LARGE–SCALE COMPUTING IN PHARMACOLOGY

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BACKGROUND

1. PHARMACOLOGICAL TARGETS – RECEPTORS
2. RECEPTORS – TRANSMEMBRANE PROTEINS
3. LARGE NUMBER OF ATOMS
4. DYNAMIC FORMS OF PROTEINS
5. FUNCTION RECOGNITION

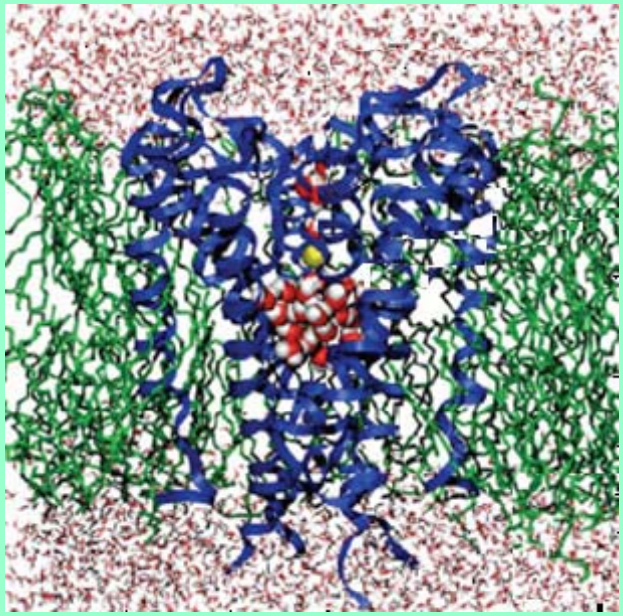
PHARMACOLOGICAL TARGETS

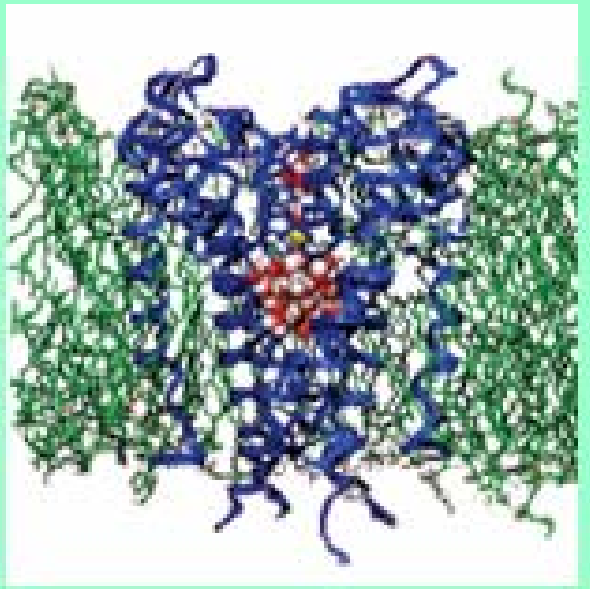
5 – 100 ATOMS

3 - 4 *10^3 ATOMS

TRANSMEMBRANE PROTEINS

$5 * 10^4$ ATOMS





$5*10^5$ ATOMS

LARGE NUMBER OF ATOMS

DYNAMIC FORMS OF PROTEINS

$$F = m\frac{d^2r}{dt^2}$$

$$\frac{dV}{dr} = m\frac{d^2r}{dt^2}$$

$$V = \sum_{bonds} K_{bi}(b_i - b_{oi})^2 + \sum_{angles} K_{ai}(\Theta_i - \Theta_{oi})^2$$

$$+ \tfrac{1}{2} \sum_{dihedral} U_n[1 + \cos(n\Phi_n - \gamma_n)]$$

$$+ \sum_{non-bonding} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{C_{ij}}{r_{ij}^{6}} + \frac{q_i q_j}{\varepsilon r_{ij}}\right)$$

DYNAMIC FORMS OF PROTEINS

TRANSMEMBRANE PROTEIN – RHODOPSIN

MIN TIME PERIOD – 2 ns
TIME STEP – 1 fs
GROMAX FORCE FIELD

PROTEIN	320 RESIDUES
	3 530 ATOMS
MWP SYSTEM	35 381 ATOMS

DYNAMIC FORMS OF PROTEIN

SIMULATIONS

1. VACUUM
2. MWP - Membrane – Water – Protein
3. FOD – „Fuzzy Oil Drop” Model

FUZZY OIL DROP MODEL

THEORETICAL DISTRIBUTION

$$Ht_j = \frac{1}{Ht_{sum}} \exp\left(\frac{-(x_j - \bar{x})^2}{2\sigma_x^2}\right) \exp\left(\frac{-(y_j - \bar{y})^2}{2\sigma_y^2}\right) \exp\left(\frac{-(z_j - \bar{z})^2}{2\sigma_z^2}\right)$$

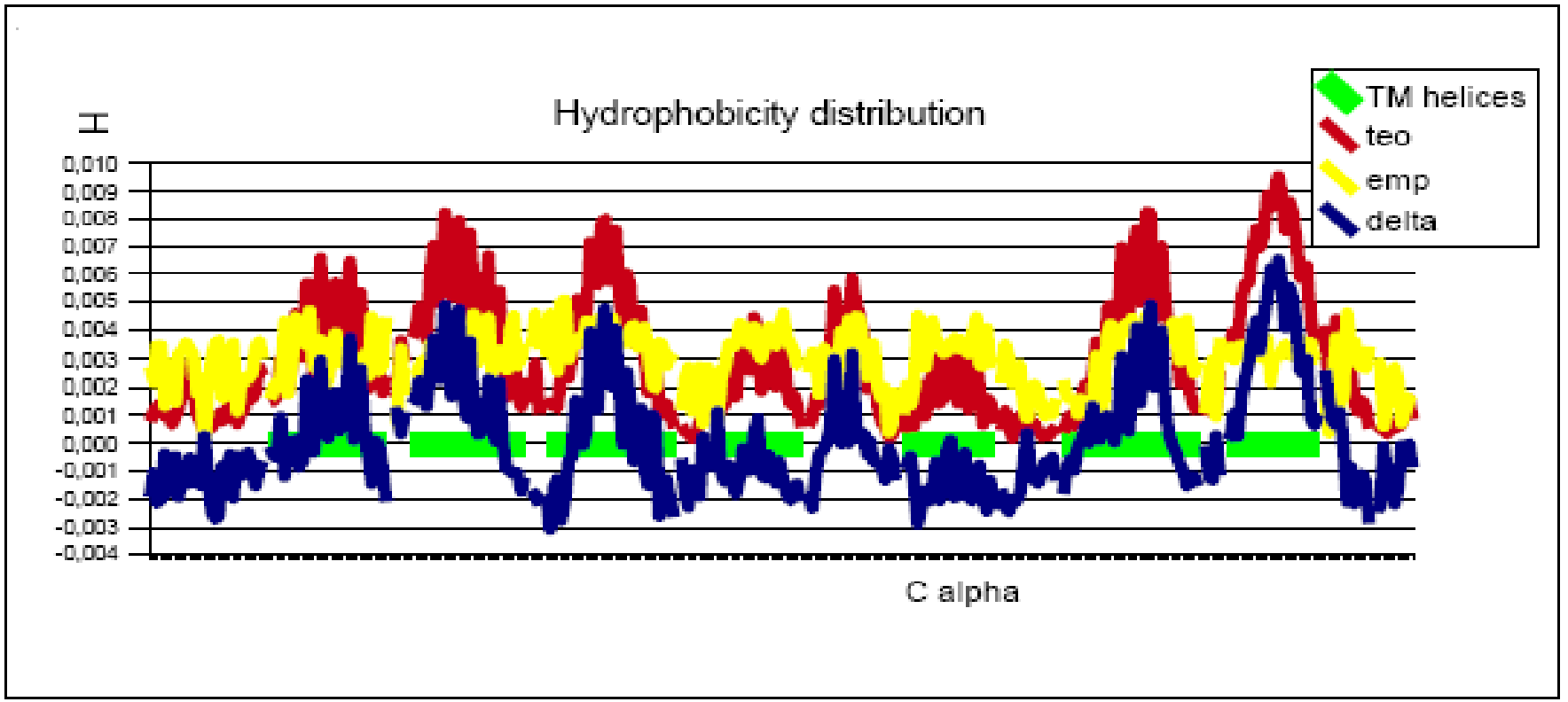
EMPIRICAL DISTRIBUTION

$$\tilde{Ho}_j = \frac{1}{\tilde{Ho}_{sum}} \sum_{i=1}^{N} (H_i^r + H_j^r) \begin{cases} \left[1 - \frac{1}{2}\left(7\left(\frac{r_{ij}}{c}\right)^2 - 9\left(\frac{r_{ij}}{c}\right)^4 + 5\left(\frac{r_{ij}}{c}\right)^6 - \left(\frac{r_{ij}}{c}\right)^8\right)\right] & \text{for } r_{ij} \le c \\ 0 \text{ for } r_{ij} > c \end{cases}$$

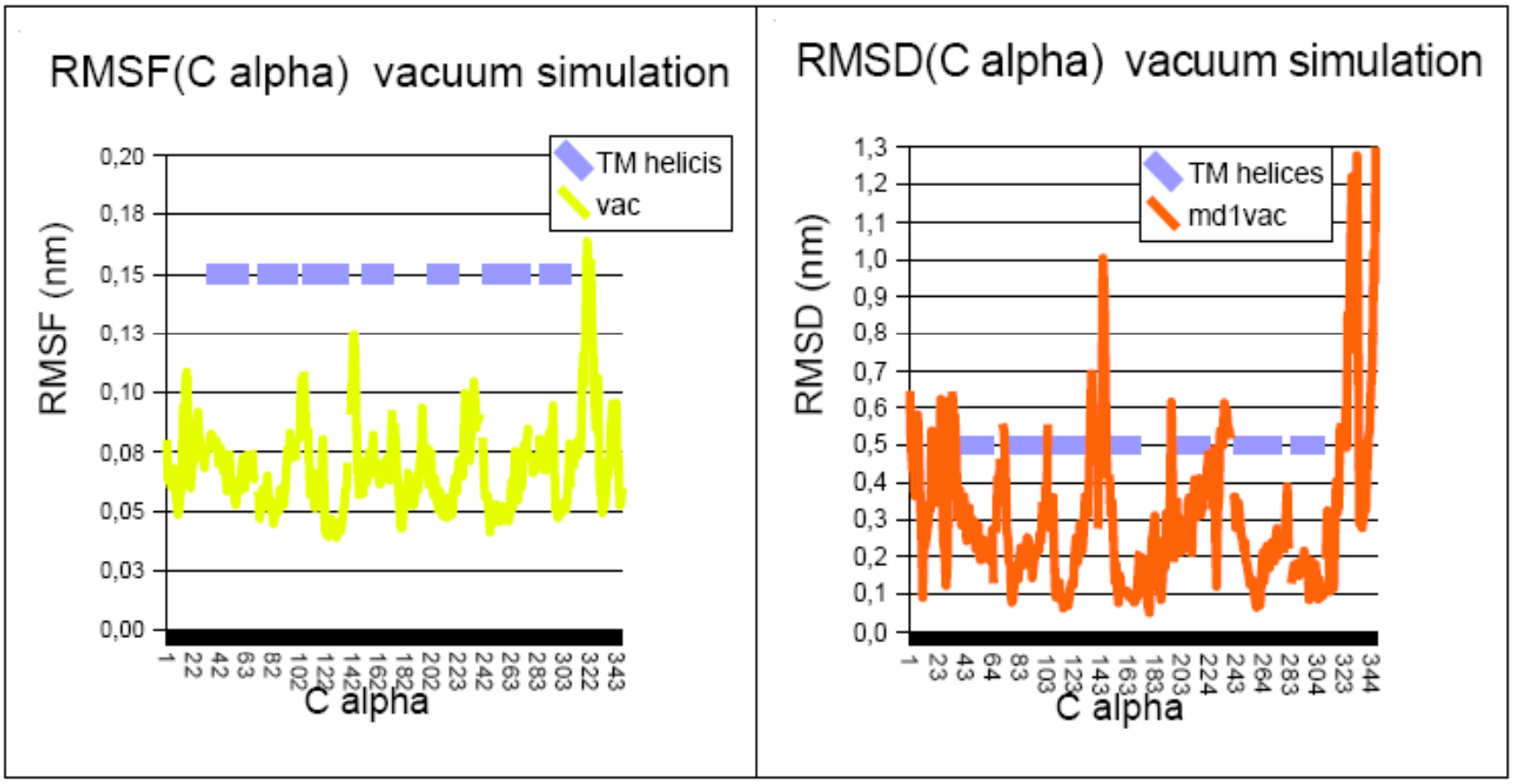
FUZZY OIL DROP MODEL

IRREGULARITY

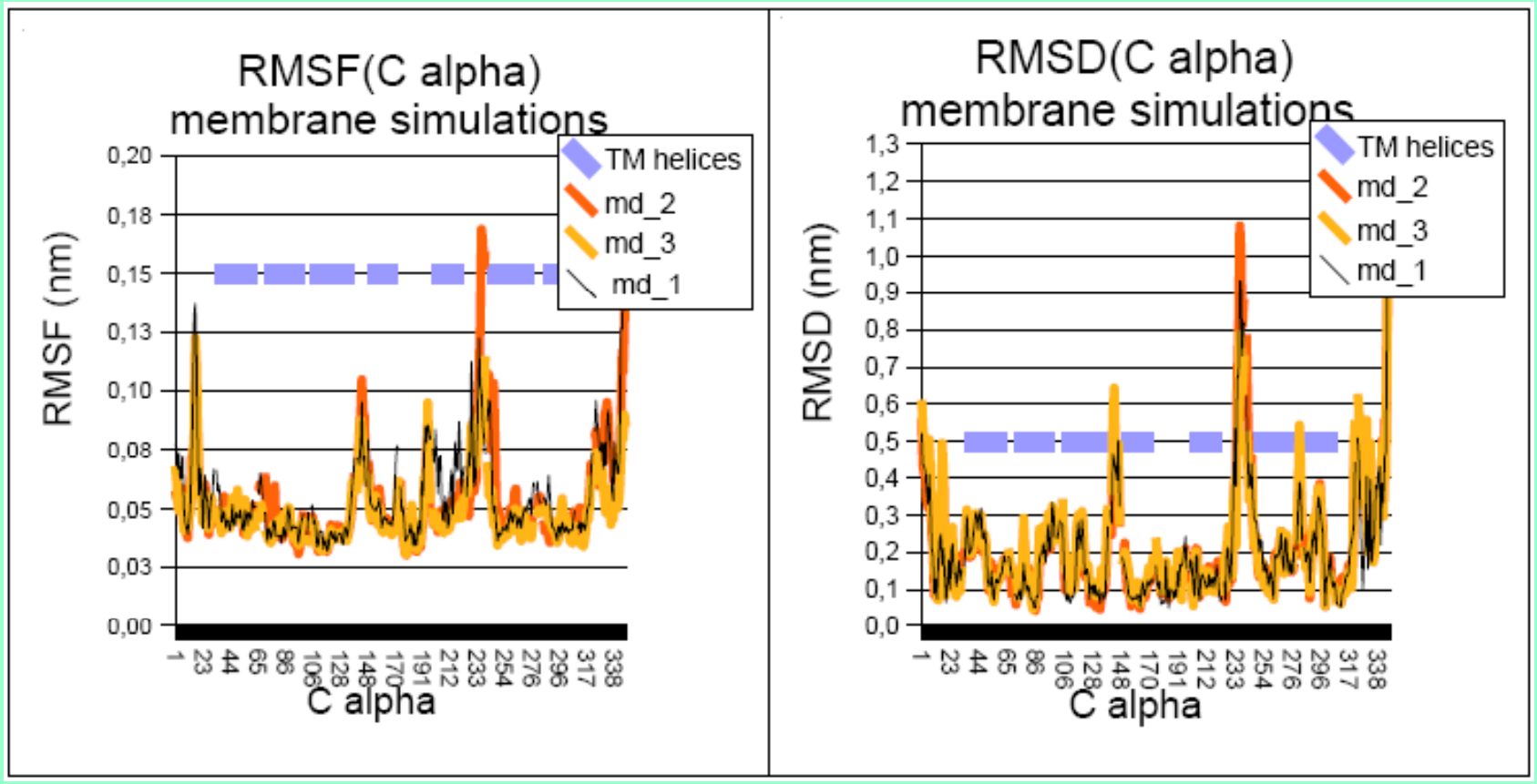
$$\Delta\tilde{H}_i = Ht_i - Ho_i$$



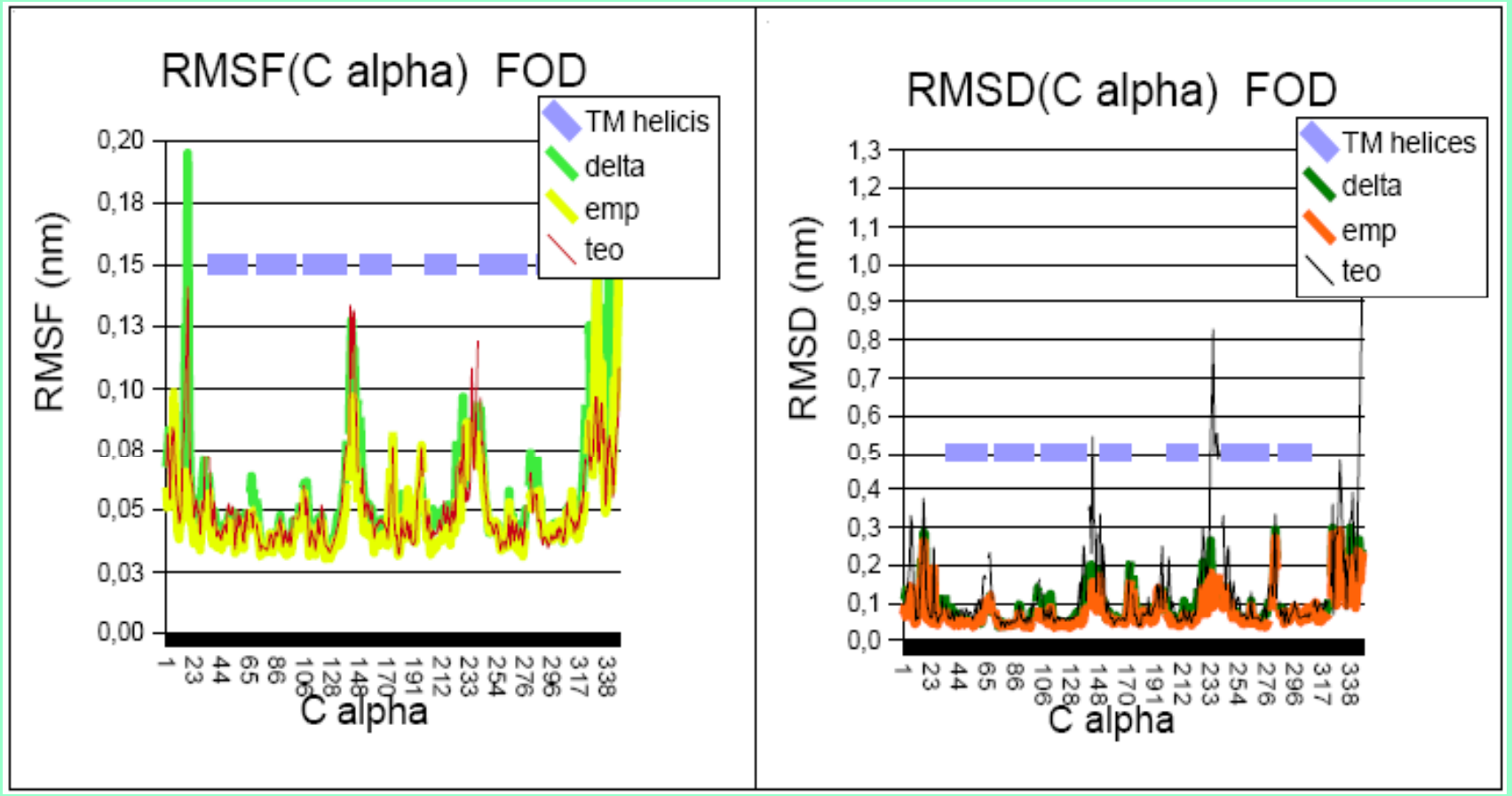
VACUUM SIMULATION



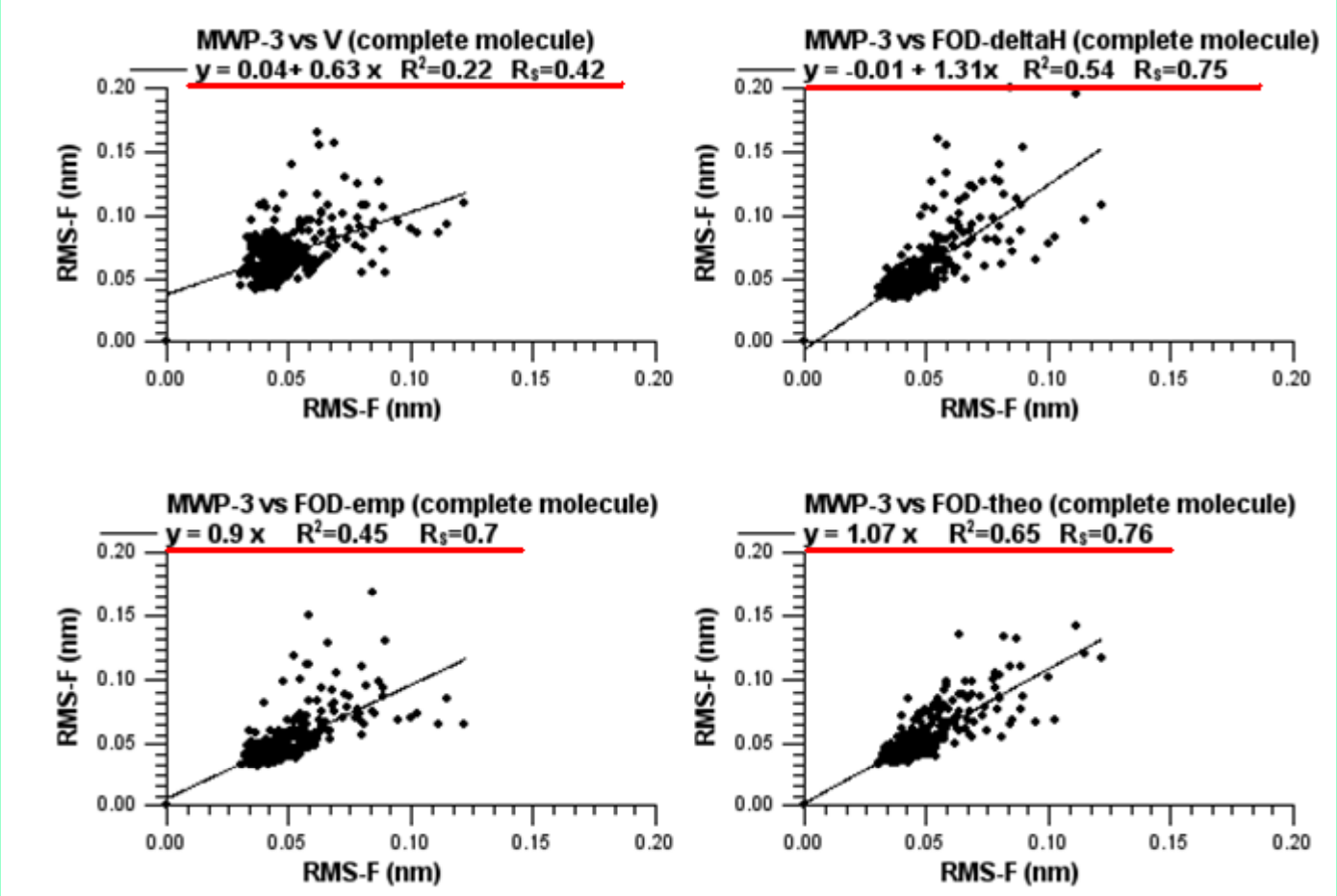
MWP SIMULATION



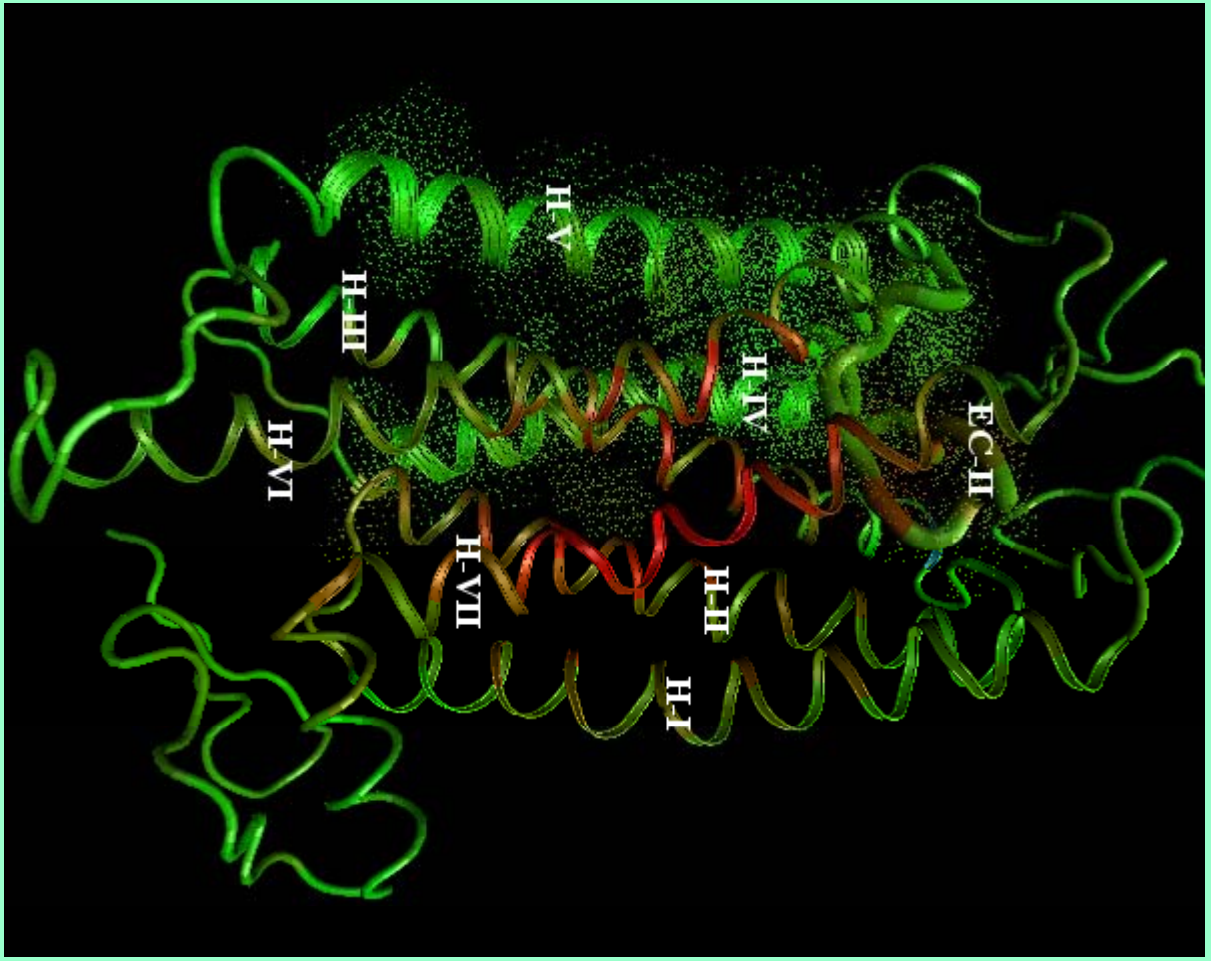
„FOD” DYNAMICS



COMPARISON


MWP-3 vs V (complete molecule)
y = 0.04+ 0.63 x R²=0.22 Rs=0.42
MWP-3 vs FOD-deltaH (complete molecule)
y = -0.01 + 1.31x R²=0.54 Rs=0.75
MWP-3 vs FOD-emp (complete molecule)
y = 0.9 x R²=0.45 Rs=0.7
MWP-3 vs FOD-theo (complete molecule)
y = 1.07 x R²=0.65 Rs=0.76
RMS-F (nm)
RMS-F (nm)
0.00
0.05
0.10
0.15
0.20

BIOLOGICAL FUNCTION RECOGNITION



CALCULATION TIME

VERSION	V	MWP	FOD
number of atoms	3530	35381	3530
duration	2 ns	2 ns	2 ns
performance	~18 hour/ns	~43 hour/ns	~18 hour/ns
wall time	~1 d 10 h	~3 d 10 h	~1 d 10 h

COLLABORATION

VERONICA ZOBNINA

currently RomaTre University - PhD student

The results presented are published in:

Zobnina V, Roterman I.

Application of the fuzzy-oil-drop model to membrane protein simulation

Proteins: Structure, Function and Bioinformatics 2009 - in press

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MANY THANKS

FOR YOUR ATTENTION