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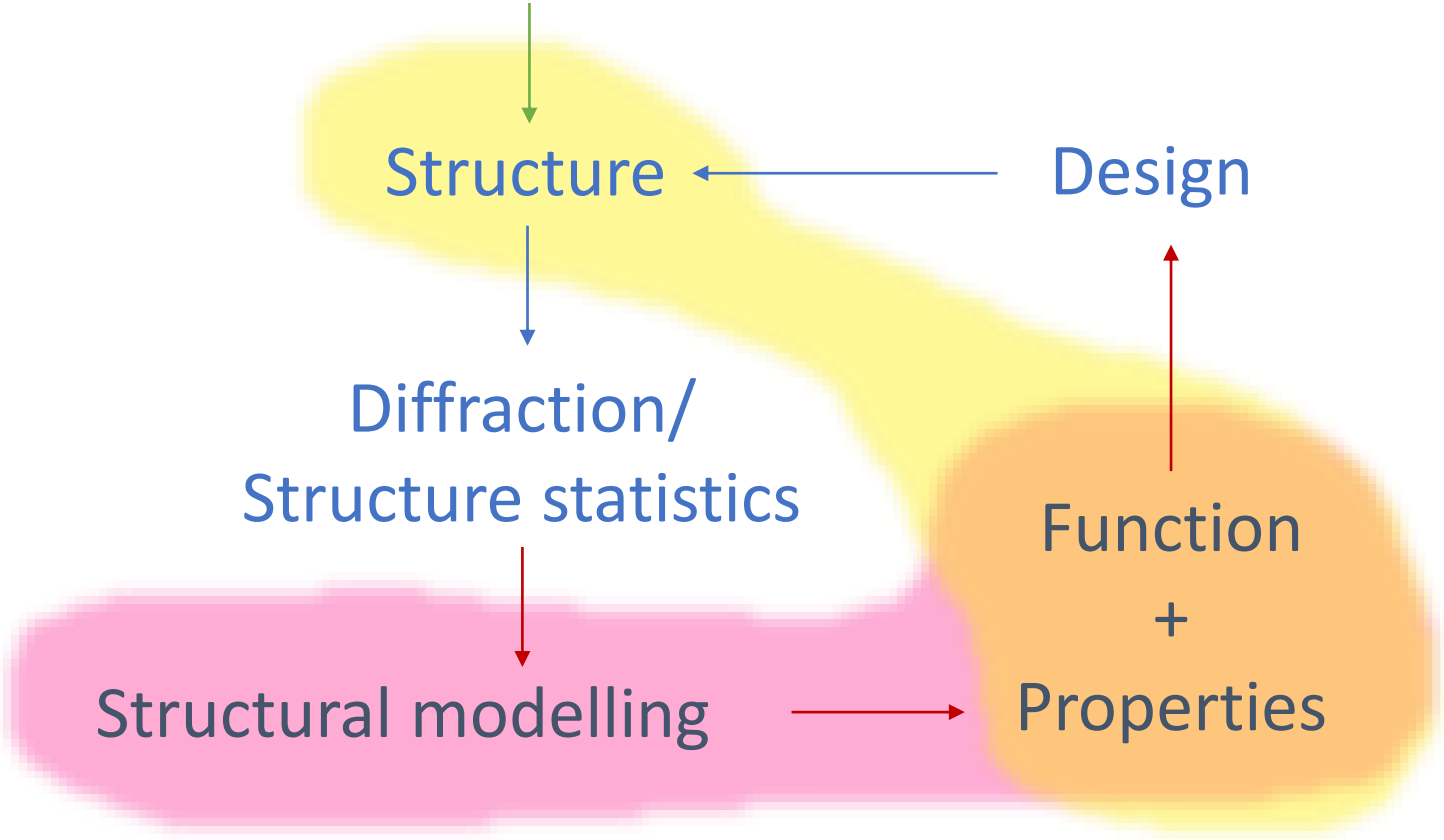
Park Innovaare · Paul Scherrer Institute · Villigen

SWITZERLAND INNOVATION
PARK INNOVAARE

mml molecular modelling laboratory

R&D mandate:
develop hybrid computational/experimental solutions for the Life Sciences



MML applies:

- High-throughput quantum chemical modelling
- State-of-the-art electron microscopy
- Artificial Intelligence (AI) heuristics

to the research and development of:

- Drug design
- Immune Interventions

pivoting on:

- Big Data
- Big infrastructures: High Performance Computing (HPC)
- Big Collaborations (HPC Vendors)

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Yes! : opportunity to develop of disruptive decision-support for drug design: are you Quantum-ready?

Classical molecular modelling

Force fields
- Ad hoc API/excipient interactions possible
- Generalized API/excipient interactions not possible:
Thermodynamics → kinetics(API T_g, ASD density, APS)

High-performance Computing (HPC)

INNOVATION

Quantum-ready

Quantum chemical modelling + Spectroscopy

- Bond breaking/formation
- Exact thermodynamics/kinetics
- Direct comparison to spectroscopical properties

- Training of Reactive potentials
- Reactive trajectories (RMC, QMD)
- A priori applicable to any API/excipient combination

Artificial Intelligence

Quantum Chemistry
- Exchange/Correlation parameters
- Reactive potential calibration

Drug design
- Unprocessed API/excipient: interactions (QMC/QMD database)
- Unprocessed API/excipient: properties (API Tg, ASD density)
- Unprocessed API/excipient: APS trends

Quantum Computing

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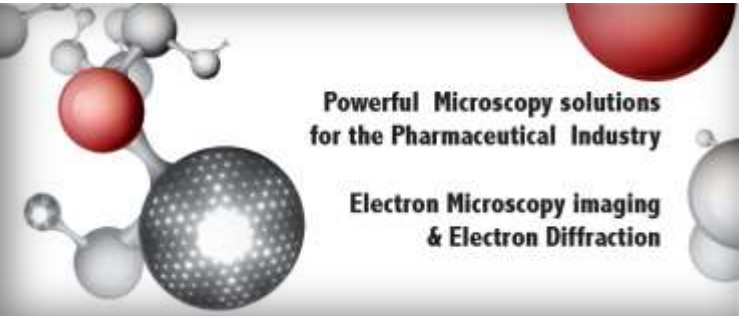
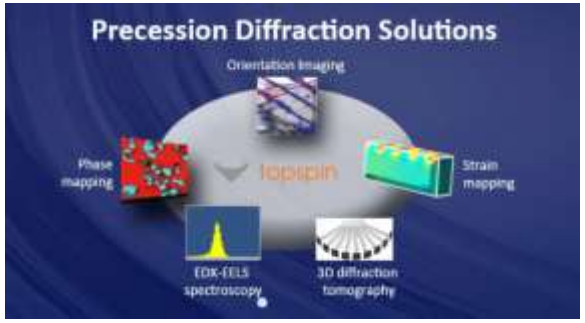
NanoMEGAS

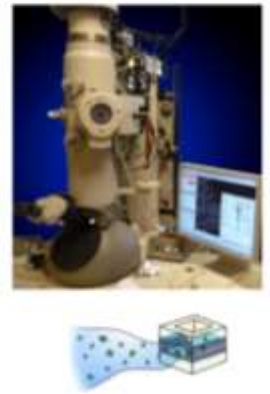
Advanced Tools for electron diffraction



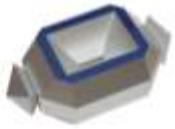


Imaging structures in native liquid

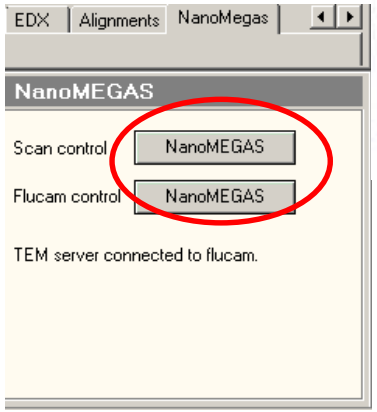
Liquid Cells (LC) in TEM allow to do image , electron diffraction and EDS analysis of samples in liquid



(Top) Poseidon Liquid cell holder (image courtesy Protochips Inc) LC-TEM schematics (bottom) showing native liquid solution contained between two amorphous SiN thin layers (50 nm).Liquid can be sealed and imaged in TEM

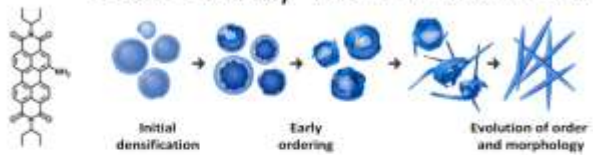


Patented holder



NanoMEGAS TEM button!

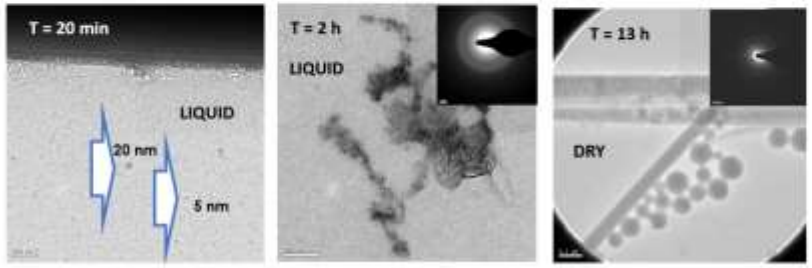
Case study : Chemical reaction pathway in liquid



Crystallization mechanism of perylene diimide has been studied by cryo-TEM

Schematic representation of crystallization pathway of perlylene dimide (left) three main stages of continuous order development are depicted (Coutesy Dr. Tsarfati Weizmann Inst Science, Israel)

Crystallization pathway /crystal nucleation) is different (regarding size/shape of crystals) in standard conditions compared with one at LC-TEM , where crystallization emerges after 13 h



Crystal growth experiment of perylene diimide with LC-TEM at different time frames.

- > 190 installations worldwide
- > 850 articles in 15 years

NanoMEGAS was found in 2004 , Brussels , Belgium and provides advanced electron diffraction (hardware/software) solutions to TEM microscopes worldwide

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Microsoft Azure

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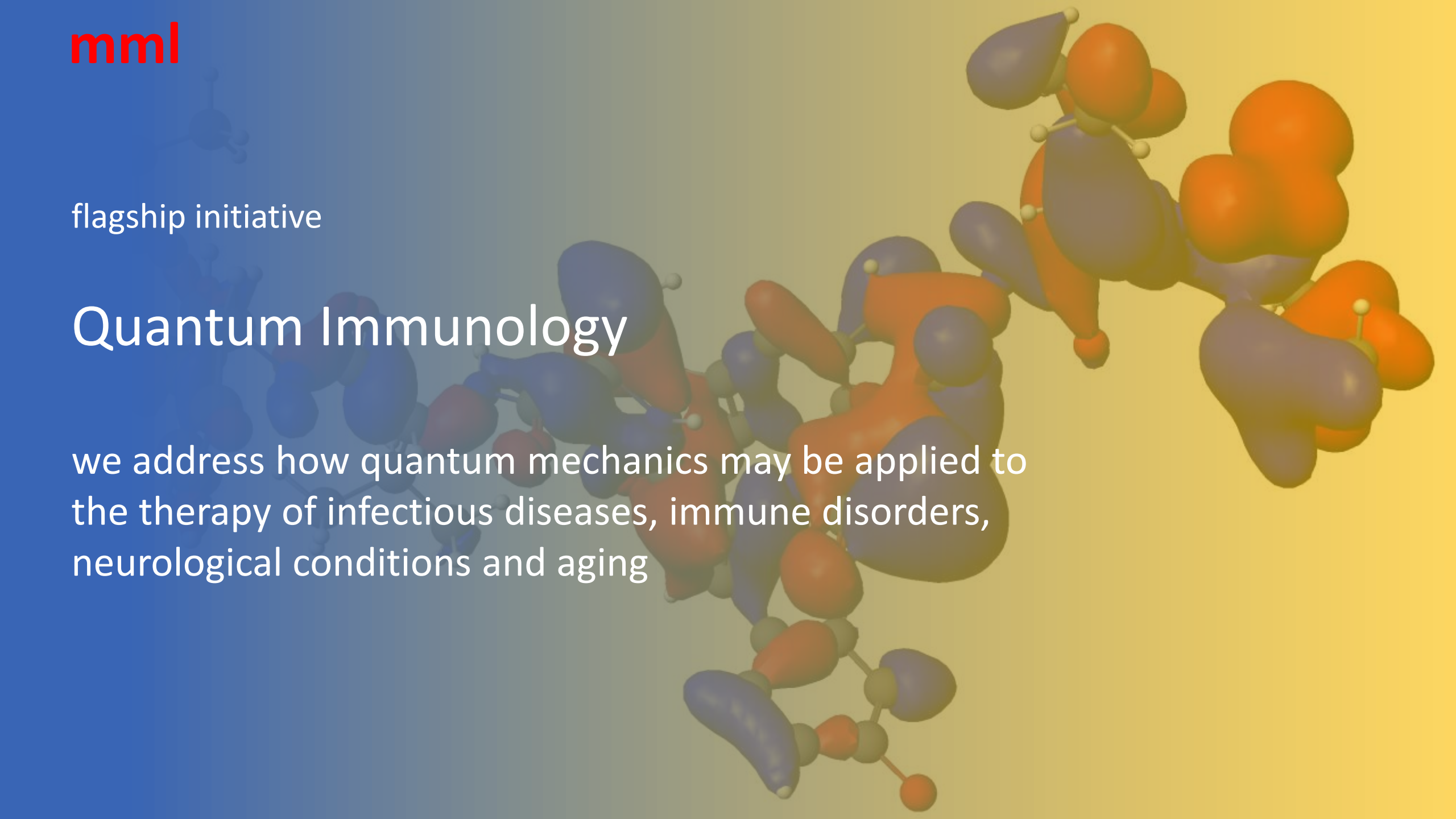
flagship initiative

Quantum Immunology

we address how quantum mechanics may be applied to the therapy of infectious diseases, immune disorders, neurological conditions and aging



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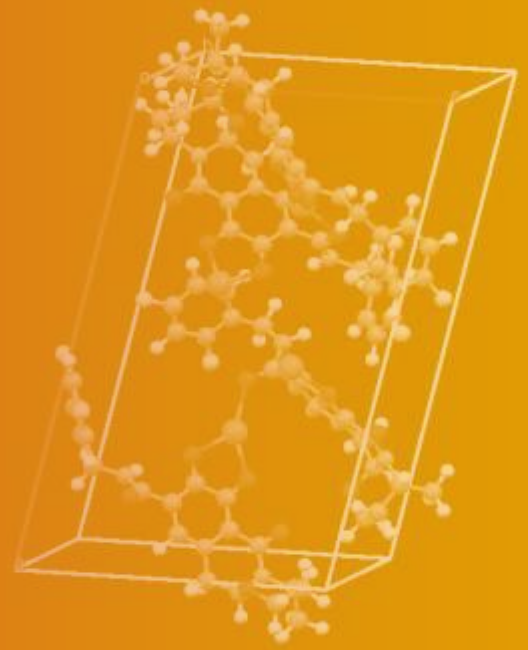
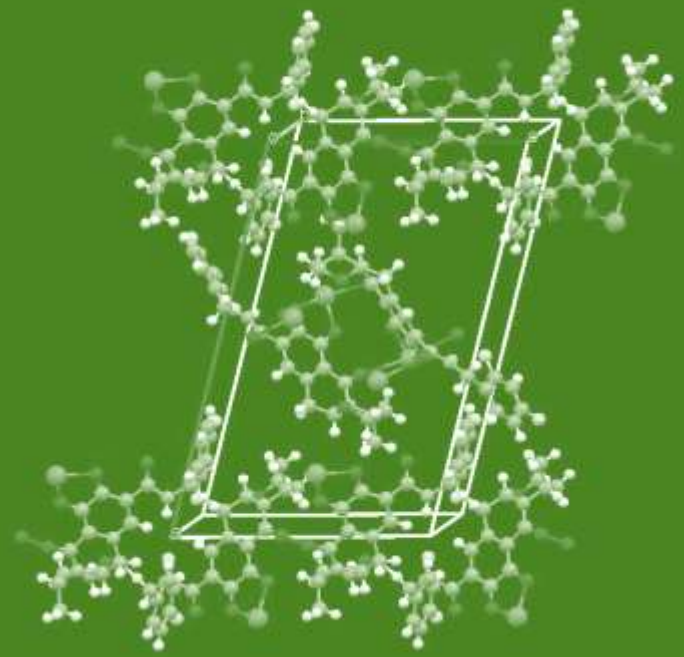
drug discovery

Organic polymorphs

we apply inverse modelling, Electron Energy Loss Spectroscopy (EELS) DFT-TD first-principles to detect new pharmaceutical polymorphs





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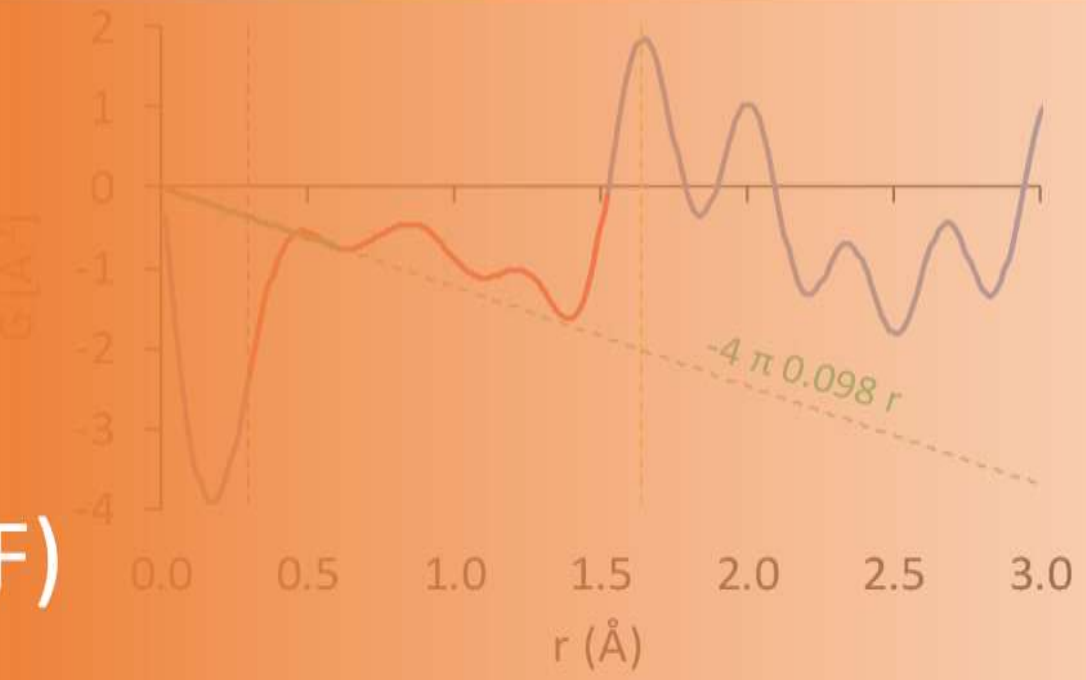
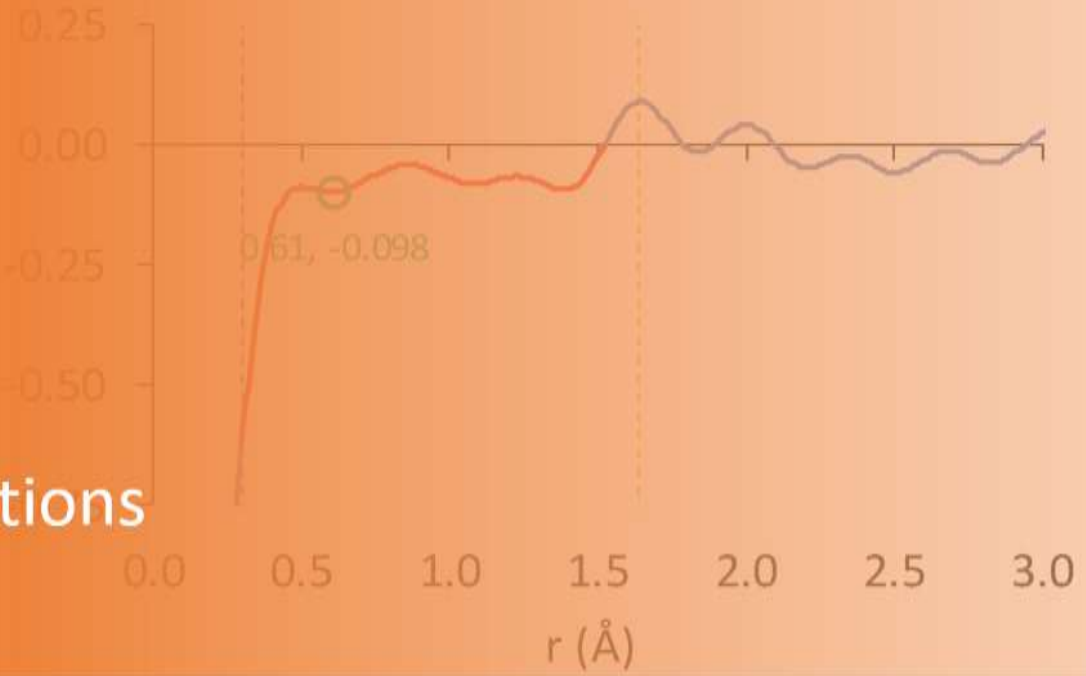
pharmaceutical phase quantification

Pair Distribution Function (PDF)



a combination of state-of-the-art electron spectroscopy and High-Performance Computing enabling the quantification of phases and the detection of solid-state miscibility and stability in pharmaceutical compounds via use of pair correlation functions



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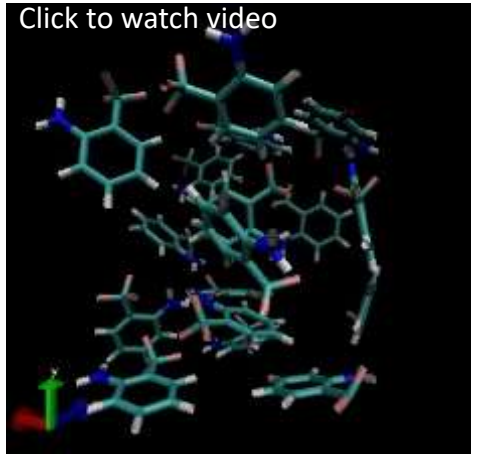
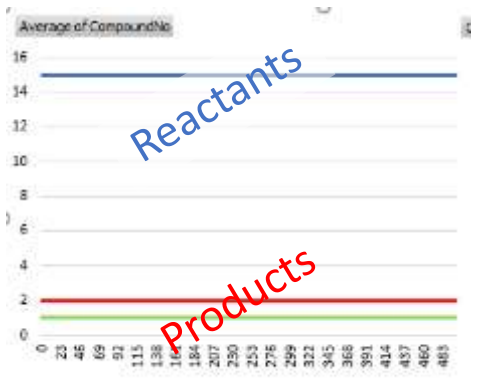
Chemical reactivity (e.g. API degradation, mesoscale dynamics)

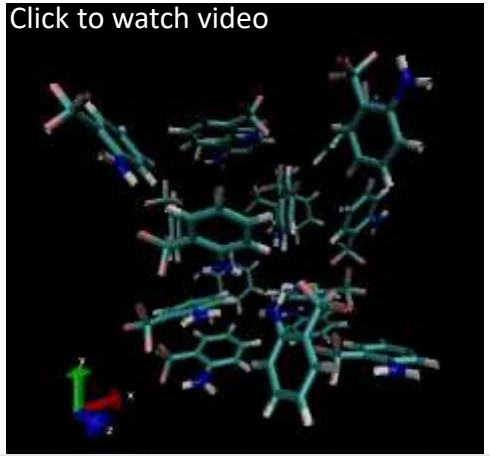
In an initial trial of the applicability of this method, we screened the chemical behavior of a molecular liquid. The system was known to be stable at room temperature, exhibiting a seemingly autocatalytic decomposition, commencing at high temperatures, accompanied by pressure buildup and in the absence of detectable chemical etching. Among other physical properties provided, the system's mass density at room temperature was known. On the basis of the results comprising 500 Monte Carlo frames each, we were successful in predicting the system's density (not shown) and chemical degradation as a function of increasing temperature while at the same time accounting for reaction products formed. All results were in full accordance with experimental data.

Room temperature (RT)
no reactivity

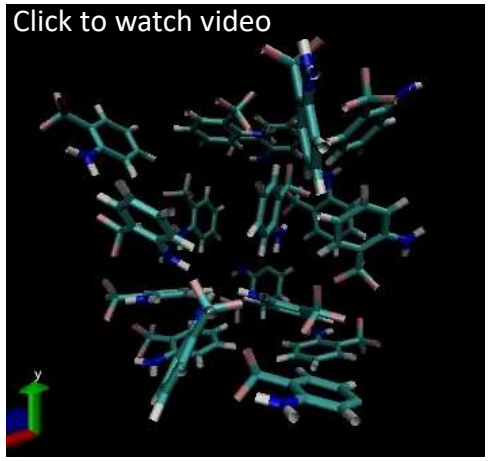


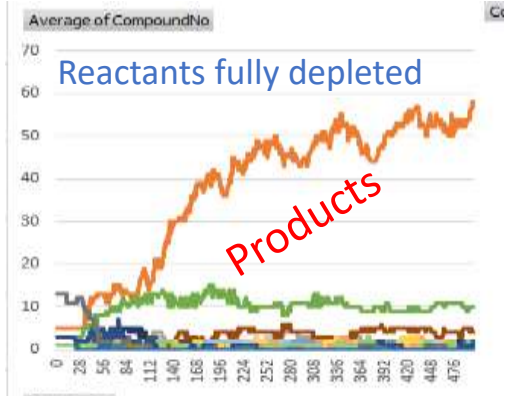


~ 2 x RT
limited reactivity

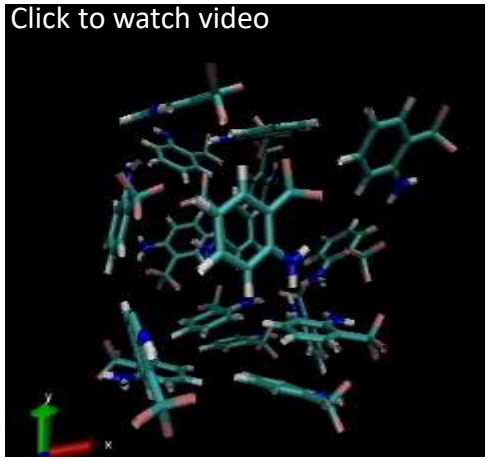


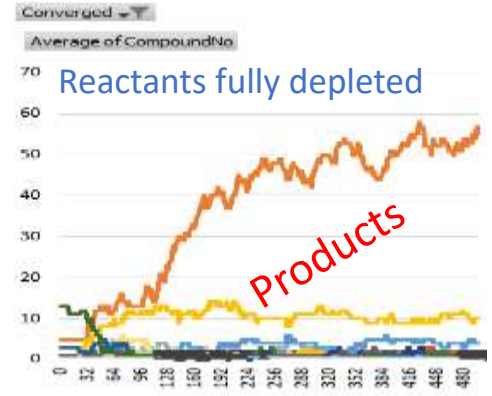
Intermediate temperature
decomposition onset





High temperature
complete decomposition





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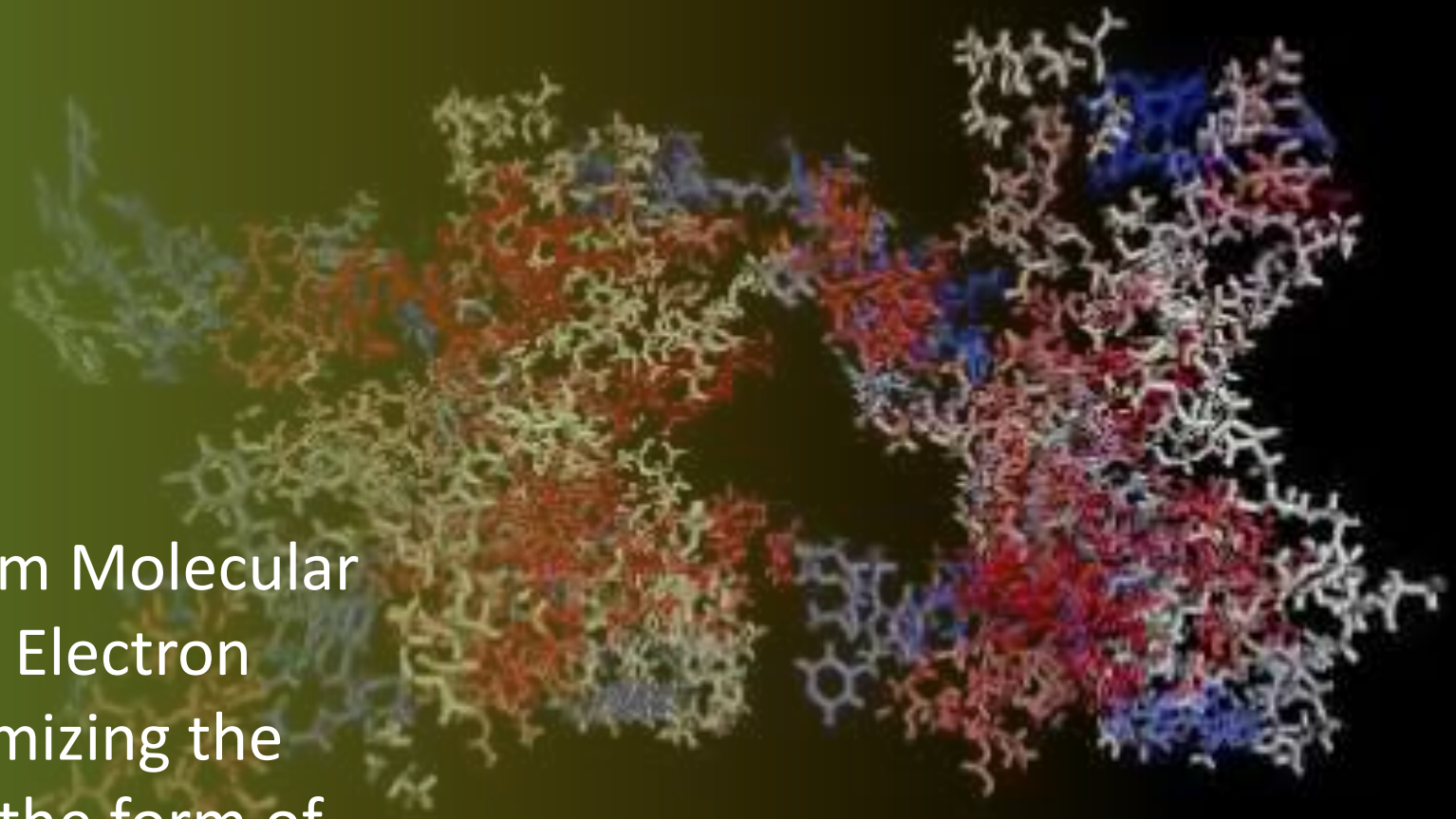
drug design

Amorphous Solid Dispersions (ASD)



High-throughput Quantum Molecular Dynamics constrained by Electron Diffraction aimed at optimizing the design of drugs dosed in the form of ASDs

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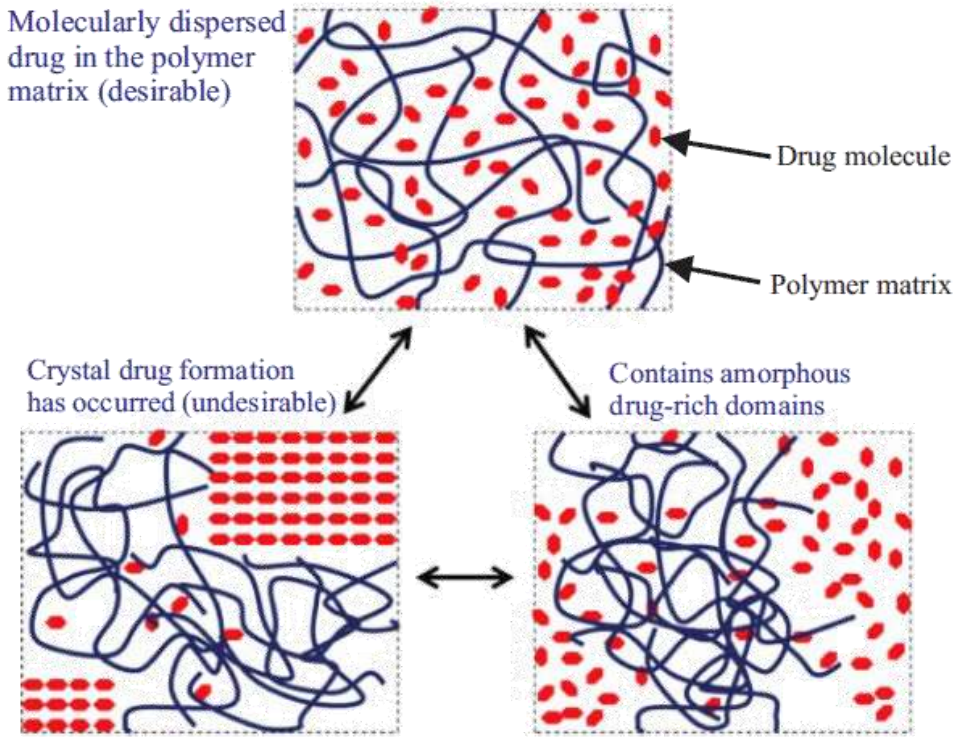
Prediction of ASD physical stability

- API solubility limit (-> API recrystallization time)
- Unattended + high-throughput
- Directly comparable to ASD stress tests
- Purely ab initio -> No semi/empirical correlations/term fitting required
- Avoid modelling the API crystalline phase (polymorphism)

Aim: Pre-formulation screening tool for optimal excipient selection



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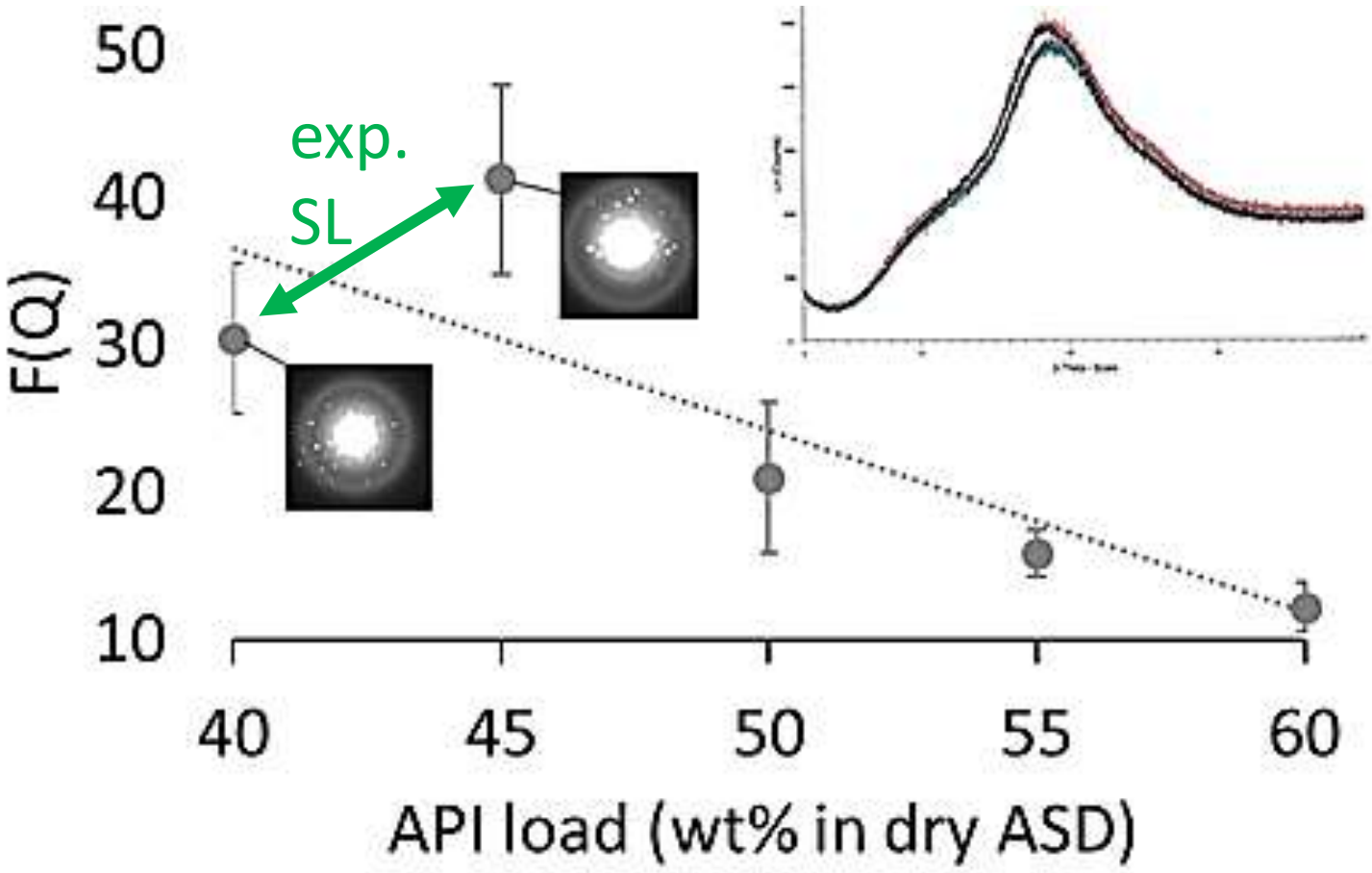
First-principles' prediction of ASD physical stability

Background + motivation

- PXRD-amorphous ≠ TEM-amorphous
- TEM electron diffraction of purely amorphous (am) ASD sites flags a correlation of API SL vs. am ASD structure



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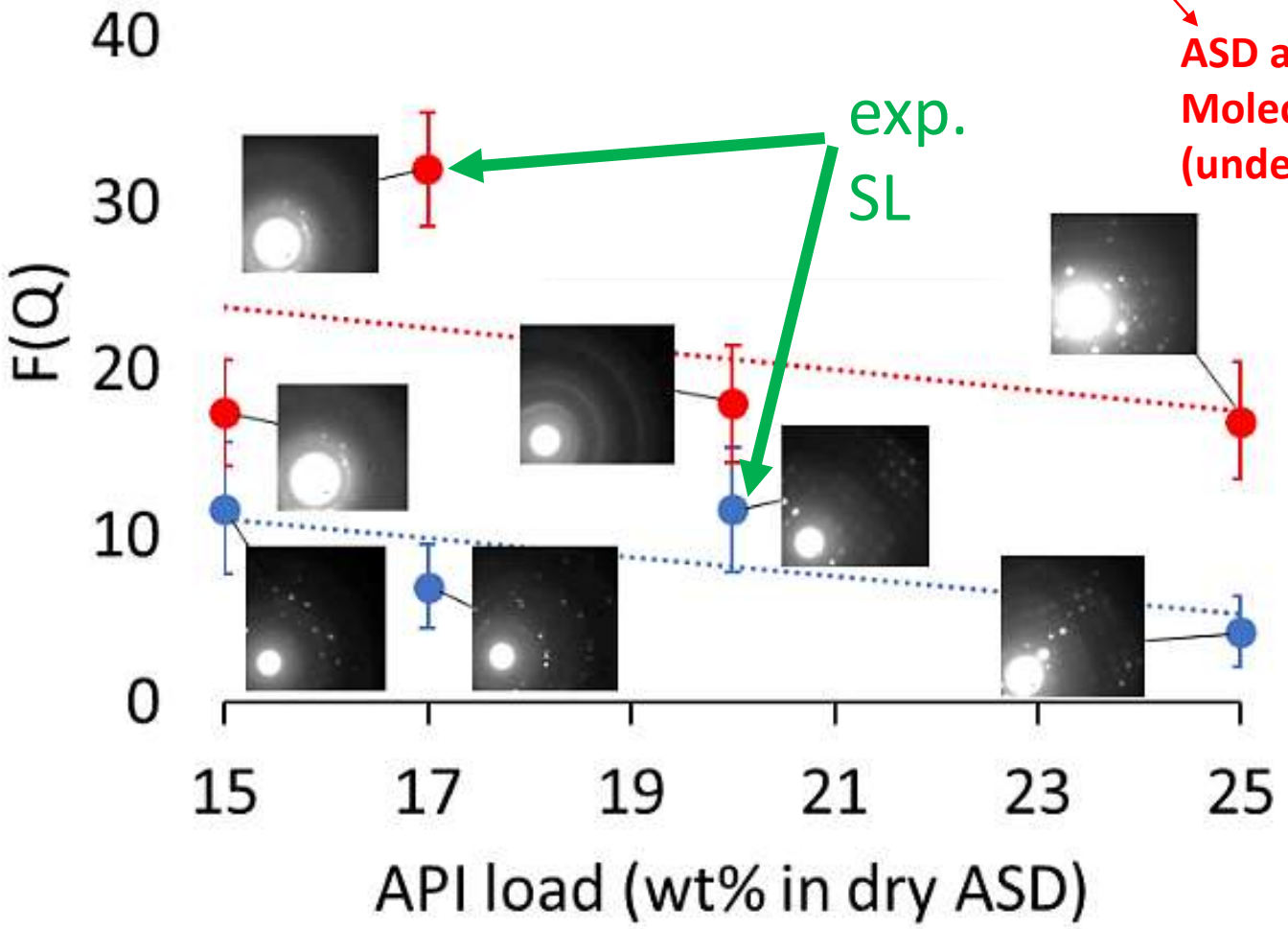
First-principles' prediction of ASD physical stability

Background + motivation

- PXRD-amorphous ≠ TEM-amorphous
- TEM electron diffraction of purely amorphous (am) ASD sites flags a correlation of API SL vs. am ASD structure

ASD am structure
Molecular Modelling energ. + kin.
(under the effect of thermal motion)



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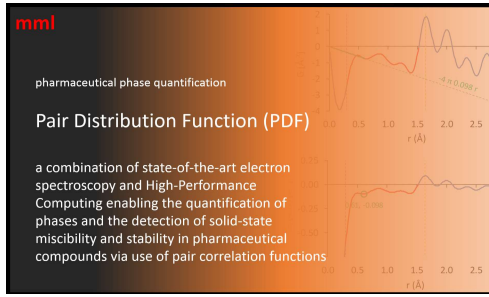
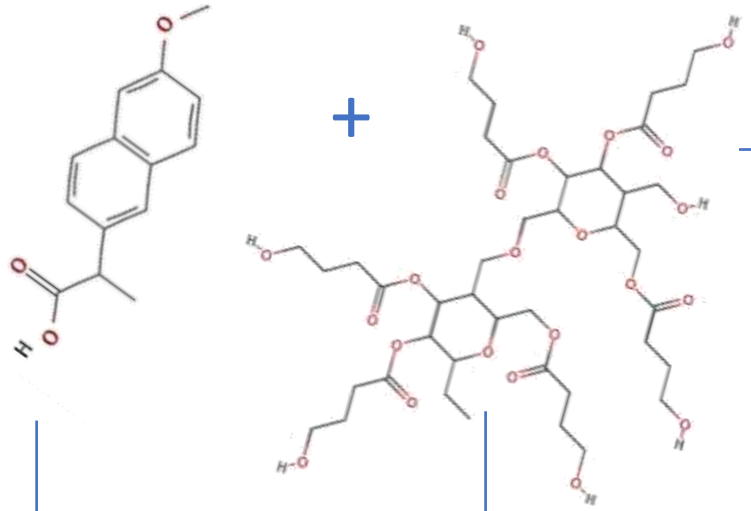
Molecular Modelling: creating simulation supercells & energy functions

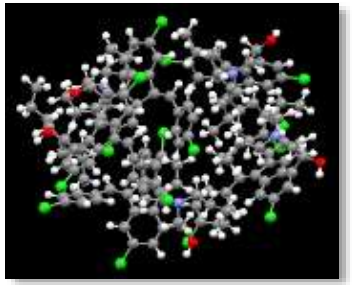


API

Excipient

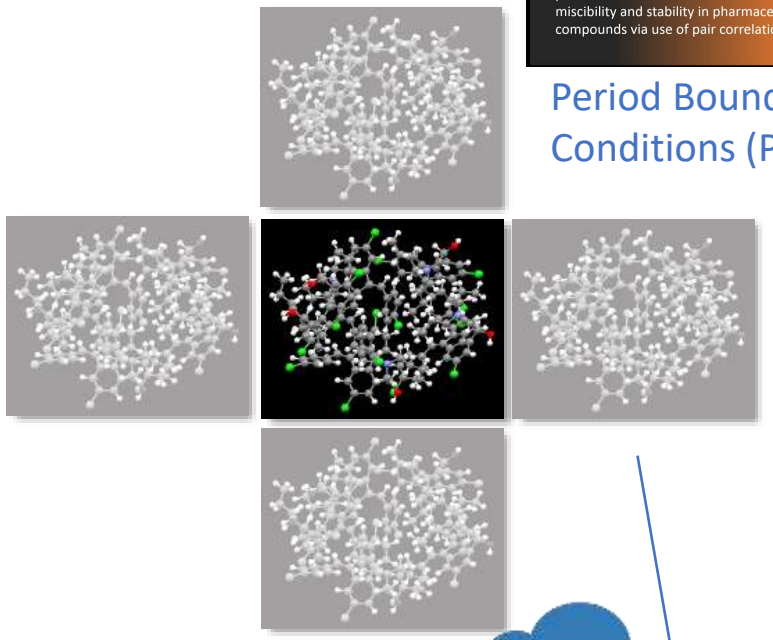


Thermal motion



Simulation supercell: Min. size physically relevant?

Period Boundary Conditions (PBC)



Microsoft Azure

API
DFT relaxation
Energy function parameters

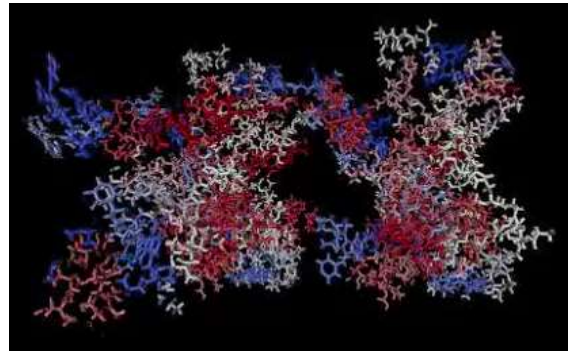
+

Excipient
DFT relaxation
Energy function parameters

Supercell
Thermal motion
(force field)
parameters

Microsoft Azure

ASD thermal motion -> energetics + kinetics



Issues to be addressed

ASD density correct ?

ASD ρ, SRO, Tg, HB

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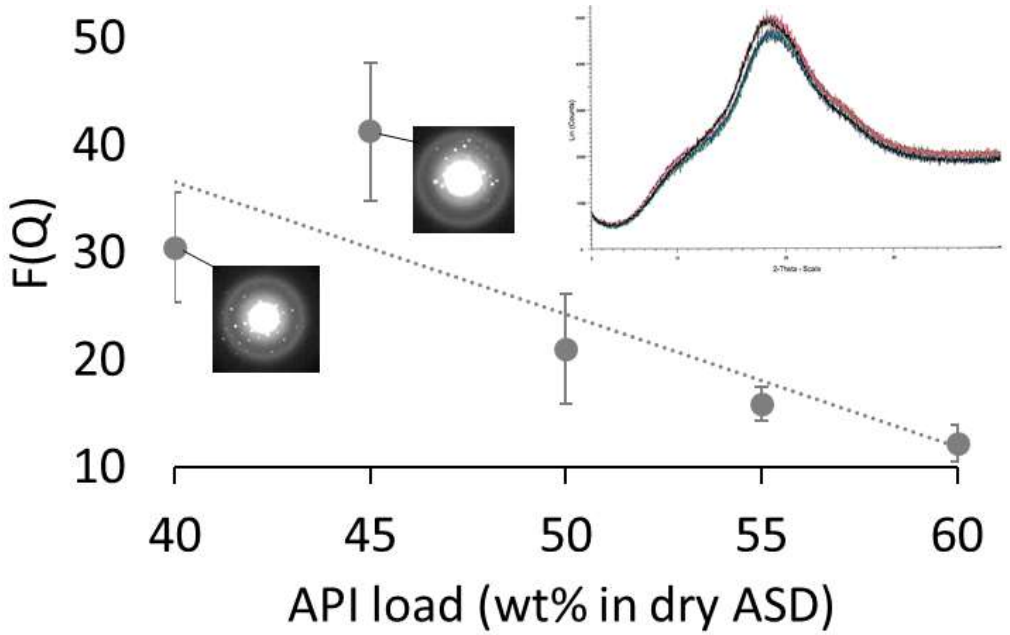
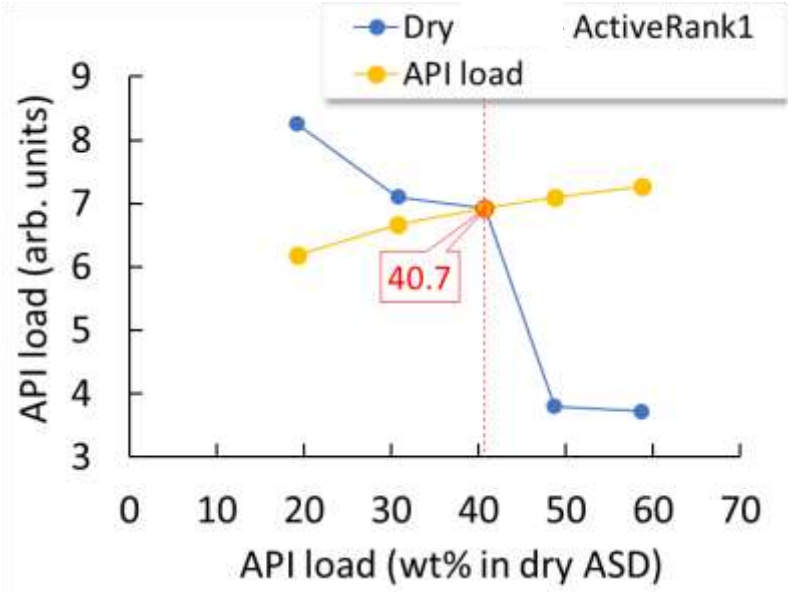
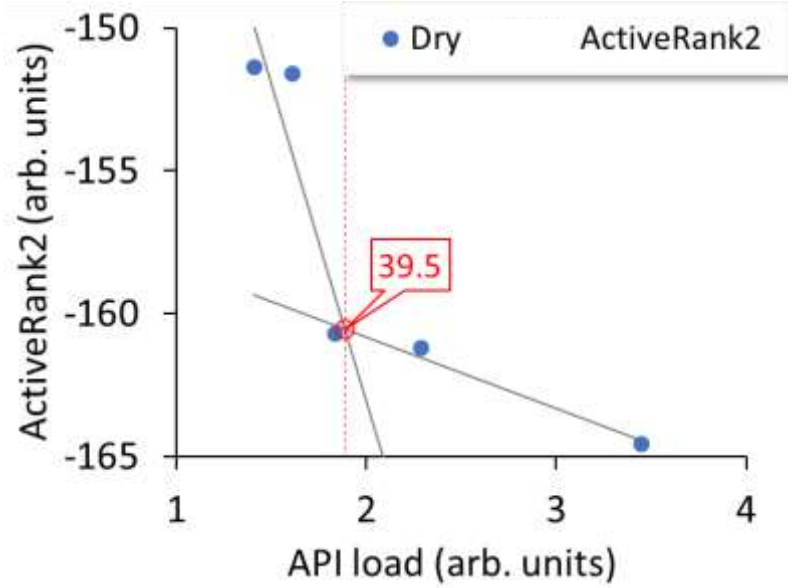
Results: ASD #1

40 < SL < 45 wt% API







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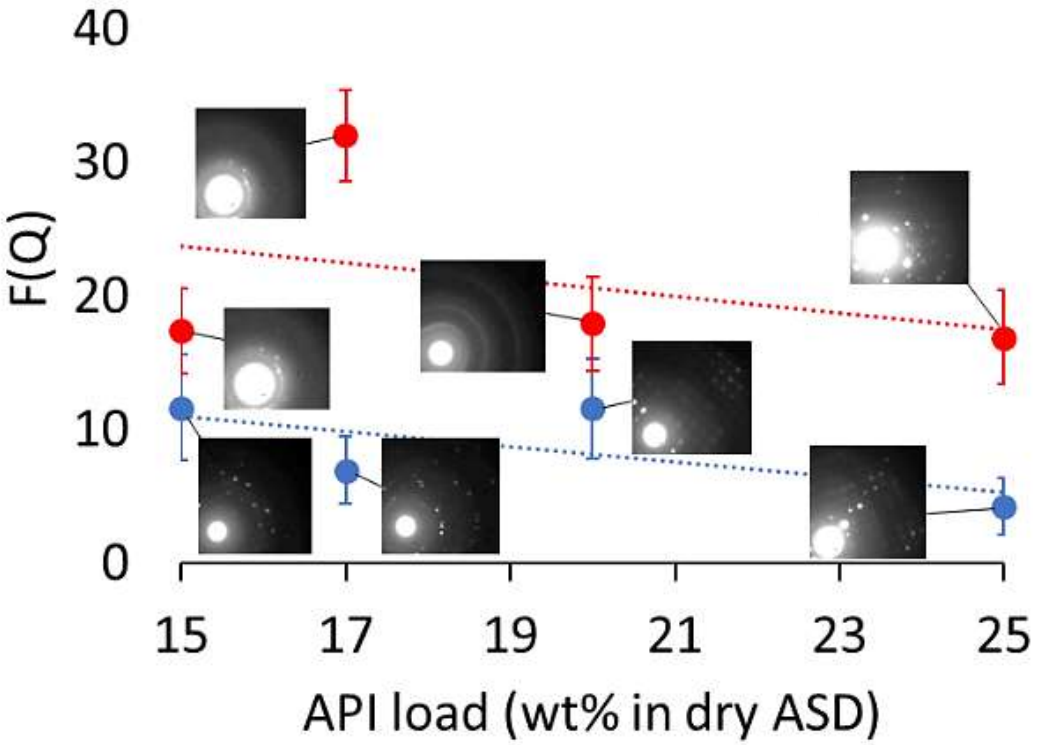
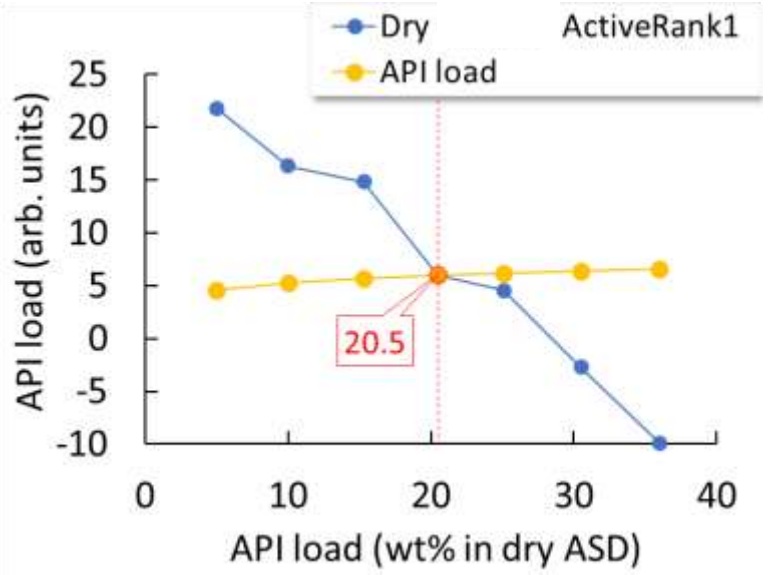
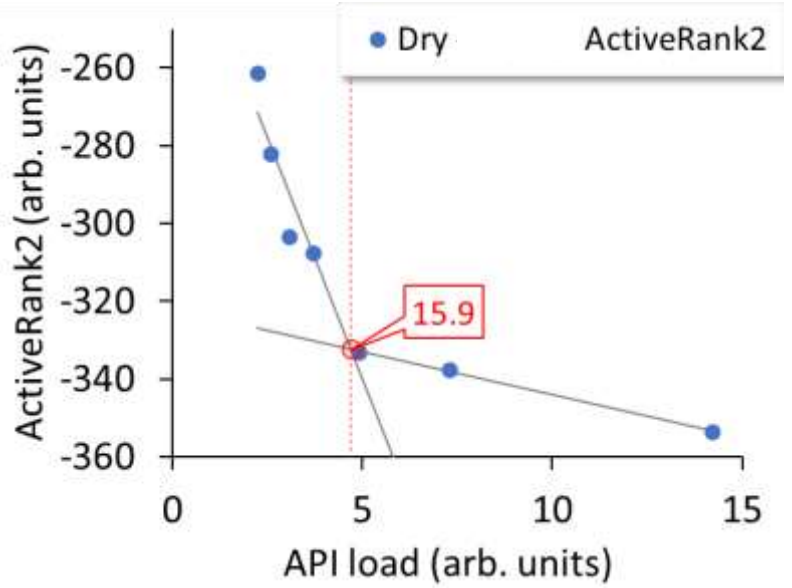
Results: ASD #2

17 < SL < 20 wt% API







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Results: ASD #3

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

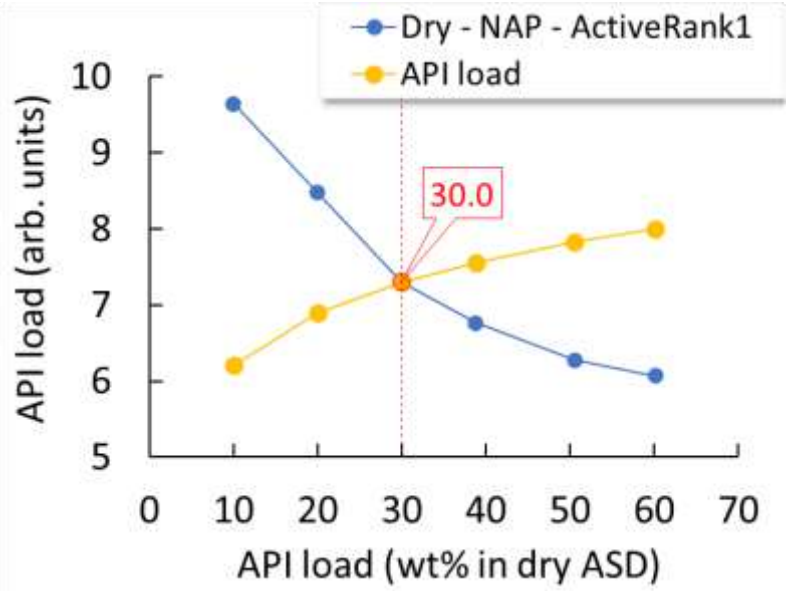
Physical stability of API/polymer-blend amorphous solid dispersions

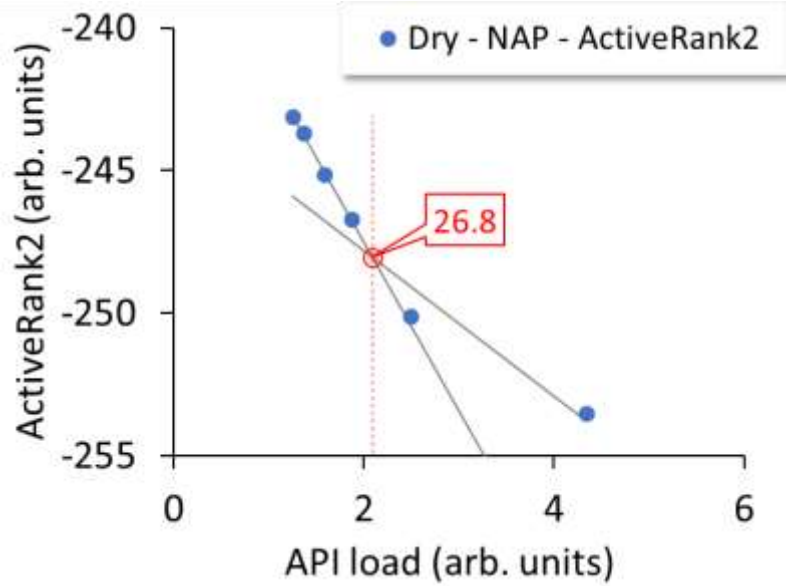
Kristin Lehmkemper[a,b], Samuel O. Kyeremateng[a,*], Mareike Bartels[b,1], Matthias Degenhardt[a], Gabriele Sadowski[b,*]

API = Naproxen (NAP)

PVP/HPMCAS (wt %/wt %)	Months of storage at 25 °C/0% RH		
	0-1	1-3	3-6
50/50	30	30	30

SL ~ 30 wt% API





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Results: ASD #4

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Research paper

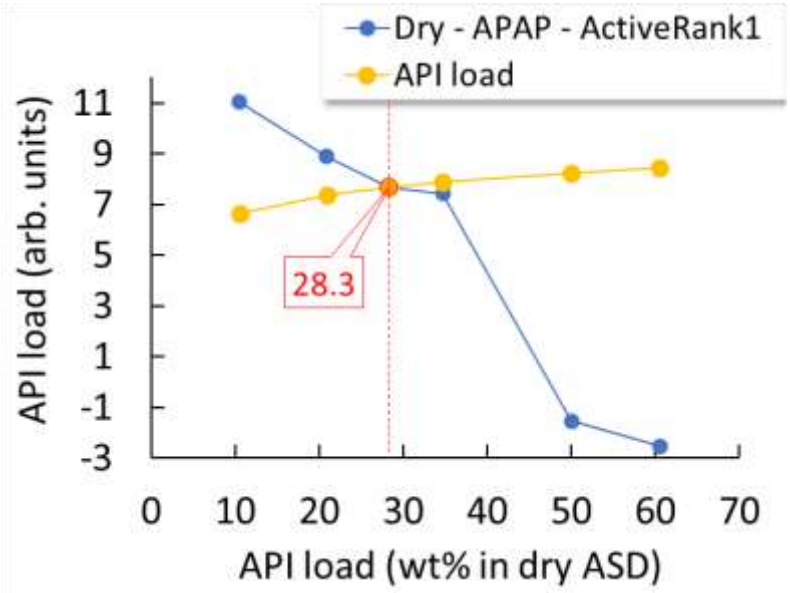
Physical stability of API/polymer-blend amorphous solid dispersions

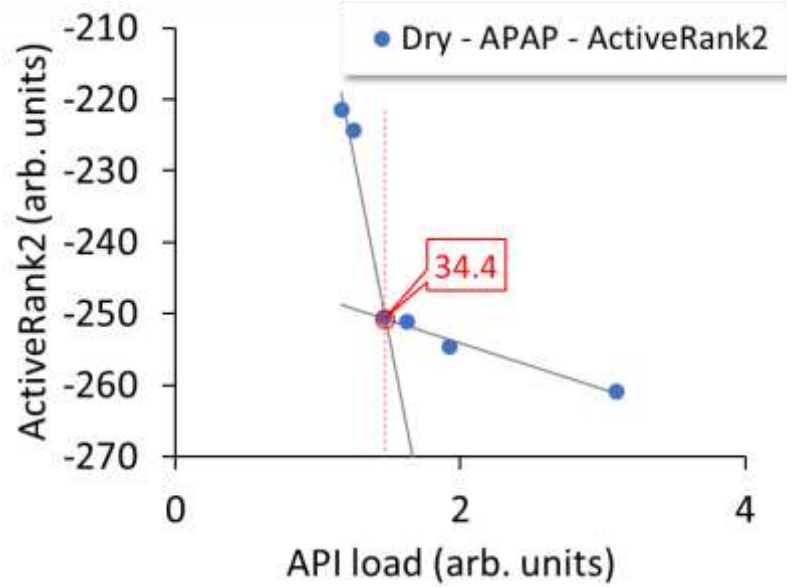
Kristin Lehmkemper[a,b], Samuel O. Kyeremateng[a,*], Mareike Bartels[b,1], Matthias Degenhardt[a], Gabriele Sadowski[b,*]

PVPVA64/HPMCAS (wt %/wt %)	Months of storage at 25 °C/0% RH		
	0-1	1-3	3-6
50/50	20 30 40	20 30 40	20 30 40

API = Acetaminophen (APAP)

30 < SL < 40 wt% API





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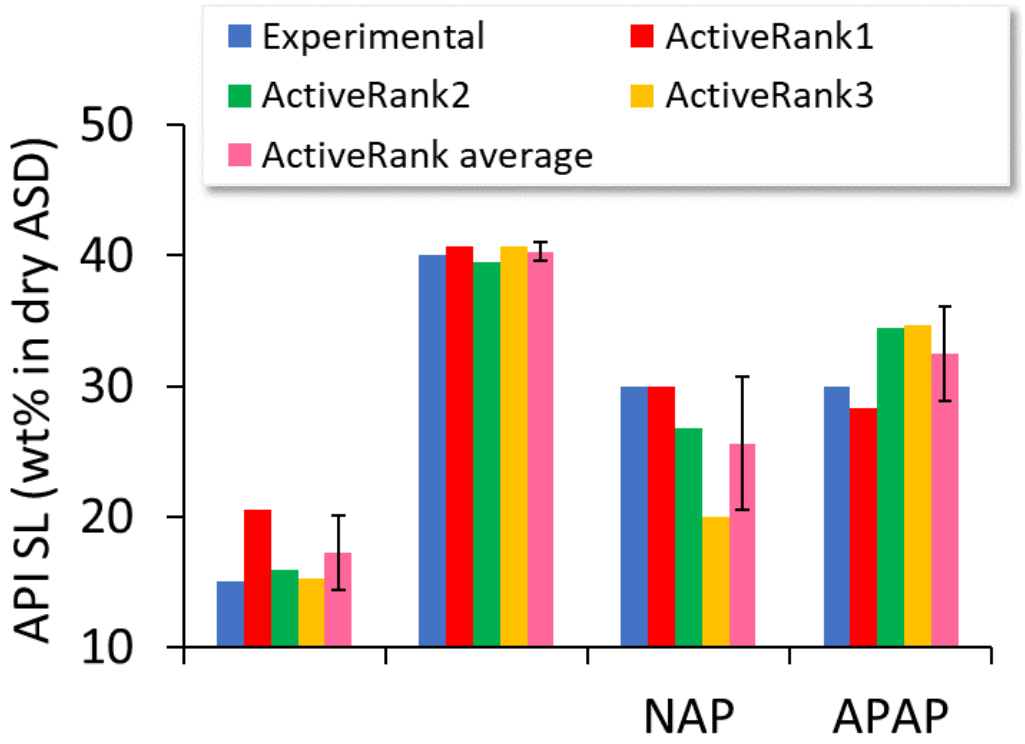
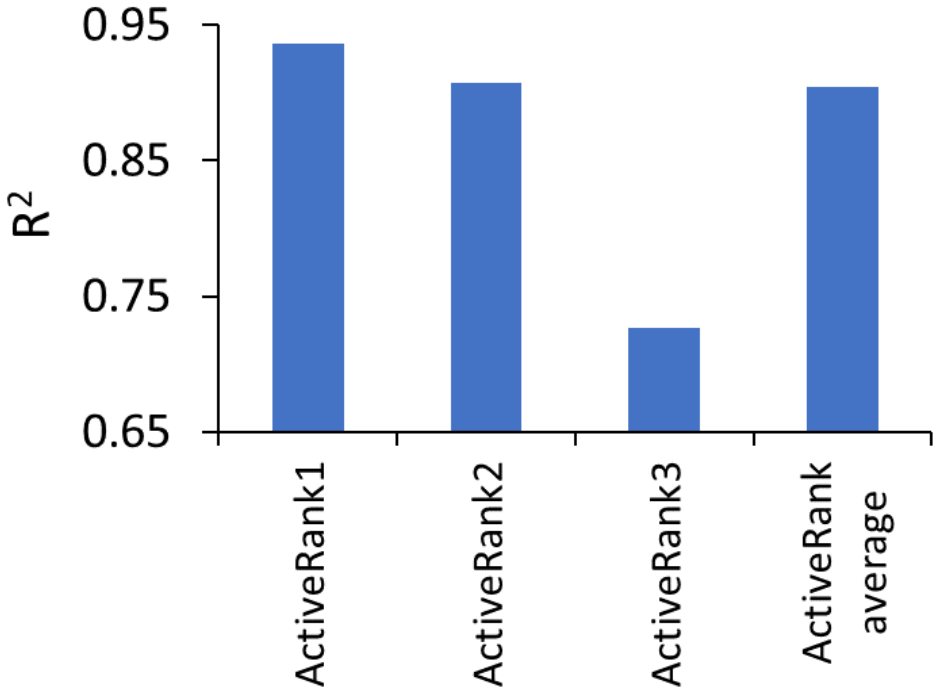
Results: ActiveRank, aggregate behavior





mml Molecular Modelling Laboratory

Forced ASD phase separation demarcates transition to the intrinsic API solubility limit

By creating Amorphous Solid Dispersion (ASD) models via homogeneous API/excipient mixing in simulation supercells equilibrated under the effect of thermal motion via large-scale molecular dynamics (MD), we previously determined that there is a firm correlation between the intrinsic behavior of the API's molar free energy (MFE) vs. API load and the experimentally observed limit of API solid solubility. This correlation was expressed as the ActiveRank family of molecular descriptors (Fig.1).

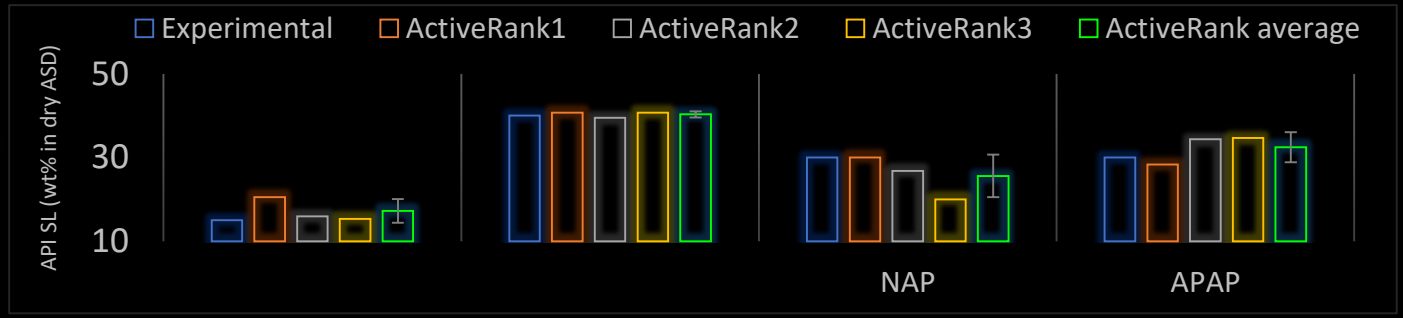


Figure 1. ActiveRank MFE descriptors vs. experimental API solubility limit NanoMEGAS Advanced Tools for electron diffraction

Extending this facility to more physically realistic systems, we recently carried out targeted MD (TMD) simulations of forced amorphous phase separation (APS) into dense API clusters (Fig.2), the latter considered precursors to the formation of API crystalline nuclei.

We found that within an interaction envelope, API energetics reached near-linear behavior at the expected API solubility limit (Fig.3). Transition to linearity is considered to demarcate the intercept between homogeneously distributed API and APS cluster MFE, beyond which APS is thermodynamically favored.

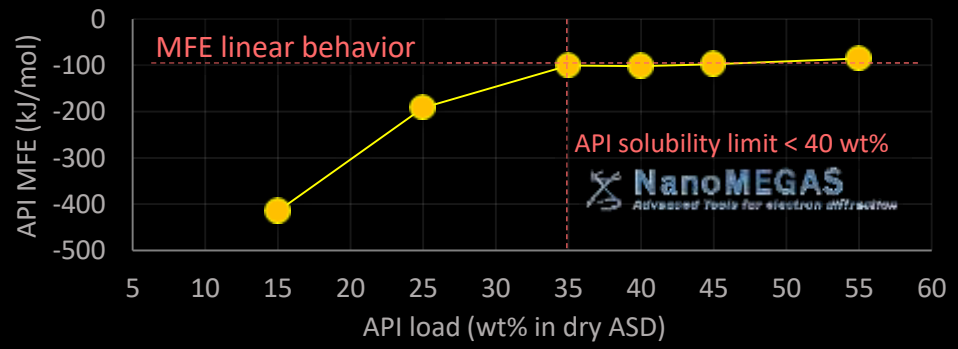


Figure 3. API MFE vs. API load under the combined effect of excipient and APS dense cluster dynamics.

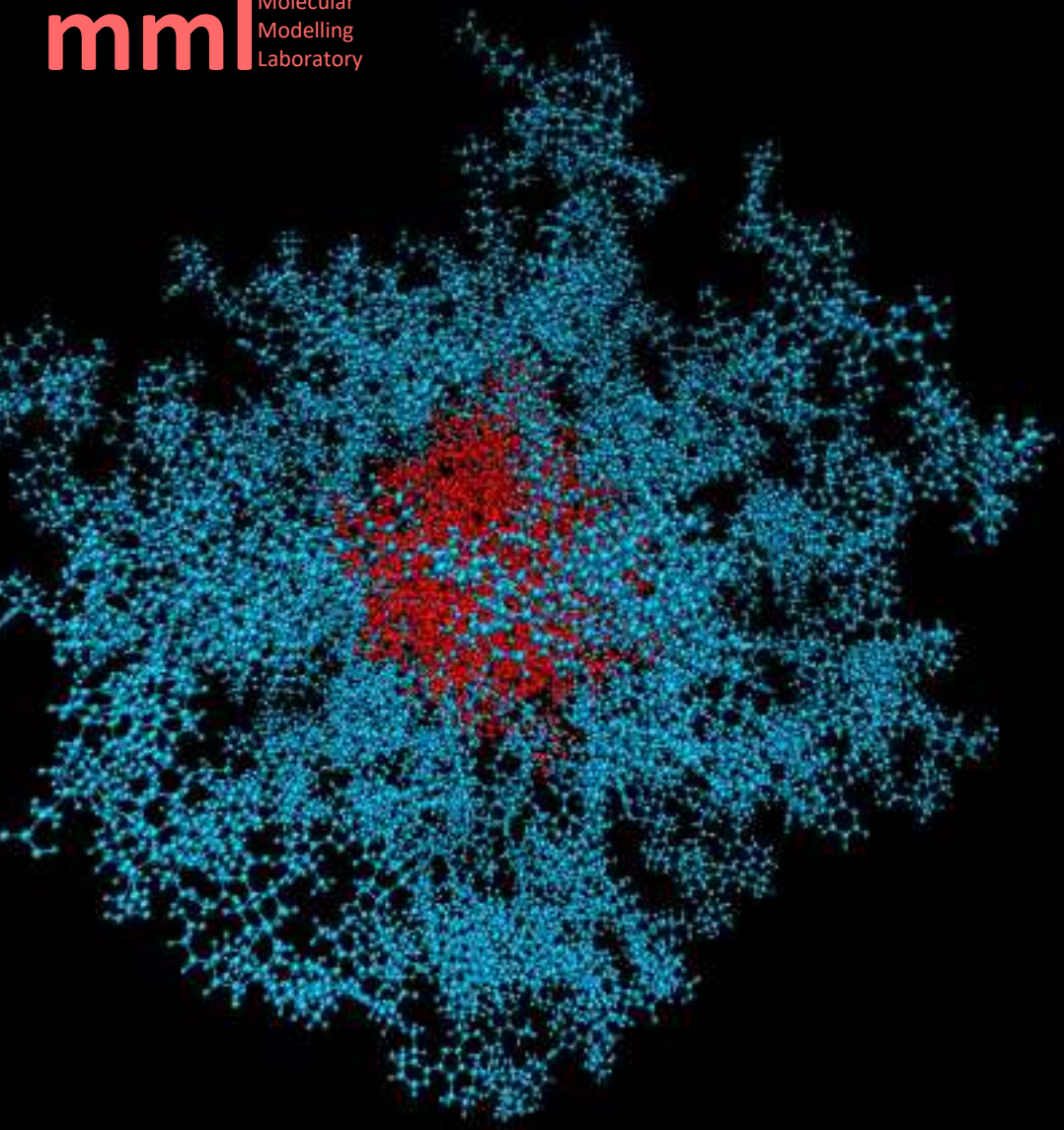


Figure 2. Homogeneously distributed API (cyan) and dense APS cluster (red). All simulations were carried out on Microsoft Azure. MML production and post-production algorithmics scaled linearly up to approx. 1000 CPU cores per MD run while linear scaling was irrespective of system size for MFE calculations.

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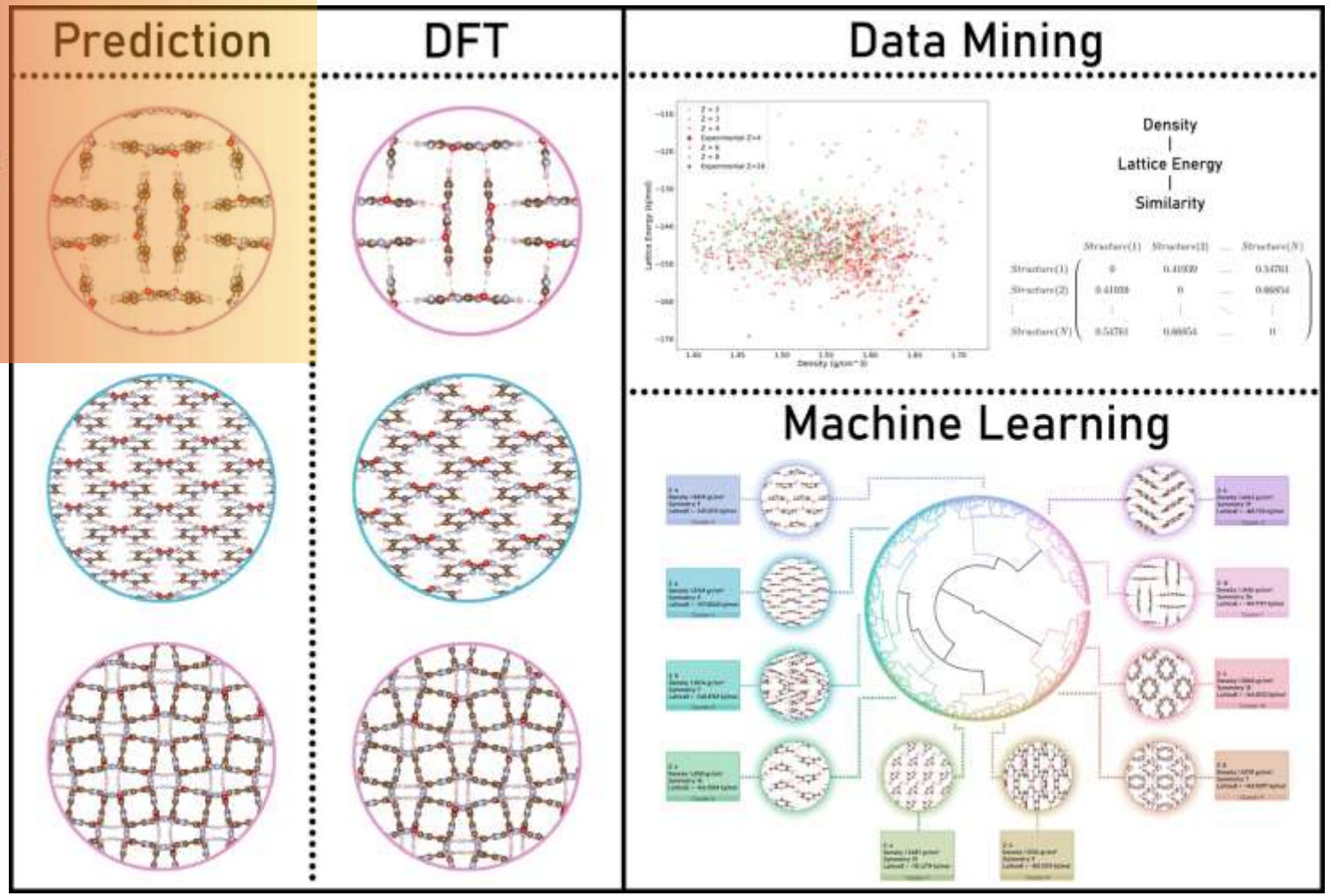
Crystal Structure Prediction (CSP)

drug discovery

Organic polymorphs

we apply inverse modelling, Electron Energy Loss Spectroscopy (EELS) DFT-TD first-principles to detect new pharmaceutical polymorphs



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Crystal Structure Prediction (CSP)

- First CSP algorithm developed in 2009.
- Currently treating covalent crystals with a knowledge-based fitness function.
- Perfroms CSP starting from seven Bravais lattice types.
- Has been used to predict the crystal structures of hydrogen storage materials.
- Written in Fortran, executed on High-performance computing clusters

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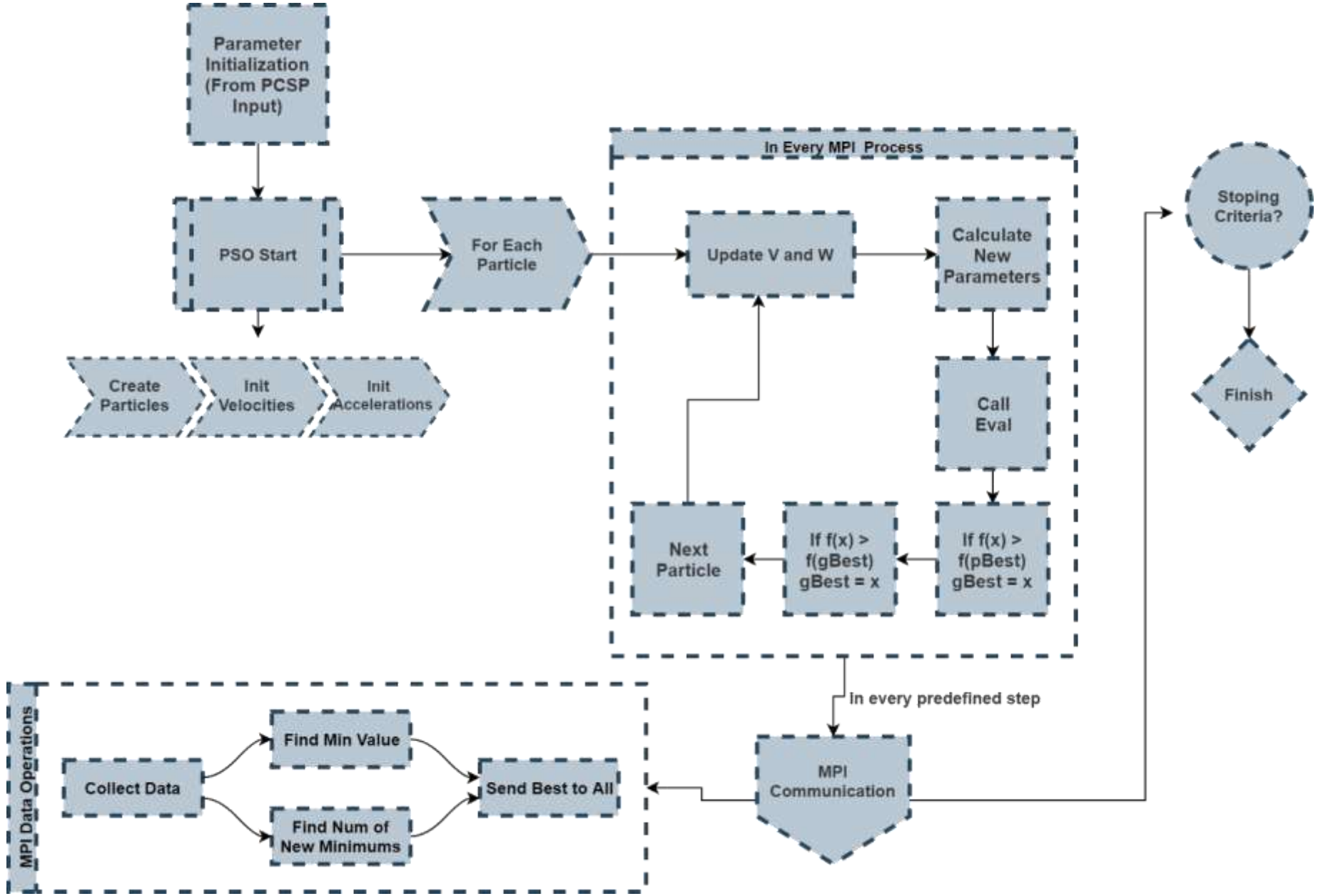
CSP flowchart



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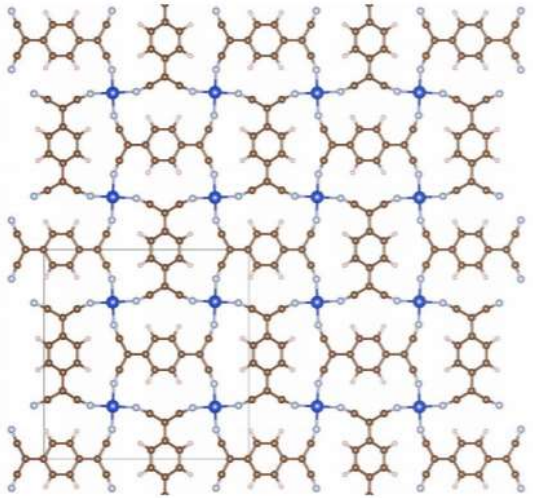
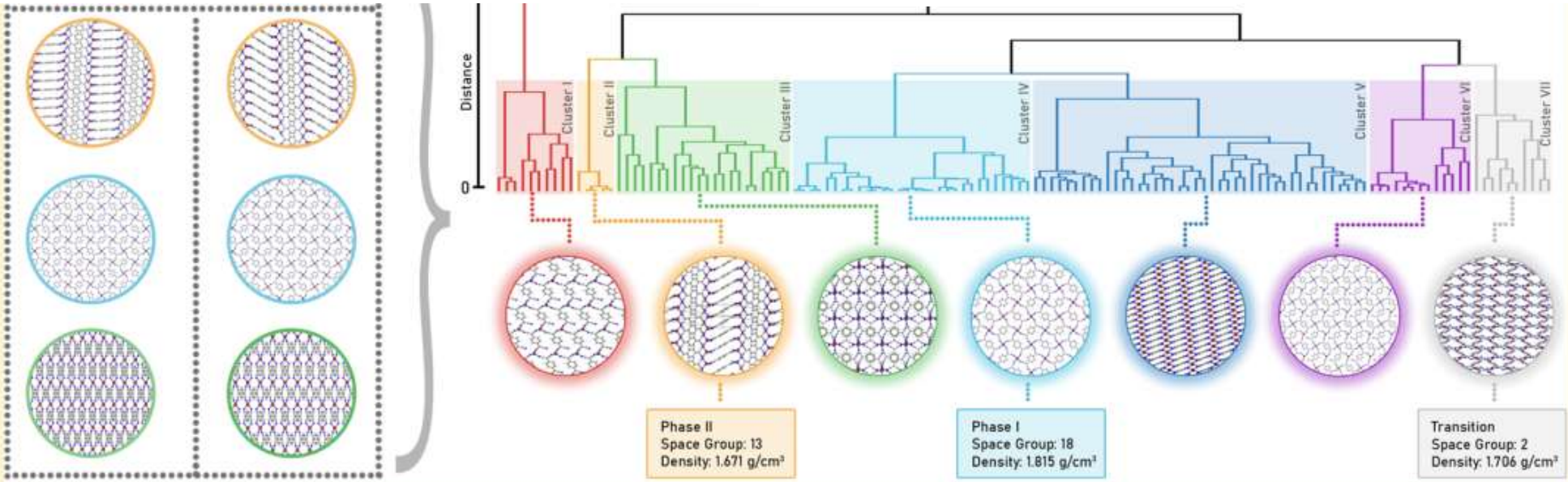
CSP applications: covalent crystals

- Tetracyanoquinodimethane (Cu-TCNQ)
- Semiconducting solid





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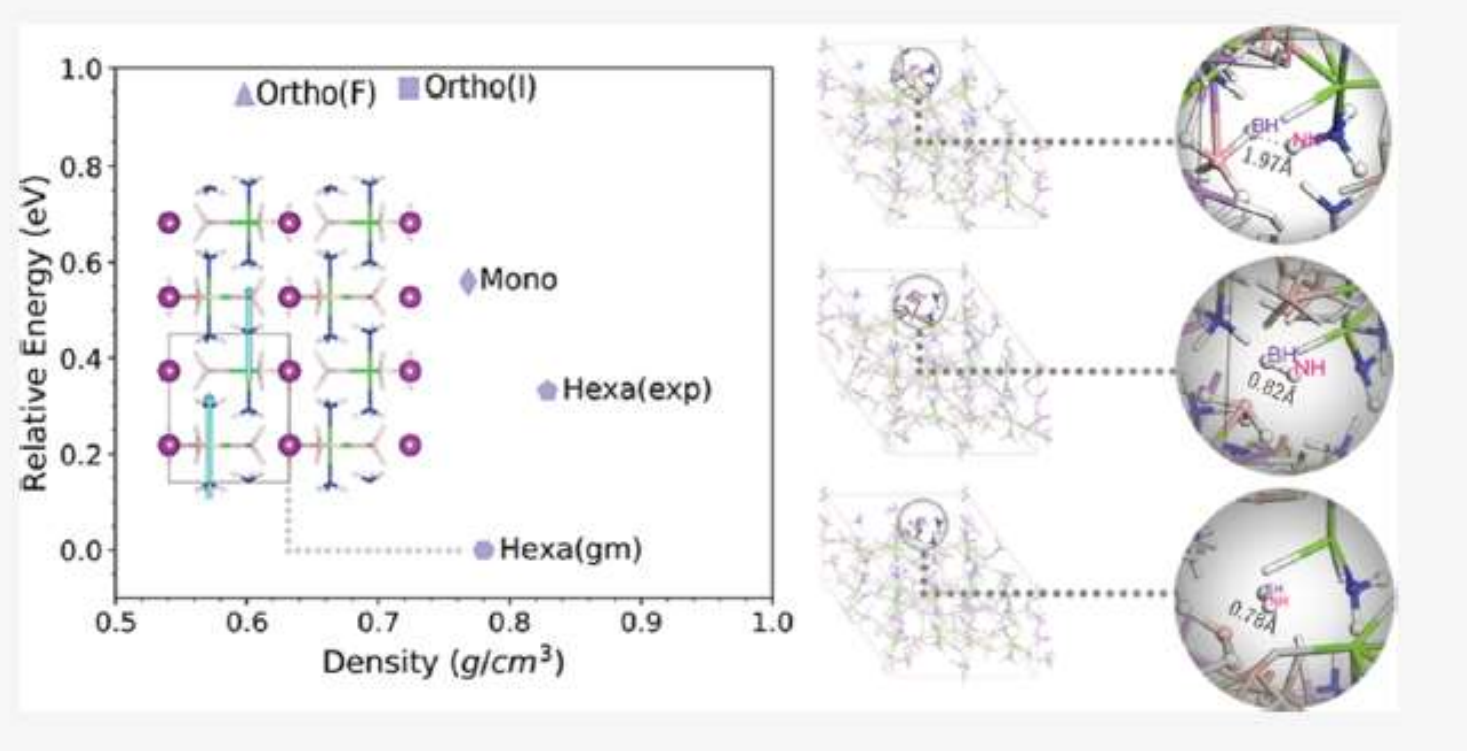
CSP applications: covalent crystals

- $LiMg(BH_4)_3(NH_3)_2$
  - Hydrogen Storage Material
  - Experimental structure detected!
  - We predicted a number structures (isoenergetic to experimental and phonon calculations show that they are stable)



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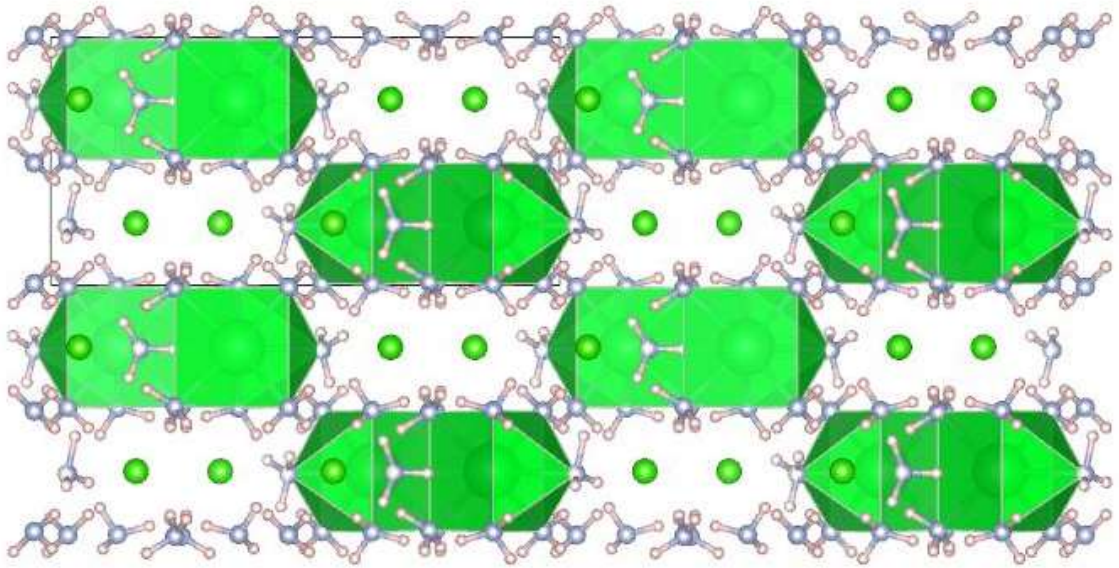
CSP applications: covalent crystals

$Sr(NH_3)_nCl_2$ (for n=8, 6, 4, 2, 1)

- Metal amine compounds for hydrogen storage



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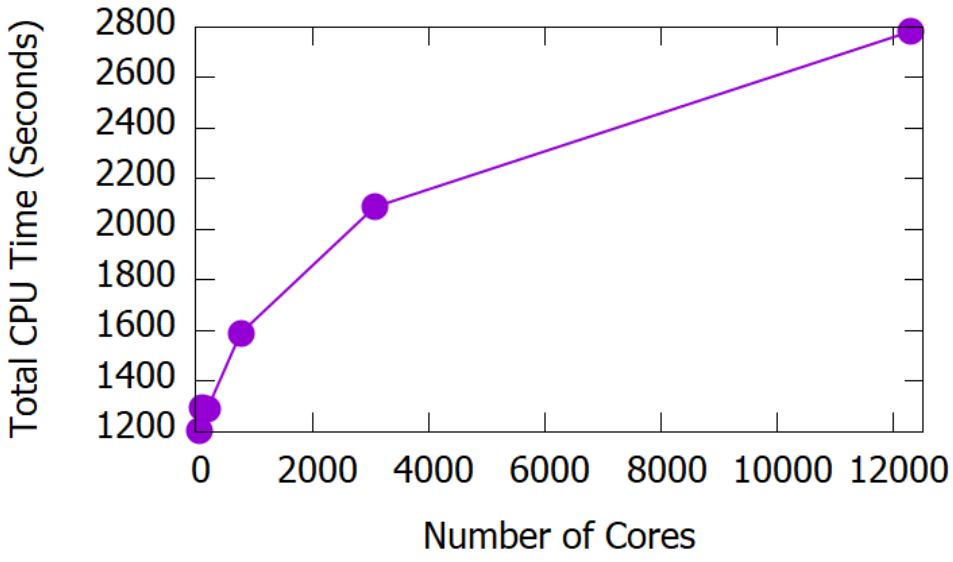
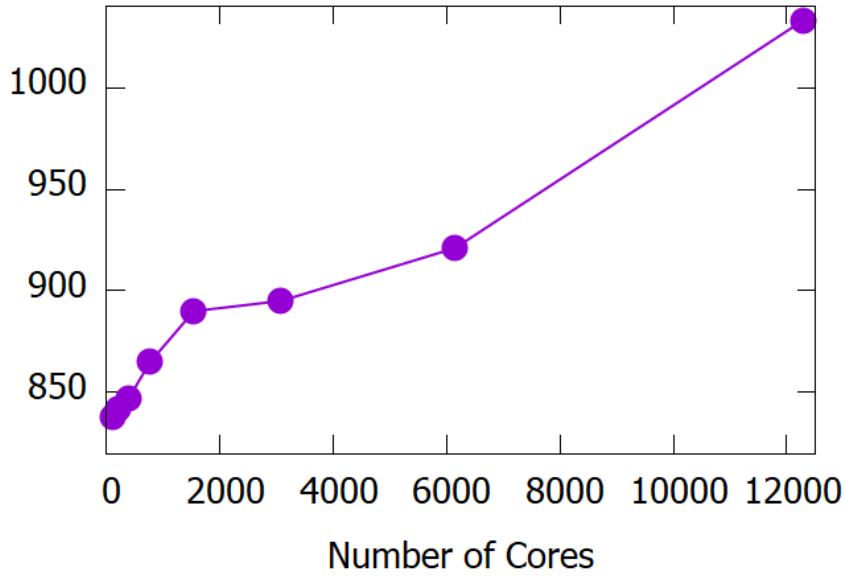
CSP scaling

- MareNostrum IV (Barcelona)
- 27th in TOP500 (June 2019)
- Intel Xeon Platinum 8160 24C at 2.1 GHz
- Intel Omni-Path
- No random seed
- 3 predictions

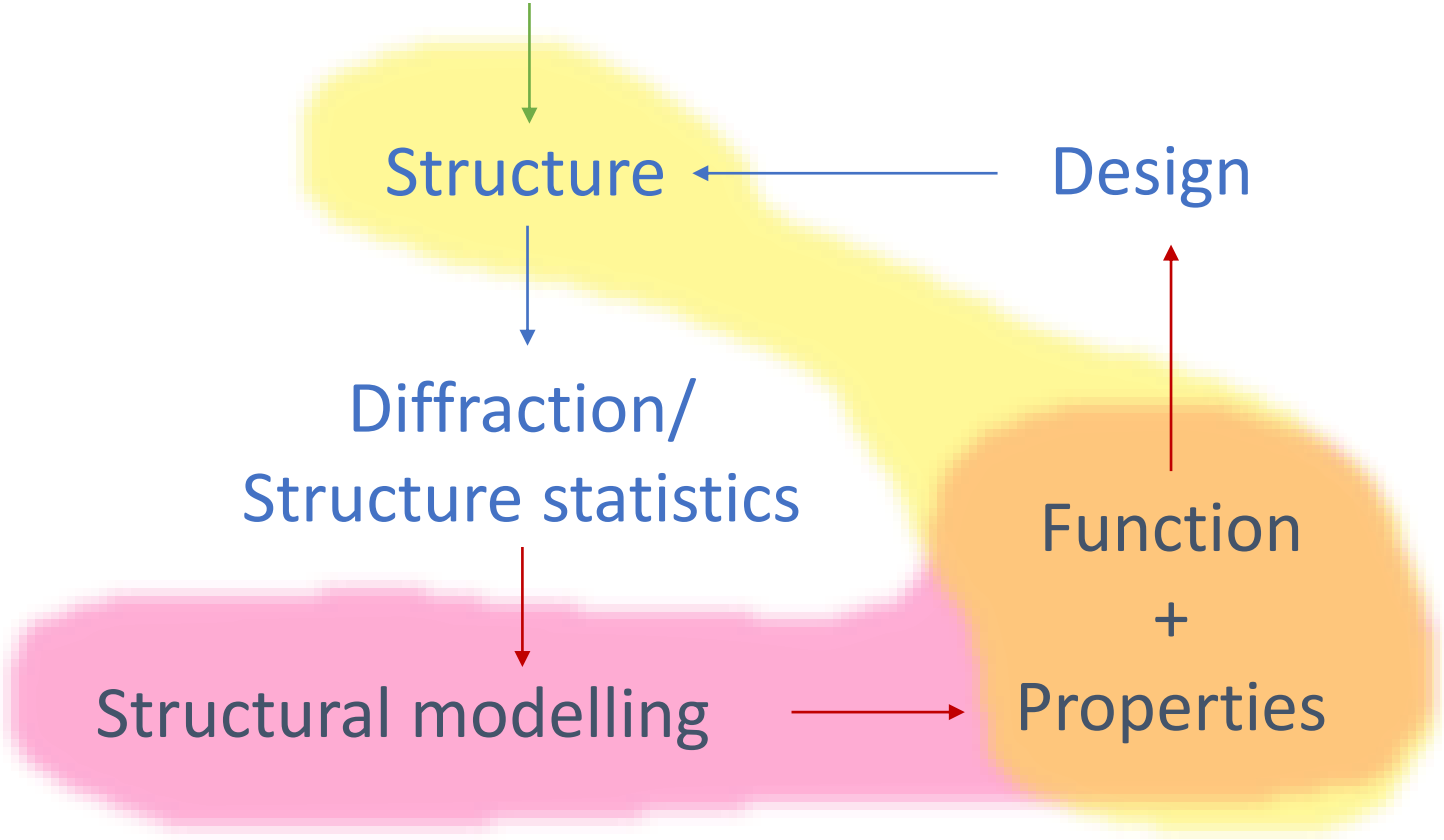


- Hazel Hen (Stuttgart)
- 34th in TOP500 (June 2019)
- Intel Xeon E5-2680v3 12C 2.5GHz
- Aries interconnect
- No random seed
- 2 predictions



mml molecular modelling laboratory

R&D mandate:
develop hybrid computational/experimental solutions for the Life Sciences



MML applies:

- High-throughput quantum chemical modelling
- State-of-the-art electron microscopy
- Artificial Intelligence (AI) heuristics

to the research and development of:

- Drug design
- Immune Interventions

pivoting on:

- Big Data
- Big infrastructures: High Performance Computing (HPC)
- Big Collaborations (HPC Vendors)