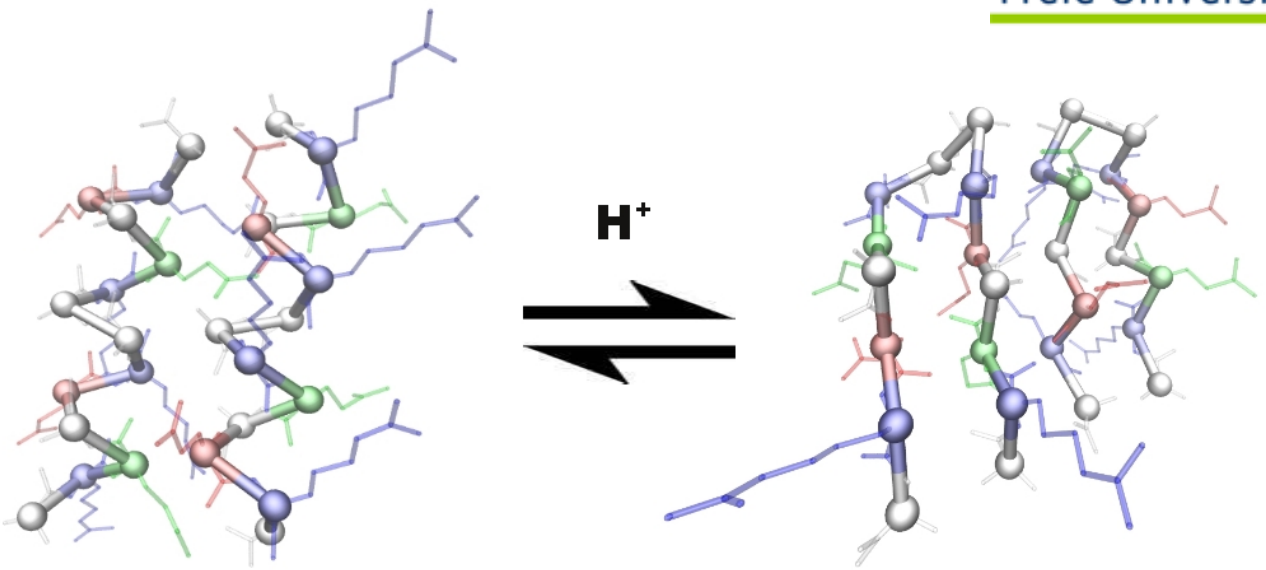
Freie Universität Berlin



pH simulations with coarse-grained resolution: peptides

Marta Enciso

Frei Universität Berlin

Outline

What

Why

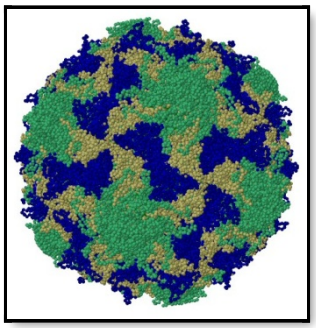
How

Where

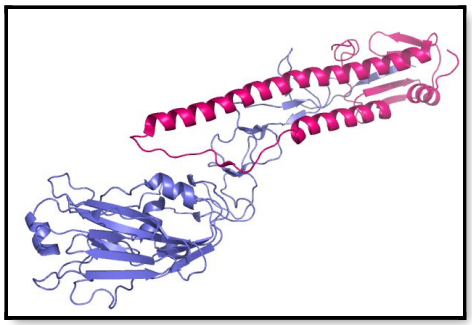
When

Who

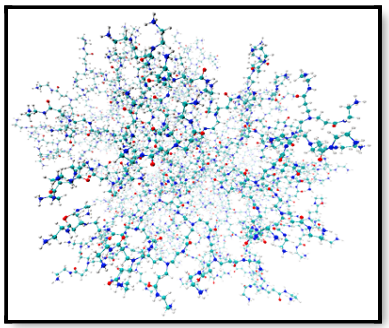
What?



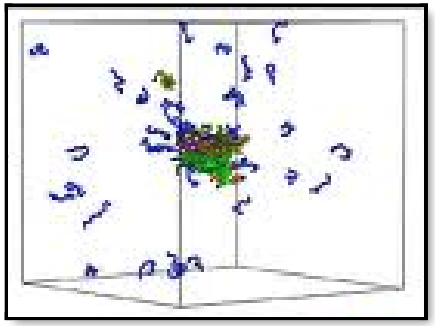
Virus capsids



Large conformational changes

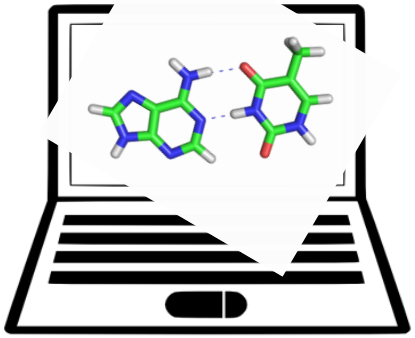


Polymer growth

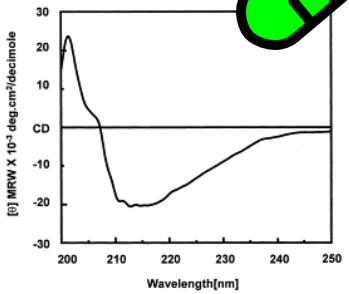


Protein/peptide stability, aggregation,…

Full atom MD



Experiments



COARSE-GRAINED SIMULATIONS

fch.upol.cz/vyzkum/hbonds_img.png
ars.els-cdn.com

Why?

1 Coarse-grained description

2 pH?????

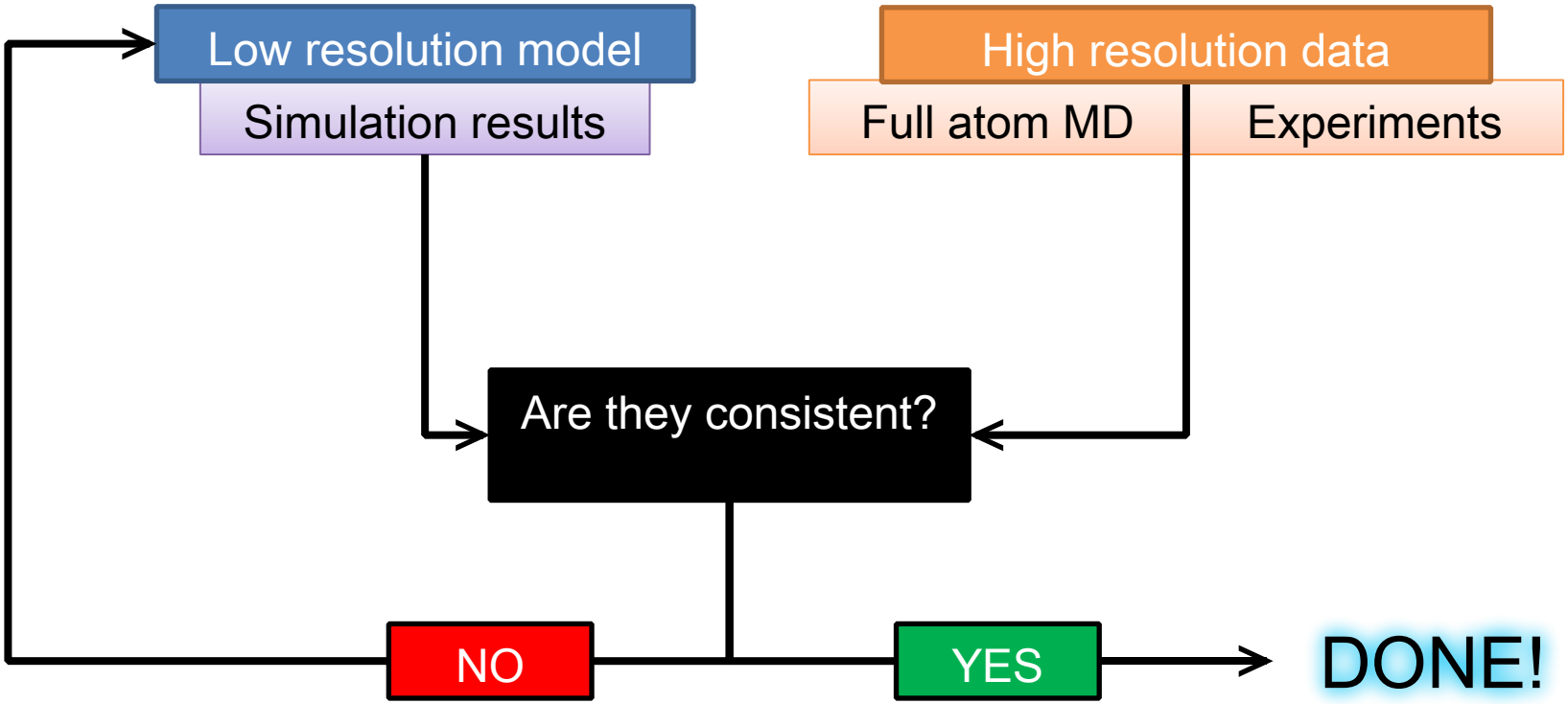
Besides…

- Accuracy vs efficiency (simplicity)
- Strong physical/theoretical base: consistency across the scales

How?

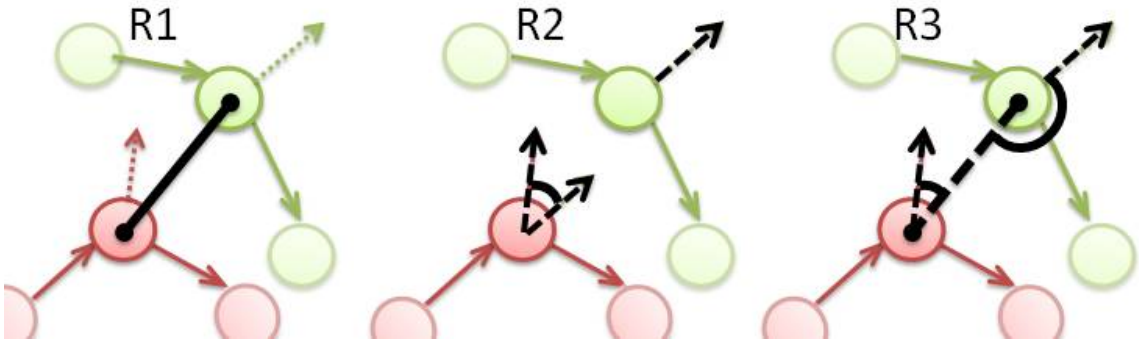
Multiscaling

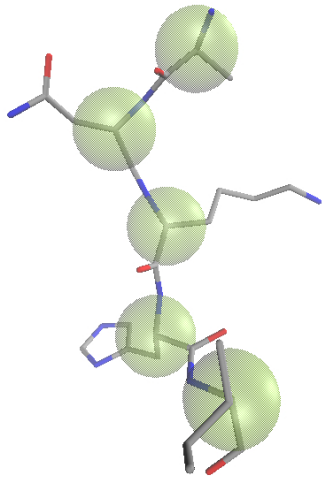
"Consistency across the scales"



How?

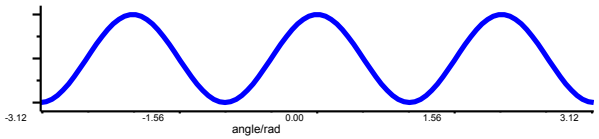
1 Starting low resolution model





Hydrogen bonds → Keep real geometry of secondary structure elements

Hydrophobic interactions → Hydrophobic, Neutral, Polar → Basic sequence information

Internal torsions → 

→ Chain flexibility

ME & Rey, J. Chem. Phys, 2010
ME & Rey, J. Chem. Phys. 2012

How?

2 Full atom MD data: what is the effect of pH?

Coulombic energy

Dispersive Lennard-Jones energy

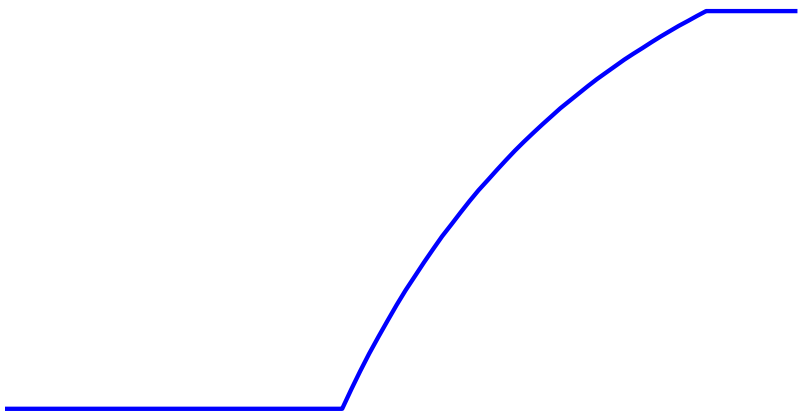
Solvent accessible surface area

Energy per hydrogen bond

How?

Hydrogen bonds + Hydrophobic interactions + Internal torsions + Electrostatic interactions

3* Statistical properties of experimental salt bridges



- Yukawa functional form

$$E = A_o \frac{q_i q_j \exp(d / A_1)}{d} + A_2$$

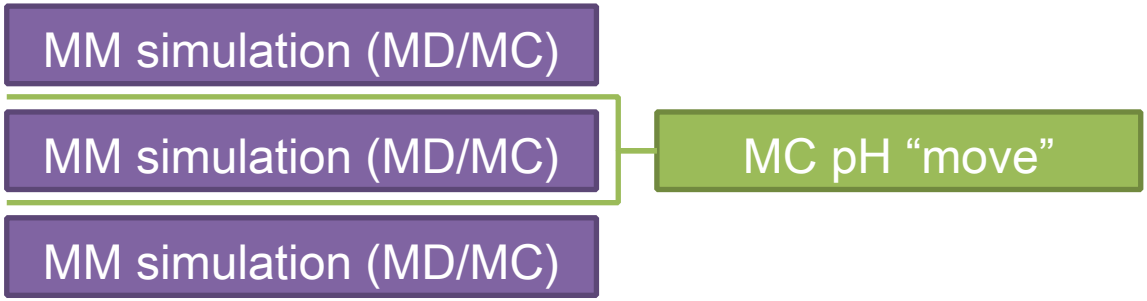
- Optimization of term weights

w^{hb}=9.5; w^{hp}=6.5; w^{tor}=6.5; w^{el}=12.5

ME, Delle Site & Schuette, Soft Matter, 2013

How?

How does our system know its pH?



$$\Delta E = \ln(10) k_B T [\mathrm{pH} - \mathrm{pK}_i] + \Delta E_{\mathrm{int}}$$

- Do I need a reference compound, thermodynamic integration, etc.? NO!
- Assumptions (and their validity)
  - * pK(amino acid in peptide) ≈ pK(isolated amino acid) !!!!!
  - * pK_a can be re-calculated

ME, Delle Site & Schuette, Soft Matter, 2013

Where can I check it?

Overview

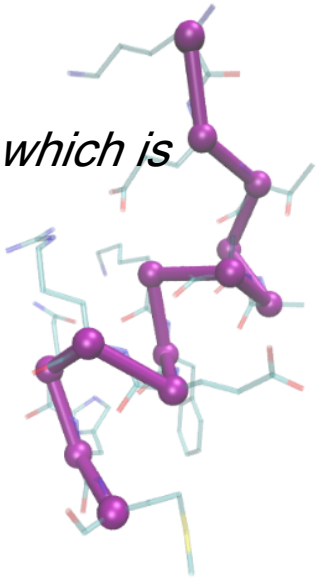
- Finding good test cases:
  - ✓ Detailed experimental and/or full atom MD information
  - ✓ Data that we can compute/compare
  - ✓ Different responses towards pH changes
- Peptide stability upon temperature/pH changes
  - Stabilized at physiological pH
  - Lower stability at physiological pH
- Peptide folding vs aggregation

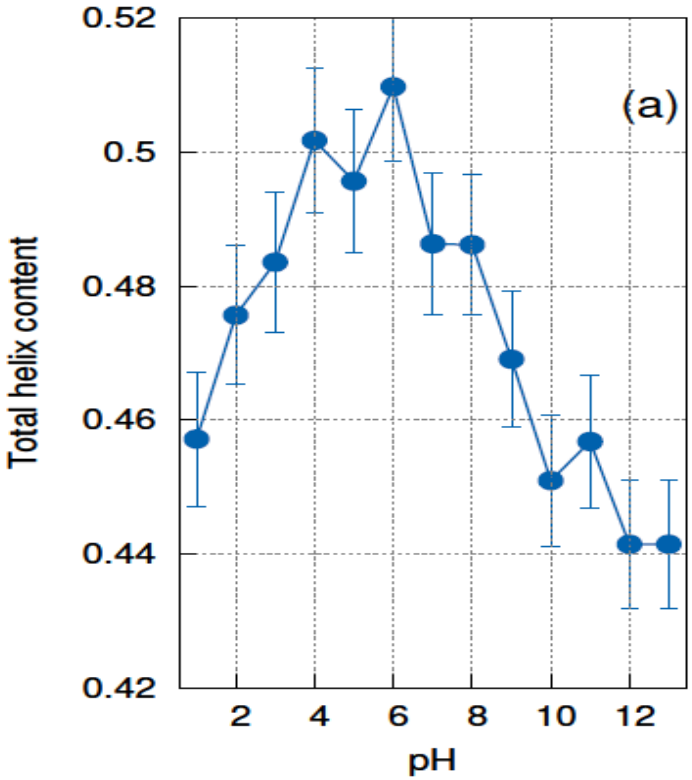
ME, Delle Site & Schuette, Soft Matter, 2013

Where?

C peptide of ribonuclease A

"The C peptide presents a helical conformation at physiological pH, which is lost in other conditions"



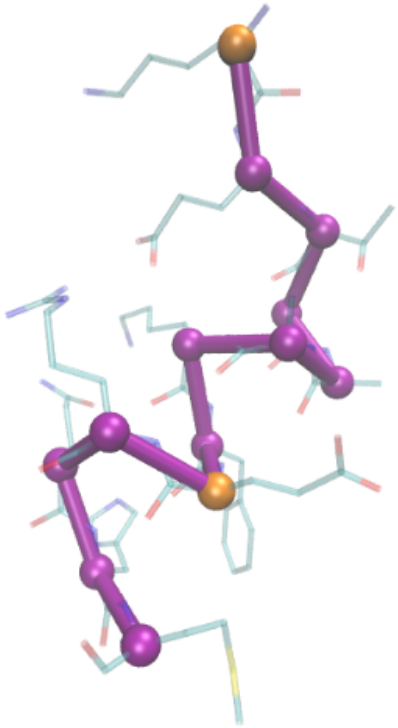


ME, Delle Site & Schuette, Soft Matter, 2013
Bierzynski et al, PNAS, 1982
Khandogin, Chen, Brooks, PNAS, 2006

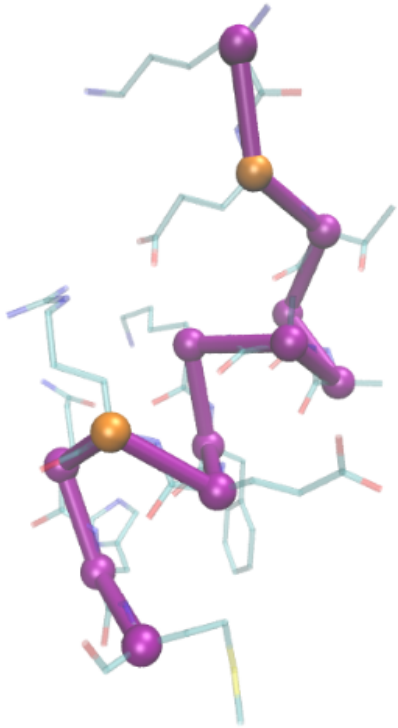
Where?

C peptide

"This change seems to be driven by a particular electrostatic interaction; there al



distance Lys1-Glu9 / nm



distance Glu2-Arg10 / nm

ME, Delle Site & Schuette, Soft Matter, 2013
Shoemaker et al, Biopolymers, 1990

Where?

Hemagglutinin fragment

"This peptide increases its helicity content at low pH values"

pH=7.2	0.41±0.01
pH=4.6	0.52±0.01

RVIEKTNEKFHQIEKEFSEVEGRIQDLEKYVEDTKI

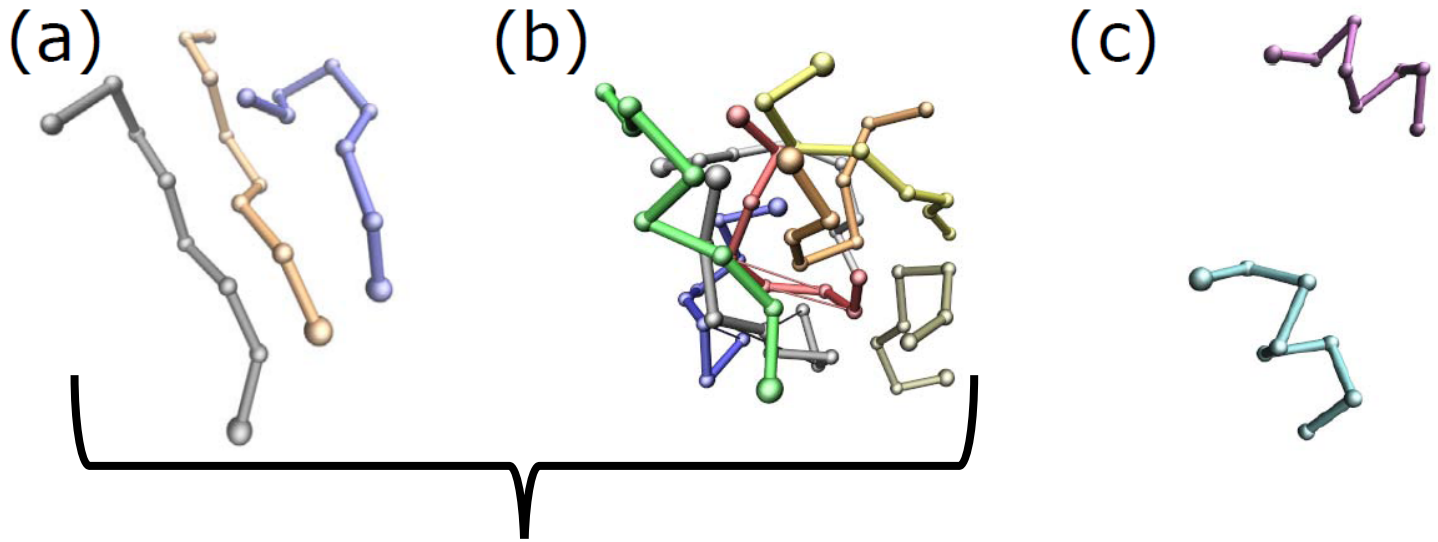
Acid
Basic

ME, Delle Site & Schuette, Soft Matter, 2013
Car & Kim, Cell, 1993

Where?

Aggregation: the human prion peptide

"The human prion peptide undergoes a conformational change under acidic conditions that is linked to aggregation processes"



pH=7.8

pH=4.5

ME, Delle Site & Schuette, Soft Matter, 2013

Zhan, J. Mol. Biol, 2003

Outline

Why

What

How

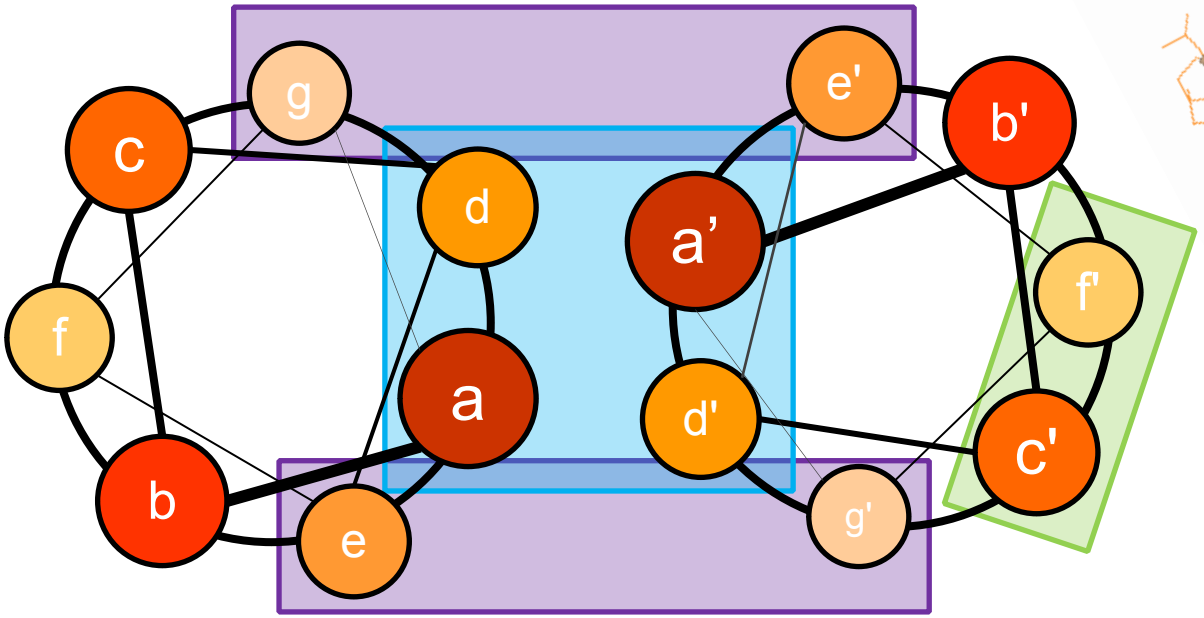
Where

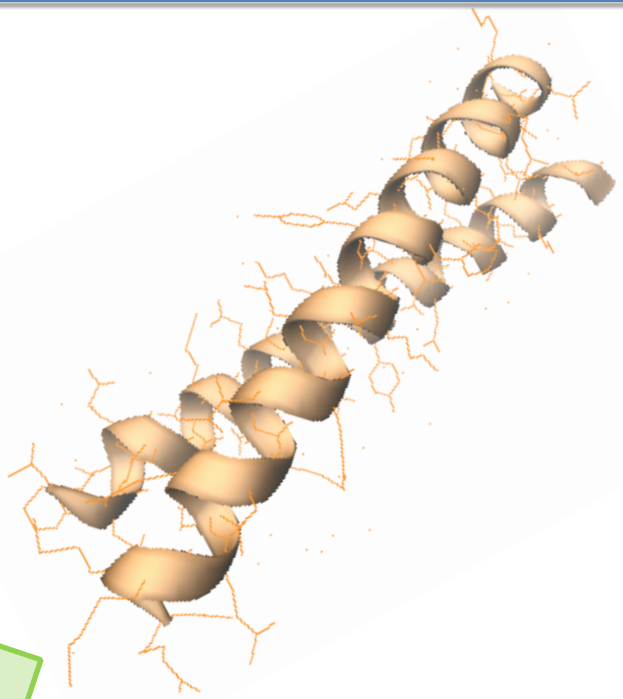
When

Who

What happens WHEN my system is different?

Application to coiled-coils





Hydrogen Bonds

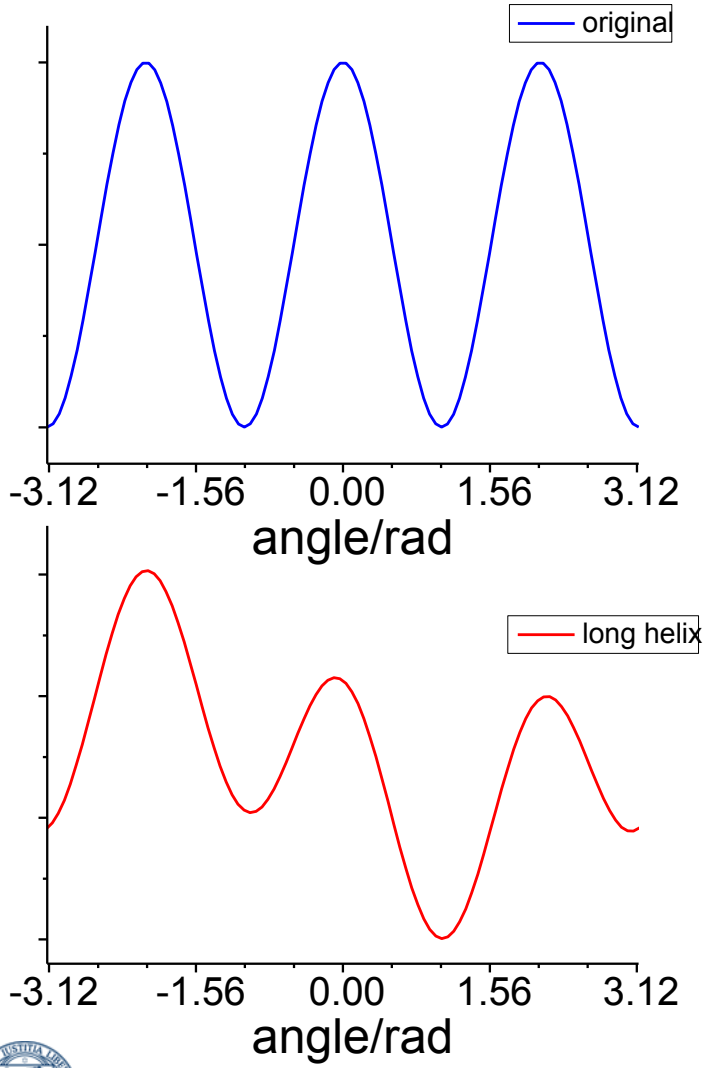
Hydrophobic interactions

Electrostatic interaction

ME, Delle Site & Schuette, Int. J. Mol. Sci., 2013

When…?

Application to coiled-coils



Hydrogen bonds

+

Hydrophobic interactions

+

Internal torsions

+

Electrostatic interactions

What if…?

Application to coiled-coils

- Generic coiled-coil systems

(ongoing)

- Particular examples

"The B-ZIP coiled-coil decreases its stability at low pH values due to the loss of electrostatic interactions between the helical interface"

pH=3

pH=7

Future work

1. Peptide simulations
    a. Coiled-coils
    b. Aggregation
2. Other pH-dependent systems
    a. Full proteins
    b. Lipoproteins
    c. Polymers
3. ???

Outline

Why

What

How

Where

When

Who

Who?

Prof. Christof Schuette
PD Dr. Luigi Delle Site

Badowski, Tomasz
Banisch, Ralf
Conrad, Dr. Tim
Durdevac, Dr. Natasa
Duwal, Sulav
Felsner, Bettina
Freder, Dr. Janine
Gul, Rahim
Gupta, Dr. Pooja
Hartmann, Prof. Dr. Carsten
Huttary, Rudolf
Hüffner, Sharon
Jürgens, Julian

Summary

1. We have developed a novel methodology to simulate constant pH conditions using a coarse-grained level resolution
2. The model design has followed the principle of “consistency across the scales”
3. Our results are consistent with experimental data and/or full atom simulation results
4. The methodology is very flexible and, therefore, can be adapted to other situations