Conformational design of self-organizing ribozymes

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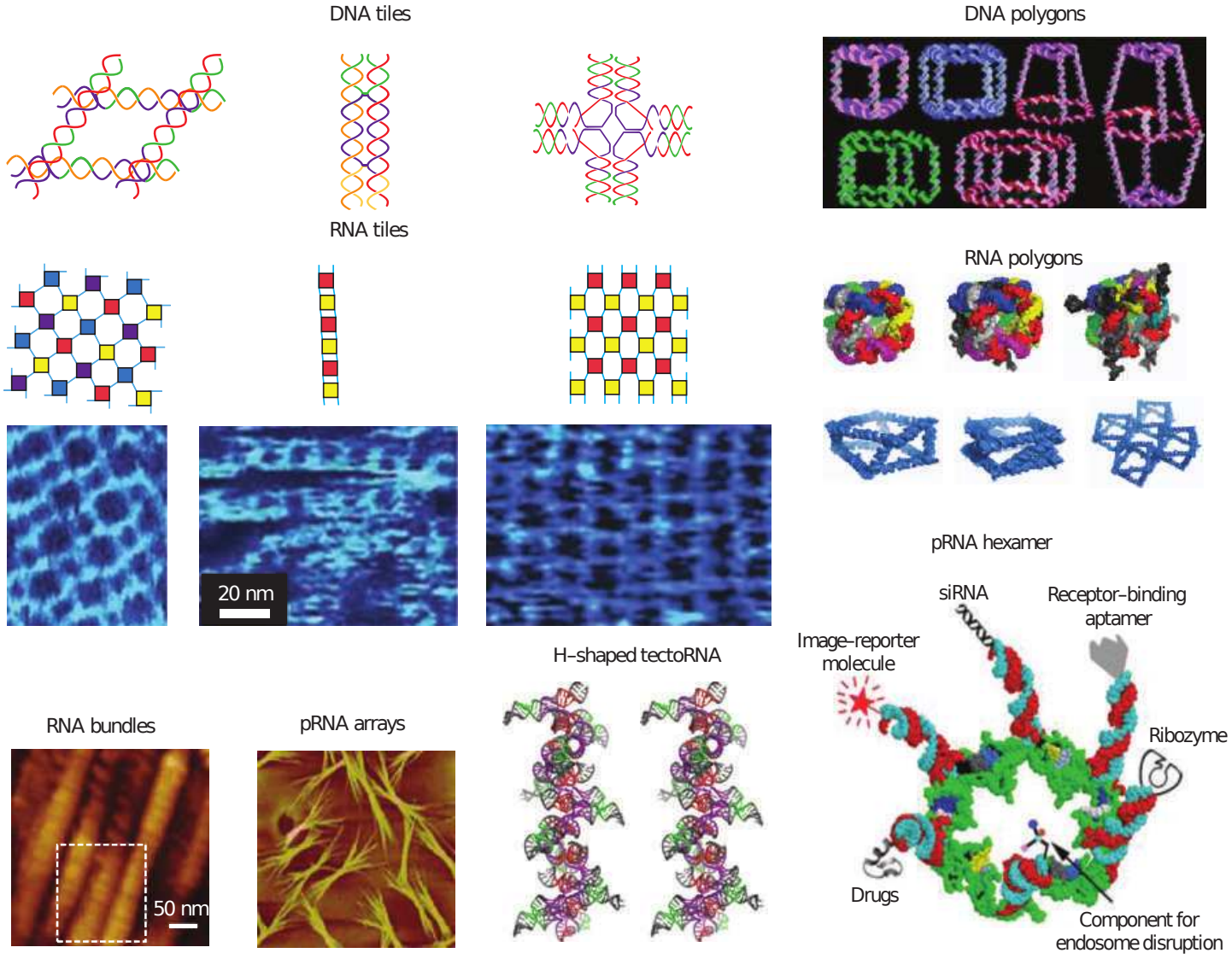
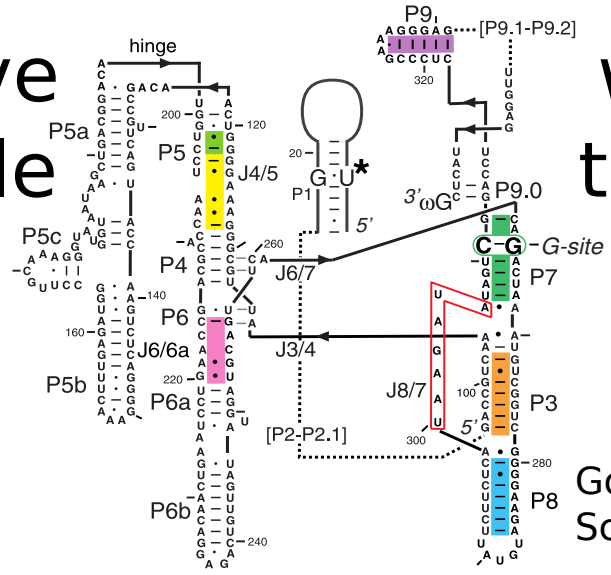
RNA nanotechnology – self-assembled RNA



Peixuan Guo, Nature Nanotechnology (2010)

Ribozymes

RNA:
an active
molecule



RNA
world
theory

Golden, BL et al.
Science (1998)

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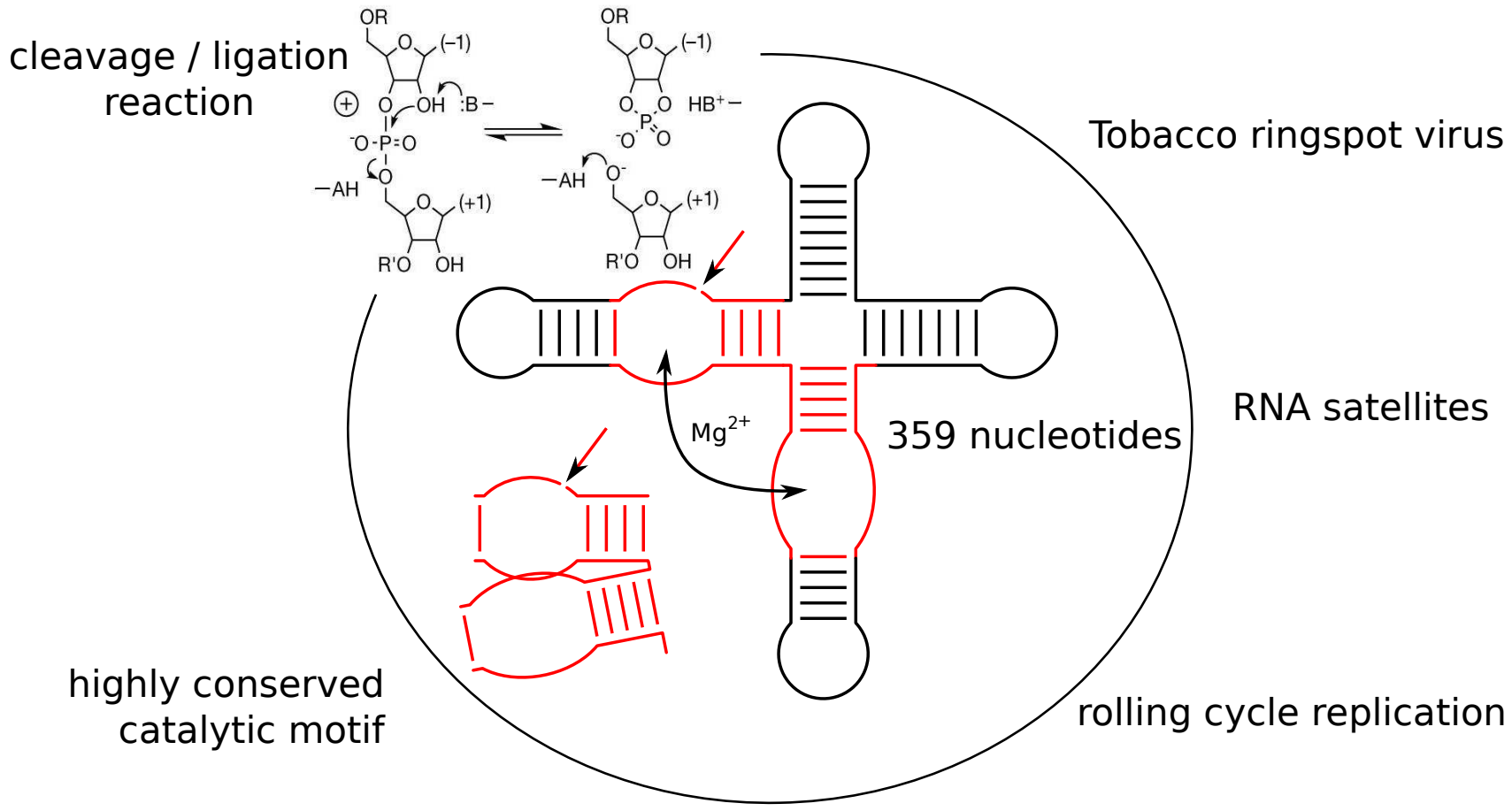
group-I
group-II
introns

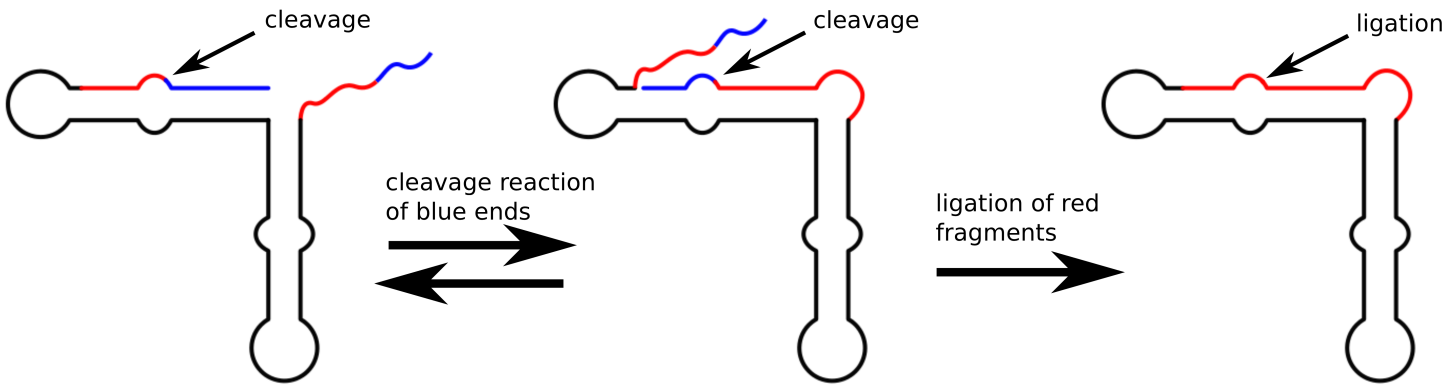
small
self-splicing
ribozymes

...

The hairpin ribozyme

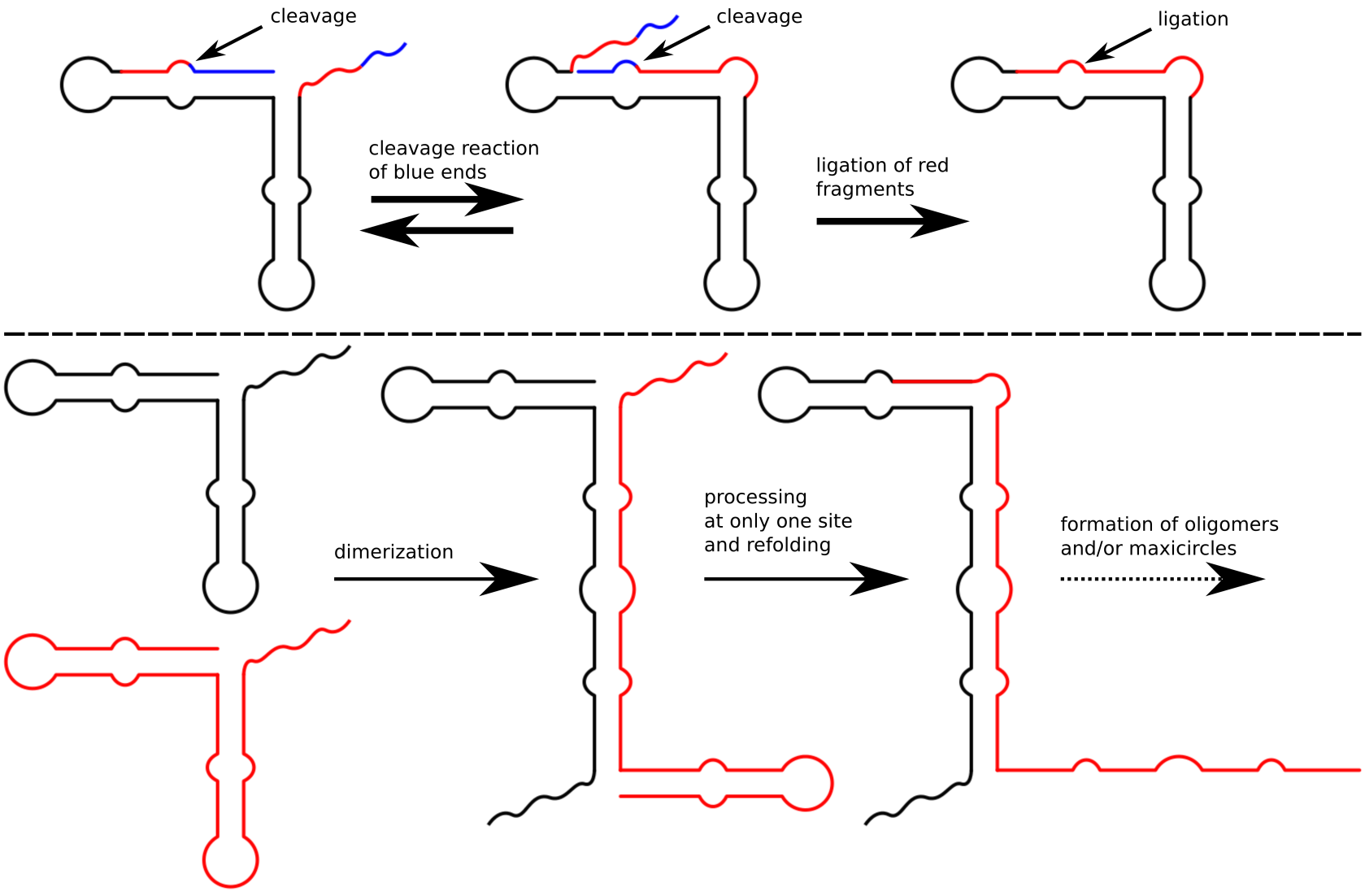


The modified hairpin ribozyme



Pieper et al. Biol. Chem. (2007)

The modified hairpin ribozyme



Pieper et al. Biol. Chem. (2007)

Summary

- small self-pocessing molecule
- minimal version $\Rightarrow$ multimeric structures
- equilibrium dependent on sequence optimization

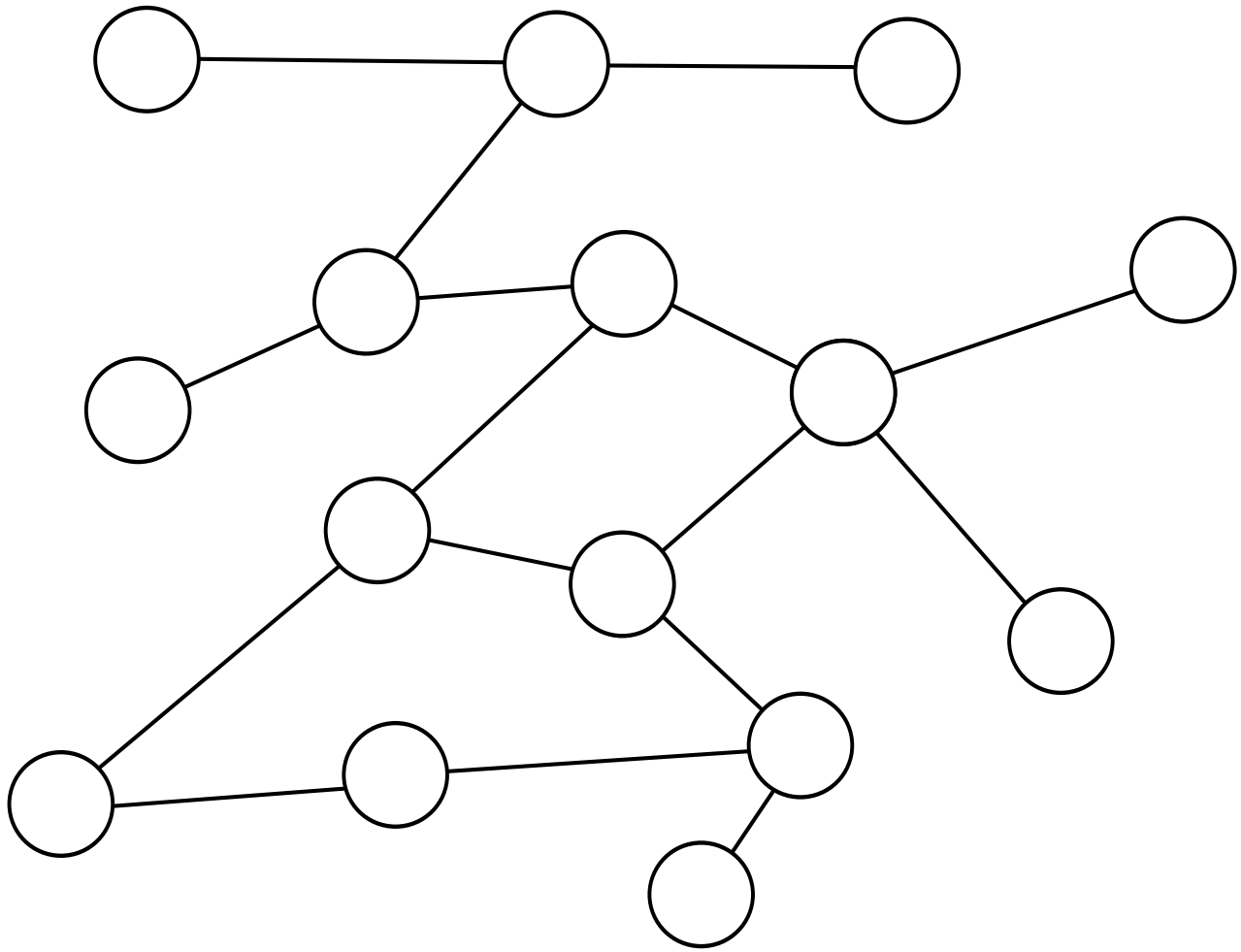
Goals

- predict the dynamics of the system
- design & optimize self-splicing ribozymes
- design & optimize multimeric structures

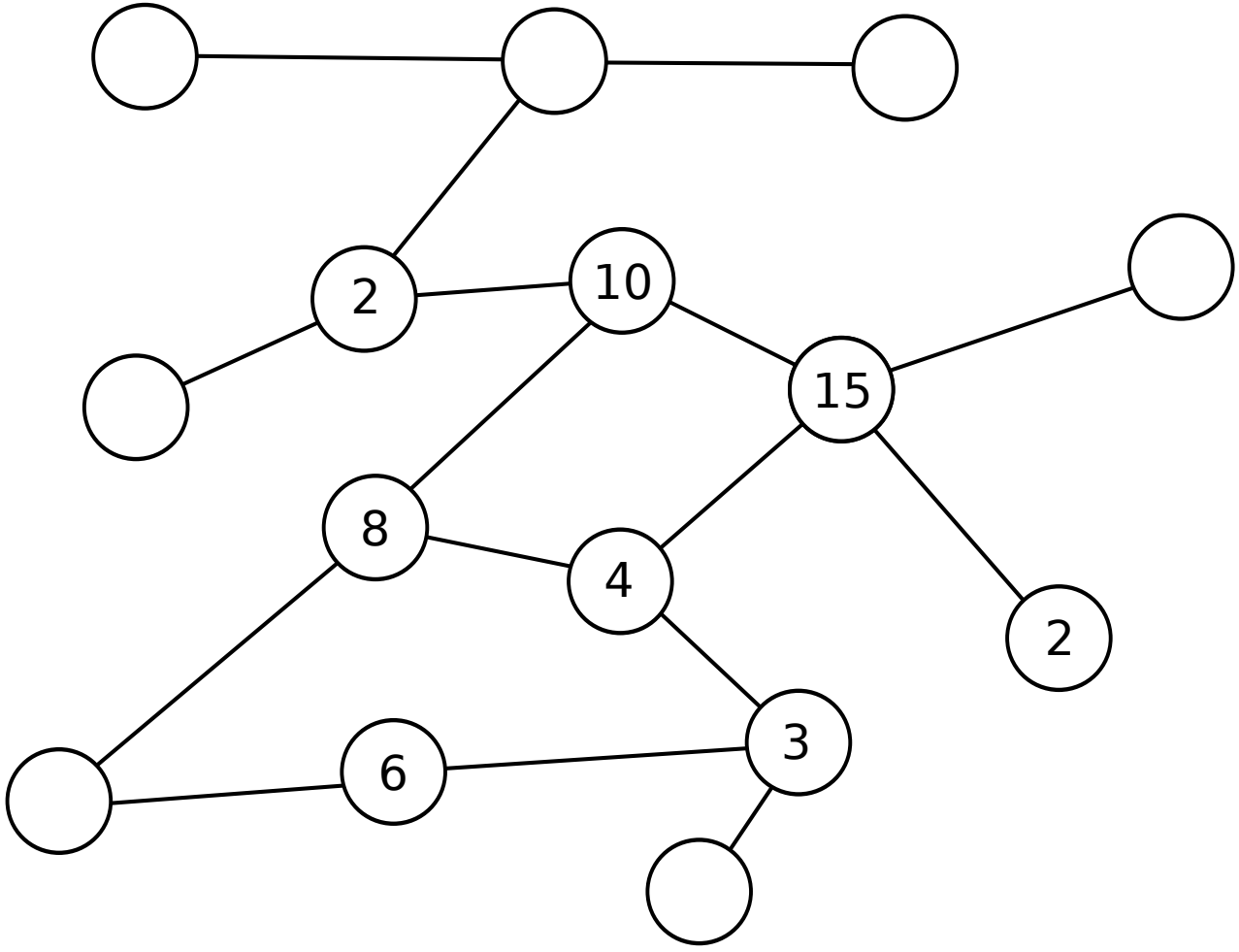
Challenges

- size of conformation space
  multimerization, catalytic activity
- coarse graining influences dynamics
- intra-/inter-molecular dynamics
- rule-based (network expansion/shrinking steps)

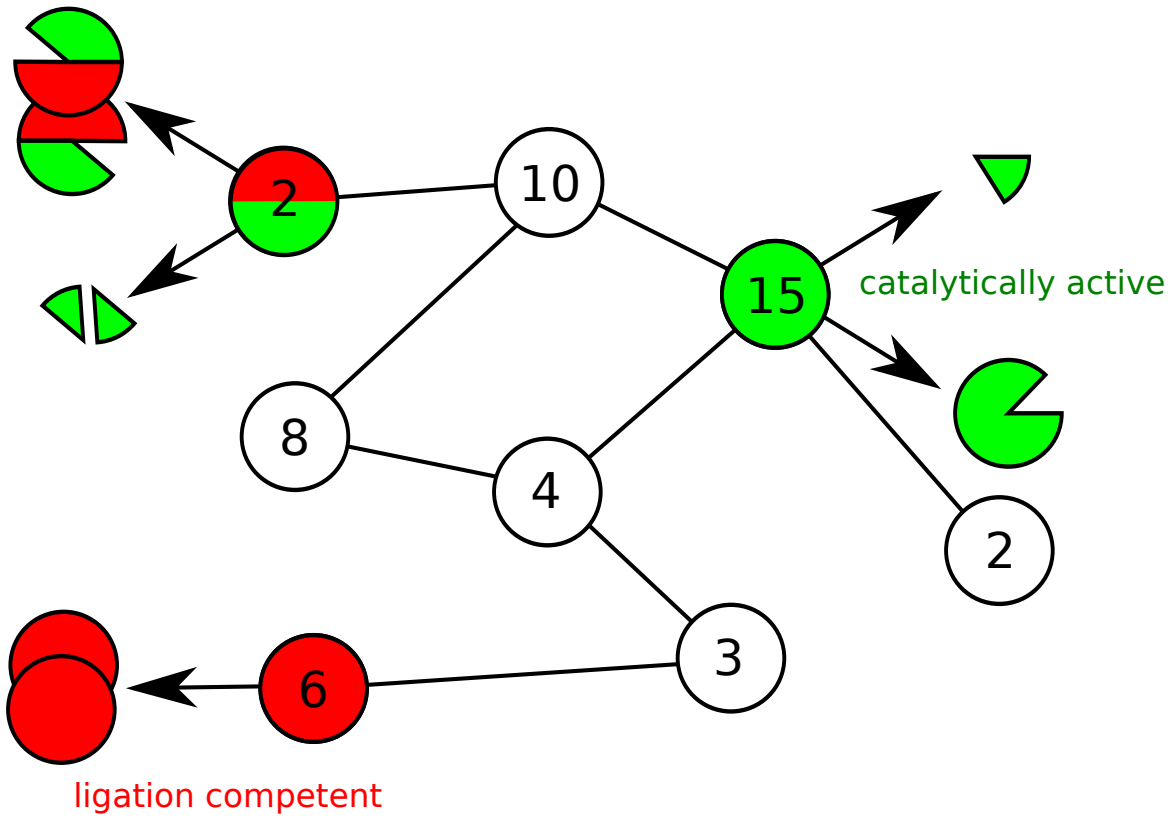
Network expansion



Stochastic simulation



Network shrinking, network expansion



Theoretical Approach

- rule-based landscape modeling
  - hypergraph
    - $\Rightarrow$ vertices: RNA secondary structures
    - $\Rightarrow$ edges: transition rates & cleavage/ligation reactions
  - rule set
    - $\Rightarrow$ sampling of RNA structures
    - $\Rightarrow$ estimate transition rates
    - $\Rightarrow$ stochastic simulation
    - $\Rightarrow$ check for catalytic activity
- sequence/landscape optimization

Current Work

- store predefined set of helices (e.g.: $len(h) > n$)
- generate suboptimal structures
- allow overlappings (zippering-, elongating- helices)
  $\Rightarrow$ nearly done :-)
- stochastic folding kinetics on helix-lists

Future Implementations

- generate a landscape with stochastic simulation (expansion, shrinking)
- intermolecular interactions
- catalytic motif finder

thanks to

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Christoph Flamm (unofficial Supervisor)
Sabine Müller (Collaboration, PhD committee)
Peter Stadler (PhD committee)
Ronny Lorenz, ... and the TBI group.

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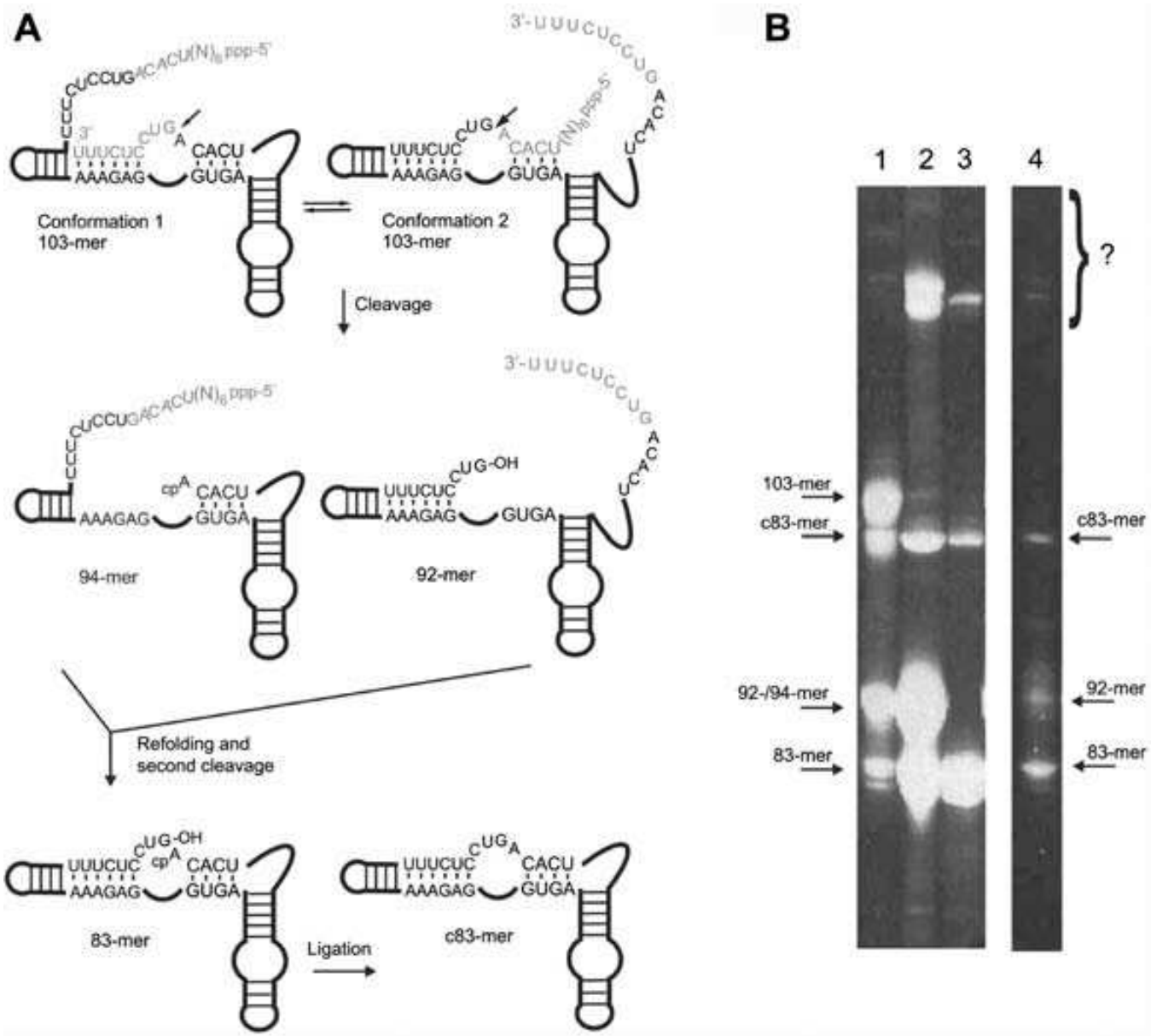
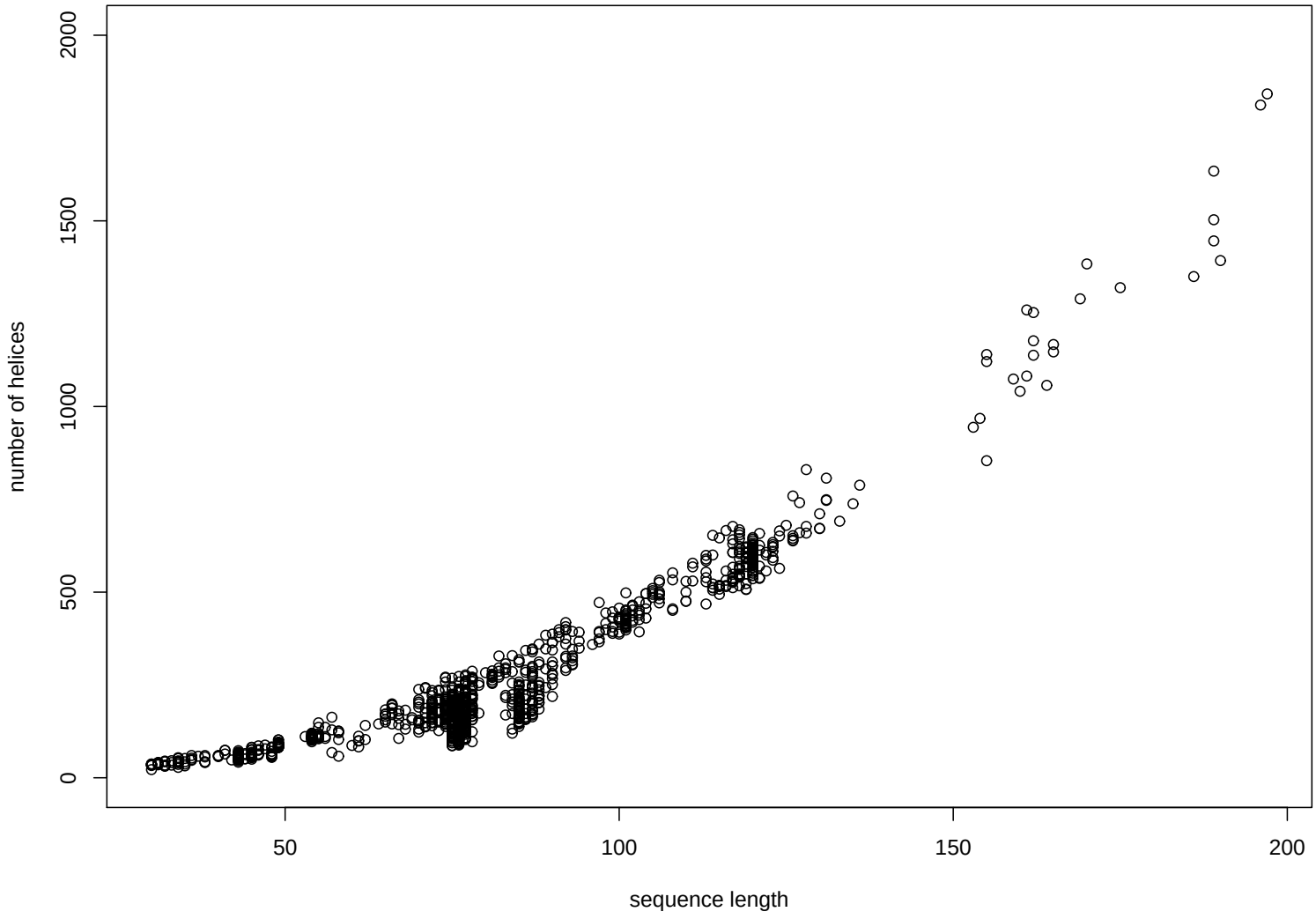
Backup Slide: modified hairpin ribozyme

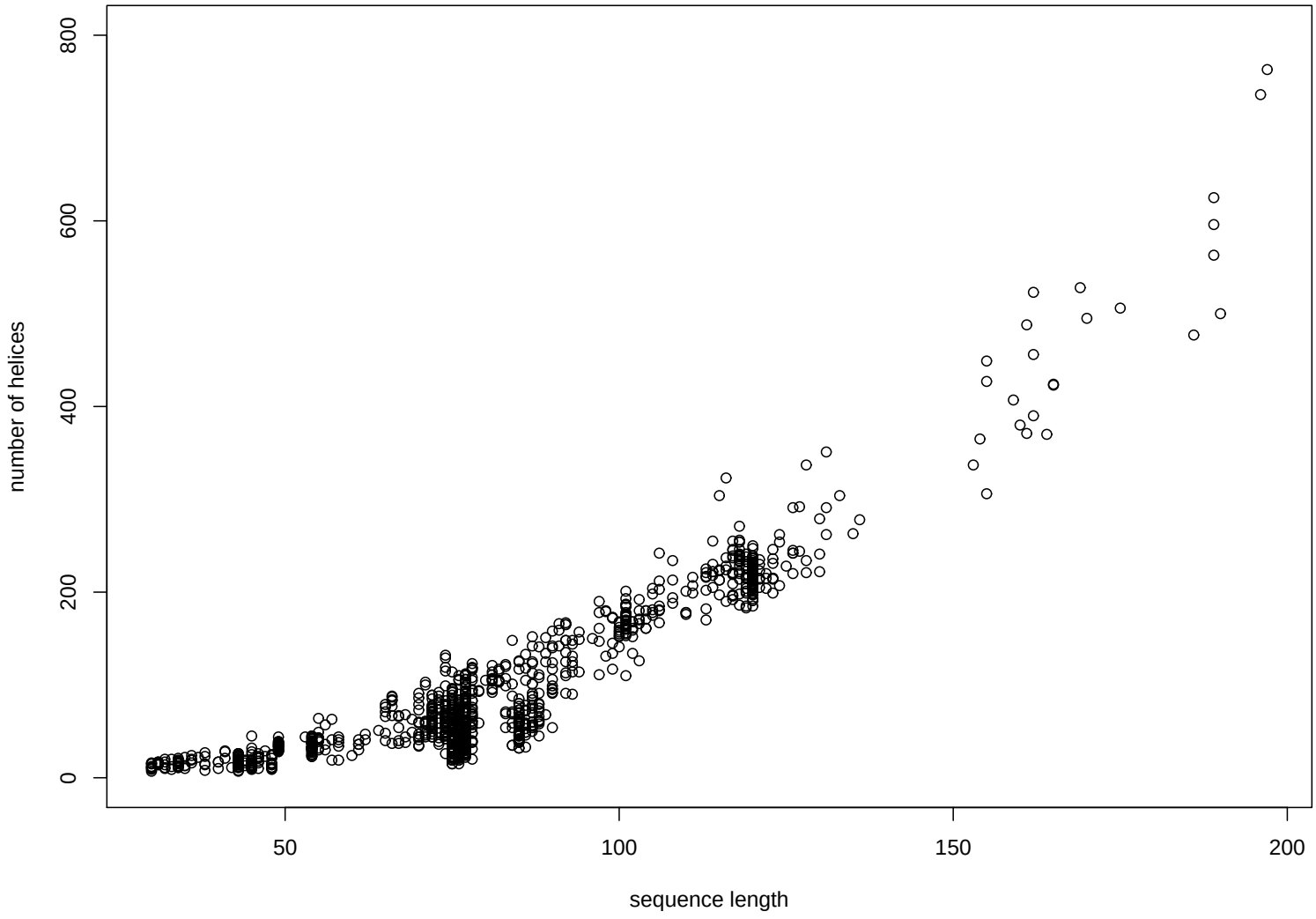


Pieper et al. Biol. Chem. (2007)

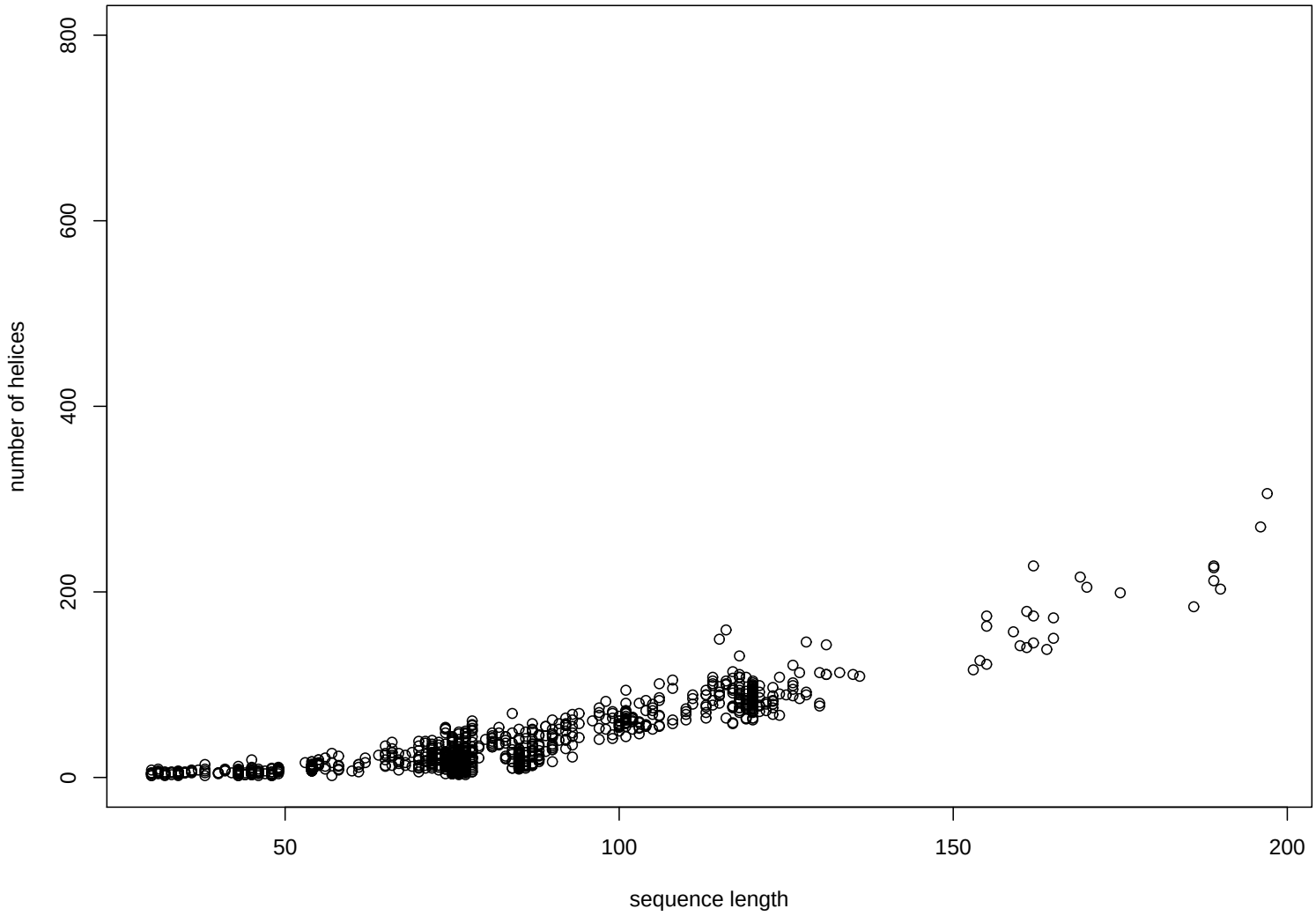
Backup Slide: minimum helix-length: 2



Backup Slide: minimum helix-length: 3



Backup Slide: minimum helix-length: 4



Backup Slide: minimum helix-length: 5