

# *Rigidity, Flexibility, and Motion in Biomolecules*

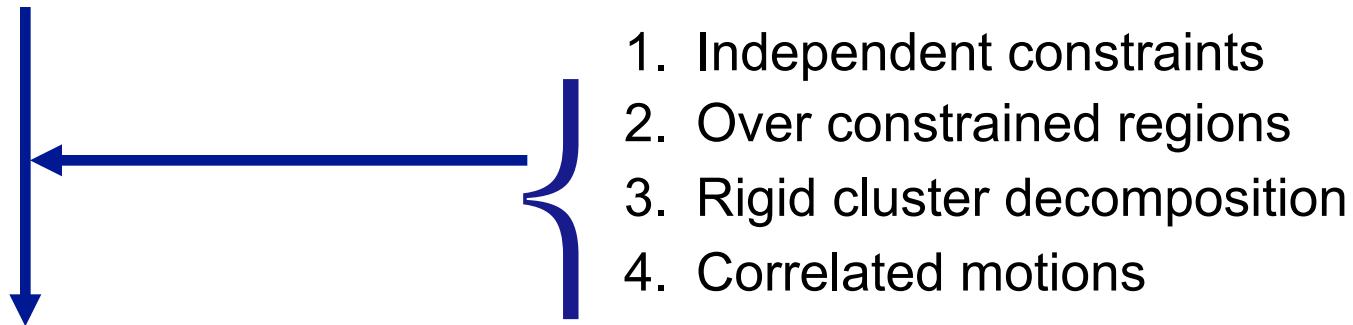
## *Workshop 2006*

## **FIRST: A Look Under The Hood**

**By Don J. Jacobs**

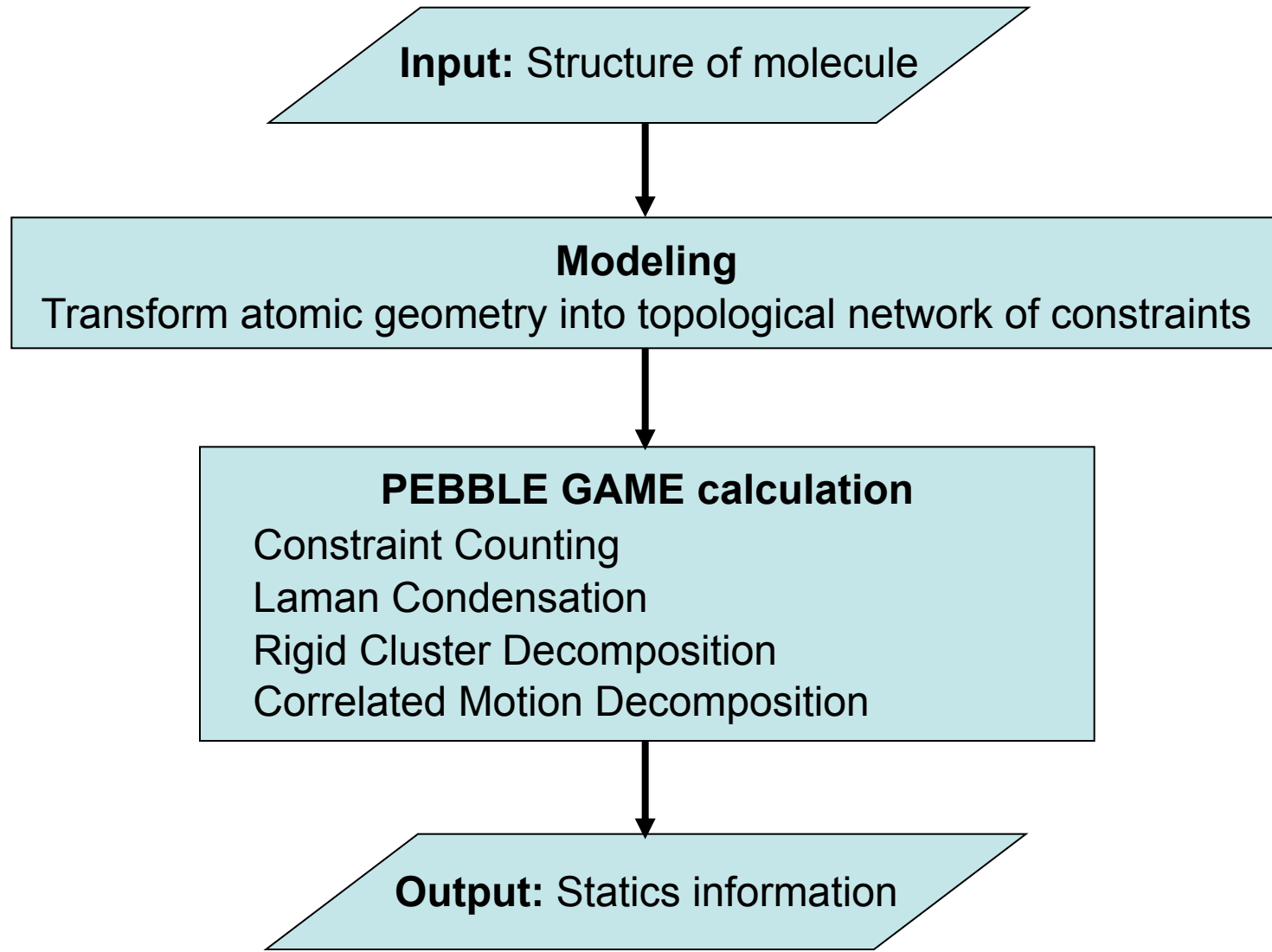
Physics and Optical Science, University of North Carolina at Charlotte

FIRST(biomolecular structure) → Detailed mechanical information



**Floppy Inclusion and Rigid Substructure Topography**

# FIRST Workflow Schematic



# Input Biomolecular structures and Modeling

Input structure

Modeling

Pebble game

Constraint counting

Laman Condensation

Rigid Cluster Decomposition

Correlated Motion Decomposition

Output

X,Y,Z coordinates of **all** atoms

Use **empirical** rules to convert geometrical information to a topological **body-bar** network.

**List of microscopic interactions to consider**

- Covalent bonding
- Hydrogen bonding and Salt bridges
- Torsion forces
- Hydrophobic interactions
- Metallic interactions
- Solvent interactions
- van der Waals interactions

# Input Biomolecular structures and Modeling

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Output

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Use **empirical** rules to convert geometrical information to a topological **body-bar** network.

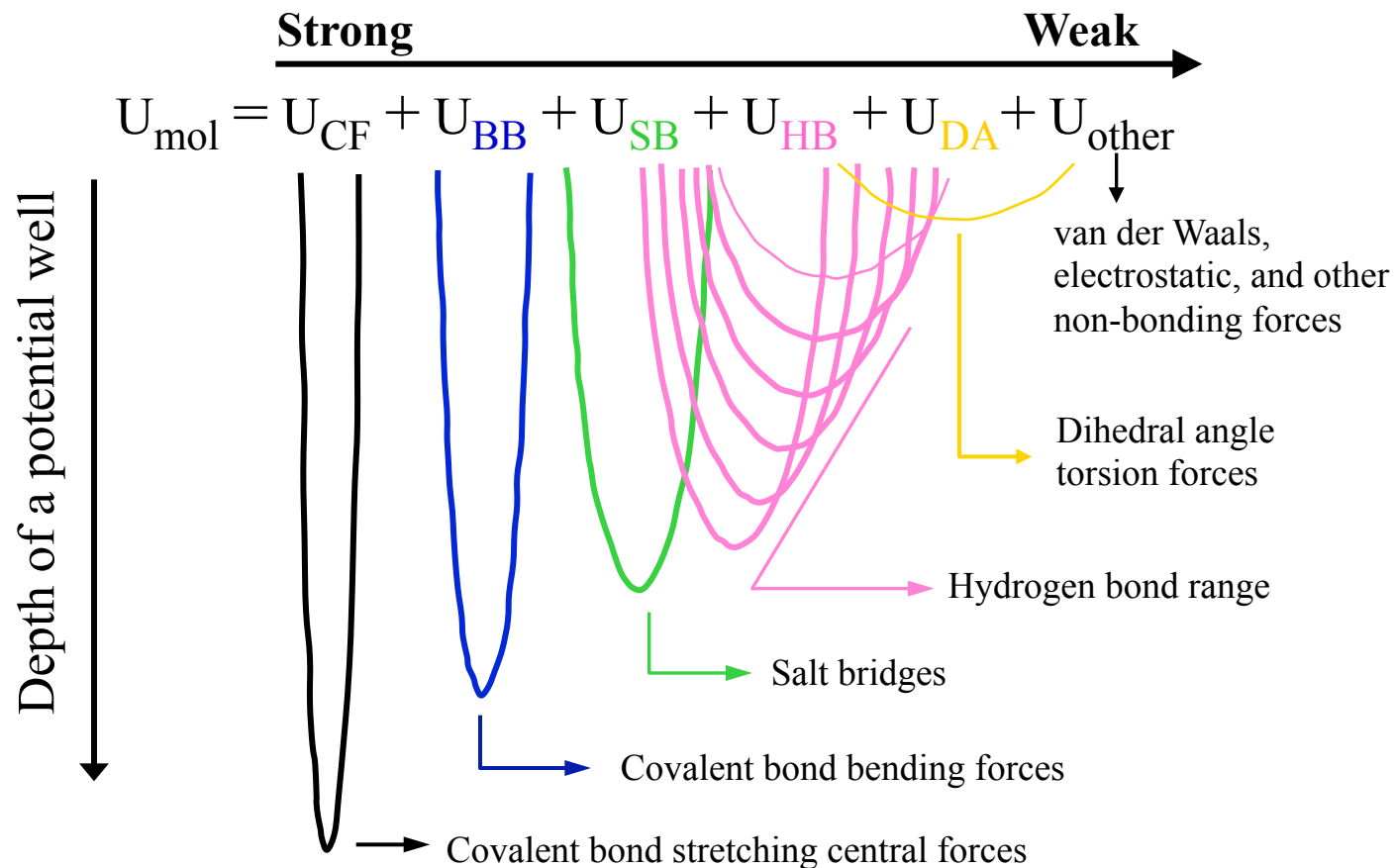
## List of microscopic interactions in FIRST

- Covalent bonding
- Hydrogen bonding and Salt bridges
- Torsion forces
- Hydrophobic interactions
- Metallic interactions
- Other (user defined)

# Modeling Interactions as Constraints

## A Tricky Business

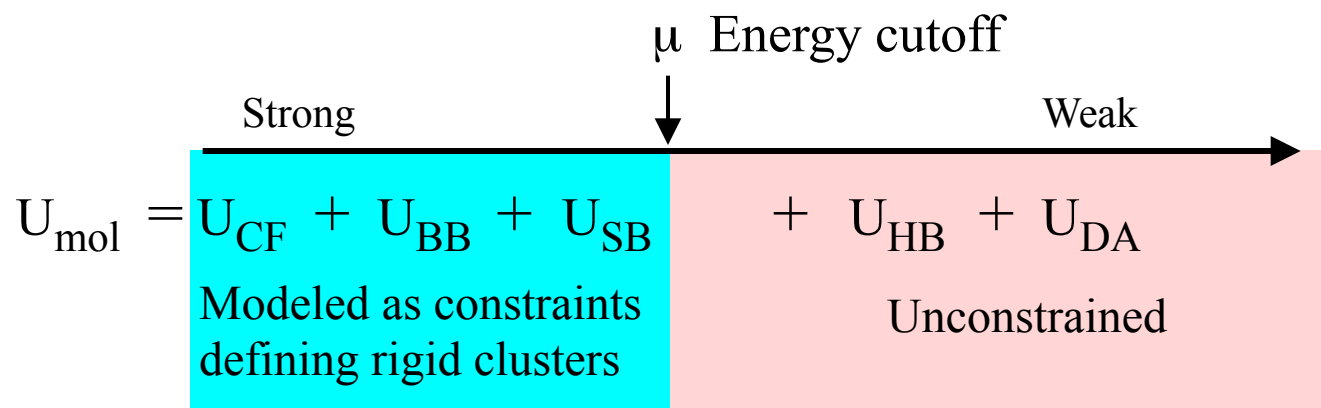
Schematic Microscopic Interaction **Strength** Scale



Jacobs, Kuhn and Thorpe, ***Flexible and rigid regions in proteins***, p357-384  
in *Rigidity Theory and Applications* (1999) Eds. Thorpe & Duxbury

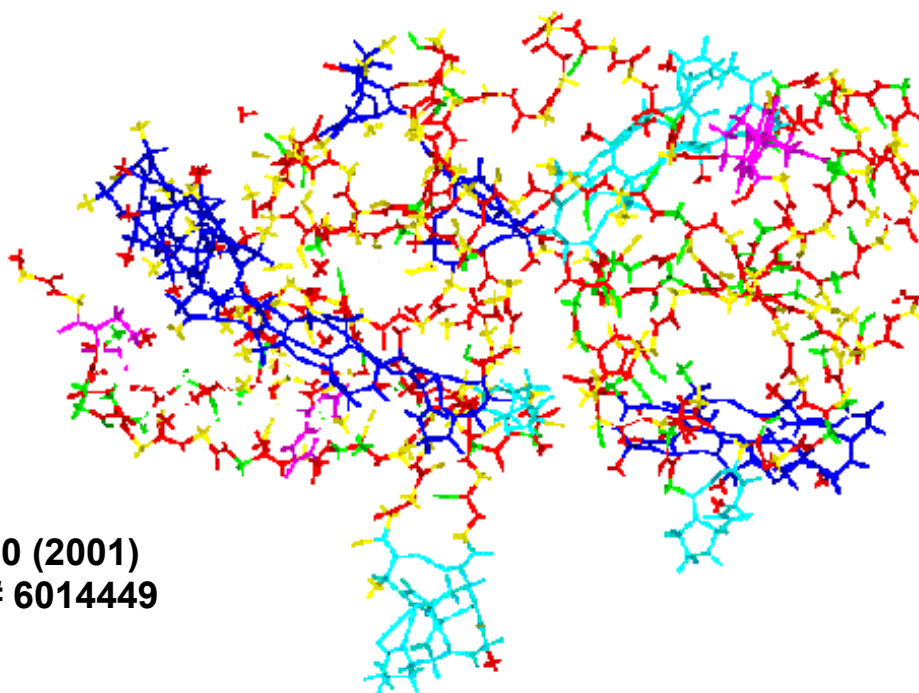
# Network Rigidity: Applied to Proteins

To be or not to be a constraint?



$$\mu = -1.8 \text{ Kcal/mol}$$

246 hydrogen bonds  
modeled as a  
constraint



Jacobs, et. al., Proteins 44, 150 (2001)  
Jacobs & Thorpe, US Patent # 6014449



# Network Rigidity: Applied to Proteins

To be or not to be a constraint?

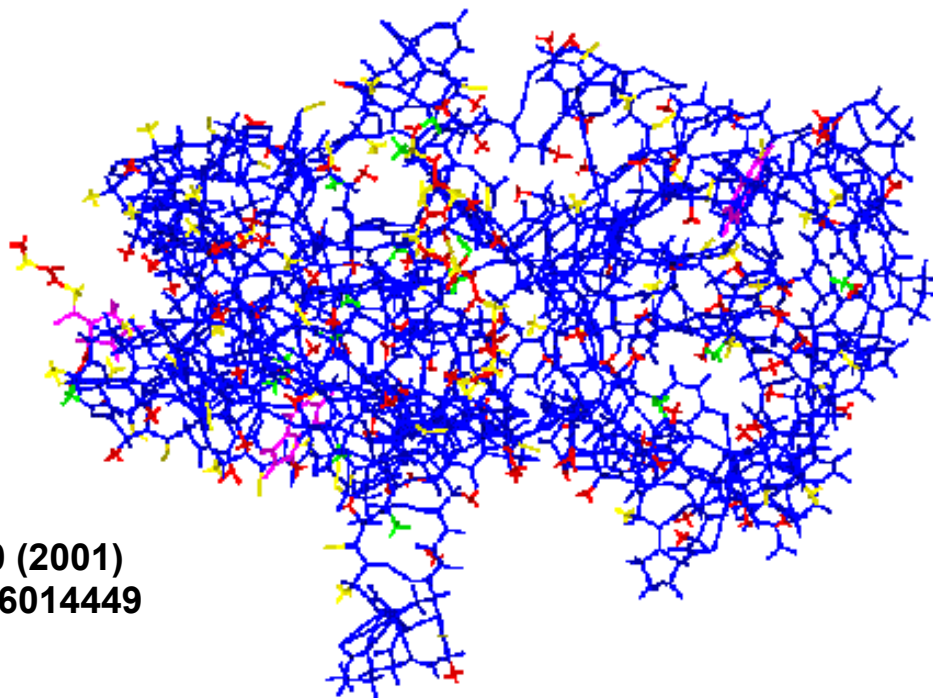
$\mu$  Energy cutoff  
↓  
Strong ← → Weak

$$U_{\text{mol}} = U_{\text{CF}} + U_{\text{BB}} + U_{\text{SB}} + U_{\text{HB}} + U_{\text{DA}}$$

Modeled as constraints defining rigid clusters      Unconstrained

$$\mu = -0.01 \text{ Kcal/mol}$$

461 hydrogen bonds modeled as a constraint



Jacobs, et. al., Proteins 44, 150 (2001)  
Jacobs & Thorpe, US Patent # 6014449



# Modeling Covalent Bonds

Input structure

**Modeling**

Pebble game

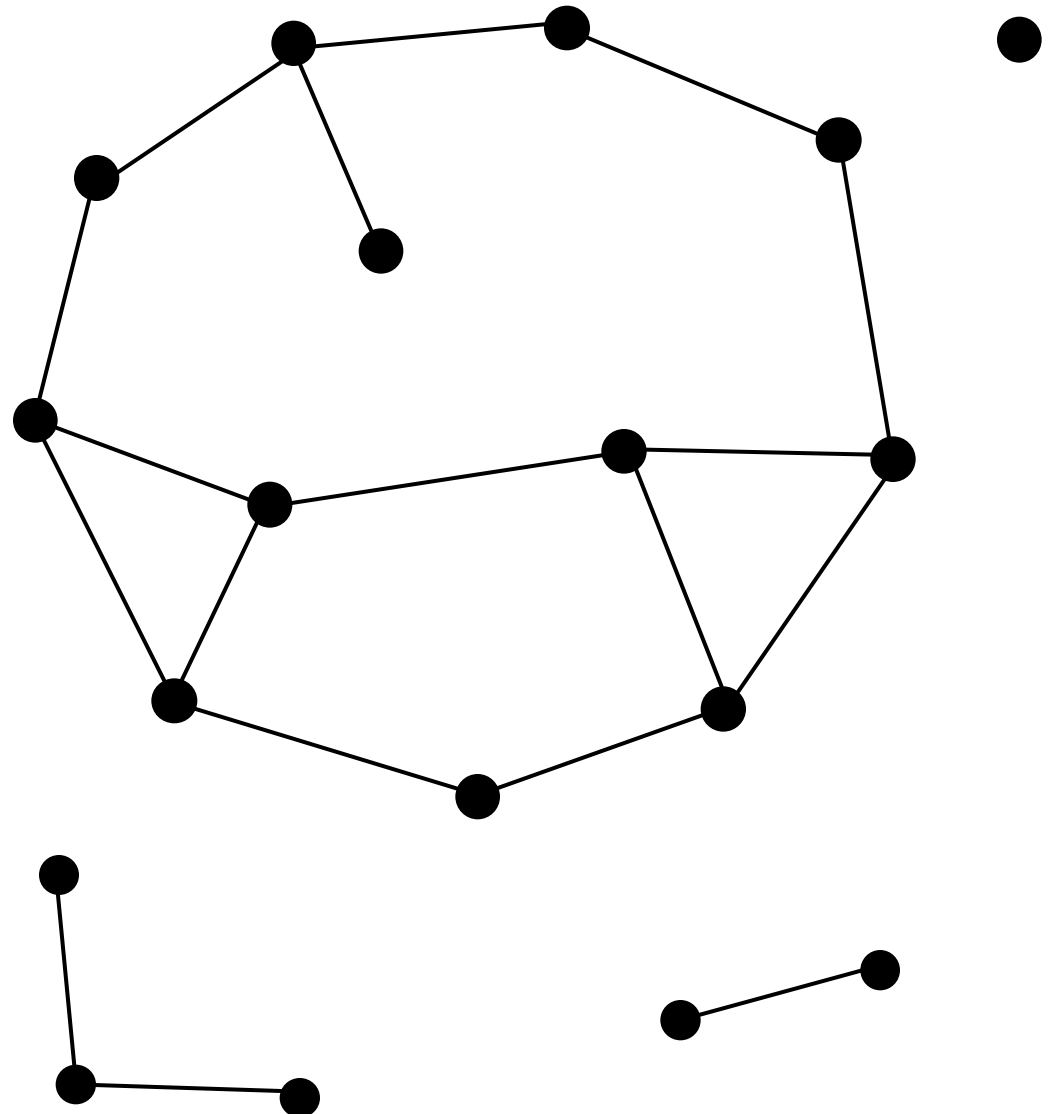
Constraint counting

Laman Condensation

Rigid Cluster Decomposition

Correlated Motion Decomposition

Output



**Covalent bonding**

Central force interactions

**Represented as a  
bar-joint network  
graph  $G$**

Jacobs, J. Phys. A 31, 6653 (1998)

UNC Charlotte

# Modeling Covalent Bonds

Input structure

**Modeling**

Pebble game

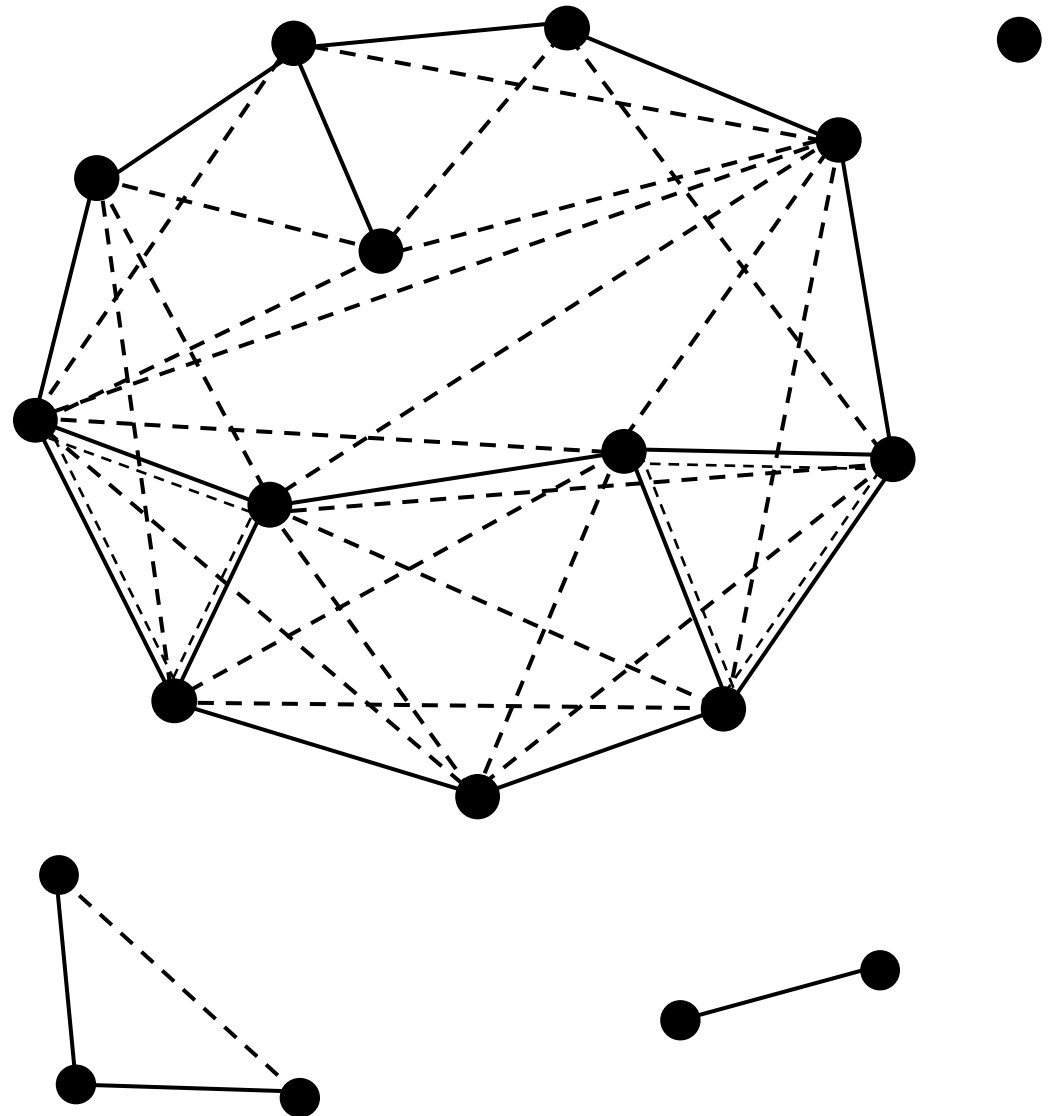
Constraint counting

Laman Condensation

Rigid Cluster Decomposition

Correlated Motion Decomposition

Output



**Covalent bonding**

Central force interactions

**Bond-bending interactions**

Represented as a  
bar-joint network

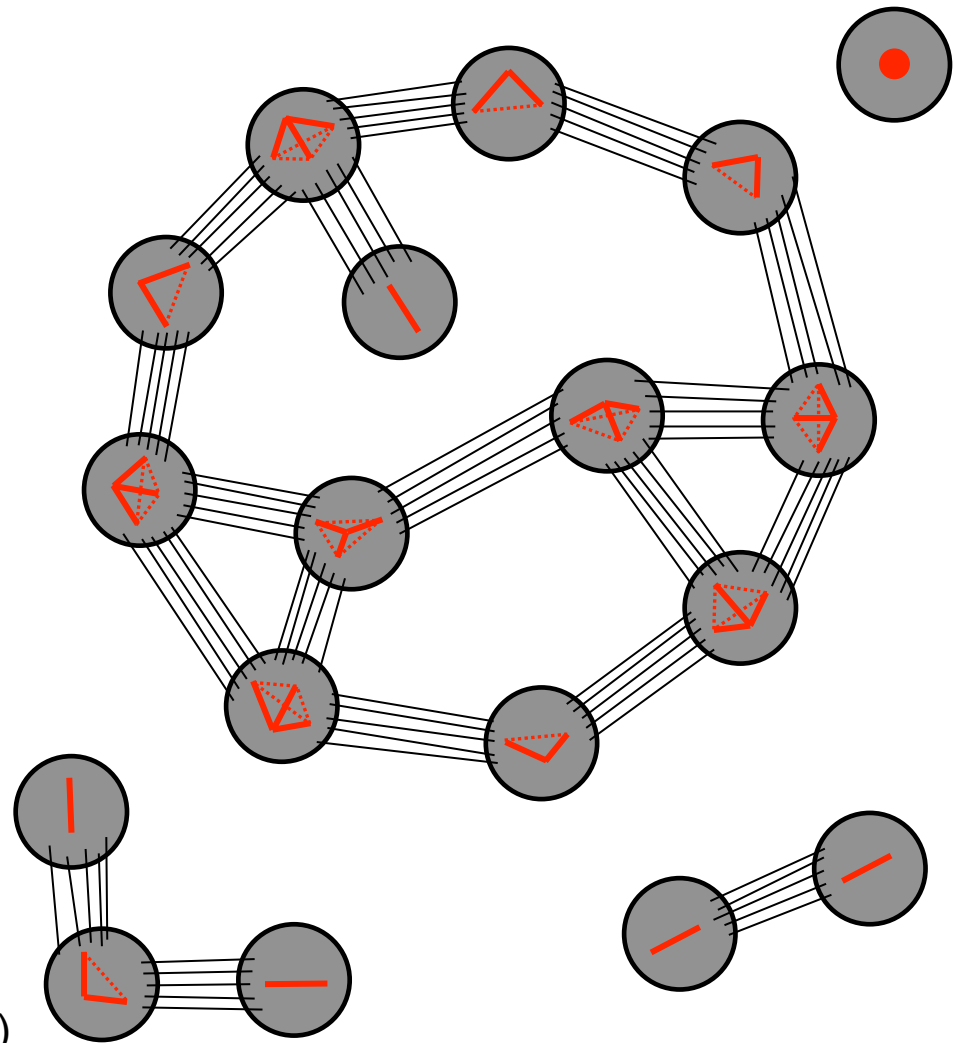
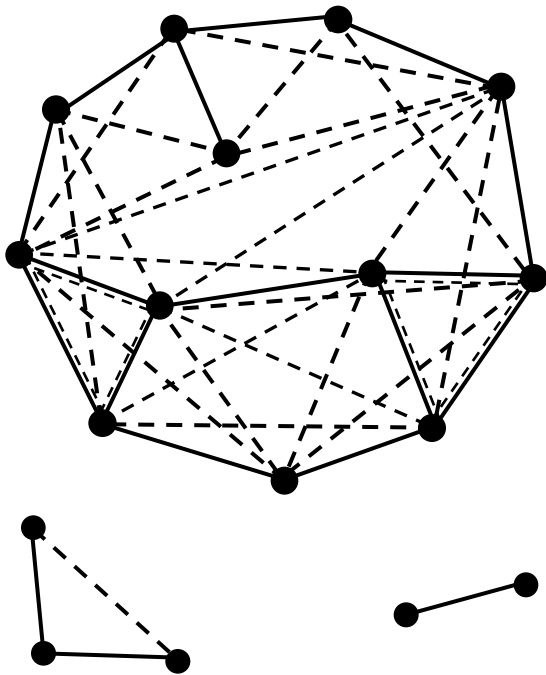
**graph  $G^2$**

Jacobs, J. Phys. A 31, 6653 (1998)

UNC Charlotte

# Modeling Covalent Bonds

Bar-joint graph  $G^2 \longrightarrow$  Body-Bar multigraph

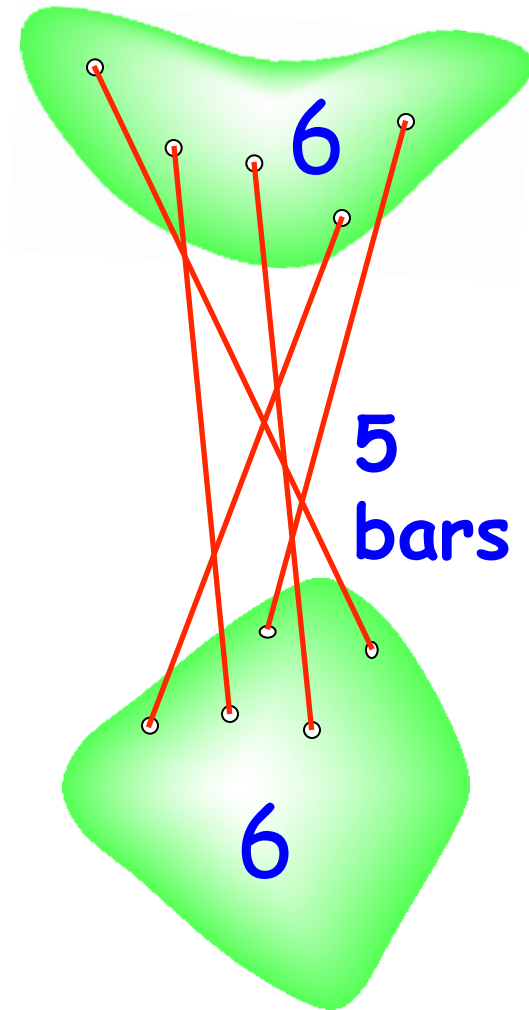
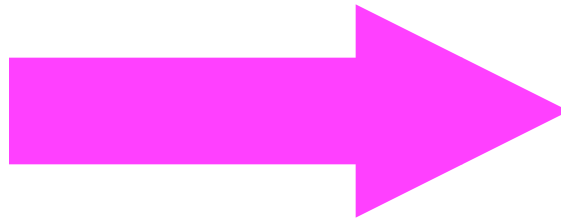
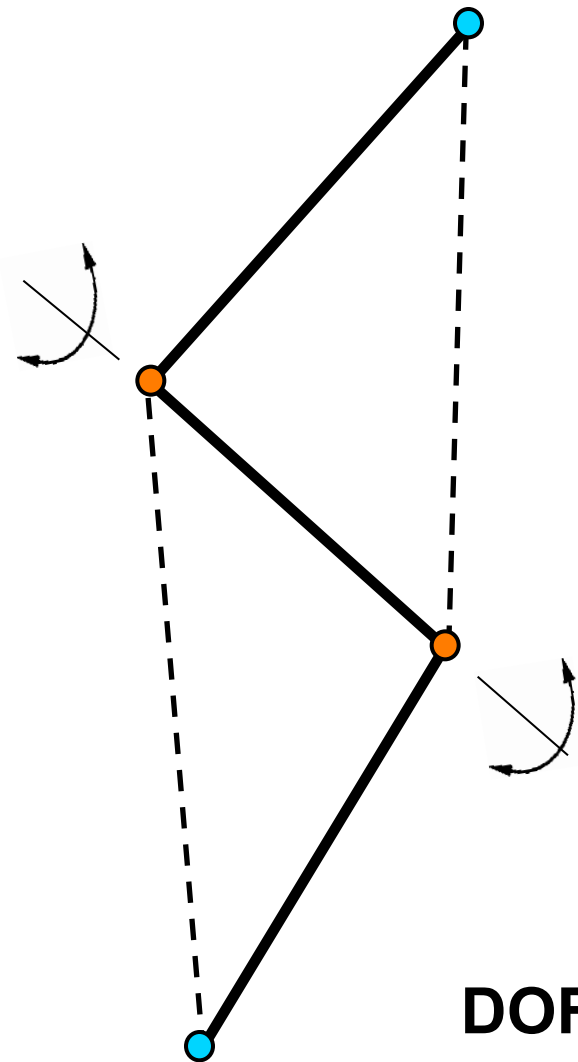


Jacobs, J. Phys. A 31, 6653 (1998)  
Tay & Whiteley, *Struct. Topol.* 9, 31 (1984)

UNC Charlotte

# Body-bar representation

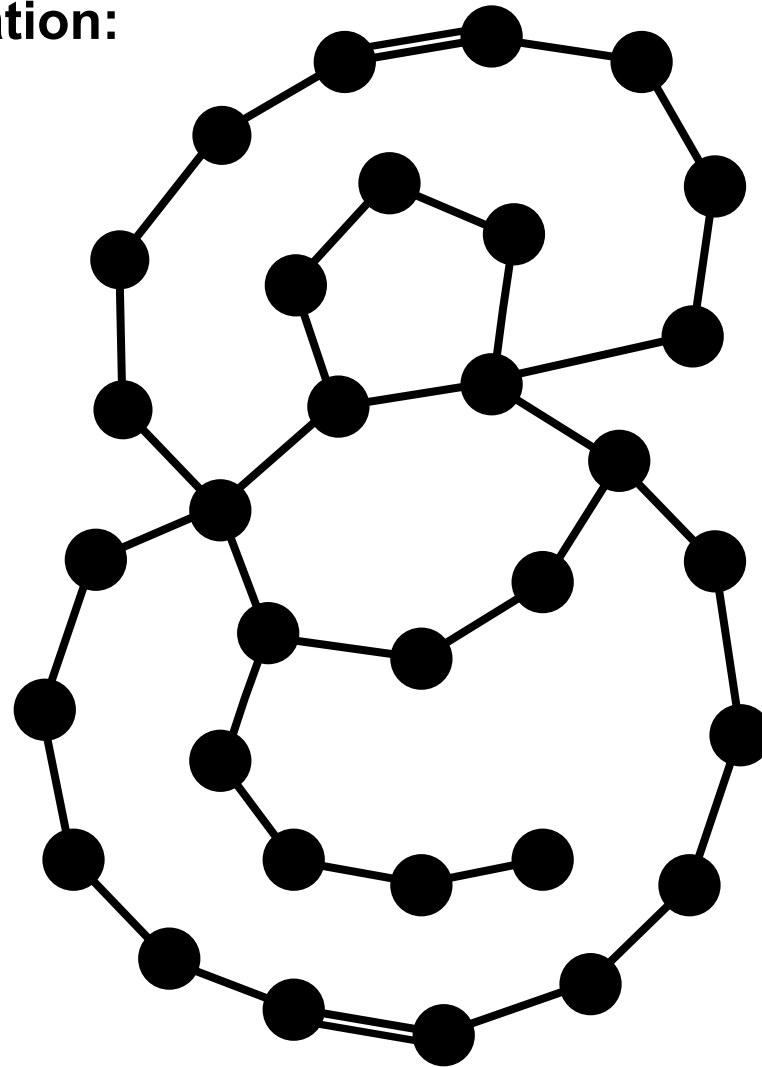
Covalent bond



$$\text{DOF} = 6 + 1 = 7 = 2 \times 6 - 5$$

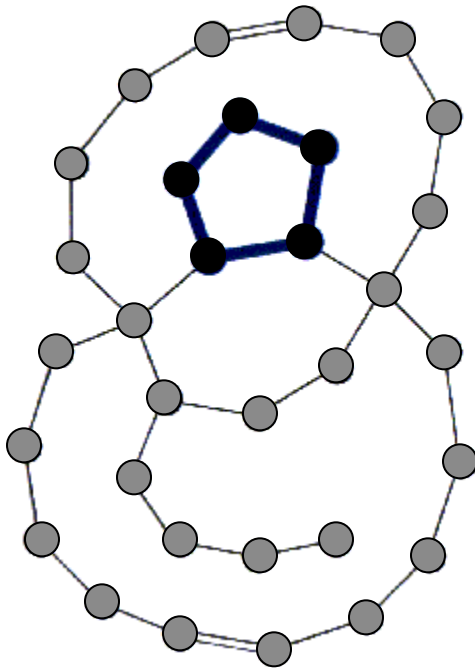
# Simple Covalent Bonded Ring System

Graph G representation:

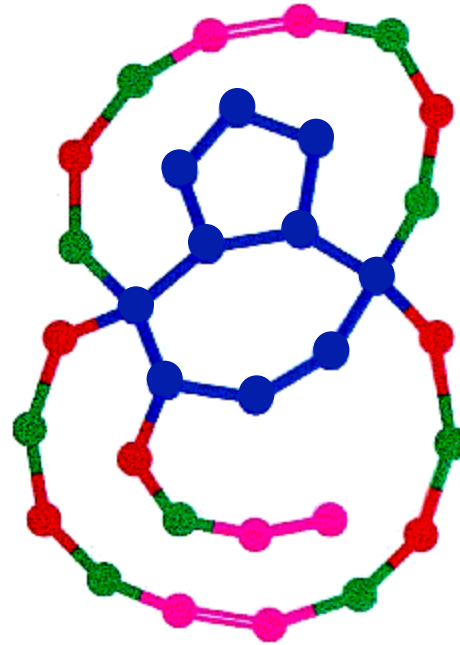


# Network Rigidity of a Simple Ring System

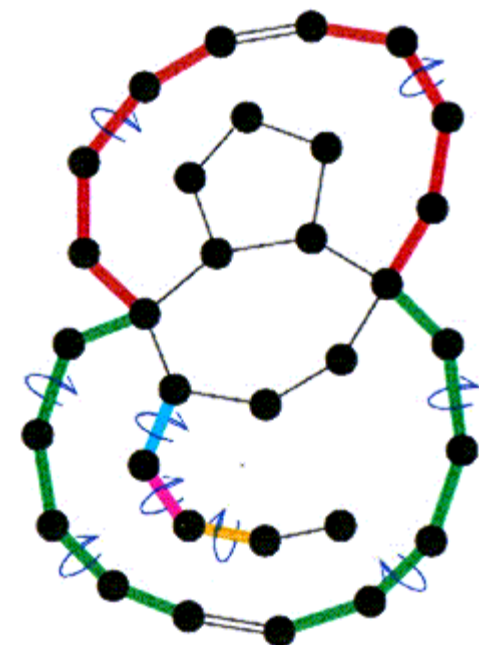
Identification of stressed regions



Rigid cluster decomposition



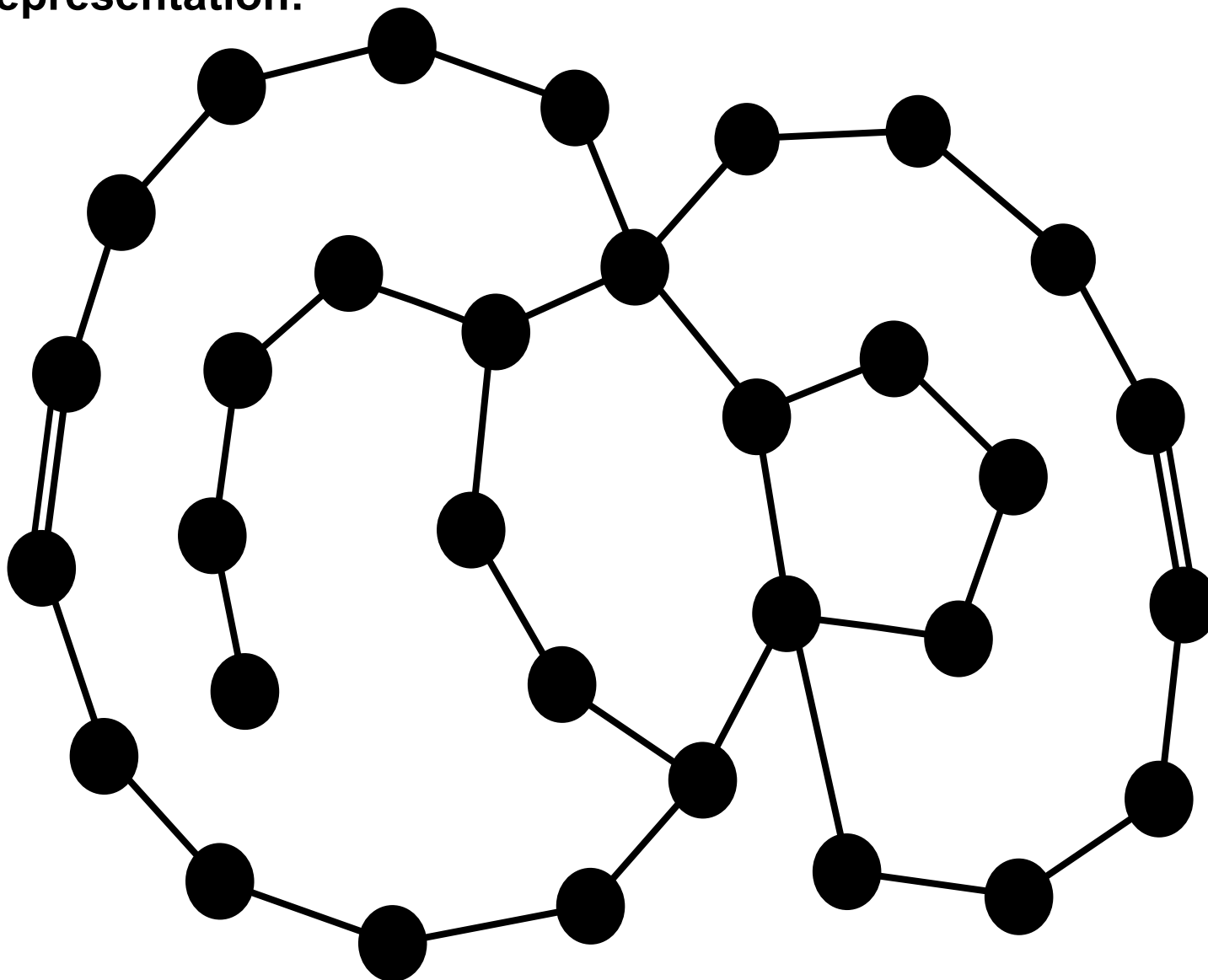
Characterization of flexible regions



Jacobs, Kuhn and Thorpe, *Flexible and rigid regions in proteins*, p357-384  
in *Rigidity Theory and Applications* (1999) (Eds. Thorpe & Duxbury)

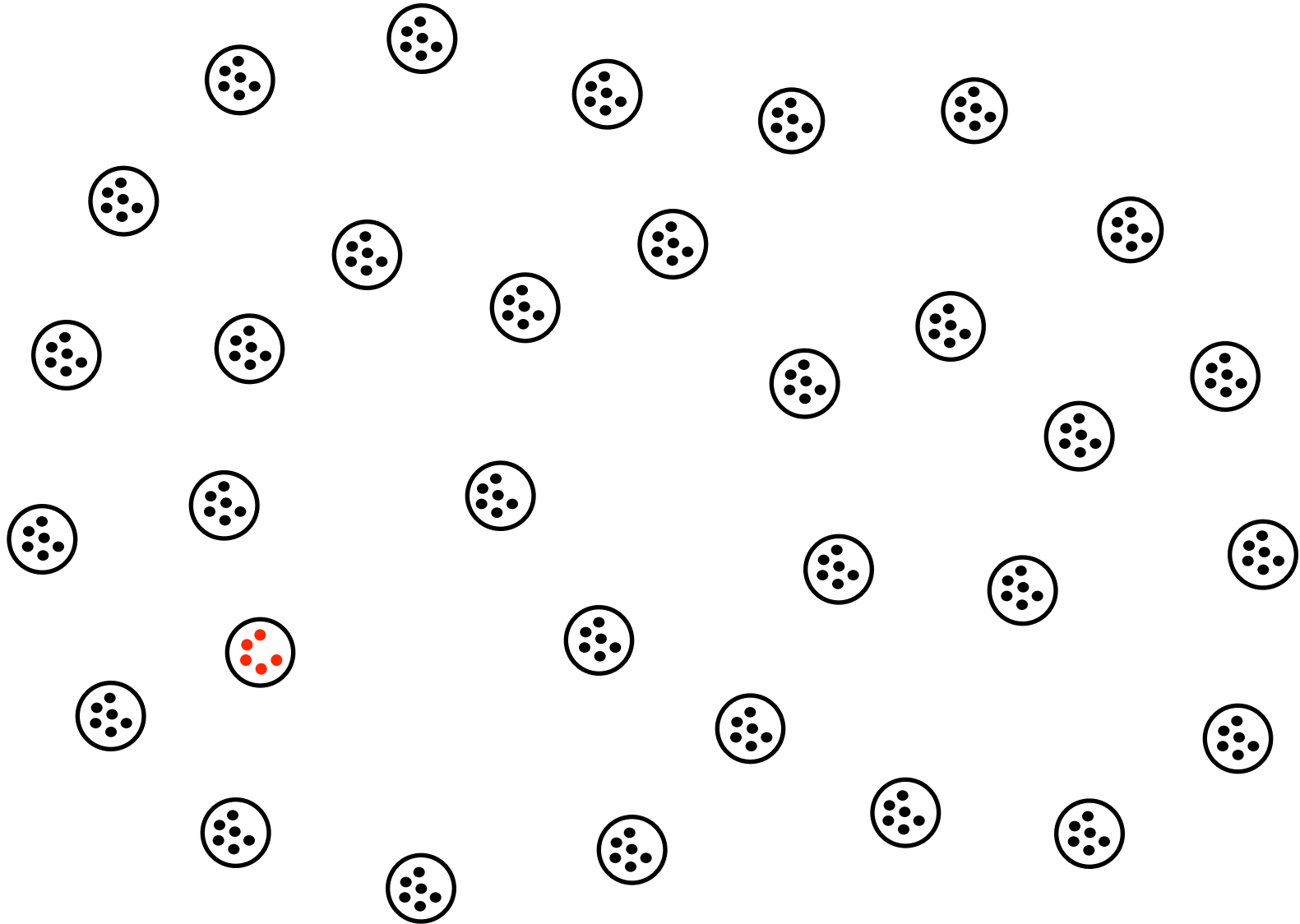
# Simple Covalent Bonded Ring System

Graph G representation:



# 3D Body-bar Pebble Game

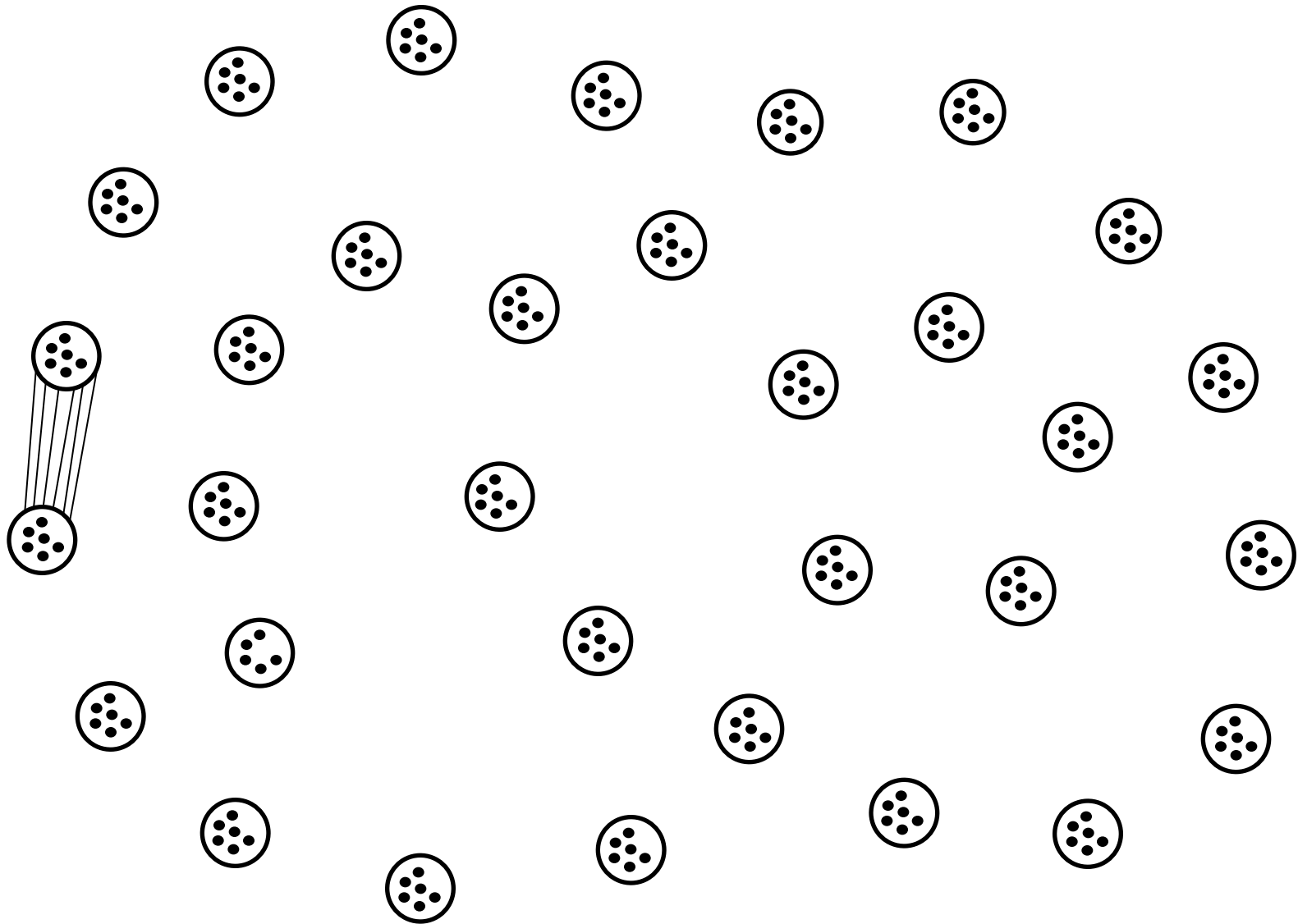
Place 6 pebbles on  $n$ -connected bodies ( $n > 1$ ) & 5 pebbles on 1-connected bodies





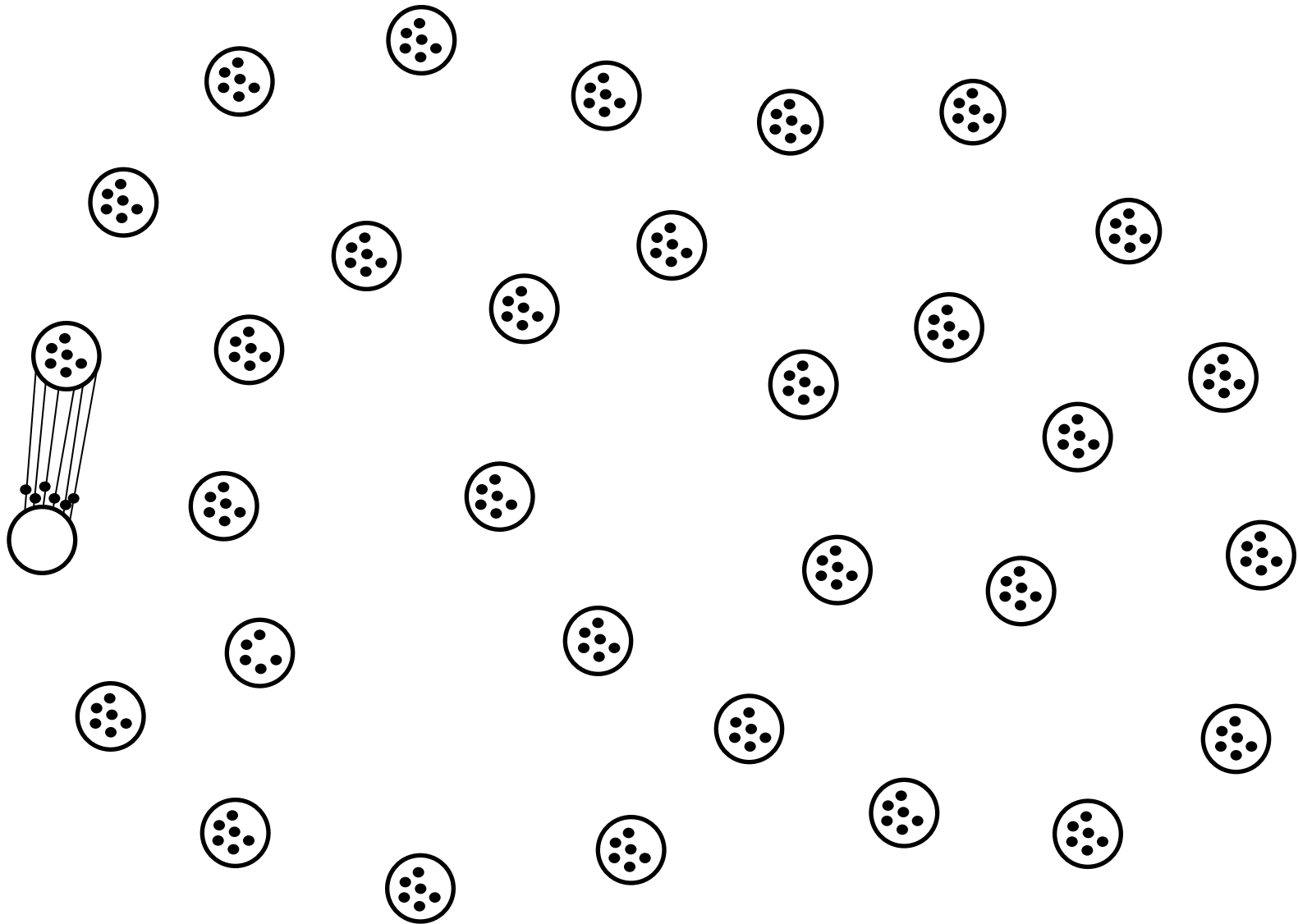
# 3D Body-bar Pebble Game

Place 6 bars at peptide bond



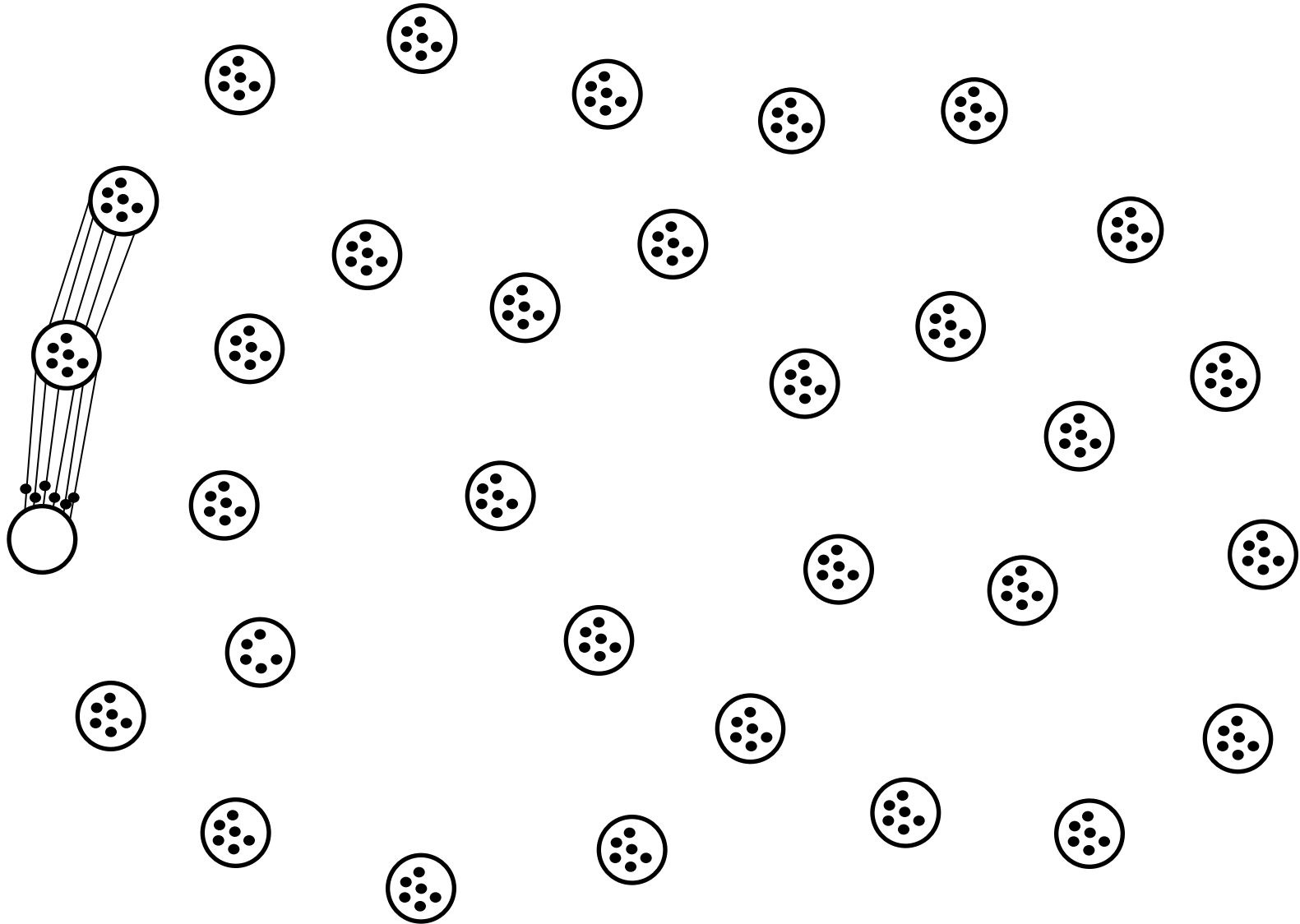
# 3D Body-bar Pebble Game

Cover all 6 bars



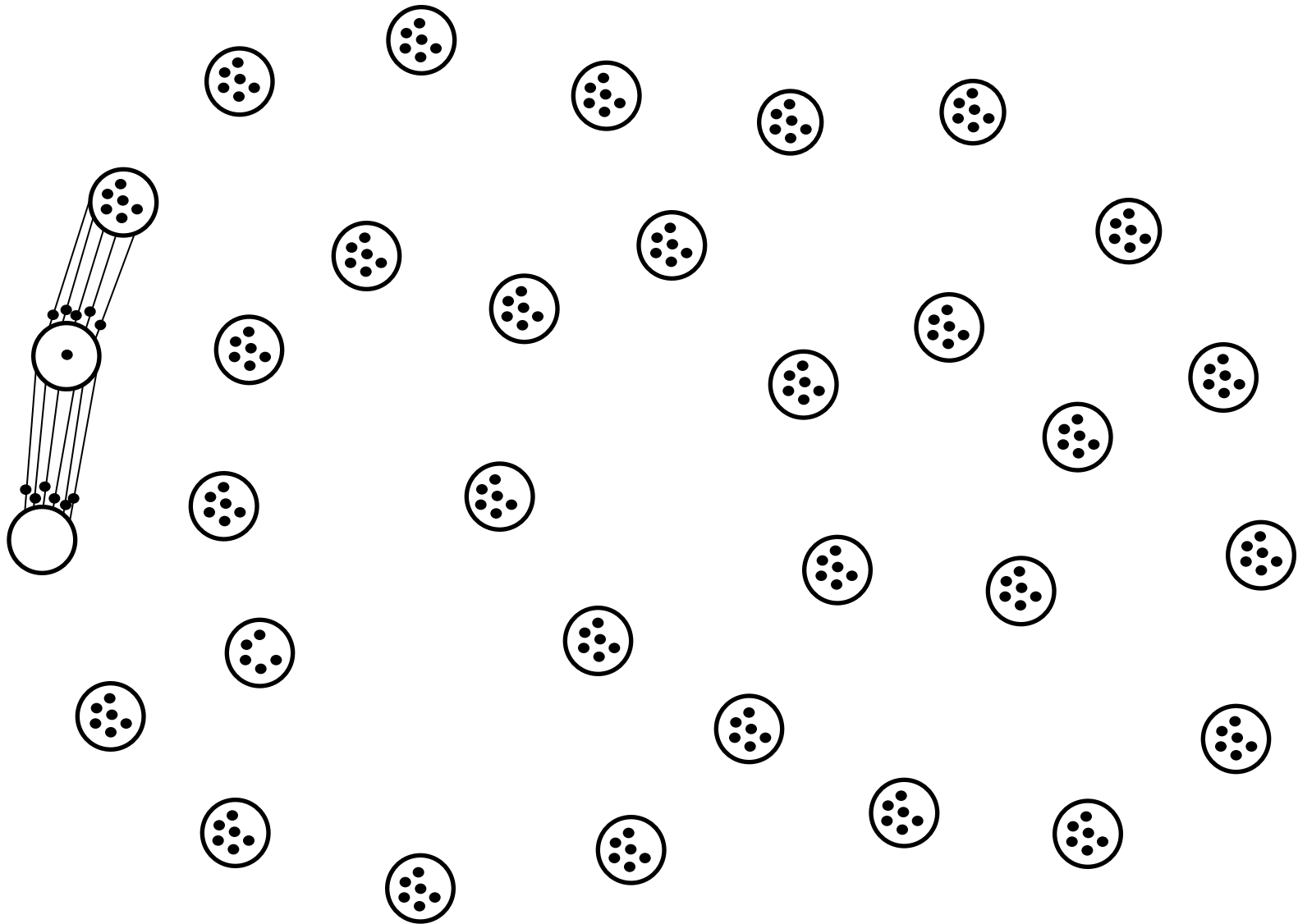
# 3D Body-bar Pebble Game

Place 5 bars for rotatable dihedral bond



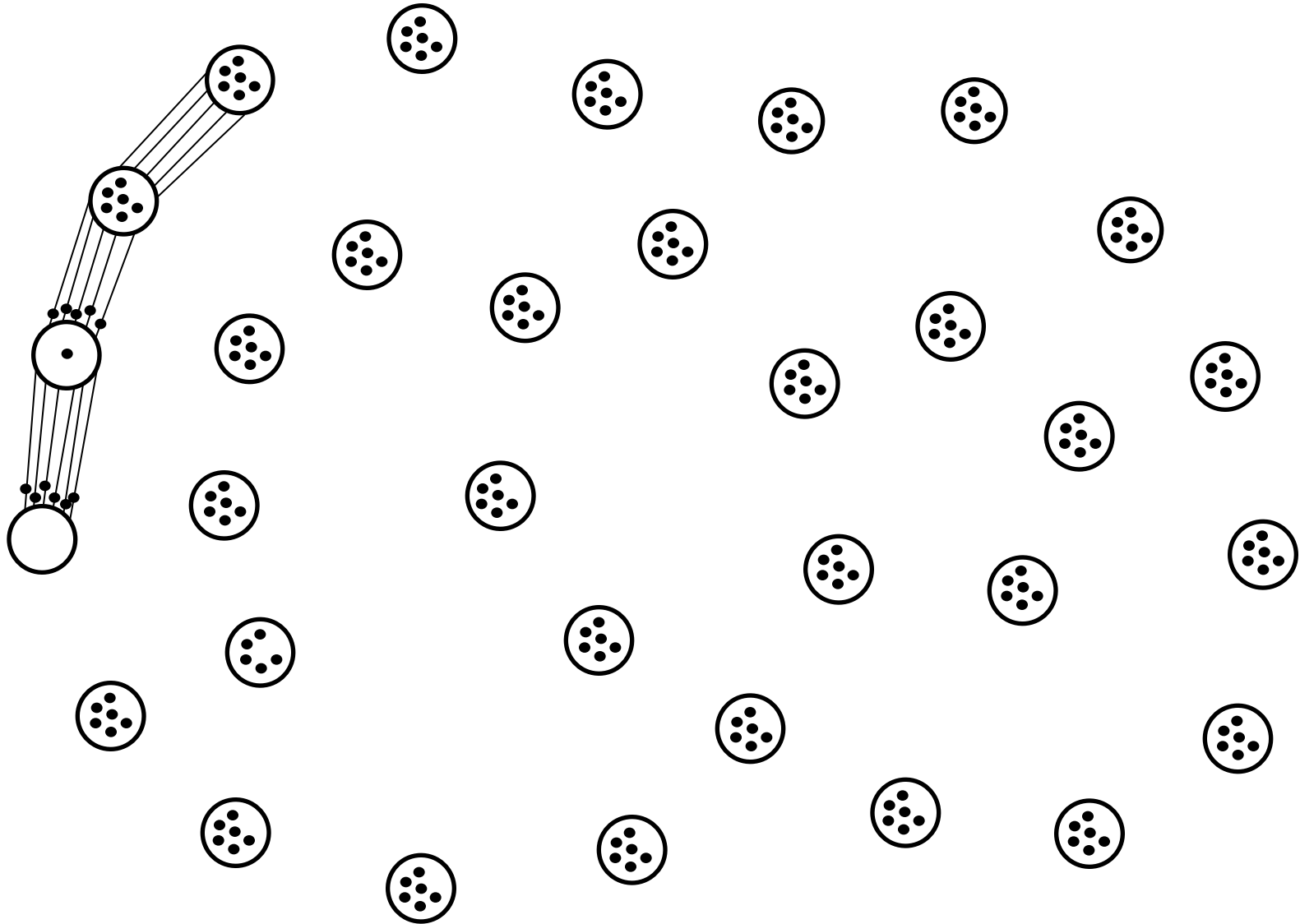
# 3D Body-bar Pebble Game

Cover all 5 bars



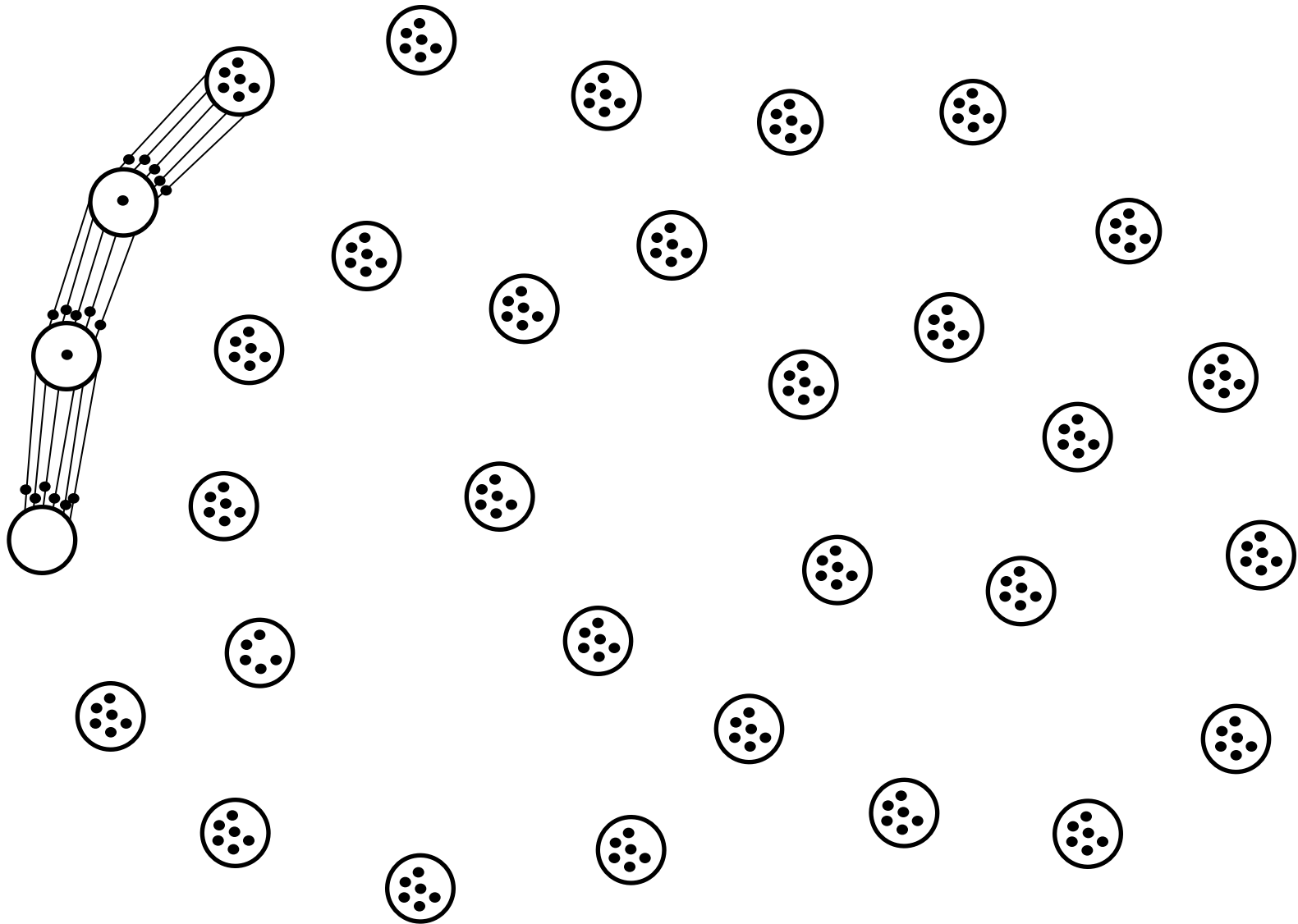
# 3D Body-bar Pebble Game

Place 5 bars for rotatable dihedral bond



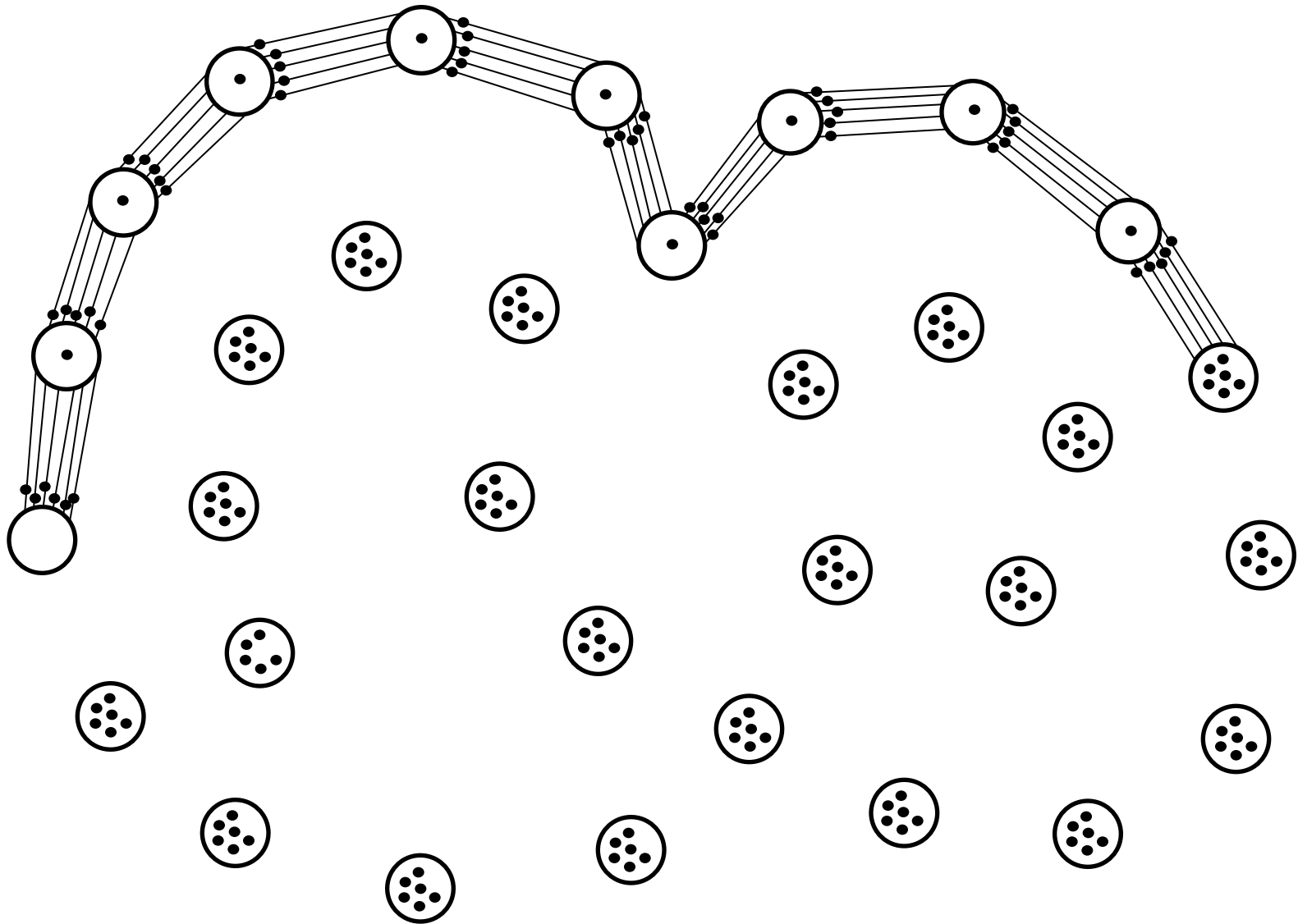
# 3D Body-bar Pebble Game

Cover all 5 bars



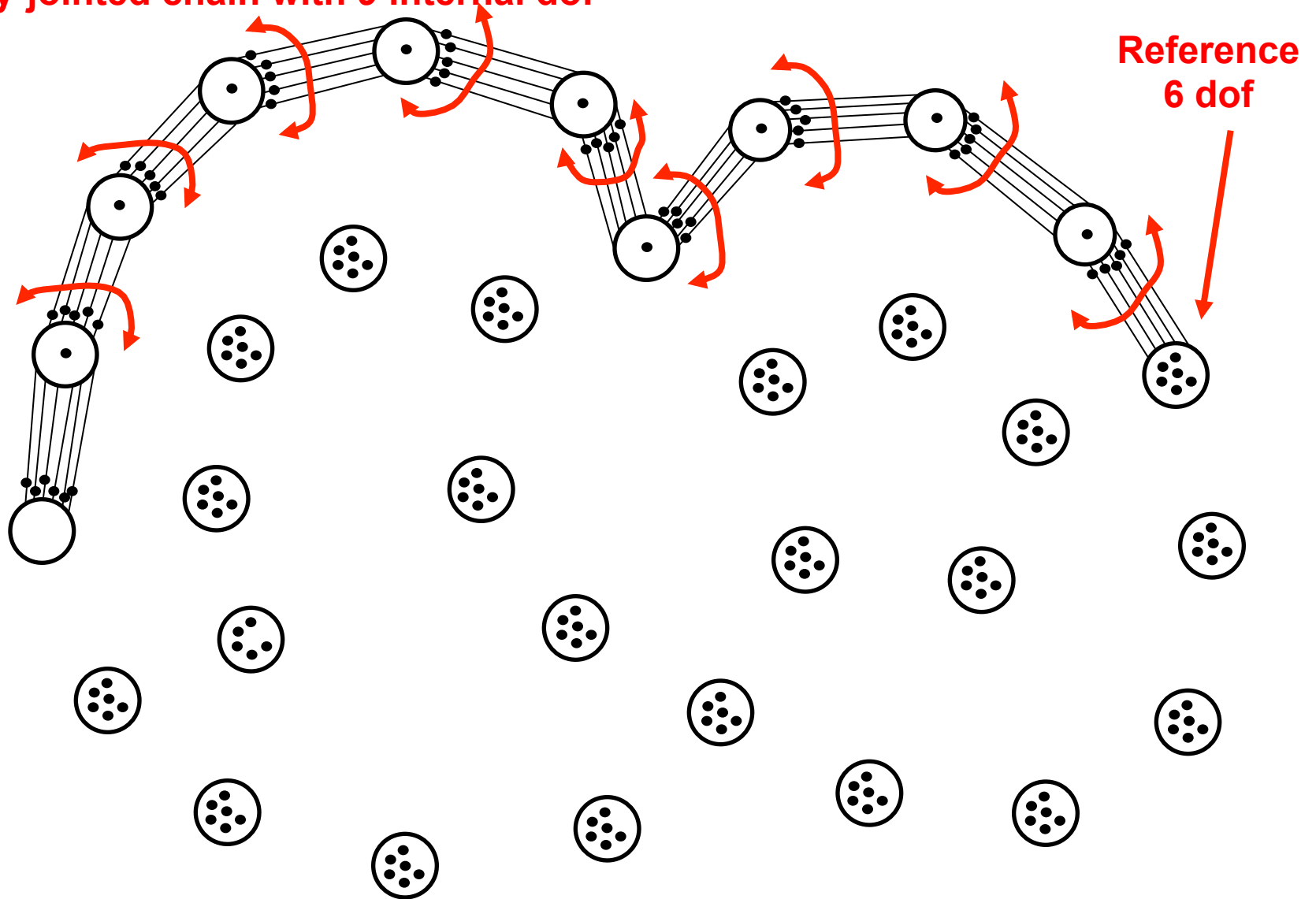
# 3D Body-bar Pebble Game

Repeat process, etc, ...



# 3D Body-bar Pebble Game

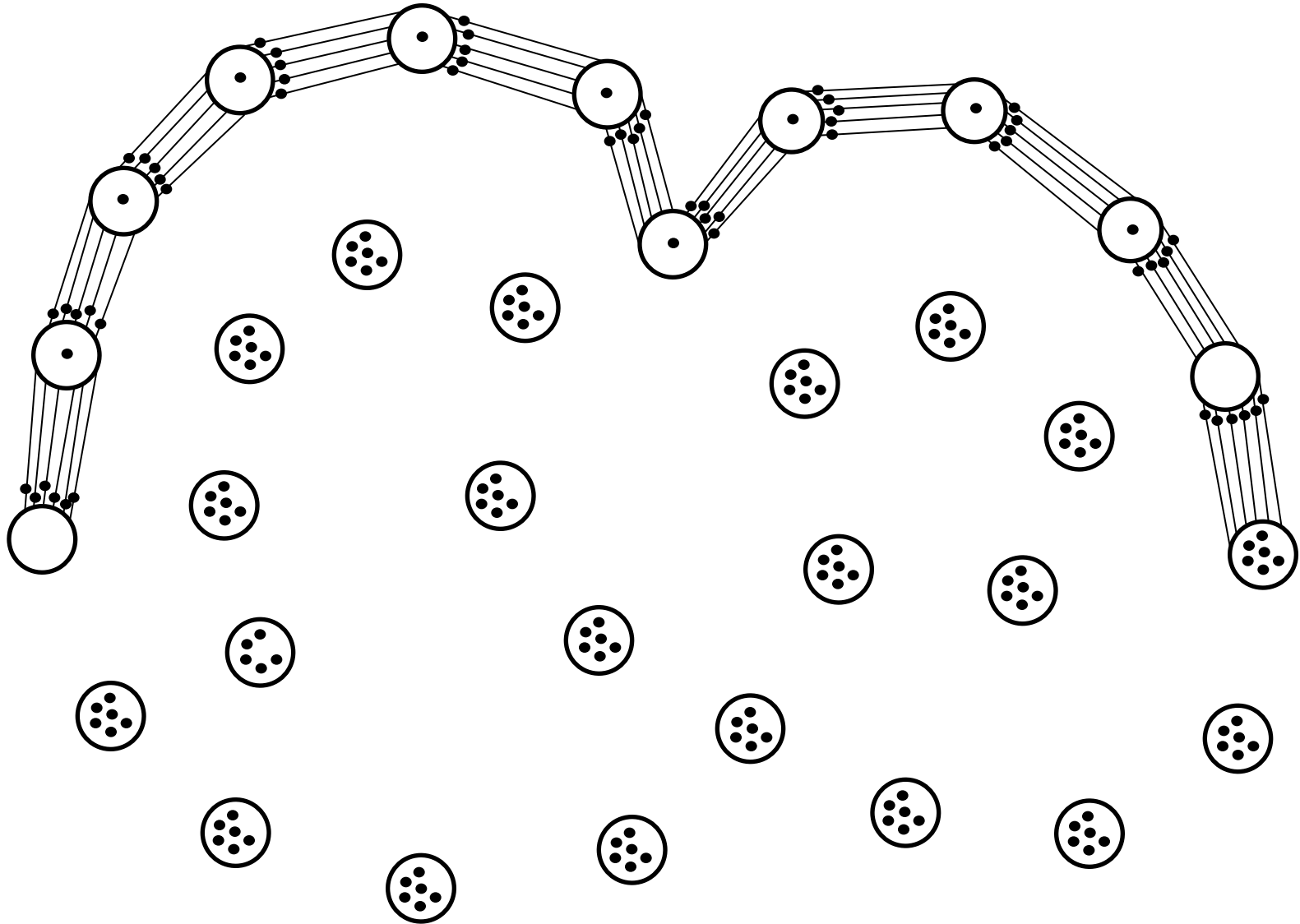
A freely-jointed chain with 9 internal dof





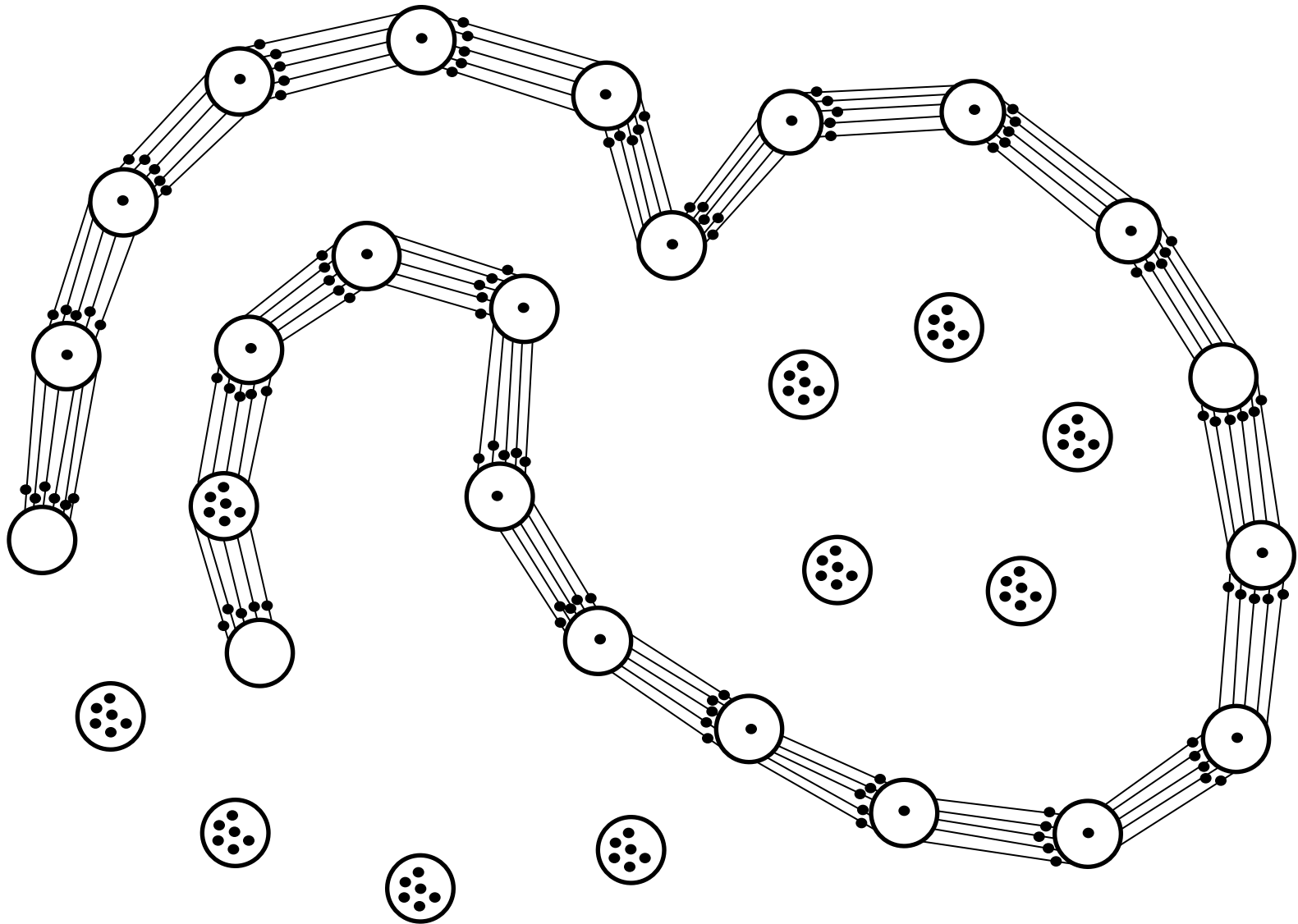
# 3D Body-bar Pebble Game

Place 6 bars at the other peptide bond and then cover all of them



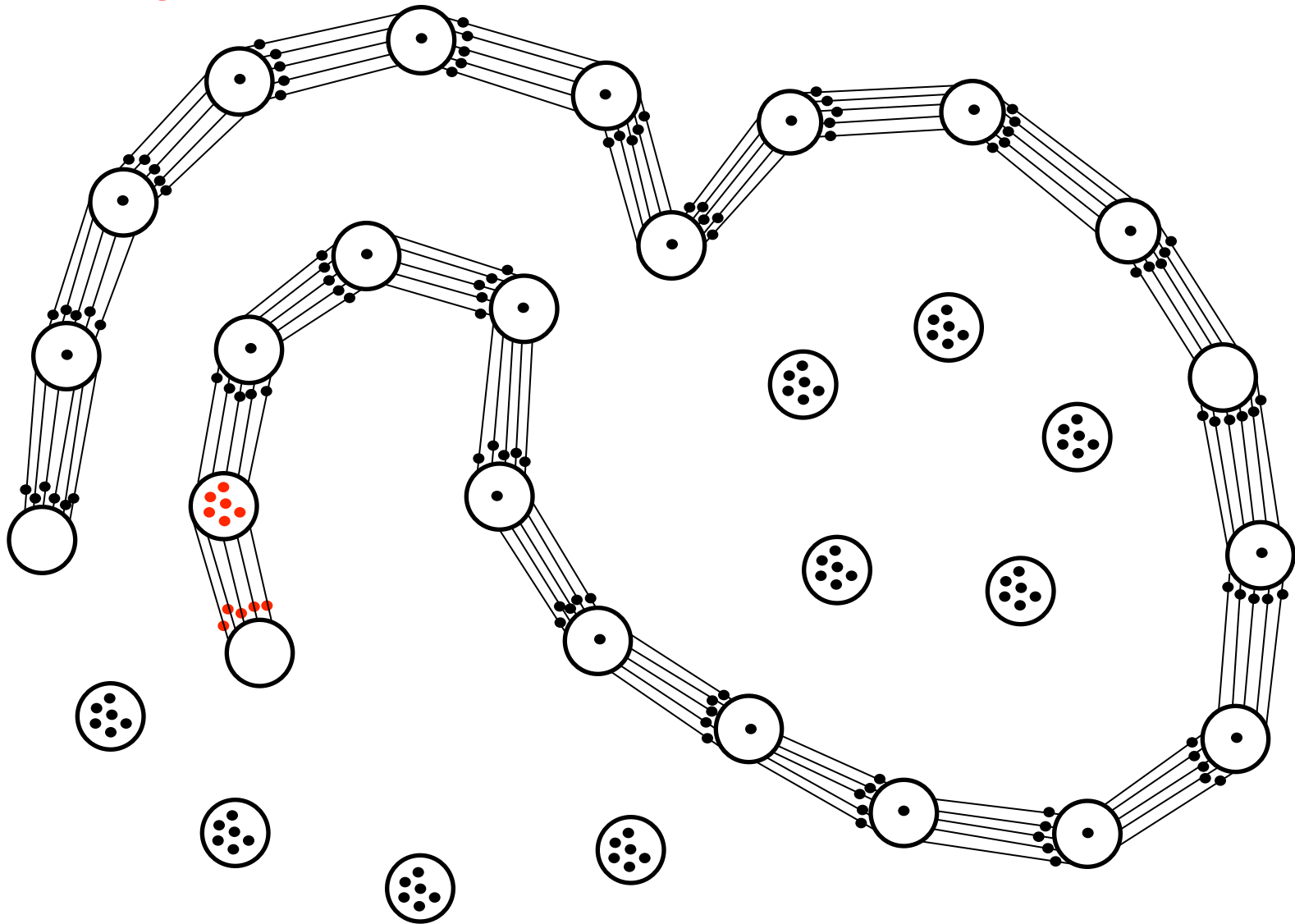
# 3D Body-bar Pebble Game

Continue process, etc, ...



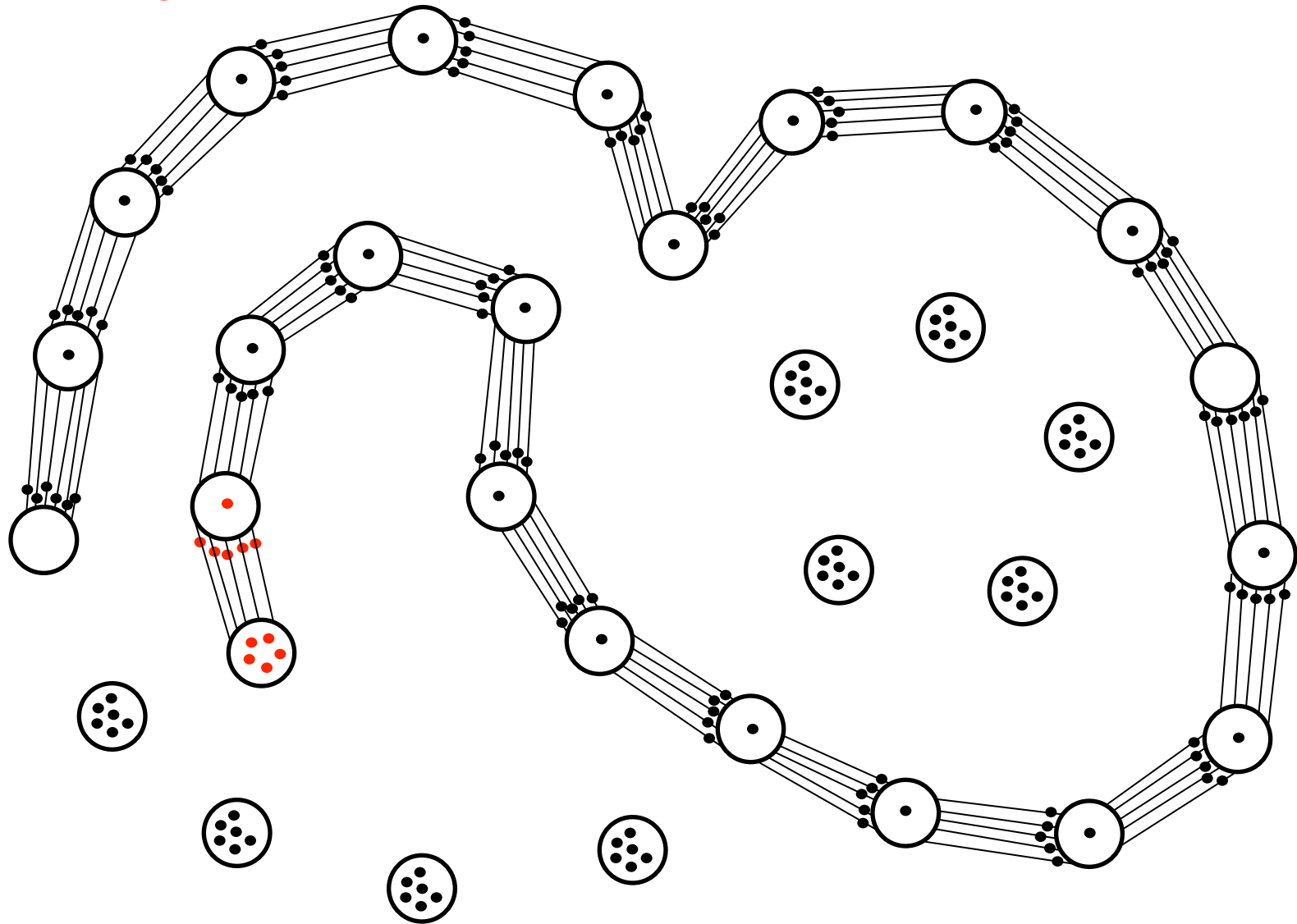
# 3D Body-bar Pebble Game

## Pebble Exchange Operation



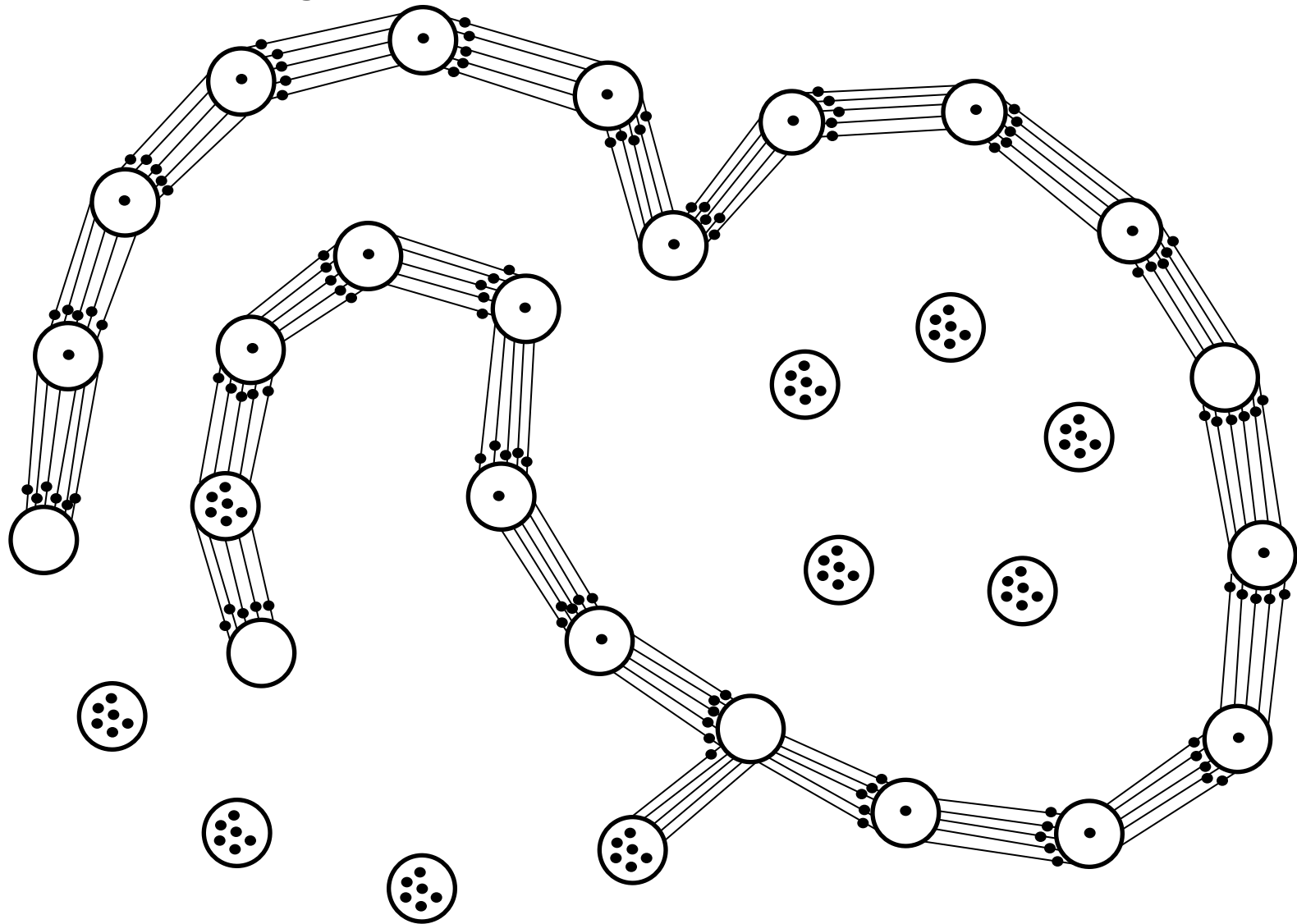
# 3D Body-bar Pebble Game

## Pebble Exchange Operation



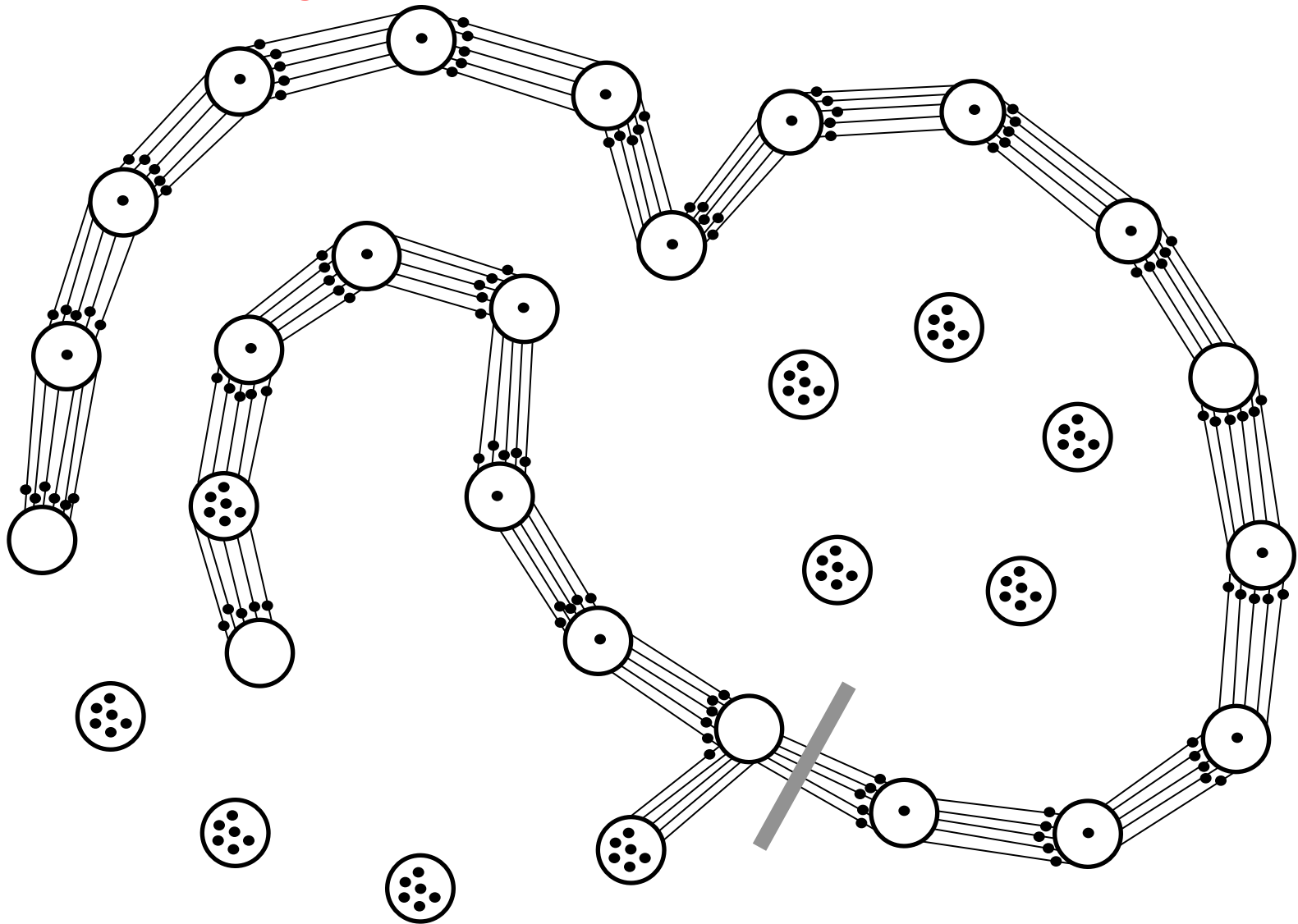
# 3D Body-bar Pebble Game

Pebble Search/Exchange Operation



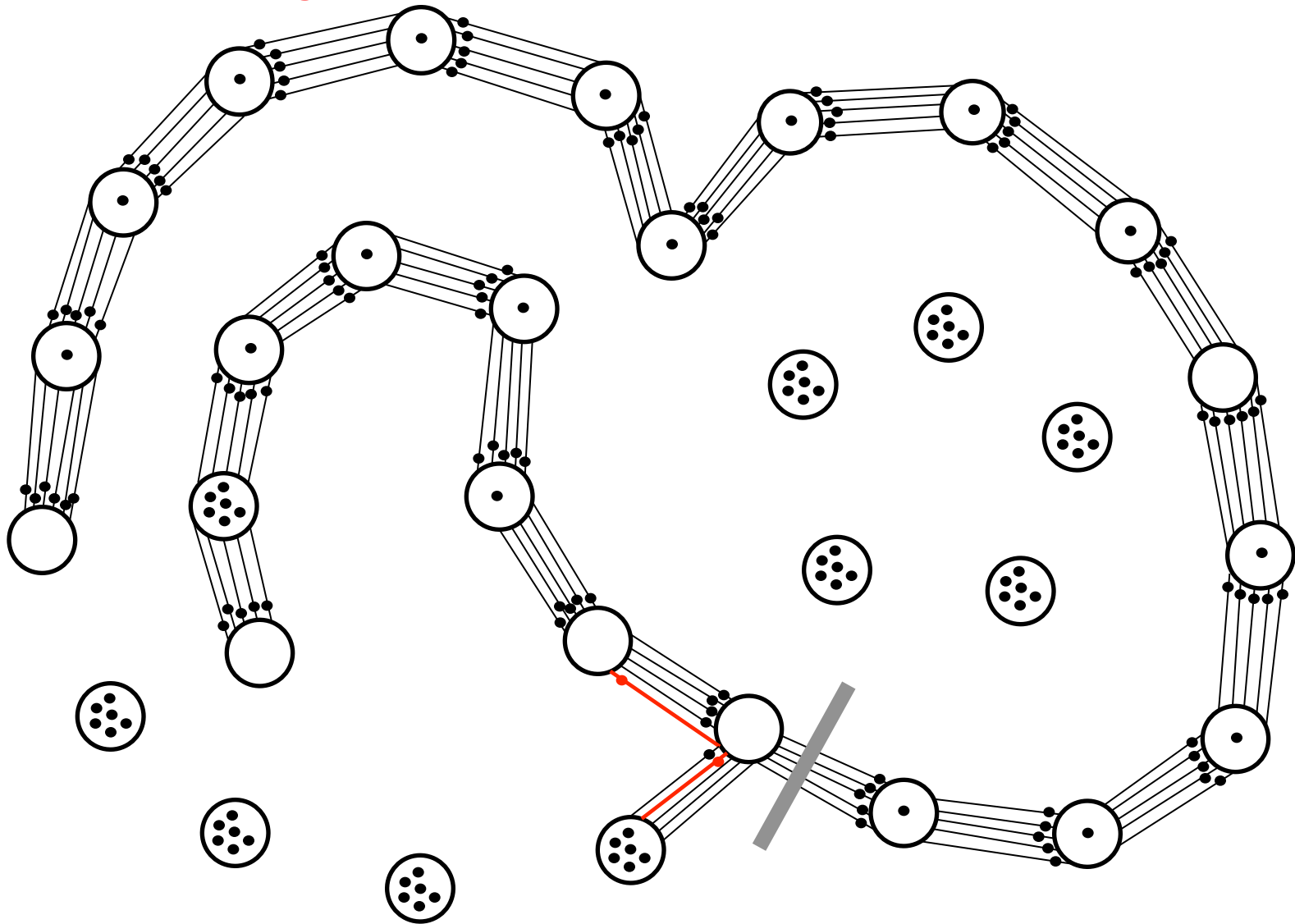
# 3D Body-bar Pebble Game

## Pebble Search/Exchange Operation



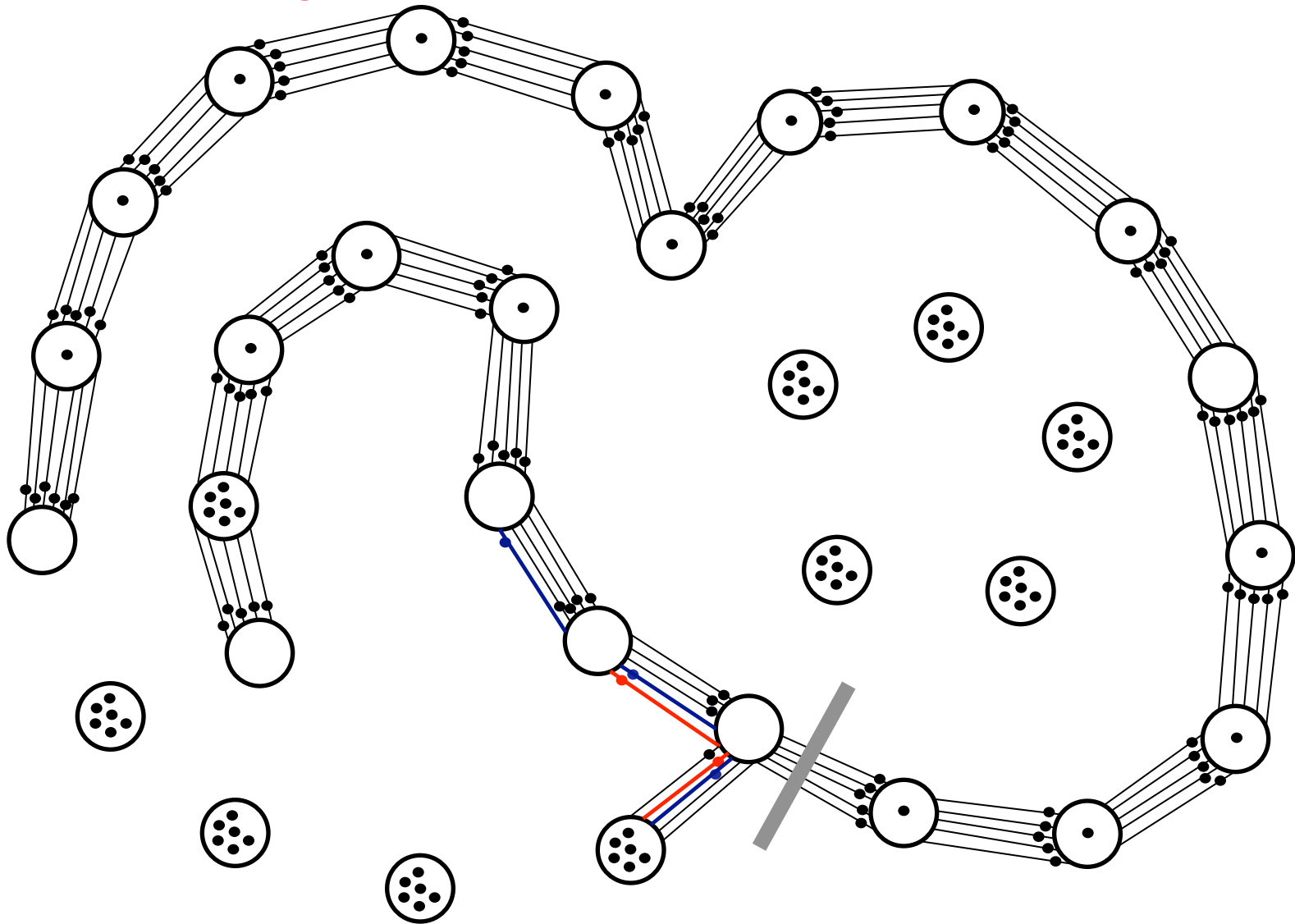
# 3D Body-bar Pebble Game

## Pebble Search/Exchange Operation



# 3D Body-bar Pebble Game

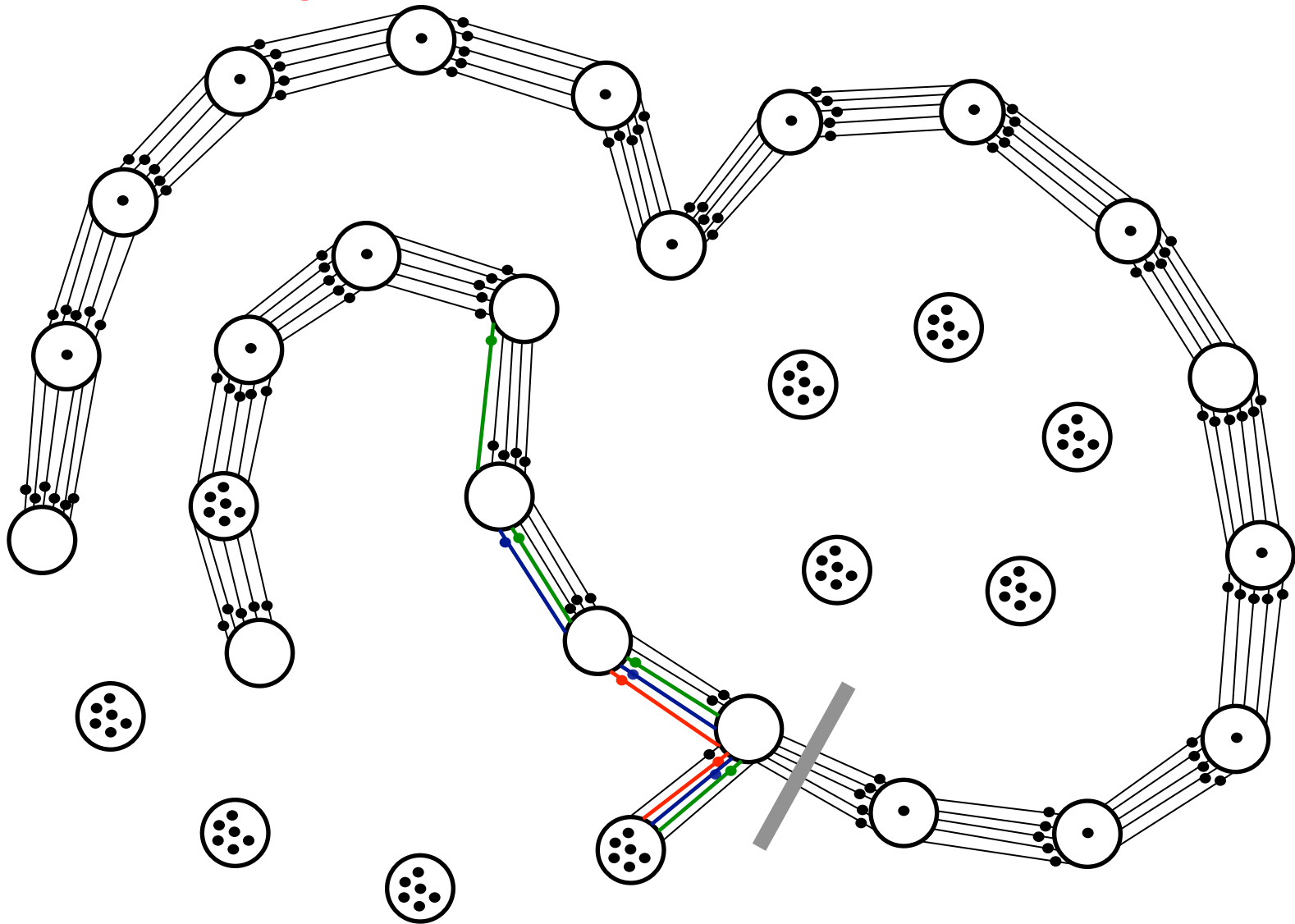
## Pebble Search/Exchange Operation





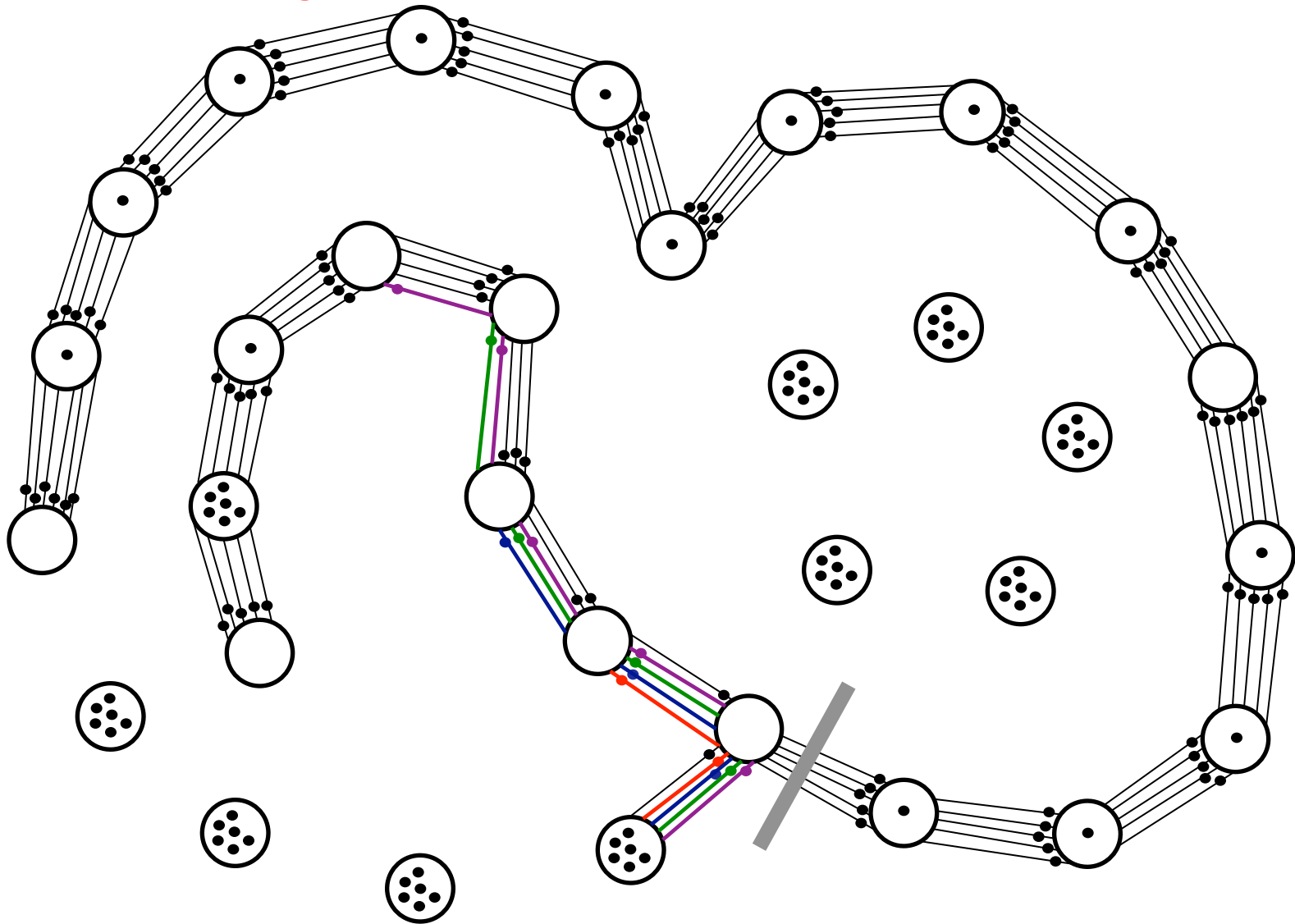
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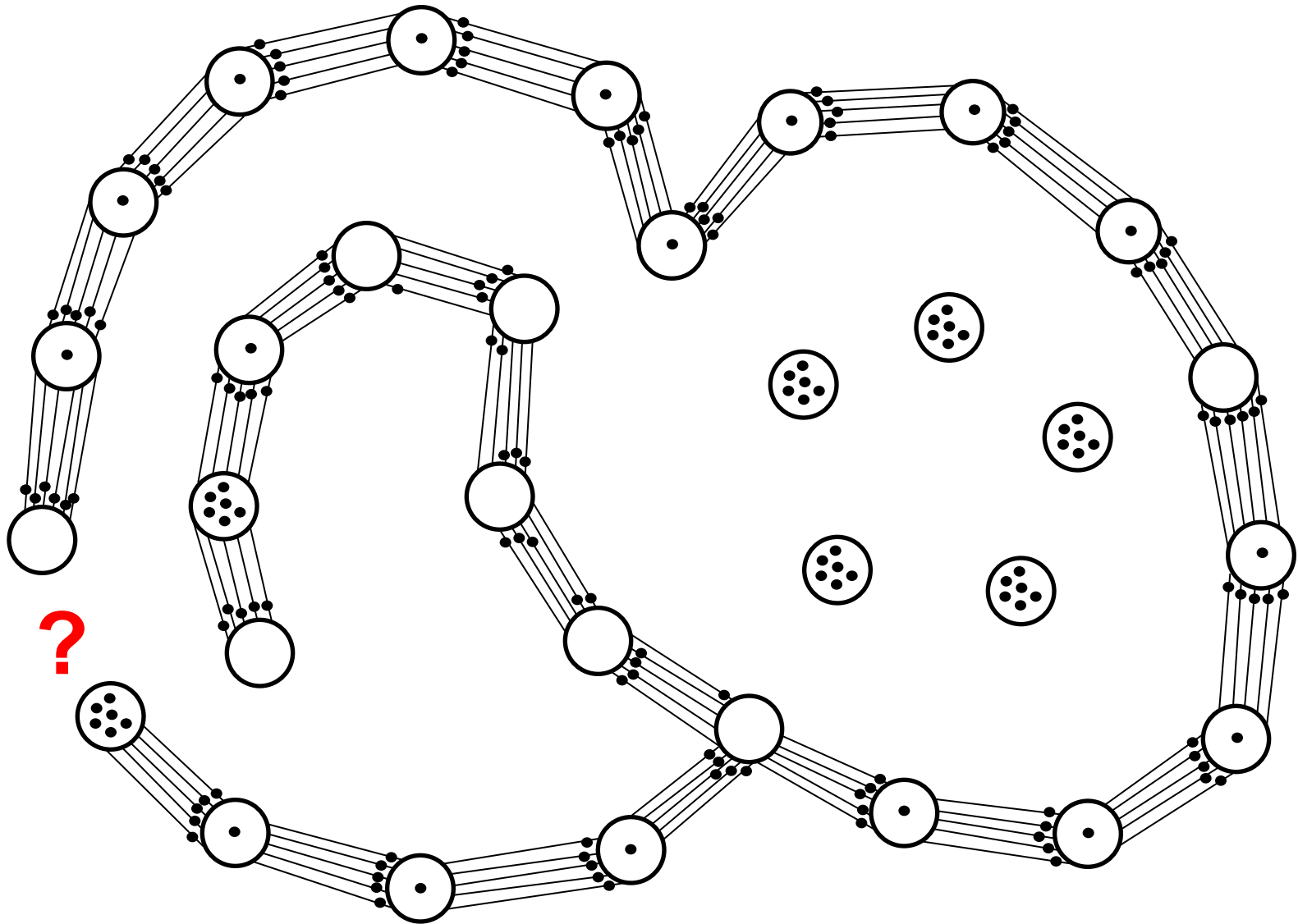
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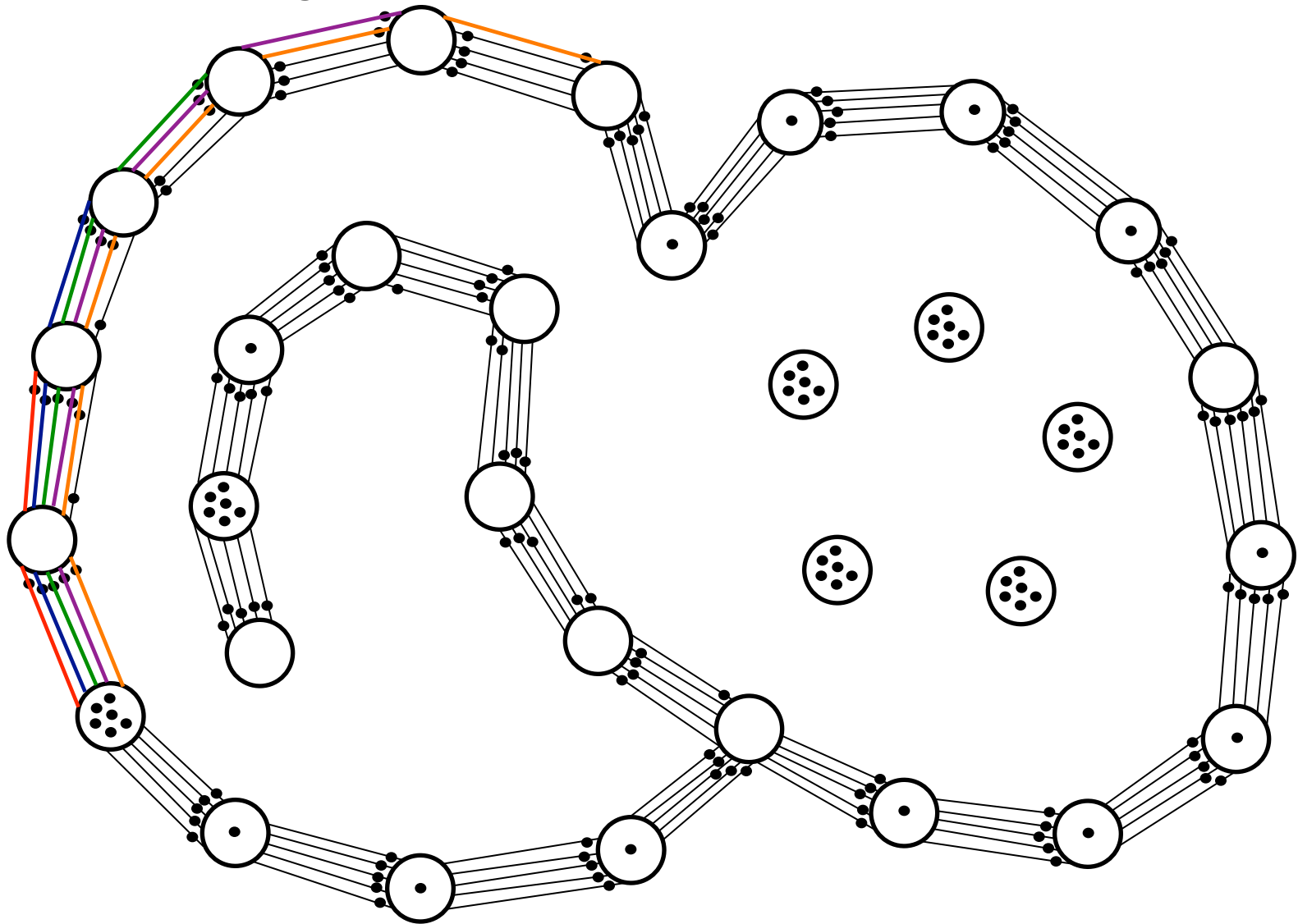
# 3D Body-bar Pebble Game

Continue process, etc, ...



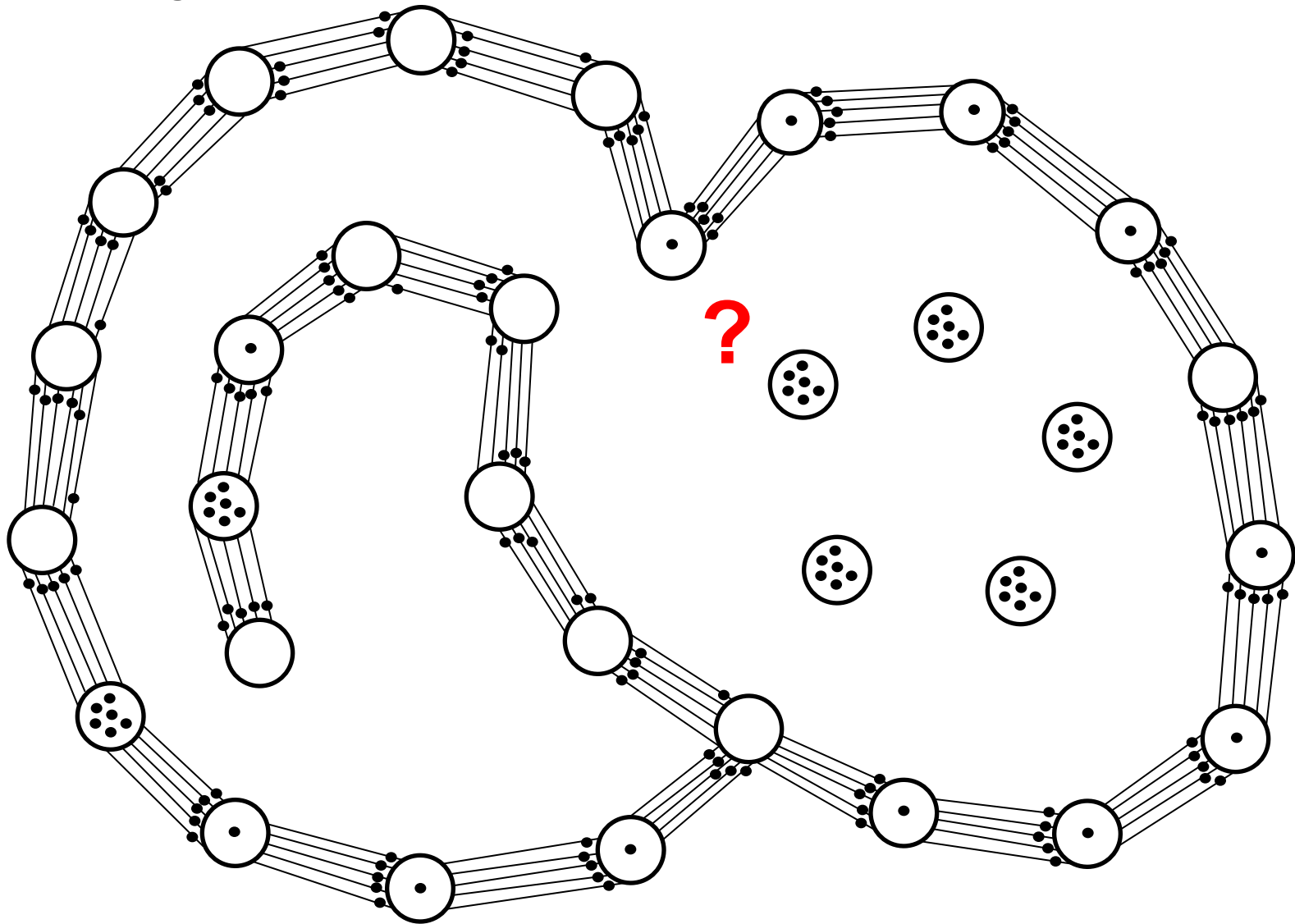
# 3D Body-bar Pebble Game

## Pebble Search/Exchange Operation



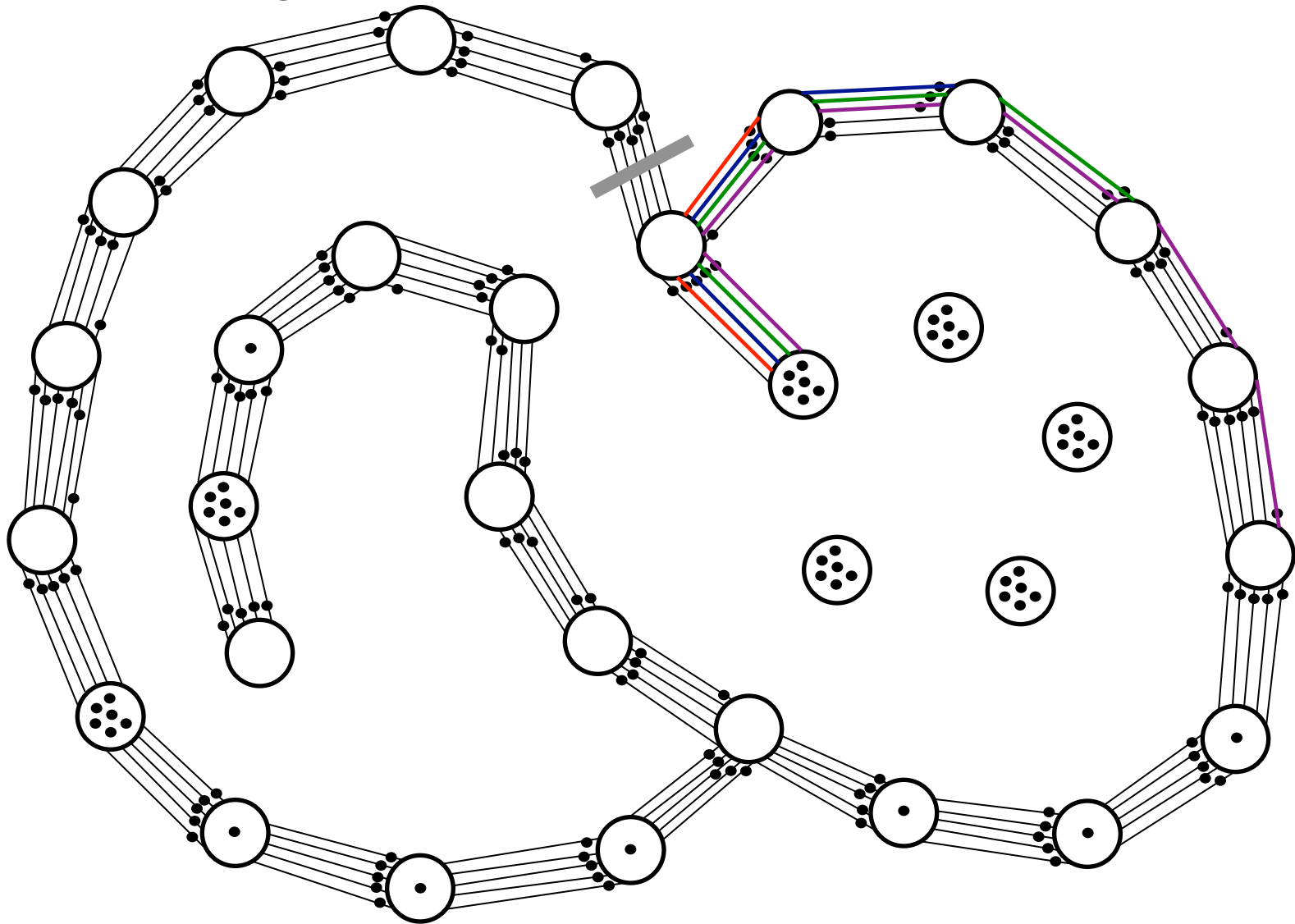
# 3D Body-bar Pebble Game

Continue placing 5 bars at rotatable bonds



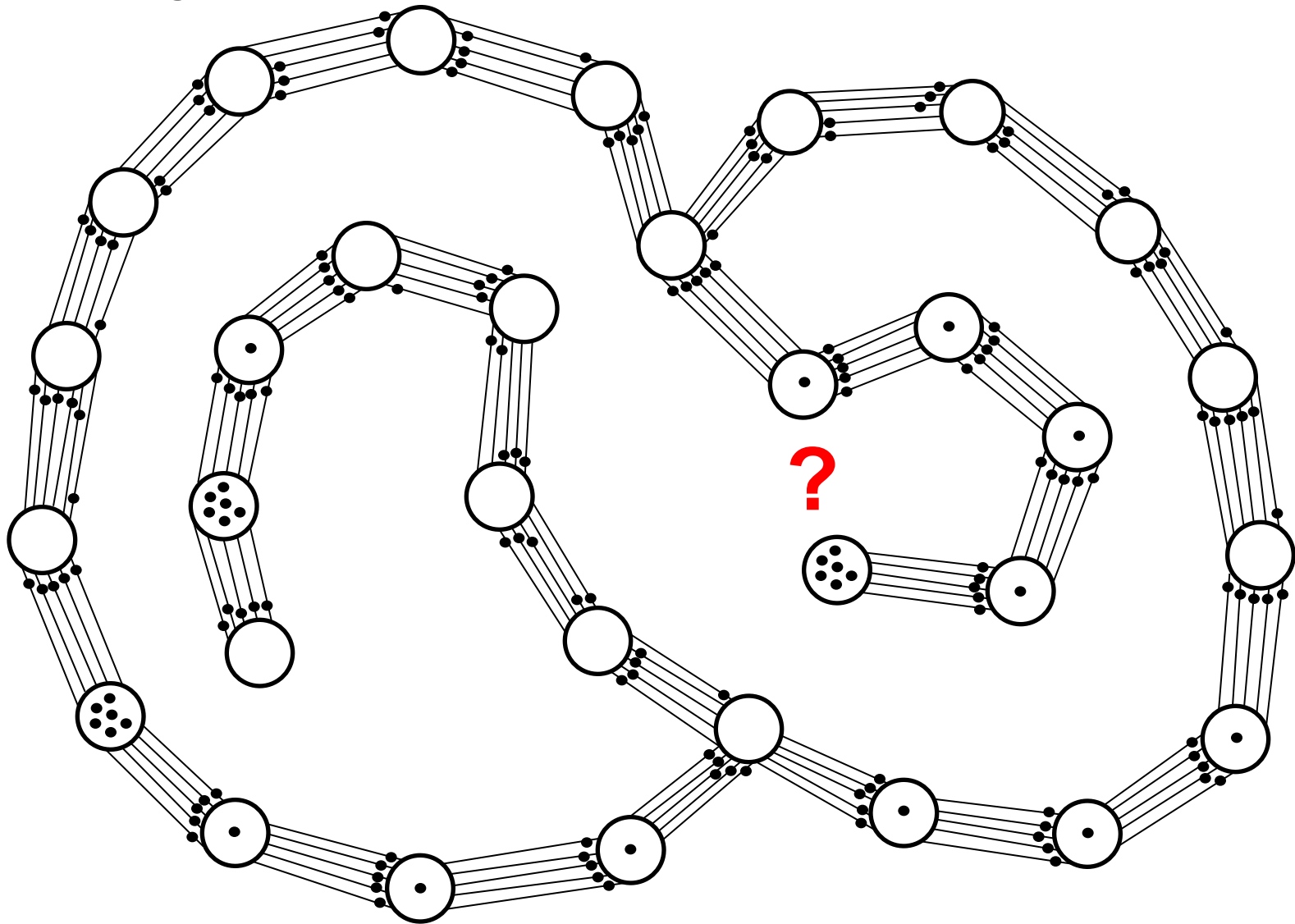
# 3D Body-bar Pebble Game

## Pebble Search/Exchange Operation



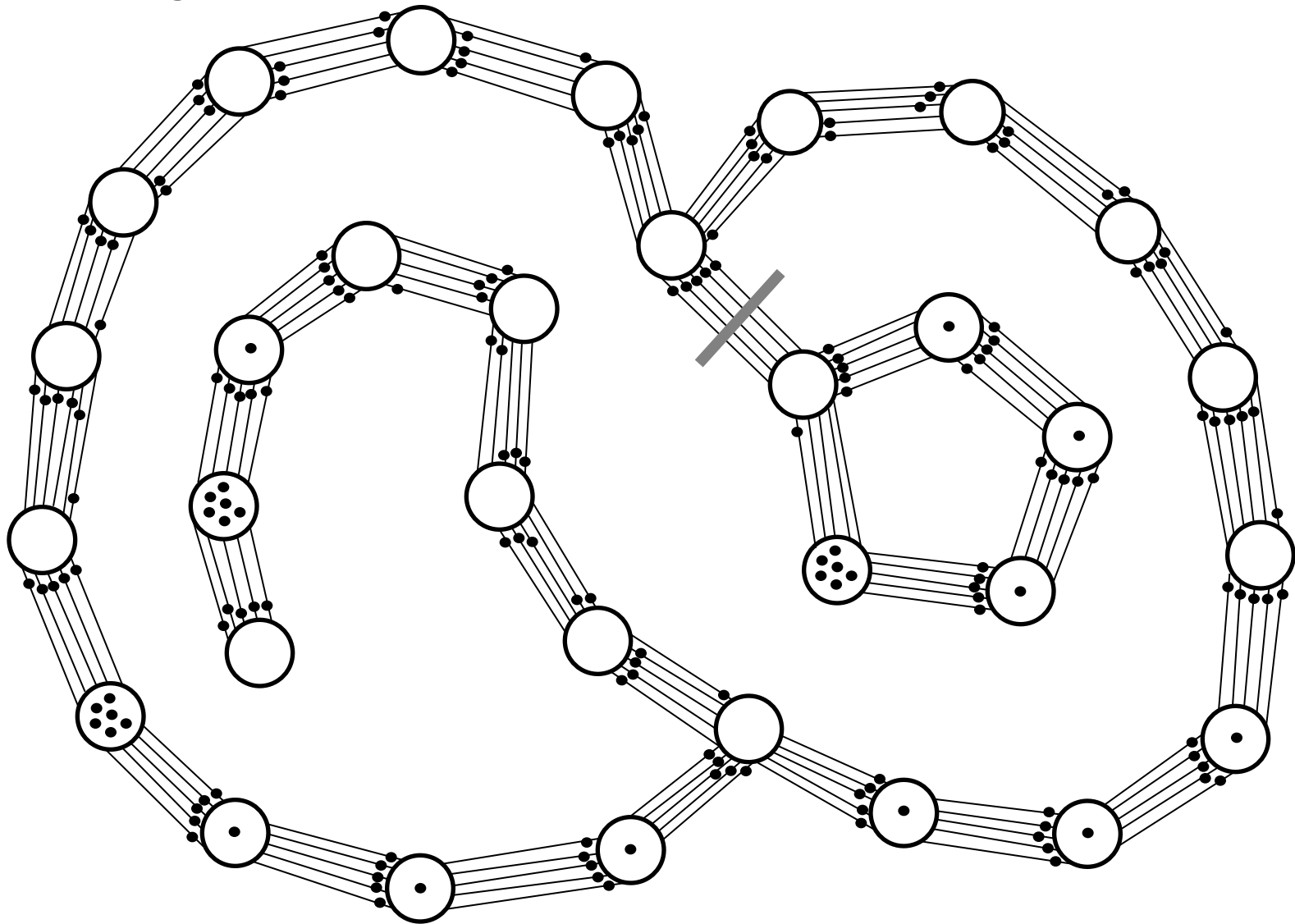
# 3D Body-bar Pebble Game

Continue placing 5 bars at rotatable bonds



# 3D Body-bar Pebble Game

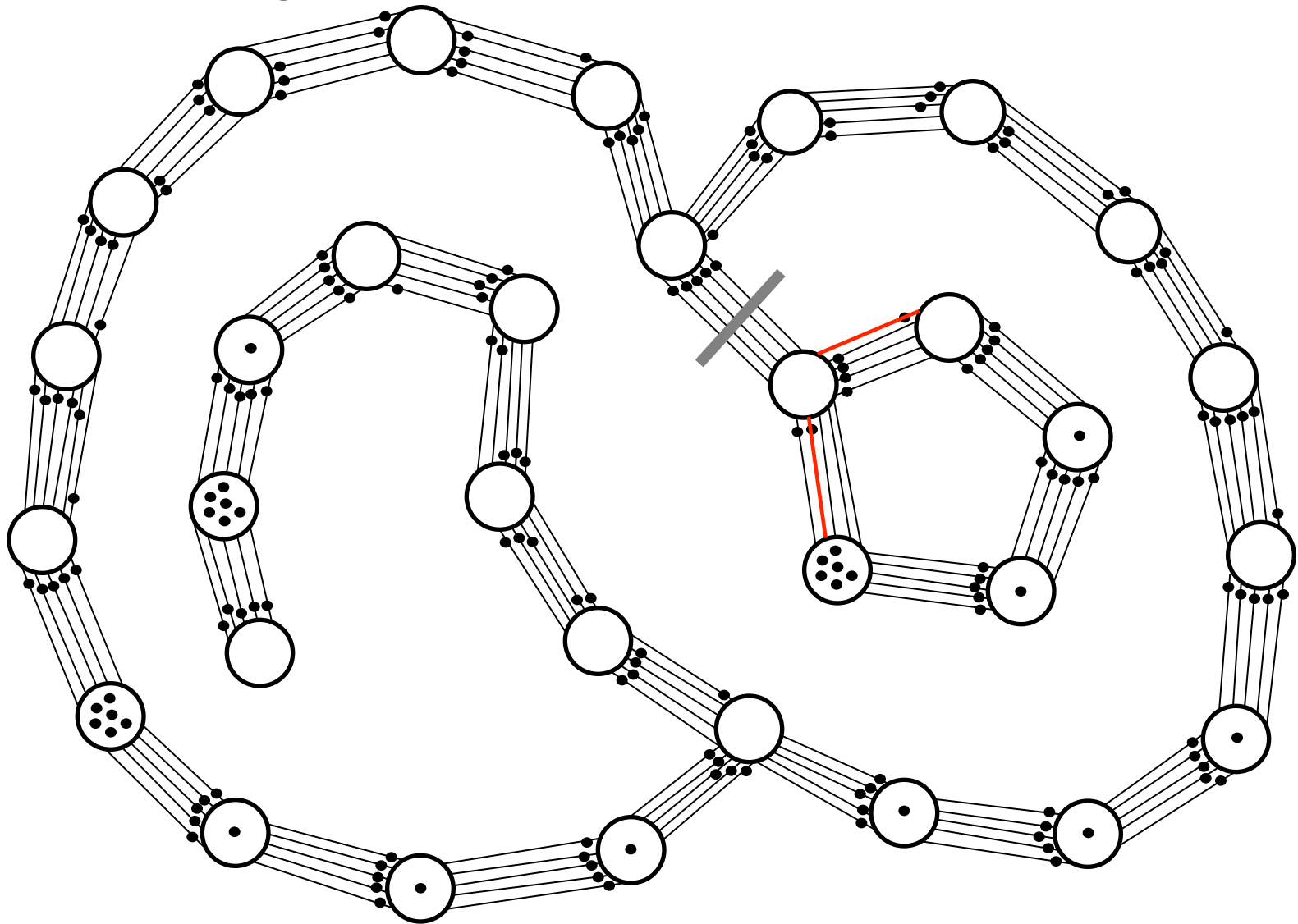
Continue placing 5 bars at rotatable bonds





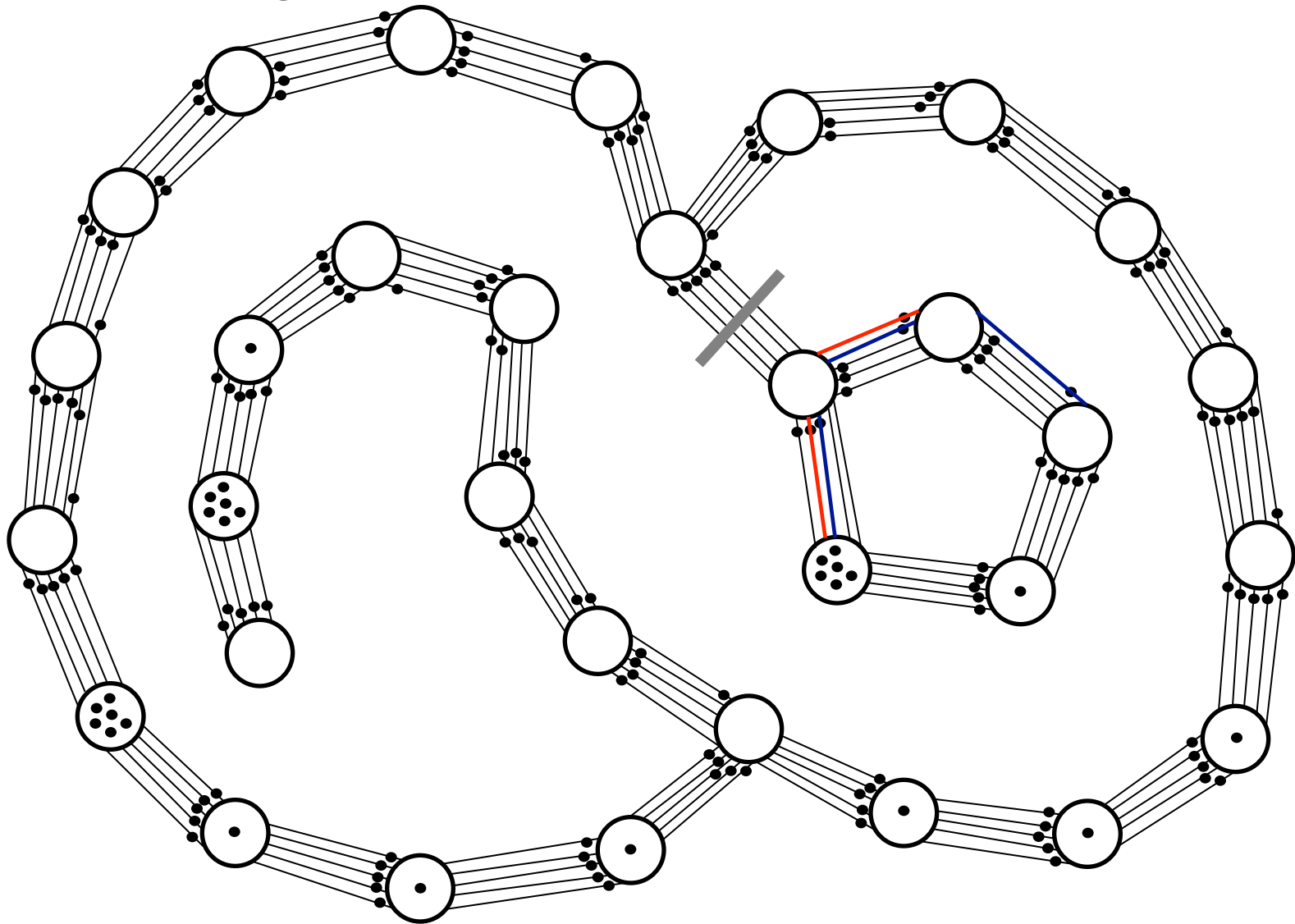
# 3D Body-bar Pebble Game

## Pebble Search/Exchange Operation



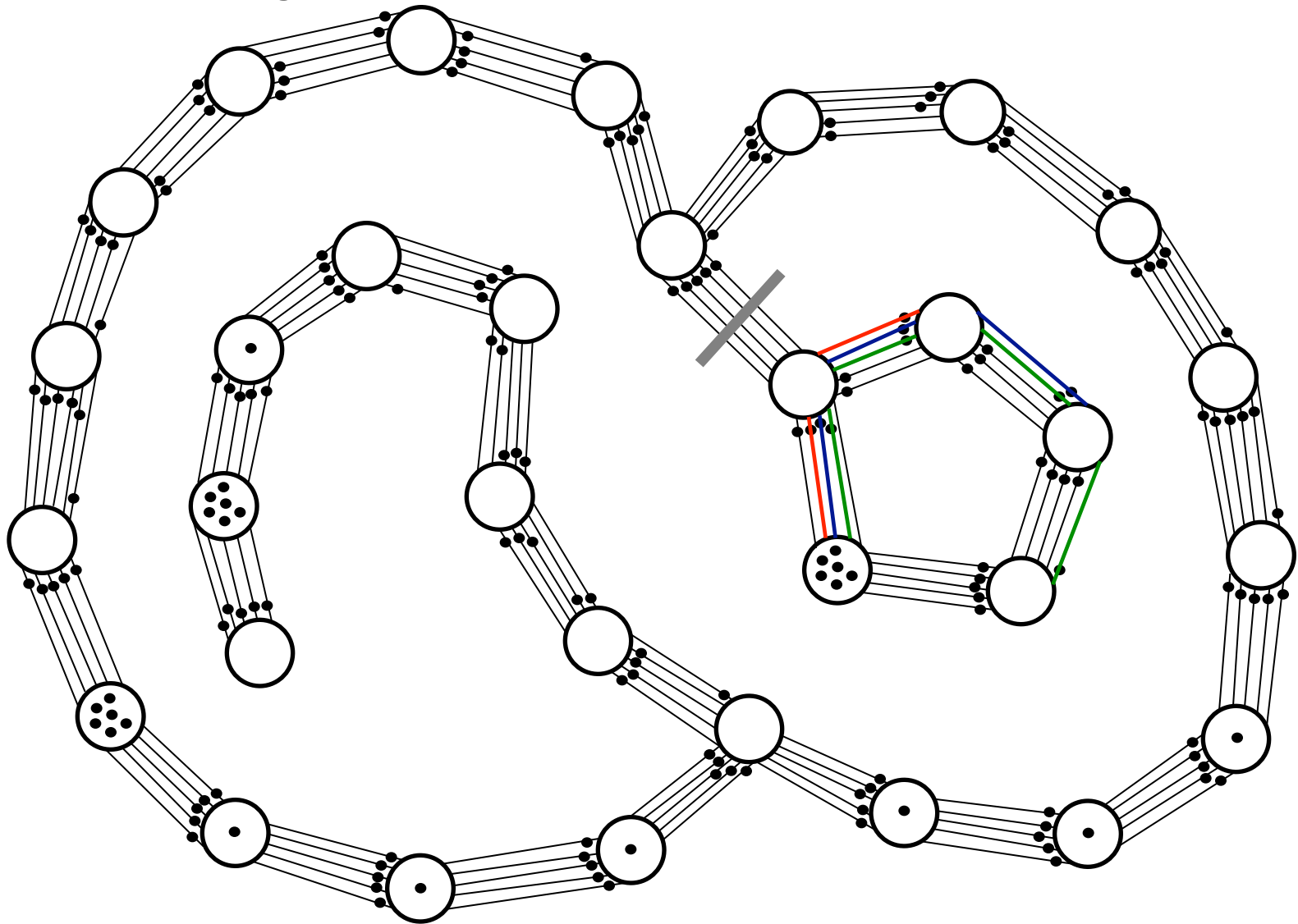
# 3D Body-bar Pebble Game

## Pebble Search/Exchange Operation



# 3D Body-bar Pebble Game

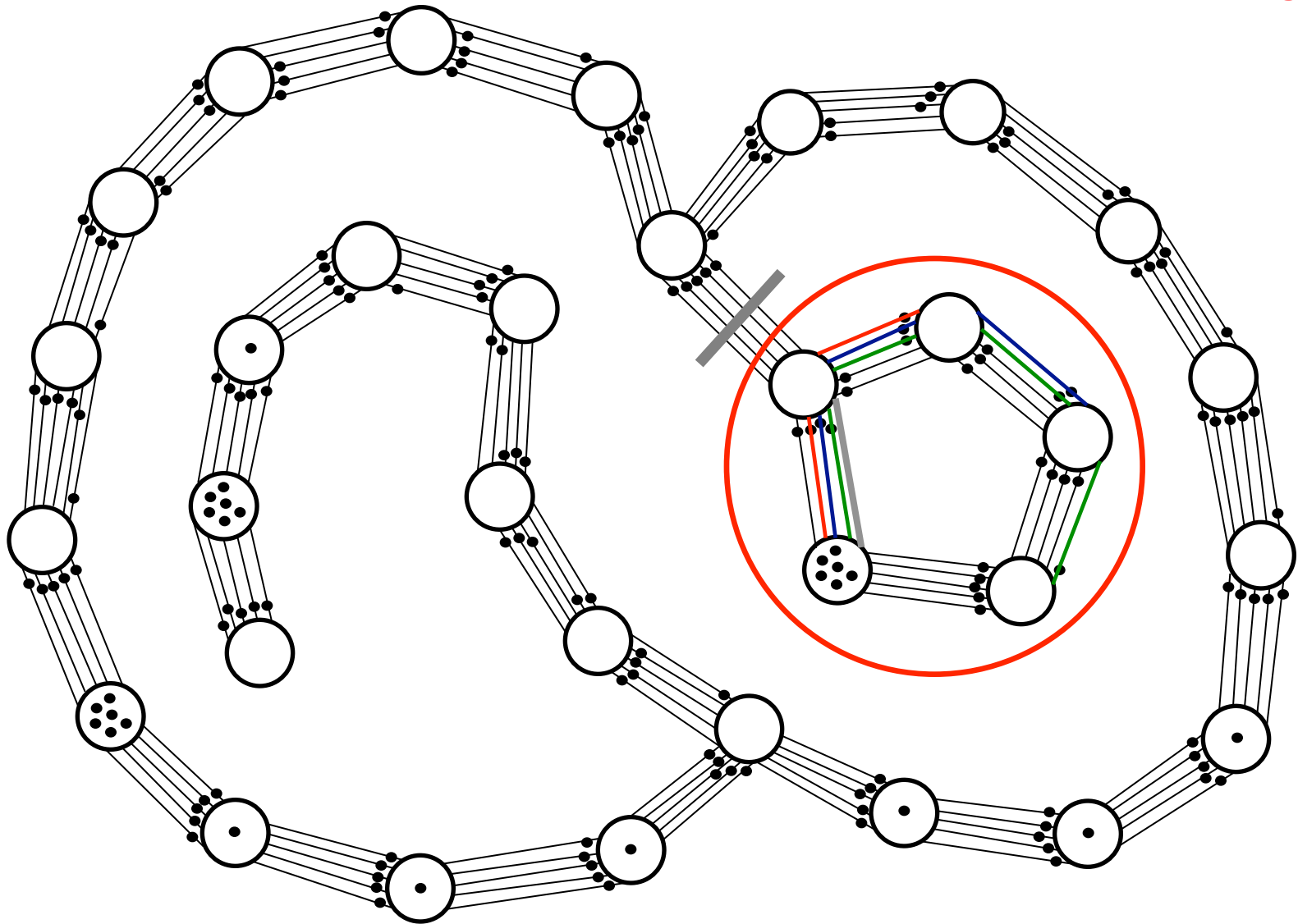
## Pebble Search/Exchange Operation



# 3D Body-bar Pebble Game

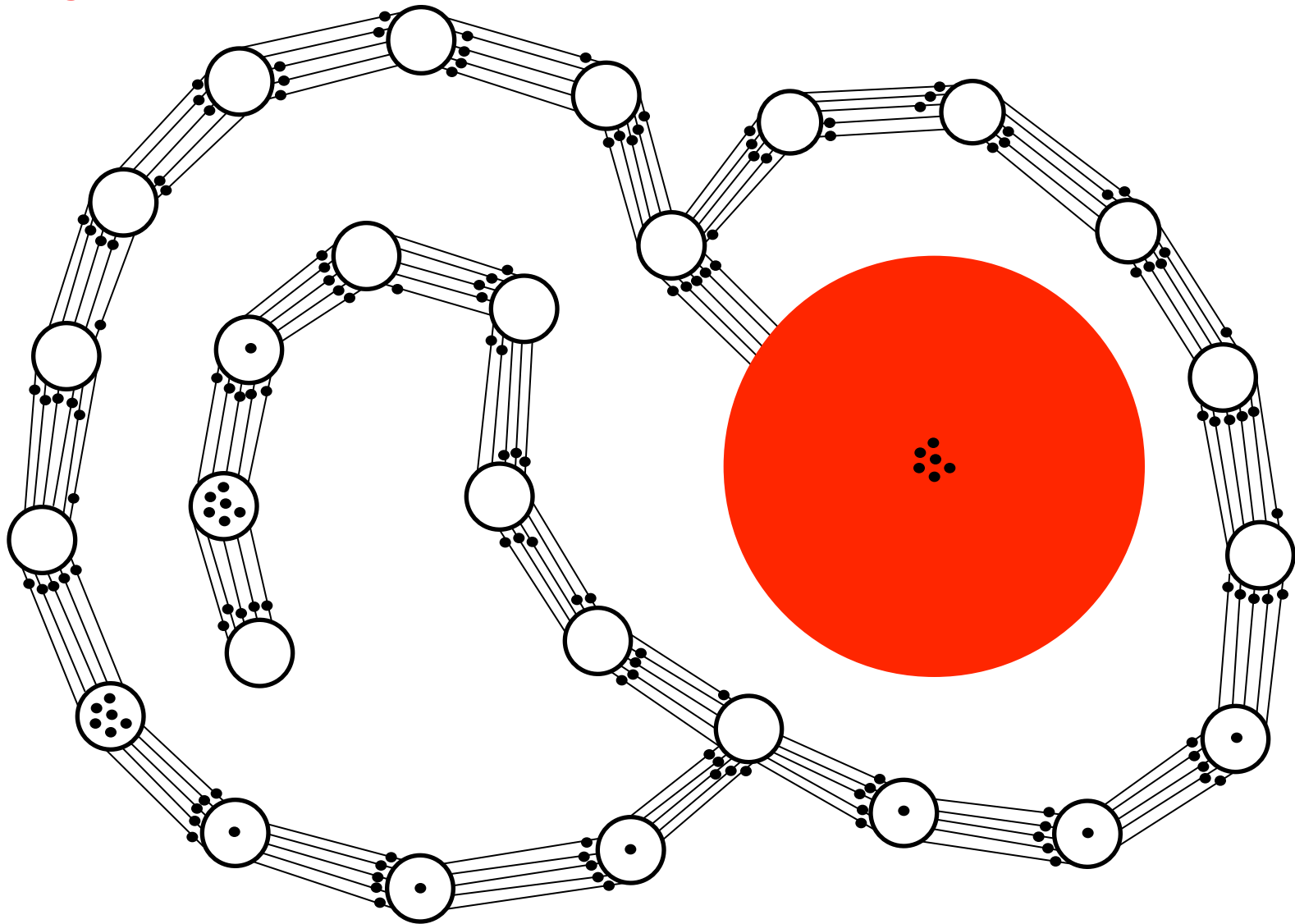
**FAILED PEBBLE SEARCH**

**RECORD Laman subgraph**



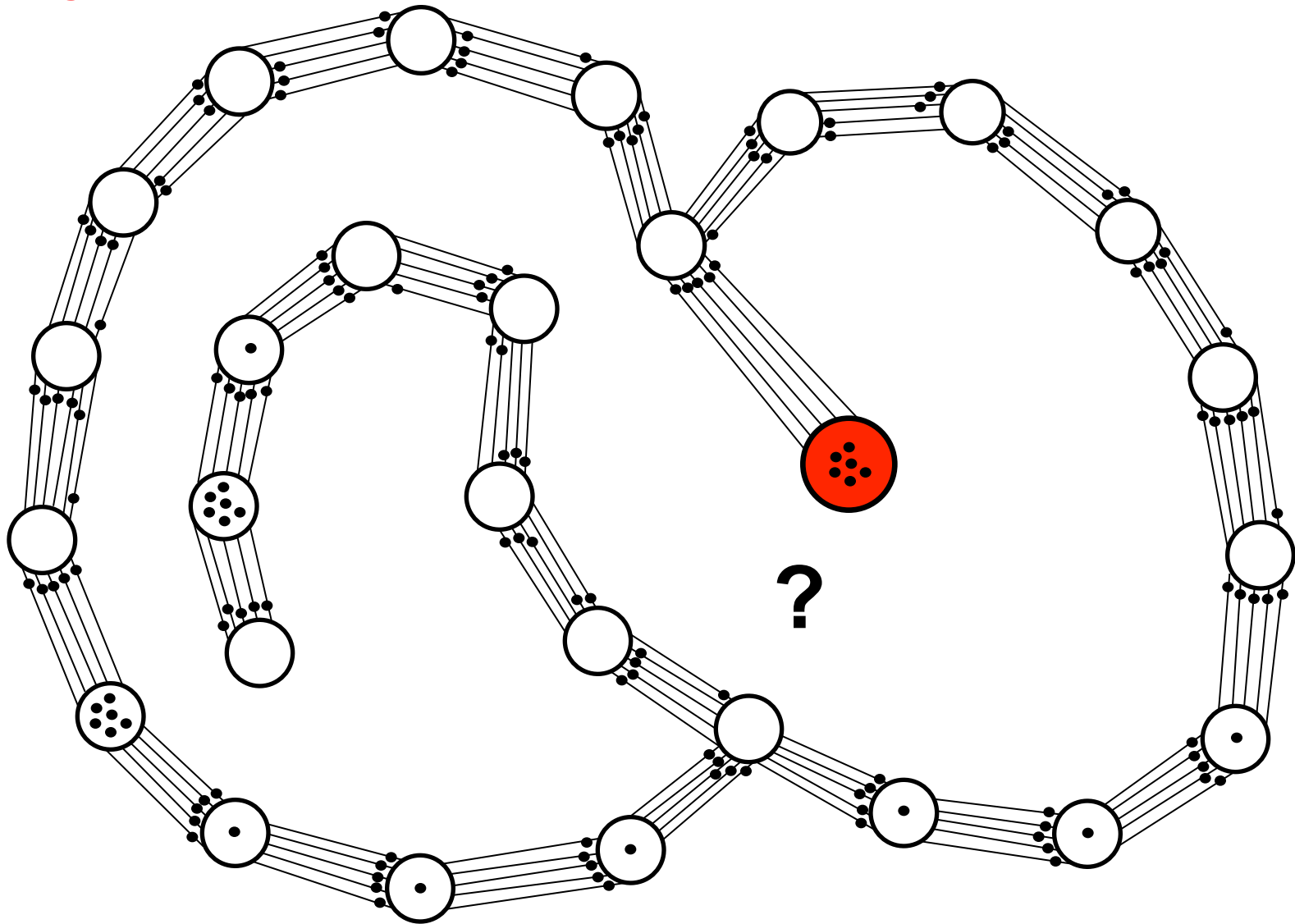
# 3D Body-bar Pebble Game

## Laman subgraph CONDENSATION



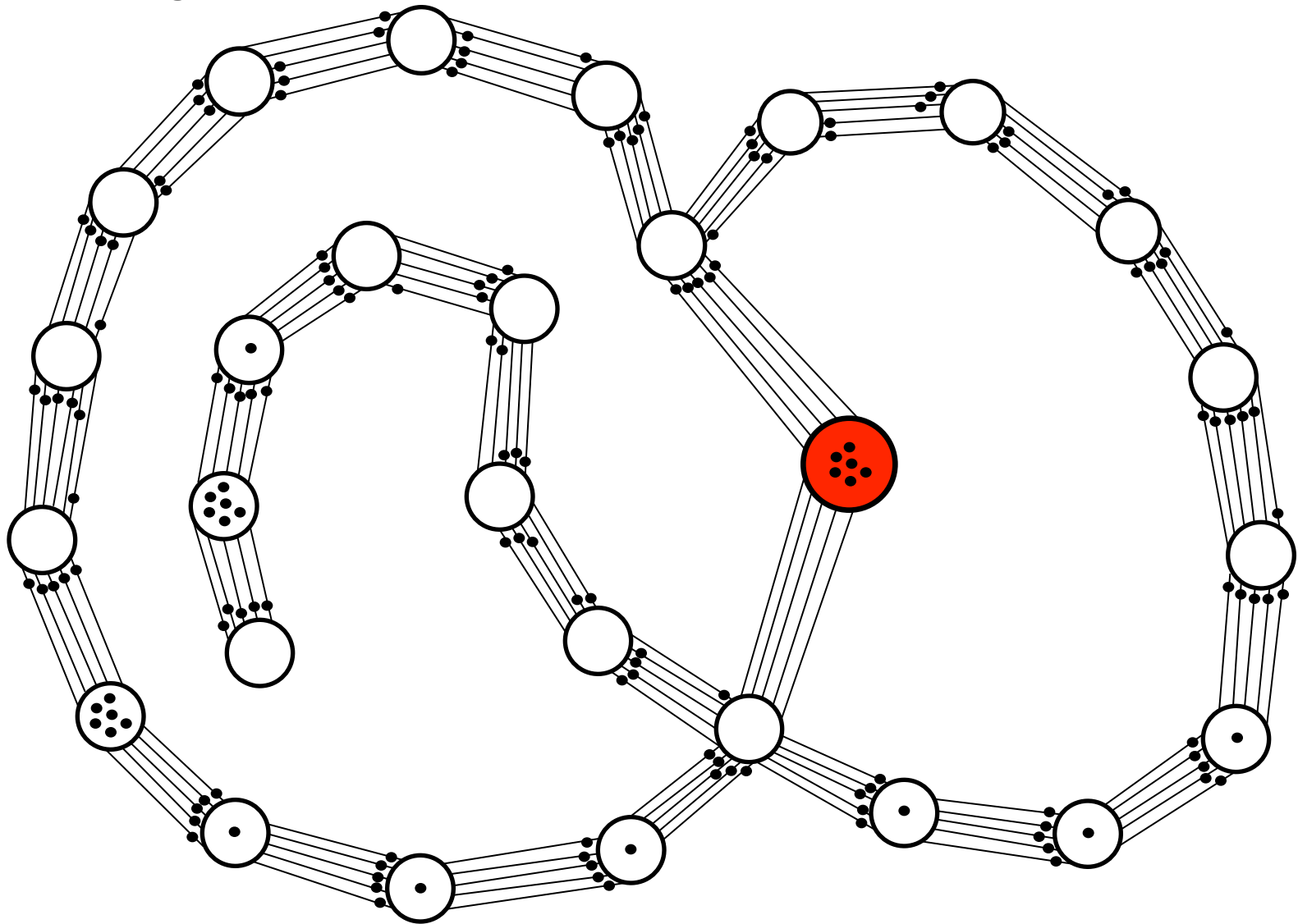
# 3D Body-bar Pebble Game

## Laman subgraph CONDENSATION



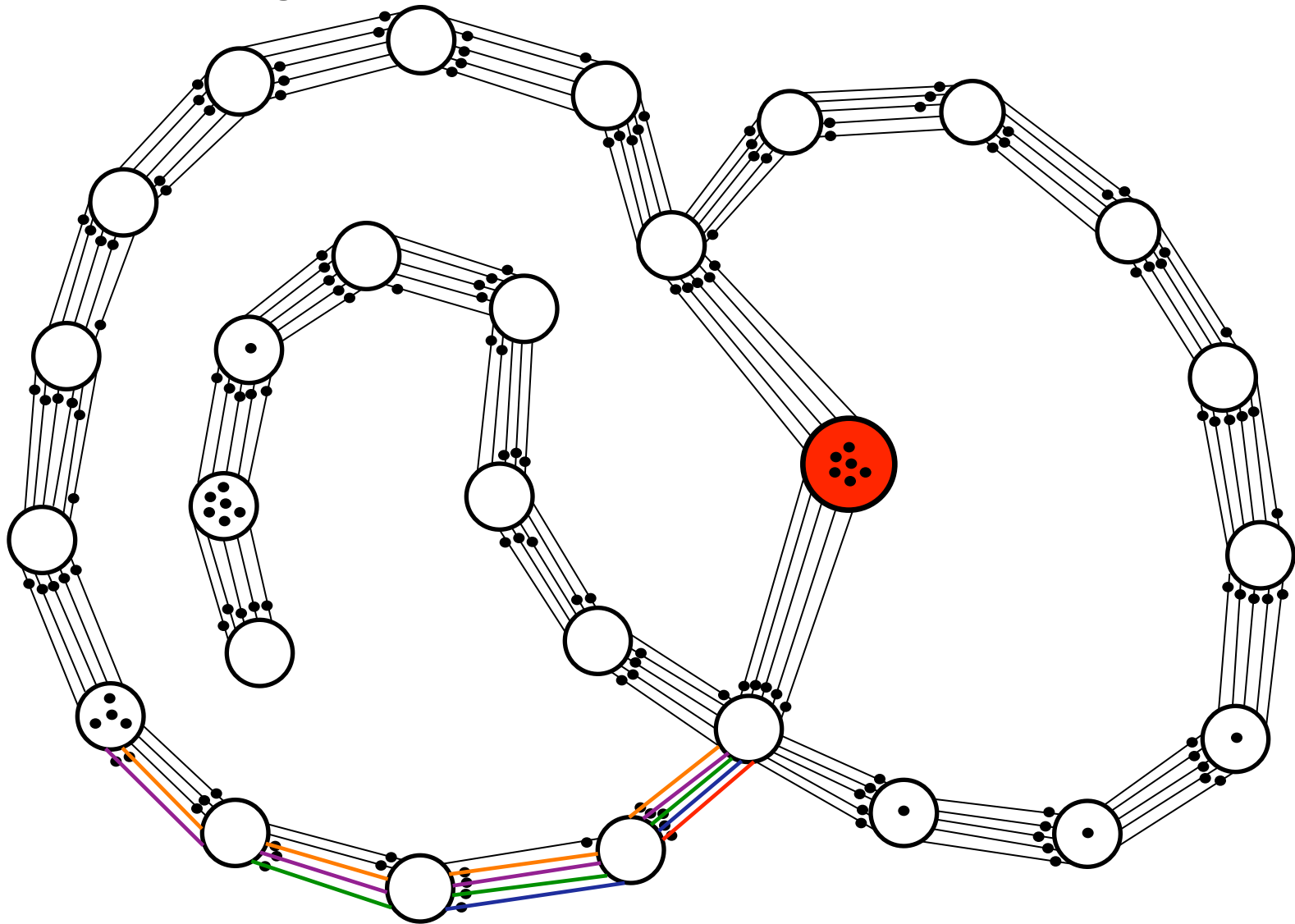
# 3D Body-bar Pebble Game

Continue placing 5 bars at rotatable bonds



# 3D Body-bar Pebble Game

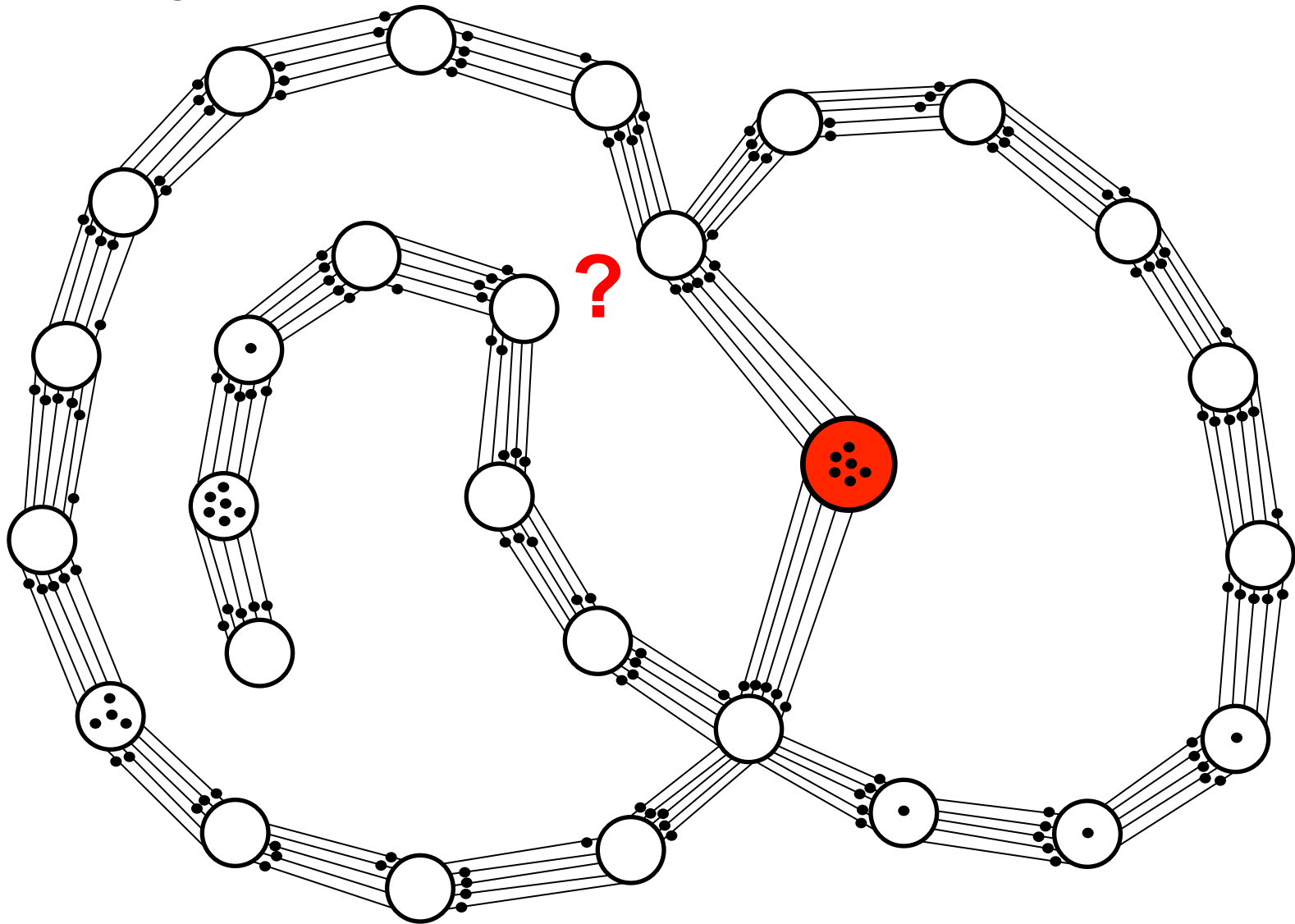
## Pebble Search/Exchange Operation





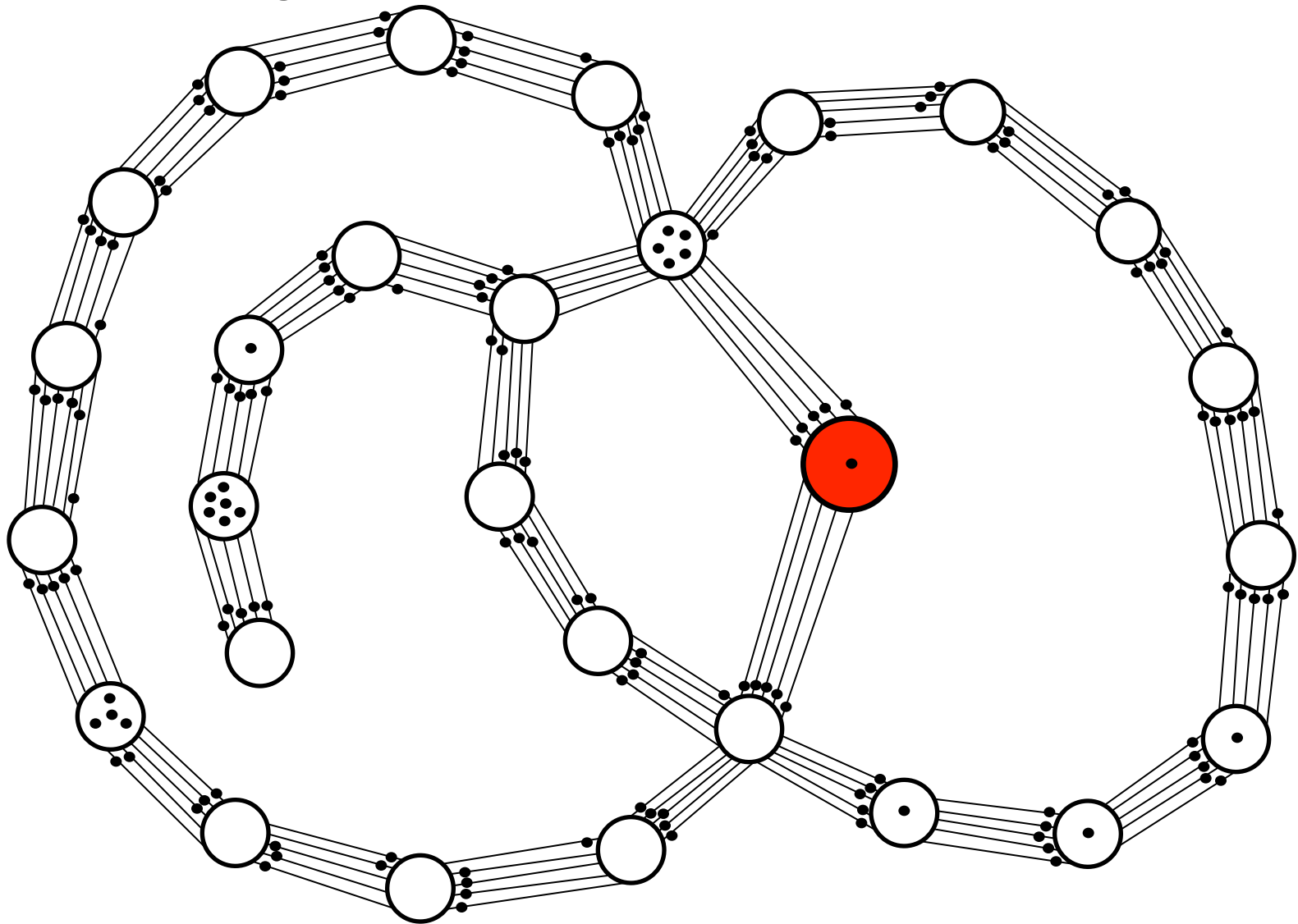
# 3D Body-bar Pebble Game

Continue placing 5 bars at rotatable bonds



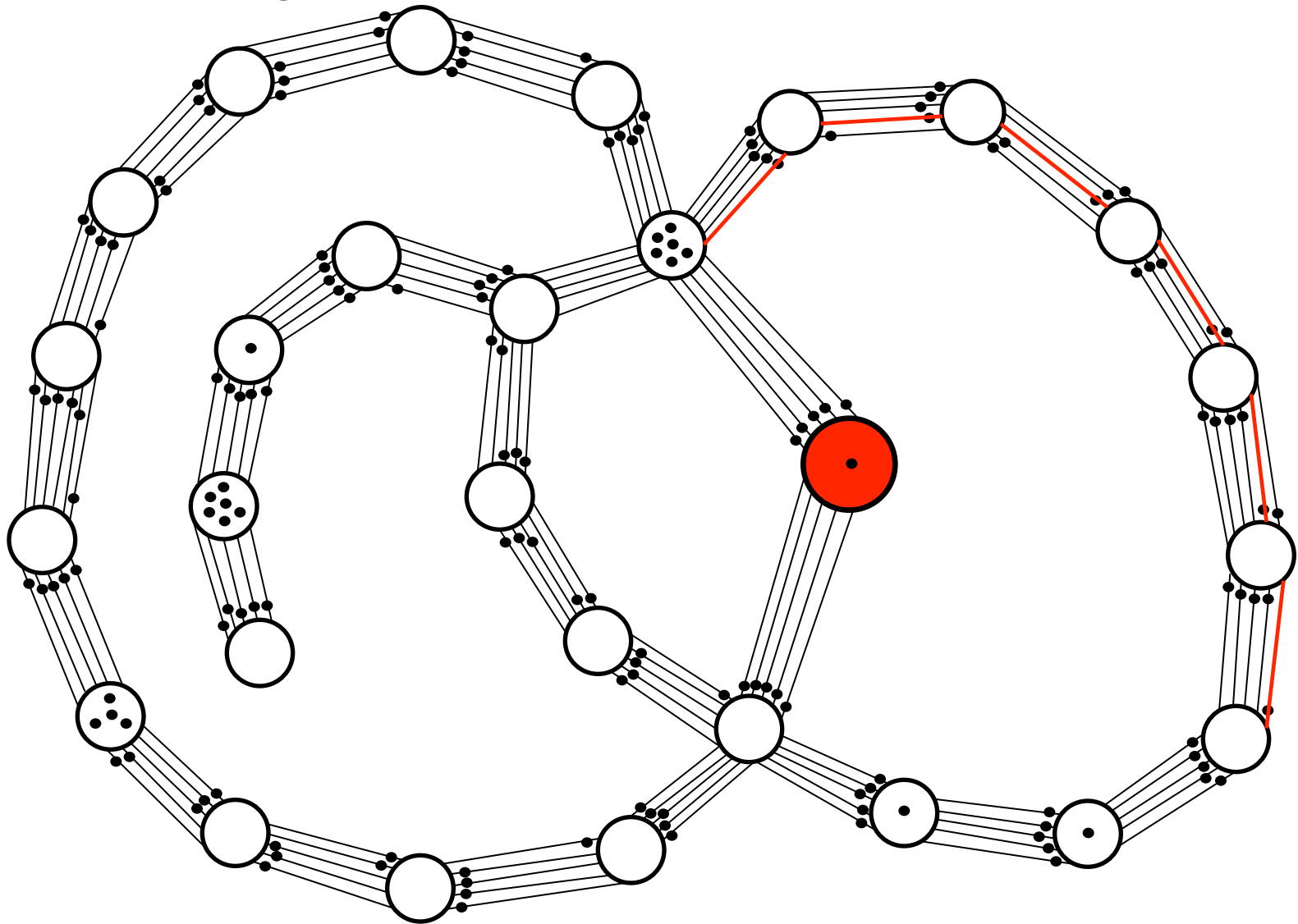
# 3D Body-bar Pebble Game

Pebble Search/Exchange Operation



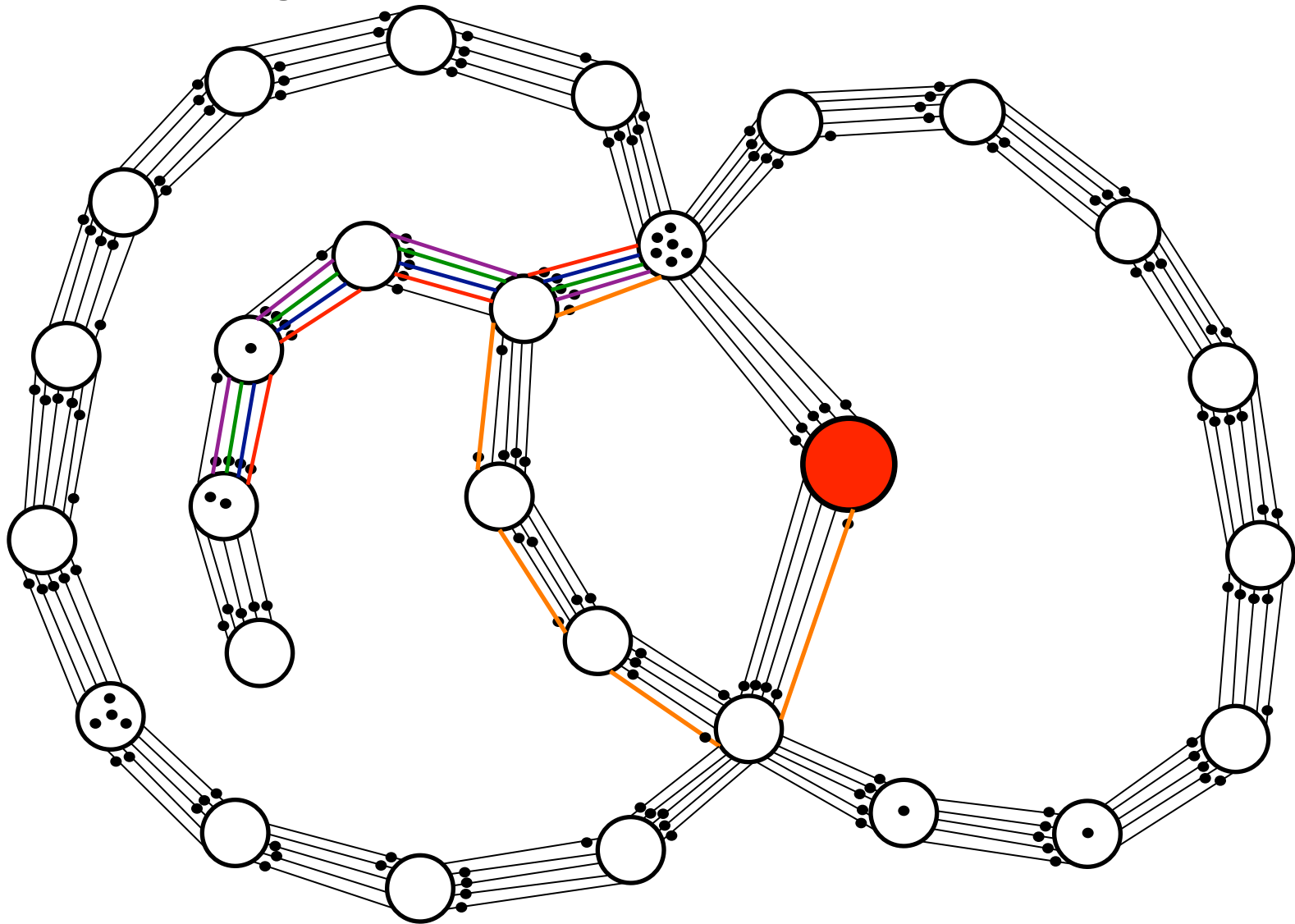
# 3D Body-bar Pebble Game

Pebble Search/Exchange Operation



# 3D Body-bar Pebble Game

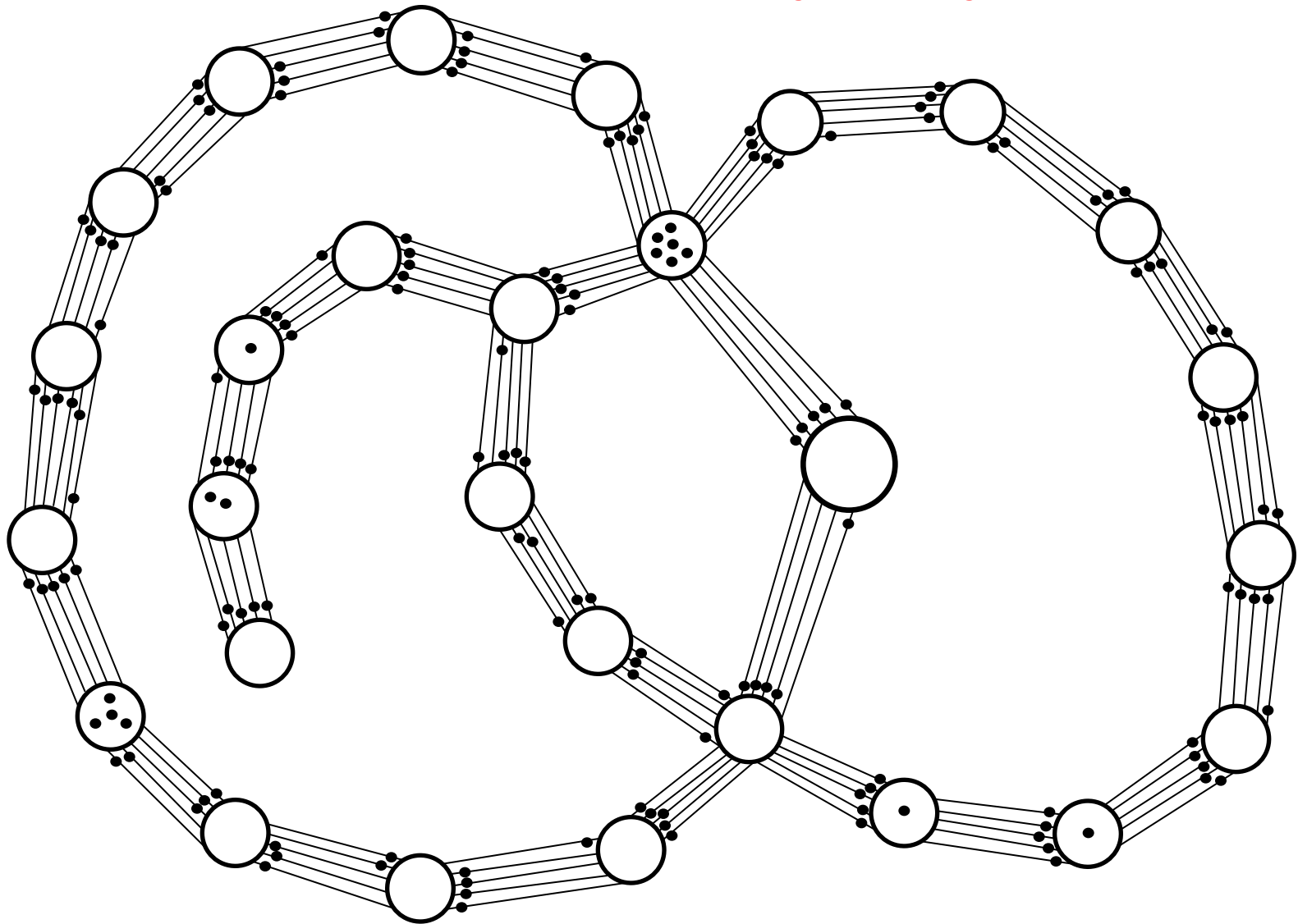
## Pebble Search/Exchange Operation



# 3D Body-bar Pebble Game

Rigid Cluster Decomposition

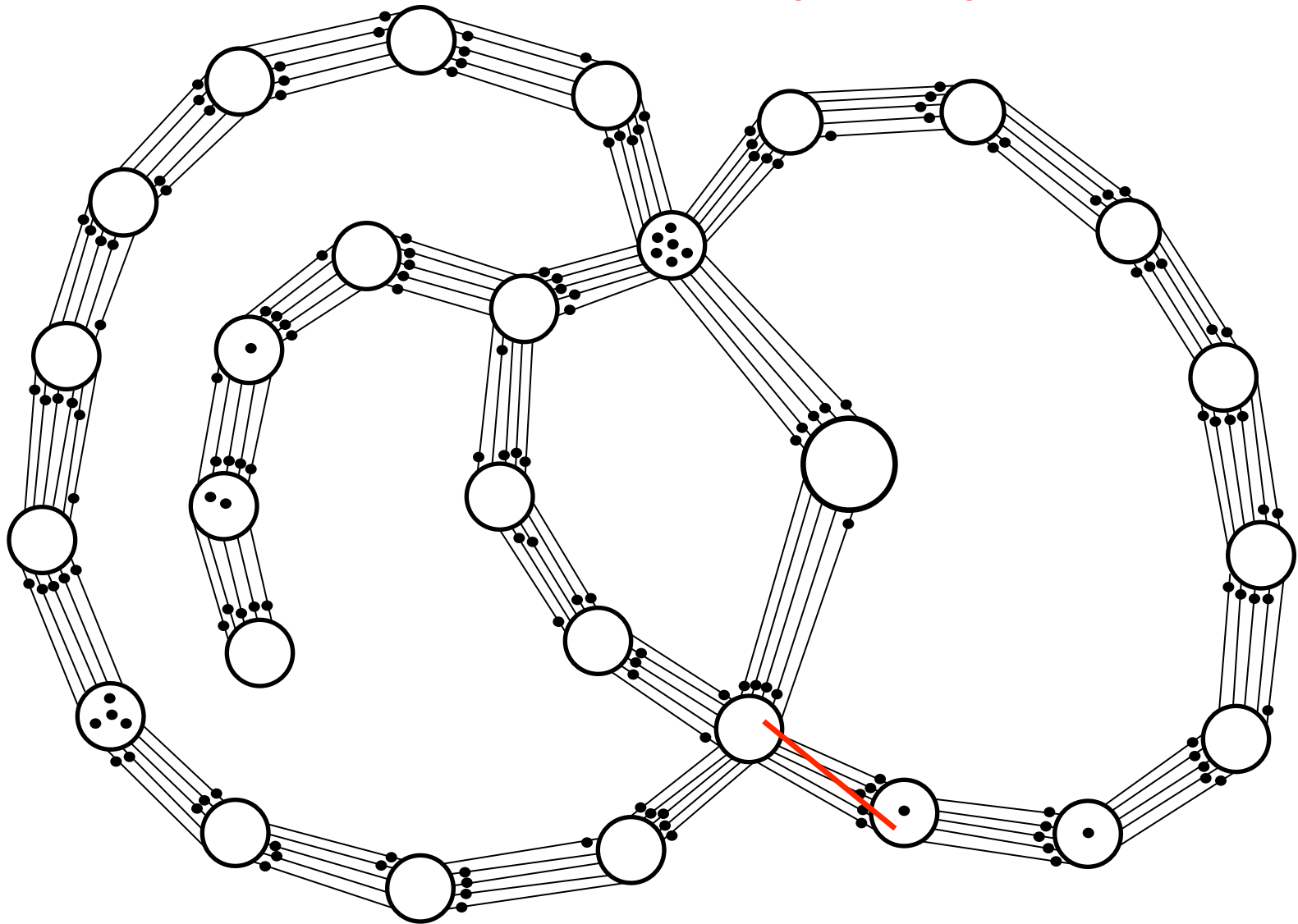
Apply auxiliary external constraint



# 3D Body-bar Pebble Game

Rigid Cluster Decomposition

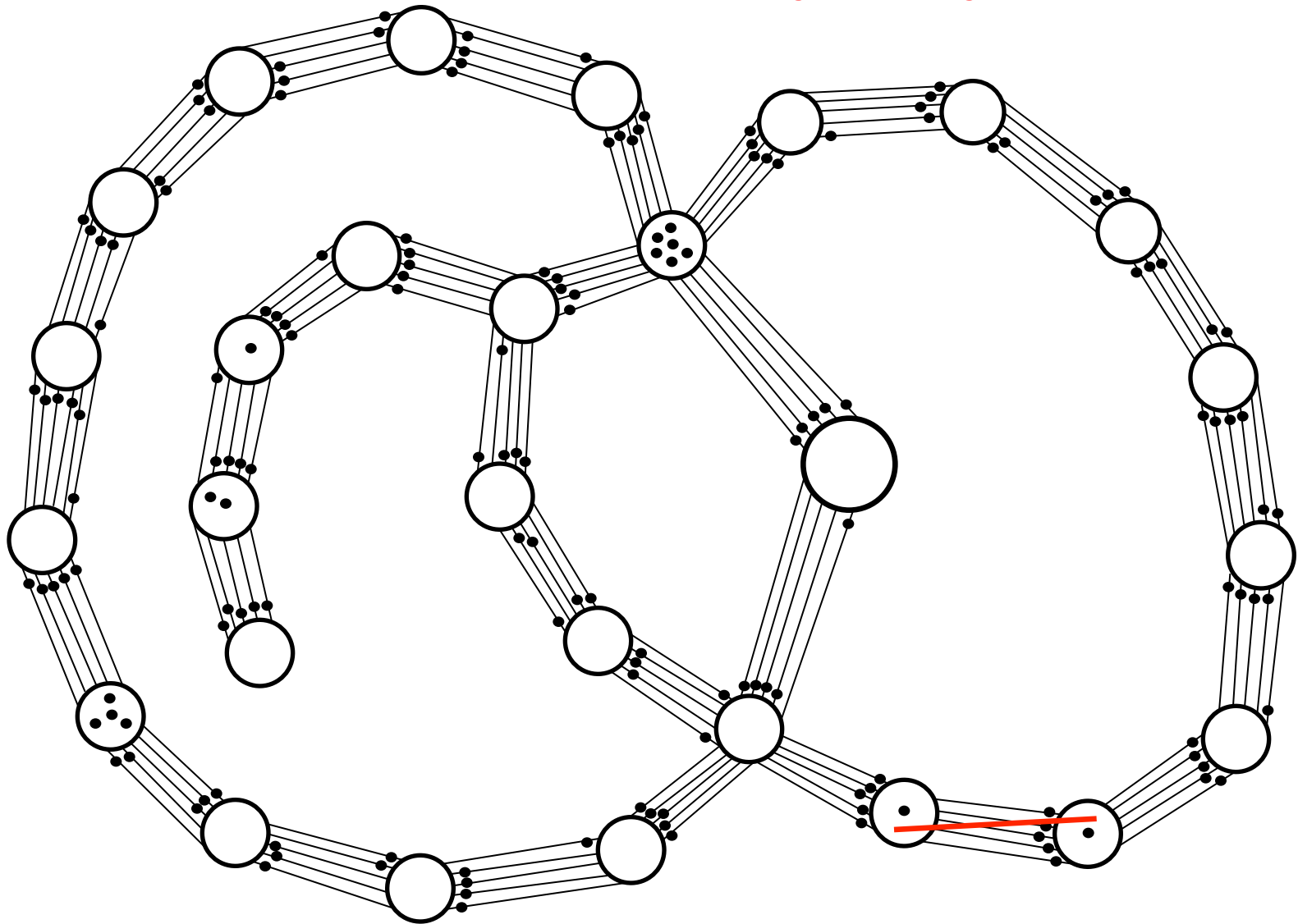
Apply auxiliary external constraint



# 3D Body-bar Pebble Game

Rigid Cluster Decomposition

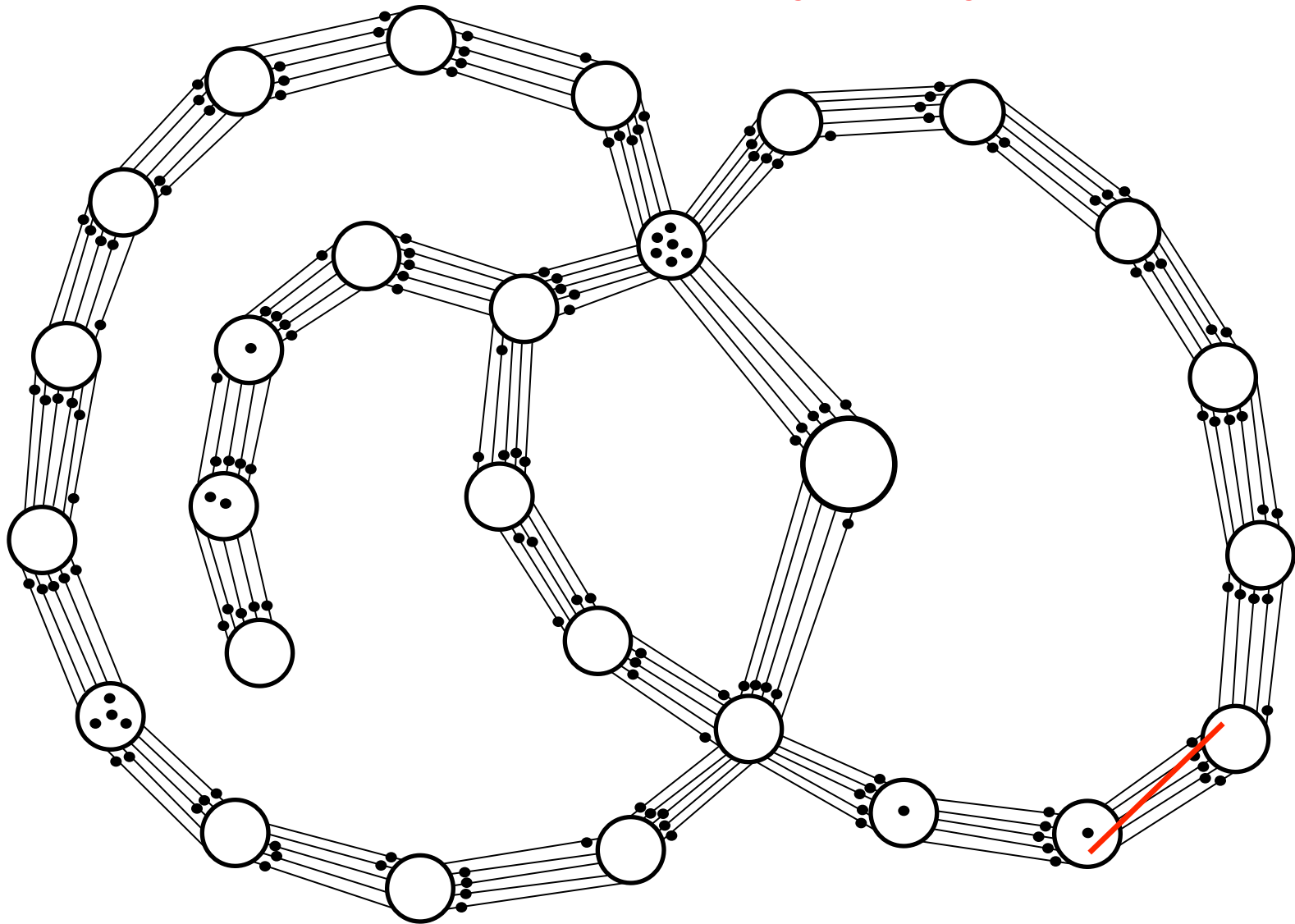
Apply auxiliary external constraint



# 3D Body-bar Pebble Game

Rigid Cluster Decomposition

Apply auxiliary external constraint

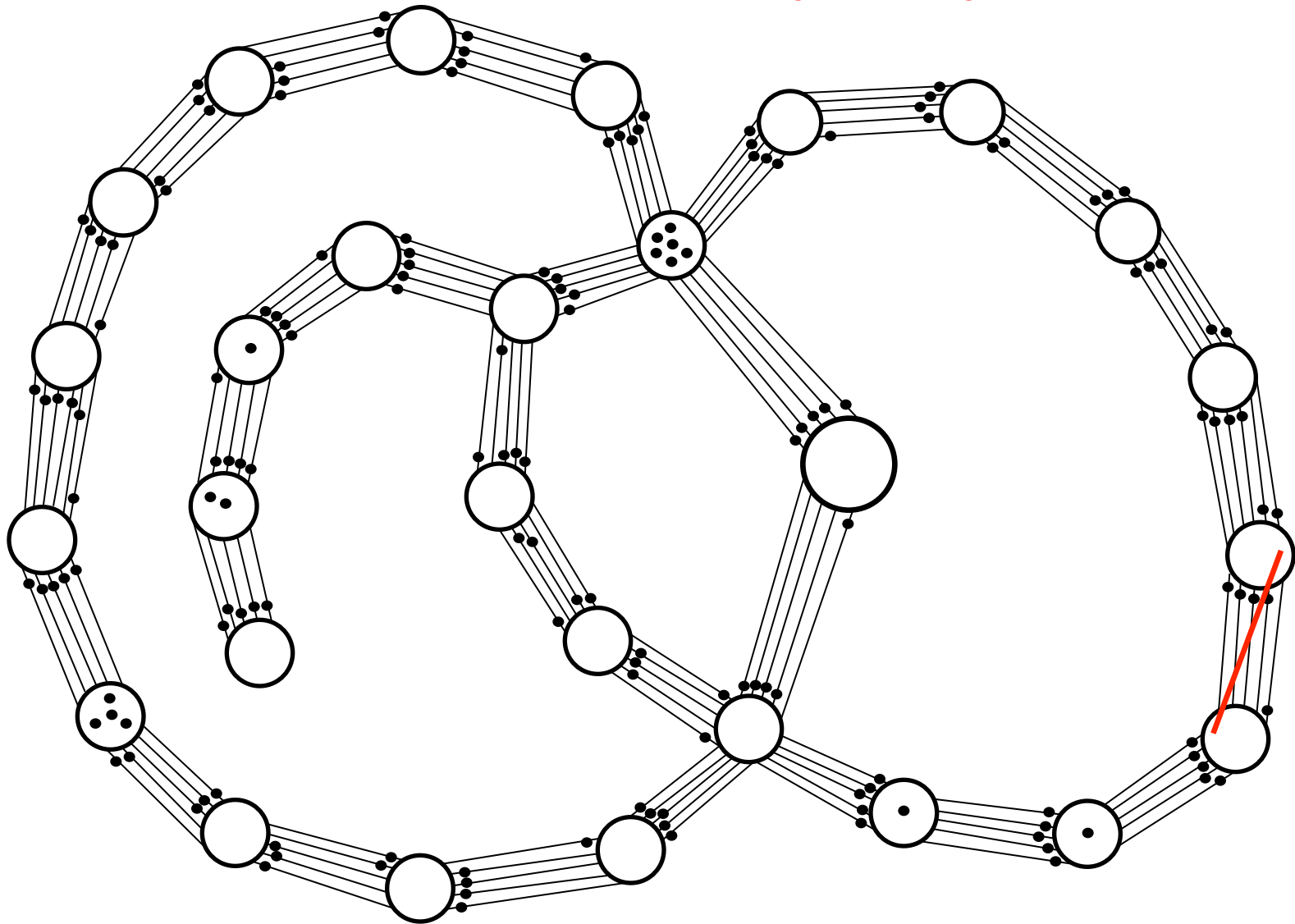




# 3D Body-bar Pebble Game

Rigid Cluster Decomposition

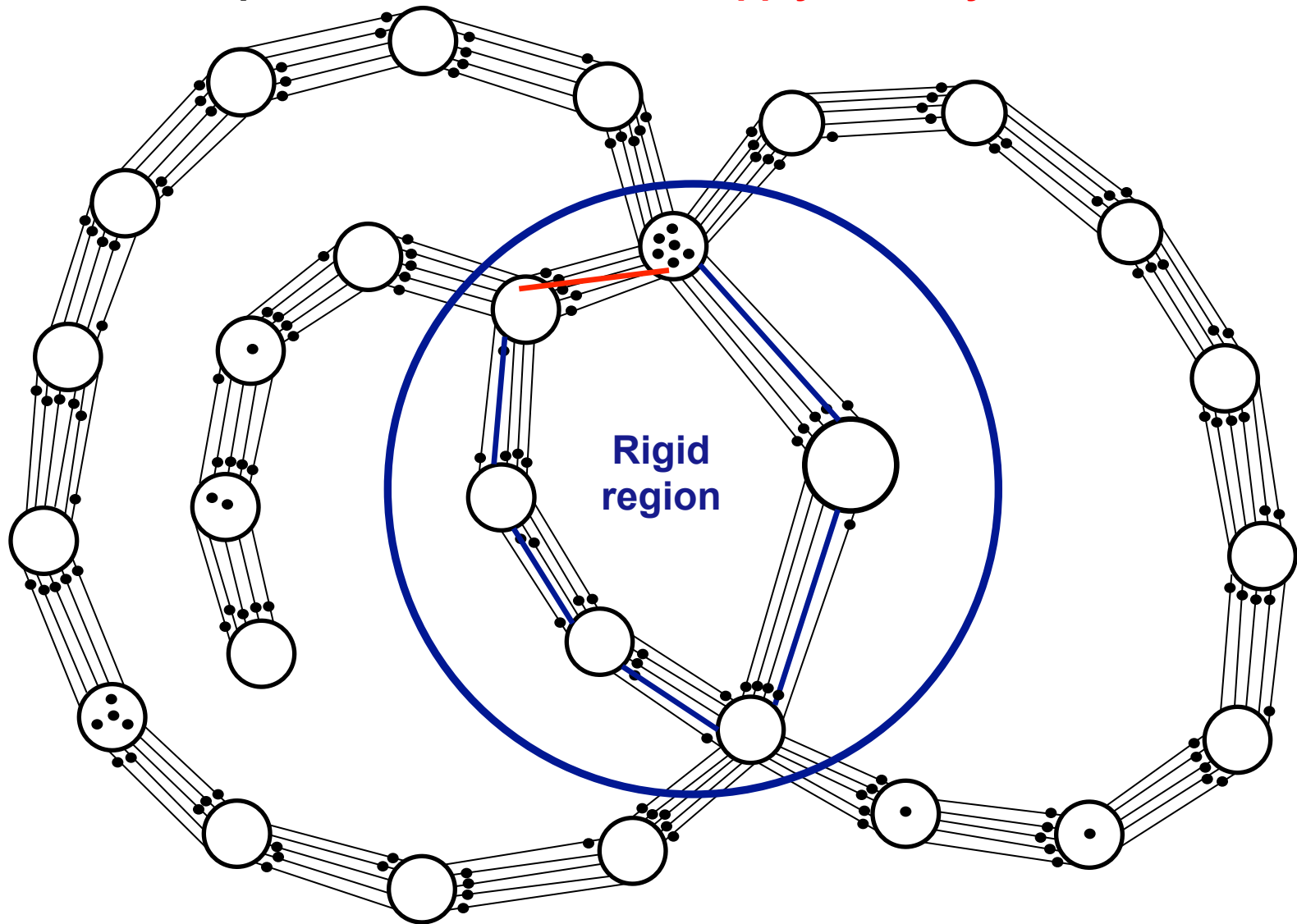
Apply auxiliary external constraint



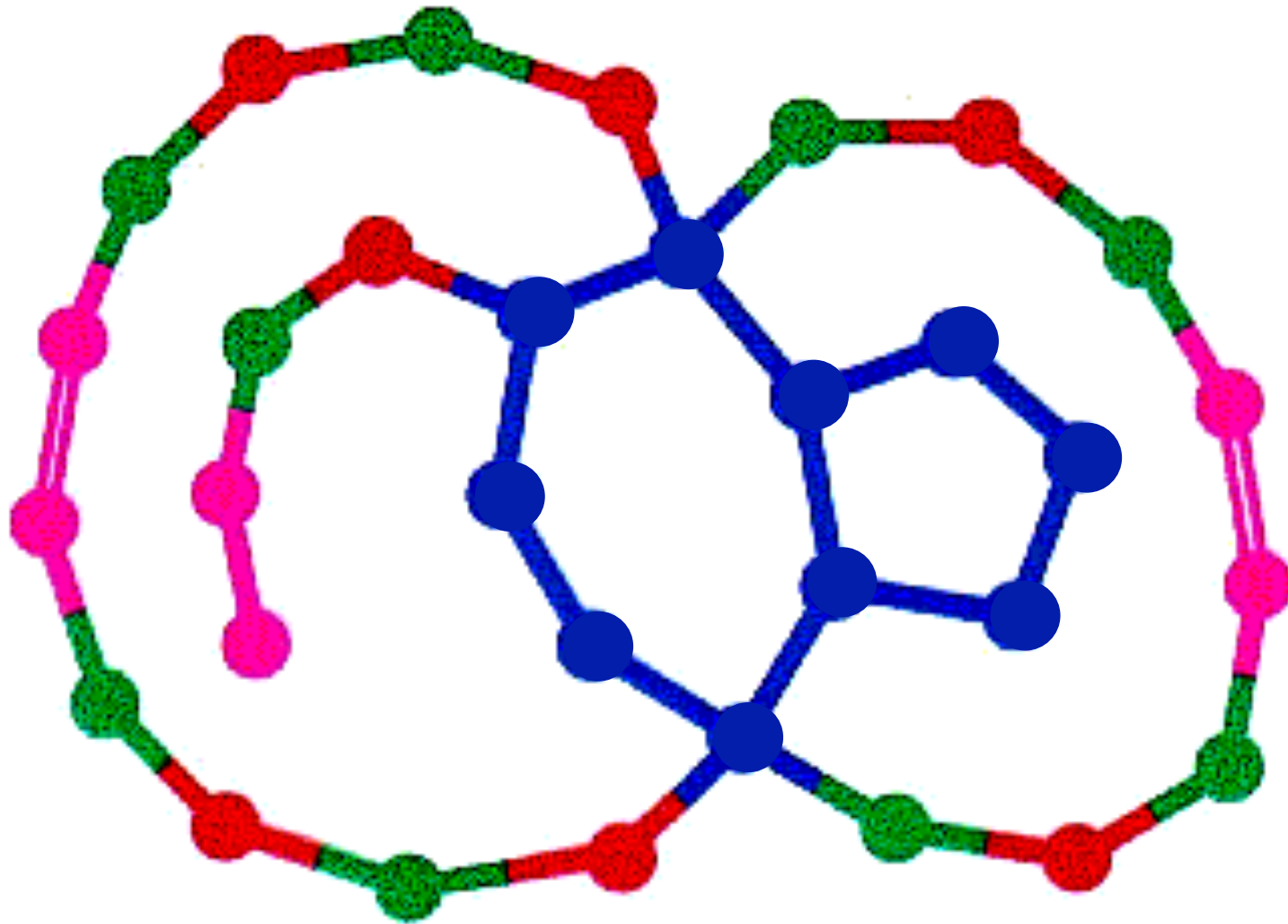
# 3D Body-bar Pebble Game

Rigid Cluster Decomposition

Apply auxiliary external constraint



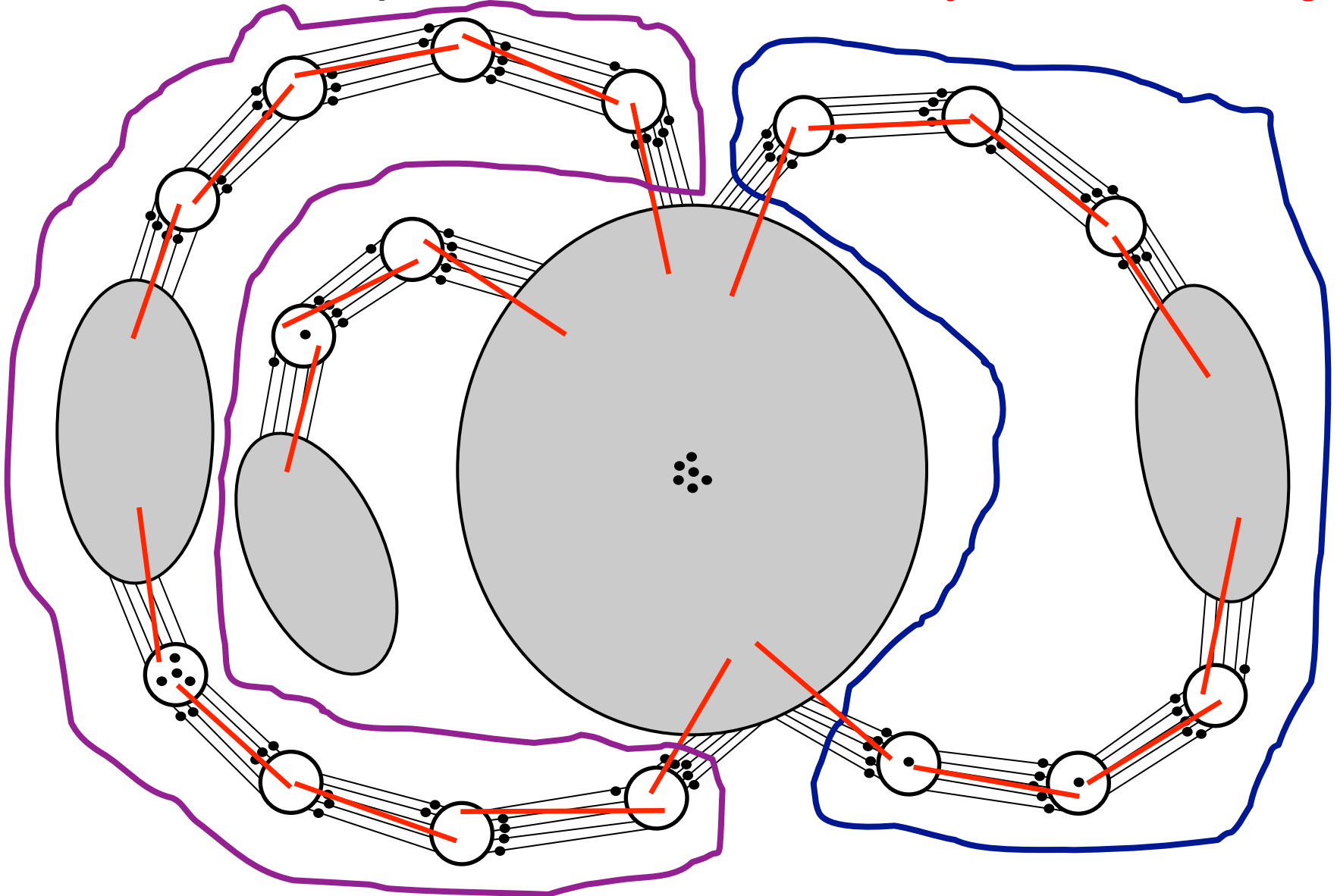
Each Rigid Body (circle) can belong to one and only one rigid substructure

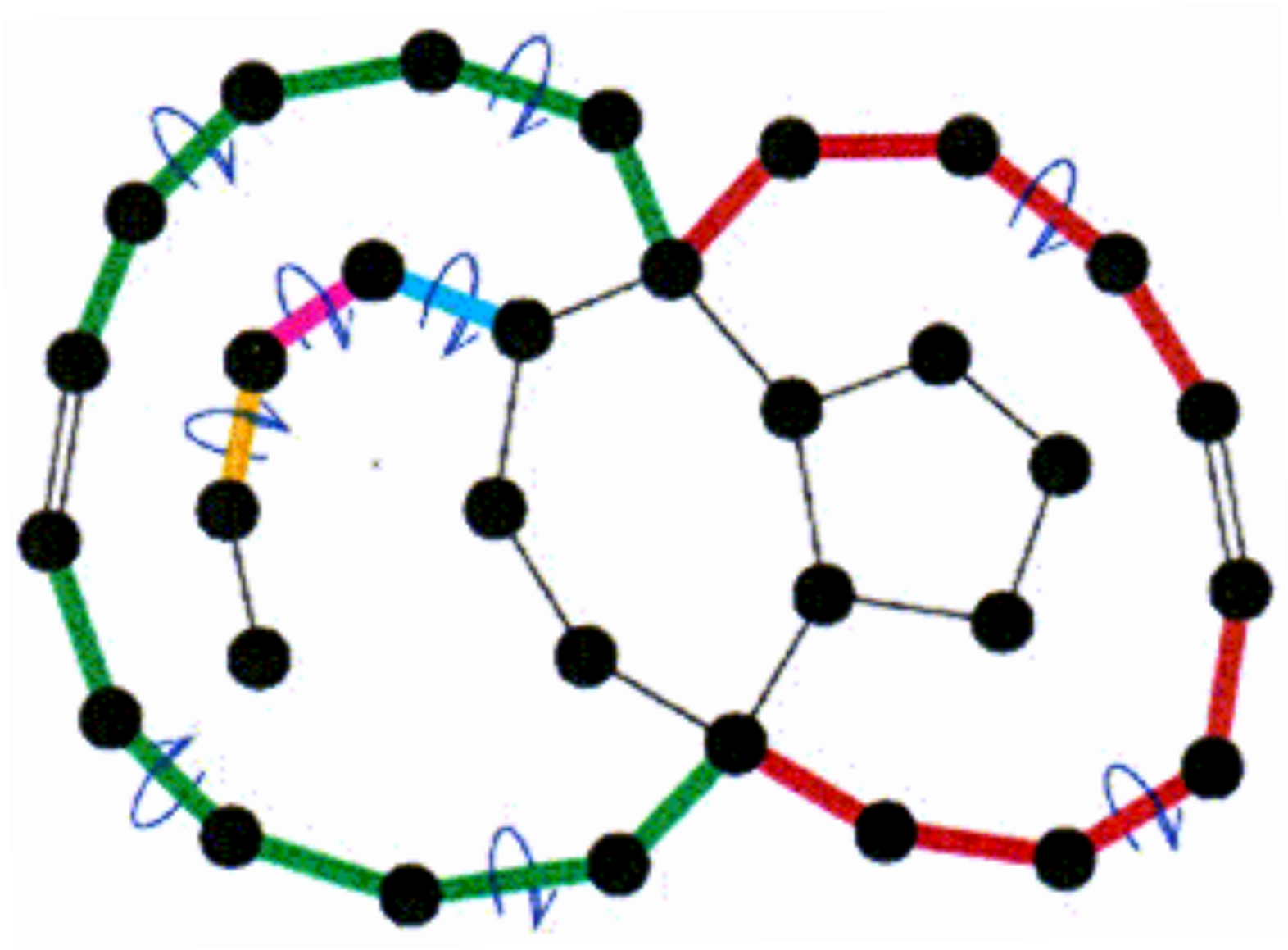


# 3D Body-bar Pebble Game

Correlated Motion Decomposition

Externally constrain each hinge





# Modeling Molecular Interactions

Input structure

**Modeling**

Pebble game

Constraint counting

Laman Condensation

Rigid Cluster Decomposition

Correlated Motion Decomposition

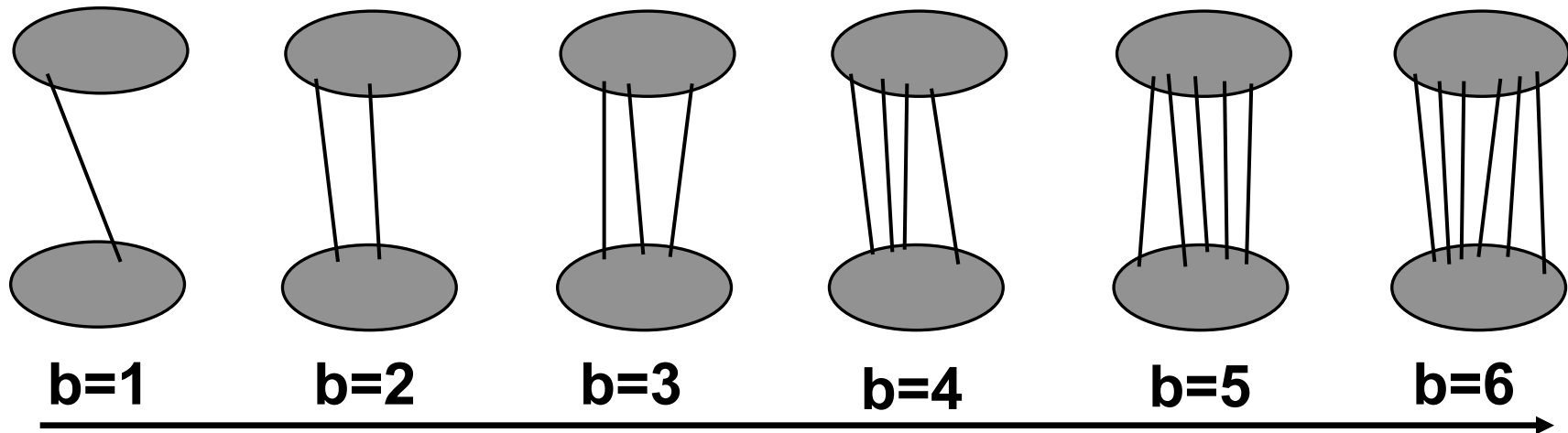
Output

0-connected bodies: assign 3 dof

1-connected bodies: assign 5 dof

n-connected bodies: assign 6 dof for  $n > 1$

Increase in mechanical relevance of a constraint



Increase in number of bars within a constraint

# Body-bar representation

# FIRST Applications

Input structure  
Modeling  
Pebble game  
  Constraint counting  
  Laman Condensation  
  Rigid Cluster Decomposition  
  Correlated Motion Decomposition  
Output

**FIRST** provides a stand-alone software that gives virtually instantaneous output for BIOLOGICAL INSIGHT.

But it is quite limited in utility

## ADDED VALUE APPLICATIONS

1. **ROCK** uses FIRST to pre-identify correlated flexible rings
2. **ENM/FIRST** allows very large spring networks to be analyzed
3. **FRODA** uses FIRST to partition protein into rigid substructures
4. **MD** analysis uses FIRST to post priori analyze atomic trajectories
5. **DCM** uses FIRST to construct accurate free energy decomposition



# Conclusion

**FIRST** has proven to be a useful tool, and has complemented many applications.

## Acknowledgements:

### **Pre-FIRST work on rigidity**

Debbie Franzblau  
Bruce Hendrickson  
Phil Duxbury

### **Key people involved in FIRST origins:**

Mike Thorpe  
Walter Whiteley  
Leslie Kuhn  
Mykyta Chubynsky  
Andrew Rader  
Brandon Hespenheide