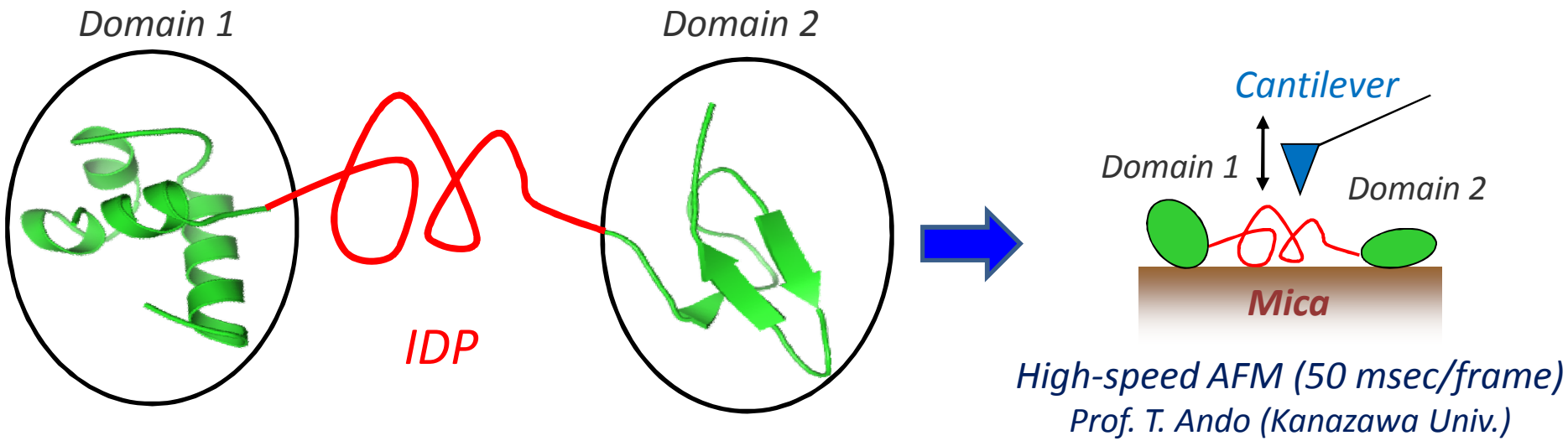
PF研究会「ERLサイエンスワークショップⅡ」
2011年4月27日－28日、KEK-PF

天然変性タンパク質をターゲットとした新しい構造生物学

―将来光源を用いた１分子解析を目指して―

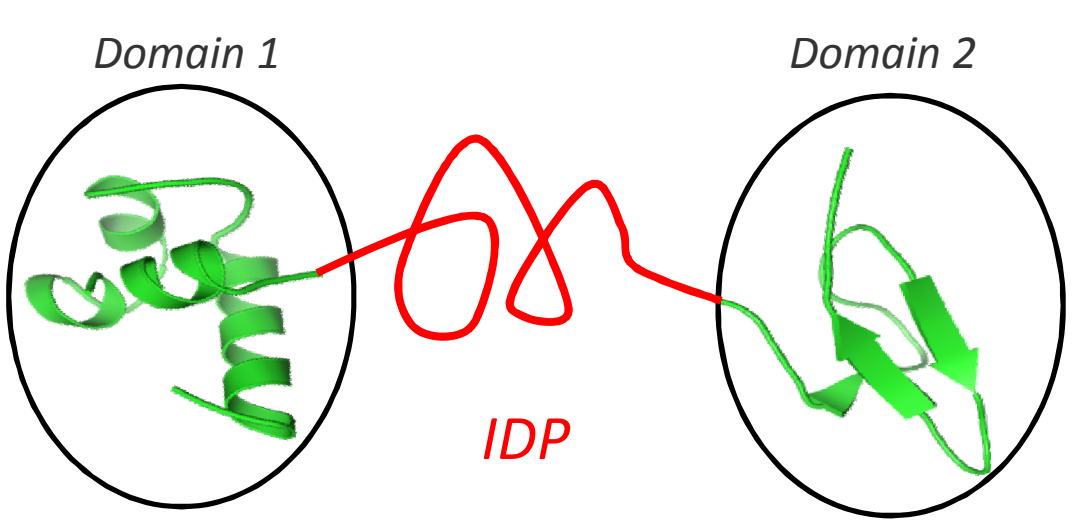
佐 藤　衛
横浜市立大学 大学院 生命ナノシステム科学研究科

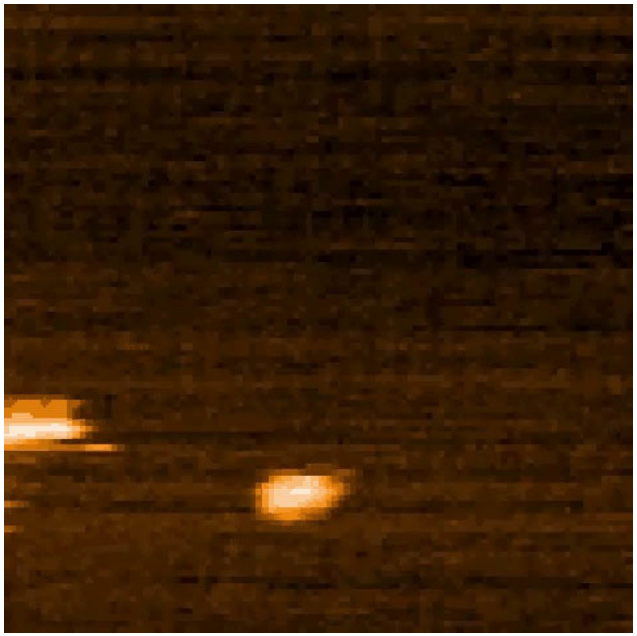
天然変性タンパク質
Intrinsically Disordered Protein: IDP

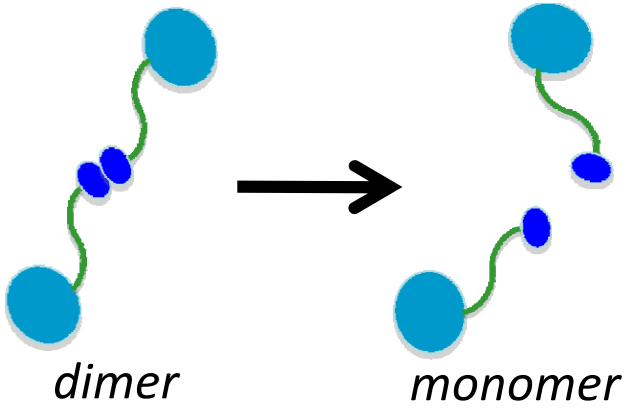


IDPs are characterized by a lack of stable folded structure along their entire lengths or in localized regions between domains, when they exist as isolated polypeptide chains under physiological conditions

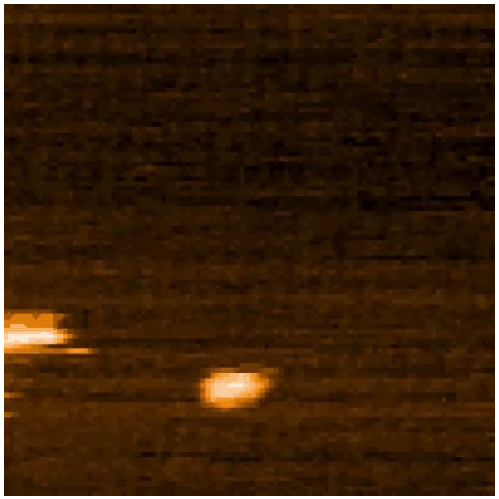
天然変性タンパク質
Intrinsically Disordered Protein: IDP







X-ray Scattering from Single IDP

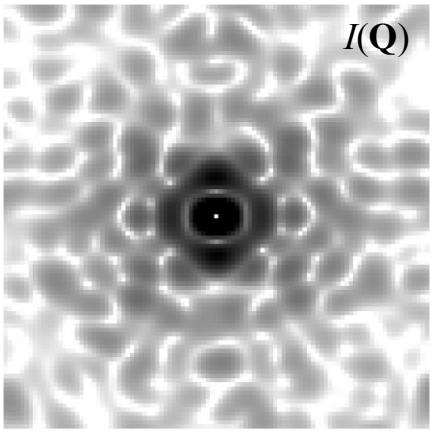


X-FEL (10 fs)

散乱因子： $F(\mathbf{Q}) = \int \rho(\mathbf{r}) e^{-i\mathbf{Q}\cdot\mathbf{r}} d^3\mathbf{r}$ $\quad |\mathbf{Q}| = (4\pi/\lambda)\sin\theta$

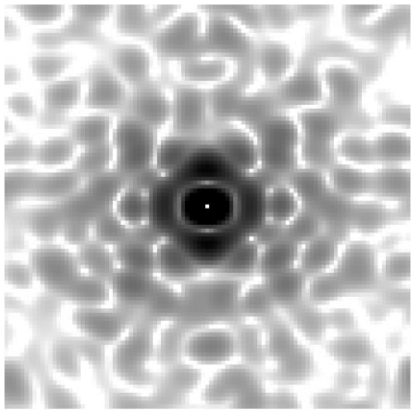
*Oversampling*による像の回復

散乱強度： $I(\mathbf{Q}) = |F(\mathbf{Q})|^2 = \int d^3\mathbf{r}' \int d^3\mathbf{r} \rho(\mathbf{r}')\rho(\mathbf{r}) e^{-i\mathbf{Q}\cdot(\mathbf{r}-\mathbf{r}')}$



二次元検出器

天然変性タンパク質をターゲットとした新しい構造生物学



コヒーレント光を用いた
新しいタンパク質溶液散乱法の提案

異方的な散乱パターンから
タンパク質構造情報が引き出せるか

研究１

フェムト秒パルスレーザーによるタンパク質１分子からの溶液散乱

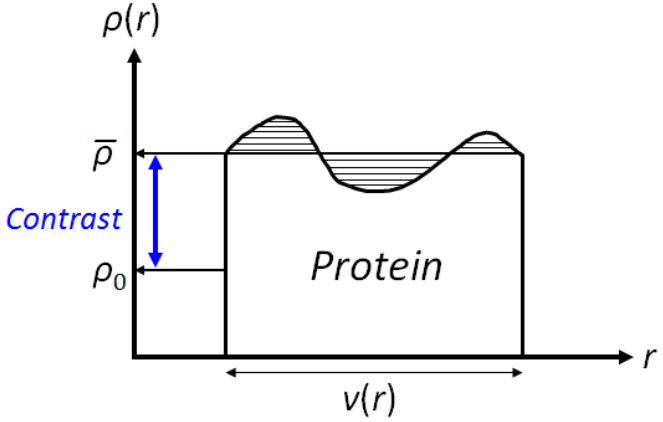
研究２

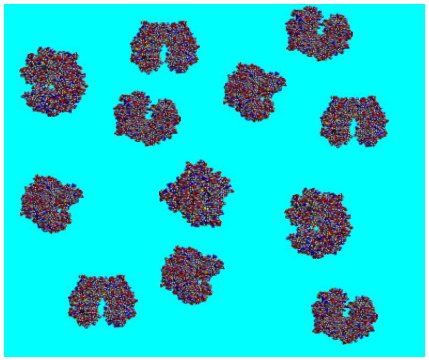
少数タンパク質分子からの溶液散乱

北大・西野吉則研究室との共同研究

Small-Angle X-ray Scattering（SAXS）

Multi-domain proteins in solution





溶媒の電子密度 ρ_0

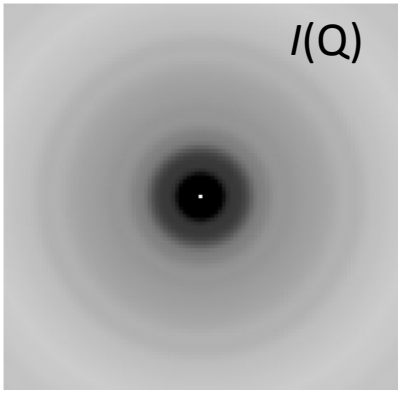
X-rays

タンパク質10^{12}分子

散乱因子： $F(\mathbf{Q}) = \int (\rho(\mathbf{r}) - \rho_0) e^{-i\mathbf{Q}\cdot\mathbf{r}} d^3\mathbf{r}$ （溶媒からの*Contrast*）

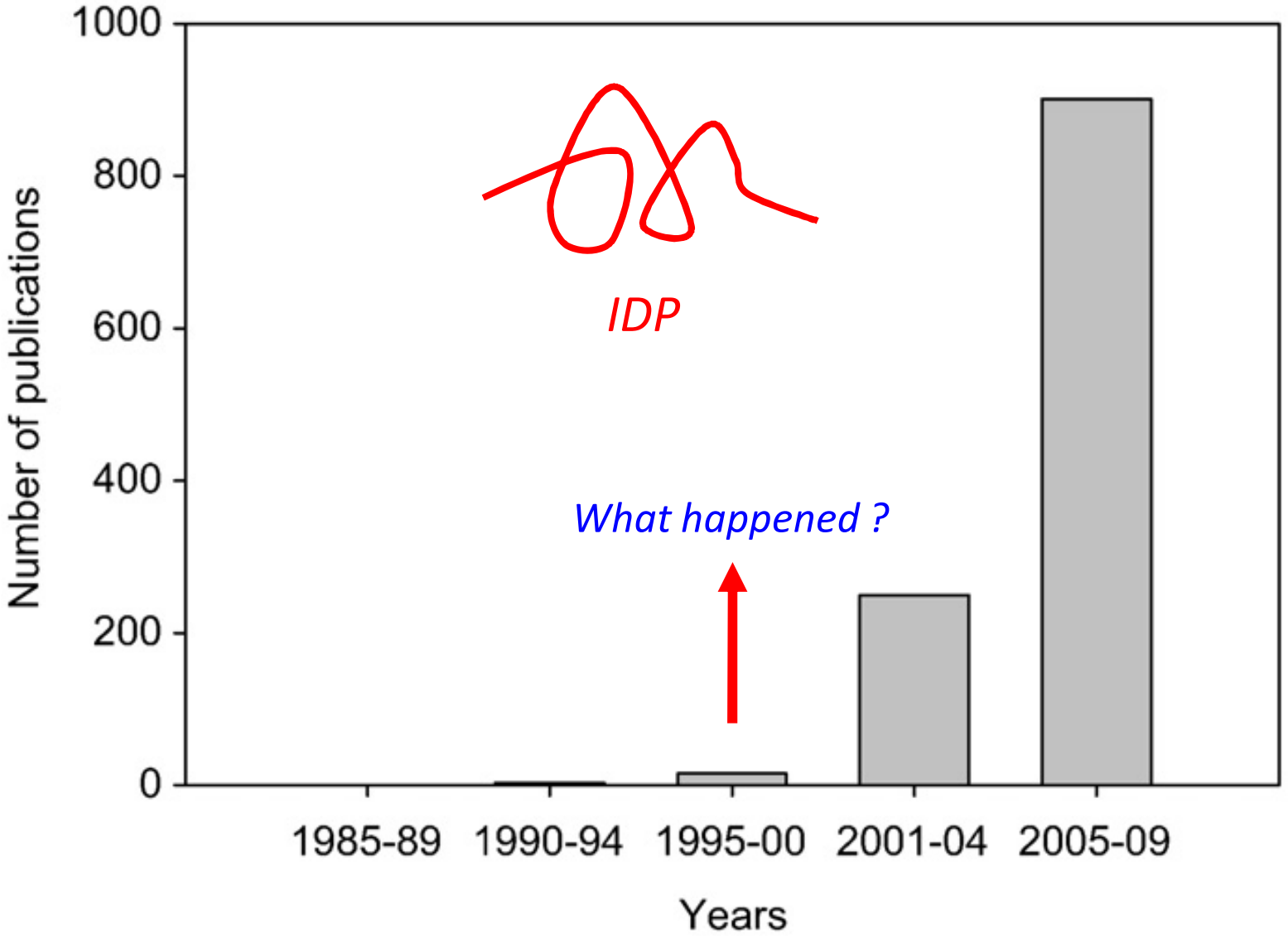
回転平均
&
アンサンブル平均

散乱強度： $I(Q) = \left\langle \left\langle |F(\mathbf{Q})|^2 \right\rangle_{\Omega_Q} \right\rangle_{\text{Ensemble}}$

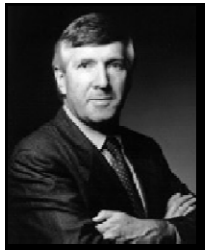


二次元検出器

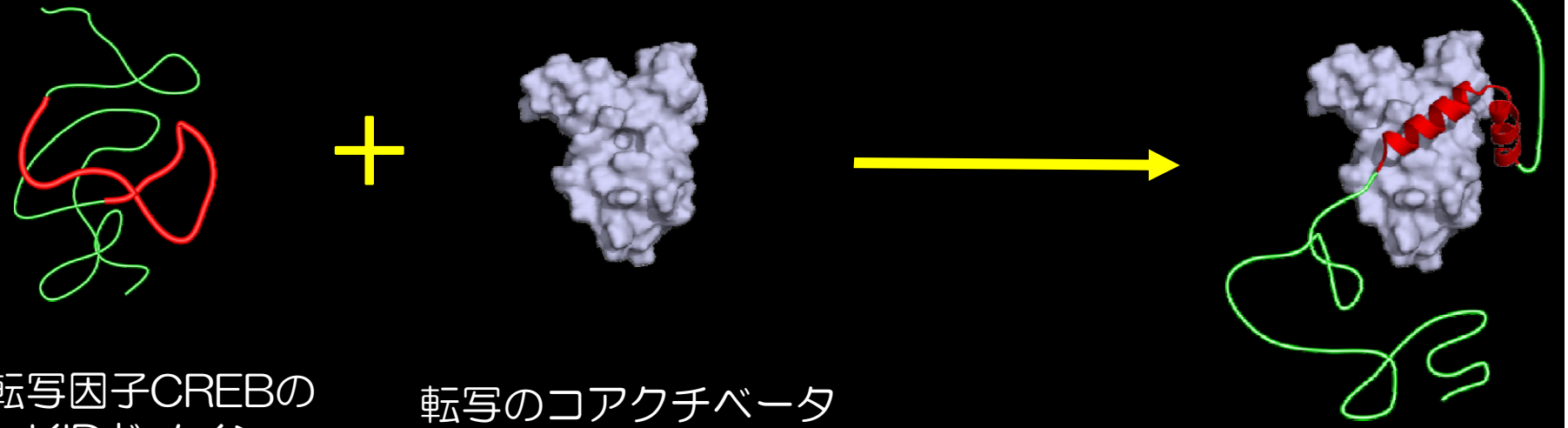
No. of PubMed hits dealing with IDPs



Biochim. Biophys. Acta, ***1804****, 1231-1264 (2010)*



*P. Wright et al. Cell **91**, 741-752 (1997)*



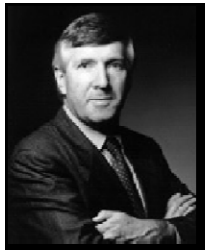
転写因子CREBの
KIDドメイン
（天然変性タンパク質）

転写のコアクチベータ
CBPのKIXドメイン

特異的複合体

天然変性タンパク質は他のタンパク質やリガンドと
相互作用すると立体構造が形成される

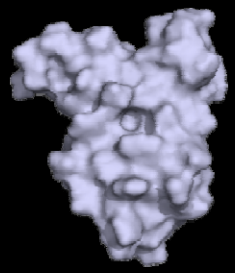
Coupled folding & binding



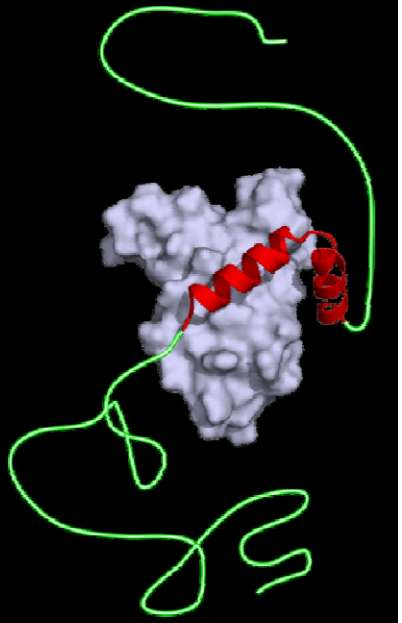
Coupled Folding & Binding

転写因子CREBの
KIDドメイン
（天然変性タンパク質）

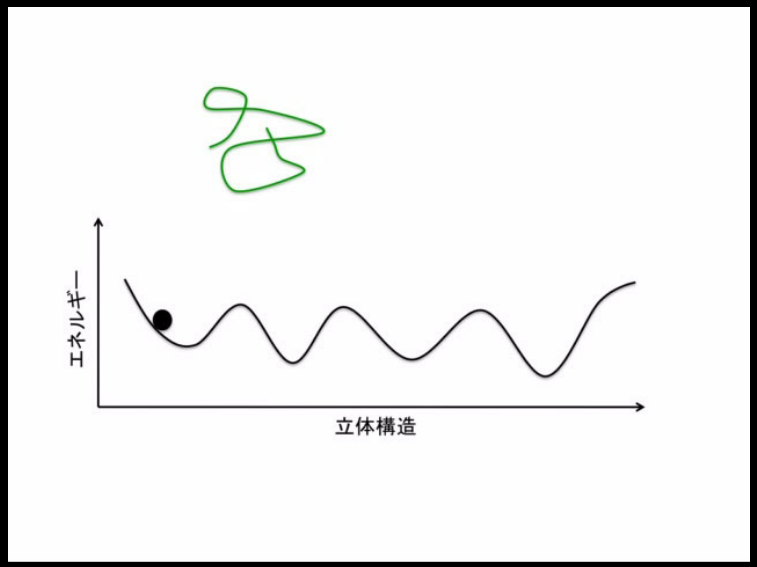
+



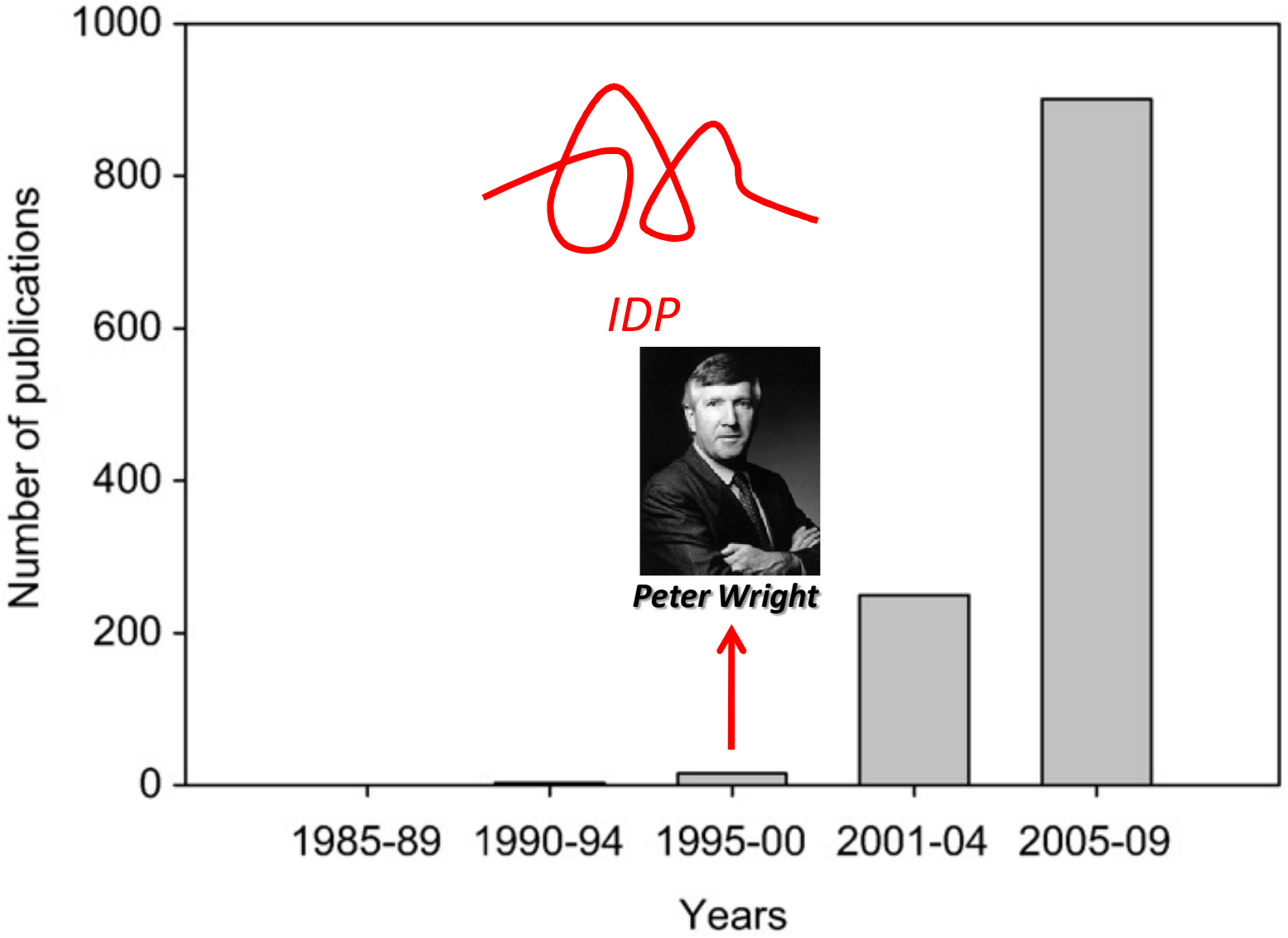
転写のコアクチベータ
CBPのKIXドメイン



特異的複合体



No. of PubMed hits dealing with IDPs



Intrinsically Disordered Protein: IDP

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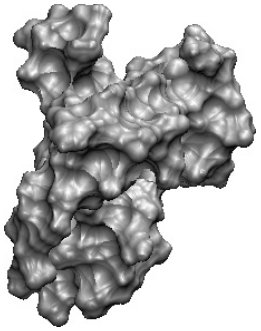
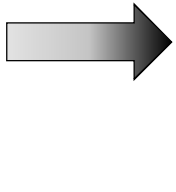
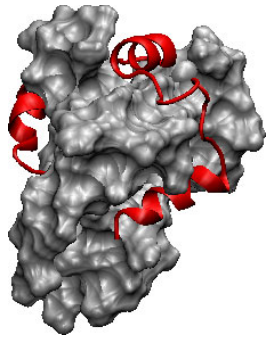


コアクチベータ *CBP*
の*TAZ1*ドメイン





（*Proc. Natl. Acad. Sci. USA* 2002）

天然変性タンパク質は複数のタンパク質やリガンドと相互作用し
それぞれ異なる立体構造を形成して機能する

低酸素誘導因子*HIF1α*
（*IDP*）

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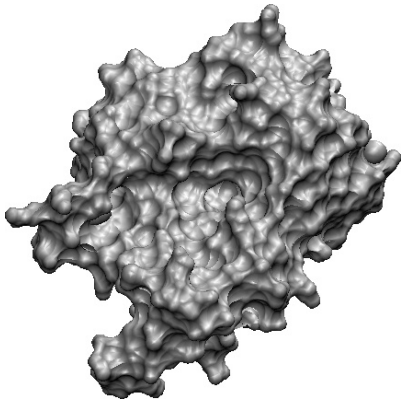
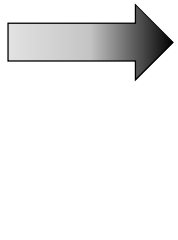
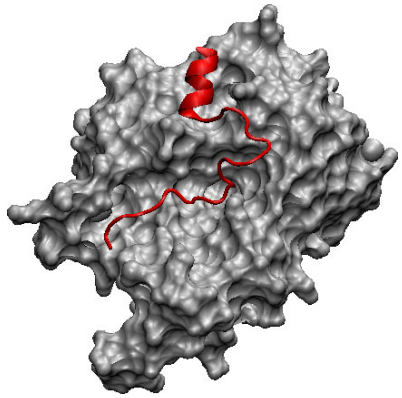


Asparagine Hydroxylase





（*J. Biol. Chem.* 2003）

天然変性タンパク質は生体内ネットワークにおける
ハブ（中核）タンパク質として機能する

A Recent Review Article on IDP

*Biochim. Biophys. Acta, **1804**, 1231-1264 (2010)*

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbapap

Review

Understanding protein non-folding

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ARTICLE INFO

Article history:
Received 21 November 2009
Received in revised form 9 January 2010
Accepted 21 January 2010
Available online 1 February 2010

Keywords:
Intrinsically disordered protein
Disorder prediction
Partially folded protein

ABSTRACT

This review describes the family of intrinsically disordered proteins, members of which fail to form rigid 3-D structures under physiological conditions, either along their entire lengths or only in localized regions. Instead, these intriguing proteins/regions exist as dynamic ensembles within which atom positions and backbone Ramachandran angles exhibit extreme temporal fluctuations without specific equilibrium values. Many of these intrinsically disordered proteins are known to carry out important biological functions which, in fact, depend on the absence of a specific 3-D structure. The existence of such proteins does not fit the prevailing structure–function paradigm, which states that a unique 3-D structure is a prerequisite to function. Thus, the protein structure–function paradigm has to be expanded to include intrinsically disordered proteins and alternative relationships among protein sequence, structure, and function. This shift in the paradigm represents a major breakthrough for biochemistry, biophysics and molecular biology, as it opens new levels of understanding with regard to the complex life of proteins. This review will try to answer the following questions: how were intrinsically disordered proteins discovered? Why don't these proteins fold? What is so special about intrinsic disorder? What are the functional advantages of disordered proteins/regions? What is the functional repertoire of these proteins? What are the relationships between intrinsically disordered proteins and human diseases?

Gordon Research Conference on IDP

Functional Repertoires of IDPs

IDPs as hubs in protein signaling networks

p53 regulates over 150 gene transcriptions (p21, MDM2, BAX ….)

IDPs and PTMs (post-translational modifications)

PTMs frequently occur in ID regions

Substrates for many PM enzymes such as kinases are ID proteins

IDPs and AS (alternative splicing)

AS region of mRNA code for ID regions

AS is likely to be involved in cell differentiation

IDPs are mainly found in eukaryotes

Eukaryotes contain far more intrinsic disorder than prokaryotes

IDPs and human diseases

Alzheimer disease and amy-β, tau, α-synuclein

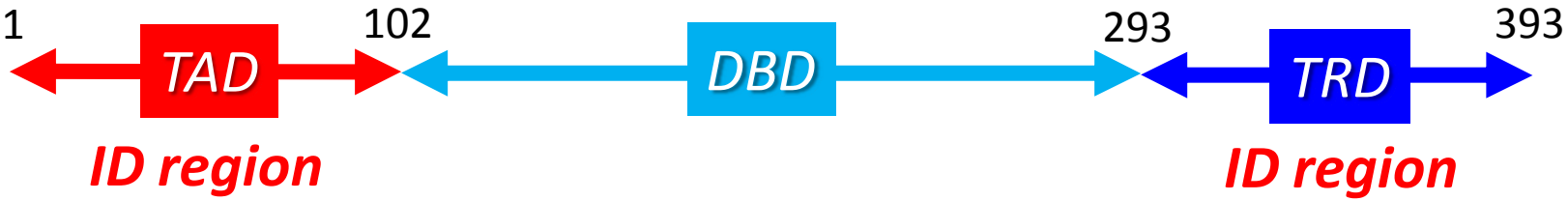
IDPs as novel drug targets

One partner is disordered and the second is structured

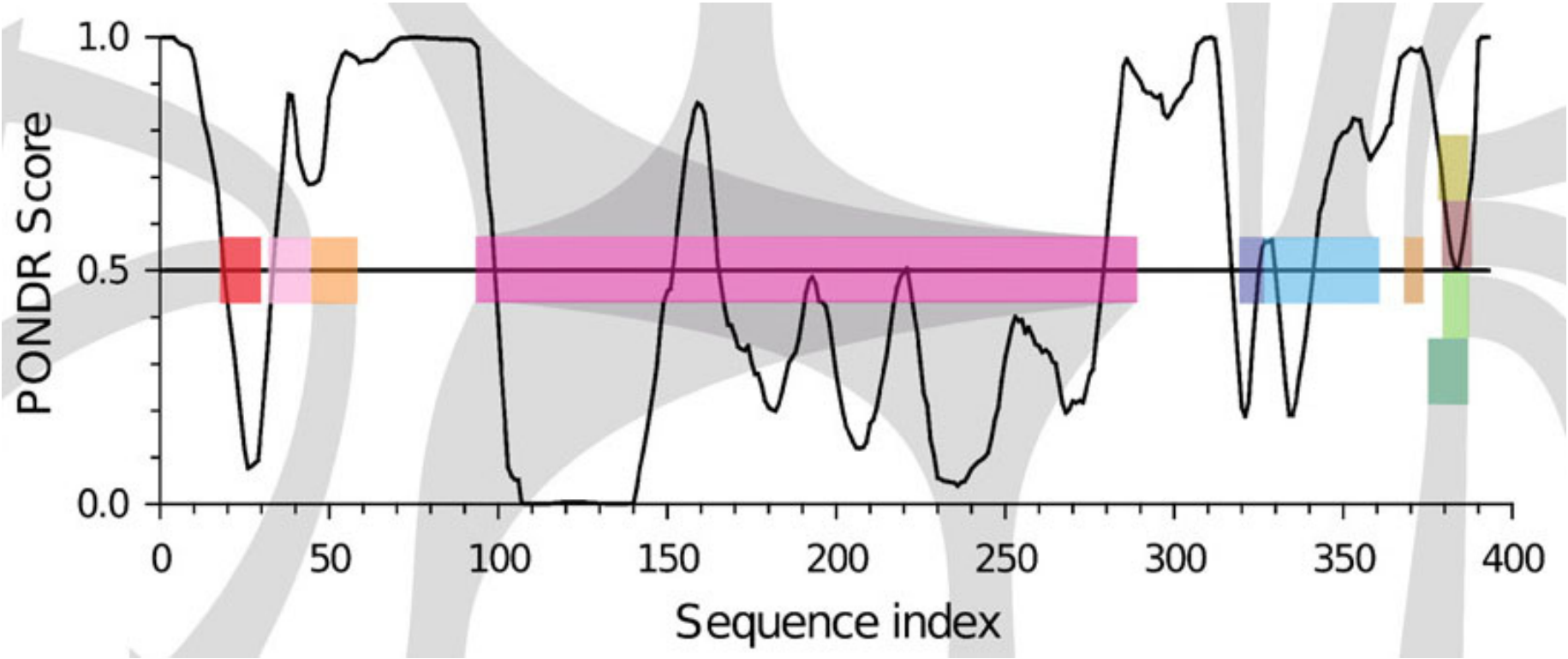
Both partners lacks fixed structures

D^2-concept: disorder in disorders

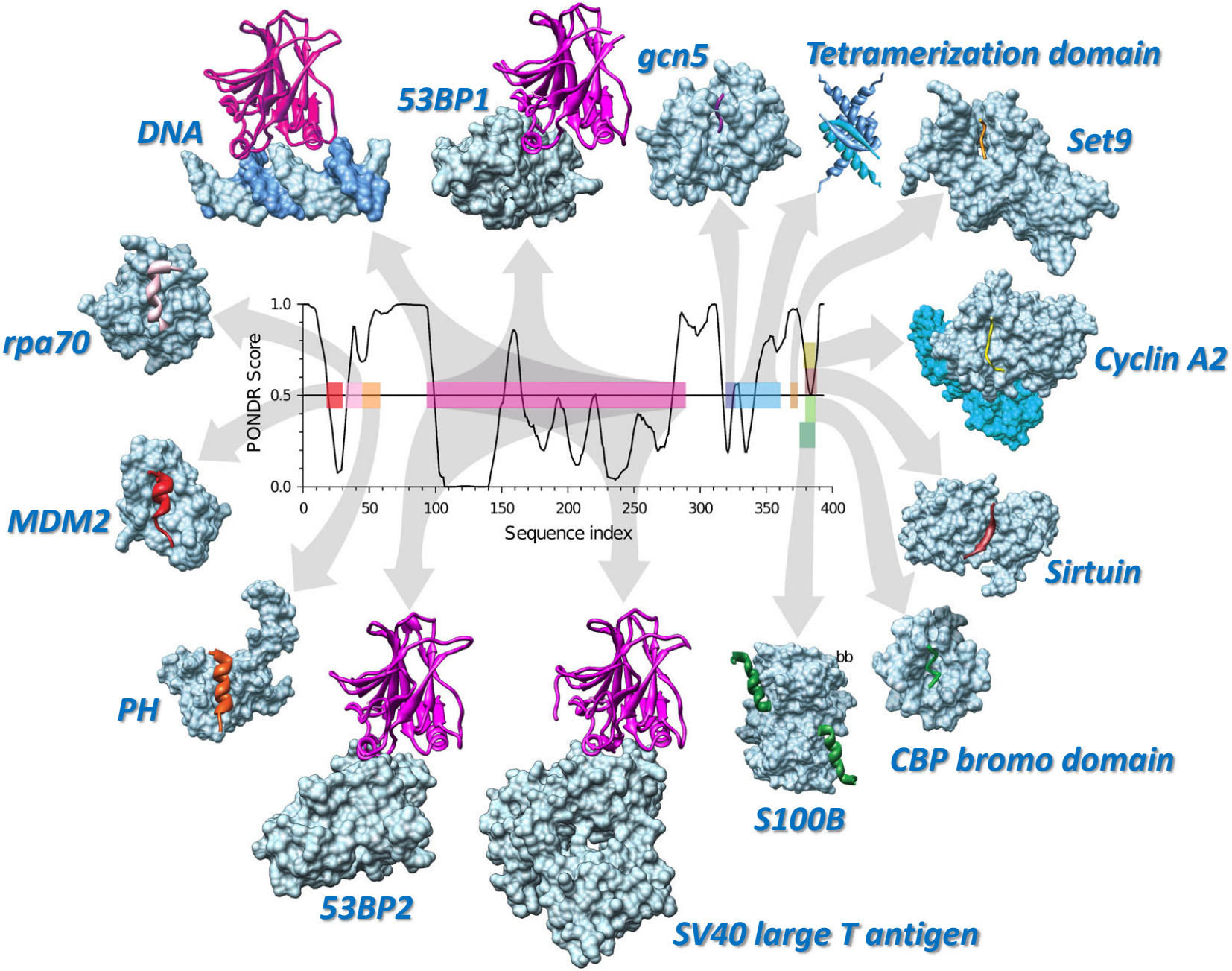
Domain Structure of p53



ID Prediction of p53 by PONDR

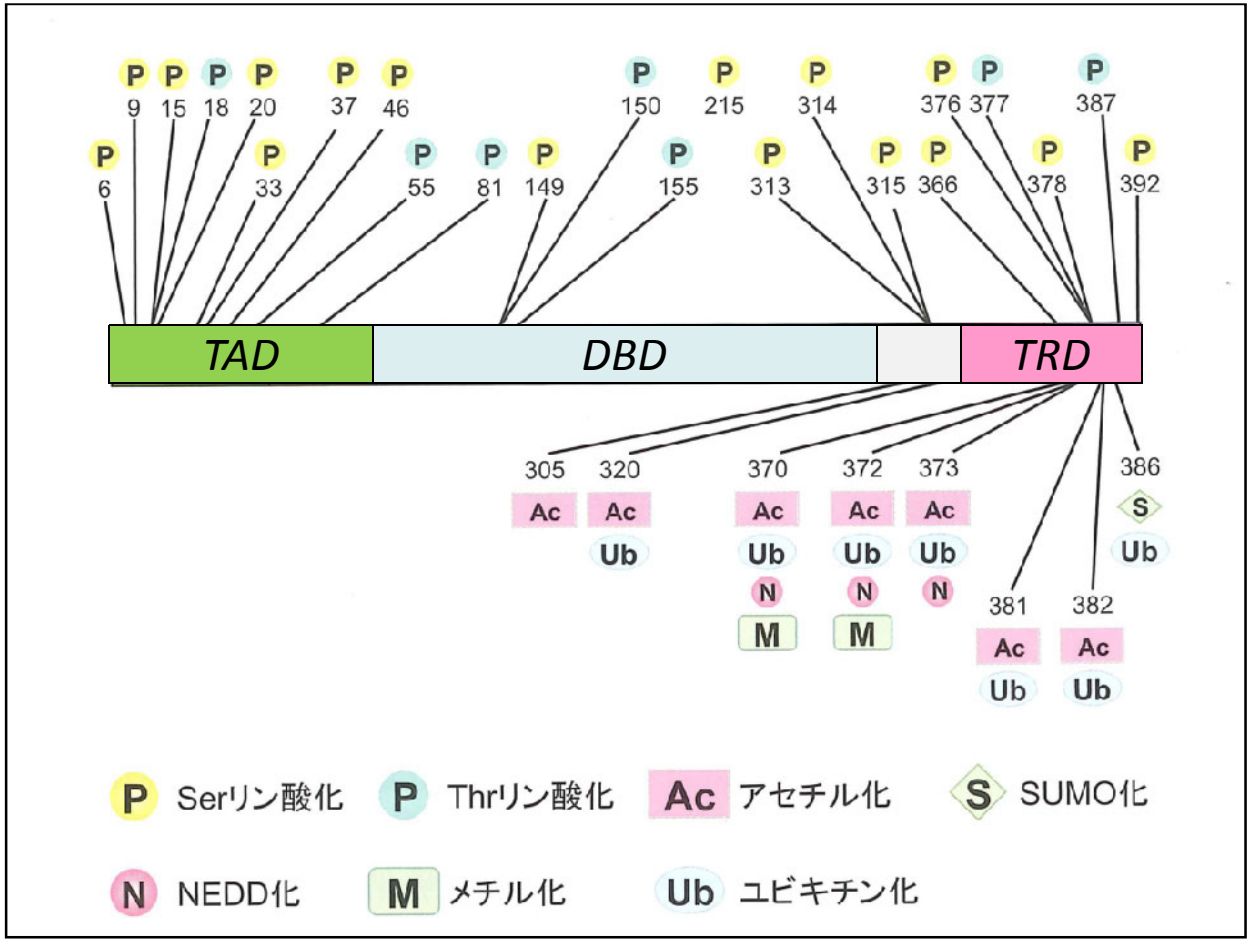


p53 interacts with 14 different partners



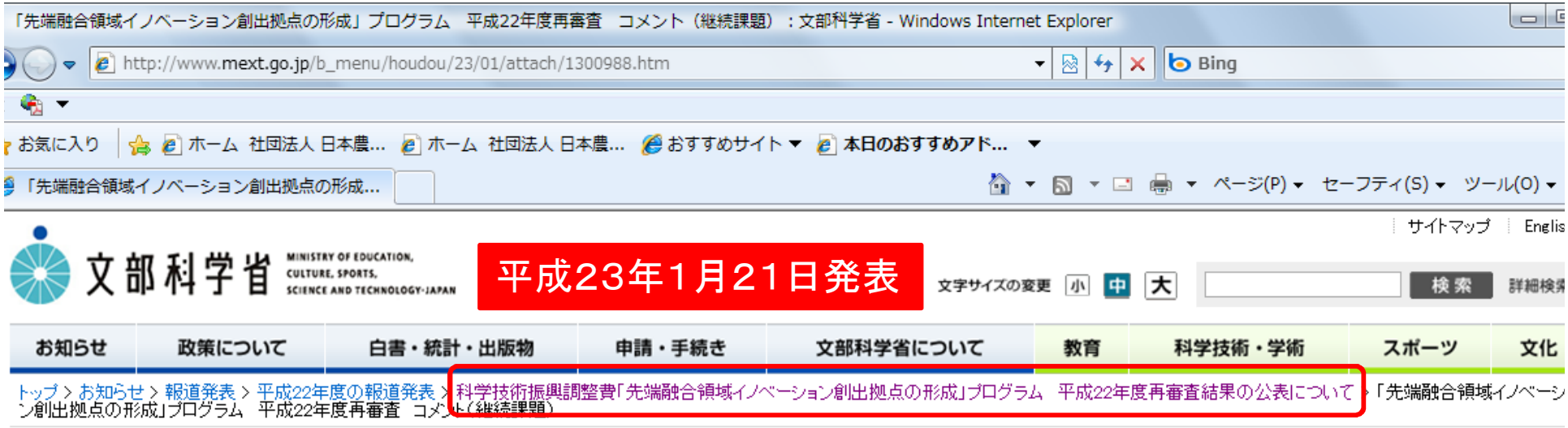
PTMs frequently occur in ID regions

PTMs of p53



*R. Kamata & K. Sakaguchi, Seikagaku, **82**, 484-493 (2010)*
(Partially modified)

PTMs frequently occur in ID regions



●「先端融合領域イノベーション創出拠点の形成」プログラム　平成22年度再審査　コメント（継続課題）

【継続課題】横浜市立大学「翻訳後修飾プロテオミクス医療研究拠点の形成」

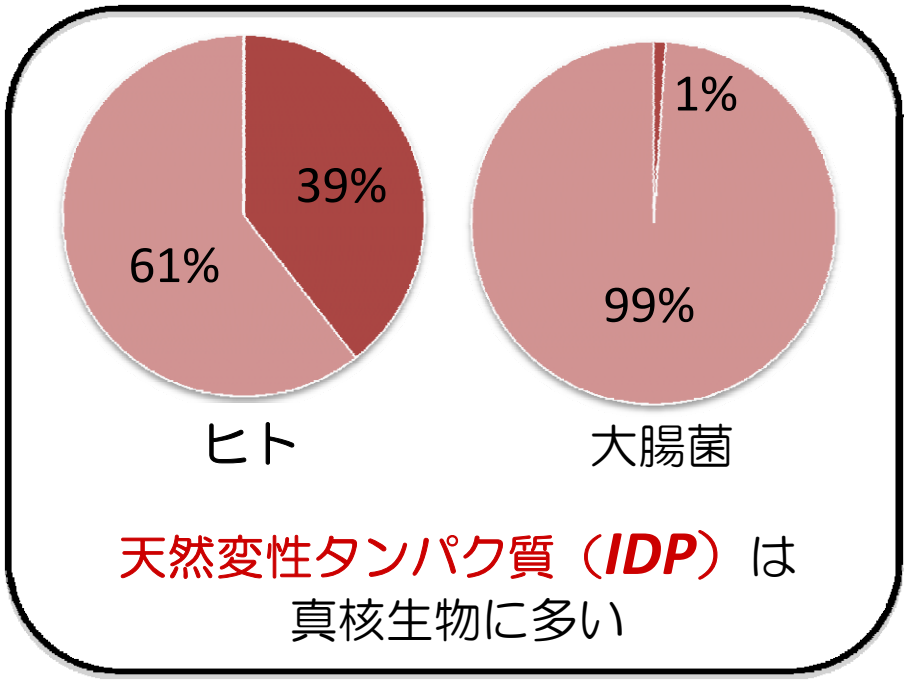
本課題は、タンパク質解析技術を基盤として、翻訳後修飾と疾患の関係を明らかにし、診断マーカーの発見や創薬を産学協働で継続的に実施する拠点形成を目指す取組である。本拠点にはタンパク質の翻訳後修飾の解析成果を医療・創薬・機能性食品・化粧品などへ応用するための協働機関が参加しており、高度なプロテオミクス拠点を形成して産業界の開発研究の推進を図るために必要な解析技術を揃えている。特に大規模分析による診断マーカー探索とそれに基づく診断薬、治療薬の開発は一定の競争力を持つことから、事業化を促進する研究拠点の形成が期待される。プロジェクト全体としての構想や今後の方向性が明確で、協働機関ともよく連携して活動が進められており、協働機関の大学に対する評価や期待も大きい。本課題については、これまでの進捗状況及び今後の見通しから判断して、本プログラムの趣旨に合致した成果を実現することが十分期待されるため、来年度から本格的実施に移行することが適当である。

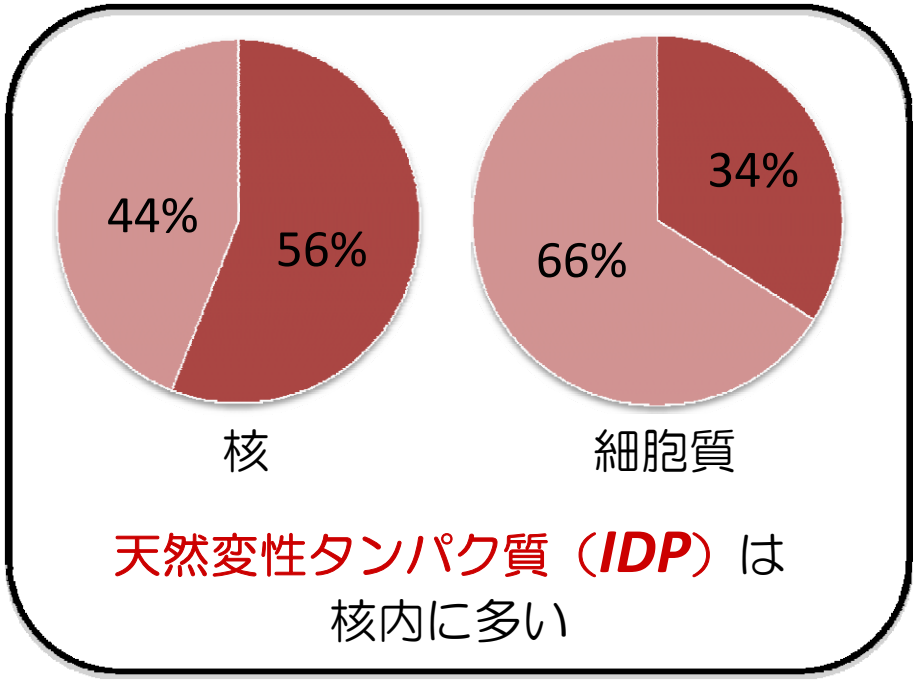
(1)目標達成度（1.ミッションステートメントの達成度、2.研究・技術開発の達成度、3.システム改革の進捗状況、4.人材育成の進捗状況）

タンパク質の翻訳後修飾の解析と医療への応用について、これまで集中的に研究が進められてきたリン酸化ペプチドに関する学術論文の質・量が共に優れており、学術的な研究成果として高く評価される。修飾タンパク質の質量分析等の要素技術基盤の確立に向けた着実な進捗が認められる等の目標は達成されている。

(2)協働機関との関係

IDPs are mainly found in eukaryotes





Fukuchi et al. unpublished data

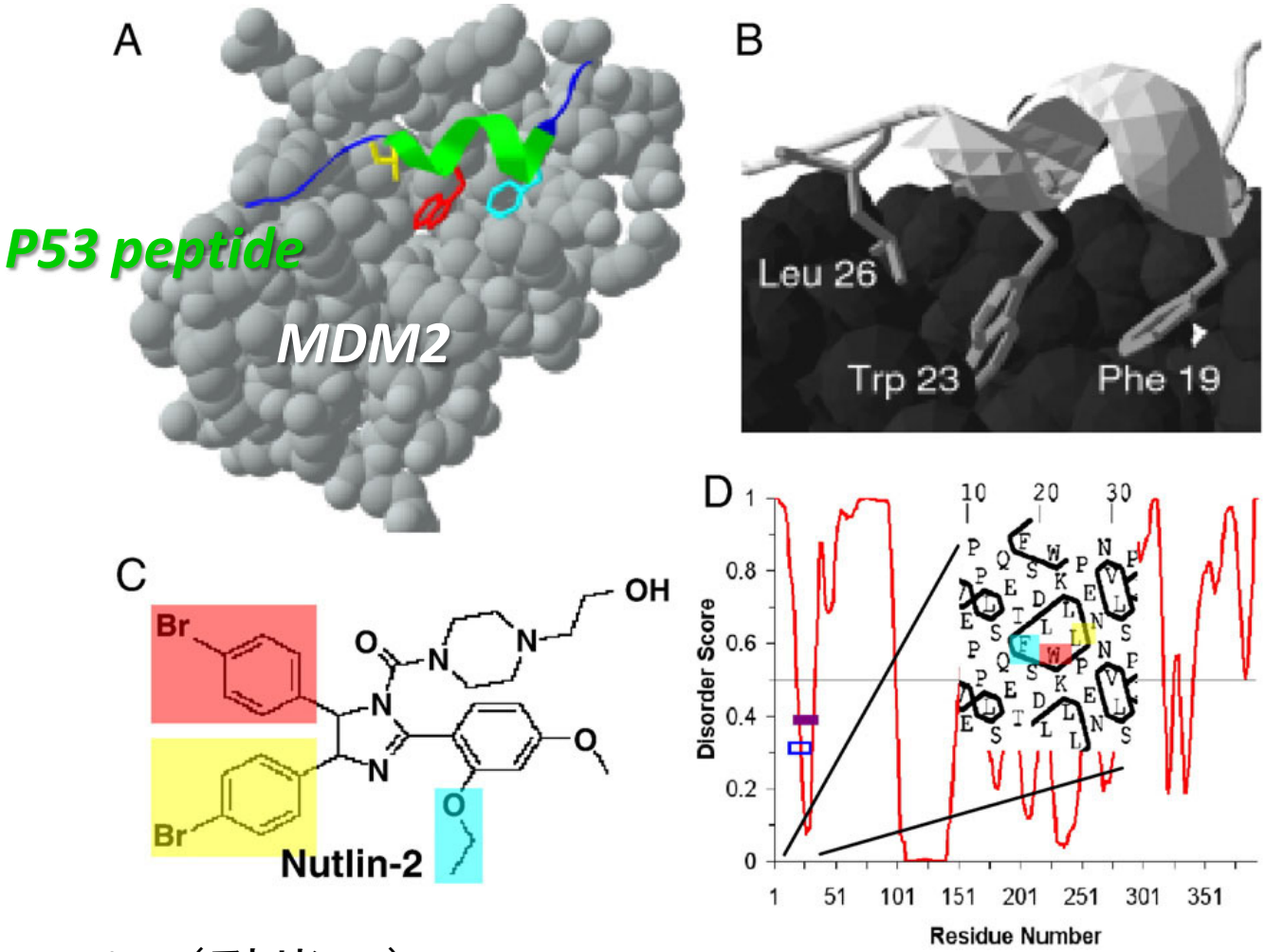
DNAの複製・転写・修復・組換やヒストン修飾などに関与する
核内タンパク質の多くは分子内に長大な天然変性領域をもっている

Minezakiらは、膜タンパク質において天然変性領域が膜の細胞質側に
顕著に見られることを発見した。

IDPs as novel drug targets

One partner (p53) is disordered

& the second (E3: MDM2) is structured



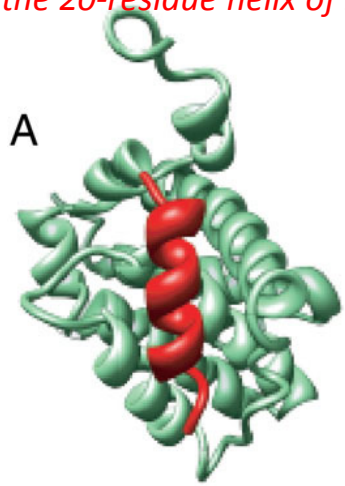
Nutlin-2（ヌトリン-2）:MDM2 Antagonist

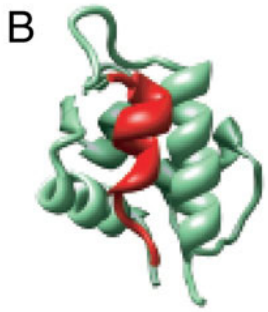
IDPs as novel drug targets

One partner is disordered & the second is structured

Bcl-xL & BAK fragment

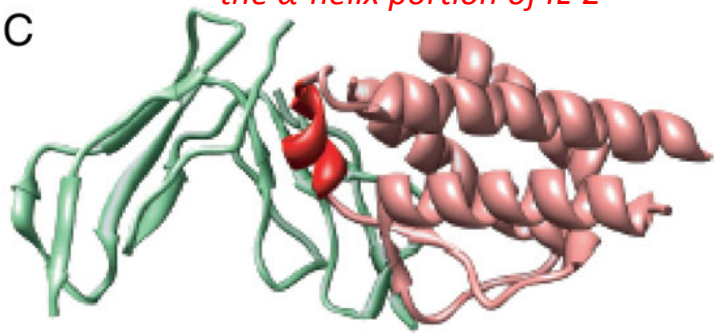
Small molecules were designed based on the 20-residue helix of BAK



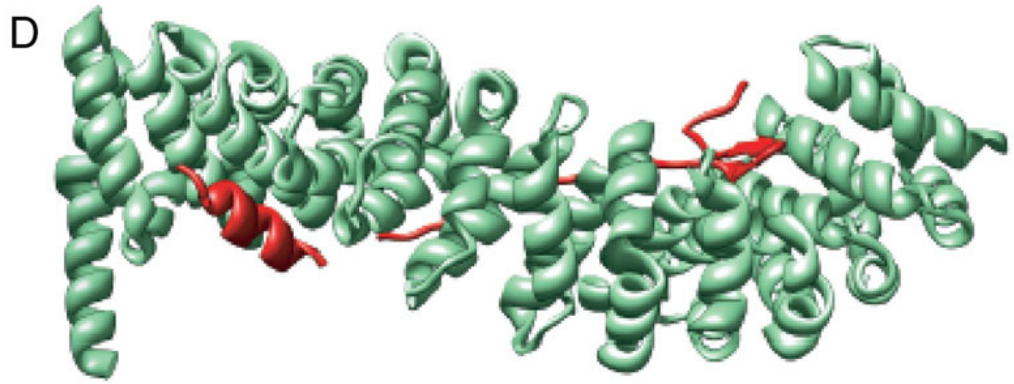


IL-2 receptor α & IL-2

Small molecules were designed based on the α-helix portion of IL-2

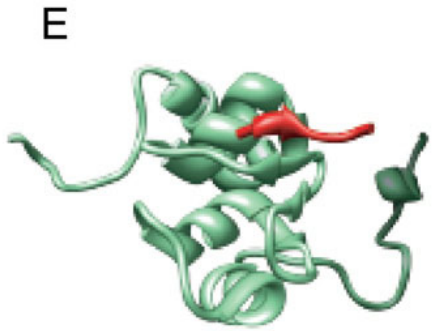


MDM2 & P53 fragment



β-catenin & T cell factor

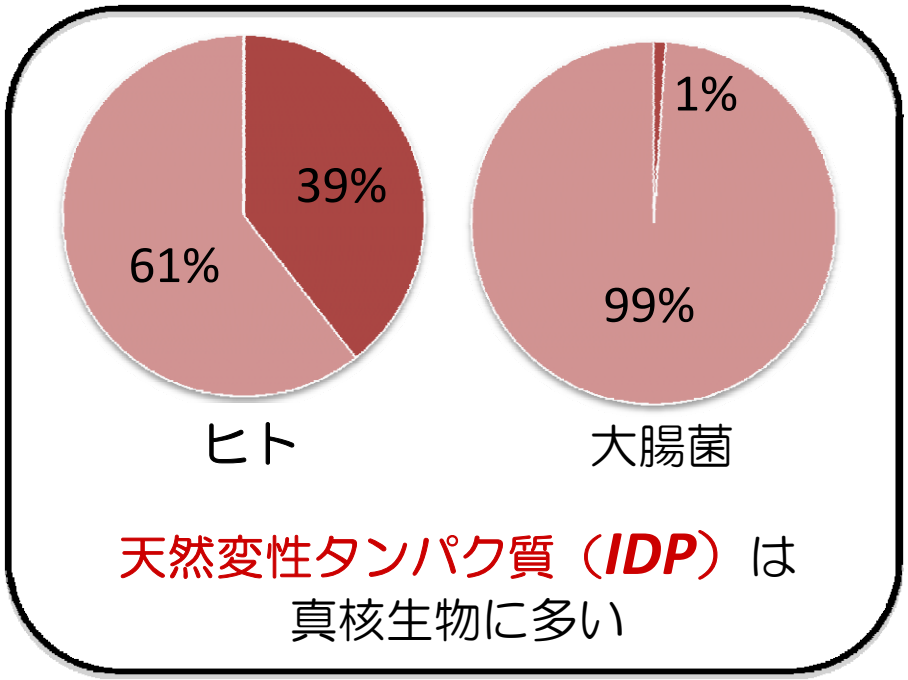
Binding sites of small molecules were not clear

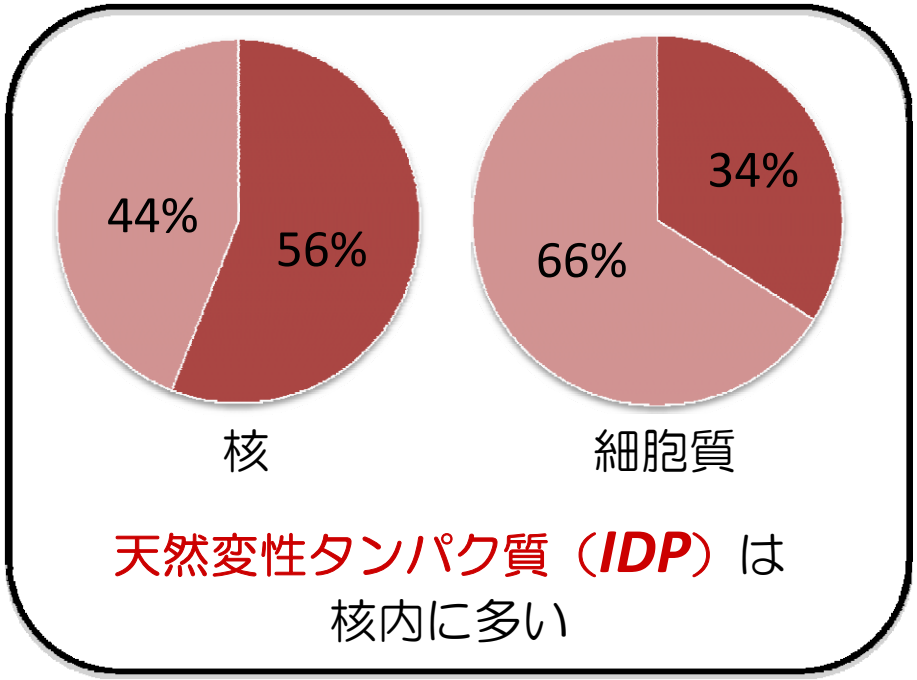


XIAP & Smac fragment

Small molecules were designed based on the β-strand fragment (AVPIAQKSE) of Smac

IDPs are mainly found in eukaryotes





Fukuchi et al. unpublished data

DNAの複製・転写・修復・組換やヒストン修飾などに関与する
核内タンパク質の多くは分子内に長大な天然変性領域をもっている

*80% of the proteins in the human cancer-associated proteins database contain **ID region** (The Scientist **23**, 47, 2009)*

Functional Repertoires of IDPs

IDPs as hubs in protein signaling networks

p53 regulates over 150 gene transcriptions (p21, MDM2, BAX ….)

IDPs and PTMs (post-translational modifications)

PTMs frequently occur in ID regions

Substrates for many PM enzymes such as kinases are ID proteins

IDPs and AS (alternative splicing)

AS region of mRNA code for ID regions

AS is likely to be involved in cell differentiation

IDPs are mainly found in eukaryotes

Eukaryotes contain far more intrinsic disorder than prokaryotes

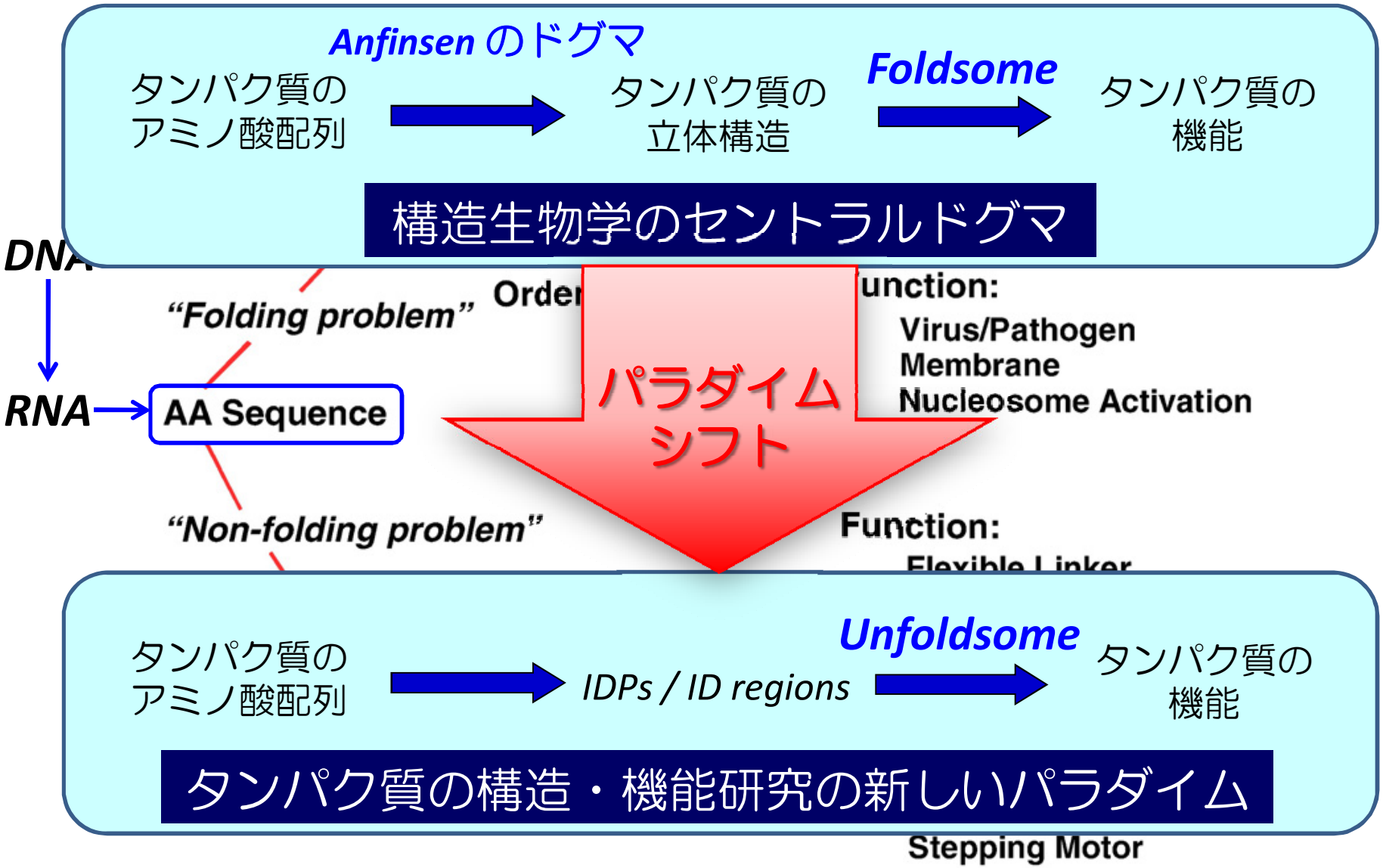
IDPs and human diseases

Alzheimer disease and amy-β, tau, α-synuclein

IDPs as novel drug targets

One partner is disordered and the second is structured

Protein Structure-Function Analysis



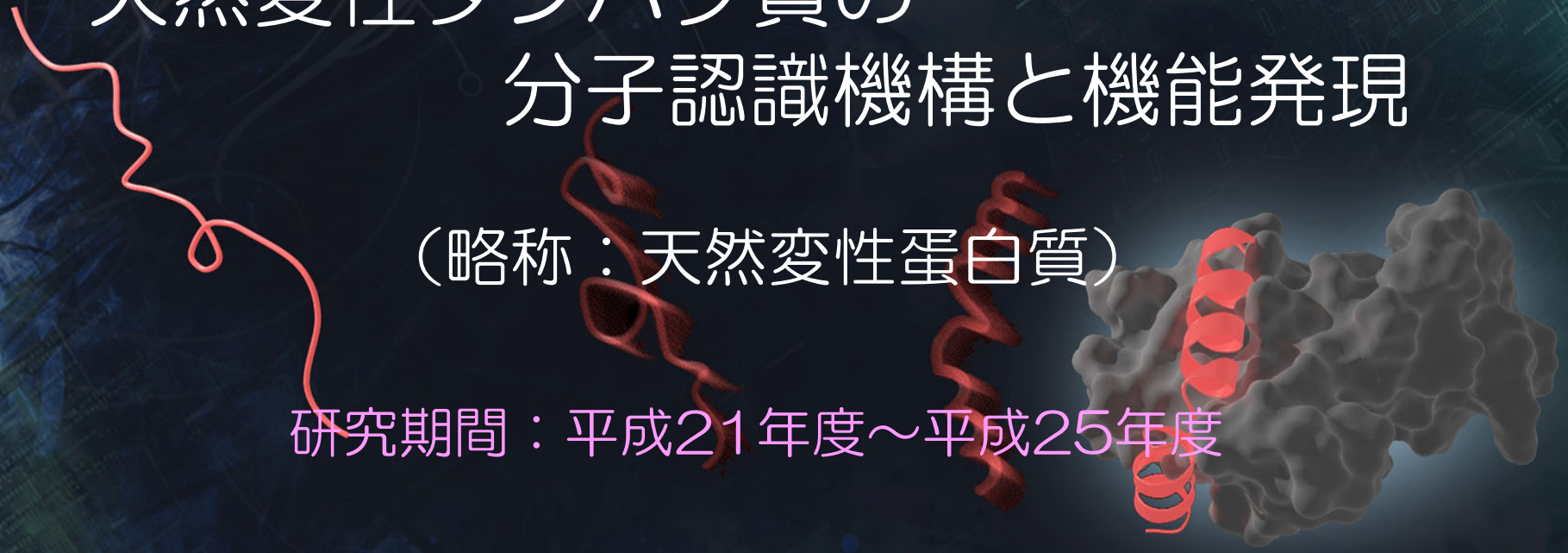
Biochim. Biophys. Acta, ***1804****, 1231-1264 (2010)*

平成21年度（2009年度） 科研費

「新学術領域研究」

天然変性タンパク質の分子認識機構と機能発現

（略称：天然変性蛋白質）



研究期間：平成21年度～平成25年度

領域代表者：佐 藤　衛

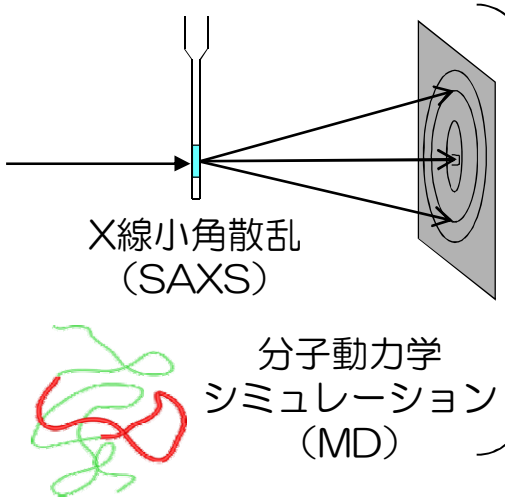
（横浜市立大学 大学院 生命ナノシステム科学研究科）

研究グループの研究内容

構造生物学グループ　**動的構造解析**

X線小角散乱, 高速AFM, NMR, 質量分析で天然変性タンパク質の動的構造を決定

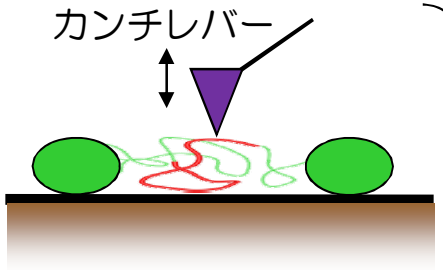
天然変性タンパク質の動的構造解析はX線結晶構造解析法などの従来の手法だけでは困難で、新しい手法の開発が不可欠



MD-SAXS法を発展させた新しい方法の開発

↓

天然変性タンパク質の原子分解能での動的構造解析



高速原子間力顕微鏡
（高速AFM）
50 msec/frame

高速AFM法を発展させた新しい方法の開発

↓

天然変性タンパク質1分子のナノ解像度での動的構造解析

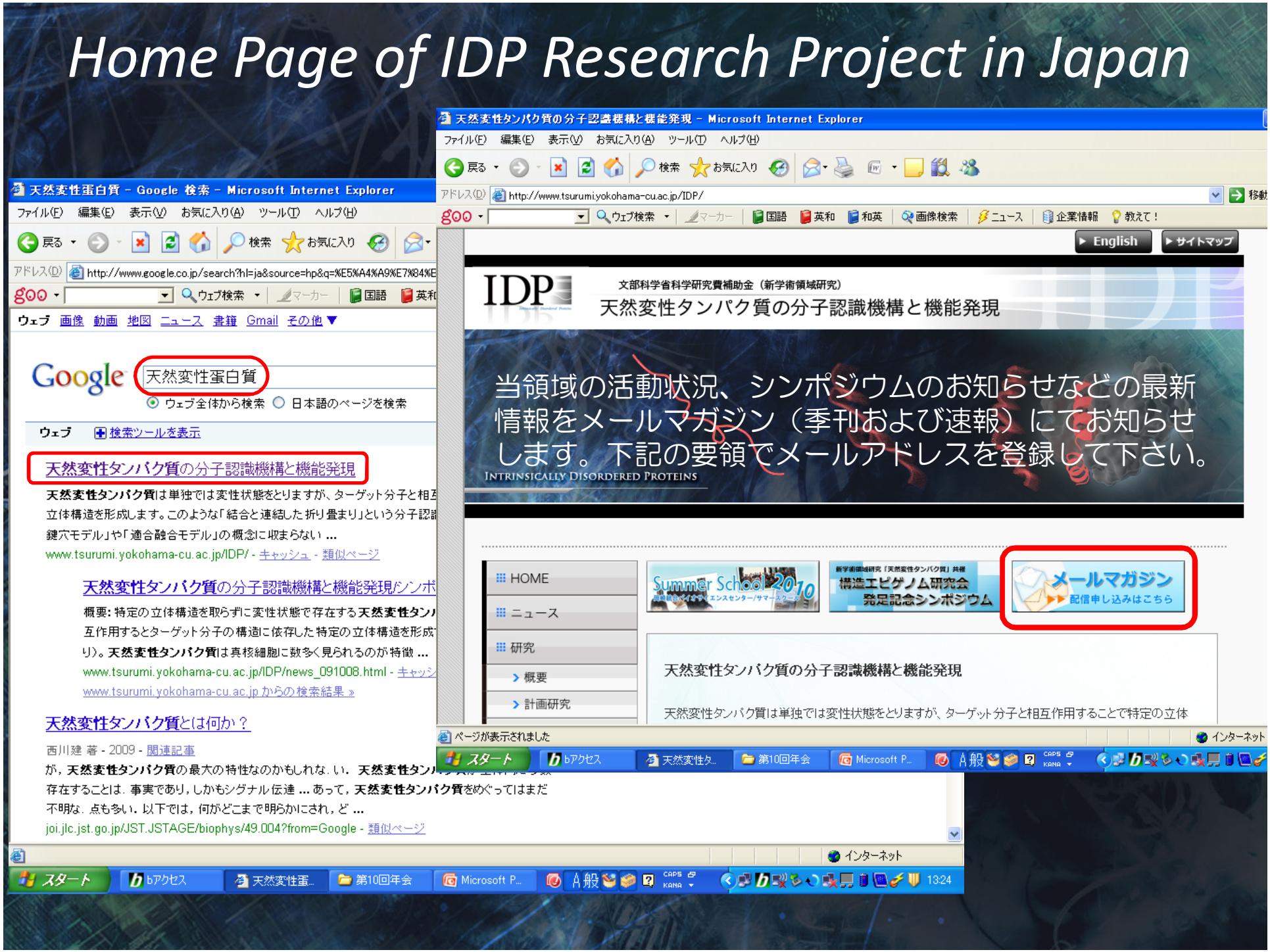
分子生物学グループ　**機能解析**

分子生物学、生化学、分子遺伝学的手法を用いて核内でDNA複製・転写・組換・修復に関与する天然変性タンパク質の機能を解明

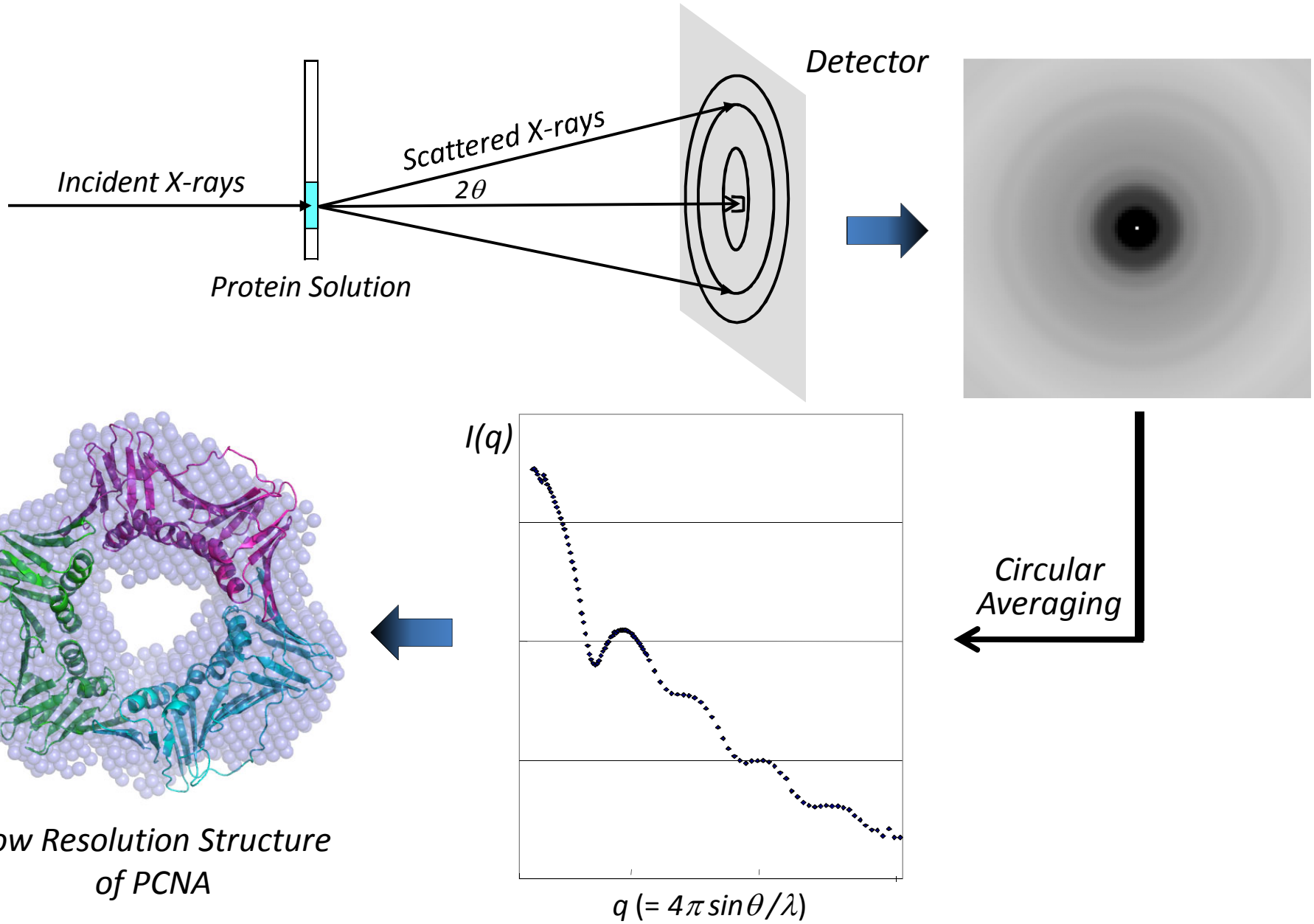
情報生物学グループ　**構造・機能予測**

分子動力学的シミュレーションなどの計算科学的手法および質・量ともに充実したデータベースを構築して天然変性タンパク質の構造・機能を予測

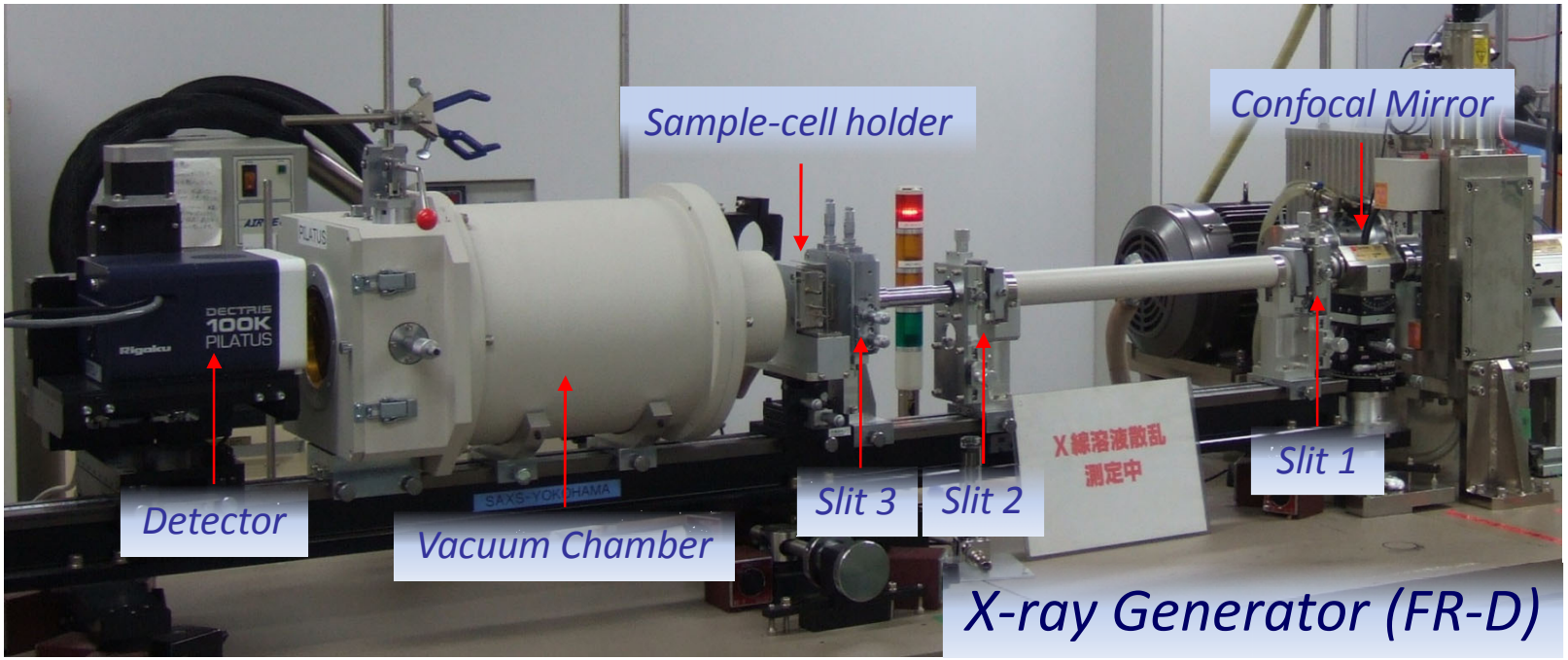
Home Page of IDP Research Project in Japan



Small-Angle X-ray Scattering（SAXS）



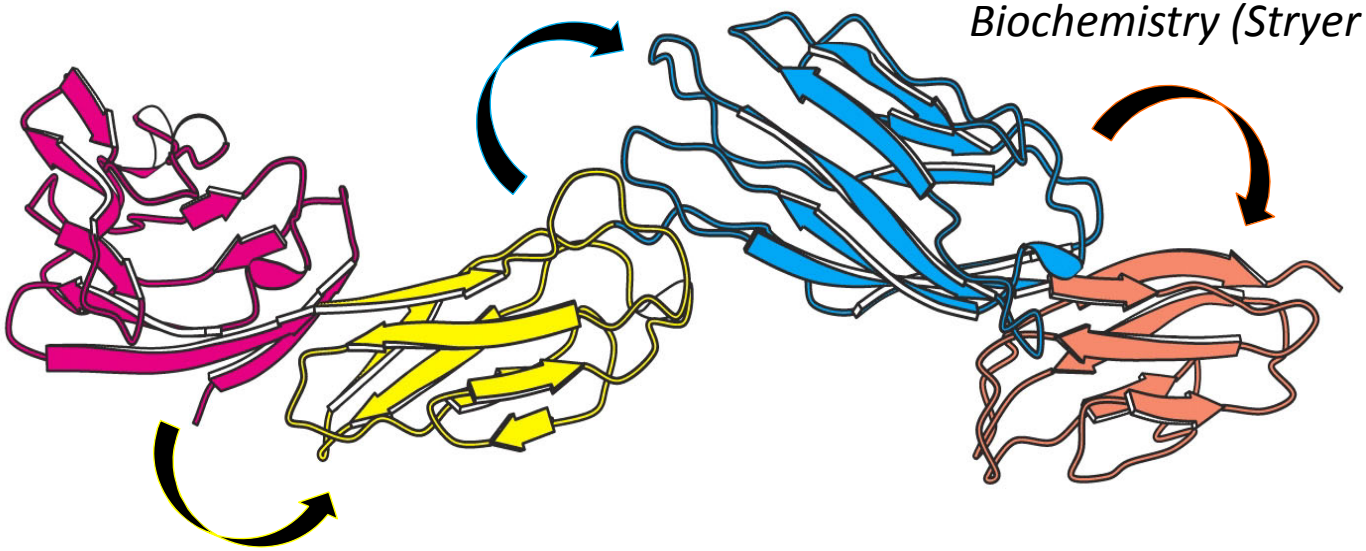
SAXS in Yokohama City University



Detector	*PILATUS 100K*
Energy range	*3 – 30 keV*
Active area	*83.8 x 33.5 mm*
Pixel number	*512 x 256*
Efficiency	*100% at 8keV 35% at 17keV*
Spatial resolution	*172 μm*

Small-Angle X-ray Scattering（SAXS）

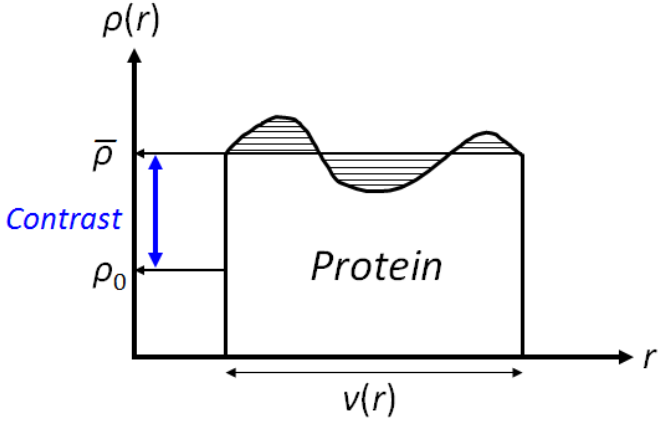
Biochemistry (Stryer et al., 5 ed.)

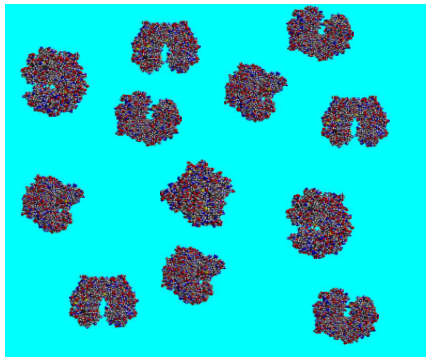


Most of multi-domain proteins are largely fluctuated in solution

Small-Angle X-ray Scattering（SAXS）

Multi-domain proteins in solution





溶媒の電子密度 ρ_0

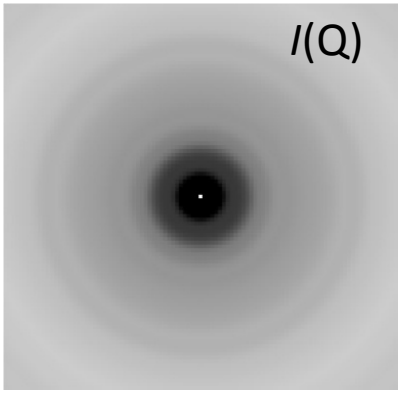
X-rays

タンパク質10^{12}分子

散乱因子： $F(\mathbf{Q}) = \int (\rho(\mathbf{r}) - \rho_0) e^{-i\mathbf{Q}\cdot\mathbf{r}} d^3\mathbf{r}$ （溶媒からの*Contrast*）

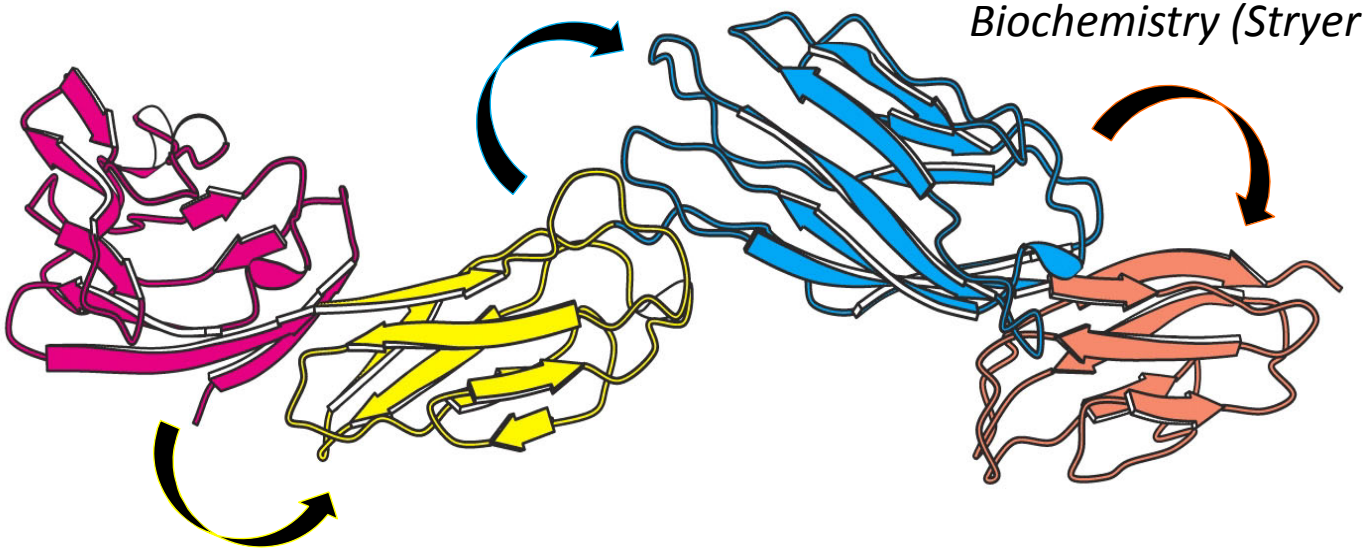
回転平均
&
アンサンブル平均

散乱強度： $I(Q) = \left\langle \left\langle |F(\mathbf{Q})|^2 \right\rangle_{\Omega_Q} \right\rangle_{\text{Ensemble}}$



二次元検出器

Small-Angle X-ray Scattering（SAXS）

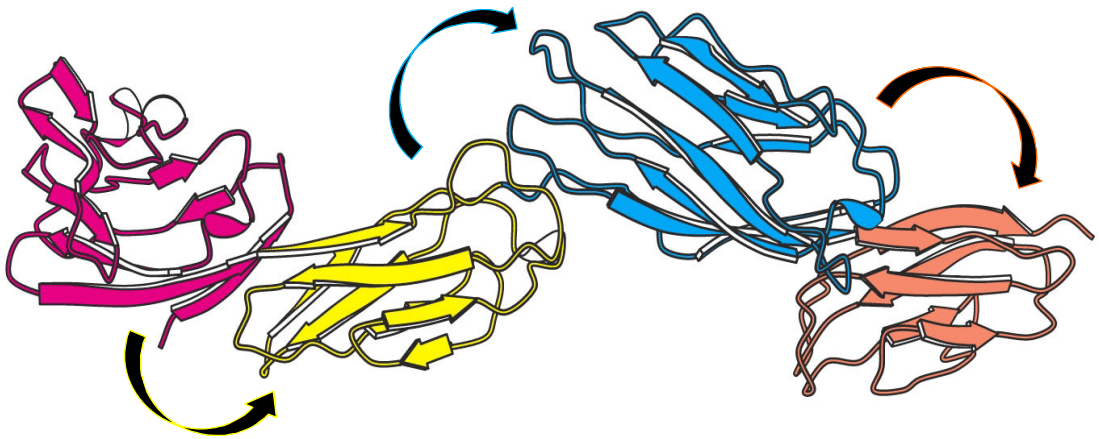


Biochemistry (Stryer et al., 5 ed.)

Most of multi-domain proteins are largely fluctuated in solution

Time-averaged

No structural & functional information !



Develop "MD-SAXS" to analyze the dynamical structure of multi-domain protein in solution

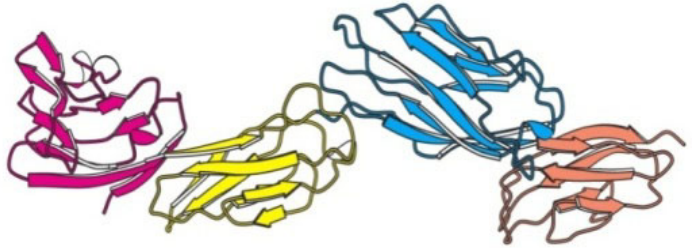
MD simulation of the multi-domain protein

The initial structure is constructed from the crystal structure of each domain

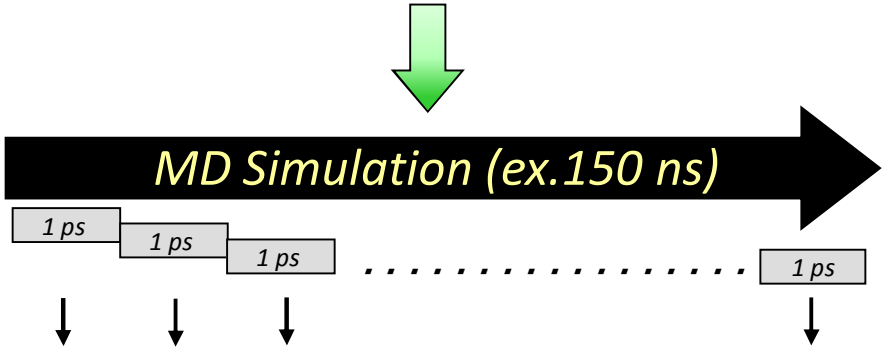
The result is assessed experimentally by SAXS

Principle of MD-SAXS

Construction of Initial Atomic Structure

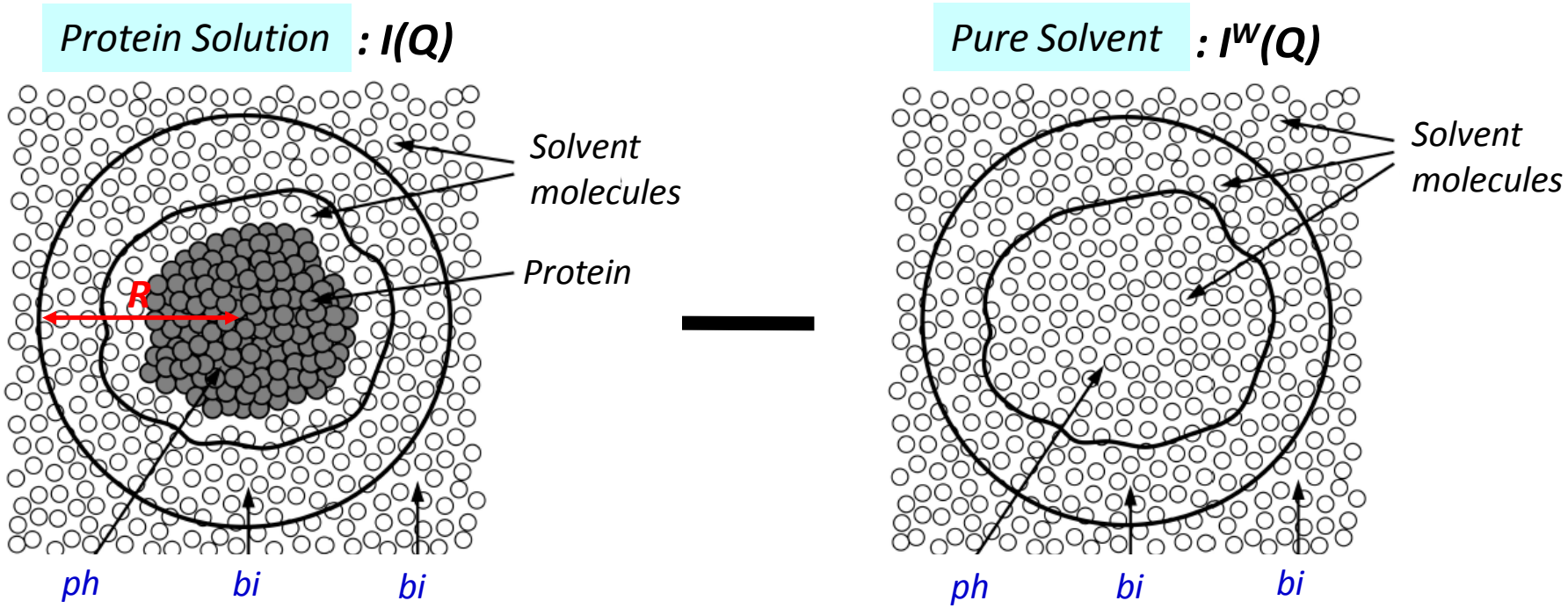


Each domain structure: Crystallographic analysis



Calculation of I(q) from each snap-shot structure

Calculation of I(q) from Each Snap Shot Structure



ph : Region for protein and hydration water molecules

bi : Region for water molecules not perturbed by protein

$$I(Q) - I^{W}(Q) = \Delta I_{ph,ph}(Q) + \Delta I_{ph,bi}(Q) + \boxed{\Delta I_{ph,bo}(Q) + \Delta I_{bi,bi}(Q) + \Delta I_{bi,bo}(Q) + \Delta I_{bo,bo}(Q)}$$

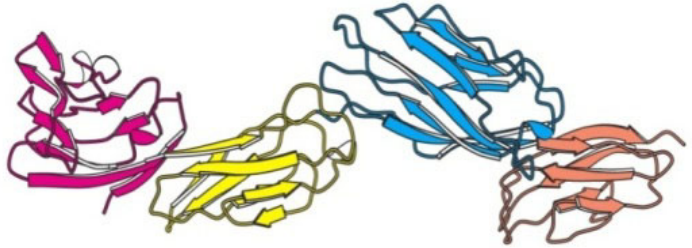
Expansion of Debye formula by spherical harmonics

= 0 for R >> Region: bi

Oroguchi et al. Biophys. J. ***96****, 2808-2822 (2009)*

Principle of MD-SAXS

Construction of Initial Atomic Structure



Each domain structure: Crystallographic analysis

MD Simulation (ex.150 ns)

1 ps 1 ps 1 ps . . . . . 1 ps

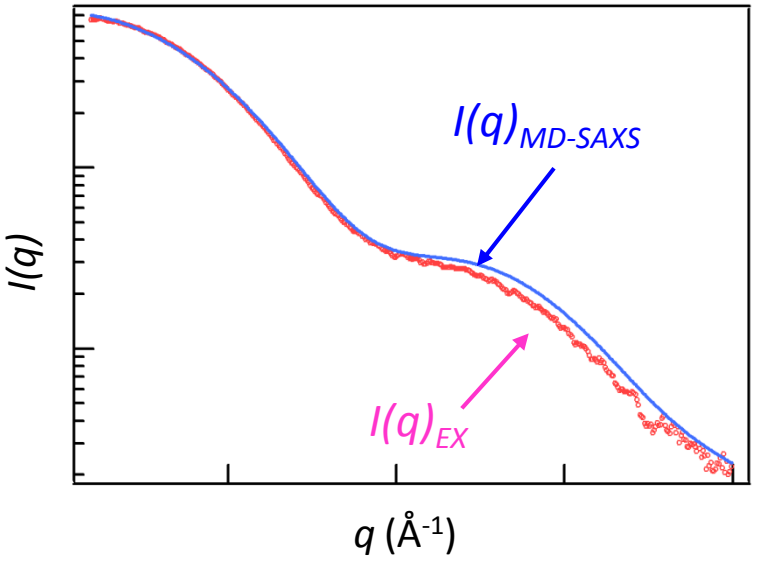
Calculation of I(q) from each snap-shot structure

I(q) q q q . . . . . I(q) q

Average the I(q) data-sets: $I(q)_{MD\text{-}SAXS}$

Inconsistent

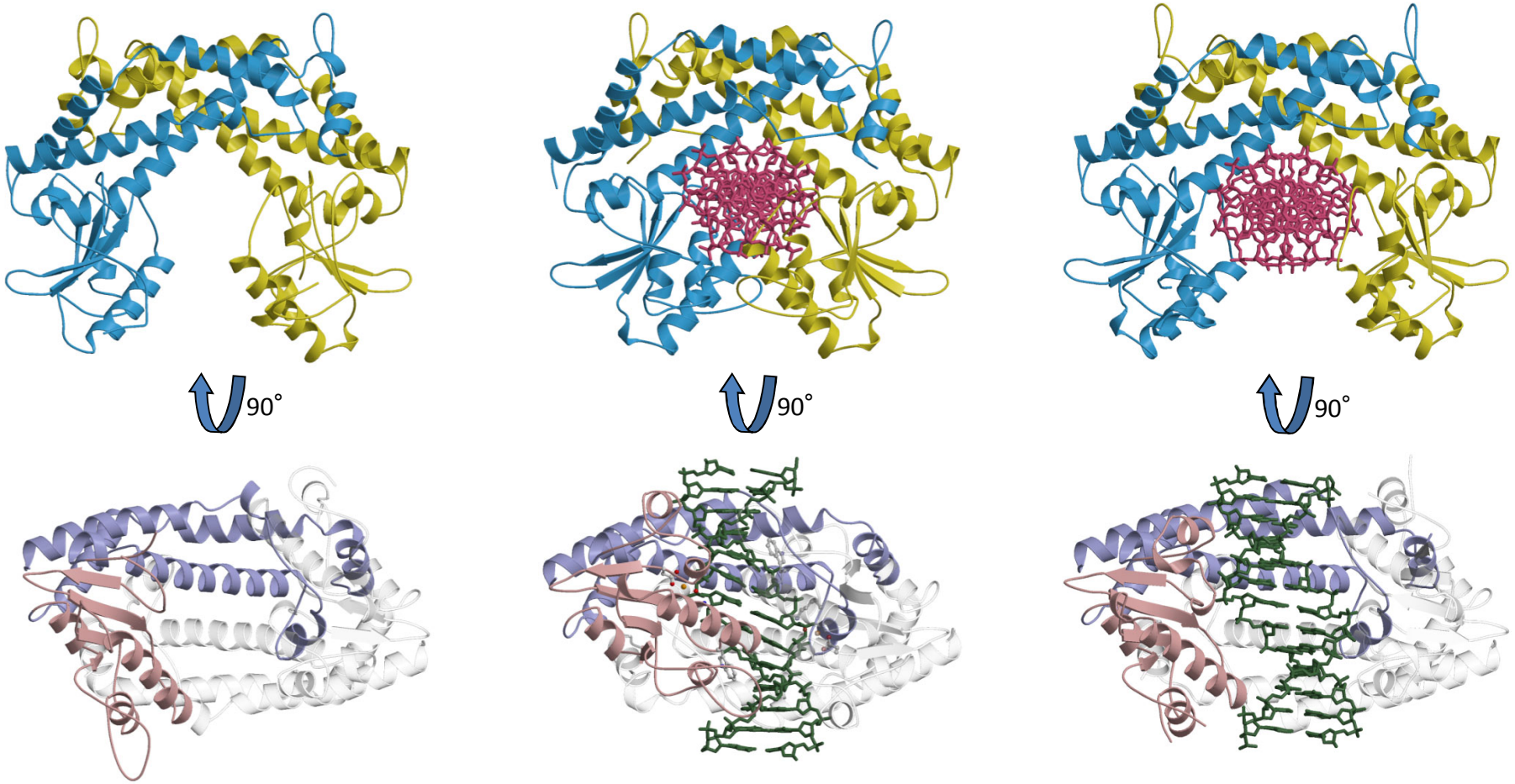
Consistent
Each snap-shot structure is the dynamical structure of the protein



Compare $I(q)_{MD\text{-}SAXS}$ *with* $I(q)_{EX}$

Example 1: Restriction Endonuclease, EcoO109I

EcoO109I consists of 272 residues (Mr 31,000) and exists as a dimer in solution

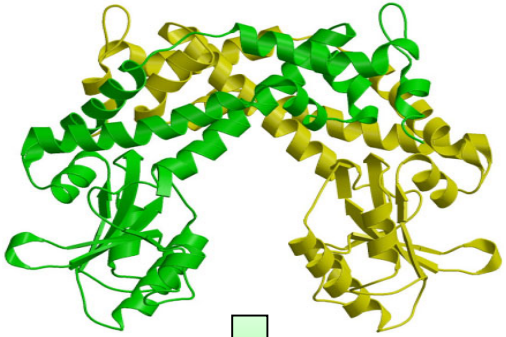


EcoO109I | *EcoO109I (WT)-DNA* | *EcoO109I (D77A)-DNA*

Hashimoto et al. J. Biol. Chem. ***280****, 5605-5610 (2005)*

Principle of MD-SAXS

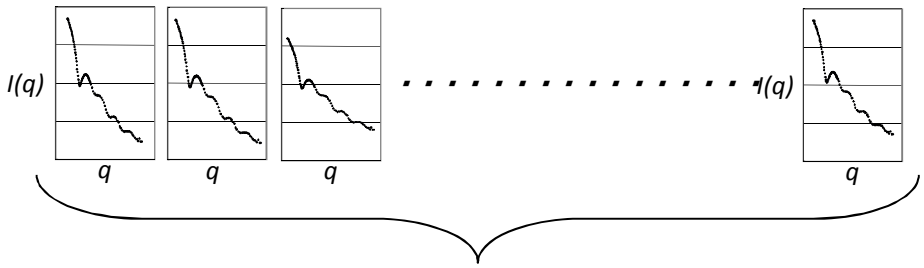
Construction of Initial Atomic Structure



MD Simulation (ex.150 ns)

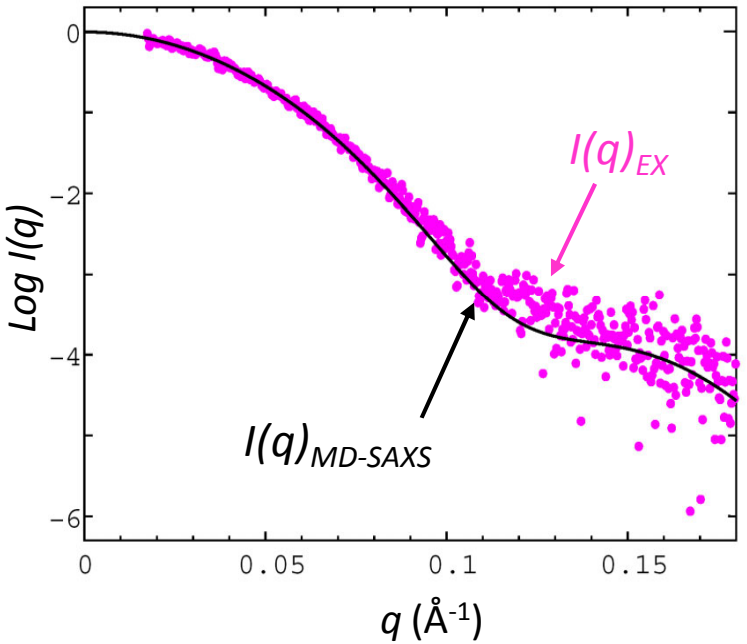
1 ps 1 ps 1 ps . . . . . 1 ps

Calculation of I(q) from each snap-shot structure



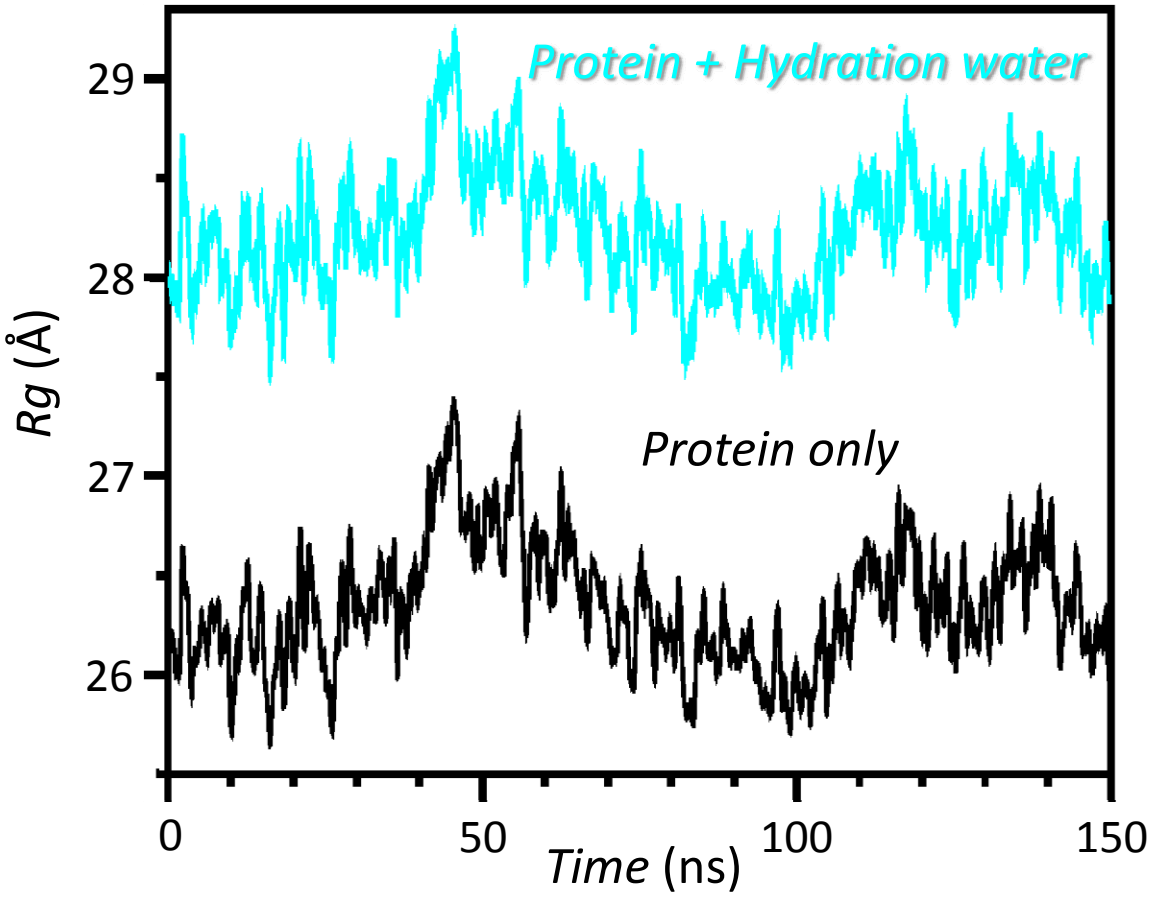
Average the I(q) data-sets: $I(q)_{MD\text{-}SAXS}$

Consistent
Each snap-shot structure is the dynamical structure of the protein



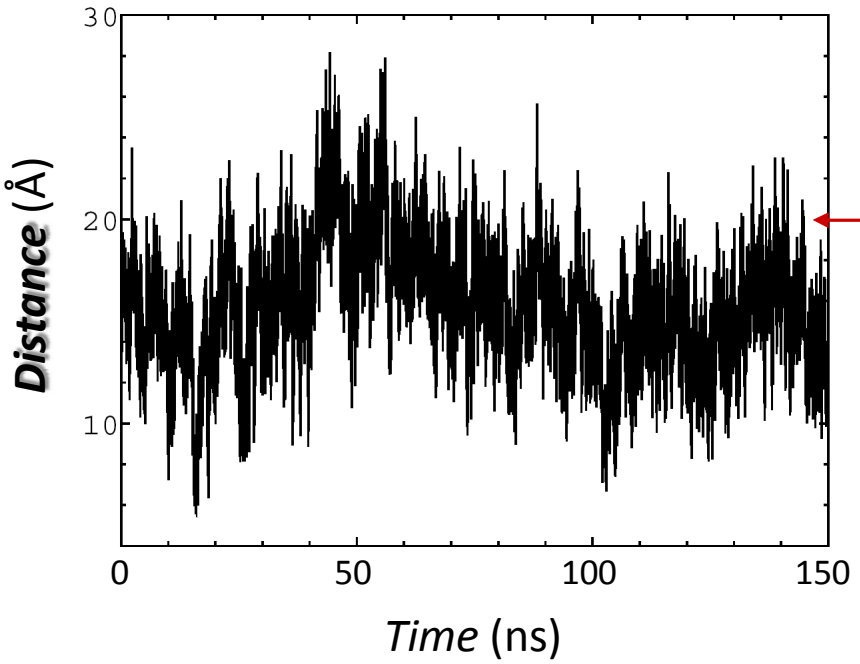
Compare $I(q)_{MD\text{-}SAXS}$ *with* $I(q)_{EX}$

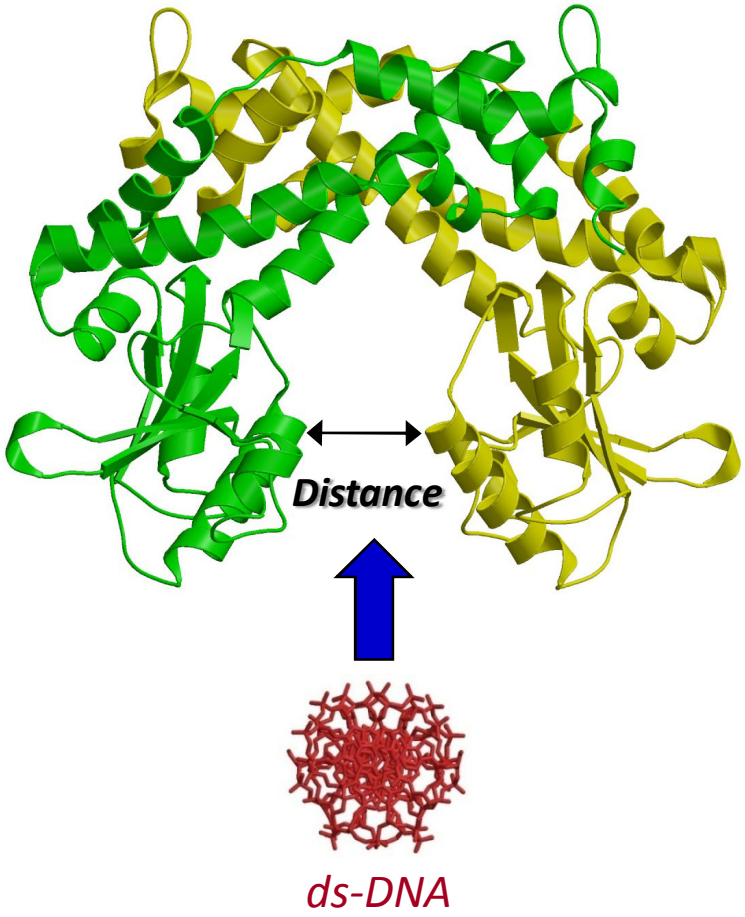
Rg as a Function of Simulation Time



- *Structure (Rg) is fluctuated with a cycle of about 100 ns*
- *Hydration shell width is about 2 Å*

Distance *as a Function of Simulation Time*

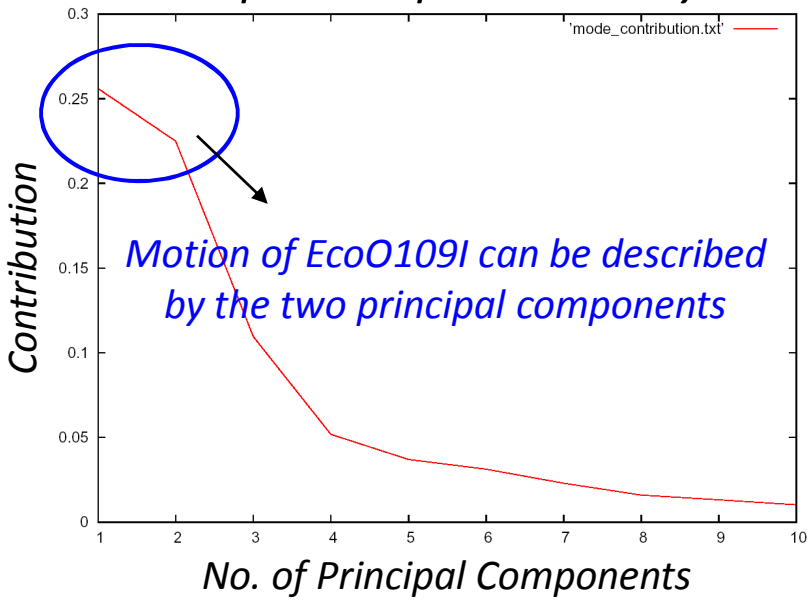


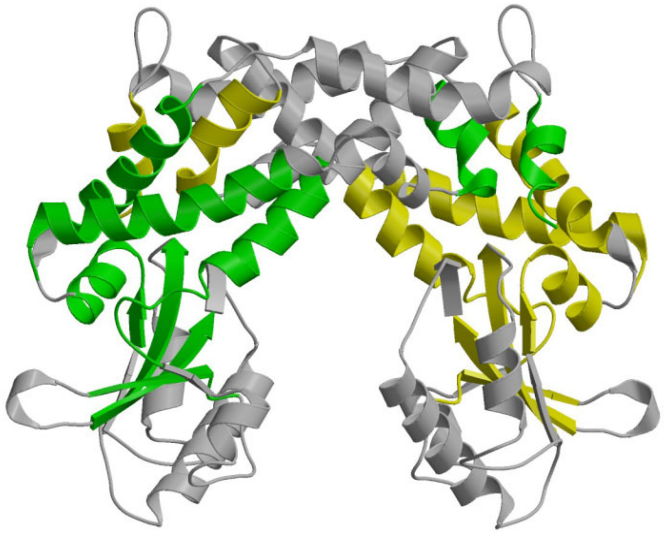


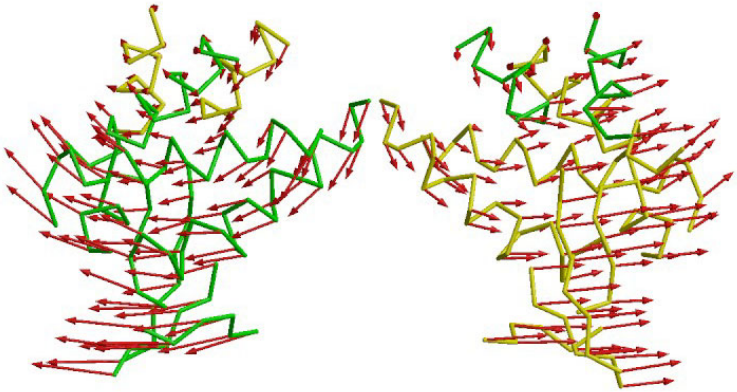
- *Structure (**Distance**) is fluctuated with a cycle of about 100 ns*
- *ds-DNA can enter within EcoO109I during about 100 ns*

Motion between Subunit A and Subunit B

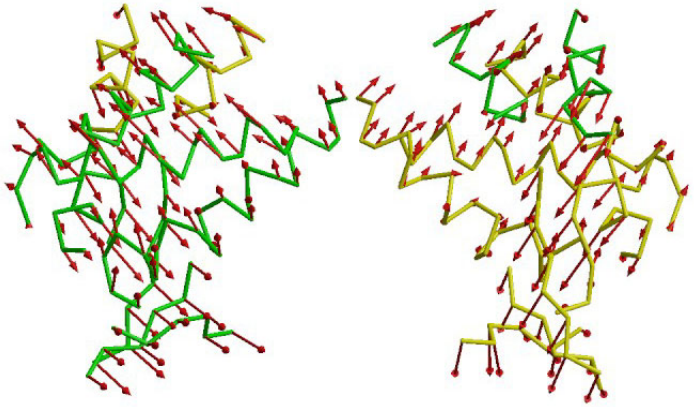
Principal Component Analysis







The first principal component: open-close motion

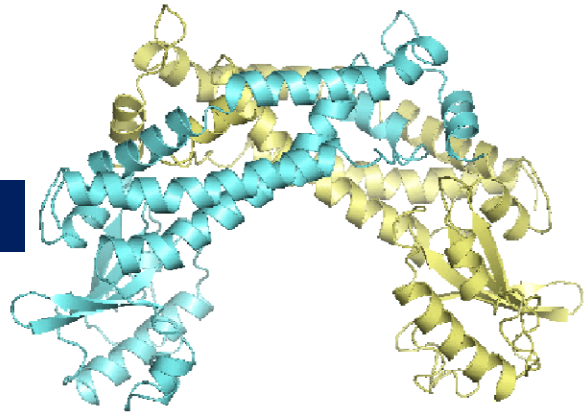


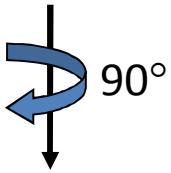
The second principal component: twisting motion

Oroguchi et al. Biophys. J. ***96****, 2808-2822 (2009)*

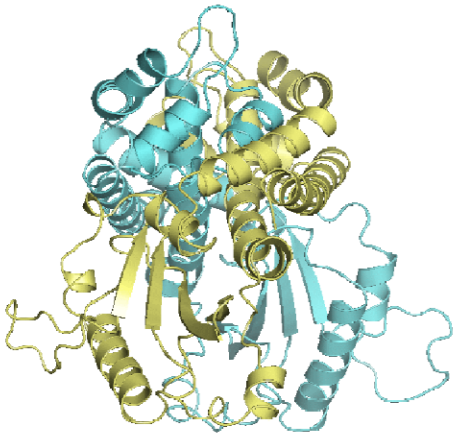
Motion between Subunit A and Subunit B

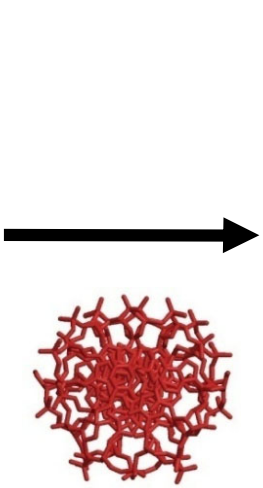
Open-close Motion



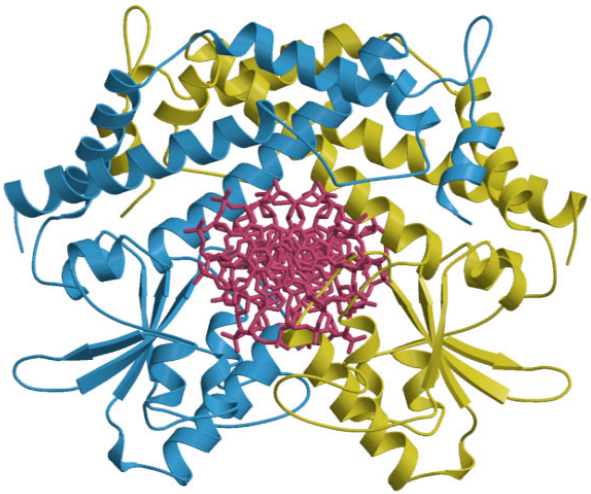


Twisting Motion





ds-DNA

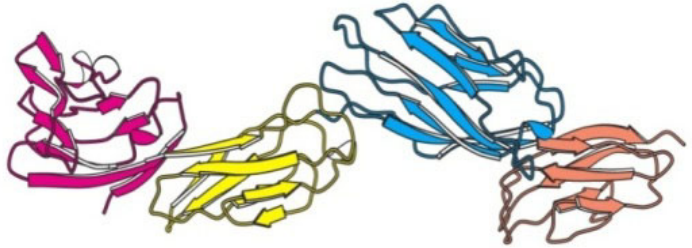


Population-Shift Model

Monod et al. J. Mol. Biol. (1965)

Principle of MD-SAXS

Construction of Initial Atomic Structure



Each domain structure: Crystallographic analysis

MD Simulation (ex.150 ns)

1 ps 1 ps 1 ps . . . . . 1 ps

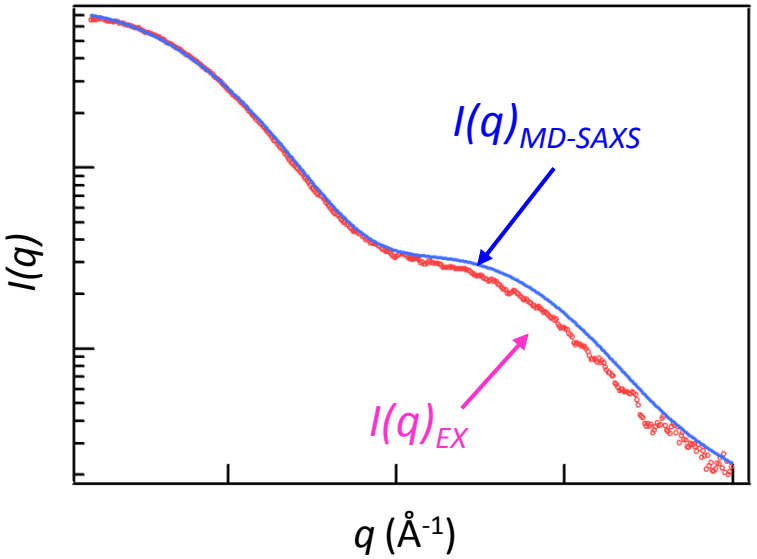
Calculation of I(q) from each snap-shot structure

I(q) q q q . . . . . I(q) q

Average the I(q) data-sets: $I(q)_{MD\text{-}SAXS}$

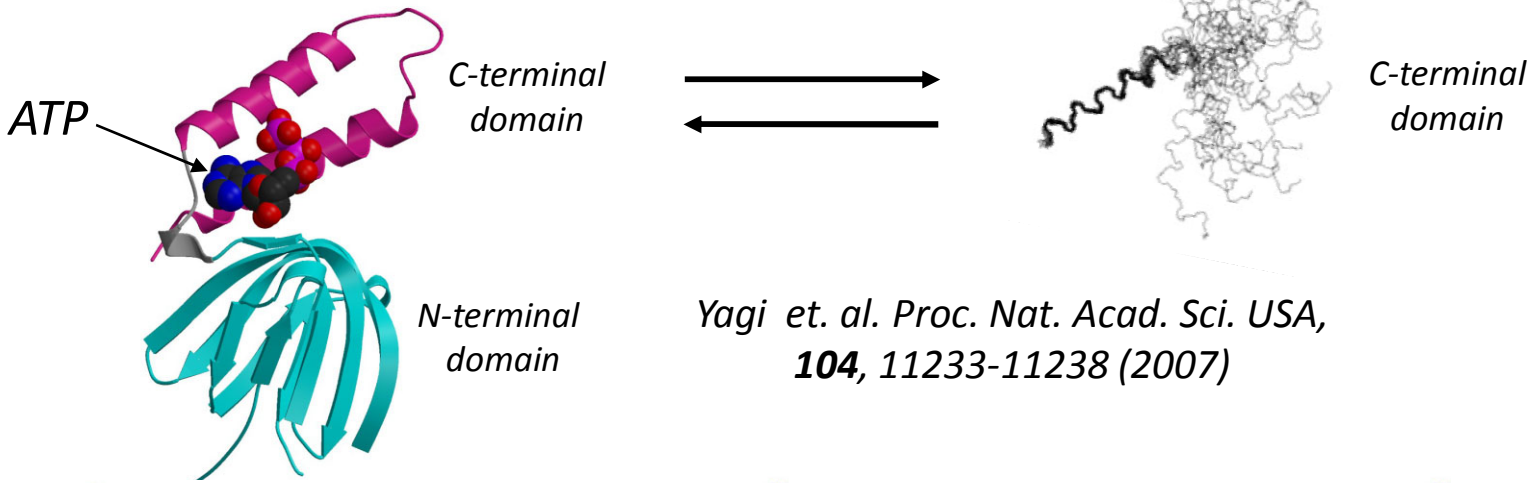
Inconsistent

Consistent
Each snap-shot structure is the dynamical structure of the protein

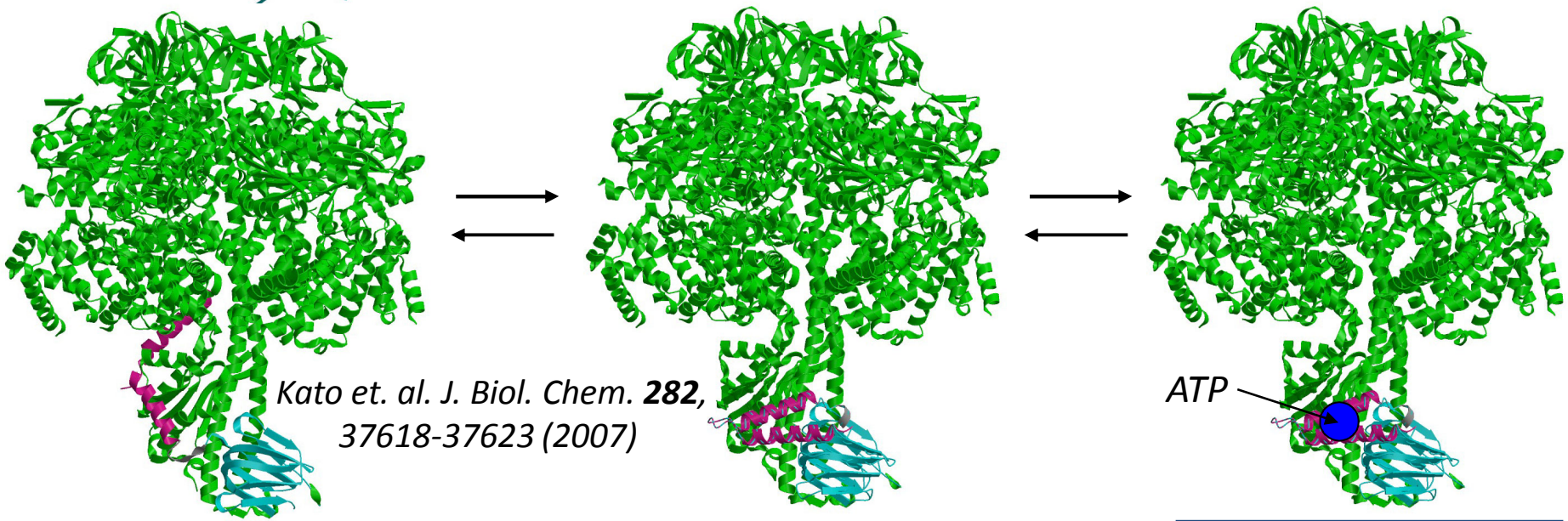


Compare $I(q)_{MD\text{-}SAXS}$ *with* $I(q)_{EX}$

Example 2: ε subunit of thermophilic F1-ATPase



*Yagi et. al. Proc. Nat. Acad. Sci. USA, **104**, 11233-11238 (2007)*



*Kato et. al. J. Biol. Chem. **282**, 37618-37623 (2007)*

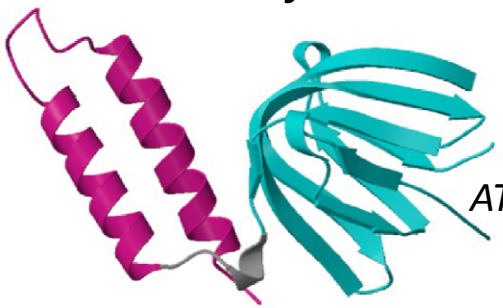
ATP-free Inactive Form

ATP-free Active Form

ATP-bound Active Form

MD-SAXS of ε subunit of F1-ATPase

Construction of Initial Atomic Structure



Crystal structure of ATP-free Active ε subunit

MD Simulation (ex.150 ns)

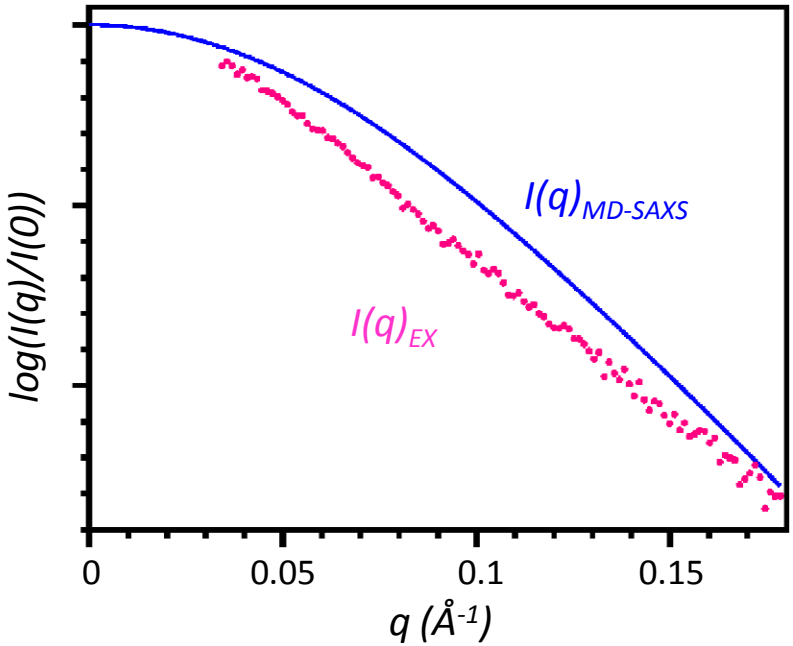
1 ps 1 ps 1 ps . . . . . 1 ps

Calculation of I(q) from each snap-shot structure

I(q) q q q . . . . . I(q) q

Average the I(q) data-sets: $I(q)_{MD\text{-}SAXS}$

Inconsistent



Compare $I(q)_{MD\text{-}SAXS}$ *with* $I(q)_{EX}$

MD-SAXS of ε subunit of F1-ATPase

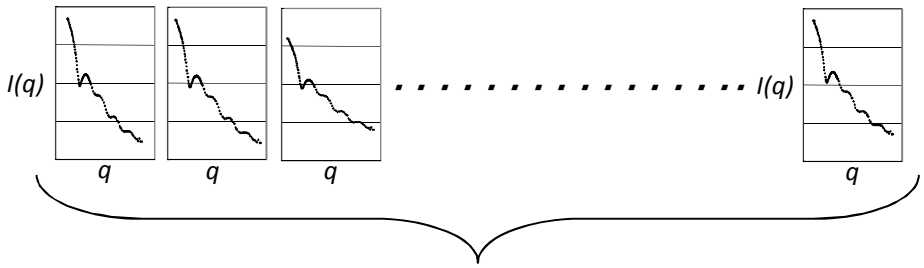
Construction of Initial Atomic Structure

Predicted structure of ATP-free inactive ε subunit

MD Simulation (ex.150 ns)

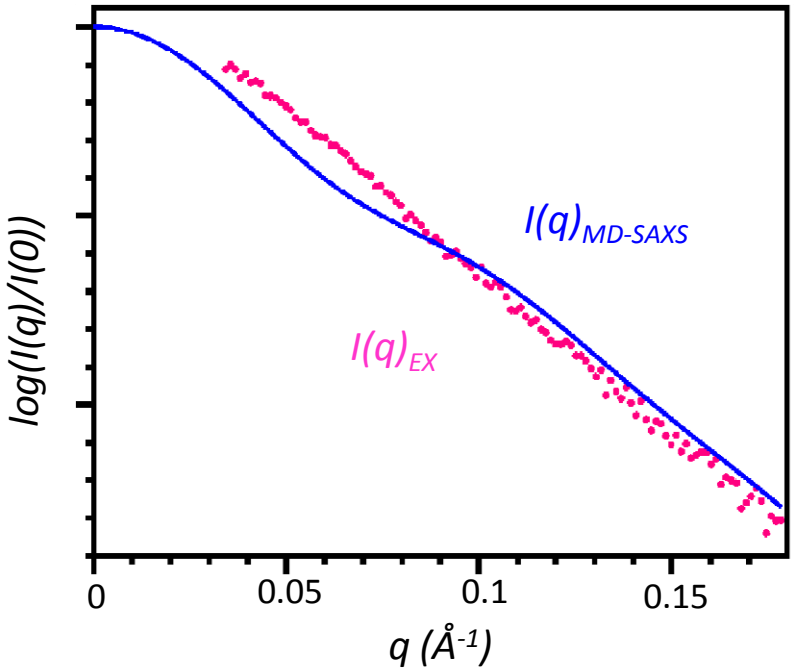
1 ps 1 ps 1 ps . . . . . 1 ps

Calculation of I(q) from each snap-shot structure



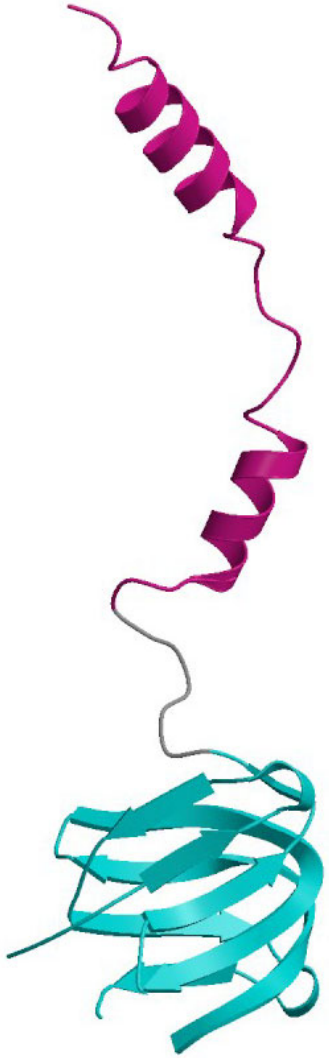
Average the I(q) data-sets: $I(q)_{MD\text{-}SAXS}$

Inconsistent

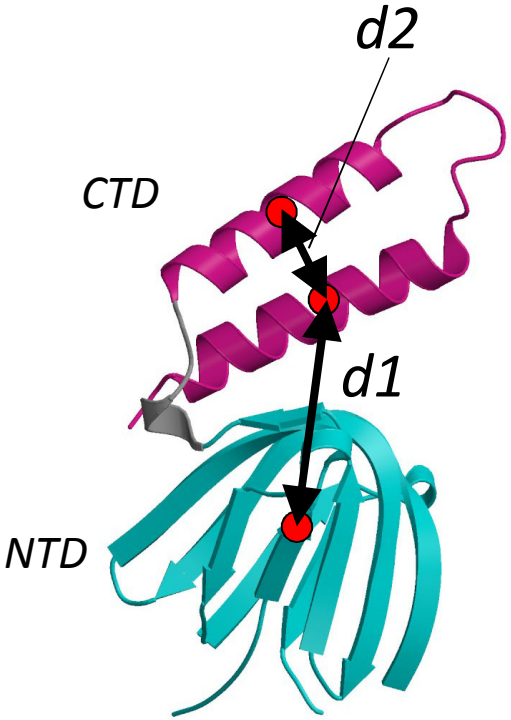


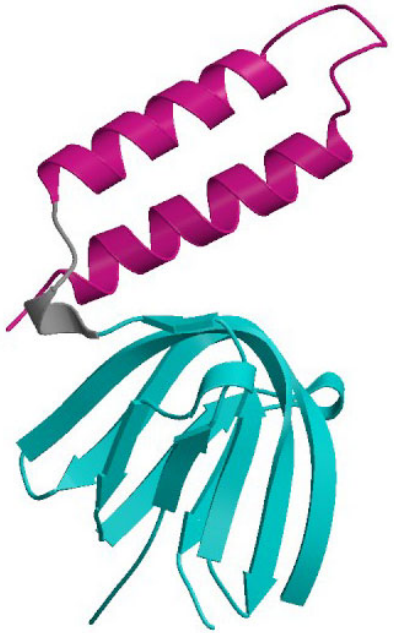
Compare $I(q)_{MD\text{-}SAXS}$ with $I(q)_{EX}$

Reconstruction of Initial Atomic Structure



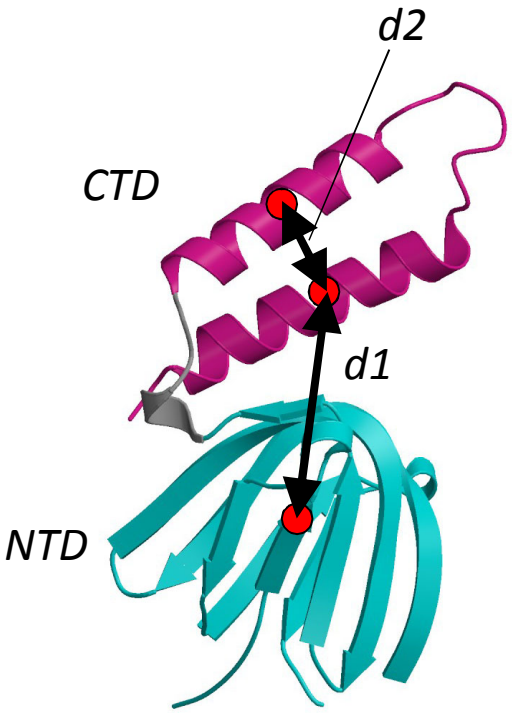
Predicted structure of
ATP-free Inactive ε subunit

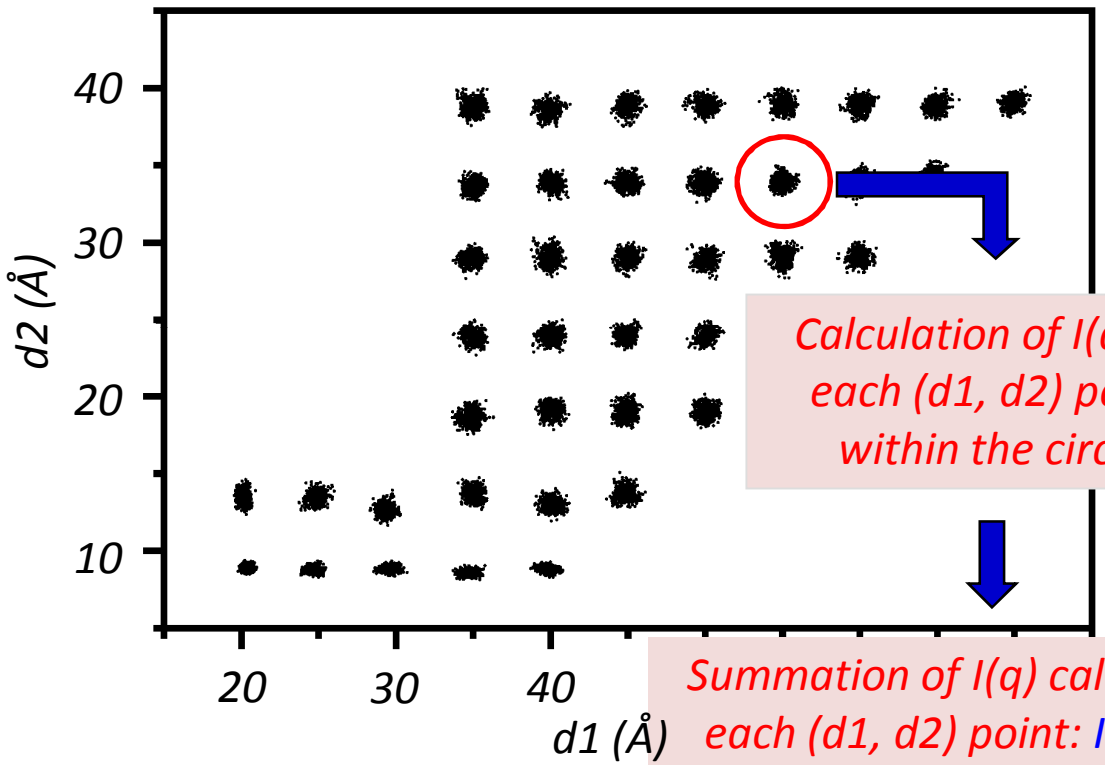




Crystal structure of
ATP-free active ε subunit

Reconstruction of Initial Atomic Structures





Calculation of I(q) at each (d1, d2) point within the circle

Summation of I(q) calculated at each (d1, d2) point: $I(q)_{MD\text{-}SAXS}$

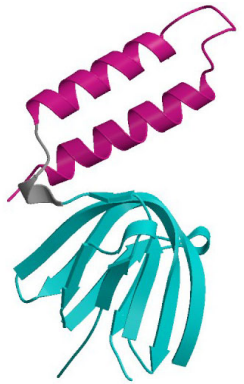
Each of d1 & d2 was changed at an interval of 5 Å (total 41 initial atomic structures), and MD simulation was carried out using each initial atomic structure.

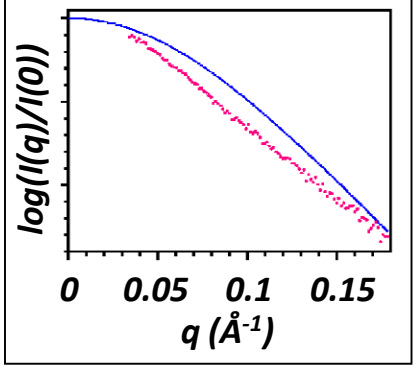
Compare $I(q)_{MD\text{-}SAXS}$ *with* $I(q)_{EX}$

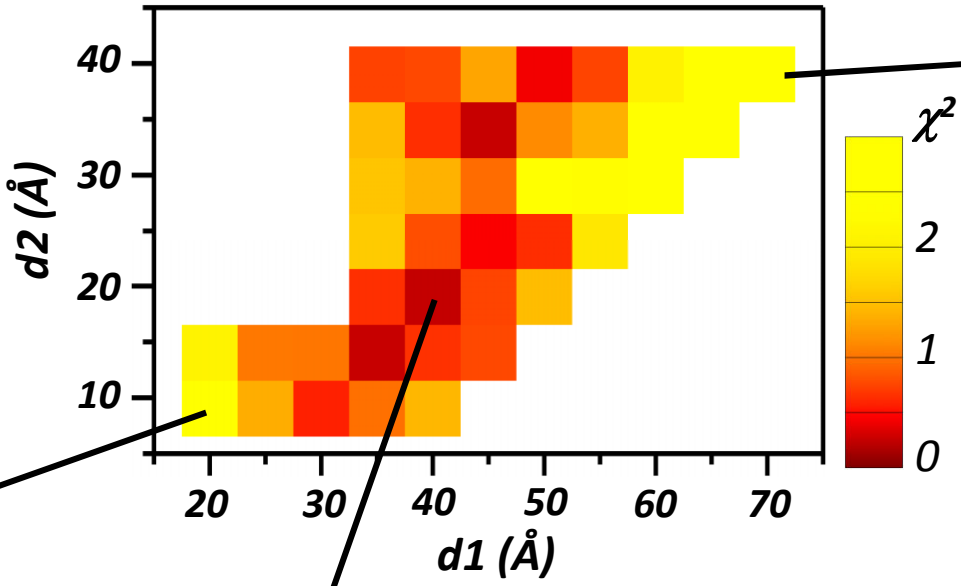
Comparison of $I(q)_{MD\text{-}SAXS}$ with $I(q)_{EX}$

Crystal structure of ATP-free active form

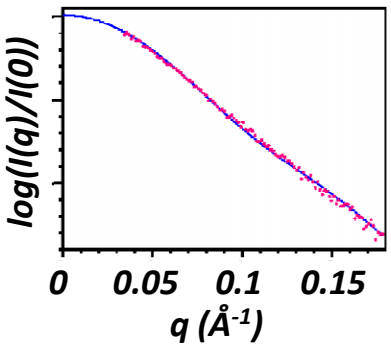
d1= 20 Å, d2= 10 Å





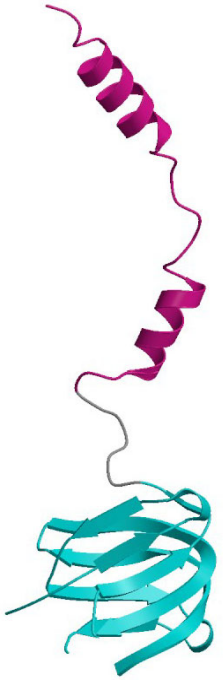


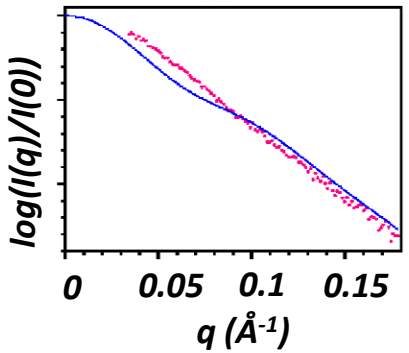
d1= 40 Å, d2= 20 Å



Predicted structure of ATP-free Inactive form

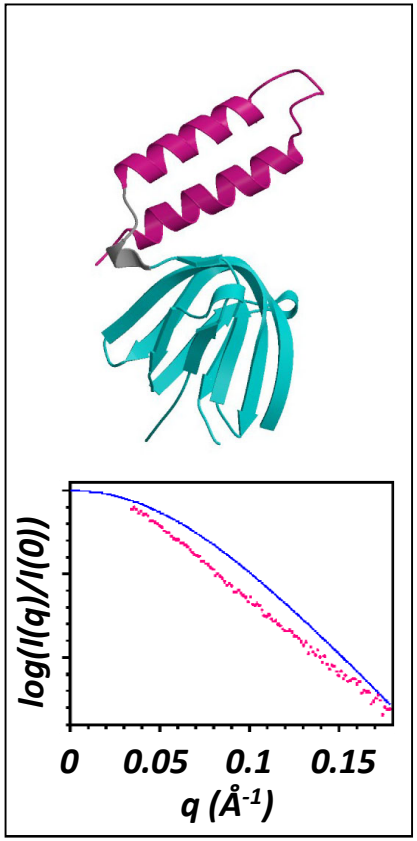
d1= 70 Å, d2= 40 Å



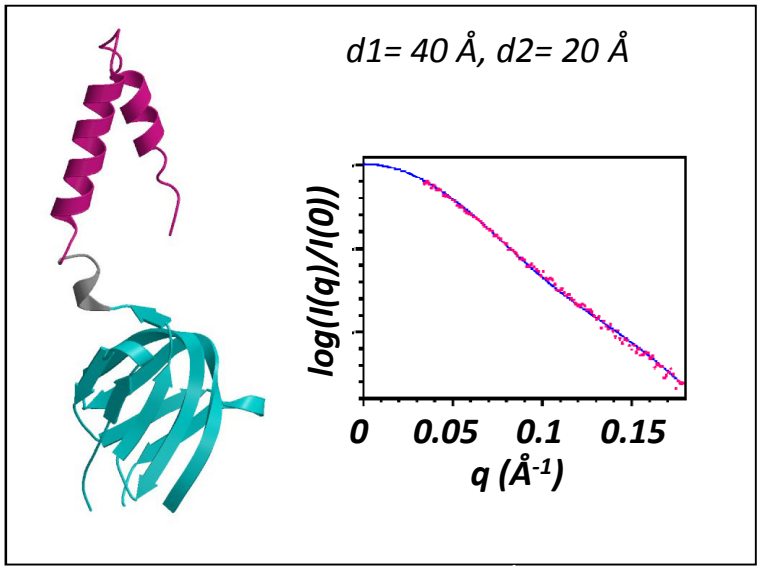


ATP-free ε subunit structure in solution

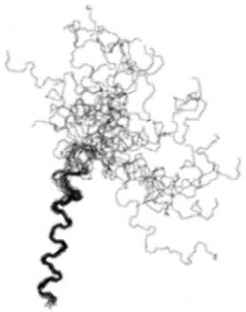
Crystal structure of ATP-free active form



but, fluctuates around

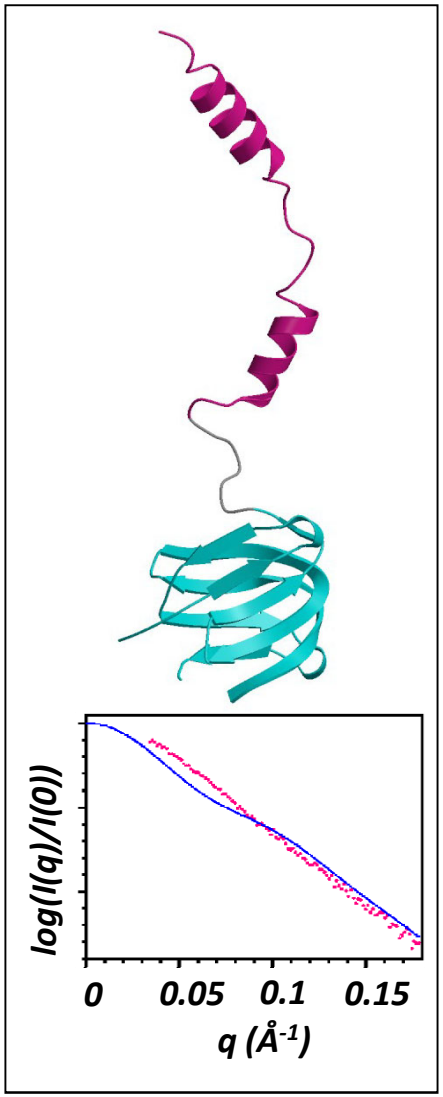


C-terminal domain



Yagi et. al. Proc. Nat. Acad. Sci. USA, ***104****, 11233-11238 (2007)*

Predicted structure of ATP-free Inactive form



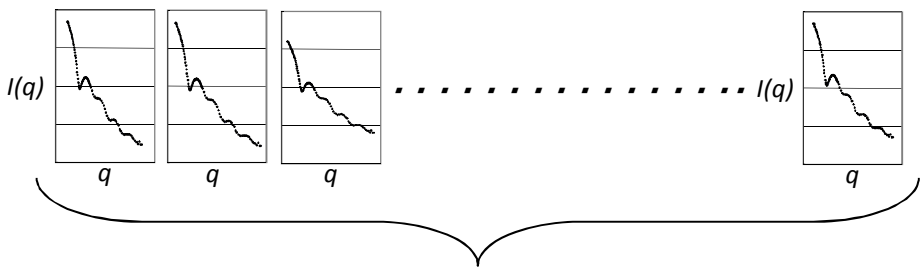
MD-SAXS of Multi-Domain Protein with ID Region

Construction of Initial Atomic Structure

MD Simulation (ex.150 ns)

1 ps 1 ps 1 ps . . . . . 1 ps

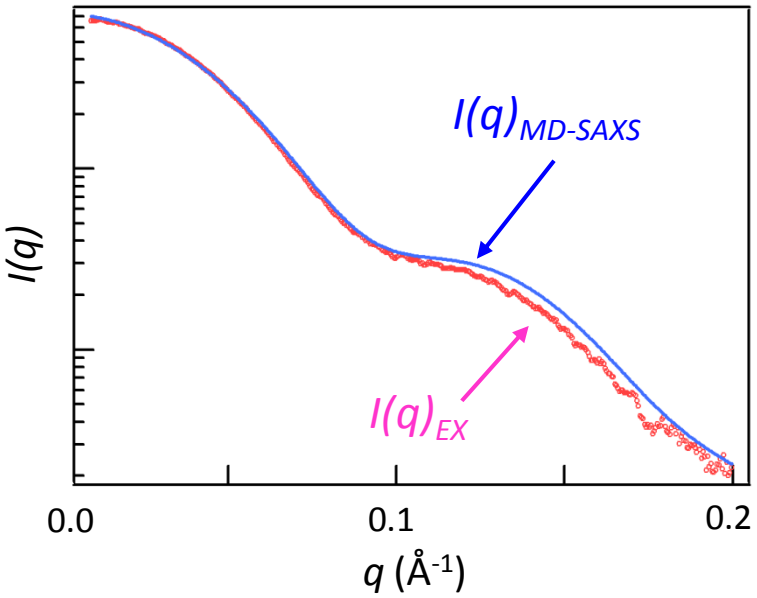
Calculation of I(q) from each snap-shot structure



Average the I(q) data-sets: $I(q)_{MD\text{-}SAXS}$

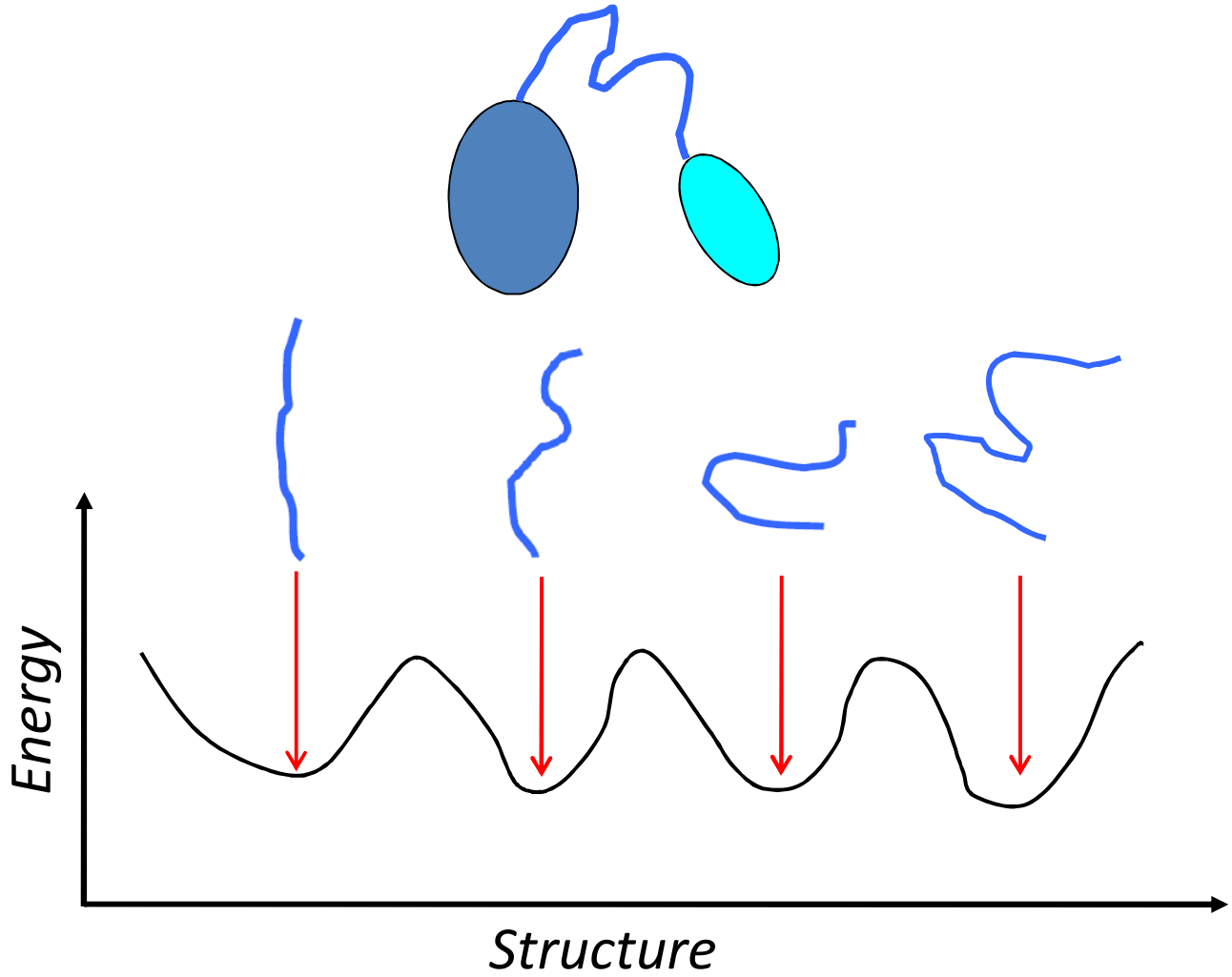
Inconsistent

Consistent
Each snap-shot structure is the dynamical structure of the protein



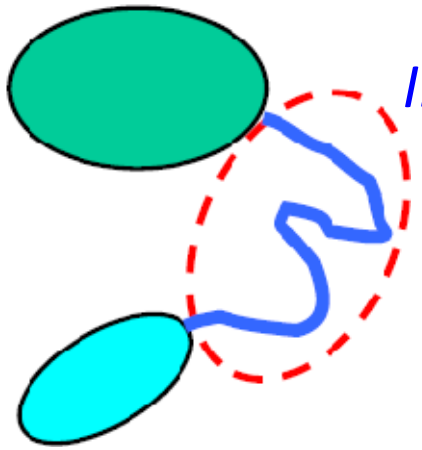
Compare $I(q)_{MD\text{-}SAXS}$ *with* $I(q)_{EX}$

Construction of Initial Atomic Structure



ID regions exist as dynamic ensembles and exhibit extremely temporal fluctuations, therefore extending the MD-SAXS method to characterize IDPs (Extended MD-SAXS)

Construction of ID Region in Extended MD-SAXS

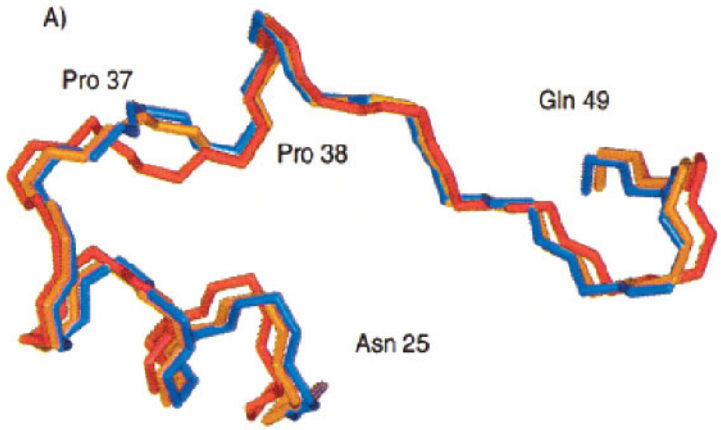


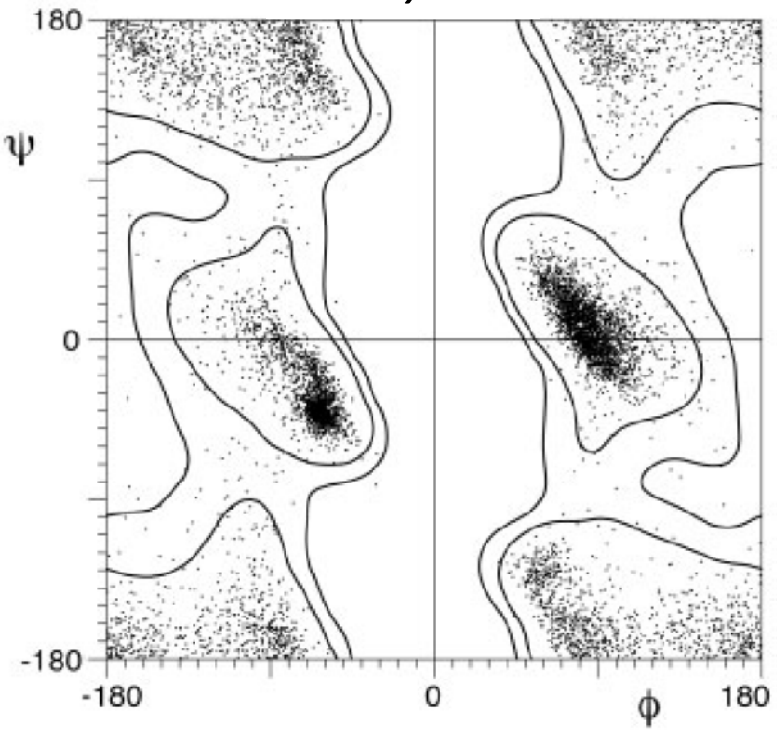
Bernado et. al. J. Am. Chem. Soc. ***129****, 5656-5664 (2007)*

ID Region:

is constructed using data-base of dihedral angles
for each amino acid residue
based on high resolution loop structures in PDB

Ex. Glycine

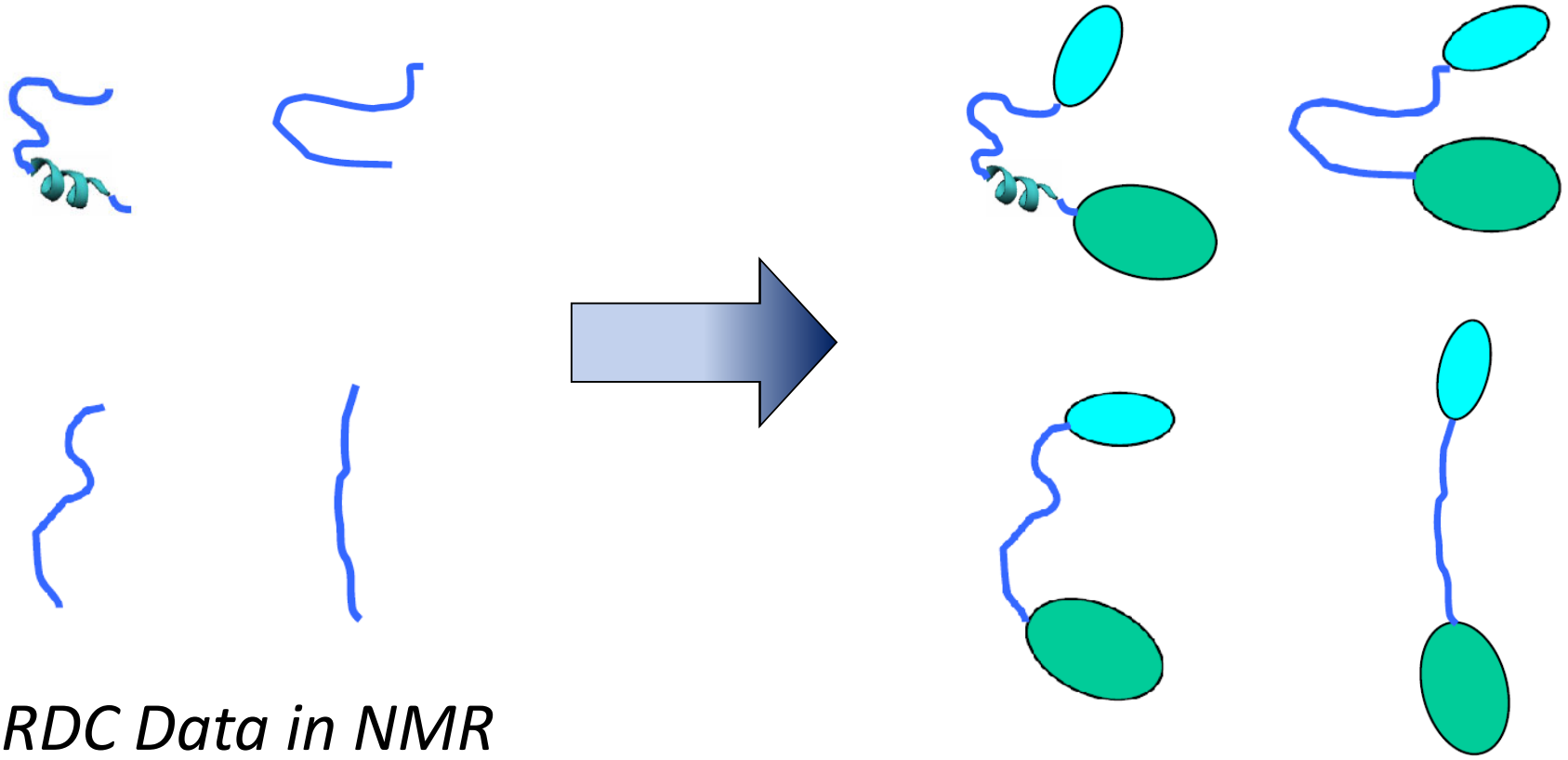




Construction of Whole Structure in Extended MD-SAXS

Constructed ID region structures

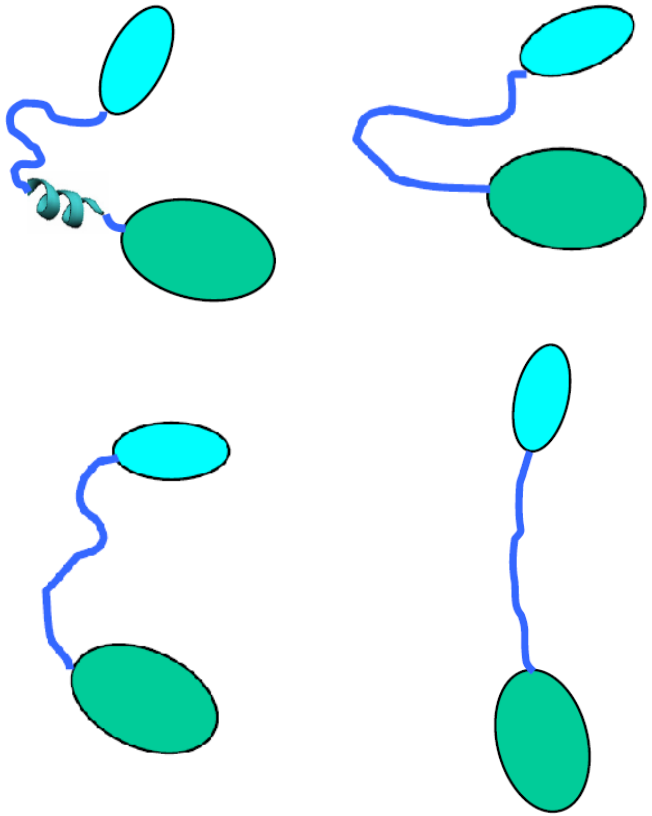
Constructed whole structures



+ RDC Data in NMR

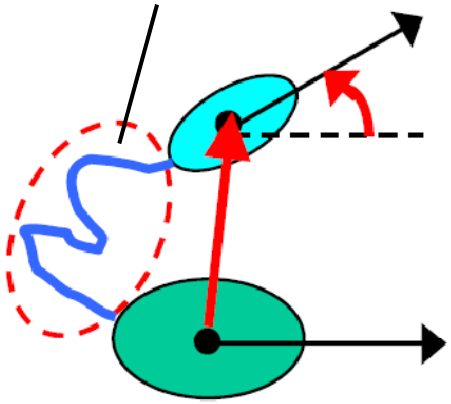
Description of the Whole Structure in Extended MD-SAXS

Constructed whole structures



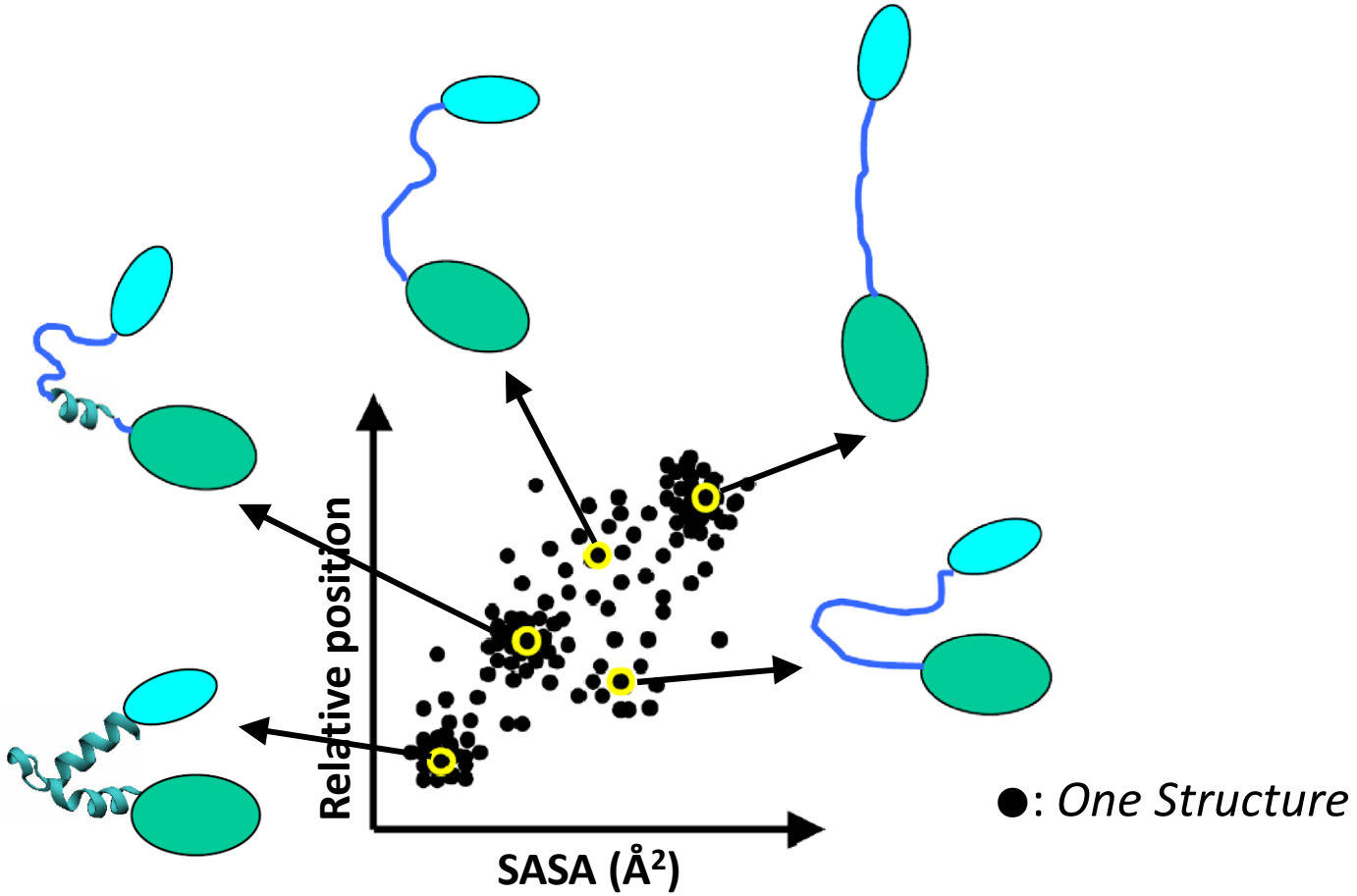
Description of the whole structure by the collective coordinate

Solvent accessible surface area (SASA)

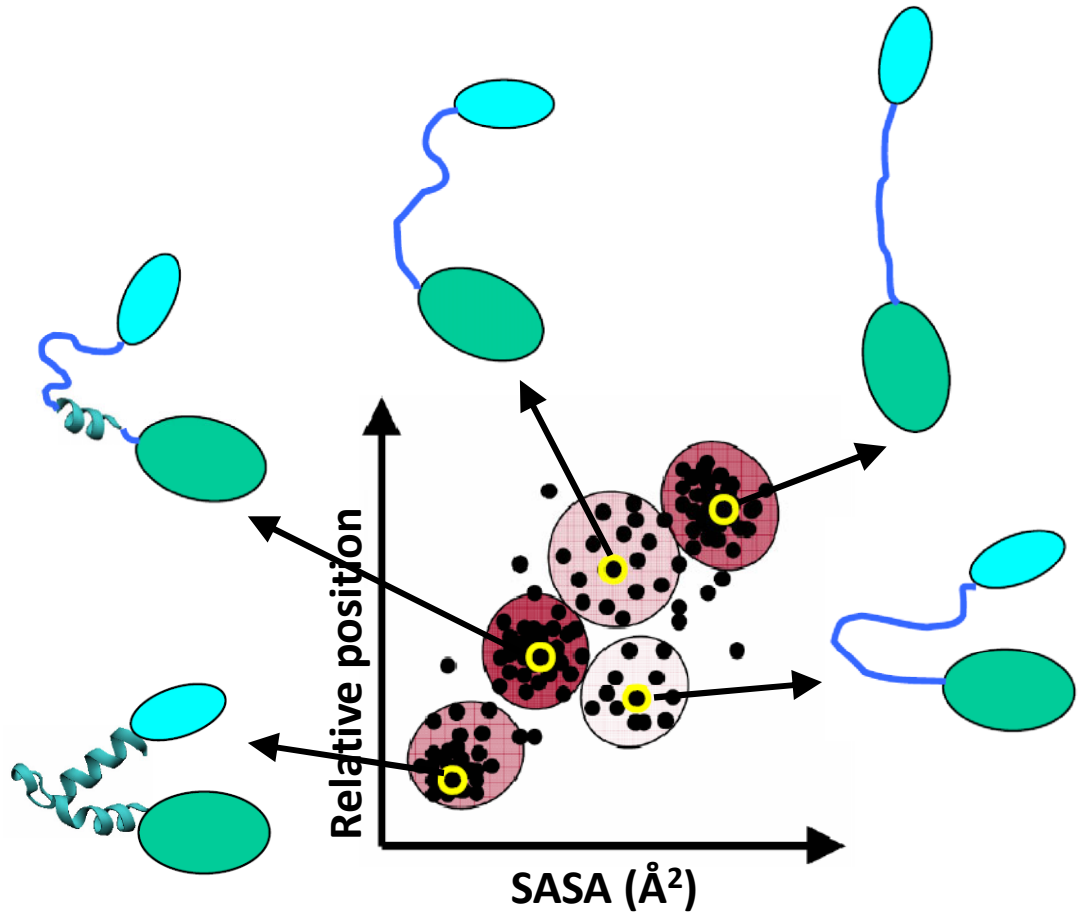


Relative position between the two domains

Initial Models of Structural Ensemble in Extended MD-SAXS

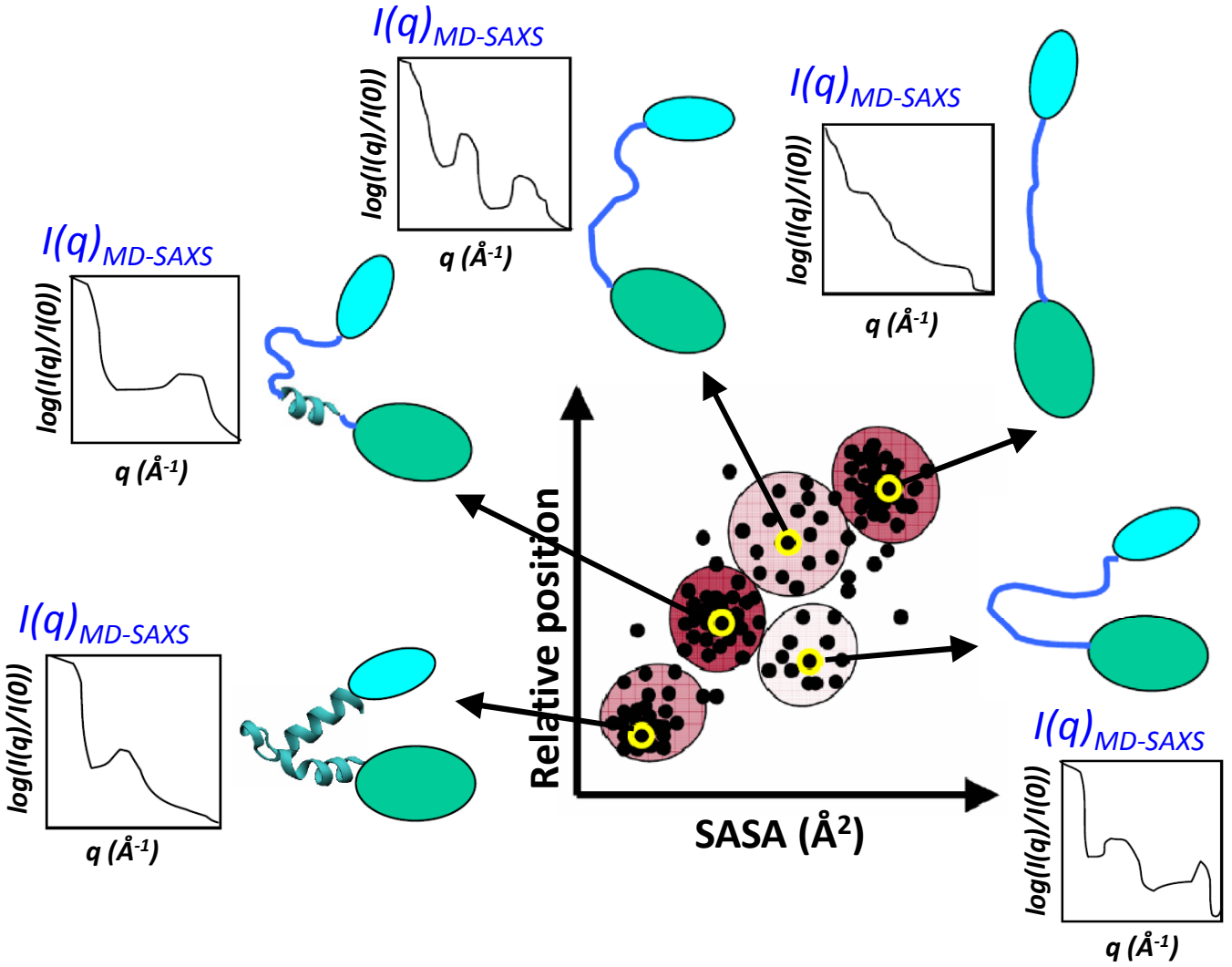


Classification of the Structural Ensemble into Sub-Groups



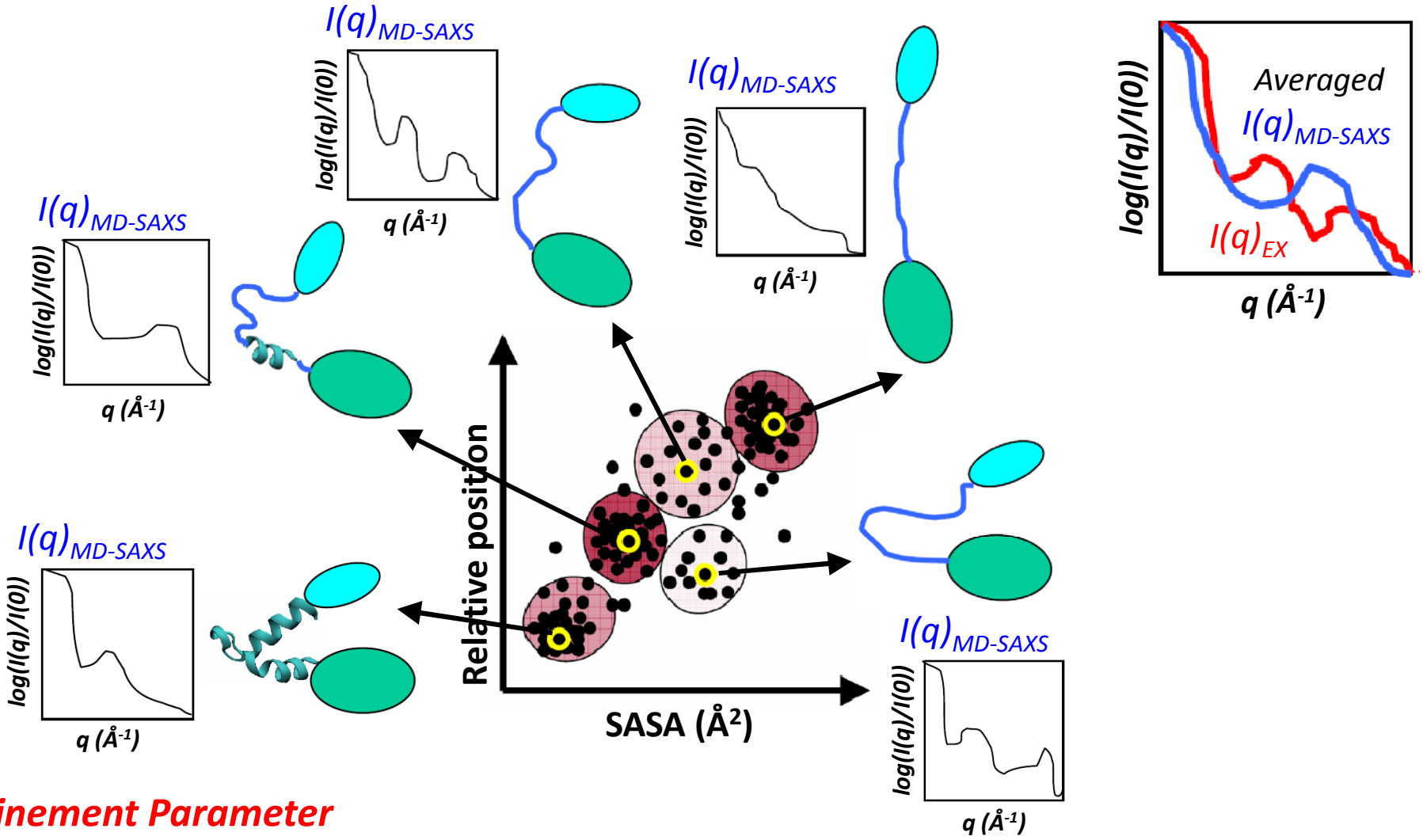
The number of structures belonging to each structural sub-group

Calculation of $I(q)_{MD\text{-}SAXS}$ for Each Sub-group



The number of structures belonging to each structural sub-group

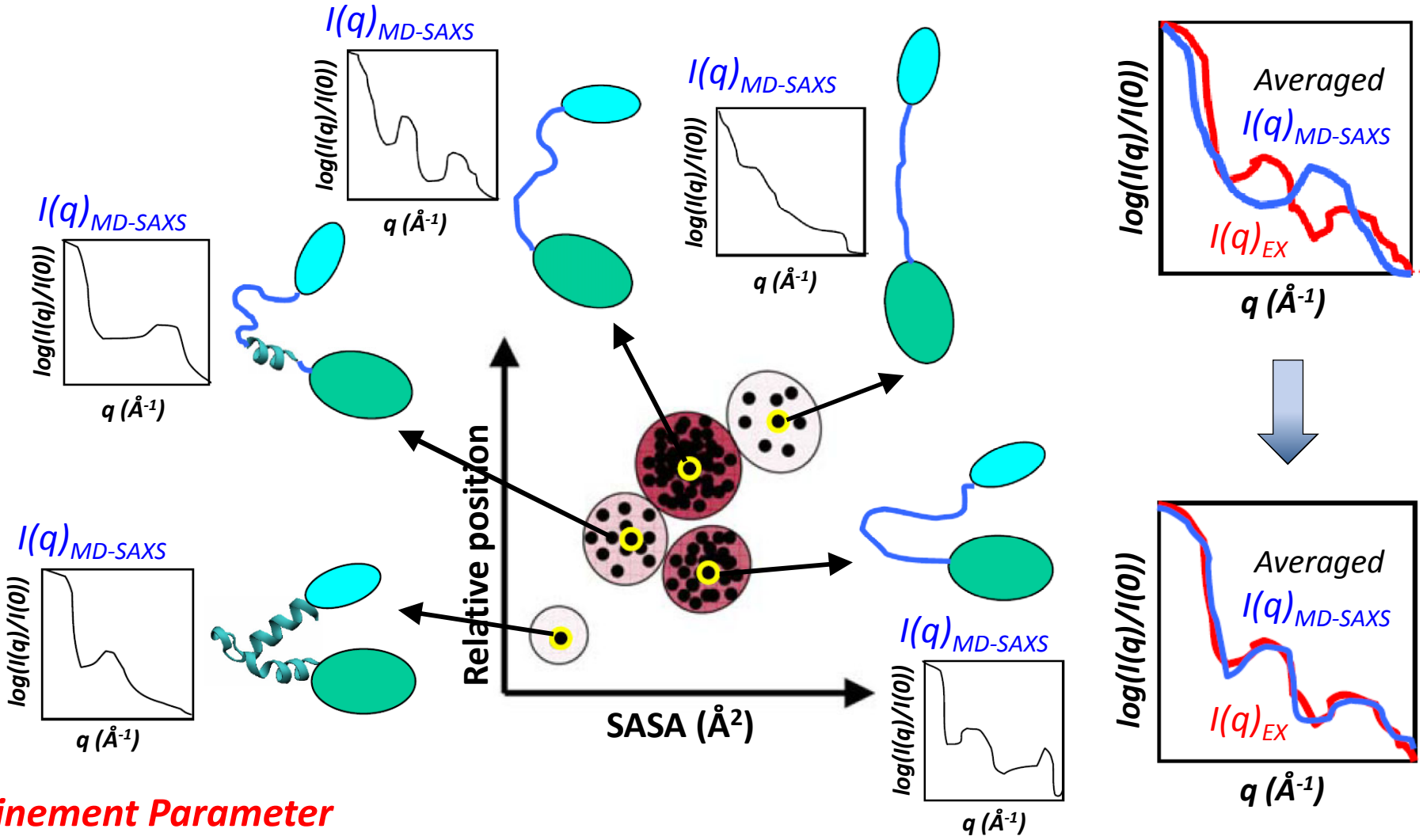
Average $I(q)_{MD\text{-}SAXS}$ & Compare with $I(q)_{EX}$



Refinement Parameter

The number of structures belonging to each structural sub-group

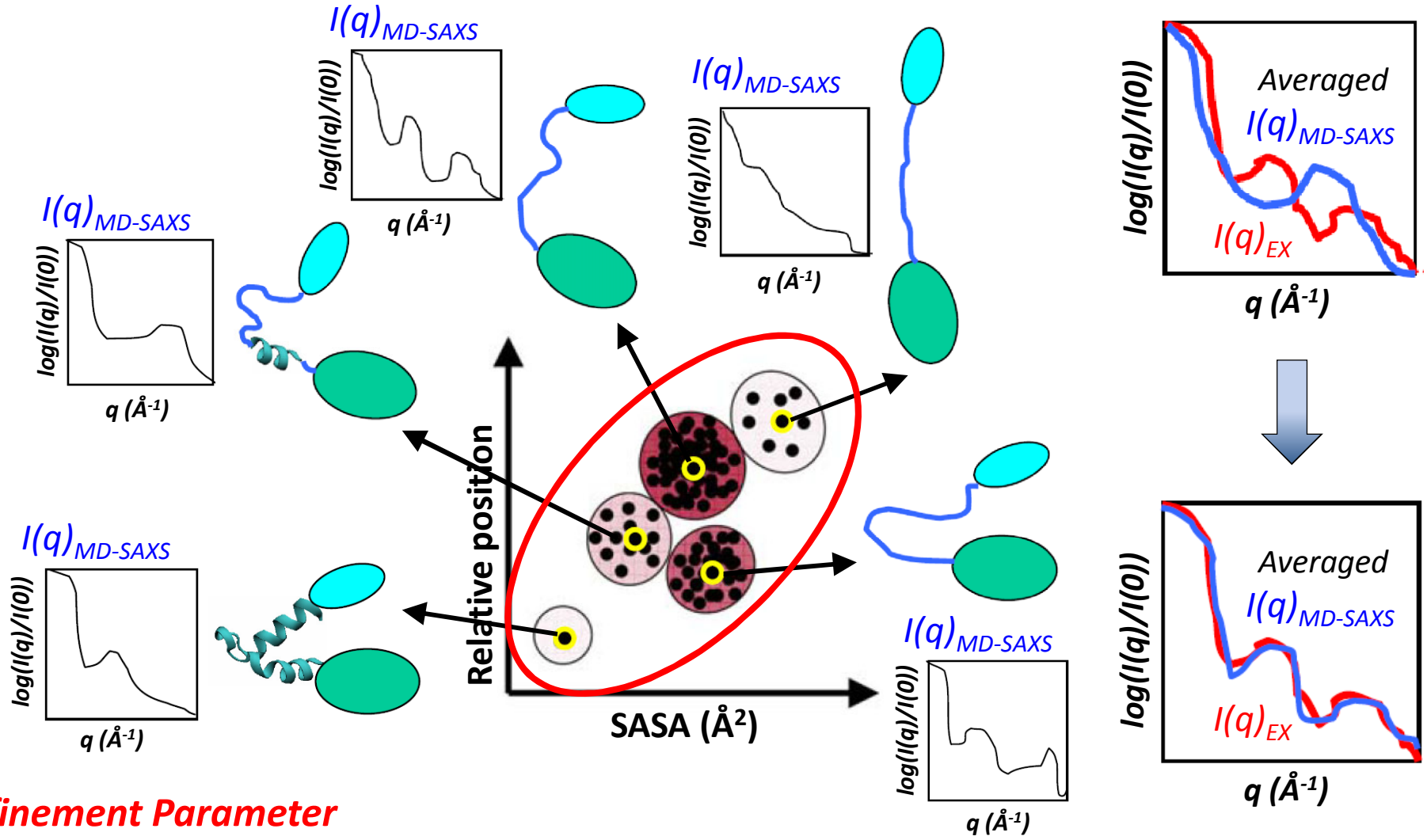
Refinement of Structural Ensemble



Refinement Parameter

The number of structures belonging to each structural sub-group

Structures (Ensemble) of IDP in Solution



Refinement Parameter

The number of structures belonging to each structural sub-group