Computer Simulation of Peptide Adsorption

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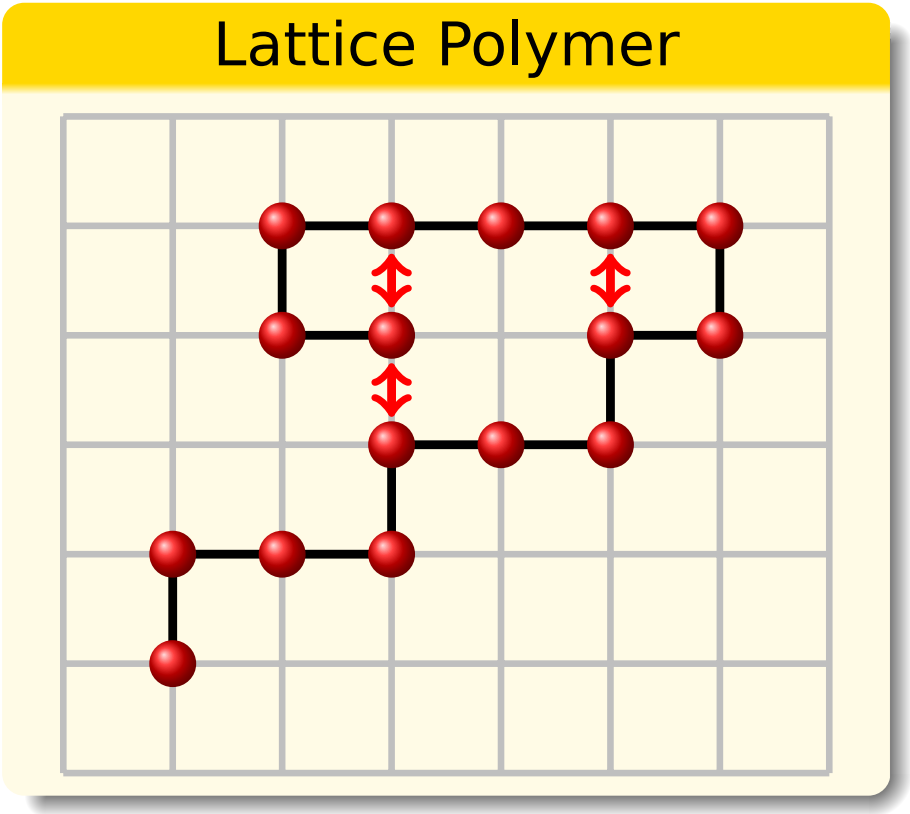
Outline

1 Lattice Peptide Monte Carlo

2 Surface Adsorption

3 Example Results

Simple Polymer Models

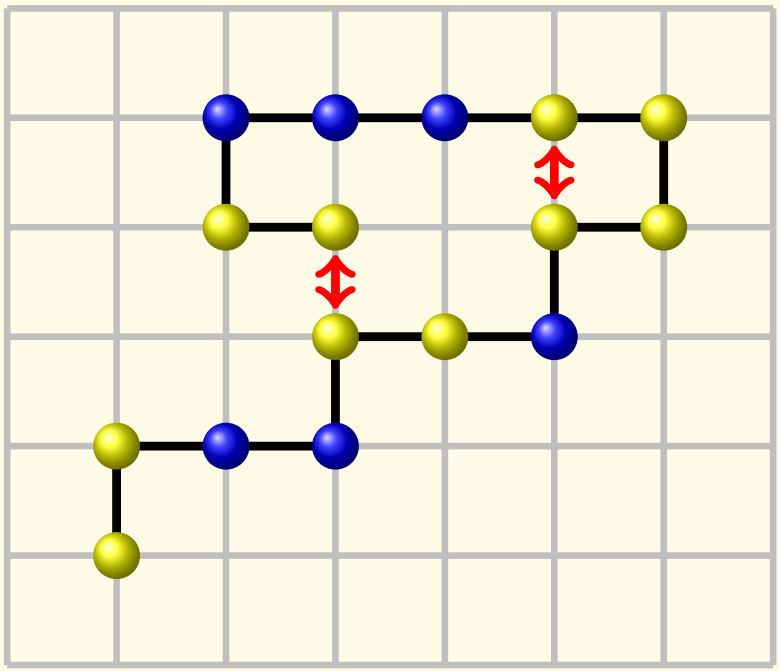


- Defined on a lattice
- Sites may be occupied or unoccupied
- Nearest-neighbour interactions
- Connectivity defines polymer chains
- Chains may not cross

- Off-lattice versions are also commonly used.

The HP Model

HP Model



- Self-avoiding chain of hydrophobic ● and polar ● residues,
- living on a 2D (square) or 3D (cubic) lattice.
- Each contact pair of non-bonded H residues contributes one unit $-\epsilon$ of favourable energy ↔.
- Encapsulates the basic problems of folding.

K Lau, KA Dill, *Macromolecules,* **22,** 3986 (1989).

KZ Yue, KA Dill, *Phys. Rev. E,* **48,** 2267 (1993).

Pull Moves

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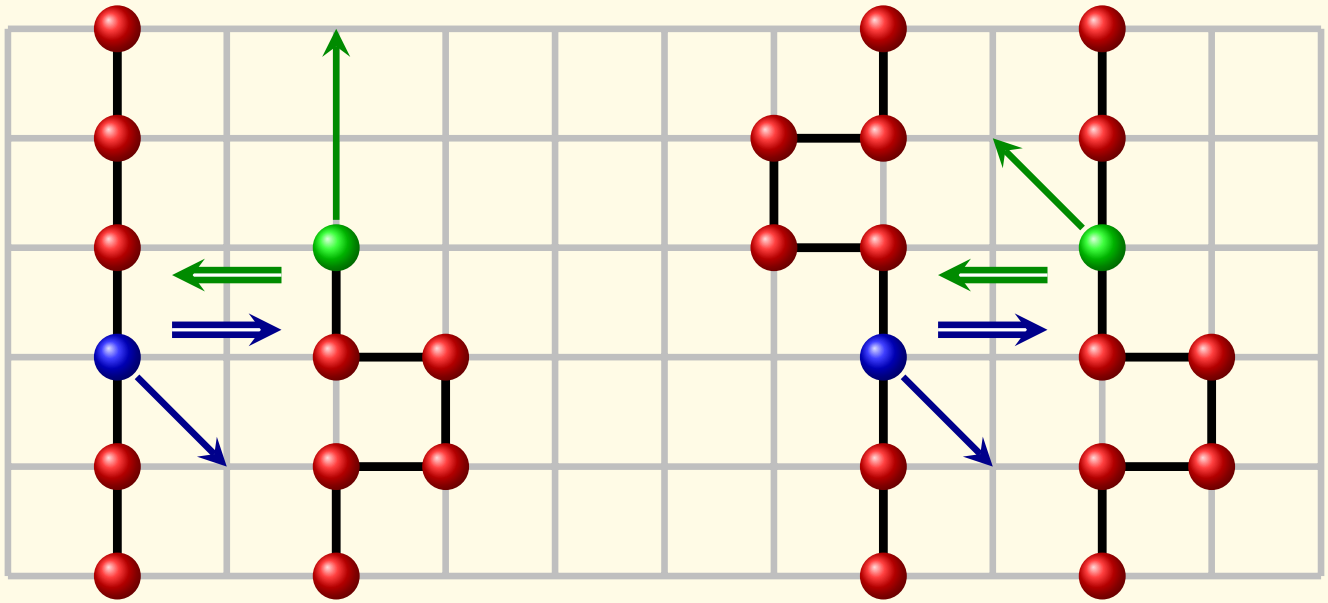
Defined by Single-Atom Move



M Lesh, M Mitzenmacher, S Whitesides, *Proc. 7th Ann. Int. Conf. on Research in Computational Molecular Biology,* p188 (2003).

Pull Moves

- Pull moves allow local contacts to form.
- They are ergodic, and improve efficiency.
- Especially important when chain is closely packed.
- Include some conventional moves, e.g. corner-flip.
- This is a *biased* sampling method, and the way the moves are selected must be included in the acceptance/rejection criterion.
- Counting the available pull moves (forward and reverse) is a critical part of the method.

M Lesh, M Mitzenmacher, S Whitesides, *Proc. 7th Ann. Int. Conf. on Research in Computational Molecular Biology,* p188 (2003).

Pull Moves

Pull Move Metropolis Equation

$$\mathcal{P}_{\text{acc}}(\Gamma' \leftarrow \Gamma) = \min\left(1, \frac{\alpha_{\text{pull}}(\Gamma \leftarrow \Gamma')}{\alpha_{\text{pull}}(\Gamma' \leftarrow \Gamma)} e^{-\Delta E/k_B T}\right)$$

$$\alpha_{\text{pull}}(\Gamma' \leftarrow \Gamma) = \frac{N_{\text{pull}}(\Gamma' \leftarrow \Gamma)}{N_{\text{pull}}(\Gamma)}, \quad \alpha_{\text{pull}}(\Gamma \leftarrow \Gamma') = \frac{N_{\text{pull}}(\Gamma \leftarrow \Gamma')}{N_{\text{pull}}(\Gamma')}$$

ΔE is change in energy associated with $\Gamma' \leftarrow \Gamma$

- $N_{\text{pull}}(\Gamma' \leftarrow \Gamma) =$ number of pull moves to Γ' from Γ
- $N_{\text{pull}}(\Gamma) =$ total number of pull moves from Γ
- $\dfrac{N_{\text{pull}}(\Gamma \leftarrow \Gamma')}{N_{\text{pull}}(\Gamma' \leftarrow \Gamma)} = 1 \quad \Rightarrow \quad \dfrac{\alpha_{\text{pull}}(\Gamma \leftarrow \Gamma')}{\alpha_{\text{pull}}(\Gamma' \leftarrow \Gamma)} = \dfrac{N_{\text{pull}}(\Gamma)}{N_{\text{pull}}(\Gamma')}$

Need to consider both forward and reverse moves.
Counting these is quite time consuming!

Pull Moves

We improve the method by simplifying the counting (and rejecting some moves).

- Ignore chain overlaps when generating pull moves
- $\alpha_{\text{pull}}(\Gamma \leftarrow \Gamma') = \alpha_{\text{pull}}(\Gamma' \leftarrow \Gamma)$
- Still need to select moves with equal probability
- Number of available pull moves depends on location of initiating bead (terminal / non-terminal).
- It does not depend on Γ.
- Some moves will be rejected due to overlap, but overall the method is faster.

Can also proceed by selecting initial bead first, and choose amongst non-overlapping pull moves (if any) second, but it seems to be a bit slower.

Density-of-States Sampling

- Covers energy scale uniformly: $\mathcal{P}(E) = \text{constant}$.
- Uses an iterative method to achieve this.
- Promotes low-energy $\longleftrightarrow$ high-energy exchange.
- Effectively counts accessible states $\mathbb{W}(E)$.
- Gives entropies $S(E) \propto \ln \mathbb{W}(E)$, free energies.

FG Wang, DP Landau, *Phys. Rev. E*, **64**, 056101 (2001).

A D Swetnam, M P Allen, *Phys. Chem. Chem. Phys.*, **11,** 2046 (2009).

A D Swetnam, M P Allen, *J. Comput. Chem.*, **32,** 816 (2011).

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2 Surface Adsorption

3 Example Results

Literature Background

An active field: several groups use a variety of techniques (e.g. chain-growth, multicanonical, WL) and models (both on-lattice and off-lattice). Examples:

- M Bachmann, W Janke “Substrate specificity of peptide adsorption: A model study”, *Phys. Rev. E,* **73,** 020901 (2006).
- T Wüst, DP Landau, “The HP model of protein folding: A challenging testing ground for Wang-Landau sampling”, *Comp. Phys. Commun.,* **179,** 124 (2008).
- M Möddel, W Janke, M Bachmann “Systematic microcanonical analyses of polymer adsorption transitions”, *Phys. Chem. Chem. Phys.,* **12,** 11548 (2010).
- YW Li, T Wüst, DP Landau, “Generic folding and transition hierarchies for surface adsorption of hydrophobic-polar lattice model proteins”, *Phys. Rev. E,* **87,** 012706 (2013).

Surface Adsorption and Confined Geometry

Two common approaches to study adsorption of peptides and polymers from solution onto a surface.

1. Tether (or graft) one end of polymer to surface.
2. Add a second confining wall (slab or slit geometry).

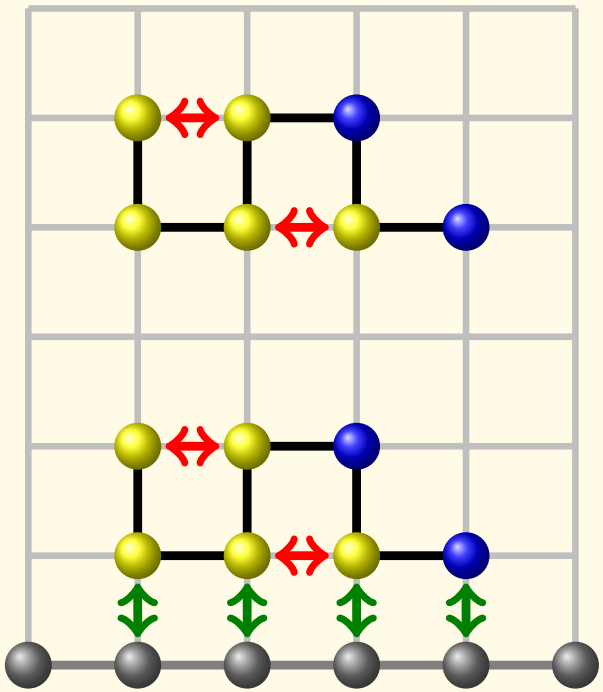
Approach #1 simulates the “wrong” system!
Approach #2 involves some inefficiencies:

- Need to separate walls so as not to interfere.
- Long excursions away from the surface of interest.
- Moves can be rejected due to wall overlap.

Polymers & Peptides on Surfaces

Our “wall-free” method avoids slit geometry altogether.

Surface Geometry



- Internal configuration Γ
- Energy $E = -n\epsilon - s\sigma$
- $n = n(\Gamma) =$ number of H-H contacts for Γ;
- $-\epsilon =$ contact energy $\leftrightarrow$.
- $s = s(\Gamma) =$ number of lower-surface beads for Γ;
- $-\sigma =$ surface energy $\leftrightarrow$.
- Count states: $\mathbb{W}_{\text{ads}}(n, s)$

Simultaneously investigates molecule in contact with, and out of contact with, surface of interest.

Polymers & Peptides on Surfaces

- Significant improvement of the method.
- There is no need for the second confining wall.

Surface Monte Carlo Algorithm

1. Standard pull move on isolated polymer
   - Count the monomer-monomer interactions n
   - No overlap with any walls
2. Translate the surface to the plane of contact
   - Count the monomer-surface interactions s
3. Look up "adsorbed" density of states $\mathbb{W}_{\text{ads}}(n, s)$.
4. Accept or reject

- There is scope to improve sampling through choice of surface orientation or transverse position.
- Method can be generalized to off-lattice case.

Polymers & Peptides on Surfaces

We get the "desorbed" density of states for free:

$$\mathbb{W}_{\text{des}}(n) = \sum_s \mathbb{W}_{\text{ads}}(n,s)$$

For neutral confining wall, slit height $H > h_{\max}$

$$\mathbb{Q}_H = \sum_n \sum_s \mathbb{W}_{\text{ads}}(n,s)\, \mathrm{e}^{+n\beta\epsilon}\, \mathrm{e}^{+s\beta\sigma} + \sum_n \sum_s \big(H - \bar{h}(n,s)\big)\, \mathbb{W}_{\text{ads}}(n,s)\, \mathrm{e}^{+n\beta\epsilon}$$

- unit cross-sectional area
- $h(\Gamma)$ is polymer "height"
- $\bar{h}(n,s)$ is the average h for given n, s.
- $h_{\max} = \max_{\Gamma} h(\Gamma)$

Statistical Mechanics of Adsorption

Partition functions for adsorbed and desorbed states

$$\mathbb{Q}_{\text{ads}}(T) = \sum_{n,s} \mathbb{W}_{\text{ads}}(n,s) \mathrm{e}^{+n\beta\epsilon} \mathrm{e}^{+s\beta\sigma}$$

$$\mathbb{Q}_{\text{des}}(T) = \sum_{n} \mathbb{W}_{\text{des}}(n) \mathrm{e}^{+n\beta\epsilon} \quad \text{(internal)}$$

Grand canonical ensemble, activity $\lambda = \mathrm{e}^{\beta\mu}$.

Grand partition function, non-interacting molecules

$$\mathbb{X}(\lambda, T) = \sum_{N \geq 0} \frac{\lambda^N \mathbb{Q}^N}{N!} = \mathrm{e}^{\lambda \mathbb{Q}}, \quad \langle N \rangle = \lambda \frac{\partial \mathbb{X}}{\partial \lambda} = \lambda \mathbb{Q}$$

$$\langle N_{\text{ads}} \rangle / \langle N_{\text{des}} \rangle = \mathbb{Q}_{\text{ads}} / \mathbb{Q}_{\text{des}}$$

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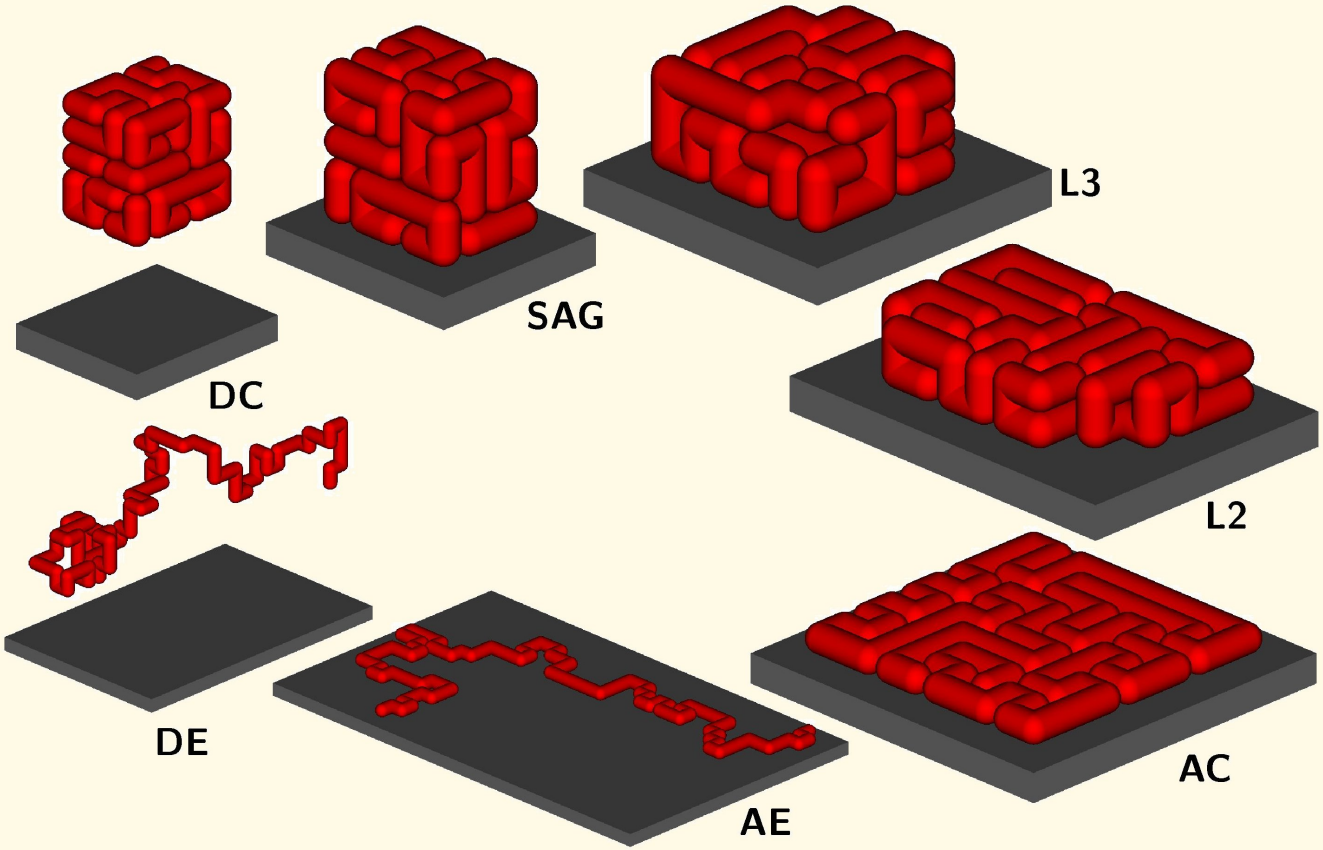
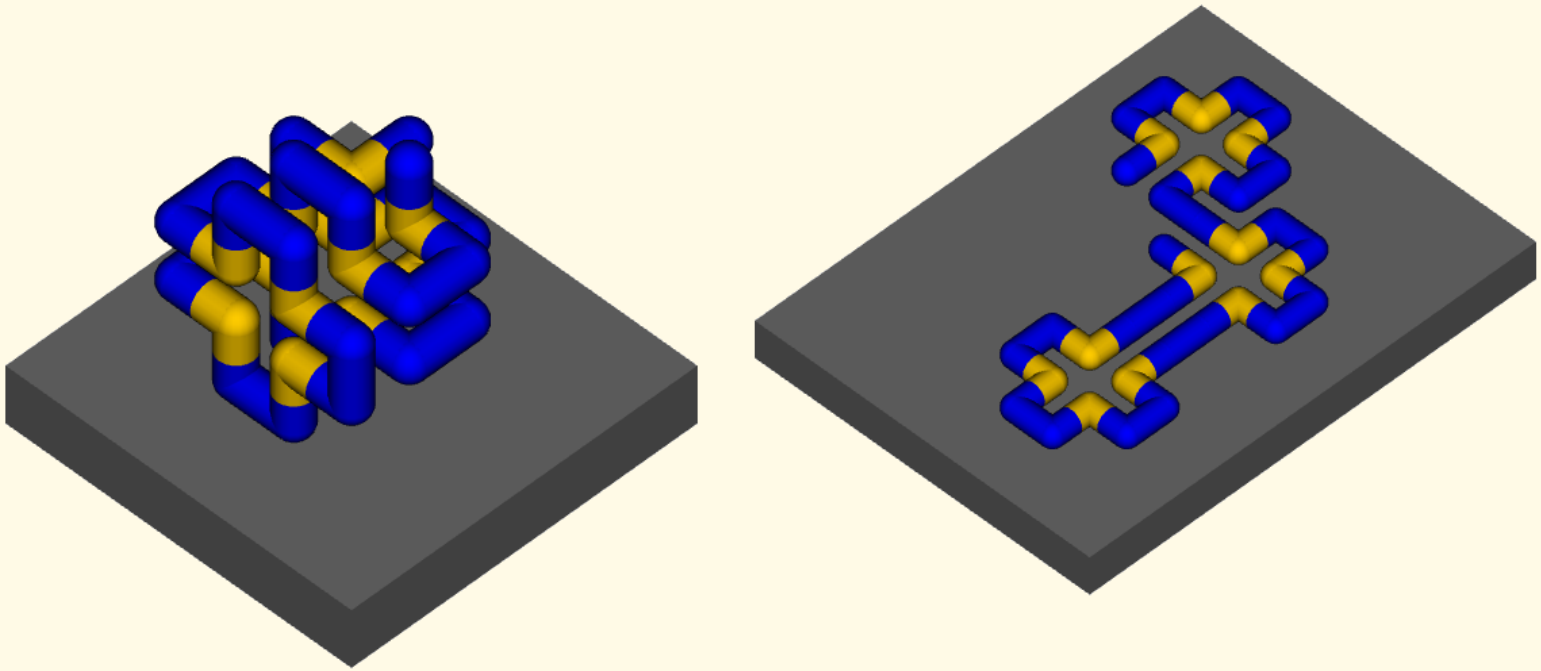
H_{100} Homopolymer

Desorbed/Adsorbed Expanded/Compact Configurations



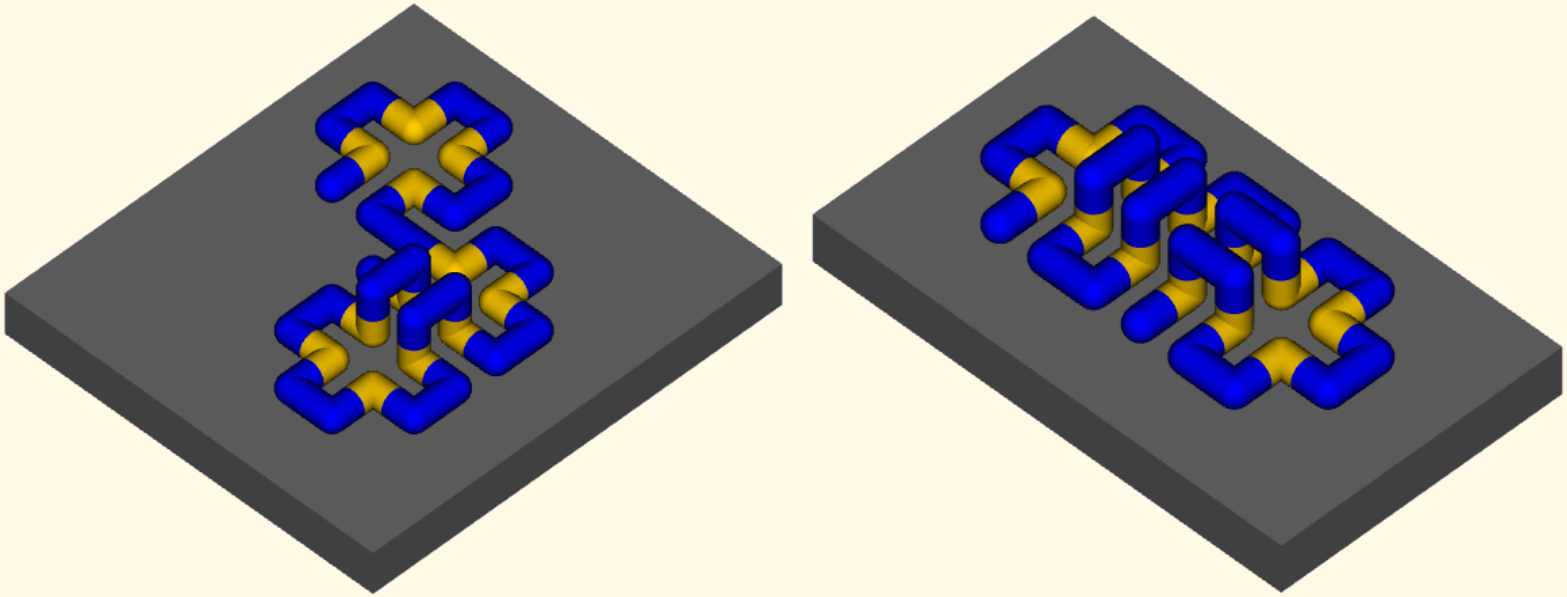
36-bead Peptide PHPPHP. . . PHP

Surface Attracts H&P Beads: DC and AC phases



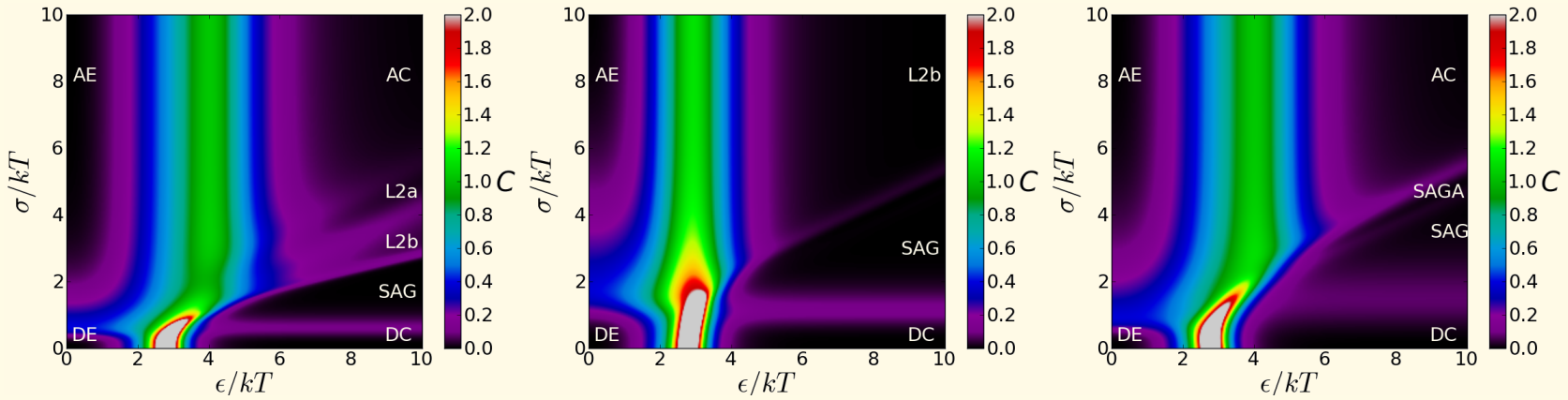
36-bead Peptide PHPPHP. . . PHP

Surface Attracts H&P Beads: L2a and L2b phases



Uniform Surface: Heat Capacities

H&P H P



- Native bulk state is cuboid with H inside, P outside.
- H&P: some P-bead flexibility, L2a, L2b phases.
- Fewer attractions (H,P) ⇒ stretched along σ axis.
- H: more P bead flexibility, L2b phase dominates.
- P: no L2 phases.

Adsorption on Patterned Surfaces

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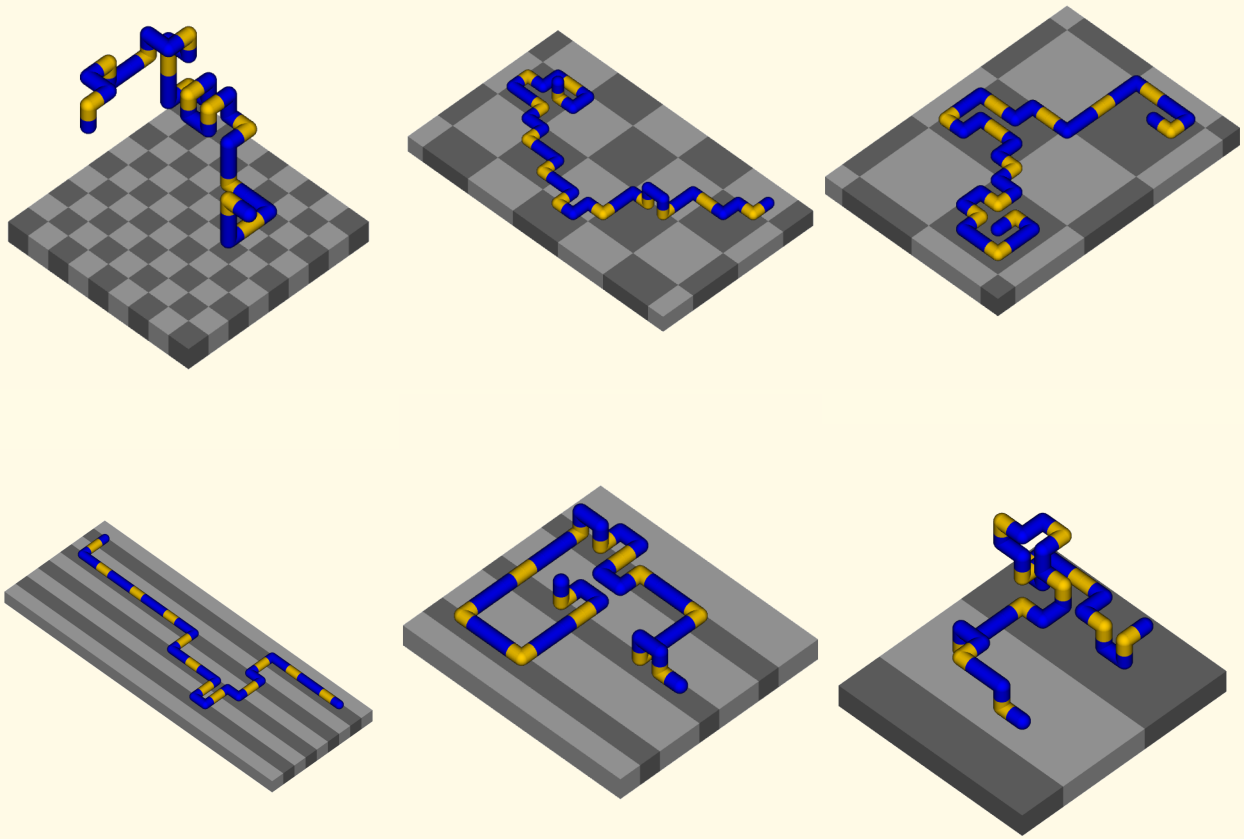
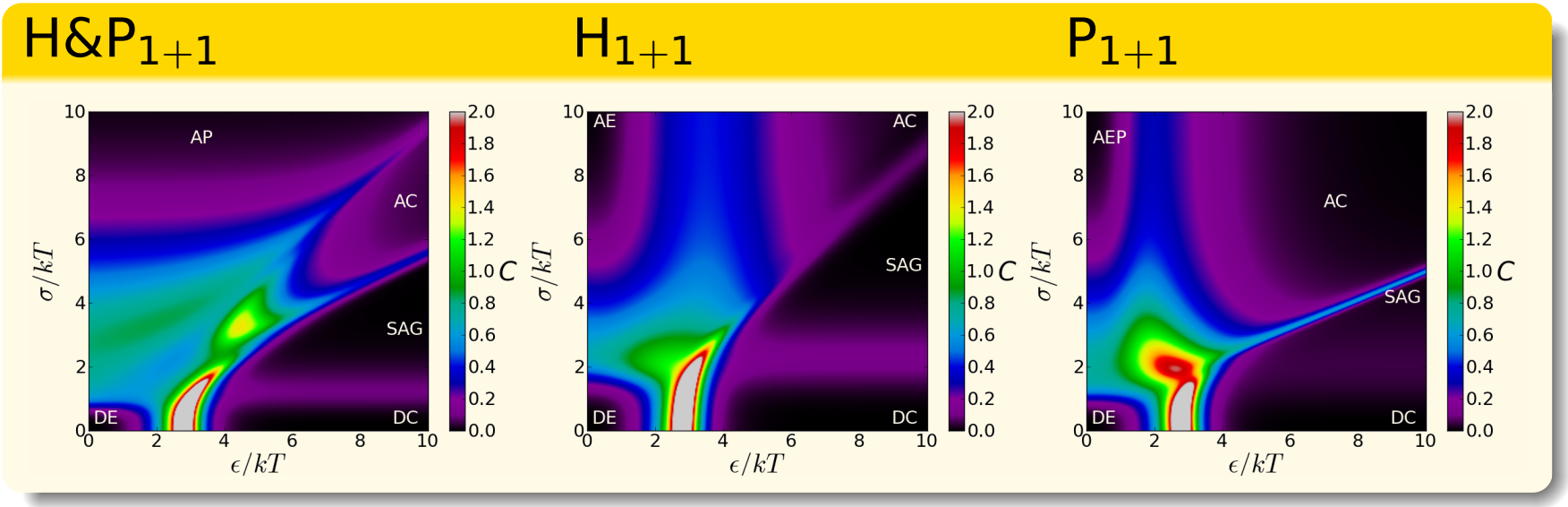
Checks and Stripes



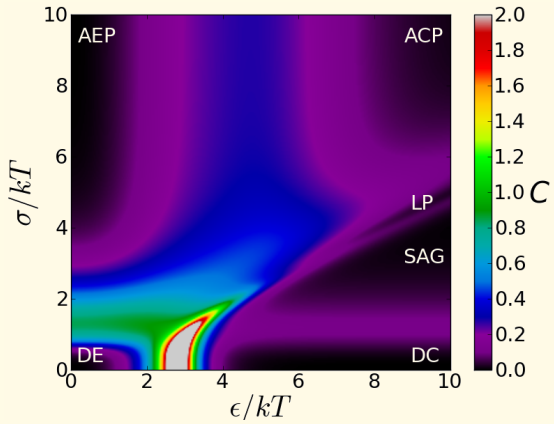
Narrow Stripes: Heat Capacities



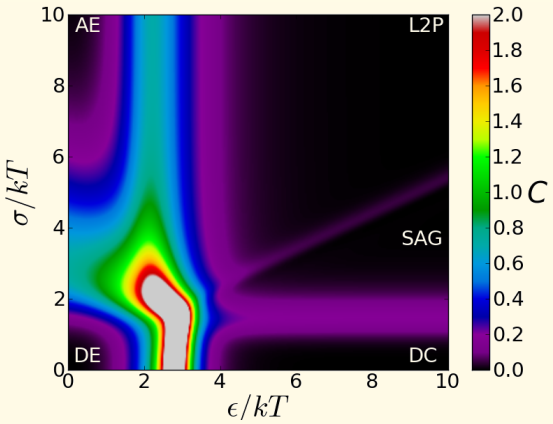
- Fewer attractions ⇒ stretched along σ axis.
- $H\&P_{1+1}$: in AP (patterned) phase all beads lie along one stripe; in AC phase, internal contacts compete, spans three stripes
- H_{1+1}: AE – AC transition does not change number of surface contacts; broad due to flexibility in P beads
- P_{1+1}: AC phase spans three stripes, AEP spans several.

Wider Stripes: Heat Capacities

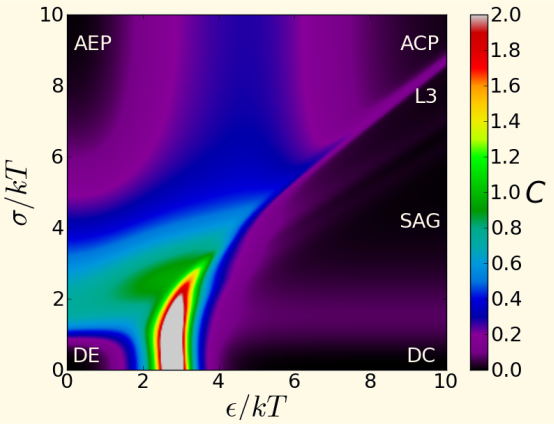
$H\&P_{2+2}$



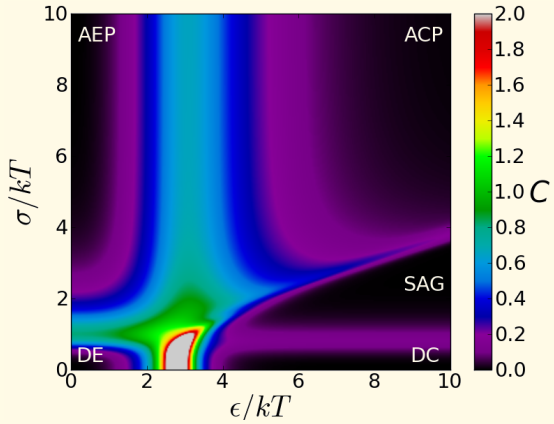
H_{2+2}



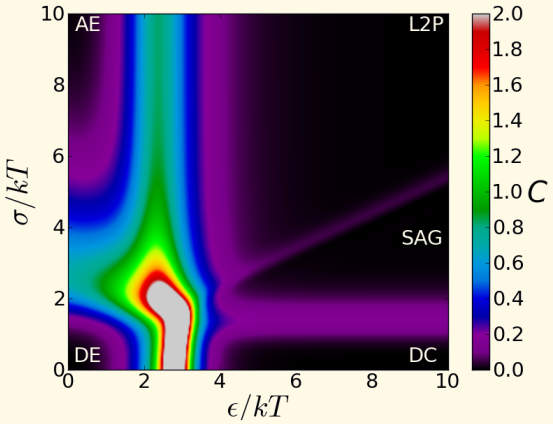
P_{2+2}



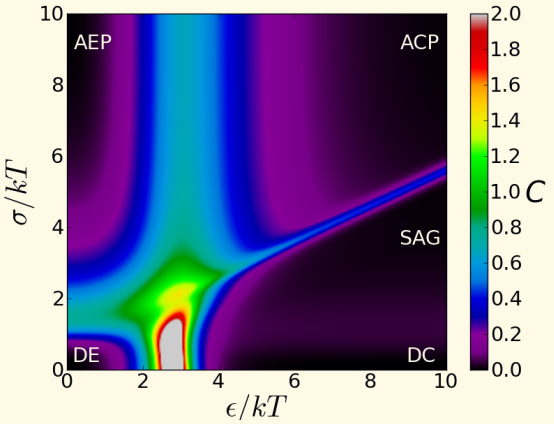
$H\&P_{3+3}$



H_{3+3}

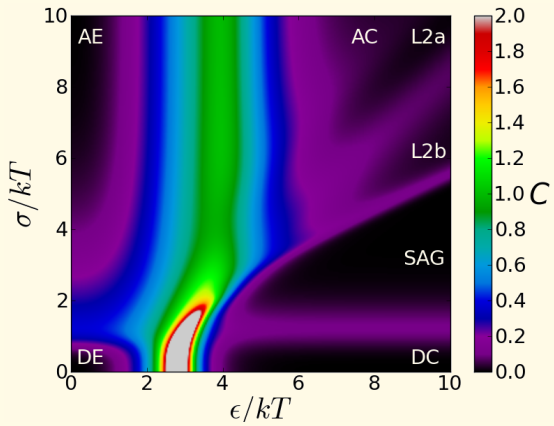


P_{3+3}

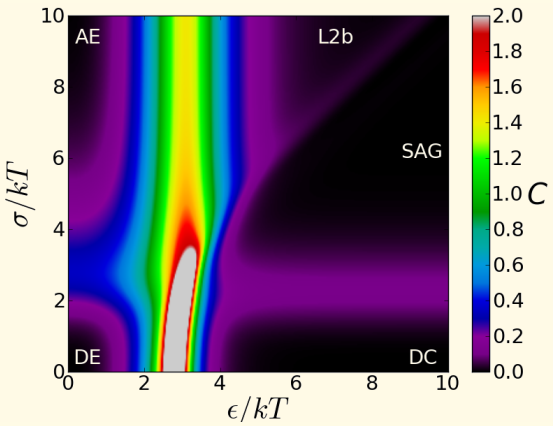


Checkerboard: Heat Capacities

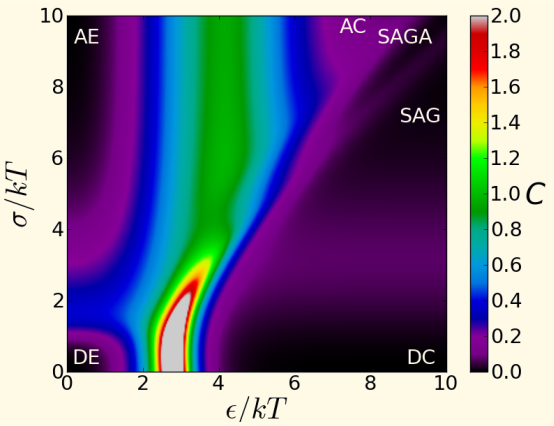
$H\&P_{1\times1}$



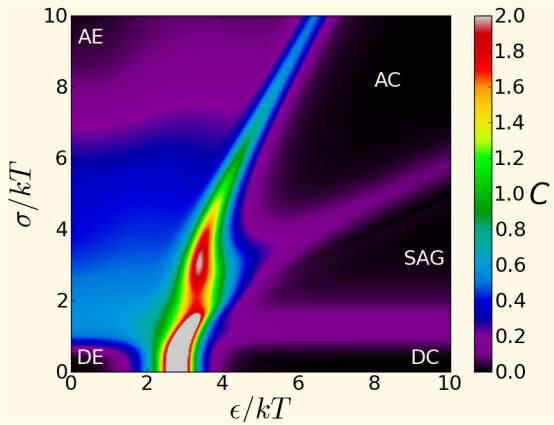
$H_{1\times1}$



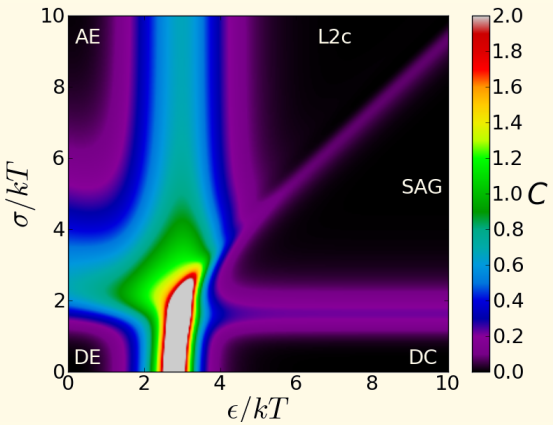
$P_{1\times1}$



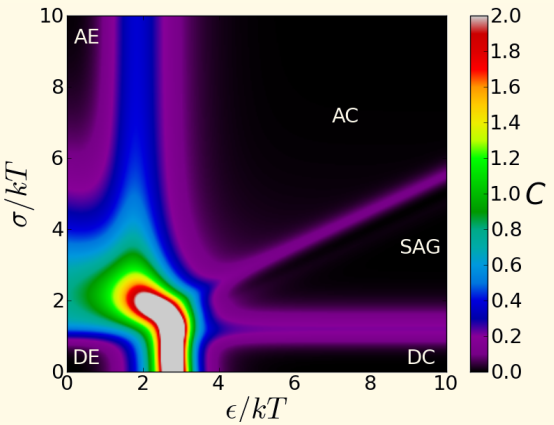
$H\&P_{2\times2}$



$H_{2\times2}$

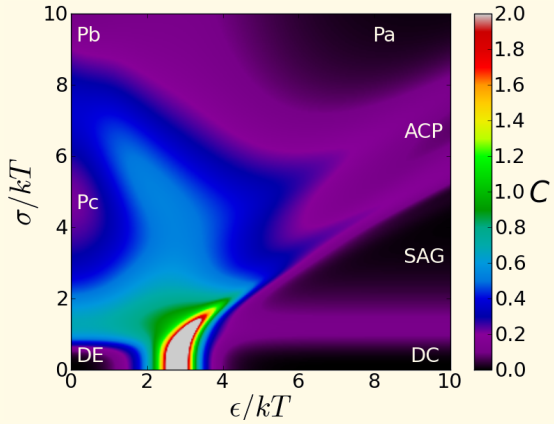


$P_{2\times2}$

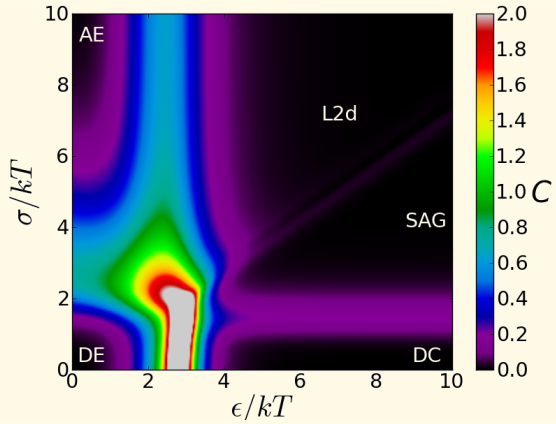


Checkerboard: Heat Capacities

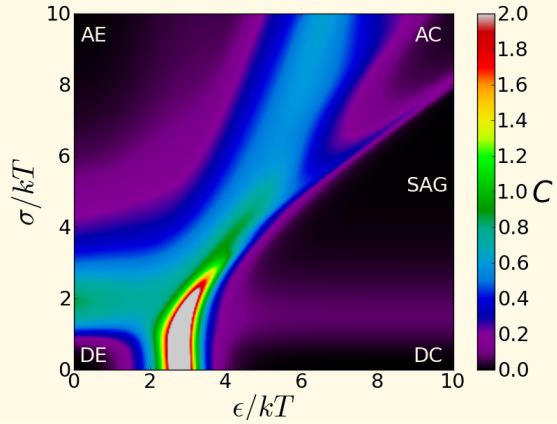
H&P$_{3\times3}$



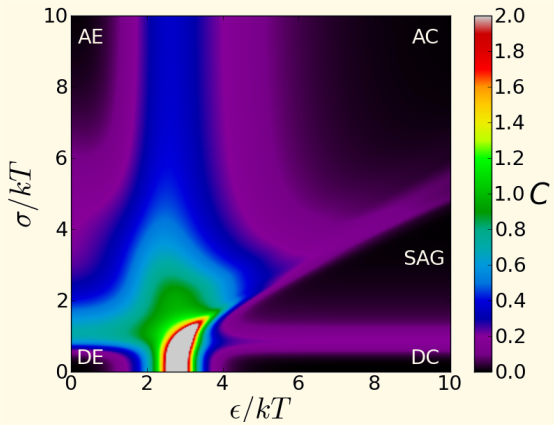
H$_{3\times3}$



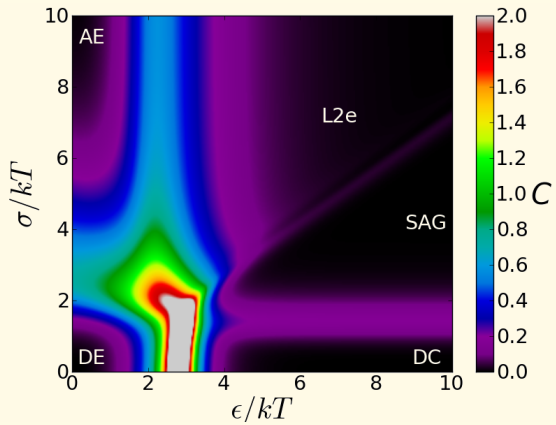
P$_{3\times3}$



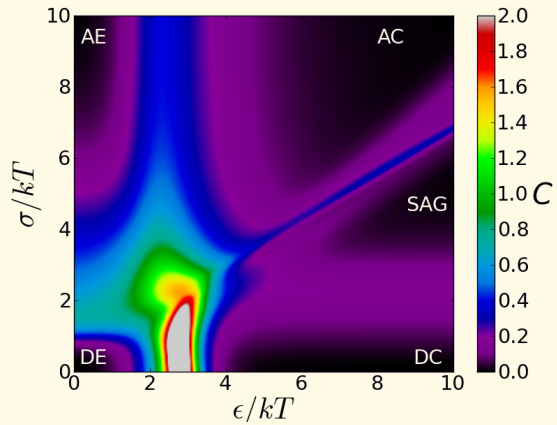
H&P$_{4\times4}$



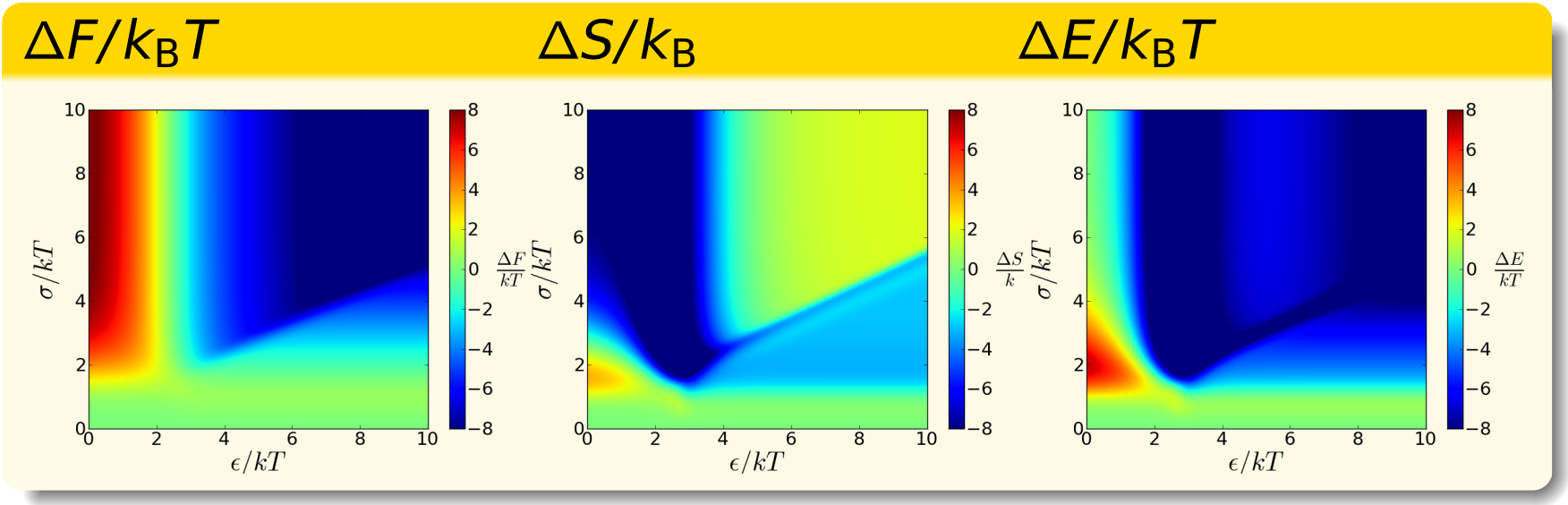
H$_{4\times4}$



P$_{4\times4}$

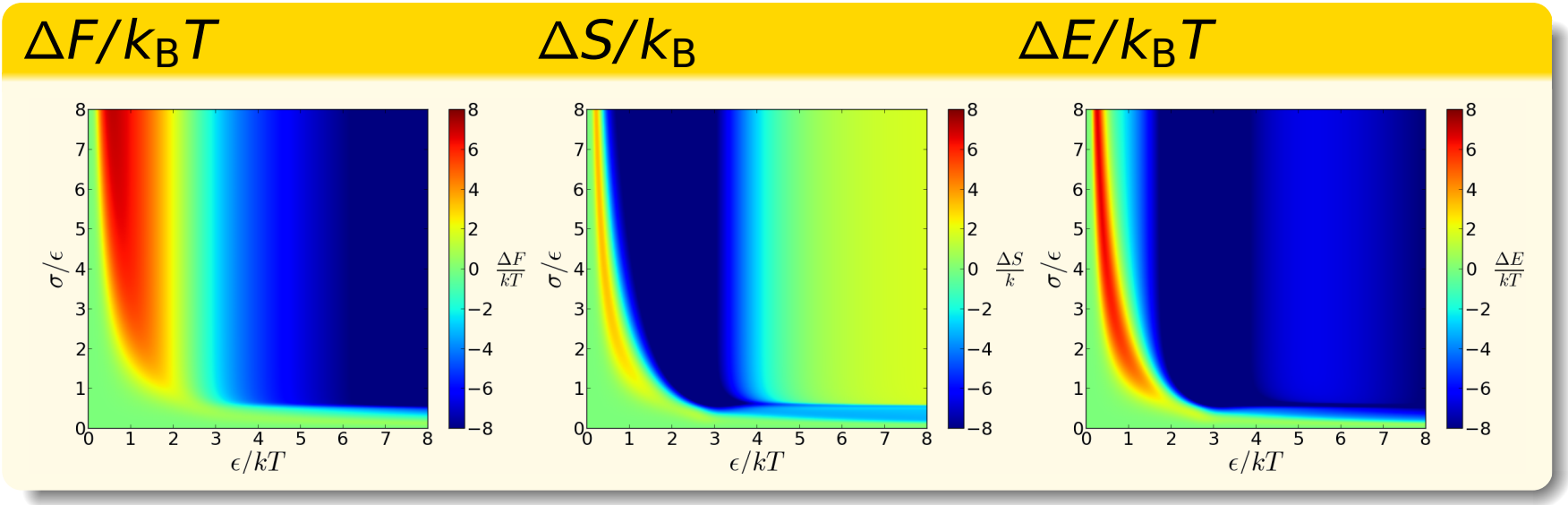


Checks $P_{2\times2}$ Relative to Stripes P_{3+3}



- Adsorbed expanded phase prefers Stripes P_{3+3}.
- Adsorbed compact phase prefers Checks $P_{2\times2}$.
- For $\sigma/\epsilon \gtrsim 1$ can switch preferred adsorption surface simply by varying T.

Checks $P_{2\times2}$ Relative to Stripes P_{3+3}



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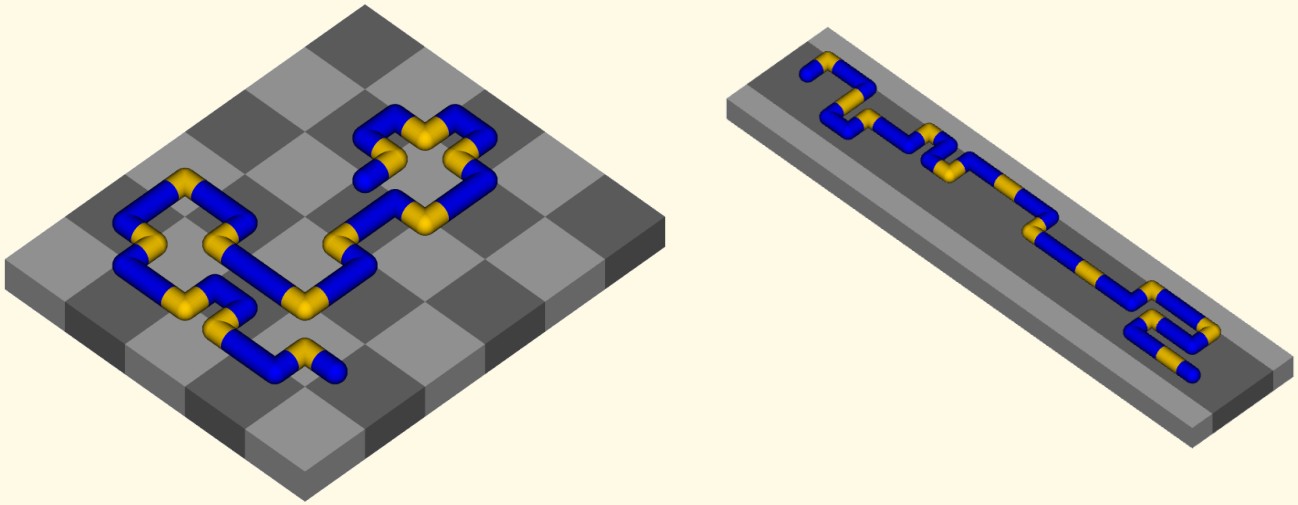
Checks $P_{2\times2}$ Relative to Stripes P_{3+3}

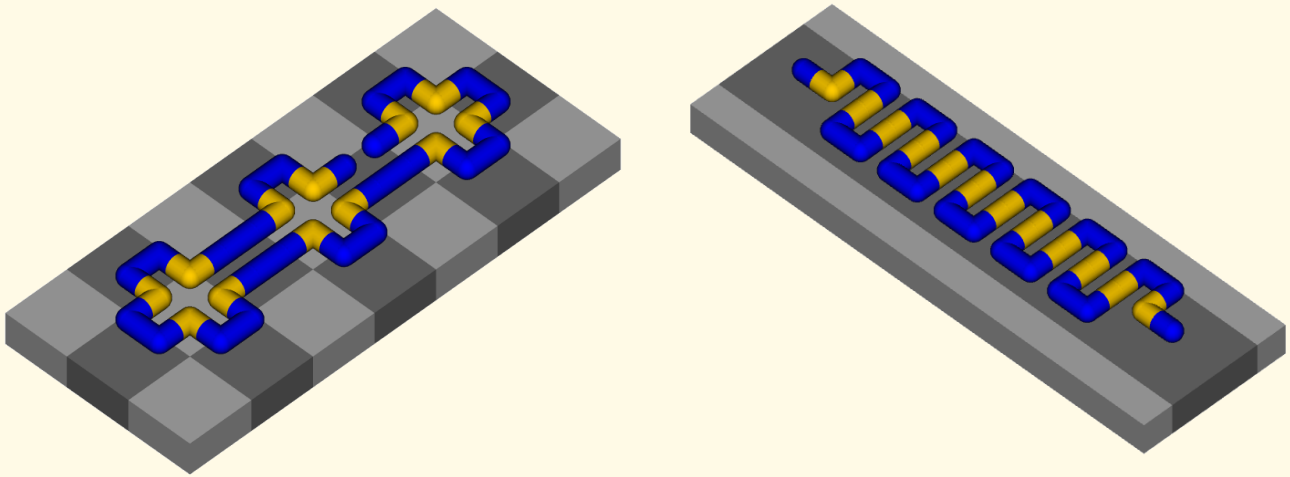
Adsorbed Expanded Configurations



In the expanded phase, on the checked surface, the peptide has lower entropy and similar energy compared with the striped surface.

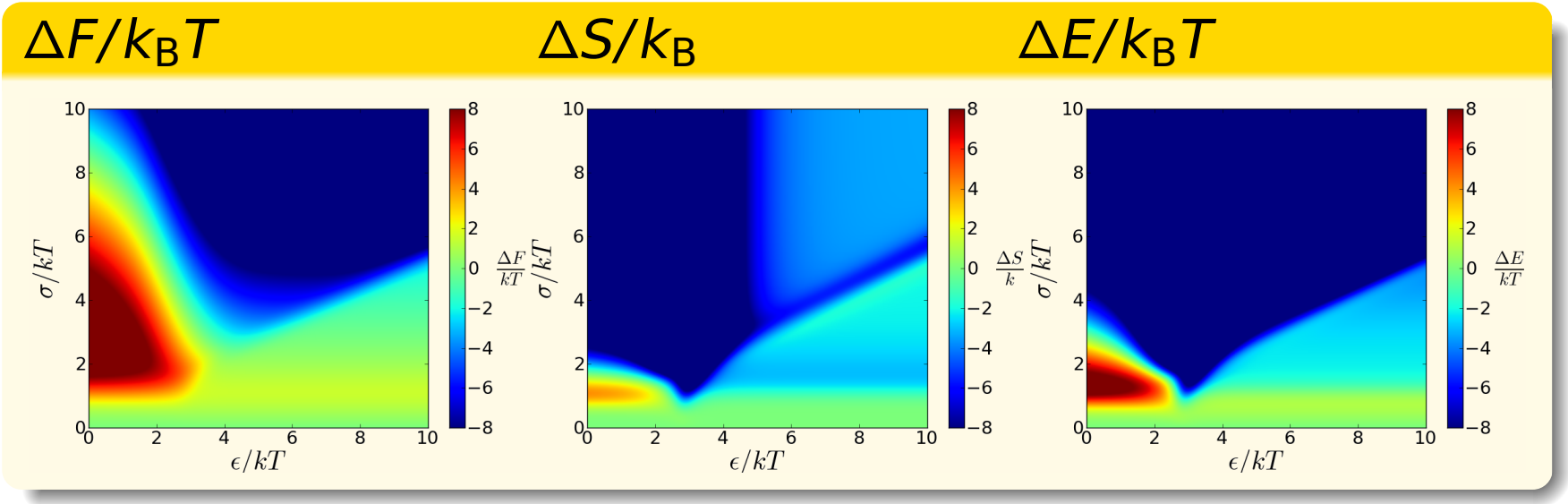
Checks $P_{2\times2}$ Relative to Stripes P_{3+3}

Adsorbed Compact Configurations



In the compact phase, on the checked surface, the peptide has similar entropy and lower energy compared with the striped surface.

Checks $P_{2\times2}$ Relative to Uniform P

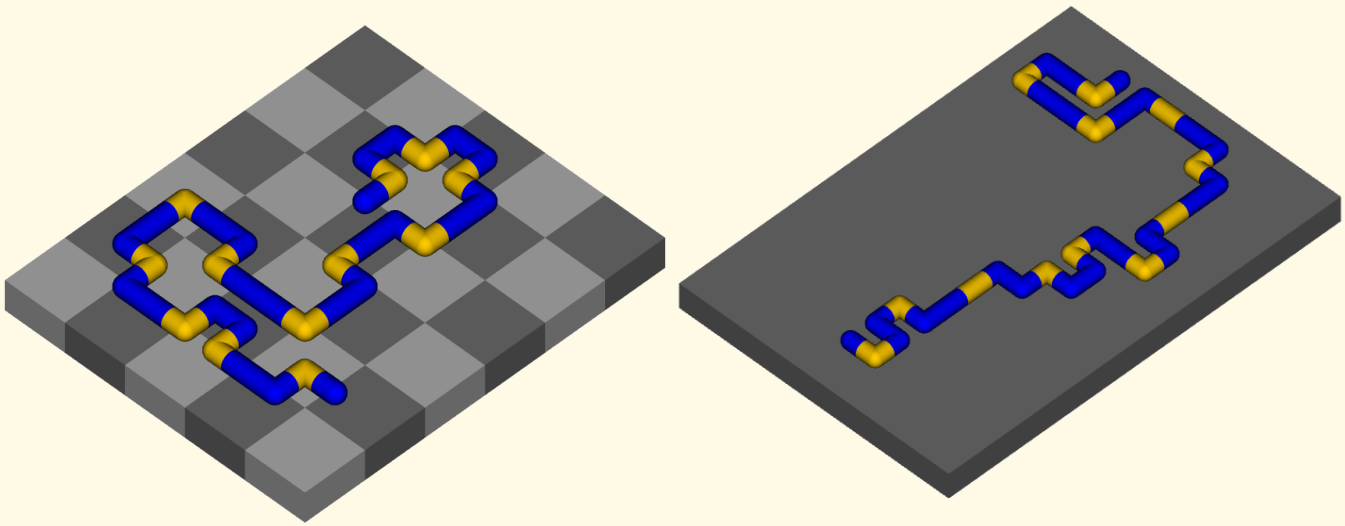


Uniform surface attraction reduced by a factor 0.9.

- Adsorbed expanded phase prefers Uniform P phase.
- Adsorbed compact phase prefers Checks $P_{2\times2}$.
- For $\sigma/\epsilon \gtrsim 0.6$ can switch preferred adsorption surface simply by varying T.

Checks $P_{2\times2}$ Relative to Uniform P

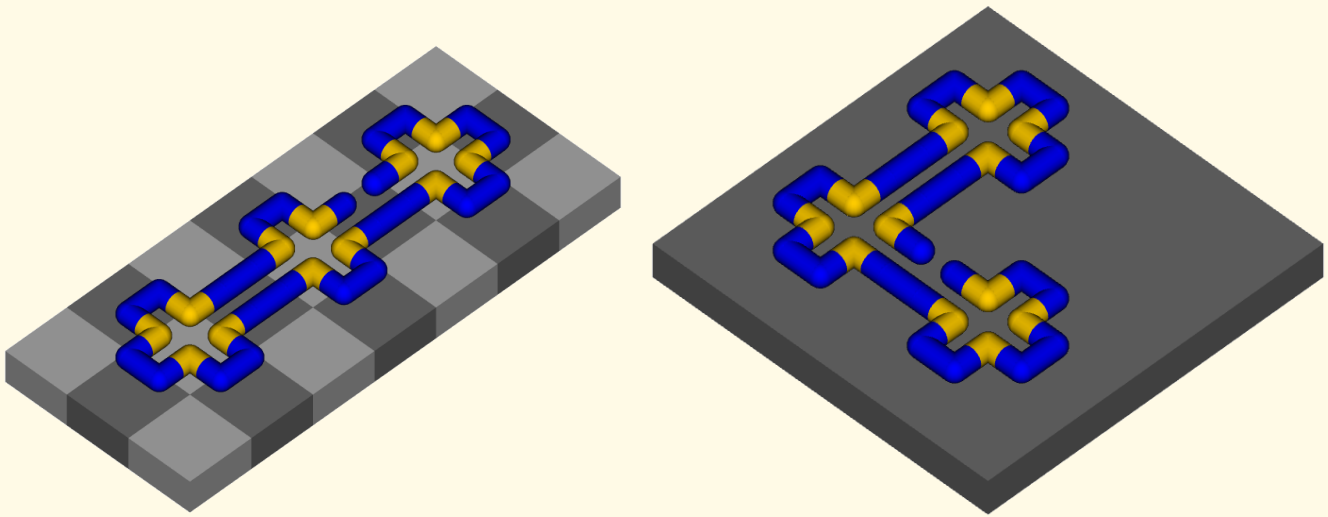
Adsorbed Configurations



In the expanded phase, on the checked surface, the peptide has much lower entropy and somewhat lower energy compared with the (weakened) uniform surface.

Checks $P_{2\times2}$ Relative to Uniform P

Adsorbed Configurations



In the compact phase, on the checked surface, the peptide has similar entropy and lower energy compared with the (weakened) uniform surface.

References

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