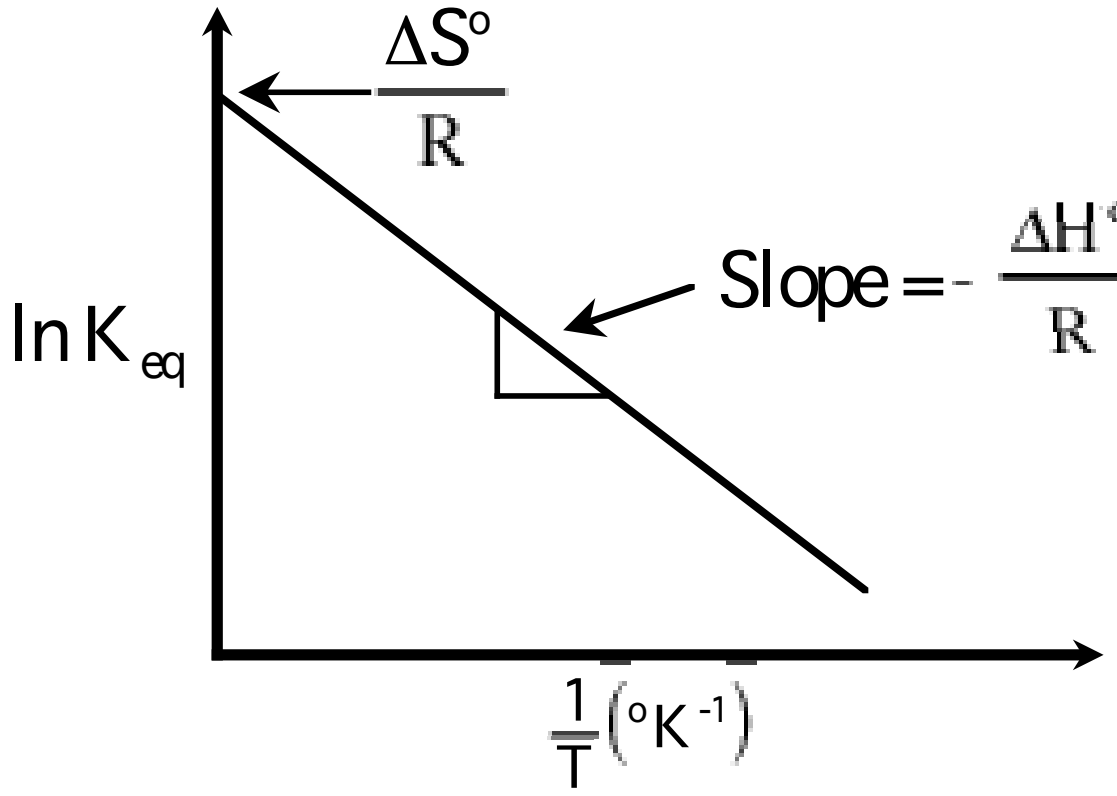
Enthalpy and entropy of protein binding to DNA

The temperature dependence of the binding constants reveals ΔH and ΔS in a van't Hoff plot if ΔH and ΔS are independent of temperature



$$\Delta G = \Delta H - T \cdot \Delta S$$

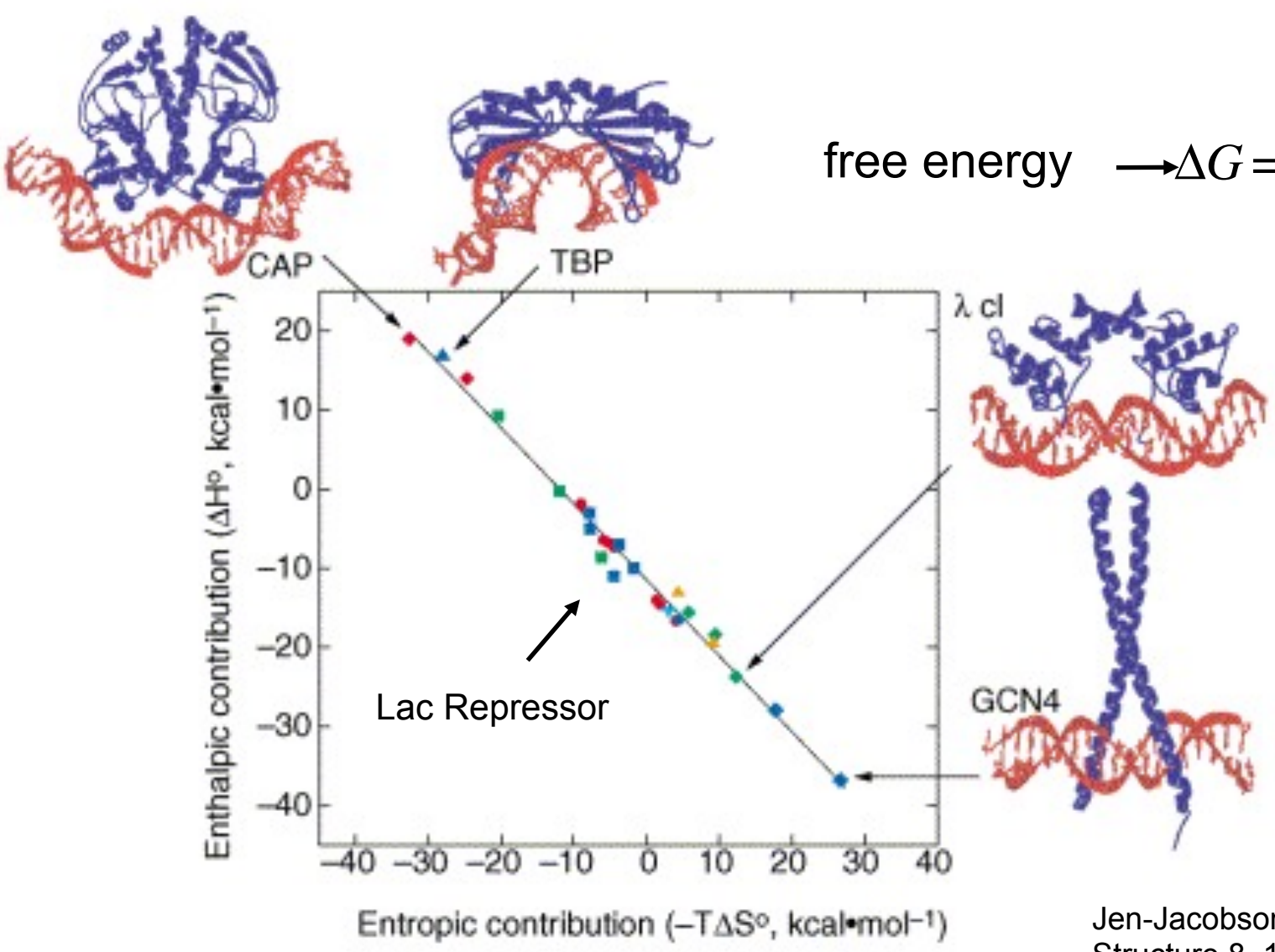
$$\Delta G = -R \cdot T \cdot \ln K_{eq}$$

$$\ln K_{eq} = -\frac{\Delta H}{RT} + \frac{\Delta S}{R}$$

$$\frac{\partial(\ln K_{eq})}{\partial(1/T)} = -\frac{\Delta H}{R}$$

From the slope of ln K_{eq} vs. 1/T (usually from 0 to 40 °C) one can determine the ΔH and from extrapolation also ΔS . Is the van't Hoff plot curved then ΔH is temperature dependent and it can be determined from the derivative.

Contribution of enthalpy and entropy to binding energies of different protein-DNA complexes



enthalpy

free energy $\longrightarrow \Delta G = \Delta H - T \cdot \Delta S$

entropy

Jen-Jacobson et al. (2000). Structure 8, 1015-1023

K_D and ΔG values for protein-DNA binding per site

Specific binding of a protein to DNA varies over a relatively small range:

$\Delta G_{bind,sp}$ = -9 to -16 kcal/mol, with ~60 kcal/mol for ΔH and $T\Delta S$

$\Rightarrow \Delta G_{bind,sp} \approx$ const. (-11.7 ± 1.6 kcal/mol)

$\Rightarrow \Delta H = -T \cdot \Delta S$ - 11.7 kcal/mol

Protein needs to select specific binding site from unspecific sites

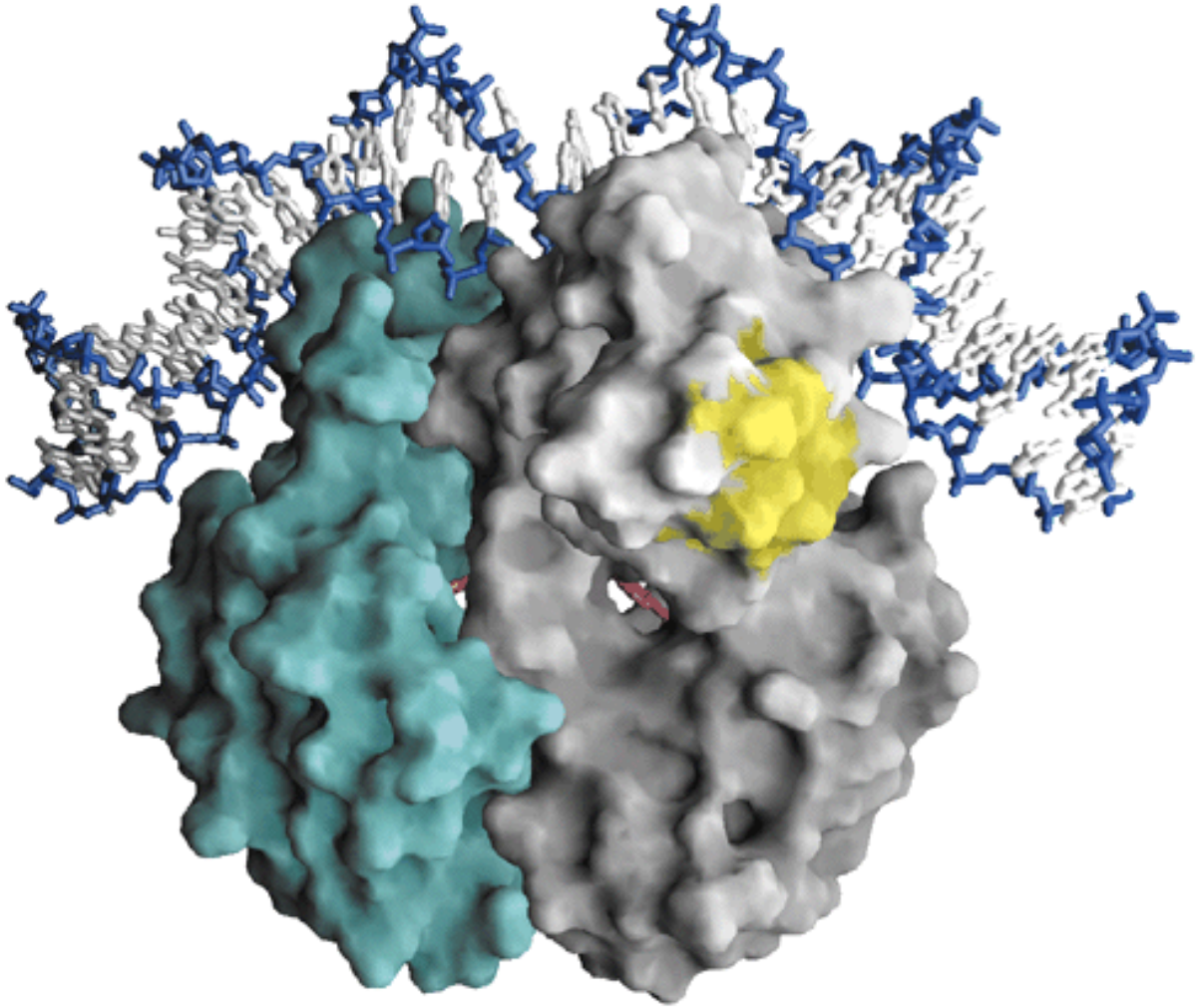
$\Rightarrow \Delta\Delta G$(specific - unspecific) ~ -5 to -9 kcal/mol

Protein binding must be reversible on the cell's time scale

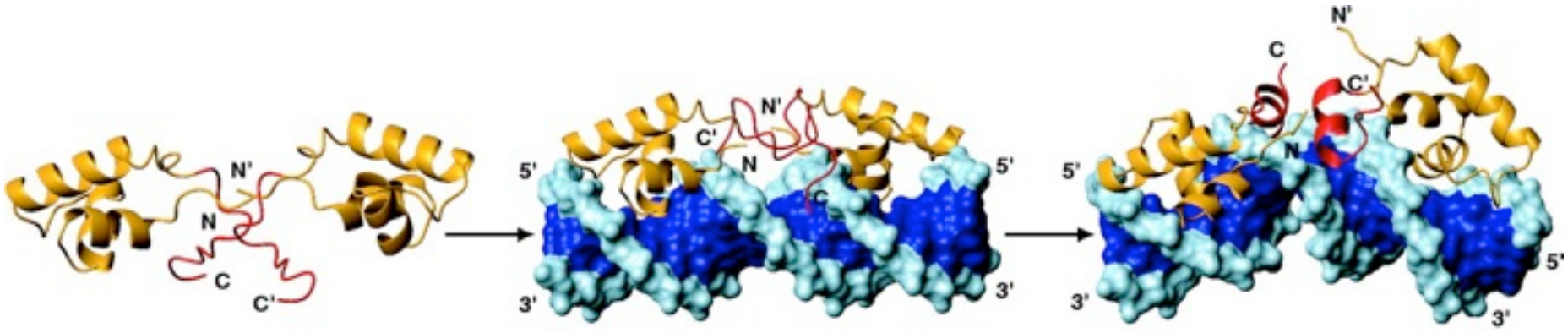
$\Rightarrow \Delta G_{bind,sp} \leq$ -16 kcal/mol

Rotational/translation entropy loss ("rigid bodies"): 15 kcal mol^{-1}

Molecular structure of E. coli CRP (also called CAP for catabolite gene activator protein)



The hinge region (50-62 in red) of Lac-DBD is folded only in the specific complex with DNA



free lac DBD nonspecific complex, straight DNA specific complex , curved DNA

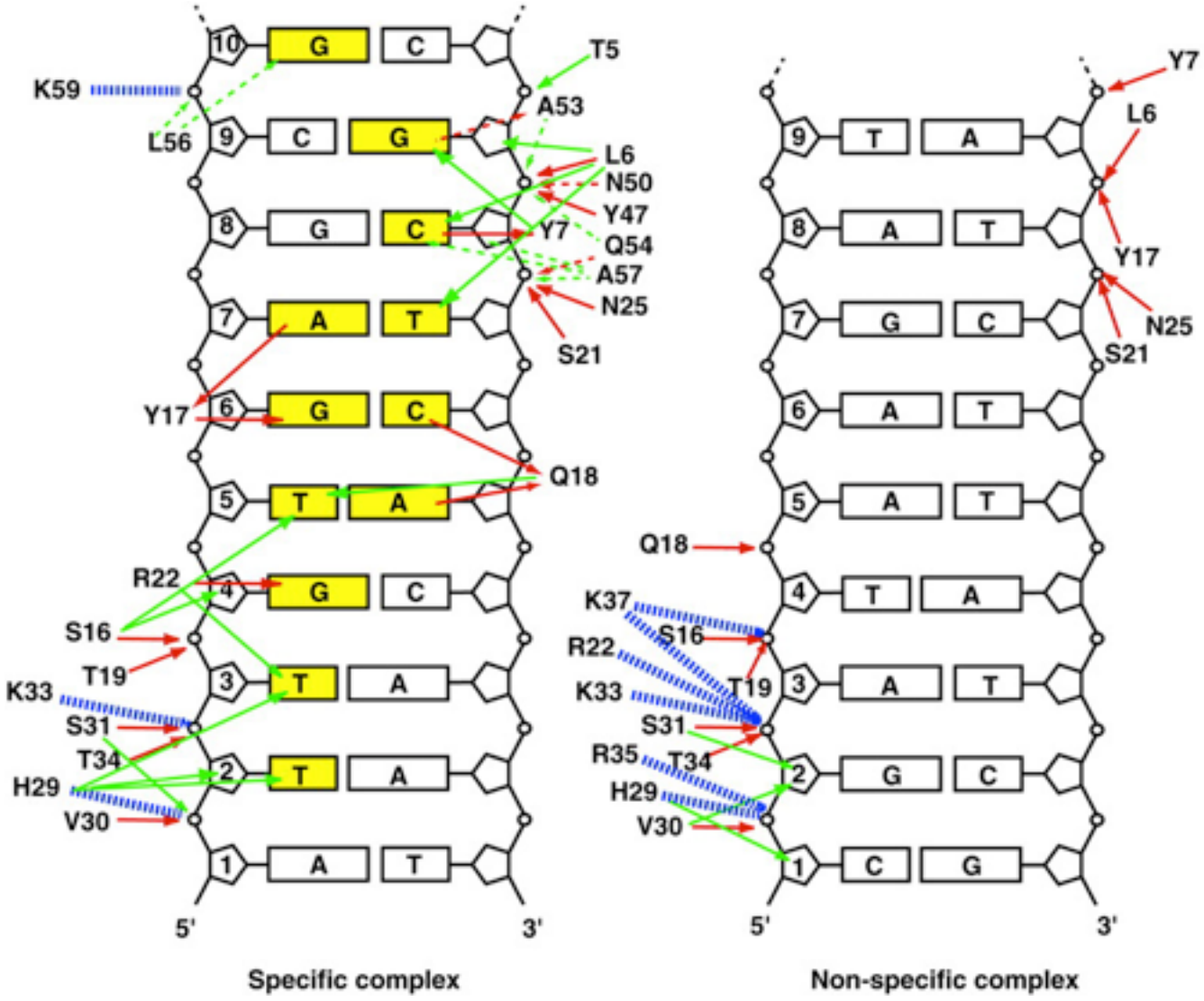
- folding of hinge region with specific contacts in minor groove
- specific interactions major groove
- less electrostatic interactions
- curvature of DNA

Specific (left) and nonspecific (right) protein-DNA contacts of Lac-DBD repressor with DNA

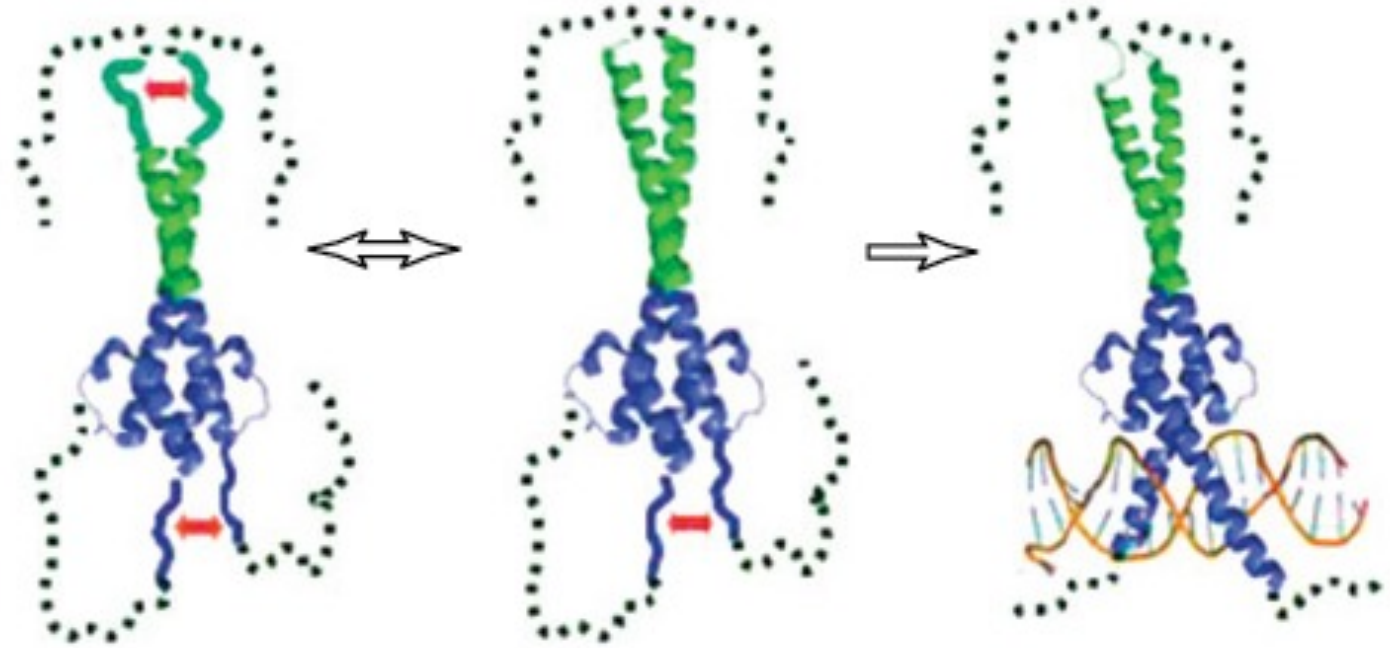
red:
hydrogen bonds

green:
hydrophobic
contacts

dashed blue:
electrostatic
contacts

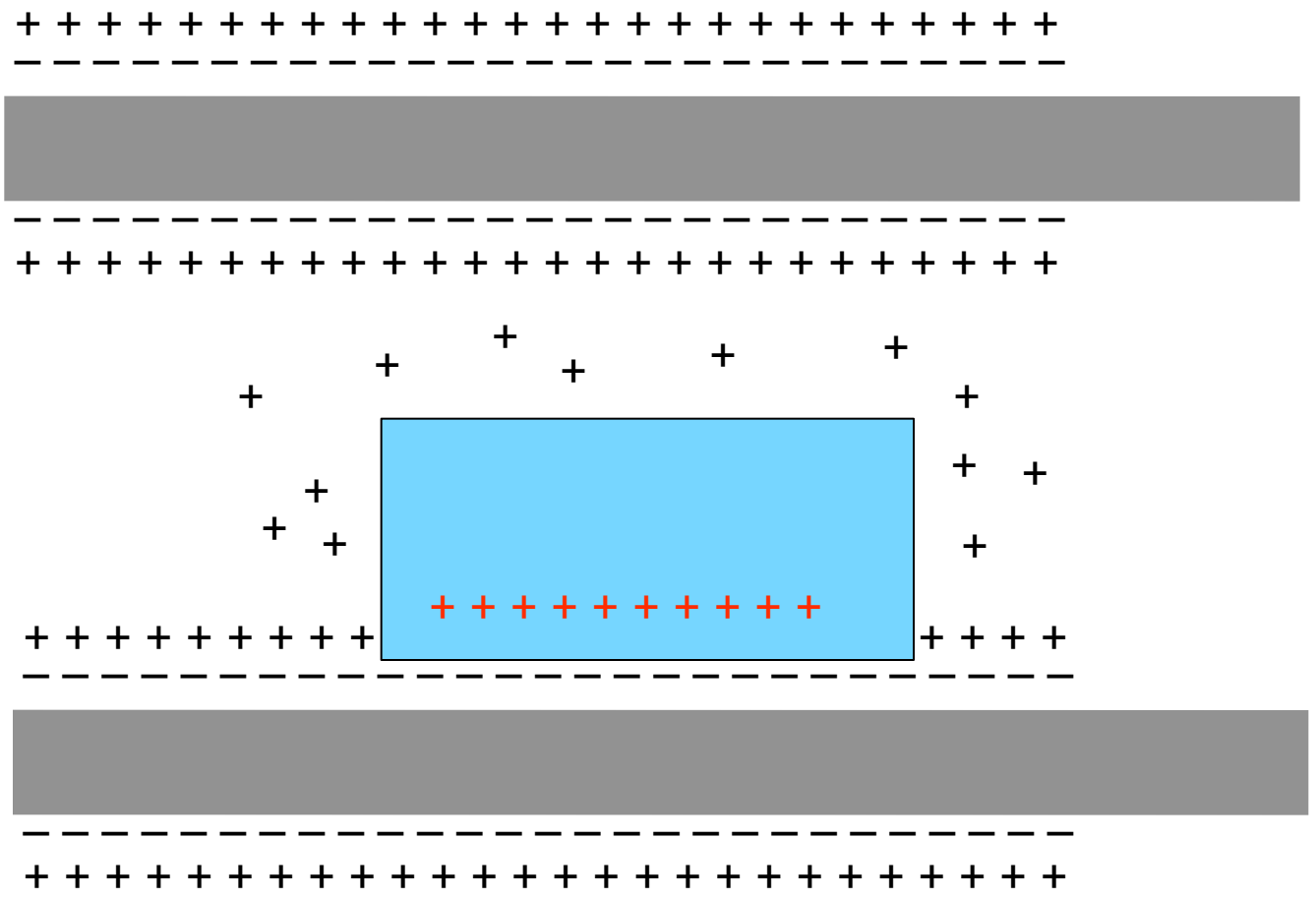


Local folding of the Max transcription factor (“leucine zipper” motif) upon dimerization and binding



The Max transcription factor (PDBcode: 1NKP) binds DNA as a dimer. The disordered N-terminal region (upper dotted line) reduces the electrostatic repulsion (red arrows) between the two monomers, and increases the population of the folded state at the flanking leucine zipper (green). This also stabilizes the bHLH region (blue) and thus improves binding affinity for DNA.

ΔS_{PE}: Favorable displacement of ions from the DNA



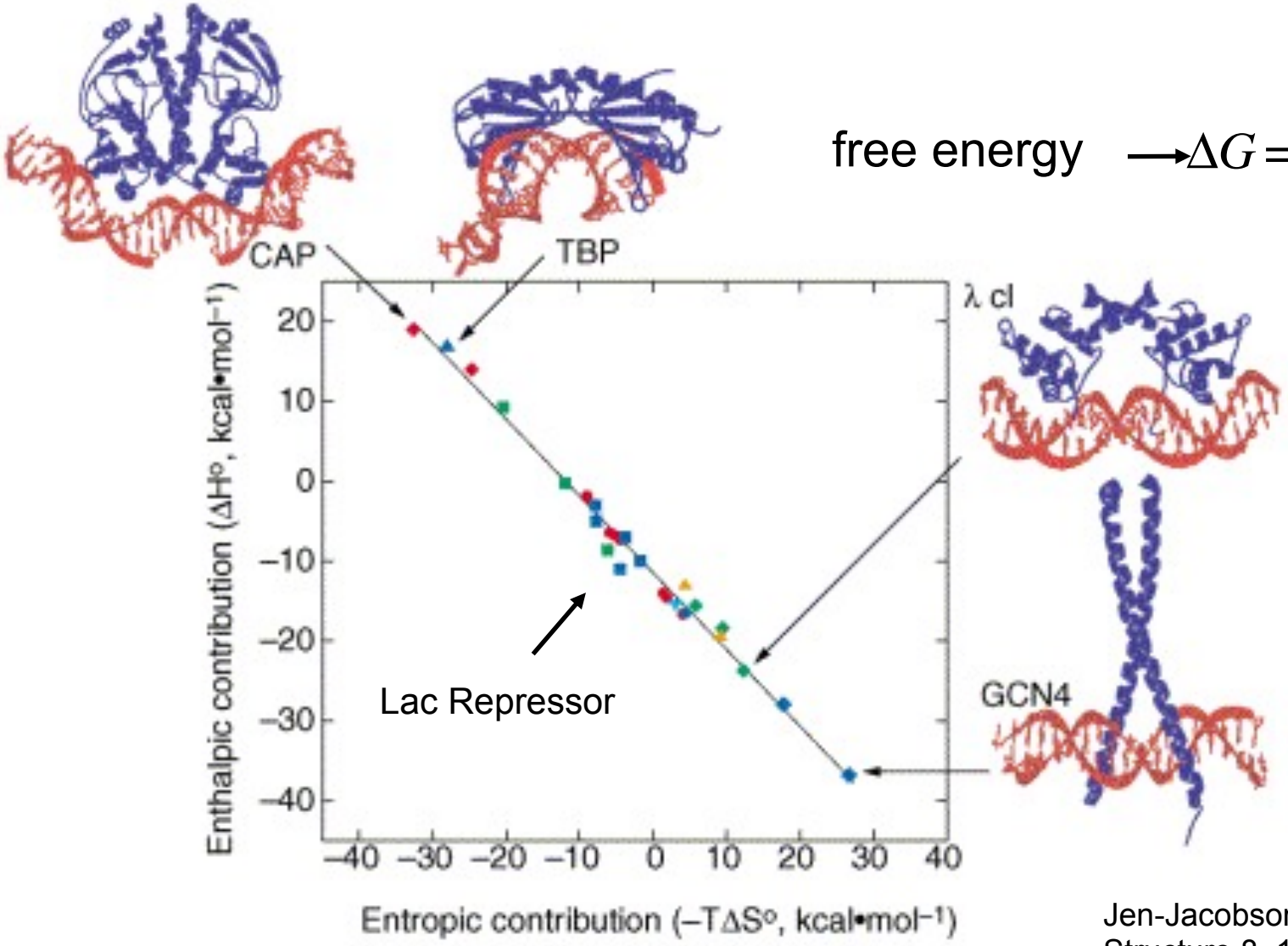
$-T\Delta S_{PE}$ = 6 to 18 kcal/mol

The unfavorable enthalpy contribution associated with DNA distortion is compensated by a favorable entropy

enthalpy

free energy $\longrightarrow \Delta G = \Delta H - T \cdot \Delta S$

entropy



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Summary of protein-DNA binding energies

- $\Delta G_{bind,specific}$: -12 ± 2 kcal mol^{-1} and $\Delta G_{bind,unspecific}$: -7 ± 2 kcal mol^{-1}

- Rotational/translation entropy loss (“rigid bodies”): 15 kcal mol^{-1}

- very different ΔH and ΔS for protein-DNA binding but similar ΔGs due to variations in induced protein folding and binding site length

- Unfavorable conformational entropy of folding per residue or 1.7 kcal mol^{-1} (Tanford estimated 1.2 kcal mol^{-1} with three flexible sites)

- Can be partly compensated by the hydrophobic effect or the “release” of water on burial of nonpolar surfaces

- Displacement of counter-ions upon protein binding to DNA: 6-18 kcal mol^{-1} entropy gain, depending on size of interaction surface