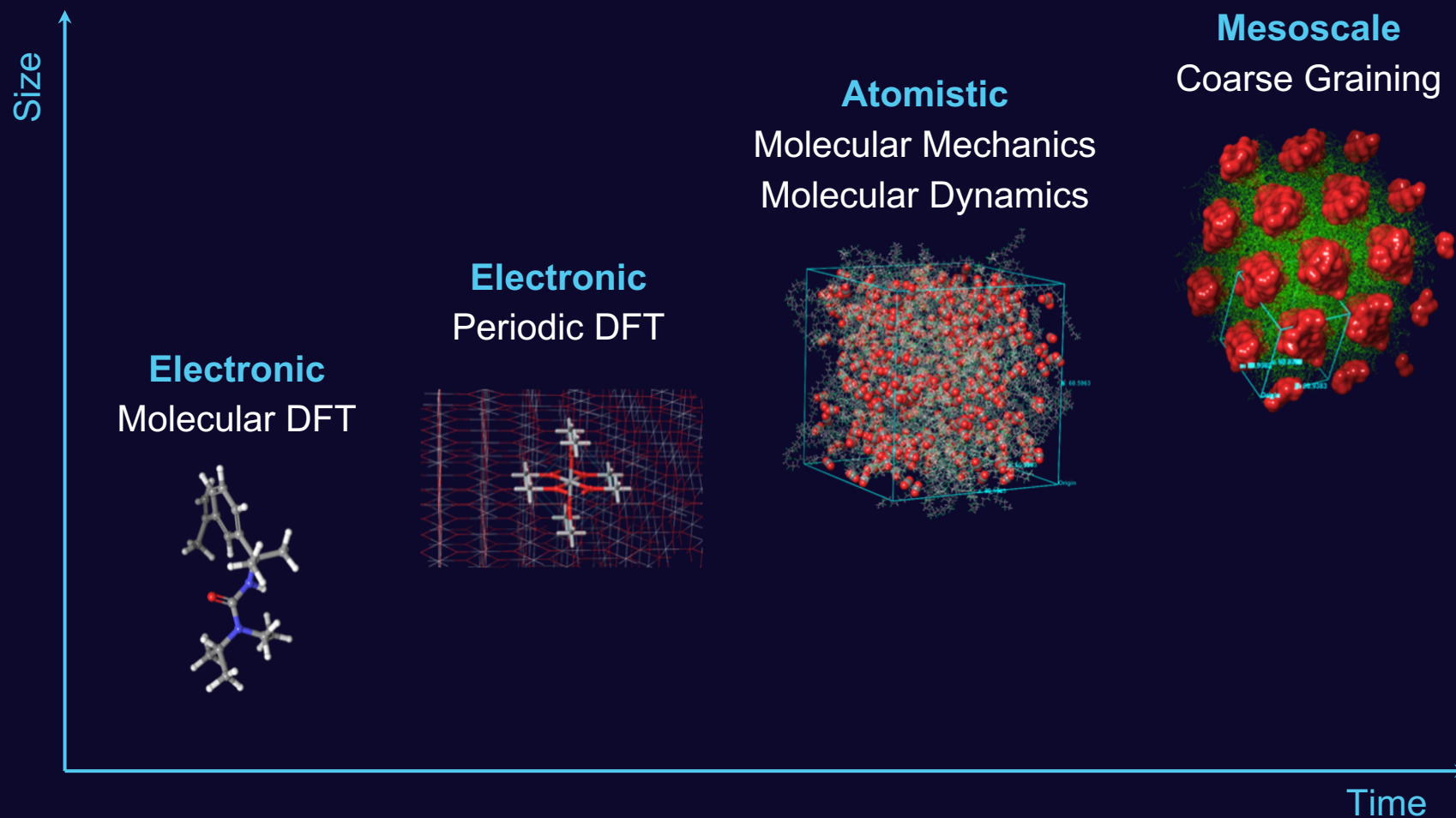


**Machine
learning**



**Collaborative
informatics**

Simulate: access all methods in a single platform



Amplified by



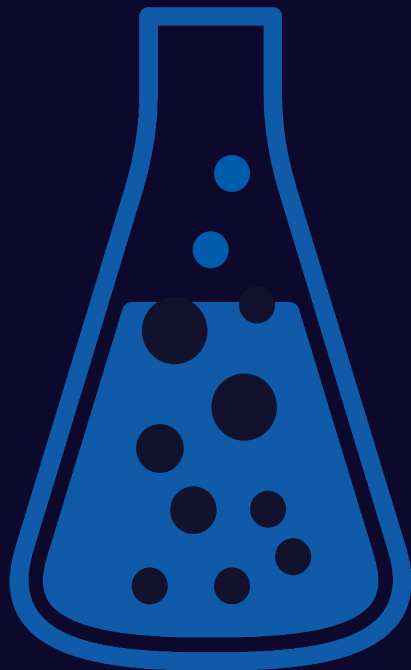
Machine
Learning



Enumeration /
Library generation

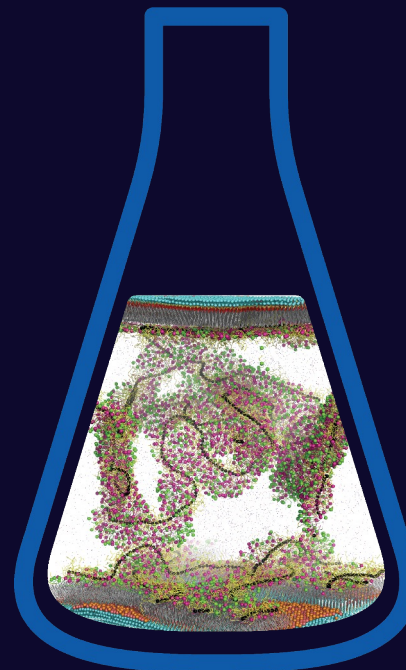
Increased understanding

Traditional R&D



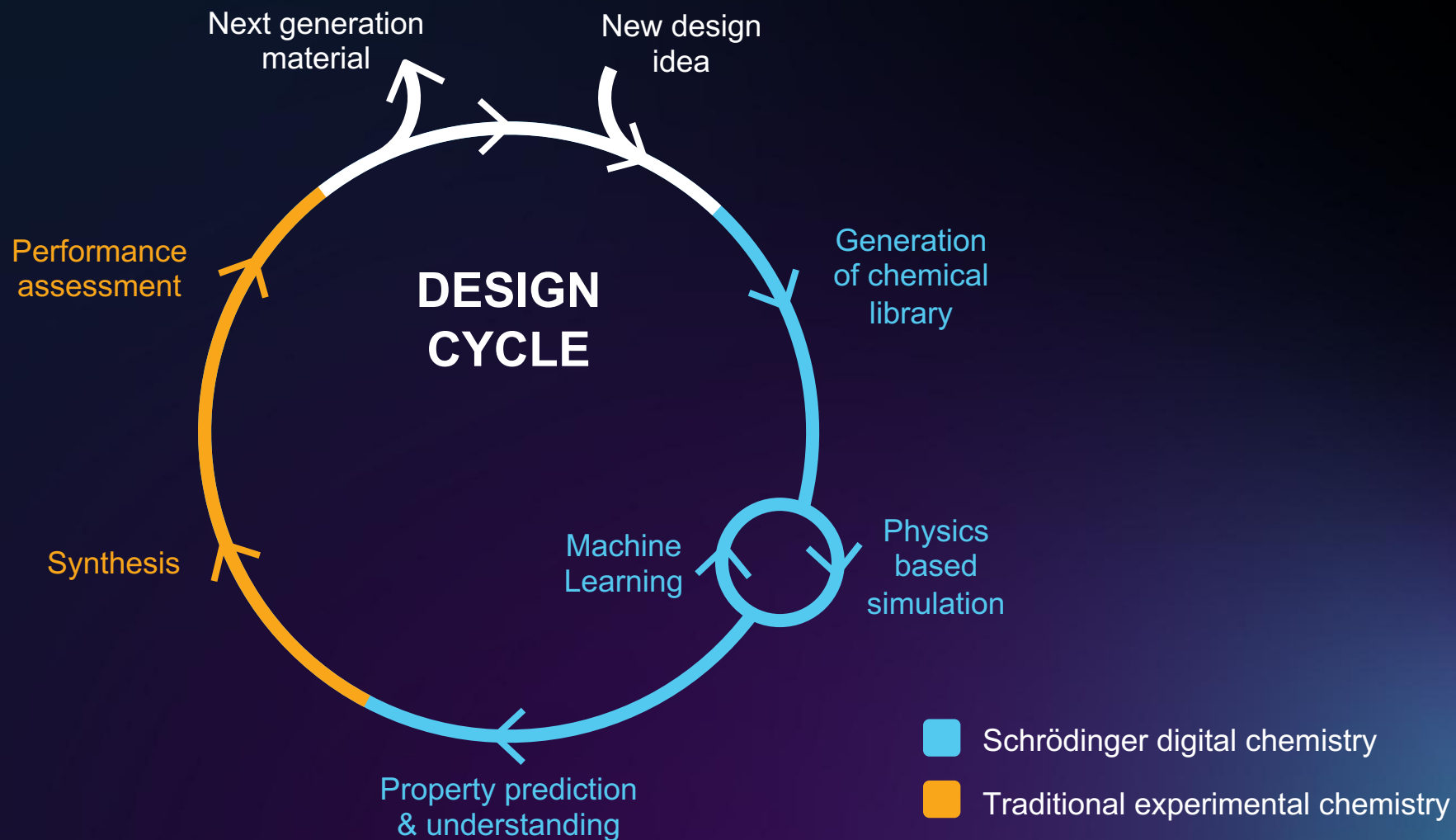
Large-scale systematic testing

Incorporating Computation

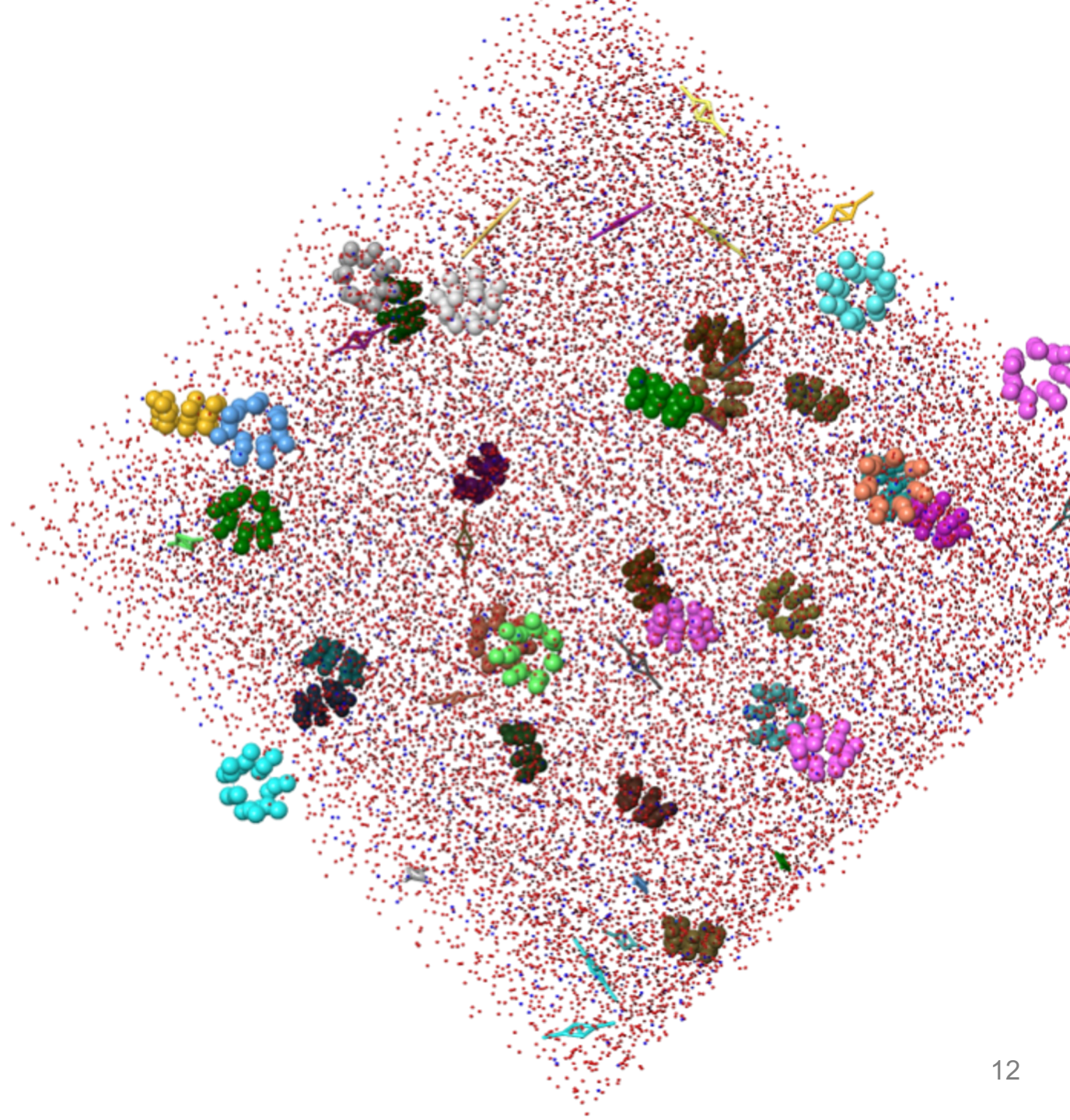


Simulation reveals molecular-level resolution, linking structure to function

Accelerate your design cycle



Pharmaceutical Formulation & Delivery



Capabilities for drug characterization and formulation

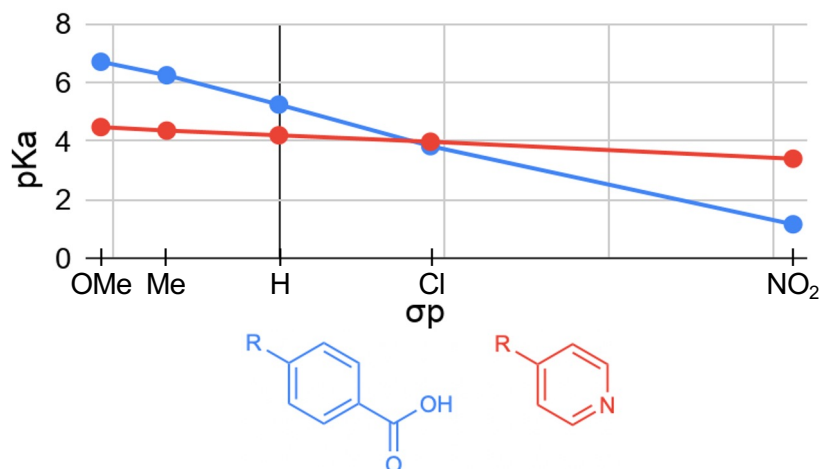
Application	Capabilities
Characterization	pK_a , powder X-ray diffraction (XRPD), crystal morphology, density of crystalline or amorphous phases
Catalysis, Reactivity, Degradation	QM multistage workflow, bond dissociation energy, nanoreactor (API degradation), AutoTS (transition state searching), reaction channel enumeration, Auto Reaction Workflow (catalyst design), conformational search
Spectroscopy	VCD, solution-state NMR, solid-state NMR, IR, UV-Vis
Crystal Structure Prediction	Crystal structure prediction
Formulation and Delivery	Creating machine learning models for formulations, system builders (mixtures, polymers, surfactants, lipids, etc.), aqueous and solvent solubility of amorphous/crystalline API, API aggregation, glass transition temperature, mechanical properties, wettability (contact angle), separation during solvent removal (evaporation), API encapsulation in cyclodextrin, etc., excipient selection and ASD formulation, API solubility and LogP in excipient, solubility parameters, API — excipient mixing enthalpy, ASD separation and dissolution, protein/biologics excipients selection, hygroscopicity (moisture sorption) in amorphous solid dispersions, APIs, tablet coatings, solution viscosity, protein/polymer interactions, lipid nanoparticles, liposomes

Characterization

pK_a prediction technologies at Schrödinger

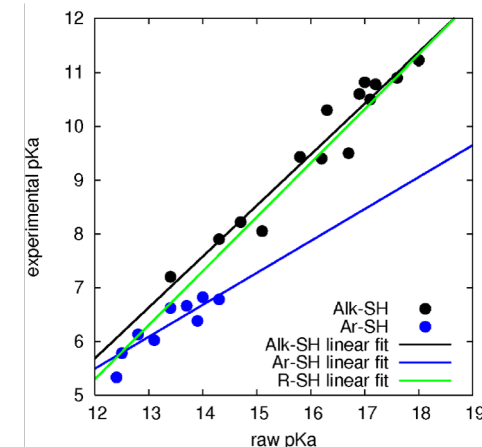
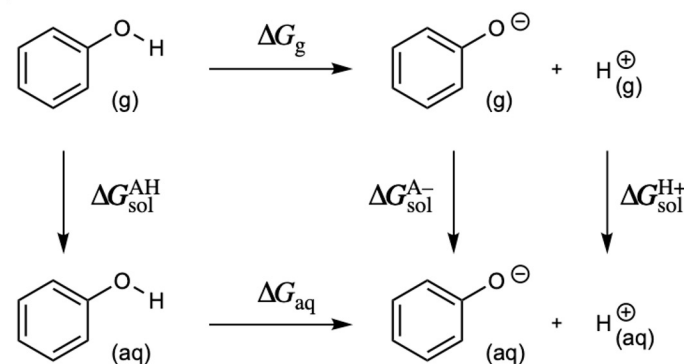
Epik (Classic)

Tech: Empirical linear free energy relationships



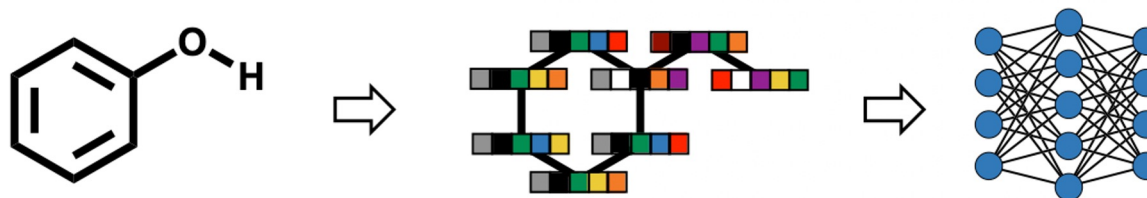
Jaguar pK_a

Tech: DFT thermodynamic cycle + conformational search + empirical corrections

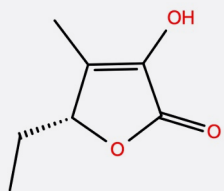


Epik 7

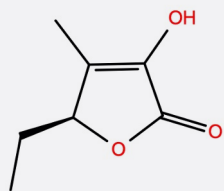
Tech: Atomic graph convolutional neural network (AGCNN) regression model



VCD spectroscopy for assigning stereochemistry

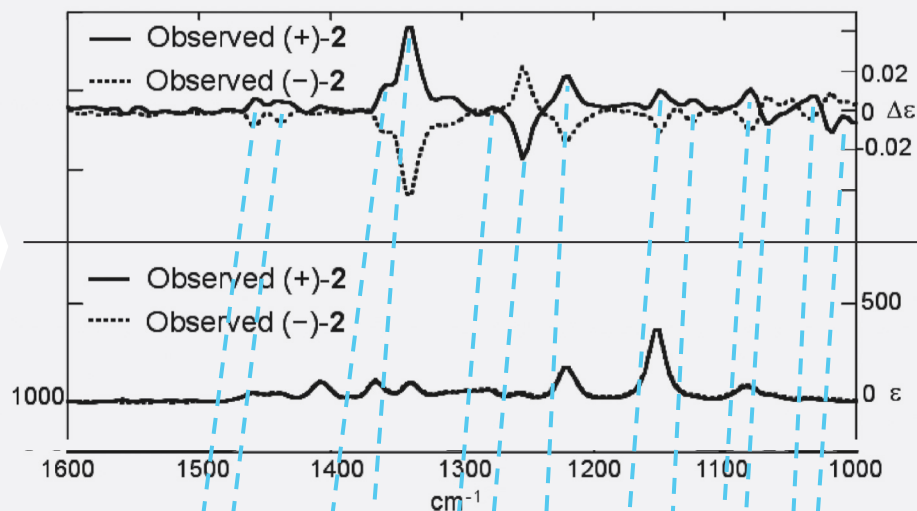


R-maple
furanone



S-maple
furanone

Which is (+) and which is (-)?

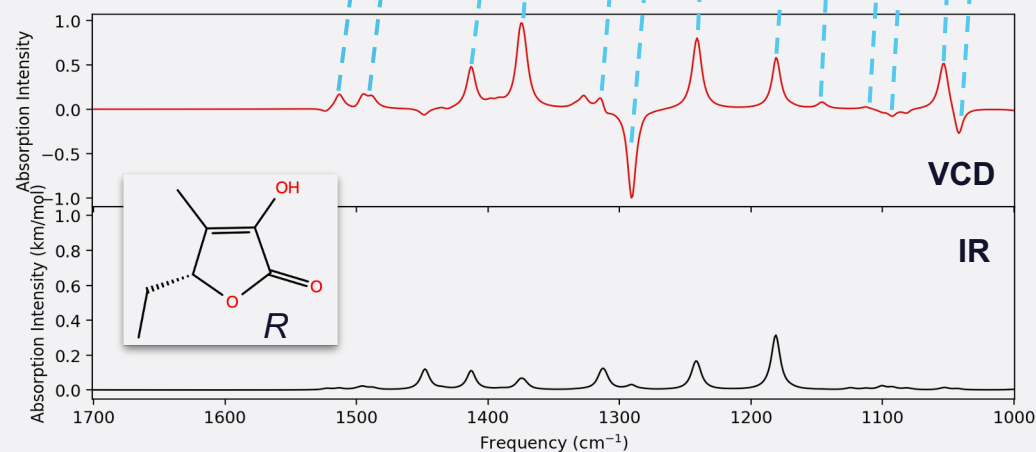


Experimental VCD spectra
of (+) and (-) maple
furanones in CCl₄

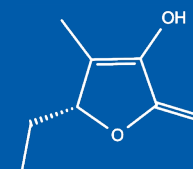
Experimental IR spectra of
enantiomers are the same, but
VCD spectra are mirror images

Jaguar Spectroscopy
Simulated VCD/IR of
the *R*-enantiomer

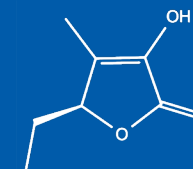
B3LYP-D3/LACVP** in CHCl₃



Assignment



R-maple
furanone
(+)

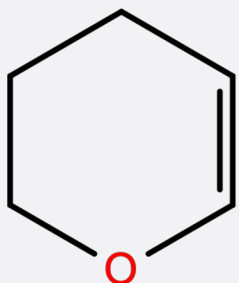


S-maple
furanone
(-)

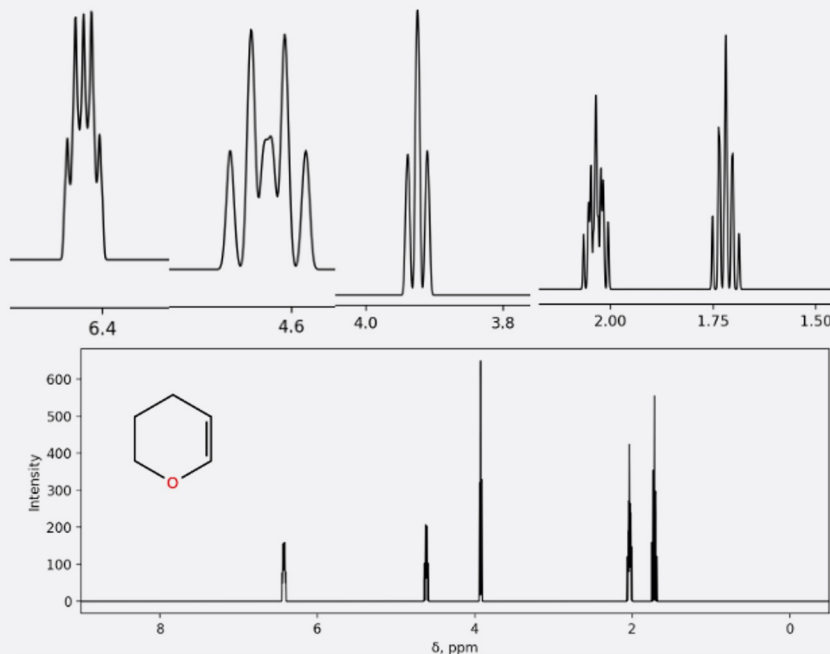
NMR calculations: spectra simulation

Simulation effectively captures fine structure of NMR signals, e.g. 3,4-dihydropyran

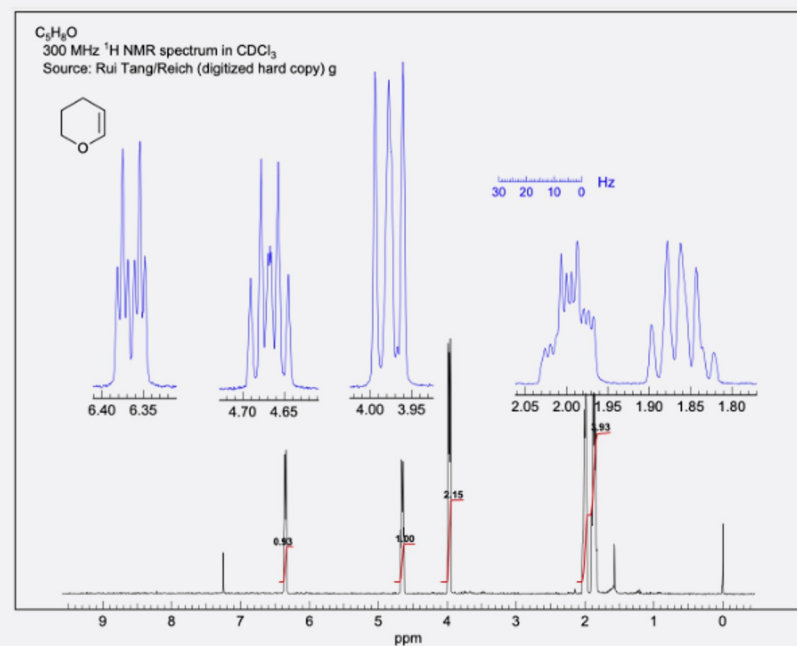
3,4-dihydropyran



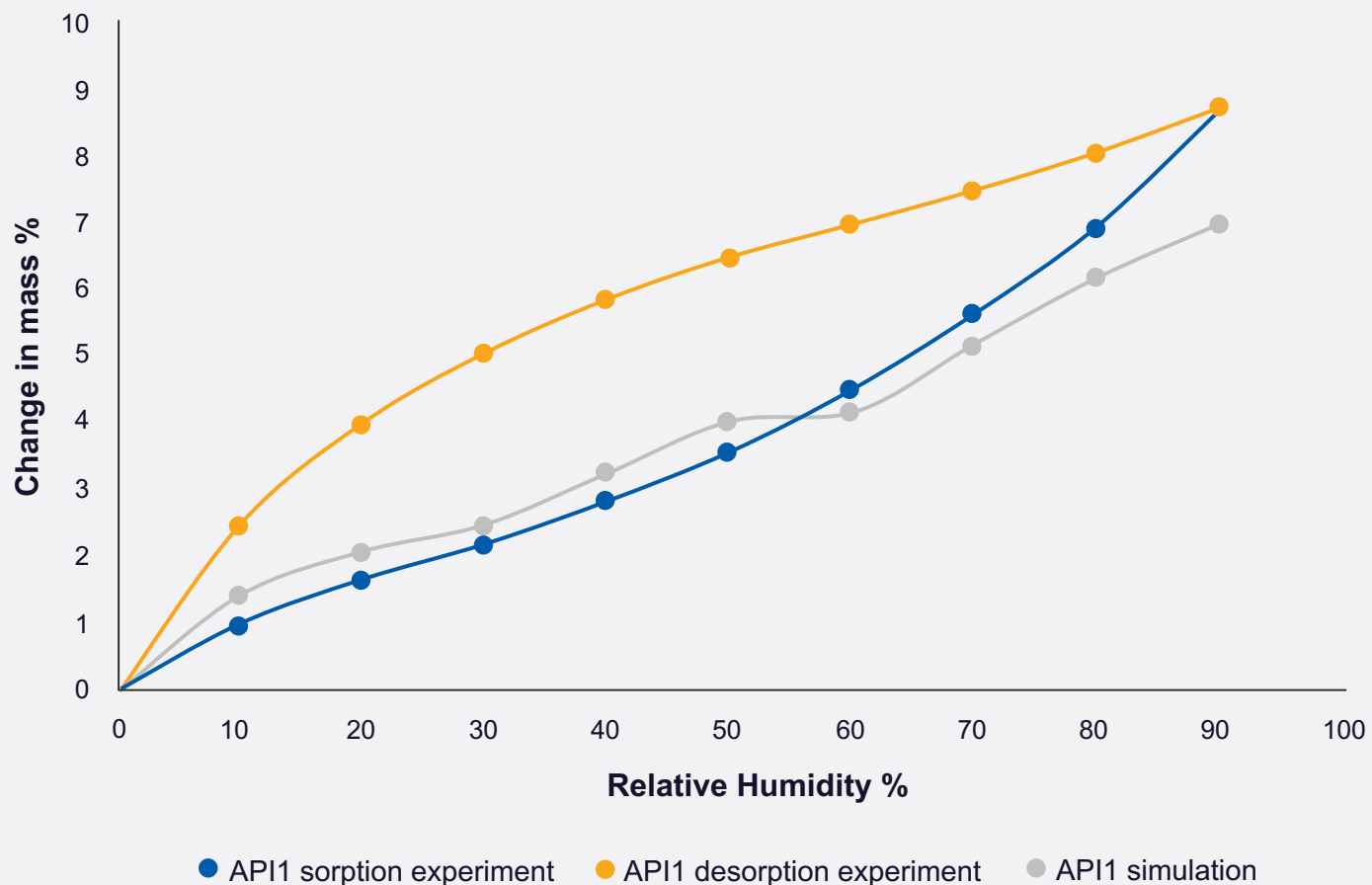
Simulation



Experiment



Hygroscopicity for an amorphous API



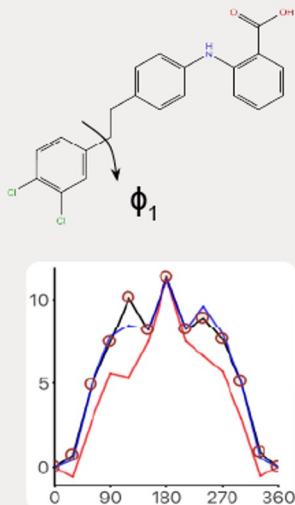
Water loading simulation agrees well with experimental sorption data across a range of relative humidity values

Crystal structure prediction (CSP) workflow

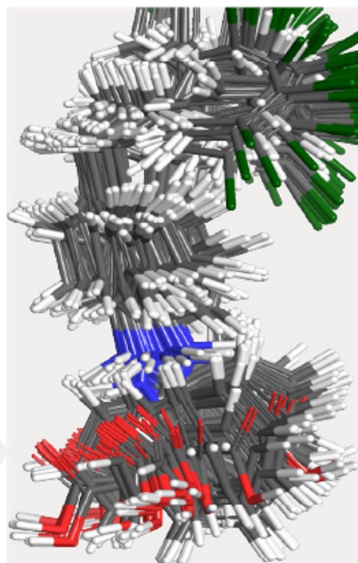
CAPABILITY



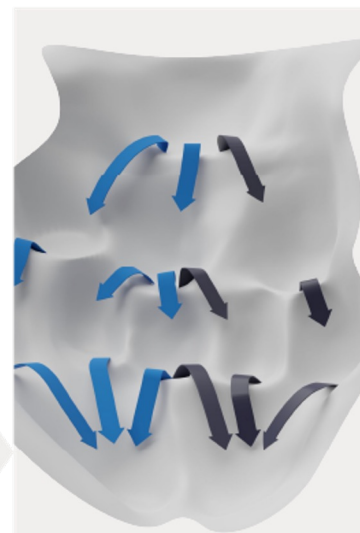
Required input:
2D structure



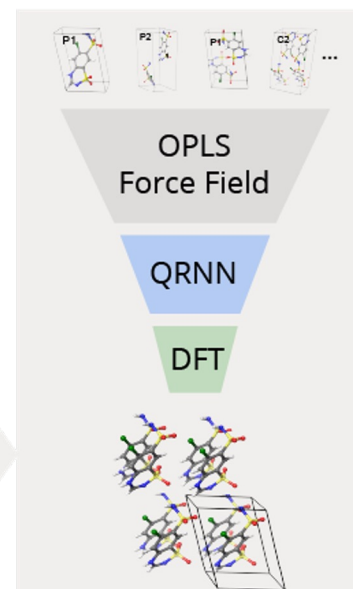
Torsion Space
Exploration
with OPLS4



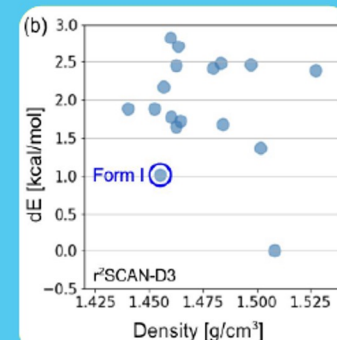
Extensive
Conformer
Generation



Systematic
Packing
Search



Hierarchical
Energy
Ranking

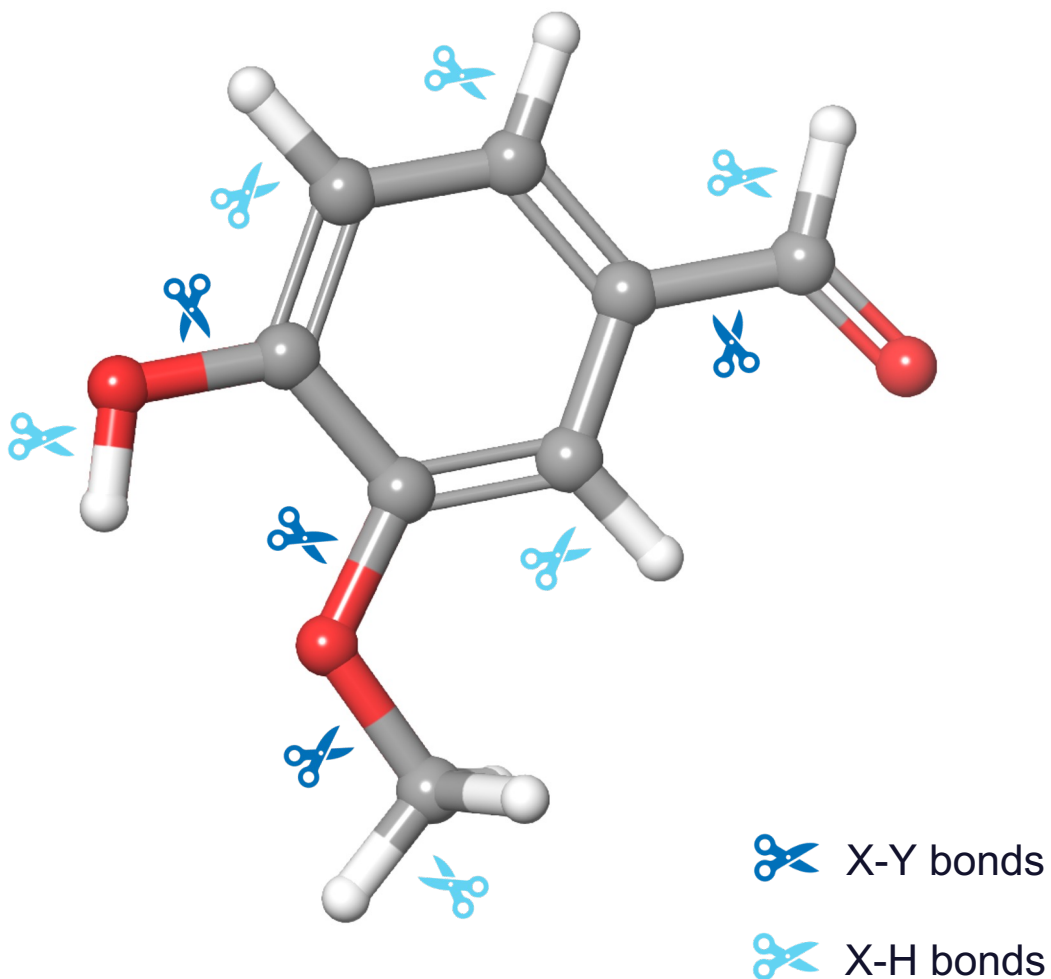


Deliverable:
CSP landscape
at 0K and RT

Catalysis, Reactivity, Degradation

Bond dissociation energy

Automated quantum mechanical solution for identification of bond strengths and insight into degradation mechanisms



Input GUI

Bond and Ligand Dissociation

Use structures from: Project Table (57 selected entries)  

Dissociation sites

☒ Single, acyclic bonds Recalculate

☒ Exclude bonds to hydrogen 

☐ Include only bonds to atoms that match one of these SMARTS patterns:  Append from workspace selection

☐ Exclude bonds to atoms that match one of these SMARTS patterns:  Append from workspace selection

☒ Ligands complexed to metals Recalculate

Initial reactant states:

Closed shell charge: 0 

☒ Singlet ground state

☐ Lowest triplet state via SCF

☐ Reduced

☐ Oxidized

☐ Excited state via TD-DFT ☒ Singlet ☐ Triplet State: 1 

Jaguar

☐ Free energies at SATP

☐ Freeze products at reactant geometry

Jaguar Options... B3LYP/LACV3P**

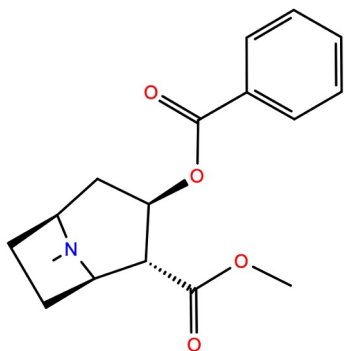
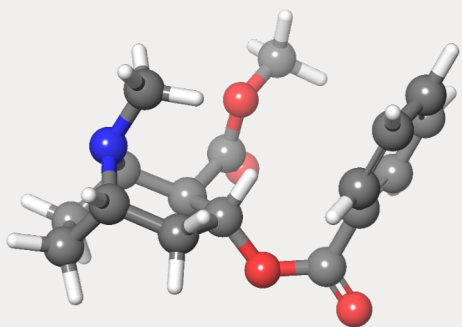
Job name: bde  Run

 Host=bolt_cpu:4, Incorporate=Append new entries as a new group 

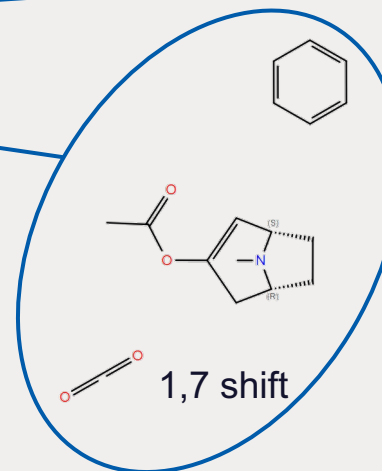
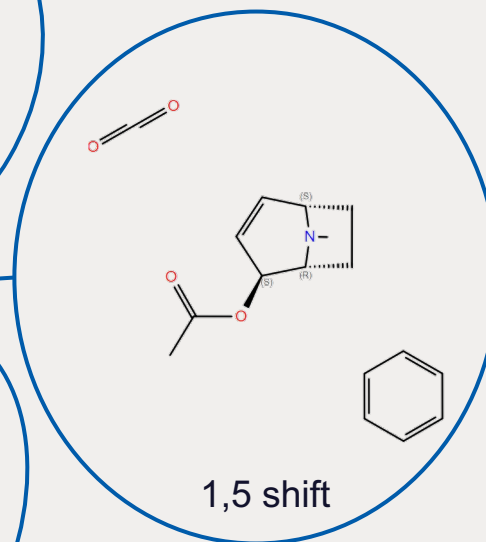
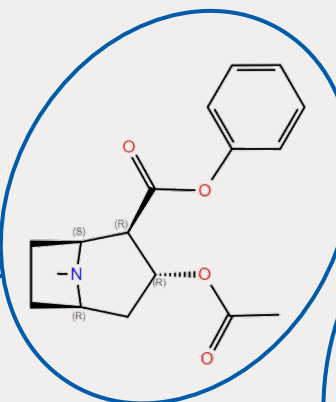
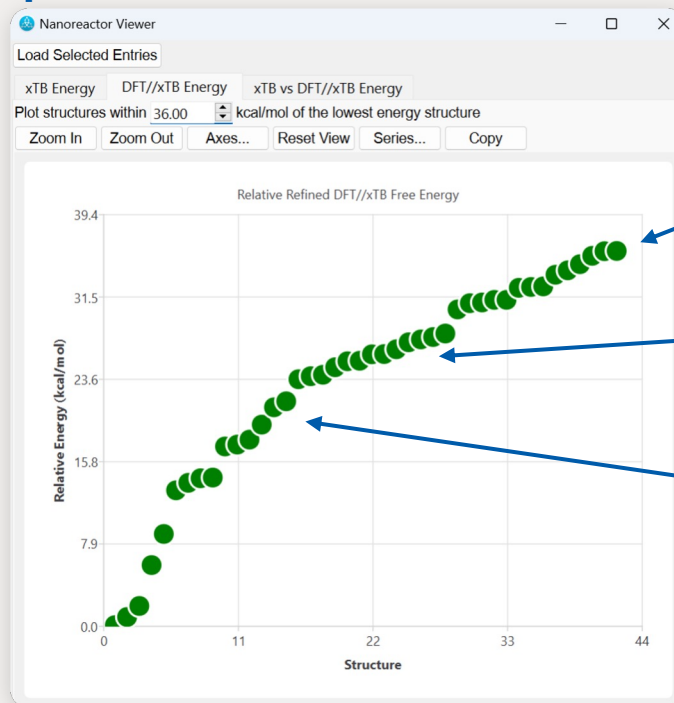
Nanoreactor: thermal decomposition of cocaine

Predict plausible degradation products of active pharmaceutical ingredients using xTB metadynamics. Optionally identify their thermodynamic sorting with free energy refinement.

Input



Output



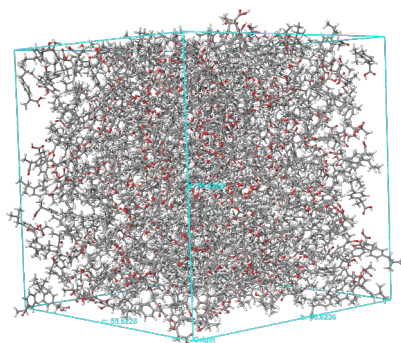
Formulation and Delivery

Solubility parameters

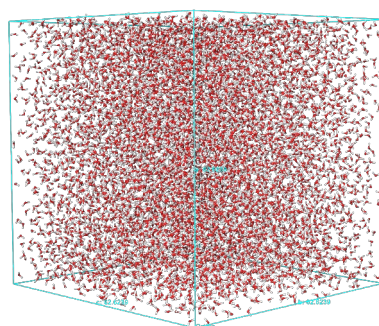
Calculation of cohesive energy density allows for prediction of Hansen/Hildebrand solubility parameter (δ).
Smaller differences in δ ($< \sim 7 \text{ MPa}^{1/2}$) indicate miscibility

- Fast miscibility screening for API / solvent combinations
- Screening of 100s-1000s of solvents enables construction of a miscibility matrix
- API input can be amorphous and/or crystalline

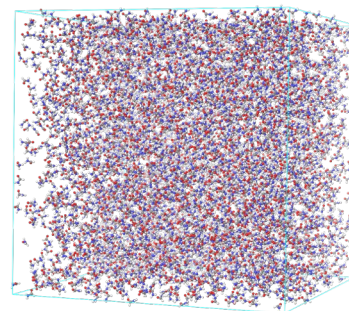
Drug	Solvent	$\Delta\delta \text{ (MPa)}^{1/2}$ (predicted)	Miscible? (experiment) ¹
Ibuprofen	Water	25.4	No ($1.5 \times 10^{-6} \text{ M}$)
	Formamide	14.9	No ($1.4 \times 10^{-3} \text{ M}$)
	Cyclohexane	6.1	Yes (0.15 M)
	Ethyl Acetate	2.9	Yes (0.33 M)



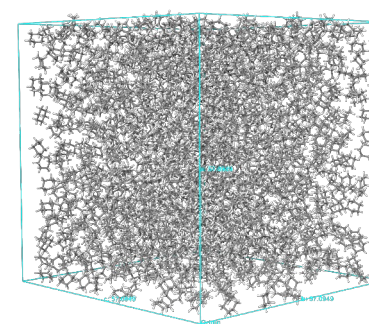
ibuprofen



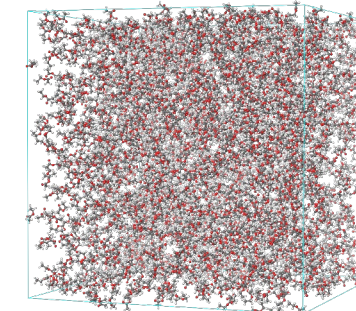
water



formamide



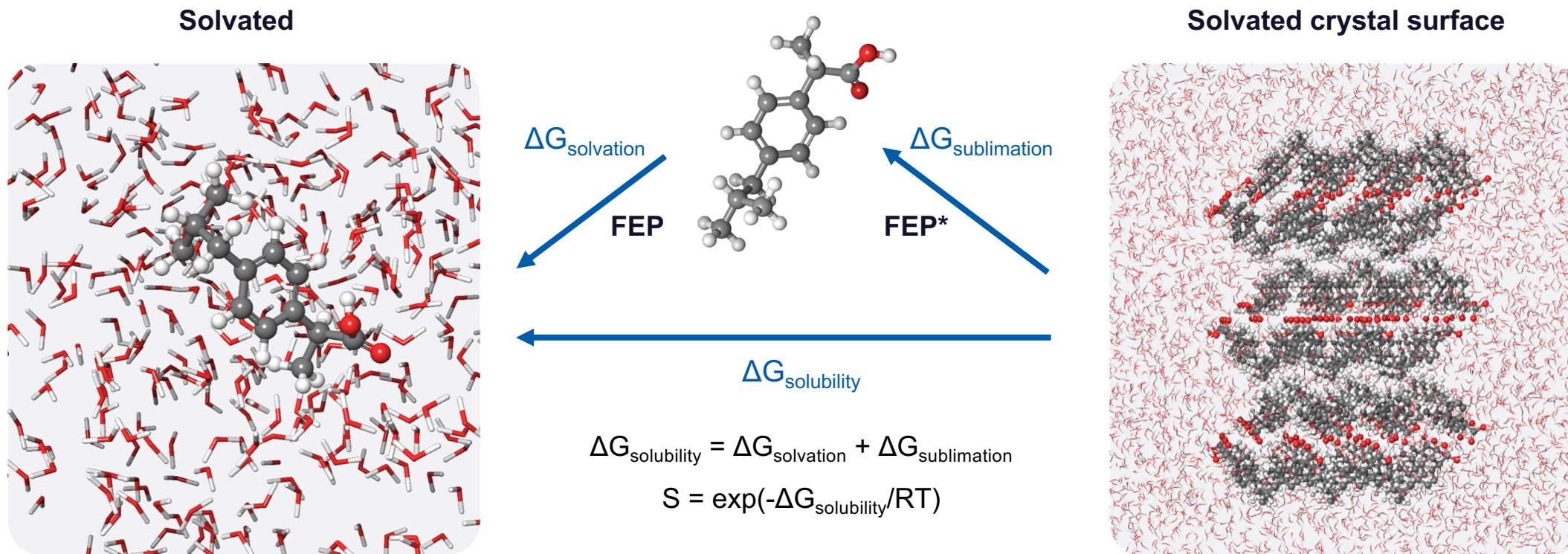
cyclohexane



ethyl acetate

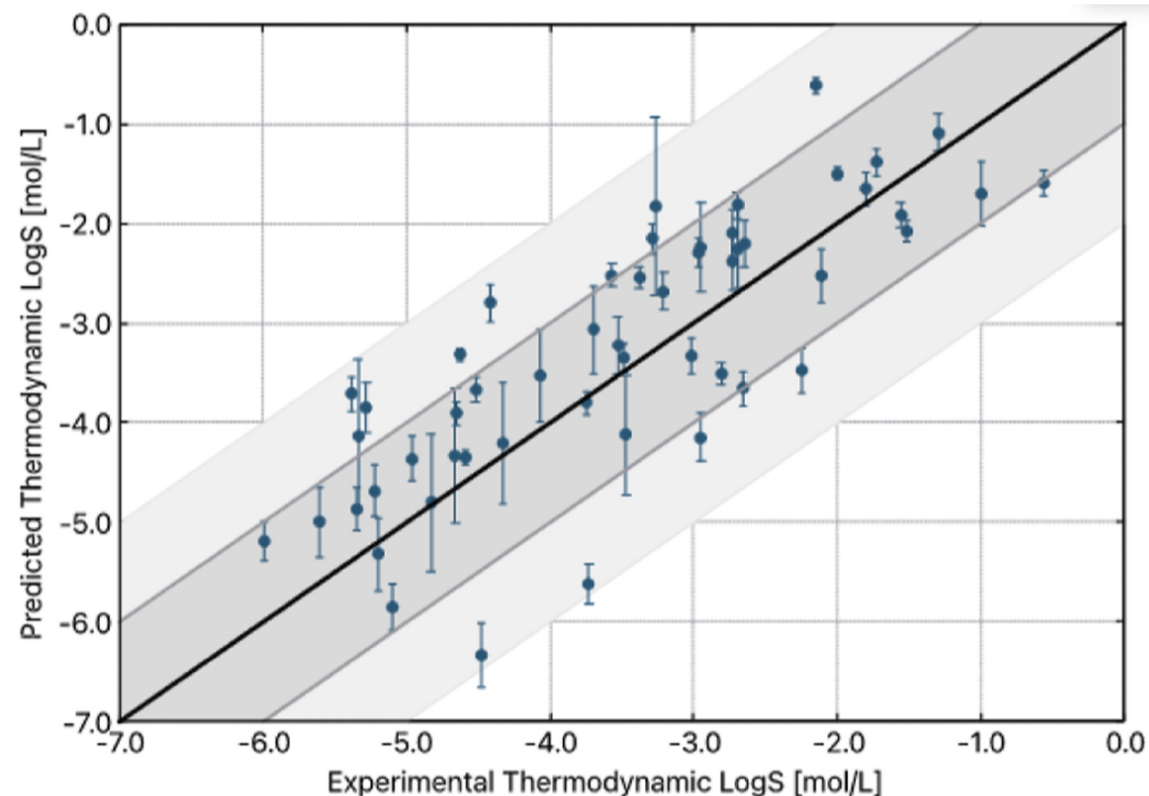
FEP Solubility: crystalline API in water

Calculate the free energy to move molecule from the crystal into the solvent via constructing a thermodynamic cycle

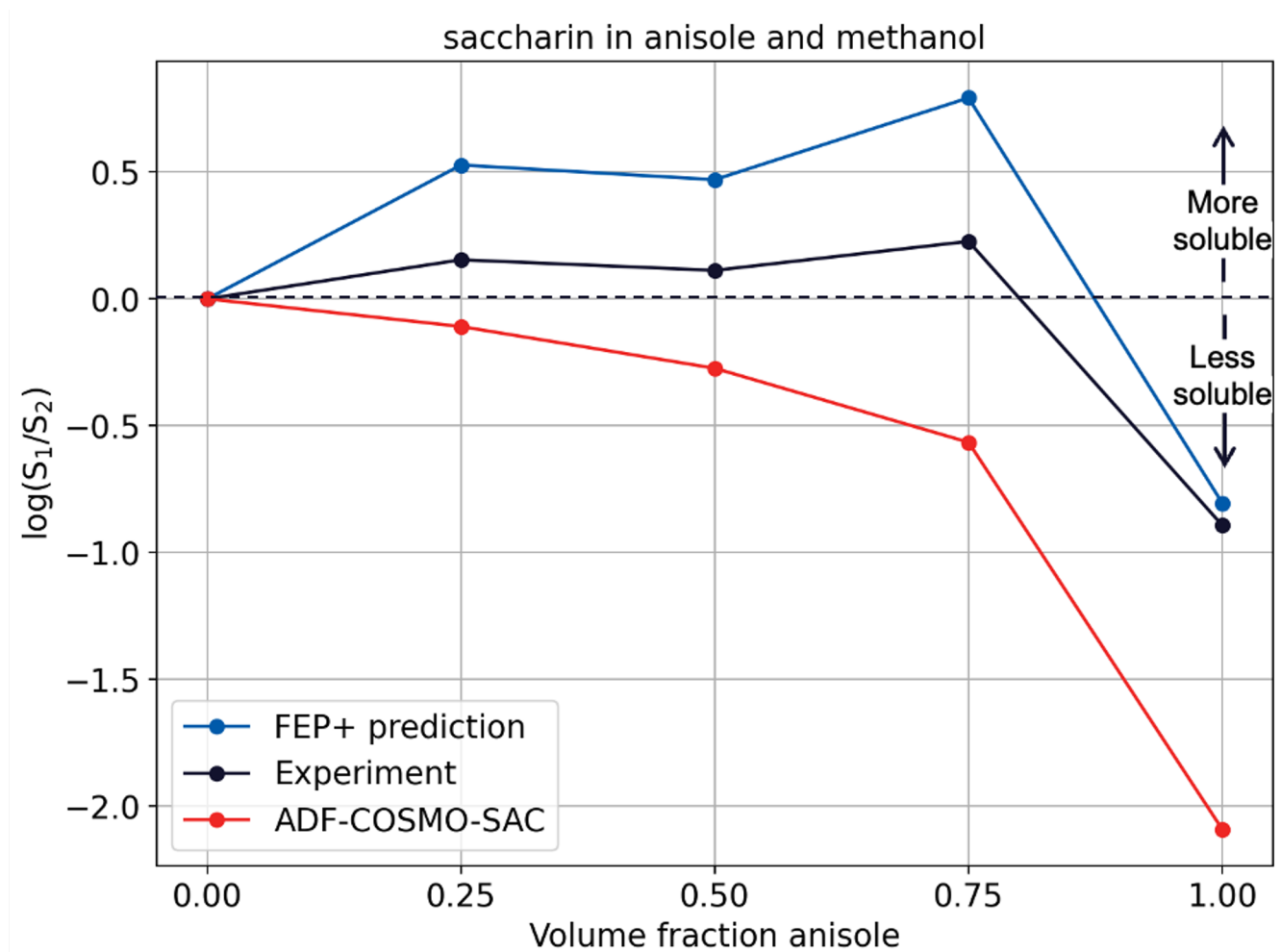


FEP Solubility: crystalline API in water

- Dataset includes drug-like molecules from:
 - DLS100 and Sol Challenge datasets (53 data points)
 - AbbVie proprietary compounds (17 datapoints)
- Molecular weight range: 250 – 445 g/mol



FEP+ captures cosolvent synergy



Solubility ratio (S_1/S_2) computed relative to saccharin in pure methanol

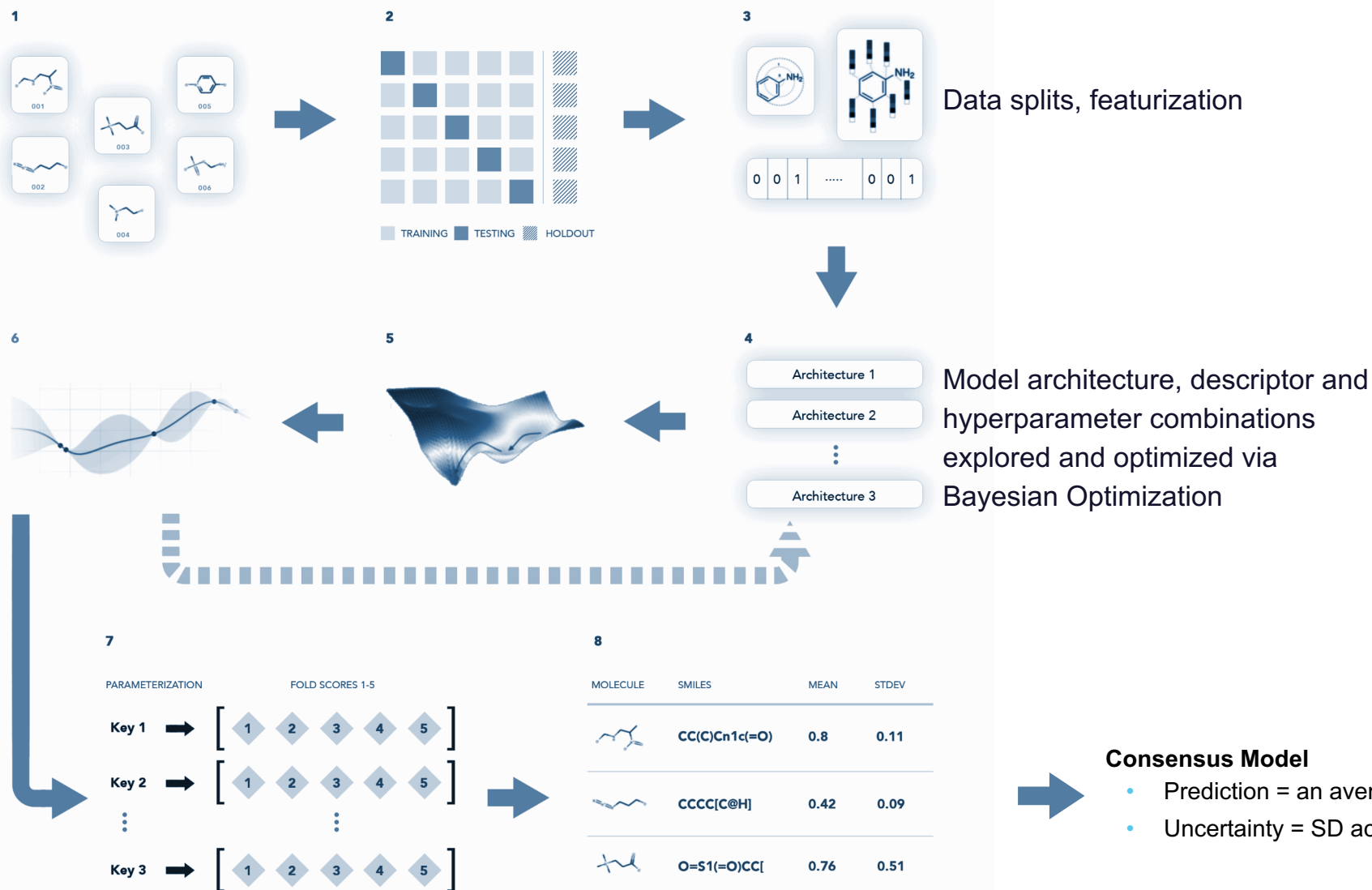
Method	Highest solubility combination (anisole:methanol)
Experiment	75:25
COSMO-RS	0:100
FEP+	75:25



- FEP+ captures shape of solubility ratio versus volume fraction curve
- FEP+ correctly identifies that 75/25 anisole:methanol results in the highest solubility

Machine Learning for Formulations

Automated machine learning: DeepAutoQSAR



Models Sampled

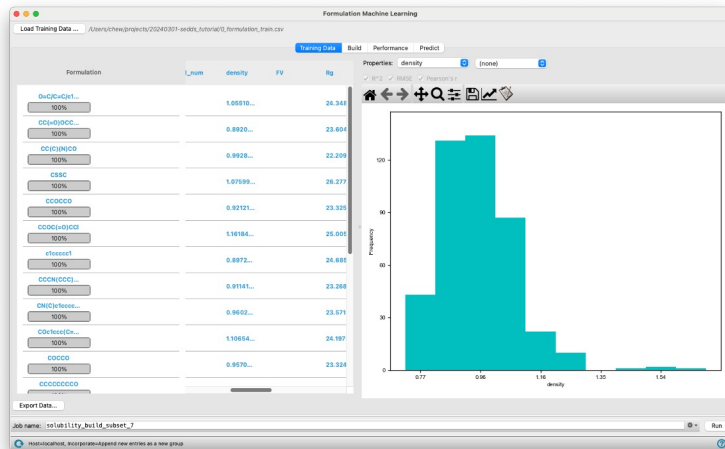
- Dense Neural Network
- Random Forest Regressor
- XGBoost
- TorchGraphConv
- GCN
- GraphSAGE
- GIN
- TopK
- SAGPool
- EdgePool
- GlobalAttention
- Set2Set
- SortPool

Consensus Model

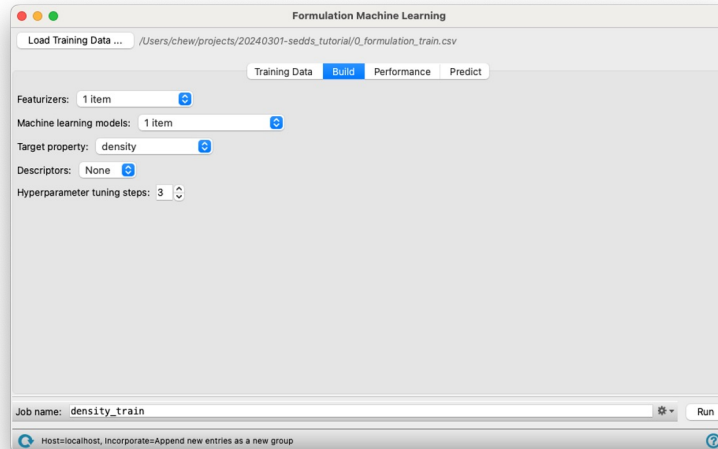
- Prediction = an average of the predictions for 5 best models
- Uncertainty = SD across the 5 predictions

Formulation machine learning

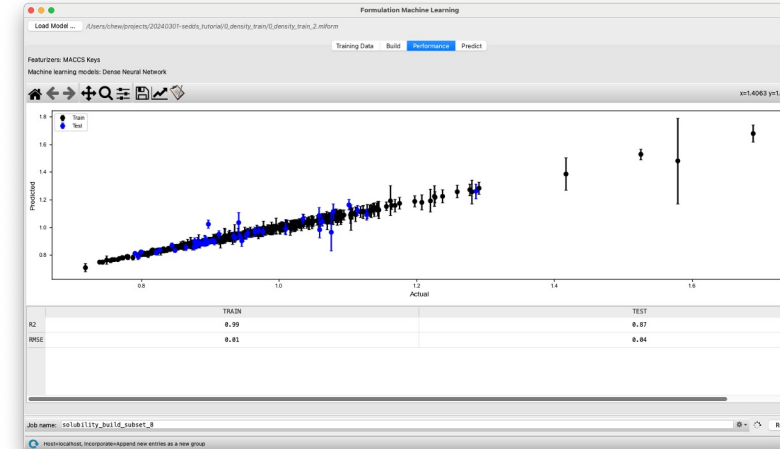
Data loading/visualization



Model training



Model evaluation/prediction

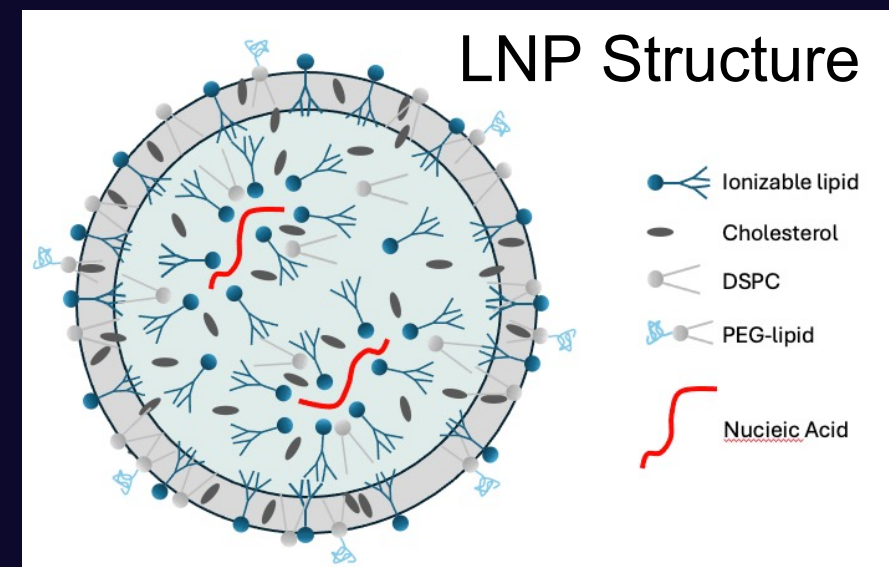


- Build, validate, and apply machine learning models based on chemistry and composition to predict any formulation property (e.g. density, viscosity)
- Allows input of external conditions, such as temperature, pressure, and so on
- Fully automated machine learning approach with automatic hyperparameter tuning

Modeling the formation, structure and behavior of mRNA-containing lipid nanoparticles

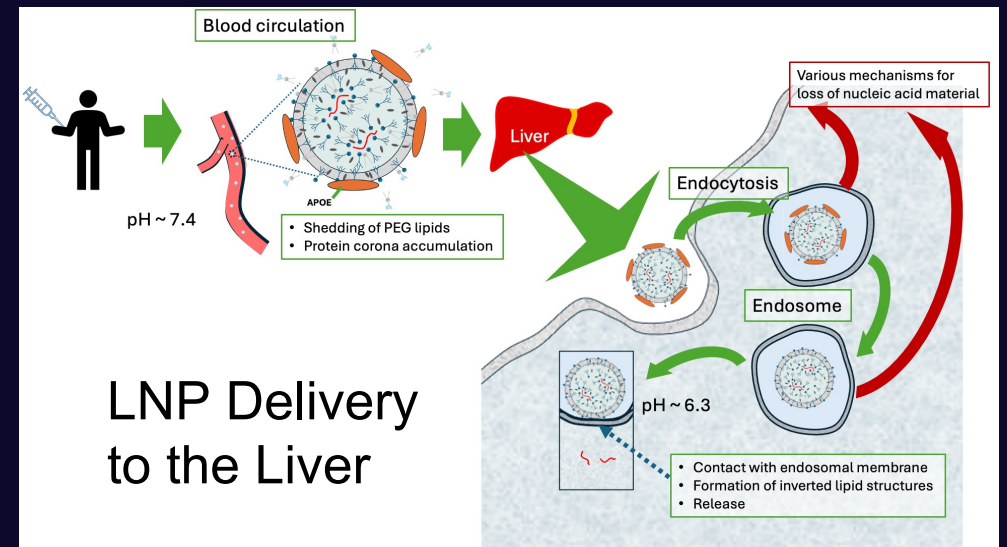
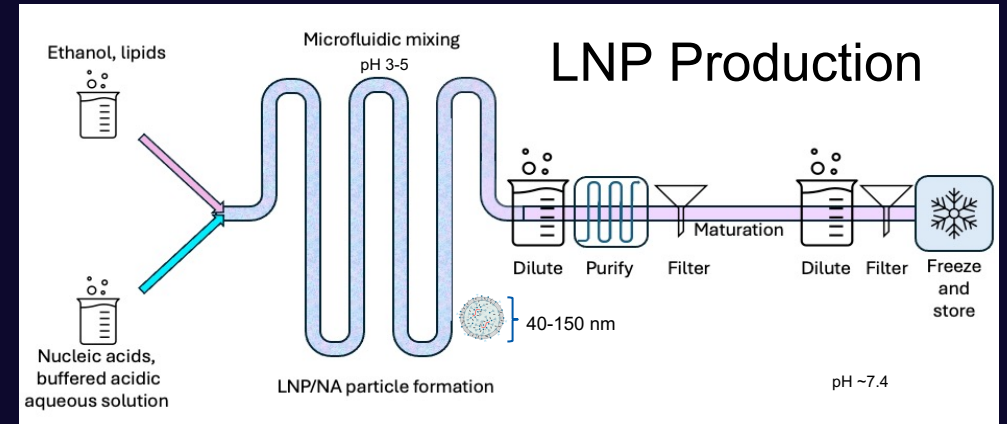
Nucleic acid LNPs

- Improve bioavailability of nucleic acid-based polymers (RNA/DNA)
- Components:
 - RNA/DNA
 - Cationic ionizable lipid (2 protonation states)
 - Cholesterol
 - 'Helper' phospholipid (often DSPC)
 - PEGylated lipid
 - Solvent(s) + counterions/salt
- RNA-loaded LNPs as therapeutics:
 - mRNA: Covid Vaccines
 - siRNA: Onpattro (treatment of hereditary transthyretin-mediated amyloidosis)
 - Many preclinical and clinical programs for delivering siRNA, miRNA, mRNA, saRNA, DNA



LNP Technology

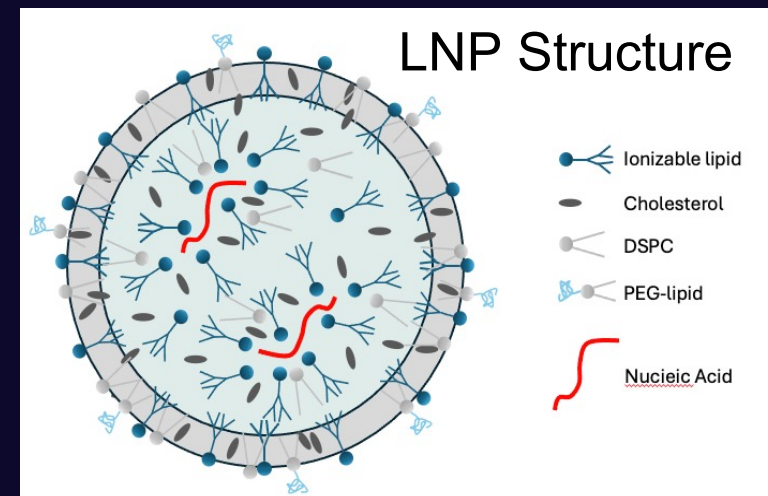
- Improve bioavailability of nucleic acid-based polymers (RNA/DNA)
- Composition affects structure
 - Structure affects transfection potency
- Motivation for computational modeling:
 - Aid in understanding
 - High-throughput computational screening



Simulating LNP self-assembly and structure

Why simulate LNP self-assembly and structure?

- LNP structure is relatively poorly characterized
 - Basic structural understanding should facilitate innovation
- Current reliance on composition/structure/activity relationships
 - Determined from extensive experiments using systematic variation in composition
 - Some experimental studies have characterized LNP structure
 - Significant effort, time and expense employing specialized equipment
 - This is far from routine
- Modeling can generate structural information that is hard to obtain from experiment
 - Complementary to experimental studies



COMMUNICATION | August 15, 2024

Coarse-Grained Simulation of mRNA-Loaded Lipid Nanoparticle Self-Assembly

Molecular Pharmaceutics 2024 21 (9), 4747-4753

Douglas J. Grzetic*, Nicholas B. Hamilton, and John C. Shelley*

<https://pubs.acs.org/doi/abs/10.1021/acs.molpharmaceut.4c00216>

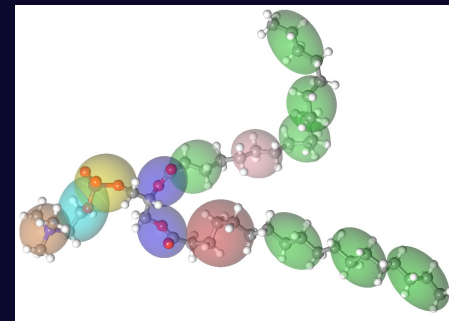
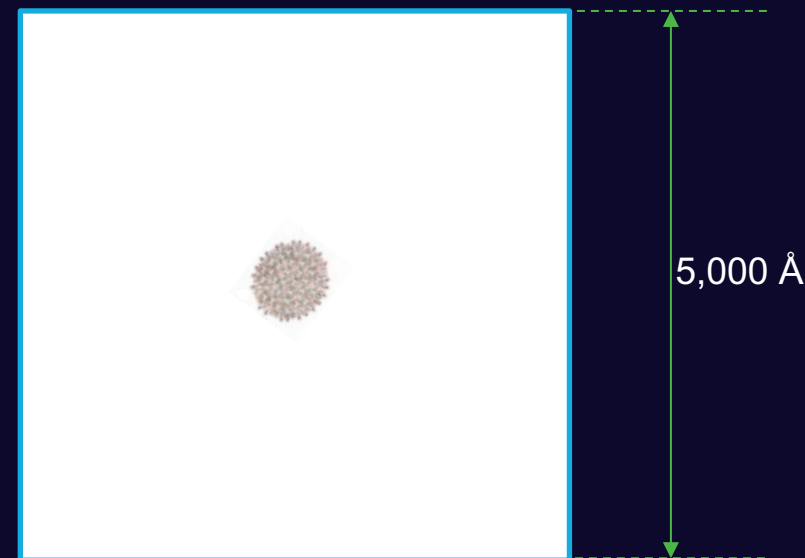
Modeling perspectives

- Self assembly occurs on μs to ms time frame
- To simulate the self assembly of a single 650 Å diameter LNP (typical for Pfizer/BioNtech Covid-19 vaccine) at the concentration used in the vaccine would require a system containing $\sim 12,000,000,000$ atoms
- Even simulating the formation of smaller LNPs at higher concentrations likely requires $> 10,000,000$ atoms for $> 1 \mu\text{s}$.
 - Challenging to employ all-atom simulations for LNP as a whole

Coarse-graining is widely used for simulating lipids

- Permits the simulation of larger systems for longer times

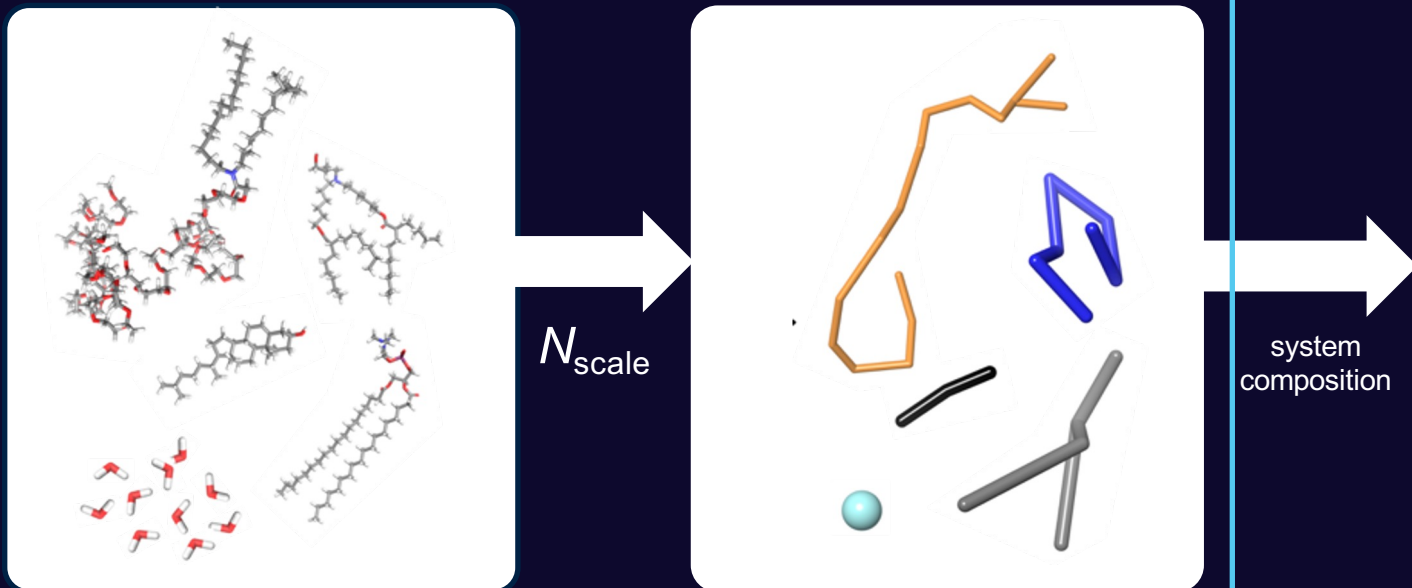
∴ Coarse-grain (CG) modeling studies have a role to play



Automated Coarse-Graining workflow

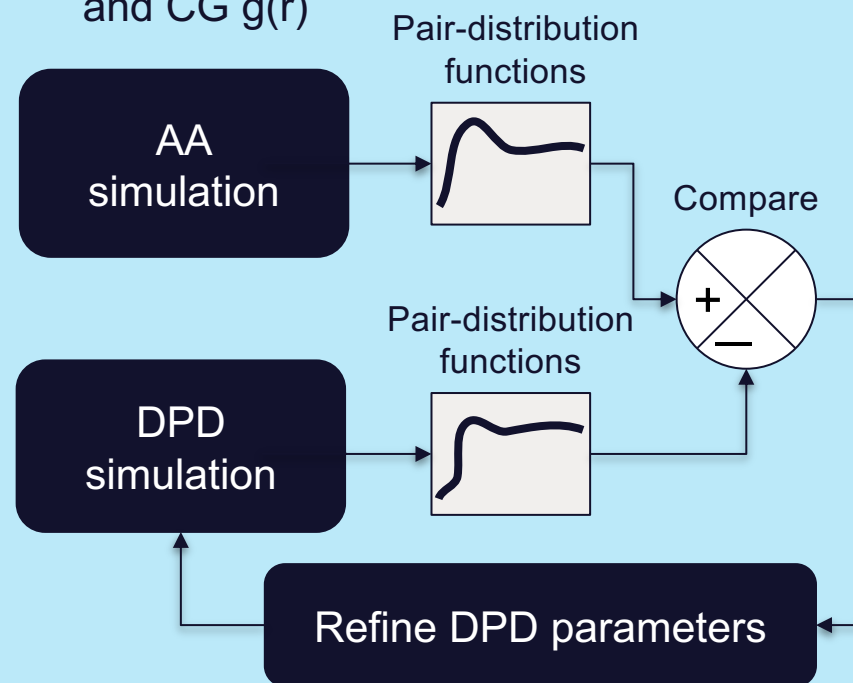
Automated Mapping

- Graph theory-based method generates AA to CG mapping for given mapping scale N_{scale}



Automated Parameterization

- Iterative Boltzmann inversion matches AA and CG $g(r)$



- AA and CG simulations conducted using Desmond
- CG mapping and parameterization done using Schrödinger MS Maestro: *Coarse-Grained Force-Field Builder*
 - Nonbond, bond and angle parameters trained against OPLS4

Creating a CG model for a mRNA / LNP vaccine is practical!

Methodology paper in preparation

Model system for Pfizer-BioNTech COVID-19 vaccine

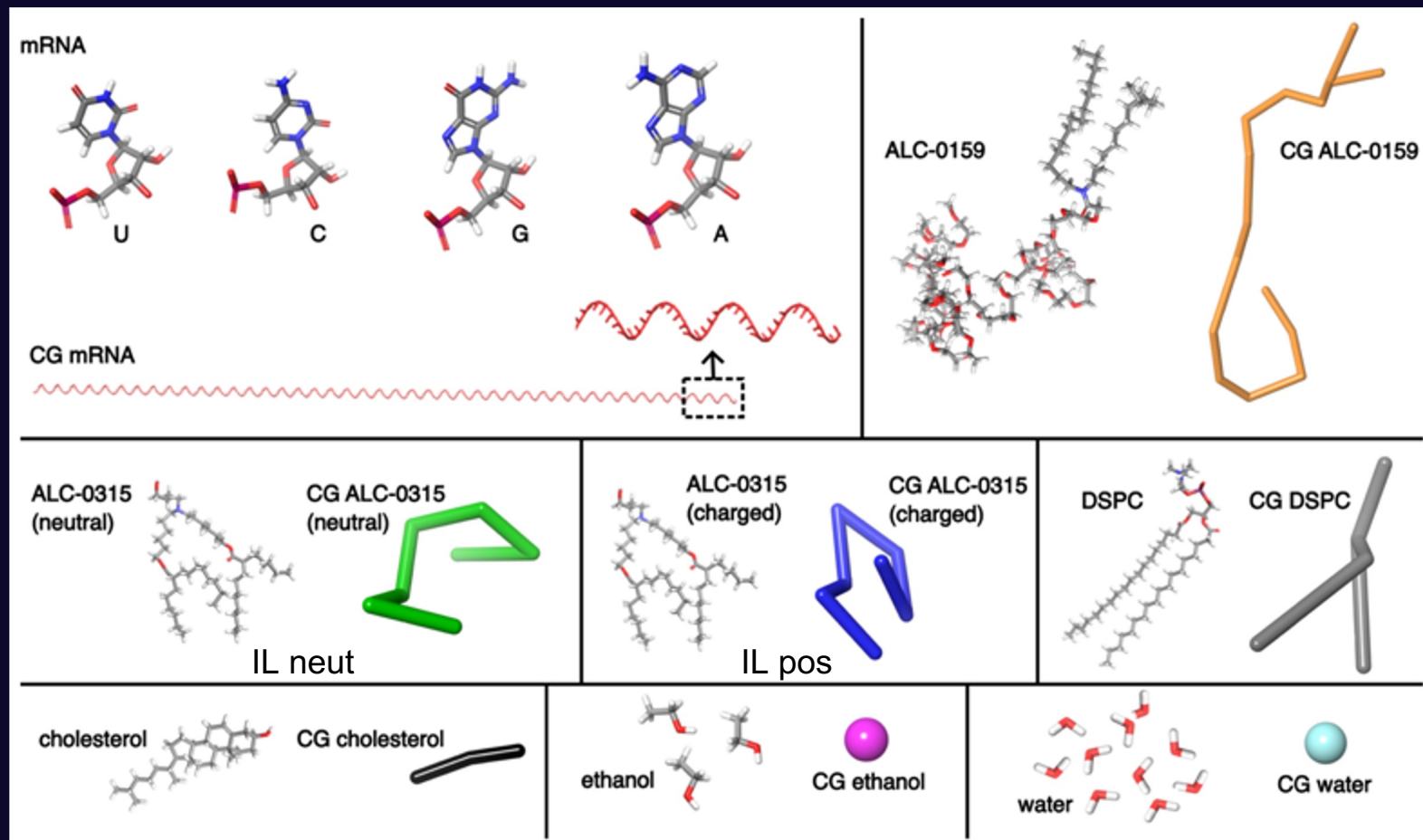
- AA reference system contains:

- mRNA fragments
- Cationic ionizable lipid (ALC-0315, 50% protonated)
- Helper lipid (DSPC)
- PEGylated lipid (ALC-0159)
- Cholesterol
- Ethanol
- Water
- Na^+ , Cl^- ions

- ~72,000 atom system simulated for 1.5 μs . Takes ~ 10 days

- Mapped to CG using a 10 heavy atoms to 1 CG particle mapping scale

- CG parameterization run for 100 iterations (200 ns per CG iteration). Completes in ~ 2.5 days

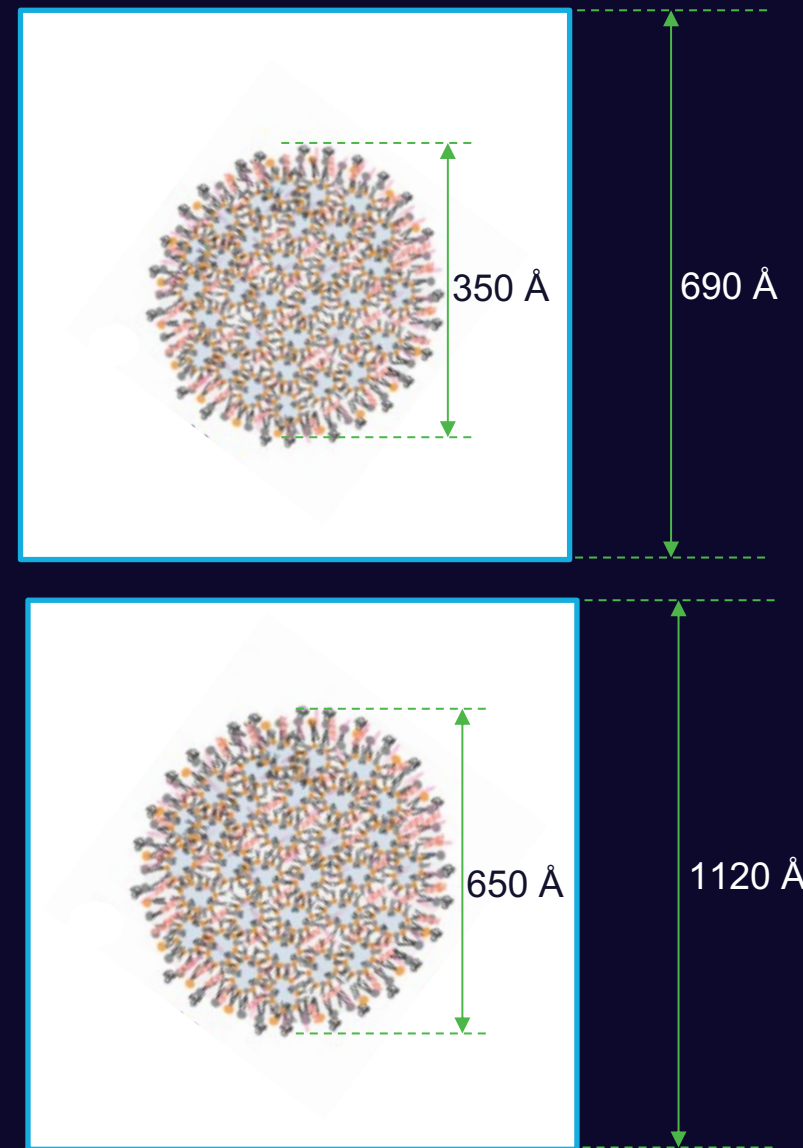


Grzetic, Hamilton, Shelley Molecular Pharmaceutics 2024 21 (9), 4747-4753

2 sizes of LNP simulations

Focus on Pfizer/BioNTech Covid-19 vaccine

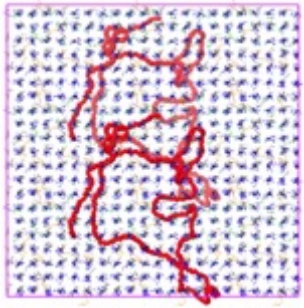
- Efficient
 - ~ 1,000,000 CG particles corresponding to ~30,000,000 atoms with enough lipids to form a LNP ~350 Å in diameter with 2 mRNA molecules each 475 nucleotides long
 - About 20 x more concentrated than the actual formulation
 - This can run on inexpensive GPGPUs
 - 425 ns/day
- Large / Full sized
 - ~ 4,600,000 CG particles corresponding to ~140,000,000 atoms with enough lipids to form a LNP ~650 Å in diameter with 1 mRNA molecules each ~4000 nucleotides long
 - This requires GPGPUs with more memory
 - 100 ns/day



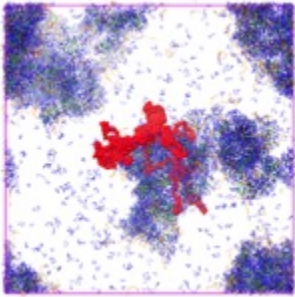
Assembly in acidic ethanol/water mixture

ALC-0315 90% protonated

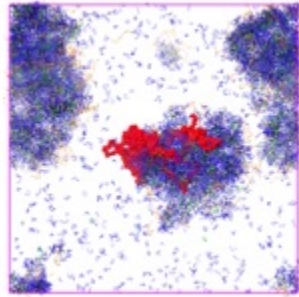
Efficient



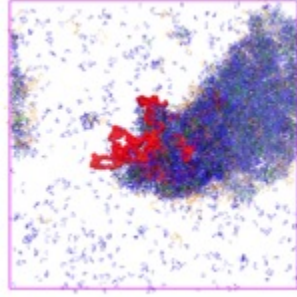
0 ns



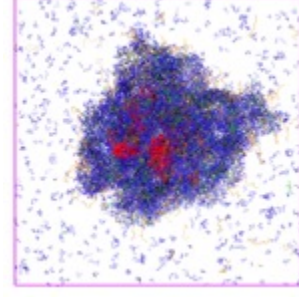
600 ns



1200 ns

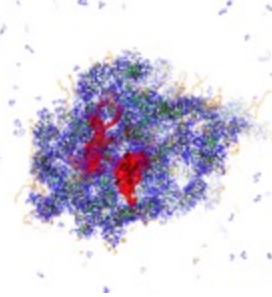


1800 ns



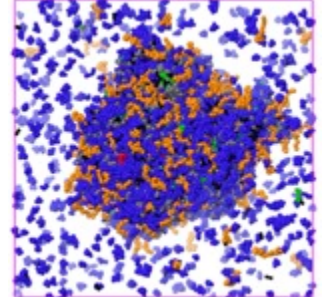
2500 ns

Cross-section



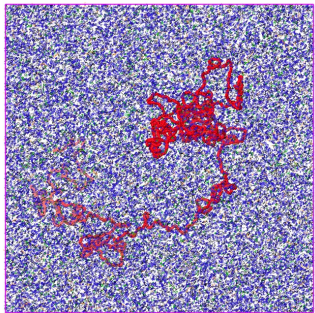
2500 ns

All vdW

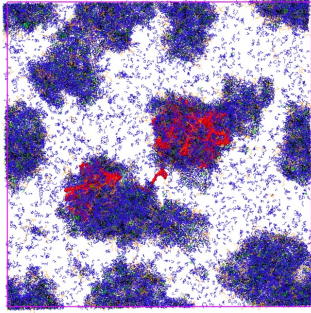


2500 ns

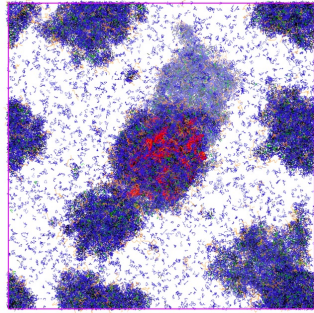
Large / Full Sized



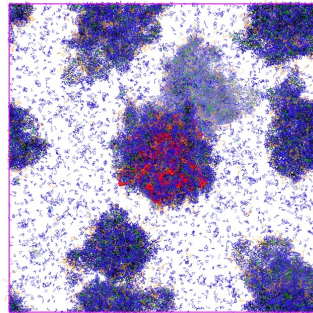
0 ns



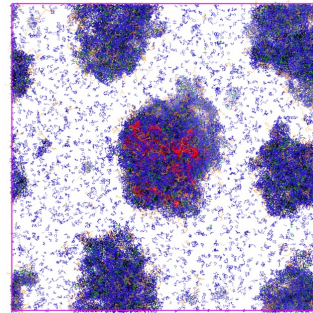
1000 ns



2000 ns

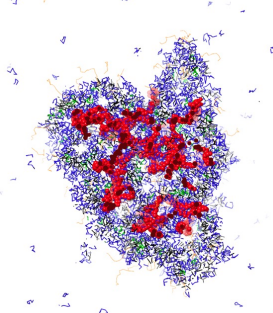


3000 ns



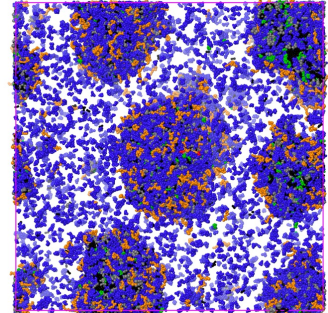
4000 ns

Cross-section



4000 ns

All vdW



4000 ns

- Assembly into pre mRNA/LNP structures (smaller with more internal solvent) observed in ethanol/water
- mRNA mostly buried
- PEG-lipid on surface



IL pos



IL neut



DSPC



cholesterol



PEG-lipid



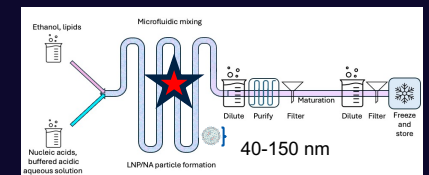
RNA



ethanol



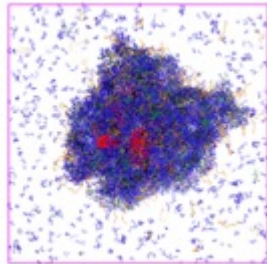
water



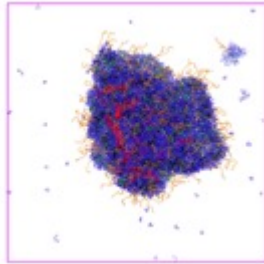
Assembly in acidic water after replacing ethanol with water

ALC-0315 90% protonated

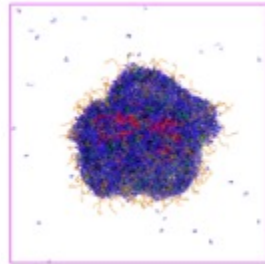
Efficient



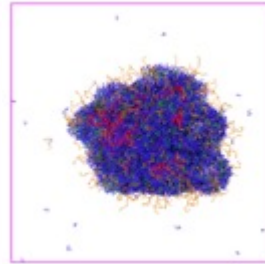
0 ns



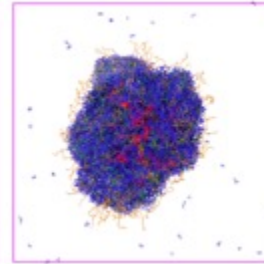
600 ns



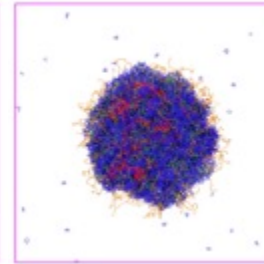
1200 ns



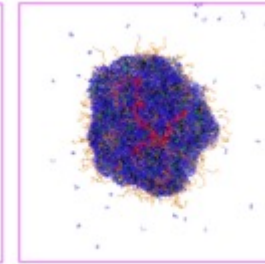
1800 ns



2400 ns

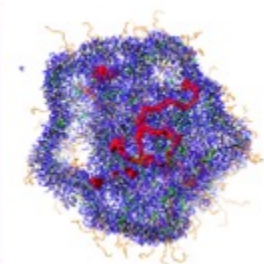


3000 ns



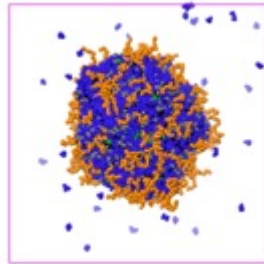
6000 ns

Cross-section



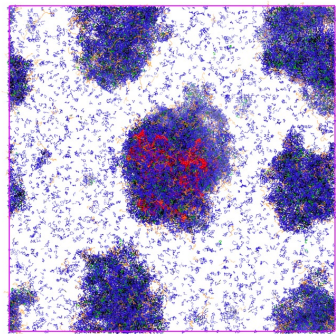
6000 ns

All vdW

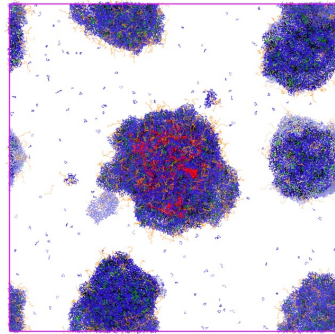


6000 ns

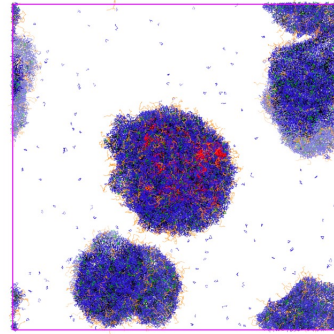
Large / Full sized



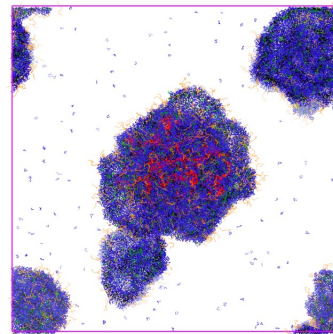
0 ns



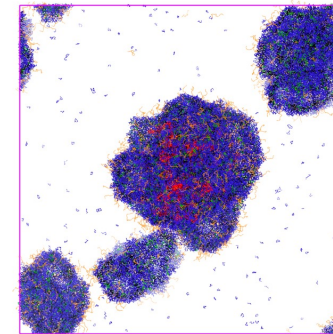
1000 ns



3000 ns



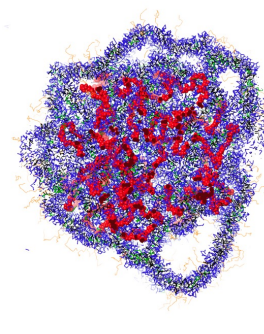
5000 ns



6000 ns

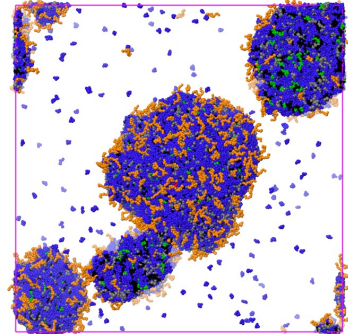
Need to run longer....

Cross-section



6000 ns

All vdW



6000 ns

- Less solvent in LNP structures
- Merging of small LNPs to form larger LNPs



IL pos



IL neut



DSPC



cholesterol



PEG-lipid



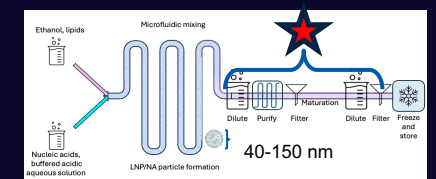
RNA



ethanol



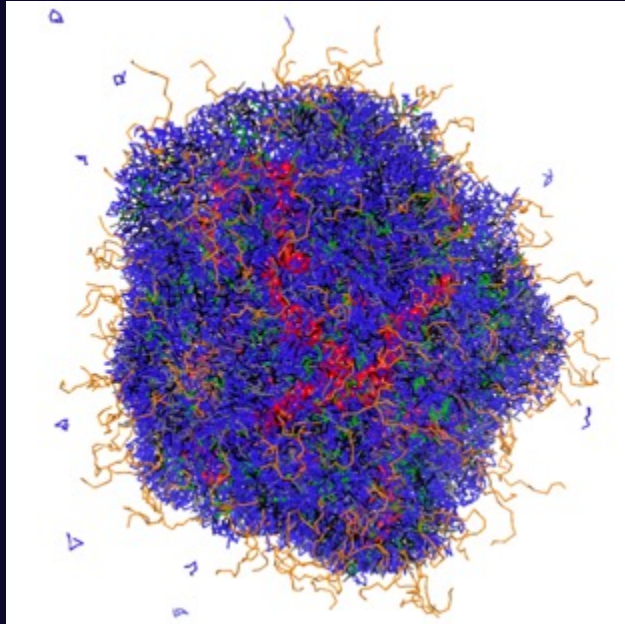
water



LNP self-assembly simulation from random solution

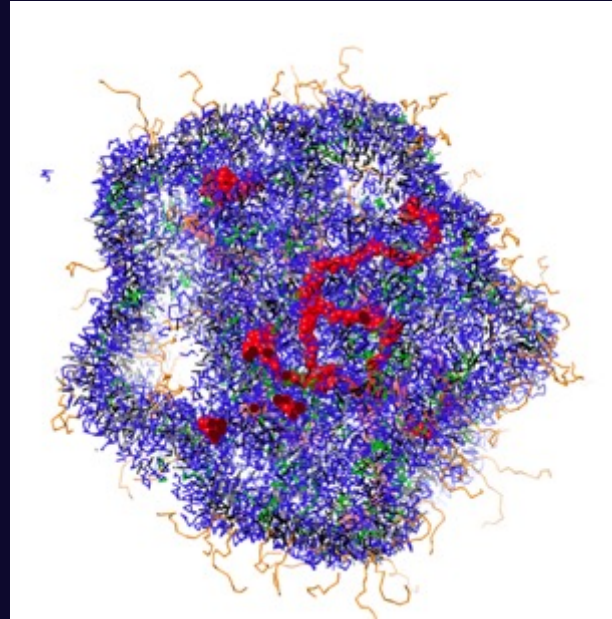
Pfizer/BioNTech formulation

Whole LNP

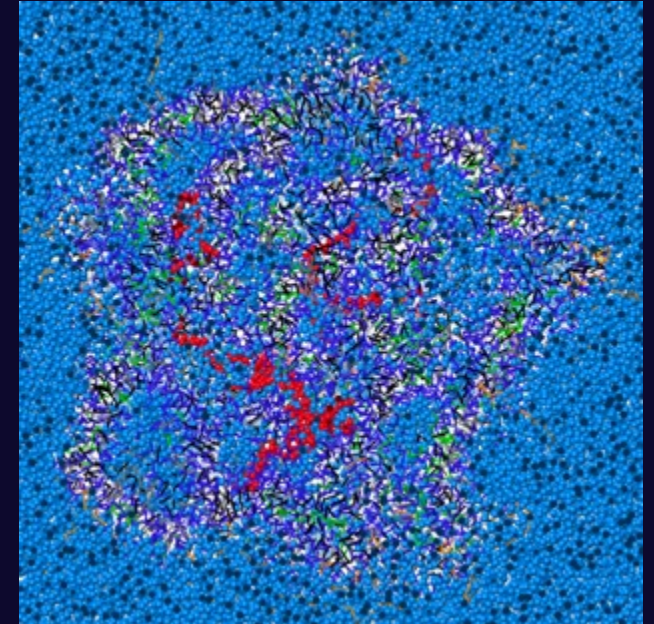


50 nm

Cross section



Cross section with water



- ✓ mRNA buried in LNP inside water channels
- ✓ Water channels that lack mRNA also present
- ✓ LNP core is about 25% water
- ✓ Nearly all PEG lipids on exterior of LNP
- ✓ Little or no neutral ALC-0315 surface exposed

Molecular Pharmaceutics 2024 21 (9), 4747-4753



IL pos



IL neut



DSPC



cholesterol



PEG-lipid



RNA



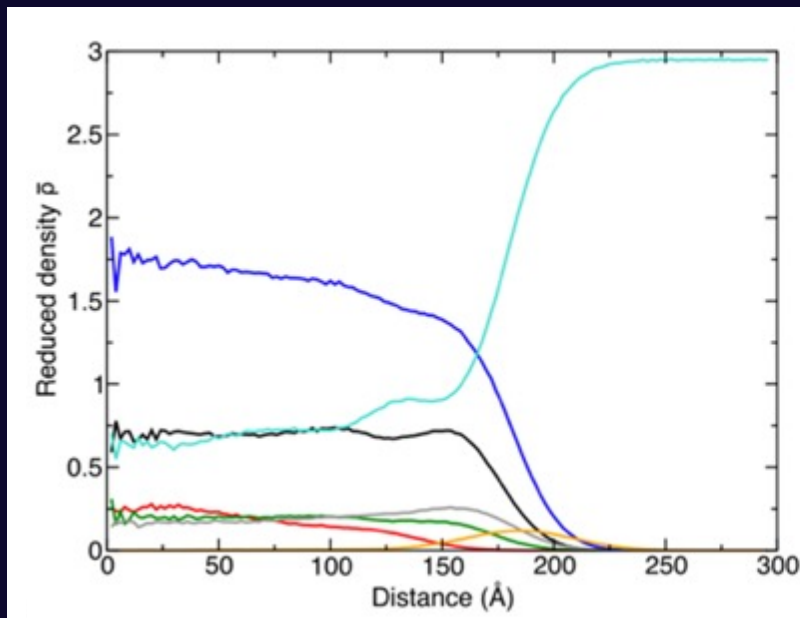
ethanol



water

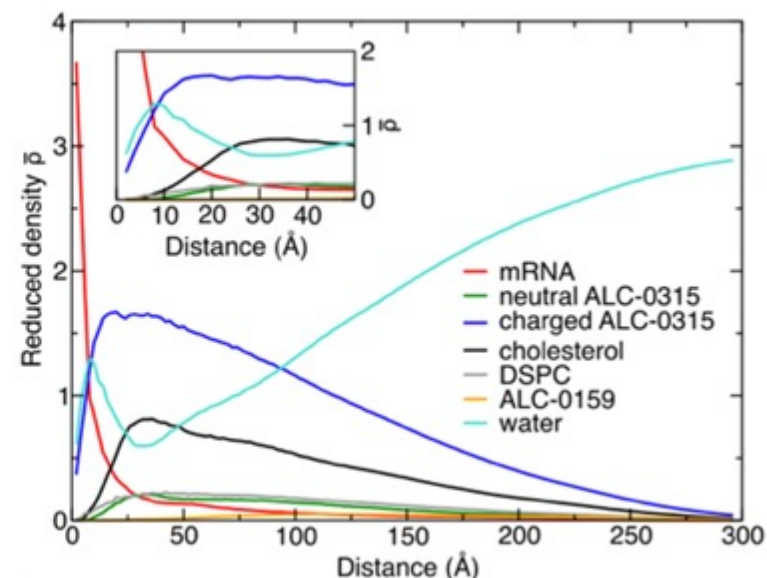
Structural analysis

Radial densities w.r.t. the LNP COM



- ✓ LNP core is about 25% water
- ✓ PEG lipids on exterior of LNP
- ✓ mRNA buried
- ✓ Neutral ALC-0315 is not surface exposed

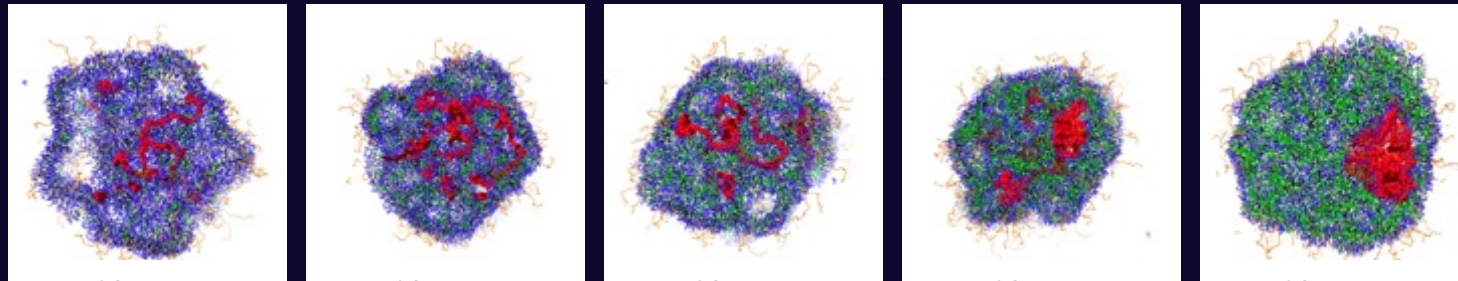
Radial densities w.r.t. the RNA backbone



- ✓ mRNA resides in water channels
- ✓ Water channels predominantly lined with positive ALC-0315 and cholesterol
- ✓ Relatively little neutral ALC-0315, DSPC, cholesterol near mRNA
- ✓ No PEG lipid in contact with mRNA
- ✓ Weak hint of pore-pore organization

Charge neutralizing ALC-0315: IL pos $\Rightarrow$ IL neut, raising the pH

Cross-section
of LNP



90% IL pos

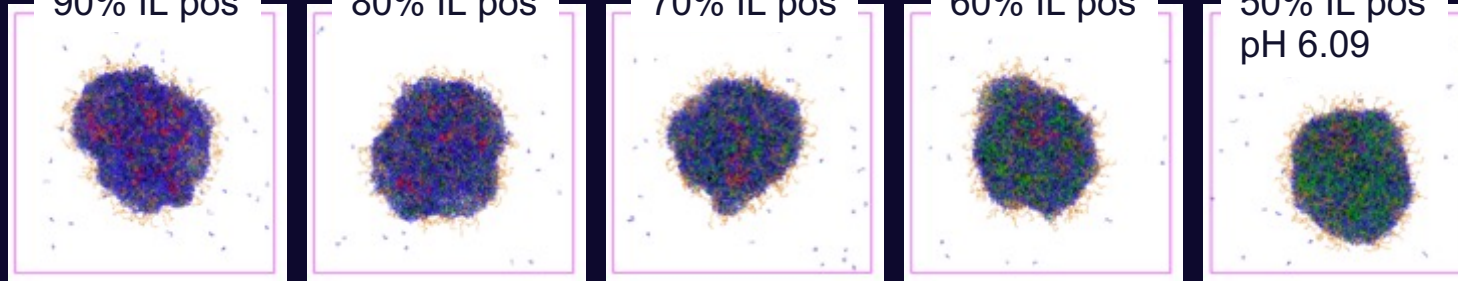
80% IL pos

70% IL pos

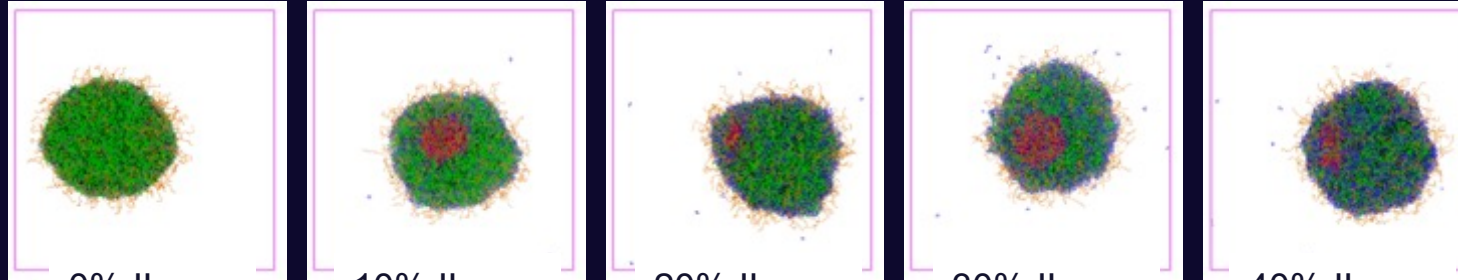
60% IL pos

50% IL pos
pH 6.09

Whole LNP



Whole LNP



0% IL pos

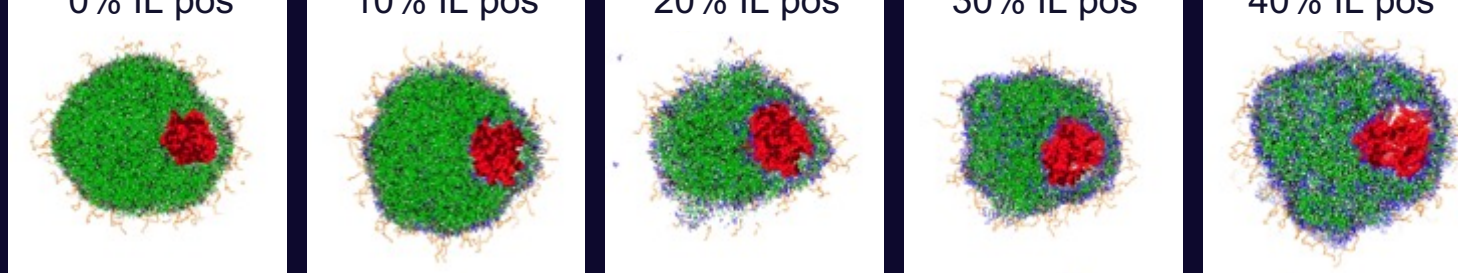
10% IL pos

20% IL pos

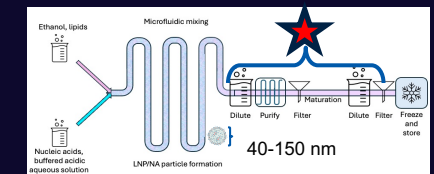
30% IL pos

40% IL pos

Cross-section
of LNP



- LNP has similar behavior for 90 - 70 % IL pos
- At 60 % IL pos, the mRNA starts to cluster
- 50 % - 0 % IL pos, the mRNA separates out within an aqueous cavity



pH dependent bleb formation

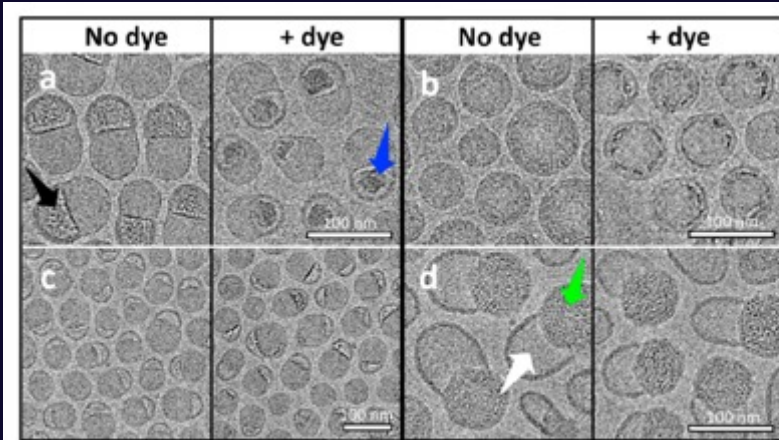
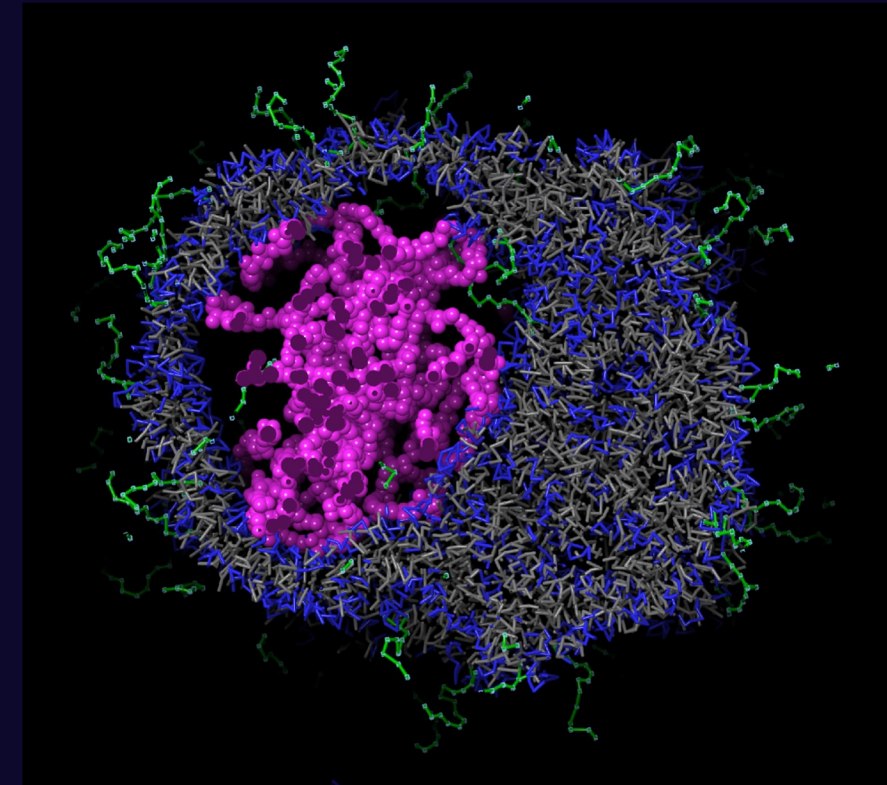


FIGURE 3 Locating encapsulated mRNA in LNPs by cryo-EM. The effect of thionine on mRNA-LNPs of different morphologies reveals that lipid-dissociated mRNA may reside in bleb compartments (a) or may be more lipid-associated in spherical (b) or less prominently blebbed particles (c). The black arrow in (a) indicates the distinctive mottled mass density of mRNA inside the bleb cavity, which itself is distinguished by a thick, dark periphery. The blue arrow indicates the significant contrast enhancement that occurs when thionine dye is present, thereby identifying mRNA within the bleb. (d) Charge-driven migration of mRNA from the bleb into the body of the LNP. When the mRNA-LNP sample of (a) (no dye) was dialyzed into pH 5 buffer, the images of (d) resulted. The mottled density is now associated with the body of the LNP (green arrow), leaving the bleb cavity devoid of mRNA (white arrow). Addition of thionine to this sample produced no notable contrast change (right), indicating that thionine did not displace lipid.

ated with the body of the LNP (green arrow), leaving the bleb cavity devoid of mRNA (white arrow). Addition of thionine to this sample produced no notable contrast change (right), indicating that thionine did not displace lipid.

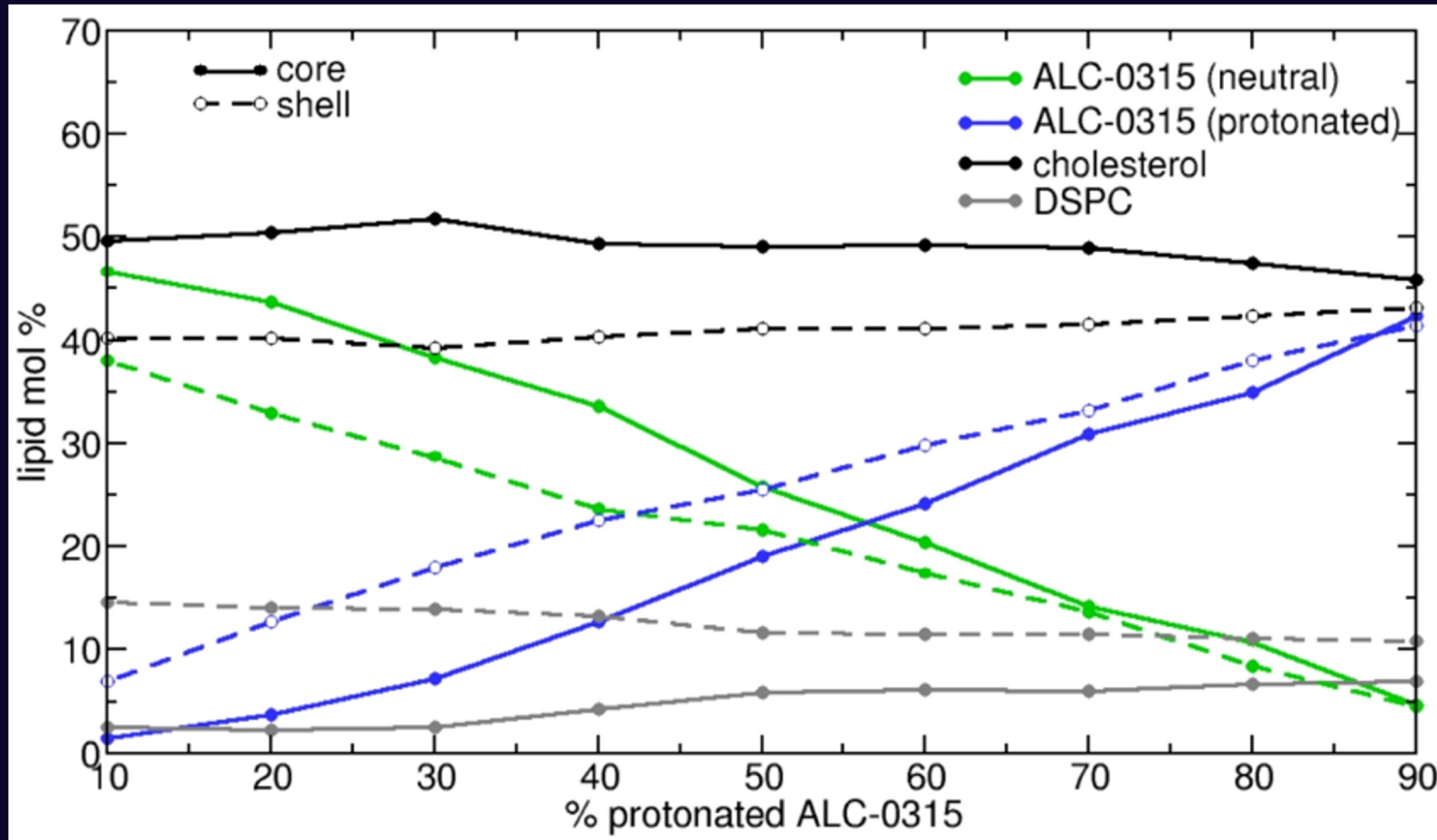
Biophys J. 2021, 120, 2766–2770



- Ionizable lipids
- PEG lipids
- mRNA
- Cholesterol, DSPC

mRNA LNP core/shell composition

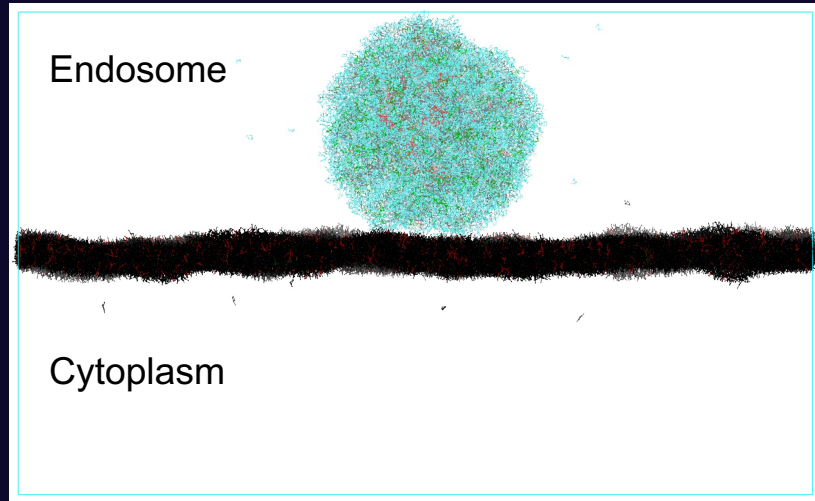
Strong preference for DSPC to reside in the LNP shell, particularly at low ionization levels (consistent with literature*)



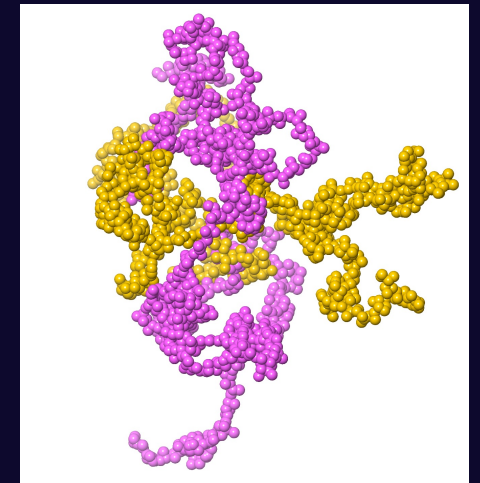
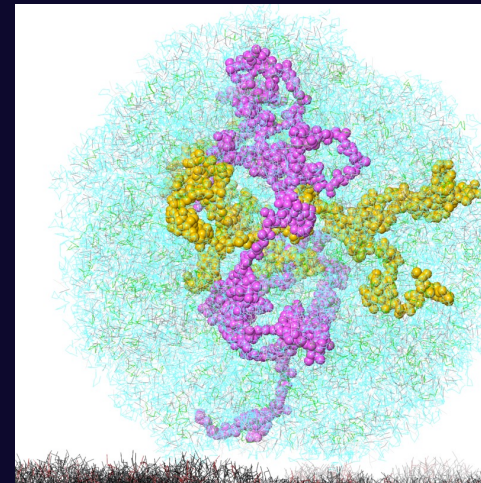
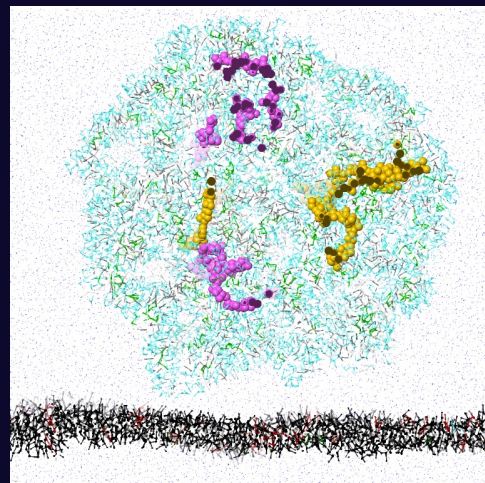
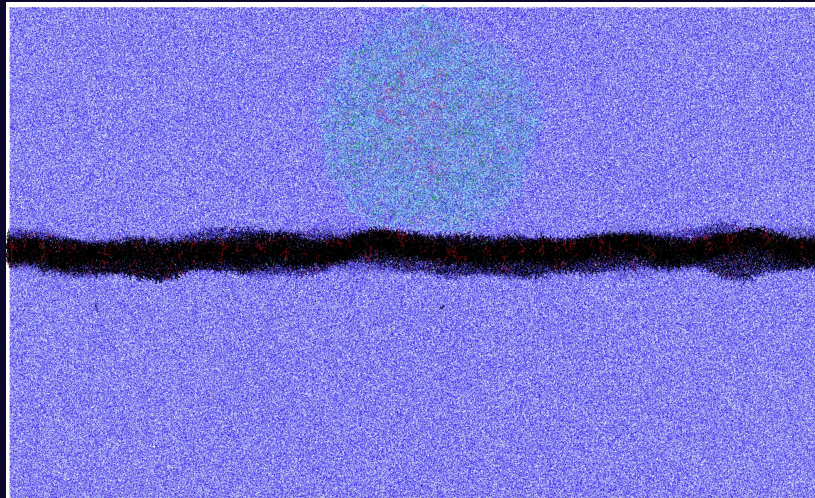
← Increasing pH

*This has been a common assumption when analyzing SANS data

Endosomal release planar geometry



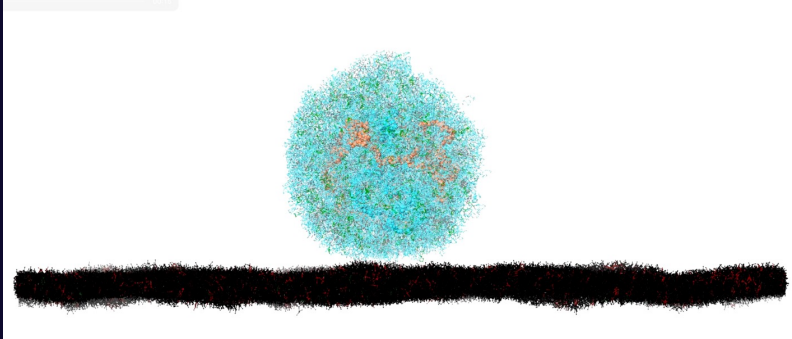
- Pfizer-BioNTech formulation
- LNP diameter ~38 nm
- 1152 mRNA residues
 - Split into 2 molecules



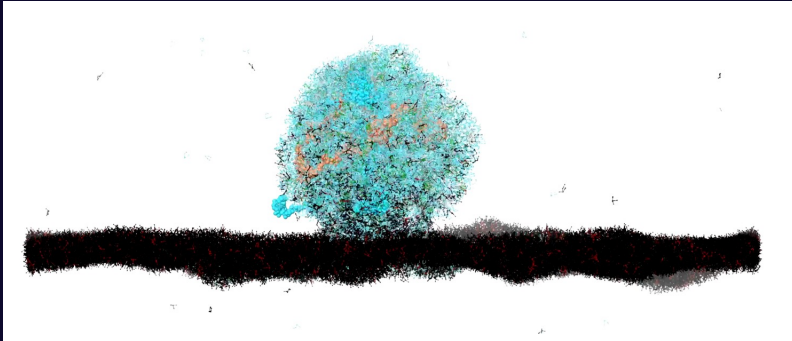
LNP + endosomal membrane

Planar geometry 2.9 μs simulation

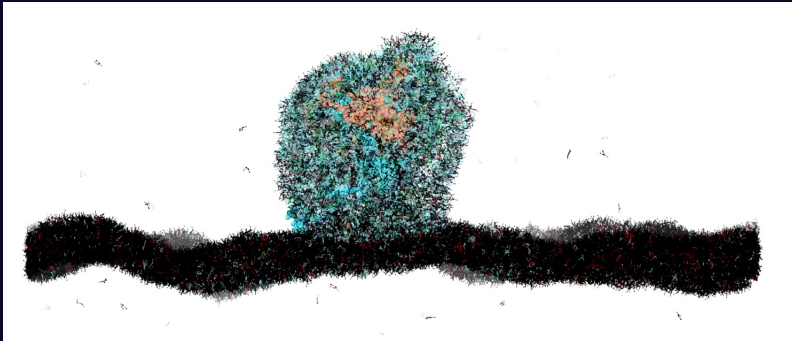
0.0 μs



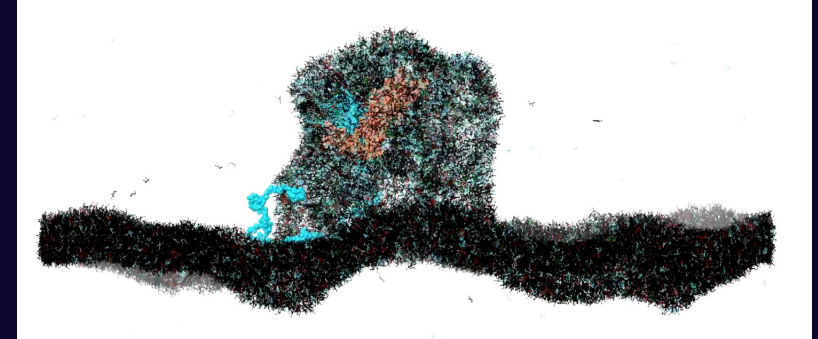
0.1 μs



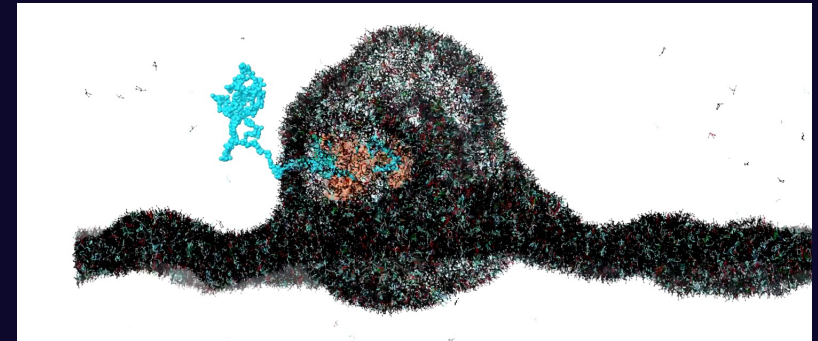
0.2 μs



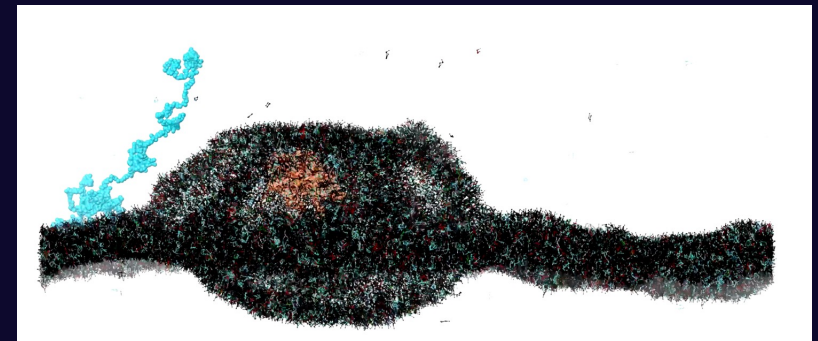
0.5 μs



1.75 μs



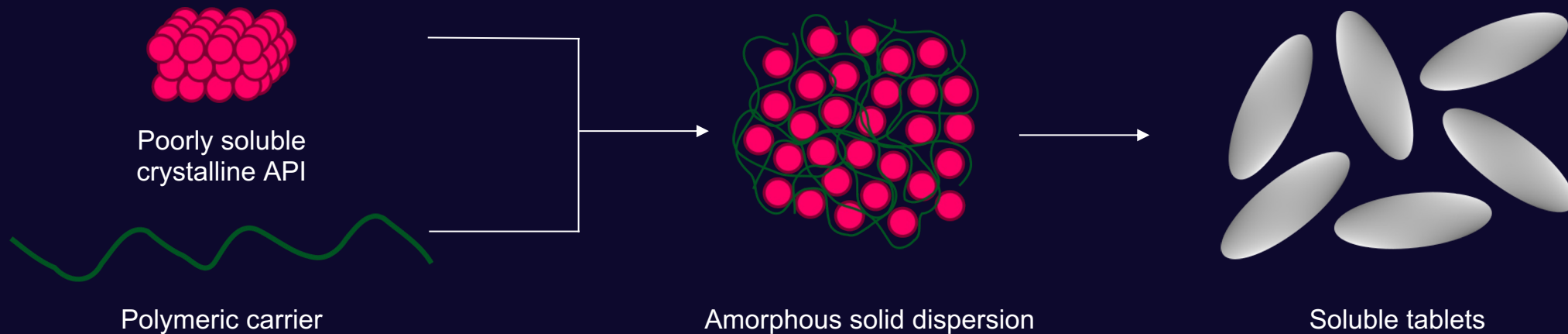
2.9 μs



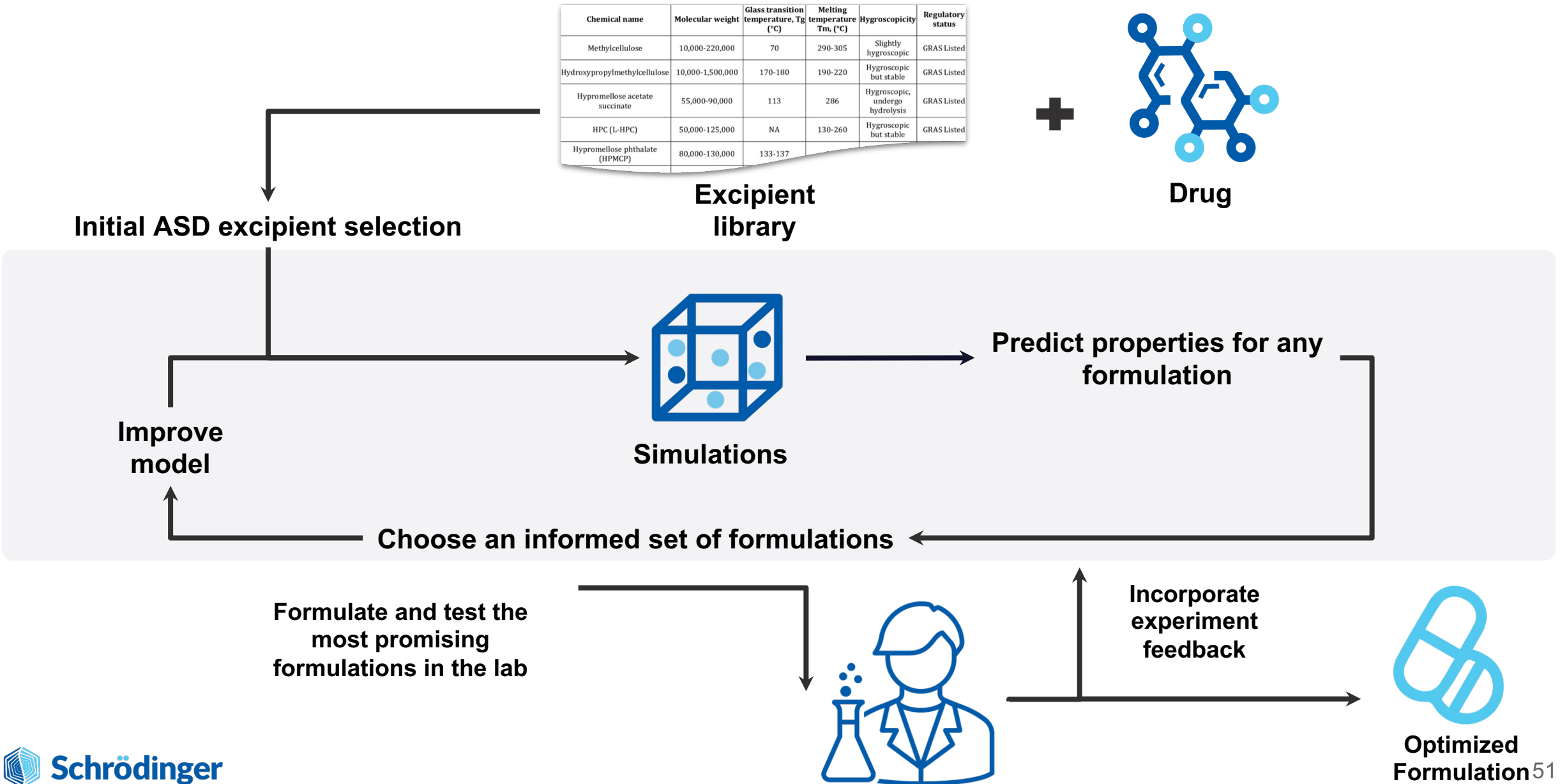
Excipient/polymer selection for small-molecule drug formulation including amorphous solid dispersions

Amorphous solid dispersions (ASDs)

- Used for drug delivery of poorly soluble Active Pharmaceutical Ingredients (APIs).
- Polymer dispersion helps prevent drug (re)crystallization.
- Excipients (e.g., surfactants) may play key roles in solubilization and/or preventing phase separation.



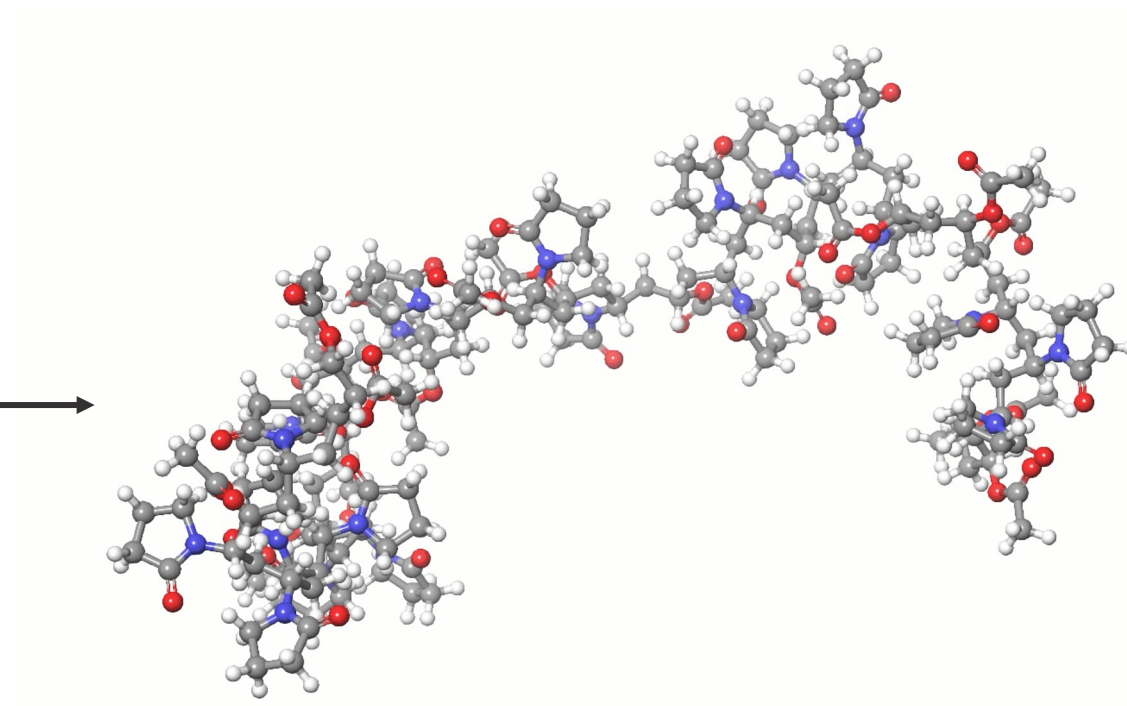
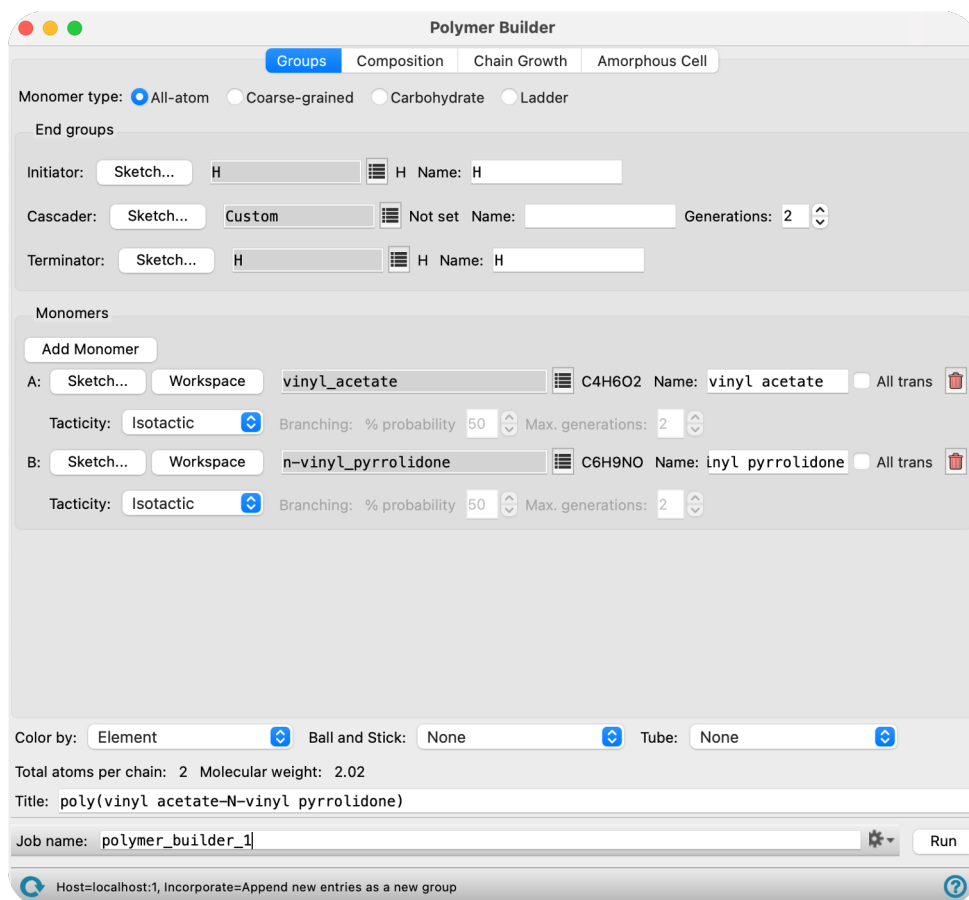
Digital first approach



*Excipient library image from S. Dhoppalapudi, *GSC Biological and Pharmaceutical Sciences*, 21, 012–021, (2022)

Polymer builder

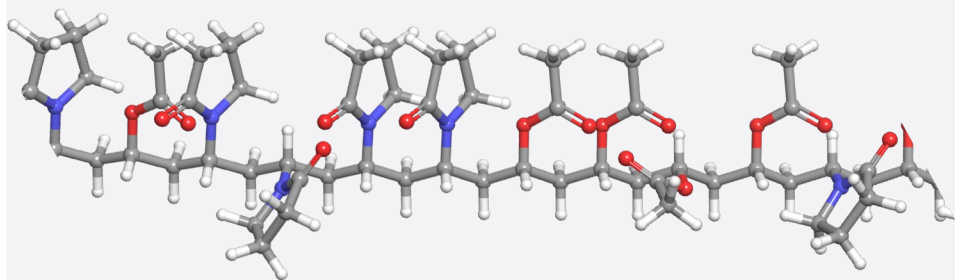
Construct polymer models (homopolymers, copolymers, ladder polymers, etc.), e.g. copovidone



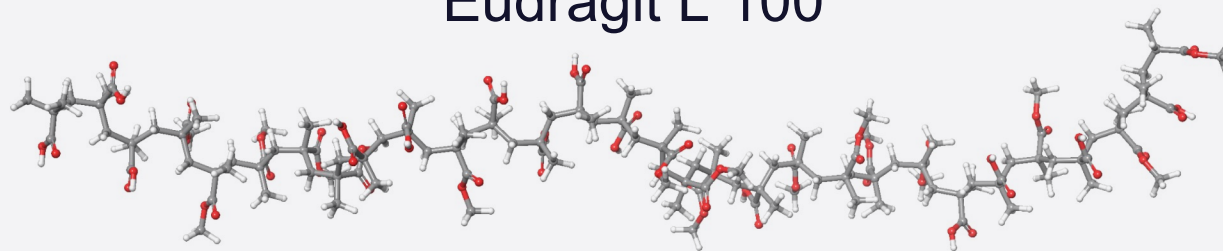
Polymer Builder included with MS Maestro

Builders include GRAS and FDA approved excipients

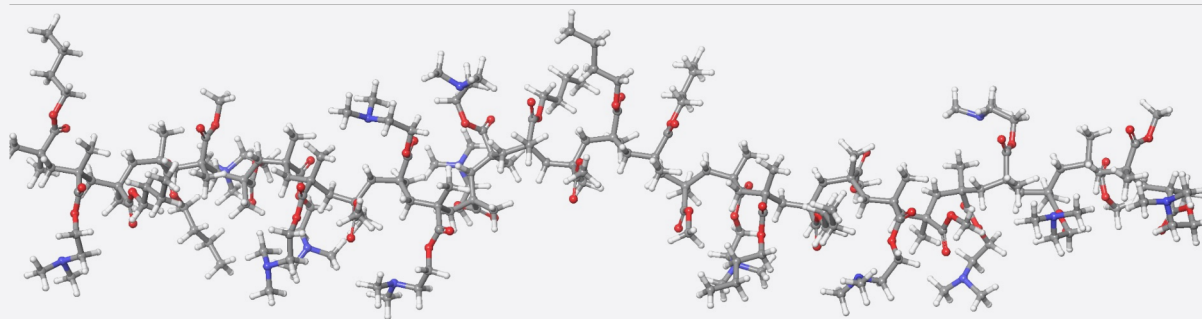
Copovidone



Eudragit L 100

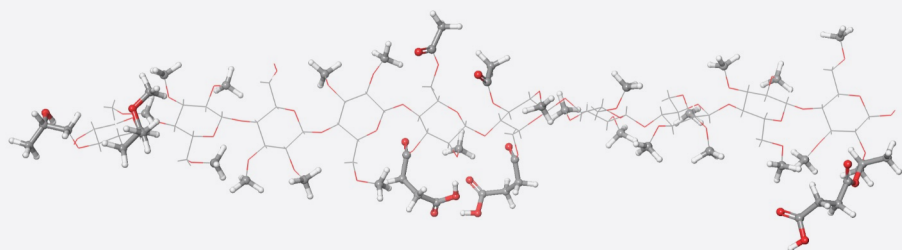


Eudragit E 100

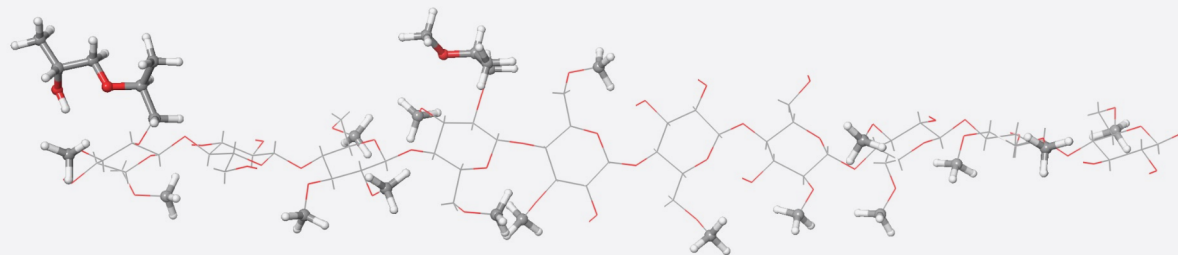


Builders include GRAS and FDA approved excipients

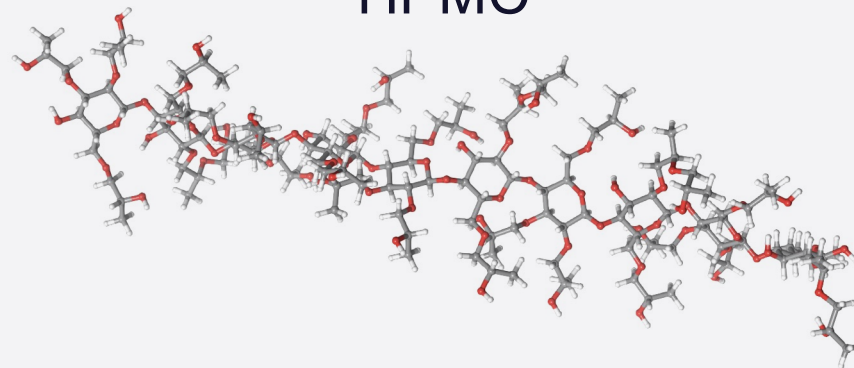
HPMCAS-M



HPMC-E5

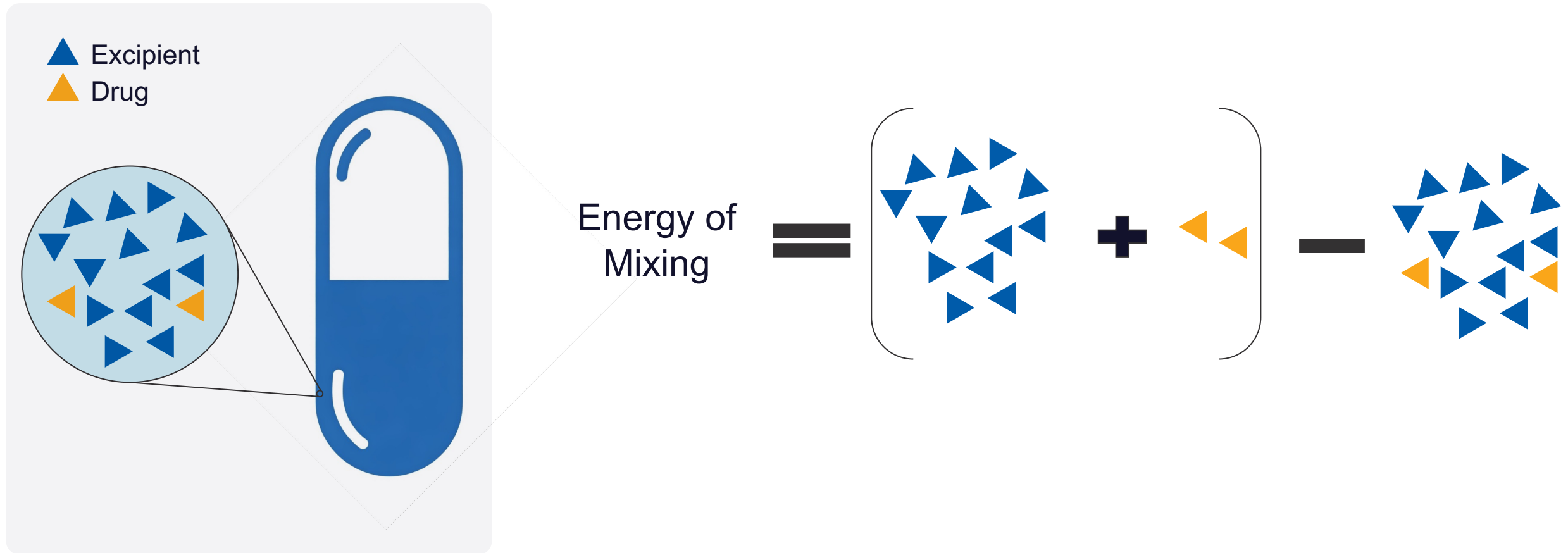


HPMC

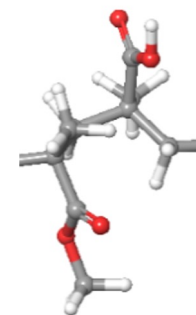
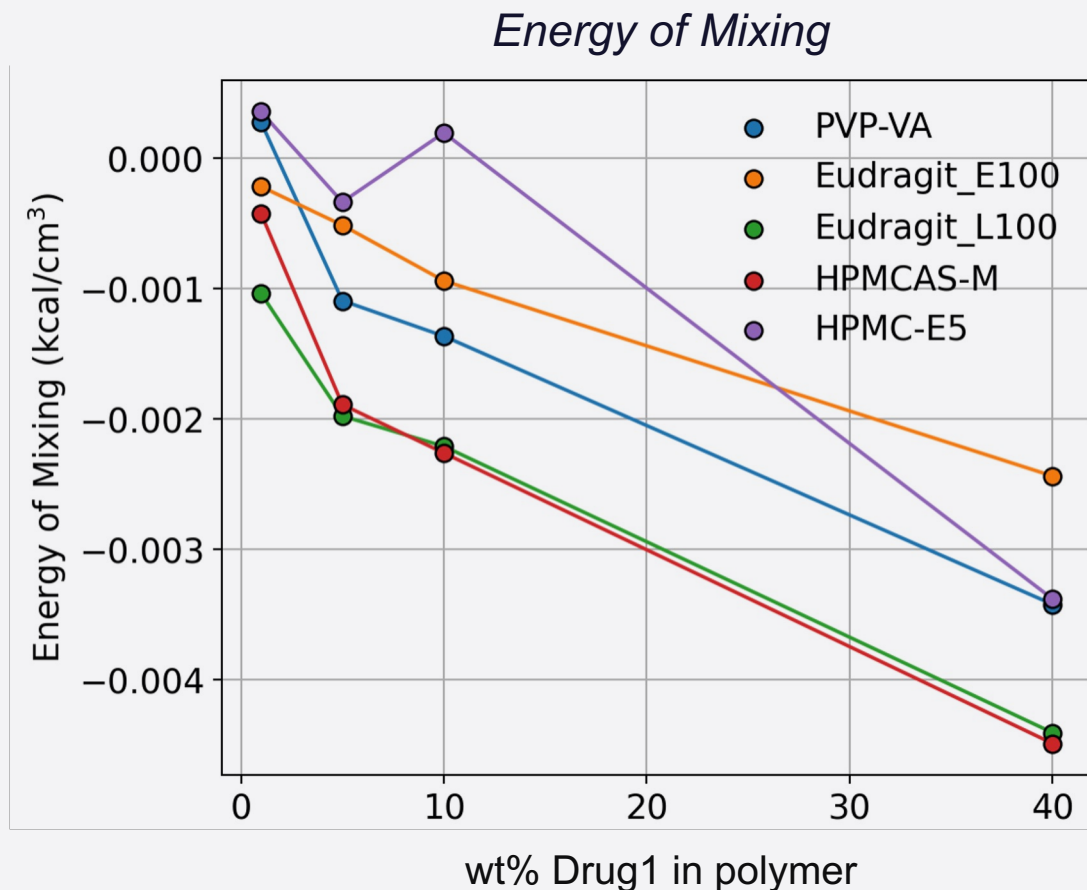


Compatibility: Mixing energy

Directly measure the enthalpic energy between excipient and drug when mixed



Compatibility: Identify a viable excipient



Eudragit L 100



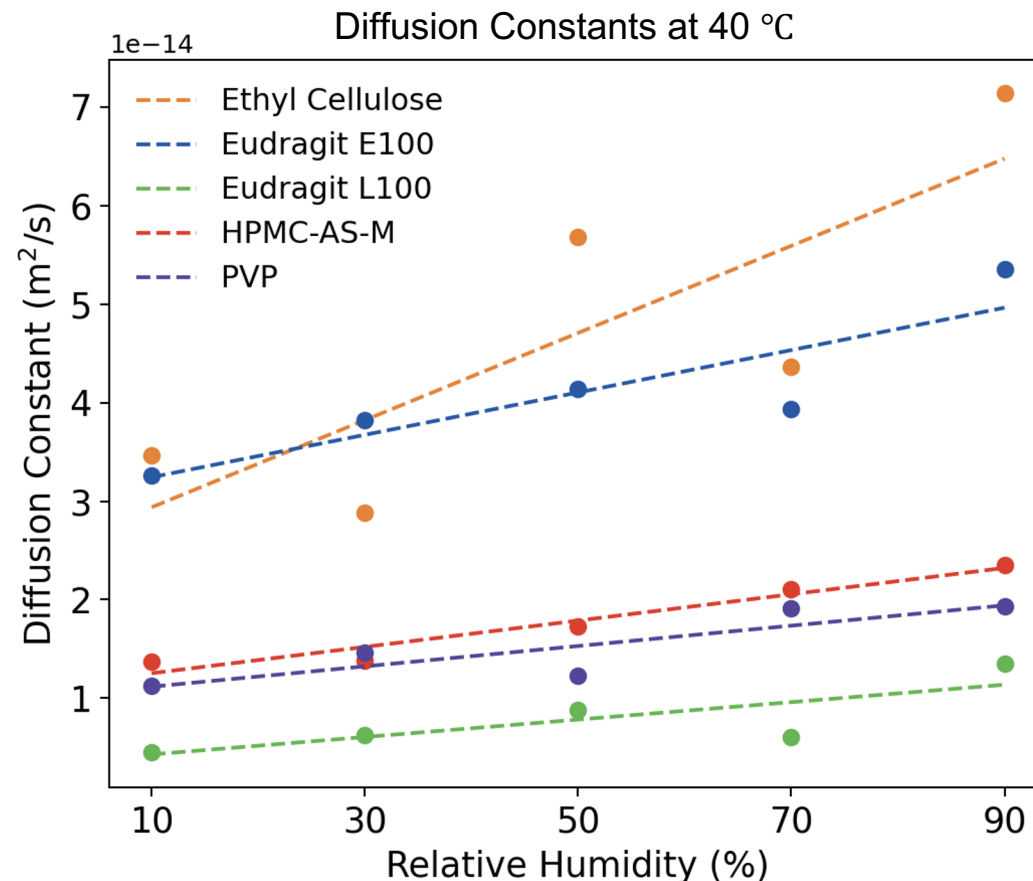
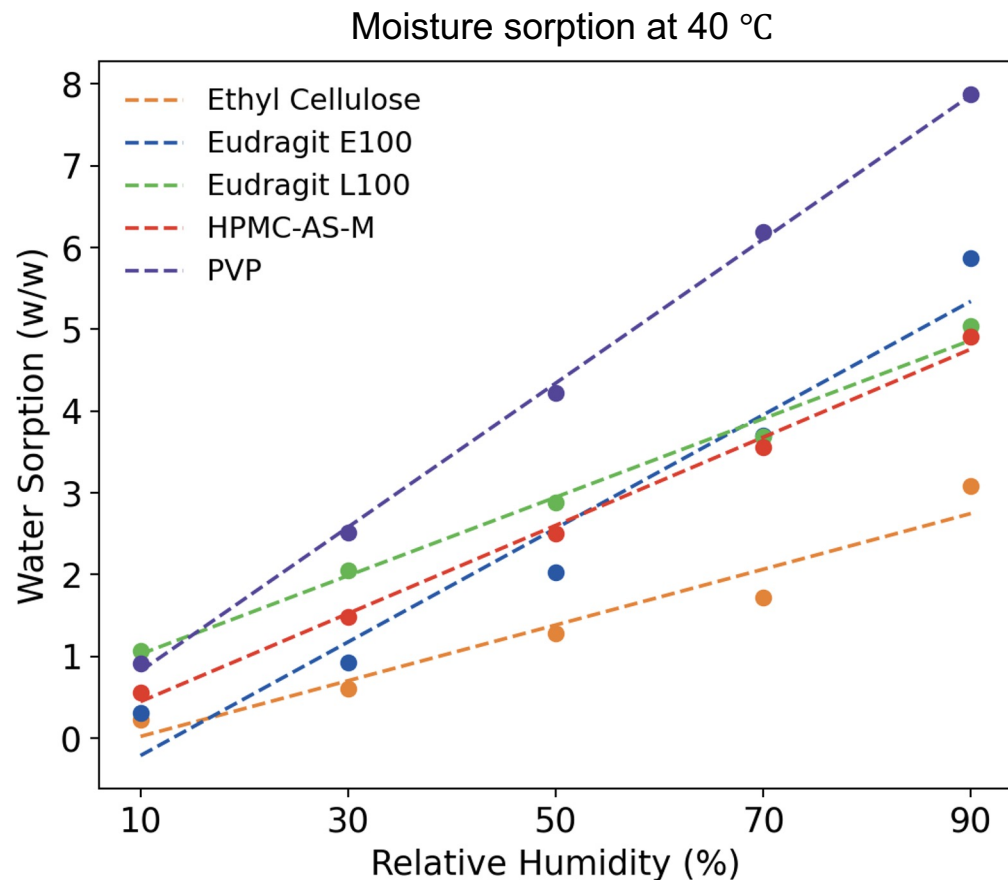
Drug1 mixes favorably with all excipients screened

HPMCAS-M and Eudragit L100 are most compatible

*Error bars hidden for visual clarity.

Property: Moisture sorption

20 w/w Indomethacin in Polymer Excipients



PVP uptakes the most water and **EC** uptakes least. However, indomethacin is most mobile in **EC** with low mobility in **PVP**

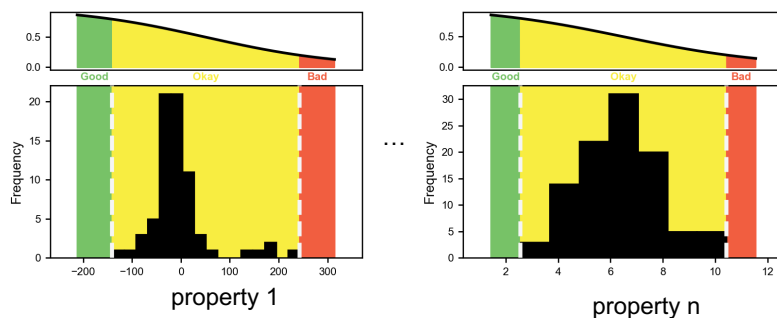
Formulation: Optimize properties with machine learning

- **MS Formulation ML Opt** allows you to optimize materials formulations for a target property
- Automated model building and validation for a given formulations vs. property dataset

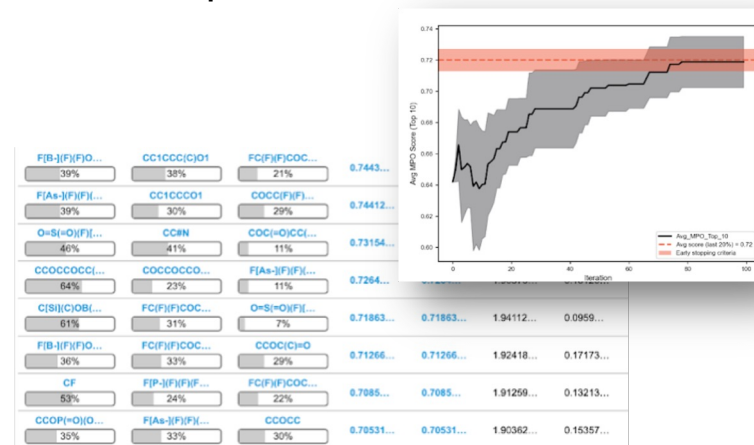
Input {SMILES | composition | property}
dataset in CSV format

Temperature Solubility (mg/ml)	DOE	SMILES_0	SMILES_1	SMILES_2	Drug_ExactMolWeight_1	ExSolvent_2_1a	ExSolvent_2_1b
278.15	0.0002	doi.org/25.15/NC1=CC(N)=CC=C1	NKCC	0	108.066748	41.8265491	18.0105667
278.15	0.002	doi.org/25.15/NC1=CC(N)=CC=C1	NKCC	0	108.066748	41.8265491	18.0105667
278.15	0.0471	doi.org/25.15/NC1=CC(N)=CC=C1	NKCC	0	108.066748	41.8265491	18.0105667
278.15	0.0678	doi.org/25.15/NC1=CC(N)=CC=C1	NKCC	0	108.066748	41.8265491	18.0105667
278.15	0.0897	doi.org/25.15/NC1=CC(N)=CC=C1	NKCC	0	108.066748	41.8265491	18.0105667
278.15	0.0629	doi.org/25.15/NC1=CC(N)=CC=C1	NKCC	0	108.066748	41.8265491	18.0105667
278.15	0.0985	doi.org/25.15/NC1=CC(N)=CC=C1	NKCC	0	108.066748	41.8265491	18.0105667
278.15	0.1181	doi.org/25.15/NC1=CC(N)=CC=C1	NKCC	0	108.066748	41.8265491	18.0105667
278.15	0.1484	doi.org/25.15/NC1=CC(N)=CC=C1	NKCC	0	108.066748	41.8265491	18.0105667
280.65	0.0047	doi.org/25.15/NC1=CC(N)=CC=C1	NKCC	0	108.066748	41.8265491	18.0105667
280.65	0.0084	doi.org/25.15/NC1=CC(N)=CC=C1	NKCC	0	108.066748	41.8265491	18.0105667

Property targets

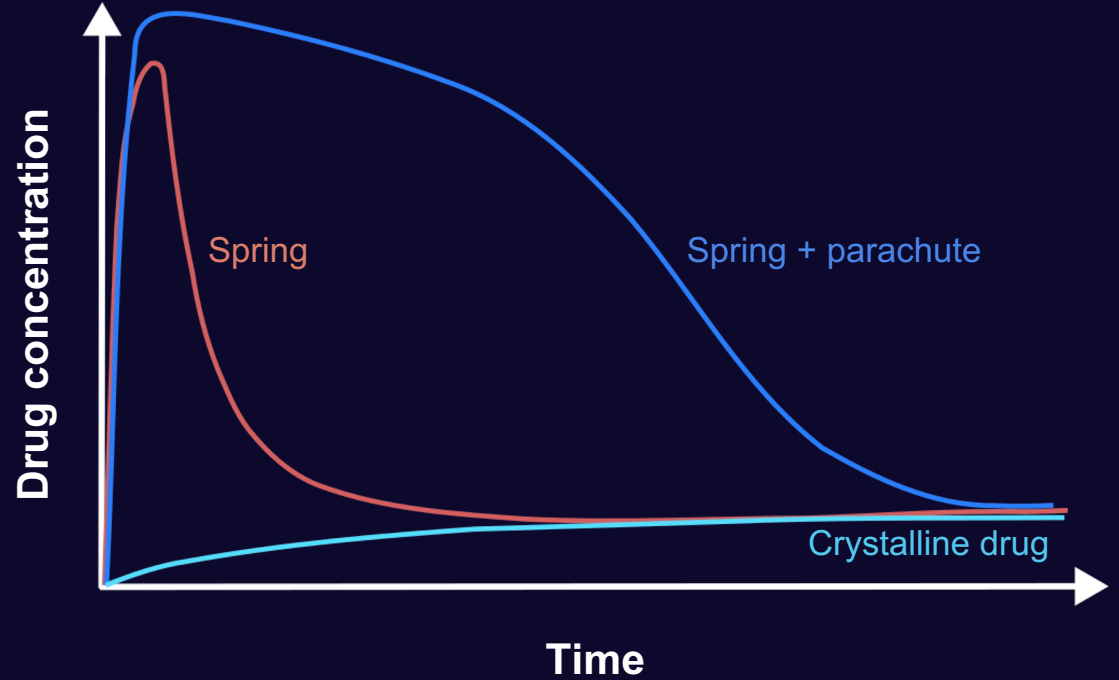
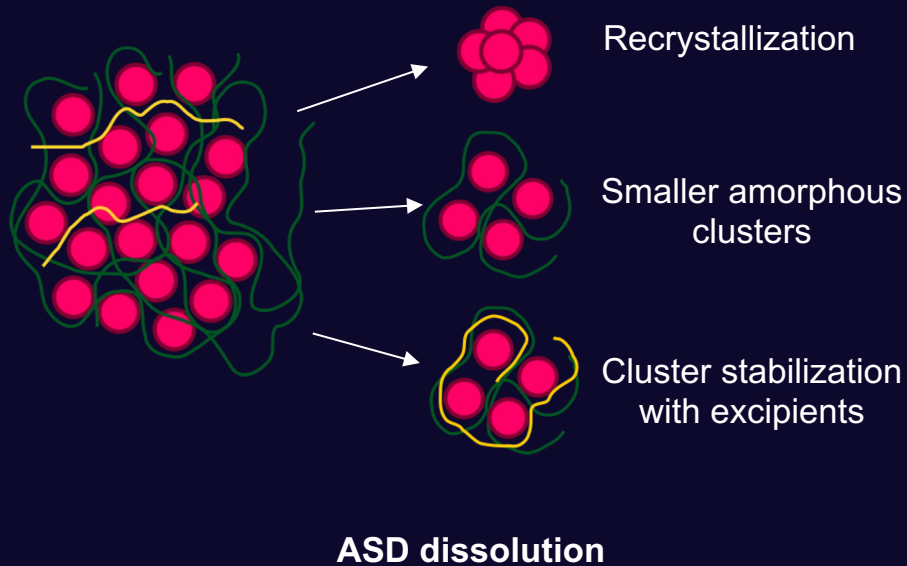


Optimized formulations



Dissolving while keeping supersaturation

- For maximal body absorption, drug solution concentration should be maintained high.
- Recrystallization in solution should be prevented.

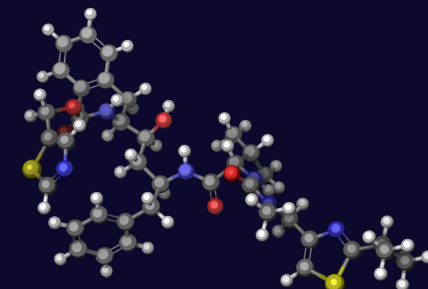


Ritonavir in copovidone

abbvie

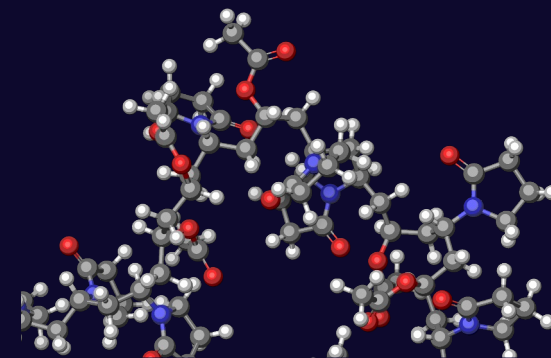
- **Ritonavir:**

- Protease inhibitor molecule acting as an antiretroviral against HIV/AIDS.
- Low aqueous solubility. [1]
- High lipophilicity. [2]
- Tendency for polymorphic transitions. [3]



- **Copovidone (PVPVA):**

- Water-soluble copolymer of vinylpyrrolidone and vinyl acetate.
- Amphiphilic properties. [4]
- Stabilization of amorphous forms. [5]
- Versatility in processing. [6]
- Biocompatibility and safety. [7]



[1] Kalepu, S. and Nekkanti, V., *Acta Pharmaceutica Sinica B*, 2015, 5(5), 442–453.

[2] Wu *et al.* *Journal of Pharmaceutical Sciences*, 2013, 102, 2444–2454.

[3] Bauer *et al.* *International Journal of Pharmaceutics*, 2001, 320, 1–9.

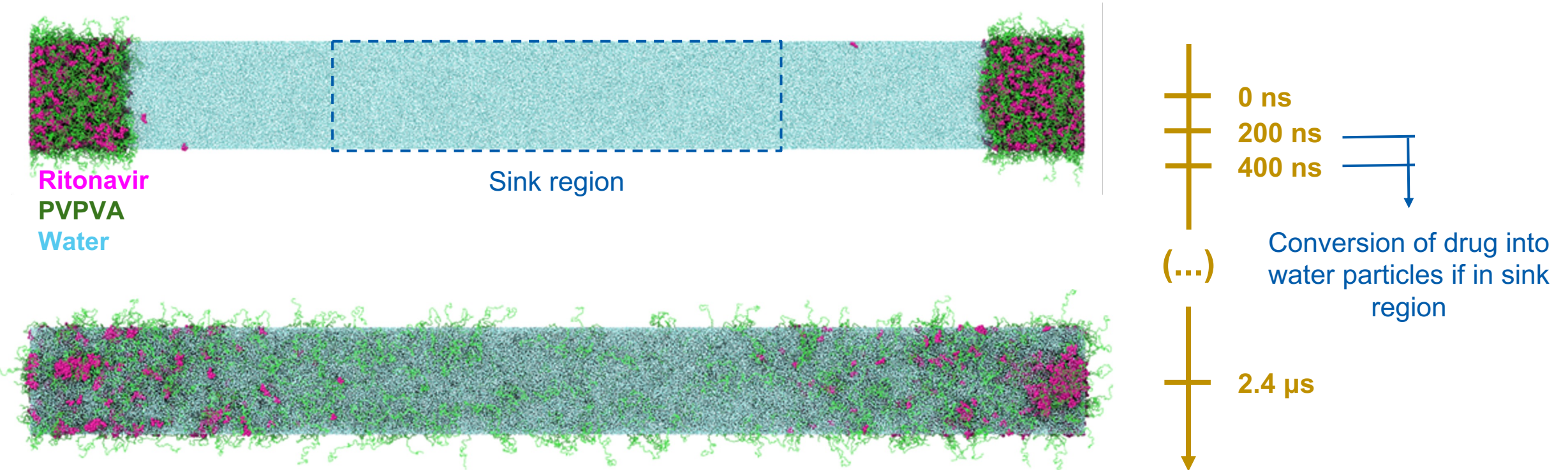
[4] Breitenbach, J., *European Journal of Pharmaceutics and Biopharmaceutics*, 2002, 54, 107–117.

[5] Baghel *et al.* *Asian Journal of Pharmaceutical Sciences*, 2016, 11, 544–559.

[6] Crowley *et al.* *Drug Development and Industrial Pharmacy*, 2007, 33, 909–926

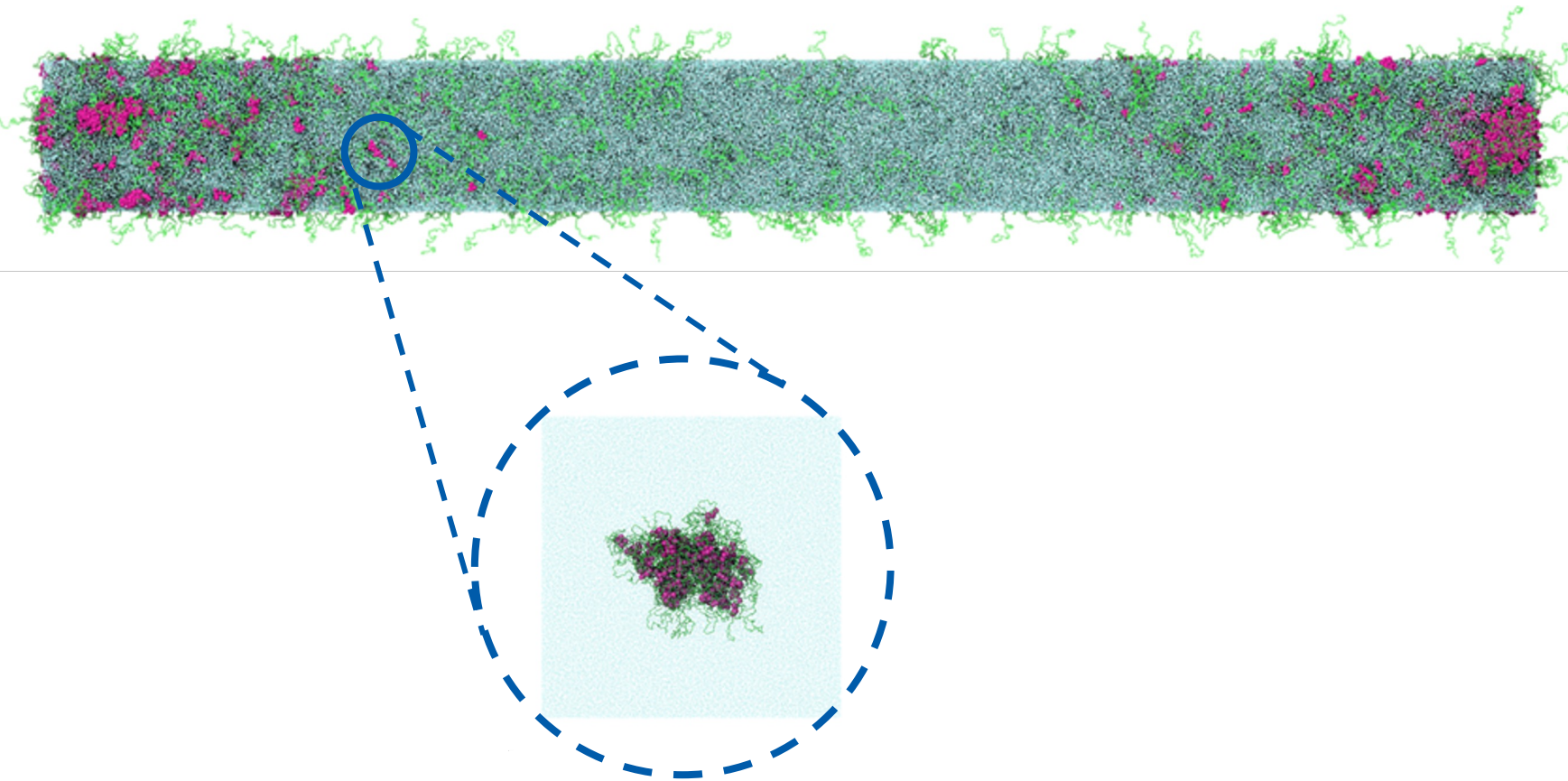
[7] Yoshihashi *et al.* *Journal of Pharmaceutical Sciences*, 2006, 95, 1364–1372.

Early stage dissolution systems



- Conversion of drug molecules into water particles to emulate the dissolution into far away regions
- Process allows studying phenomena in the ~50 nm range

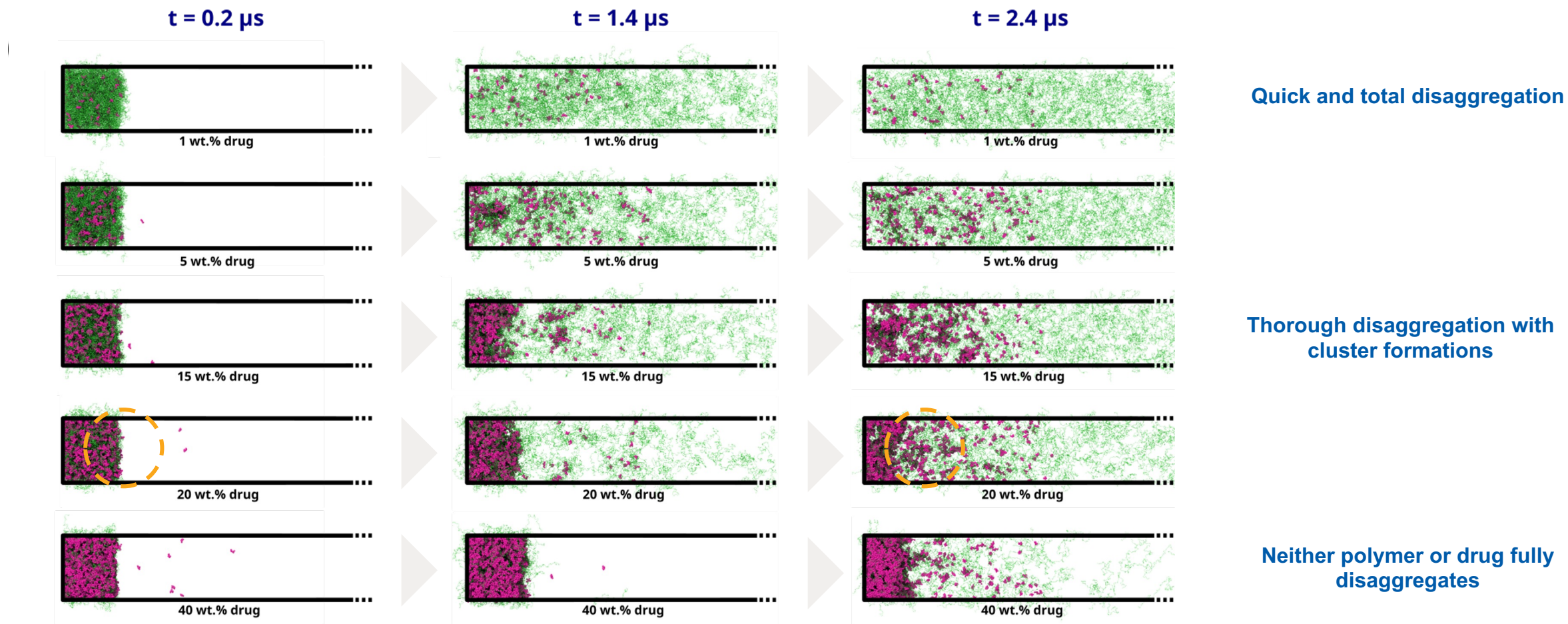
Late stage dissolution systems



- Grants information about organization of ASDs in advanced solubilization states
- Captures water-ASD and polymer-drug interactions at equilibrium

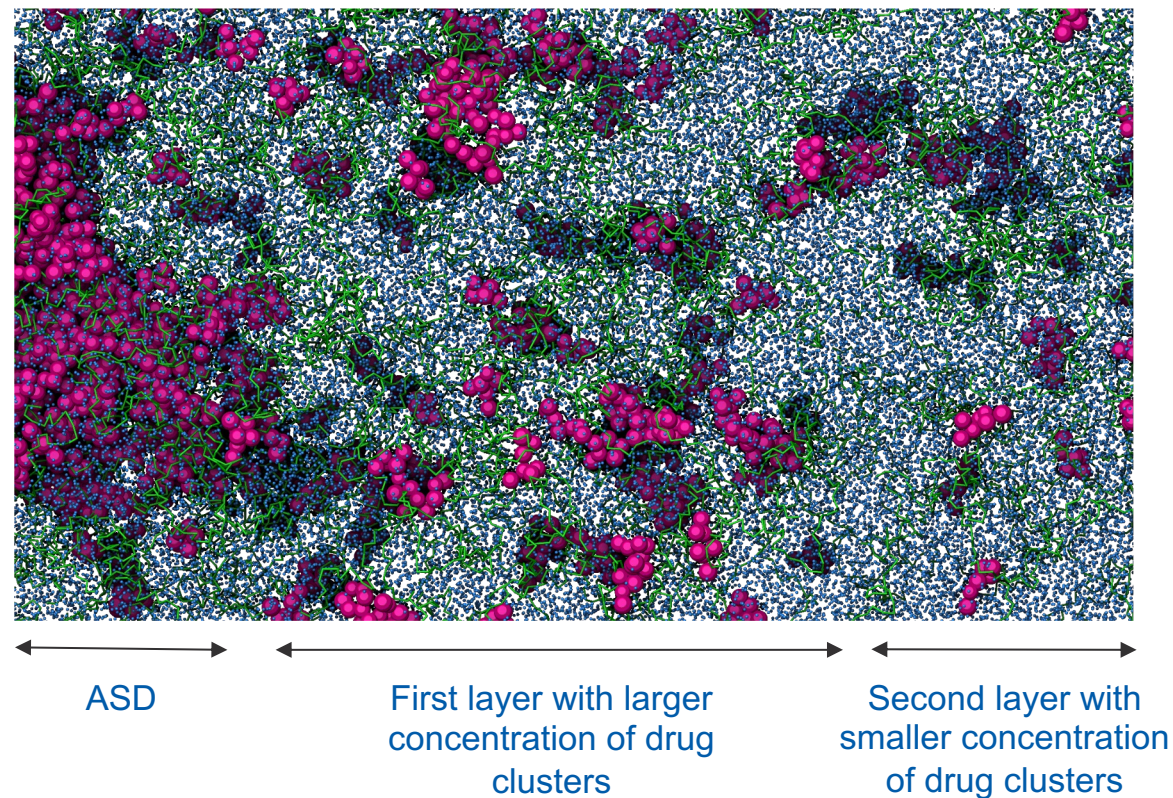
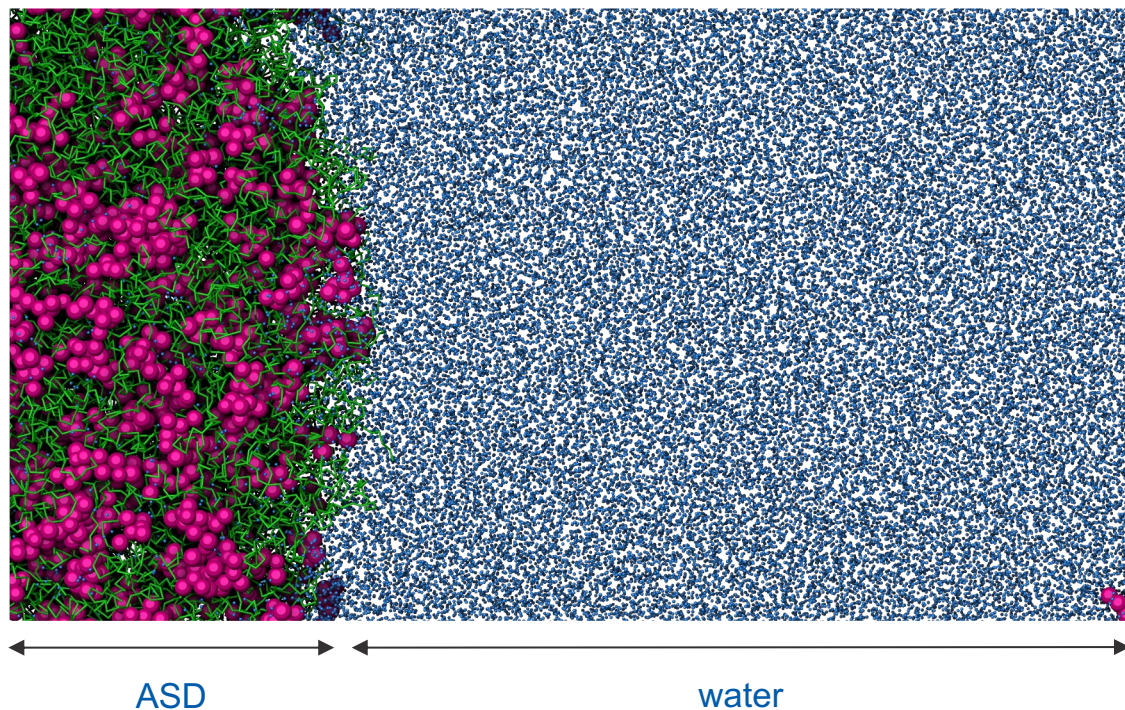
Early stage dissolution simulations

ASD dissolution process is highly dependent on drug load



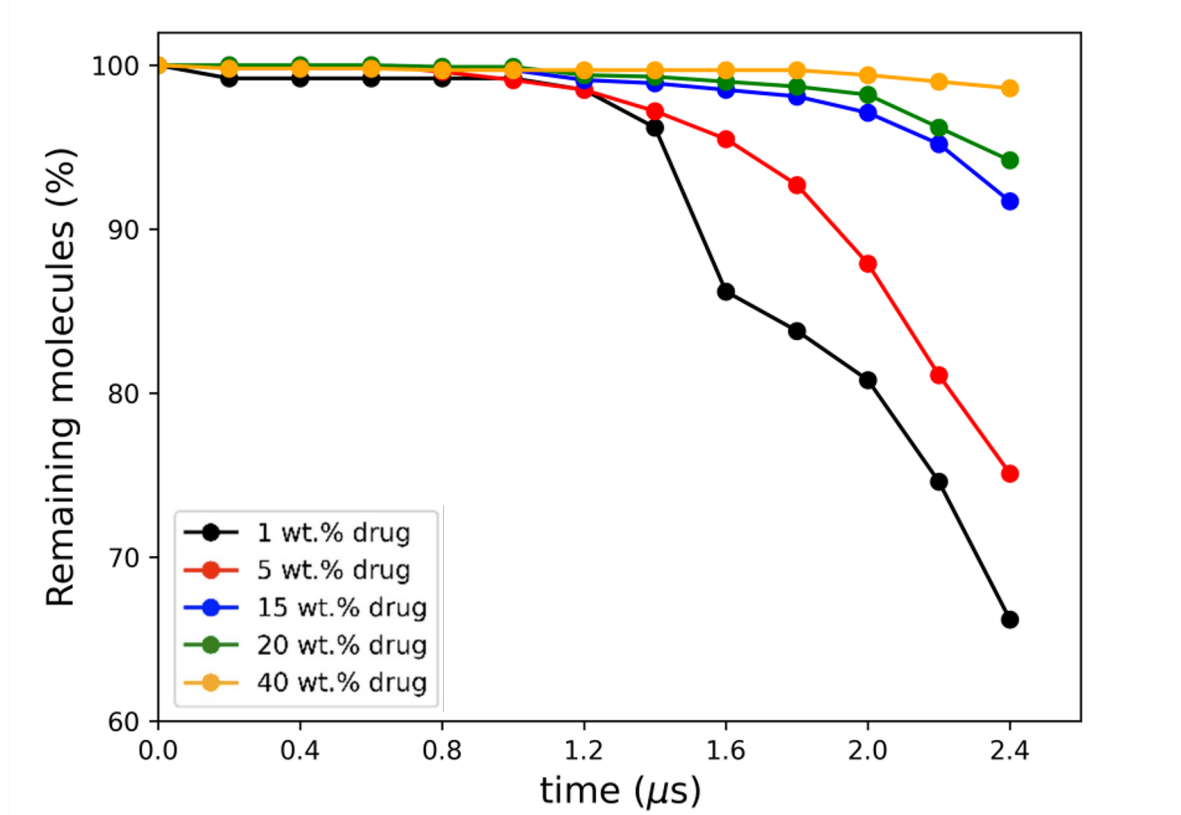
Zooming in the dissolution process

Break down of ASD occurs forming intermediate layers with different drug concentrations



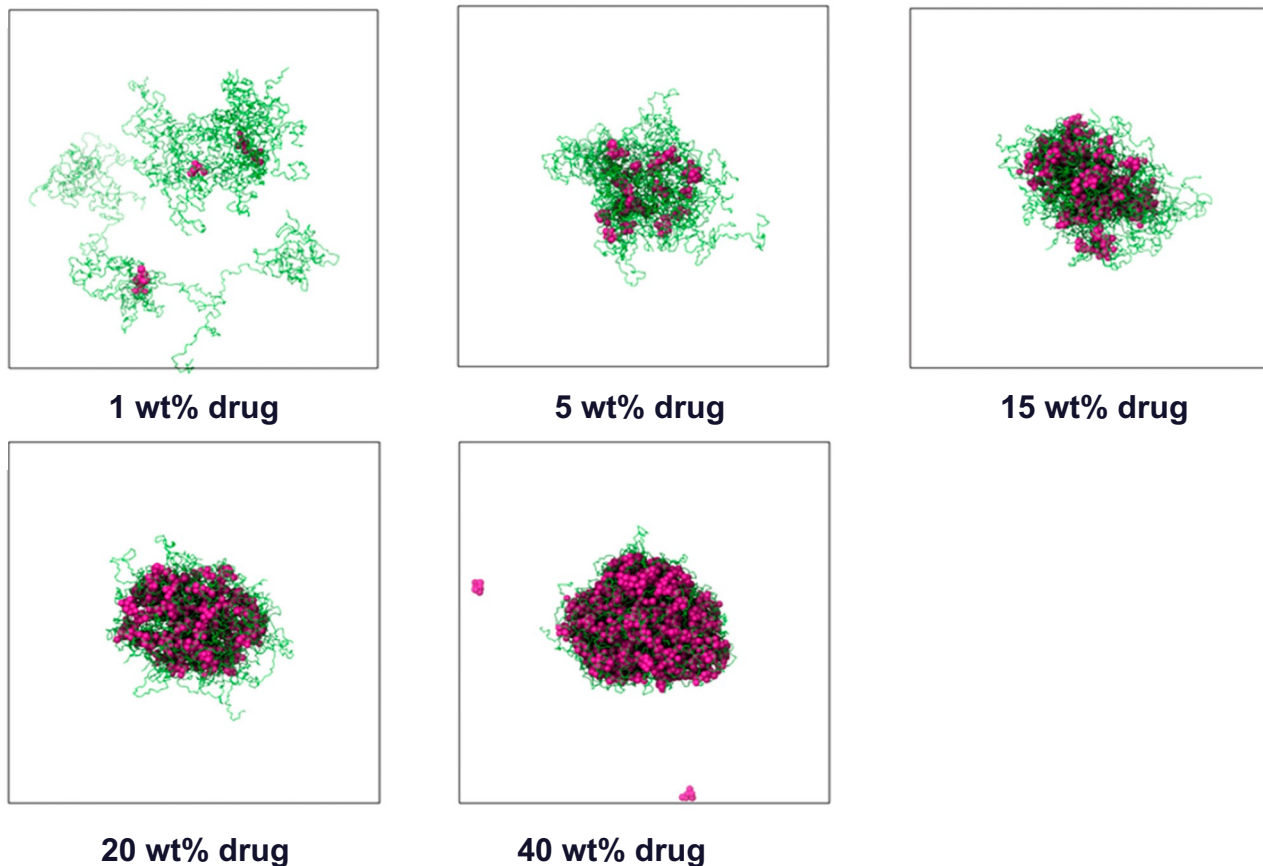
Early stage dissolution simulations

Dissolution slows down with drug load at equilibrium



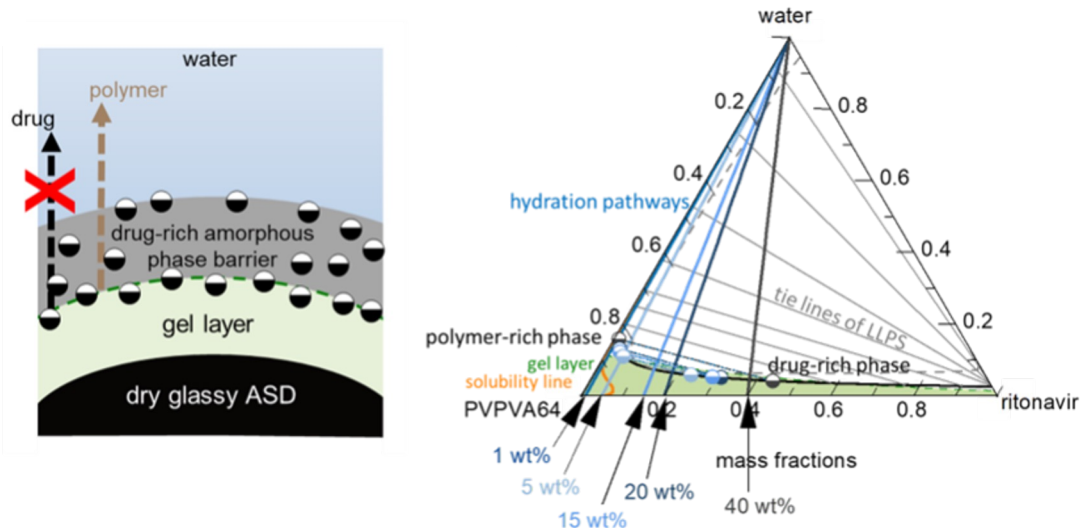
Late stage dissolution simulations

Increasing level of drug aggregation and compactness of main cluster in higher drug loads also observed in snapshots.

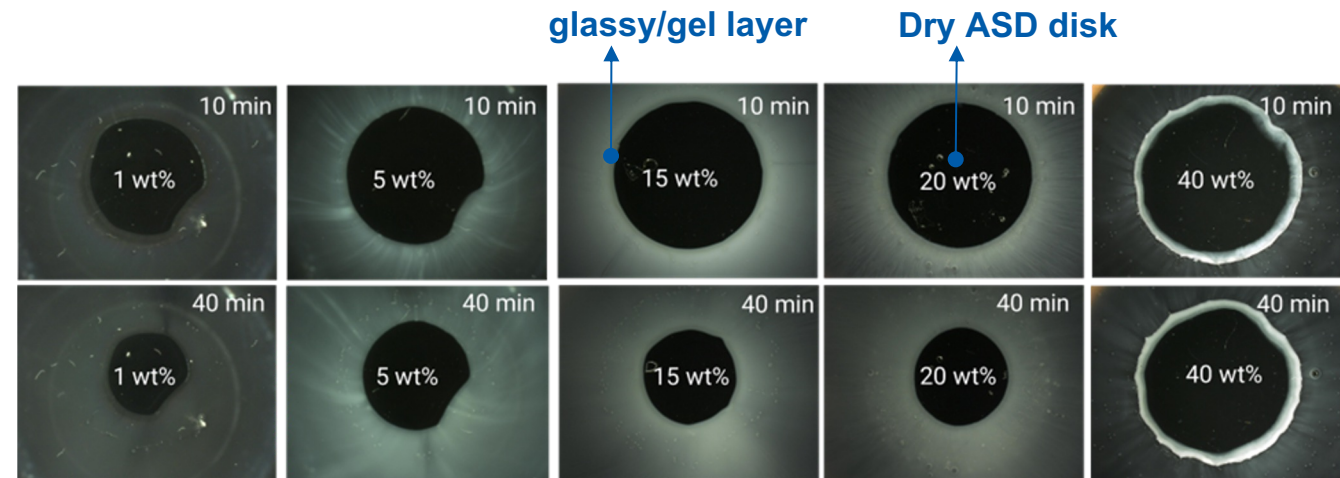


Thermodynamic modeling and experimental results

- AbbVie:
 - Thermodynamic modeling of ASD/water interface.
 - Microscopic erosion time test (METT).

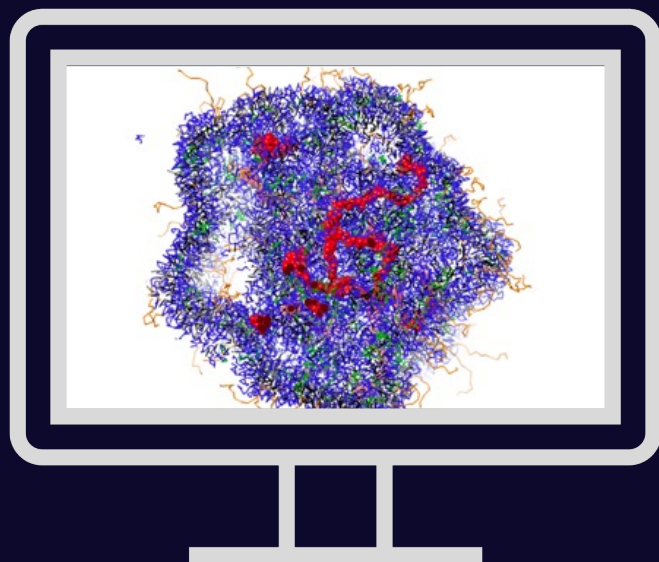


Thermodynamic modeling of ASD interface: hypothesis of intermediate gel-like API-rich layer surrounding ASD disk

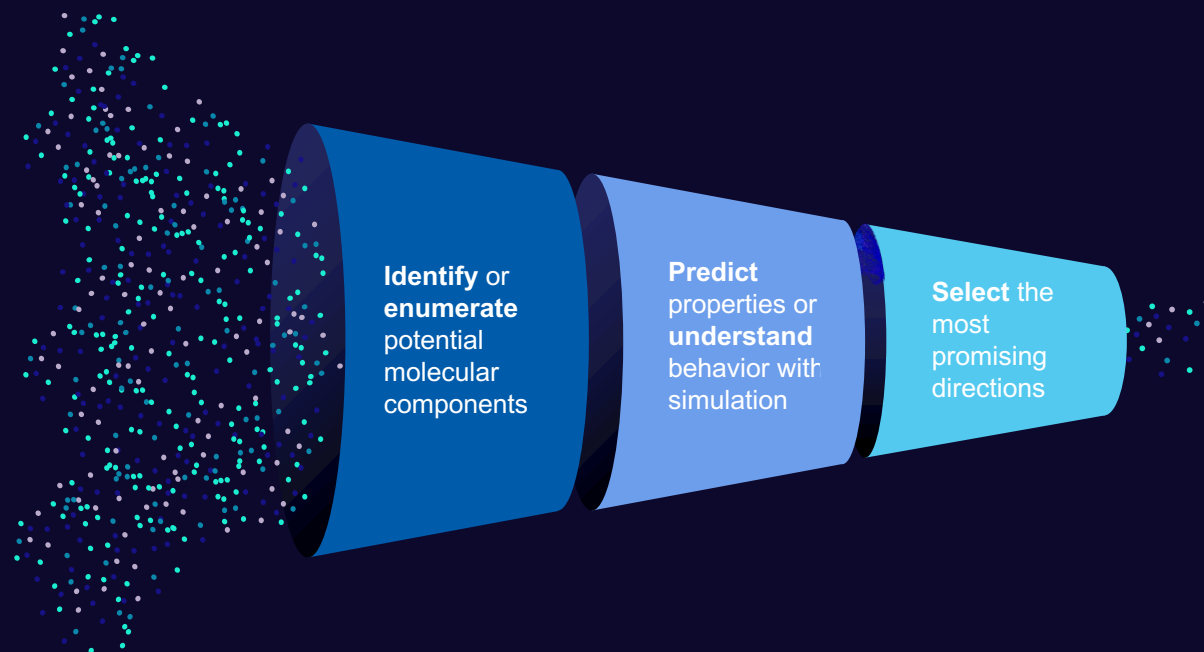


METT: Confirmation of (i) load-dependent release and (ii) formation of intermediate layer between solvent and ASD.

Conclusions



**Simulations yield understanding
of essential molecular and
nanoparticle level structure and
behavior**



**Computational screening
improves efficiency of
formulation development**

How to work with Schrödinger?

We can help with software, technology evaluation, cloud access, workflows, cluster setup, paid research, collaborations

Let's start a discussion
Booth 302

Shiva Sekharan, Sr. Director, Formulations and CSP, Shiva.Sekharan@Schrodinger.com