It’s not about DNA, It’s all about Pizza

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2nd year PhD

Supervisor: Damien Woods

CS workshop [19/06/2024]

Hamilton Institute

Maynooth University
National University of Ireland Maynooth

Fondúireacht Eolaíochta Éireann sfi Dá bhfuil romhainn

European Innovation Council

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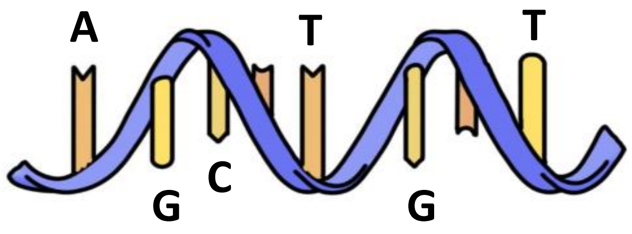
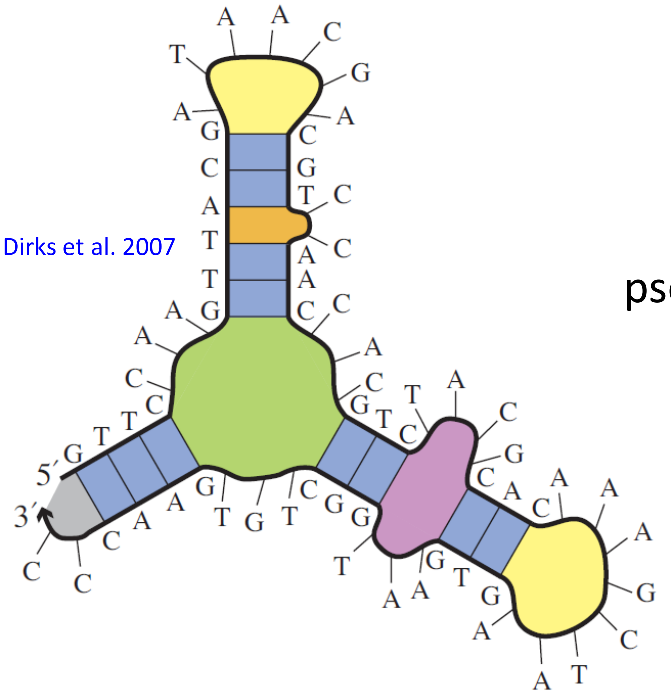
erc

Secondary structure



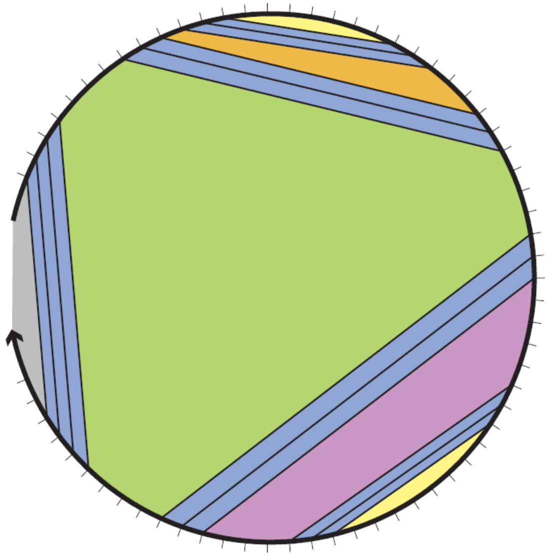
Single stranded DNA

Dirks et al. 2007



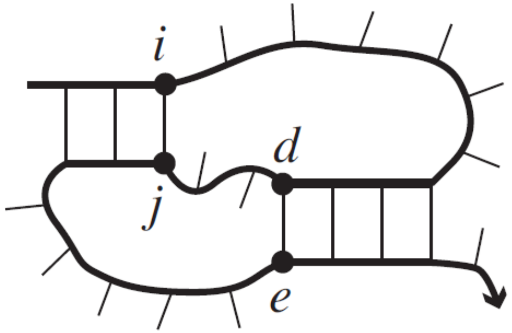
Secondary structure

pseudoknot-free



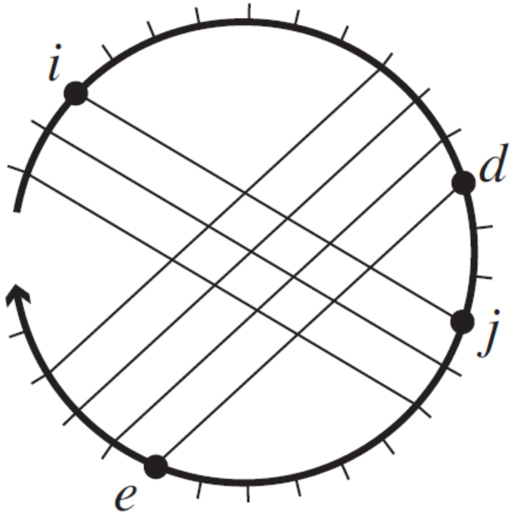
Dirks et al. 2007

Polymer graph representation



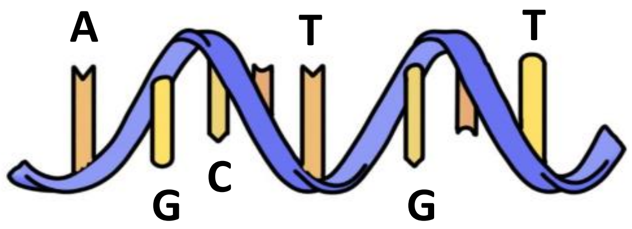
Dirks et al. 2007

pseudoknotted



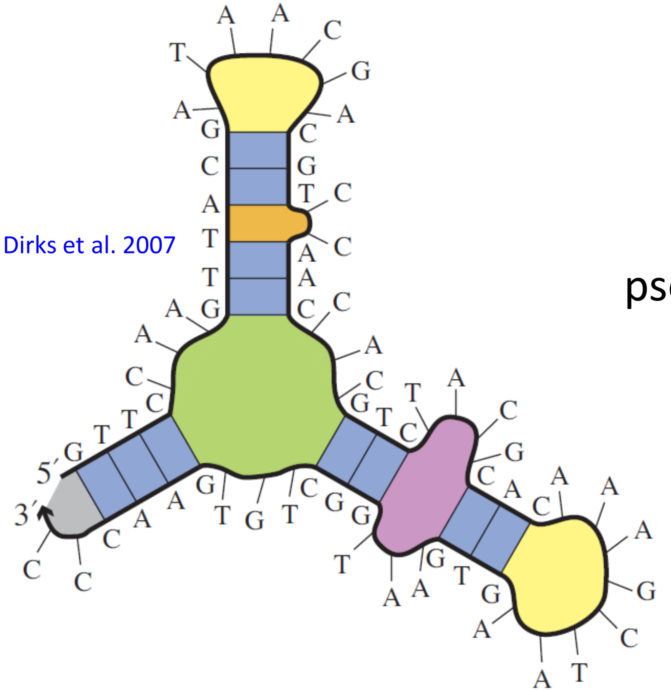
Dirks et al. 2007

Secondary structure



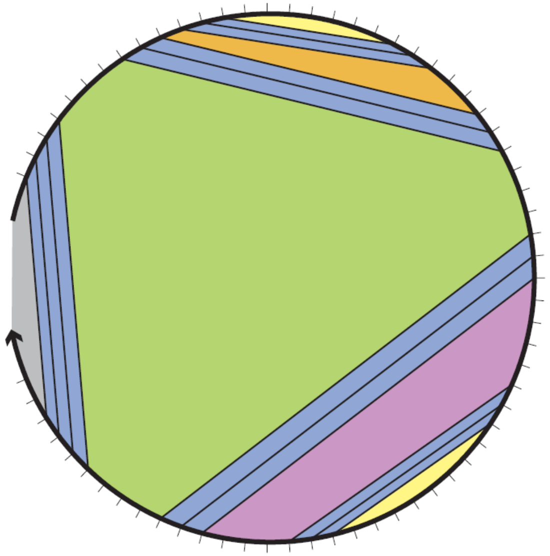
Single stranded DNA

Dirks et al. 2007



Secondary structure

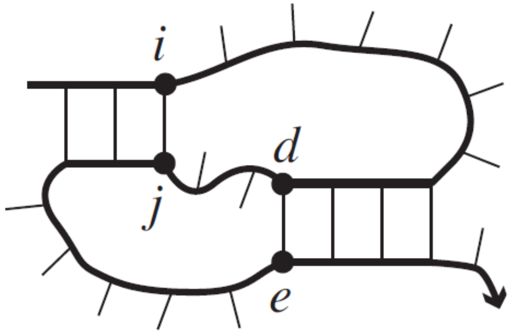
pseudoknot-free



Dirks et al. 2007

Polymer graph representation

NP – Complete



Dirks et al. 2007

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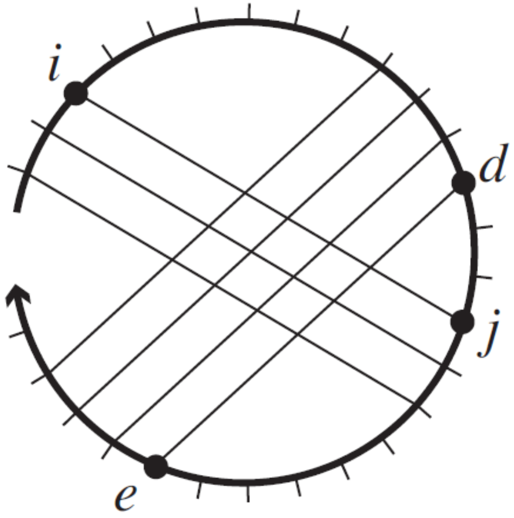
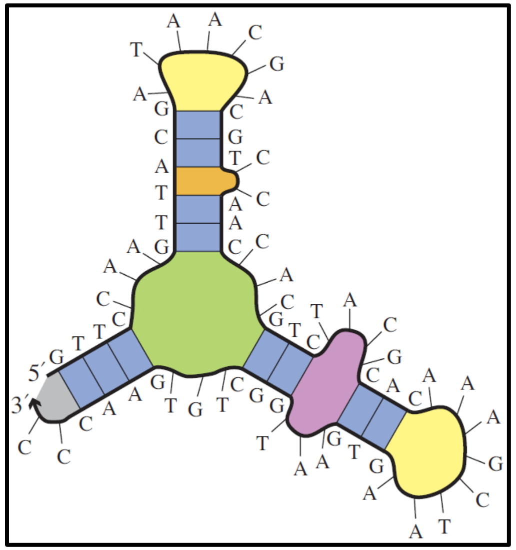
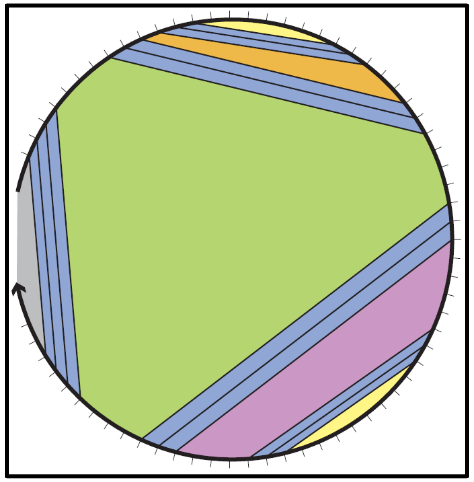


Dirks et al. 2007

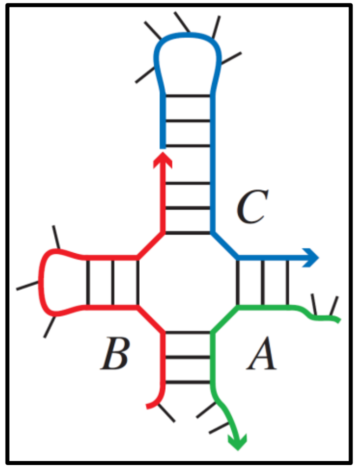
Energy models, Minimum Free Energy and Partition Function

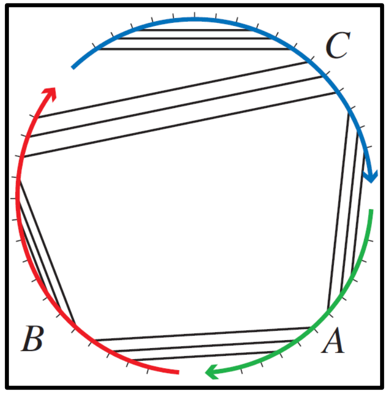
Single stranded system





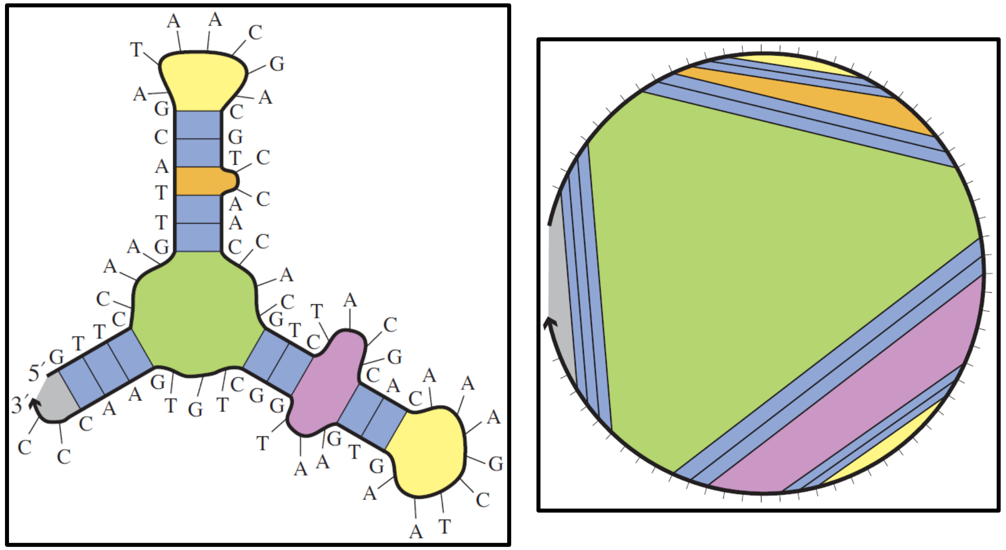
Multi stranded system of s strands





Energy models, Minimum Free Energy and Partition Function

Single stranded system

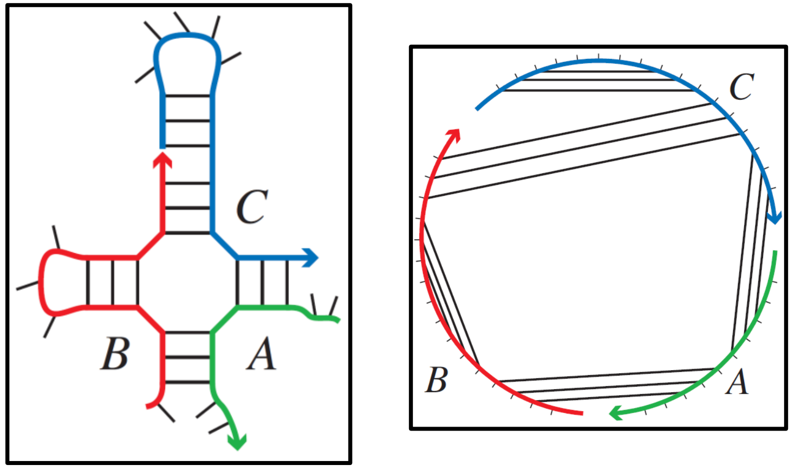


$\Delta G(S)$

Energy model

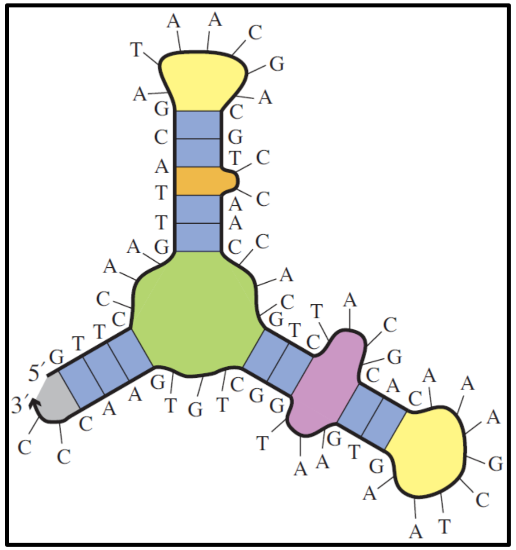
Capture the free energy of secondary structure

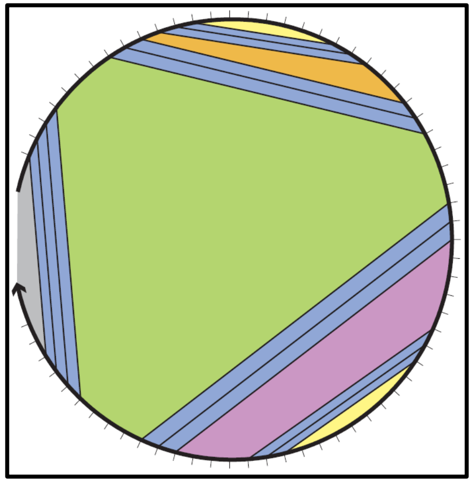
Multi stranded system of s strands



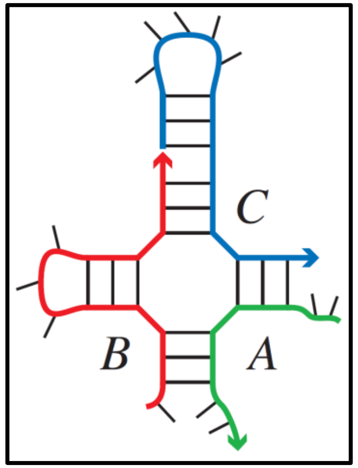
Energy models, Minimum Free Energy and Partition Function

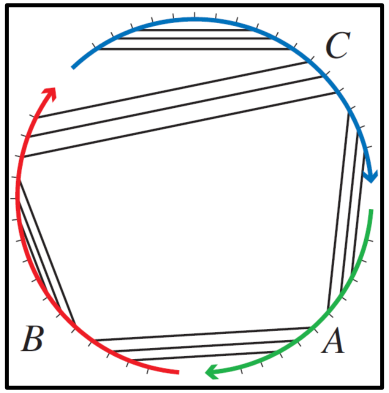
Single stranded system





Multi stranded system of s strands





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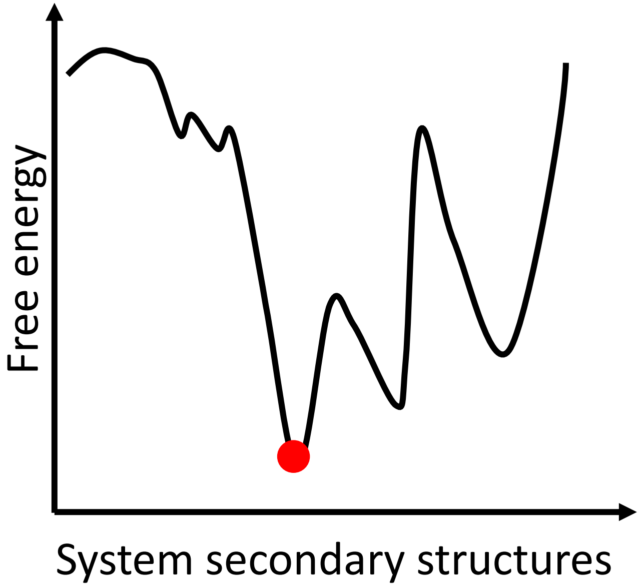
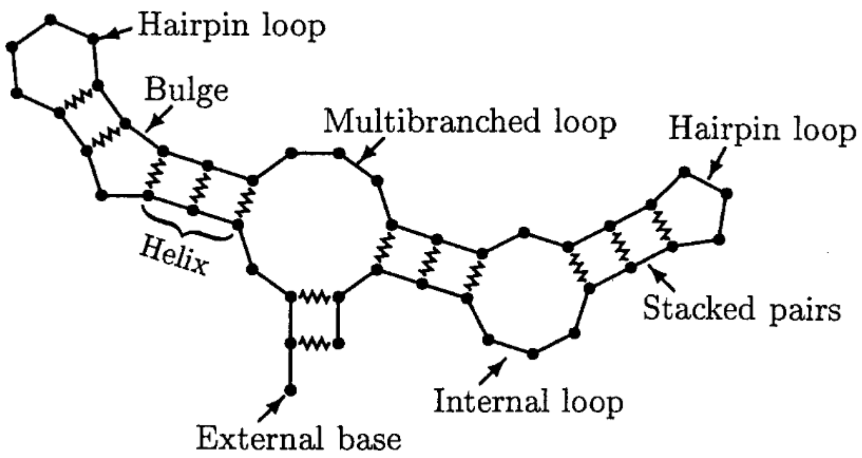
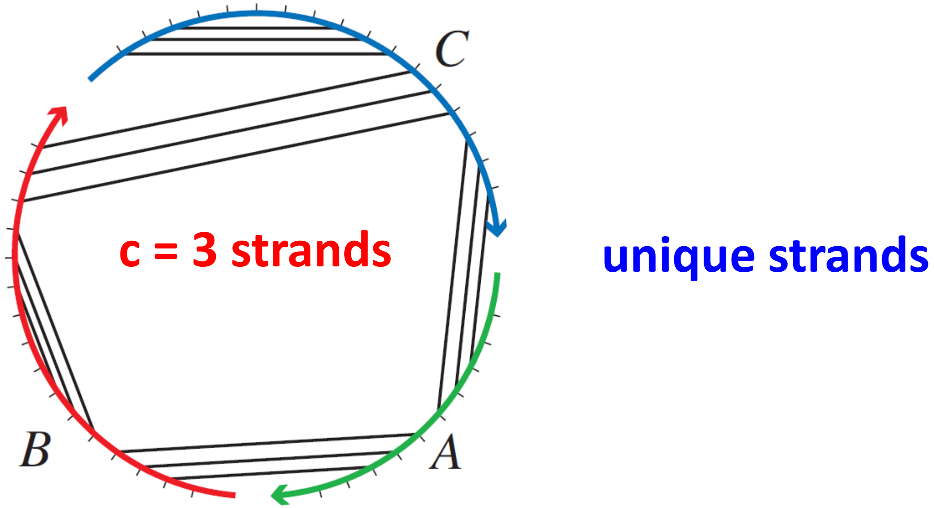


$$\text{MFE} = \min_{S\in\Omega} \Delta G(S)$$

Minimum Free Energy

Energy model: Loop model





$$\Delta G(S) = \sum_{l \in S} \Delta G(l)$$

$$\Delta G(S) = \sum_{l} \Delta G(l) + (c-1)\,\Delta G^{\mathrm{assoc}}$$

$$\min_{S \in \Omega} \Delta G(S)$$

Ω: the set of all secondary structures

Energy model: Loop model (allowing repeats)

$$\underbrace{\Delta G(S)}_{\text{Free energy}} = \sum_{l \in S} \underbrace{\Delta G(l)}_{\text{Loop energy}} + \underbrace{(c-1) * \Delta G^{\text{assoc}}}_{\text{Entropic association cost}} + \underbrace{k_B T * \log R}_{\text{Symmetry penalty}}$$

$-$ $+$ $+$

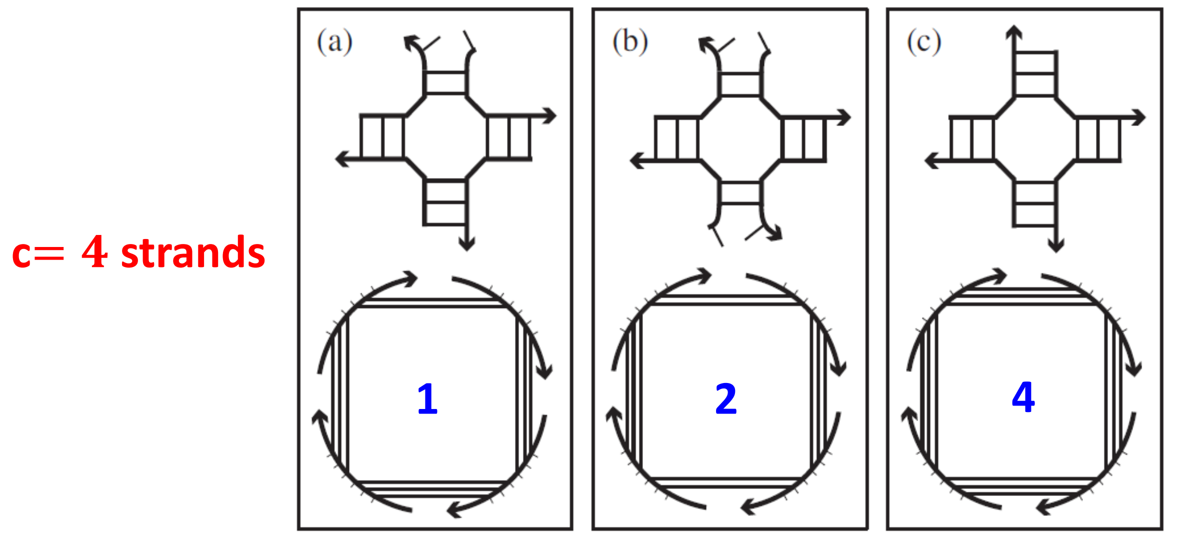


Fig. 2.2 *Sample secondary structures and polymer graphs for a complex of four indistinguishable strands. (a) 1-fold (i.e., no) rotational symmetry. (b) 2-fold rotational symmetry. (c) 4-fold rotational symmetry.*

$$\min_{S \in \Omega} \Delta G(S)$$

Ω: the set of all connected structures

R: degree of rotational symmetry

Computational complexity of Minimum Free Energy algorithms

Input Type	MFE
Single Strand	$O(N^3)$
Multiple **unique** Strands, Bounded ($\leq$ c)	$O(N^3(\mathrm{c}-1)!)$
Multiple Strands **allowing repeats**, Bounded ($\leq$ c)	?
Multiple Strands, Unbounded	$NP-\mathrm{Complete}$

N bases, c strands

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N bases, c strands

Open problem for $\approx$ 20 years

Why symmetry makes it difficult?

Input Type	MFE
Single Strand (Loop model)	$O(N^3)$
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N bases, c strands

Why symmetry makes it difficult?

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} **Dynamic programming algorithms**

N bases, c strands

All of these are dynamic programming algorithms

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} Dynamic programming algorithms

N bases, c strands

All of these are dynamic programming algorithms

Subproblems → **Big problem**

Level	Input Type	MFE
1	Single Strand (Maximum matching)	$O(N^3)$
2	Single Strand (Loop model)	$O(N^3)$
3	Multiple unique Strands, Bounded ($\leq$ c)	$O\left(N^3(c-1)!\right)$
4	Multiple Strands, Bounded ($\leq$ c)	?

N bases, c strands

All of these are dynamic programming algorithms

Subprograms → Big problem

Level	Input Type	MFE
1	Single Strand (Maximum matching)	$O(N^3)$
2	Single Strand (Loop model)	$O(N^3)$
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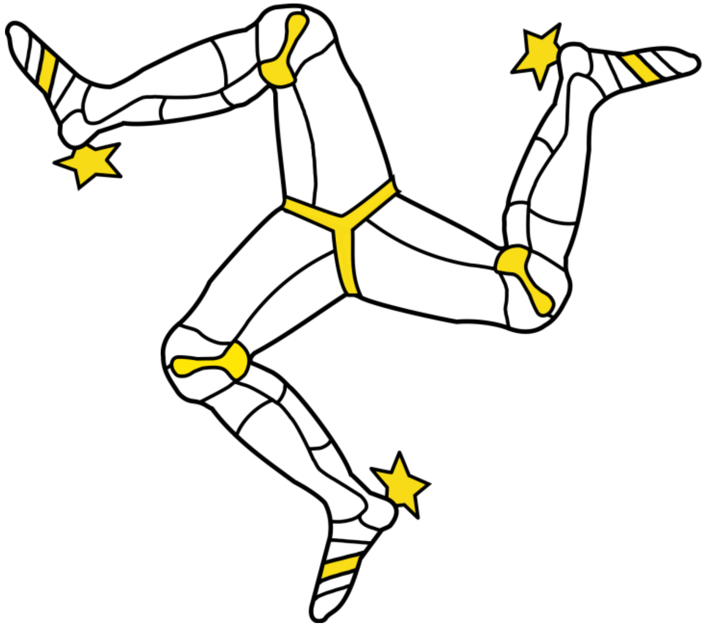
N bases, c strands

All of these are **dynamic programming** algorithms

Subproblems → **Big problem**



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N bases, c strands

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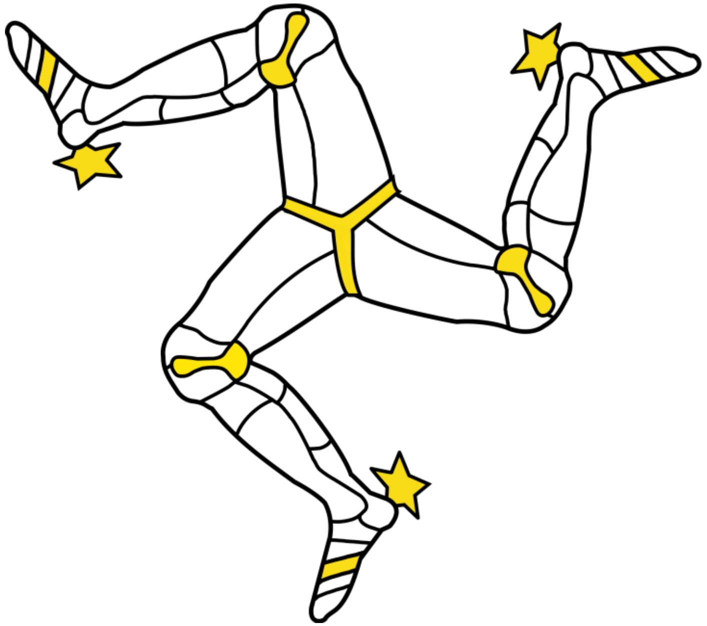

Global property

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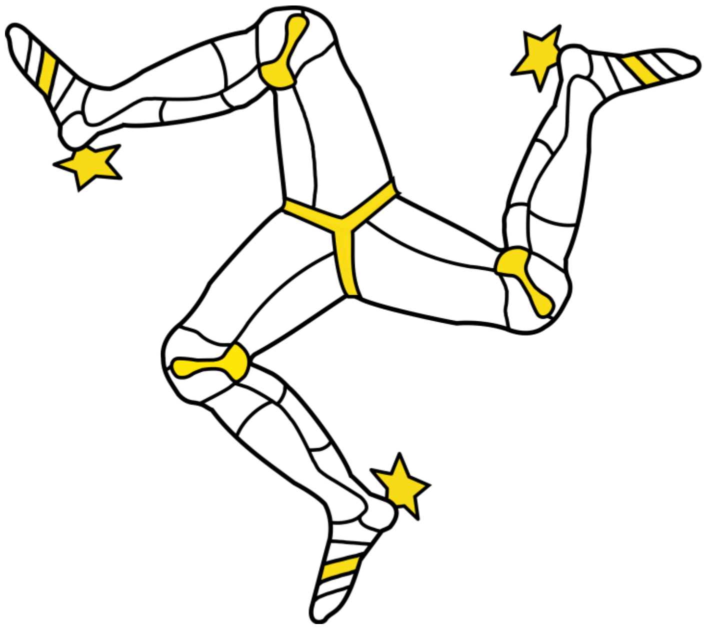
N bases, c strands

All of these are dynamic programming algorithms

Subprojects → Big problem

Local point of view



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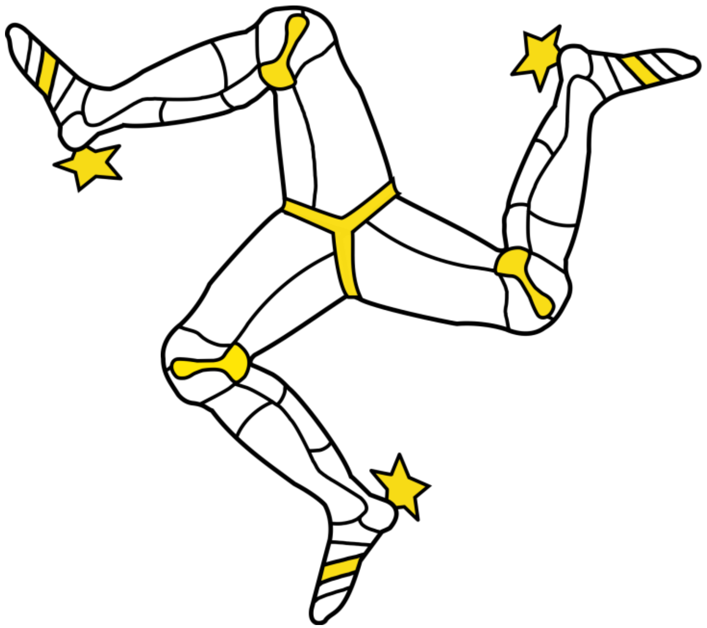
N bases, c strands

All of these are dynamic programming algorithms

Subprblems → Big problem

Local point of view → ? → Global property



Possible approach

Input Type	MFE
Single Strand (Loop model)	$O(N^3)$
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N bases, c strands

$$\Delta G(S) = \sum_{l} \Delta G(l) + (c-1)\Delta G^{\mathrm{assoc}} + \boldsymbol{k_B T * \log R}$$

Possible approach

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N bases, c strands

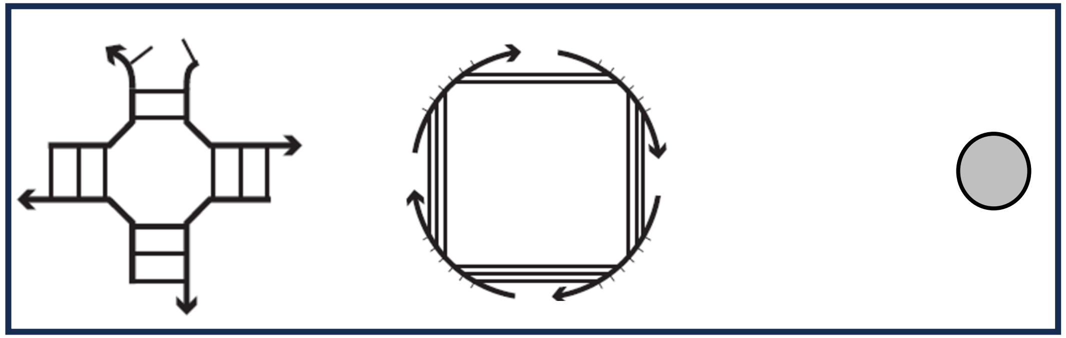
$$\Delta G(S) = \sum_l \Delta G(l) + (c-1)\Delta G^{\text{assoc}} + \boldsymbol{k_B T * \log R}$$

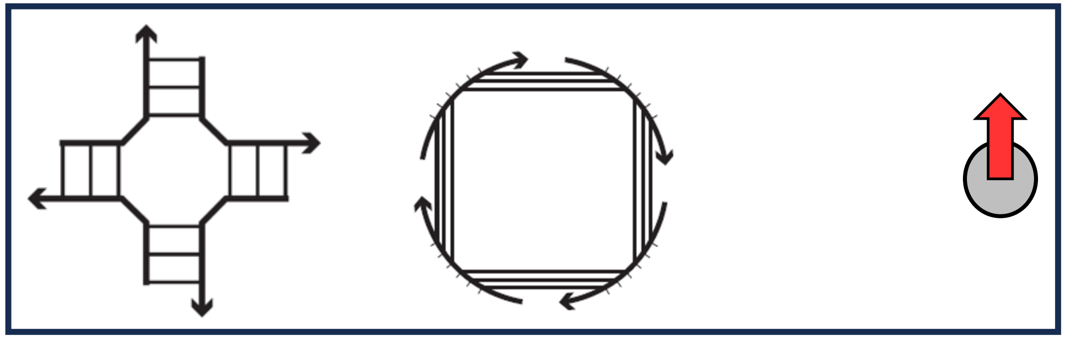
$$\Delta G'(S) = \sum_l \Delta G(l) + (c-1)\,\Delta G^{\text{assoc}}$$

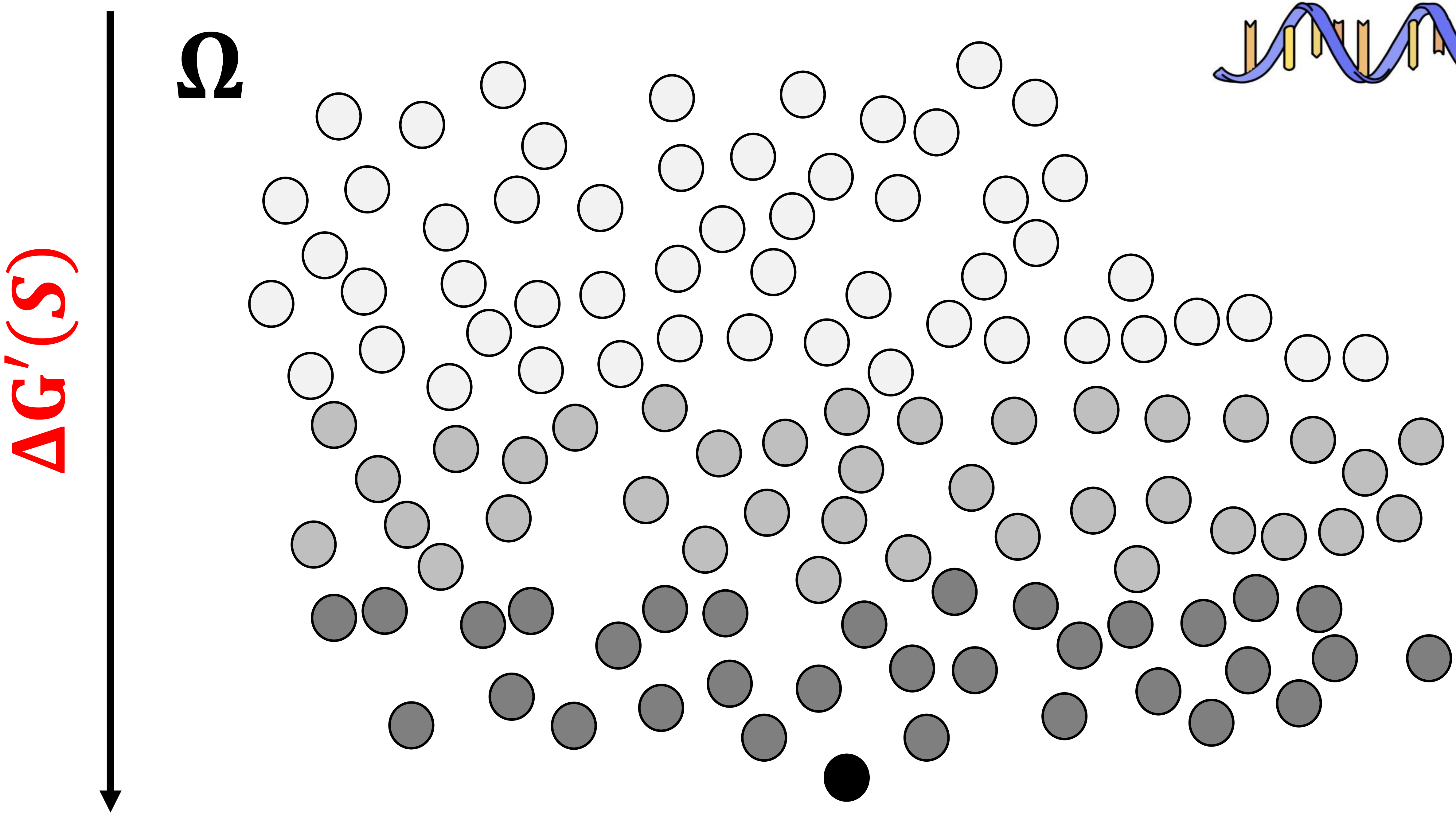
Ignore symmetry

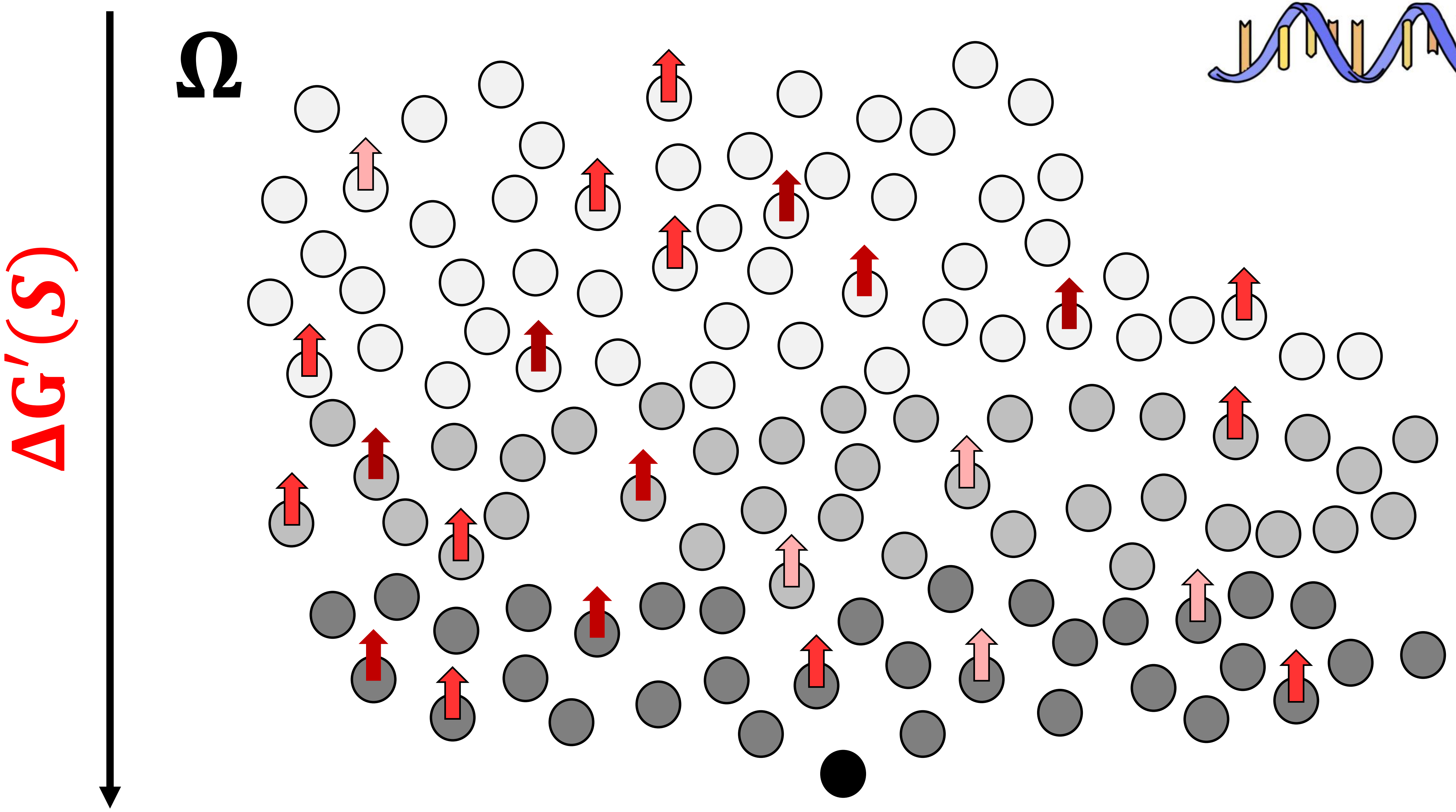
$\Delta G'(S)$

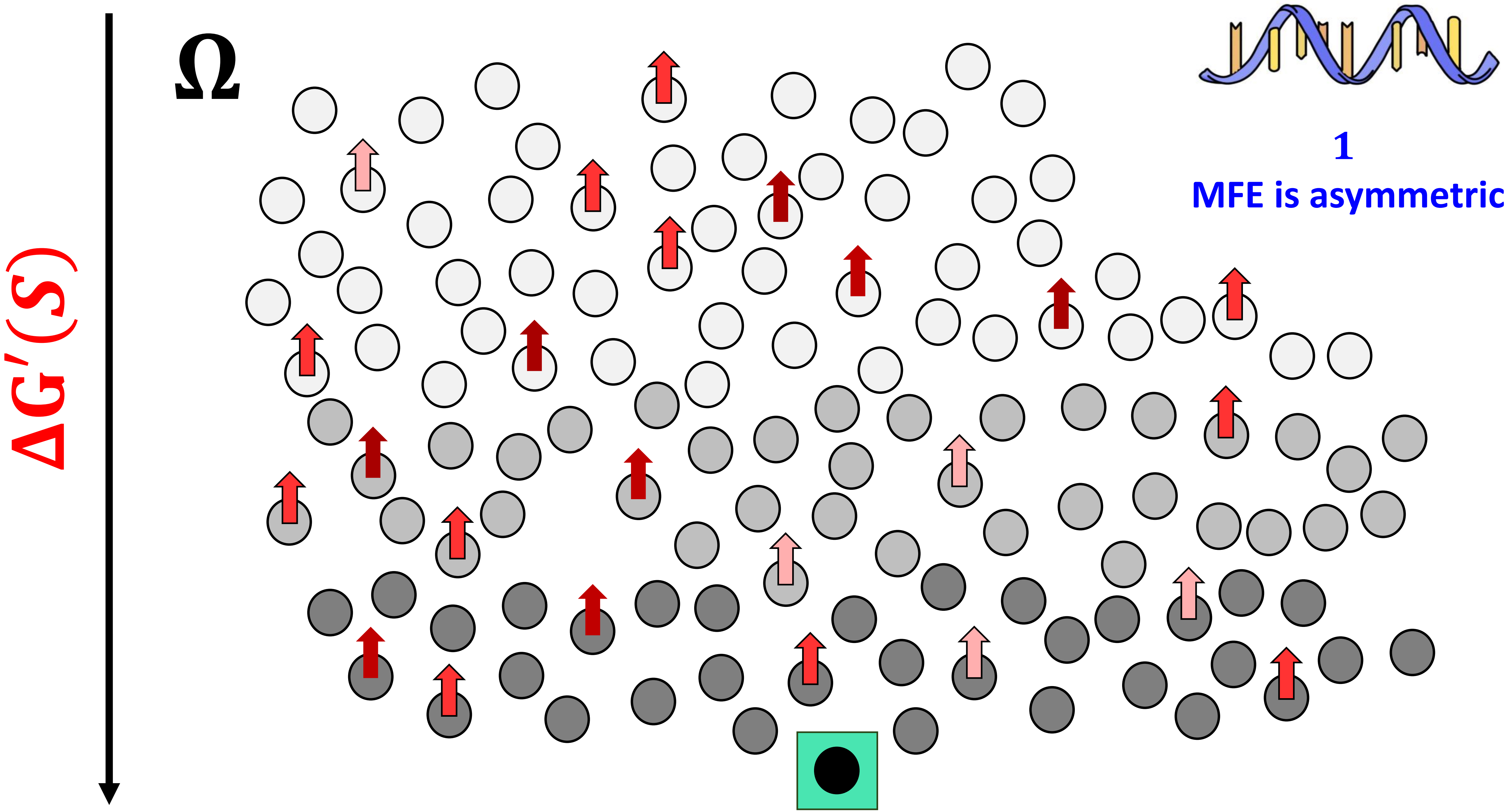
Let's ignore the symmetry for a while



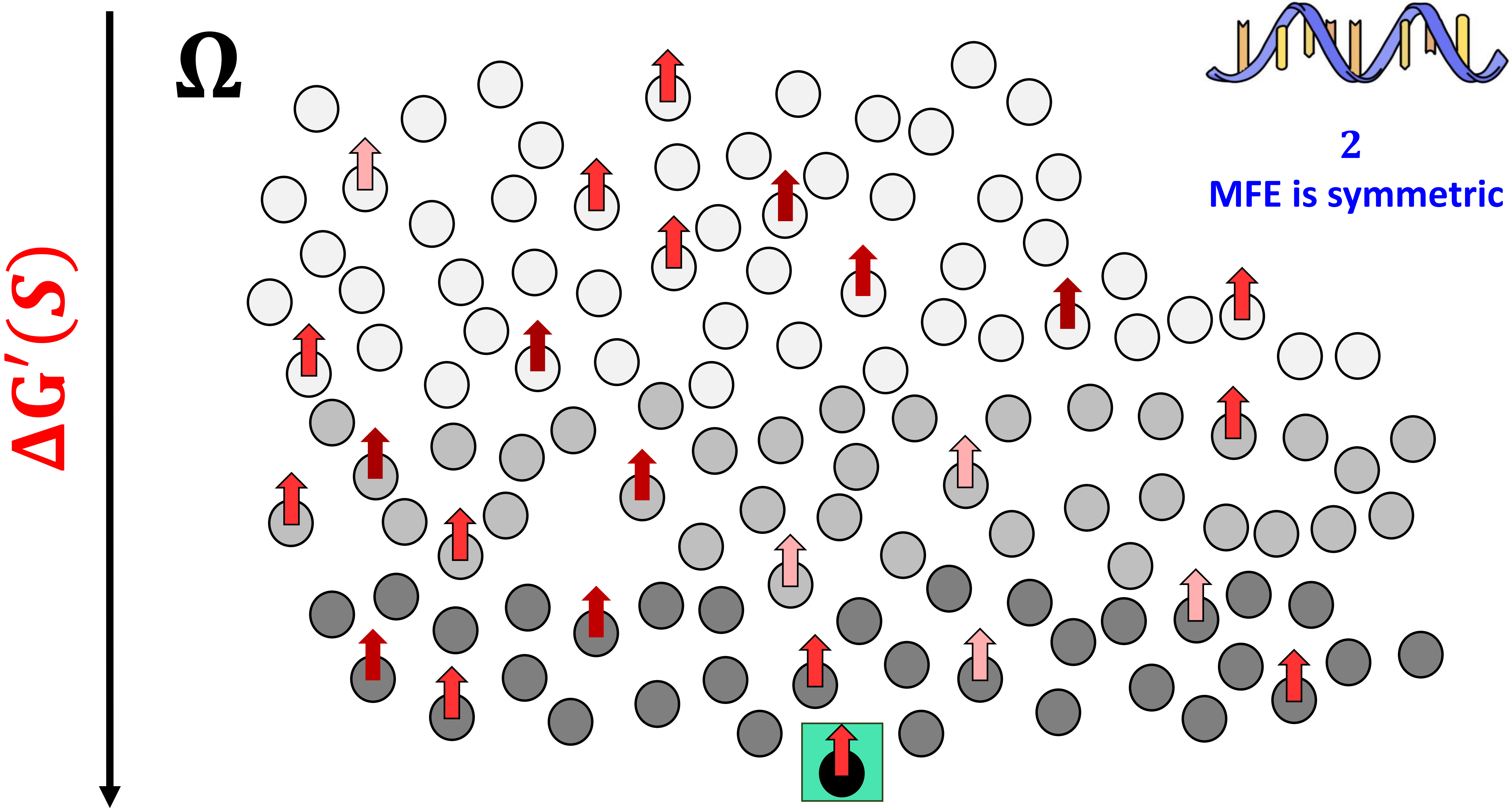


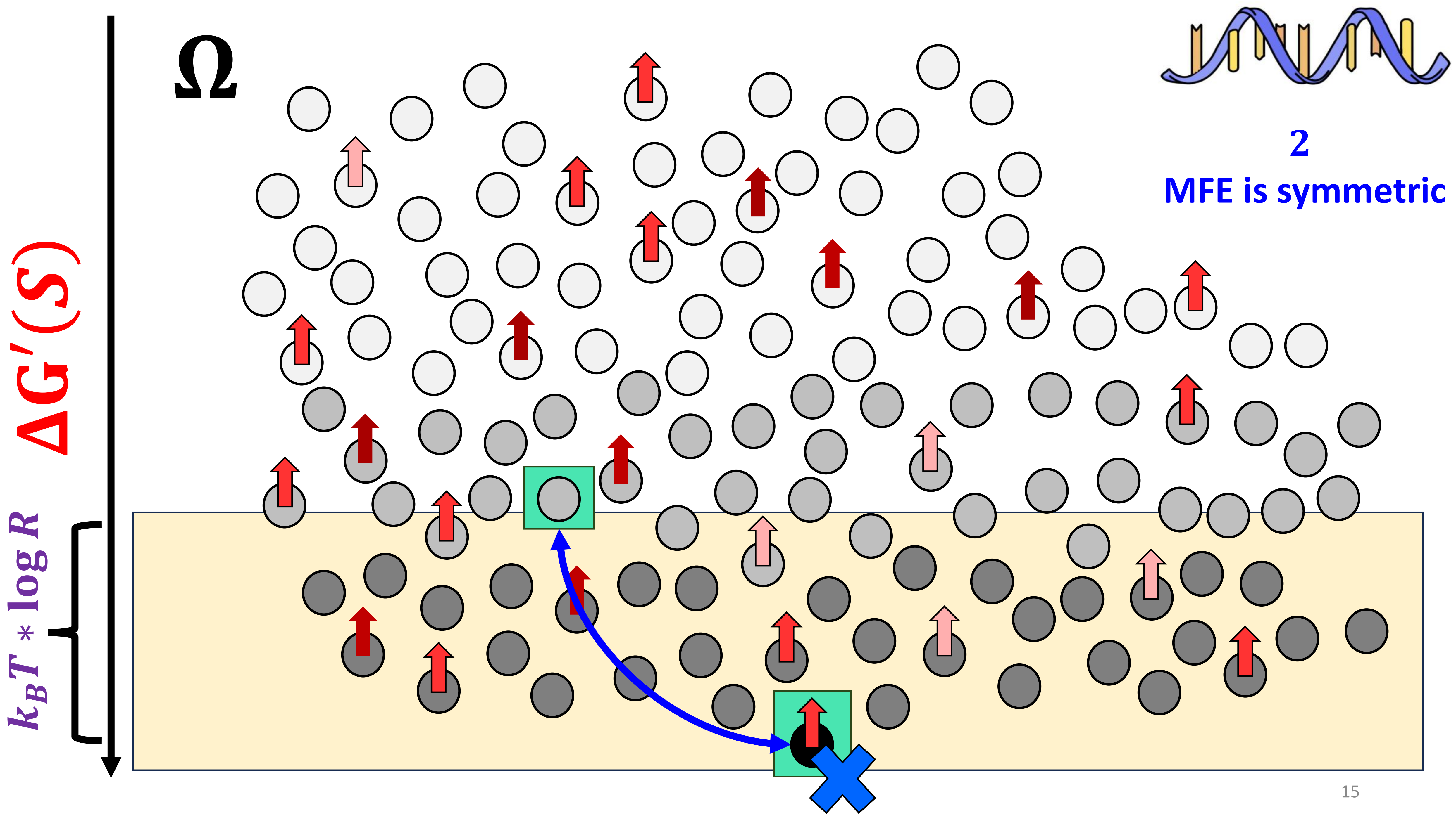

Ω
ΔG′(S)

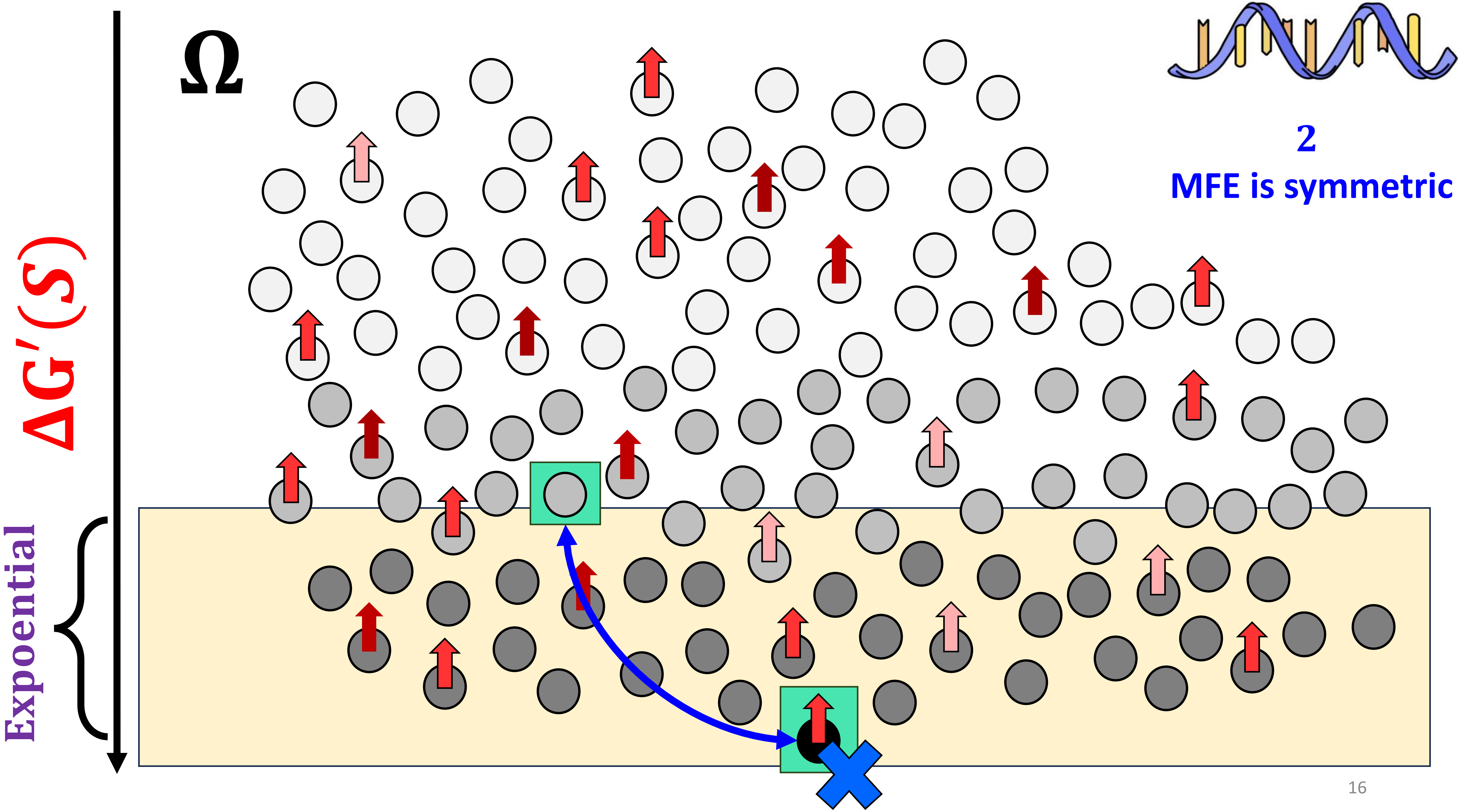

Ω
ΔG′(S)



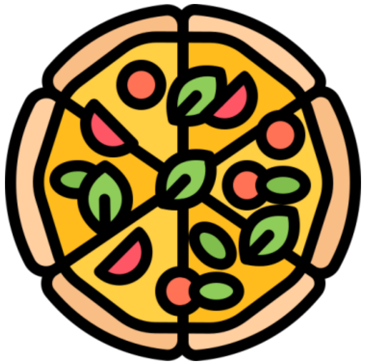
1
MFE is asymmetric

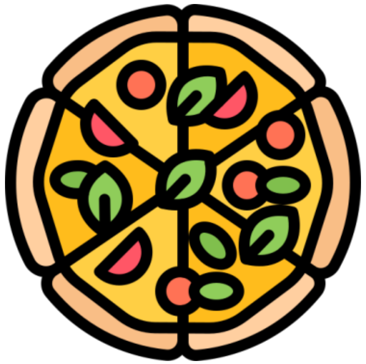

Ω
ΔG′(S)
2
MFE is symmetric


Ω
$\Delta G'(S)$
$k_B T * \log R$
2
MFE is symmetric

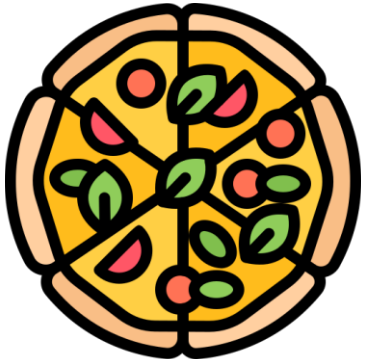

Ω
ΔG′(S)
Exponential
2
MFE is symmetric

Our solution





S_x

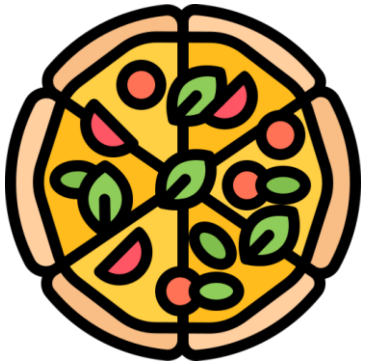


S_y

$\Delta G'(S)$

$\Delta G'(S_y) \leq \Delta G'(S_x)$

S_x

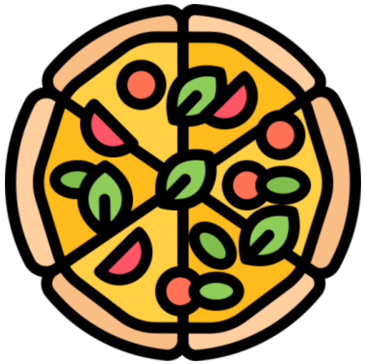


S_y

$\Delta G'(S)$

$\Delta G'(S_y) \leq \Delta G'(S_x)$

S_x **Symmetric**



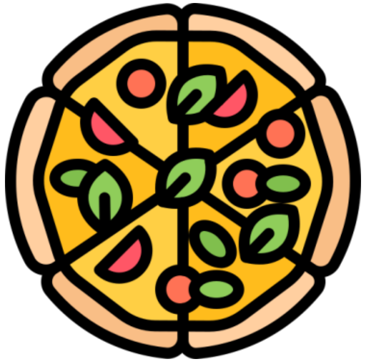
S_y **Symmetric**

$\Delta G'(S)$

$\Delta G'(S_y) \leq \Delta G'(S_x)$

S_x **Symmetric**

S_x and S_y **Admissible cut**



S_y **Symmetric**

$\Delta G'(S)$

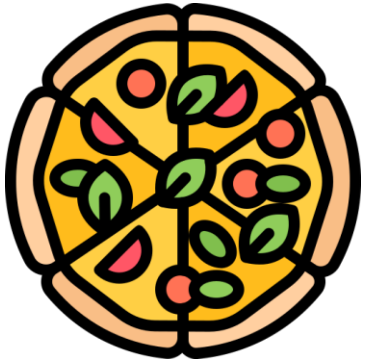
$\Delta G'(S_y) \leq \Delta G'(S_x)$

S_x Symmetric

X

S_z Asymmetric

S_x and S_y Admissible cut



S_y Symmetric

$\Delta G'(S)$

$\Delta G'(S_y) \leq \Delta G'(S_x)$

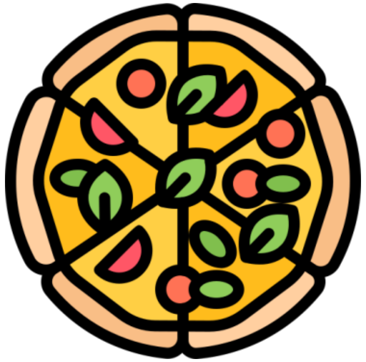
$\Delta G'(S_y) \leq G(S_z) \leq \Delta G'(S_x)$

S_x **Symmetric**

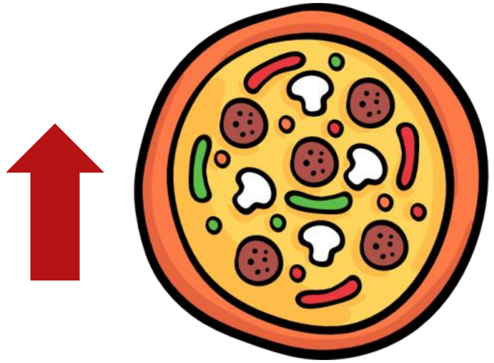
X

S_z **Asymmetric**

S_x and S_y Admissible cut



S_y **Symmetric**



S_x

Symmetric

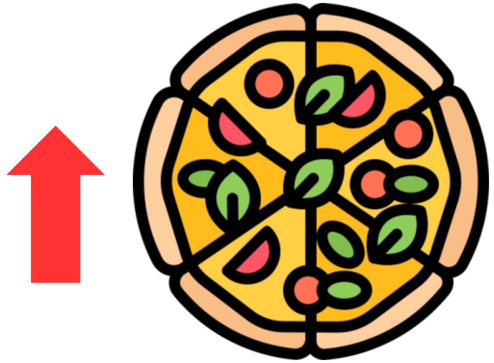
X

S_z

Asymmetric

S_x and S_y

Admissible cut



S_y

Symmetric

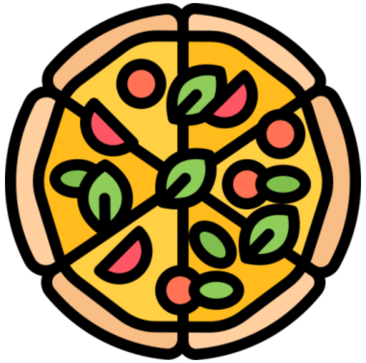
S_x

Symmetric

X 

S_z

Asymmetric



S_y

Symmetric

S_x and S_y

Admissible cut

S_x

Symmetric

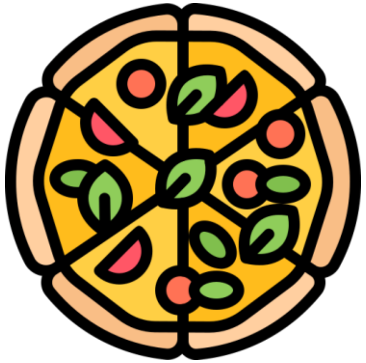
X

S_z

Asymmetric

S_x and S_y

Admissible cut



S_y

Symmetric

Upper bound

$$\boxed{\frac{N-c}{v(\pi)}\left(\sigma\left(v(\pi)\right) - v(\pi)\right)}$$

$$+$$

$$\boxed{N^2/16}$$

S_x

Symmetric

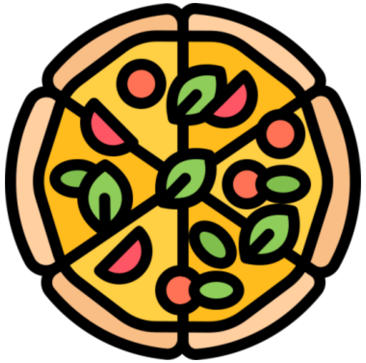
X

S_z

Asymmetric

S_x **and** S_y

Admissible cut



S_y

Symmetric

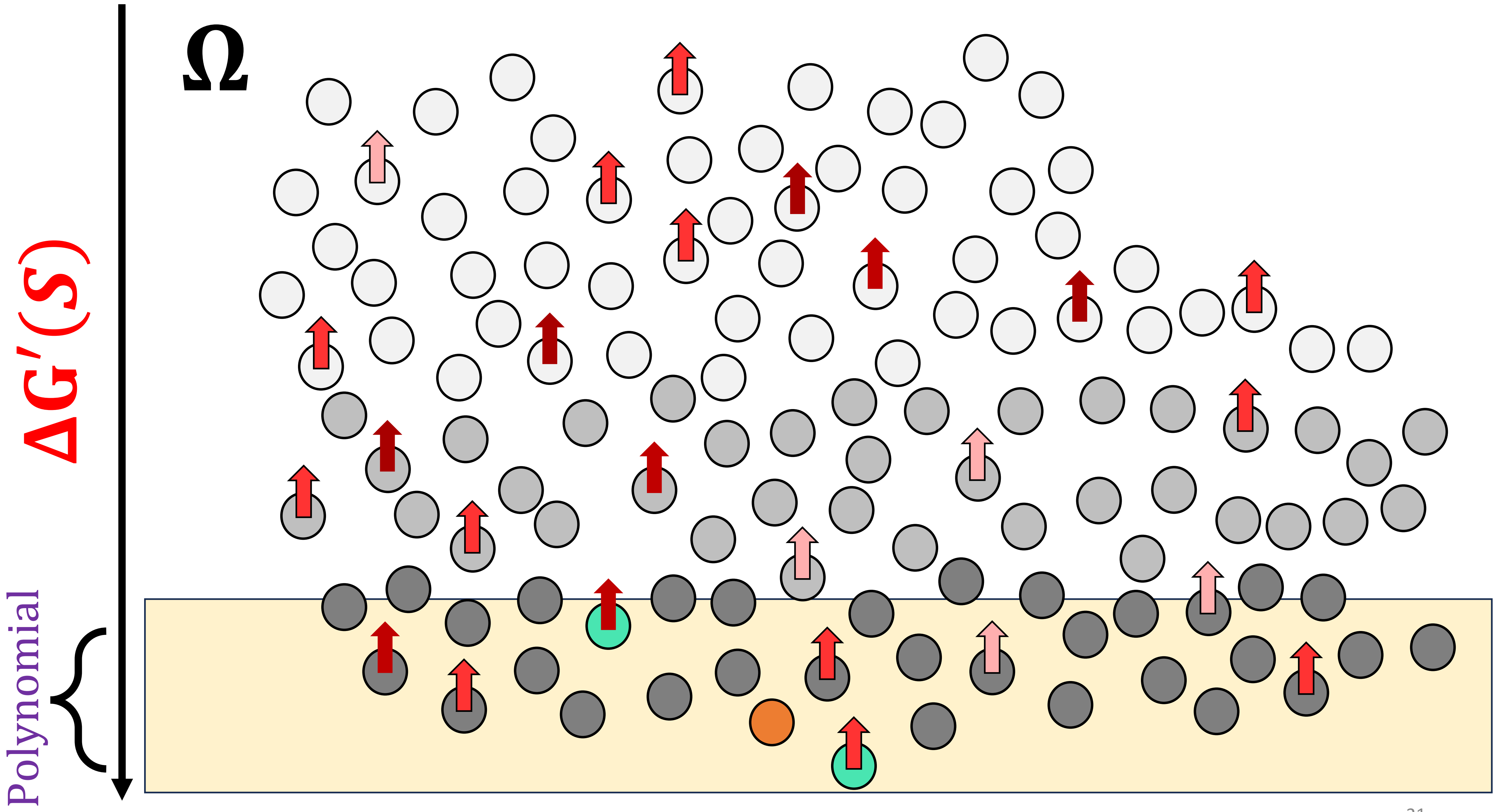
Upper bound

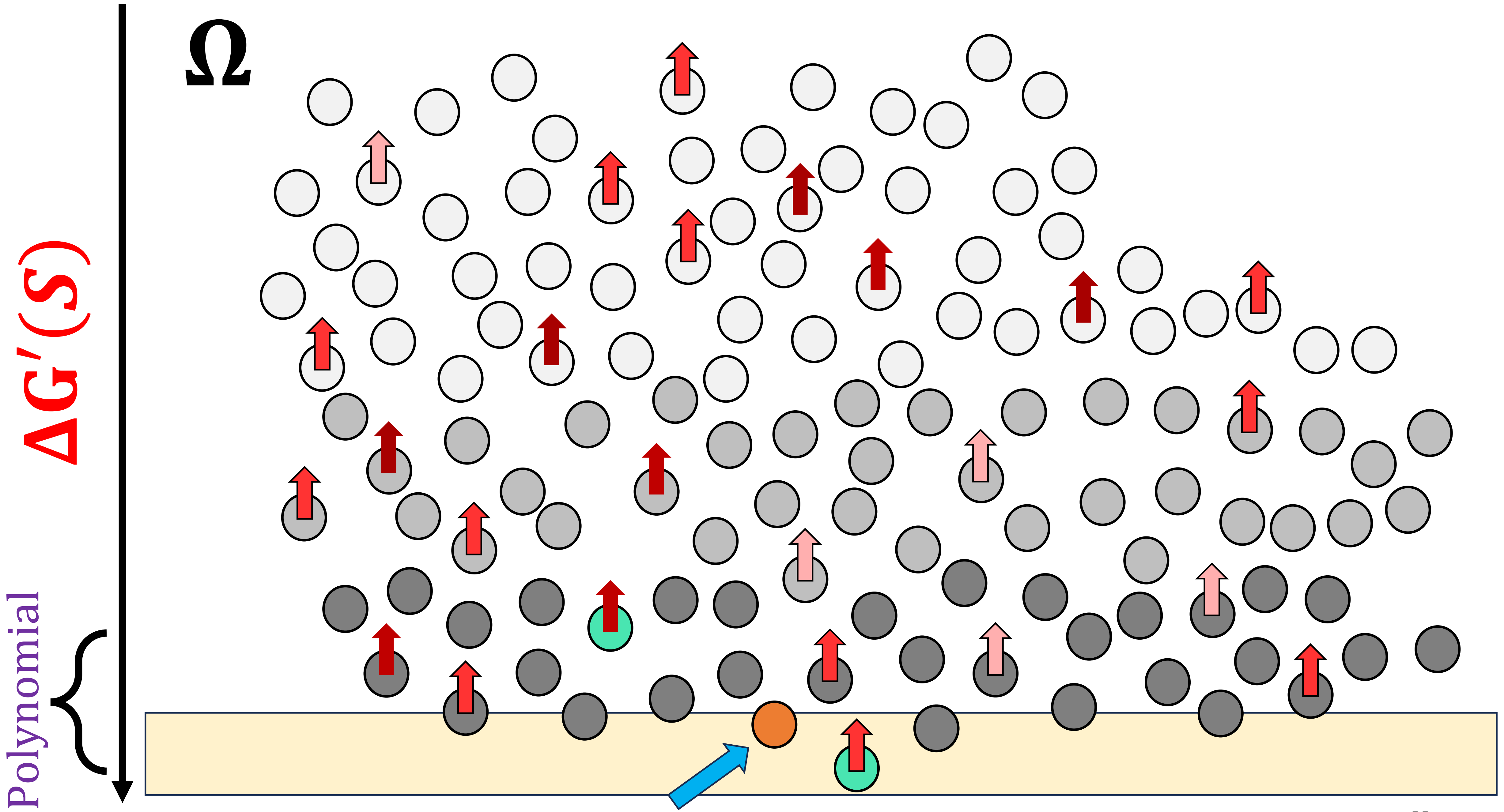
$$\boxed{\frac{N-c}{v(\pi)}\left(\sigma(v(\pi)) - v(\pi)\right)}$$

$$+$$

$$\boxed{N^2/16}$$

Adjusting the backtracking algorithm to go through energy levels sequentially starting from the MFE level.


Ω
ΔG′(S)
Polynomial


Ω
ΔG′(S)
Polynomial

Computational complexity of Minimum Free Energy algorithms

Input Type	MFE
Single Strand (Loop model)	$O(N^3)$
Multiple **unique** Strands, Bounded ($\leq$ c)	$O(N^3(c-1)!)$
Multiple Strands, Bounded ($\leq$ c)	$\mathbf{O\left(N^4(c-1)!\right)}$
Multiple Strands, Unbounded	NP – Complete

N bases, c strands

Thanks

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