

Molecular Modeling Software

PERCH NMR Software Course

Turku - 16- 17.5.2006

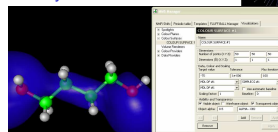
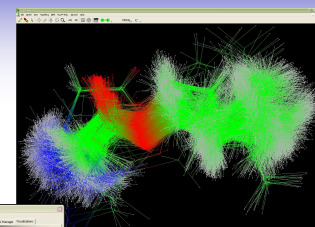


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Not only NMR - Molecular Modeling

- 4D-Structure Editor
- Molecular Mechanics
- Molecular Dynamics
- Metropolis Monte Carlo
- NMR-refined Force Field
- Conformation Analysis
- Fuzzy Force Field



- FLUFF-BALL
- Visualizations
- Link to GAUSSIAN

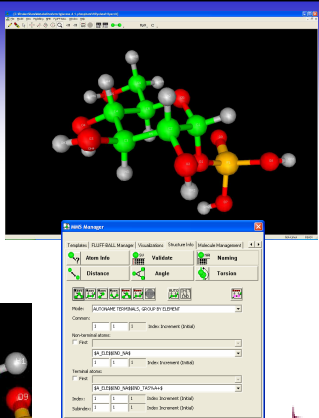


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Numbering

- Automatic / Manual
- Single, Paths
- Terminals/Non-Terminals
- First / Subsequent
- Element, Index
- Sub-Indices for Non-Terminals
- Export to MOL-file (V2000)



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MMS – General

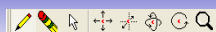
- Native Windows application. Windows NT/2000/XP fully supported. Windows 9x/ME not supported in all configurations.
- Uses OpenGL graphics, an accelerator card is recommended. The Installable Client Driver (ICD) should be enabled if available.
- Fully multithreading, for optimal performance use a multiprocessor PC.



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MMS – Tools



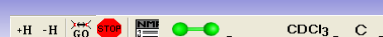
- DRAW: Click to draw atoms and Drag to draw bonds. Left button uses only the current bond type while right button will cycle bond types when repeatedly drawing a bond.
- ERASE: Left click to erase. NO CONFIRMATIONS!
- SELECT: Left/Right click will toggle selection.
- TRANSLATE & ORBIT: Left drag to affect whole model, Right drag to affect selected atoms only.
- ZOOM: Left/Right drag will zoom the model.



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MMS – Tools II



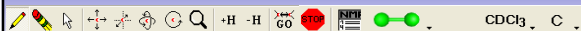
- ADD/REMOVE H: Adds or removes hydrogens. NO CONFIRMATIONS!
- GO: Shortcut equal to *Modelling/Geometry Optimizations*. Useful for launching Rubber-Band mode.
- STOP: Cancels computations.
- NMR: Shows or hides the MMS Manager dialog.
- BOND TYPE: Sets bond type to single, double, triple or conjugated (aromatic).
- SOLVENT: Sets the current solvent.
- ELEMENT: Sets the current element (Shows a periodic table of elements.)



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MMS – Tools III



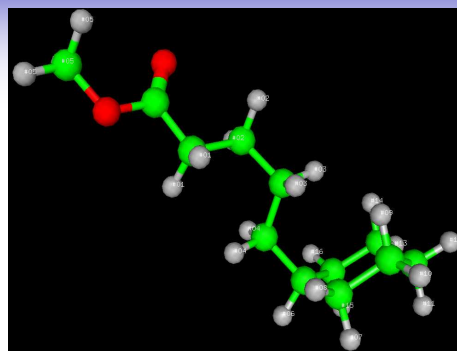
- Mouse Wheel can be used to zoom. Click on the Wheel enables a tool selection mode in which wheel can be used to cycle the tools. Second click will activate the new tool.
- Spacebar is a shortcut to *Model/Center Conformation* and can be used to center view.
- If there is a uncertainty whether to use a conjugated bonds or alternating single/double bonds draw the molecule and use *Model/Fix aromatic bonds*
- Use Rubber-Band whenever possible!



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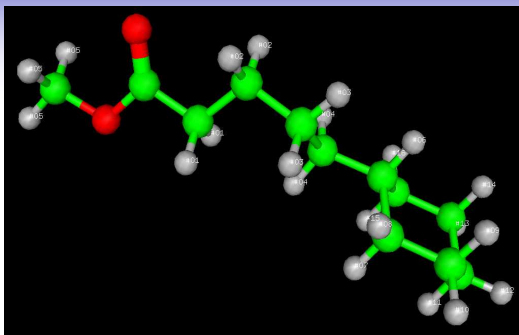
MMS – Rubber Band



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MMS – Rubber Band II



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MMS – Rubber Band III

- Rubber band is special computational mode whereby the model can be interactively manipulated while the GO is running in the continuous optimization mode.
- When translation and orbit tools are used on selected atoms it causes a “force” in the model which *dynamically* interacts with the standard molecular mechanics forces.



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MMS – Rubber Band IV

- Rubber band is very flexible and can be used to edit the conformation/configuration with unsurpassed ease.
- When the GO is running and the RIGHT button is pressed the selected atoms are subjected to the Rubber Band forces.
For rings the most useful strategy is to use sharp drag-and-release motions to “kick” the model to new conformation / configuration.
- For chains the most useful strategy is to use long drag-and-hold to slowly entice the chain to new position.



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MMS – Molecular Mechanics

- Force field is a derivative of the MMFF94 adapted specifically for use with NMR. Highly suitable for small molecules and peptides.
- Solvation is modelled using implicit solvent based on the solvent accessible surface area (SASA) and by manipulating dielectricity constant. Explicit solvations effects are not included.
- Fully supports Locking and Ghosting of atoms.



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MMS – Lock and Ghost

- Locked atoms are included in the molecular mechanics but are *locked* in space. This mode is particularly useful when dealing with side-chains of a larger system (i. e. peptides)
- Ghosted atoms are excluded from the molecular mechanics and are locked in space. This model can be used to hide a part of a large molecule in order to allow the rest seek optimal conformation unhindered.



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MMS – GO

Geometry Optimization

Maximum number of CG-steps: 650 OK

Energy convergence: 0.001 Cancel

Continuous optimization

Graphics update frequency: 10

Move locked and ghosted atoms

- Geometry optimization: Conjugate-Gradient based optimization.

NOTE: Local minima optimization only.

- NUMBER OF STEPS: The maximum number of steps to be computed. Default is usually sufficient.
- ENERGY CONVERGENCE: The residual energy gradient allowed. Dramatically shortens the GO run. For most accurate results use 0 (requires long optimization).
- CONTINUOUS OPTIMIZATION: If enabled GO runs until canceled by user.
- GRAPHICS UPDATE FREQUENCY: Steps per update. Use 2-10 (25) for Rubber-Band and 10-1000 for normal GO.
- MOVE LOCKED: If enabled the GO will disregard all lock and Ghost flags.



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MMS – Fuzzy Force Field

- Standard GO find only nearest *local minima*. This can be a problem as the molecule may “hang” on a infinitely small energy barrier.
- This is primarily caused by very weak barriers created by torsion terms.
- Usually global minima is searched using Simulated Annealing or high energy MD but both techniques are slow and non-deterministic.

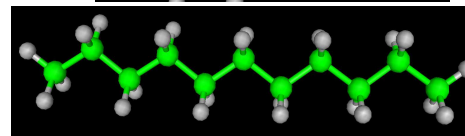
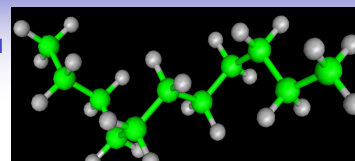


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MMS – Fuzzy Force Field

Epot= 2.08 kJ/mol



Epot= -11.89 kJ/mol



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MMS – Fuzzy Force Field II

- The Fuzzy Force Field (FFF) smoothes out the fine structure of the energy landscape by manipulating the torsion terms.
- Fuzzy MD is an *EXPERIMENTAL* implementation of the FFF in which the smoothing is performed during the balancing stage.
- The temperature is used to determine how much energy is injected into the system in order to overcome the residual barriers



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MMS – Conformational Analysis

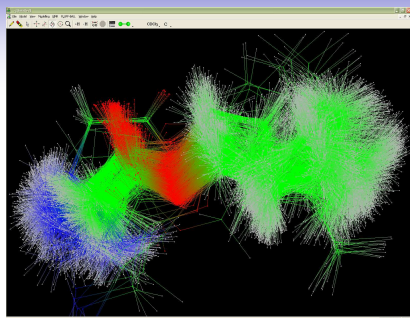
- For accurate NMR prediction it is necessary to consider the molecule as a dynamic system and map the conformational space. The conformational space can not be exhaustively mapped, but it can be adequately sampled by using a suitable method.
- MMS Provides Molecular Dynamics (MD), Metropolis Monte-Carlo (MC) and a Combined MC/MD computations.



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MMS – Conformation analysis II



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MMS – Conformation analysis III

VIEW / CONFORMATIONS

- SHOW/HIDE
 - FIRST, NEXT, PREVIOUS, LAST
 - ORIGINAL, BEST, WORST
- If desired the default wireframe rendering of the conformer swarm can be overridden in *VIEW / RENDERING* but the rendering will probably become unbearably slow.
 - NOTE: At the moment the conformations are not saved to the MMS file.

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MMS – MD

- Molecular Dynamics: Velocity-Verlet based MD.
- All atom MD without any SHAKE delimiters.

- NUMBER OF STEPS: The number of steps to be computed for balancing and production runs respectively.
- TIME STEPS/ SIMULATION TEMPERATURE : Time-Steps and temperature to be used. NOTE: a combination of long time step and high temperature may lead to complete disintegration of the model.
- SIMULATION TYPE: The type of temperature regulation to use.
- GRAPHICS UPDATE FREQUENCY: Steps per update. Use 2-10 (25) for Rubber-Band and 10-1000 for normal GO.

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MMS – MC

- Metropolis Monte Carlo
- Can be very slow on highly strained systems.

- INITIAL STEPS: The number of balancing steps to be computed.
- NUMBER OF CONFORMATIONS: The number of conformations to generate.
- CAPTURE FREQUENCY: MC steps per conformation.

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MMS – MC/MD

- Combined Metropolis Monte Carlo-Molecular Dynamics run (MC/MD).
- First initial conformations are generated by MC which are then refined by a short MD.
- Usually quite slow.

- INITIAL STEPS: The number of balancing steps to be computed.
- NUMBER OF CONFORMATIONS: The number of conformations to generate.
- CAPTURE FREQUENCY: MC steps per conformation.
- MD TEMPERATURE: The temperature for MD refinement

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