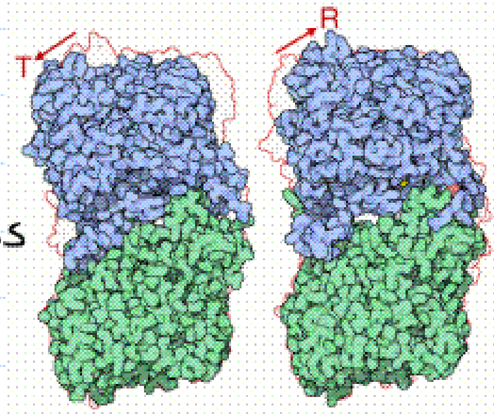
GCMB'07 Graph Rigidity for Modeling Allostery

Note Title 4/10/2007

Molecular Allostery

Glycogen phosphorylase



http://www.rcsb.org/pdb/static.do?p=education_discussion/molecule_of_the_month/pdb24_1.html

First-order rigidity of graphs

Laman conditions [L 70]

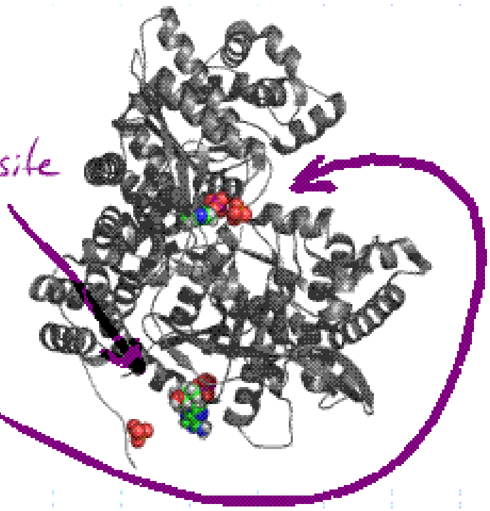
Pebble games [JH 95 & 97]

Applying to GP

Hydrogen bond strength

Allostery

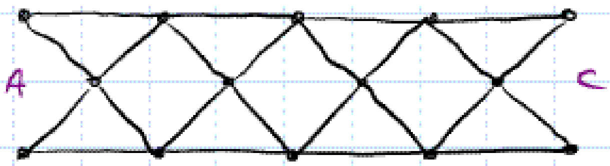
Binding a molecule at an allosteric site affects the ability to bind at another catalytic site



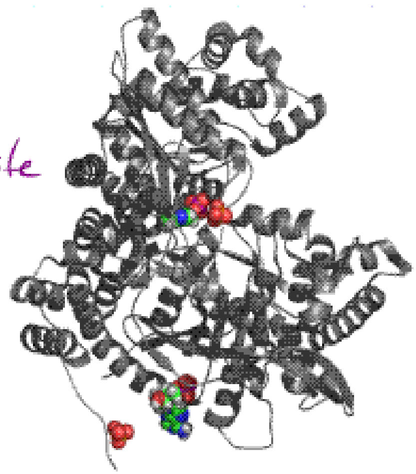
Is there a mechanical transmission that can explain allostery?

A 2-d example:

struts transmit 1 degree of freedom



Allostery



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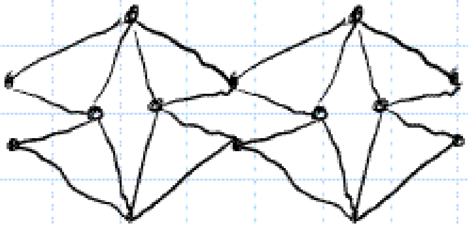
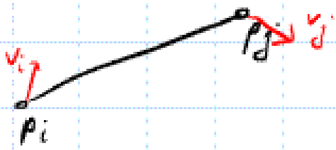


First-order Rigidity of Graphs

Let G be a graph with a straight-line embedding into R^d with vertices in general position.
Consider assigning a vector v_i to each vertex i such that $\forall (p_i, p_j) \in E,\ (p_i - p_j)\cdot(v_i - v_j) = 0$

Preserve length



$d(p_i+\epsilon v_i,\ p_j+\epsilon v_j) - \underline{d(p_i, p_j)}$

$(p_i - p_j + \epsilon(v_i - v_j))\cdot(\ )$ -

$\cancel{= (p_i - p_j)\cdot(p_i - p_j)}$

$= \cancel{(p_i - p_j)(p_i - p_j)} + 2\epsilon(p_i - p_j)(v_i - v_j) + \cancel{\epsilon^2 (v_i - v_j)(v_i - v_j)}$

$(p_i - p_j)(v_i - v_j) = 0$

First-order Rigidity of Graphs

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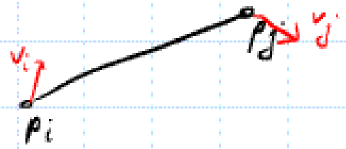


G is rigid iff the only assignments are rigid motions of R^d.

Actually, the rigidity of generic embeddings is a property of the graph – e.g. all triangles are rigid.

Degree of Freedom Counting

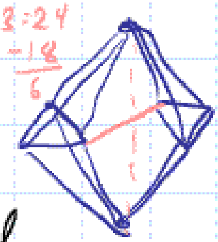
For a graph G with v vertices & e edges

	2d	3d
Vertices have	$2v$ dof	$3v$ dof
Edges remove	$-\ e$ dof	$-\ e$ dof
R^d has	3 dof	dof

$2v - e = 3$ for rigid $\qquad 3v - e = 6$ for rigid

Degree of Freedom Counting

$8 \cdot 3 = 24$
-18
6



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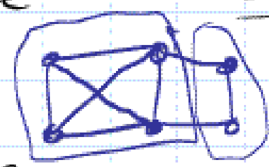


$9 = 12 - 3$ ✓

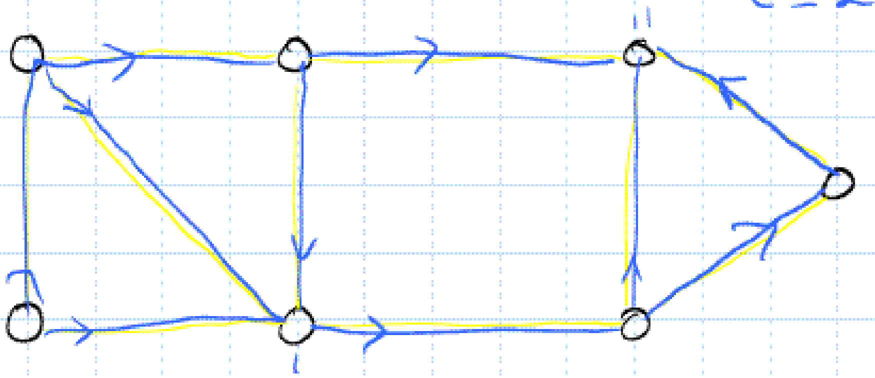
Laman [70] G is minimally rigid in 2d iff
$e = 2v - 3$ and any vertex-induced subgraph
(V', E') with $|V'| \geq 2$ satisfies $|E'| \leq 2|V'| - 3$.

Equivalent condition in R^3, $e \leq 3v - 6$, is necessary, but not sufficient.

A Pebble Game to verify Laman's condition (2D)

Every vertex has two pebbles it can place on edges
Every edge has a pebble.
To add edge (i, j), first draw four pebbles to p_i, p_j.

$e \leq 2v - 3$

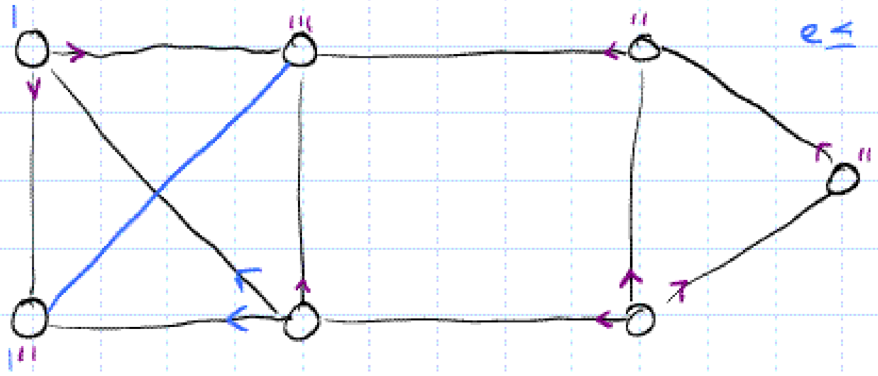


A Pebble Game to verify Laman's condition (3D)

Every vertex has ~~two~~ three pebbles it can place on edges

Every edge has a pebble.

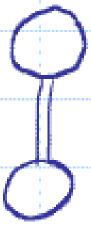
To add edge (i,j), first draw ~~four~~ six pebbles to p_i, p_j,
and one to each neighbor of p_i, p_j in turn



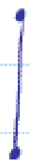
$e \le 3v-6$

Allostery: Molecules → rigid frameworks

atoms joined by bonds



ball joints connected by struts



vertices joined by edges

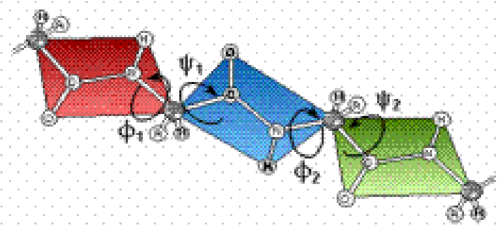
strong

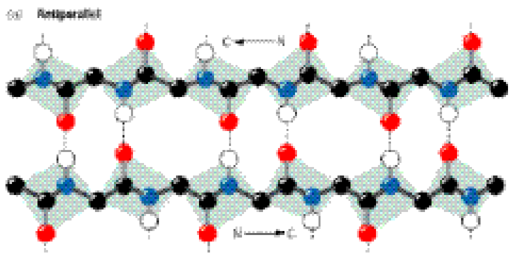
peptide bonds
- angle rotations, so add struts

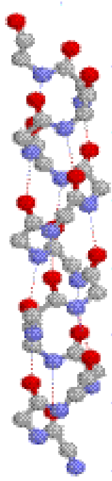
disulfide bonds

hydrogen bonds

weak

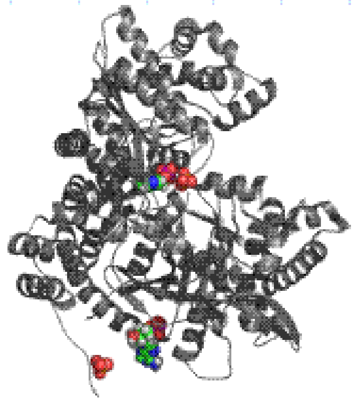






Testing Allostery

1. Add edges for bonds to G
2. Test dof at
   catalytic site #
3. Add bonds to
   allosteric site A
4. Re-test dof at
   catalytic site #



Do this for all bond strengths