A Model of Correct and Incorrect Dimer Contacts

Mobolaji Williams — Shakhnovich Group Meeting— Jan 16, 2018

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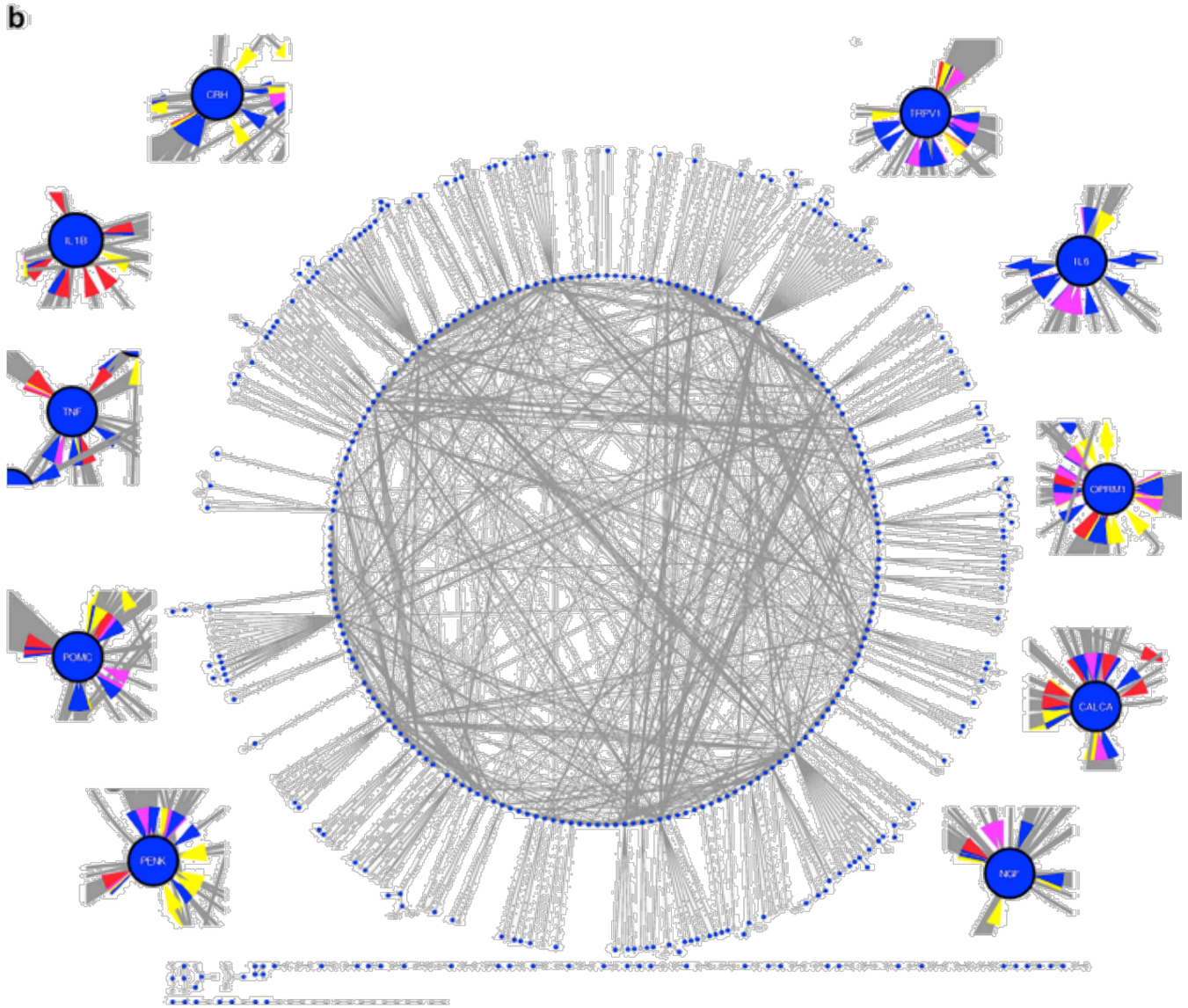
Protein Interactions and Networks

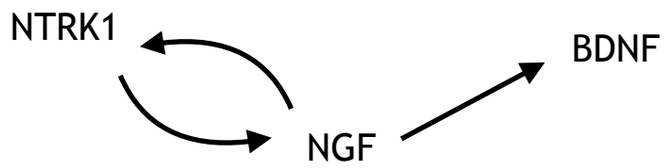
"The pain interactome: Connecting pain-specific protein interactions", Jamieson *et.al.* 2014

— 611 proteins with 1001 unique interactions.



Pain is communicated throughout the body using proteins involved in cellular signaling and signal transduction pathways

Sub-network for inflammatory pain



✳ NTRK1: Neurotrophic Kinase 1
NGF: Nerve growth factor
BDNF: Brain-derived neurotrophic growth factor

Specific protein Interactions are involved in communicating specific types of pain

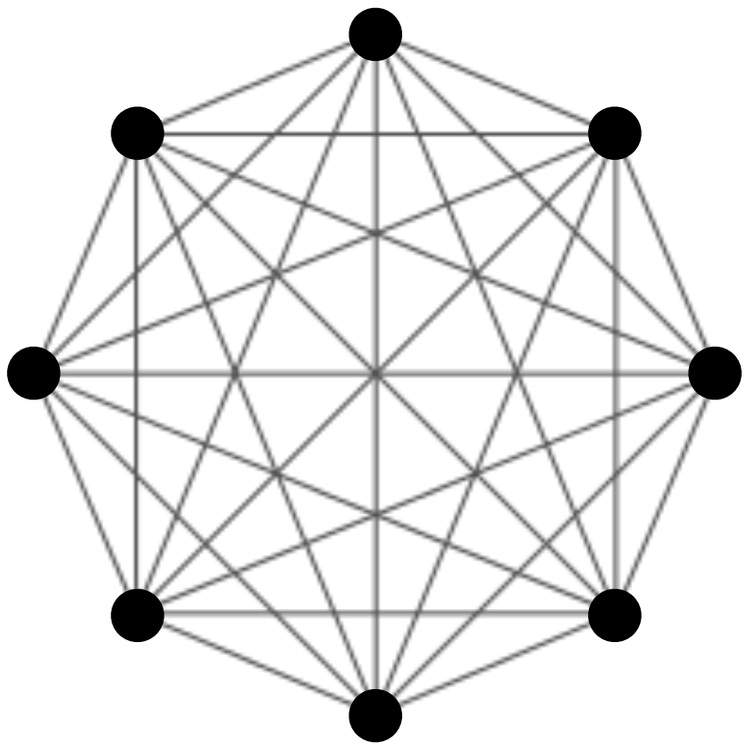
— **neuropathic** (e.g., tingling and burning pain) and **inflammatory** (i.e., associated with tissue damage) pain networks contain 127 and 157 proteins, with 80 proteins appearing in both data sets.

With so many possible interactions, how can physical constraints ensure that "correct" interactions occur?

Idealized Network

With so many possible interactions, how can physical constraints ensure that “correct" interactions occur?

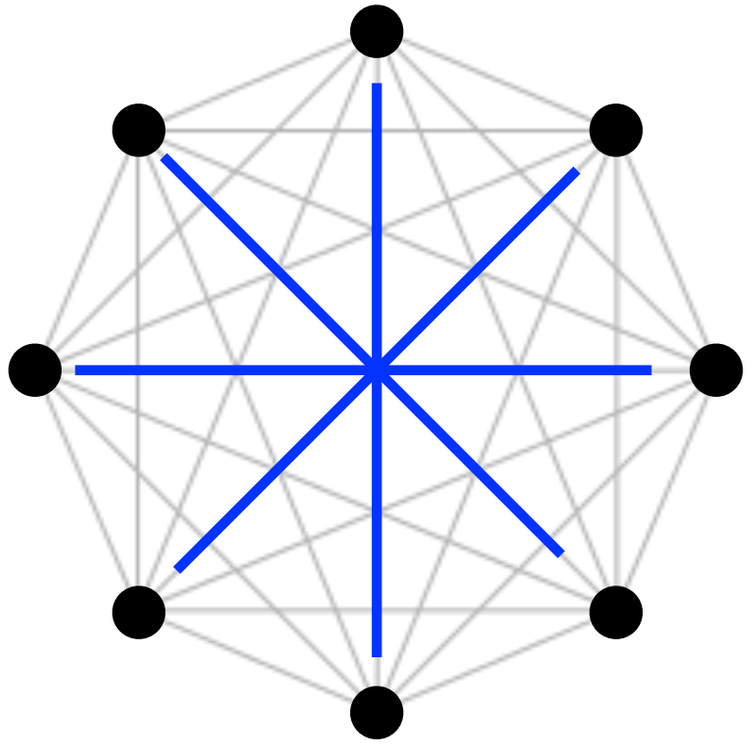
Say we have a network, where each **node** represents a subunit and each **edge** represents a possible interaction between subunits



All possible Interactions

*We take the network to be **fully connected**, each subunit can interact with any other subunit

But let’s say a single set of *N* connections are deemed to be **“correct edges”** for a particular process.



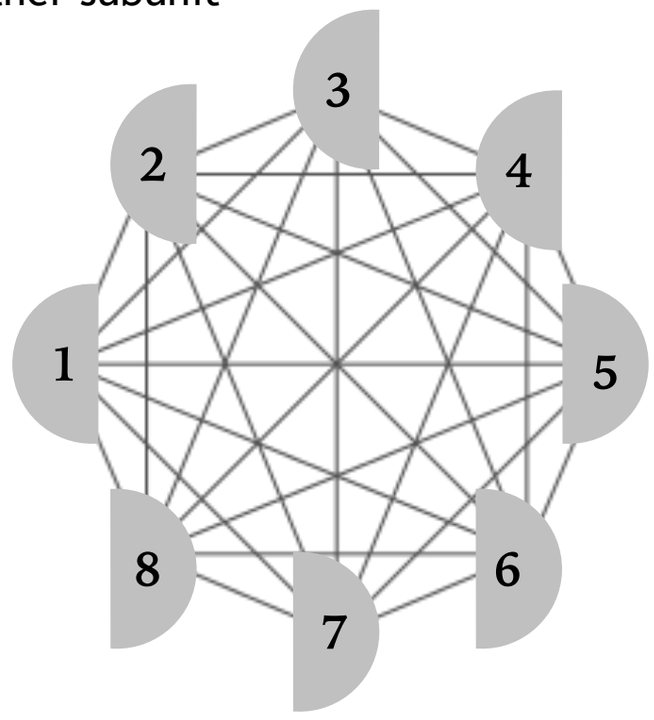
“Correct” Interactions (for some purpose)

How can we study this system physically?

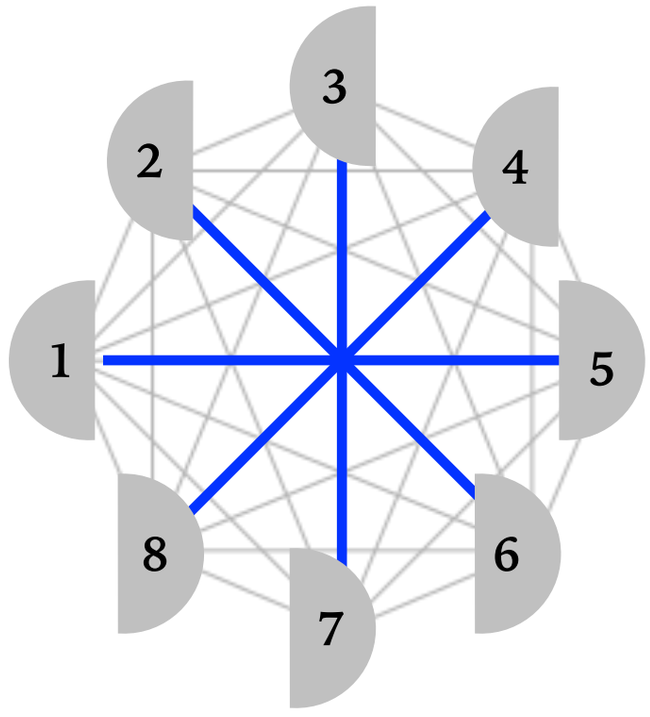
From Network to Physical Particles

To Study this System Physically:

Represent each node as a physical subunit, which can interact with any other subunit



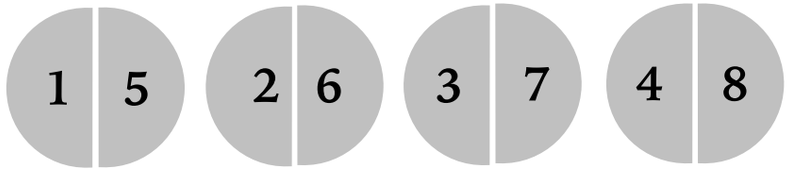
"Correct Interactions" are represented by specific interactions in this network



Introducing Physics:

"Correct" interactions occur with binding energy $-(E_0 + \Delta)$. All other interactions have binding energy $-E_0$.

e.g., Correct Bindings for 2N = 8 network



$$\text{Energy} = -4(E_0 + \Delta)$$

Main Question:

What thermodynamic constraints ensure system will have correct interactions?

Building a Model

1. There are $2N$ distinguishable monomers denoted $\alpha_1, \alpha_2, \ldots, \alpha_{2N}$ which can exist alone or as dimers (i.e., in pairs).

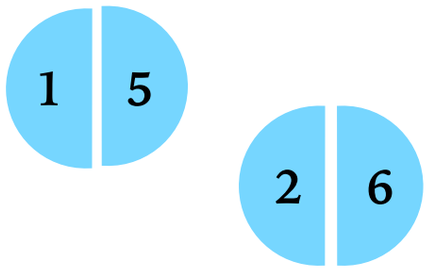
2. Each monomer has one other monomer to which it binds with energy $-(E_0 + \Delta)$. We call these pairings **"correct"** dimers, and they consist of α_k binding to α_{k+N} (or, if $k > N$, to α_{k-N}).

3. For all pairings different from a "correct" pairing, the binding energy is $-E_0$. We call these pairings **"incorrect"** dimers.

4. Dimers and monomers are otherwise non-interacting and point-like.

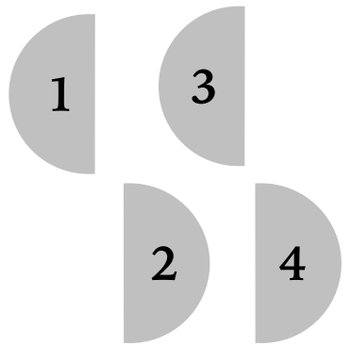
5. Each monomer has mass m_0, and the system exists in a volume V at temperature T.

e.g., for 2N = 8



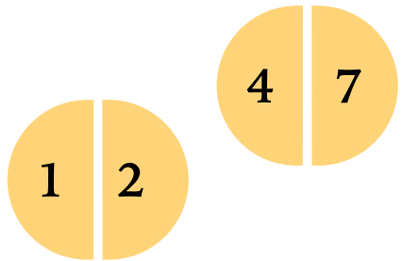
Correct dimers have binding energy

$$-(E_0 + \Delta)$$



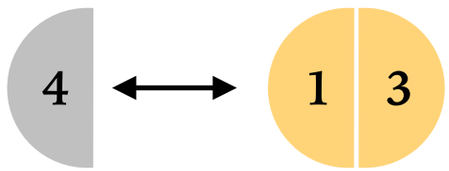
System has 2N subunits/monomers

e.g., for 2N =8



Incorrect dimers have binding energy

$$-E_0$$



No Interaction

Implies the monomers and dimers have kinetic energy.

mass: m_0

Volume *V* and temperature *T*

A Possible Microstate

Example Microstate for 2N = 30

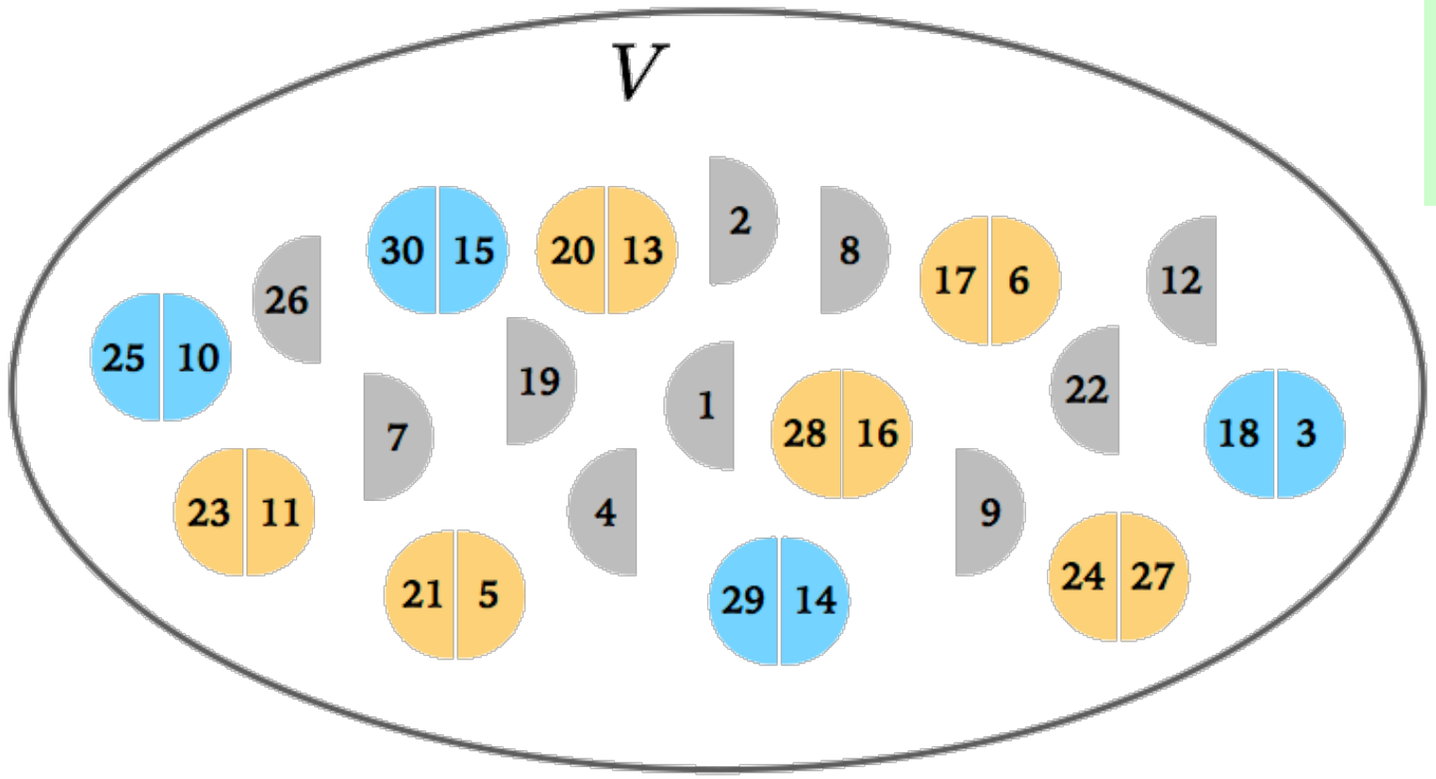
Monomers and dimers have kinetic energies of the form $\frac{1}{2m_0}\mathbf{p}^2$, $\frac{1}{2(2m_0)}\mathbf{p}'^2$ respectively.

Correct dimers have binding energy

$-(E_0 + \Delta)$

Incorrect dimers have binding energy

$-E_0$



We label the total number of dimers as *k*

For this microstate:

$k = 10$

We label the number of correct dimers as *m*

For this microstate:

$m = 4$

Energy of microstate: $\mathcal{E} = -E_0(k-m) - (E_0+\Delta)m + \frac{1}{2m_0}\sum_{i=1}^{N-k}\mathbf{p}_i^2 + \frac{1}{2(2m_0)}\sum_{j=1}^{k}\mathbf{p}'^2_j$

$= -10\,E_0 - 4\,\Delta + \frac{1}{2m_0}\sum_{i=1}^{20}\mathbf{p}_i^2 + \frac{1}{2(2m_0)}\sum_{j=1}^{10}\mathbf{p}'^2_j$

Equilibrium Thermodynamics

To investigate the equilibrium thermodynamics of this system, we need to compute the partition function

$$\sum_{\text{states}} e^{-\beta \mathcal{E}(\text{state})}$$

We need two things:

1. Boltzmann factor → Found this in previous slide.
2. Sum over states

Sum over states

1. **Momenta:** Sum over the momenta of monomers and dimers.
2. **Positions:** Sum over positions of monomers and dimers; with 1) this constitutes what is known as **"phase space"**

3. # of **Dimers:** Sum over all possible values of *k*
4. # of **Correct Dimers:** Sum over all possible values of *m*

Physics problem: What is the partition function for an ideal gas of *N* distinguishable particles with volume *V* and temp *T*?

$$Z = \frac{1}{h^{3N}} \int_V d^3\mathbf{r}_1 \dots d^3\mathbf{r}_N \int d^3\mathbf{p}_1 \dots d^3\mathbf{p}_N e^{-\beta \sum_{i=1}^{N} \mathbf{p}_i^2/2m_0}$$

$$= \left(\frac{V}{\lambda_0^3}\right)^N \quad \text{with} \quad \lambda_0 \equiv \frac{h}{\sqrt{2\pi m_0 k_B T}}$$

Combinatorics problem: How many ways can we create *k* pairs and *m* correct pairs out of a set of *2N* subunits?

$$\Omega_N(k,m) = \binom{N}{m} a_{N-m,k-m} \quad \text{with}$$

$$a_{N,\ell} = \sum_{j=0}^{\ell} (-1)^j \binom{N}{j} \binom{2N-2j}{2\ell-2j} (2\ell-2j-1)!!.$$

Computing Partition Function

Assembling these pieces, we have the partition function

$$Z_N(\beta E_0, \beta\Delta) = \sum_{k=0}^{N}\sum_{m=0}^{k} \left(\frac{V}{\lambda_0^3}\right)^{2N-2k} \left(\frac{V}{(\lambda_0/\sqrt{2})^3}\right)^{k} e^{\beta E_0(k-m)} e^{\beta(E_0+\Delta)m} \binom{N}{m} a_{N-m,k-m}$$

There is a cleaner (but less intuitive) analytical form:

$$Z_N(\beta E_0, \beta\Delta) = \frac{1}{2\sqrt{\pi}\,\Gamma\left(N+\frac{1}{2}\right)} \left(\frac{V}{\lambda_0^3}\right)^{2N} \int_0^\infty dx\,dy\, \frac{e^{-(x+y)}}{\sqrt{xy}} \left(\mathcal{M}_+^{2N} + \mathcal{M}_-^{2N}\right)$$

where

$$\mathcal{M}_\pm(x, y; \beta E_0, \beta\Delta) \equiv \sqrt{x} \pm \left(\frac{2\sqrt{2}\,\lambda_0^3}{V}\right)^{1/2} e^{\beta E_0/2} \sqrt{y\,\Phi(x;\beta\Delta)}\,,$$

and

$$\Phi(x;\beta\Delta) \equiv e^{\beta\Delta} + 2x - 1.$$

* $\lambda_0 \equiv \dfrac{h}{\sqrt{2\pi m_0 k_B T}}$

Note: This result is exact; No approximations have been made.

The continuous integrals come from using identities like $N! = \int_0^\infty ds\, e^{-s} s^N$

What physical results can we extract from this result?

Physical Results from Partition Function

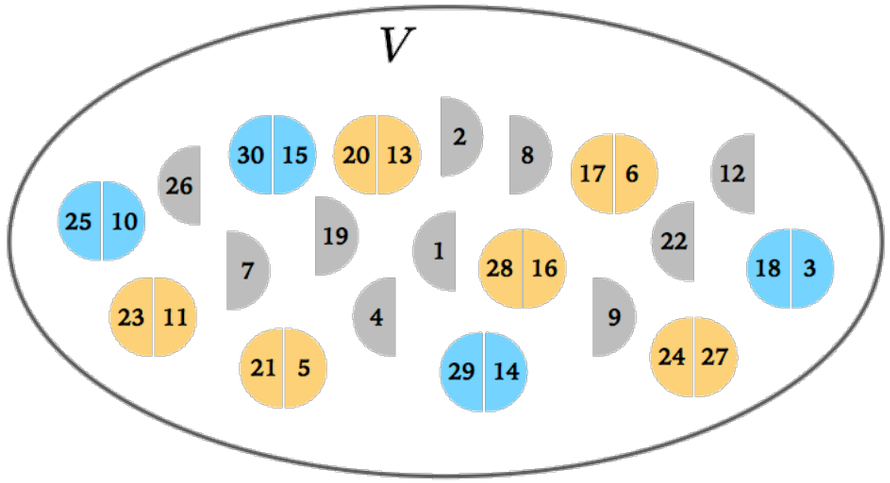
What physical results are contained in this partition function?

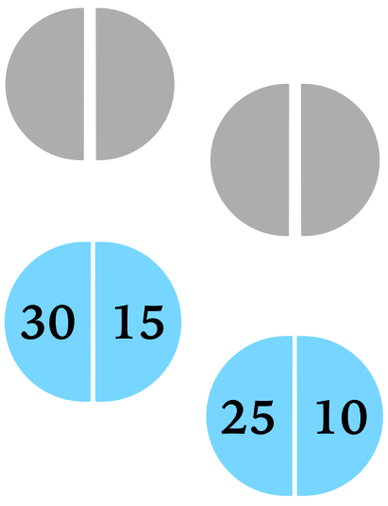
$$Z_N(\beta E_0, \beta\Delta) = \frac{1}{2\sqrt{\pi}\,\Gamma\left(N+\frac{1}{2}\right)}\left(\frac{V}{\lambda_0^3}\right)^{2N}\int_0^\infty dx\,dy\,\frac{e^{-(x+y)}}{\sqrt{xy}}\left(\mathcal{M}_+^{2N}+\mathcal{M}_-^{2N}\right)$$

Two Interesting Questions:

1. For what thermal conditions is the system composed **mostly of dimers?**

2. For what thermal conditions do these dimers consist **mostly of correct contacts?**





Partition function allows us to "easily" compute two relevant quantities:

1. The average number of **total dimers** as a function of temperature.

2. The average number of **correct dimers** as a function of temperature

Formal Definitions

$$\langle k\rangle = \frac{\partial}{\partial(\beta E_0)}\ln Z_N(\beta E_0, \beta\Delta)$$

$$\langle m\rangle = \frac{\partial}{\partial(\beta\Delta)}\ln Z_N(\beta E_0, \beta\Delta)$$

Equilibrium Conditions

From the partition function

$$Z_N(\beta E_0, \beta\Delta) = \frac{1}{2\sqrt{\pi}\,\Gamma\left(N+\frac{1}{2}\right)}\left(\frac{V}{\lambda_0^3}\right)^{2N}\int_0^\infty dx\,dy\,\frac{e^{-(x+y)}}{\sqrt{xy}}\left(\mathcal{M}_+^{2N}+\mathcal{M}_-^{2N}\right)$$

We can compute:

1. Mean number of total dimers $\langle k\rangle = \frac{\partial}{\partial(\beta E_0)}\ln Z_N(\beta E_0, \beta\Delta)$
2. Mean number of correct dimers $\langle m\rangle = \frac{\partial}{\partial(\beta\Delta)}\ln Z_N(\beta E_0, \beta\Delta)$

Problem: Requires multiple numerical integrations for each quantity.

i.e., Too computationally expensive!

Simpler Approach:

1. Use Laplace's Method to Approximate Integral
2. Find Conditions for the validity of the approximation
3. Derive equilibrium conditions for <k> and <m>

$$\int_0^\infty dx\,dy\,e^{-\beta F(x,y)} \simeq e^{-\beta F(\overline{x},\overline{y})}$$

$$0 = \partial_x F(x,y)\Big|_{x=\overline{x},y=\overline{y}} = \partial_y F(x,y)\Big|_{x=\overline{x},y=\overline{y}}$$

??

After *some* algebra

Equilibrium Conditions:

$$\frac{e^{\beta\Delta}}{2} \simeq \langle m\rangle\frac{N-\langle m\rangle}{\langle k\rangle-\langle m\rangle}, \qquad \frac{4\sqrt{2}\,\lambda_0^3}{V}e^{\beta E_0} \simeq \frac{\langle k\rangle-\langle m\rangle}{\left(N-\langle k\rangle\right)^2}$$

*Much less computationally expensive!

Equilibrium Conditions: Sanity Check #1

Mean number of total dimers $\langle k \rangle$ and mean number of correct dimers $\langle m \rangle$ are constrained by the system of equations:

$$\frac{e^{\beta\Delta}}{2} \simeq \langle m \rangle \frac{N - \langle m \rangle}{\langle k \rangle - \langle m \rangle}, \qquad \frac{4\sqrt{2}\,\lambda_0^3}{V} e^{\beta E_0} \simeq \frac{\langle k \rangle - \langle m \rangle}{\big(N - \langle k \rangle\big)^2}$$

Limit Case: No Correct Dimers

Take $\Delta \to 0$, so that there are no correct dimers.

(New system of equations)

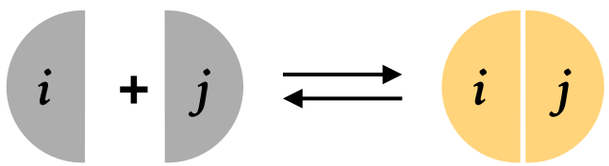
$$\langle m \rangle \simeq \frac{\langle k \rangle}{2N}, \qquad \frac{\sqrt{2}\,\lambda_0^3}{V} e^{\beta E_0} \simeq \frac{\langle k \rangle}{\big(2N - 2\langle k \rangle\big)^2}$$

Average number of dimers

Average number of monomers

$$[\text{dimers}] = \langle k \rangle / V$$
$$[\text{monomers}] = (2N - 2\langle k \rangle)/V$$

2. Reaction Equation



$$\alpha_i + \alpha_j \rightleftharpoons \alpha_i\alpha_j\,; \quad \Delta G = -E_0$$

From Chem 101: Concentrations at chemical equilibrium

$$\frac{[\alpha_i\alpha_j]}{[\alpha_i]^2} = K_{\text{eq}} \quad \text{and} \quad K_{\text{eq}} \propto e^{-\beta\Delta G}$$

From Model: Concentrations at thermal equilibrium

$$\frac{[\text{dimers}]}{[\text{monomers}]^2} = \sqrt{2}\,\lambda_0^3\, e^{\beta E_0}$$

$$\frac{[\alpha_i\alpha_j]}{[\alpha_i]^2} \propto e^{\beta E_0}$$

Model is consistent with basic chemistry.

Equilibrium Conditions: Sanity Check #2

Mean number of total dimers $\langle k \rangle$ and mean number of correct dimers $\langle m \rangle$ are constrained by the system of equations:

$$\frac{e^{\beta\Delta}}{2} \simeq \langle m \rangle \frac{N - \langle m \rangle}{\langle k \rangle - \langle m \rangle}, \qquad \frac{4\sqrt{2}\,\lambda_0^3}{V} e^{\beta E_0} \simeq \frac{\langle k \rangle - \langle m \rangle}{\big(N - \langle k \rangle\big)^2}$$

Limit Case: No Correct Dimers

Take $\Delta \to 0$, so that there are no correct dimers.

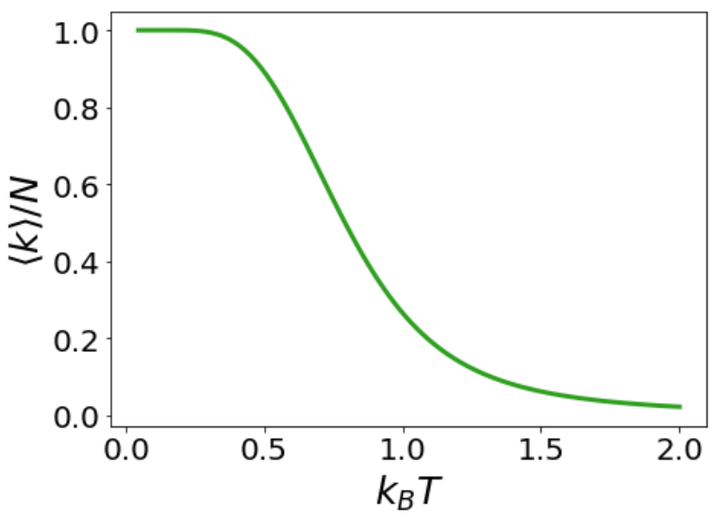
(New system of equations)

$$\langle m \rangle \simeq \frac{\langle k \rangle}{2N}, \qquad \frac{\sqrt{2}\,\lambda_0^3}{V} e^{\beta E_0} \simeq \frac{\langle k \rangle}{\big(2N - 2\langle k \rangle\big)^2}$$

Average number of dimers

Average number of monomers

2. "Melting Temperature" of Dimers:



Melting temperature $T_{1/2}$ is the temperature where $\langle k \rangle = N/2$.

$$k_B T_{1/2} = \frac{2E_0}{3} \left[W_0 \left(\frac{4\pi m_0 E_0}{3h^2 \big(2N\sqrt{2}/V\big)^{2/3}} \right) \right]^{-1}$$

* $W_0(x)$ is the Lambert-W function defined by the condition $W_0(xe^x) = x$.

Numerical Example:
From *OligoCalc* the numerical values for 20bp DNA dissociation:

(Dissoc. Energy) $E_0 = (20 \pm 3)$ kcal/mol $= (1.4 \pm .21) \times 10^{-22}$ kJ

(Mass of ssDNA) $m_0 = 9.7 \times 10^{-24}$ kg

(Molarity of solution) $N/V = 50.0 \times 10^{-3}$ mol/m^3 $= 3.01 \times 10^{22}$ m^{-3}

$$T_{1/2} = (352 \pm 50)\ \text{K}$$

(For 20 base-pair strand of DNA)

**OligoCalc* melting temperature: ≈ 310 K

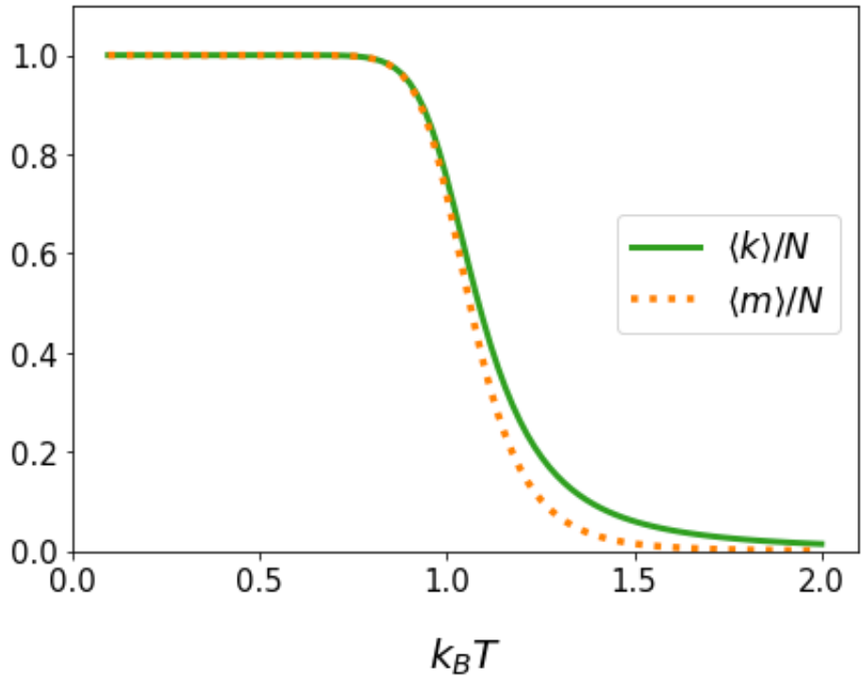
Prediction is consistent with results of online software

Solving Equilibrium Conditions Generally

To determine the equilibrium behavior more generally, we need to numerically solve the system of coupled quadratic equations.

$$\frac{e^{\beta\Delta}}{2} \simeq \langle m \rangle \frac{N - \langle m \rangle}{\langle k \rangle - \langle m \rangle}, \qquad \frac{4\sqrt{2}\,\lambda_0^3}{V} e^{\beta E_0} \simeq \frac{\langle k \rangle - \langle m \rangle}{\left(N - \langle k \rangle\right)^2}$$

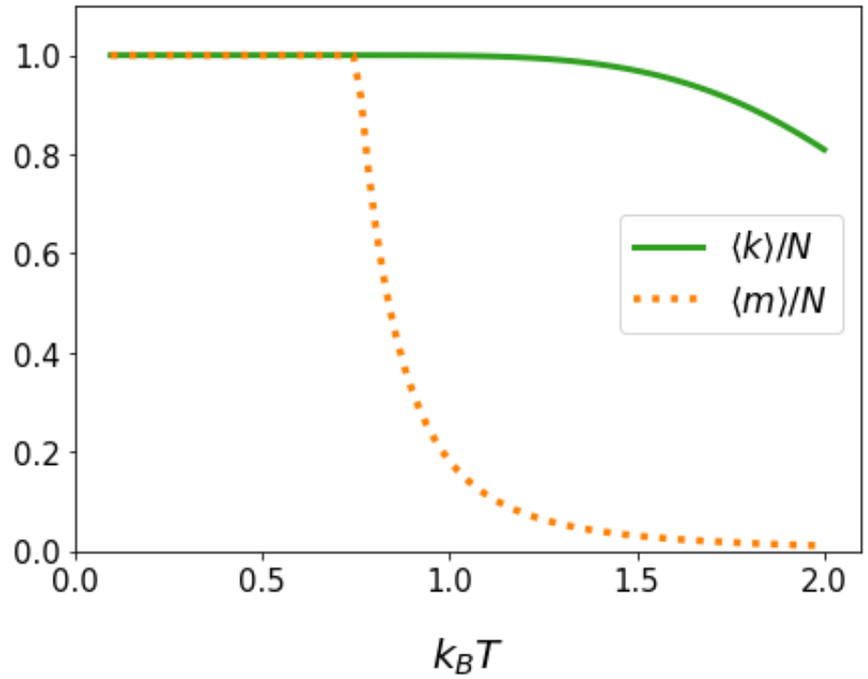
Doing so and exploring the solutions we find that the solutions fall into two general forms



(Type-I dimer system)

As we increase *T,* the **number of correct dimers decays away <u>with</u> the number of total dimers**

"Soft Transition"



(Type-II dimer system)

As we increase T, the number of **correct dimers decays away <u>before</u> the number of total dimers**

"Sharp Transition"

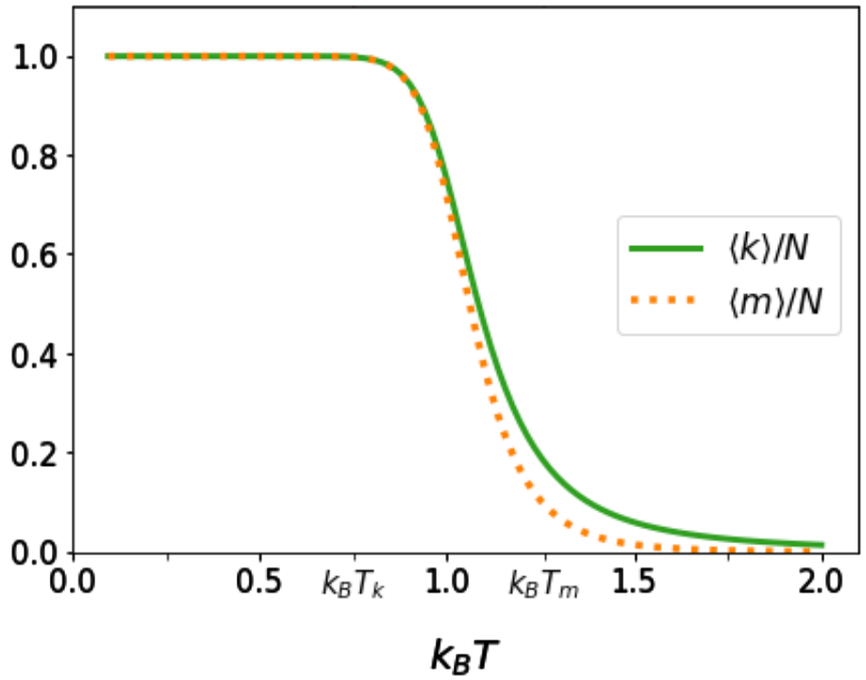
Type-I and Type-II Dimer Systems

Quantitatively, what distinguishes these two types of systems?

From the system of equations, we can compute two temperatures:

$$k_B T_m = \frac{\Delta}{\ln(2N)} \qquad (T_m\text{: Temperature at which } \langle m \rangle \simeq N)$$

$$k_B T_k = \frac{2}{3}(E_0 + \Delta)\left[W_0\left(\frac{2}{3}\beta(E_0+\Delta)\left(\frac{NV}{2\lambda_0^3\sqrt{2}}\right)^{2/3}\right)\right]^{-1} \qquad (T_k\text{: Temperature at which } \langle k \rangle \simeq N)$$



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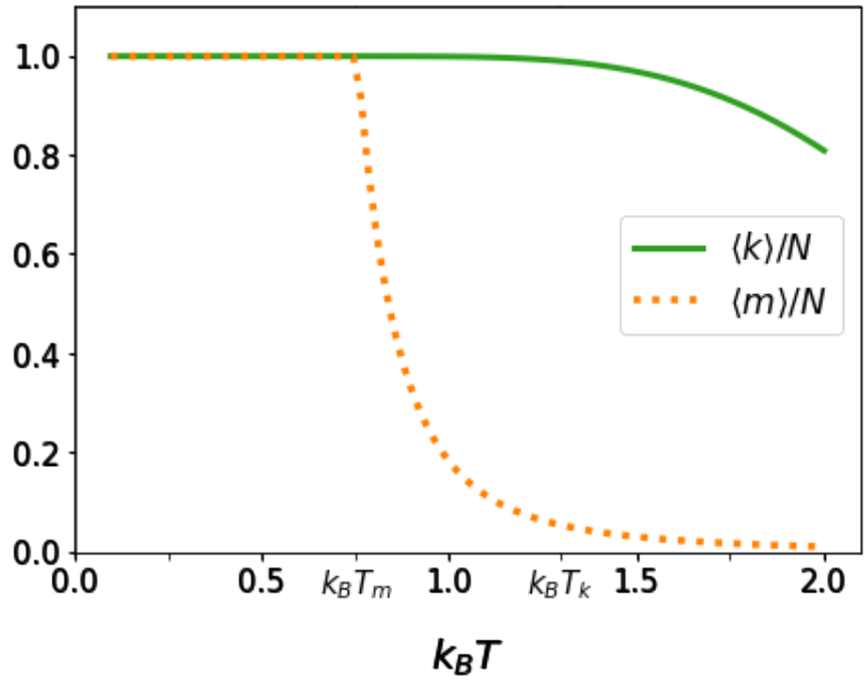
$T_k < T_m$

"Soft Transition"



(Type-II dimer system)

As we increase T, the number of **correct dimers decays away <u>before</u> the number of total dimers**

$T_m < T_k$

"Sharp Transition"

Phases of Dimer System

These systems are characterized by **four different phases**

– which are themselves defined by temperatures

(T_m: Temperature at which $\langle m \rangle \simeq N$)

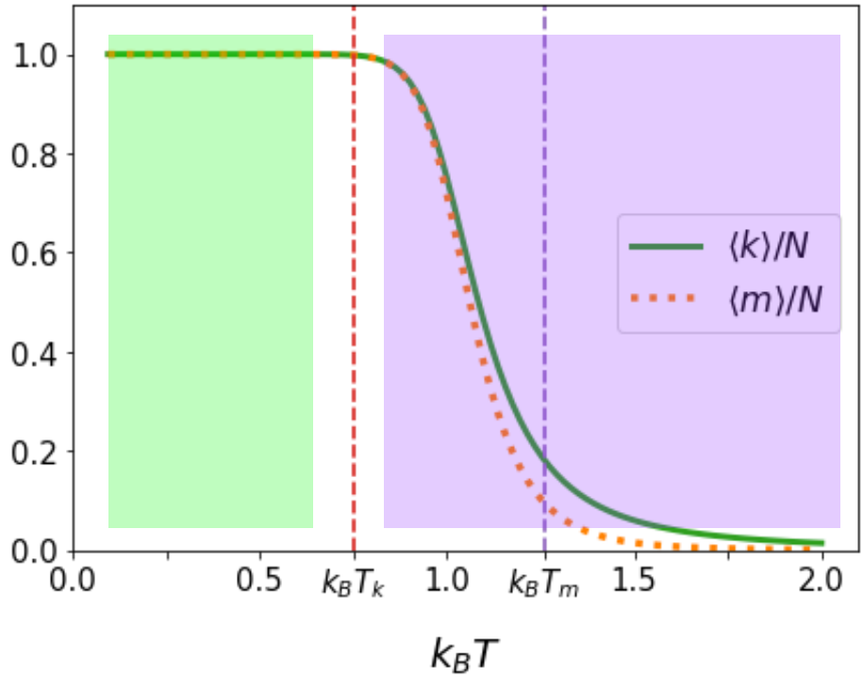
(T_k: Temperature at which $\langle k \rangle \simeq N$)

Completely dimerized and completely correct $T < T_m, T_k$

Partially dimerized and partially correct of Type I $T_k < T, T_m$

Completely dimerized and partially correct of Type II $T_m < T < T_m$

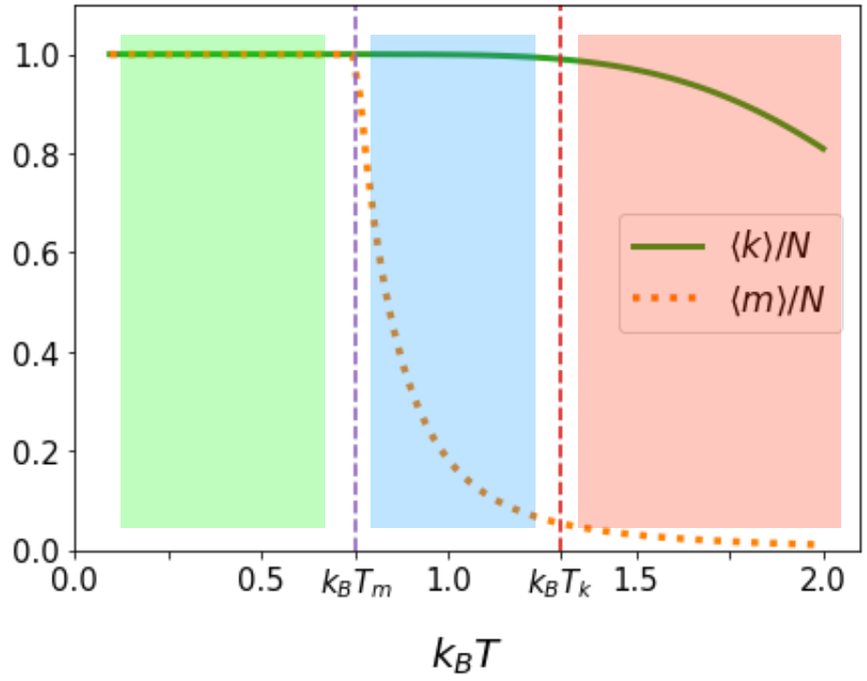
Partially dimerized and partially correct of Type II $T_k < T_m < T$



(Type-I dimer system)

As we increase *T*, the **number of correct dimers decays away <u>with</u> the number of total dimers**

$$T_k < T_m$$



(Type-II dimer system)

As we increase T, the number of **correct dimers decays away <u>before</u> the number of total dimers**

$$T_m < T_k$$

Phases of Dimer System

These systems are characterized by **four different phases**

— which are themselves defined by temperatures

(T_m: Temperature at which $\langle m \rangle \simeq N$)

(T_k: Temperature at which $\langle k \rangle \simeq N$)

Completely dimerized and completely correct $T < T_m, T_k$

Partially dimerized and partially correct of Type I $T_k < T, T_m$

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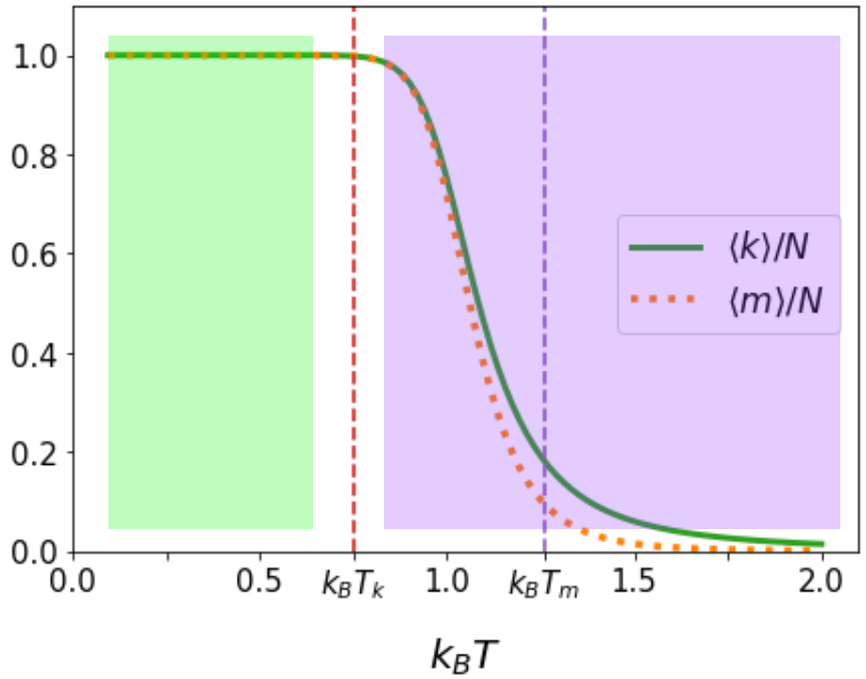
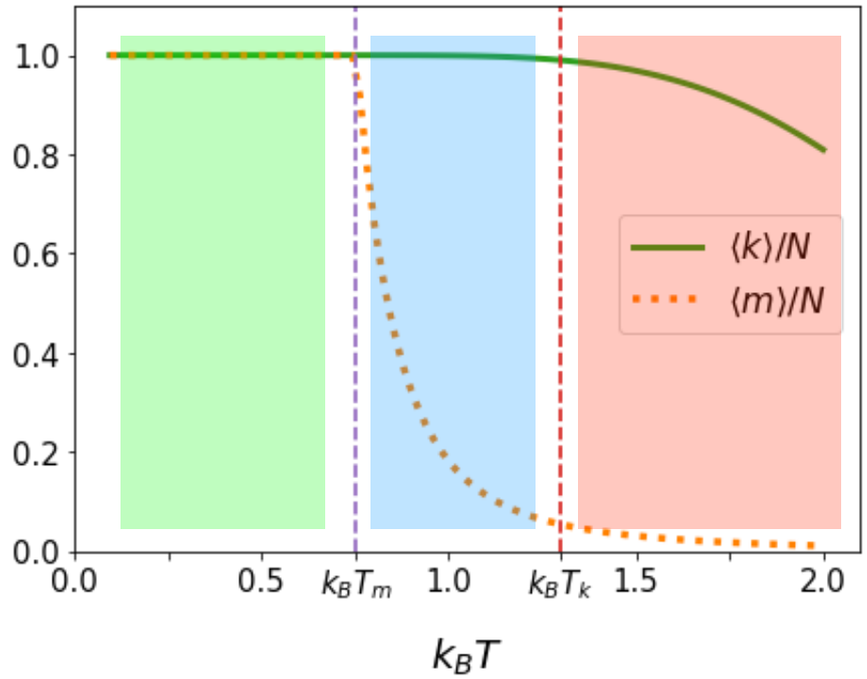
Partially dimerized and partially correct of Type II $T_k < T_m < T$



(Type-I dimer system)



(Type-II dimer system)

As we increase *T*, the **number of correct dimers decays away <u>with</u> the number of total dimers**

$$T_k < T_m$$

We can display these phases in a phase diagram.

As we increase T, the number of **correct dimers decays away <u>before</u> the number of total dimers**

$$T_m < T_k$$

These systems are characterized by **four different phases**

– which are themselves defined by temperatures

(T_m: Temperature at which $\langle m \rangle \simeq N$)

(T_k: Temperature at which $\langle k \rangle \simeq N$)

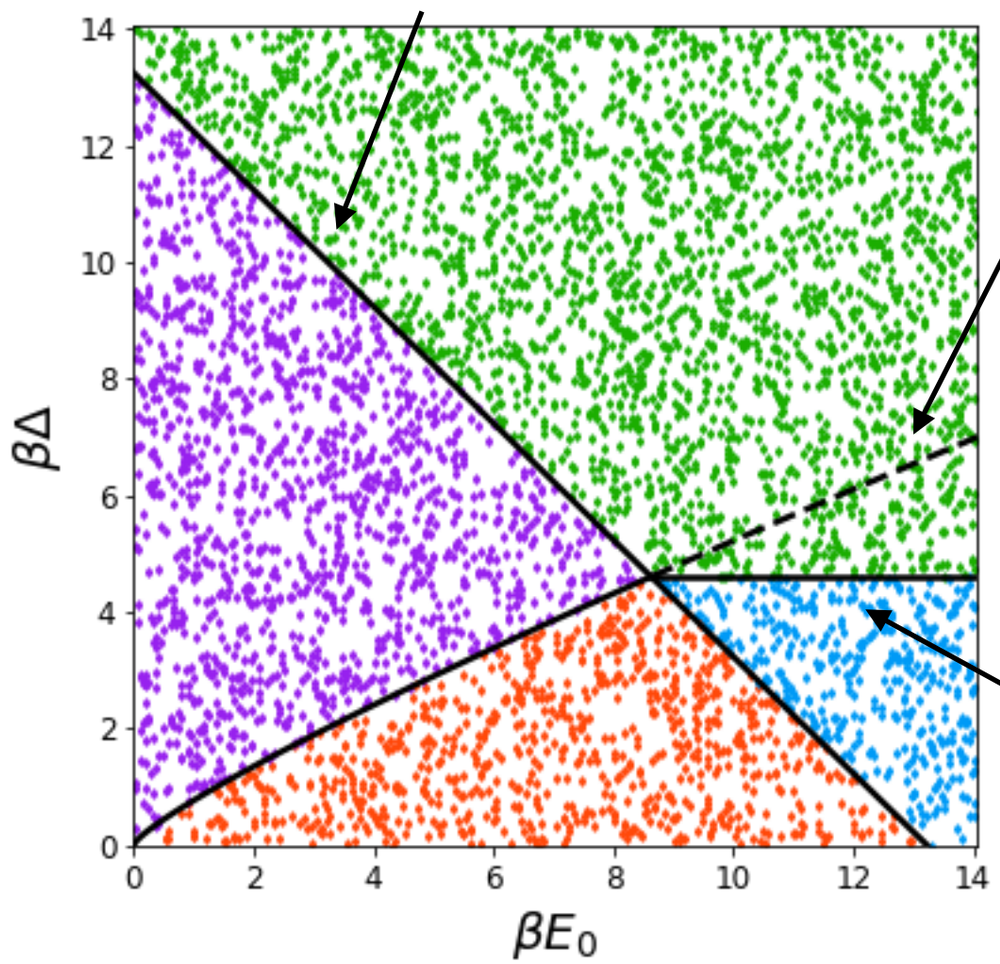
Completely dimerized and completely correct $T < T_m, T_k$

Partially dimerized and partially correct of Type I $T_k < T, T_m$

Completely dimerized and partially correct of Type II $T_m < T < T_m$

Partially dimerized and partially correct of Type II $T_k < T_m < T$

βE_0–$\beta\Delta$ space (Fixed N, V, and T)



Conditions to be completely dimerized and completely correct

$$\beta\Delta \geq \begin{cases} -\beta E_0 + \ln\left[NV/2\sqrt{2}\lambda_0^3\right] & \text{if } \beta E_0 < -\ln\left[4\sqrt{2}\,\lambda_0^3/V\right], \\ \ln(2N) & \text{if } \beta E_0 \geq -\ln\left[4\sqrt{2}\,\lambda_0^3/V\right] \end{cases}$$

$$(\beta\Delta)_{\min} = \ln(2N)$$

Particle Number and Phase-Space Density

These systems are characterized by **four different phases**

– which are themselves defined by temperatures

(T_m: Temperature at which $\langle m \rangle \simeq N$)

(T_k: Temperature at which $\langle k \rangle \simeq N$)

Completely dimerized and completely correct $\quad T < T_m, T_k$

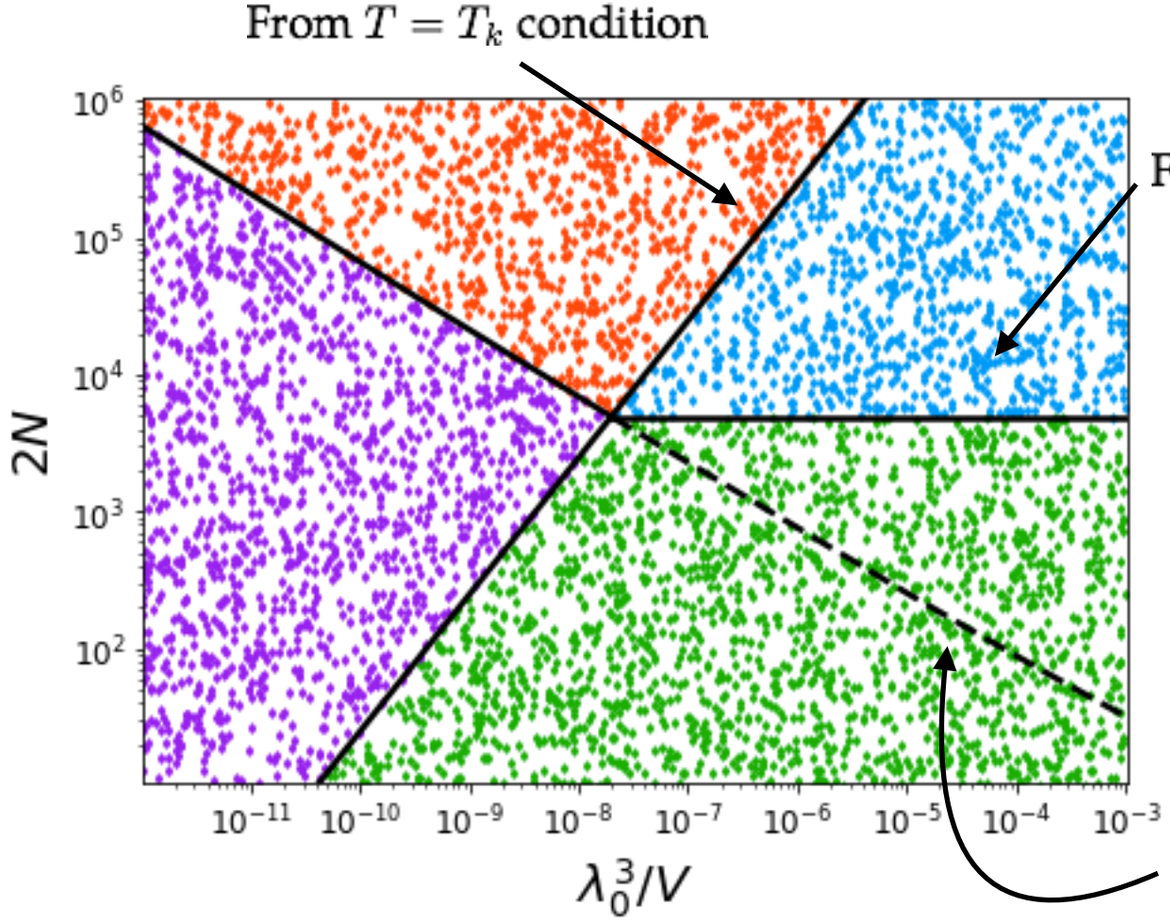
Partially dimerized and partially correct of Type I $\quad T_k < T, T_m$

Completely dimerized and partially correct of Type II $\quad T_m < T < T_m$

Partially dimerized and partially correct of Type II $\quad T_k < T_m < T$

$2N$–λ_0^3/V space (Fixed E_0, Δ, and T)

$$\lambda_0 = \frac{h}{\sqrt{2\pi m_0 k_B T}}$$



λ_0^3/V: represents the number of particles per unit phase space. Think of it as a dimensionless temperature-dependent volume density.

Conditions to be completely dimerized and completely correct

$$2N \leq \begin{cases} \dfrac{4\sqrt{2}\lambda_0^3}{V} e^{\beta(E_0+\Delta)} & \text{if } \lambda_0^3/V < e^{-\beta E_0}/(4\sqrt{2}), \\ e^{\beta\Delta} & \text{if } \lambda_0^3/V \geq e^{-\beta E_0}/(4\sqrt{2}) \end{cases}$$

$$(2N)_{\max} = e^{\beta\Delta}$$

Biophysical Systems: Proteins in a Cell

The **offset binding-energy** determines **maximum number** of correctly interacting monomers you can have in a system.

$$(2N)_{\max} = e^{\beta\Delta}$$

What do these results tell us about biophysical systems?

Proteins in a Cell

Cell signaling pathways require proteins to find and distinguish their correct partners from a sea of incorrect partners

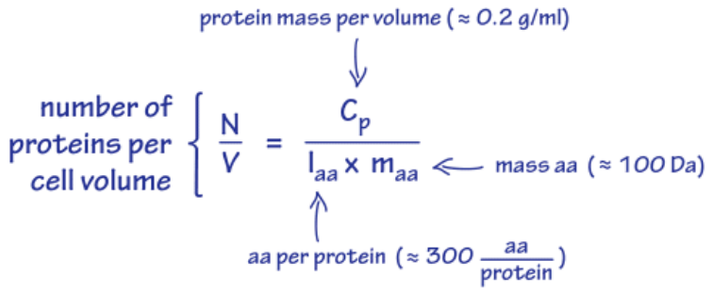
how many proteins are in a cell?

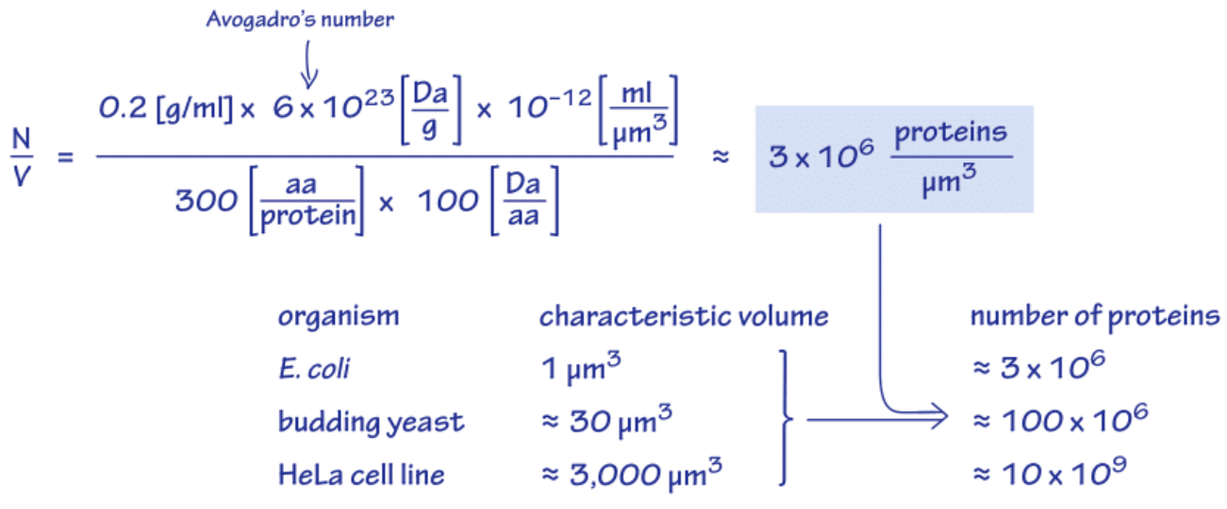
Estimate offset binding-energy: $\Delta \approx 10$ kcal/mol

Maximum number of proteins: $(2N)_{\max} \approx 2 \times 10^7$

Of similar order of magnitude.

Inference?
Protein density/volume constraints approximately match combinatorial constraints.





Cell Biology By the Numbers, Phillips and Milo

Estimation Caveats

— Proteins have a spectrum of binding energies
— Cell has 1000s of different types of proteins with different abundances
— Not all proteins form transient and non-obligate dimers
— Proteins are spatially localized within a cell

…last but not least…

— Cellular environments are not in equilibrium

Biophysical Systems: Abundance and Stability

The offset binding-energy determines maximum number of correctly interacting monomers you can have in a system.

$$(2N)_{\max} = e^{\beta\Delta}$$

What do these results tell us about biophysical systems?

Abundance and Stability

Being incredibly non-rigorous about this…

* Same caveats apply

$$\text{dimer abundance} \sim \exp(\text{offset binding-energy})$$

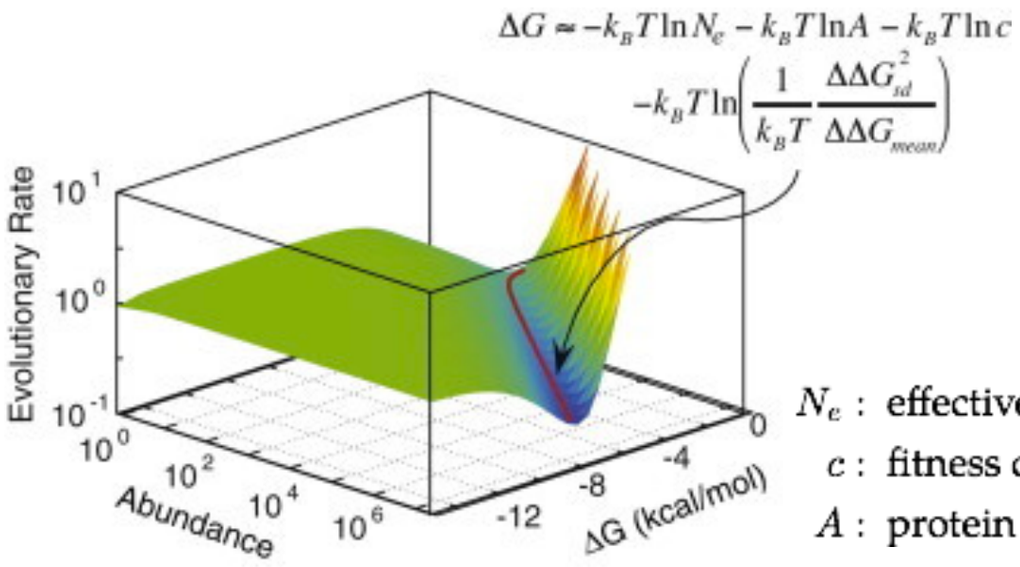
Serohijos, Rimas, and Shakhnovich, 2013

— Highly abundant **proteins** are more stable because they are more necessary to cellular function and thus **evolved so as to protect against misfolding.**

Correct and Incorrect Dimer Model

— Highly abundant **dimers** have higher offset binding energies because they need **to distinguish incorrect contacts from correct contacts.**

Experimental Tasks?
— **Dimer abundances:** Measure binding energies and abundances of dimer systems in proteins?
— **Evolution:** Consider evolutionary explanation for relationship



N_e : effective population size
c : fitness cost per misfolded protein
A : protein abundance

Biophysical Systems: Cellular Death

The offset binding-energy determines maximum number of correctly interacting monomers you can have in a system.

$$(2N)_{\max} = e^{\beta\Delta}$$

What do these results tell us about biophysical systems?

Proteins and Cellular Death

Bhattacharyya, Bershtein et. al., 2016

"…*in vitro* measurements clearly point to spurious protein-protein interactions between the over expressed DHFR and other metabolically and functionally related proteins in *E. coli* as the most probable cause of GDT."

i.e., Too many (essential) DHFRs leads to incorrect protein-protein interactions, thus leading to cell death

Essential fact reflected in the model

Correct and Incorrect Dimer Model

Over expressing a protein beyond constraints which allow for correct PPIs, leads to incorrect interactions (which may be damaging to the cell)

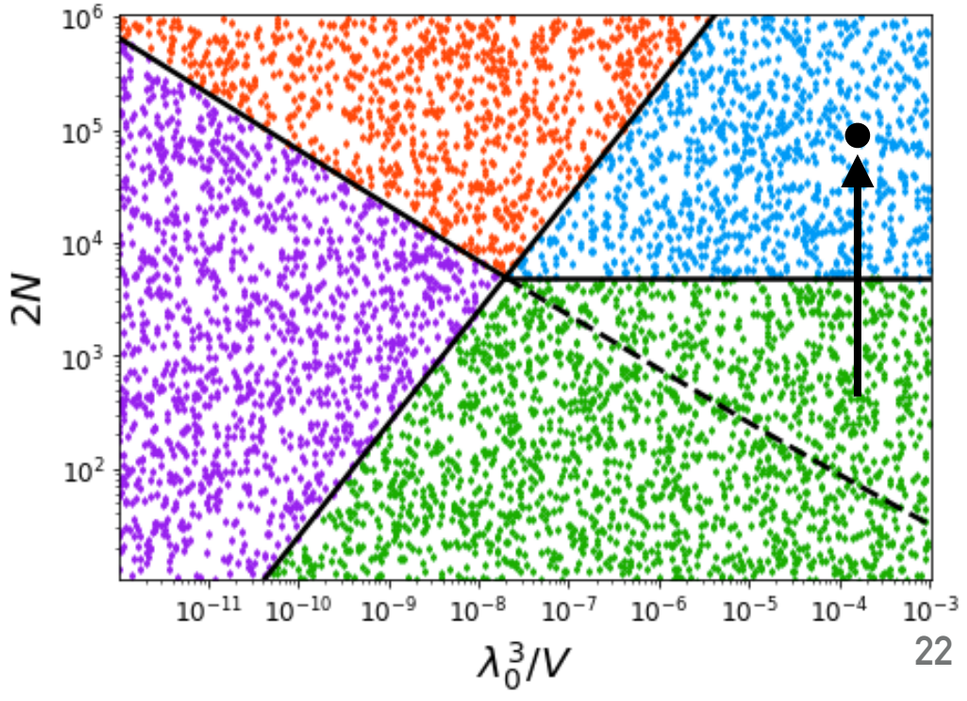
Completely dimerized and completely correct

Partially dimerized and partially correct of Type I

Completely dimerized and partially correct of Type II

Partially dimerized and partially correct of Type II

Increasing N

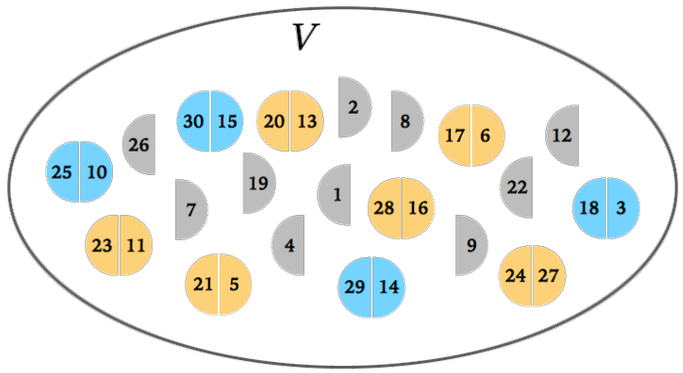


Biophysical Systems: Self Assembly

The system we've studied bears some of the features of self-assembly

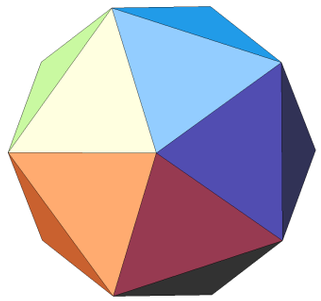
<u>Model of Correct and Incorrect Dimers</u>

System of many **monomers** coming together in **correct dimers/contacts**



<u>Self-Assembly</u>

System of **many** different subunits coming together in **correct contacts** to form some larger structure.



Icosahedron "virus capsid" from <u>math.wikia.com</u>

The similarity suggests some questions we can ask about Self-Assembly systems:

– **Subunits Limit:** Is the number of subunits (and hence the size of the object) constrained by the energies of the contacts?

– **Energy-Scales of Self-Assembly:** Is there an energy scale at which the structure disassembles different from the energy scale at which incorrect contacts dominate?

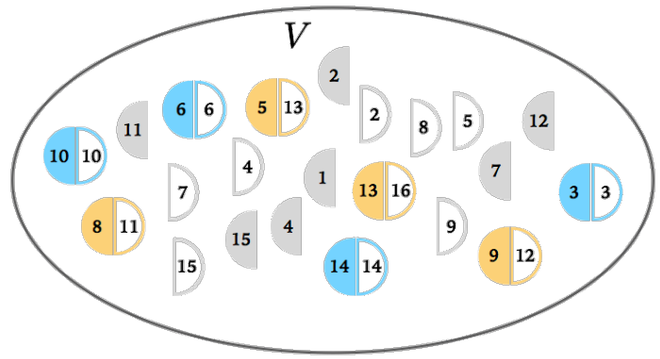
– **Phases of Self-Assembly:** How can we quantitatively categorize the various stages toward self-assembly in phases?

What's Next?

Future Possible Theoretical Work:

1. **Non-Ideal Gas:** We assumed that the subunits did not have volume and did not interact with one another. What results would we get for more realistic assumptions?

$$\left(\frac{V}{\lambda_0^3}\right)^N \rightarrow \frac{(V-Nb)^N}{\lambda_0^{3N}} e^{-N\beta\phi}$$

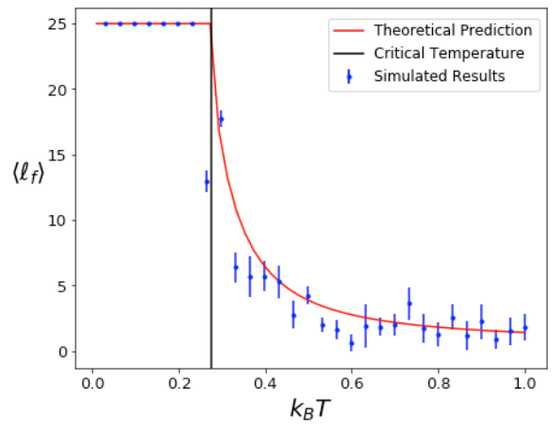


2. **Gendered/Typed Model:** What if subunits came in two-types, and dimers were formed by one of each kind?

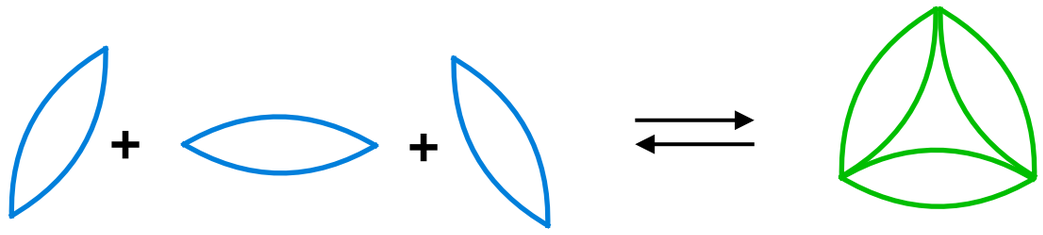
3. **Complexes:** Can we consider models where more than two subunits bind together?

1 2 3

4. **Simulations:** This system should be simple to simulate. Can we compare the results with those of a simulations?



6. **Analytical Model of Self-Assembly:** Using this system as a motivation can we develop a soluble analytical model of self-assembly?



Ending Remarks

END

Physicists make terrible parents.

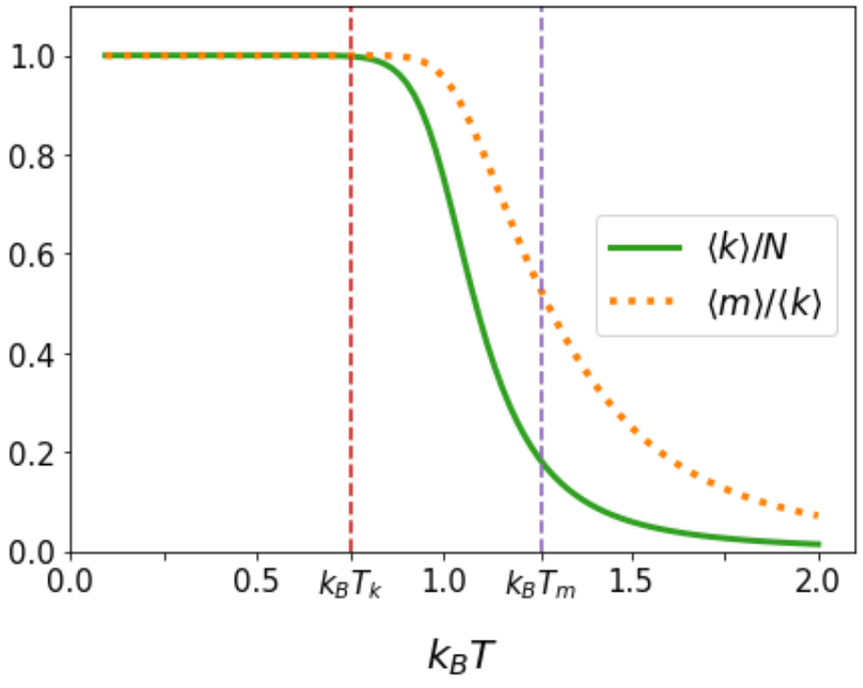
SMBC, 2013-11-26

Supplementary Slides

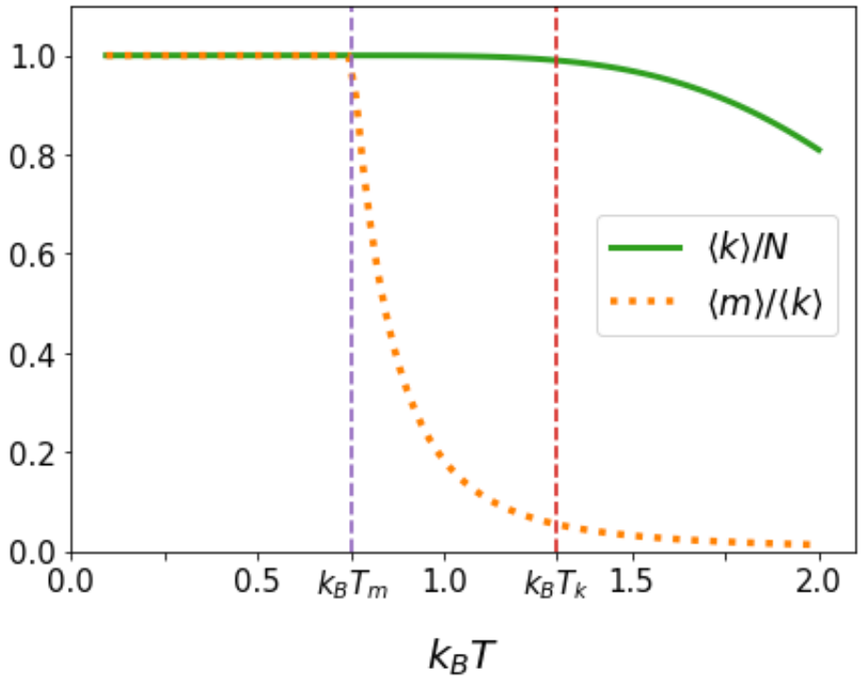
Supplementary Figures

Type-I and Type-II dimer systems, with the number of correct dimers <m> normalized by the total number of dimers <k>.

(Type-I dimer system)



(Type-II dimer system)

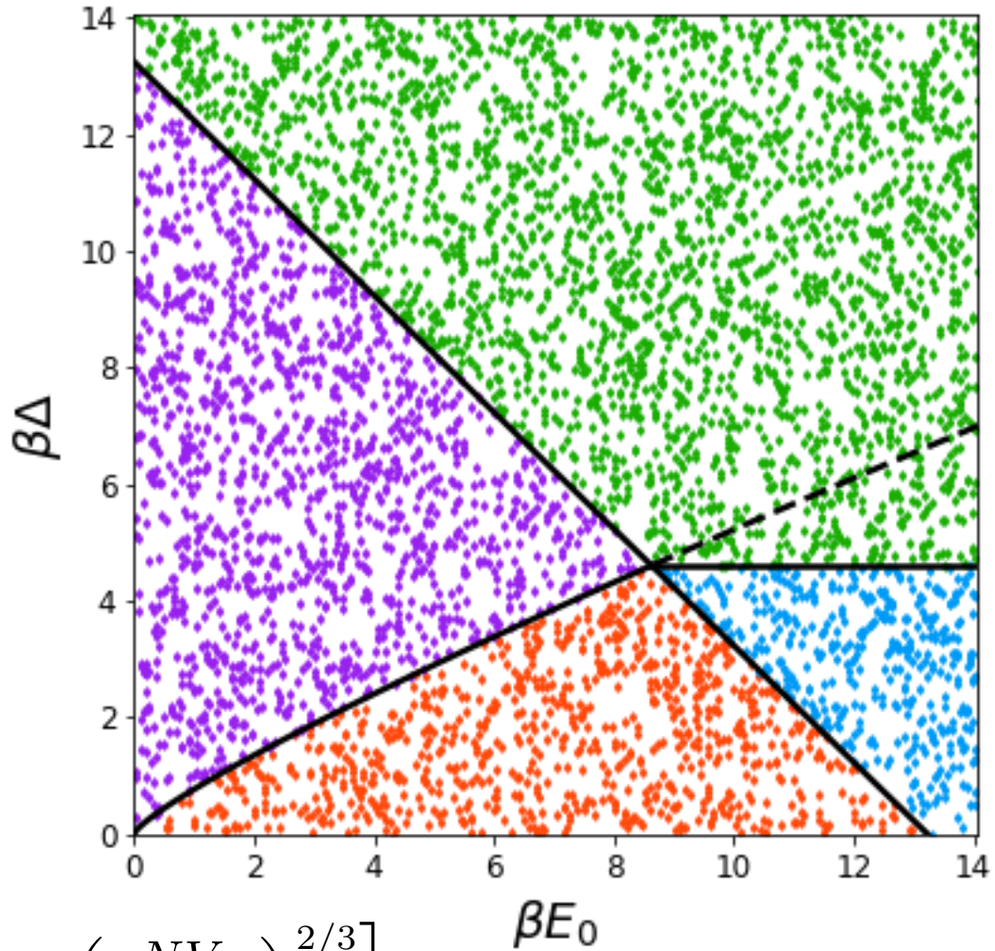


Supplementary Figures

Explicit Phase Boundary Conditions for

Energy—Offset Energy Space

$$\beta\Delta = -\beta E_0 + \frac{3}{2}\ln\left[\left(\frac{NV}{2\lambda_0^3\sqrt{2}}\right)^{2/3}\right]$$



$$\beta\Delta = \ln(2N)$$

$$\beta E_0 + \beta\Delta = \frac{3\beta\Delta}{2\ln(2N)}\ln\left[\frac{\beta\Delta}{\ln(2N)}\left(\frac{NV}{2\lambda_0^3\sqrt{2}}\right)^{2/3}\right]$$

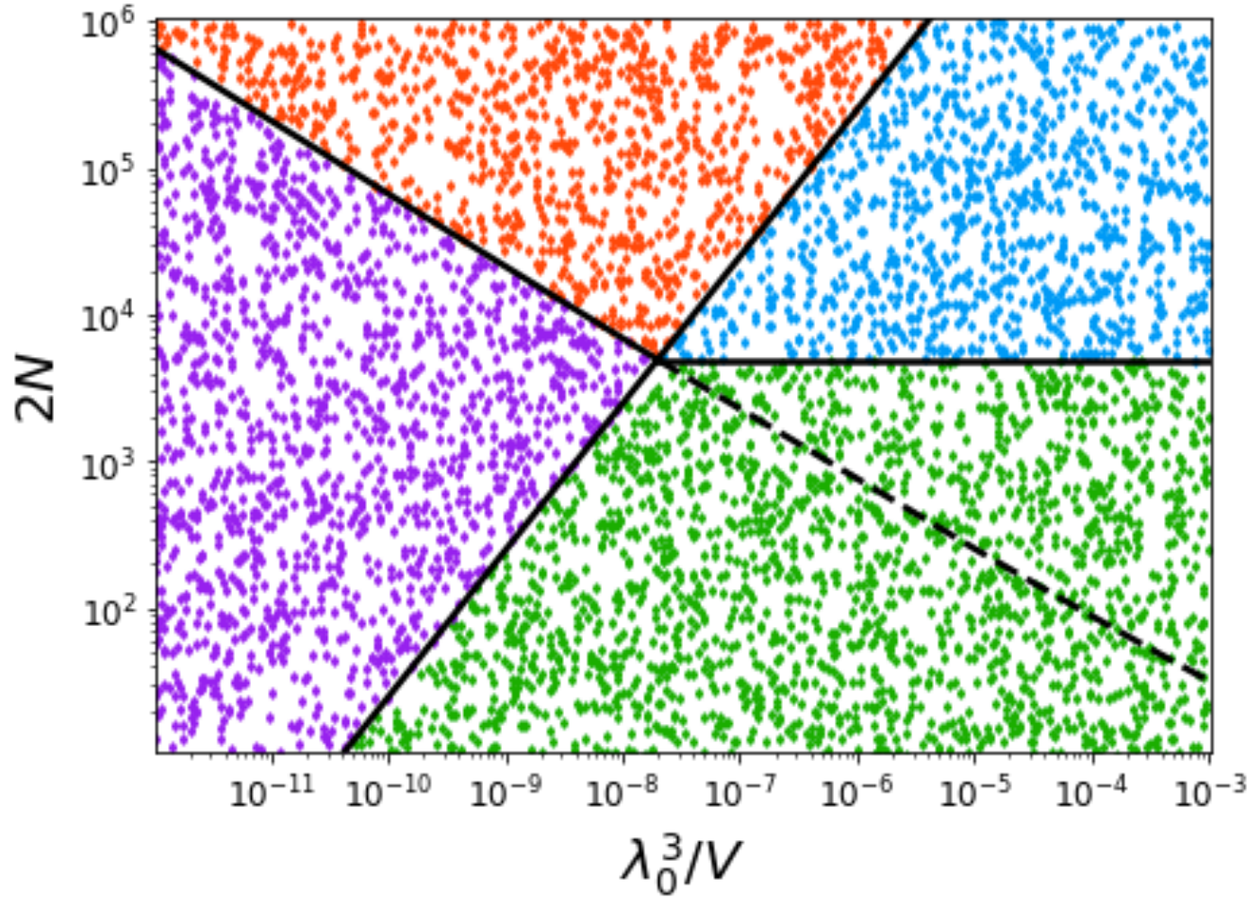
Supplementary Figures

Explicit Phase Boundary Conditions for

Number—Phase Density Space

$$2N = \frac{4\sqrt{2}\lambda_0^3}{V} e^{\beta(\Delta + E_0)}$$

$$2N = \exp\left[3W_0\left(\frac{9}{4}\frac{\beta\Delta e^{-(E_0/\Delta+1)}}{(4\lambda_0^3\sqrt{2}/V)^{2/3}}\right)\right]$$



$$2N = e^{\beta\Delta}$$