



3DEXPERIENCE



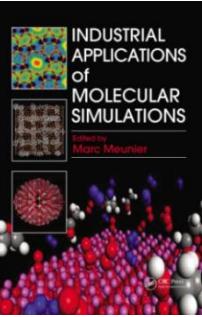
The 4th International Conference on Molecular Simulation

Oct. 23 - 26, 2016

Shanghai, China

Molecular Modelling of Polymers and Nanocomposites

Dr MARC MEUNIER
Principal Application Scientist & Fellow
BIOVIA, Cambridge, U.K.



Agenda



Dassault Systèmes BIOVIA



Multi-scale modelling



Polymer modelling



Epoxy Networks: modelling cross-linking reactions



Environmental Stress Cracking of polymers



Polymer Nanoparticles for Drug Delivery



| Virtual BioSphere and Materials



accelrys®
becomes
DS BIOVIA

BIOVIA provides a **scientific** collaborative environment for advanced biological, chemical and materials experiences. The sophisticated enterprise system of modelling, simulation, laboratory and quality management enables **innovation** for science-based industries.



VISUALIZATION

Molecular and Crystallographic View Generators. BIOVIA Materials Studio is a graphical environment that enables researchers in materials science and engineering to visualize and analyze their data along with its properties and behavior. Using Materials Studio's visualization tools, users can view and analyze materials of all types, including pharmaceuticals, catalysts, polymers, ceramics, semiconductors, metals, minerals, cells, nanoparticles, and more.

Materials Studio's most advanced, yet easy

to-use environment for modeling and visualizing materials science requires the following benefits:

- A highly graphical user interface with physical modeling and experimentation through "Virtual Screening" of candidate molecules.

- An integrated environment for performing, monitoring, performing, monitoring, and controlling the materials simulation process.

- Improved fundamental understanding of the relationship between structure and function, and the resulting properties and behavior.

- Access to new materials capabilities through adoption of computational materials science as a companion to traditional experimental methods.

Materials Studio includes a complete collection of tools for Materials Studio Collection for BIOVIA Pipeline Pilot, as well as the Materials Studio API.

SOLUTION TECHNOLOGIES

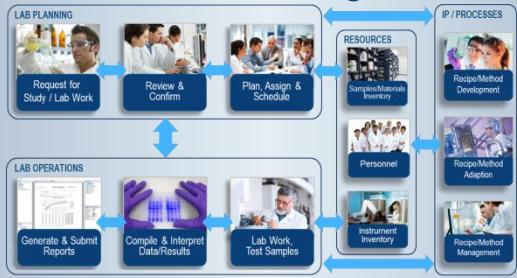
Materials Studio offers a complete range of simulation capabilities from quantum, atomic-scale, molecular, statistical, and continuum modeling. Materials Studio also includes valuable tools such as a reaction mechanism or surface particle to store, analyze, and evaluate performance in the shortest time possible.



The Laboratory Workflow



Unified Lab Management



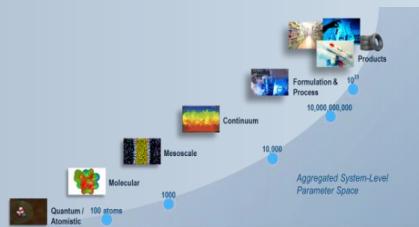
Process Production Operations



Quality and Regulatory



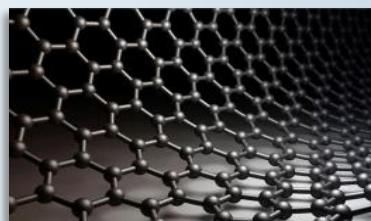
Collaborative Science



Predictive Models



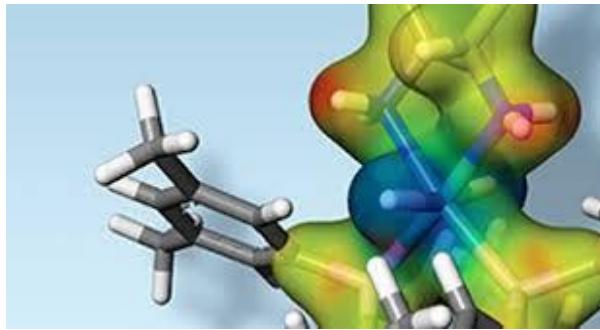
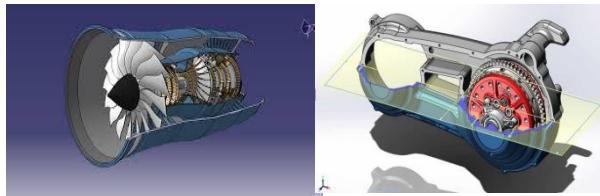
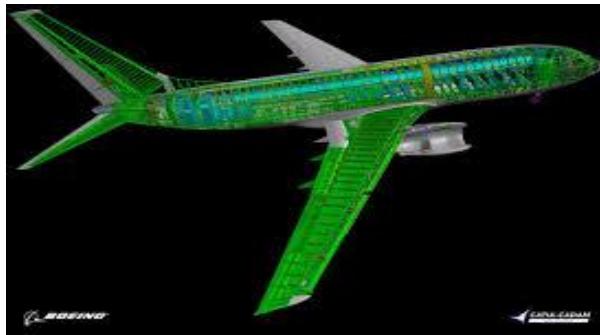
Novel Therapeutics



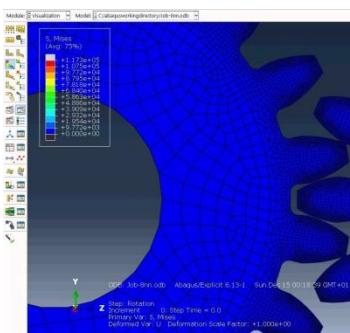
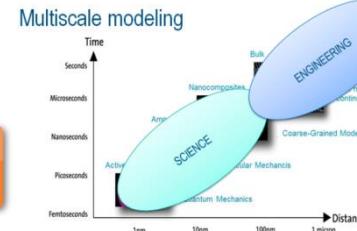
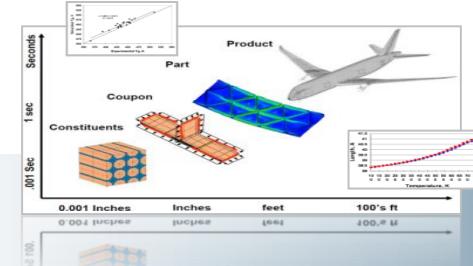
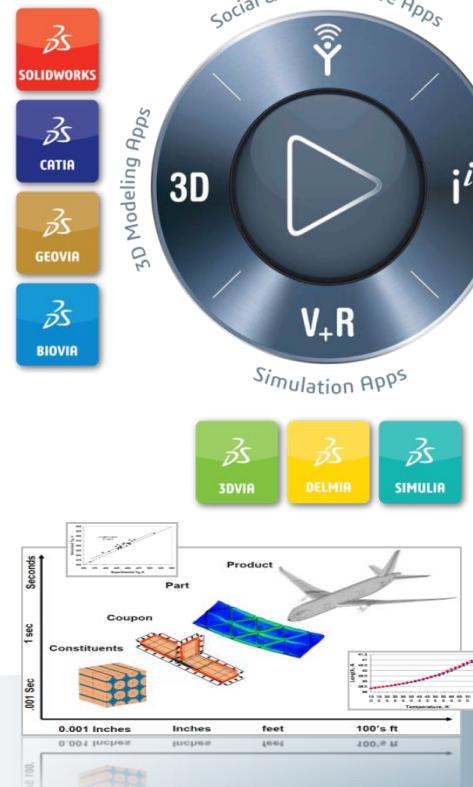
Engineered Materials



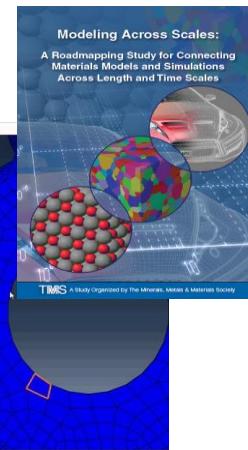
Chemicals & Formulations



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BOEING Frontiers 2010



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Multi-Scale Simulations

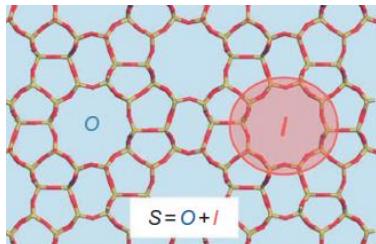
The Nobel Prize in Chemistry 2013

Martin Karplus, Michael Levitt and Arieh Warshel

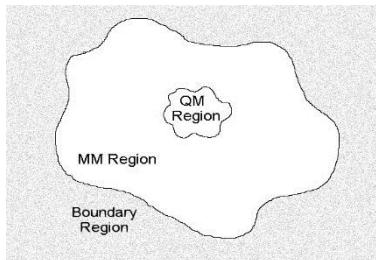


"for the development of multiscale models for complex chemical systems"

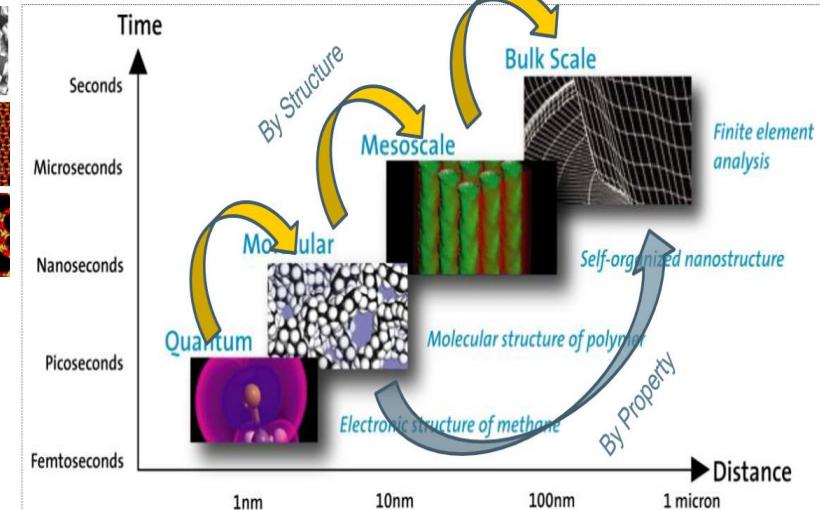
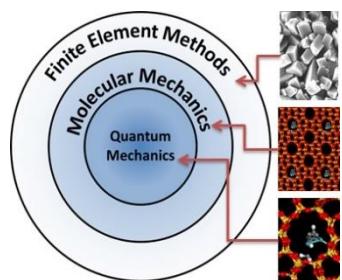
Hybrid: Mixture (e.g. QM/MM)



$$E_{\text{tot}} = E_{\text{QM}} + E_{\text{MM}} + E_{\text{QMMM}}$$



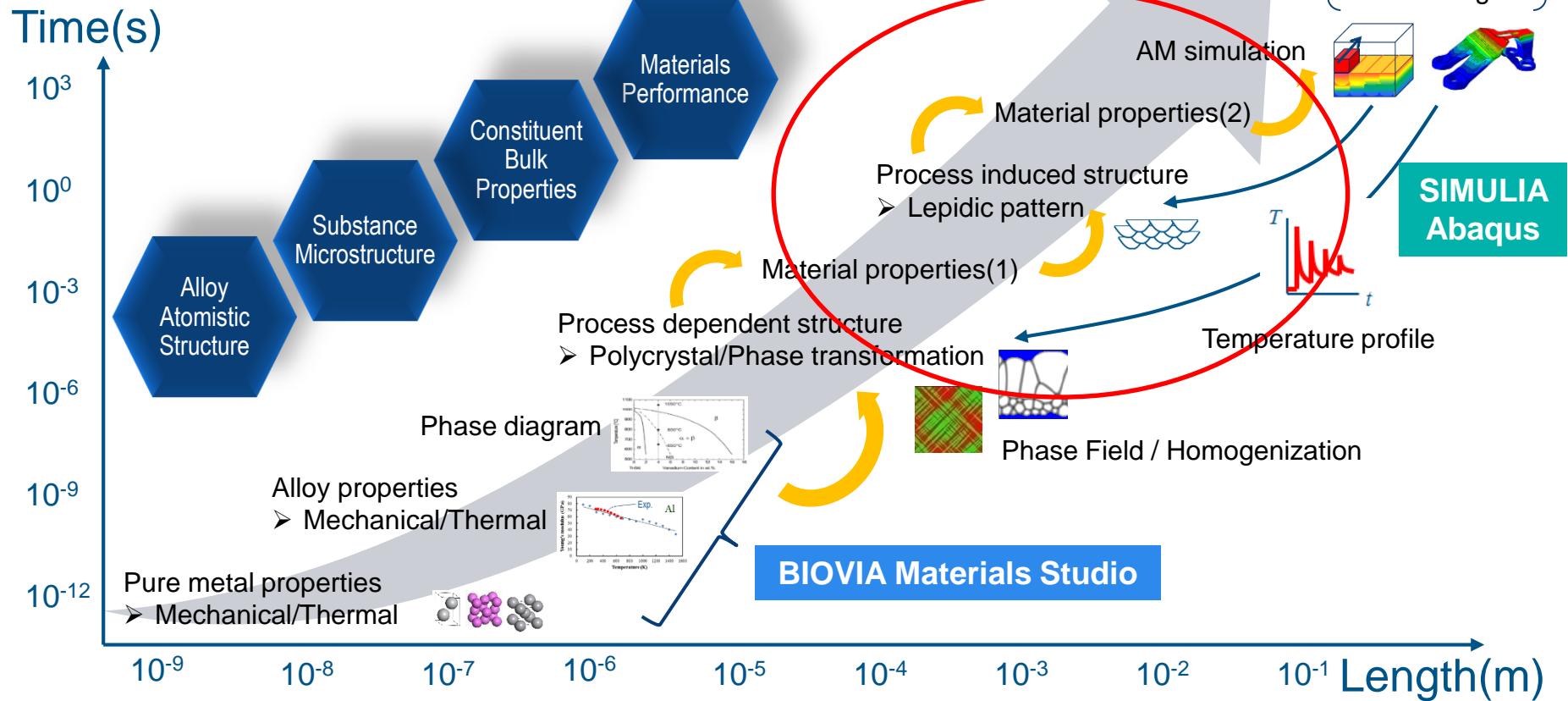
Hierarchical: One method at a time going up (or down) scale



Multiscale modeling of nanomaterials: recent developments and future prospects

G. Fitzgerald¹, J. DeJoannis², M. Meunier³
¹Accelrys, Inc., San Diego, CA, USA; ²Accelrys, Inc., Burlington, MA, USA; ³Accelrys Limited, Cambridge, UK

Multiscale Modeling in Additive Manufacturing

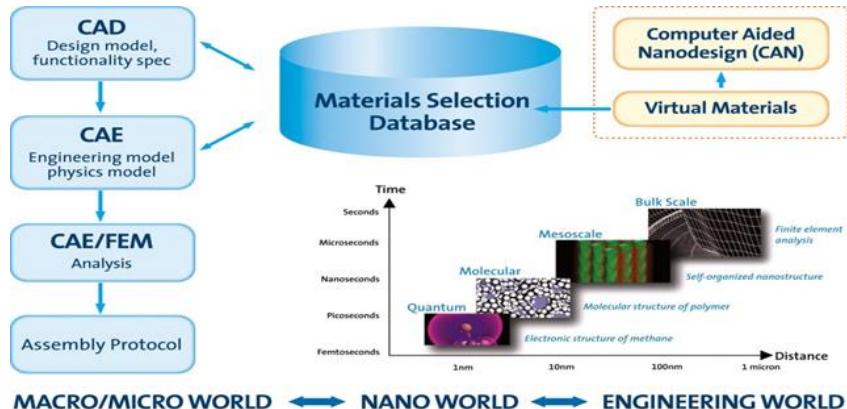
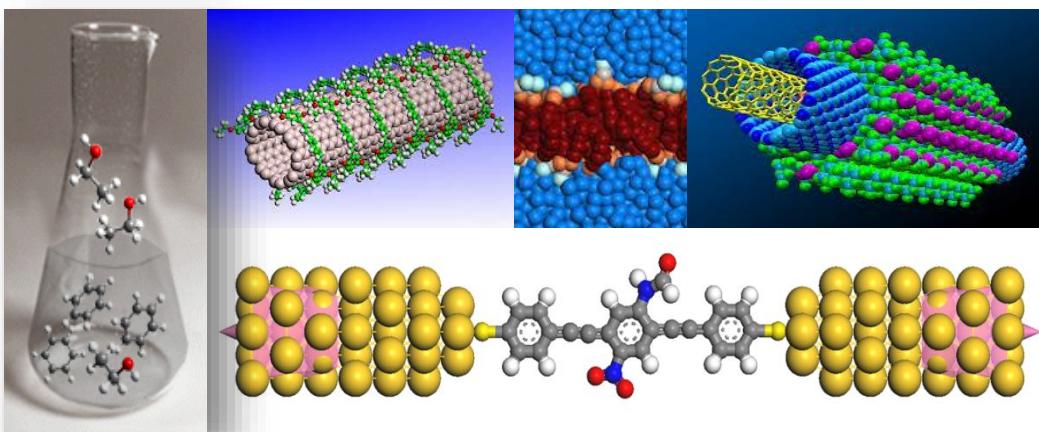


Predictive Materials Science

Molecular modelling tools allow for the simulation of chemicals and materials and to predict their properties and behaviour.

There is a wide variety of computational tools:

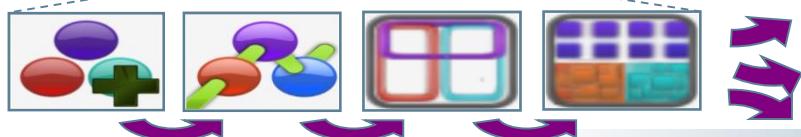
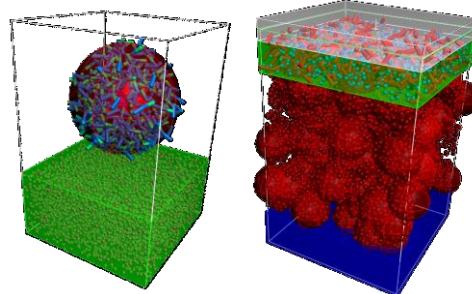
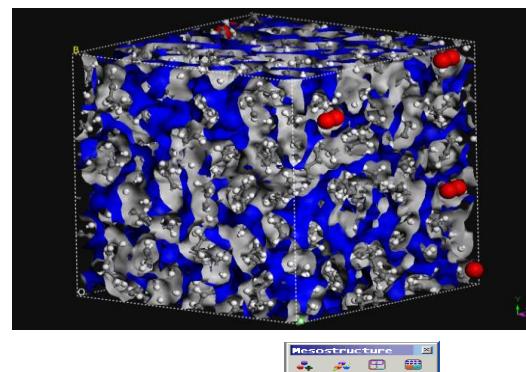
1. Visualization
2. Quantum Mechanics
3. Classical Mechanics
4. Mesoscale
5. Crystallisation
6. QSAR & Statistics...



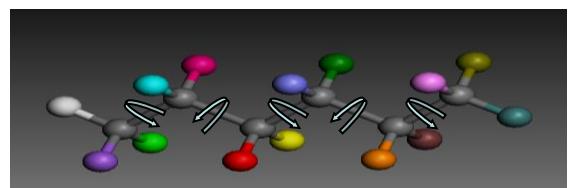
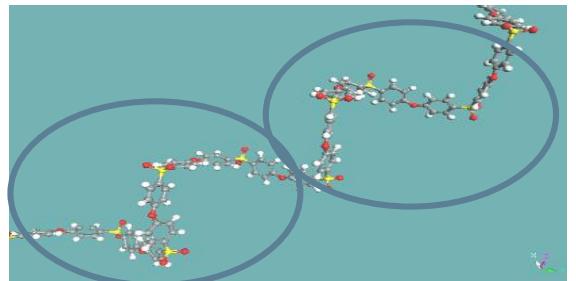
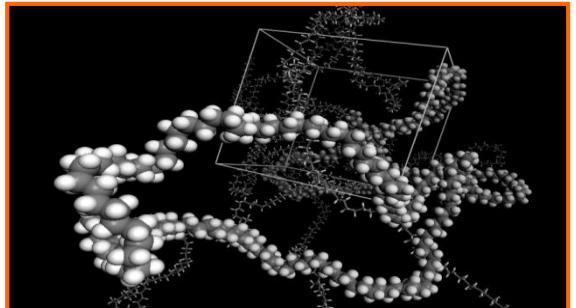
POLYMERS MODELLING



- Comprehensive tools for model building and simulating
- Modelling bulk amorphous systems, mixtures, blends, liquid crystals, etc.



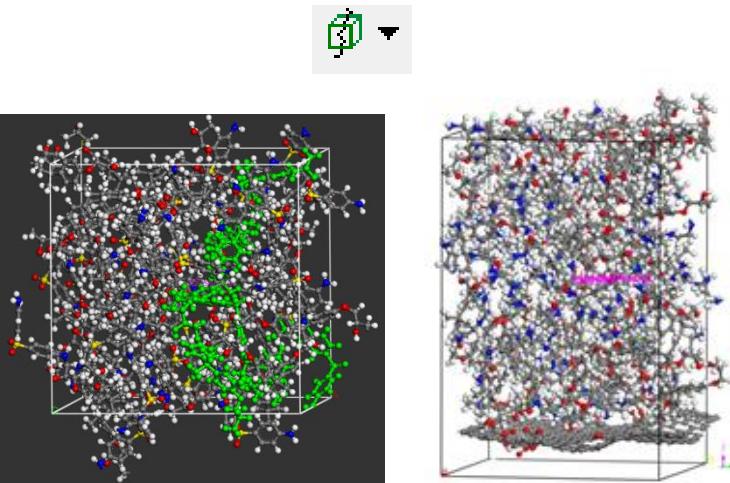
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Polymer Builder

- Build Polymers from existing library of Repeat Units or sketch your own.
- Build one or more chains, select Tacticity, Chain Length, etc.
- Then, use Monte-Carlo based approach to ‘mix’ models together (Additives, solvent, nanomaterials, etc.)
 - Build a new phase
 - Build ‘into’ an existing phase (“Packing”)

<u>Build Polymers</u>	▶
Build Analogs	▶
Build Nanostructure	▶
Build Transport Device	▶
Build Mesostructure	▶
<u>Crystals</u>	▶
<u>Homopolymer</u>	
<u>Block Copolymer</u>	
<u>Random Copolymer</u>	
<u>Dendrimer</u>	
<u>Repeat Unit</u>	
<u>Branch Points</u>	



Atomistic Simulations

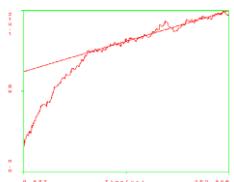
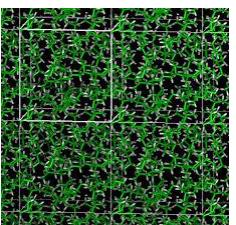
Atomistic Simulations: allows you to construct and characterize models of isolated chains or bulk polymers, either crystalline or amorphous, and predict key properties.

Applications include nanocomposites, coatings, lubricants, food packaging, gels, and adhesives...

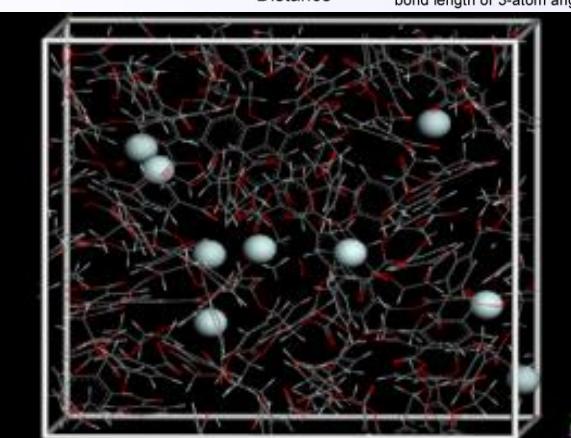
LIMITS:

- ❖ Force fields are valid for a 'limited' type of material (e.g. organics or zeolites)
- ❖ Size of system $\sim 10^4$ atoms or a few nanoseconds

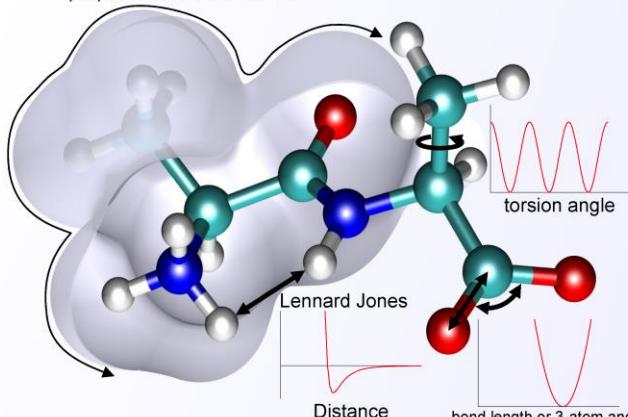
$$\begin{aligned}
 V(R) = & \sum_b D_b [1 - e^{-(b-b_0)}]^2 + \sum_\theta H_\theta (\theta - \theta_0)^2 + \sum_\phi H_\phi [1 - s \cos(n\phi)] \\
 & + \sum_x H_x x^2 + \sum_b \sum_{b'} F_{bb'} (b - b_0)(b' - b'_0) + \sum_\theta \sum_{\theta'} F_{\theta\theta'} (\theta - \theta_0)(\theta' - \theta'_0) \\
 & + \sum_b \sum_\theta F_{b\theta} (b - b_0)(\theta - \theta_0) + \sum_\phi F_{\phi\theta\theta'} \cos(\theta - \theta_0)(\theta' - \theta'_0) \\
 & + \sum_x \sum_{x'} F_{xx'} x x' + \sum_i \sum_{j>i} \left[\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^6} - \frac{q_i q_j}{r_{ij}} \right]
 \end{aligned}$$



$$-\frac{dV}{dr_i} = m_i \frac{d^2 r_i}{dt^2}$$



Hydrophobic effect is roughly proportional to surface area



COMPASS II Forcefield

J Mol Model (2016) 22:47
DOI 10.1007/s00894-016-2909-0



ORIGINAL PAPER

- Extensions to COMPASS (I) include:
 - Maybridge screening database
 - Heterocyclics, sulphur containing molecules
 - Ionic liquids
 - NIST database
 - Improved parameters for oximes, azo bonds etc.
- Maintains quality of original forcefield
- Developed in collaboration with Prof Huai Sun (SJTU)

COMPASS force field (J Phys Chem B 102(38):7338–7364, 1998)

COMPASS II: extended coverage for polymer and drug-like molecule databases

Huai Sun¹ · Zhao Jin¹ · Chunwei Yang¹ · Reinier L. C. Akkermans² ·
Struan H. Robertson² · Neil A. Spenley² · Simon Miller² · Stephen M. Todd²

Maybridge Screening DB



Unknown quality parameters



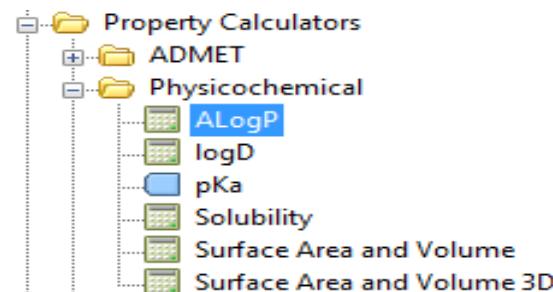
Fully parameterized

Table 1
Theoretical methods used for the calculation of physicochemical properties of compounds

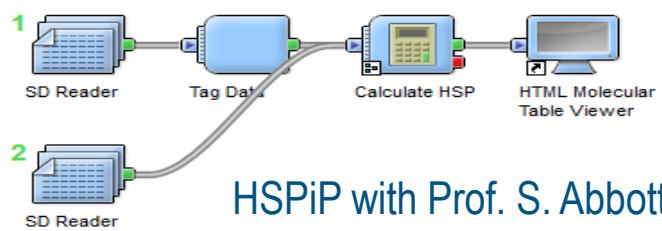
Theoretical relations	Component symbols	Refs
Solubility parameter	$\delta_{\text{em}} = \frac{E_{\text{coh}}}{V} = \sqrt{CED}$ $\delta_{\text{HAN}} = (\delta_d^2 + \delta_p^2 + \delta_h^2)$ $4(\delta_{d1} - \delta_{d2})^2 + (\delta_{p1} - \delta_{p2})^2 + (\delta_{h1} - \delta_{h2})^2 \leq R_o^2$ $\delta = \frac{E_{\text{coh}}}{V} = \frac{(E_{\text{vac}} - E_{\text{bulk}})C}{V} = \sqrt{CED}$	(1a) (1b) (1c) (1d)
	δ_{em} , Hildebrand solubility parameter E_{coh} , cohesive energy V , total volume CED , cohesive energy density	31,48
	δ_{HAN} , Hansen solubility parameter δ_d , partial dispersion component δ_p , partial dipole-dipole component δ_h , partial hydrogen-bonding component R_o , radius of interaction sphere in Hansen space 1 or 2 – (subscript) indicates compound 1 or 2, respectively δ , solubility parameter E_{coh} , cohesive energy E_{vac} , energy of molecule in vacuum state E_{bulk} , energy of molecule in amorphous state V , total volume C , unit conversion factor CED , cohesive energy density	49
Flory-Huggins interaction parameter	$\chi_{FH} = \frac{\Delta H_{\text{mix}}}{kTN_1\phi_2}$ $\chi_{FH} = \frac{V_{\text{ref}}(\phi_1 CED_1 + \phi_2 CED_2 - CED_{12})}{RT}$ $\chi_{FH} = \frac{VA_{12}}{RT} + \beta$ $A_{12} = (\delta_1 - \delta_2)^2 \text{ or } A_{12} = (\delta_{d1} - \delta_{d2})^2 + 0.25(\delta_{p1} - \delta_{p2})^2 + 0.25(\delta_{h1} - \delta_{h2})^2$ $\beta = 0.0$ or 0.34 when Hansen and Hildebrand solubility parameters are used, respectively	(2a) (2b) (2c)
	χ_{FH} – Flory-Huggins interaction parameter ΔH_{mix} – enthalpy change upon creation of a binary mixture k , Boltzmann constant T , absolute temperature N_1 , number of molecules of solvent ϕ_2 , volume fraction of polymer	55
	χ_{FH} – Flory-Huggins interaction parameter V_{ref} – molar volume of the smaller molecule in the binary mixture ϕ_i – volume fraction of compound i in the binary mixture CED – cohesive energy density 1 or 2 – (subscript) indicates compound 1 or 2, respectively	58,59
	χ_{FH} – Flory-Huggins interaction parameter V – the molar volume of the solute R – gas constant T – absolute temperature δ_{em} – Hildebrand solubility parameter of compound i δ_d – partial dispersion component (Hansen) δ_p – partial dipole-dipole component (Hansen) δ_h – partial hydrogen-bonding component (Hansen) β – correction to the Flory combinatorial entropy 1 or 2 – (subscript) indicates compound 1 or 2, respectively	31,49, 55
Enthalpy	$\Delta H_{\text{mix}} = \chi_{FH}RT\phi_1\phi_2$ $\Delta H_{\text{mix}} = H_{12} - n_1H_1 - n_2H_2$	(2d)
	ΔH_{mix} , enthalpy change upon creation of a binary mixture χ_{FH} , Flory-Huggins interaction parameter R , gas constant T , absolute temperature ϕ_1 , volume fraction of component i n_i , mole fraction of component i H_1 , enthalpy of component i at pure-state H_{12} , enthalpy of mixture of component 1 and 2 1 or 2 – (subscript) indicates compound 1 or 2, respectively	55,57
Lipophilicity	$\log P = \sum_{i=1}^n a_i \cdot f_i + \sum_{i=1}^M k_i \cdot C_m$	(3)
	P , partition coefficient n , functional groups of the molecule f_i , hydrophobic fragmental constant a_i , incidence of functional group C_m , the Correction factor ($CM = 0.219$) K_m , the frequency of Cm R_g , radius of gyration of linear polymer R , end-to-end distance a , bond length of monomer N , degree of polymerization of polymer α , swelling exponent	28,65,66
Radius	Flory's theory: $R_g = \frac{R}{\sqrt{6}}$, where : $R = aN^{\alpha}$	(4)
		55,79

SOLUBILITY PREDICTION

Group Contributions:
 $\log S = \sum a_i n_i + a_0$



PP Chemistry Collection

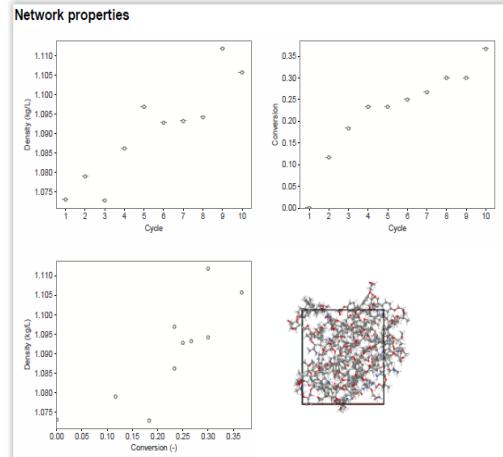
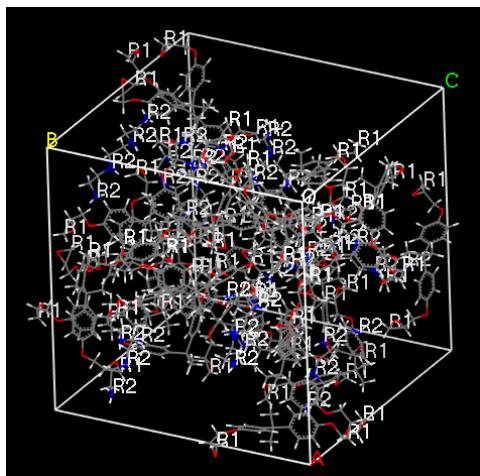
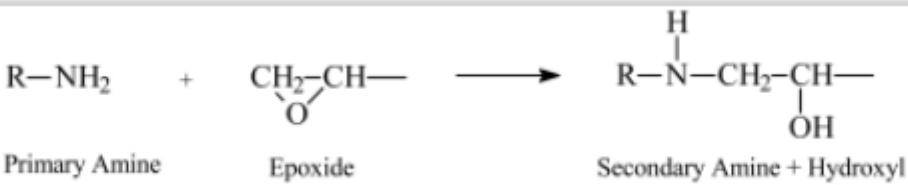
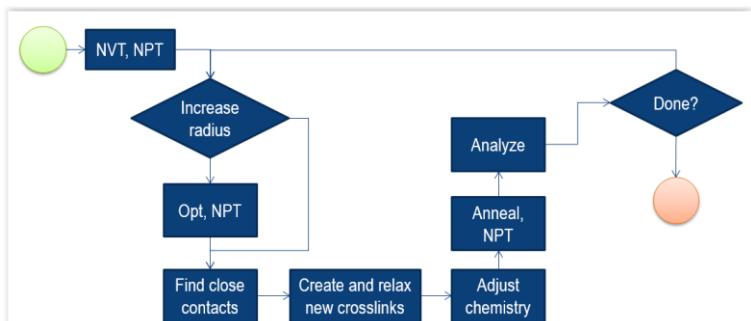
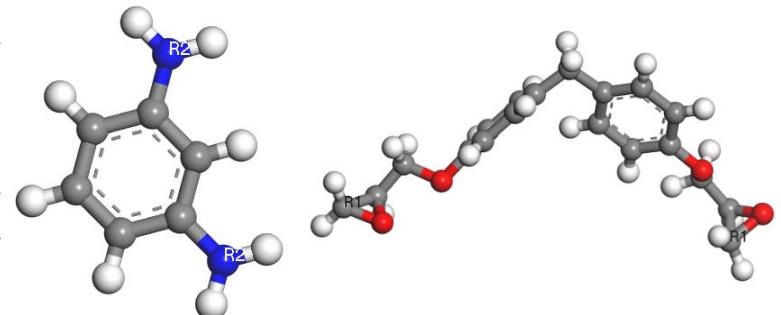


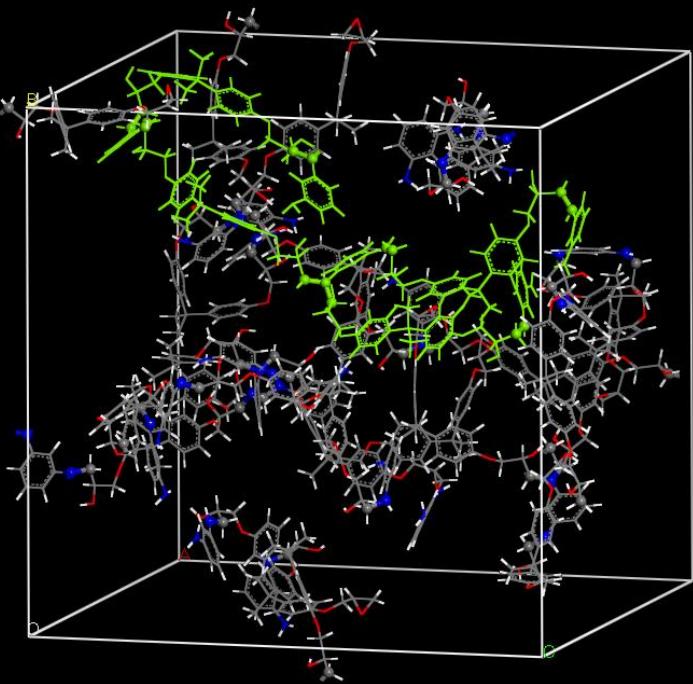
HSPiP with Prof. S. Abbott

Building Polymer Networks

Step 1: Build a 3D model of the mixture

Step 2: Allow for cross-linking reactions to happen whilst running successive MDs simulations

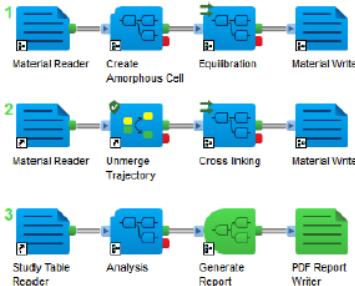




SIMULATING THE CURING OF AN EPOXY POLYMER NETWORK

BIOVIA MATERIALS STUDIO

Polymer Network



Given the structure of a base resin and a curing agent molecule, the following steps will be performed:

1. Create an amorphous cell containing the specified loading for base resin and curing agent molecules
2. Allow the reactive sites in the molecules to react during a dynamics simulation up to the specified conversion
3. Analyze the data for the density versus conversion and cycle number

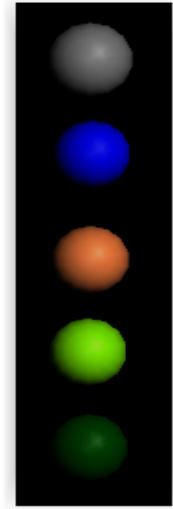
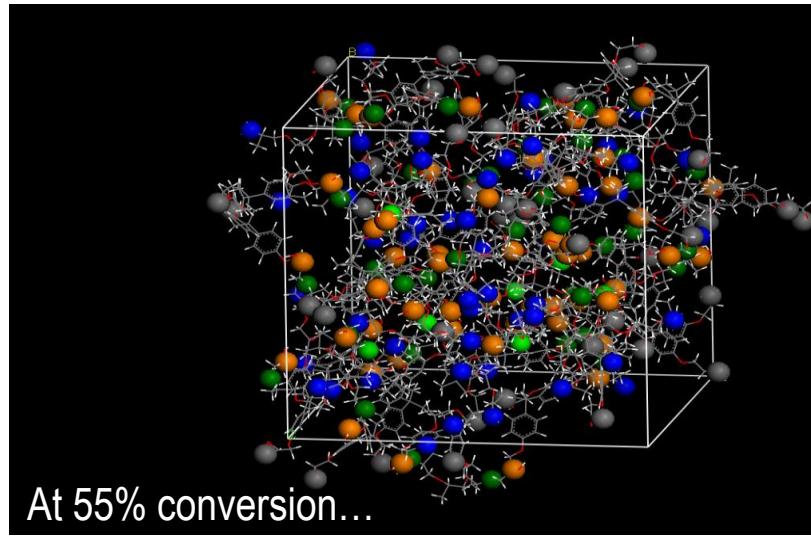
The base resin is an oligomer (prepolymer) containing two or more reactive sites such as epoxide rings. The curing agent, also known as hardener or cross-linker, is typically a small polyfunctional molecule that reacts with the resin to form a polymer network. In addition a solvent can be added to the reacting system.

The reactive sites on the resin and the curing agent must be specified in the input structures before they can be used in the protocol. This is done by assigning a unique name to the primary atom in each functional group, for example N1 for nitrogen atoms in a primary amine group. All names should be listed in the Species parameter, so they can be used to define reactions. The Species list can also contain names of intermediate groups, such as secondary amines. A default species X indicates an unreactive atom and should not be used to define reactive atoms.

Different types of reactions may be specified:

- Ring-opening: A reaction in which a ring is opened by breaking a ring bond.
- Addition: A reaction in which a double bond is reduced to a single bond.
- Condensation: A reaction in which a bond with a small functional group is broken, leaving a condensation product.

For each reaction a *Probability* can be specified as a number between 0 and 1. This can be used to express a difference in activation energies.



Unreacted Epoxy ring

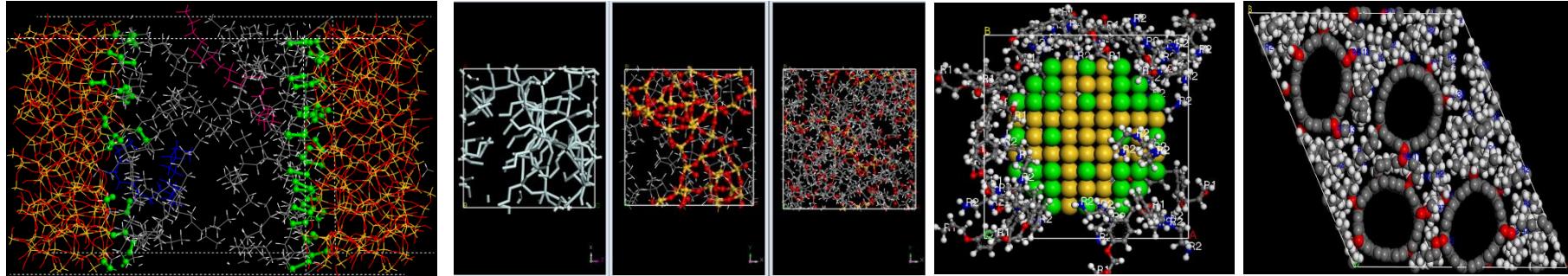
Primary Amine

Crosslinked Epoxy

Tertiary Amine

Secondary Amine

Other 'networks'



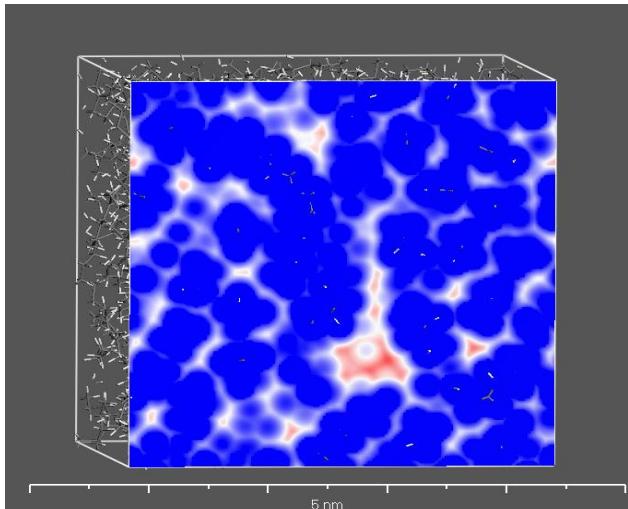
Environmental Stress Cracking of Polymers

- Environmental Stress Cracking (ESC) is one of the most common causes of unexpected brittle failure of thermoplastic (especially amorphous) polymers.
- ESC is linked to the polymer Moduli:
 - elastic: $E=3K(1-2v)$ and
 - bulk $K = \frac{8.04(e_{coh}+x_c\Delta H_m)}{V}$
- So that, $E \sim e_{coh} / V = \delta_{HIL}$
- “the solubility parameter affects both the modulus and the surface energy and has a major role in ESC mechanism”



ESC of Polymers

- ▶ Atomistic simulations (MD) allow for the computation of:
 - ▷ Free Volume
 - ▷ Fluids Diffusion
 - ▷ Solubility parameters (w%)
 - ▷ Solvation Free Energies
- ▶ “a general efficiency approach that combines all results into a single efficiency number could distinguish between an ESC fluid and a non ESC fluid in all the systems tested”



Polyethylene model with water (1.2 wt%) - free volume display (2D slice, blue is highly dense, red: low density or free volume).

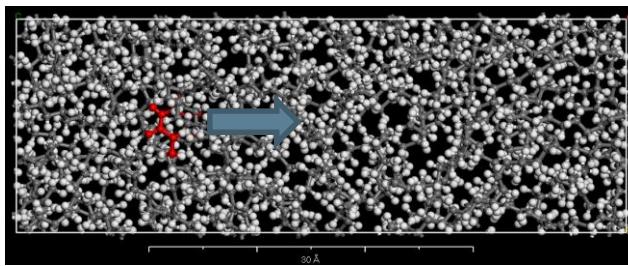


Figure 2: Toluene molecule (red) in amorphous PE, the blue arrow indicates the direction of the applied external force.

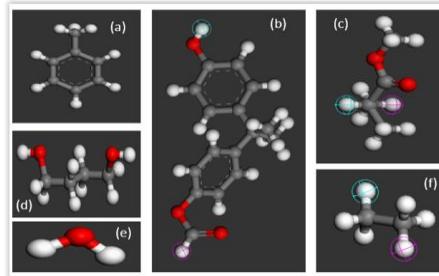


Figure 1: Atomistic models used in the simulations: (a) Toluene (b) PC repeat unit (c) PMMA repeat unit (d) 1,4 Butane diol (e) Water (f) Polyethylene repeat unit.

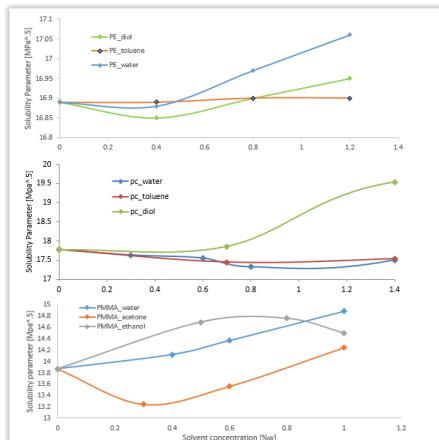


Figure 3: Solubility parameters of the polymer-ESC fluids mixtures versus ESC fluids concentration (%v/v).

D. Alperstein and M. Meunier. Atomistic simulations of environmental stress cracking in polymers. Molecular Simulation, ICMS 2016 Special Issue – submitted.

In silico modelling to predict drug affinity to PLA-PEG nanoparticle core

- Intended to be a “virtual screening” for potential drug
- Focus only on non-covalent encapsulation.

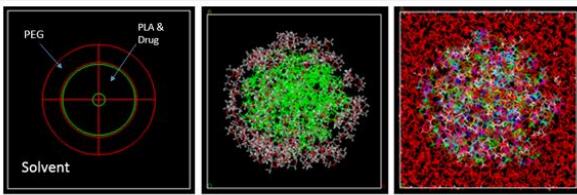
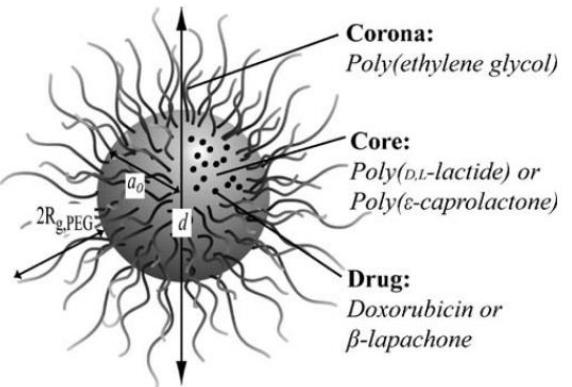
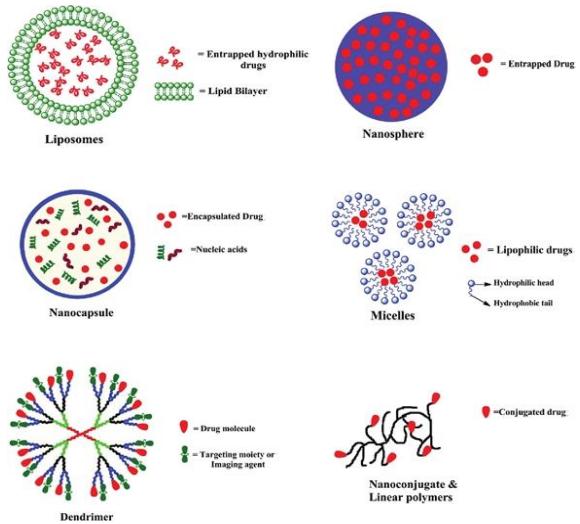
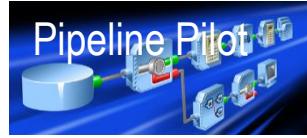
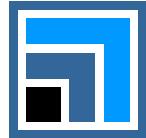


Figure 2: Schematic display of the PLA-PEG nanoparticle (a) micelles regions (b) unsolvated atomistic micelle model (c) solvated atomistic micelle model.

M. Meunier, A. Goupil and P. Lienard. Predicting drug loading in PLA-PEG nanoparticles. To be submitted.

Methodology



- Literature analysis reports many predictive approaches:
 - Combination of molecular dynamics simulations and docking (Monte-Carlo)

$$\delta = \sqrt{\frac{\Delta H_v - RT}{V_m}}$$

- Using Solubility parameters:

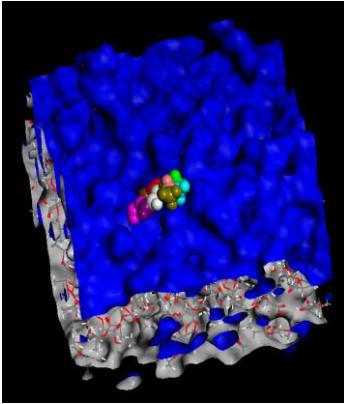
- Flory-Huggins Chi (χ) parameter calculation

$$\chi = \frac{V}{RT} (\delta_i - \delta_j)^2$$

- Hansen Solubility Parameters

$$\delta^2 = \delta_D^2 + \delta_P^2 + \delta_H^2$$

$$(Ra)^2 = 4(\delta_{d2} - \delta_{d1})^2 + (\delta_{p2} - \delta_{p1})^2 + (\delta_{h2} - \delta_{h1})^2$$

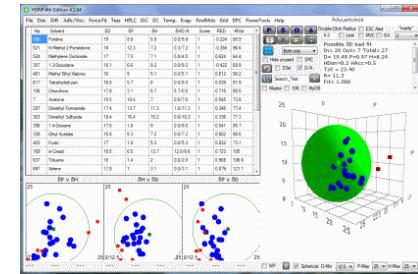


- QSAR

- Log P



- Compare results from different simulations methods with experimental results of drug loading



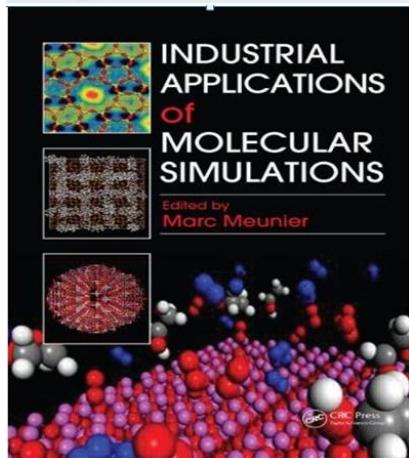
HSPiP

More Information

Virtual Biosphere and Materials

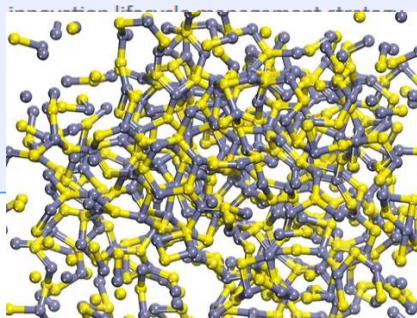
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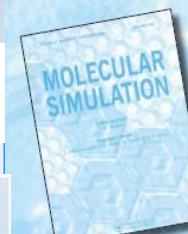
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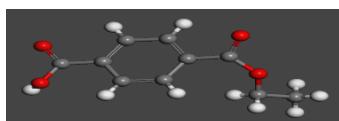
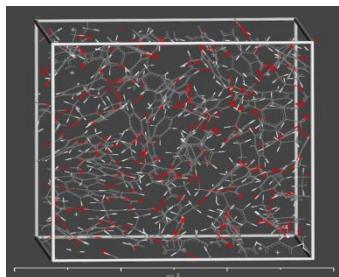
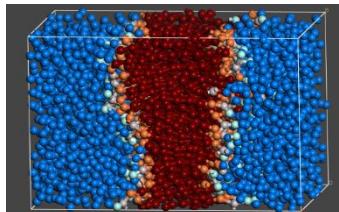
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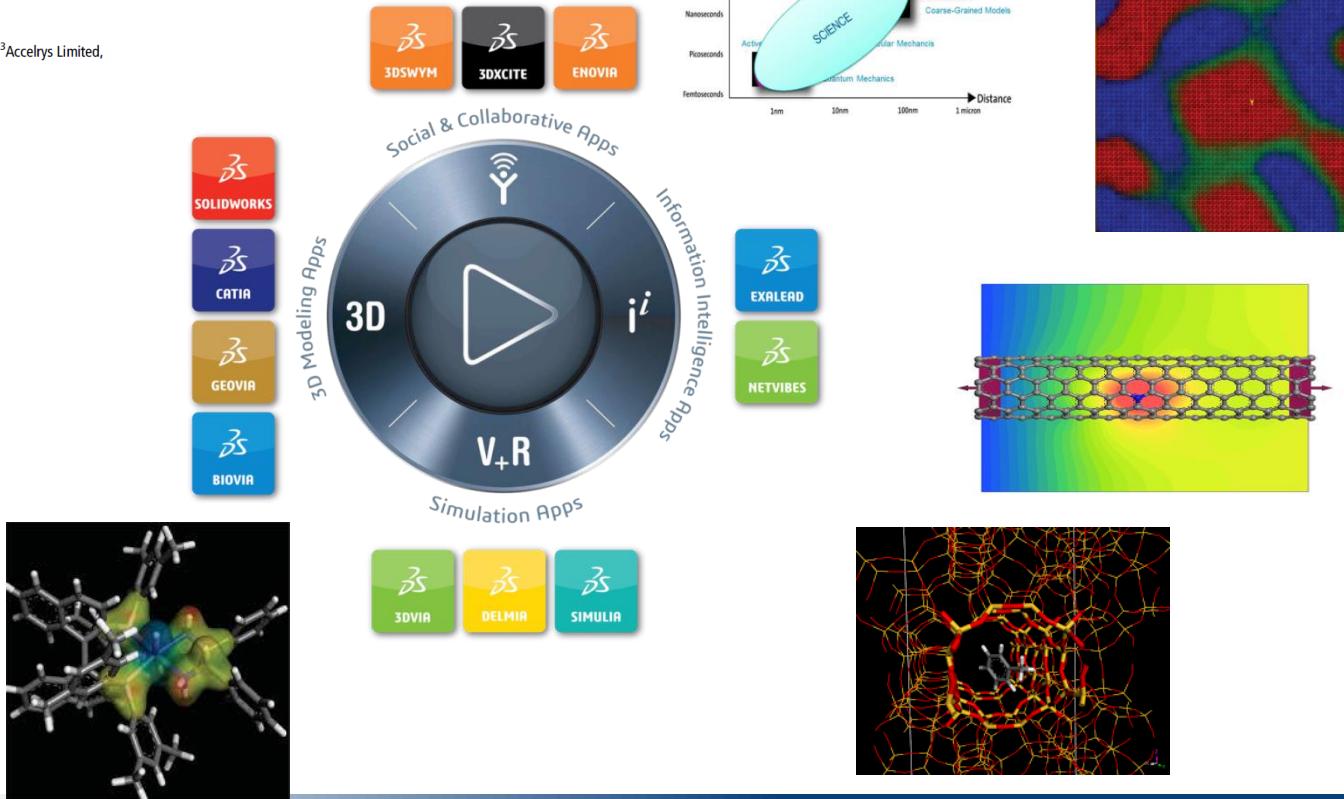
Multiscale modeling of nanomaterials: recent developments and future prospects

G. Fitzgerald¹, J. DeJoannis², M. Meunier³

¹Accelrys, Inc., San Diego, CA, USA; ²Accelrys, Inc., Burlington, MA, USA; ³Accelrys Limited, Cambridge, UK



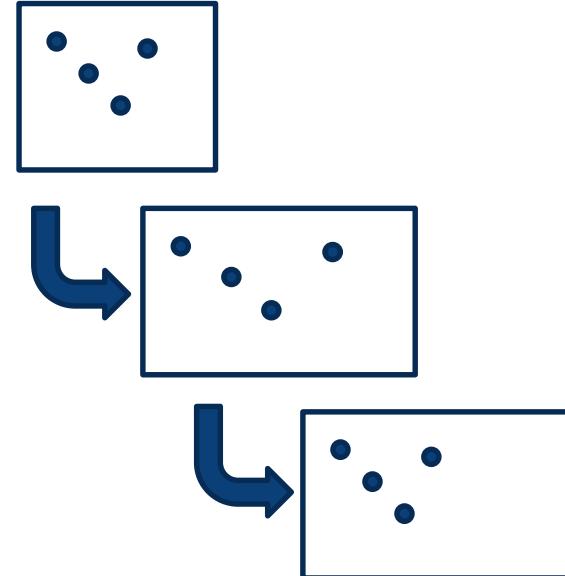
1 Multi-Scale at DS BIOVIA



Extended Mechanical Properties

- Constant Strain
 - Apply several different small finite strains, measure stress
 - Plot stress Vs strain
- Static method (using Hessian)
 - Assumes that energy is quadratic in neighbourhood of current configuration
 - Faster than constant strain
 - Requires well optimized structure]

OK

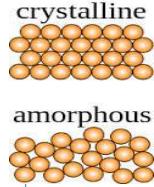


- Stress fluctuation
 - Relates stiffness tensor to fluctuations in stress
 - NVE - adiabatic elastic constants
 - NVT – isothermal elastic constant
 - Requires trajectory

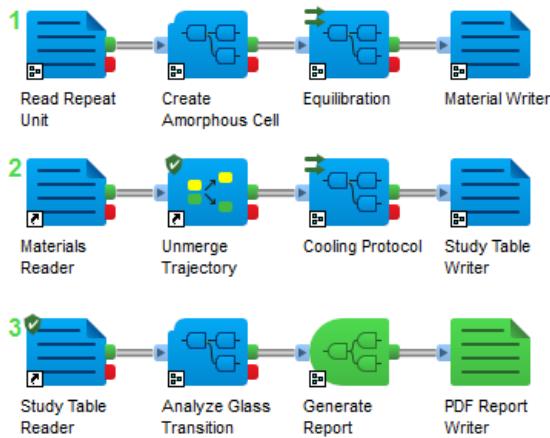
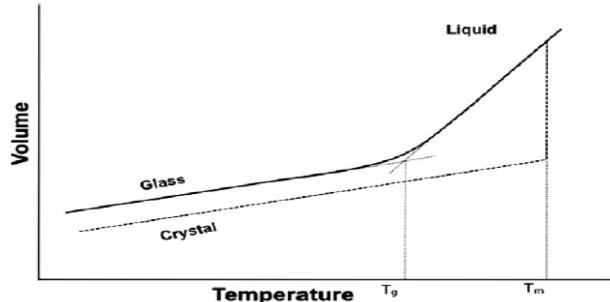
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Energy and derivatives are recomputed by Mechanical Properties task. Hessian need not be precomputed (unlike Vibrational Analysis)

Glass Transition Temperature Prediction



- The glass transition temperature (T_g) of an amorphous solid is a critical physical property which can dramatically influence its physical stability and viscoelasticity properties.
- Study the effect of humidity on T_g (water acting as a plasticizer).



Dilatometric Analysis

Property	Value
Glass transition temperature (K)	534.07 ± 11.06
Specific volume at T_g (L/kg)	1.03 ± 0.29
Thermal expansion in glass state (1/10K)	0.41 ± 0.72
Thermal expansion in rubber state (1/10K)	3.24 ± 0.72
Transition temperature range (K)	2.68 ± 276.95

