Coil-Helix Transformation

homogeneous and heterogeneous environments

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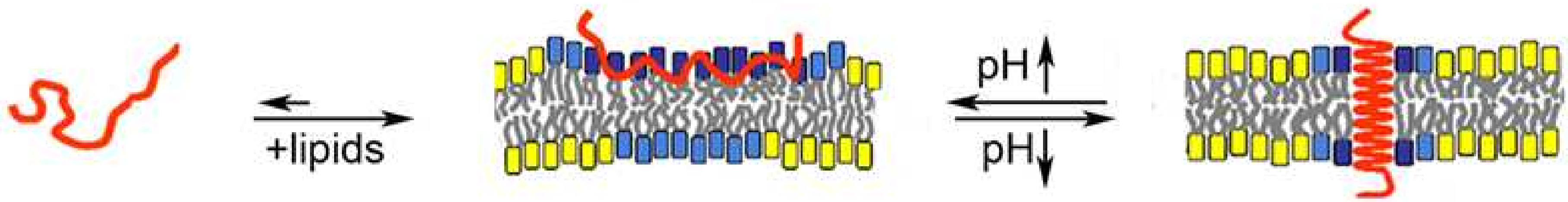
pHLIP: pH - Low - Insertion Peptide

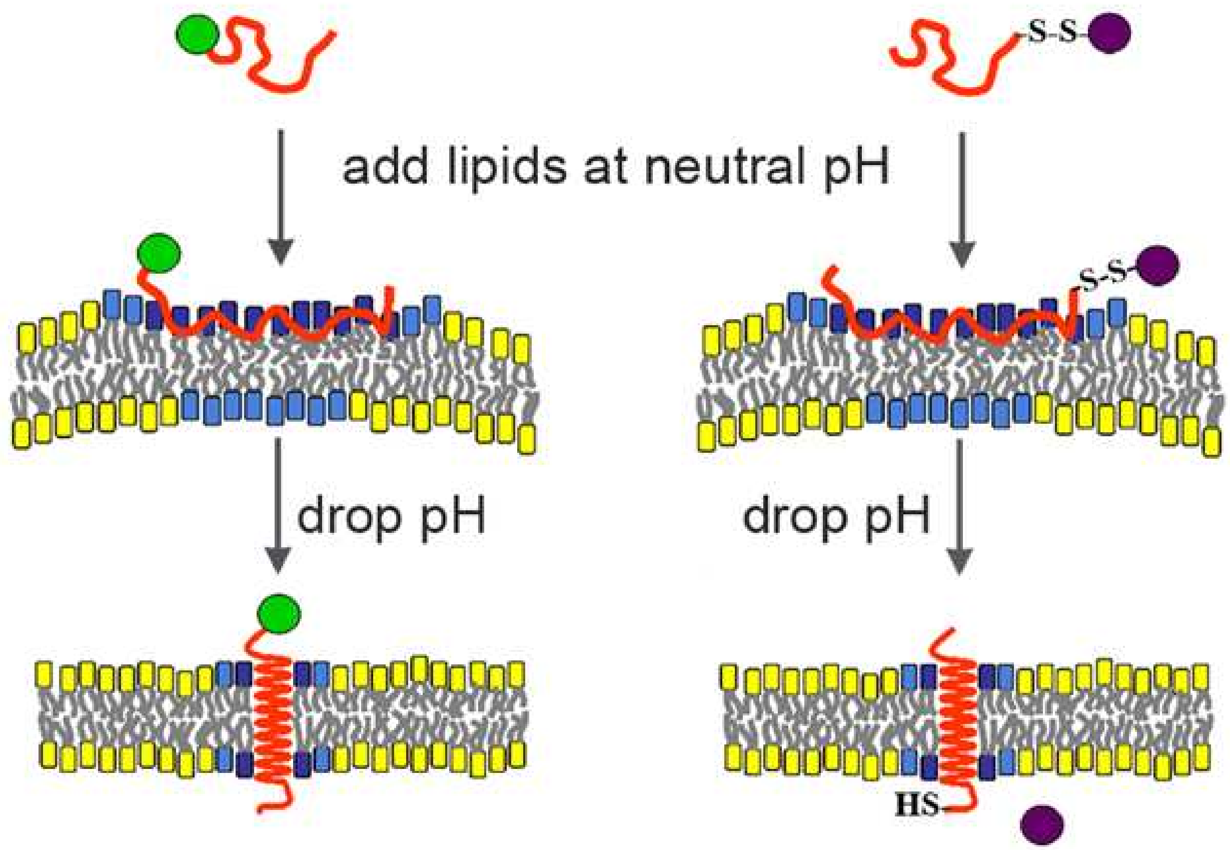
N terminus

A E Q N P I Y W A R Y A D W L F T T P L L L L D L A L L V D A D E G T

C terminus

flanking | trans−membrane | flanking





diagnostic agent

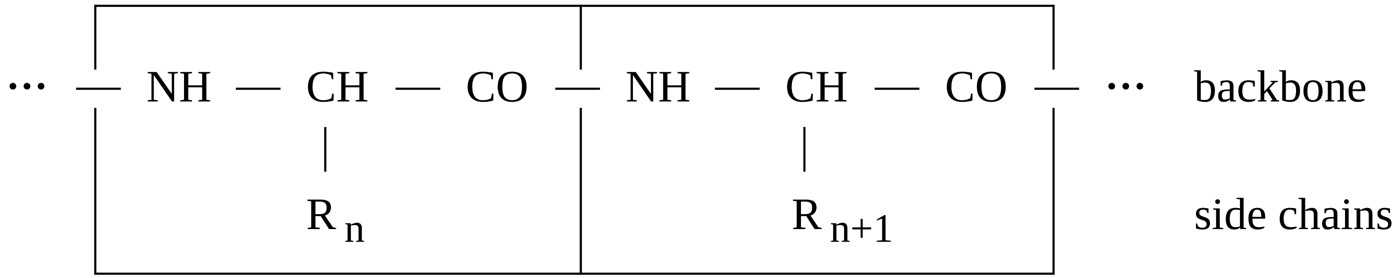
cargo $\longrightarrow$ marker

therapeutic agent

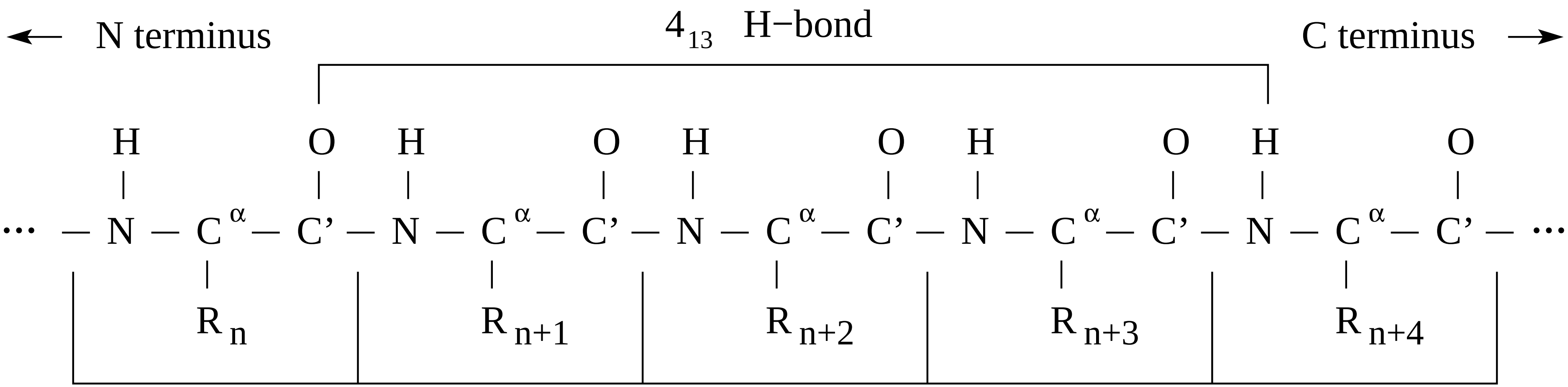
cargo $\longrightarrow$ drug

Proteins and Peptides

Amino acids linked into polymer.
Backbone $\rightarrow$ periodic. Side chains $\rightarrow$ aperiodic.
Residues n and $n+1$ coupled by peptide bond.

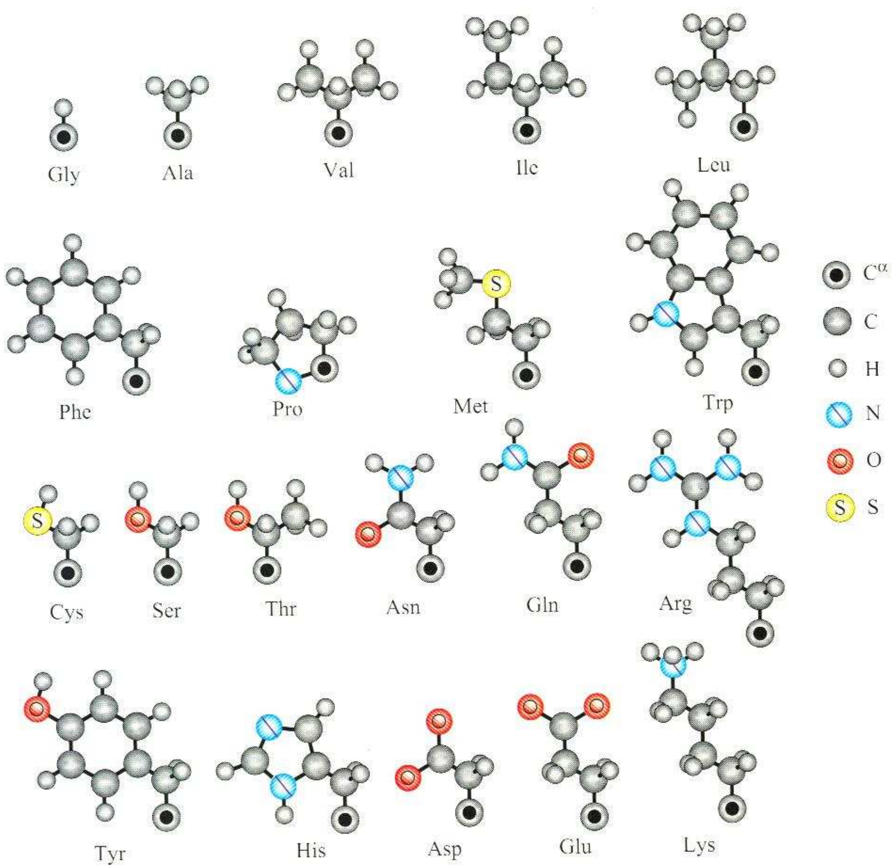


α-helix stabilized by internal H-bonds ($\sim 9k_BT$).

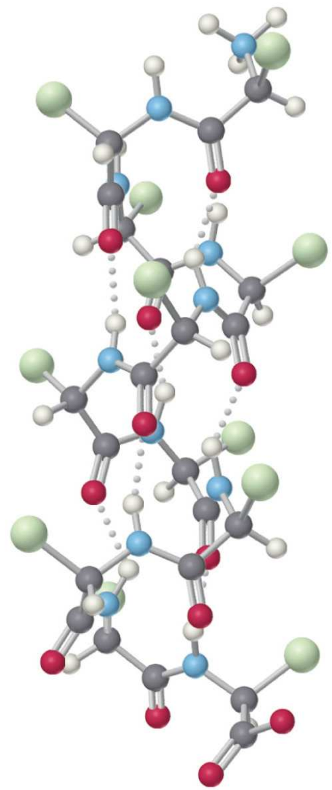


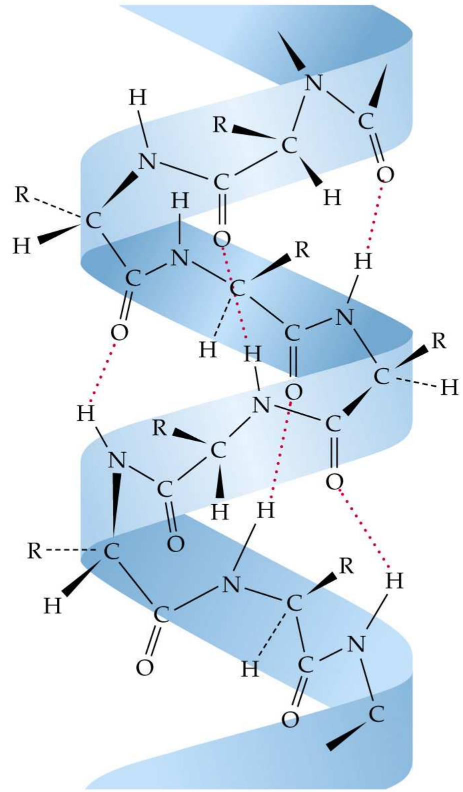
Amino Acid Residues

side chains



backbone





Length per residue: $\ell_e \simeq 4$Å (extended), $\ell_h \simeq 1.5$Å (helical).

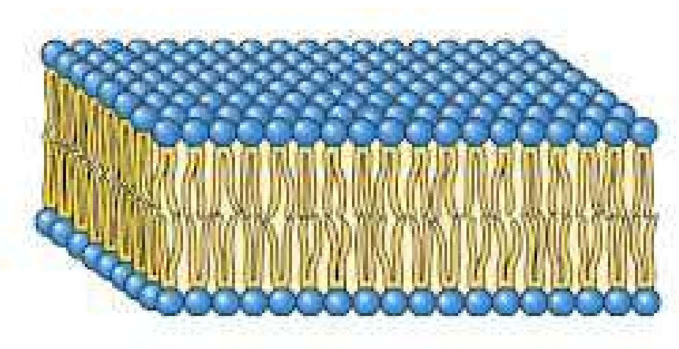
Conformational Change: Coil vs Helix

Conformation with lower free energy is realized.

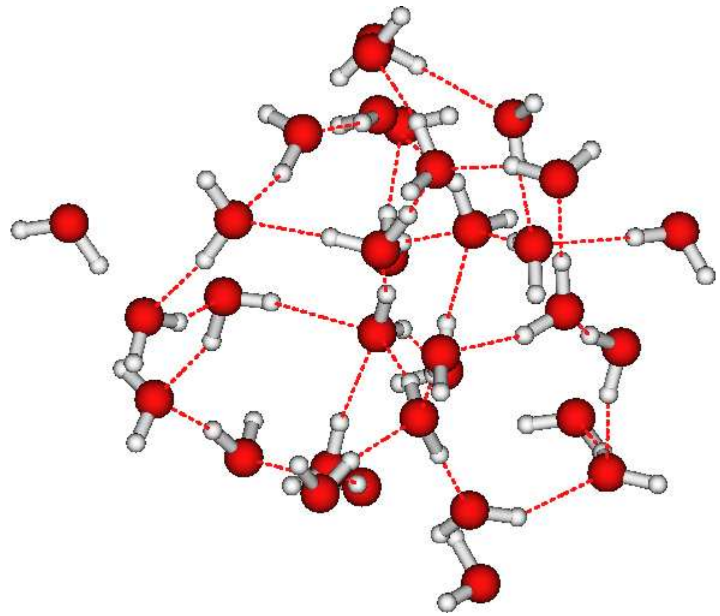
$$\Delta G \doteq G_{coil} - G_{helix} = \Delta H - T\Delta S.$$

ΔH: enthalpic contribution, $T\Delta S$: entropic contribution.

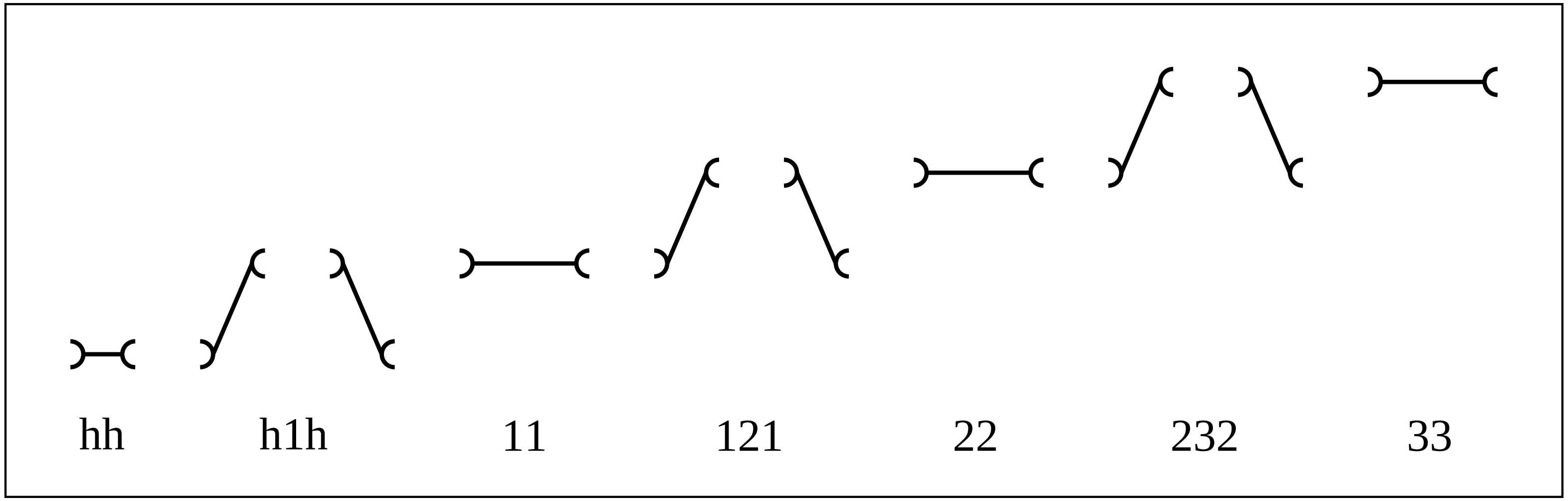
non-polar environment: $|\Delta H| \gg |T\Delta S|$

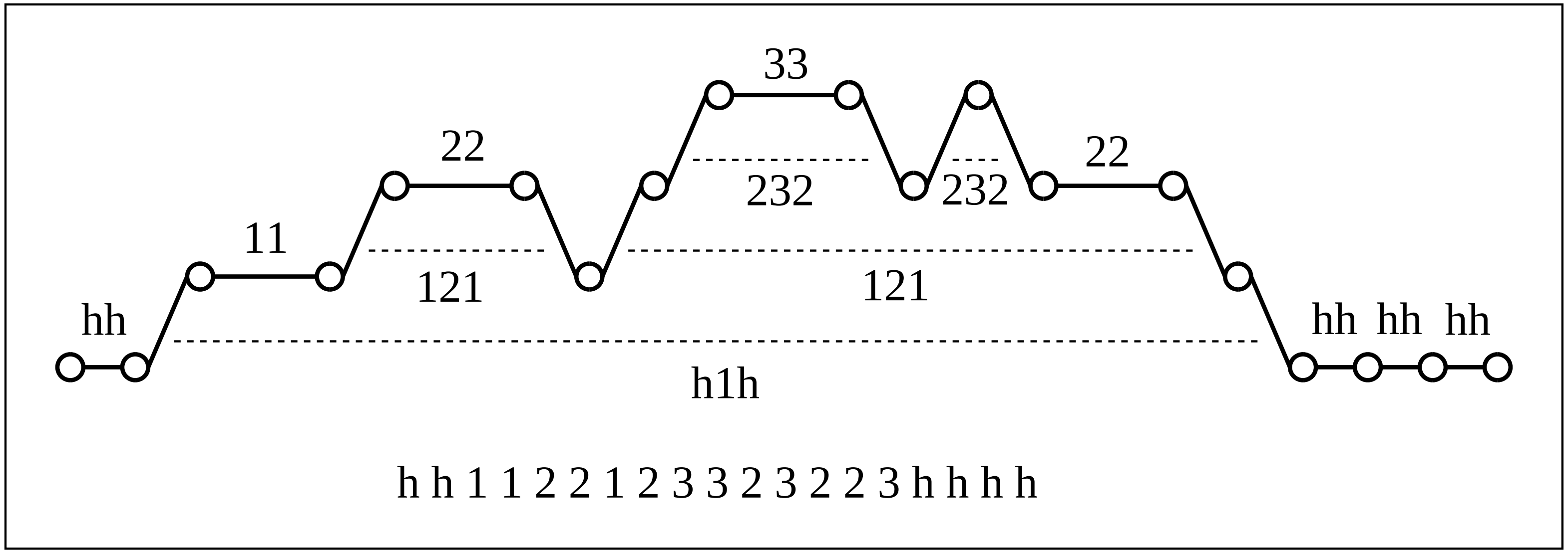


polar environment: $|\Delta H| \lesssim |T\Delta S|$



Mathematical Model (1)





Statistical Interaction

Generalized Pauli principle [Haldane 1991]

How is the number of states accessible to one particle of species m affected if particles (of any species m') are added?

$$\Delta d_m \doteq -\sum_{m'} g_{mm'} \Delta N_{m'} \qquad \Rightarrow \; d_m = A_m - \sum_{m'} g_{mm'} (N_{m'} - \delta_{mm'})$$

Energy and multiplicity of many-body states

$$E(\{N_m\}) = E_{pv} + \sum_{m=1}^{M} N_m \epsilon_m, \qquad W(\{N_m\}) = \prod_{m=1}^{M} \underbrace{\binom{d_m + N_m - 1}{N_m}}_{\frac{\Gamma(d_m + N_m)}{\Gamma(N_m + 1)\Gamma(d_m)}}$$

- E_{pv}: energy of reference state
- N_m: number of particles from species m
- ϵ_m: particle activation energies
- $g_{mm'}$: statistical interaction coefficients
- A_m: capacity constants
- d_m: number of open slots for a particle of species m

Thermodynamics with Statistical Interaction

System specifications:

- particle energies ϵ_m
- statistical interaction coefficients $g_{mm'}$
- capacity constants A_m

Two tasks:

- combinatorial problem: $W(\{N_m\})$
- extremum problem: $\delta(U - TS - \mu\mathcal{N}) = 0$

Partition function [Wu 1994]: $Z = \sum_{\{N_m\}} W(\{N_m\}) e^{-\beta E(\{N_m\})} = \prod_m \left(\frac{1+w_m}{w_m}\right)^{A_m}$

$$e^{\epsilon_m/k_BT} = (1+w_m) \prod_{m'=1}^{M} \left(1 + w_{m'}^{-1}\right)^{-g_{m'm}}, \quad m = 1, \ldots, M.$$

Average number of particles: $w_m \langle N_m \rangle + \sum_{m'} g_{mm'} \langle N_{m'} \rangle = A_m, \quad m = 1, \ldots, M$

Configurational entropy [Isakov 1994]:

$$S(\{N_m\}) = k_B \sum_{m=1}^{M} \Big[(N_m + Y_m) \ln (N_m + Y_m) - N_m \ln N_m - Y_m \ln Y_m \Big]$$

$$Y_m \doteq A_m - \sum_{m'=1}^{M} g_{mm'} N_{m'}$$

Mathematical Model (2)

Specifications for combinatorics: $d_m = A_m - \sum_{m'} g_{mm'}(N_{m'} - \delta_{mm'})$.

motif	cat.	m	ϵ_m	A_m
h1h	host	1	ϵ_1	$N-2$
121	hybrid	2	$2\epsilon_4$	0
232	hybrid	3	$2\epsilon_4$	0
11	tag	4	ϵ_4	0
22	tag	5	ϵ_4	0
33	tag	6	ϵ_4	0

$g_{mm'}$	1	2	3	4	5	6
1	2	2	2	1	1	1
2	-1	0	0	0	0	0
3	-0	-1	0	0	0	0
4	-1	-1	0	0	0	0
5	0	-1	-1	0	0	0
6	0	0	-1	0	0	0

Specifications for energetics: $E(\{N_m\}) = E_{pv} + \sum_{m=1}^{M} N_m \epsilon_m,$

- Nucleation parameter: $\tau \doteq e^{(\epsilon_4 - \epsilon_1)/k_B T}$ (gauge of cooperativity).
- Growth parameter: $t \doteq e^{\epsilon_4/k_B T}$ (gauge of preferred conformation).

Mathematical Model (3)

Polynomial equation for solution of ν-state model with $\nu = 2, 3, \ldots$:

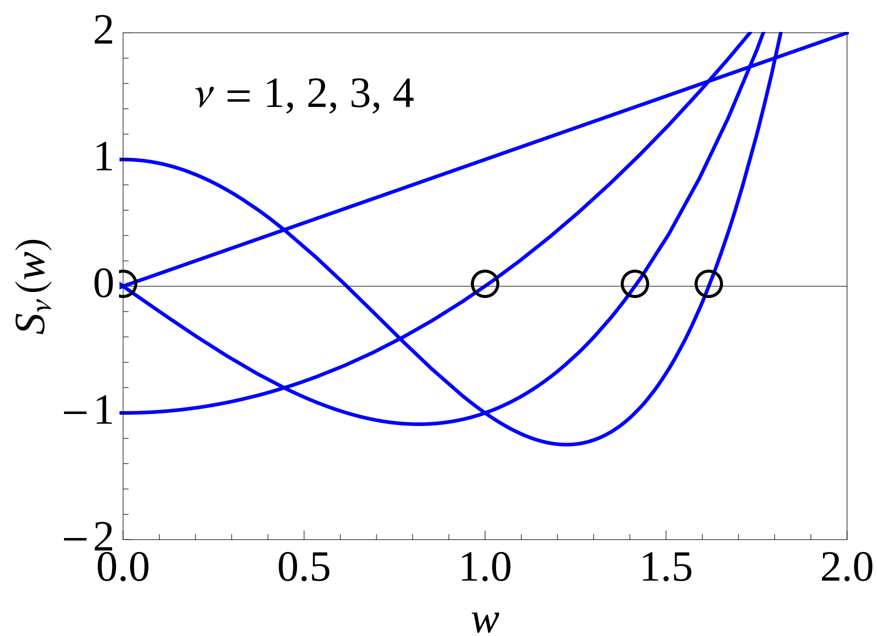
$$(1 + w_\nu - t) S_{\nu-1}(w_\nu) = t\tau S_{\nu-2}(w_\nu) \qquad \Rightarrow \; w_\nu(t, \tau).$$

$$\Rightarrow \; w_1 = \frac{S_{\nu-1}(w_\nu)}{\tau S_{\nu-2}(w_\nu)}; \quad w_\mu = \frac{S_{\nu-\mu+1}(w_\nu)}{S_{\nu-\mu-1}(w_\nu)}, \quad \mu = 2, \ldots, \nu - 1;$$

$$w_\nu = w_{\nu+1} = \cdots = w_{2(\nu-1)}.$$

Chebyshev polynomials of the 2^{nd} kind:

- $S_0(w) = 1, \quad S_1(w) = w,$
- $S_{\nu+1}(w) = w S_\nu(w) - S_{\nu-1}(w),$
- $S'_\nu(w) = \dfrac{2(\nu + 1) S_{\nu-1}(w) - \nu w S_\nu(w)}{4 - w^2}.$



Mathematical Model (4)

Free energy: $\bar{G}(t,\tau) = -k_B T \ln\left(1 + w_1^{-1}(t,\tau)\right).$

Population densities from

$$w_m(t,\tau)\bar{N}_m(t,\tau) + \sum_{m'} g_{mm'}\bar{N}_{m'}(t,\tau) = \delta_{m,1}, \quad m = 1,\ldots,2(\nu-1).$$

Helicity: $\bar{N}_{hl}(t,\tau) = 1 - \bar{N}_1 - 2\sum_{\mu=2}^{\nu-1}\bar{N}_\mu - \sum_{\mu=\nu}^{2(\nu-1)}\bar{N}_\mu = 1 - \left(\frac{\partial \bar{G}}{\partial \epsilon_1}\right)_T - \left(\frac{\partial \bar{G}}{\partial \epsilon_\nu}\right)_T.$

Entropy: $\bar{S}(t,\tau) = \bar{S}\left(\{\bar{N}_m\}\right) = -\left(\frac{\partial \bar{G}}{\partial T}\right)_{\epsilon_1,\epsilon_\nu}.$

Enthalpy $\bar{H}(t,\tau) = \sum_m \bar{N}_m \epsilon_m = \bar{G}(t,\tau) + T\bar{S}(t,\tau).$

First-Order Transition

Solution for $\tau = 0$ and any ν.

High-cooperativity limit.

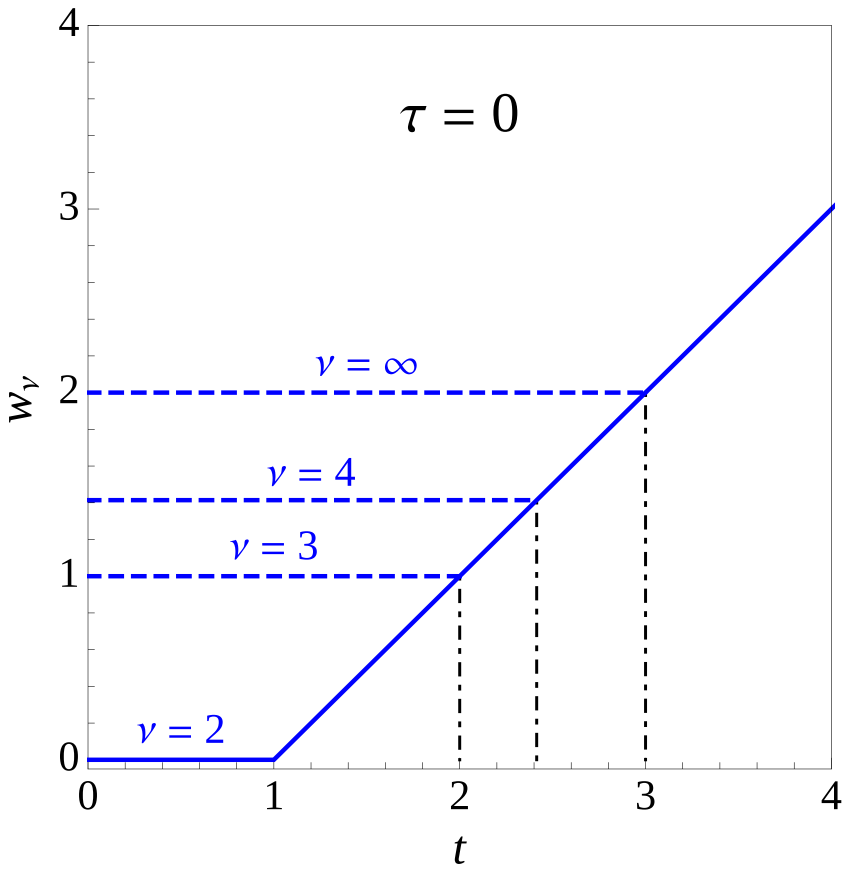
$$(1 + w_\nu - t)S_{\nu-1}(w_\nu) = 0, \quad \nu = 2, 3, \ldots$$

Physical solution $w_0^{(\nu)}$ switches at $t_c^{(\nu)}$.

- $t \leq t_c^{(\nu)}$: $w_0^{(\nu)}$ from $S_{\nu-1}(w_0^{(\nu)}) = 0$.
- $t \geq t_c^{(\nu)}$: $t = 1 + w_0^{(\nu)}$.

Transition point:

$$t_c^{(2)} = 1, \quad t_c^{(3)} = 2, \quad t_c^{(4)} = 1 + \sqrt{2},$$
$$t_c^{(5)} = \frac{1}{2}[1 + \sqrt{5}], \quad \ldots, \quad t_c^{(\infty)} = 3.$$

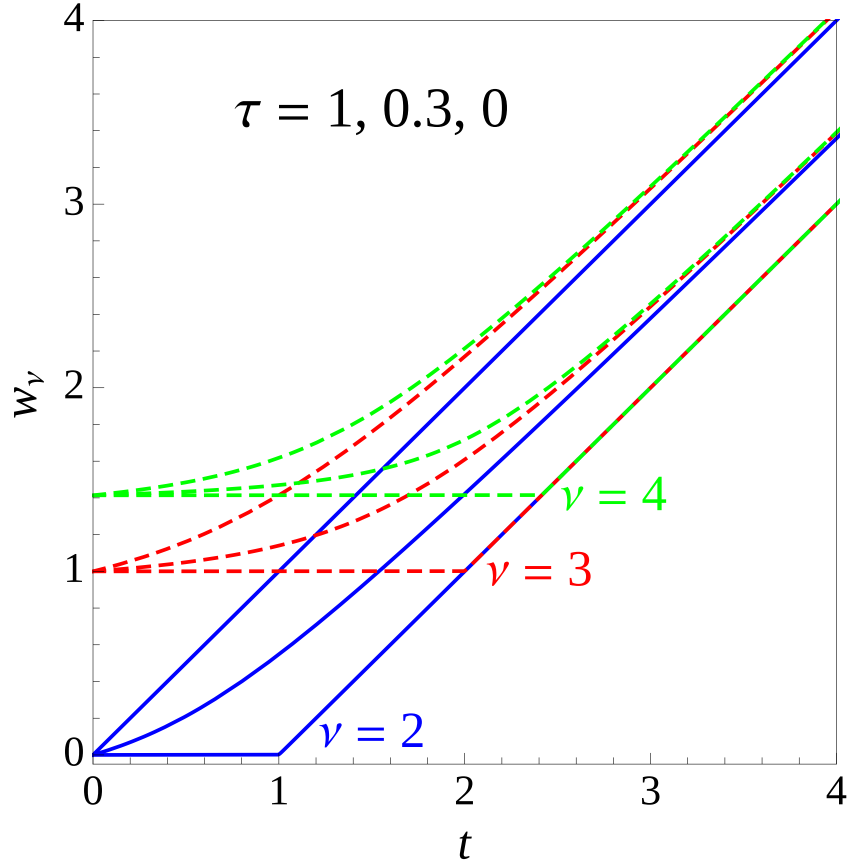


Crossover

Solution for $0 \le \tau \le 1$ and $\nu < \infty$.

Thermal fluctuations soften
$1^{\rm st}$-order transition into crossover.

$$t(\nu, w_\nu, \tau) = \frac{(1+w_\nu)S_{\nu-1}(w_\nu)}{S_{\nu-1}(w_\nu) + \tau S_{\nu-2}(w_\nu)}.$$



Limit $\nu \to \infty$ for special values of w_ν:

$$t(\nu, 2, \tau) = \frac{3\nu}{\nu + (v-1)\tau} \overset{\nu\to\infty}{\longrightarrow} \frac{3}{1+\tau}.$$

$$t(\nu, 3, \tau) = \frac{4 f_{2\nu}}{f_{2\nu} + \tau f_{2\nu-2}} \overset{\nu\to\infty}{\longrightarrow} \frac{4}{1 + \frac{2\tau}{3+\sqrt{5}}}.$$

Fibonacci numbers:

$$f_n = 0, 1, 1, 2, 3, 5, 8, \ldots$$

Second-Order Transition

Solution for $0 < \tau \leq 1$ and $\nu \to \infty$.

Proliferation of states sharpens crossover into 2^{nd}-order transition.

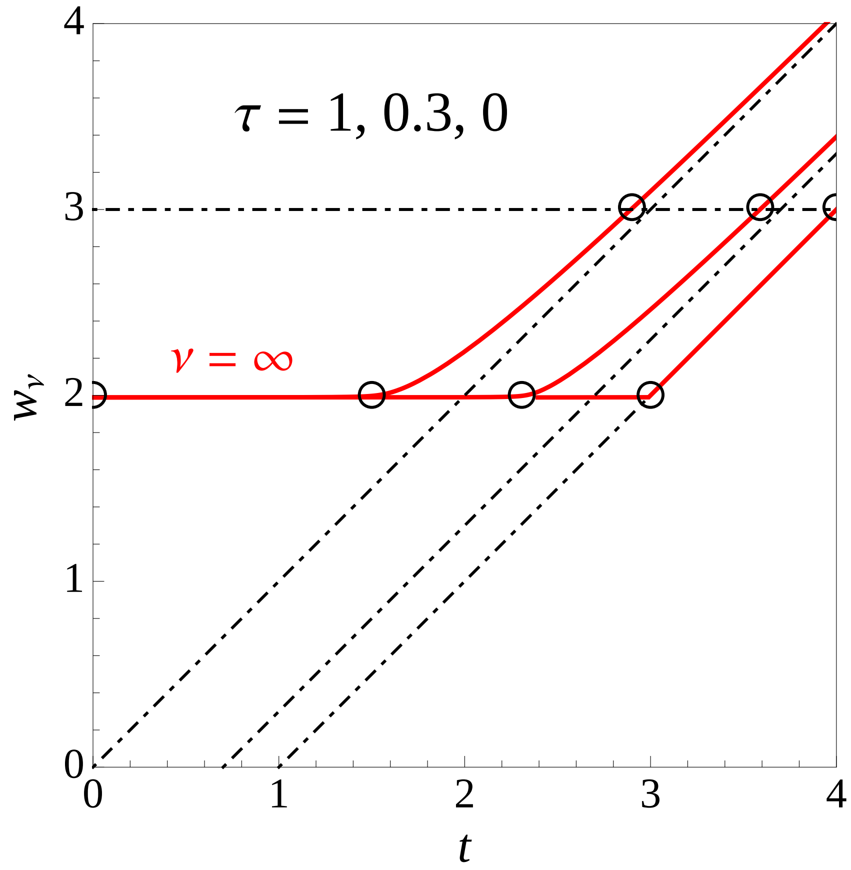
$$t(\nu, w_\nu, \tau) = \lim_{\nu\to\infty} \frac{(1+w_\nu)S_{\nu-1}(w_\nu)}{S_{\nu-1}(w_\nu) + \tau S_{\nu-2}(w_\nu)}.$$

Transition point for $\tau > 0$:

$$t_c^{(\infty)} = \frac{3}{1+\tau}.$$

Asymptotics for $t \gg 1$:

$$w_0^{(\infty)} = t + \tau - 1.$$



Helicity and Entropy: Parametric Representations

Helicity: $\bar{N}_{hl} = 1 - \dfrac{t}{w_1(1+w_1)} \dfrac{\partial w_1}{\partial t}.$

Entropy: $\bar{S}/k_B = \ln\left(1 + w_1^{-1}\right) + \dfrac{1}{w_1(1+w_1)} \left[t \ln t \dfrac{\partial w_1}{\partial t} + \tau \ln \tau \dfrac{\partial w_1}{\partial \tau} \right].$

- $t = \dfrac{S_{\nu-1}(w_\nu)[1+w_\nu]}{S_{\nu-1}(w_\nu) + \tau S_{\nu-2}(w_\nu)}, \qquad w_1 = \dfrac{S_{\nu-1}(w_\nu)}{\tau S_{\nu-2}(w_\nu)},$
- $\dfrac{\partial w_1}{\partial t} = \dfrac{\partial w_1}{\partial w_\nu} \dfrac{\partial w_\nu}{\partial t}, \qquad \dfrac{\partial w_1}{\partial \tau} = \dfrac{\partial w_1}{\partial w_\nu} \dfrac{\partial w_\nu}{\partial \tau} - \dfrac{w_1}{\tau}.$

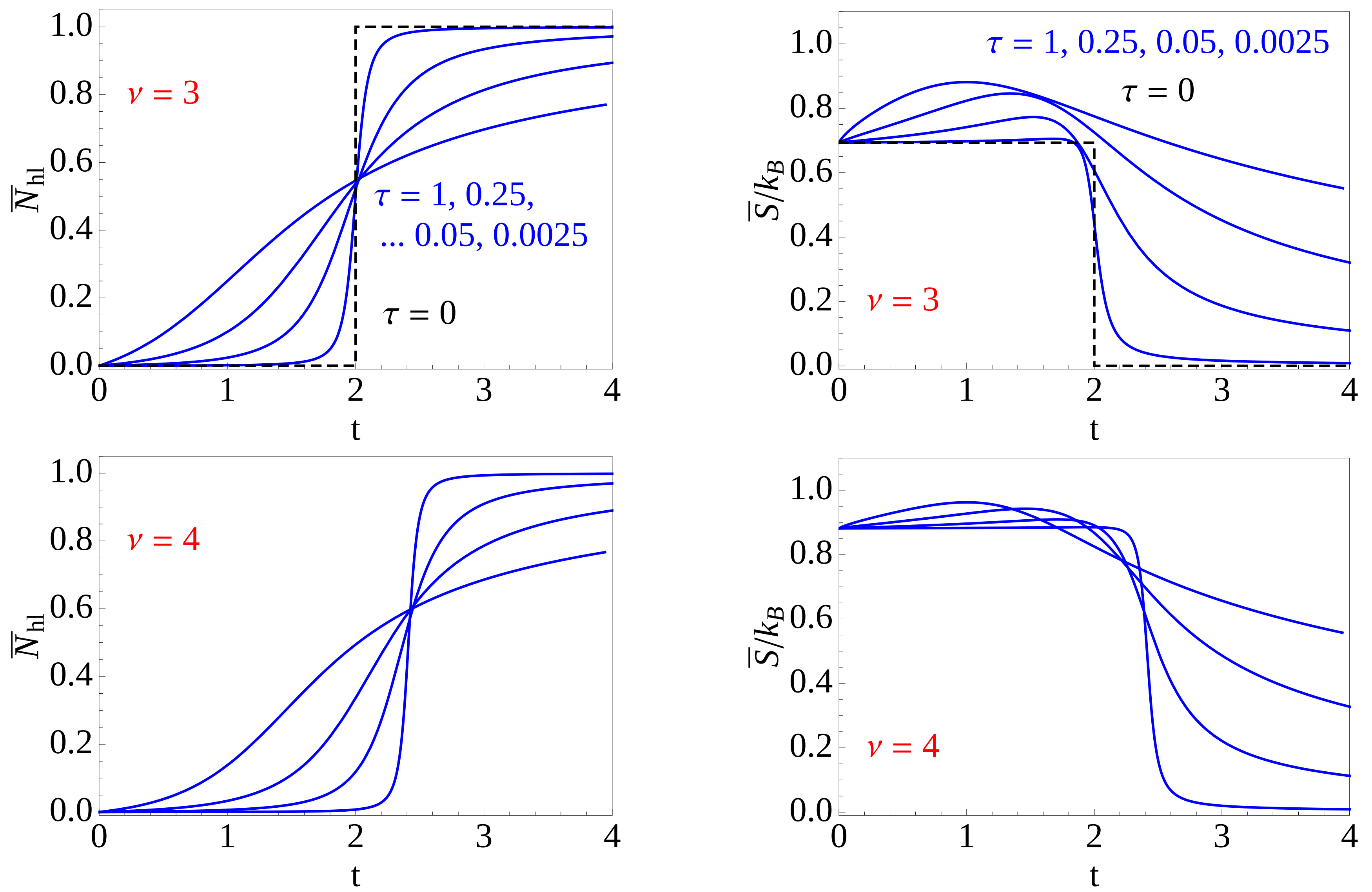
Parametric representations for $\bar{N}_{hl}(t,\tau)$ and $\bar{S}(t,\tau)/k_B$:

$$\bar{N}_{hl}(\nu, w_\nu, \tau), \quad \bar{S}(\nu, w_\nu, \tau)/k_B, \quad t(\nu, w_\nu, \tau),$$

$$w_0^{(\nu)} < w_\nu < \infty.$$

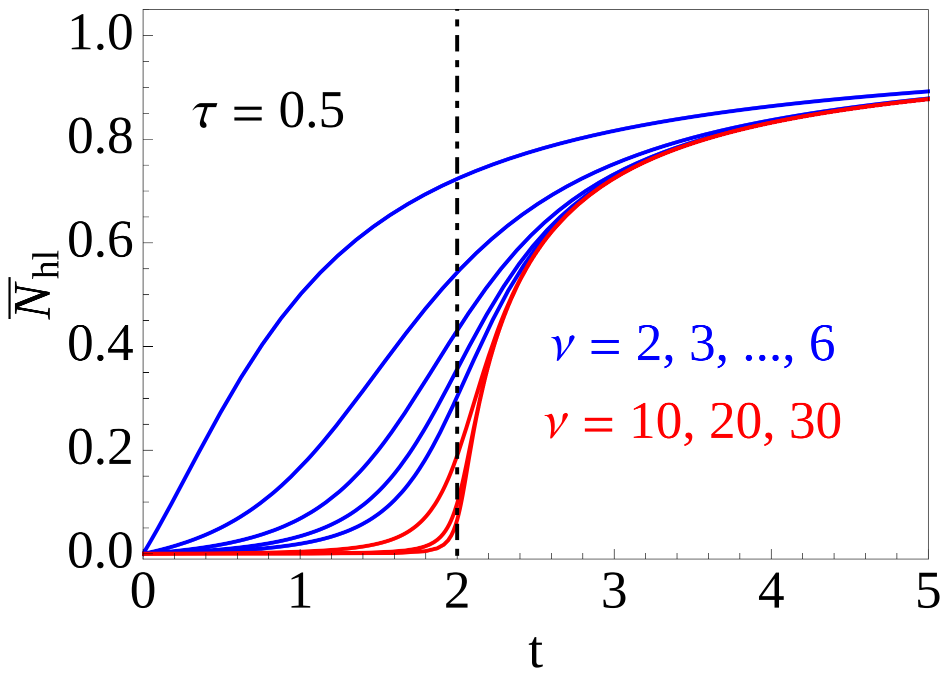
Helicity and Entropy: First Order Transition

Helicity   Entropy

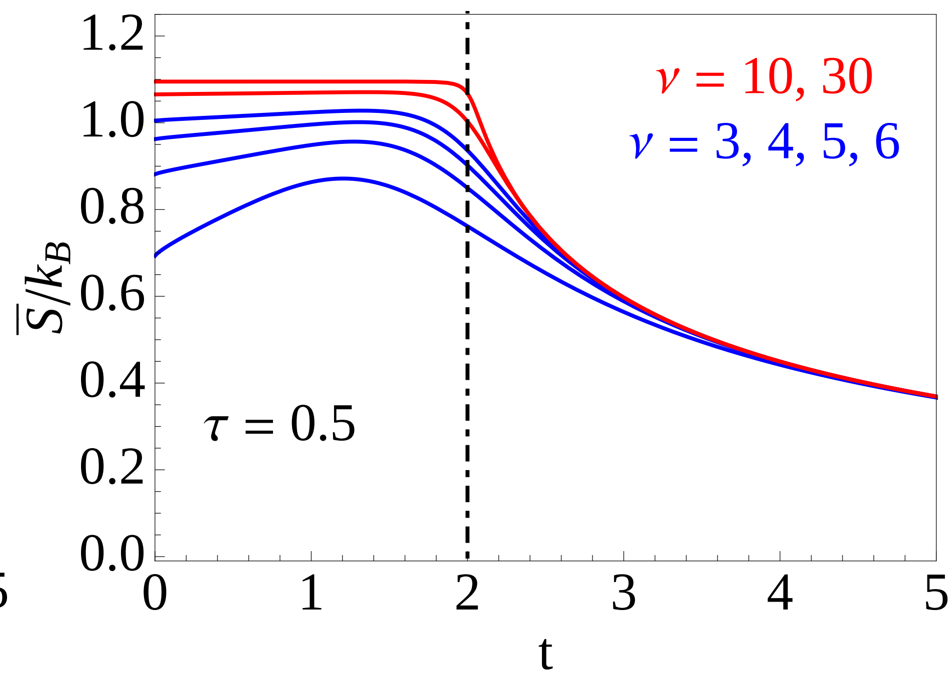


Helicity and Entropy: Second Order Transition

Helicity



Entropy



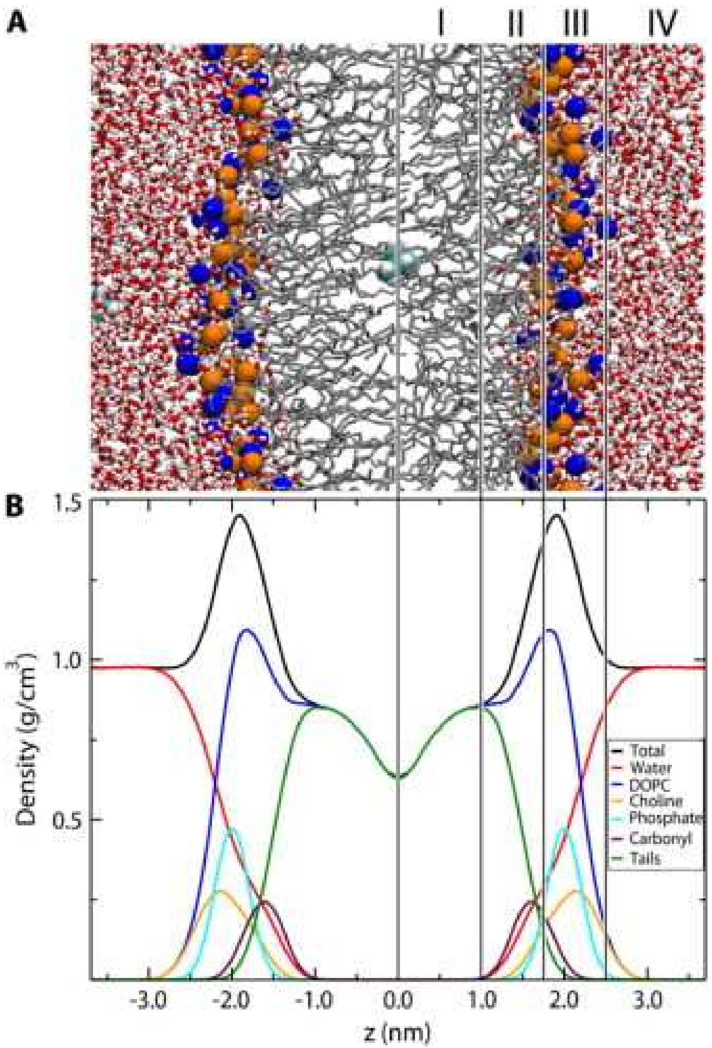
helical order parameter

cusp singularity for $t \to t_c^+$ and $\nu = \infty$

divergence for $\nu \to \infty$ and $t < t_c$

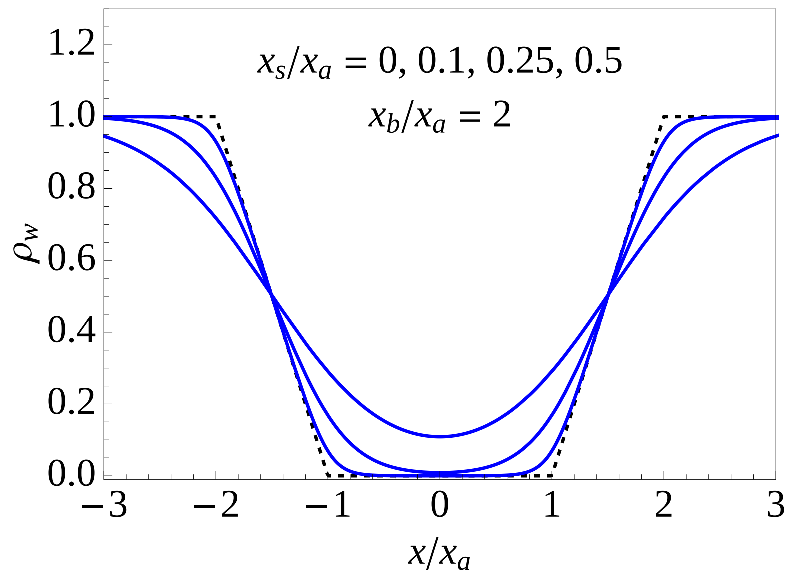
divergence for $t \to t_c^+$ and $\nu = \infty$

Heterogeneous Environment



MacCallum et al. (2008)

profile of $\mathrm{H_2O}$ density across lipid bilayer



$$\rho_w(x) = 2 + \frac{x_s}{x_b - x_a}\left[\ln\left(\frac{1+e^{(x_a-x)/x_s}}{1+e^{(x_b-x)/x_s}}\right) + \ln\left(\frac{1+e^{(x_a+x)/x_s}}{1+e^{(x_b+x)/x_s}}\right)\right].$$

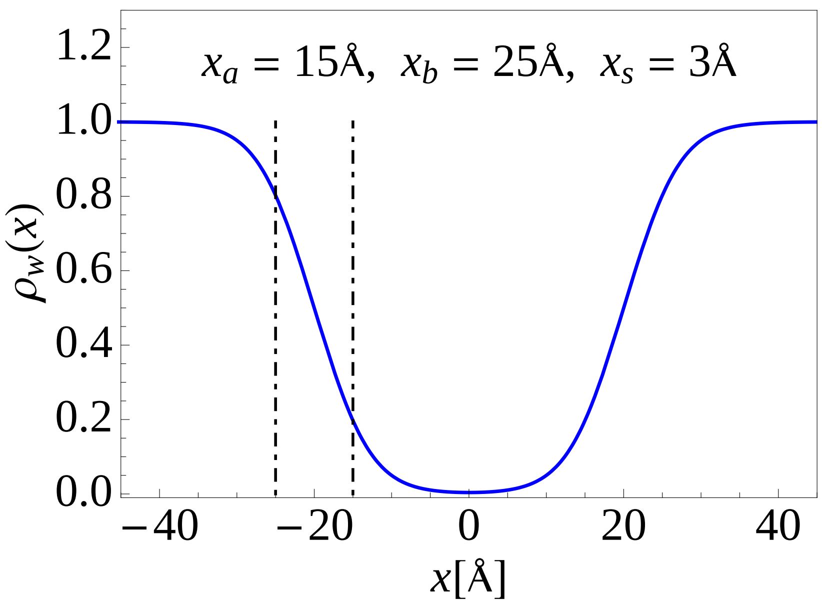
Profiles (1)

Activation energies: $K_\nu(x) = \dfrac{\epsilon_H}{k_B T}\left[1 - \alpha_H \rho_w(x)\right]$

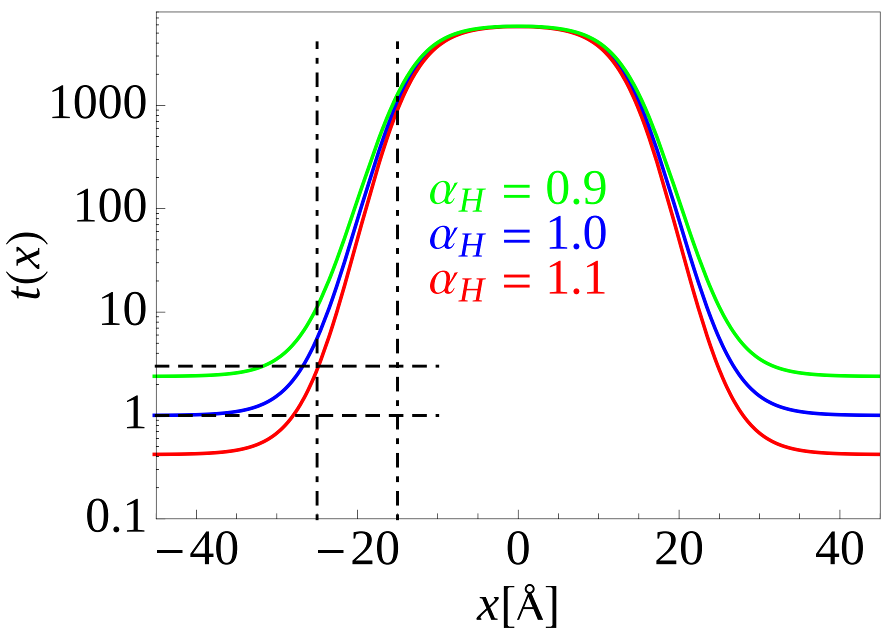
Growth parameter: $t(x) = e^{K_\nu(x)}$. Cooperativity: $\tau = e^{K_\nu(x) - K_1(x)}$, $(0 \leq \tau \leq 1)$

Energy parameter: $\dfrac{\epsilon_H}{k_B T} \simeq 9$. Enthalpy parameter: $\alpha_H \simeq 1$.

Density of water



Growth parameter

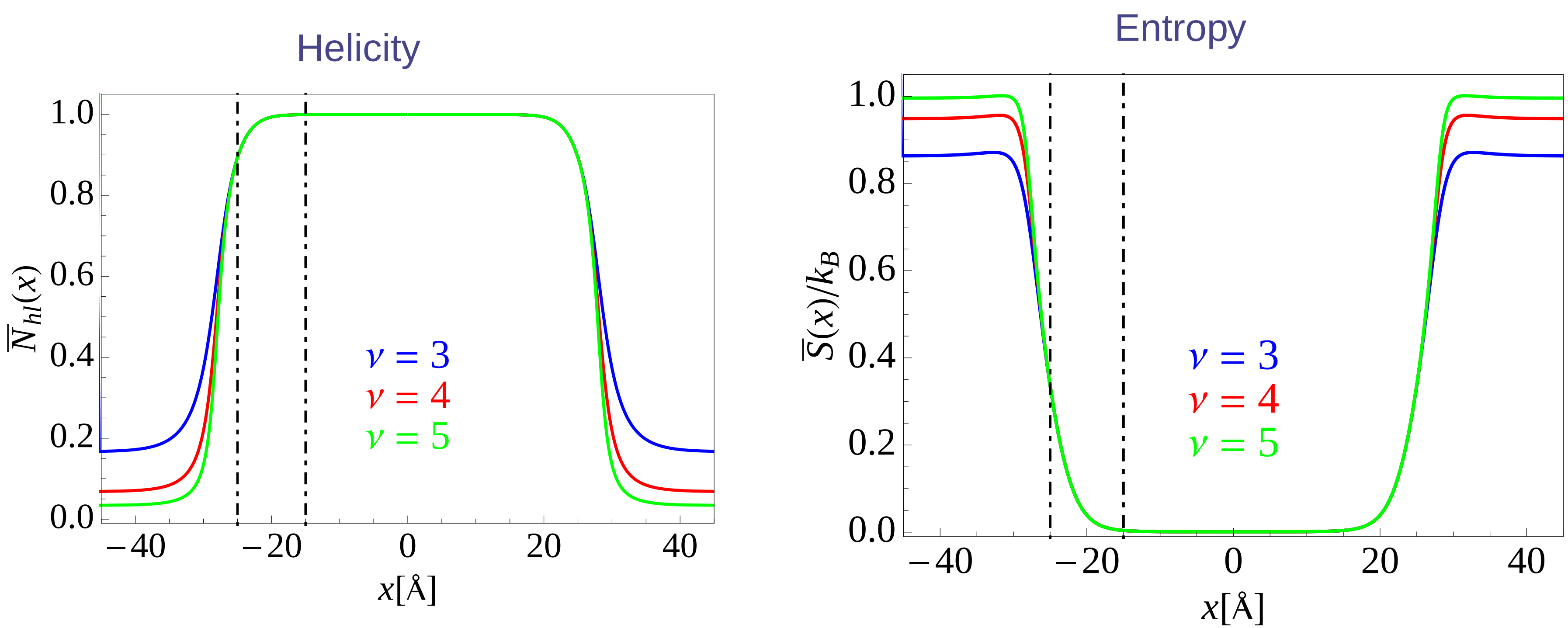


Profiles (2)

Local helicity: $\bar{N}_{hl}(t,\tau)$ with $t = t(x)$.

Entropy density: $\bar{S}(t,\tau)/k_B$ with $t = t(x)$.

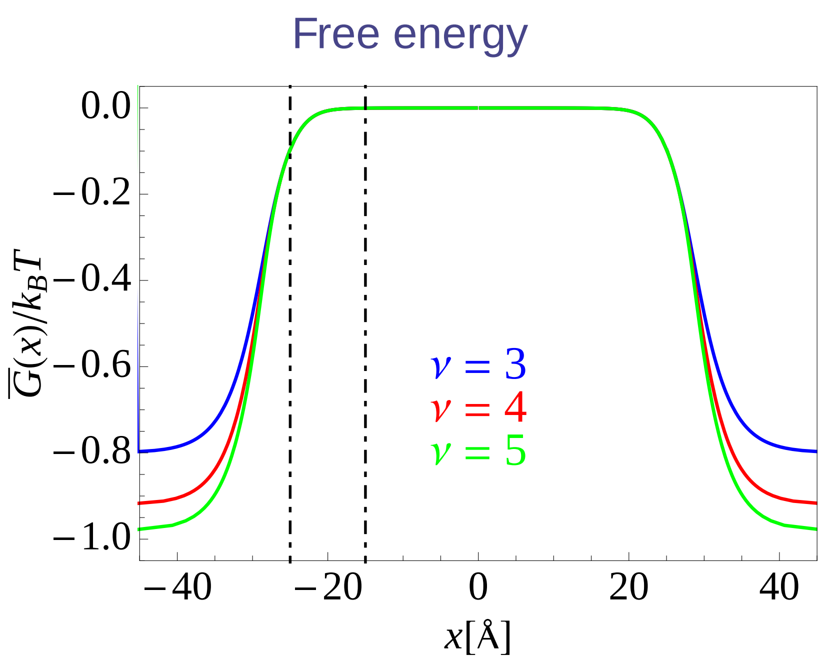
Parameter values used: $\dfrac{\epsilon_H}{k_B T} = 8.7, \quad \alpha_H = 1, \quad \tau = 0.5.$

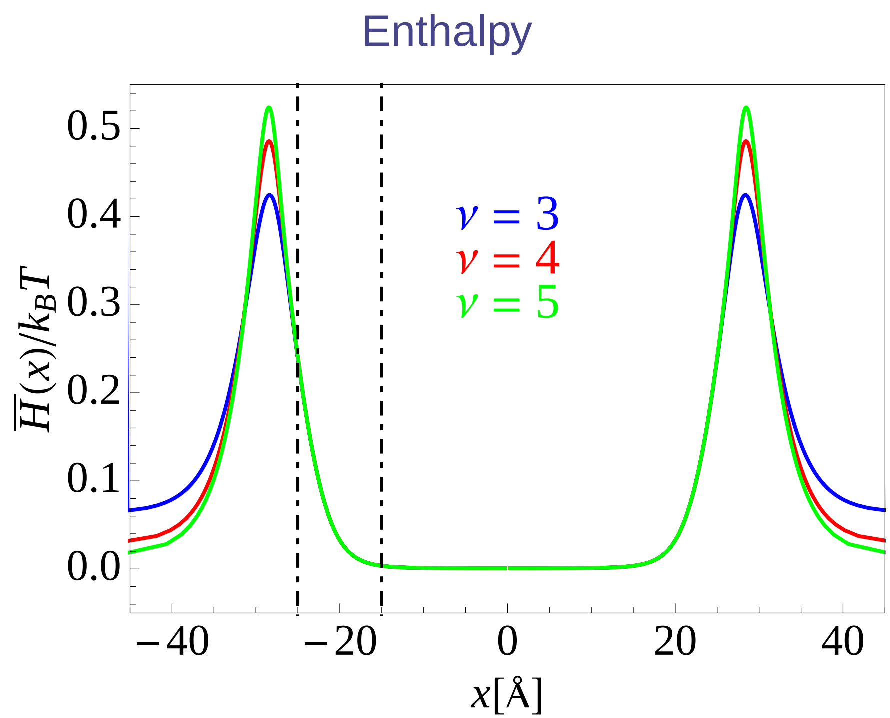


Profiles (3)

Free energy density: $\frac{\bar{G}(t,\tau)}{k_B T} = -\ln\left(1 + w_1^{-1}(t,\tau)\right)$ with $t = t(x)$.

Enthalpy density: $\frac{\bar{H}(t,\tau)}{k_B T} = \frac{\bar{G}(t,\tau)}{k_B T} + \frac{\bar{S}(t,\tau)}{k_B}$ with $t = t(x)$.

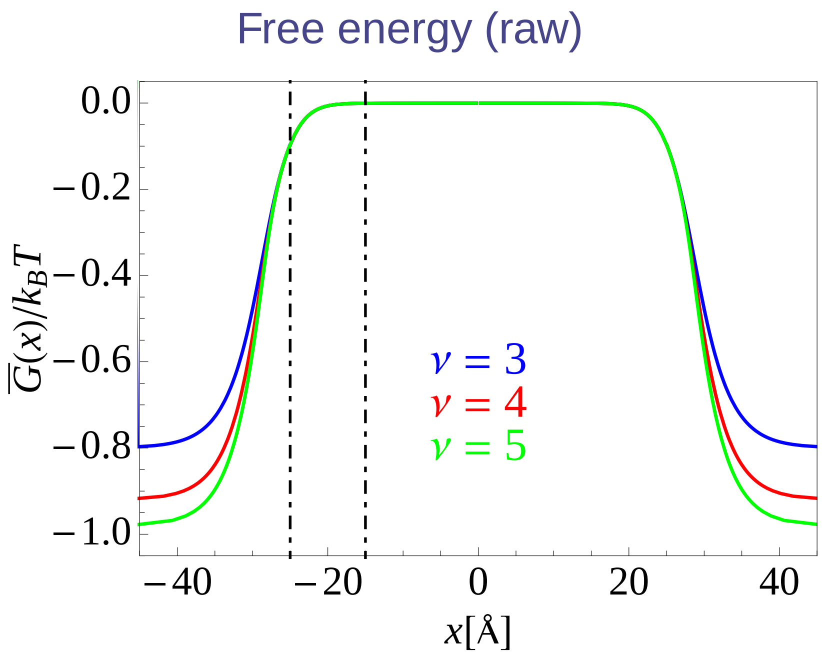


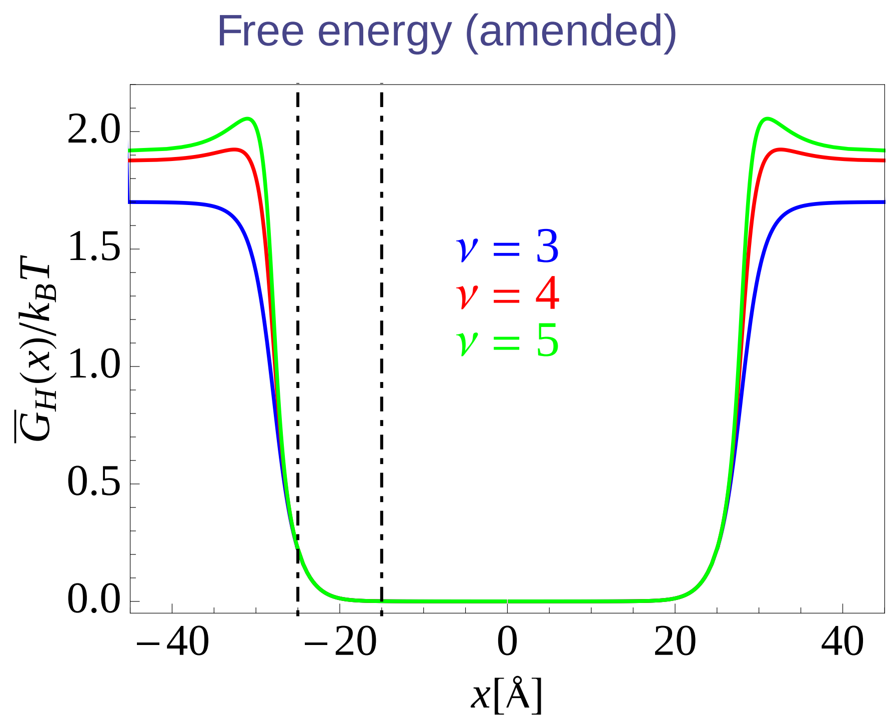


Profiles (4)

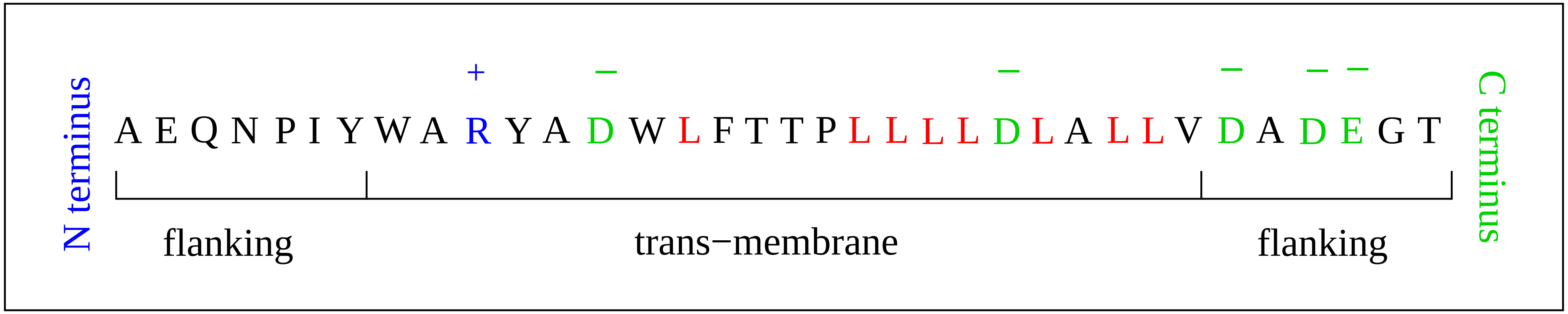
Entropic cost of external H-bond: $\dfrac{T\Delta\bar{S}_H}{k_BT} \simeq 1.5.$

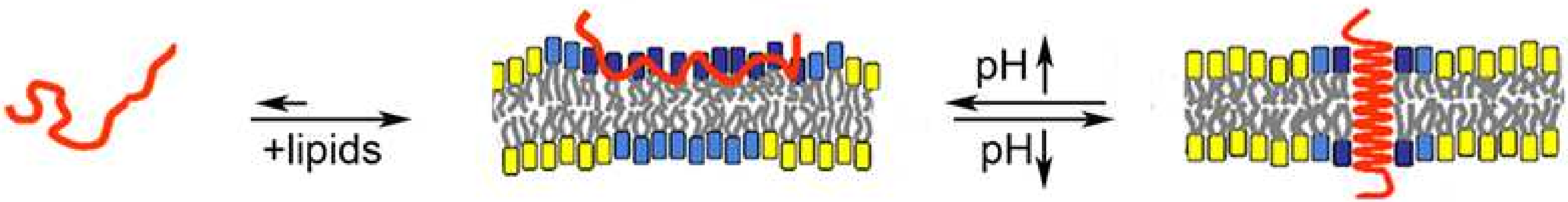
Amended free energy: $\dfrac{\bar{G}_H(x)}{k_BT} = \dfrac{\bar{G}(x)}{k_BT} + 2\dfrac{\Delta\bar{S}_H}{k_B}\left[1 - \bar{N}_{hl}(x)\right]$





pHLIP: pH - Low - Insertion Peptide



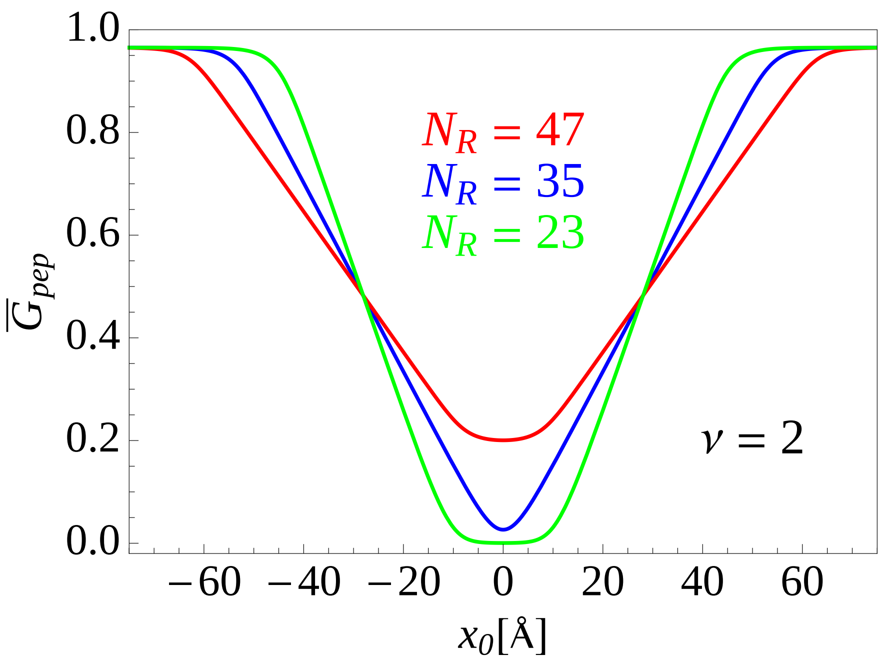


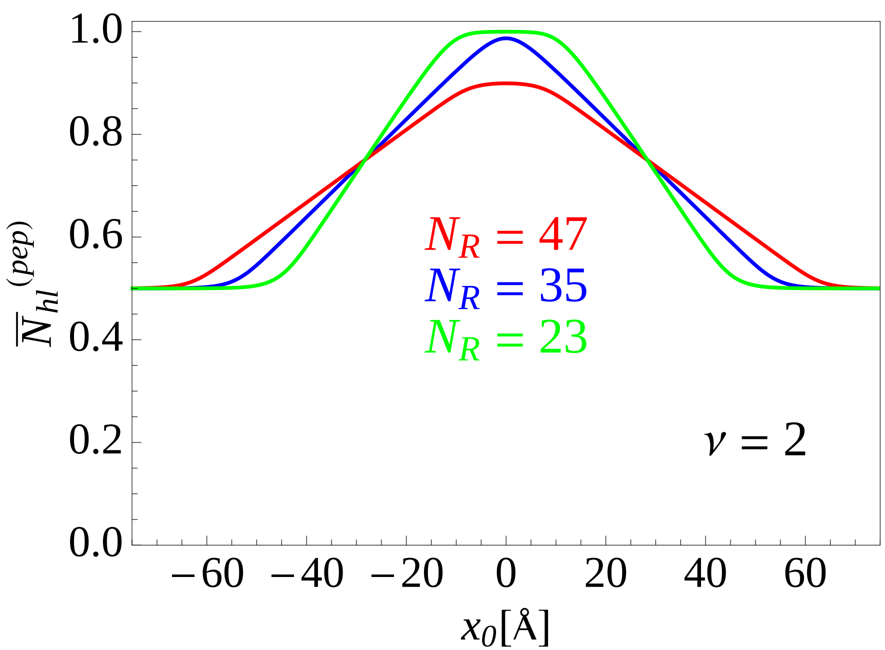
Landscapes (1)

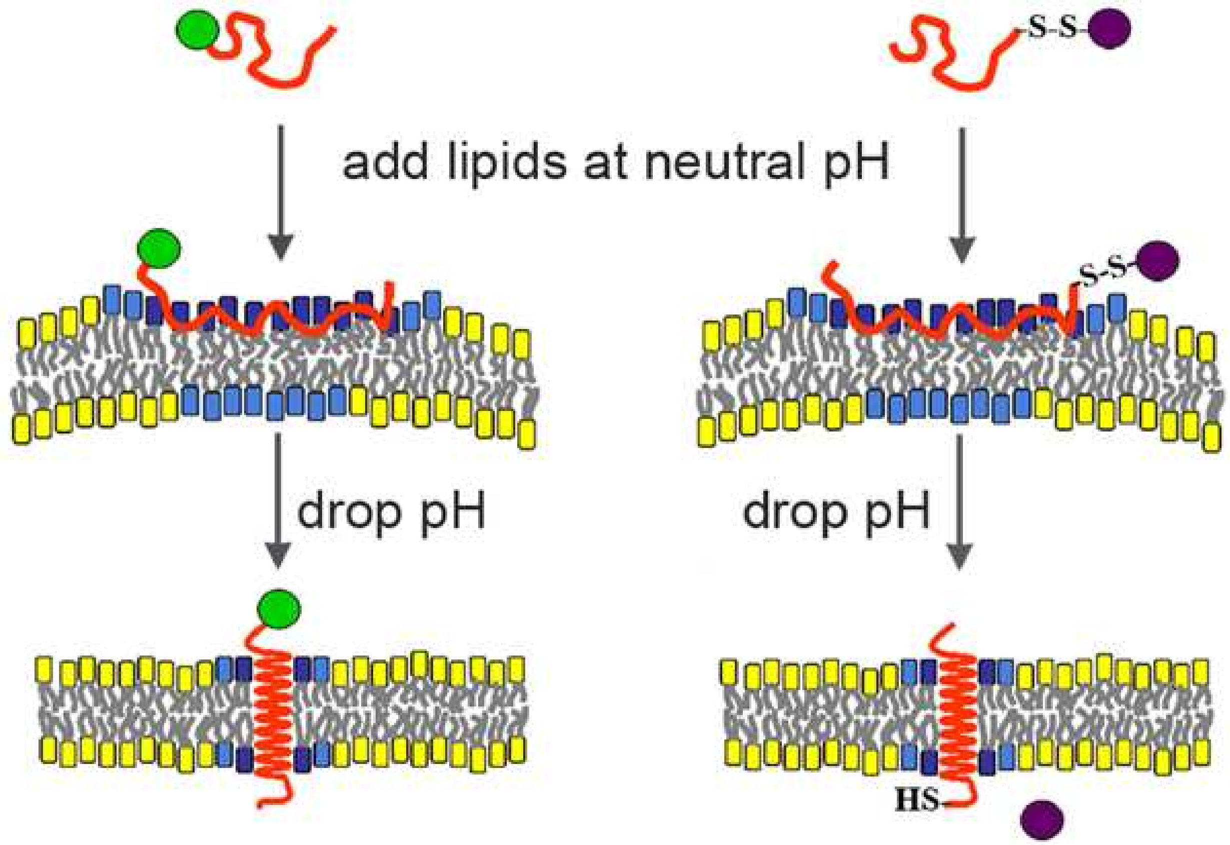
Helicity of peptide: $\bar{N}_{hl}^{(pep)}(x_0) = \sum_{n=-(N_R-1)/2}^{+(N_R-1)/2} \frac{\bar{N}_{hl}(x_0 + nl_h)}{N_R}.$

Free energy of peptide: $\bar{G}_{pep}(x)/k_BT = \sum_{n=-(N_R-1)/2}^{+(N_R-1)/2} \frac{\bar{G}_H(x_0 + nl_h)}{N_R k_B T}.$

Assumption: $x_{n+1} - x_n = l_h = 1.5\,\text{Å}$ (independent of conformation)







diagnostic agent

cargo $\longrightarrow$ marker

therapeutic agent

cargo $\longrightarrow$ drug