DNA base pairing

What generates and maintains the pairing rules?

DNA

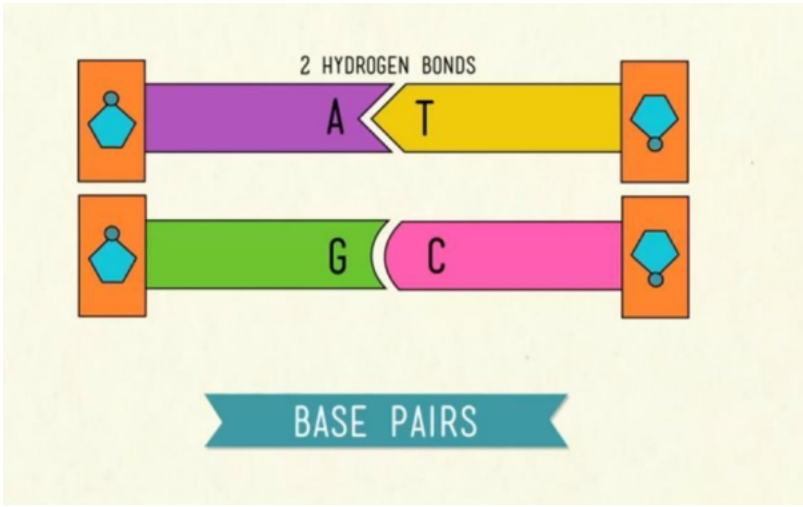
4 bases

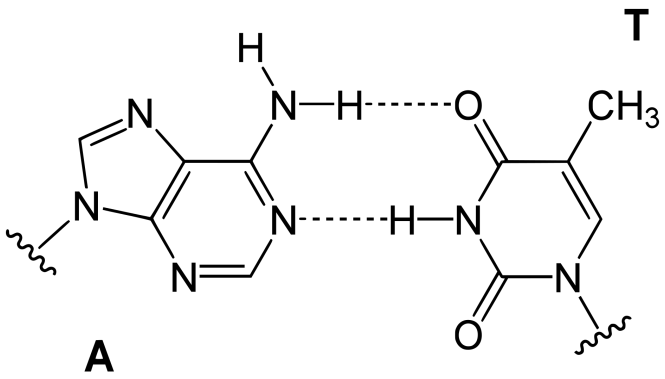
Pairing:

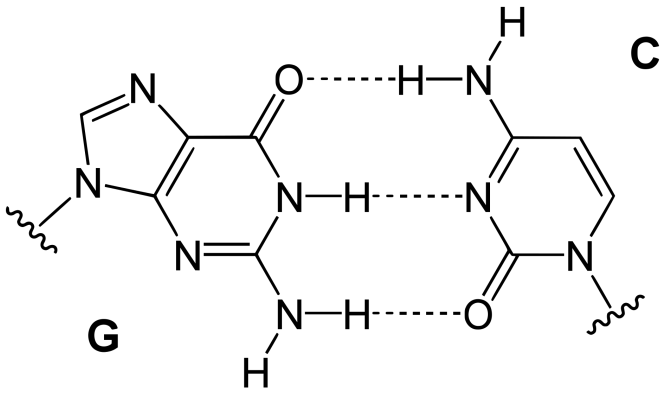
G - C
A - T

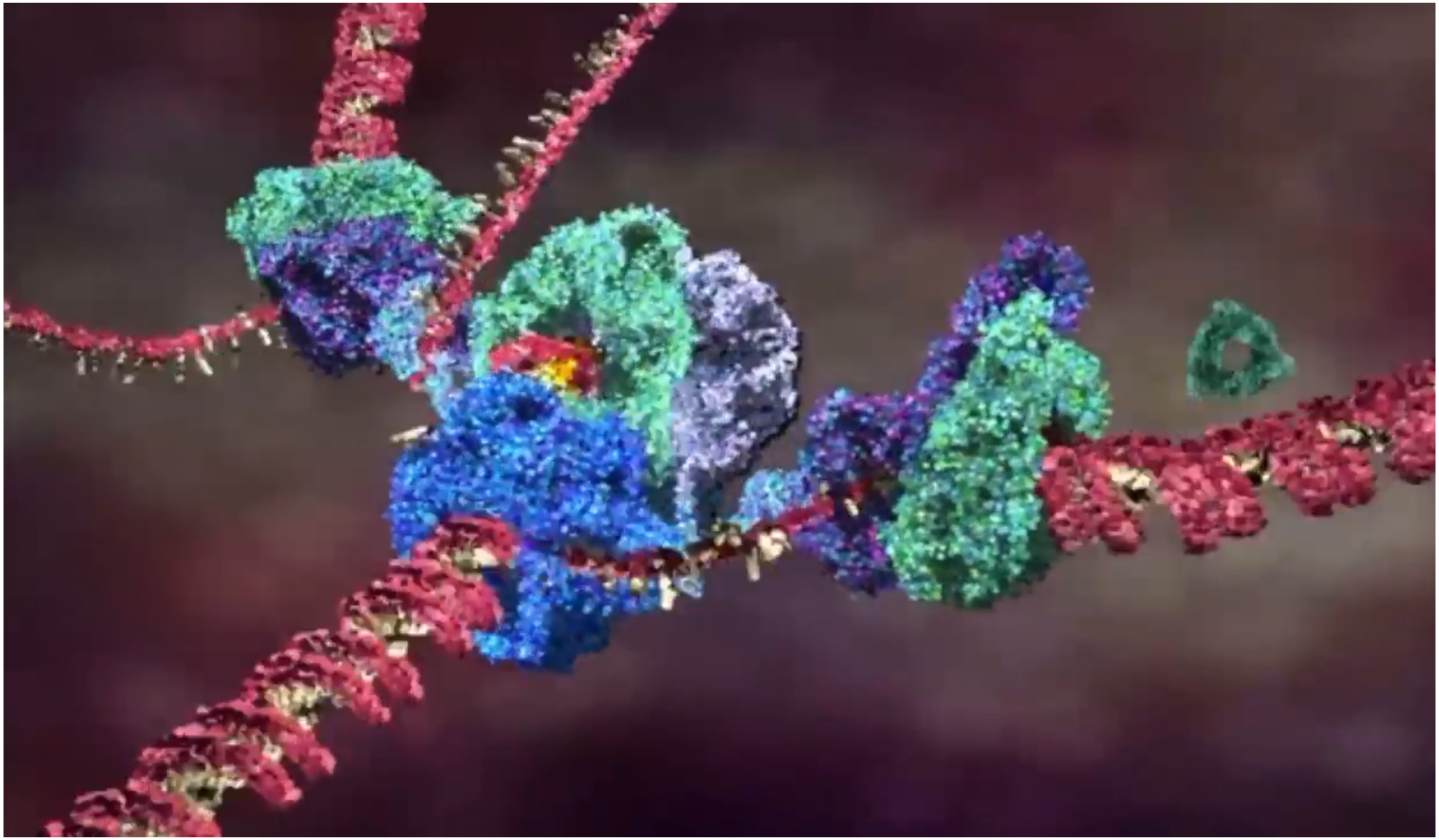
Mutation rate:

10^{-10} errors/(rep*base)

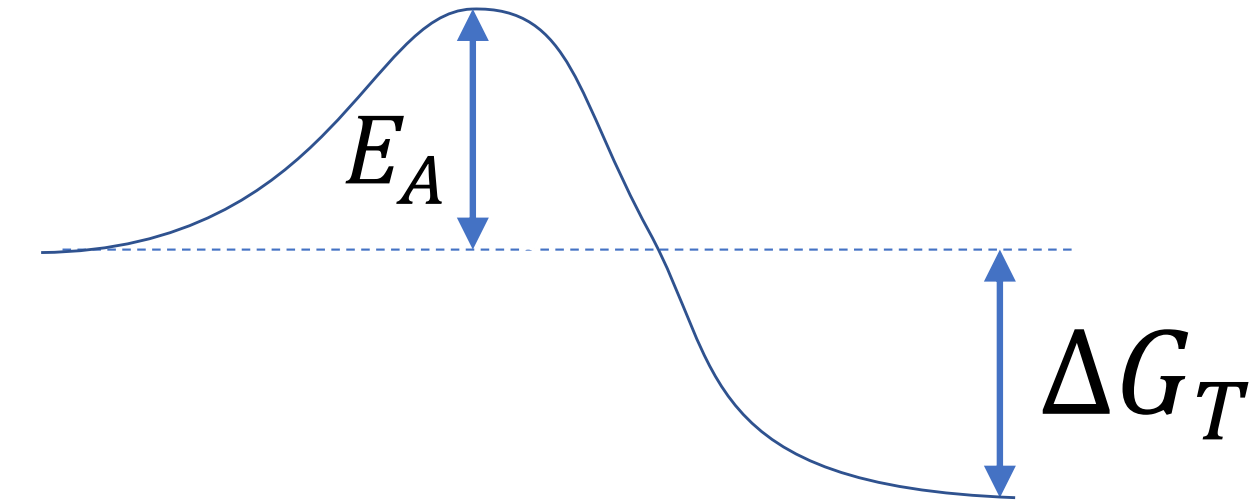

2 HYDROGEN BONDS
A
T
G
C
BASE PAIRS


T
A

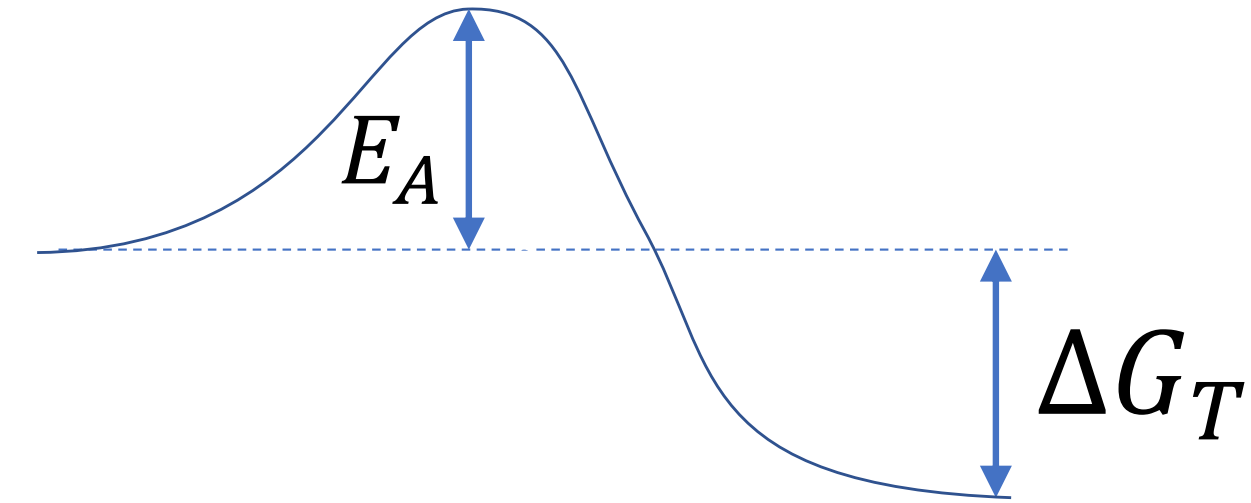

C
G



www.drewberry.com/science

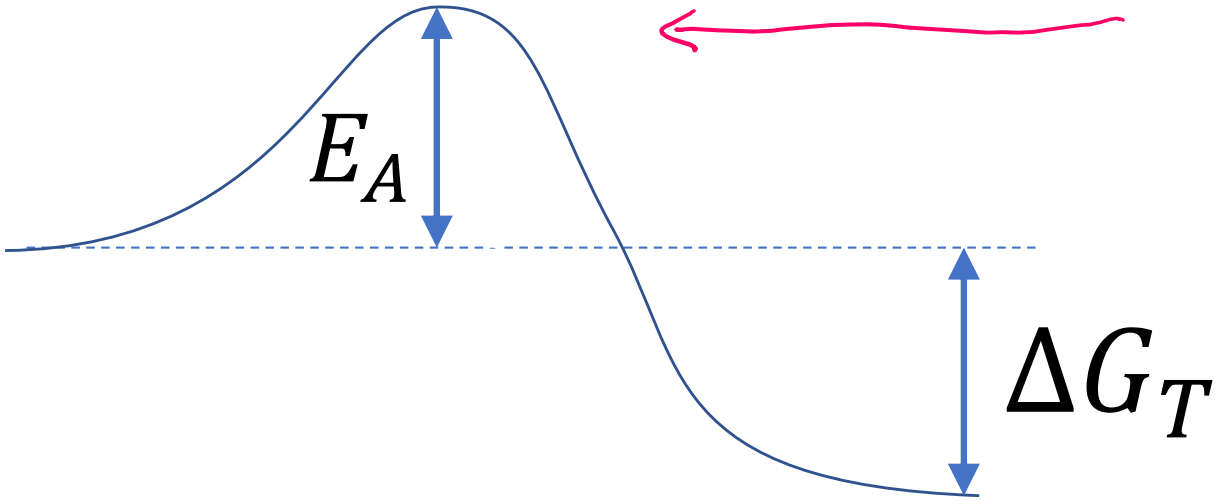

E_A
ΔG_T
Reactants
Products

$$k_1 \propto e^{-\frac{E_A}{kT}}$$



$$k_1 \propto e^{-\frac{E_A}{kT}}$$

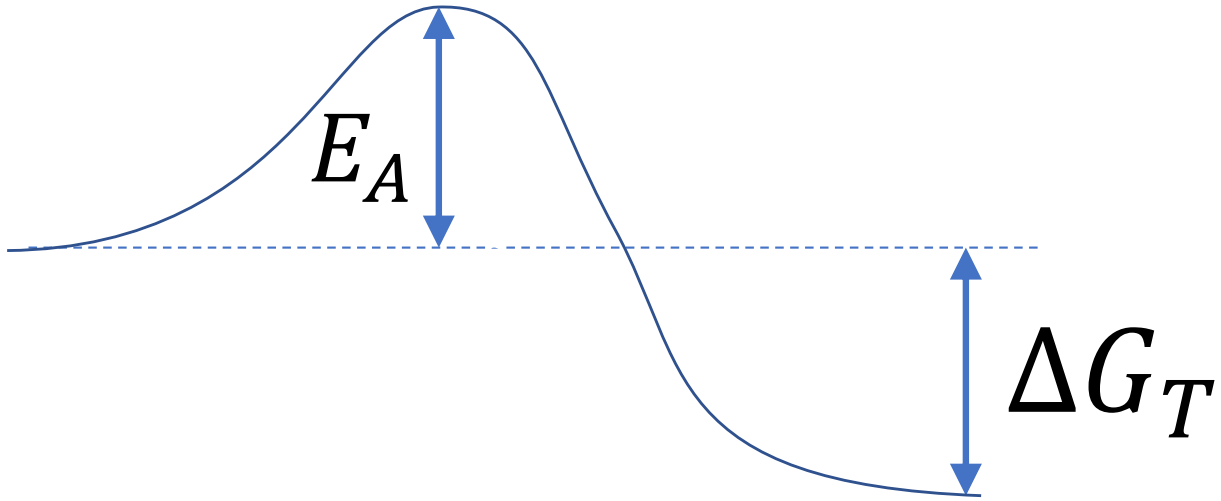
$$k_2 \propto e^{-\frac{E_A+\Delta G}{kT}}$$

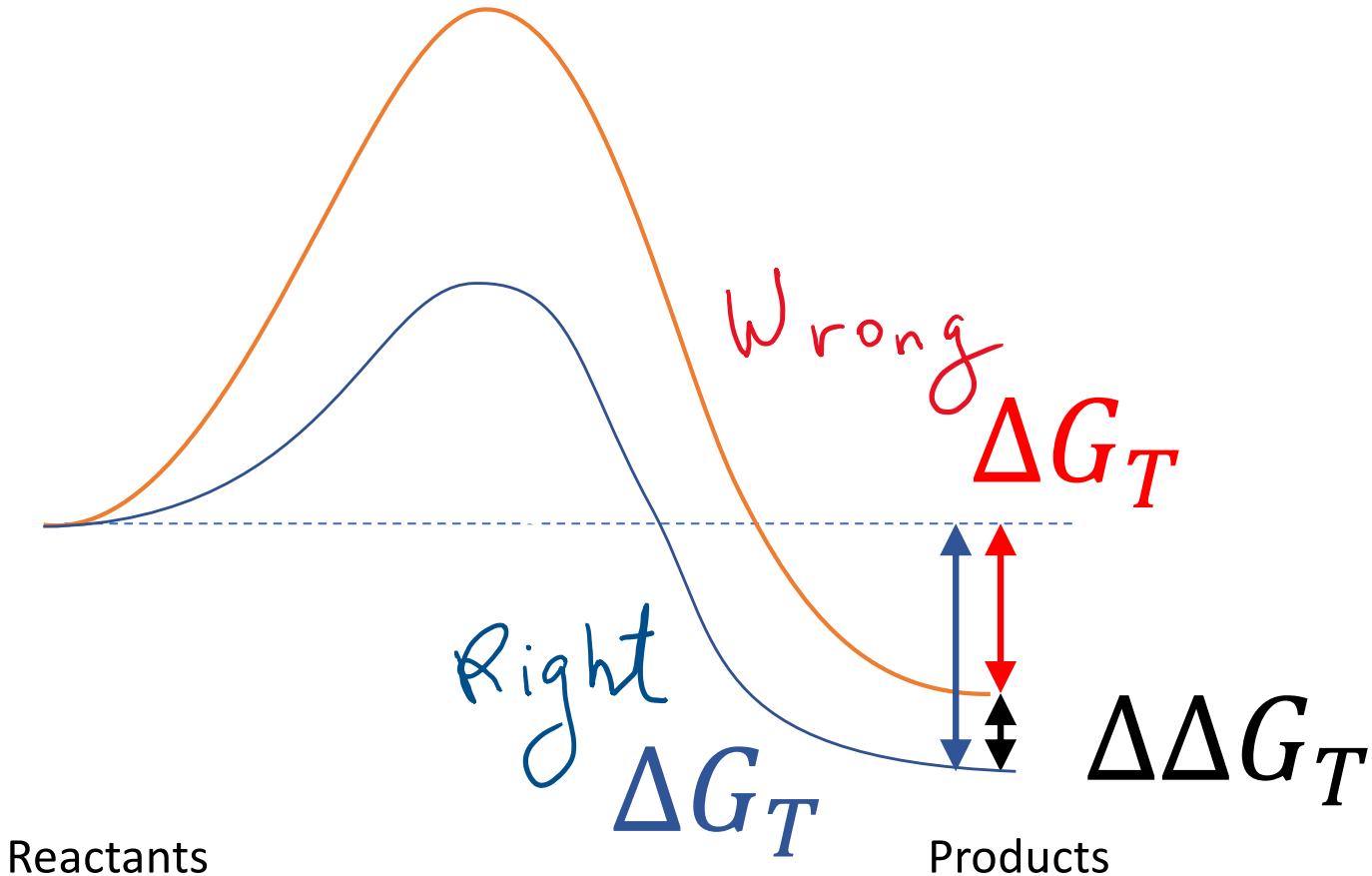


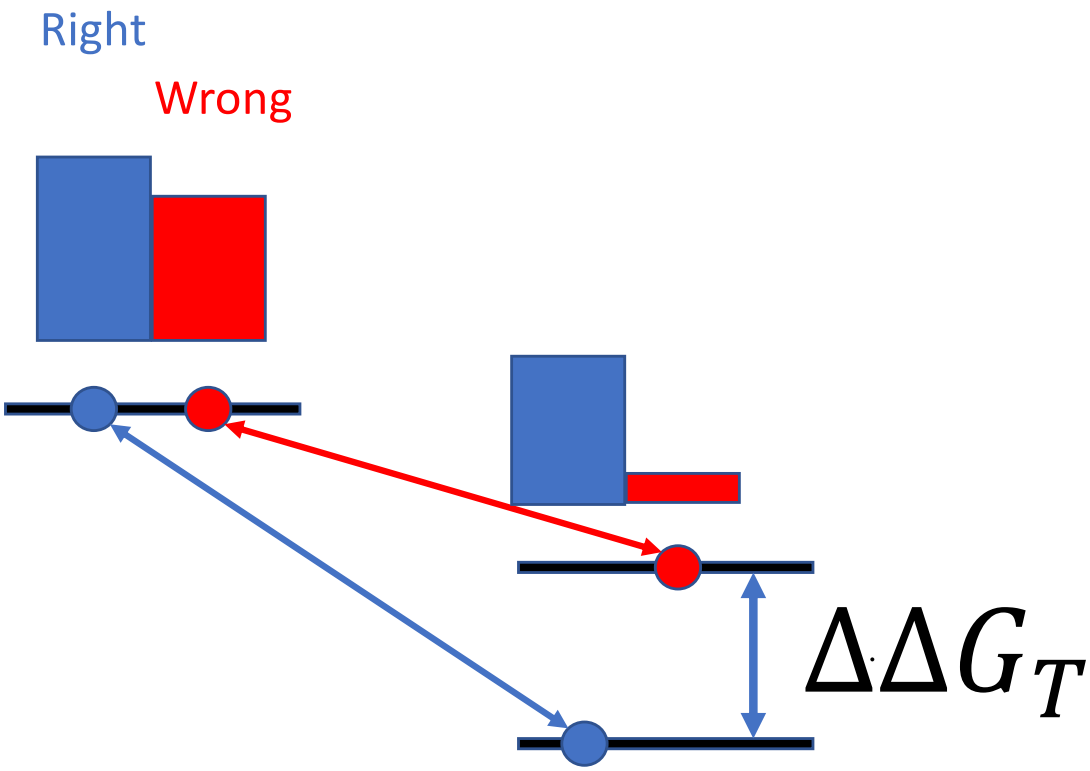
Reactants

Products

$$\frac{k_1}{k_2} = e^{-\frac{\Delta G}{kT}}$$



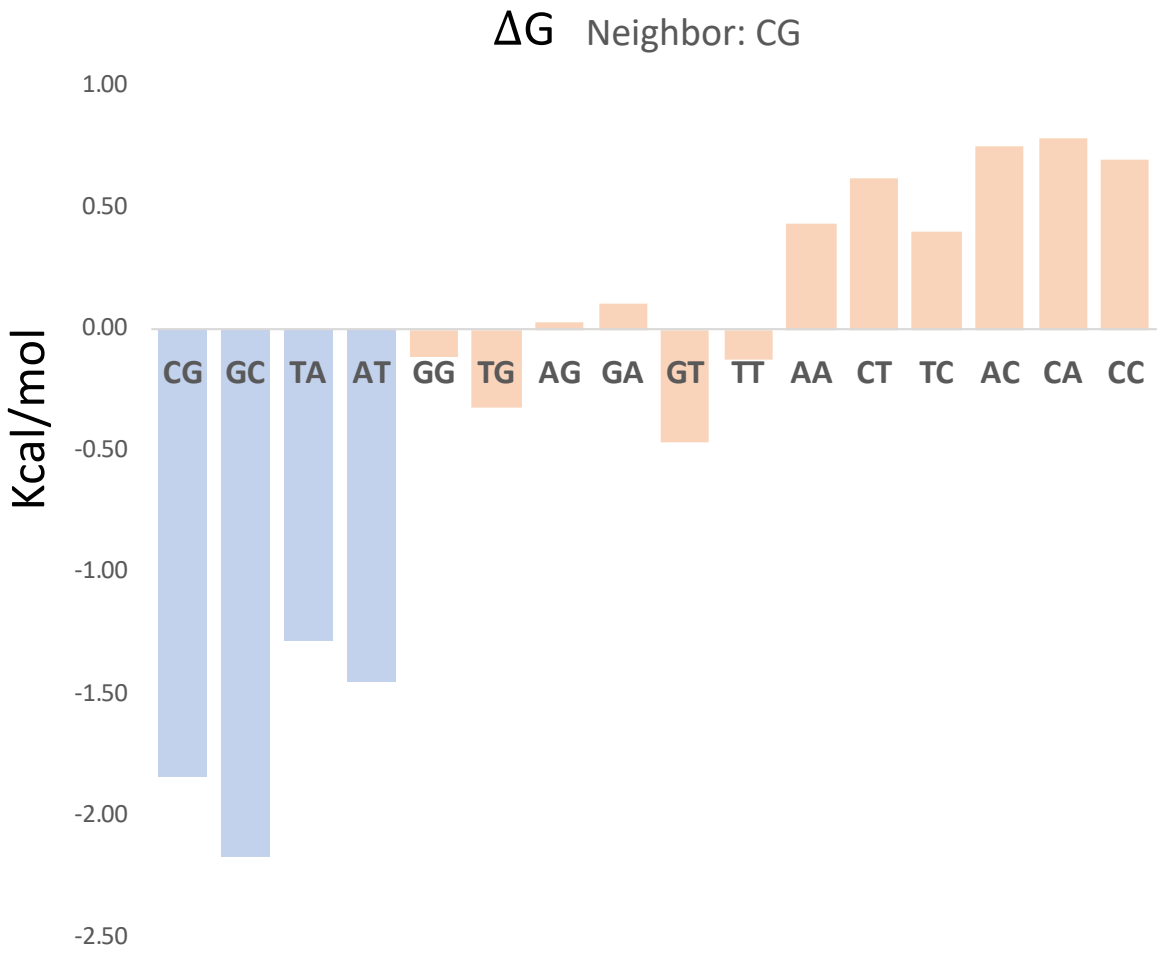

Wrong
ΔG_T
Right
ΔG_T
$\Delta\Delta G_T$
Reactants
Products



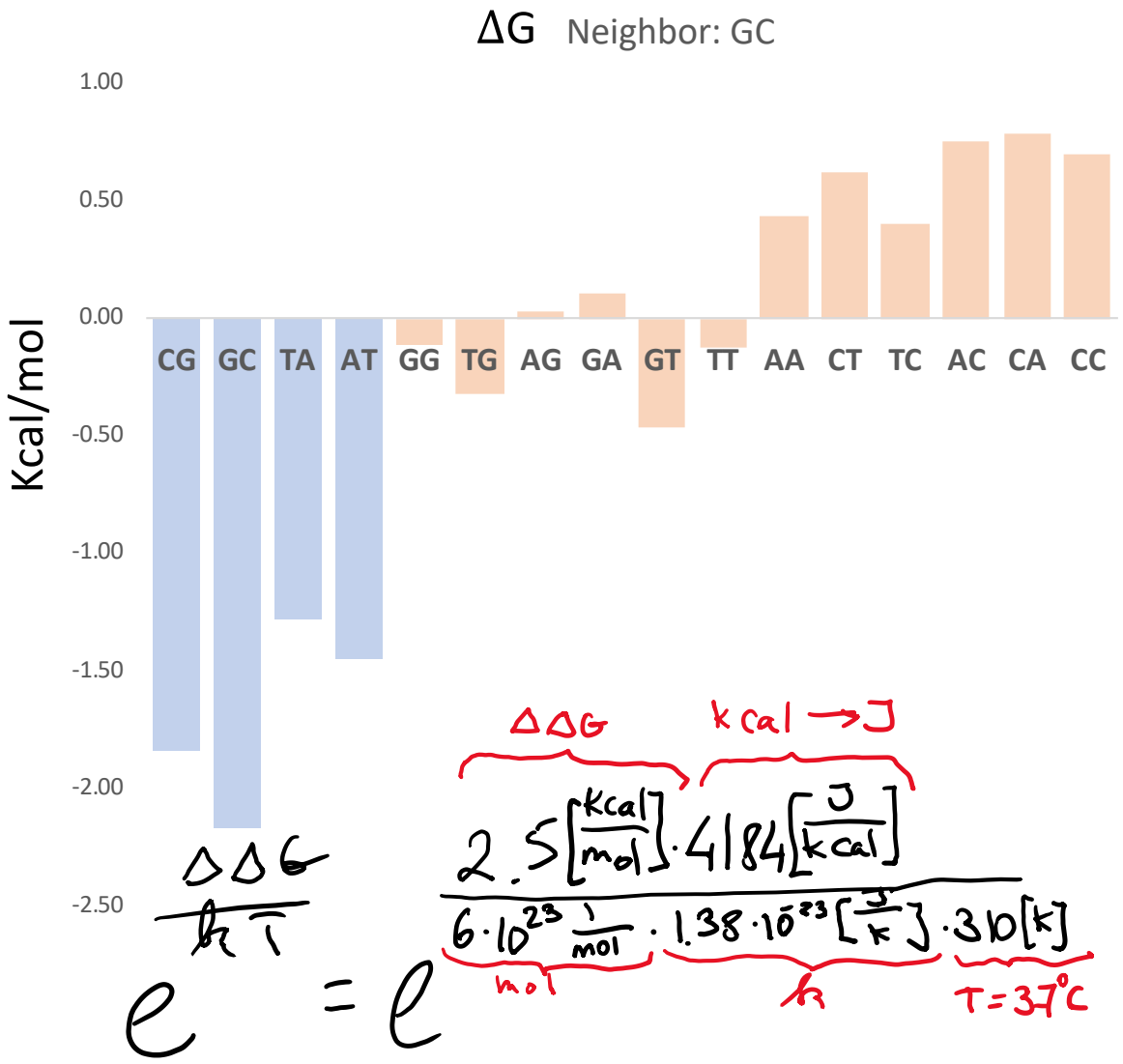
Ratio of R to W amplified by

$$e^{\frac{\Delta\Delta G}{kT}}$$

Binding difference



Binding difference



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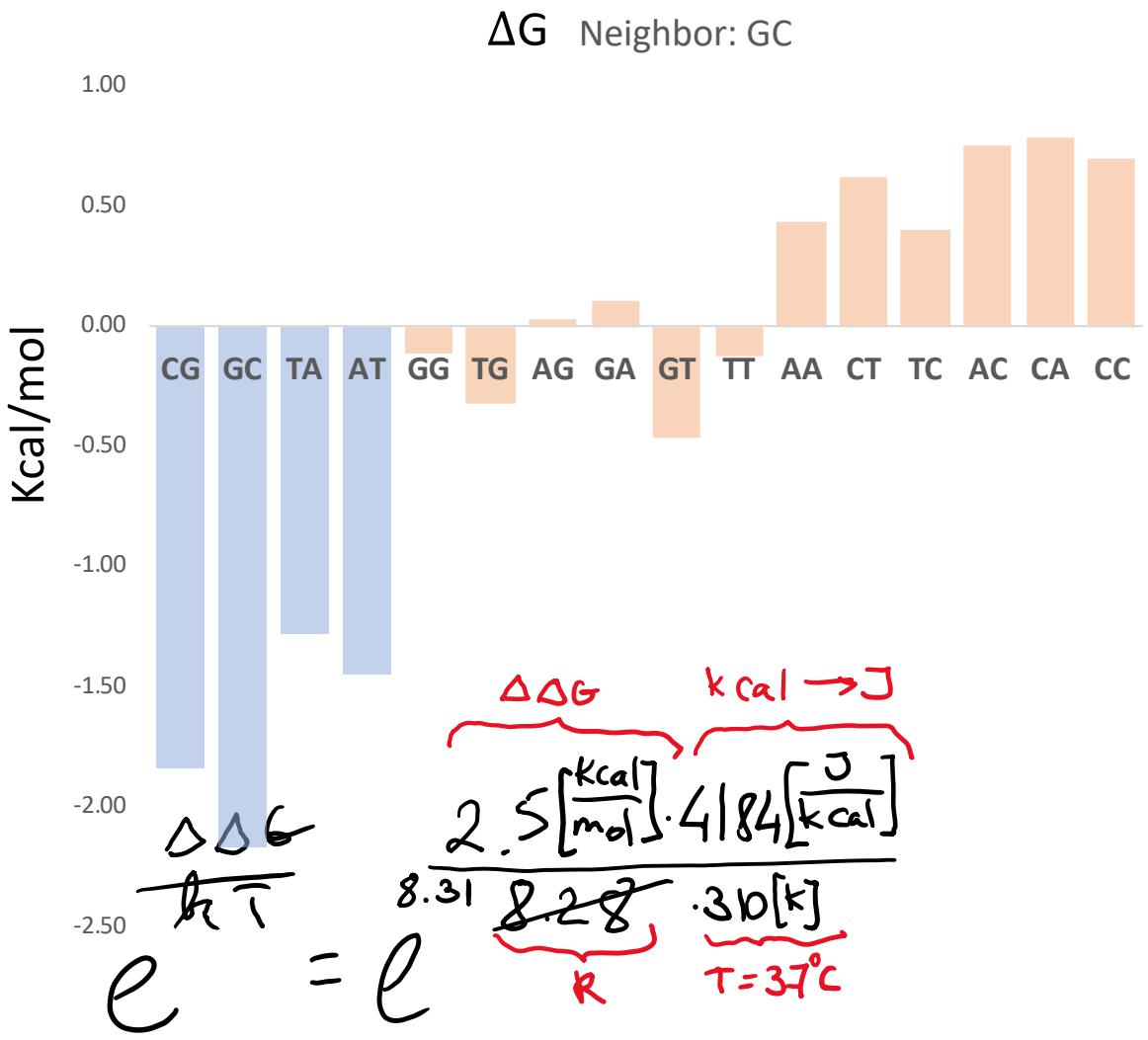
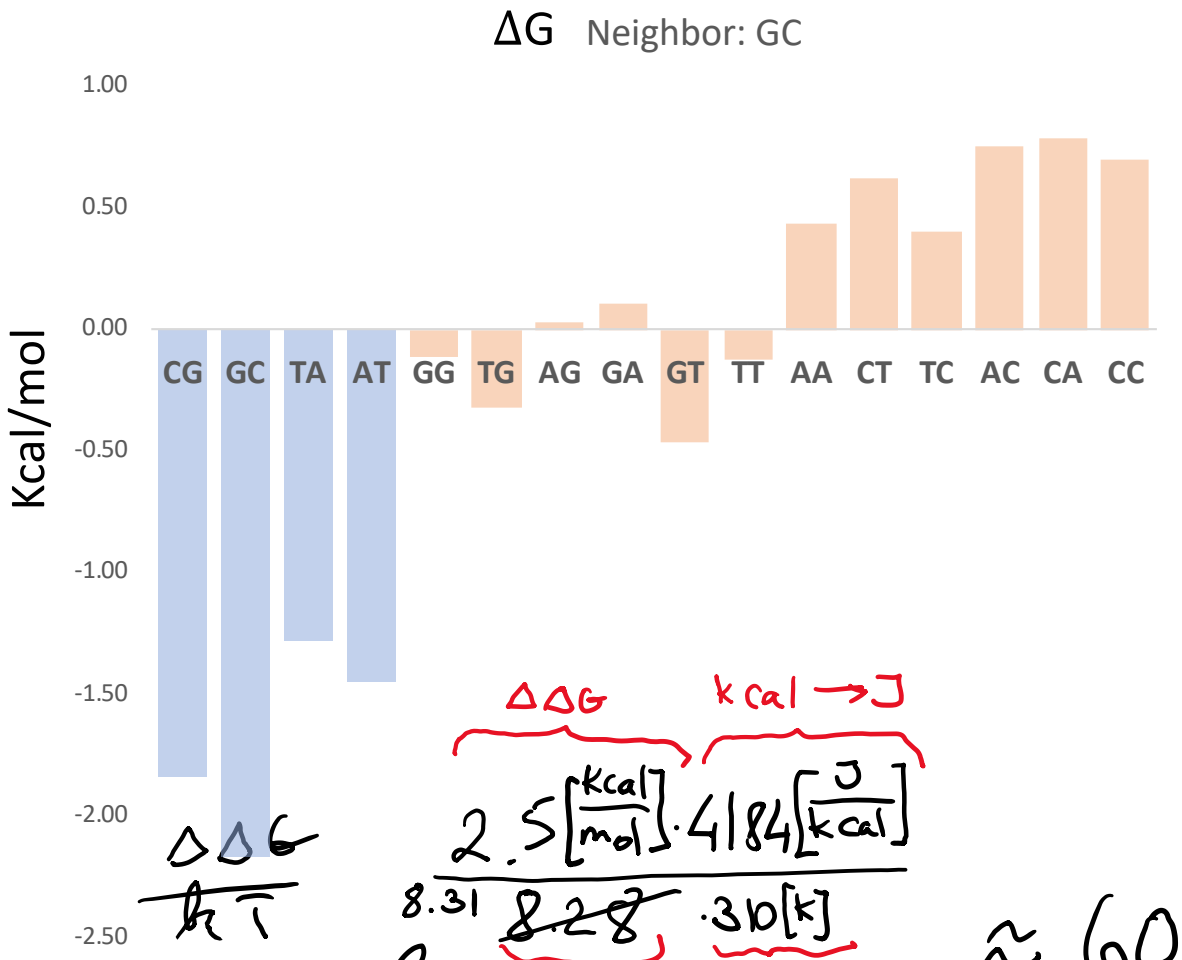


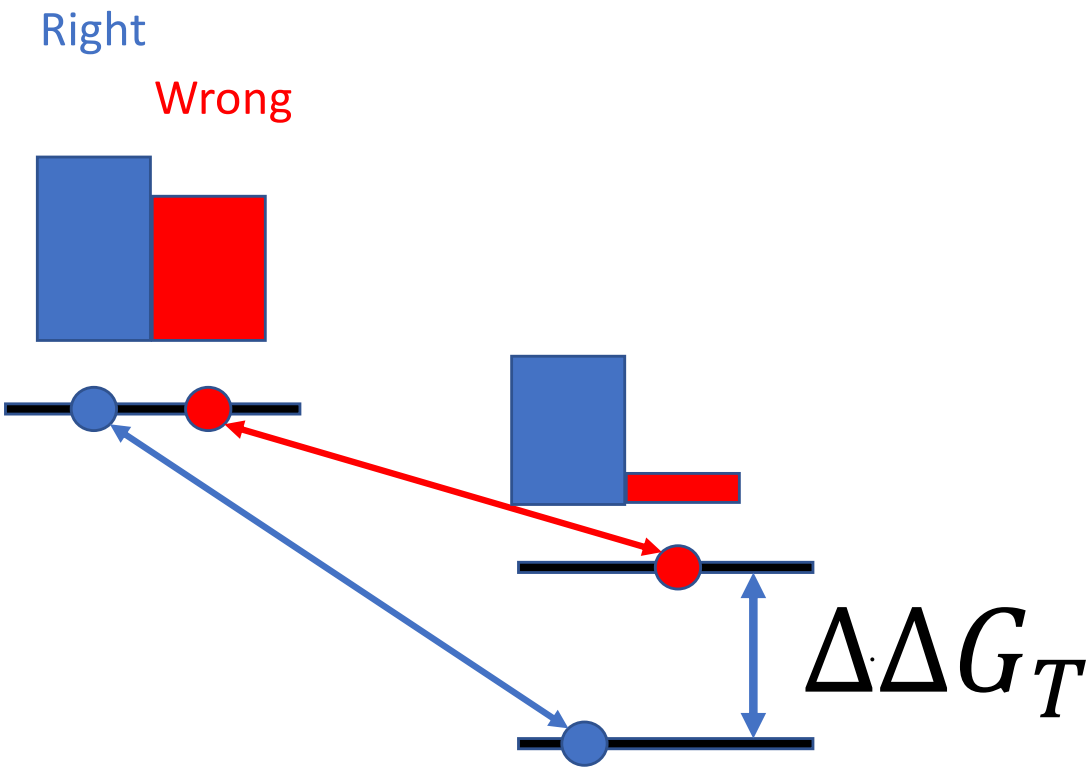
Binding difference



$$e^{\frac{\Delta\Delta G}{kT}} = e^{\frac{2.5\left[\frac{kcal}{mol}\right]\cdot 4184\left[\frac{J}{kcal}\right]}{8.31\left[\frac{J}{mol\,K}\right]\cdot 310[K]}} \approx 60$$

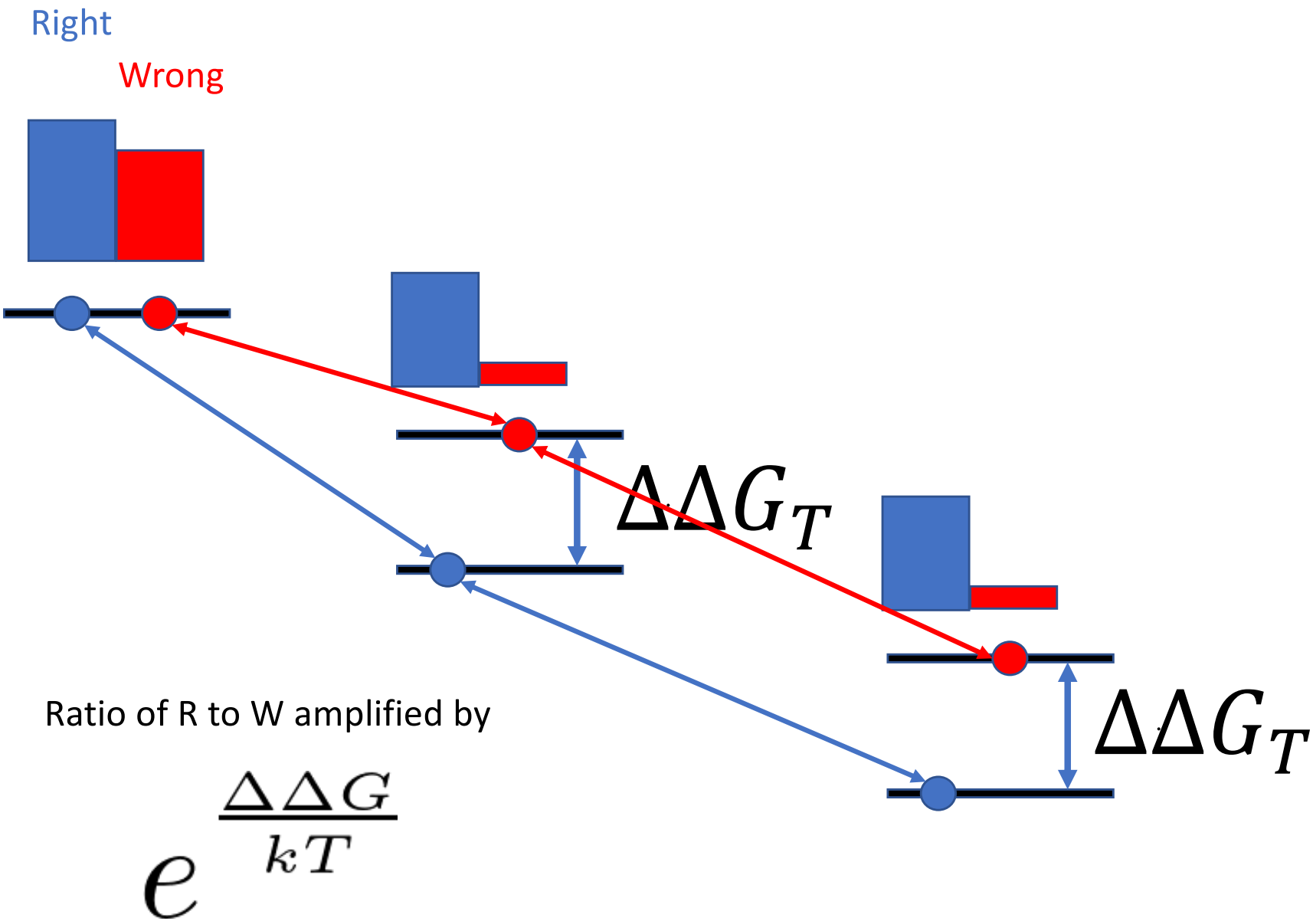
ΔΔG — kcal → J

R — T = 37°C



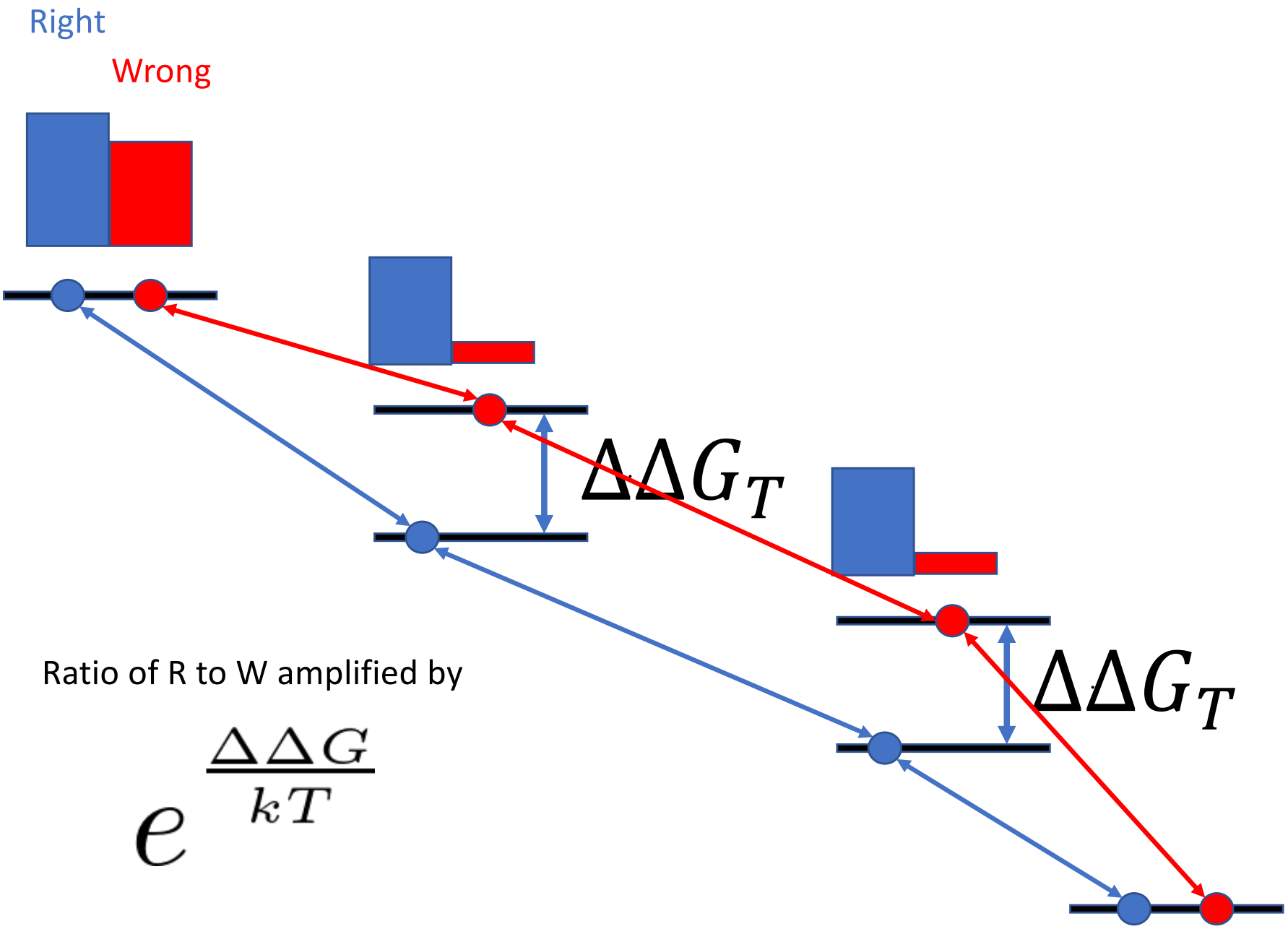
Ratio of R to W amplified by

$$e^{\frac{\Delta\Delta G}{kT}}$$



Ratio of R to W amplified by

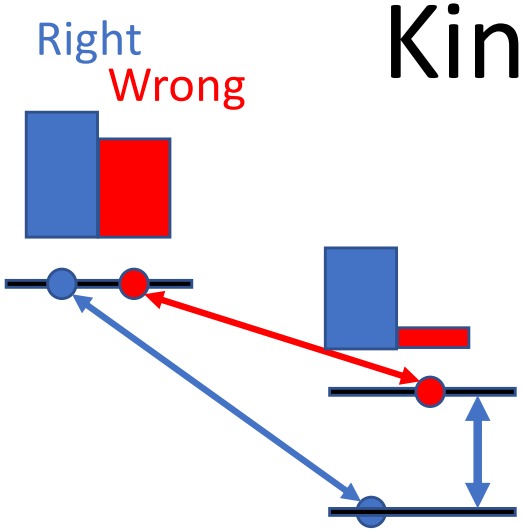
$$e^{\frac{\Delta\Delta G}{kT}}$$



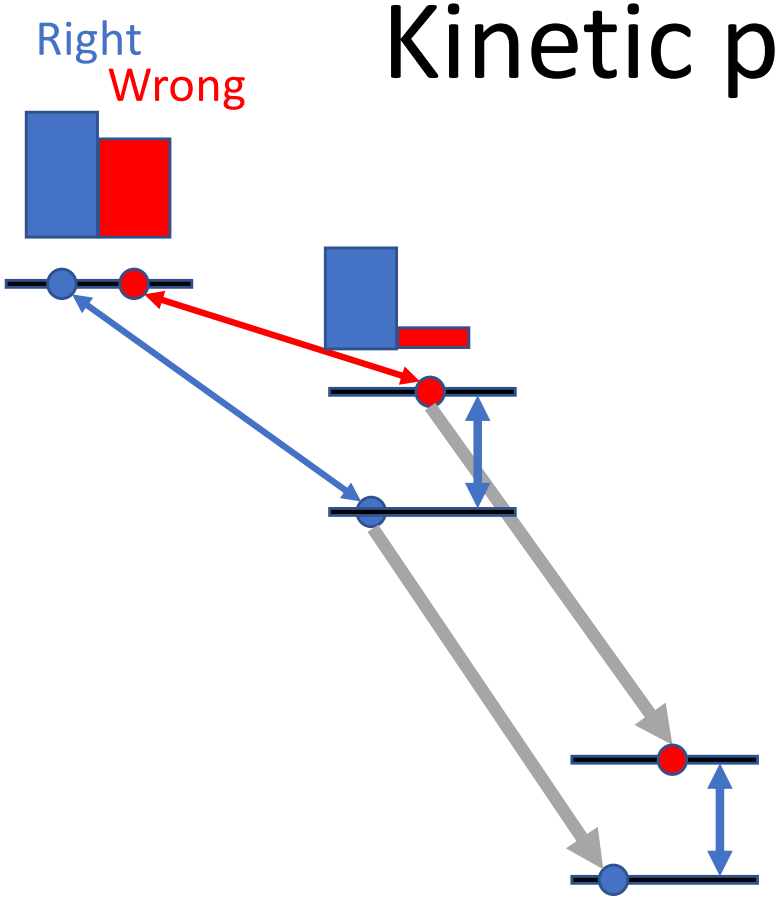
Ratio of R to W amplified by

$$e^{\frac{\Delta\Delta G}{kT}}$$

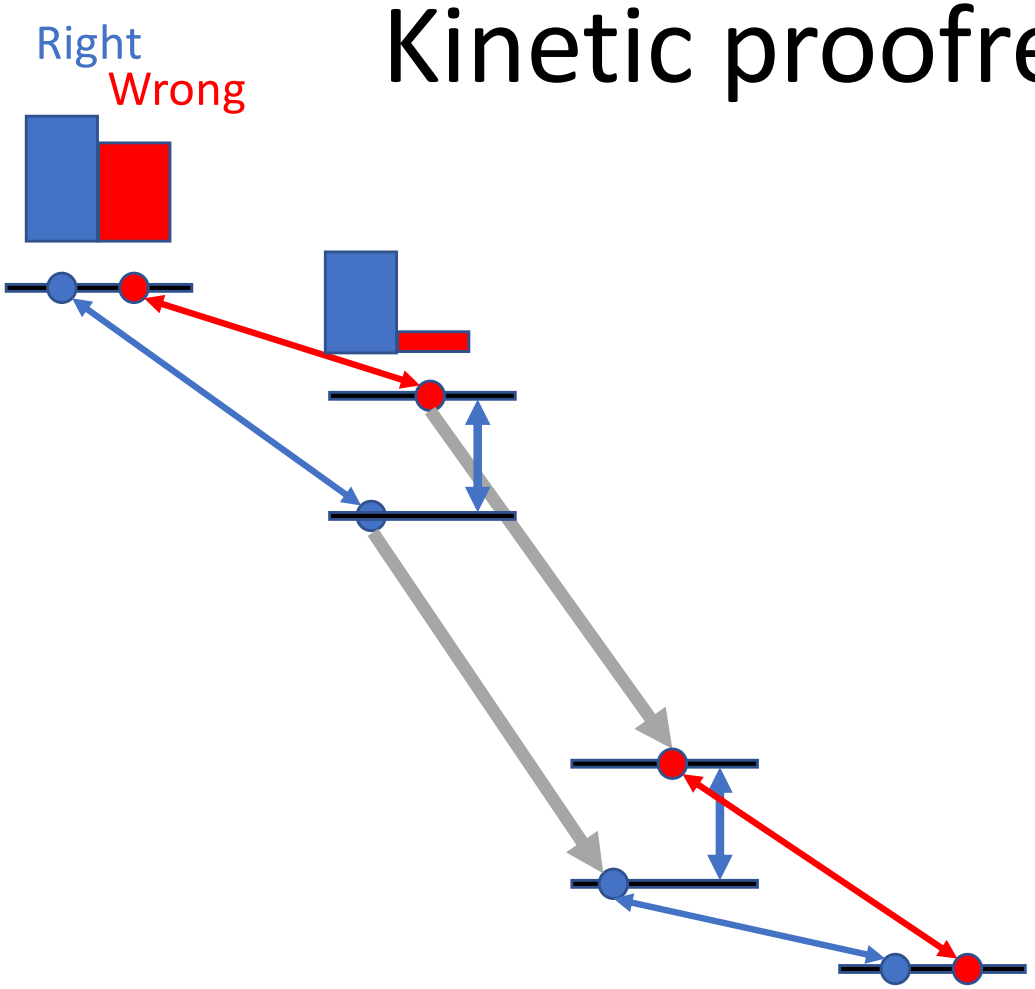
Kinetic proofreading



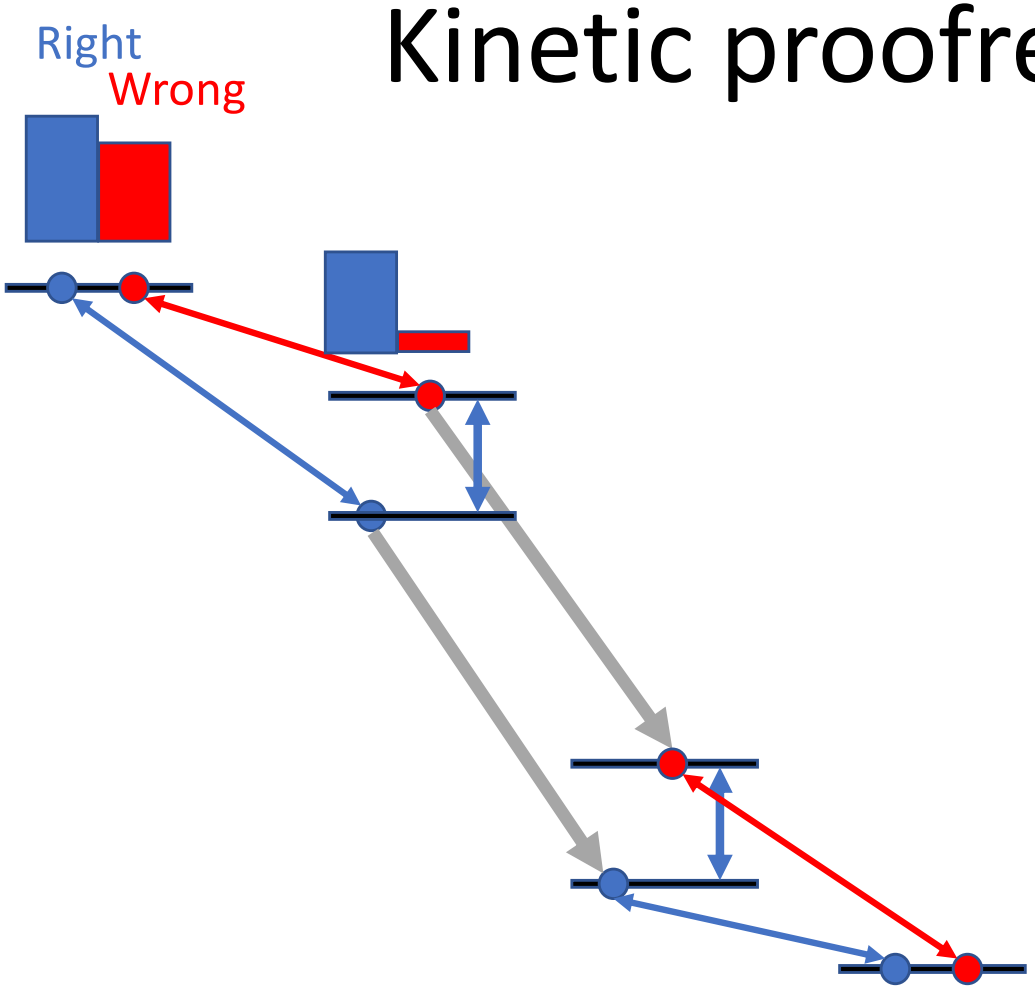
Kinetic proofreading



Kinetic proofreading

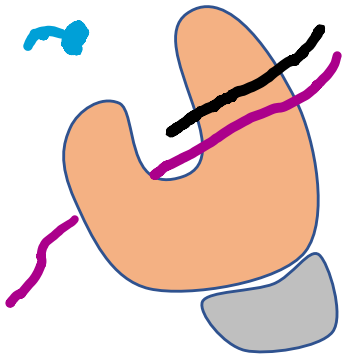


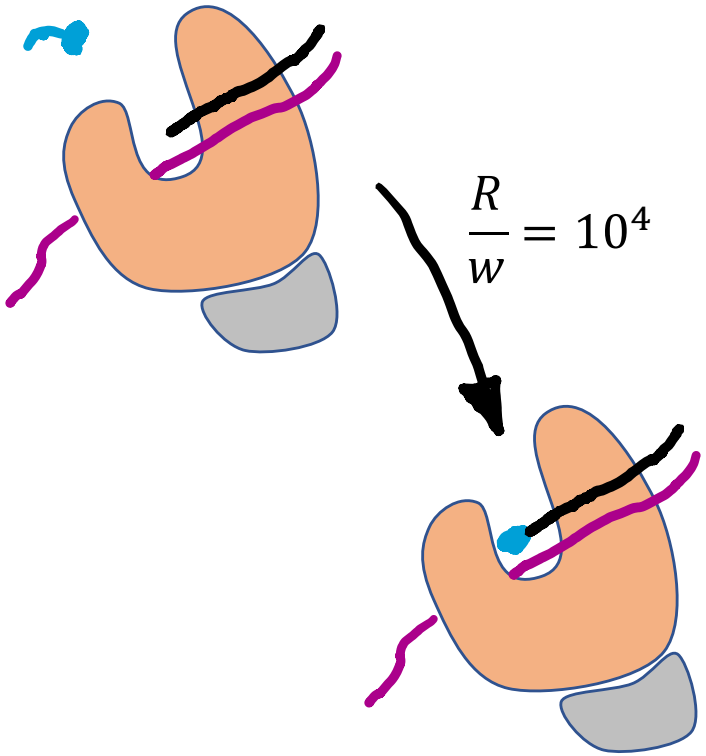
Kinetic proofreading

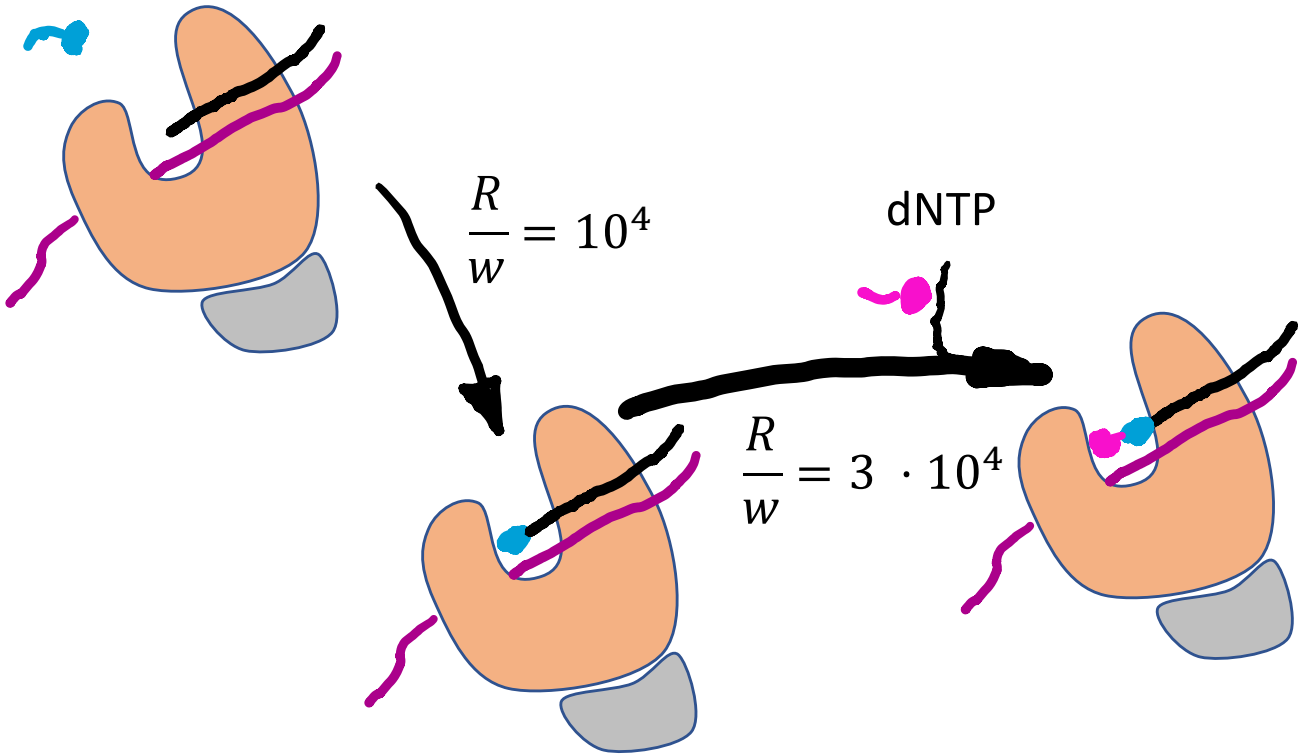


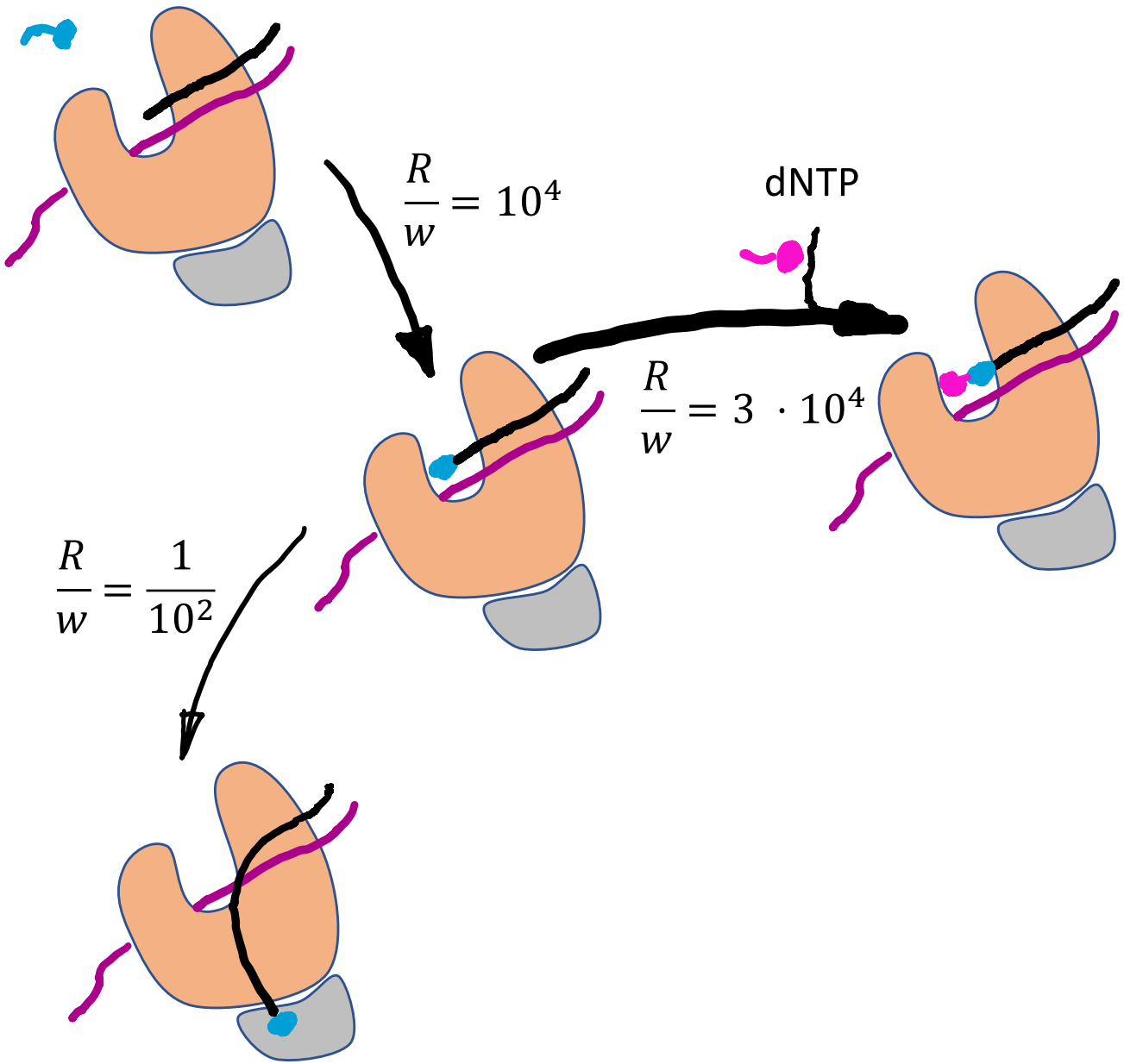
Ratio of R to W amplified by

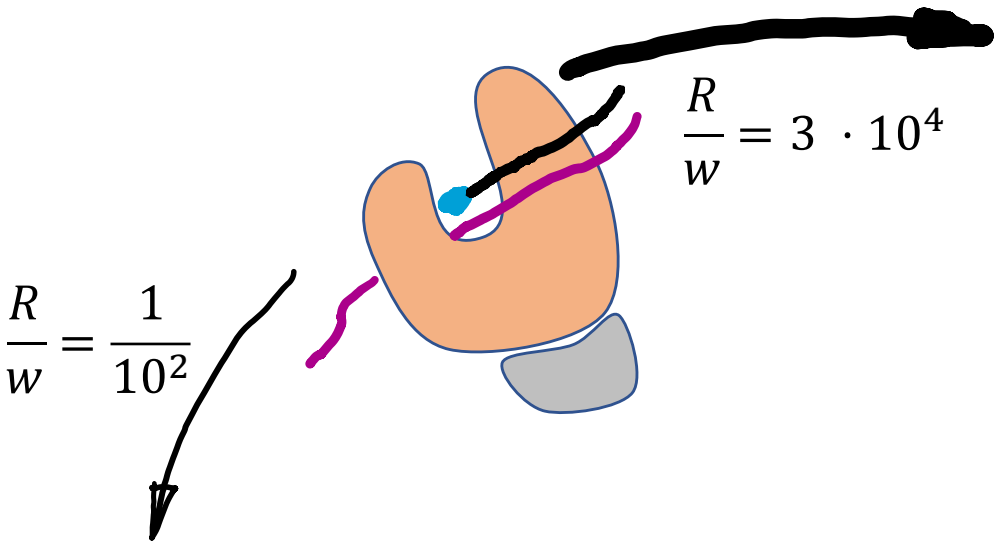
$$\left(e^{\frac{\Delta\Delta G}{kT}} \right)^2$$




$\frac{R}{w} = 10^4$

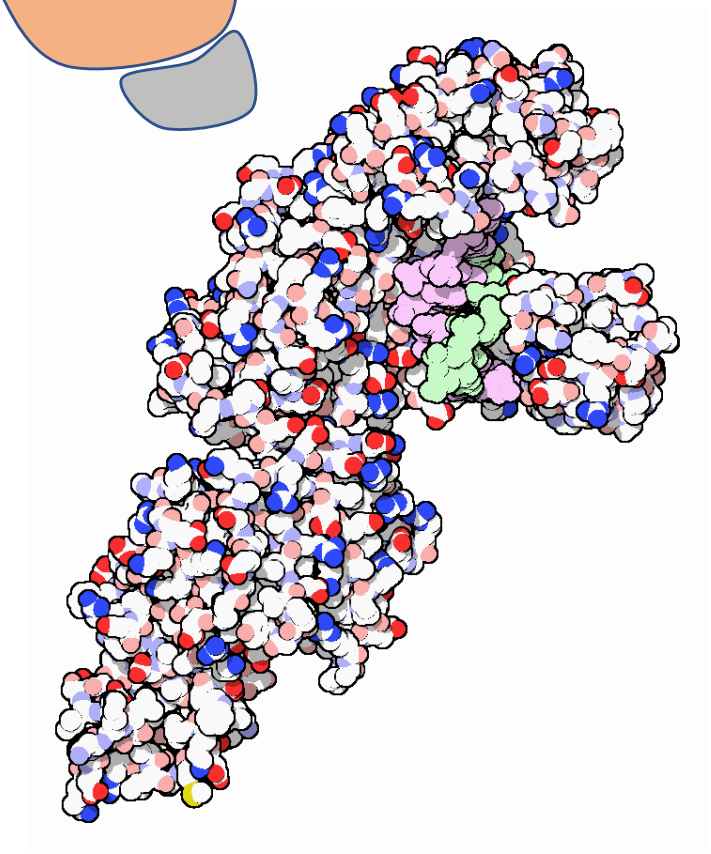

$\frac{R}{w} = 10^4$
dNTP
$\frac{R}{w} = 3 \cdot 10^4$


$\frac{R}{w} = 10^4$
dNTP
$\frac{R}{w} = 3 \cdot 10^4$
$\frac{R}{w} = \frac{1}{10^2}$


$\frac{R}{w} = 3 \cdot 10^4$
$\frac{R}{w} = \frac{1}{10^2}$

$$\frac{R}{w} = 3 \cdot 10^4$$

$$\frac{R}{w} = \frac{1}{10^2}$$



Bases encountered by DNA polymerase

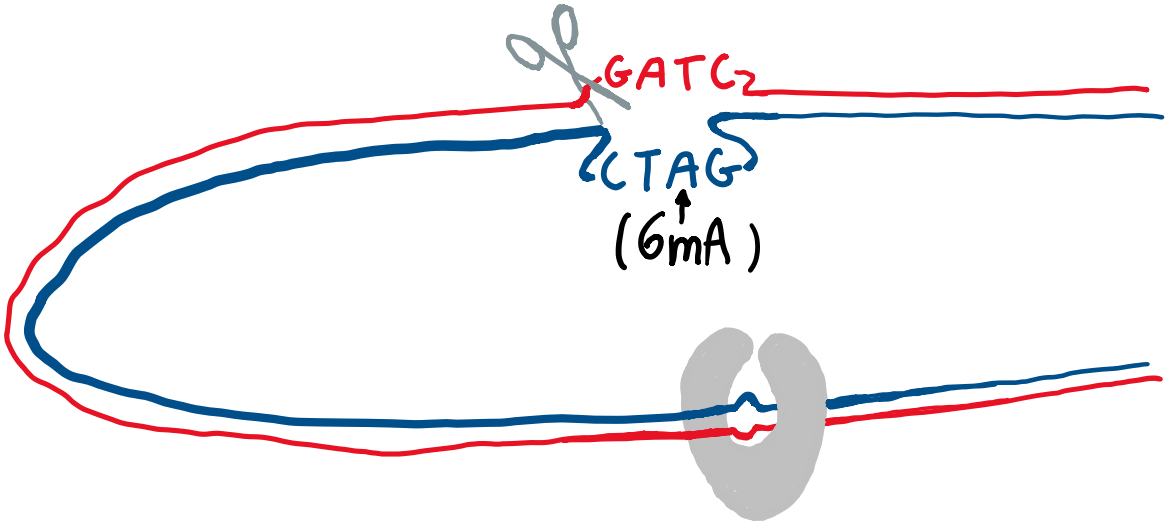
Bases encountered by DNA polymerase

- Watson Crick pairs (CATG)
  - Only ~50 fold enrichment from pairing
  - Right base at 3-fold disadvantage
  - 4 shapes valid
- “Valid” W-C extra bases (C*,6mA)
  - Additional shapes valid
- NTP from RNA
  - Frequent
  - Shape recognition
- “Nonstandard” bases
  - Rare, probably shape recognition

DNA mismatch repair (MMR)

MutS

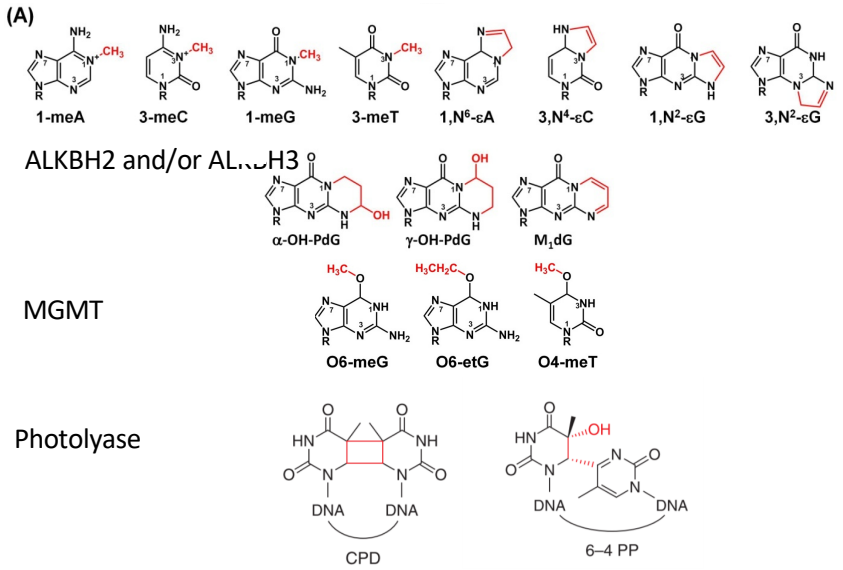
Groothuizen, eLife 2015;4:e06744 doi: 10.7554/eLife.0674



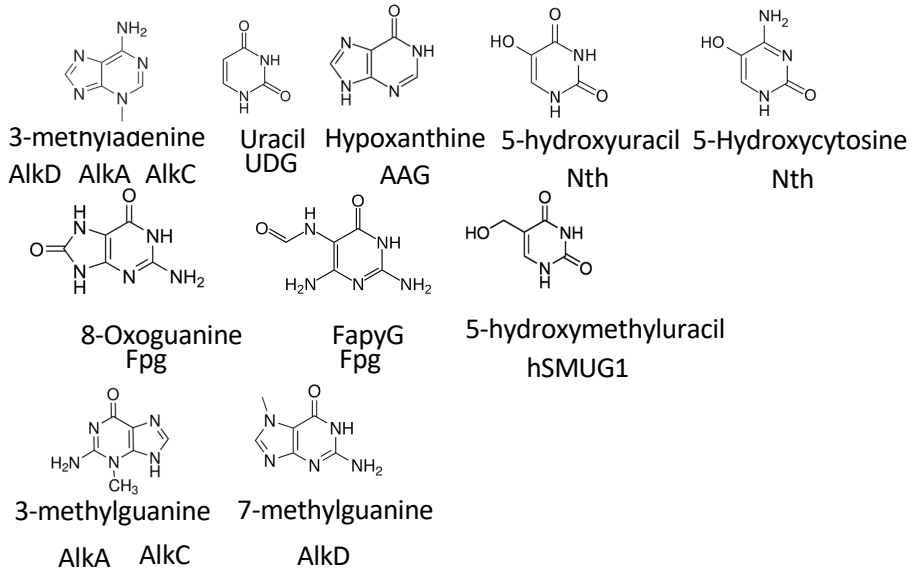
DNA mismatch repair (MMR)

MutS

Groothuizen, eLife 2015;4:e06744 doi: 10.7554/eLife.0674



Direct reversal



Base excision repair

Summary – it isn't in the bases

- Many bases exist in DNA/RNA
  - Damage, modification, insertion
- dNTP concentration is controlled
- DNA polymerase controls pairing
- Large number of specific/general repair enzymes