RNA Kinetics

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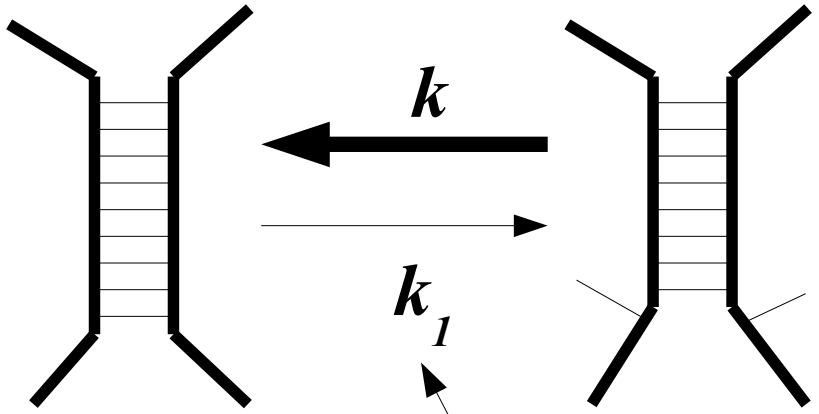
Motivation

- The structure is not fixed
- Some biological processes are based on transitions between structures: attenuation, riboswitches etc.
- Transitions between structures can be described with a rate constants
- How can we evaluate these rates?

Elementary step

Fluctuations of the terminal base pairs – a simple model

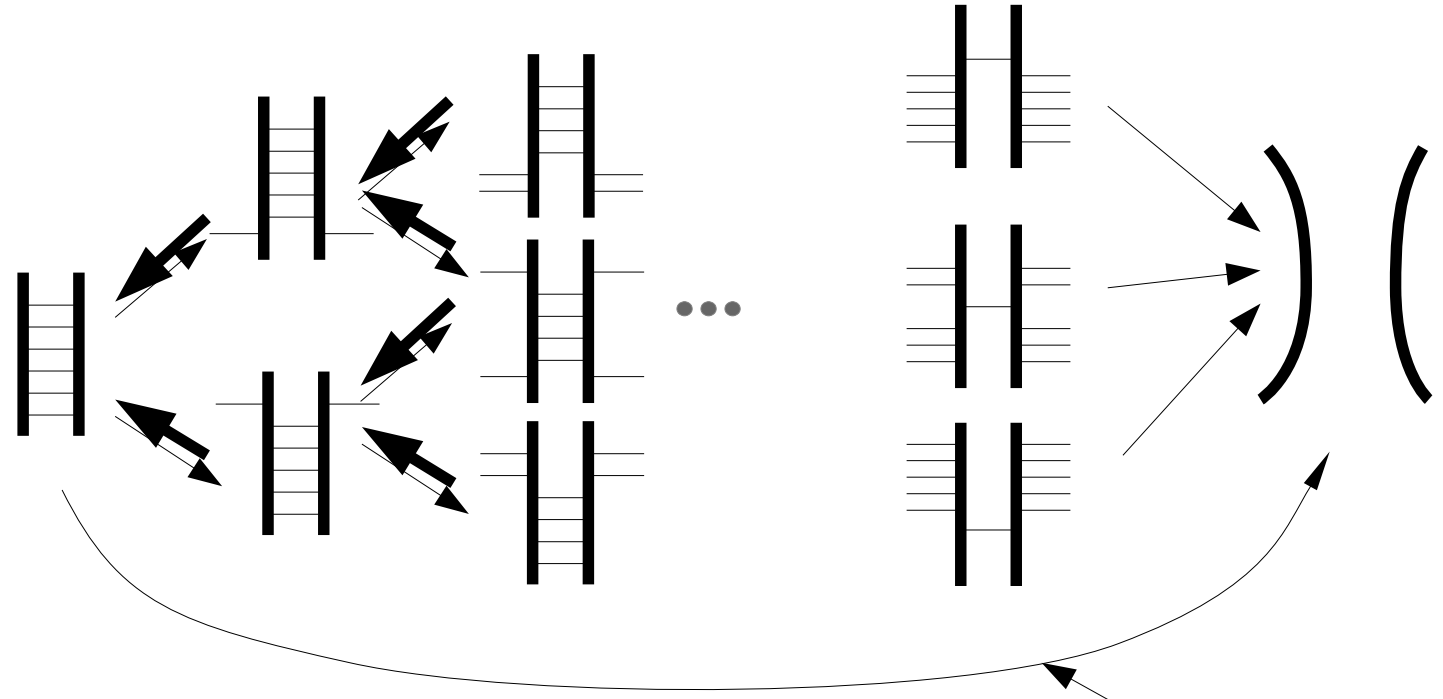


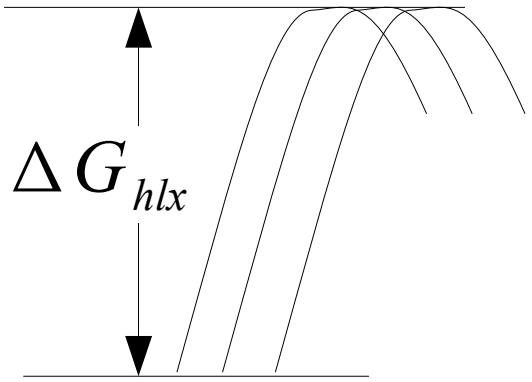
$$k_1 = k \cdot \exp \frac{\Delta G_{st}}{kT}$$

k – rate constant of "free" fluctuation. Does not depend on the stacking energy.

k_1 – rate constant of stacking disruption. Depends on the stacking energy.

Helix disruption

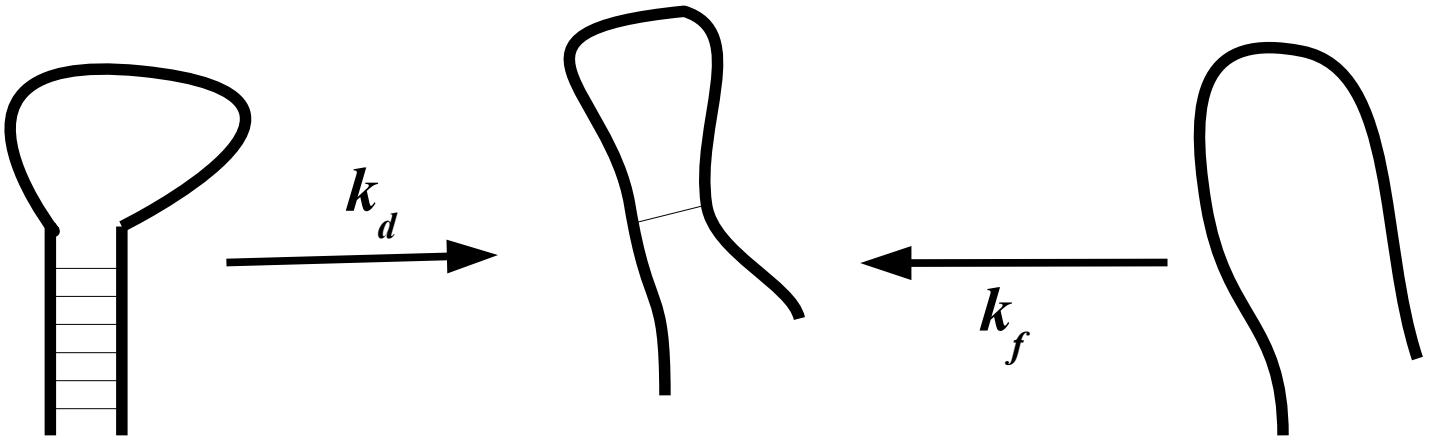


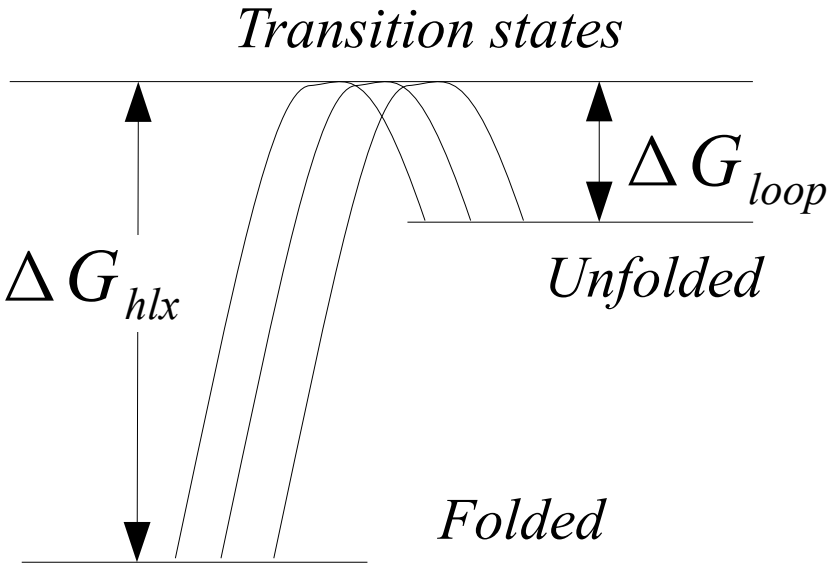


$$k_d = k \cdot N \cdot \exp \frac{\Delta G_{hlx}}{kT}$$

$$\Delta G_{hlx} = -6\,kcal/mol\,; \quad k = 10^7\,s^{-1}\,; \quad t = \frac{1}{k_d} = 2 \cdot 10^{-3}\,s$$

Helix formation





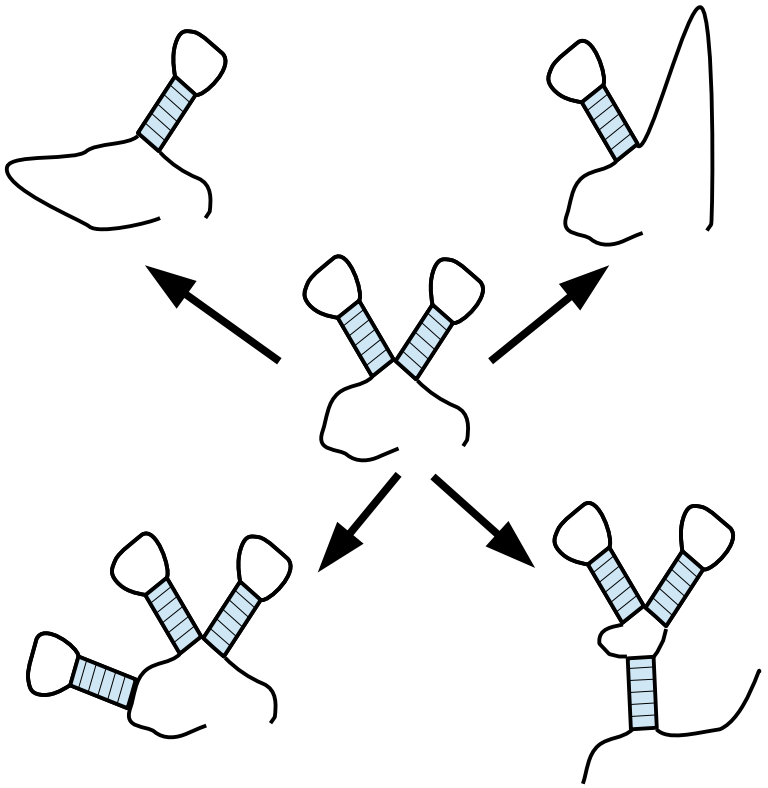
$$\frac{k_d}{k_f} = \exp\left(\frac{\Delta G_{hlx} + \Delta G_{loop}}{kT}\right)$$

$$k_d = k \cdot N \cdot \exp\left(\frac{\Delta G_{hlx}}{kT}\right)$$

$$k_f = k \cdot N \cdot \exp\left(-\frac{\Delta G_{loop}}{kT}\right)$$

Monte-Carlo Markov chain approach

The transition time is a random variable that is distributed exponentially



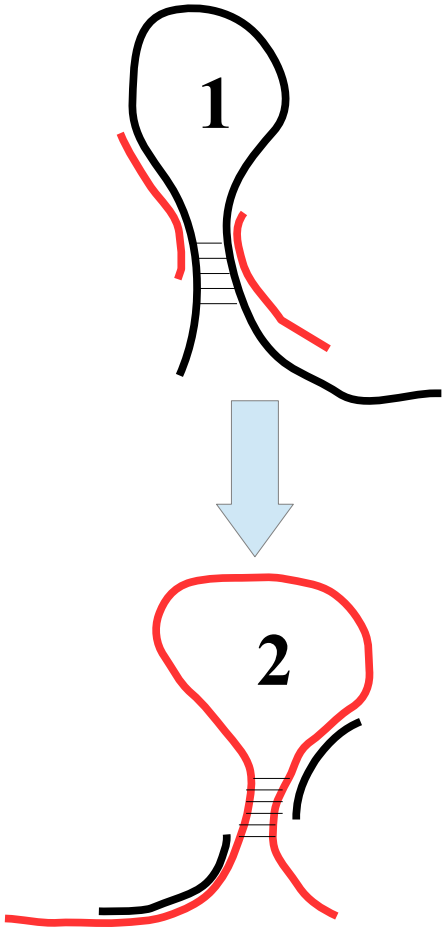
1. Select a transition

$$i_{transition} = arg\,min\left(i : r \geq \frac{k_i}{\sum k_i}\right)$$

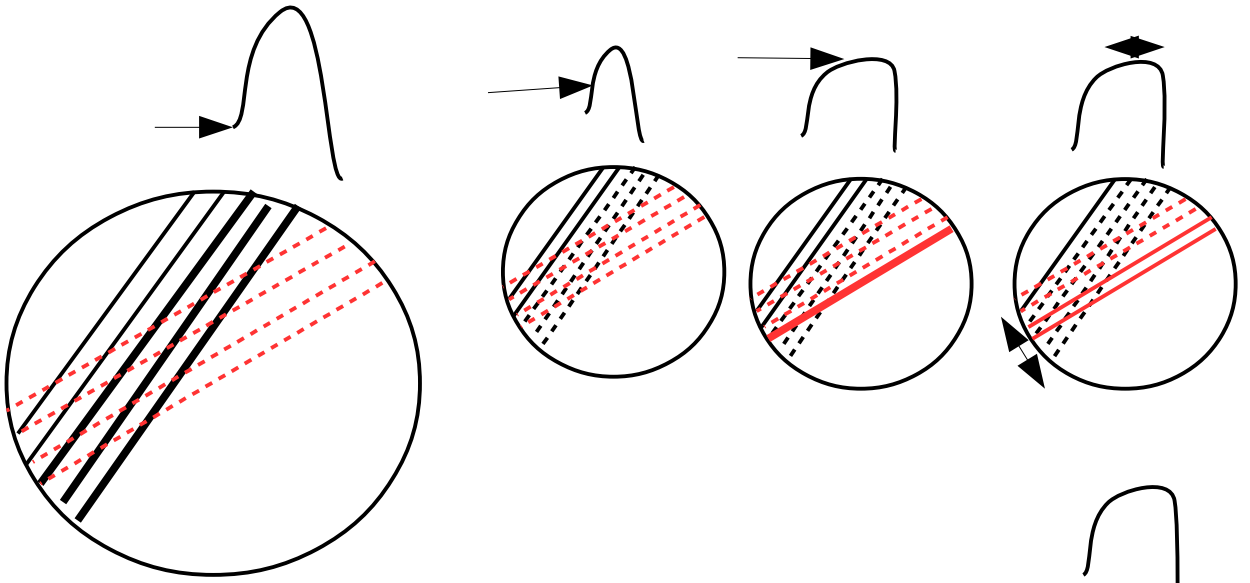
2. Simulate the transition time

$$t = -\ln(r) \cdot \left(\frac{1}{\sum k_i}\right)$$

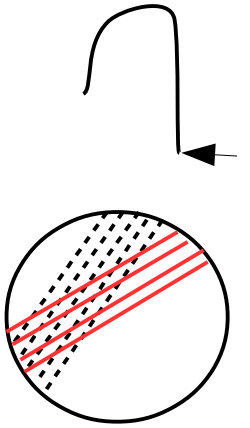
More complex transformations



New helix formation does not require disrupt entire existing helix



$$k(1 \rightarrow 2) = k \cdot \exp \frac{\Delta G_{hlx} - \Delta G_{loop1}}{kT}$$



General case

There are exist many different paths between valleys

Effective rate constant is sum of rate constants over all possible paths

General case

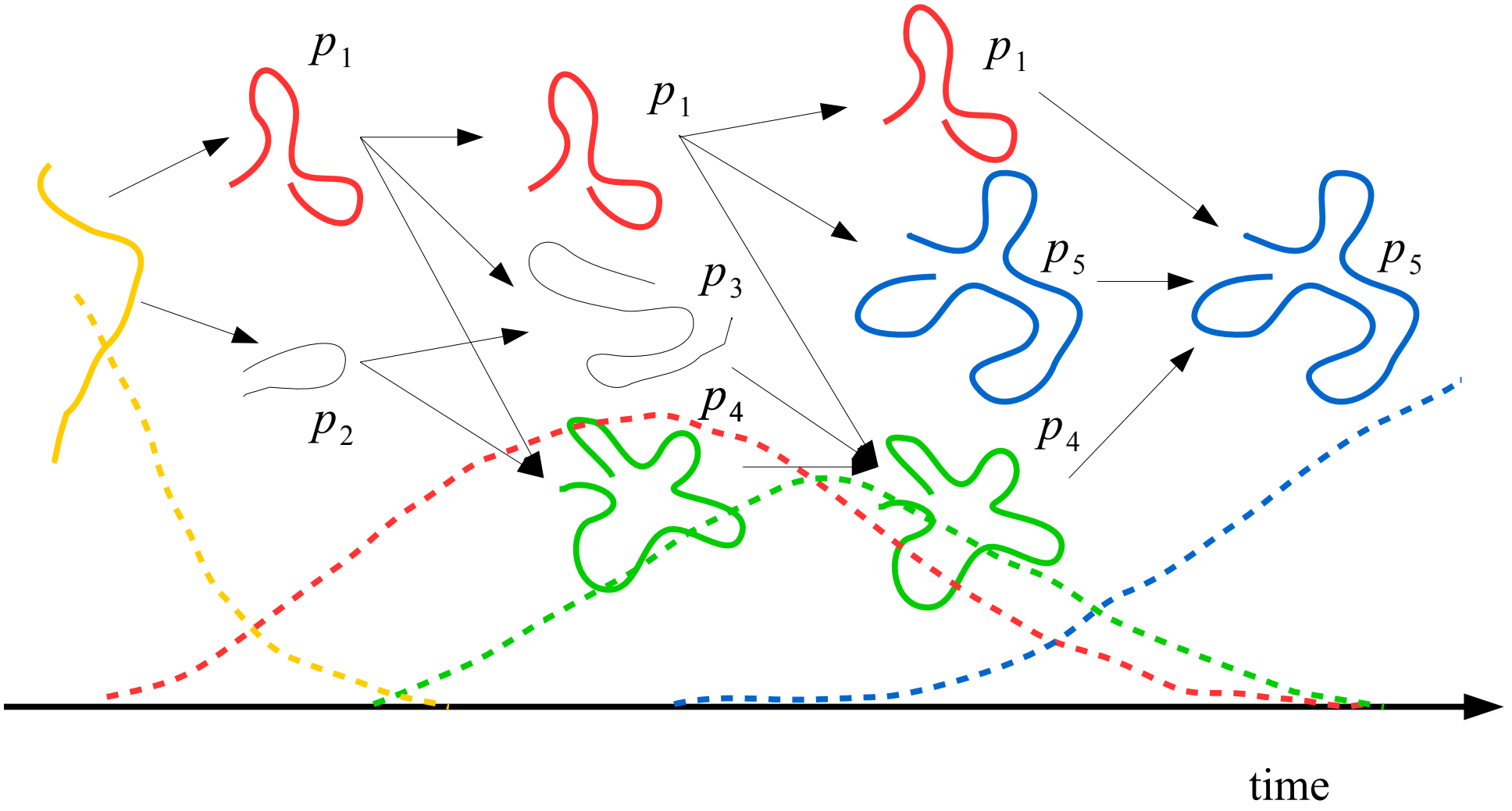
Transition from one structure to another

- Enumerate the transition states
- Calculate all transition energies
- Calculate the transition rate constant

$$k_{transition} = k \cdot \sum_{all\ transition\ states} \exp \frac{-\Delta G_{trans}}{kT}$$

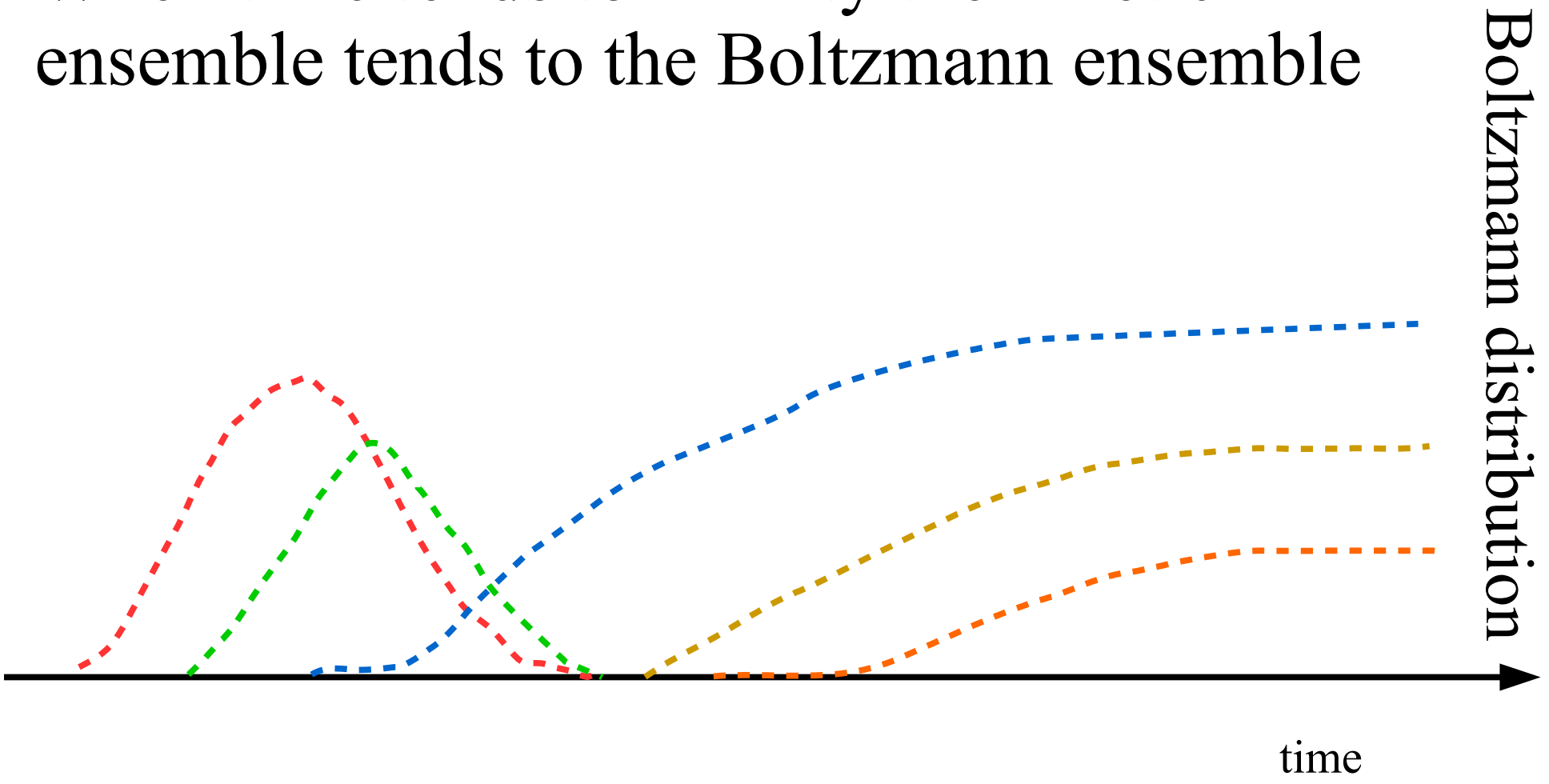
Kinetic ensemble

The probability of structure existence depends on time



Kinetic ensemble

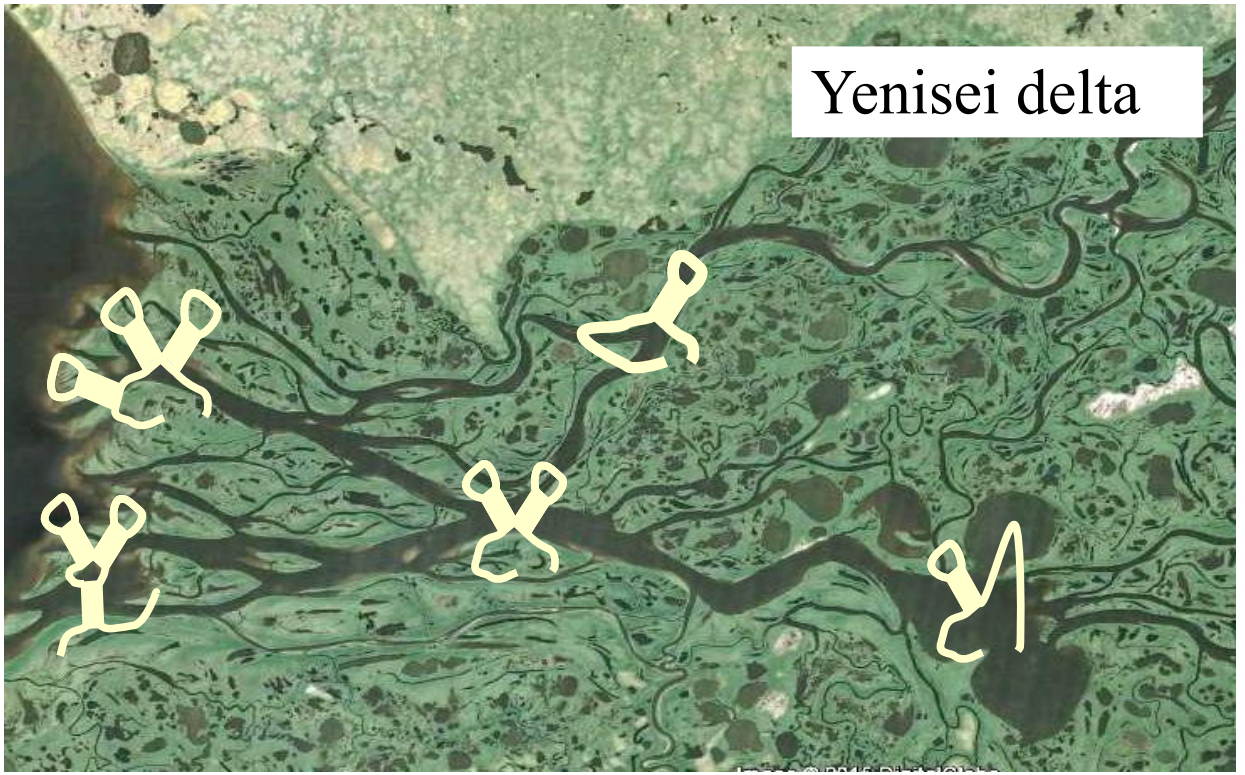
When time tends to infinity the kinetic ensemble tends to the Boltzmann ensemble



Relaxation

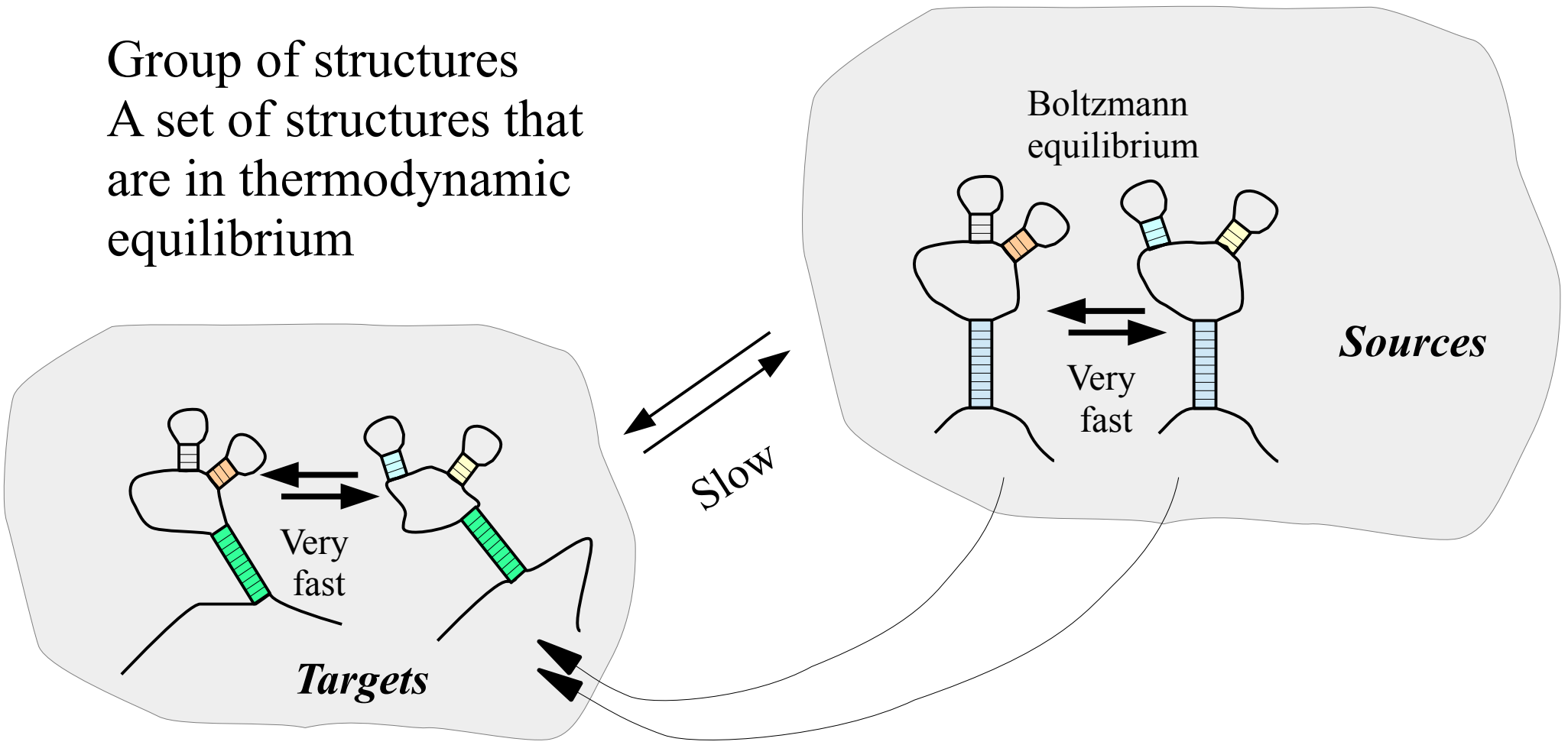
- There are many different ways to the Boltzmann distribution

the Boltzmann's ocean



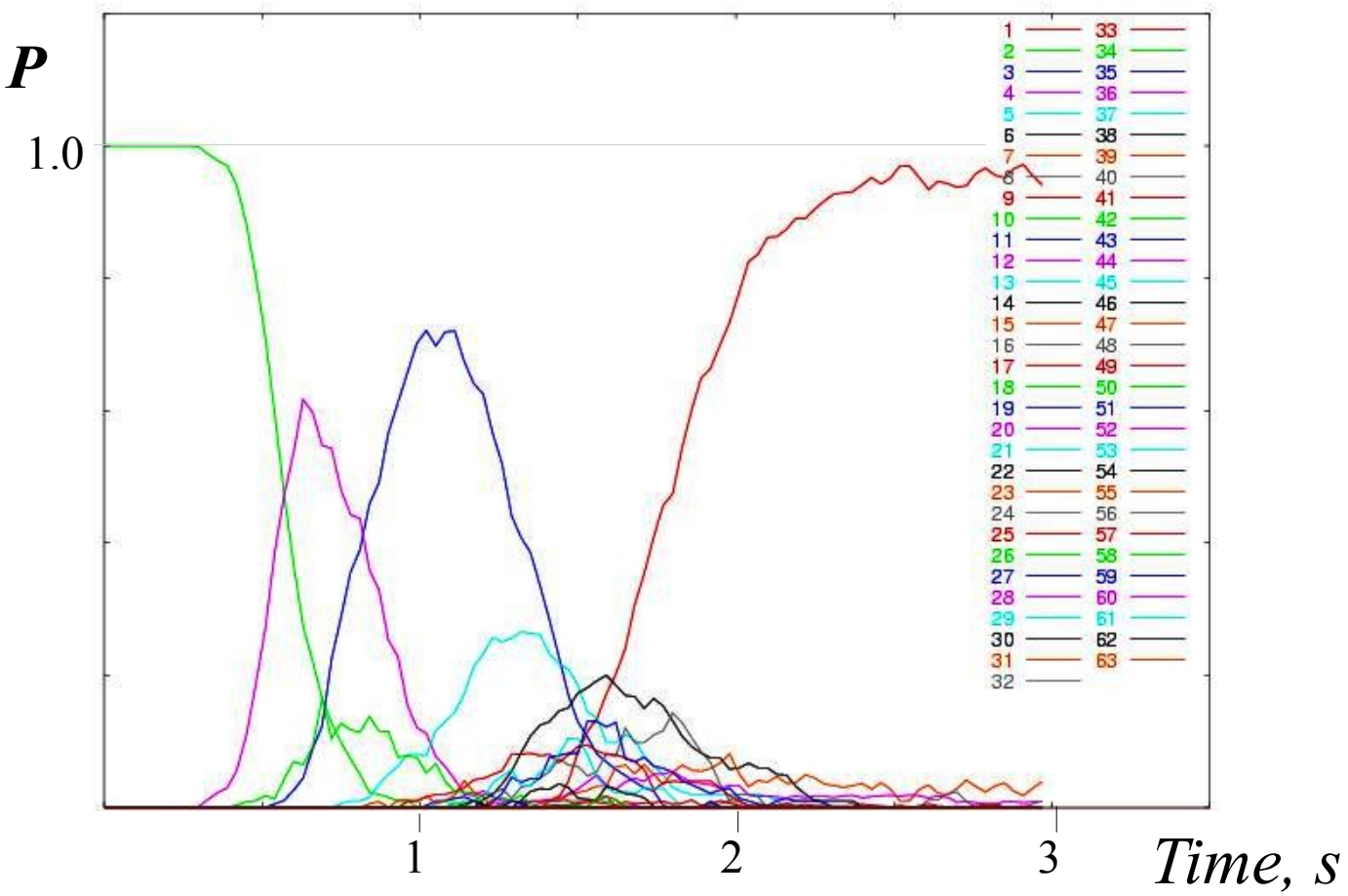
Group of structures

Group of structures
A set of structures that are in thermodynamic equilibrium



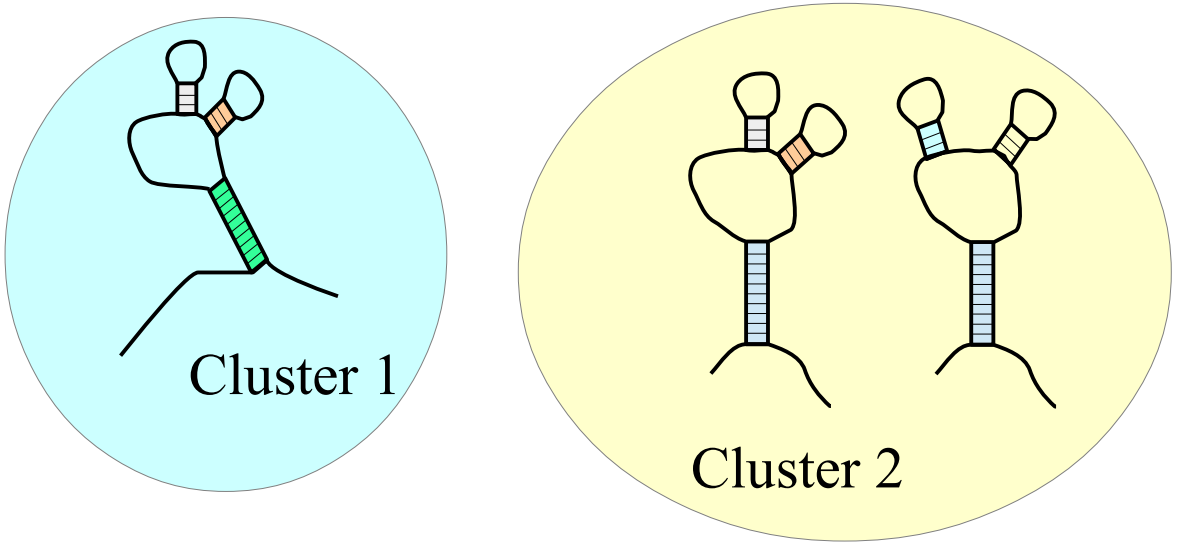
$$k_{transition} = \sum_{source} \sum_{targets} k(souce \rightarrow target) P_{source} P_{target}$$

Example of a simulation



Conclusion remarks and questions

- Structure clustering should be based on kinetic characteristics



- How we can effectively enumerate kinetically neighbor structures?
- How we effectively enumerate the transition states?
- How we can take into account the RNA kinetics on data analysis

Team

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- Dmitri Pervouchine
- Alexander Favorov