(Non)-Degenerate Ground States in the H–P model

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University of New Brunswick

Outline

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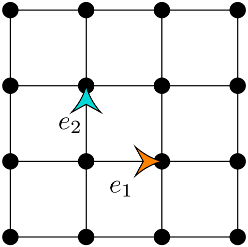
Lattices

Lattice

Given linearly independant vectors $B = \{ b_1 \dots b_d \}$ in $\mathbb{R}^d$, the *lattice*

$$L(B) := \{ \sum_{i=1}^{d} z_i b_i \mid z_i \in \mathbb{Z} \}$$



Lattice Graphs

Given l.i. $B \subset \mathbb{R}^d$, the *lattice graph*

$$G(B) = (L(B), \{ (p, q) : \|p - q\| = 1 \})$$

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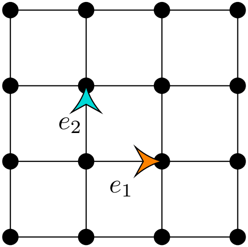

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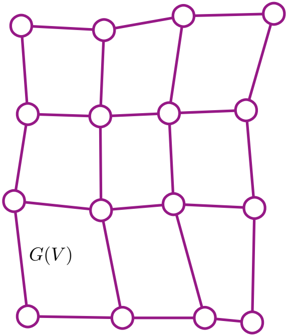

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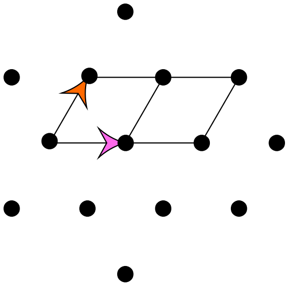

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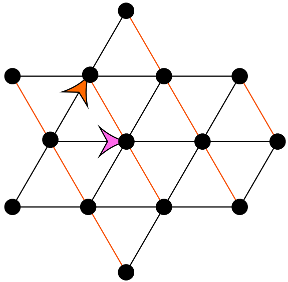


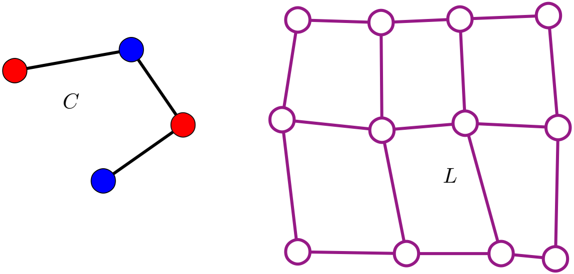
Lattice Models

Combinatorial Setting

Polymer A chain C (node sequence) with coloured (classified) nodes.

Lattice A vertex regular (sufficiently large) graph L.

Folding An embedding of C into L.



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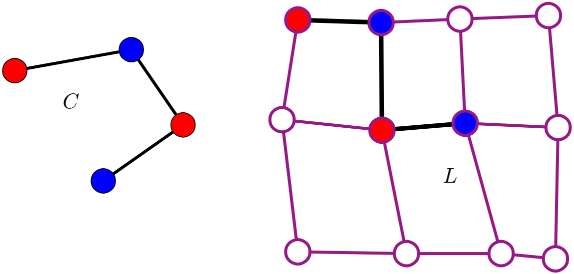

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Energy Model

Energy ϕ : embedding $\rightarrow \mathbb{R}$

Locality ϕ is usually a function of a small neighbourhood in L.

Optimality Minimum energy embeddings (*ground states*) are considered optimal.

Lattice Models: pro and contra

Pro

Physics is hard Global optimization models have $\Omega(3^n)$ local optima.

Chemistry is lattice-like Close packed proteins are crystal-like.

Thought Experiment Can a small subset of forces explain folding?

Contra

Discrete optimization is hard Computing optimal embeddings is NP-hard.

Approximation is rough Close energy $\not\Leftrightarrow$ close shape?

Lattice artifacts Crude approximation of shape. Parity. Chirality.

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What Lattice, What Energy function?

Lattice

2D square
: Some interest for ≤ 30 monomers

3D cubic
: Basic local structures (helix) are 3D.

2D triangular
: Solve parity problems

Energy Function

- Hydrophobic/Hydrophilic forces by far strongest
- Helical structures can be designed by using only hydrophobicity,
- β-sheets have few local interactions

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H–P model

Hydrophobic/Hydrophilic

- Hydrophobic (H) repels water
- Polar (Hydrophilic) (P) attracts water
- Model: H's attract each other and P's are neutral

Amino Acid	Code	Classification
Leucine	L	H
Serine	S	P
Glycine	G	H
Threonine	T	P
⋮	⋮	⋮

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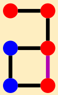

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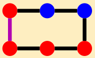

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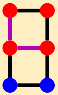

2 contacts

optimal Maximum number of contacts

stable/degenerate optimal embedding

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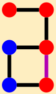

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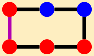

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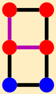

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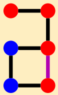

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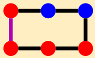

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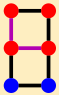


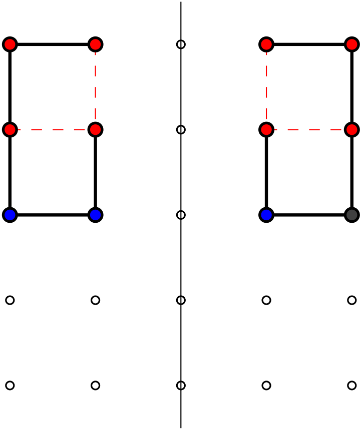
2 contacts

optimal Maximum number of contacts

unstable/degenerate Many optimal embeddings

What counts as "unique"?

- Most lattices have *isometries*, i.e. distance preserving transformations.
- Isometries preserve contacts.
- Counting contacts is oblivious to *chirality*



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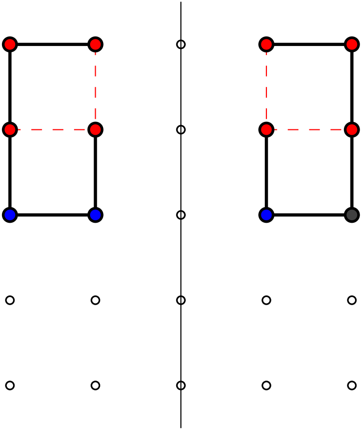

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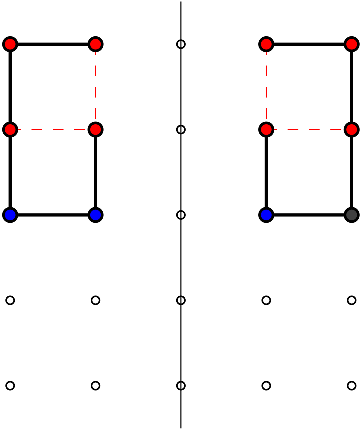

Computational Complexity of the H–P model

Algorithmic results

- NP-Complete for 3D (Berger & Leighton 1998)
- NP-Complete for 2D (Crescenzi et al., JCB 1998)
- 3/8-approximation for 3D and 1/4-approximation for 2D (Hart and Istrail, STOC 1995).

Fight hardness with more restricted problem?

- *H*-connected optimal embedding.
  - 3D NP-hard gadgets have this property
  - 2D gadgets do not
- Unique optimal embeddings
  - neither 2D nor 3D NP-hard gadgets are stable

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The Protein Folding "Paradoxes"

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There are an exponential number of foldings ("conformations"), but proteins fold quickly.

New Improved Protein Folding Paradox (1998)

Finding the optimal folding in the H–P model is NP-complete, but proteins still fold quickly.

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Why care about uniqueness?

Motivations

- An important property of real proteins
- Possible resolution to NP-hardness "paradox".
- "Sequence design: the hard part is uniqueness" (Dill et al., 1995)

Evidence

Experimental designed polymers have many optimal foldings

Algorithmic designing to fold to a shape is easy. (Kleinberg 1999)

Simulation machine designed H–P-polymers tend to collapse below design state (Yue et al. 1995)

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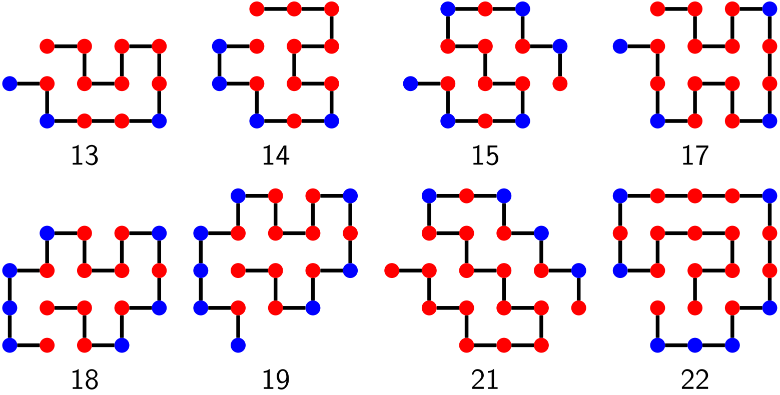
Simulation Results

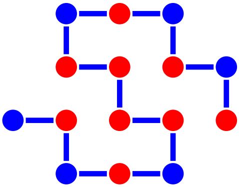
- About 2% of sequences up to length 18 length have unique optimal foldings



Outline

Terminology

- A pair of H nodes adjacent in an embedding, but not on the chain P, is called a *contact*
- *contact graph* $V =$ H nodes; $E =$ contacts
- The *conformation graph* consists of the edges of polymer P, along with the contacts.



embedding contacts conformation graph

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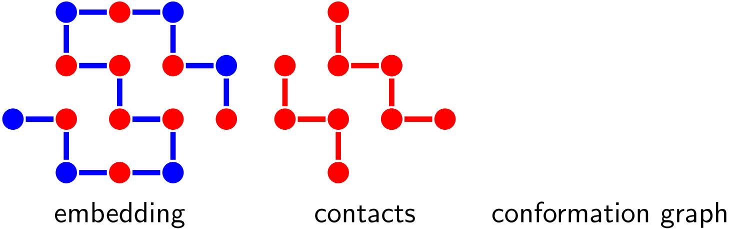

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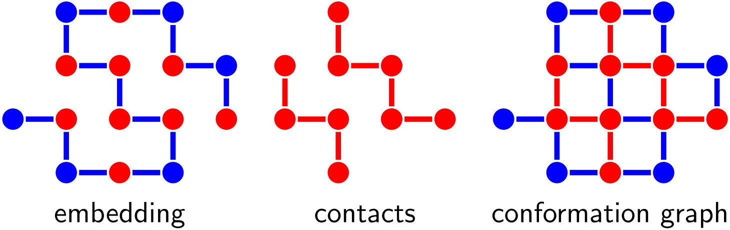
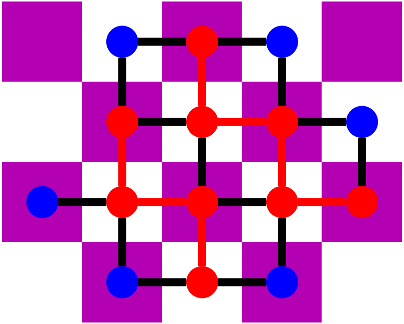


Parity and Lattice Graphs

Parity

Define the *parity* of lattice point $\sum z_i b_i$ as $\sum z_i \bmod 2$.



Bipartite Lattice Graphs

In the square and cubic lattice graphs:

- Every edge changes parity.
- Contacts exist only between H nodes of different parity.
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- The maximal contact graph of a closed chain consists of disjoint even cycles.

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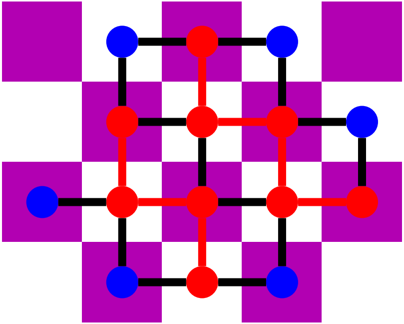

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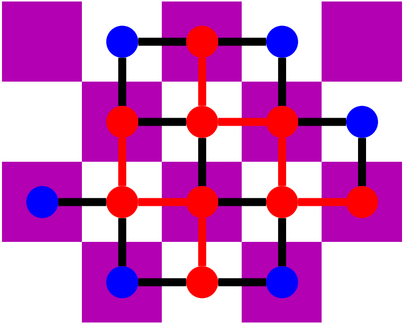

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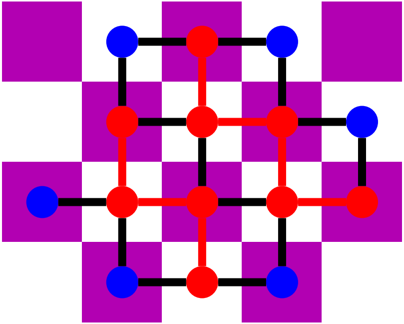

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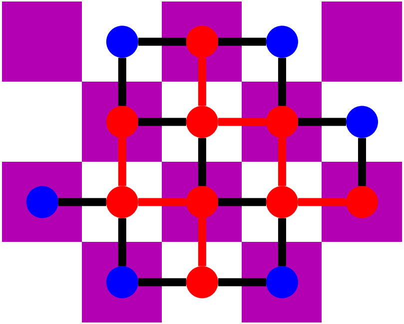

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- 2D square lattice
- open or closed chains
- Degenerate ground state ≡ many optimal embeddings

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Any embedding of P^k is optimal

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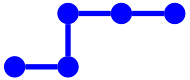

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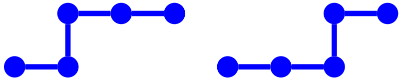

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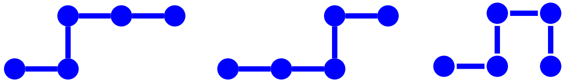
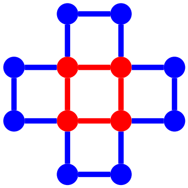


Fact

Any optimal embedding of the closed chain $(\text{PHP})^{4k}$ has a contact graph consisting of k four cycles.



Skip proof

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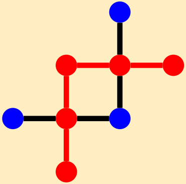

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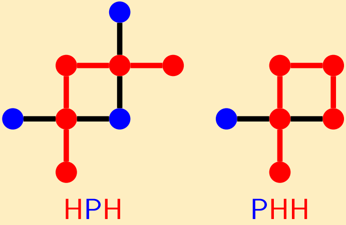

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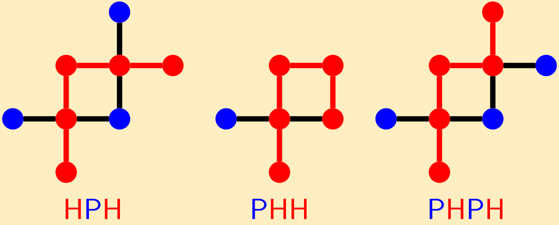

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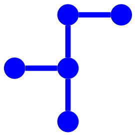
There are as many optimal embeddings of $(\mathrm{PHP})^{4k}$ *as there are (embeddings of) k-node lattice trees.*



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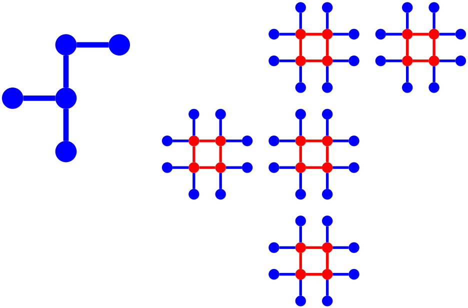

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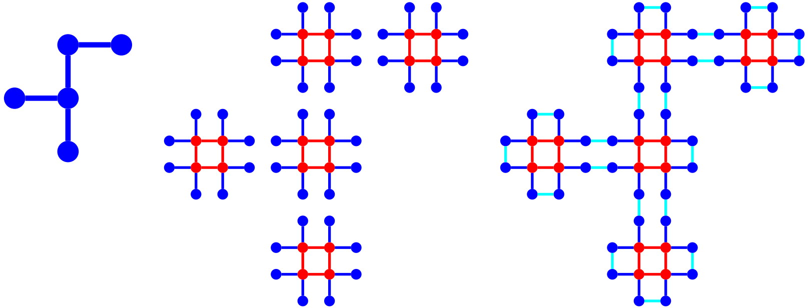
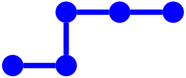


Fact (Stanley)

There are $\Omega((1+\sqrt{2})^k)$ embeddings of k-node lattice trees.



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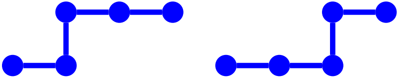

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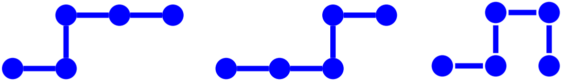

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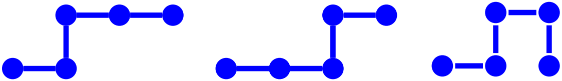
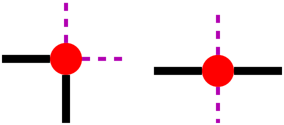


- and probably lots more $(\Omega\left(\frac{3.79^k}{k}\right))$

Outline

Missing Contacts and Perimeter



Missing Contact Neighbouring lattice point that is neither

- An H node
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Pseudocontacts H-H neighbours (on chain or otherwise). For a given chain, maximizing contacts is equivalent to

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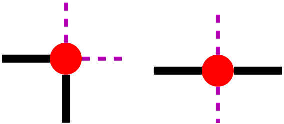

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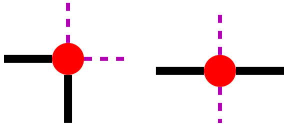

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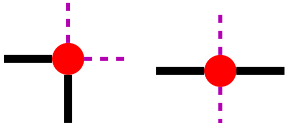

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Square Contact Graphs

Fact

A chain with s^2 H nodes embedded in the square lattice has at most $2s^2 - 2s$ pseudocontacts, and this is achieved exactly when H nodes are embedded in a $s \times s$ square grid.

$$\min 2x + 2y$$

subject to

$$x \cdot y \geq s^2$$
$$x \geq 1$$
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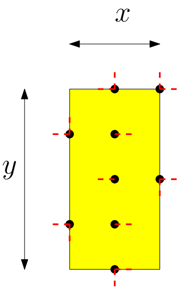

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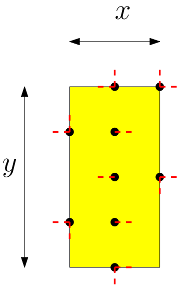

$$
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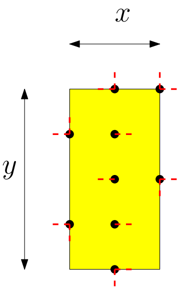

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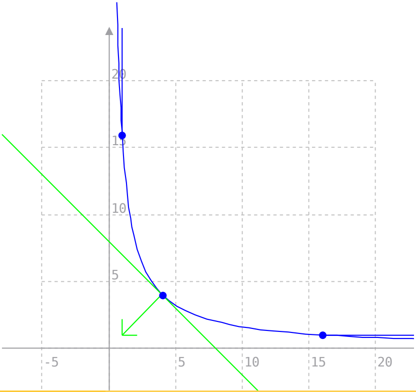
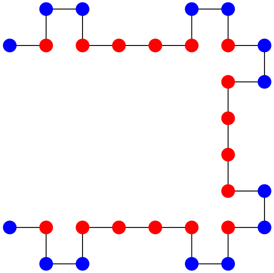


Uniquely achieving the $s \times s$ square

- Start by fixing the corners
- Make short loops of H nodes
- Repeat



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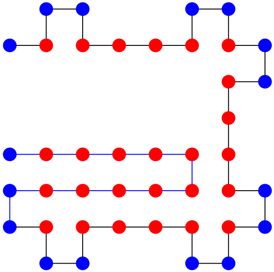

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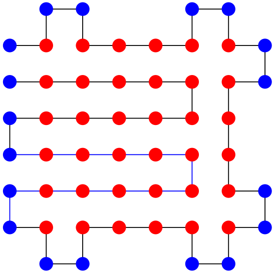
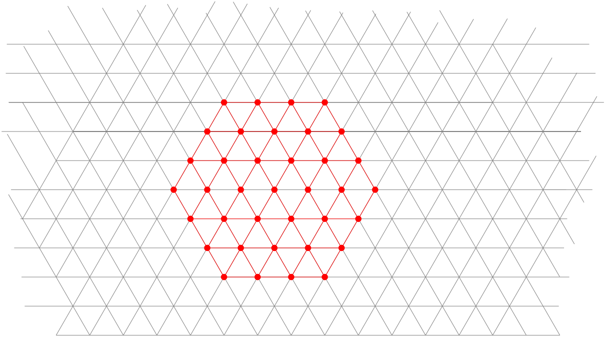


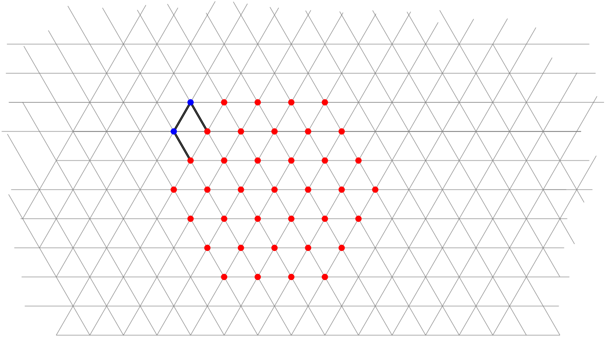
Hexagonal Contact Graphs

Fact

A chain $3s^2 - 3s + 1$ H nodes embedded in the triangular lattice has at most $9s^2 - 15s + 6$ pseudocontacts, and this is achieved exactly when the H nodes are embedded in a side-length s hexagonal grid.



Uniquely realizing the hexagon



- Sides can be fixed
- but with wiggle
- Wiggle can be fixed
- And the interior filled

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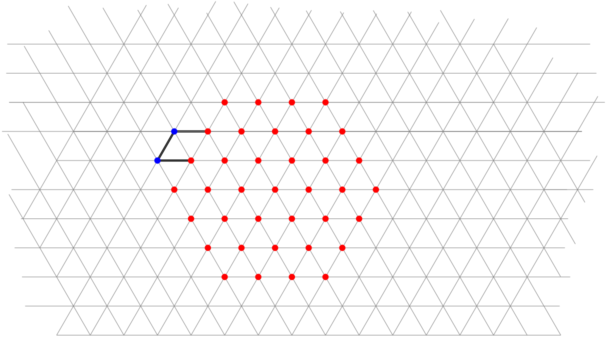

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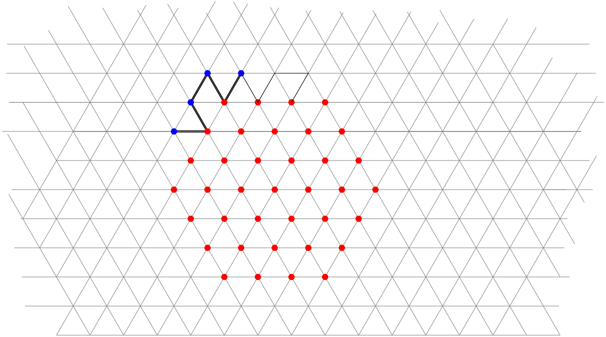

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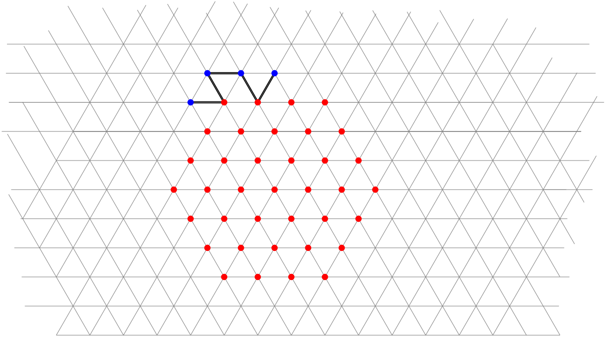

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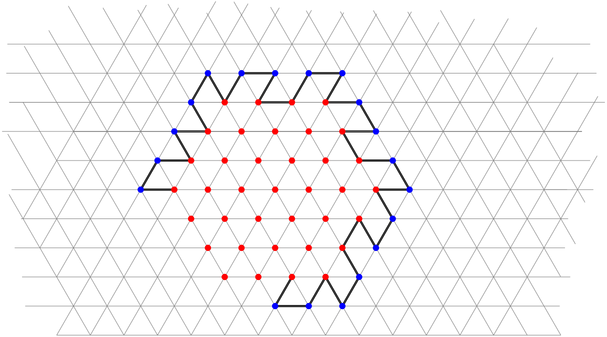

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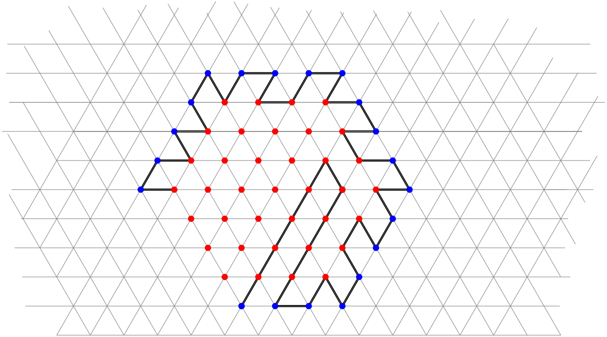

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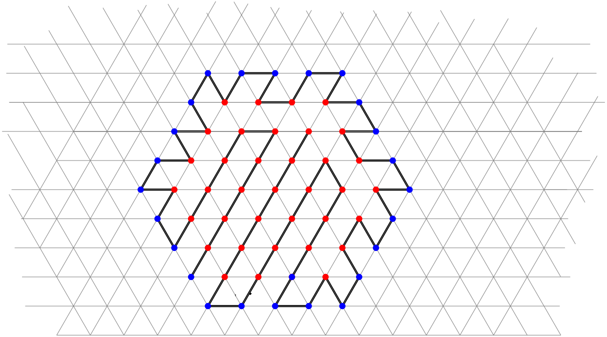

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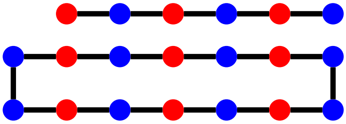
Outline

Closed Chain Examples

$$A_m = (\text{HP})^m$$

$$S_k = \text{P}\ A_{\lceil k/2 \rceil}\ \text{P}\ A_{\lfloor k/2 \rfloor}$$



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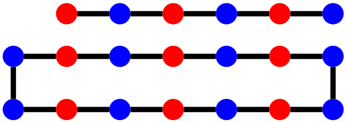
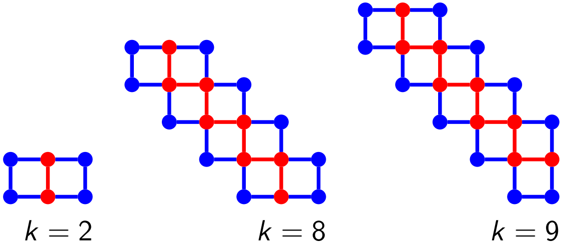
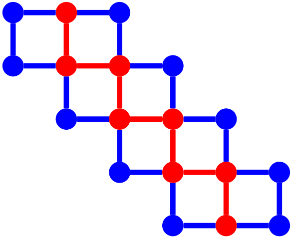




Observation

There exists an embedding of S_k with 2 missing contacts.



Corollary

In any optimal embedding of S_k, both monochrome edges are on the bounding box.

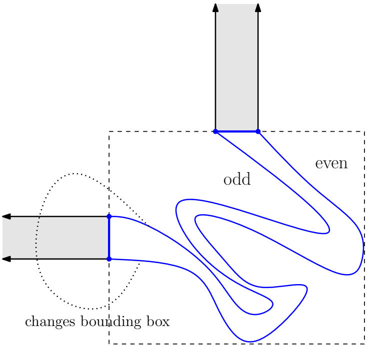
Internal and External Contacts

Definition

An exterior contact in an embedding of a closed chain C is one that does not subdivide the interior of C.

Lemma

There are no exterior contacts in an optimal embedding of S_k.



The conformation graph of S_k

Lemma

Over all optimal embeddings of S_k, the conformation graph is unique.

Theorem

There is a the unique optimal embedding (up to isometries) of S_k.

Proof.

Start with one of the four cycles, the embedding is forced. □

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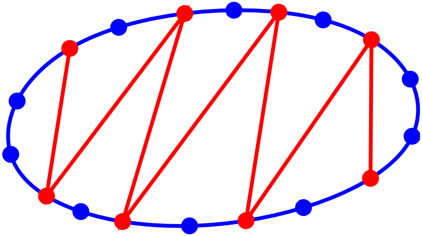

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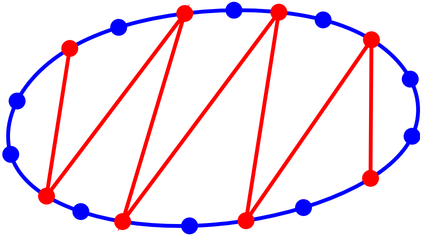

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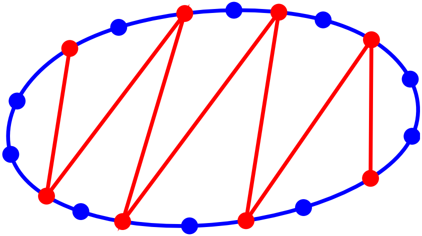

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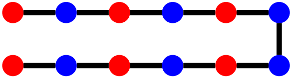

Theorem

Z_{2j} has a unique optimal embedding for all $j \geq 1$.

Skip proof

Proof.

(Sketch)

1. How can H nodes appear on the bounding box?
2. Both endpoints on the bounding box, and in contact.
3. The monochrome edge is on the bounding box.
4. The open case reduces to the closed case

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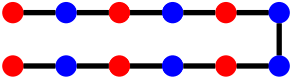

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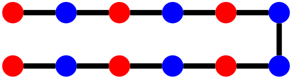

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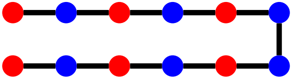

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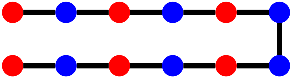

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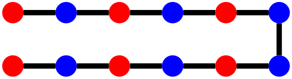

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Open and Closed Questions

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1. Do real proteins fold uniquely in the H–P model?
2. Asymptotically, what fraction of n-node H–P-sequences fold uniquely?
3. Is H–P sequence folding still NP-complete when restricted to “nice” sequences?

Not so open questions

- There exist stable H–P trees in $3D$.
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Credits

- Inspired by an article of Brian Hayes in American Scientist
- Initiated at a workshop on Molecular Reconfiguration organized by Godfried Toussaint.
- Non-globular examples with Oswin Aichholzer, Erik Demaine, Vera Sacristan and Mike Soss.
- Globular examples with Henk Meijer and Jit Bose