Anomalous dynamics of metal ions in presence of a bacterial protein

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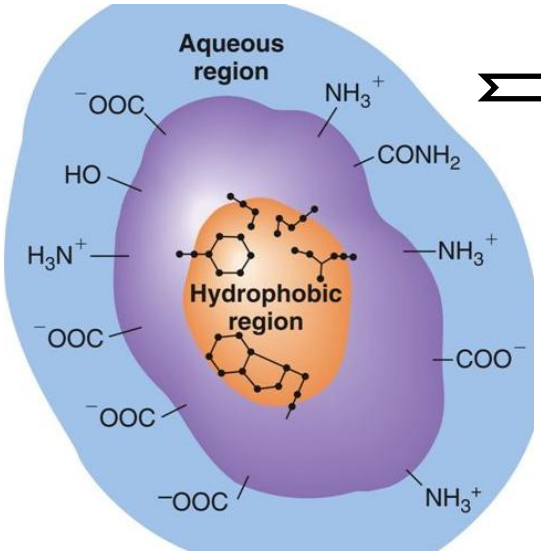
Background

- Surface induced properties: modifications in both statics and dynamics
- Nano-particles: Large surface area
- Nano-technology: Information storage, packaging, electronics, catalysis, lithium-ion batteries, solar cells
- Biomedical application: metallic, magnetic, fluorescent, polymeric and protein-based nano-particles: sensor & replacement

Proteins as nano particles



⟹ **Exposed hydrophilic groups**

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Heterogeneity in electrostatic interactions with ions

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Complicated motions of ions

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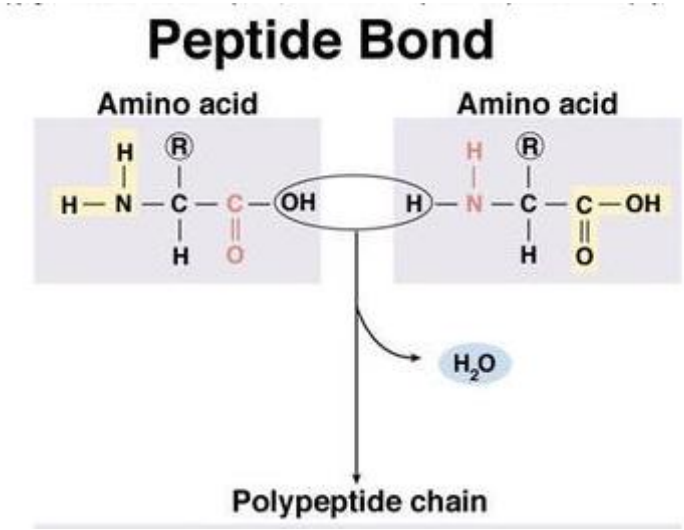
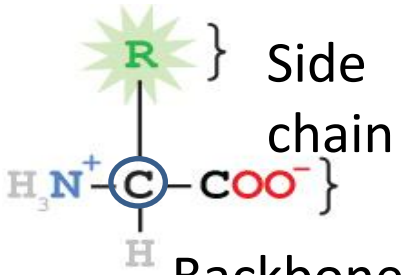
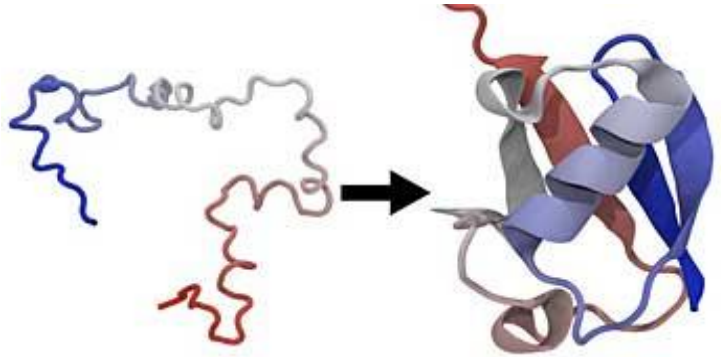
Ion-dipole interaction: functionality of protein

Basic Chemistry of Protein







Unfolded

Folded

Objective

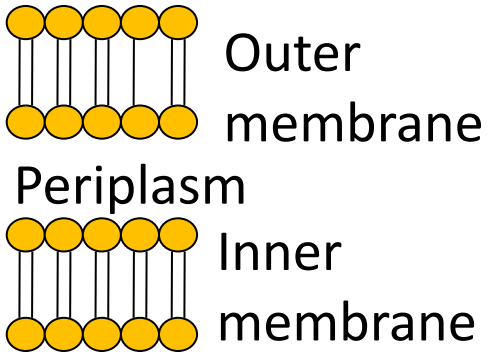
- Study motions of metal ions in presence of heterogeneous surface of a bacterial protein
- Functionality of bacterial proteins: major cause for virulence
- Metal ions in trace amount act as structural and functional scaffolds of proteins

Protein STY3178

- yfdX family from typhoid fever causing bacteria

Salmonella Typhi : unknown structure function

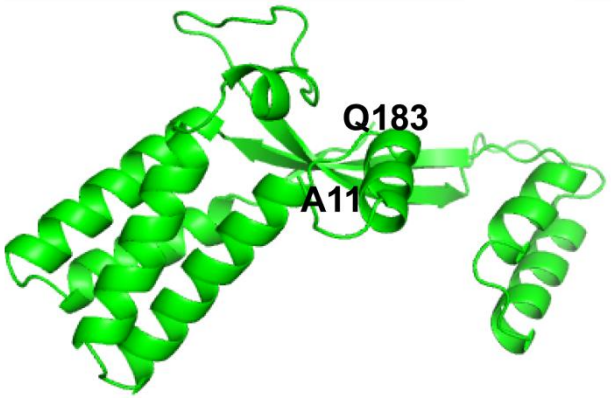
- Recent studies:
  - Interact with several antibiotics
  - Structurally stable in wide range of temperature and pH
  - Trimer in water
  - Monomer in **SDS**
  - Can act as **chaperon** protein
  - Probable to localize in periplasmic area



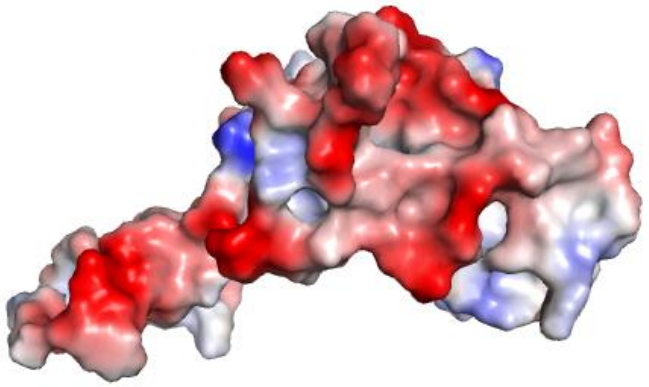
P. Saha, C. Manna, J. Chakrabarti, and M. Ghosh, Sci. Rep. **6** (2016); P. Saha, C. Manna, S. Das, and M. Ghosh, Sci. Rep. **6** (2016); P. Saha, S. Sikdar, J. Chakrabarti, and M. Ghosh, RSC Adv. **6**, 91256 (2016); P. Saha, S. Sikdar, C. Manna, J. Chakrabarti, and M. Ghosh, RSC Adv. **7**, 6209 (2017).

- **Investigate dynamics of most abundant metal ions in cellular conditions : Mg^{+2} and Ca^{+2}**

Model structure of STY3178



Model structure of STY3178



Electrostatic surface of STY3178

-ve charge distribution

+ve charge distribution

- -ve surface charge, Capable of interacting with metal ions

P. Saha, C. Manna, J. Chakrabarti, and M. Ghosh, Sci. Rep. **6** (2016); P. Saha, C. Manna, S. Das, and M. Ghosh, Sci. Rep. **6** (2016); P. Saha, S. Sikdar, J. Chakrabarti, and M. Ghosh, RSC Adv. **6**, 91256 (2016); P. Saha, S. Sikdar, C. Manna, J. Chakrabarti, and M. Ghosh, RSC Adv. **7**, 6209 (2017).

MD Simulation

- GROMOS9653a6 force field
- Solvated in cubic box: SPC 3-point water model, Electronutrality
- 0.5mM $MgCl_2$ and $CaCl_2$ experiments
- Isothermal isobaric ensemble
- Periodic boundary condition
- 1fs time step
- PME: long ranged electrostatic interaction

$$U = \sum_{bonds} \frac{1}{2} k_r (r - r_o)^2 + \sum_{angles} \frac{1}{2} k_\theta (\theta - \theta_o)^2 + \sum_{torsions} \frac{V_n}{2} [1 + \cos(n\varphi + \delta)] + \sum_{improper} \frac{V}{2} [1 + \cos(2\varphi - 180)]$$

bonded

$$+ \sum_{elec} \frac{q_i q_j}{r_{ij}}$$

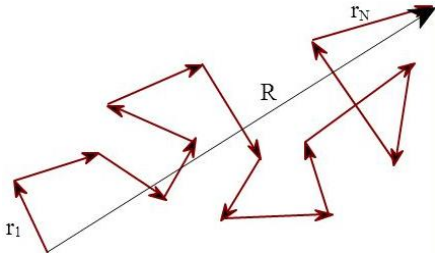
Coulomb

$$+ \sum_{LJ} 4\varepsilon_{ij} \left[\left(\frac{A_{ij}}{r_{ij}} \right)^{12} - \left(\frac{B_{ij}}{r_{ij}} \right)^{6} \right]$$

- **240ns long simulation**
- Self-vHf and msd from equilibrated trajectory averaging over different initial conditions

Analysis

- **Mean square displacement; δr^2**
- Motion of particle in fluid



- Square of displacement at t from starting position
- In long time limit ,

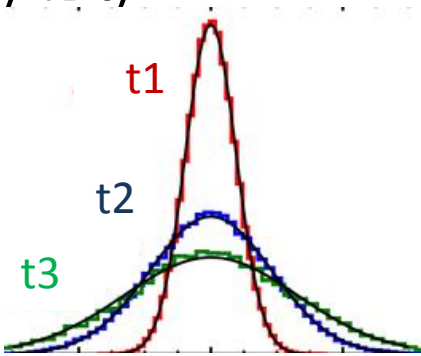
  $\delta r^2 = 6Dt$
- Measurable by DLS experiment

- **Self van Hove function; $G_s(r, t)$**
- probability of finding a particle at r at t, located at the origin at t = 0
- Neutron scattering experiment
- Normal liquid: Gaussian form

$G_s(r, t) \propto \exp(-r^2/4Dt)$

⇓

Fickian dynamics



t1< t2<t3

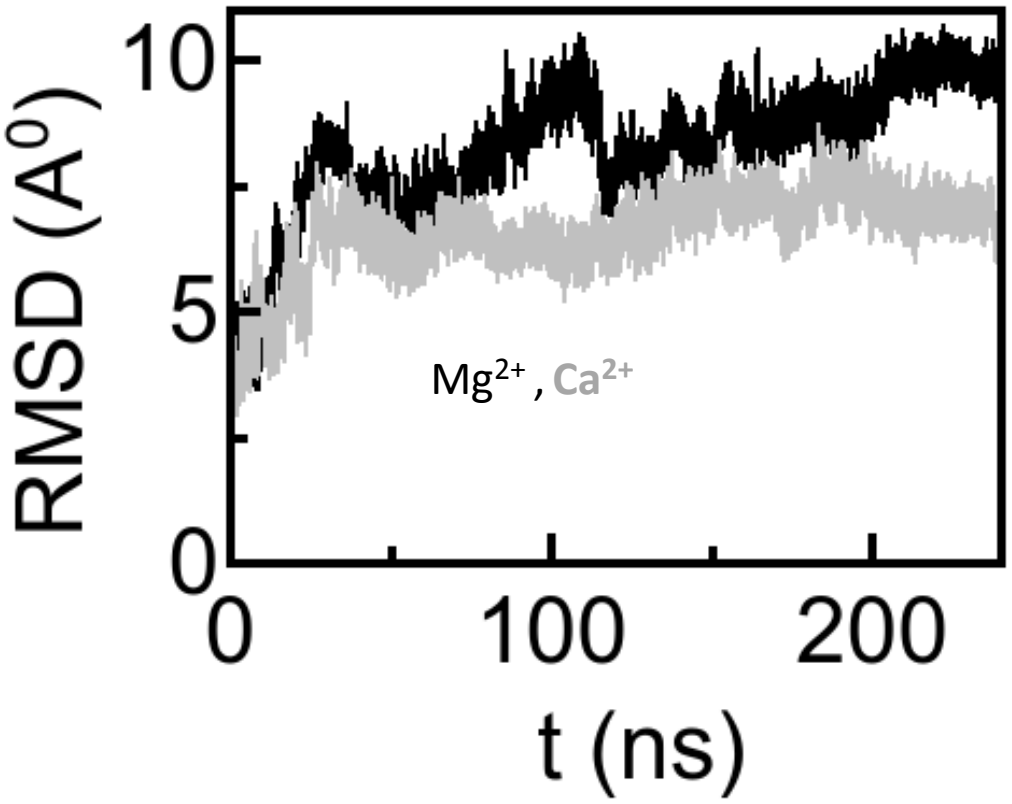
- **Deviation in msd from linear dependence on t**
- **Non-Gaussian self-vHf**
- **Linear msd on t; Non-Gaussian self-vHf: Non-Fickian diffusion dynamics**

RMSD

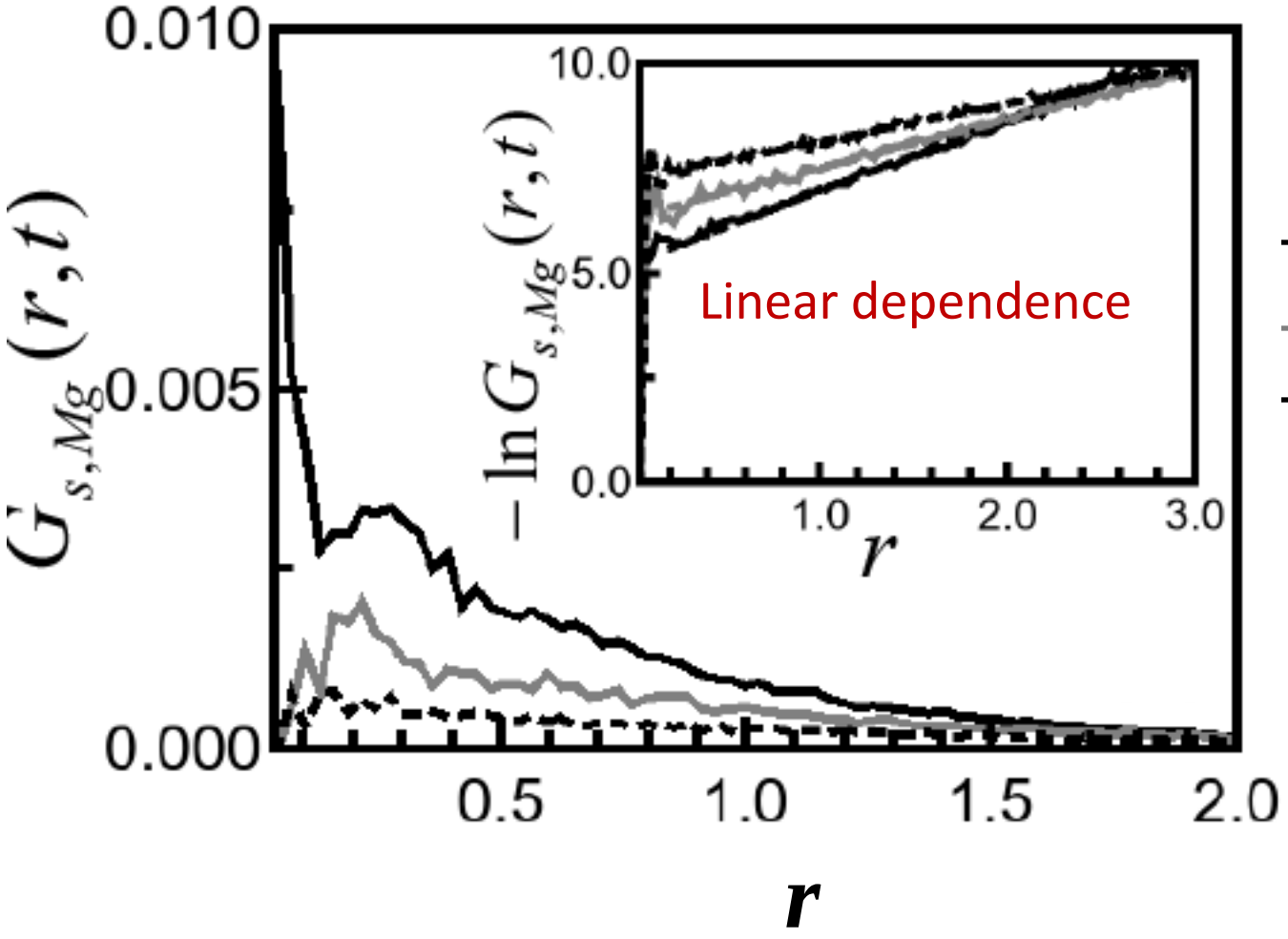
RMSD(t): deviation of a particle at a particular time t from starting point

$$\mathrm{RMSD}(t) = \frac{1}{N} < \sum_{i=1}^{N} \sqrt{\left| r_{c_\alpha}^{(i)}(t) - r_{c_\alpha}^{(i)}(0) \right|^2} >$$

Averaged over Cα atom of N number of residues



Self van Hove for Mg^{2+}



—— t =0.05 ns

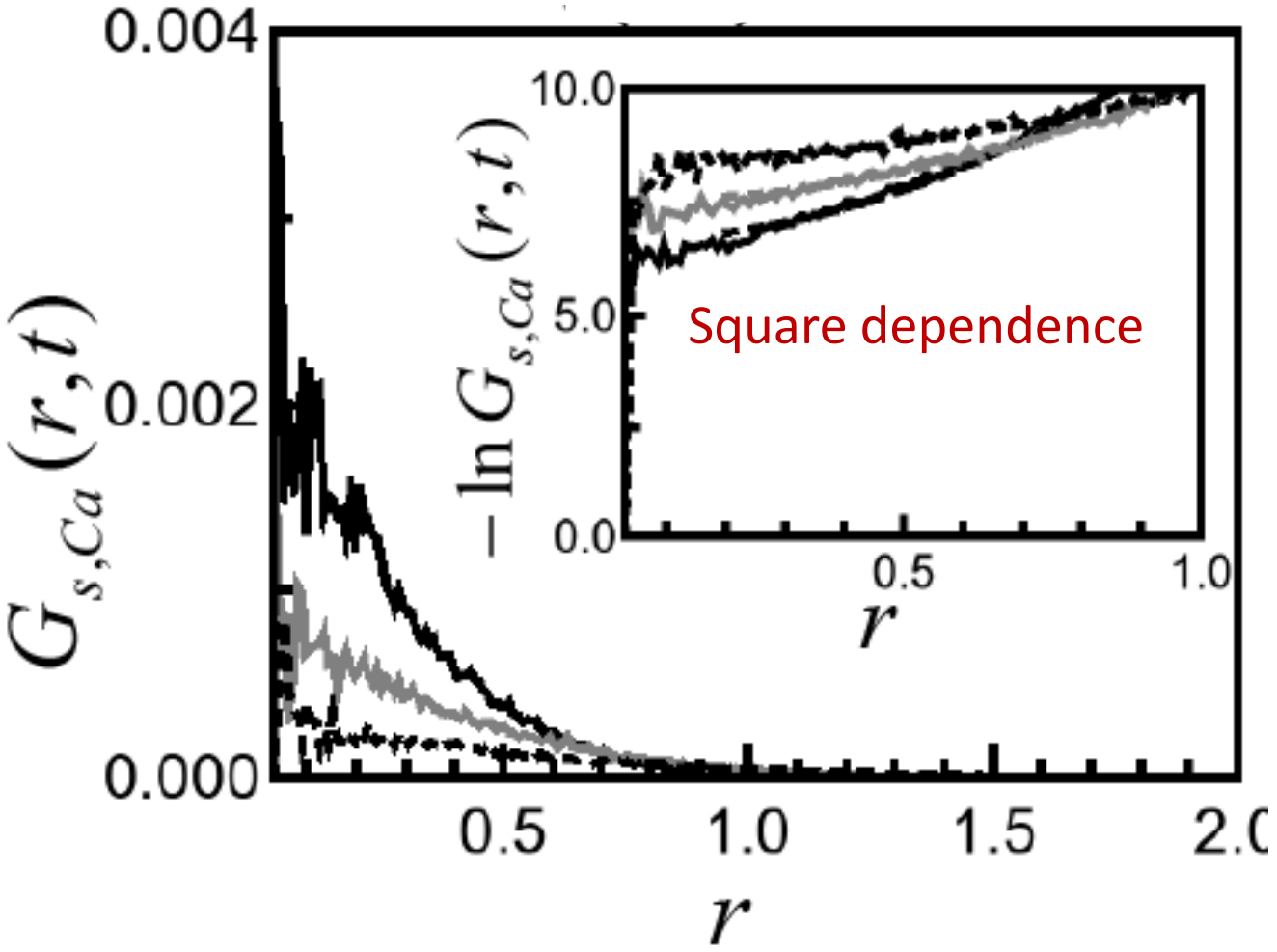
—— t =0.10 ns

------- t =0.20 ns

↓

Comparable to backbone relaxation time

Self van Hove for Ca^{2+}



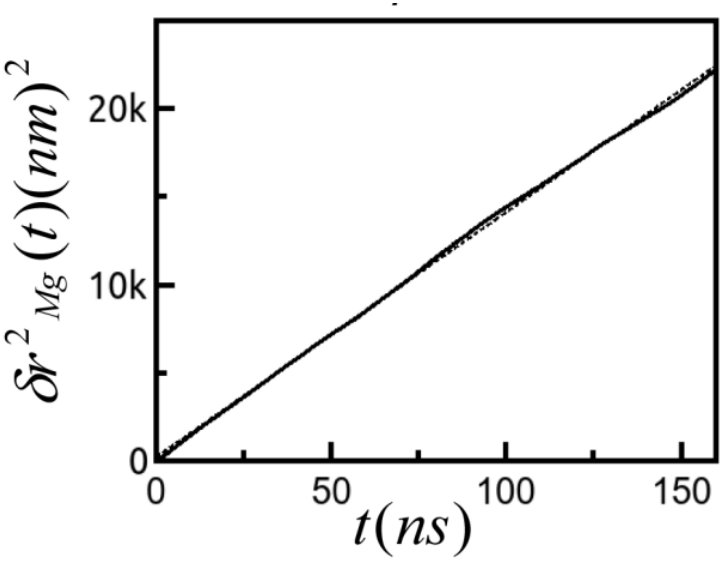
t =0.05 ns

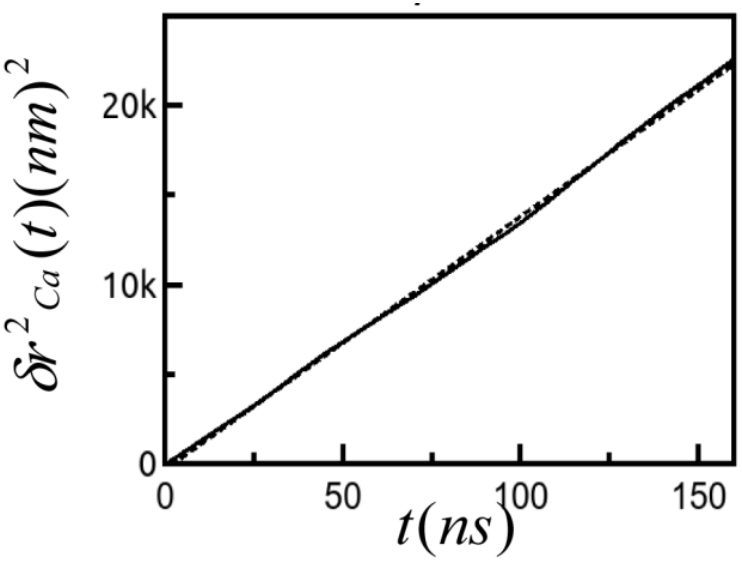
t =0.10 ns

------- t =0.20 ns

Comparable to backbone relaxation time

MSD





D : aqueous solution: 0.70×10^{-5} cm^2 s^{-1}
D : presence of STY3178: 0.20×10^{-5} cm^2 s^{-1}

D : aqueous solution: 0.79×10^{-5} cm^2 s^{-1}
D : presence of STY3178: 0.24×10^{-5} cm^2 s^{-1}

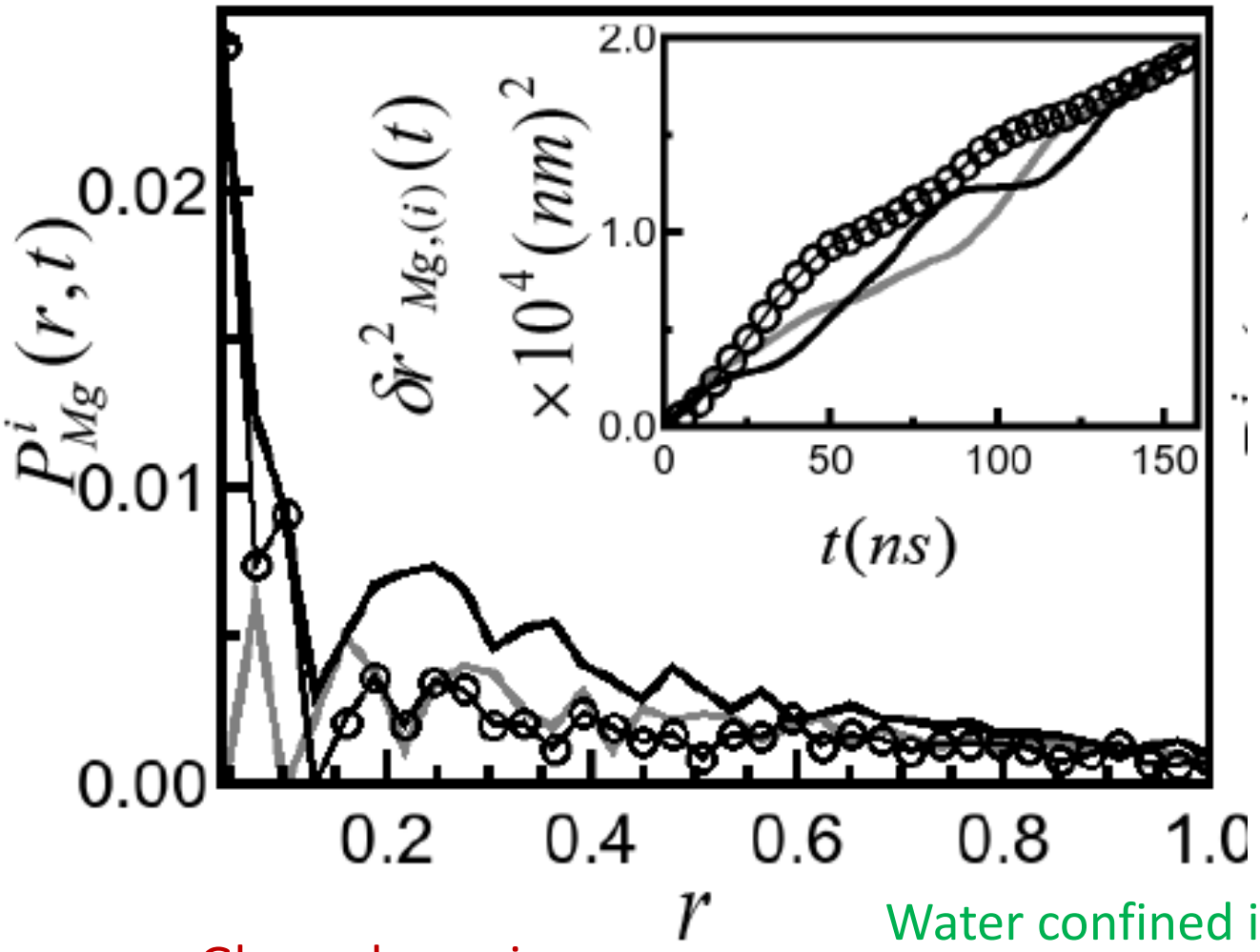
- Gaussian self-vHf & linear MSD: Fickian diffusion of Ca^{2+}
- Non-Gaussian exponential self-vHf & linear MSD: Non-Fickian diffusion of Mg^{2+}

⇩

- Dynamic heterogeneity : diffusion of colloids in lipid bilayer tube & bio-filament network

Motions of individual Mg^{2+} ions

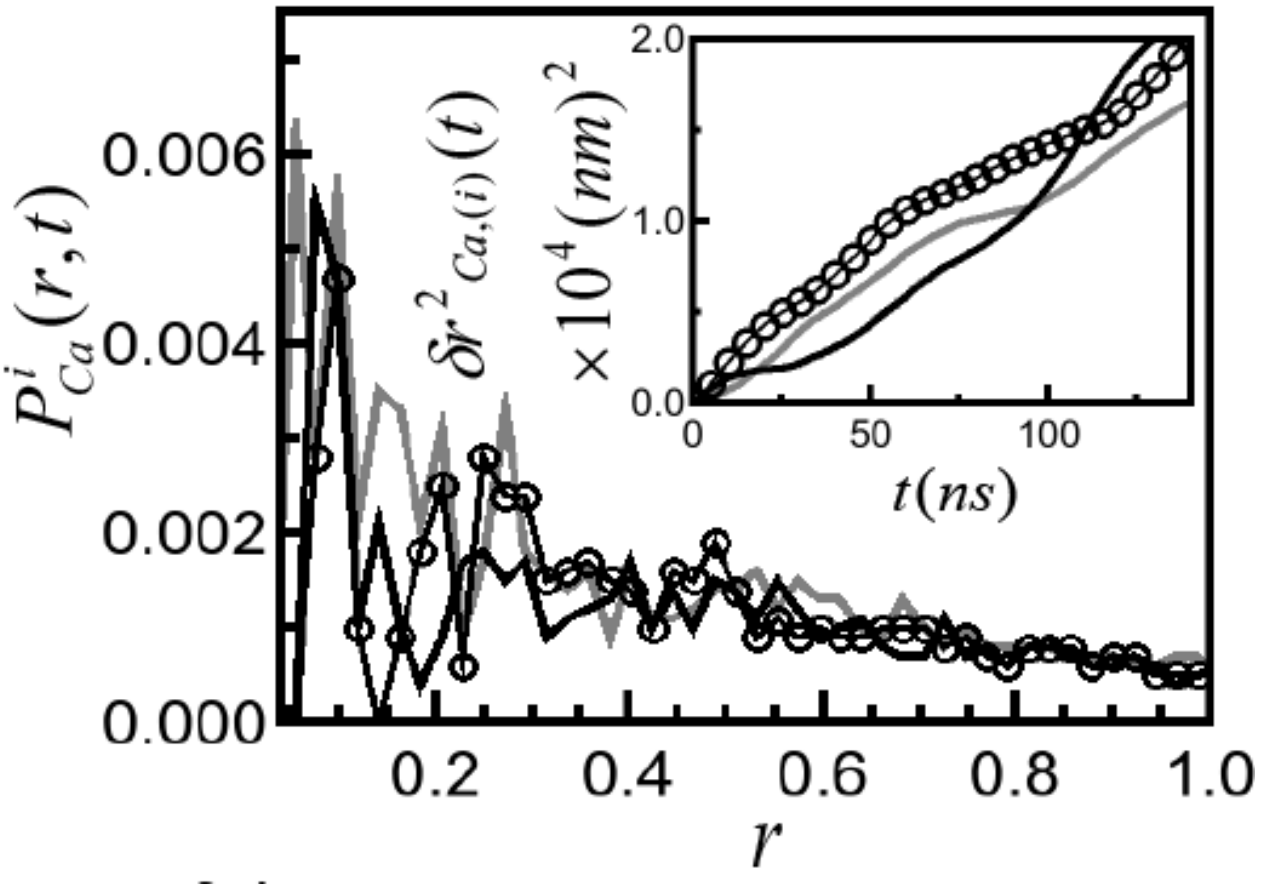
- Probability distributions of displacement at 0.05 ns time interval; msd of the same ions



Glassy dynamics → Water confined in protein-protein & protein-DNA interfaces

Motions of individual Ca^{2+} ions

- Probability distributions of displacement at 0.05 ns time interval; msd of the same ions

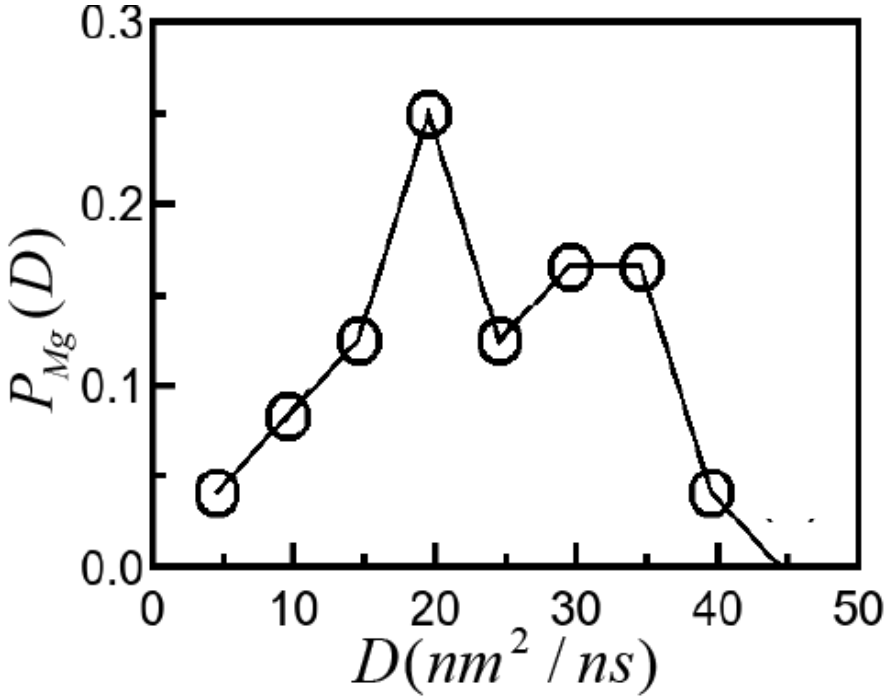


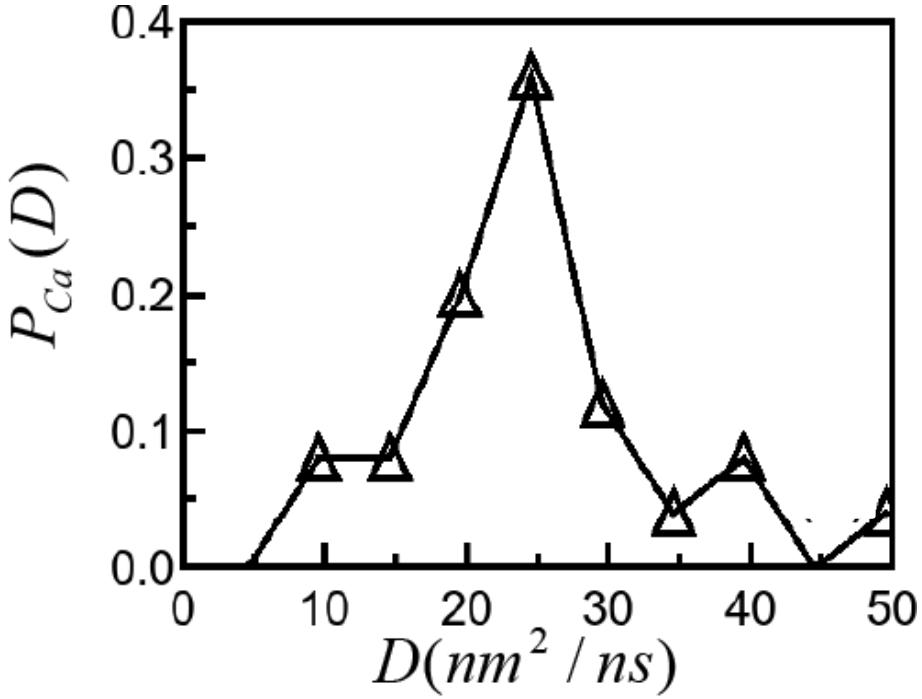
4th particle
1st particle
2nd particle

Purely diffusive motions of liquids

Dynamic heterogeneity; diffusion coefficient

Probability distributions of diffusion coefficients ; different regions in MSD data with varying slopes

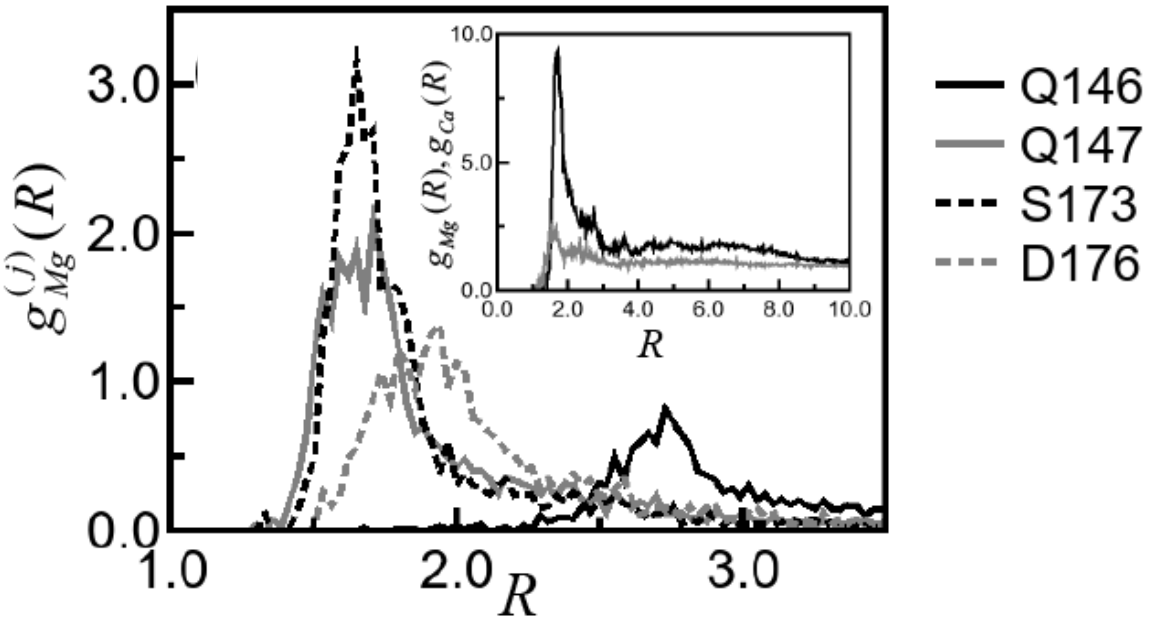


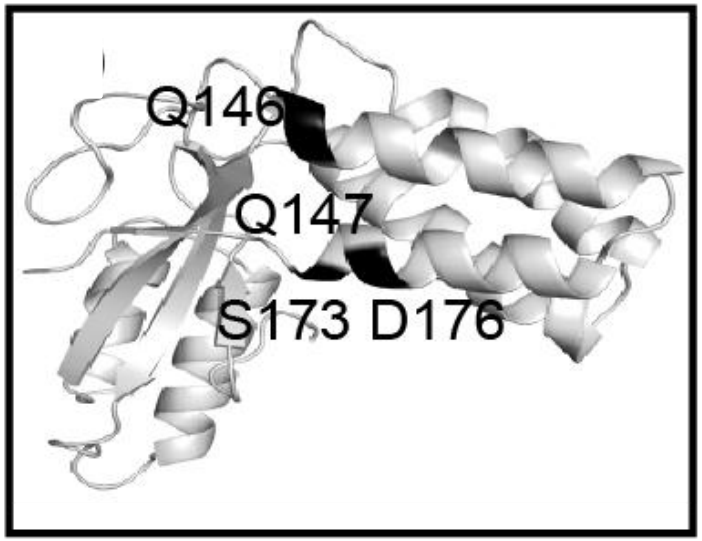


- All Mg^{2+} diffuse differently
- Similar diffusion profile for all Ca^{2+}

Interaction between ions and residue

- Surface exposed acidic and polar residues of protein using Swiss PDB
- Distributions of distance between ions around residues :
  Pair-correlation function g(r)
- Distribution of Mg^{2+} around each residues separately



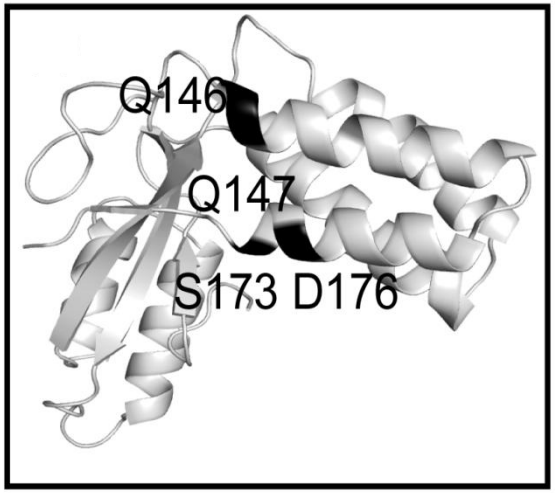


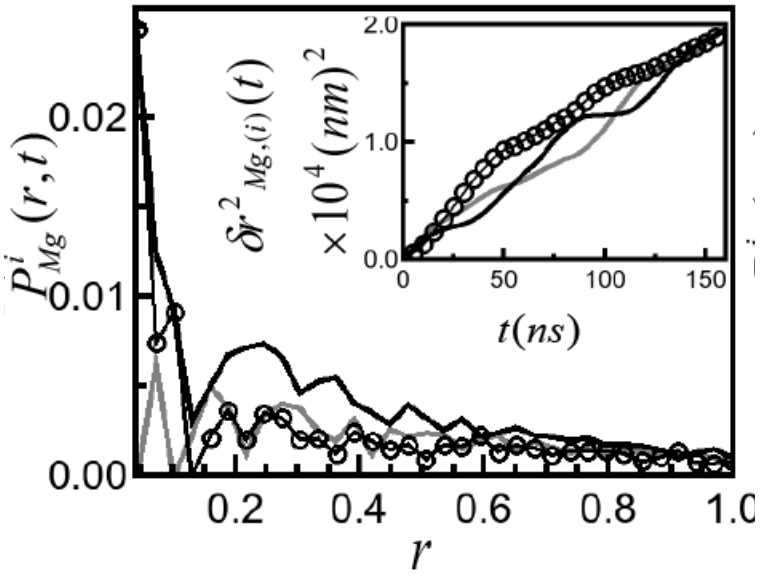
Mg^{2+} charge density 0.15 $\times 10^{11}$ coulomb m^{-3}

Ca^{2+}: charge density 0.06 $\times 10^{11}$ coulomb m^{-3}

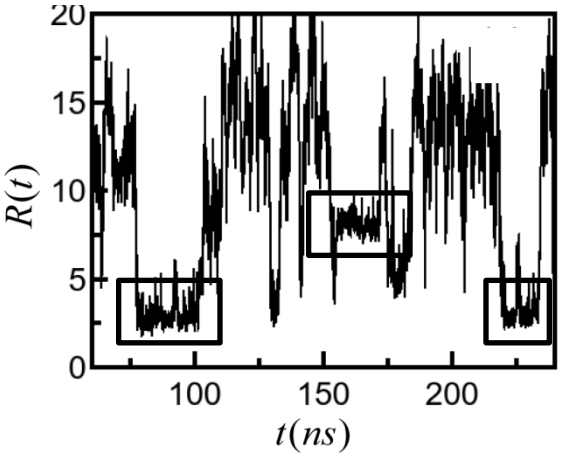
Mg^{2+} trapping patch of STY3178

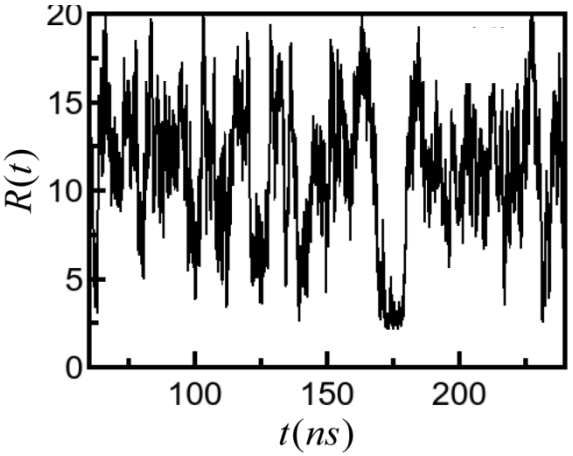
- Variation of distance between 2nd and 4th Mg^{2+} with respect to surface patch residues





Trapping

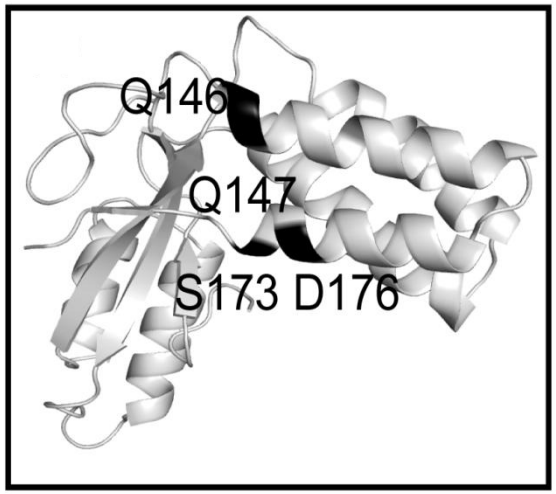


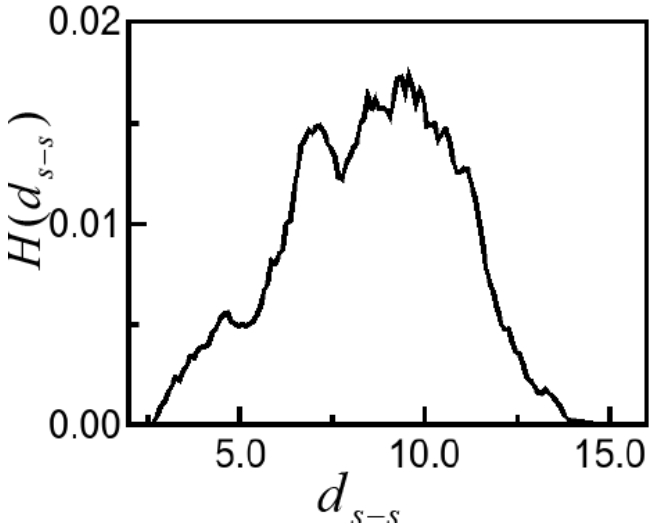


Q146-4th Mg^{2+} **Q146-2nd Mg^{2+}**

Inter-atomic distances between surface patch residues

- Mean of inter-atomic distances between Cα atoms of adjacent residues (Q146-Q147; S173-D176; ~ 6A^0)
- Minimum distance between heavy atoms of side chains of distant pairs ($d_{s\text{-}s}$-~ 5 A^0)

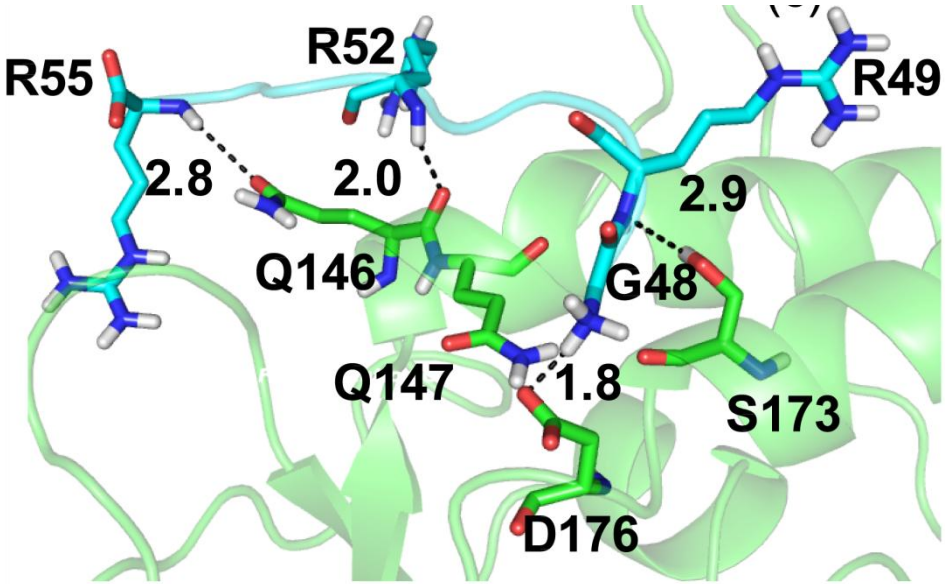




Q147-D176

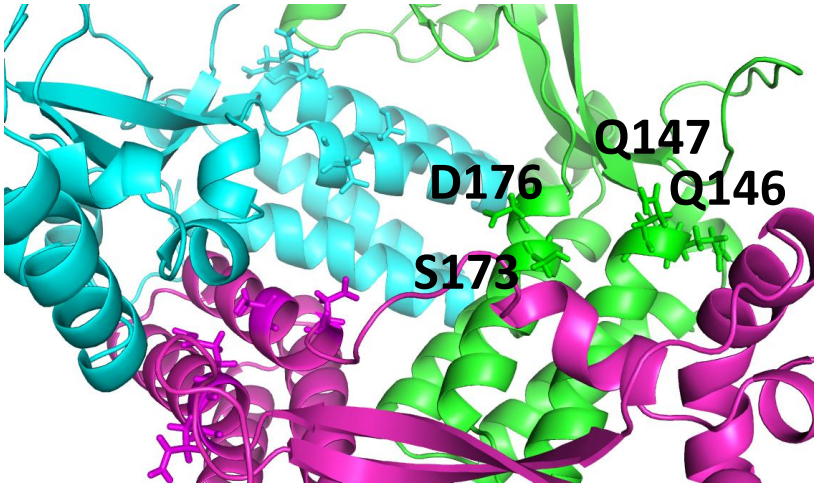
Binding sites of STY3178

- Dock basic residue rich peptides (Tat protein) with charge density 11.12×10^{11} coulomb m^{-3} to Mg^{2+} trapping sites of STY3178
- Hydrogen bonds between two peptides



Binding site of STY3178

Basic residue rich peptide



Trimeric model of STY3178

Conclusion

- Dynamic anomaly of ions
- Useful approach to reveal binding pocket over protein surface
- Ligand attached protein: template for novel functional material at nano meter range

Acknowledgement:

1. Dr. Mahua Ghosh
2. Sutapa Dutta