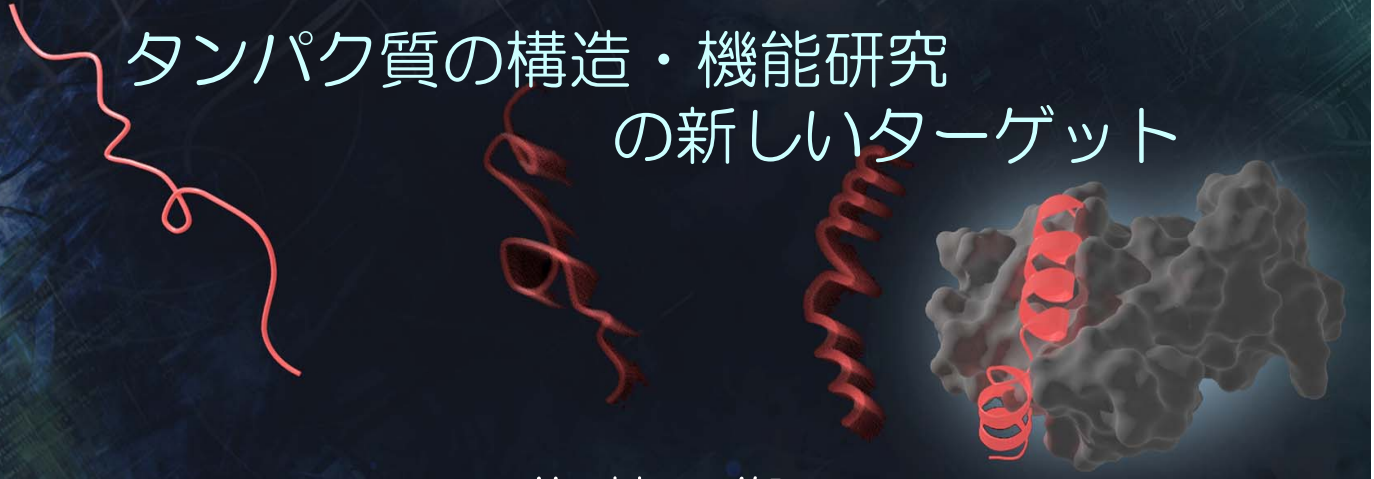
天然変性タンパク質
（*Intrinsically Disordered Protein: IDP*）

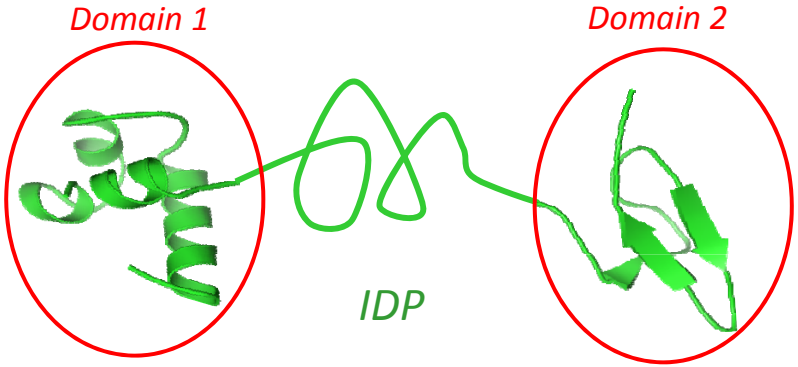
タンパク質の構造・機能研究
の新しいターゲット



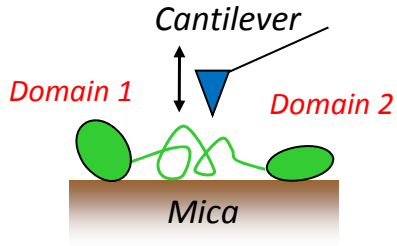
佐 藤　衛
横浜市立大学生命ナノシステム科学研究科

PF研究会（2010年7月12日-13日）

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



天然状態で特定の立体構造をとらないで
揺らいでいるタンパク質



High-speed AFM
(50 μsec/frame)
Prof. T. Ando (Kanazawa Univ.)

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

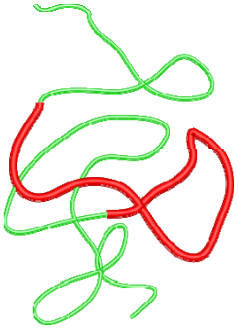
転写因子CREBの
KIDドメイン
（天然変性タンパク質）

転写のコアクチベータ
CBPのKIXドメイン

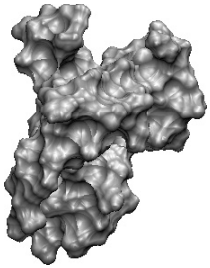
特異的複合体

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

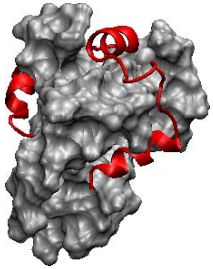
Coupled Folding & Binding



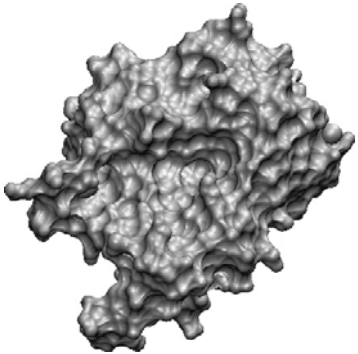
低酸素誘導因子*HIF1α*
（天然変性タンパク質）



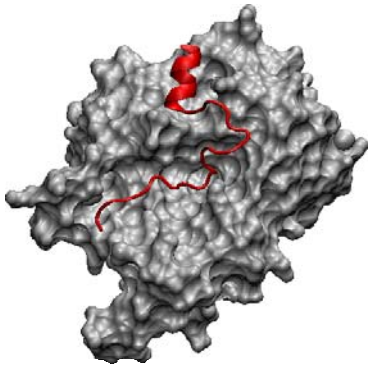
コアクチベータ *CBP*
の*TAZ1*ドメイン



（*Proc. Natl. Acad. Sci. USA* 2002）



Asparagine Hydroxylase



（*J. Biol. Chem.* 2003）

天然変性タンパク質は相互作用するタンパク質やリガンドによってそれぞれ異なる立体構造を形成する

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

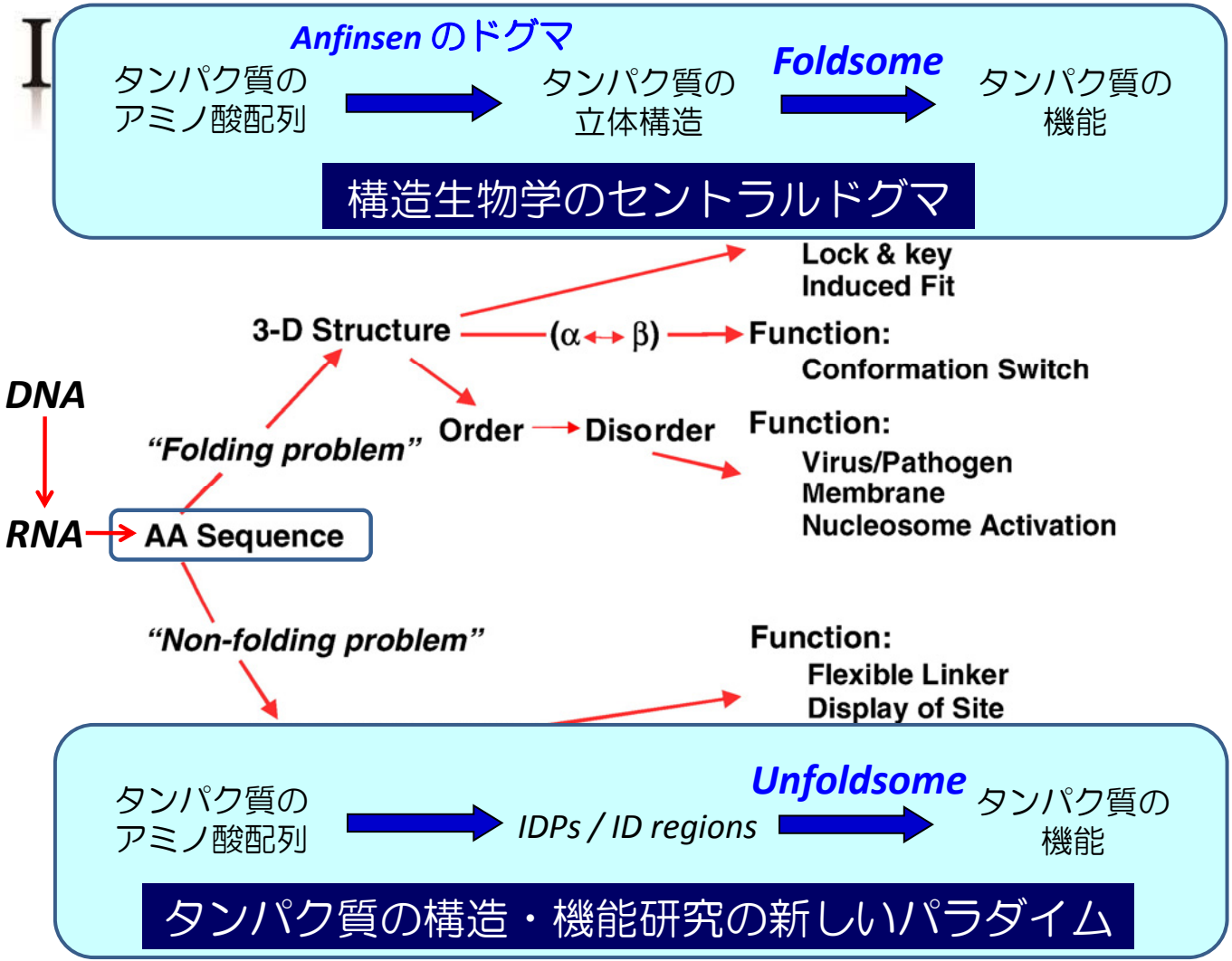
Alzheimer disease and amy-β, tau, α-synuclein

IDPs as novel drug targets

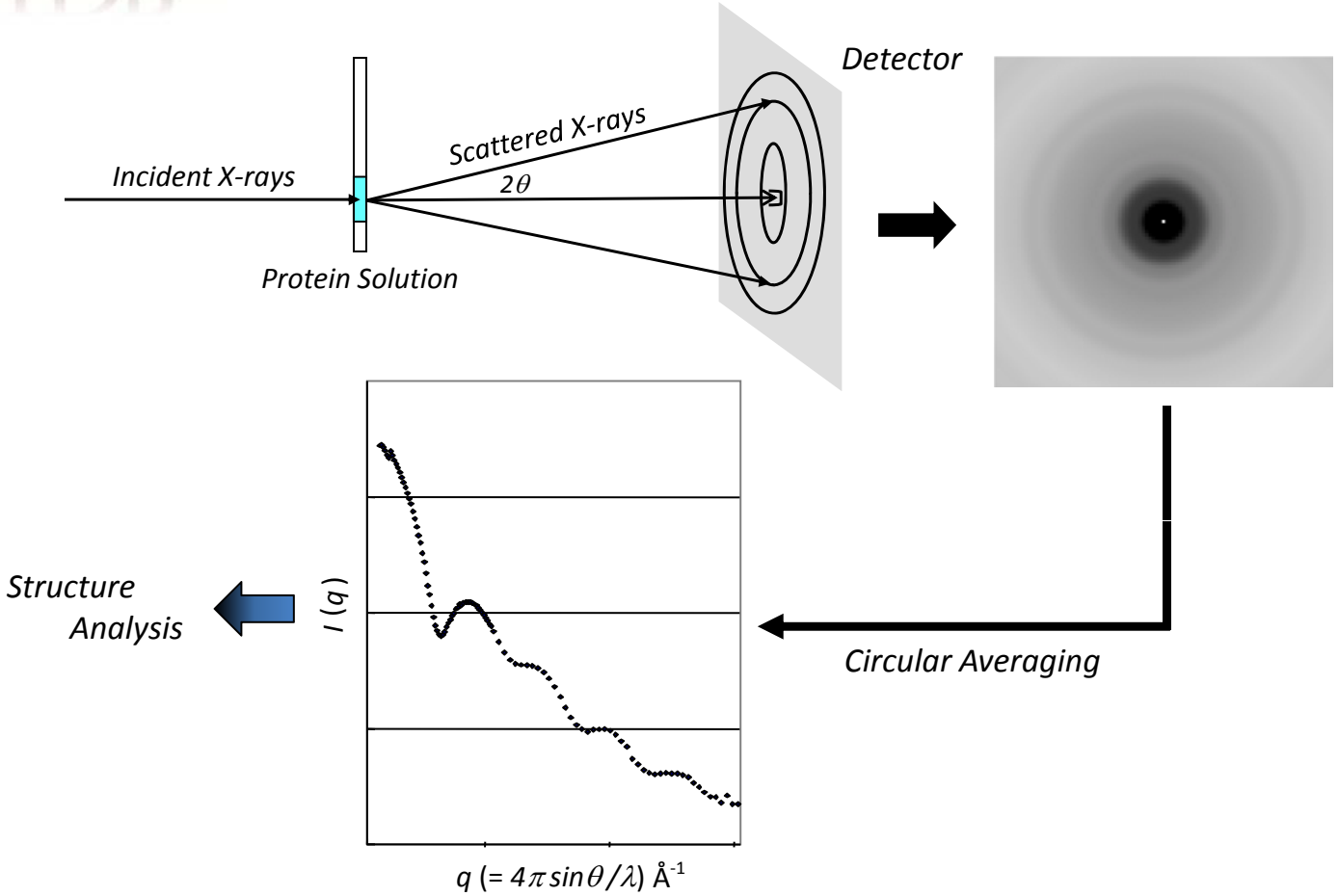
One partner is disordered and the second is structured

Both partners lacks fixed structures

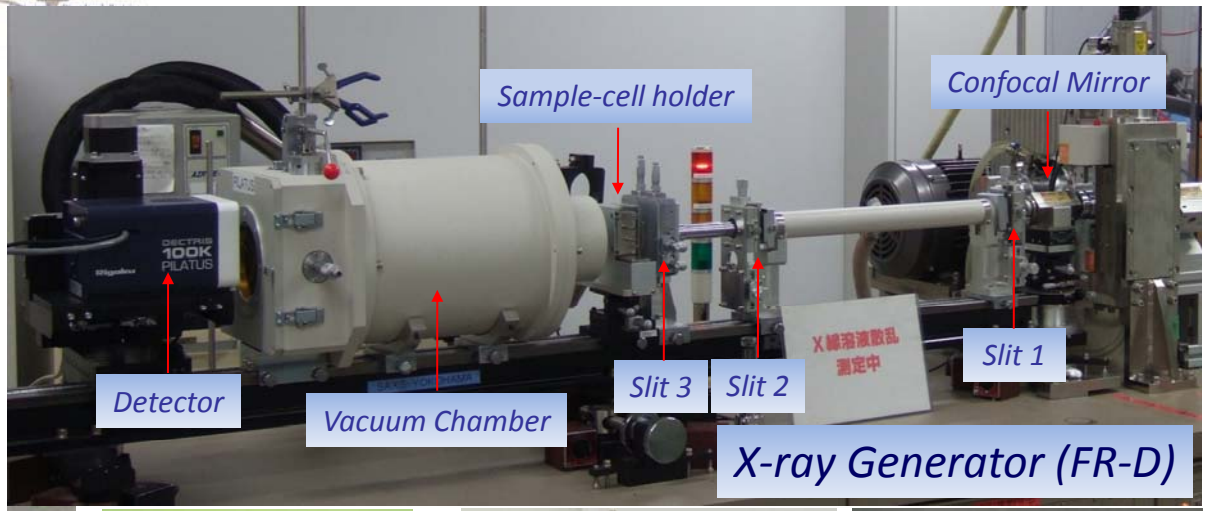
D^2-concept: disorder in disorders

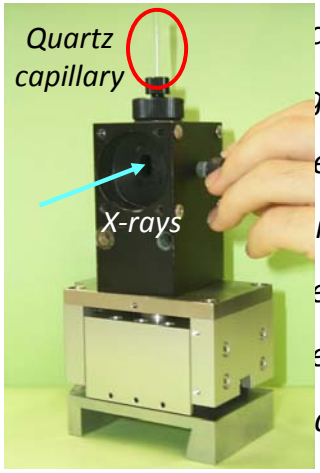

Anfinsen のドグマ
タンパク質の
アミノ酸配列
タンパク質の
立体構造
Foldsome
タンパク質の
機能
構造生物学のセントラルドグマ
Lock & key
Induced Fit
3-D Structure
(α ↔ β)
Function:
Conformation Switch
DNA
"Folding problem"
Order
Disorder
Function:
Virus/Pathogen
Membrane
Nucleosome Activation
RNA
AA Sequence
"Non-folding problem"
Function:
Flexible Linker
Display of Site
タンパク質の
アミノ酸配列
IDPs / ID regions
Unfoldsome
タンパク質の
機能
タンパク質の構造・機能研究の新しいパラダイム

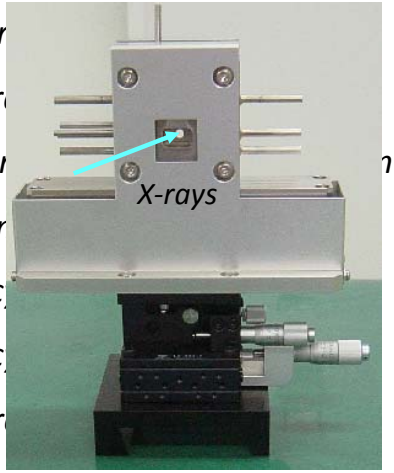
Small-Angle X-ray Scattering（SAXS）

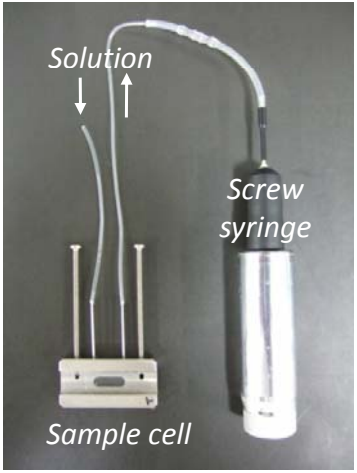


SAXS in Yokohama City University



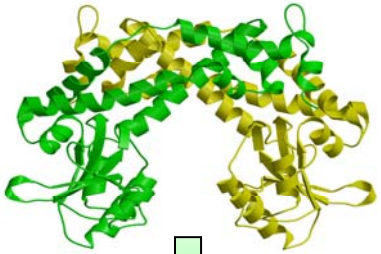






Principle of MD-SAXS

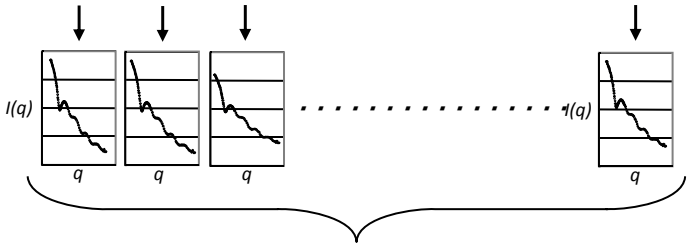
Construction of Initial Atomic Structure



MD Simulation (ex.150 ns)

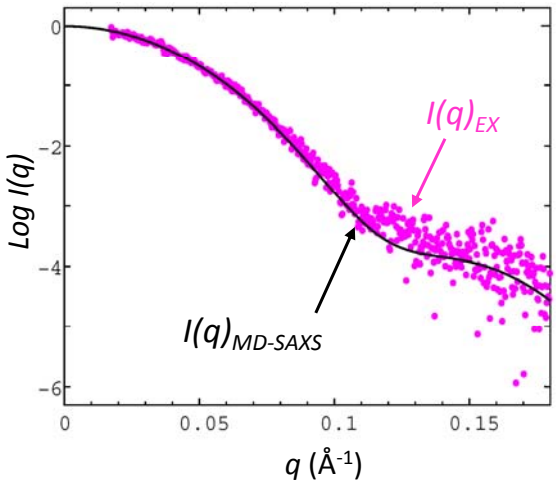
1 ps 1 ps 1 ps . . . . . 1 ps

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



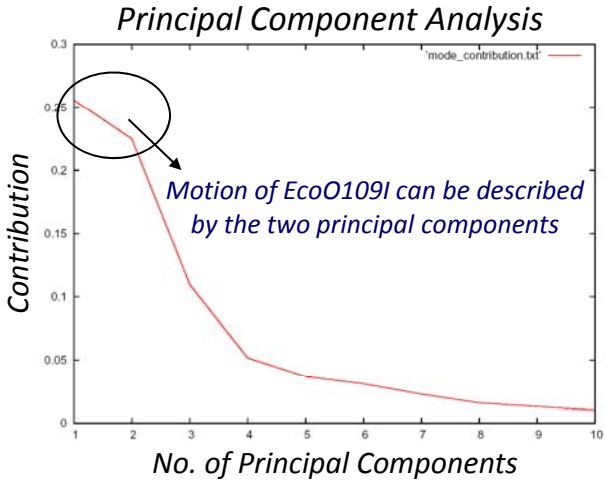
Average the I(q) data-sets: $I(q)_{MD\text{-}SAXS}$

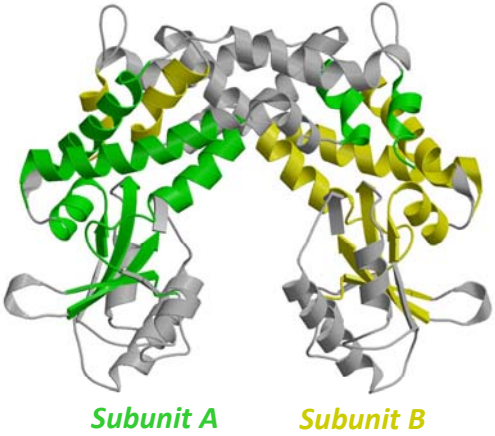
Consistent
Each snap-shot structure is the dynamical structure of the protein

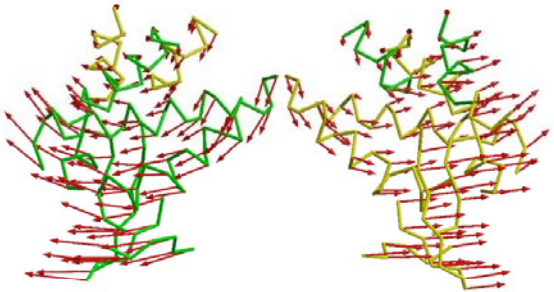


Compare $I(q)_{MD\text{-}SAXS}$ with $I(q)_{EX}$

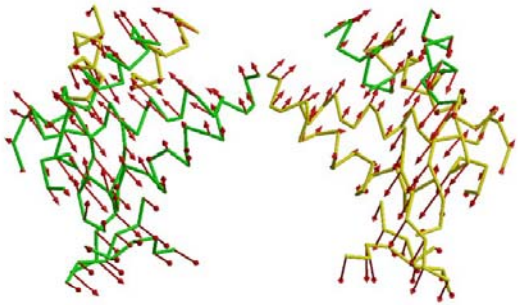
Motion between Subunit A and Subunit B







The first principal component: open-close motion

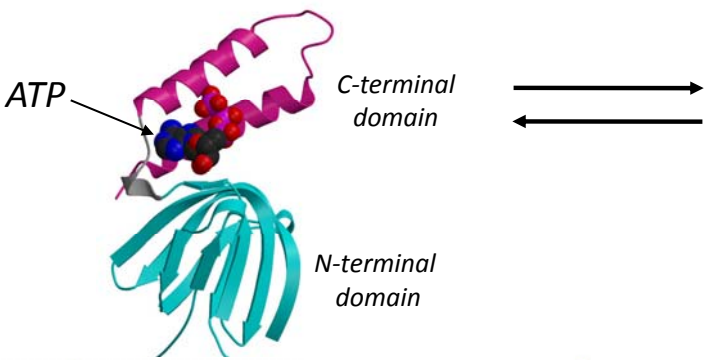


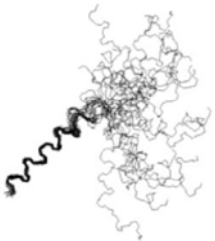
The second principal component: twisting motion

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

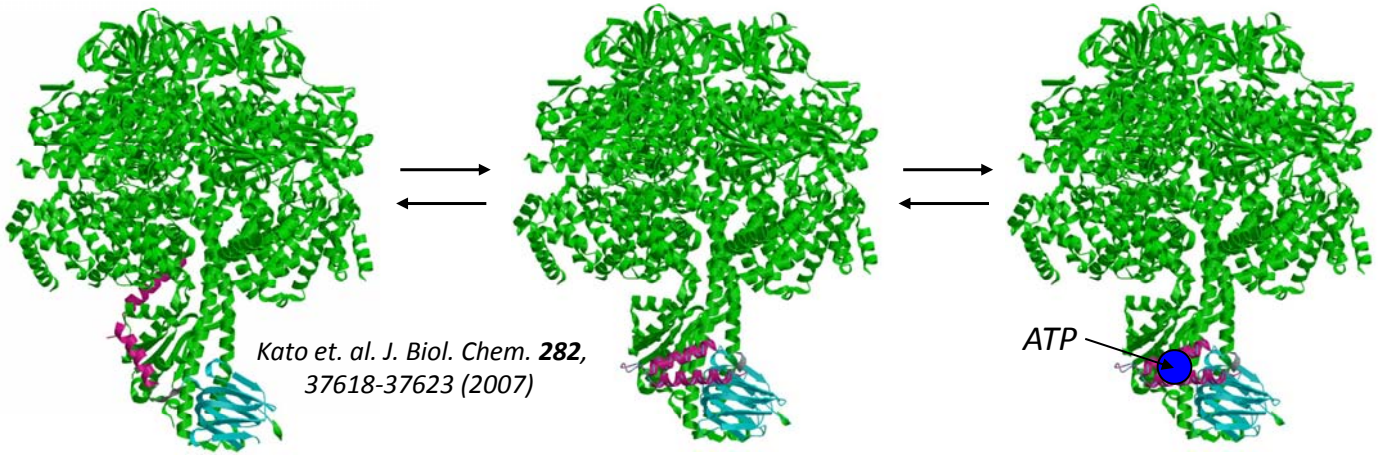
Example 2 of MD-SAXS:

ε subunit of thermophilic F1-ATPase





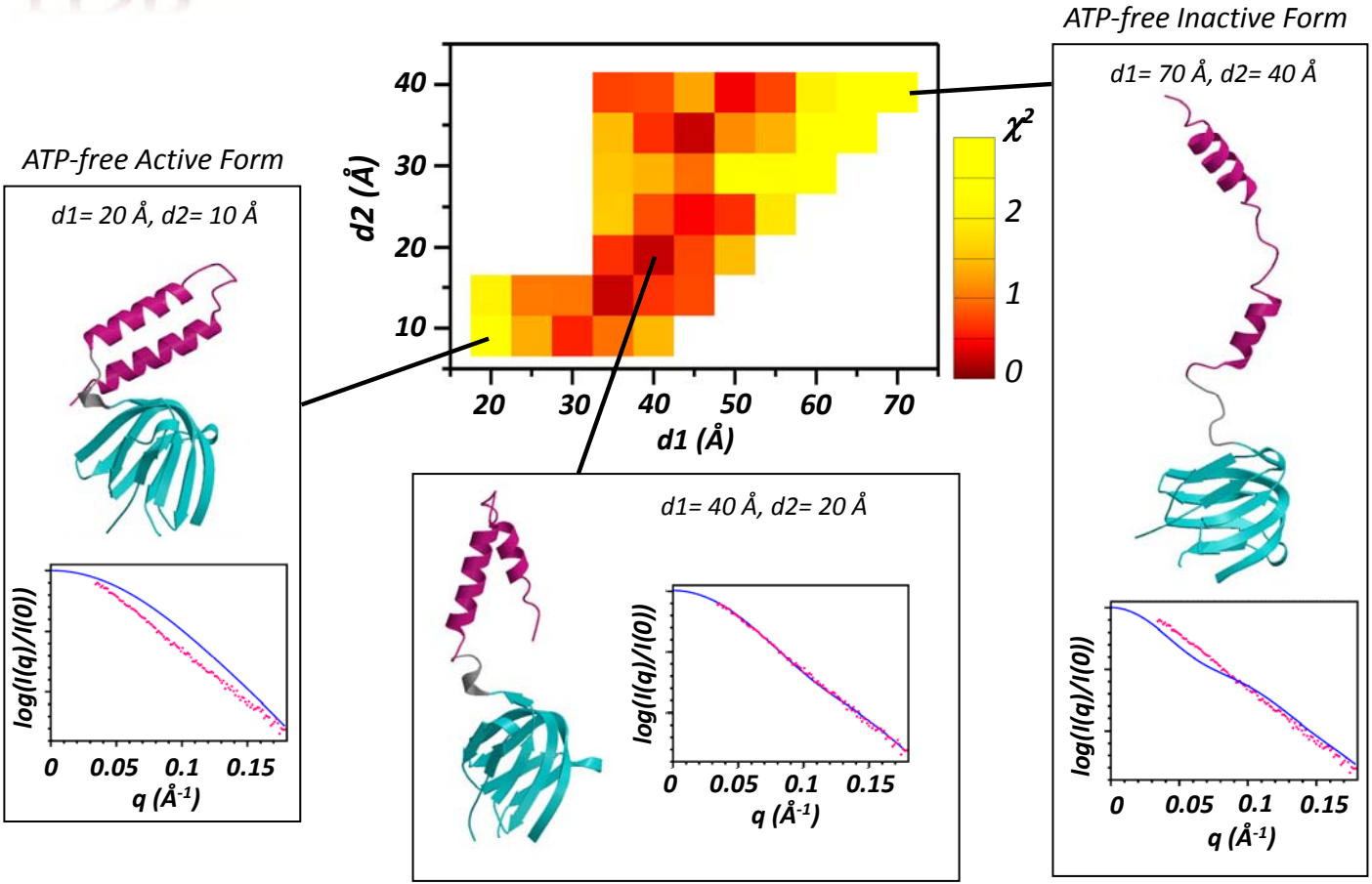
Yagi et. al. Proc. Nat. Acad. Sci. USA, ***104***, 11233-11238 (2007)



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

ATP-free Inactive Form

ATP-free Active Form

ATP-bound Active Form

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