

UltraScan: Improved 2DSA Resolution with Modified Parameter Space Grids



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Overview

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- Background

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 - Solute parameters & the Lamm Equation

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 - 2DSA

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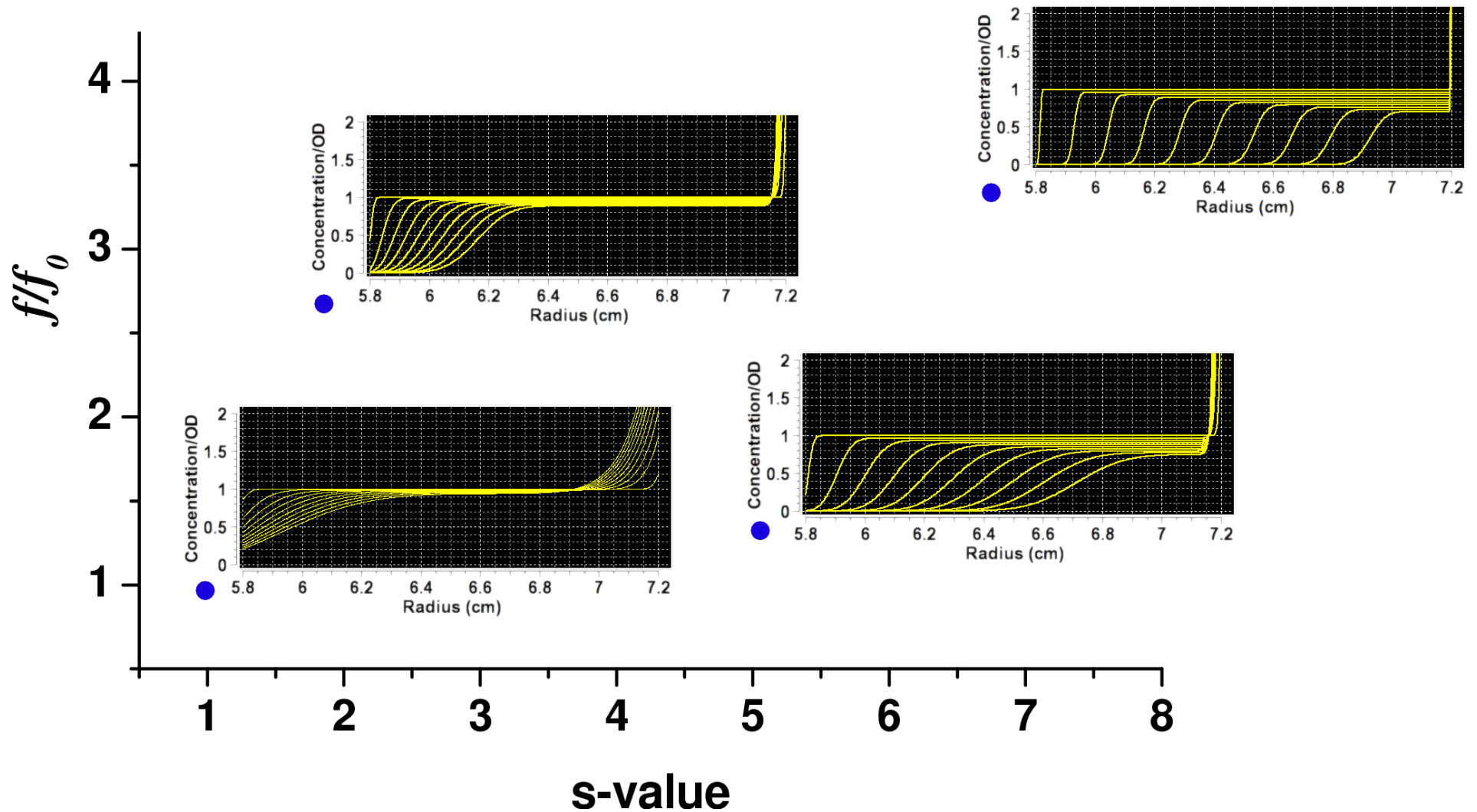
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 - Solute parameters & the Lamm Equation
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 - Algorithm to produce
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- Concept Application

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- Summary

Background: Solute Parameters & The Lamm Equation

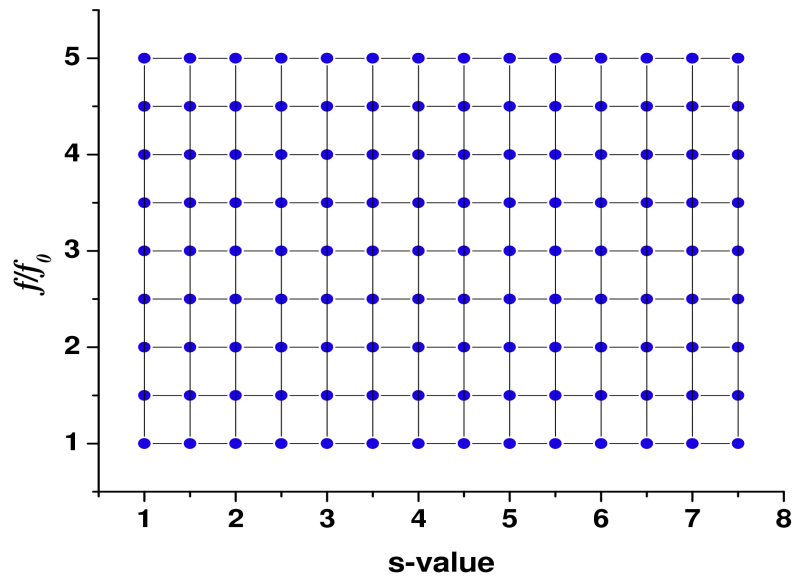
$$\left(\frac{\partial C}{\partial t}\right)_r = \frac{-1}{r} \frac{\partial}{\partial r} \left[s \omega^2 r^2 C - D r \frac{\partial C}{\partial r} \right]_t$$



Background: 2DSA

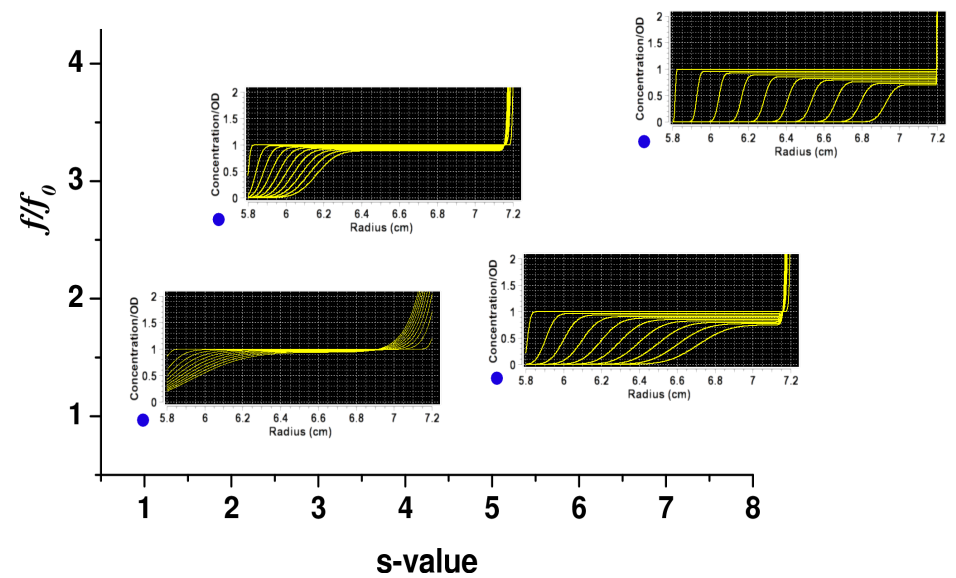
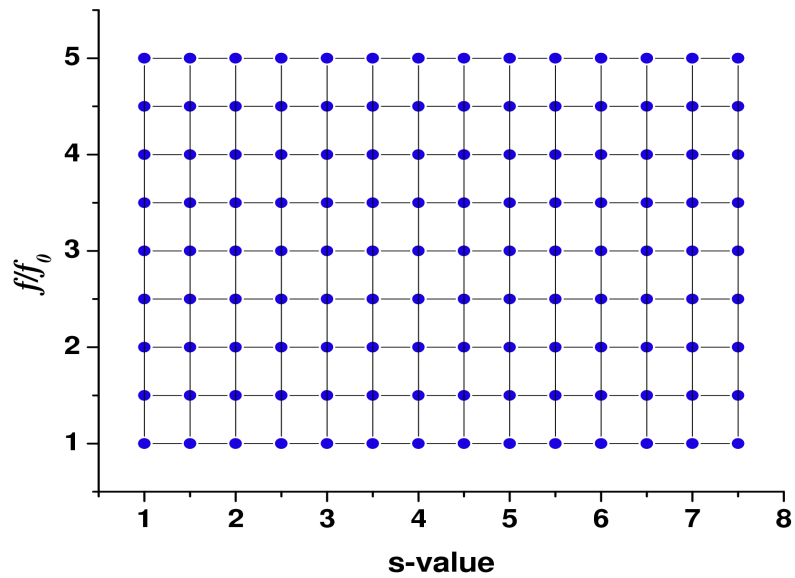
Background: 2DSA

- Put a grid on the parameter space



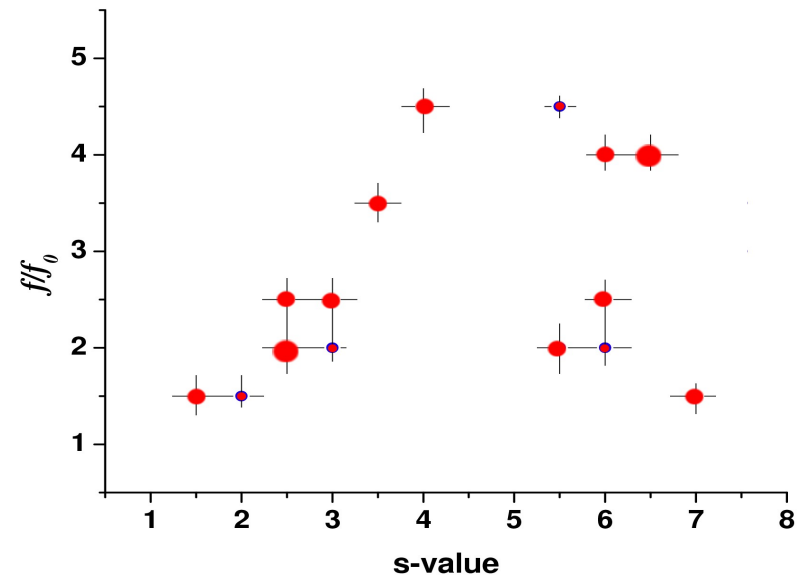
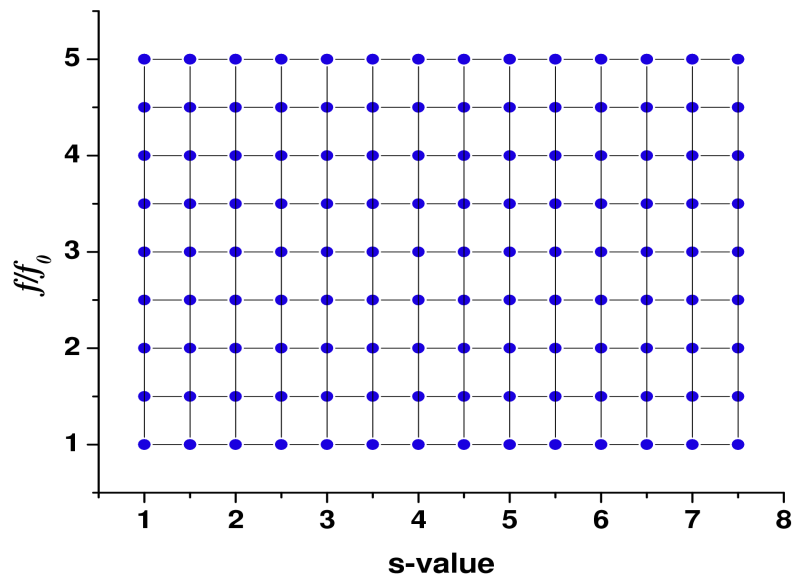
Background: 2DSA

- Put a grid on the parameter space
- Build FEM for each point of the grid



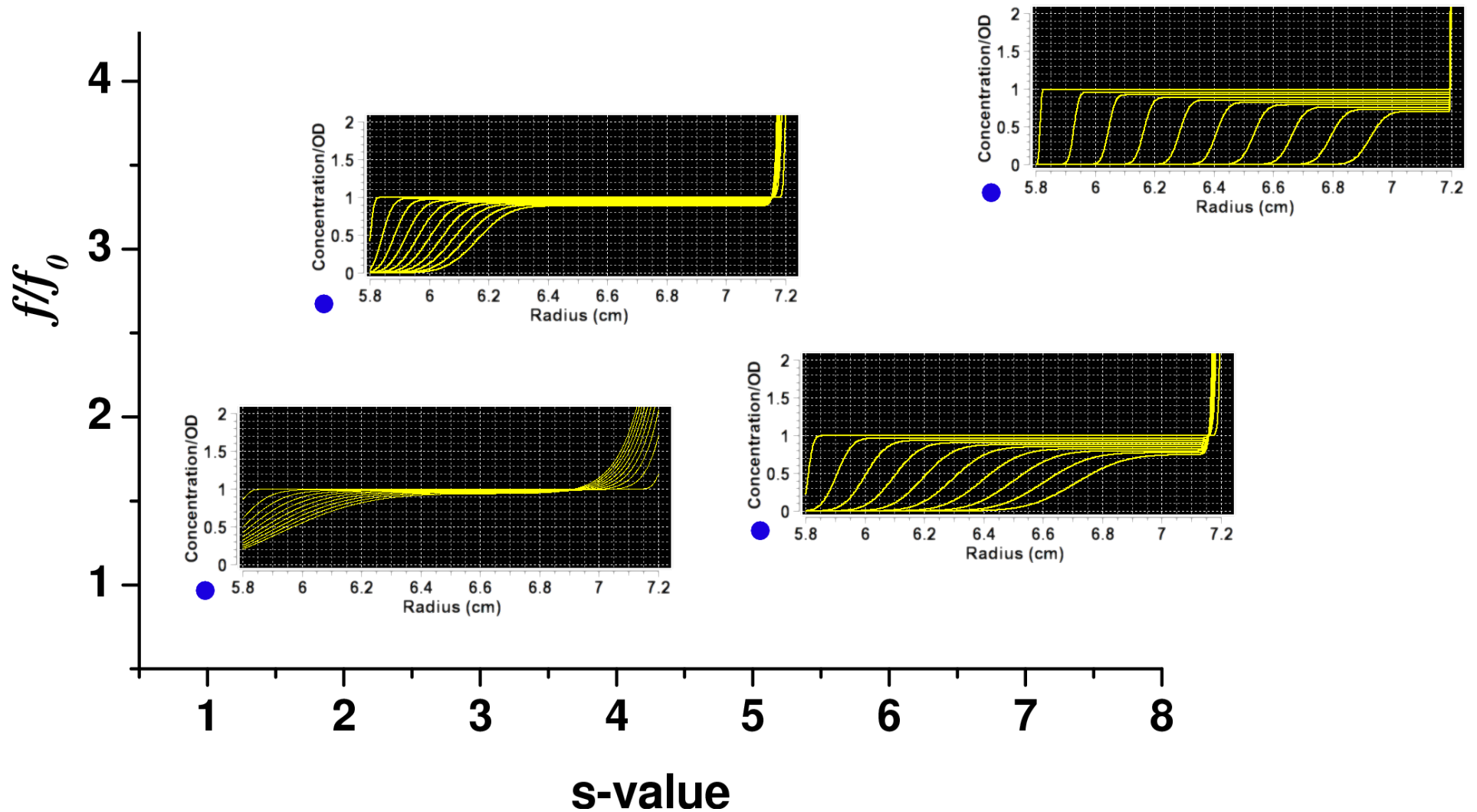
Background: 2DSA

- Put a grid on the parameter space
- Build FEM for each point of the grid
- Fit the experiment with the collection of FEMs to produce a model



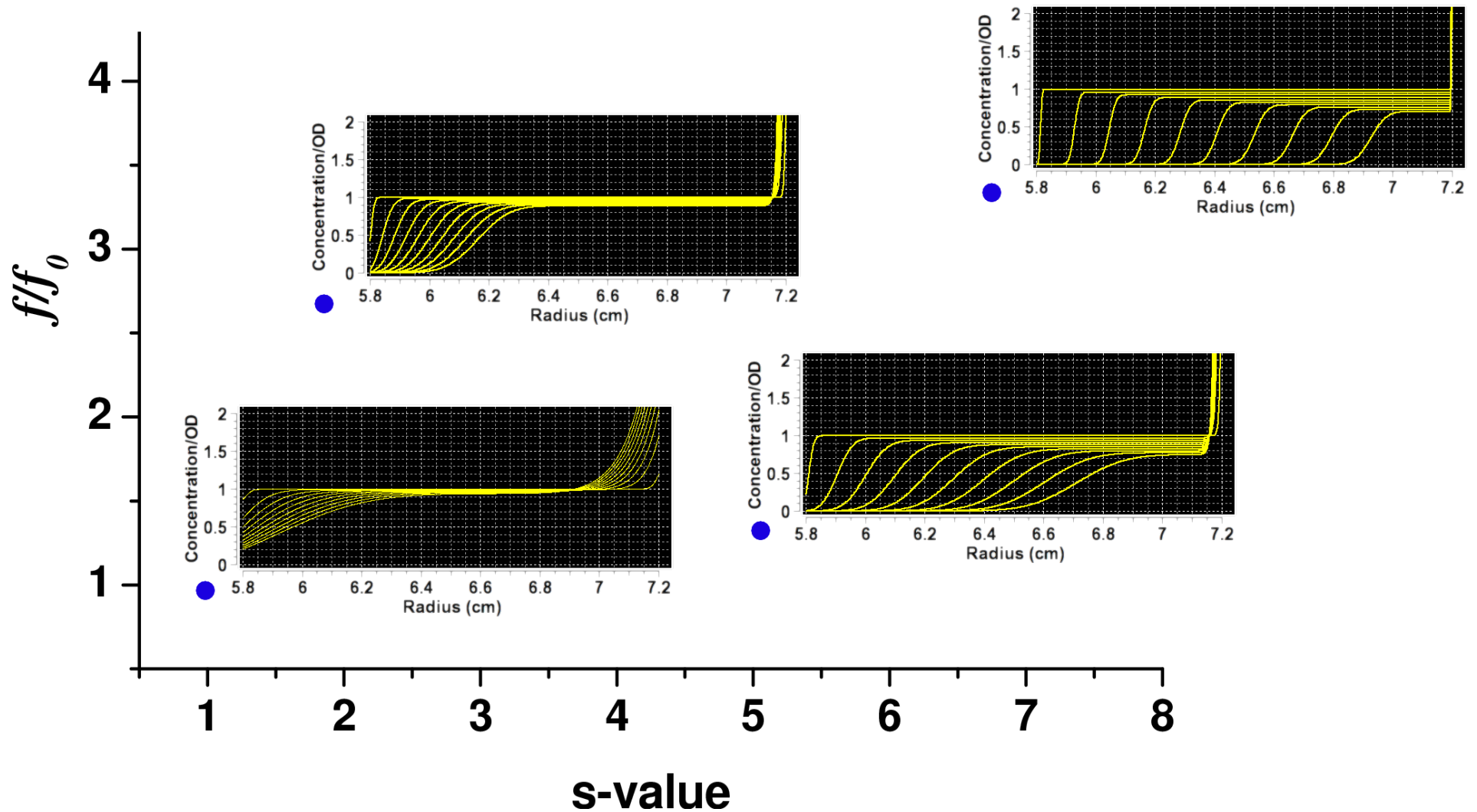
RMSD in model space

- Regular grid in parameter space is not regular in FEM space



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- FEM-RMSD



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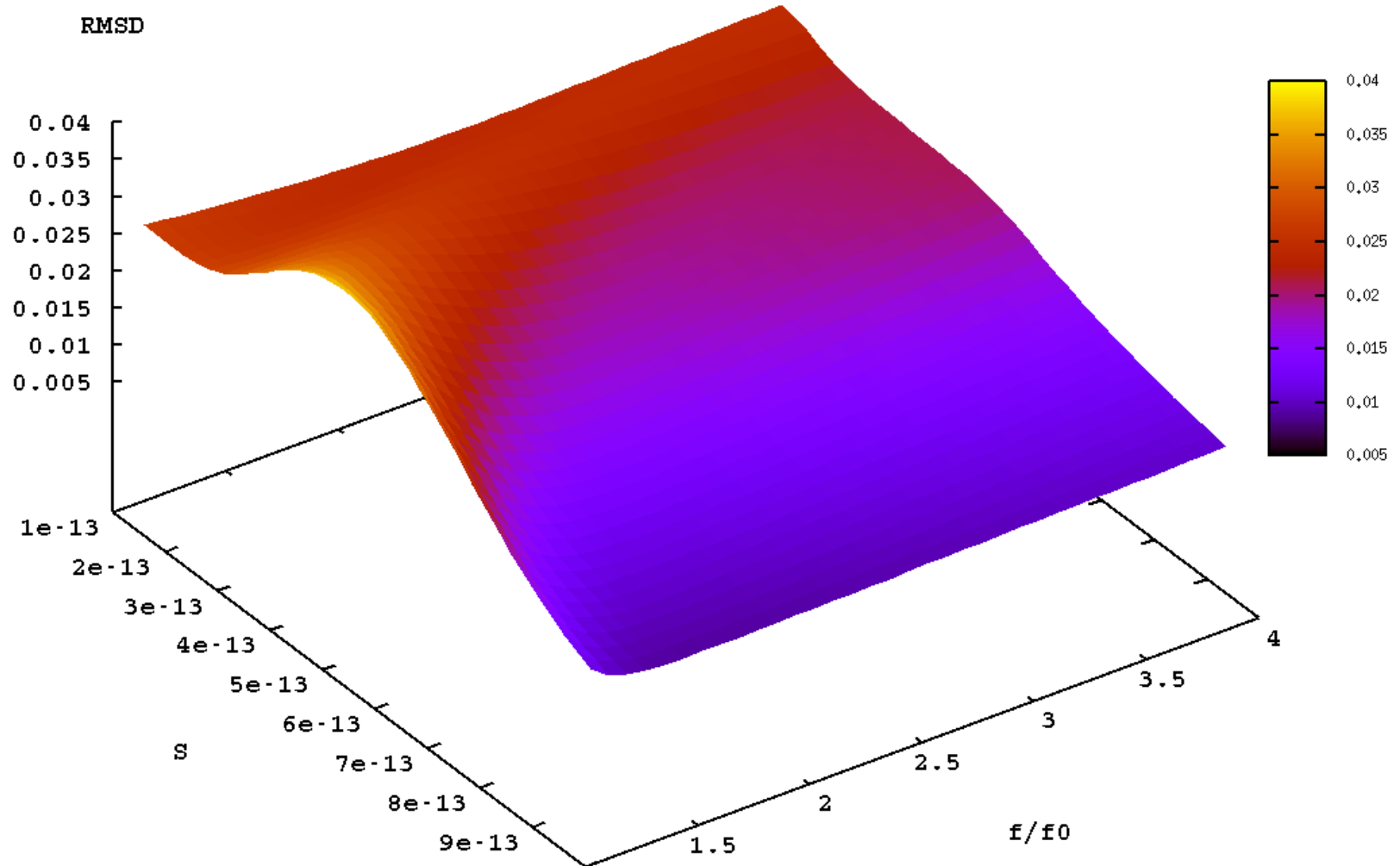
RMSD in model space

- Regular grid in parameter space is not regular in FEM space
- FEM-RMSD
 - Dependent on experimental conditions:
 - Speed
 - Number of scans, duration of experiment

RMSD in model space

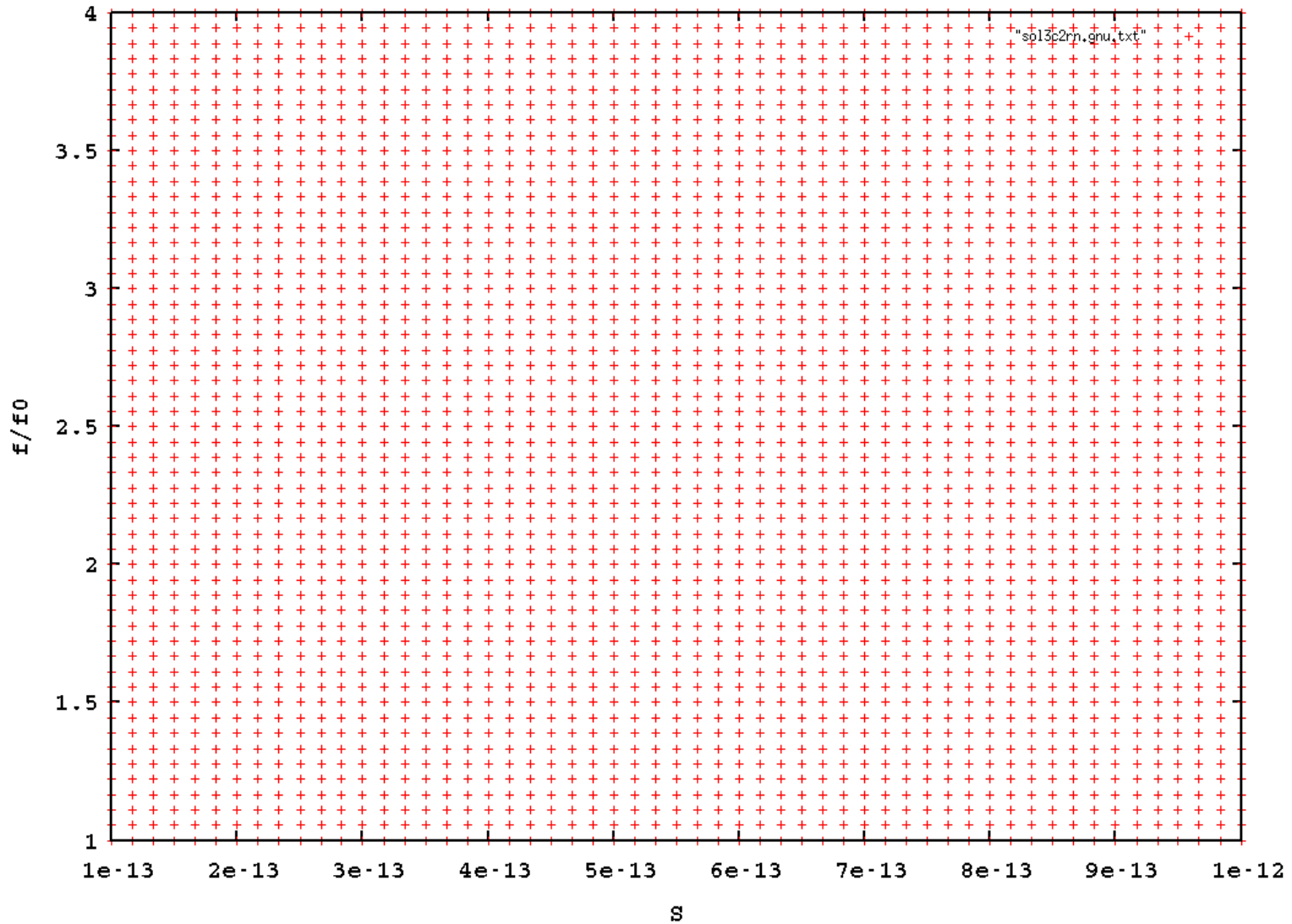
- Regular grid in parameter space is not regular in FEM space
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 - Dependent on experimental conditions:
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 - Number of scans, duration of experiment
 - Manual editing of data

Finite Element Model Vector distance in RMSD



RPM 45k, 10.5 hours, 30 scans
Meniscus 5.8 bottom 7.2, Edited to 5.82, 7.15

Original Parameter Space Grid Layout



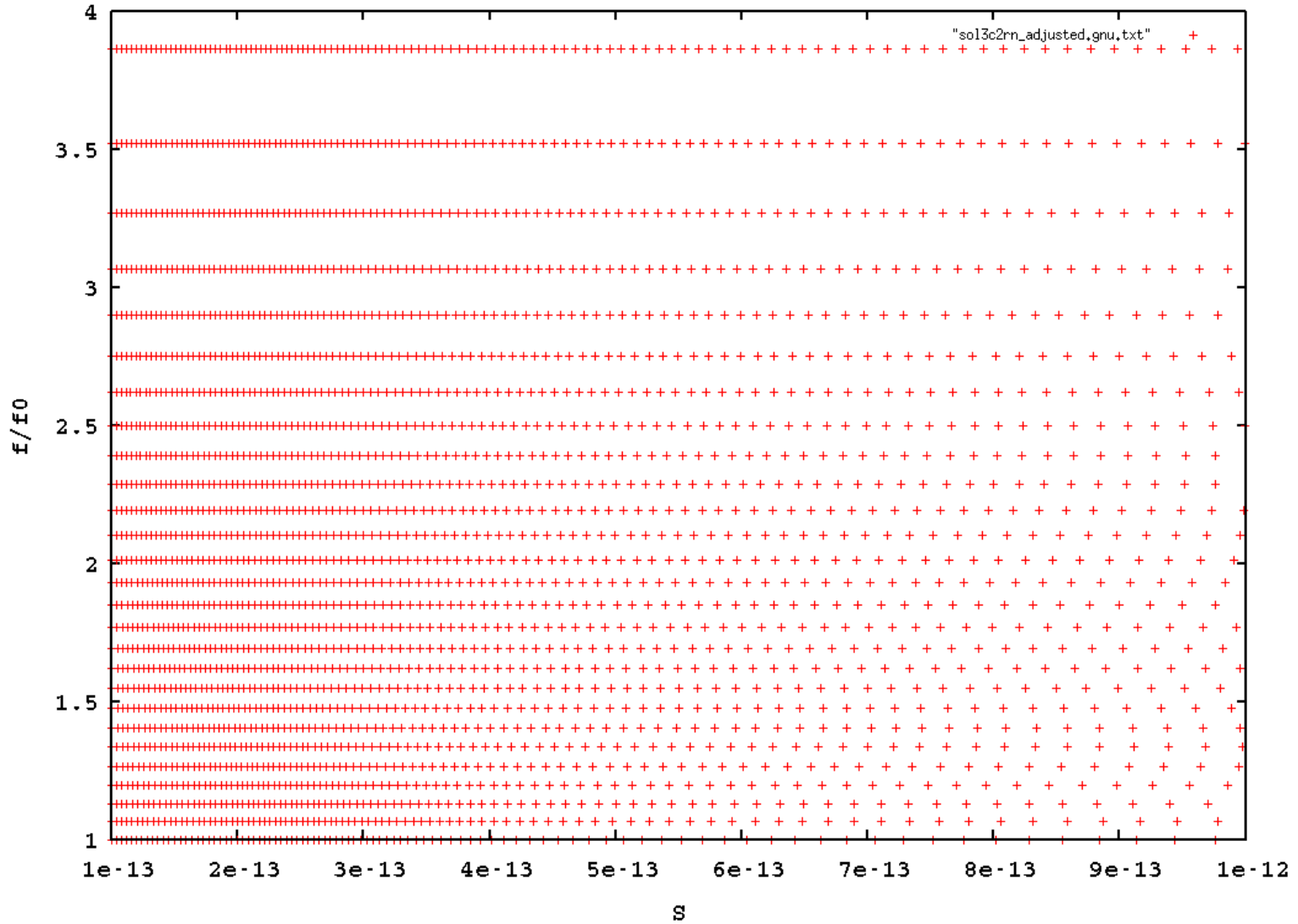
10x10 grid shifted 6^2 times, 3339 unique points*

FEM-RMSD: Average 0.0157

Minimum 0.0046

Maximum 0.0502

Modified Parameter Space Grid Layout



Modified grid, 2622 unique points (20% fewer)

FEM-RMSD: Average 0.0157

Minimum 0.0149

Maximum 0.0158

Producing the FEM-RMSD equalized grid

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 - repeat until new point is within FEM-RMSD tolerance

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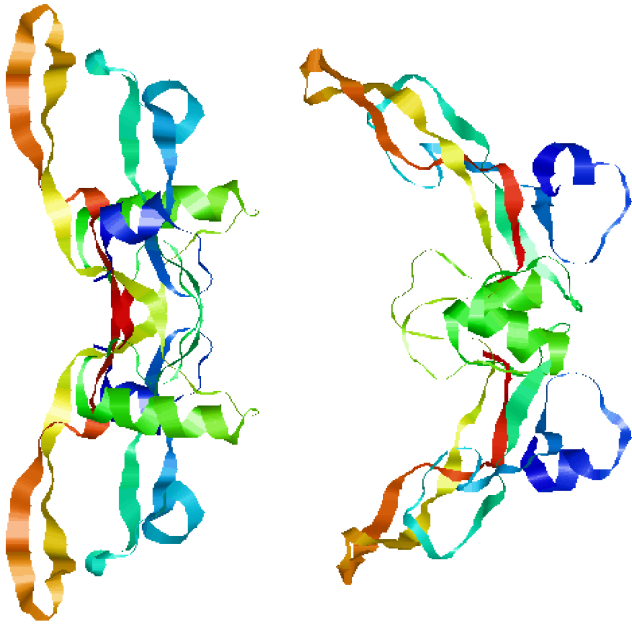
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- Results:
 - Original grid: 36 points, RMSD of 2DSA model 0.02783

Producing the FEM-RMSD equalized grid

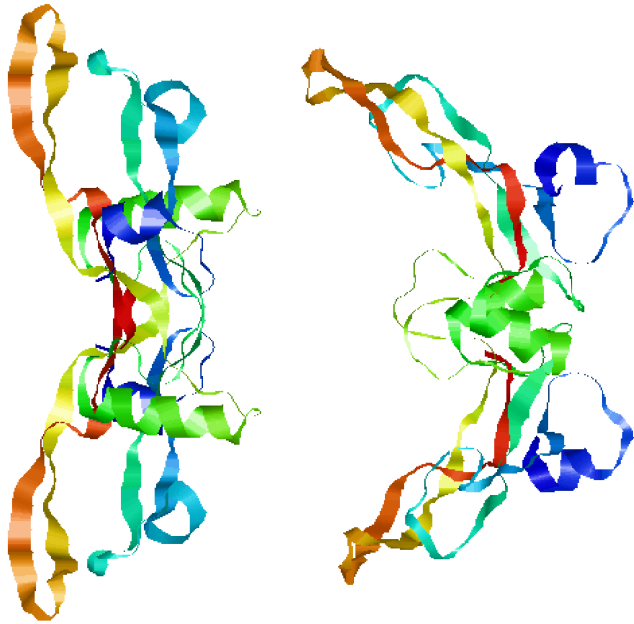
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 - repeat until new point is within FEM-RMSD tolerance
- Results:
 - Original grid: 36 points, RMSD of 2DSA model 0.02783
 - Modified grid: 30 points, RMSD of 2DSA model 0.02039

Concept Application

- Transforming growth factor betas (TGF β s) are 25 kDa disulfide-linked dimers that regulate cell proliferation, cell differentiation, and expression of extracellular matrix proteins.

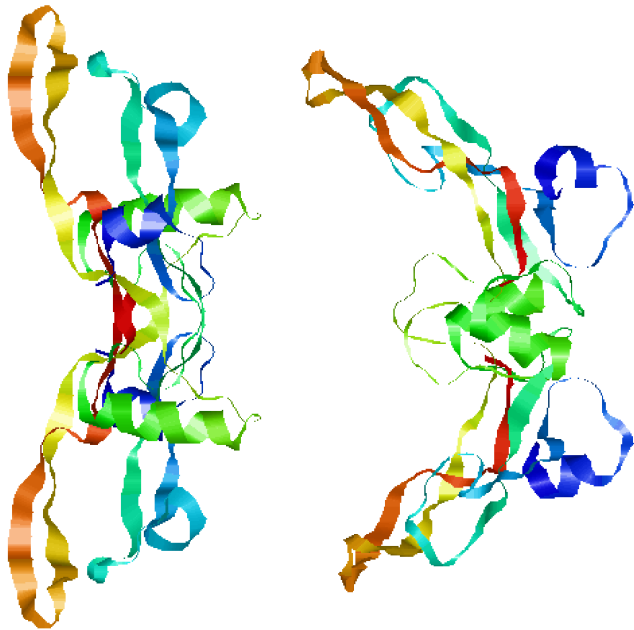


Concept Application



- Transforming growth factor betas (TGF β s) are 25 kDa disulfide-linked dimers that regulate cell proliferation, cell differentiation, and expression of extracellular matrix proteins.
- TGF β isoforms signal through two cell surface receptors, known as the TGF β type I and type II receptors (TR β I and TR β II, respectively)

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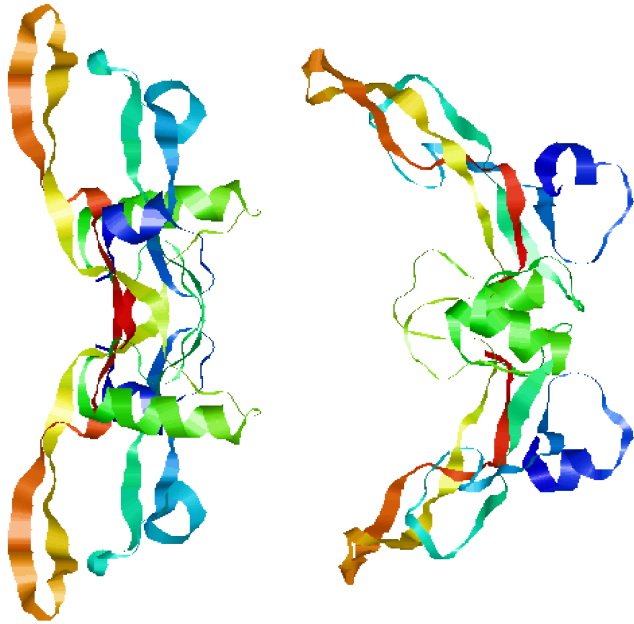
Open
2.44 S
1.3 f/f0

Closed
2.5 S
1.27 f/f0

FEM-RMSD: 0.016425

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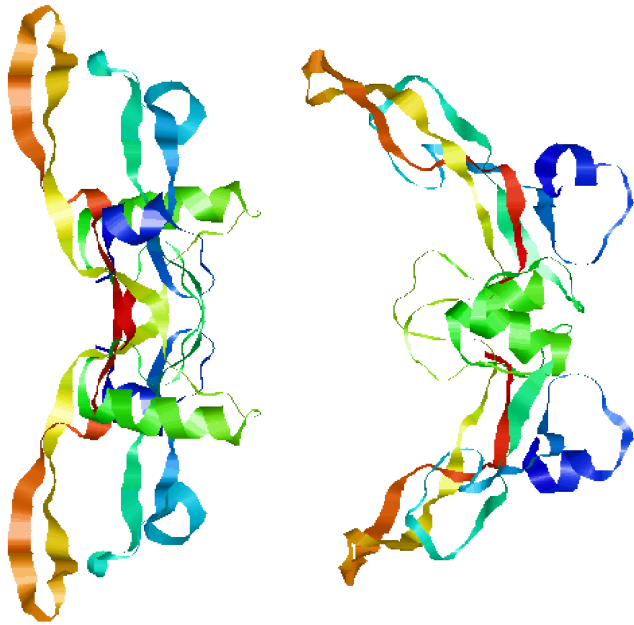
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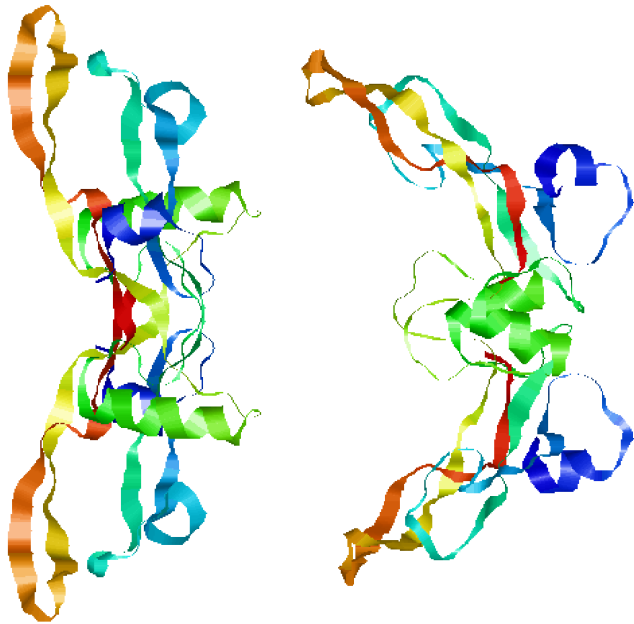
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- We wanted to know if we can determine relative concentration of open and closed states of TGFβ via AUC.

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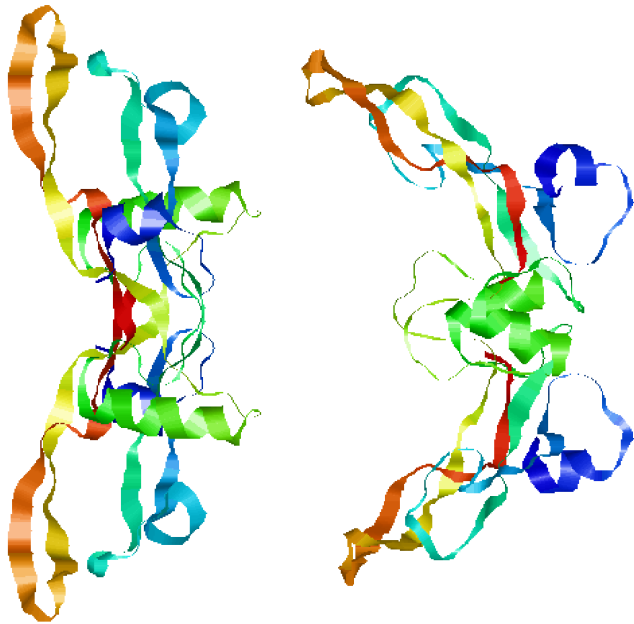
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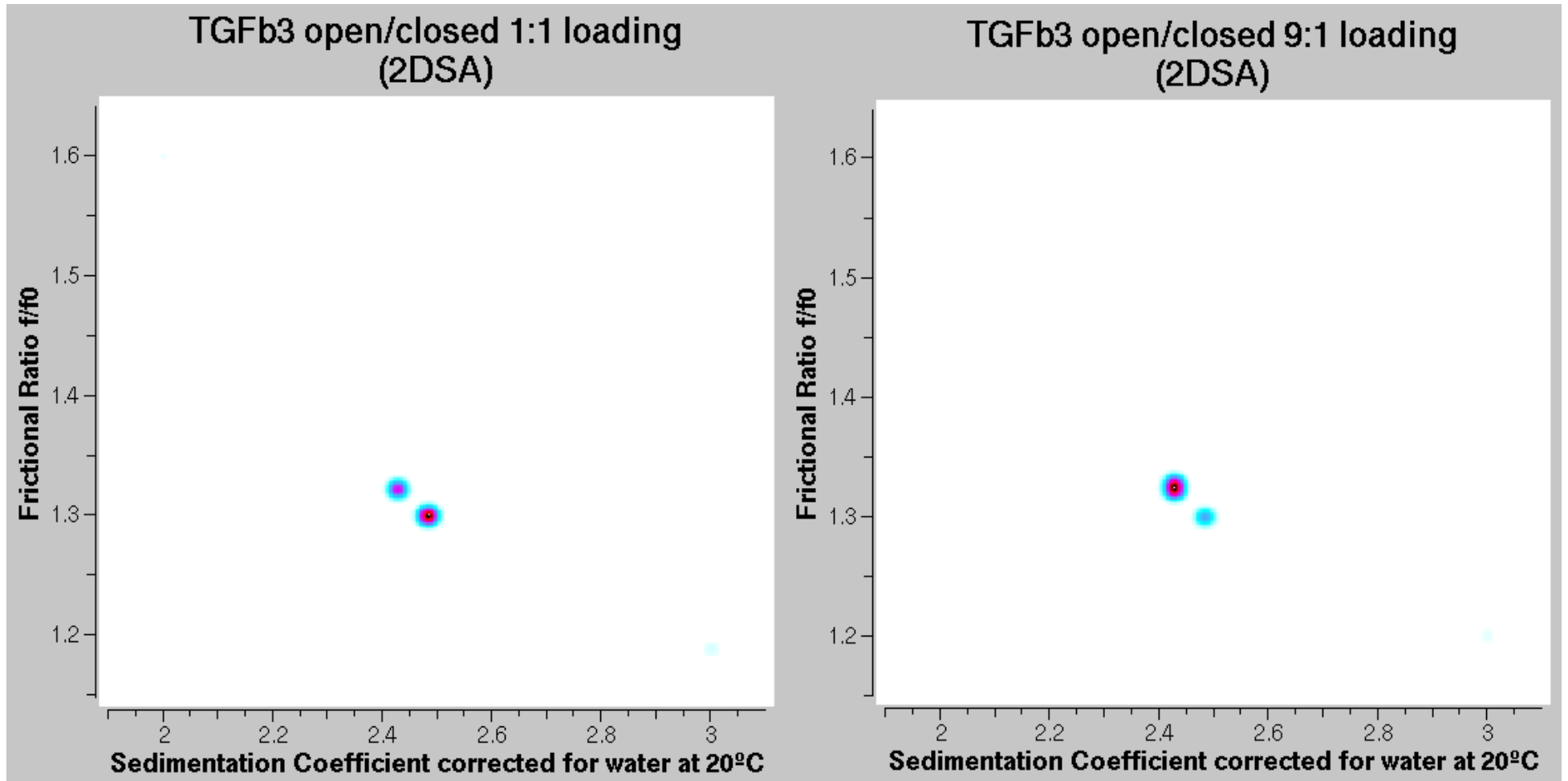
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- .5 % random noise, 60k RPM
- FEM-RMSD >> noise

Concept Application



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 - Dependent on experiment and editing
- Preparatory modeling can determine if 2DSA can resolve components.
- Not yet implemented in UltraScan
 - Contact me if you are interested in utilizing adaptive grids and preparatory modeling steps

Acknowledgments

Thanks to:

- Our team at UTHSCSA:
 - Jeremy Mann, Bruce Dubbs, Dan Zollars, Gary Corbet, Virgil Schiff.
- Supported by
 - To Demeler:
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 - To Brookes
 - NIH/NIGMS 1K25GM090154-01A1