MODELLING MIXTURES @IFF

Using computers to build better formulations

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OUTLINE

Background to Modelling@IFF

Examples of Mixture Modeling

- Predicting flashpoints and making them useful….

IFF'S DATA AND ANALYTICS TEAM

Started approximately 8 years ago within Corporate R&D.

Mission to support corporate R&D projects and act as subject matter experts within the wider business.

Currently 6 scientists

Mix of capabilities and domain expertise;

Molecular Design – Fragrance molecule synthesis and structure-property relationships.

Computational Materials Science - Fragrance delivery, Emulsions and Mixtures

Research Automation and Information Systems – Making knowledge accessible, building applications

Machine Learning – Prediction of spectra and sensory properties

IFF'S VALUE CHAIN

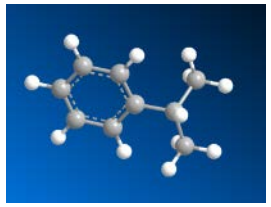
A materials chemistry perspective

Captive Molecule →

Neat Oils, Fine Fragrance →

Flavor Emulsions →

Fragrance Capsules
Laundry, Personal Wash, Beauty Care
Flavor Powders →

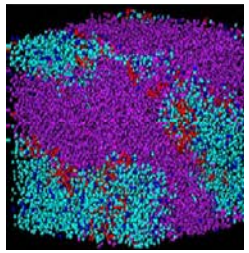


Molecules

↓

Simple Mixture
(e.g. flavor accord)

↓



Emulsion
(e.g. water/oil emulsions)

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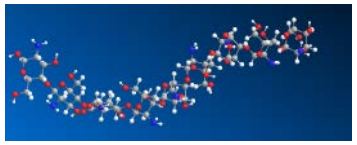
Polymers



Delivery System
(e.g. capsule slurry, spray dried powder)

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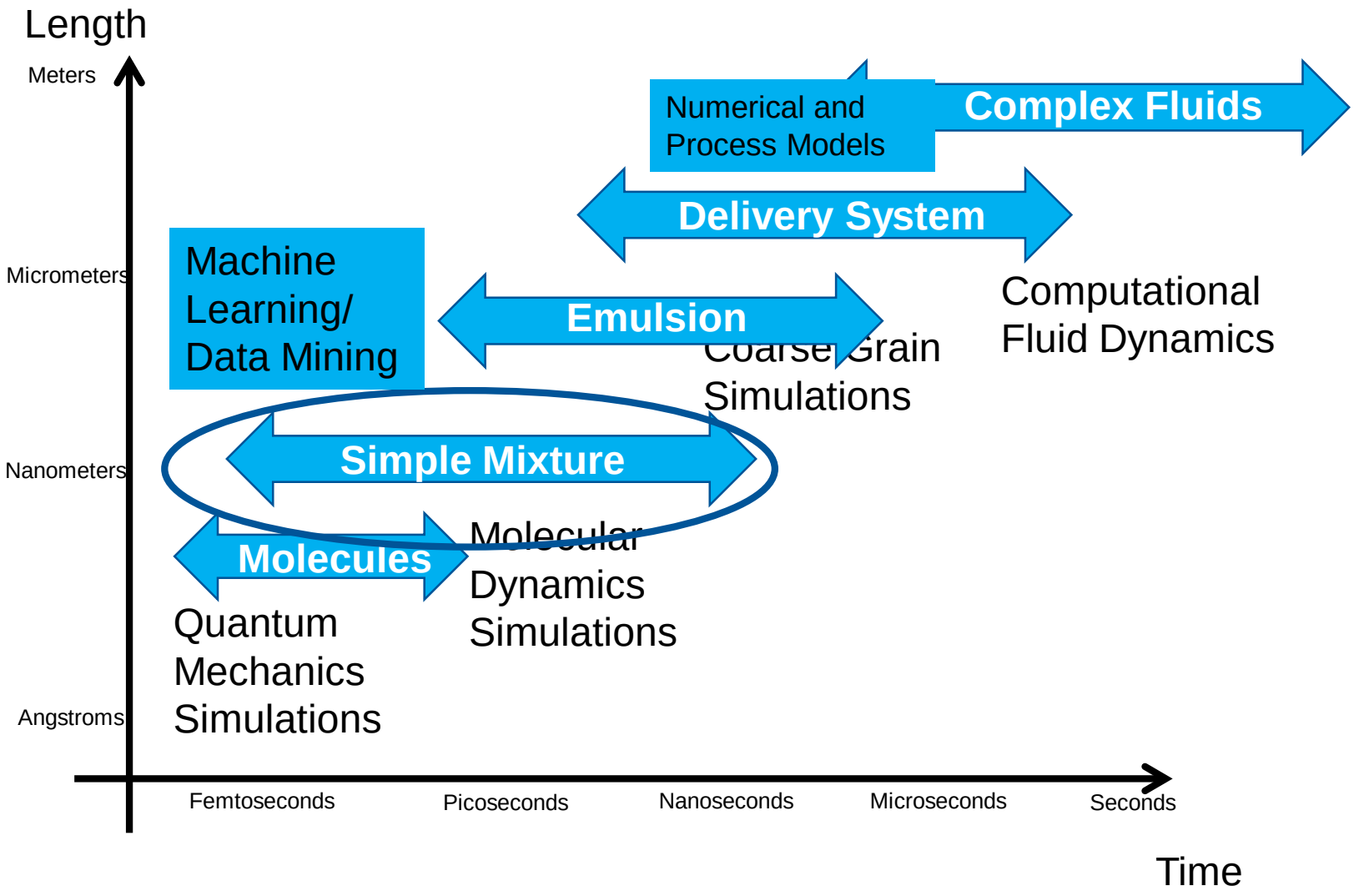
Complex Fluid
(Fab Con, LLD, Dough, Beverage)

Chemistry

Materials Science

COMPUTATIONAL MATERIALS SCIENCE SIMULATIONS



BUILDING DIGITAL INTO FORMULATIONS WORKFLOWS

Our experiences….

Applications

Formulators aren't going to learn expert chemistry tools;

Act as their 'go to' person. Often need fast turn around times and doesn't lead to regular use

Building accessible tools (e.g. Web based tools).

Tools need to be scalable and fit into existing workflows of the target users.

Tools must add value

Be faster than current workflow
Provide more information

Most accurate/scientifically correct solution is not always required

Data

Terminology is not universal, e.g. a fragrance ingredient means different things to a perfumer as it does to a chemist.

Data developed for other purposes may not be always be usable for modeling studies.

Is it fit for purpose?

Building correlative models

Comparing to other calculations

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MIXTURE MODELING@IFF

Formula Optimization using mathematical modeling

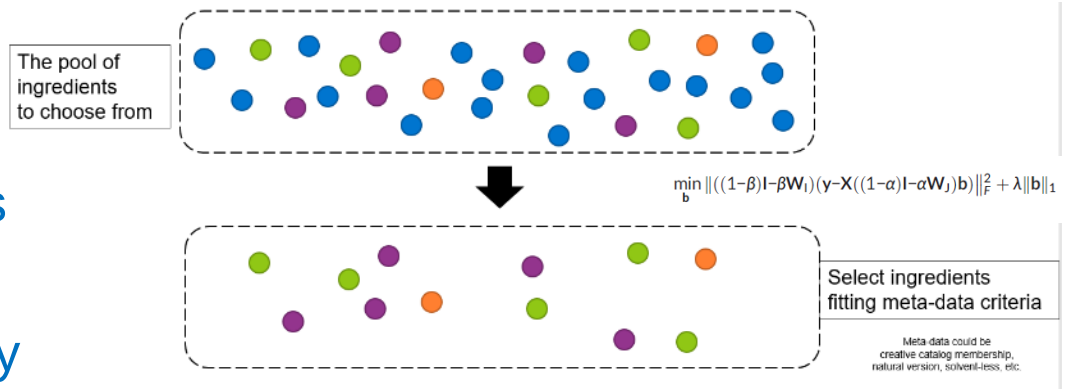
Reconstruction of formulations from Analytical results (e.g. natural oil)

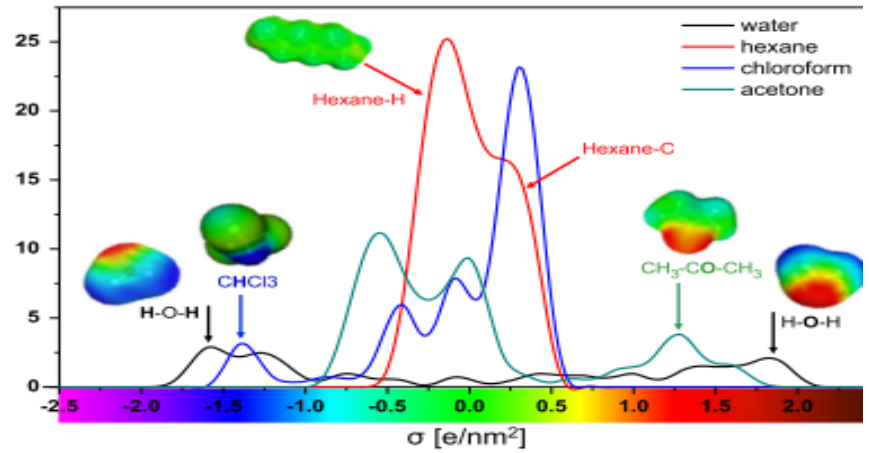
Reformulating to reduce cost or improve sustainability

(e.g. bioderived molecules)

Optimization based on minimization algorithm

(e.g. Silva BS, Tøstesen M, Petersen MA, Bäckman A, Flavour and Fragrance Journal 32[4] July 2017, 286-293)

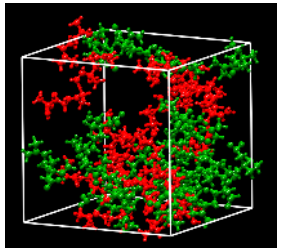




Thermodynamics of mixtures - COSMO-RS

Fundamental Understanding using Computational Chemistry

Intermolecular interaction, co-solvation, conformations



USES OF COSMO-RS@IFF

Green Chemistry

- Replacement of solvents
- pKa prediction

Headspace Concentration above a fragrance mixture

- Vapour-Liquid Equilibrium
- Activity Coefficient Calculation

Flashpoint Prediction

- Assisting formulators

COSMO Theory – Conductor Screening Model

Theory developed in the early 90's;

based on Quantum Mechanics

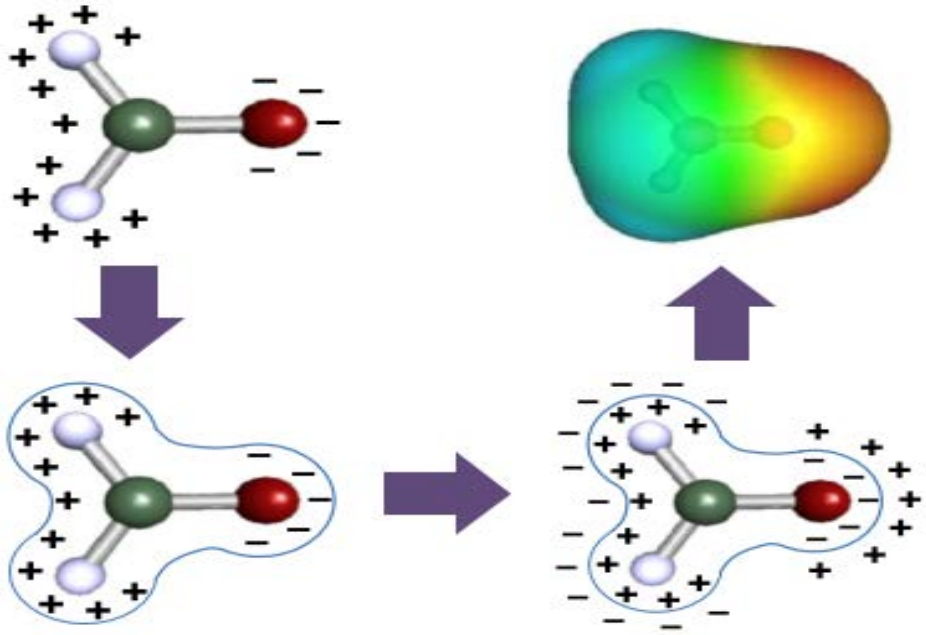
Embeds a molecule in a dielectric medium that represents the solvent.

Solves a simplified version Schrodinger Equation.

Taking into account the polarization of the charge in the molecule, due to the solvent

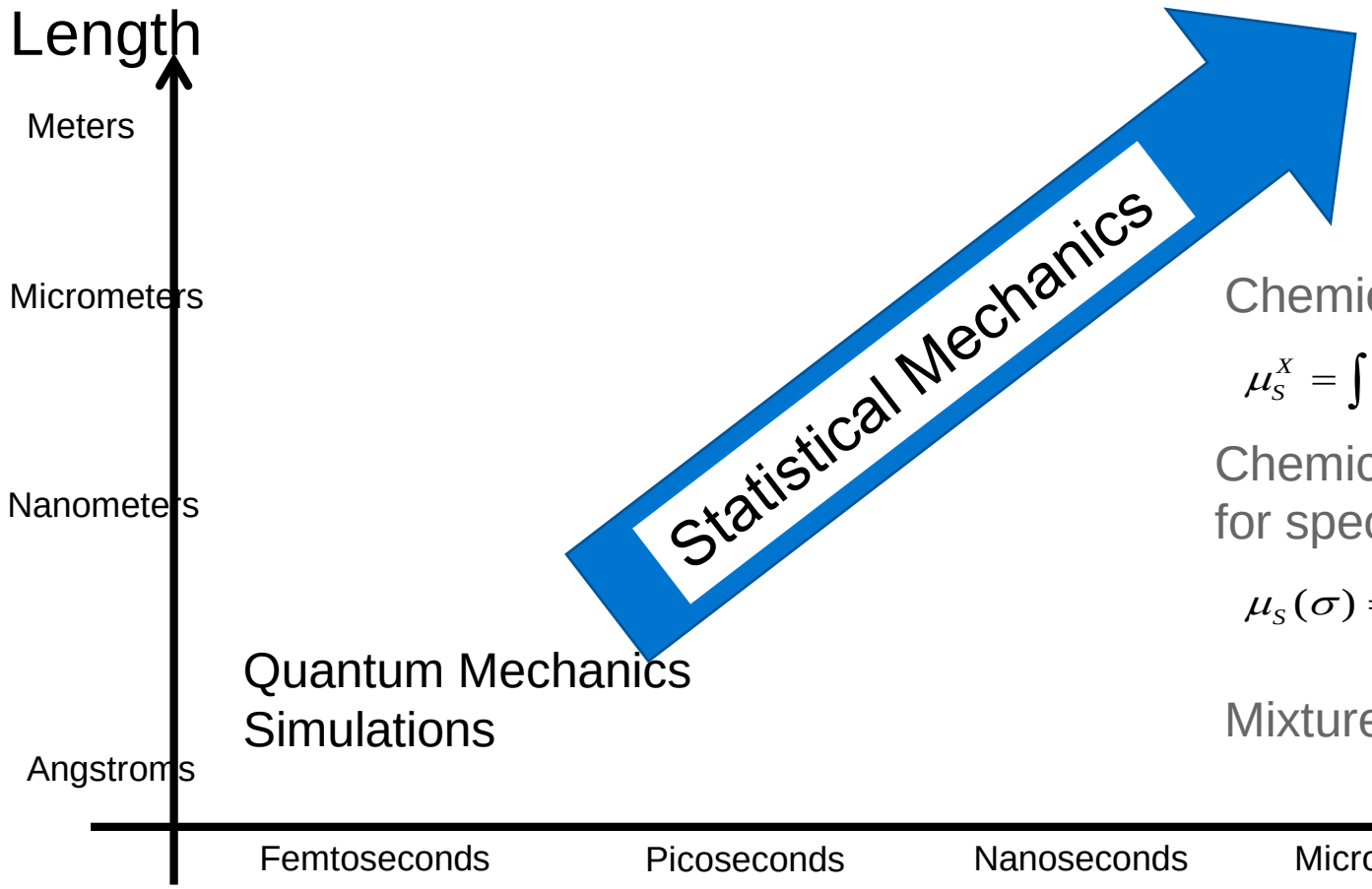
Also the polarization of the solvent to account for the molecule.

Polarization charge density, σ = polarization charge / area



Klamt, A. The COSMO and COSMO-RS Solvation Models.
Wiley Interdiscip. Rev. Comput. Mol. Sci. **2018**, *8* (1).
https://doi.org/10.1002/wcms.1338.

COSMO-RS (REAL SOLVENT)



Macroscopic thermodynamic properties; e.g. Solubility, Activity Coefficients, LogP

Chemical potential of solute X in S

$$\mu_S^X = \int d\sigma p^X(\sigma)\mu_S(\sigma) - \lambda kT \ln A^S$$

Chemical potential affinity of solvent for specific polarity σ (σ-potential)

$$\mu_S(\sigma) = -kT \ln \int d\sigma' p_S(\sigma') \exp\left\{-\frac{E_{\text{int}}(\sigma,\sigma') - \mu_S(\sigma')}{kT}\right\}$$

Mixture σ-potential $p_S(\sigma) = \frac{\sum_i x^i p^i(\sigma)}{\sum_i x^i area^i}$

FLASHPOINT PREDICTION - INTRODUCTION

For safety reasons flashpoint temperature of most fragrance/flavor formulations must be above a certain threshold (e.g. 70°C)

Flashpoints are often influenced by minor amounts of high vapor pressure components in a mixture

Measuring flashpoints for mixtures can be very inefficient when looking at a large number of formulations

Provide guidance of how changes to the formulation alter the flashpoint and if possible by how much can be a great time saver.

Use COSMO-RS based methodology

Reinisch, J.; Klamt, A., Ind. Eng. Chem. Res. 54, 12974 (2015).

FLASHPOINT PREDICTION - THEORY

Flashpoints can be calculated from the Antoine equation;

$$LogP_{sat} = A - \frac{B}{T+C}$$

$$P_{sat}(T) - P_{sat}(FPT) = 0$$

where A, B, and C are specific constants.

Where $P_{sat}(T)$ is the saturated vapor pressure of the pure compound at a given temperature, $P_{sat}(FPT)$ is the saturation vapor pressure at the flashpoint temperature.

This can be applied to a mixture using the equation;

$$1 = \sum_{i \neq k} \frac{x\gamma P_{Sat,i}}{P_{Sat,i,fp}}$$

Where, x is the mole fraction, γ is the activity coefficient, i are the flammable components in the mixture and k the non-flammable components

The activity coefficient is calculated from the Quantum Mechanics calculations.

Reinisch, J.; Klamt, A., Ind. Eng. Chem. Res. 54, 12974 (2015).

Chen, H.-Y.; Liaw, H.-J. Procedia Eng. 45, 507 (2012)

VALIDATION (INGREDIENTS)

Understanding limitations

Tested approximately 50 pure compounds from IFF's catalog.

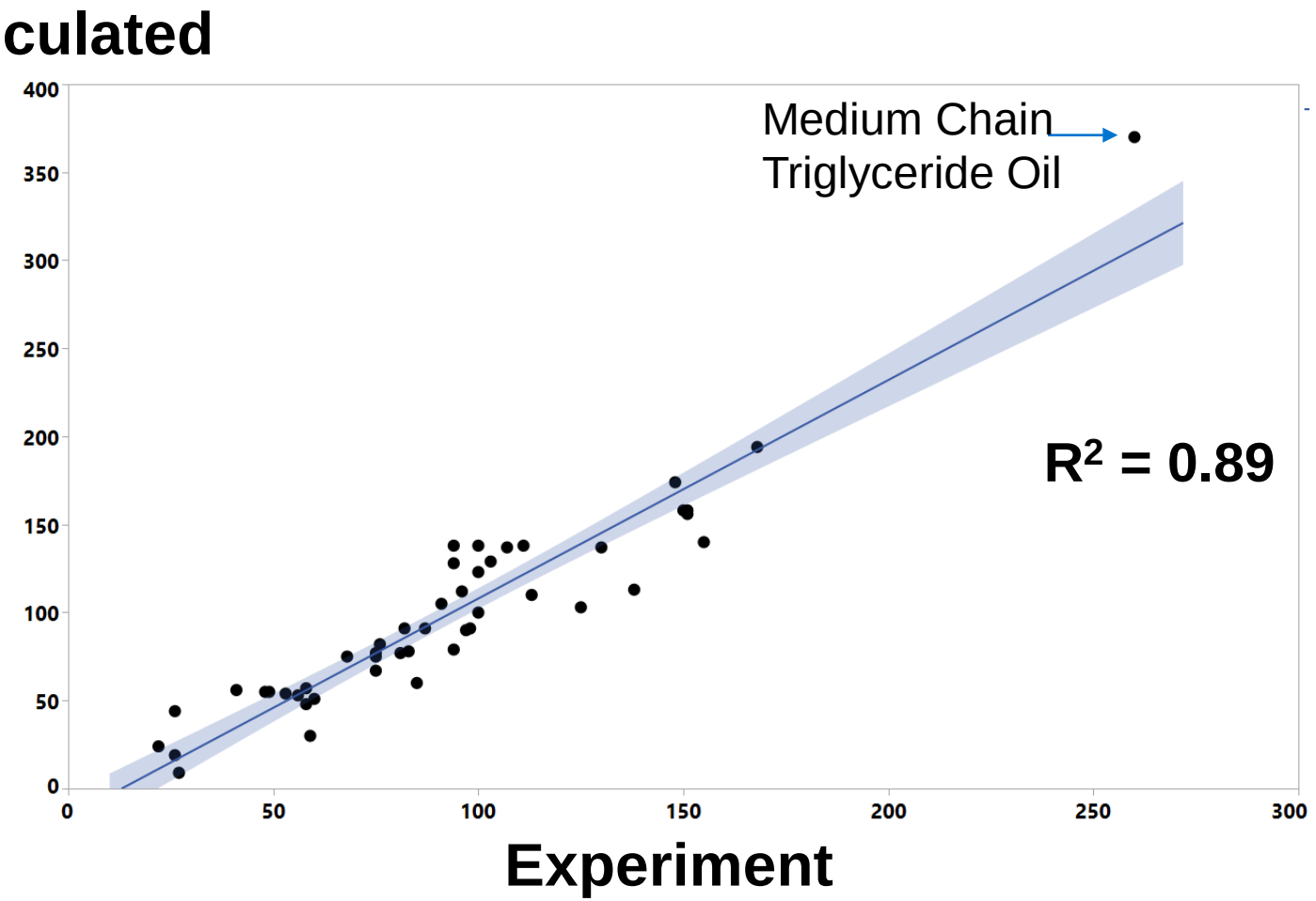
Overall results show good agreement with experimental measurements

Model doesn't not overpredict or underpredict flashpoints

Some significant differences

Medium Chain Triglyceride Oil – molecule possible to large for COSMO methodology.

Some ingredients may not be completely pure when tested (e.g. isomers)



VALIDATION (FULL FORMULAE)

10 full fragrance formulation

Each containing approximately 30-50 components

Predictions provide **directional guidance** and in some cases are **semi-quantitative**

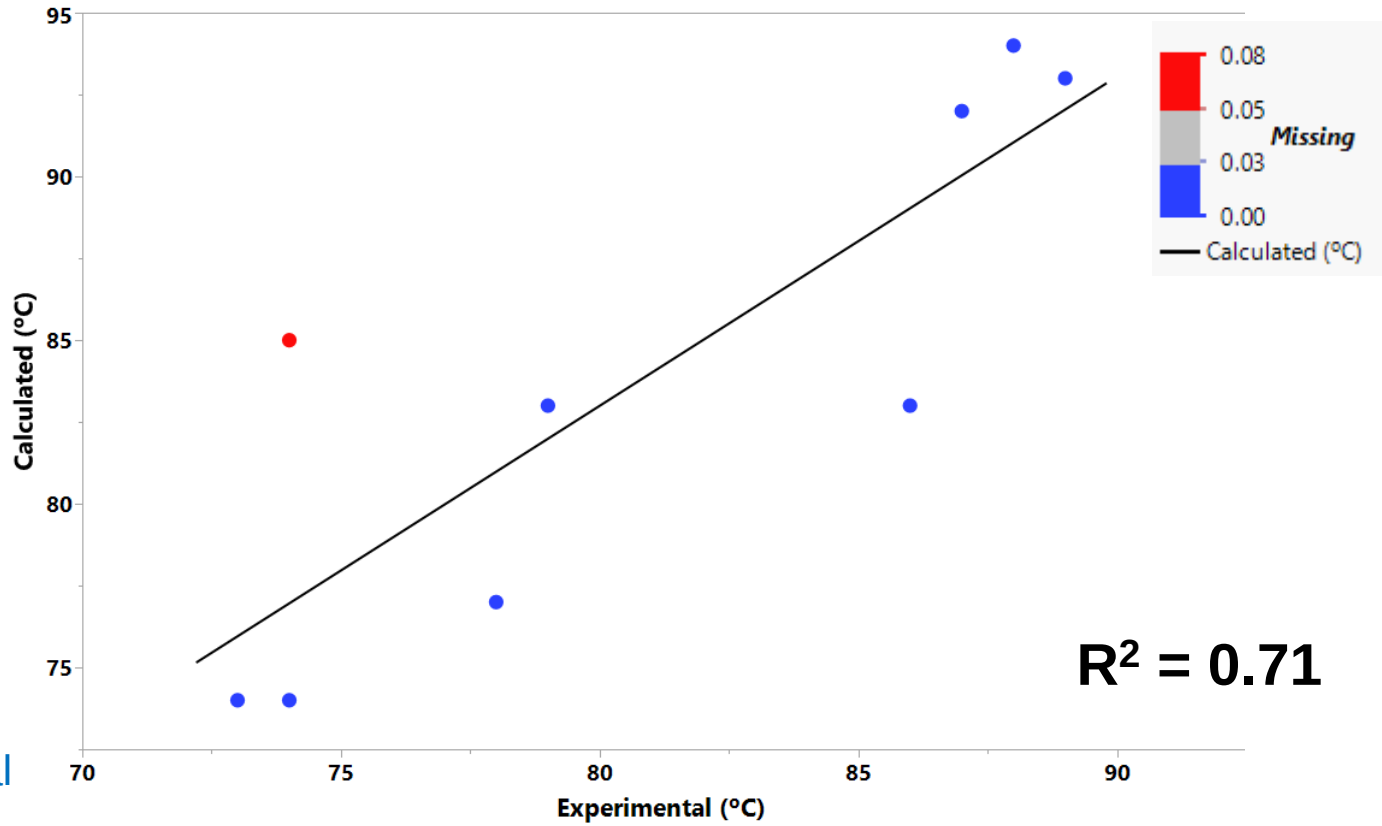
Worst prediction is about 11°C away from experiment

Three possible reasons for poor correlation

Very narrow range of flashpoint data (20°C)

Amount of missing components in system (e.g. natural oils)

Measurement error, accuracy of flashpoint experiment is ±3°C.



VALIDATION - TERNARY MIXTURE

	Exp (ºC)	Calc (ºC)
Glycerol	160	129
Ethyl Lactate	46	48
Water	NA	NA

Pure Components

Predictions in line with full formulations

May be underpredicting strength of H-bonds in Glycerol

Reproduce directional trend of increasing Ethyl Lactate results in lower flashpoint

Glycerol : Water : Ethyl Lactate	Exp (ºC)	Calc (ºC)	Difference (ºC)
6 : 3 : 1	90	79	-11
7 : 2 : 1	83	82	-1
8 : 1 : 1	72	83	11
4 : 3 : 3	71	63	-8
6.5 : 1.5 : 2	67	71	4
5 : 2 : 3	67	65	-2
6.5 : 0.5 : 3	65	65	0
5 : 1 : 4	63	62	-1
4 : 1 : 5	62	60	-2
2 : 2 :5	61	59	-2

VALIDATION – TERNARY MIXTURE

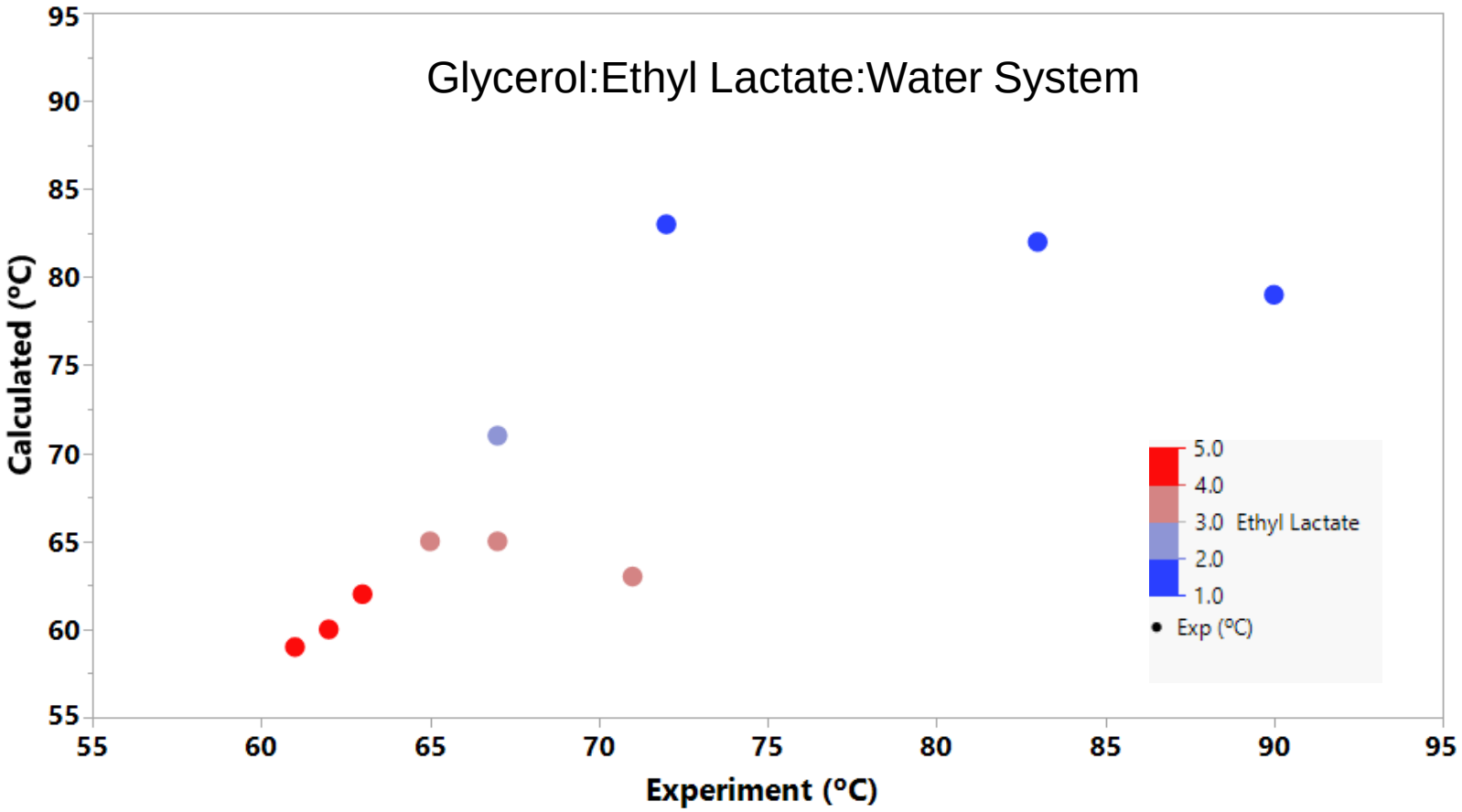
Broadly – error of prediction increases as concentration of ethyl lactate decreases.

Poor prediction of Glycerol flashpoint

Simple mixtures (2 or 3 component) less accurately predicted compared to full formula

Propagation of errors.

More studies on simple mixtures needed.



ACCESSIBILITY

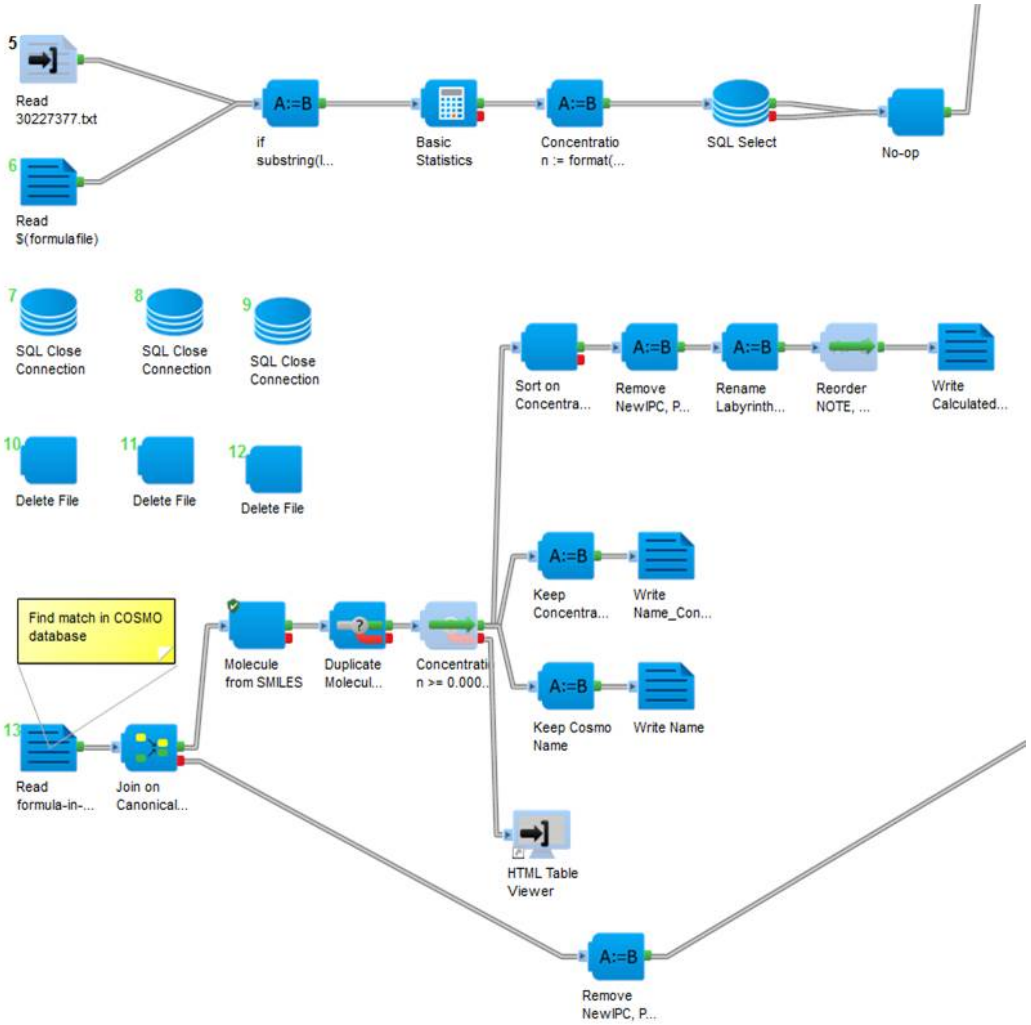
Use Pipeline Pilot to automate calculation & provide API.

COSMO-RS is an expert tool. Can only really be used by a small subset of individuals

Formulators resistant to learning a new software tool

Need to make the tool available in a simple to use format without laborious data input steps

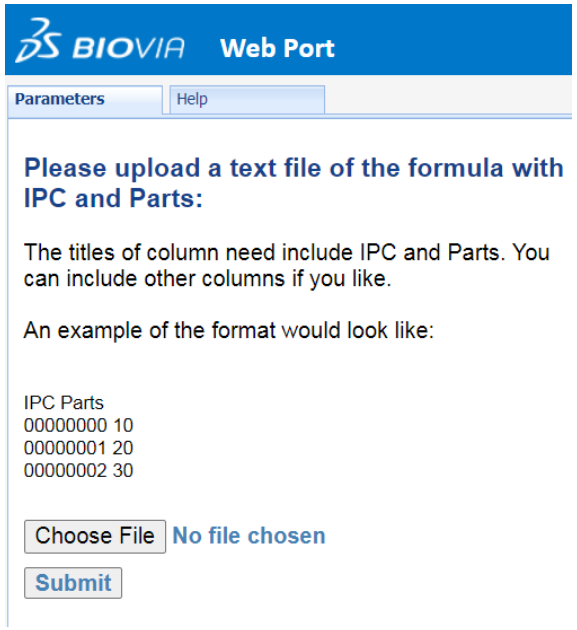
Used Biovia's Pipeline Pilot to create a workflow accessible via a Webpage



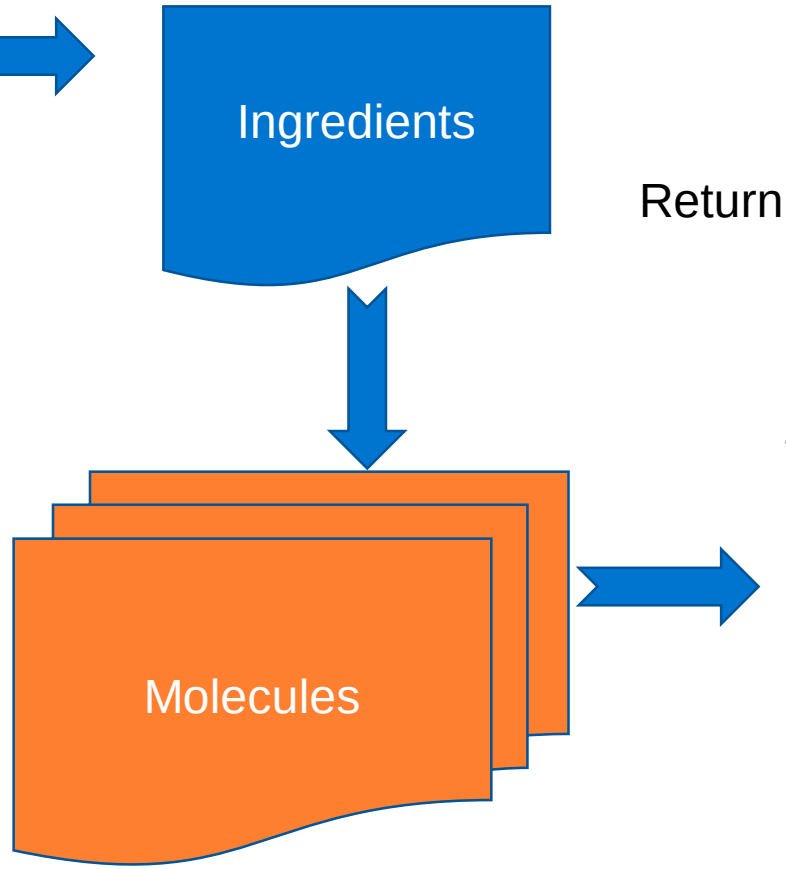
PIPELINE PILOT WEBPORT TOOL

Pipeline Pilot enables the creation of web based tools.

Only requirement is a spreadsheet with a formulation

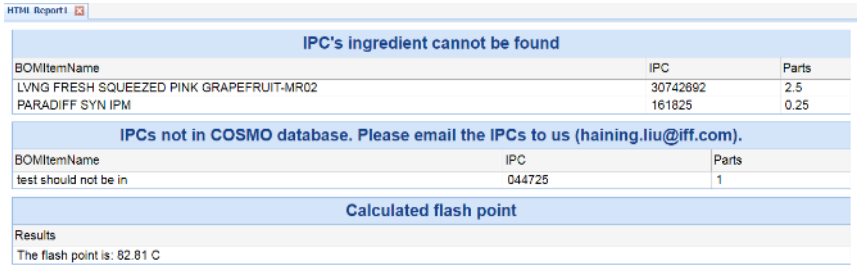


Upload of formulation




```
BOMItemName      IPC      Parts
ALD C-10 TOCO    13199    4
GALBASCONE PRG BHT        71328    0.25
VELTOL PLUS      222199   2
VANILLIN FRG     220617   2
IONOL CP         94006    10
ALD C-18         13566    1
ALD C-16 STRAWB#2         12461    4
"DECALACTONE, GAMMA"      41424    10
DELPHONE         42280    0.5
UNDECALACTONE GAMMA COEUR          162511   30
THIAZOLE (2-ISO PROP 4-METH) 1% IPM(MB) 92029    20
ETH BUTY         50139    7.5
BUTYL ACET       26800    2.5
ETH CAPROATE     50290    7.5
ISO AMYL ISO VAL          90262    7.5
ETH-2-METH BUTY 59178    2.5
MANZANATE        51650    1.25
ALLYL CAPROATE   13338    1.25
ALLYL HEPTANOATE          13876    7.5
VERDOX  222496   100
ALD C-8 TOCO     13099    2
ALD C-9 TOCO 10% IPM (MB)          11817    0.25
```

Creation of COSMO input file



IPC's ingredient cannot be found

BOMItemName	IPC	Parts
LVNG FRESH SQUEEZED PINK GRAPEFRUIT-MR02	30742692	2.5
PARADIFF SYN IPM	161825	0.25

IPCs not in COSMO database. Please email the IPCs to us (haining.liu@iff.com).

BOMItemName	IPC	Parts
test should not be in	044725	1

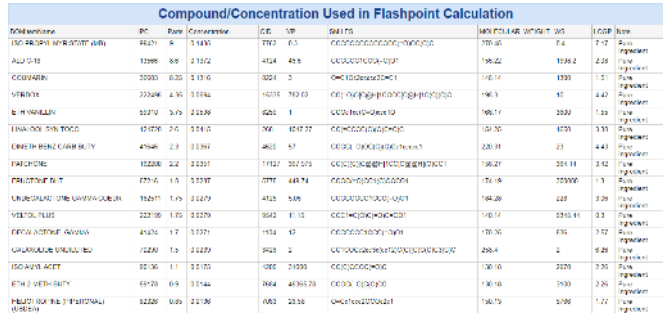
Calculated flash point

Results

The flash point is: 82.81 C

Flashpoint

Return of results



Extra Information (e.g. FP of pure components)

CONCLUSION

The modeling of mixtures is a relatively new area of research

It is key in increasing the efficiency of formulation design

We have had some initial success using COSMO-RS to predict flashpoints.

More importantly, tools must be accessible in an easy to use format for our formulators.

ACKNOWLEDGEMENTS

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