Multiscale modeling of crystalline dynamics and the corresponding diffuse X-ray scatter from biological molecules

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Lawrence Berkeley National Laboratory

Molecular Context

Crystal as metaphor

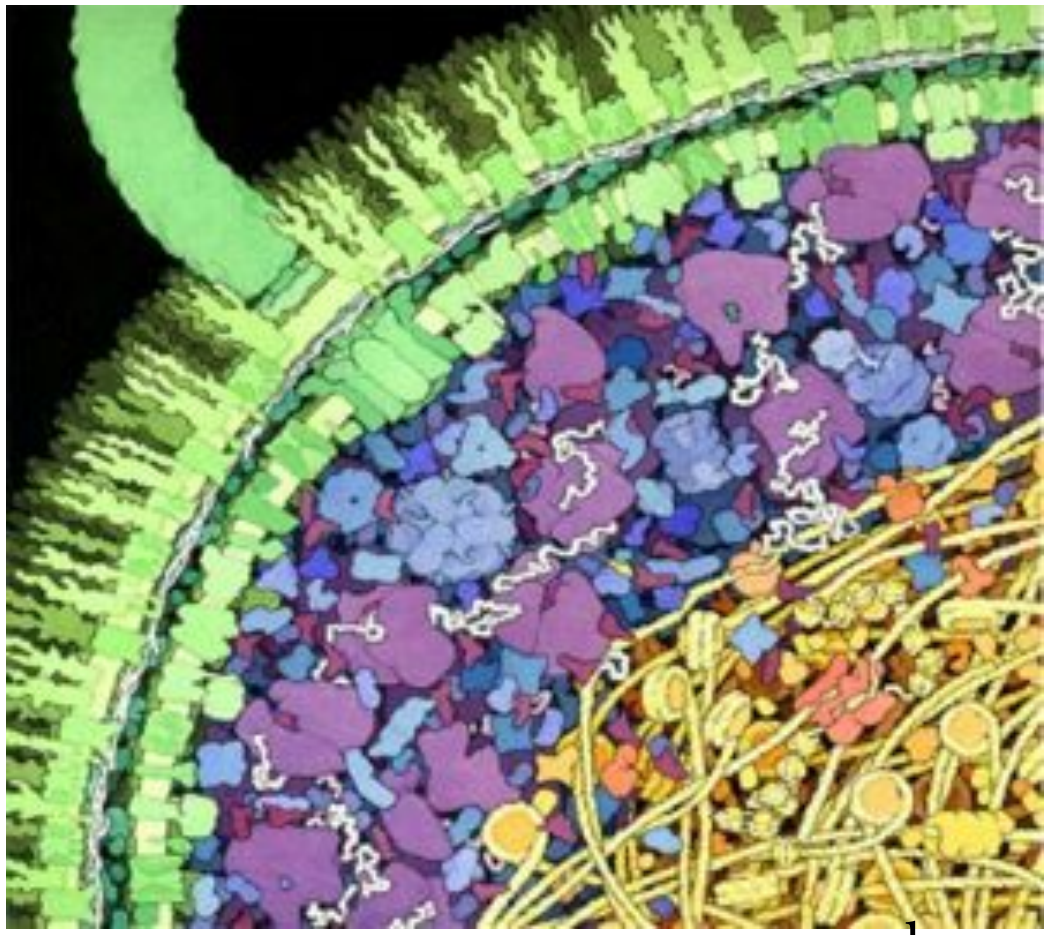
Phillips, Fillers, and Cohen, BiophysJ (1980)

30-70% water

Similar to cytoplasm

Record Jr., M. T. et. al. TiBS (1998)

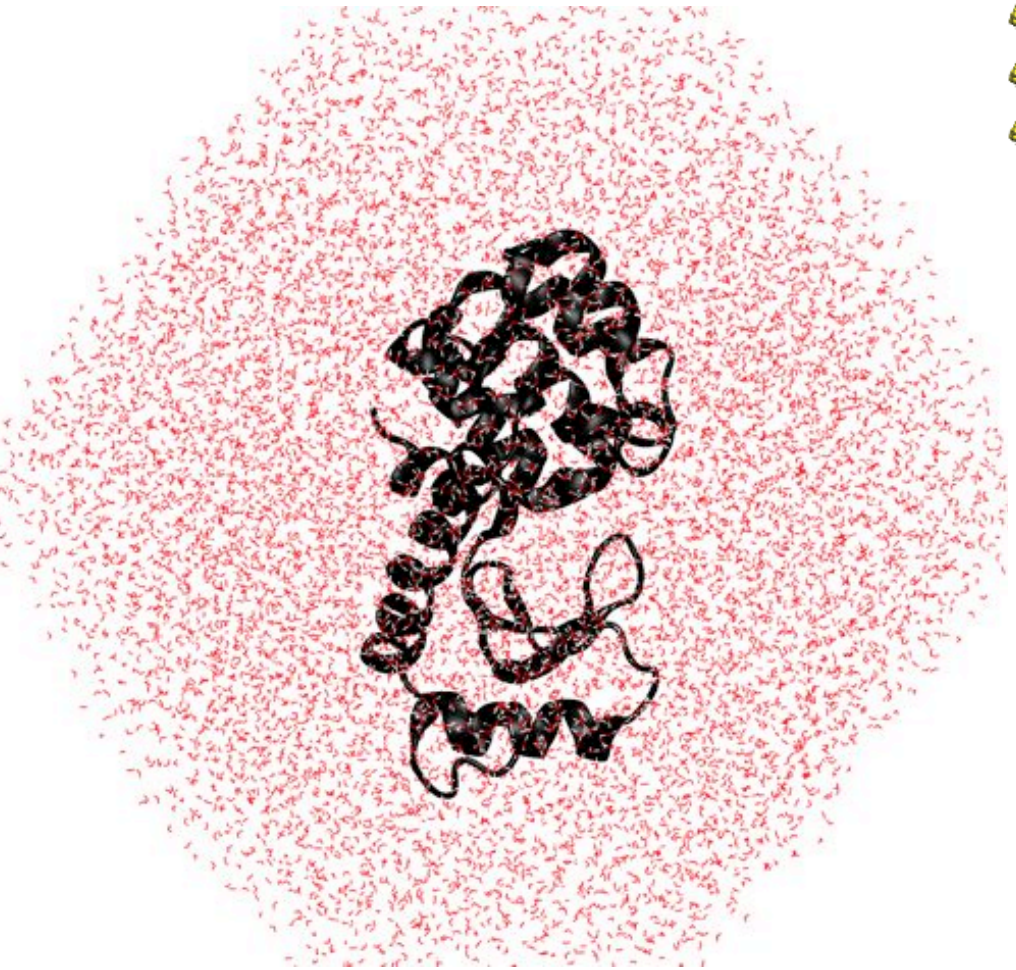
Structure/Dynamics/Function



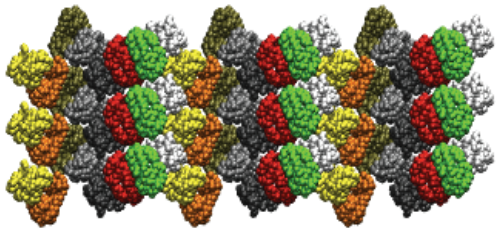
anl.gov

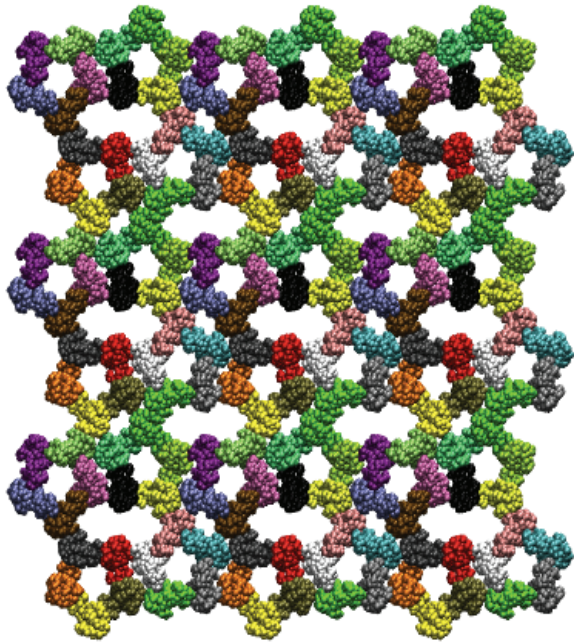
"The difference is comparable to skipping through an open field or being crammed into a crowded elevator" -Lee Makowski

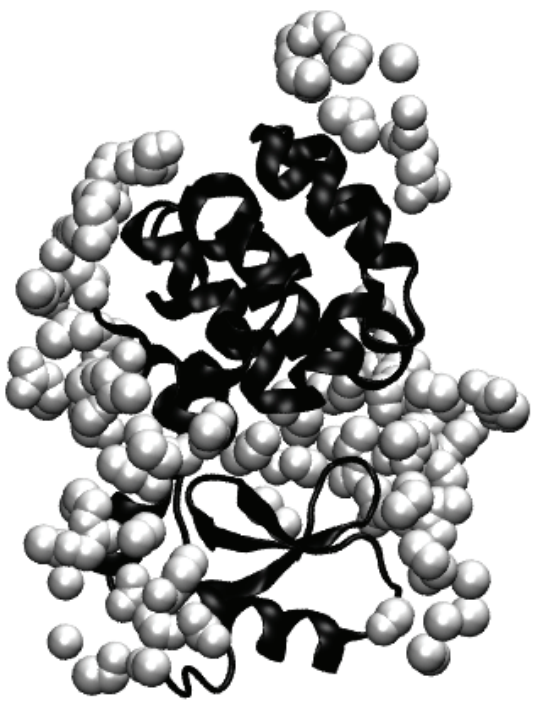
Molecular Context

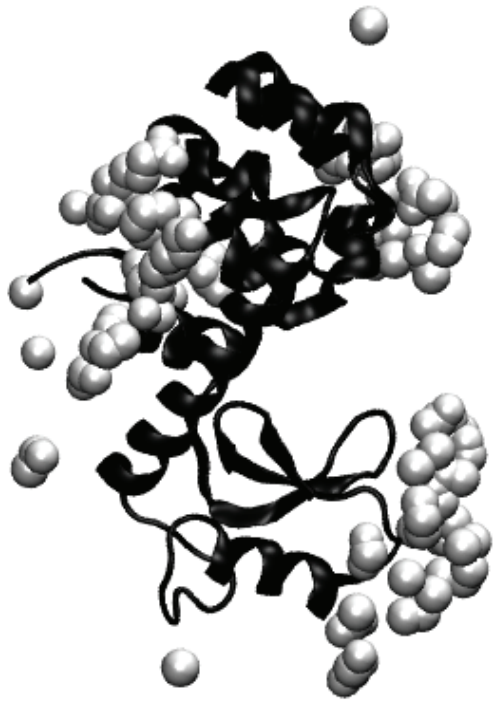


T4 Lysozyme









Zhang, Wozniak, and Matthews JMB (1995)

Elastic Network Model

Typical representation of potential energy

$$V = V_{bonds} + V_{angles} + V_{dihedrals} + V_{nonbond}$$

Just use simple springs between interacting atoms!

$$V_{sprng}(\mathbf{r}_a, \mathbf{r}_b) = \frac{C}{2}(|\mathbf{r_a} - \mathbf{r_b}| - |\mathbf{r_a^0} - \mathbf{r_b^0}|)^2 \quad \text{if } |\mathbf{r_a^0} - \mathbf{r_b^0}| \leq R_{cut}$$

$$V = \sum_{a,b} V_{sprng}(\mathbf{r}_a, \mathbf{r}_b)$$

Harmonic approximation: in terms of Hessian Matrix

$$V(\mathbf{r}) = \frac{1}{2}\mathbf{r}^T \mathbf{\Phi} \mathbf{r}$$

MM Tirion, PRL (**1996**)

ENM variations

Isolated Lysozyme

Cutoff: 8Å

Cutoff: 16Å

Most common:

$$k(R) = \begin{cases} R^{-c} & \text{if } R \leq R_{cut} \\ 0 & \text{if } R > R_{cut} \end{cases}$$

-The network
- -coarse-graining
- -more or less “chemistry”

-The force constant
- -relative interaction strength
- -can be more detailed

Surprising efficacy: low frequency modes dominate

No energy minimization

Normal Mode Analysis

Go, Noguti, and Nishikawa, PNAS (1983)
Brooks and Karplus, PNAS (1983)
Levitt, Sander, and Stern, JMB (1985)

Eigen values and vectors

$$L^T \Phi L = \Lambda$$

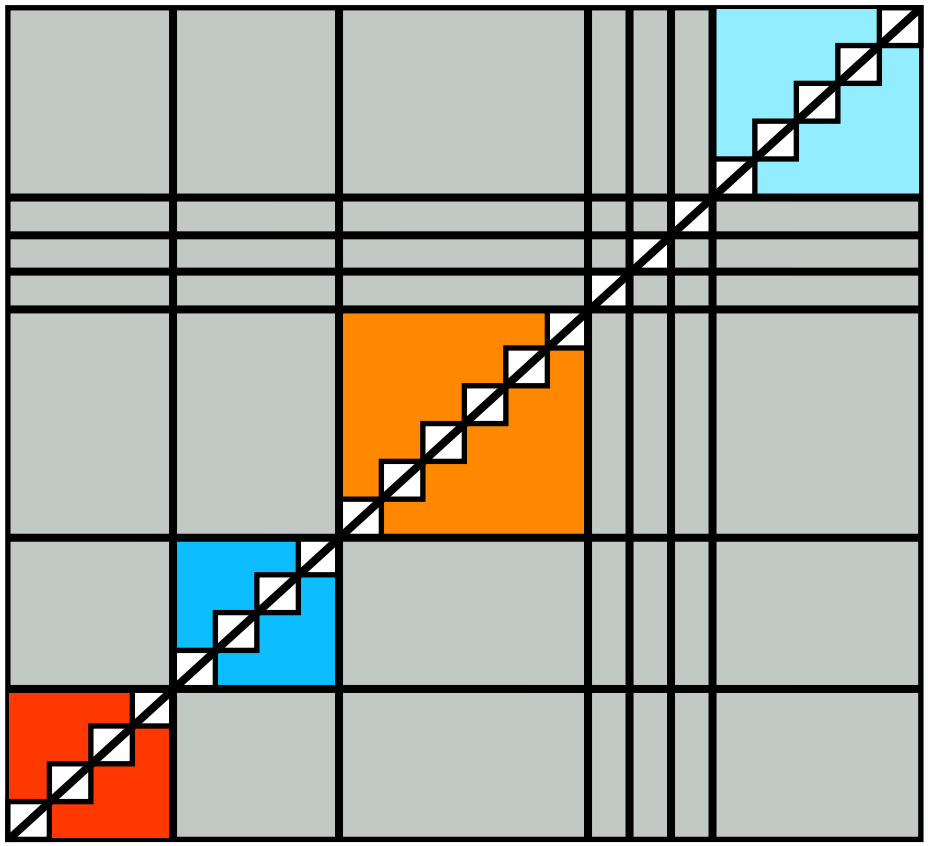
Variance-covariance matrix!

$$\langle \mathbf{u}\mathbf{u}^T \rangle = k_B T \times \mathbf{L}\mathbf{\Lambda}^{-1}\mathbf{L}^T$$

Ichiye and Karplus, Proteins (1991)

But try and do this on the entire crystal...

Some useful information from ENM NMA



Variance-covariance matrix

Temperature Factors

$$\langle \mathbf{u}_i \mathbf{u}_i^T \rangle = \begin{pmatrix} \langle \delta x_i \delta x_i \rangle & \langle \delta x_i \delta y_i \rangle & \langle \delta x_i \delta z_i \rangle \\ \langle \delta y_i \delta x_i \rangle & \langle \delta y_i \delta y_i \rangle & \langle \delta y_i \delta z_i \rangle \\ \langle \delta z_i \delta x_i \rangle & \langle \delta z_i \delta y_i \rangle & \langle \delta z_i \delta z_i \rangle \end{pmatrix}$$

Atom-Atom correlations

$$\Phi_{ij} = \sqrt{u_i^2 u_j^2} \frac{\langle \delta r_i \delta r_j \rangle}{\sqrt{\langle \delta r_i^2 \rangle \langle \delta r_j^2 \rangle}}$$

CDOS

$$G(\omega_f) = \sum_i^f g(\omega_i)$$

"Liquid like" correlations

Caspar, Clarage, Salunke, and Clarage Nature (1988)

$$C(r) = C_0(1 - \lambda_0)e^{-\frac{r}{\lambda}} + \lambda_0$$

Meinhold and Smith Proteins (2007)

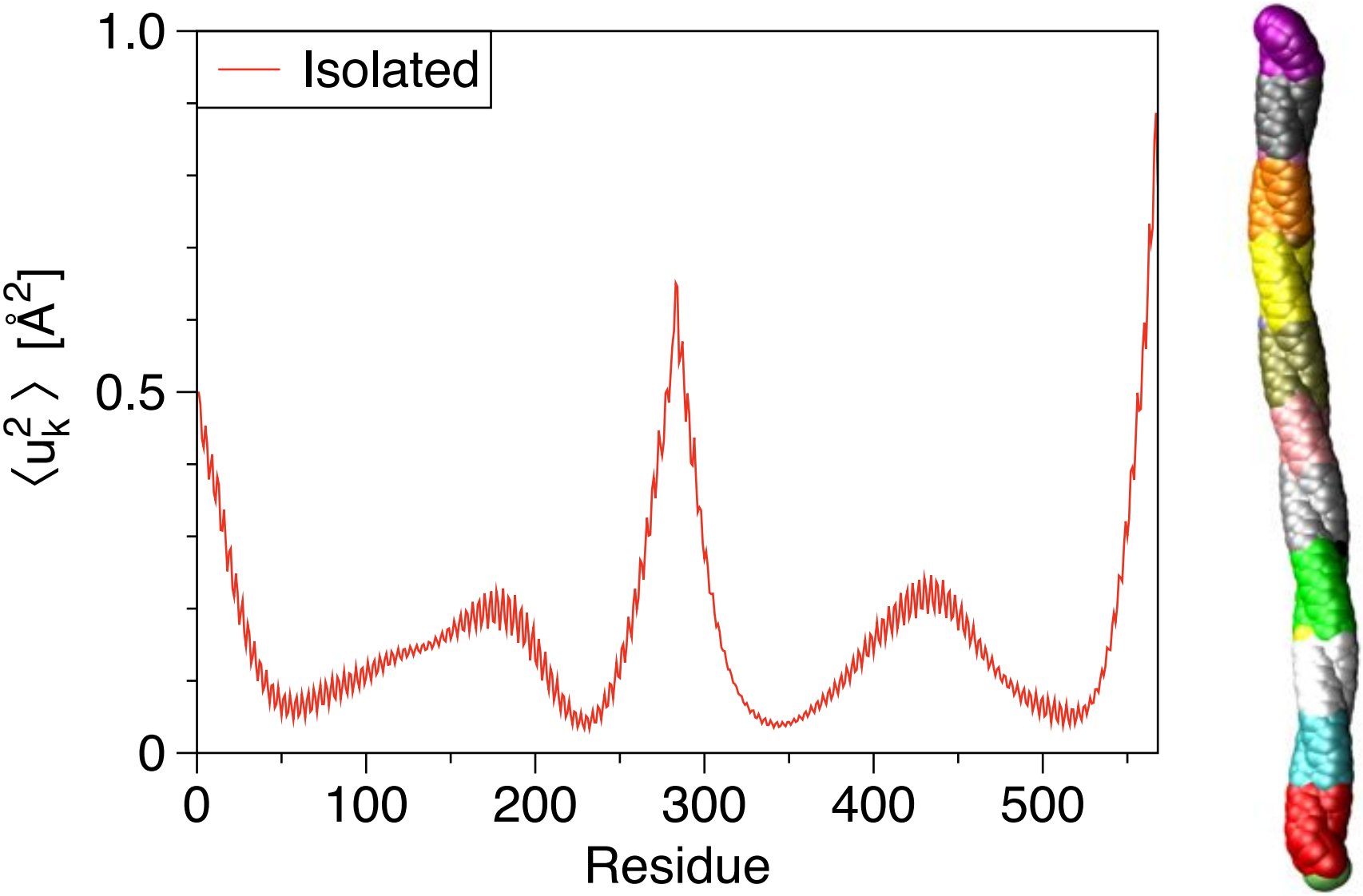
Diffuse X-ray scattering

Example: Tropomyosin

PDBID: 2TMA

Phillips, JMB (1986)

Isotropic Temperature Factor

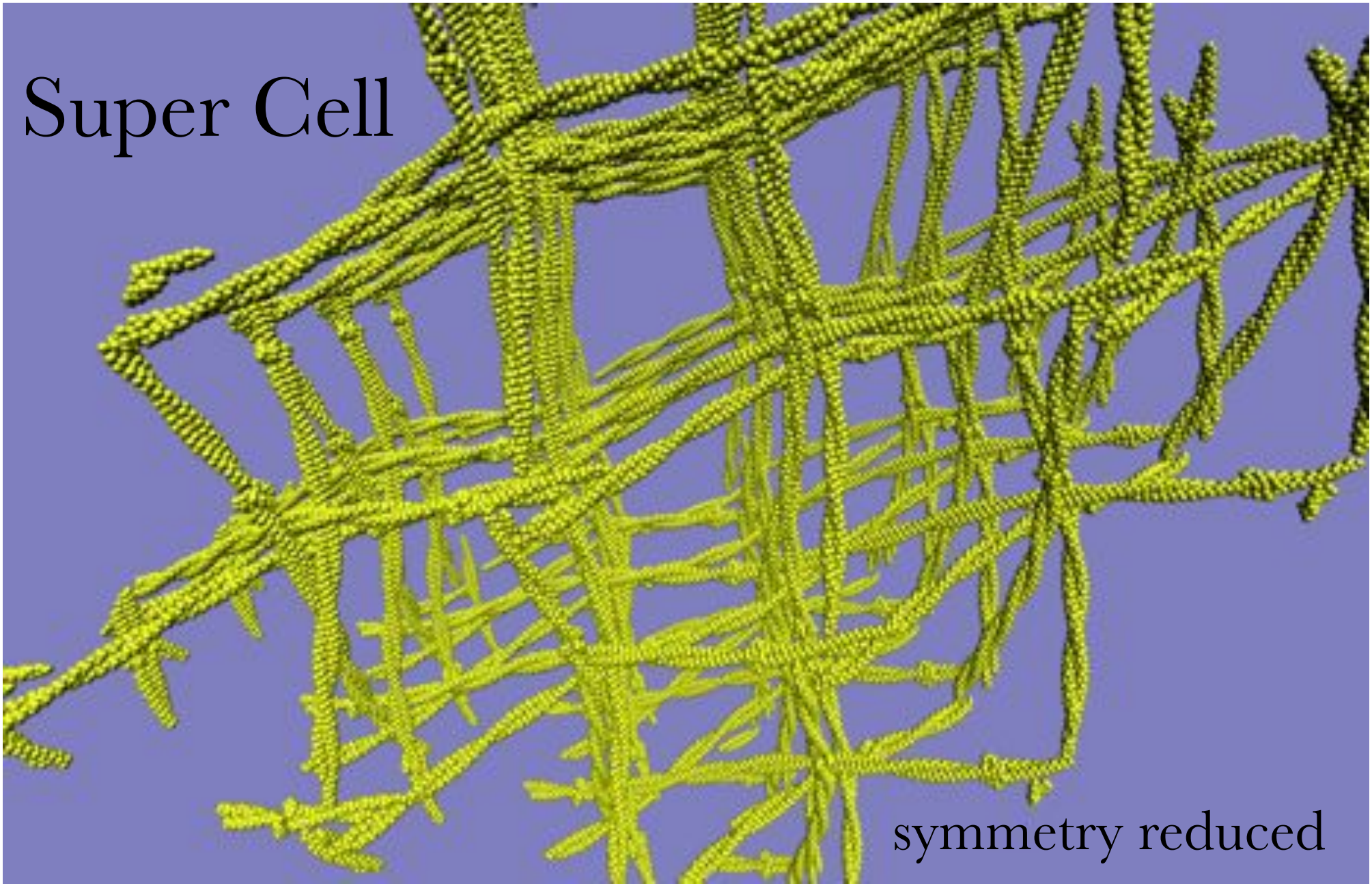


Tropomyosin

P1 Unit Cell

symmetry reduced

Tropomyosin



Crystalline Context: BVK boundary conditions

Construct the dynamic matrix from Hessian

$$\mathbf{D}(kk', \mathbf{q}) = \sum_{l'} \mathbf{\Phi}\binom{kk'}{0l'} e^{i\mathbf{q}\cdot(\mathbf{R}(k'l') - \mathbf{R}(k0))}$$

"Thermal vibrations in Crystallography",Willis and Pryor (1975)

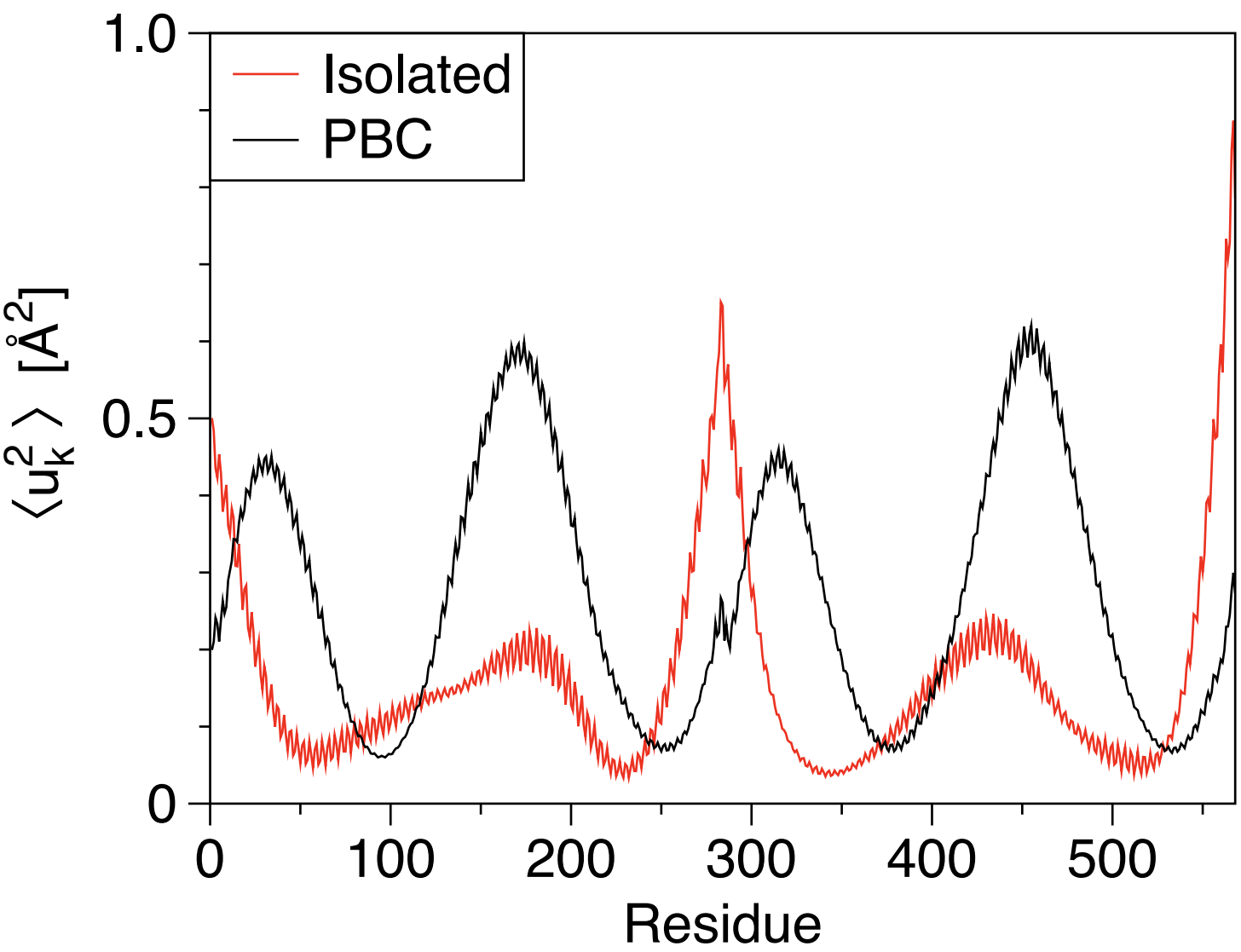
Dimensions: 3nN to 3n

$$\mathbf{L}(\mathbf{q})^T \mathbf{D}(\mathbf{q}) \mathbf{L}(\mathbf{q}) = \Lambda(\mathbf{q})$$

Sample wavevectors to construct variance-covariance matrix

$$\langle \mathbf{u}\mathbf{u}^T \rangle = k_B T \times \langle \mathbf{L}(\mathbf{q}) \mathbf{\Lambda}^{-1} \mathbf{L}(\mathbf{q})^\dagger \rangle_{\mathbf{q}}$$

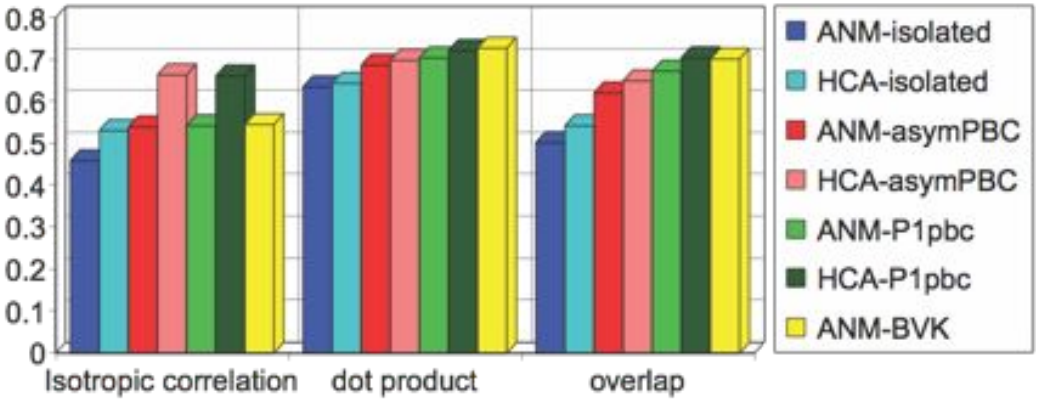
Isotropic Temperature Factor

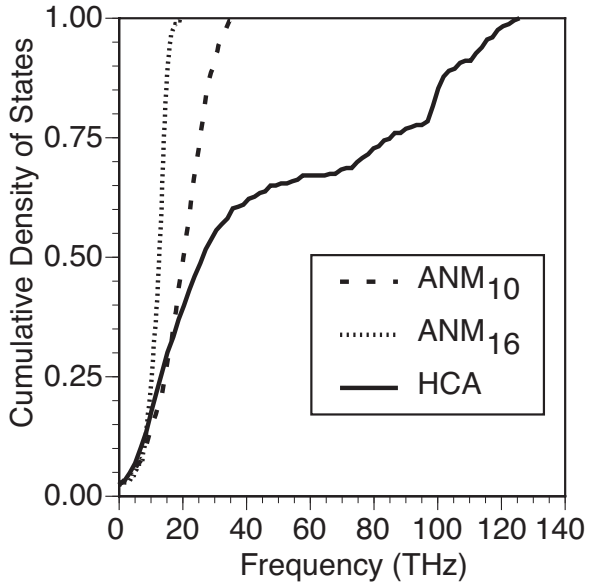


PBC: $q = 0$

Variances and DOS

83 high resolution structures





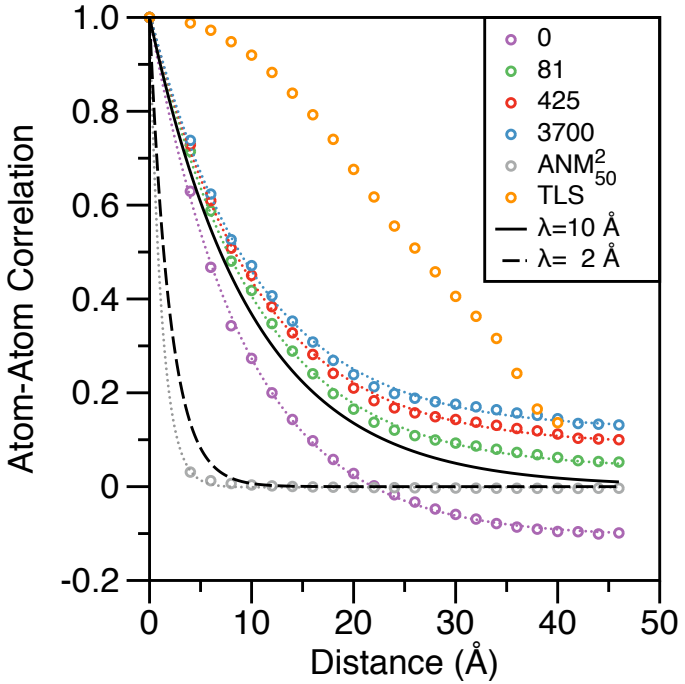
Riccardi, Cui, Phillips, Biophys J (2009)

-Some popular ENMs that are unphysical.

-Relative interaction strength! →Simplest: $1/R^6$

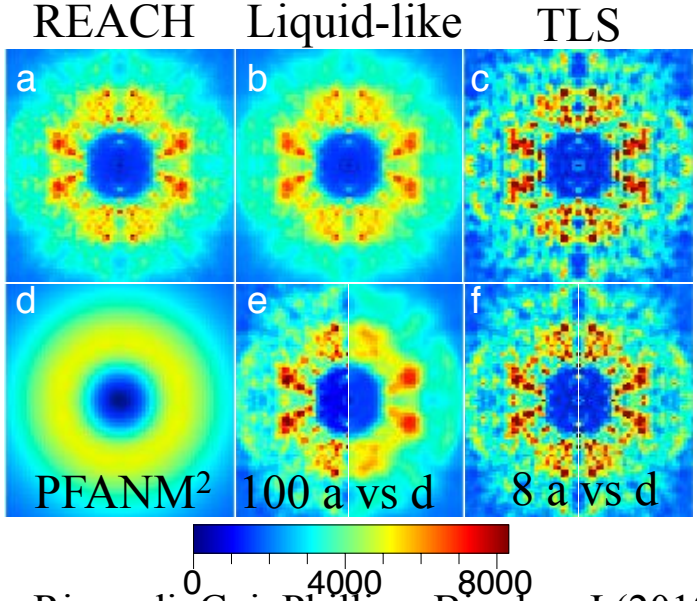
-Crystal context for crystalline observables

Covariances and correlations



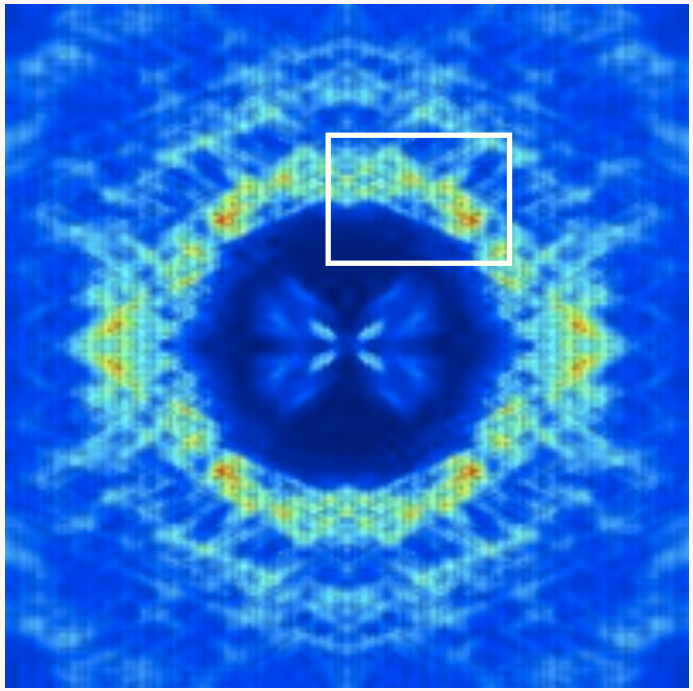
Staph Nuclease

Wall, Ealick, Gruner, PNAS (1997)



Riccardi, Cui, Phillips, Biophys J (2010)

Crystallographers Tricks



Subtract the background:

$$I_{Bragg} = I_{Total} - I_{Diffuse}$$

Multiscale modeling of Diffuse X-ray scattering

$$I_D = I_T - I_B$$

From the entire crystal:

$$I_D = \sum_{kl}\sum_{k'l'} f_k(\mathbf{Q}) e^{-\frac{1}{2}\mathbf{Q}^T\langle \mathbf{u}_{kl}\mathbf{u}_{kl}^T\rangle \mathbf{Q}} f_{k'}(\mathbf{Q}) e^{-\frac{1}{2}\mathbf{Q}^T\langle \mathbf{u}_{k'l'}\mathbf{u}_{k'l'}^T\rangle \mathbf{Q}} e^{i\mathbf{Q}\cdot(\mathbf{r}_{kl}-\mathbf{r}_{k'l'})} \times (e^{\mathbf{Q}^T\langle \mathbf{u}_{kl}\mathbf{u}_{k'l'}^T\rangle \mathbf{Q}} - 1)$$

Equations simplified in the following:

$$I_D = \sum_{kl}\sum_{k'l'} B_{lk,l'k'}(\mathbf{Q})(e^{\mathbf{Q}^T\langle \mathbf{u}_{kl}\mathbf{u}_{k'l'}^T\rangle \mathbf{Q}} - 1)$$

Independent unit cells

Atoms not correlated if in different unit cells

$$\langle \mathbf{u}_k \mathbf{u}_{k'} \rangle = \langle \mathbf{u}_{k,l} \mathbf{u}^T_{k',l'} \rangle \times \delta_{l,l'}$$

Correlations within unit cell

$$I_D(\mathbf{Q}) = N \sum_k \sum_{k'} B_{k,k'}(\mathbf{Q}) (e^{\mathbf{Q}^T \langle \mathbf{u}_k \mathbf{u}^T_{k'} \rangle \mathbf{Q}} - 1)$$

Independent Blocks of Atoms

Atoms not correlated if in different blocks

$$\langle \mathbf{u}_k \mathbf{u}_{k'} \rangle = \langle \mathbf{u}_{k,m} \mathbf{u}^T_{k',m'} \rangle \times \delta_{m,m'}$$

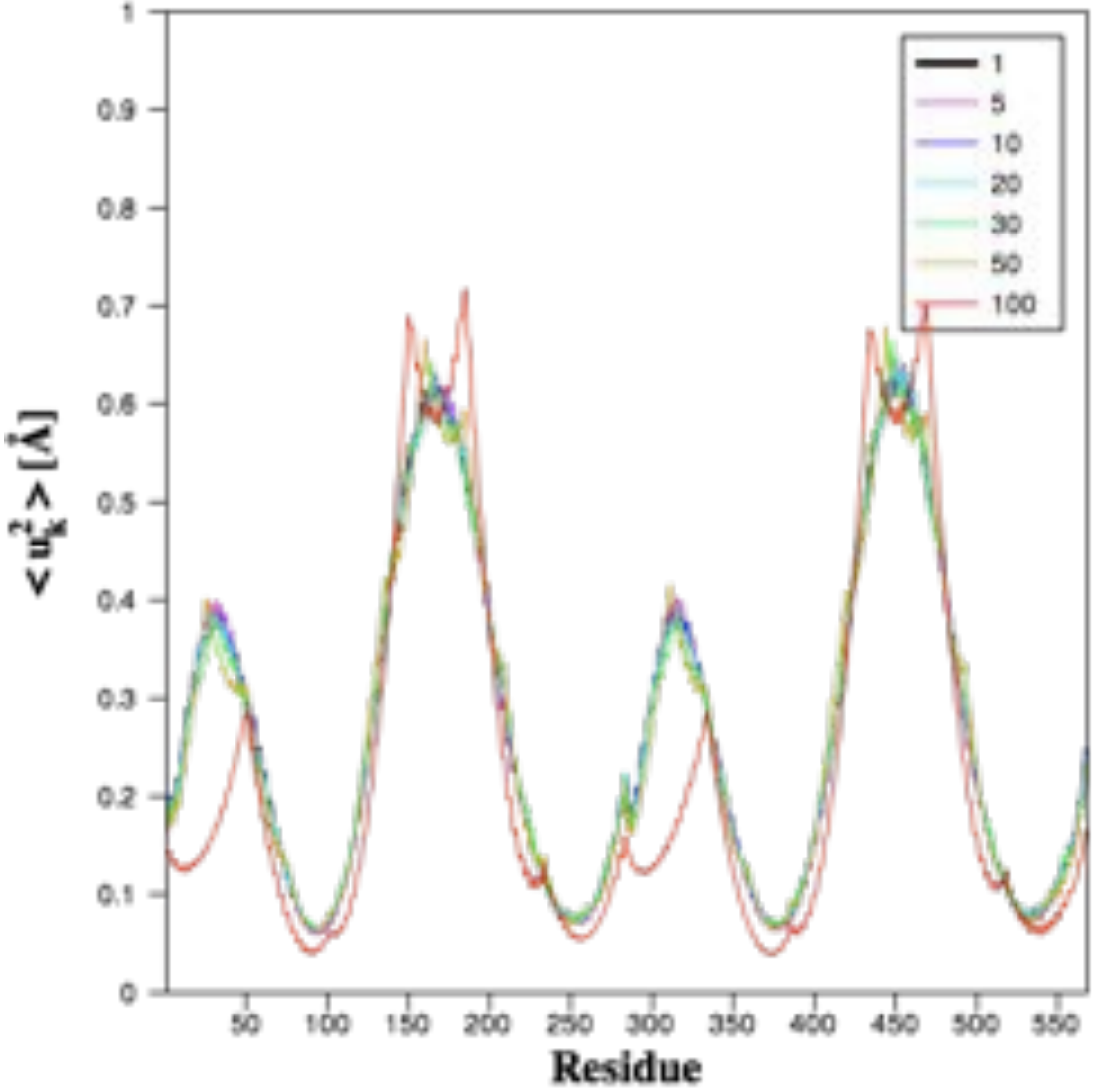
Correlations within blocks

$$I_{D,blocks}(\mathbf{Q}) = N \sum_{m}^{blocks} \sum_{k,k' \in m} B_{k,k'}(\mathbf{Q})(e^{\mathbf{Q}^T \langle \mathbf{u}_k \mathbf{u}^T_{k'} \rangle \mathbf{Q}} - 1)$$

E.g. One atom per block$\left(\times \delta_{k,k'}\right)$

$$I_{D,atoms}(\mathbf{Q}) = N \sum_{k} f_k^2(\mathbf{Q})(1 - e^{-\mathbf{Q}^T \langle \mathbf{u}_k \mathbf{u}^T_k \rangle \mathbf{Q}})$$

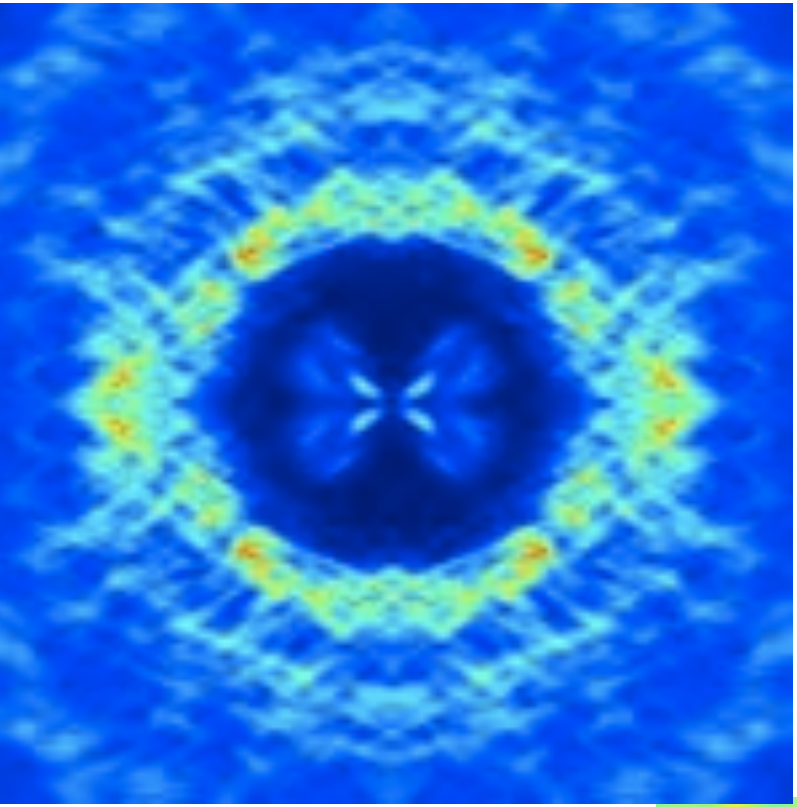
Example: Block NMA of Tropomyosin



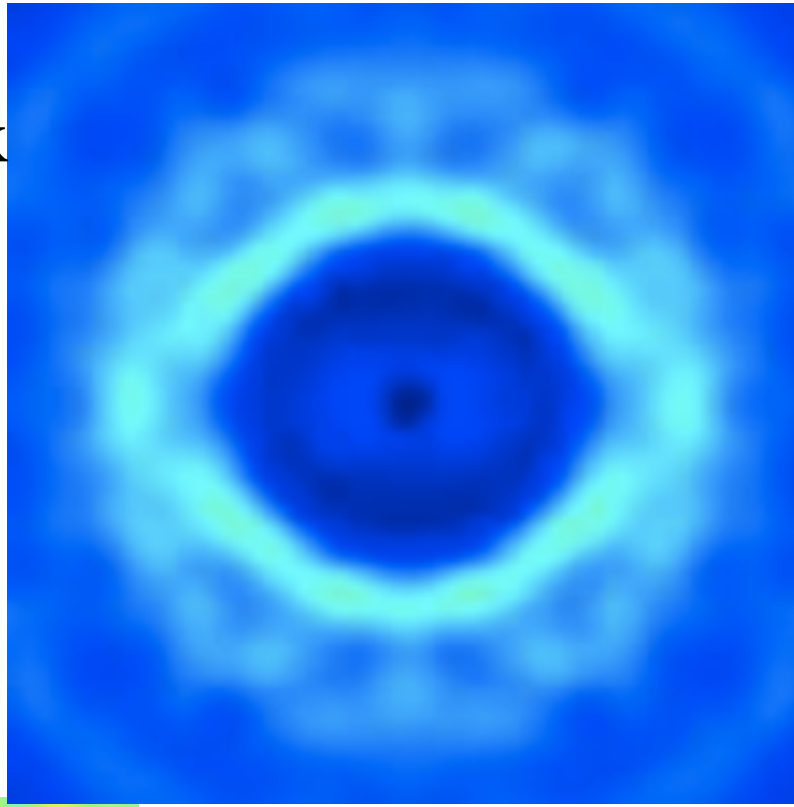
PBC: $q = 0$

Project Hessian into space of rigid block TransRots

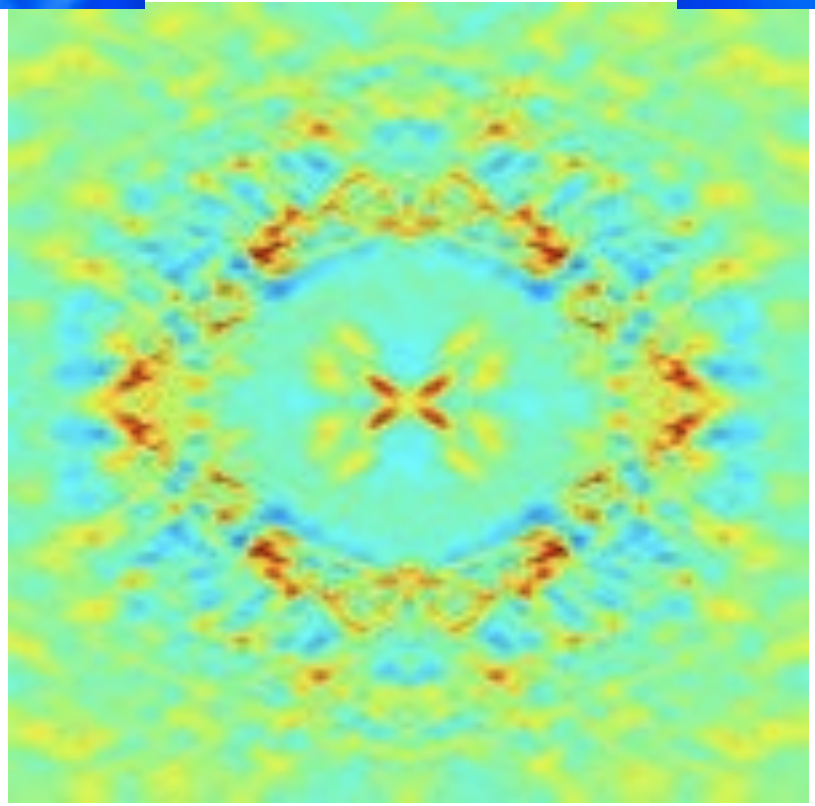
Tama, Gadea, Marques, Sanejouand, Proteins (2000)
Li and Cui Biophys J (2002)



10 atoms/block

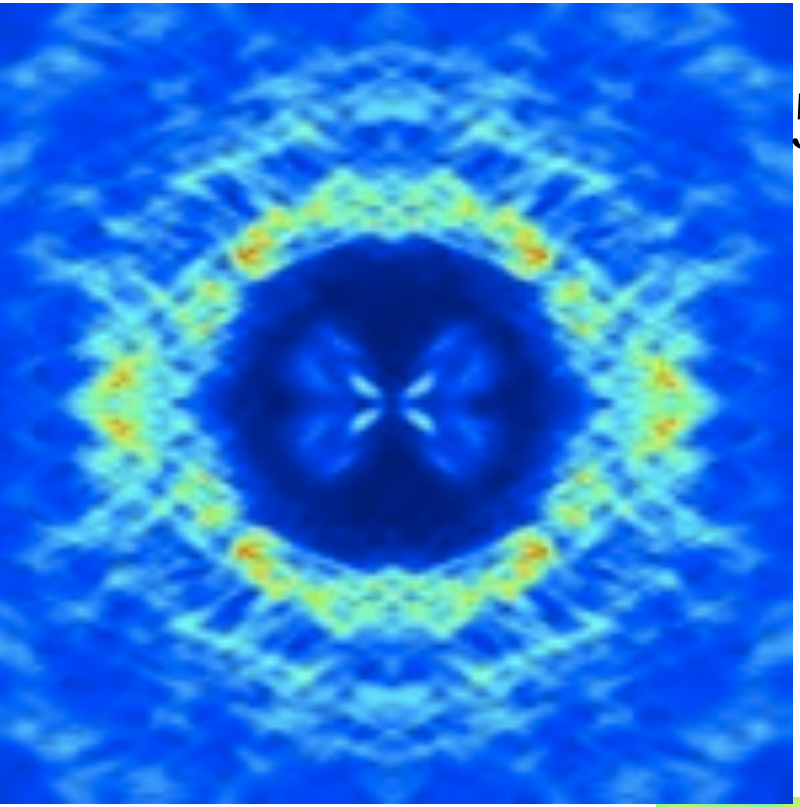


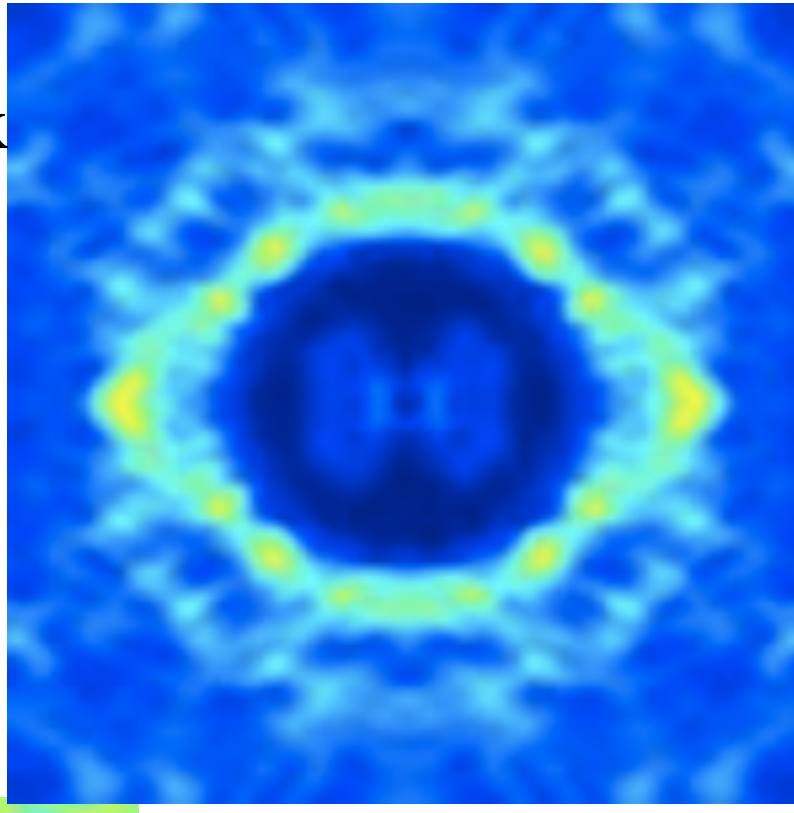
To all atom
$R_I \times 100 = 0.1\%$



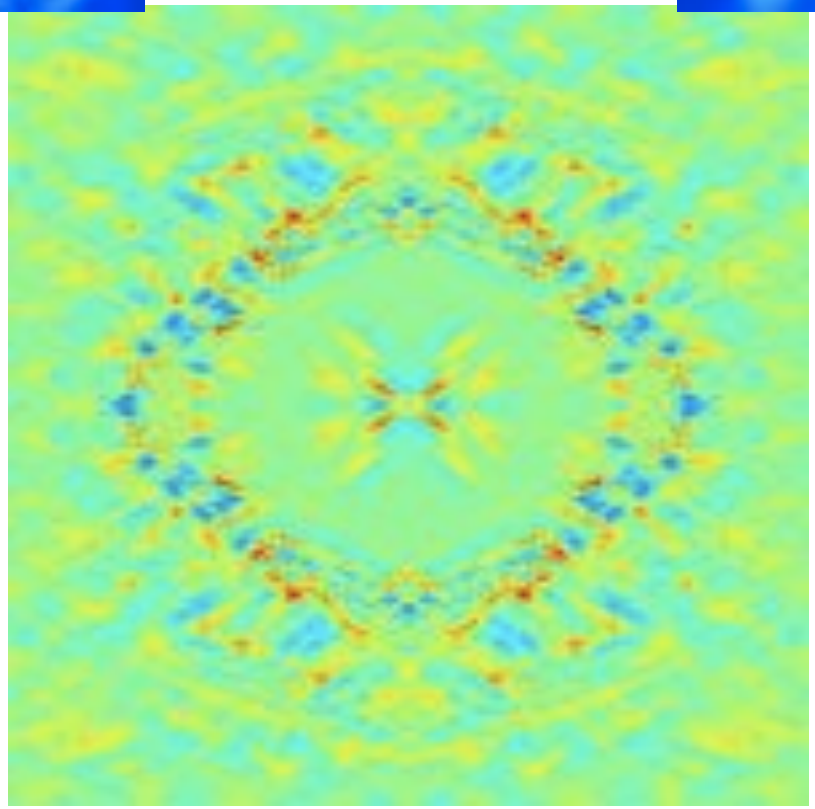
To all atom
$R_I \times 100 = 24.6\%$

50 atoms/block



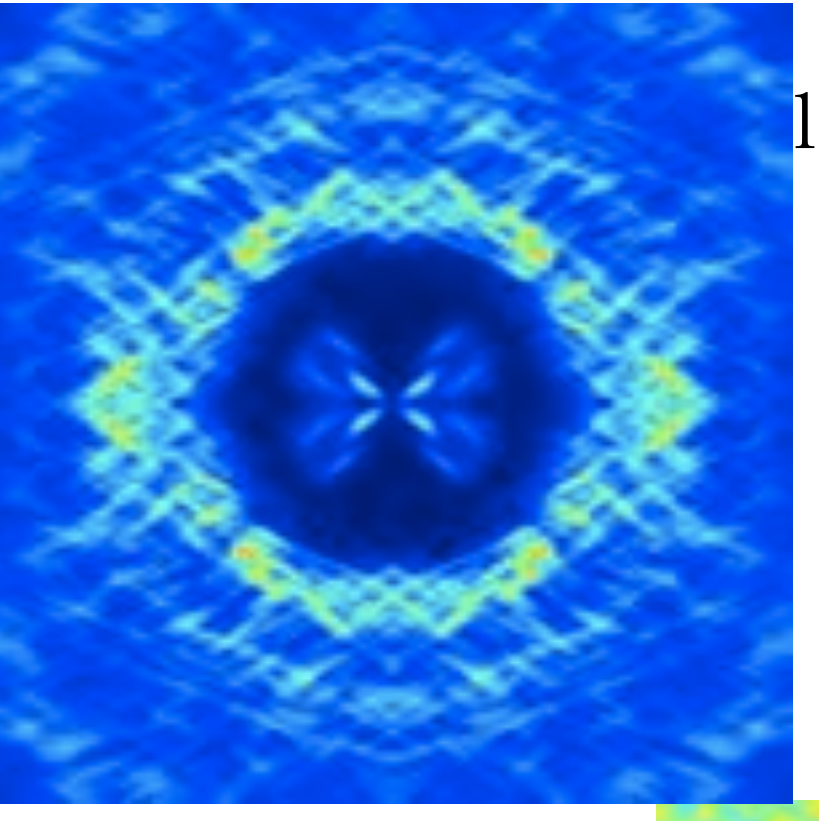


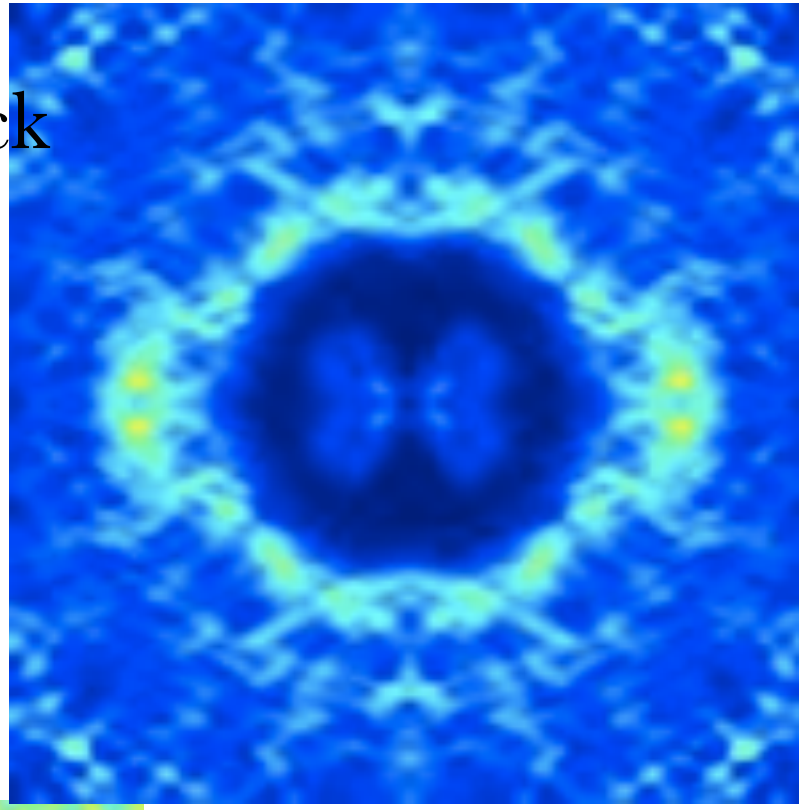
To all atom
$R_I \times 100 = 2.5\%$



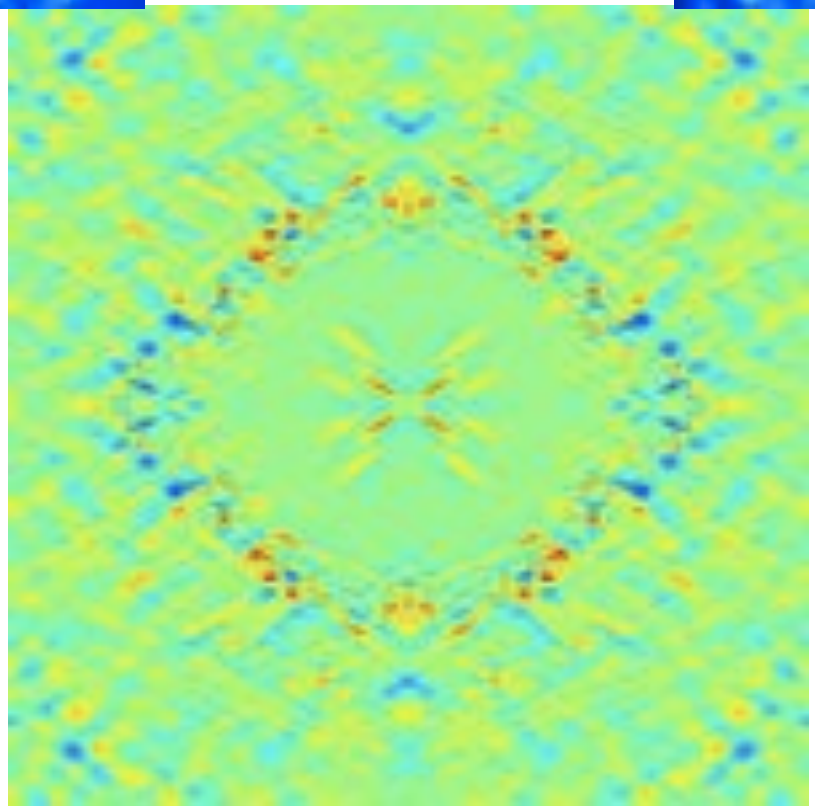
To all atom
$R_I \times 100 = 19.3\%$

100 atoms/block





To all atom
$R_I \times 100 = 8.5\%$



To all atom
$R_I \times 100 = 20.0\%$

Correlations between blocks

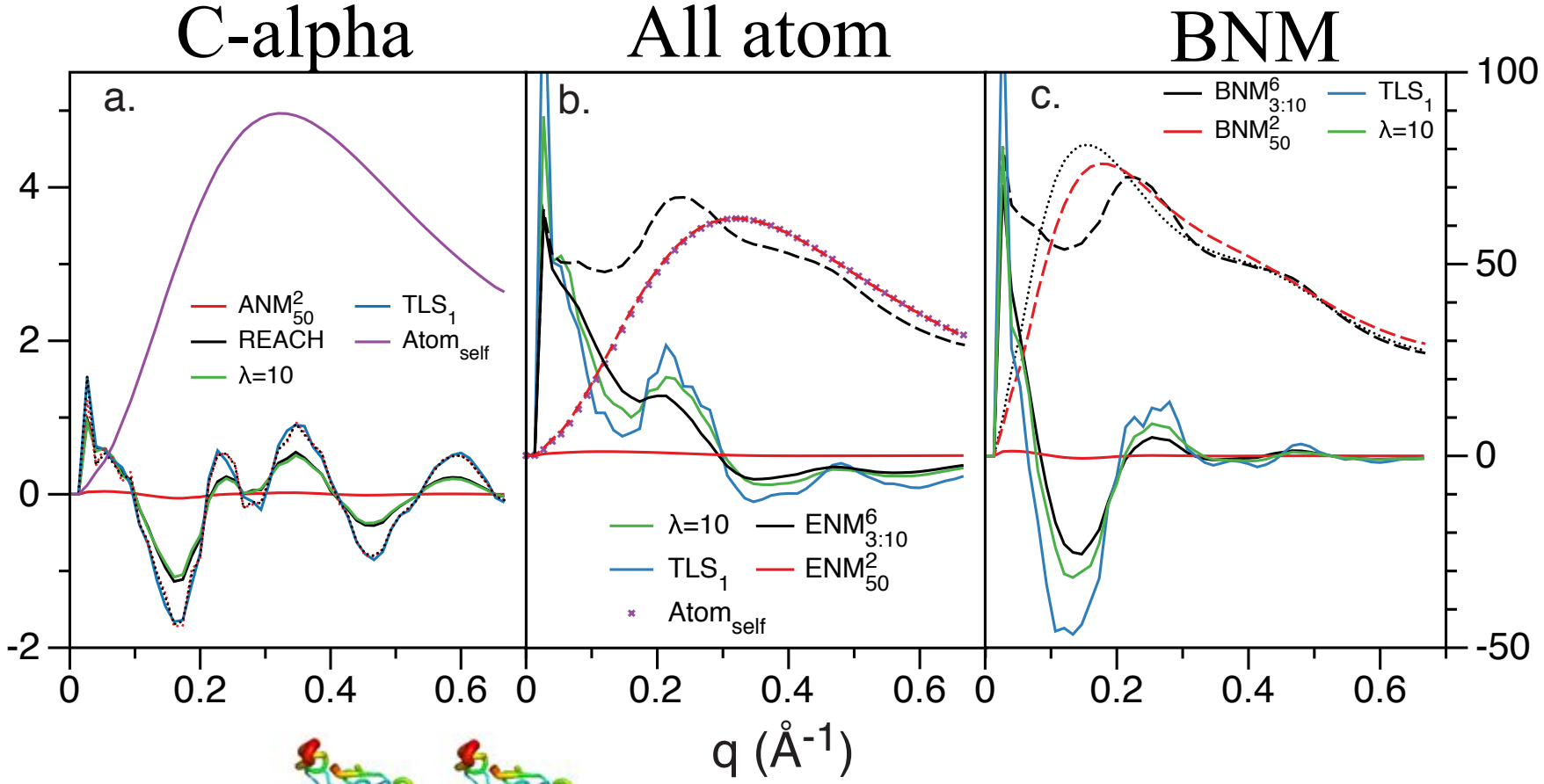
$$I_{D,blocks}(\mathbf{Q}) = N \sum_{m}^{blocks} \sum_{k,k' \in m} B_{k,k'}(\mathbf{Q})(e^{\mathbf{Q}^T \langle \mathbf{u}_k \mathbf{u}_{k'}^T \rangle \mathbf{Q}} - 1)$$

$$I_{D,interatomic}(\mathbf{Q}) = I_D(\mathbf{Q}) - I_{D,atoms}(\mathbf{Q})$$
$$I_{D,interresidue}(\mathbf{Q}) = I_D(\mathbf{Q}) - I_{D,intraresidues}(\mathbf{Q})$$
$$I_{D,inter2ndary}(\mathbf{Q}) = I_D(\mathbf{Q}) - I_{D,intra2ndary}(\mathbf{Q})$$

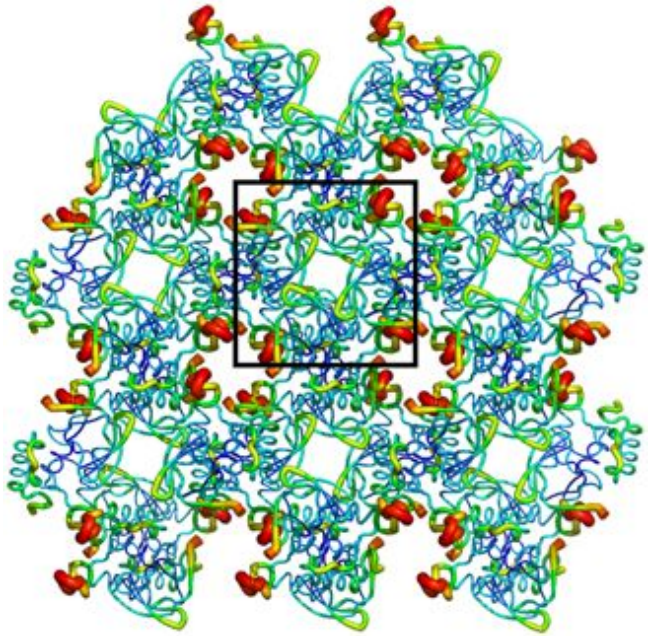
Remix it

Contribution to the diffuse scattering from interblock correlation

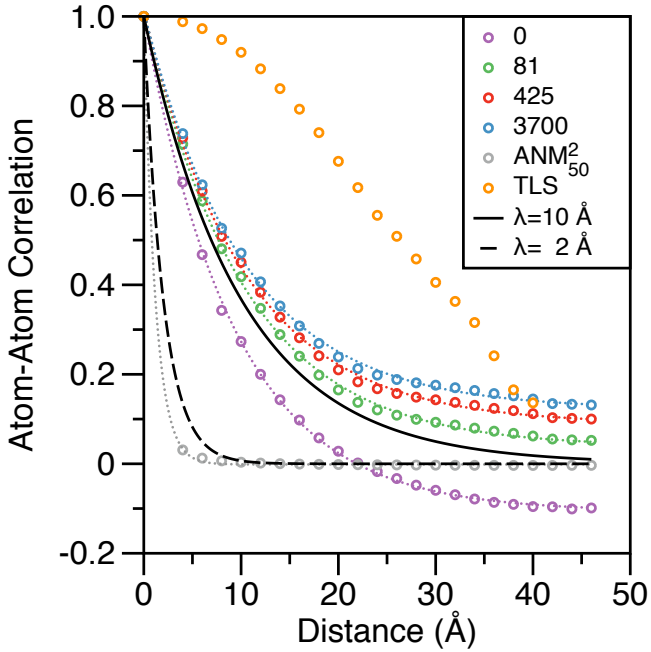
$$I_{D,interblock}(\mathbf{Q}) = N \sum_{m}^{blocks} \sum_{k \in m} \sum_{m' \neq m}^{blocks} \sum_{k' \in m'} B_{k,k'}(\mathbf{Q})(e^{\mathbf{Q}^T \langle \mathbf{u}_k \mathbf{u}_{k'}^T \rangle \mathbf{Q}} - 1)$$

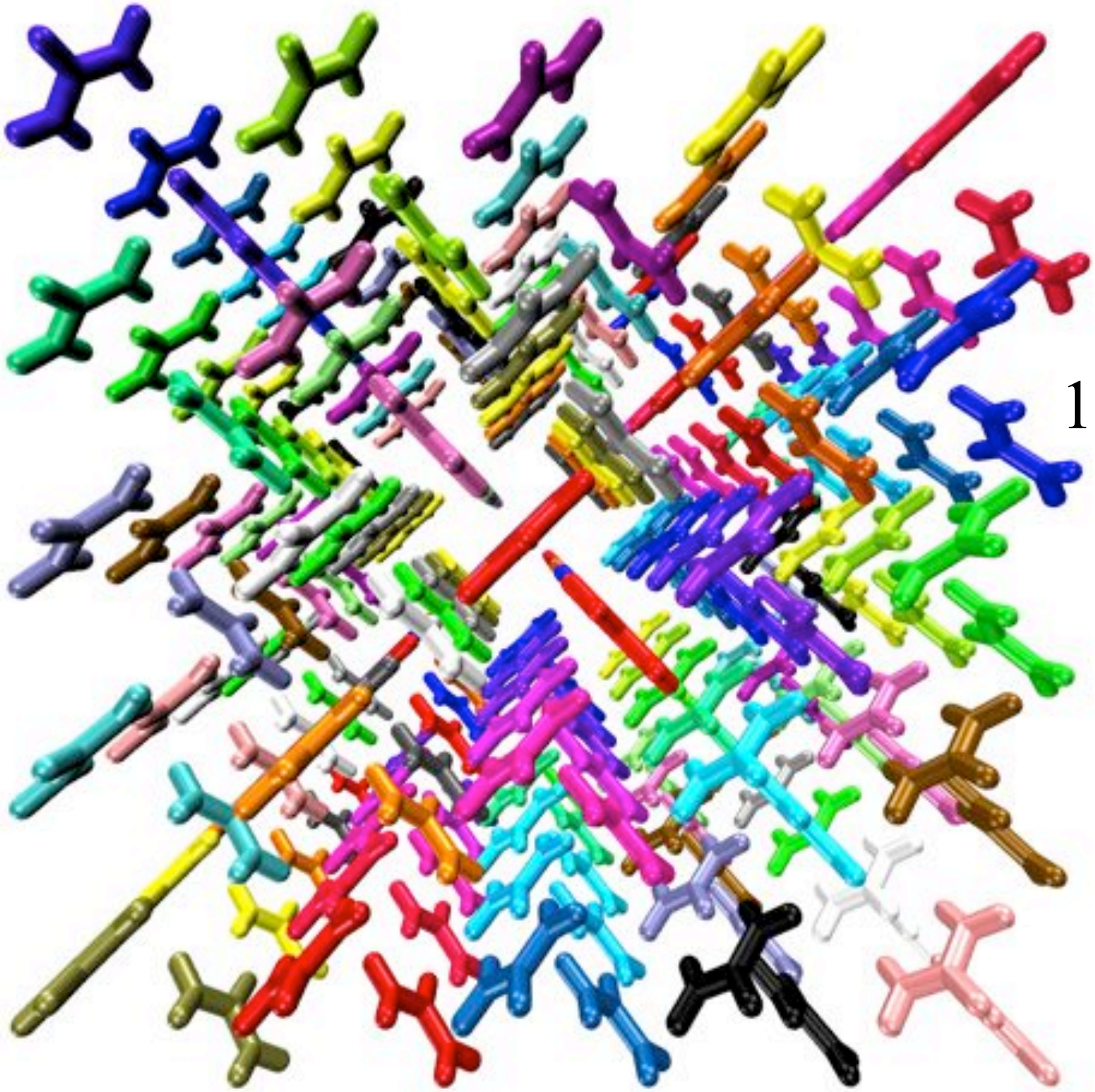


Wall, Ealick, Gruner, PNAS (1997)
Meinhold and Smith Proteins (2007)



Riccardi, Cui, Phillips, Biophys J (2010)





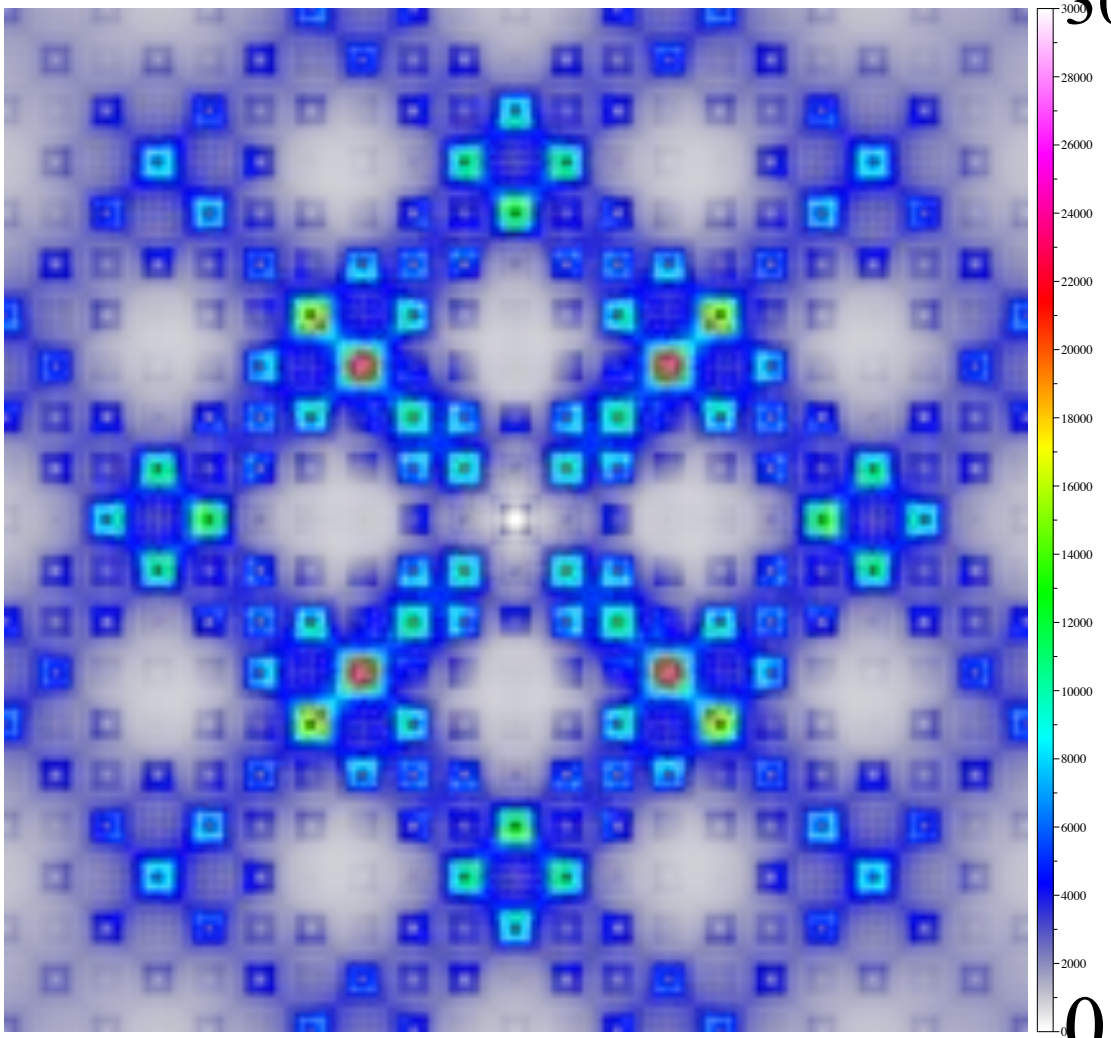
1 Urea per block

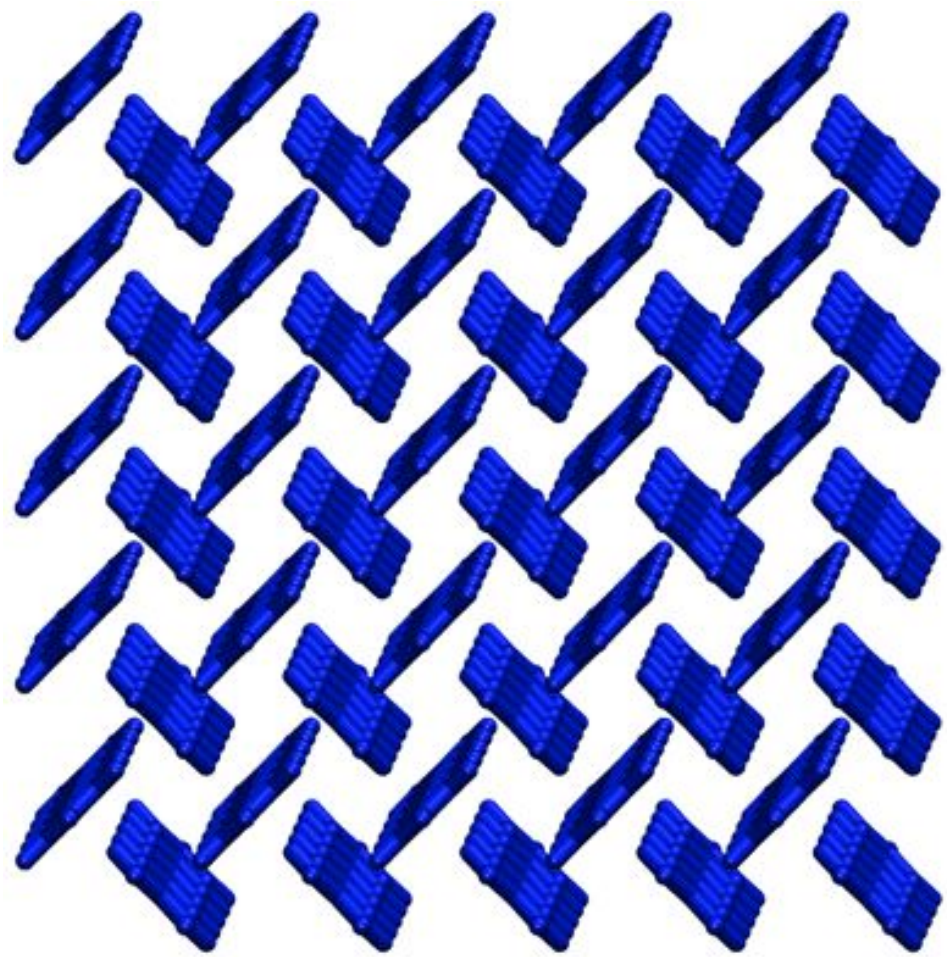
3.5 Å cutoff

$1/R^6$

Wavevectors!

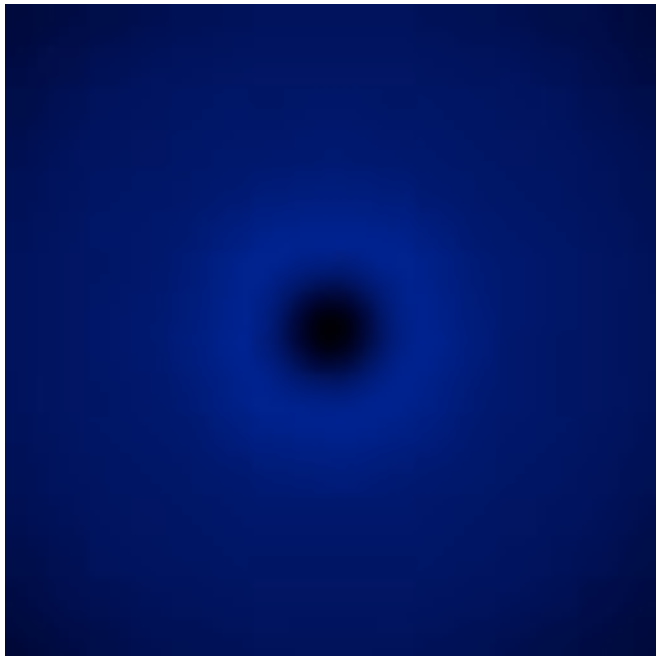
Swaminathan, Craven, and McMullan, Acta D (1984)



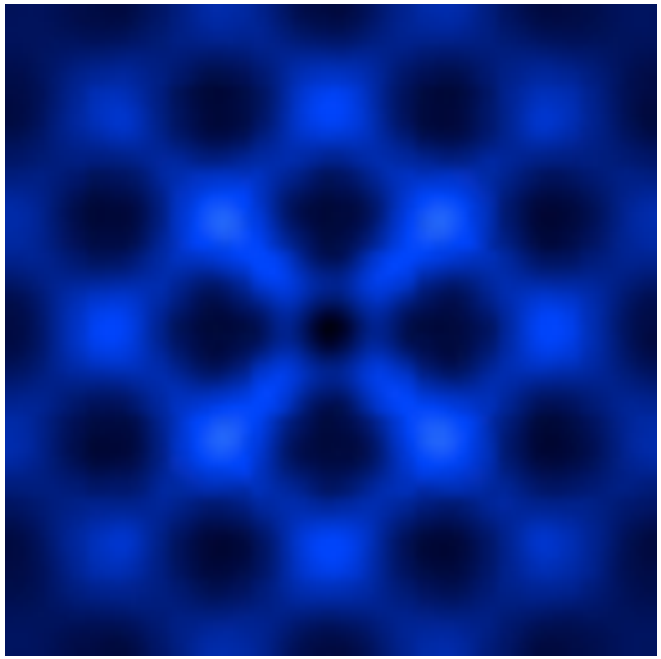


I_D hk0

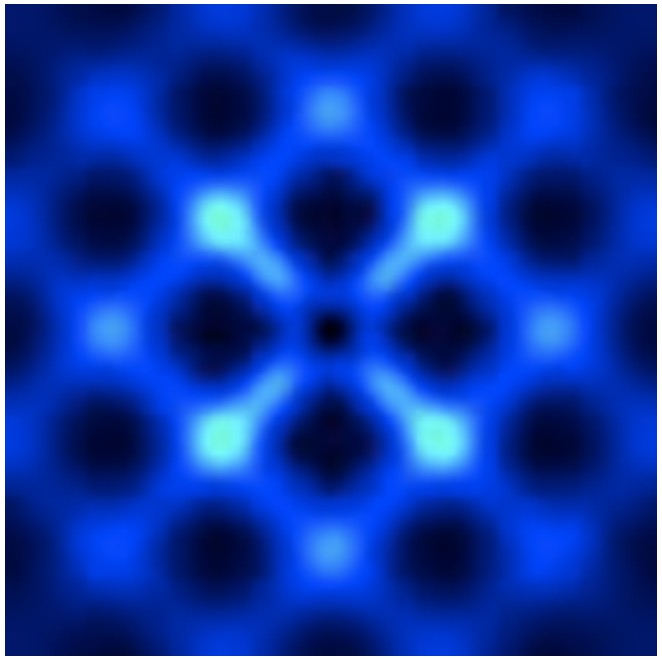
One block
Tipped a little to visualize



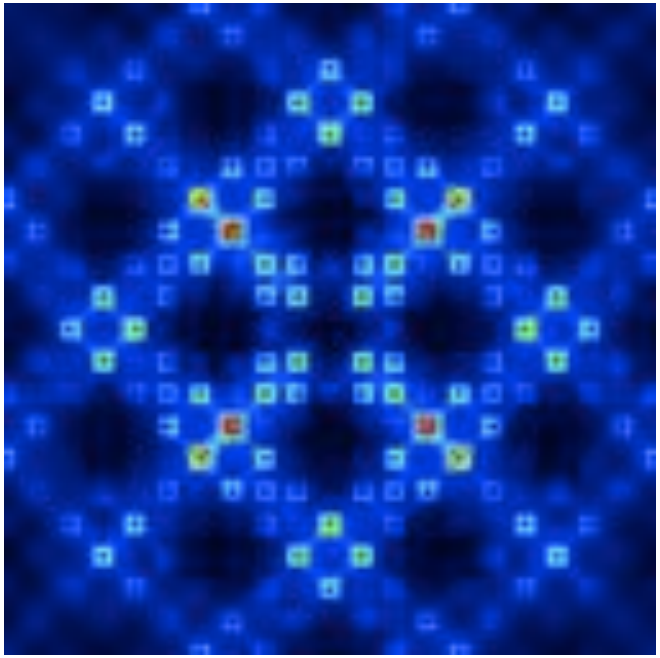
$I_{atom,self}$



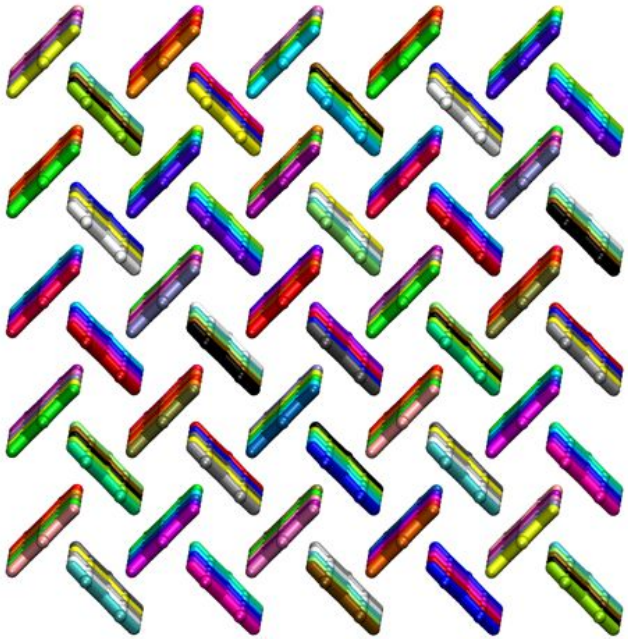
$I_{urea,self}$

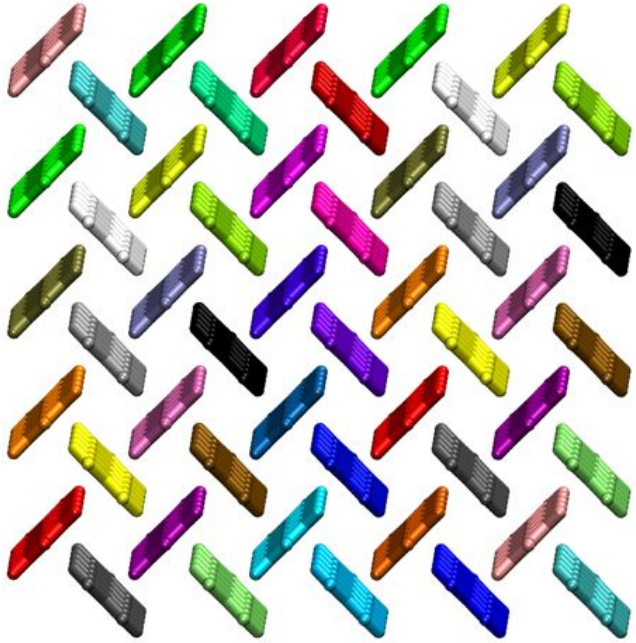


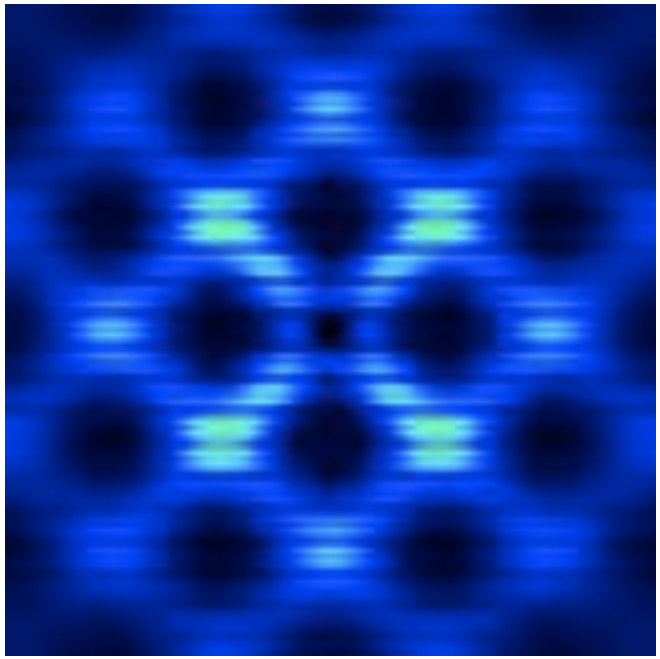
I_{rows}



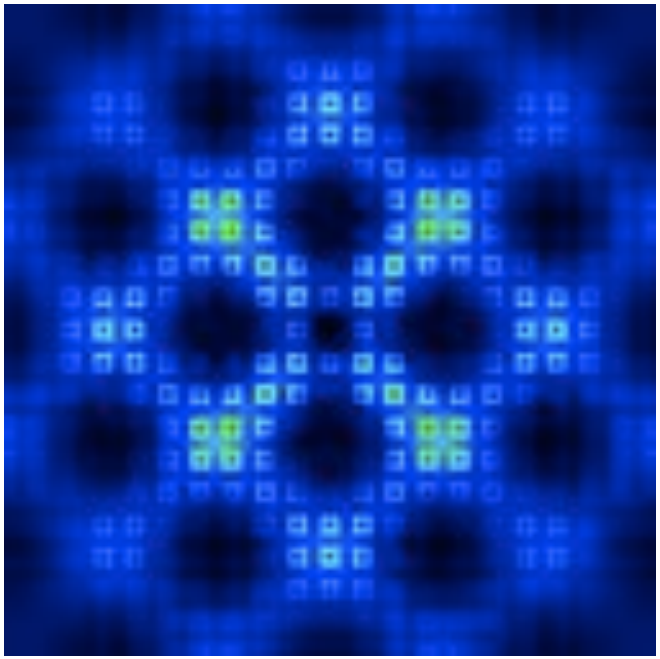
I_D



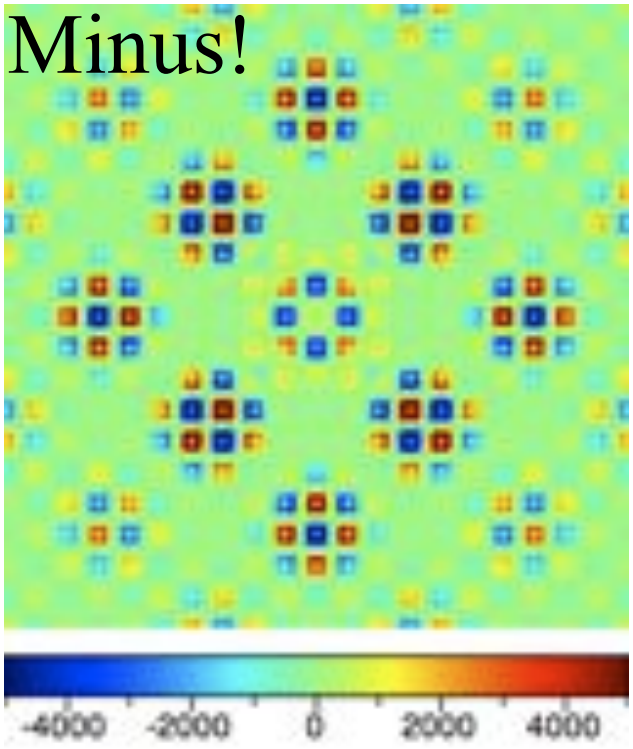


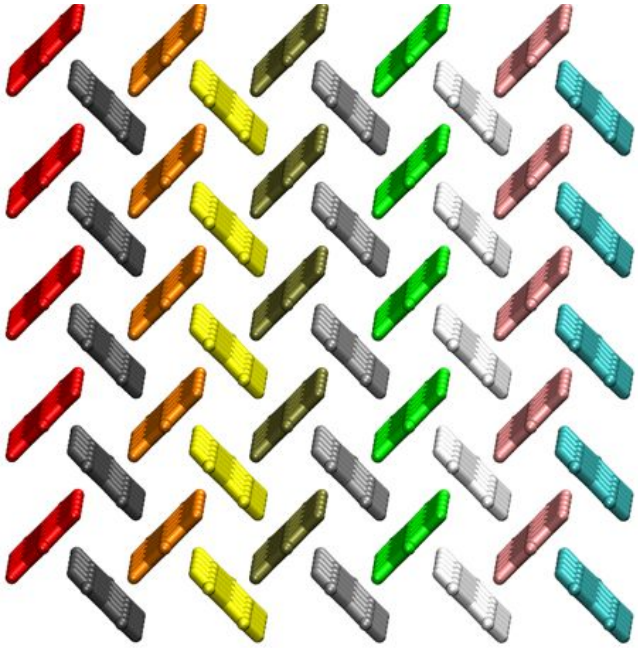


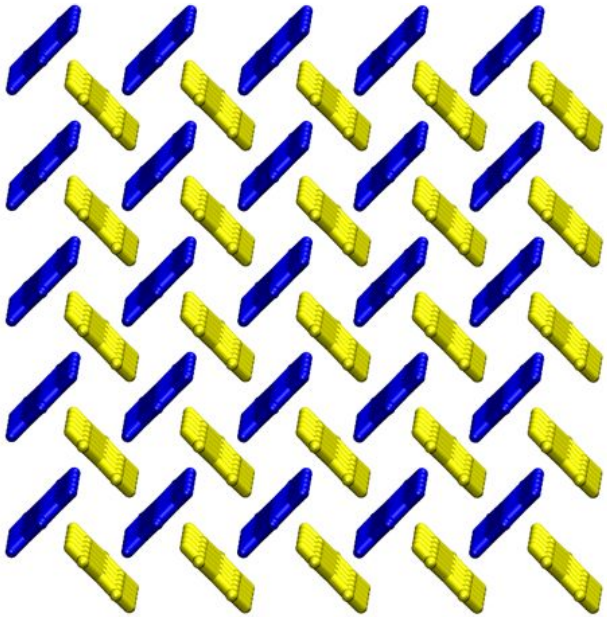
I_{planes}

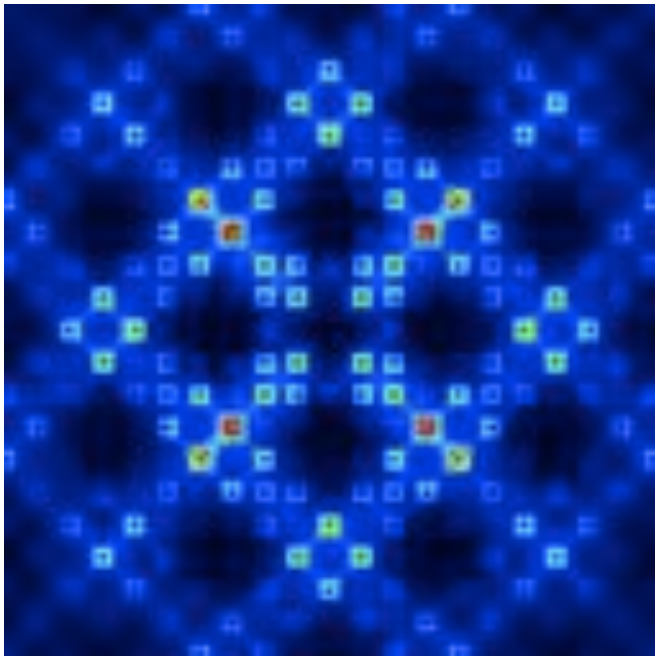


I_{xblox}

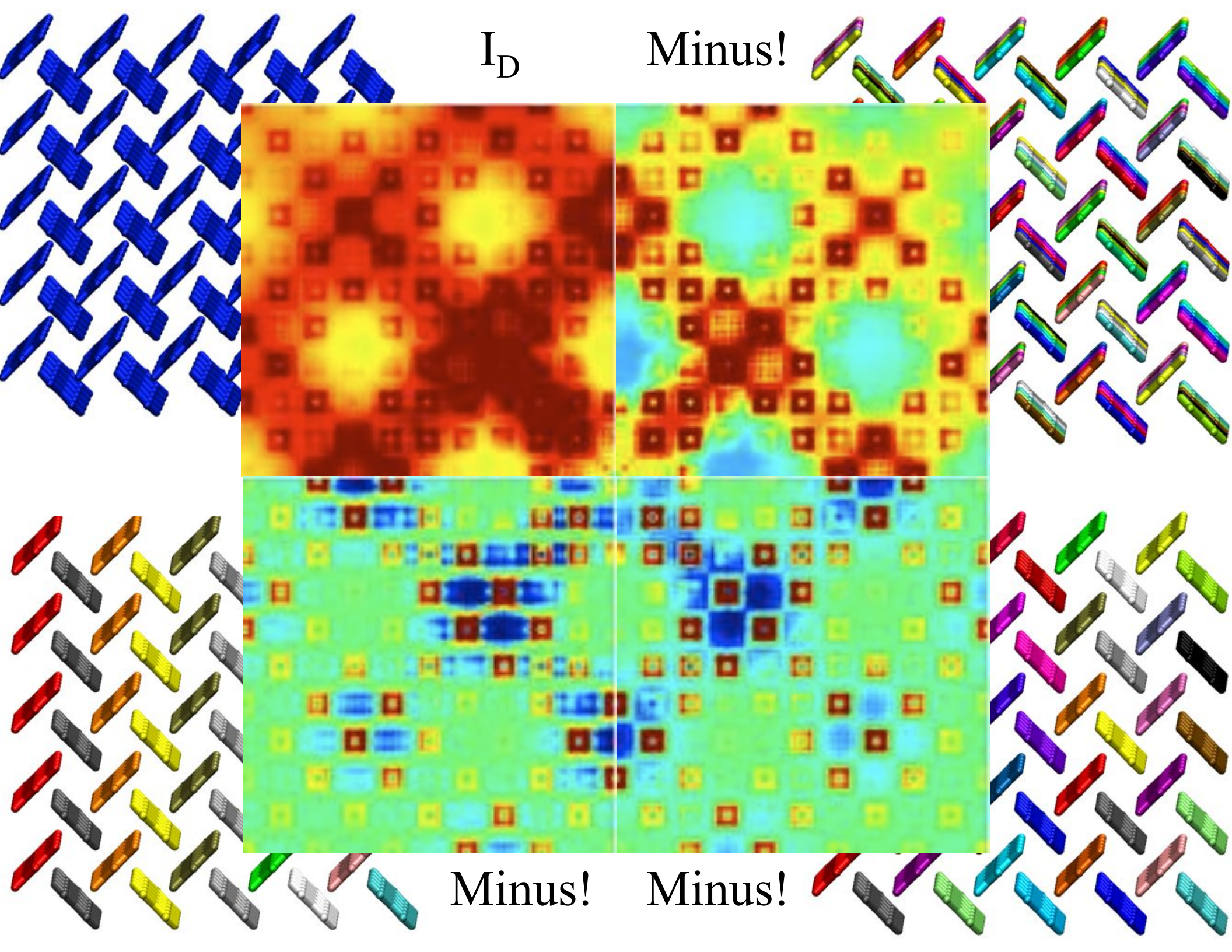


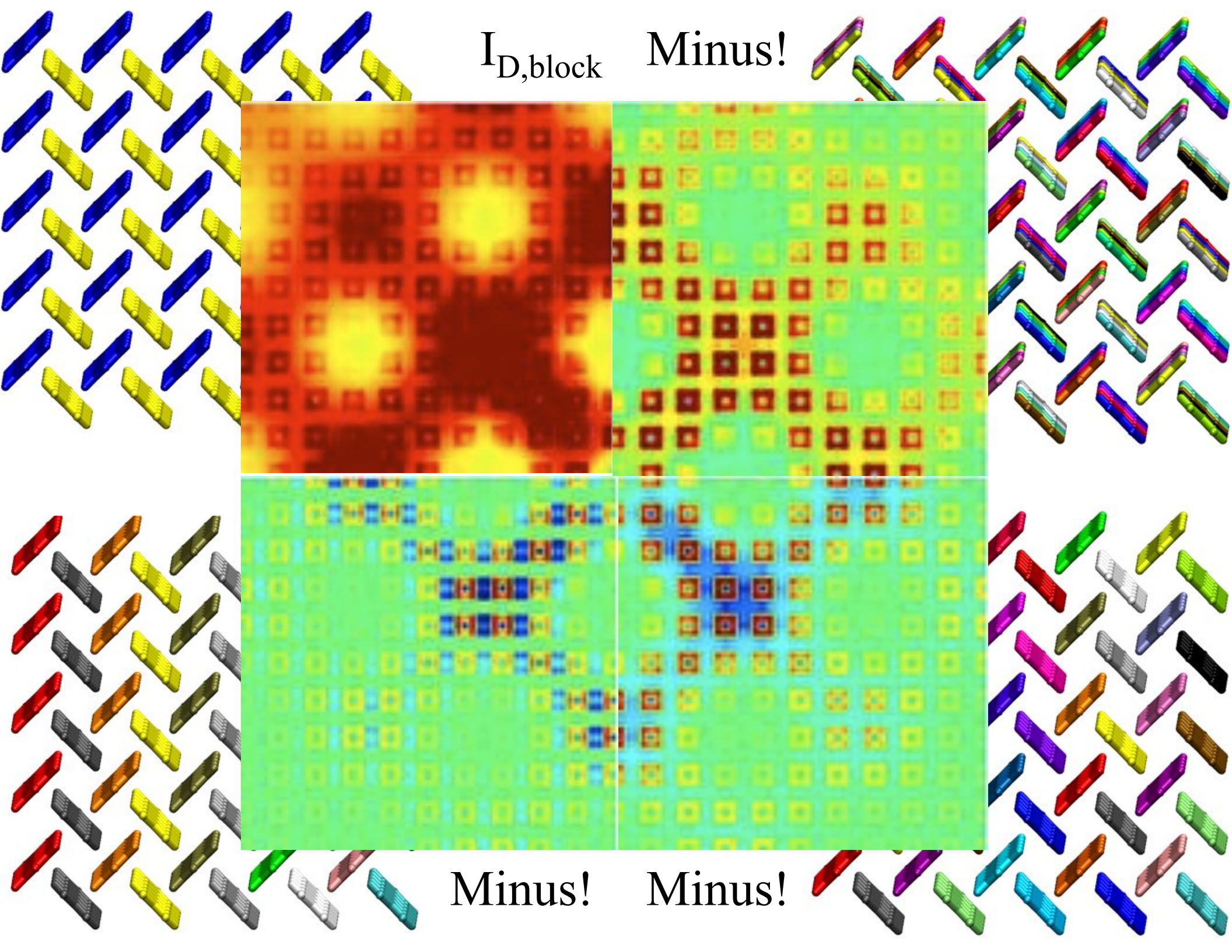




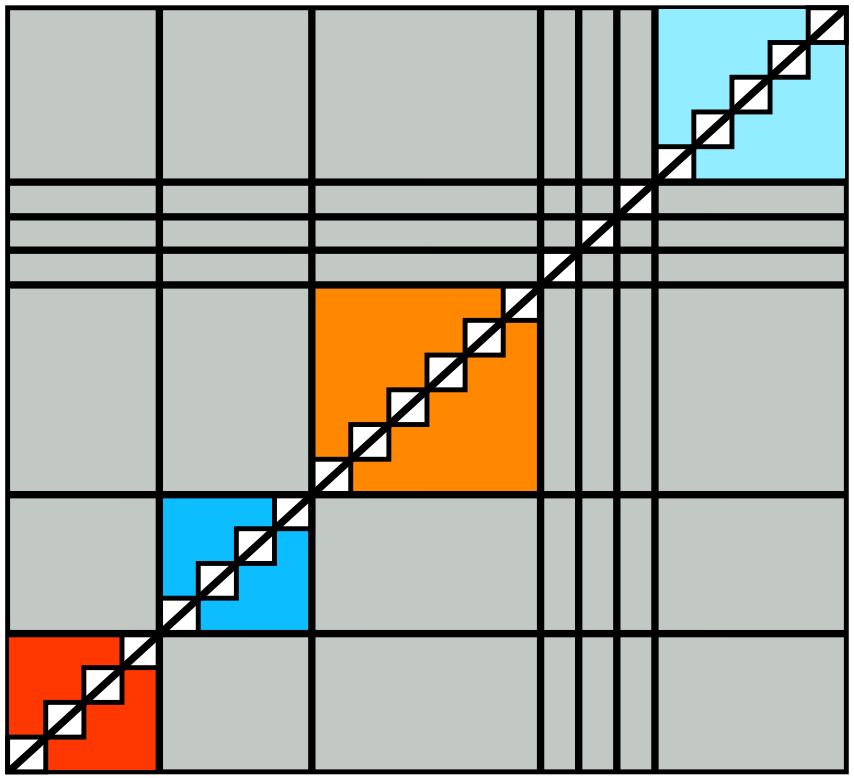


I_D


I_D
Minus!
Minus!
Minus!


$I_{D,block}$
Minus!
Minus!
Minus!

Conclusions



Multiscale Modeling of I_D

TMTOWDI

Vary the model VCOV

Vary the atom groups of VCOV

Dissect the pattern

$$I_{D,blocks}(\mathbf{Q}) = N \sum_{m}^{blocks} \sum_{k,k' \in m} B_{k,k'}(\mathbf{Q})(e^{\mathbf{Q}^T \langle \mathbf{u}_k \mathbf{u}_{k'}^T \rangle \mathbf{Q}} - 1)$$

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