Monte Carlo Simulations of the Hyaluronan-Aggrecan Complex in the Pericellular Matrix

Marcel Hellmann

BIOMS Group Cellular Biophysics, Deutsches Krebsforschungszentrum (DKFZ)

Theoretical Biophysics Group, Universität Heidelberg

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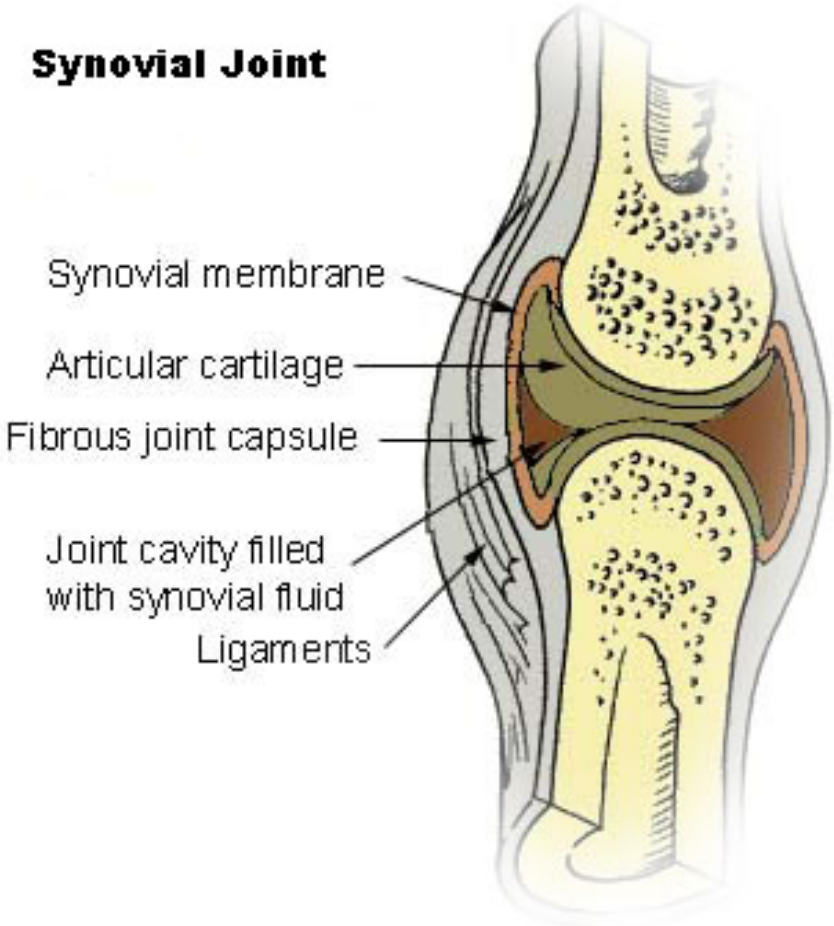
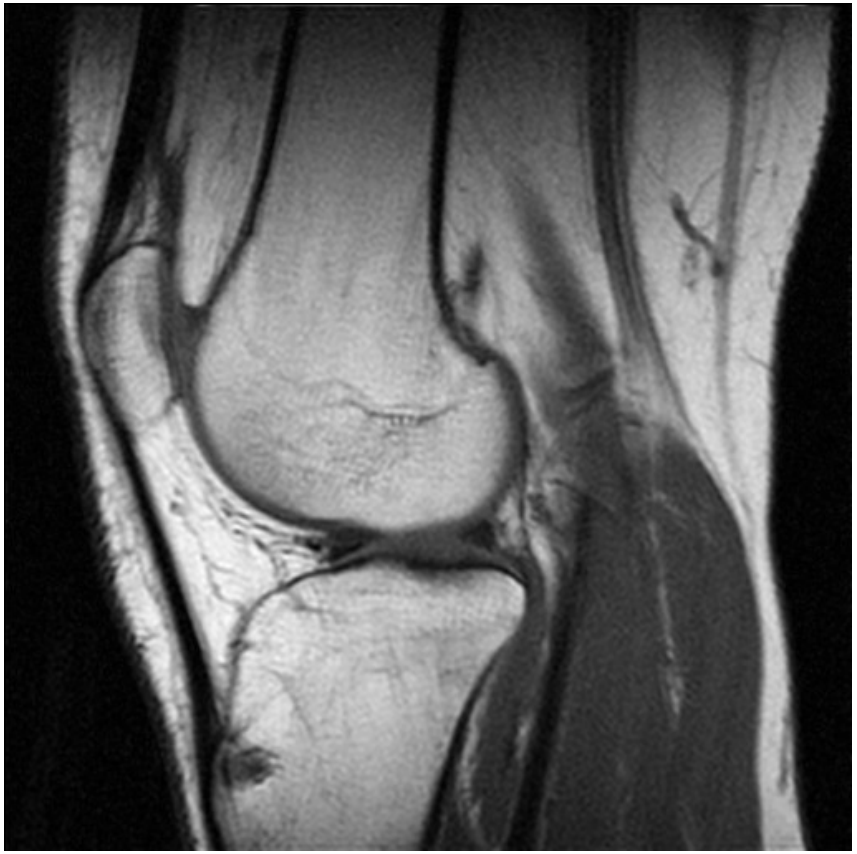
Content

The Human Knee Joint





www.wikipedia.org

Articular Cartilage

macroscopic observations:

- articular cartilage forms *menisci* in synovial joints
- highly elastic cushion
- serves as a rampart against pressure (e.g. during movements)
- damage results in disease (e.g. osteoarthritis)

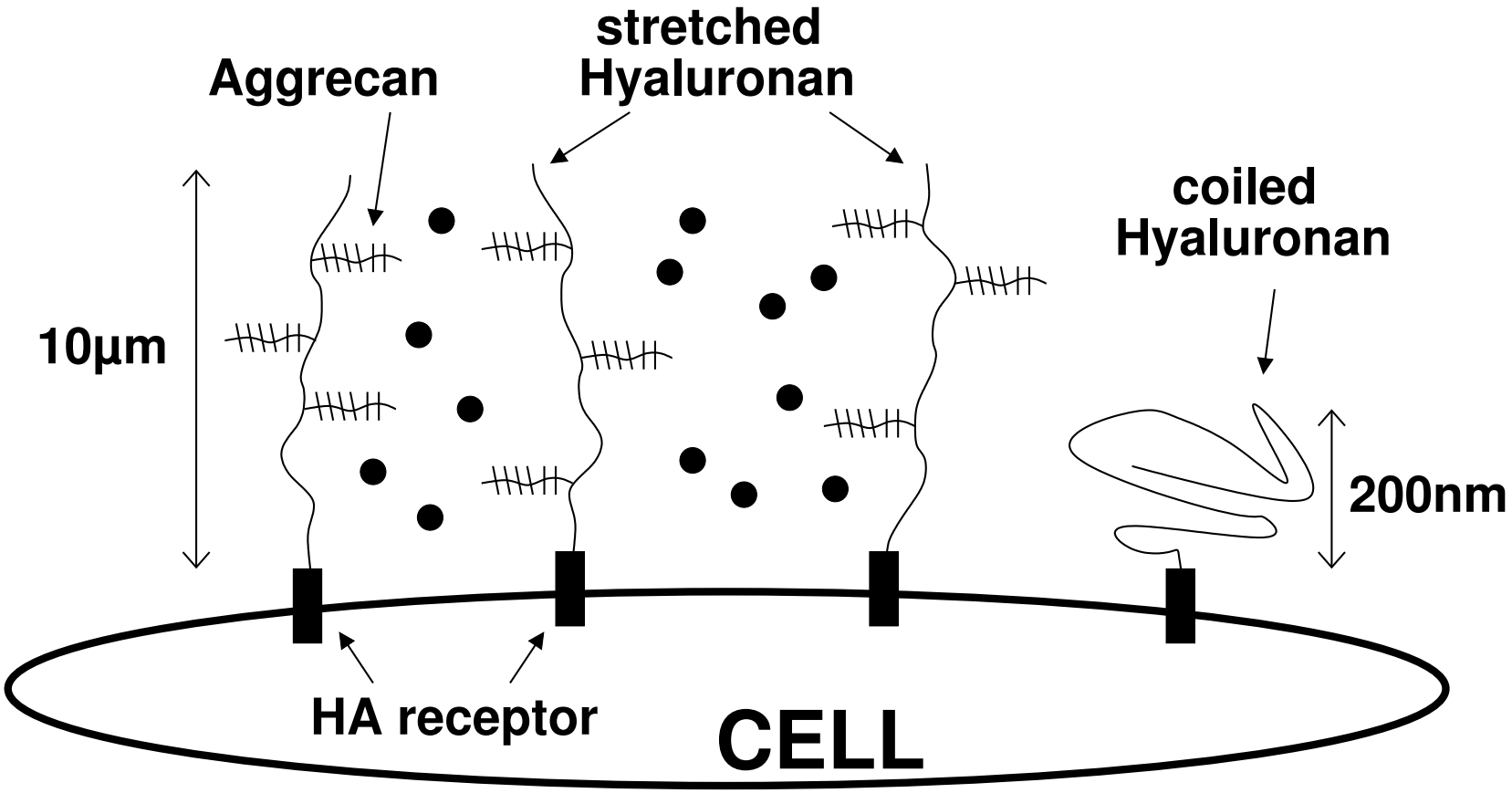
microscopic nature:

- highly entangled polymer network
- origin of synthesis: pericellular matrix arround specialized cells (fibroblasts)

How do the macroscopic properties emerge from the microscopic structure?

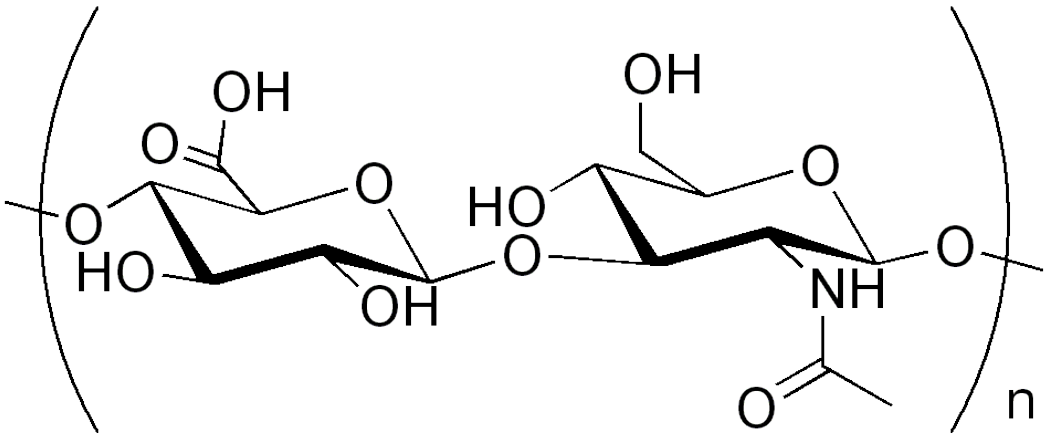
The Pericellular Matrix - A Simple Model

A simplyfied model of the pericellular matrix (PCM) arround a fibroblast [1]



[1] Lee et al. 1993

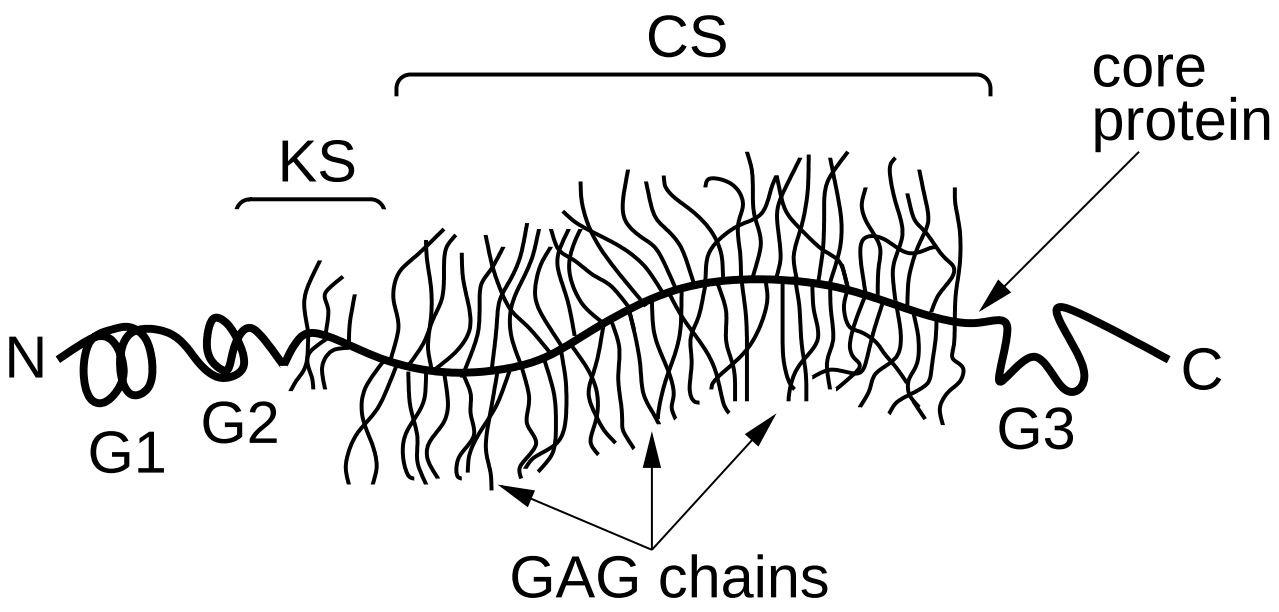
Hyaluronan (hyaluronic acid, HA)



- chain of sugars, total molecular weight: $\sim 10^6$ u
- contour length: $\sim 10\mu$m; persistence length: ~ 8 nm
- can be tethered to the membran by HA receptor protein

$\Longrightarrow$ **HA is a long, flexible polymer chain**

Aggrecan ('large aggregating proteoglycan')



- $\sim$ 300 ku core protein with $\sim$ 100 side chains attached
- contour length: $\sim$ 400 nm; persistence length: $\sim$ 110 nm
- core protein can bind to HA via linker protein

$\Longrightarrow$ **Aggrecan is a rather rigid 'polymer comb'**

Model Characteristics

- backbone (HA) fully flexible with length N; end-grafted on flat substrate (cell)
- side chain (Aggrecan) fully rigid with length S
- branching site b

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- good athermal solvent $\Leftrightarrow$ no interactions between monomers besides self-avoidance; no adsorbtion

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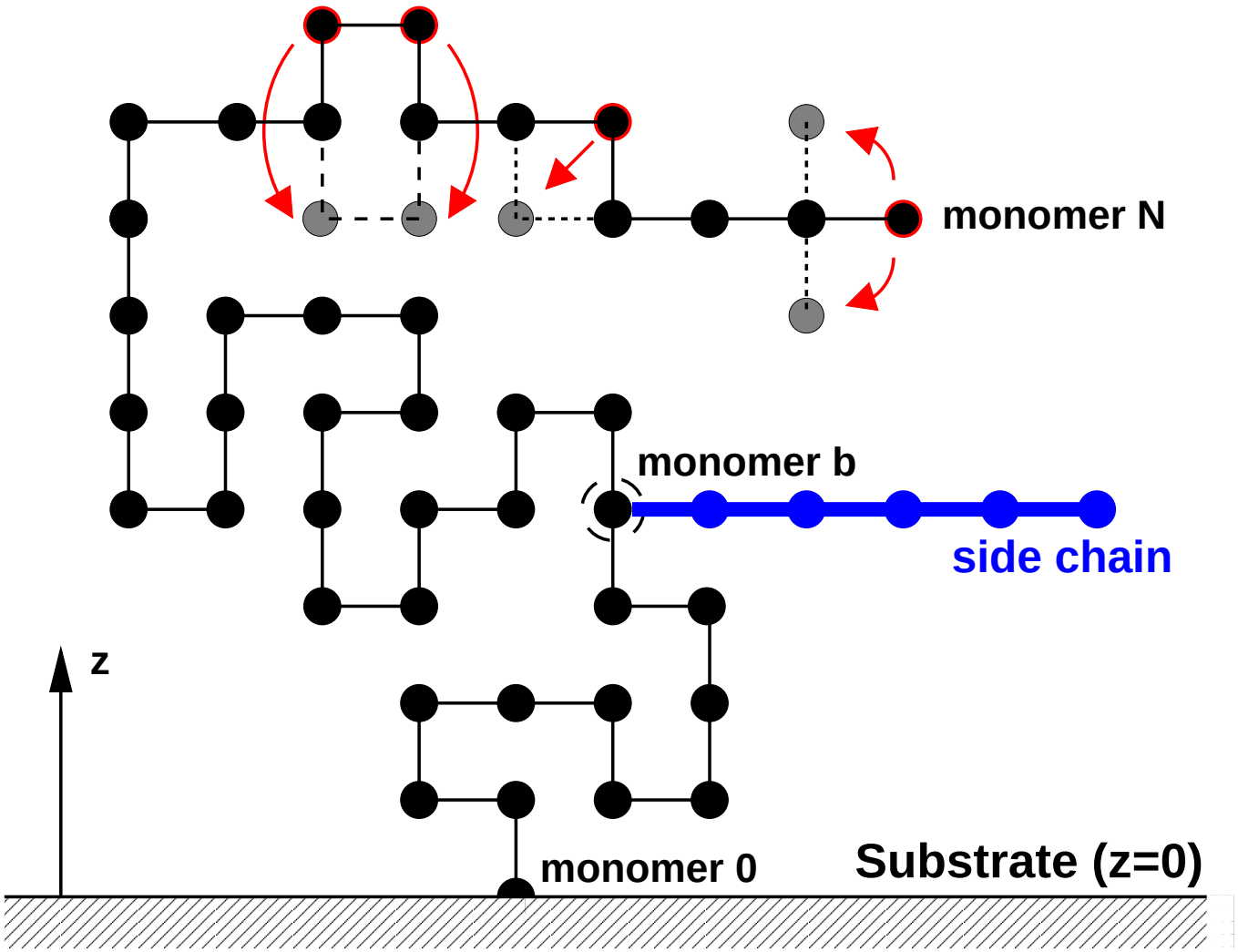
- Dynamical Monte Carlo to generate independent configuartions: Verdier-Stockmayer-type algorithm and random rotations of side chain

Simulation Model, 2D-sketch



Shape of a Polymer

polymer shape described by gyration tensor[2]:

$$S_{mn} = \frac{1}{N} \sum_{i=1}^{N} r_m^{(i)} r_n^{(i)}$$

- diagonalisation yields principle axes of gyration, $\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3$ defining the triaxial gyration ellipsoid

[2] Šolc & Stockmayer 1971
[3] Bruns 1992

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- ratios between the lengths of these axes ($L_1 \leq L_2 \leq L_3$) quantify the asphericity
- MC simulations reveal[3]

$$\text{RW:} \quad \langle L_1^2 \rangle : \langle L_2^2 \rangle : \langle L_3^2 \rangle \xrightarrow{N \to \infty} 1 : 2.7 : 12$$

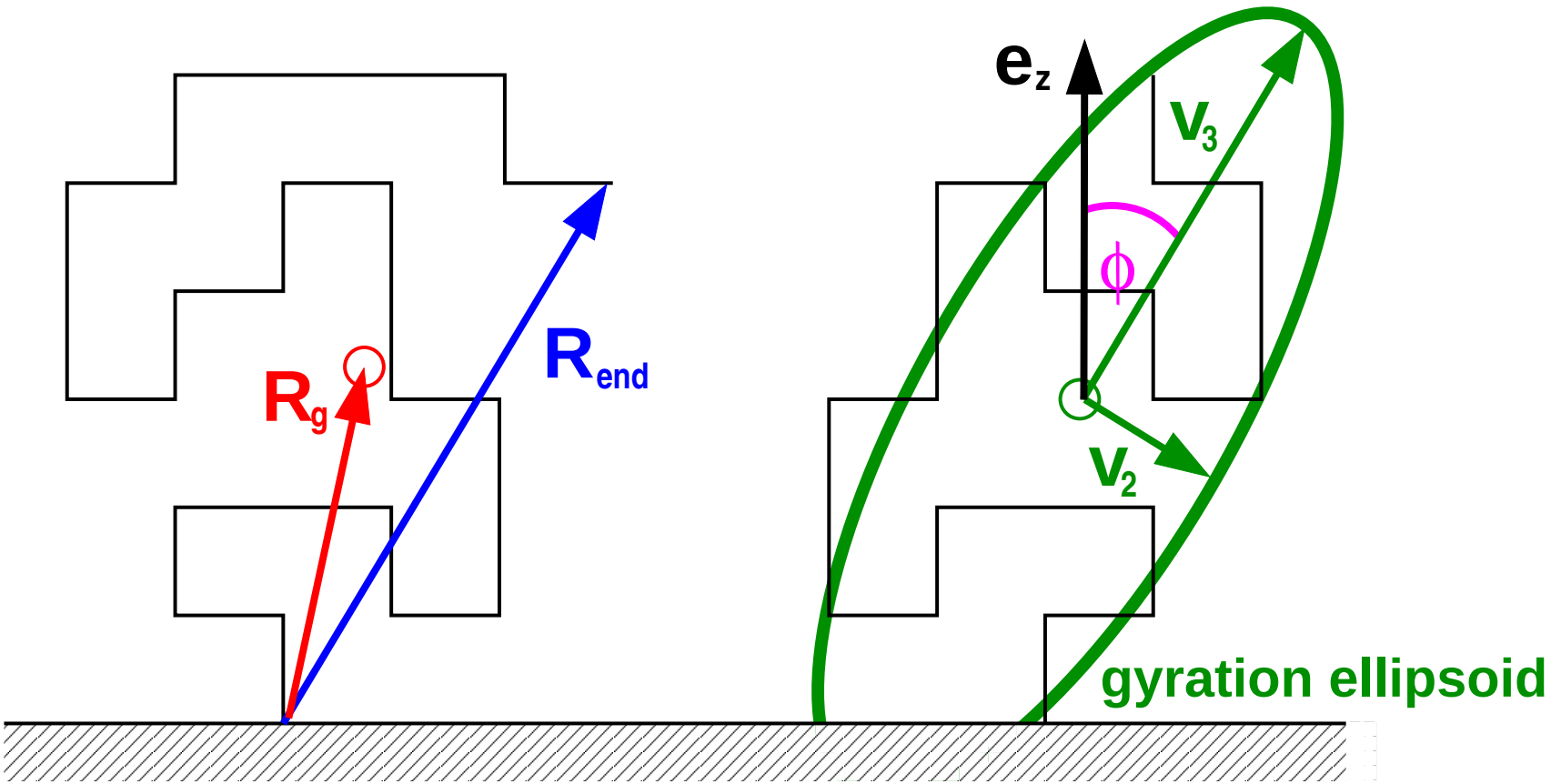
$$\text{SAW:} \quad \langle L_1^2 \rangle : \langle L_2^2 \rangle : \langle L_3^2 \rangle \xrightarrow{N \to \infty} 1 : 3.0 : 14$$

[2] Šolc & Stockmayer 1971

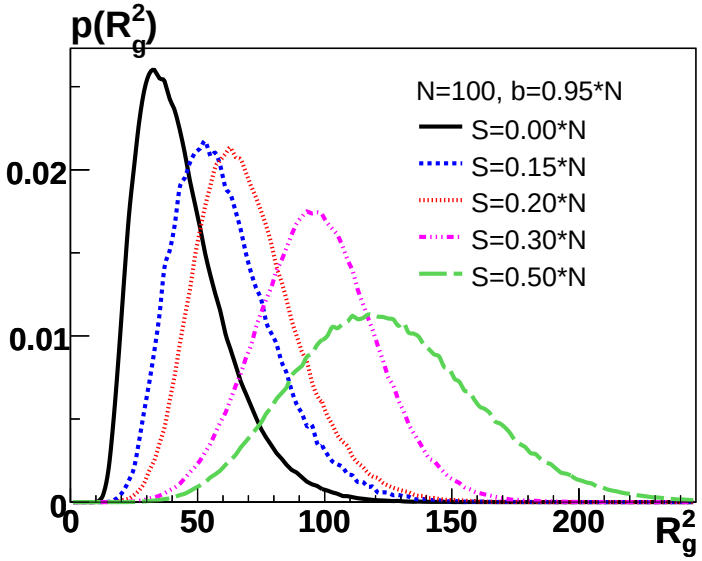
[3] Bruns 1992

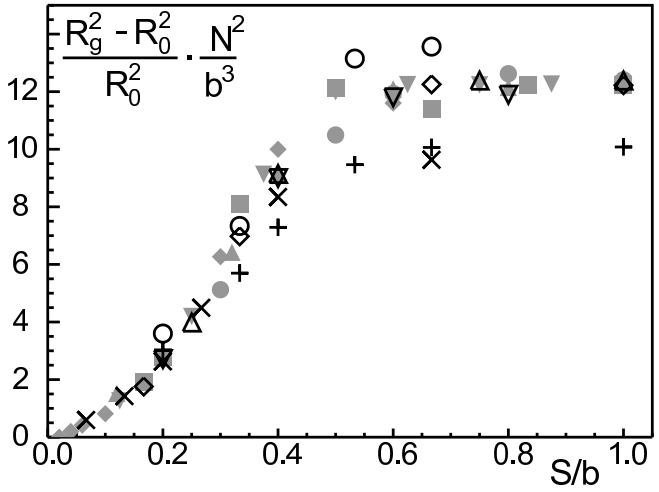
Read Outs

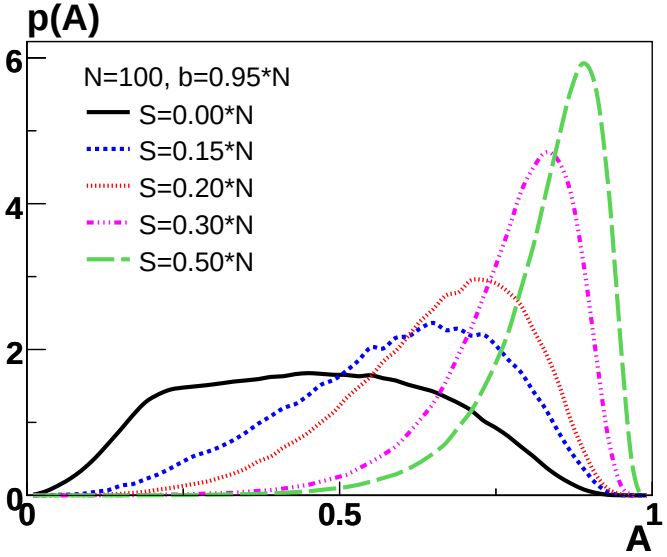
only backbone monomers are used for calculations!

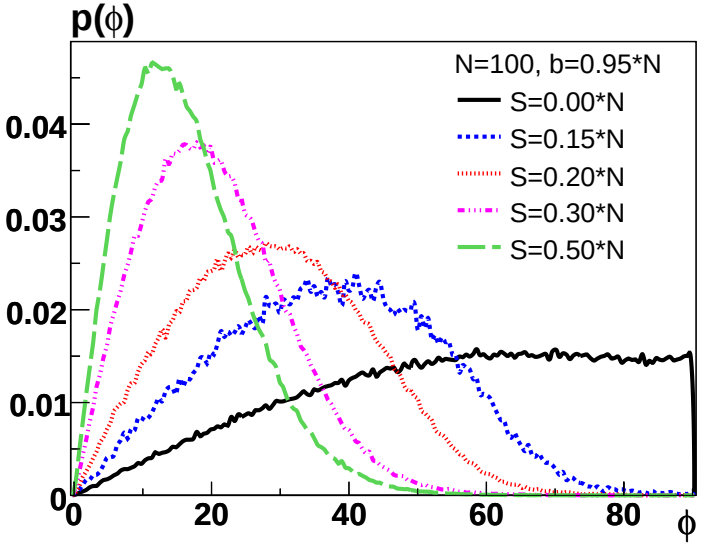


Simulation Results









Summary: Isolated HA-aggrecan Complex

Conformational changes due to rigid side chain:

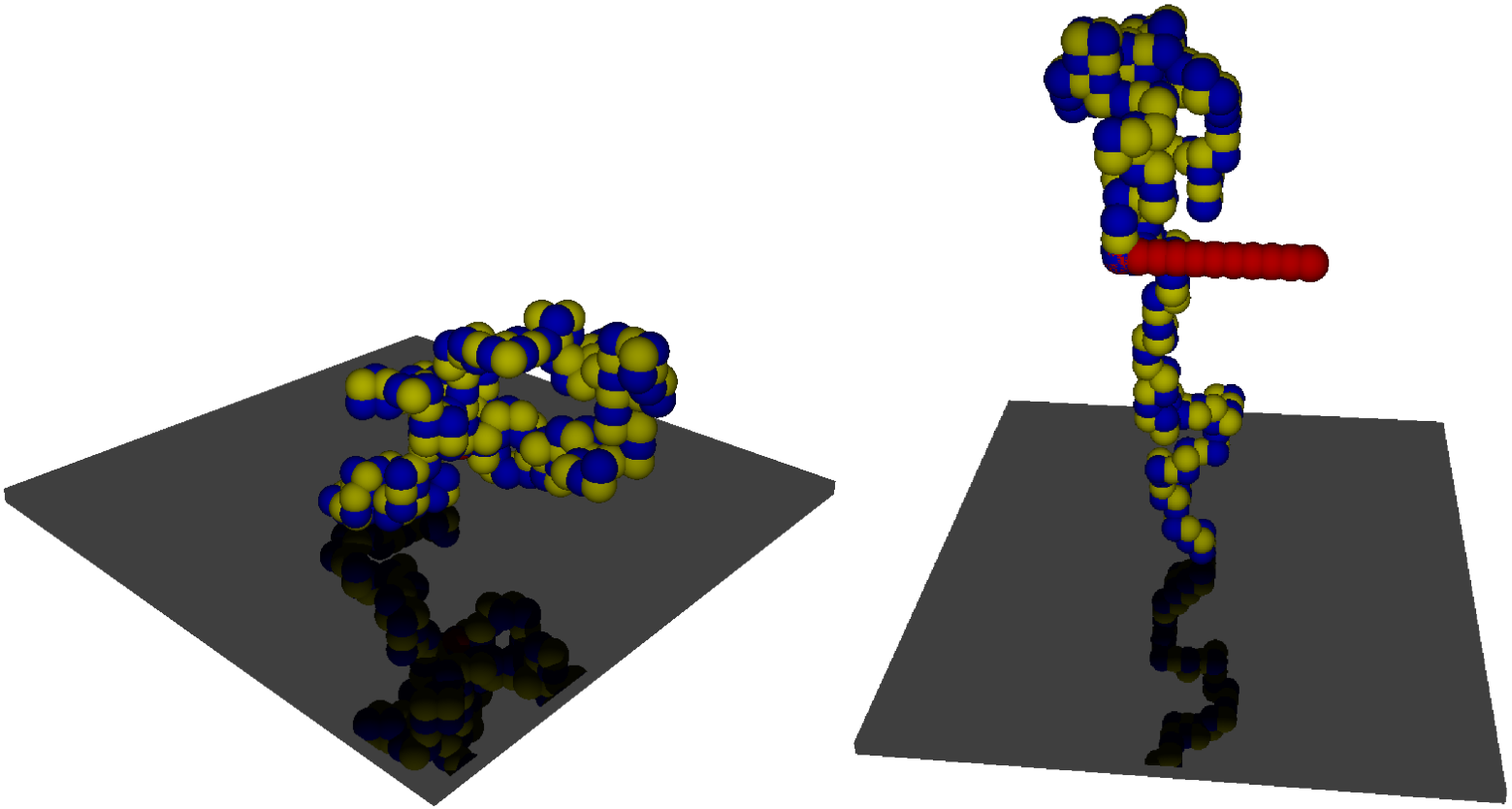
1. $\mathbf{R}_g$, $\mathbf{R}_{end}$ $\Rightarrow$ increase in size
2. asphericity $\Rightarrow$ pronounced rod-like shape
3. angle ϕ $\Rightarrow$ backbone orientates towards z-axis
4. increased persistency below side chain
5. additional side chains $\Rightarrow$ streightening largely caused by uppermost side chain

- all changes depend on b and S
- strongest effect for $b \approx N$, $S \geq 0.5 \cdot N$

M. H., M. Weiss, and D. W. Heermann, *Phys. Rev. E* **76**, 021802

Isolated HA-aggrecan Complex: 3D-Representation

Conformational changes due to rigid side chain:



Towards Dense Systems

observed streightening not sufficient to explain full extension of PCM

next: account for interactions between neighbouring complexes

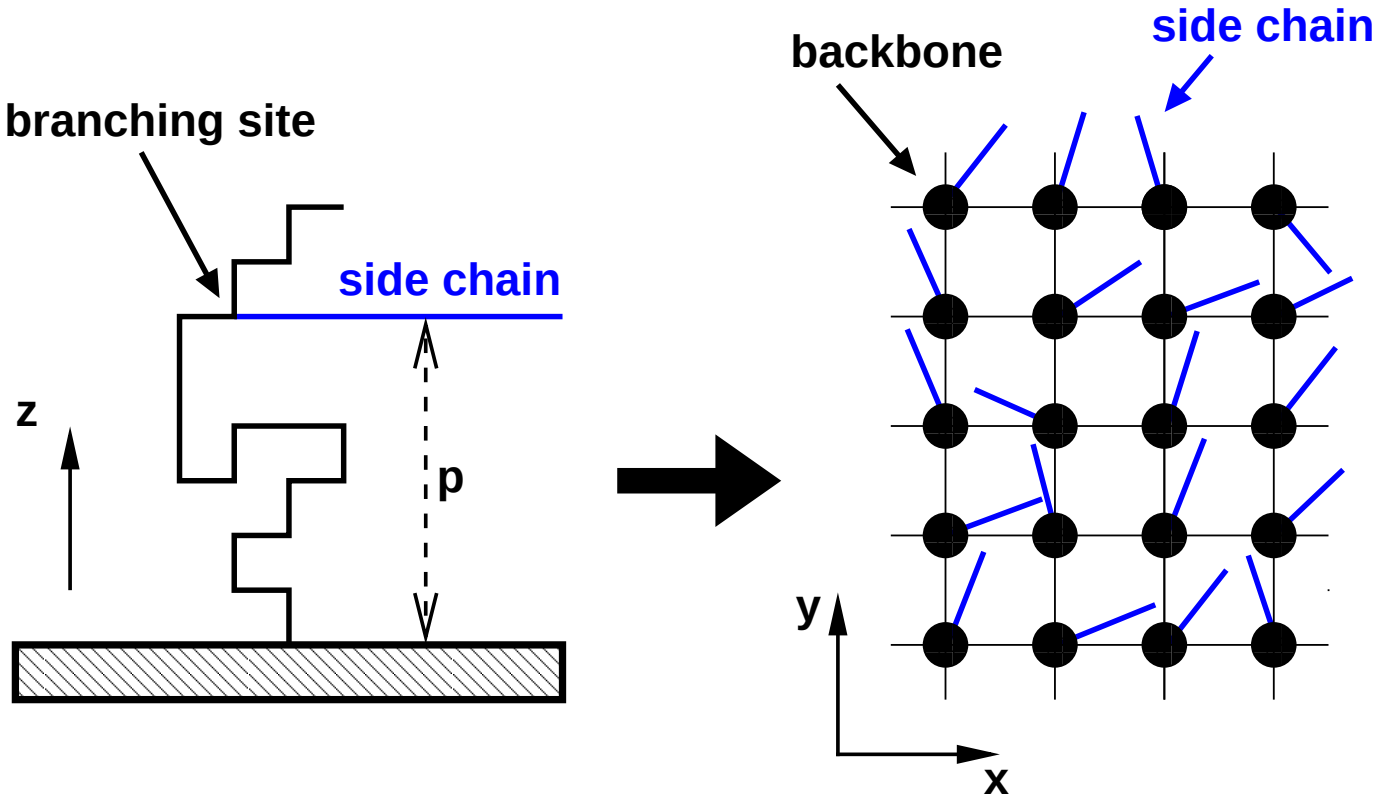
tasks/problems:

- simulations with single chain resolution are much too expensive!
- new model necessary: only account for 'most important' degrees of freedom

$\Longrightarrow$ *physically interesting side project*

New Model

idea: polymer with side chain $\longrightarrow$ rotating rods



New Model

- account for height p above the substrate: only side chains on the same level may interact $\rightarrow$ Potts model

$$\mathcal{H}_{Potts} = -J_P \sum_{\langle i,j \rangle} \delta_{p_i p_j} \quad \text{with } p_i \in \{0, 1, \ldots, q-1\}$$

- particular interaction between side chains unknown

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- particular interaction between side chains unknown
- consider NN-ferromagnetic interaction (prefers parallel alignment) $\rightarrow$ planar rotator model (XY-model)

$$\mathcal{H}_{XY} = -J_{XY} \sum_{\langle i,j \rangle} \mathbf{S}_i \mathbf{S}_j = -J \sum_{\langle i,j \rangle} S_i S_j \cos\theta_{i,j}$$

New Model

$\Rightarrow$ hybrid model:

$$\mathcal{H}_{Hybrid} = -J_H \sum_{\langle i,j \rangle} \delta_{p_i p_j} \cdot S_i S_j \cos\theta_{i,j} \quad \text{with } p_i \in \{0, 1, \ldots, q-1\}$$

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- parameters:
  - rotator length S_i — fix: $S_i = 1$,
  - number of Potts levels q — fix: $q = 3$,
  - system size $N = L \times L$ — vary,
  - interaction strength J_H ($\Leftrightarrow$ temperature T) — vary.

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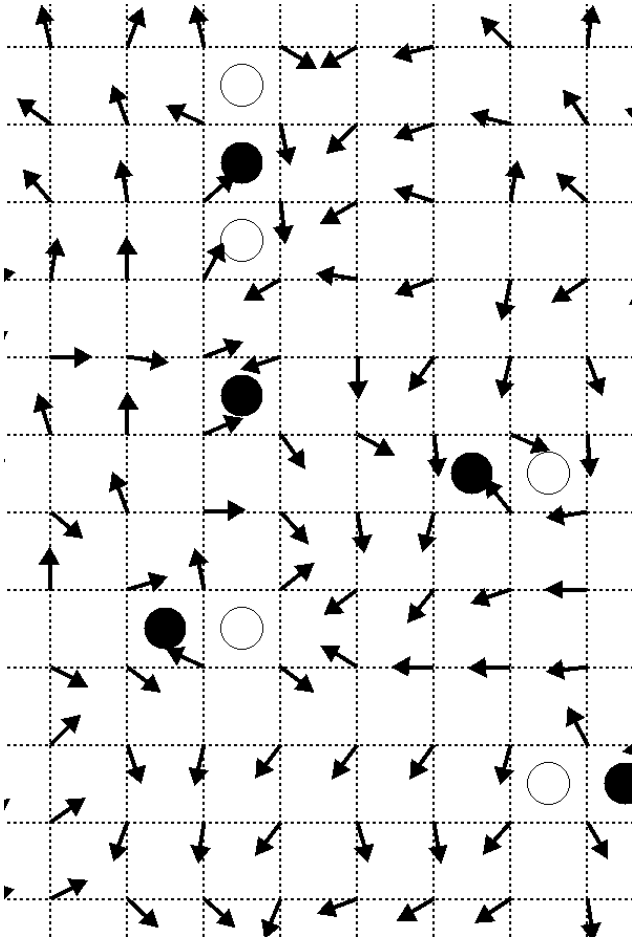
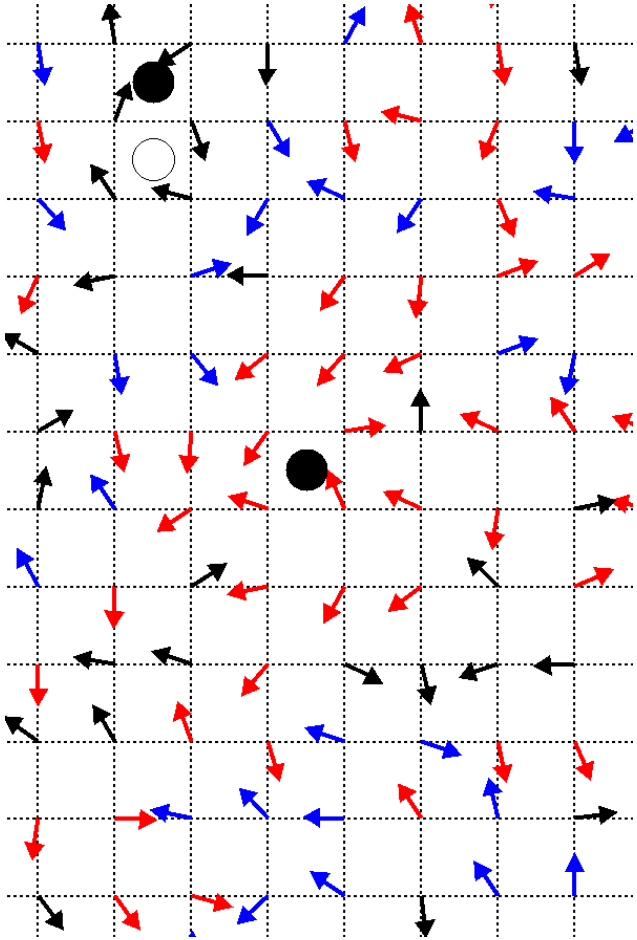
- behaviour in dependence on temperature and system size?
  1. XY model, NN-ferromagnetic $\rightarrow$ KT-transition
  2. 2D q-state Potts model: $q \leq 4 \rightarrow$ 2nd order
  3. hybrid: KT, 1st or 2nd order?

Vorticity: XY model and hybrid model

a) $q = 1$ (XY model, $T > T_{KT}$)

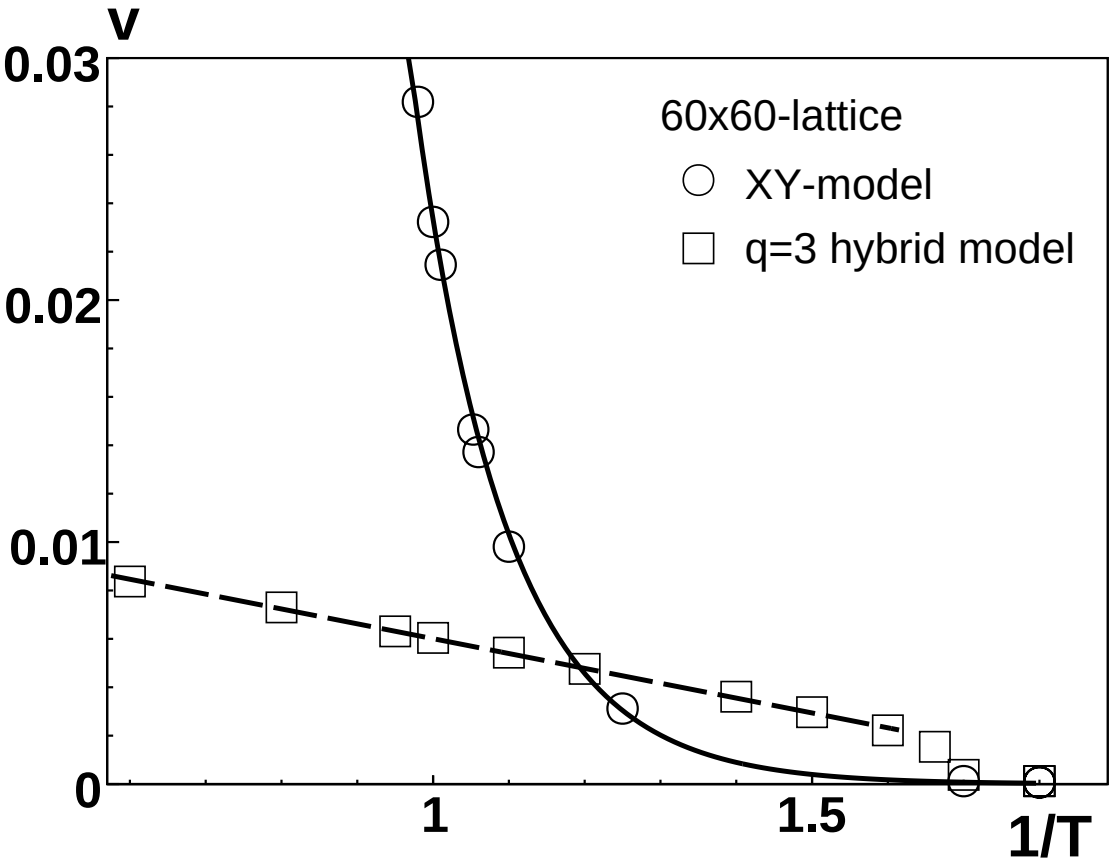


b) $q = 3$ (hybrid model)



Vortex Density

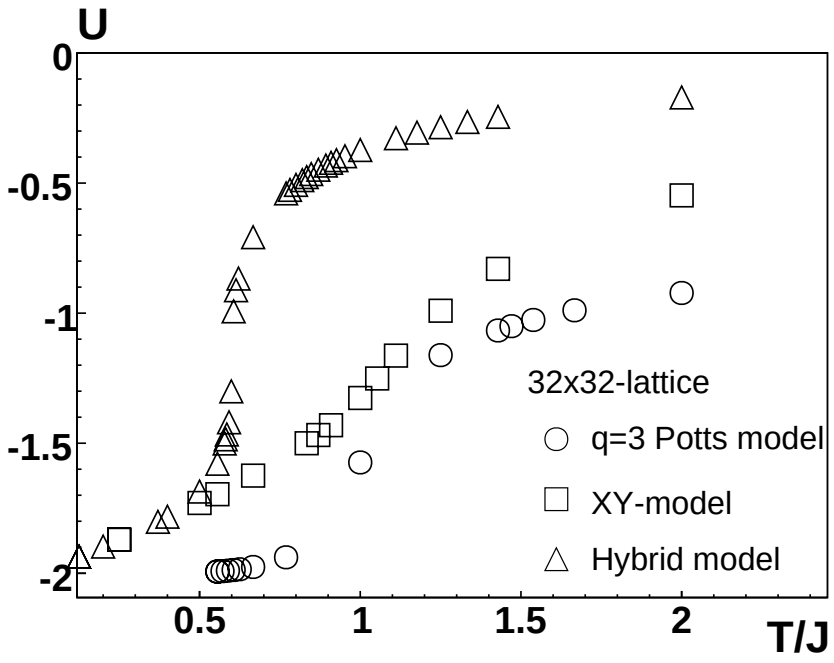
Vortex density $\equiv$ (#vortices + #antivortices) / lattice size

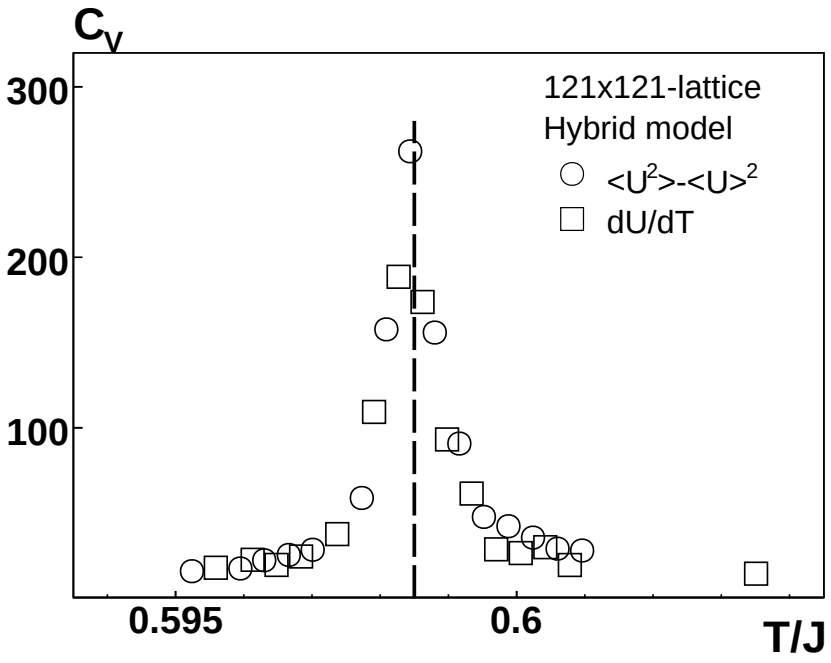


- XY model:
  $v \sim \exp(-2\mu/T)$
- hybrid:
  $v \sim -6.14 \cdot 10^{-3}/T$

Thermodynamics: Inner Energy and Specific Heat

results of **Metropolis MC**





$\Rightarrow$ transition temperature: $\boxed{T_c \approx 0.5985}$

Wolff's Cluster Algorithm[4]

Wolff Cluster Flipping

- randomly choose a lattice site
- draw bonds to all nearest neighbours with probability

$$P = 1 - \exp\left(-K\delta_{p_i,p_j}\right)$$

  (with $K \equiv J/k_B T$)
- proceed recursevily until no more new bonds are created
- flip all spins in the cluster

hybrid model has two *dof*: p (discrete) and θ (continuous)
$\Rightarrow$ flip cluster with respect to embedded variables

[4] Wolff, 1989

Embedding I

XY degree of freedom

embedding procedure for XY model well known (Wolff Embedding Trick)

- consider projection of spin vector onto x-axis
  $\Rightarrow$ Ising model of projected spins
- add bond between nearest neighbour sites with

$$P = 1 - \exp\left(\delta_{p_i,p_j} \cdot \min[0, 2K \cdot S_i^x \cdot S_j^x]\right)$$

- invert the x-component of all spins in the cluster
- to provide ergodicity rotate all spins by the same angle

Embedding II

Potts degree of freedom

- choose randomly a pair of p-values: (0,1), (0,2), (1,2)
- calculate effective interaction strength:

$$J_{eff} = J_H \cdot S_i S_j \cos\theta_{i,j}$$

- if $J_{eff} > 0 \Rightarrow$ ferromagnetic coupling:

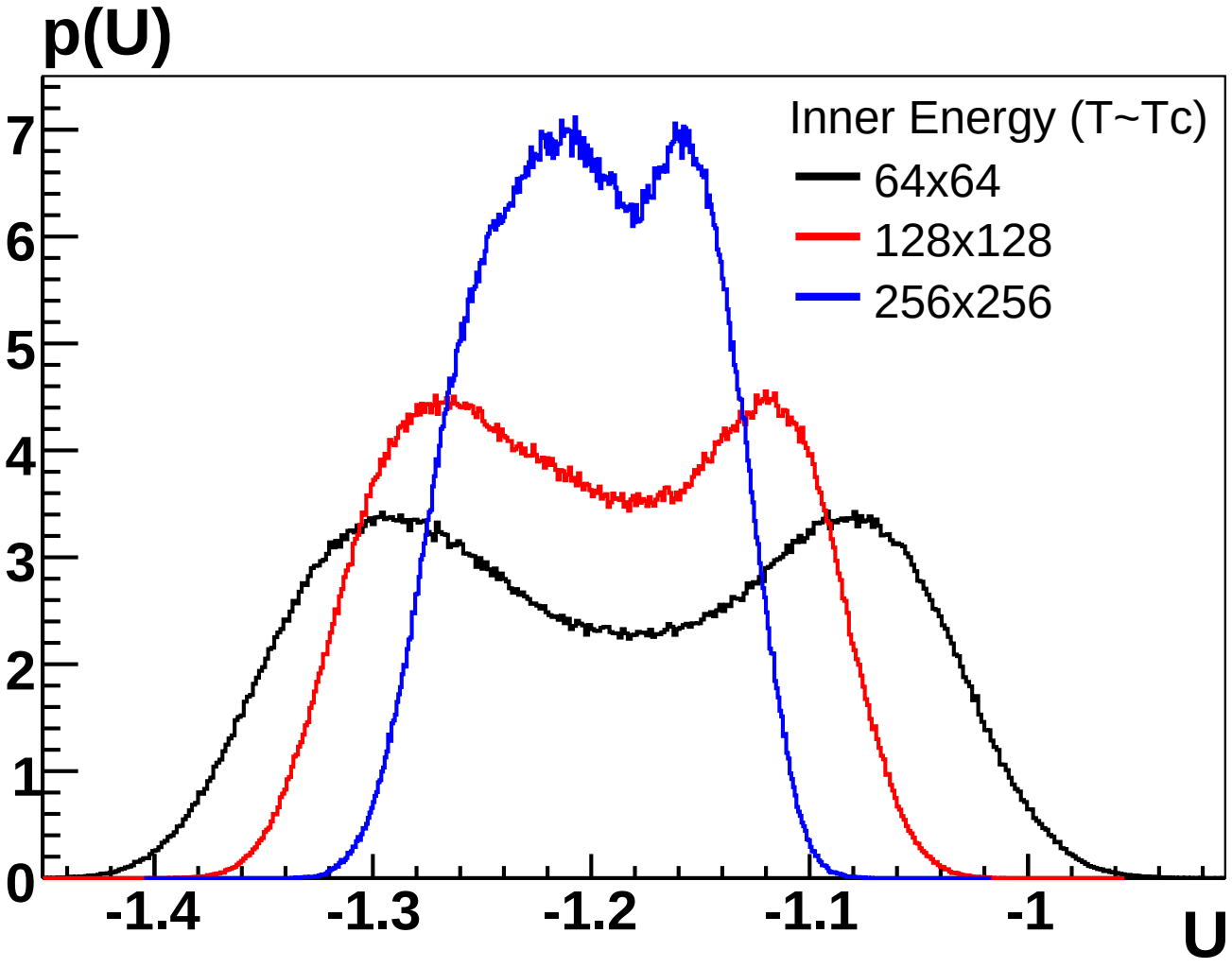
$$P = 1 - \exp\left(-K_{eff}\delta_{p_i=p_j}\right)$$

- if $J_{eff} < 0 \Rightarrow$ anti-ferromagnetic coupling:

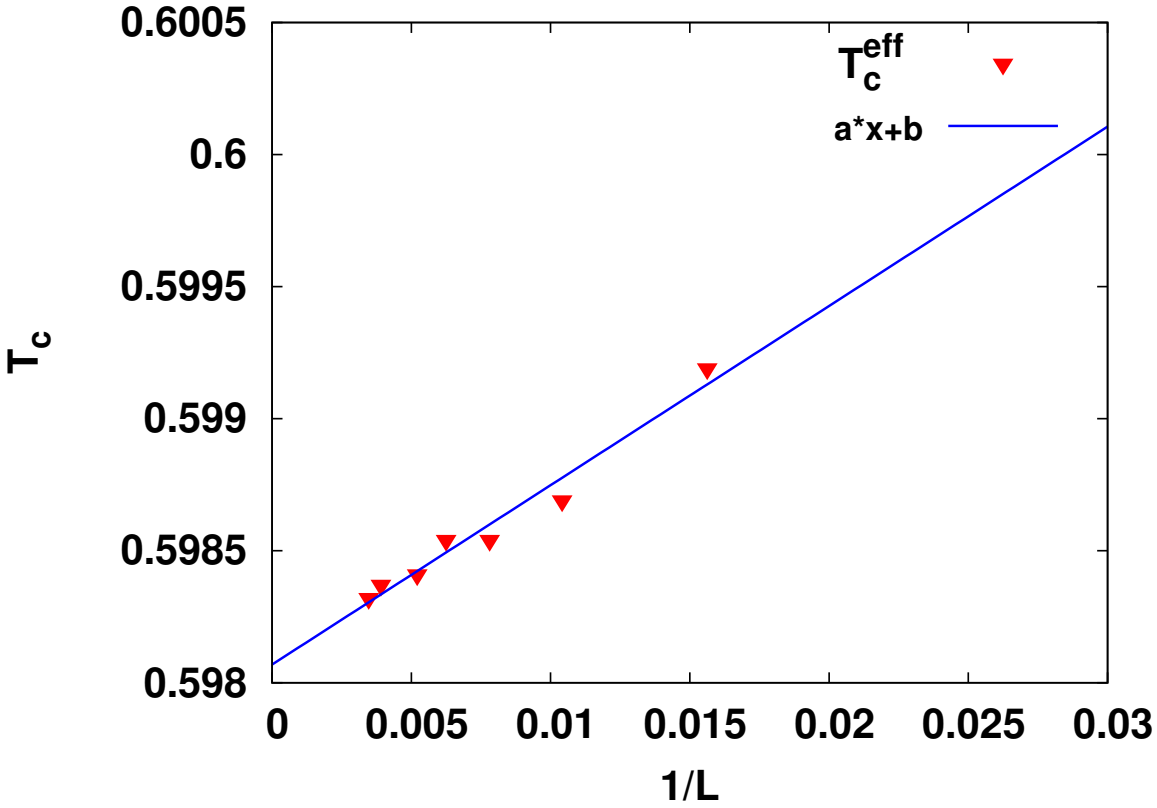
$$P = 1 - \exp\left(K_{eff}\delta_{p_i\neq p_j}\right)$$

- switch all Potts spins in the cluster

Recent Results: Inner Energy Distribution



Recent Results: Transition Temperature



linear fit $\Rightarrow$ $\boxed{T_c^{eff}(L \to \infty) = 0.598069}$

Open Questions/Problems/Ideas

- character/order of phase transition? Weak 1st order or 2nd order?
- order parameter?
- use results obtained for isolated complex (distribution for p)
- biologically motivated interaction (e.g. steric, electrostatic)?
- obtain macroscopic quantities (e.g. disjoining force)
- biological/biophysical implications?

Thank You for Your Attention!

Supervisors

Prof. Dr. D. W. Heermann,
Theoretical Biophysics Group,
Universität Heidelberg

Dr. Matthias Weiss,
BIOMS Group Cellular Biophysics,
Deutsches Krebsforschungszentrum

Collab. partner

Dr. Youjin Deng,
Univ. Heidelberg

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Dennis Große

Manfred Bohn

Contact

hellmann@tphys.uni-heidelberg.de
m.hellmann@dkfz-heidelberg.de

dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT