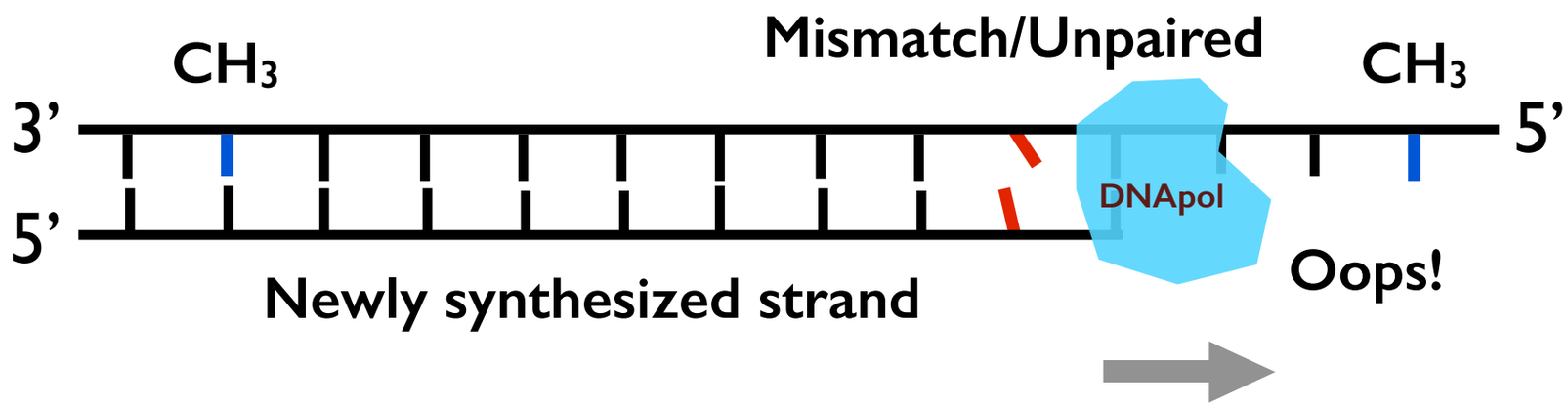
Dynamic Regulation of Mismatch Excision in DNA Mismatch Repair

POSTECH

Physics & IBIO

Jong-Bong Lee

During DNA Replication



Error rate ~ 10^{-4} /bp

After its proofreading
Error rate ~ 10^{-7} /bp

Proofreading speed: ~ 2 nt/s
Proofreading processivity: ~ 500 nt
(Part *et al.* unpublished)

Deficient DNA mismatch repair function

- Genome in a human cell: 3 billion base pairs
- Error rate of DNA polymerase: 1 error per 10^7 bp

3,000 errors

protein-coding RNA
(1.5 % of genome)

Non-coding RNA
(tRNA, rRNA, microRNA, etc)

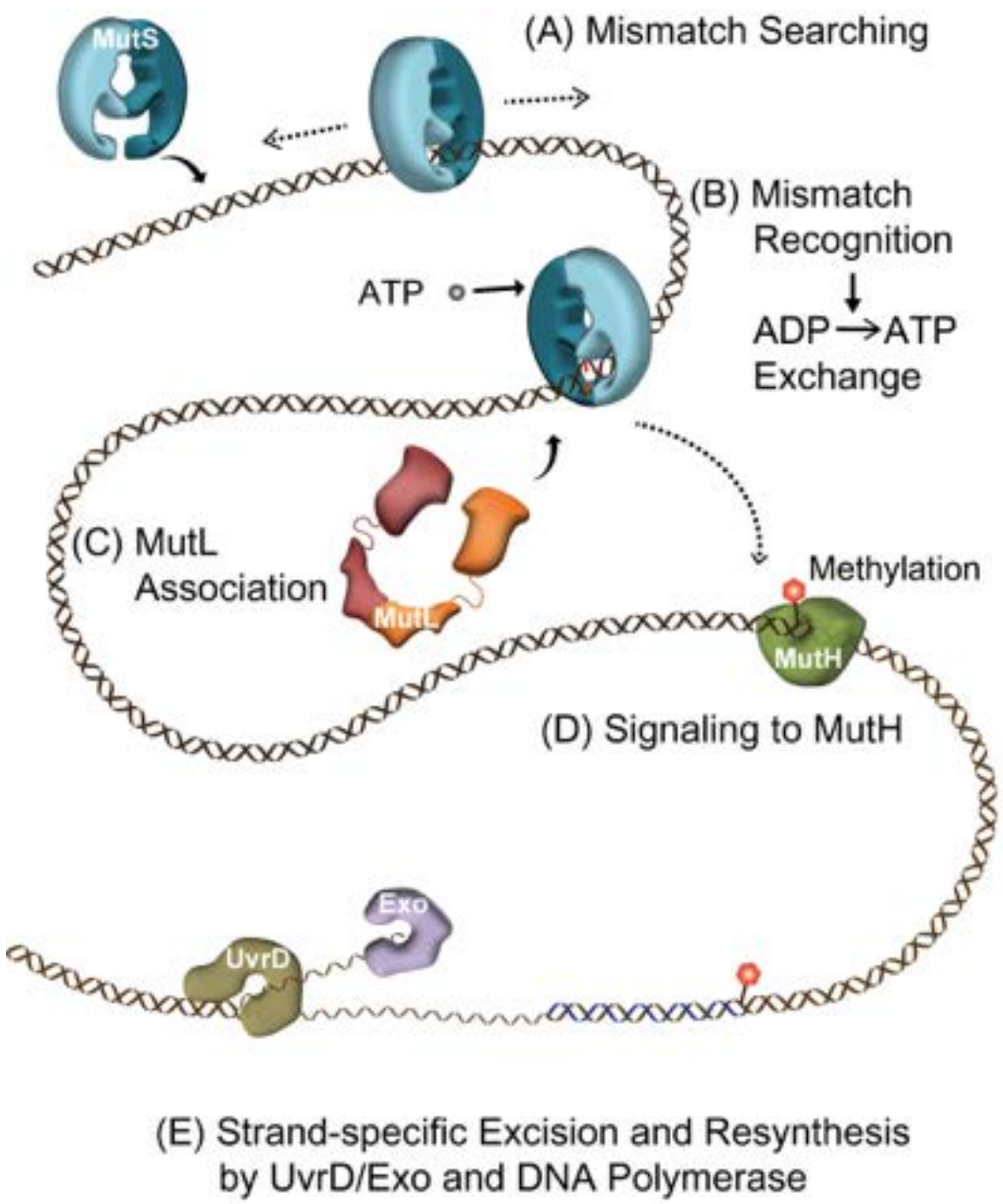
Mutant Proteins

Colon Cancer,
Endometrial, Ovarian and upper unitary tract tumors

DNA mismatch repair increases the fidelity of DNA replication up to 1,000 times.

Error rate ~ **10^{-10} /bp**

DNA Mismatch Repair



Mismatch finding

↓

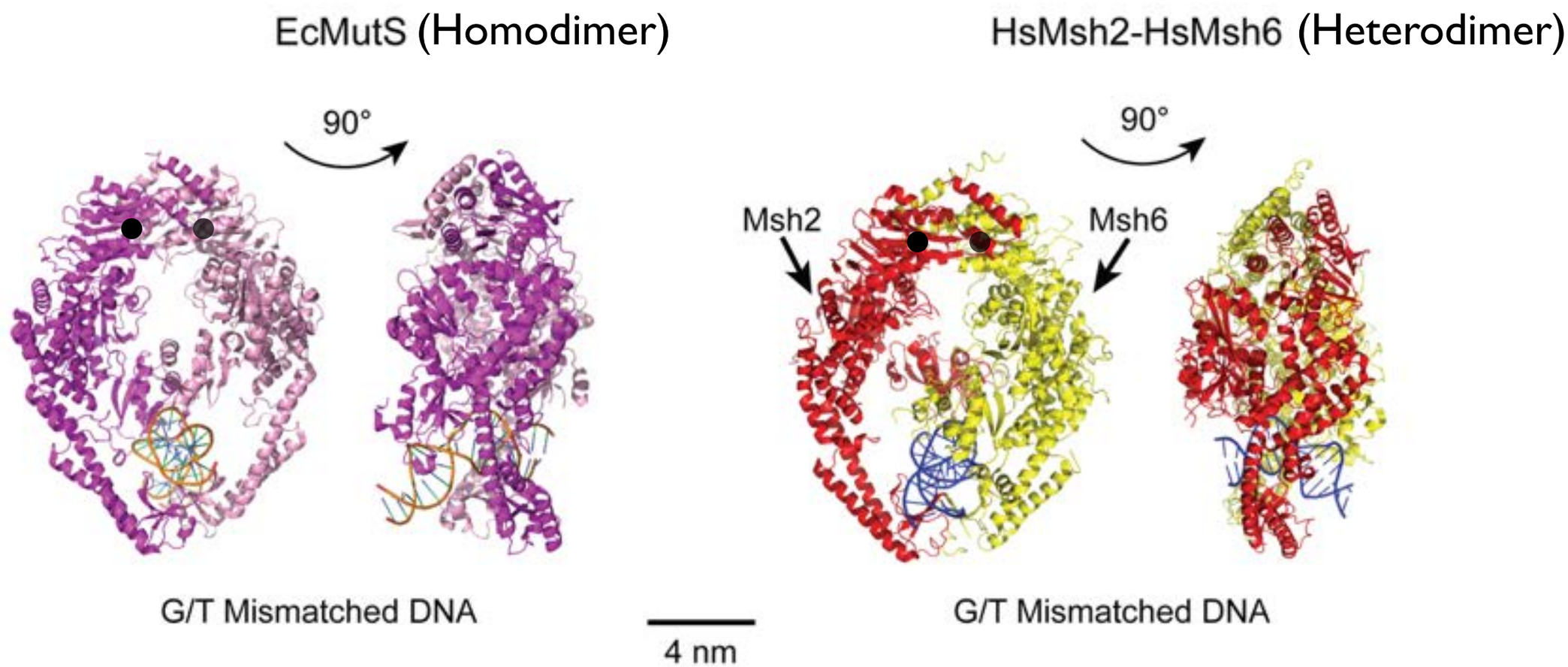
Strand scission

↓

Mismatch Removal

MutS

- ATP binding sites

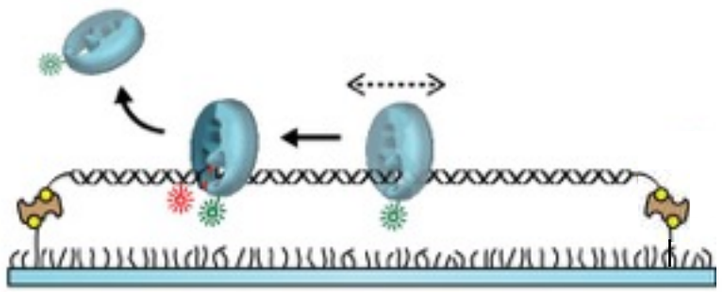


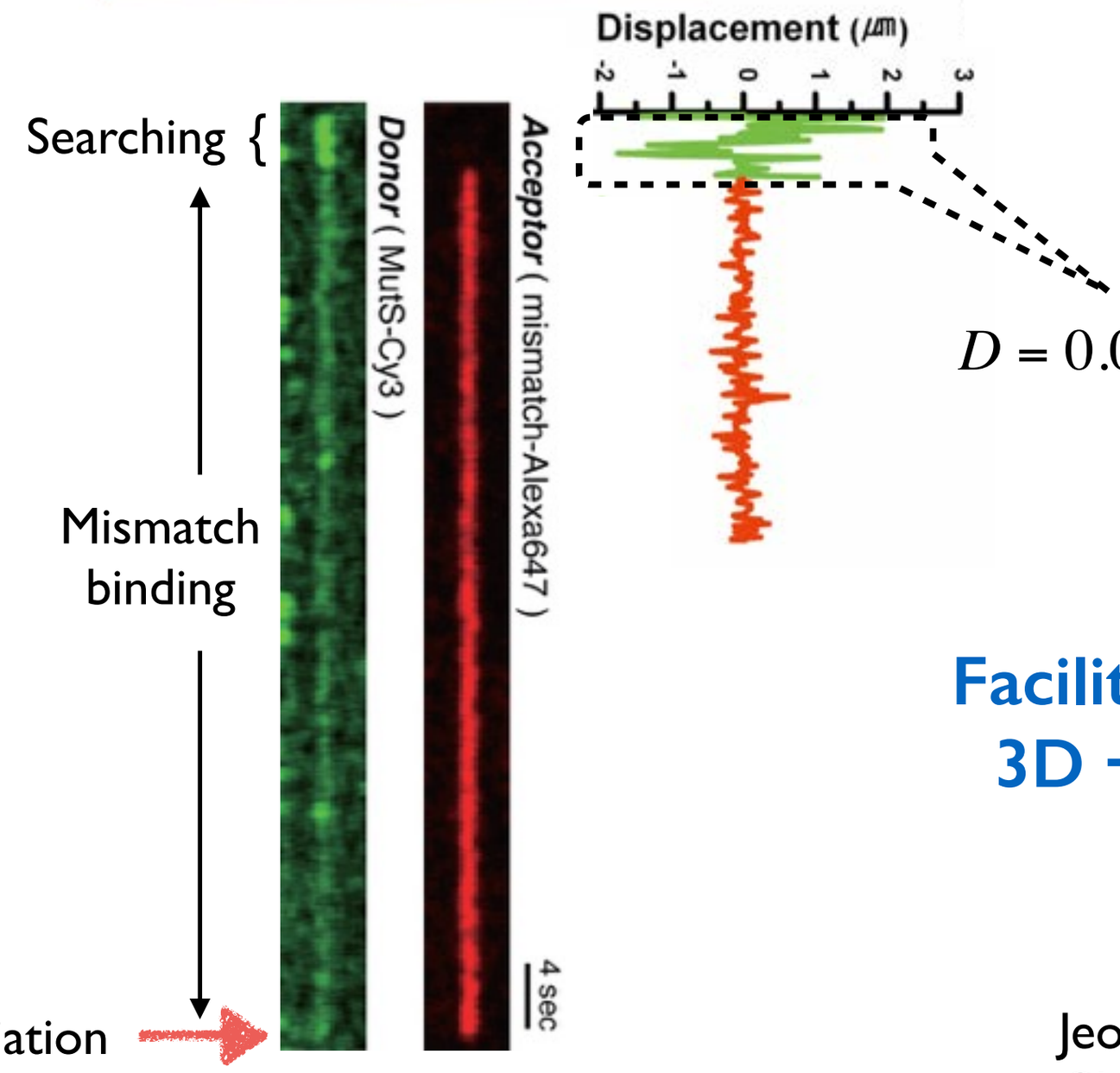
9 X 7 X 12 nm

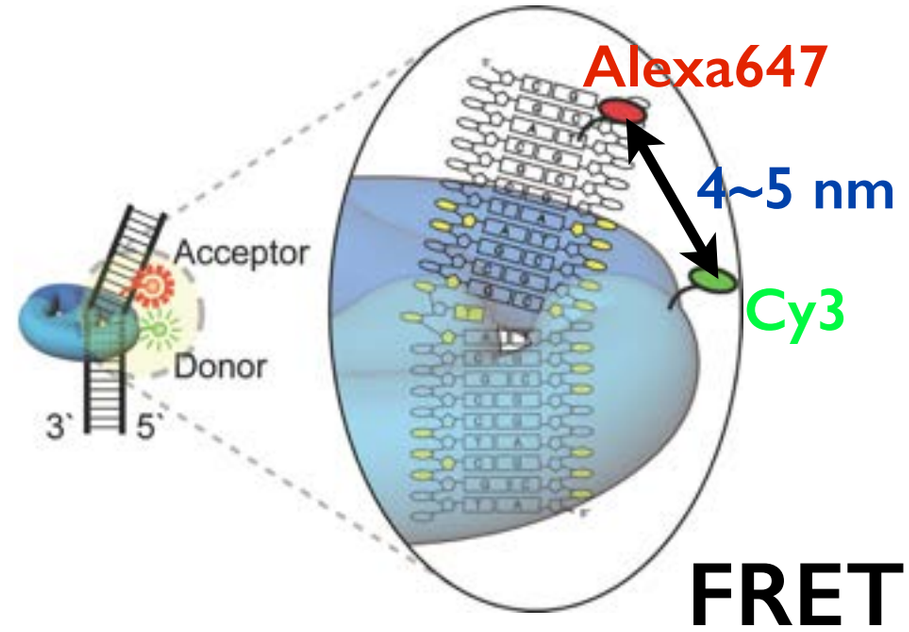
Footprint: 24 bp

Lamers et al. Nature (2001)
Warren et al. Mol Cell (2007)

Searching MutS (No ATP)







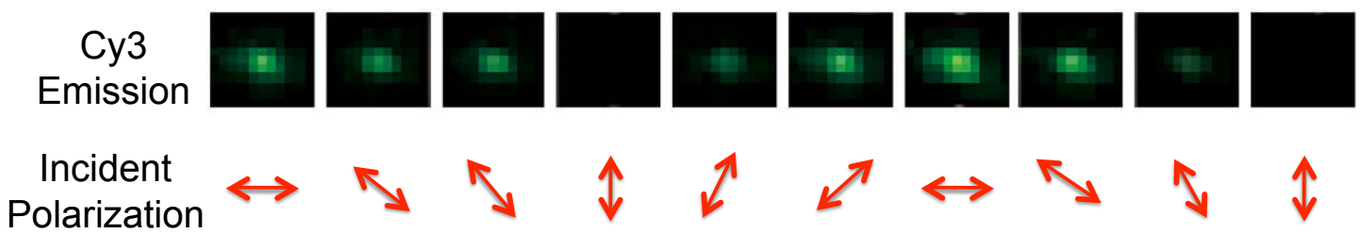
$$D = 0.032\ \mu m^2 / s$$

Facilitated Diffusion:
3D + 1D diffusion

Jeong et al. Nature Struct Mol Biol (2011)
Cho et al. Structure (2012)

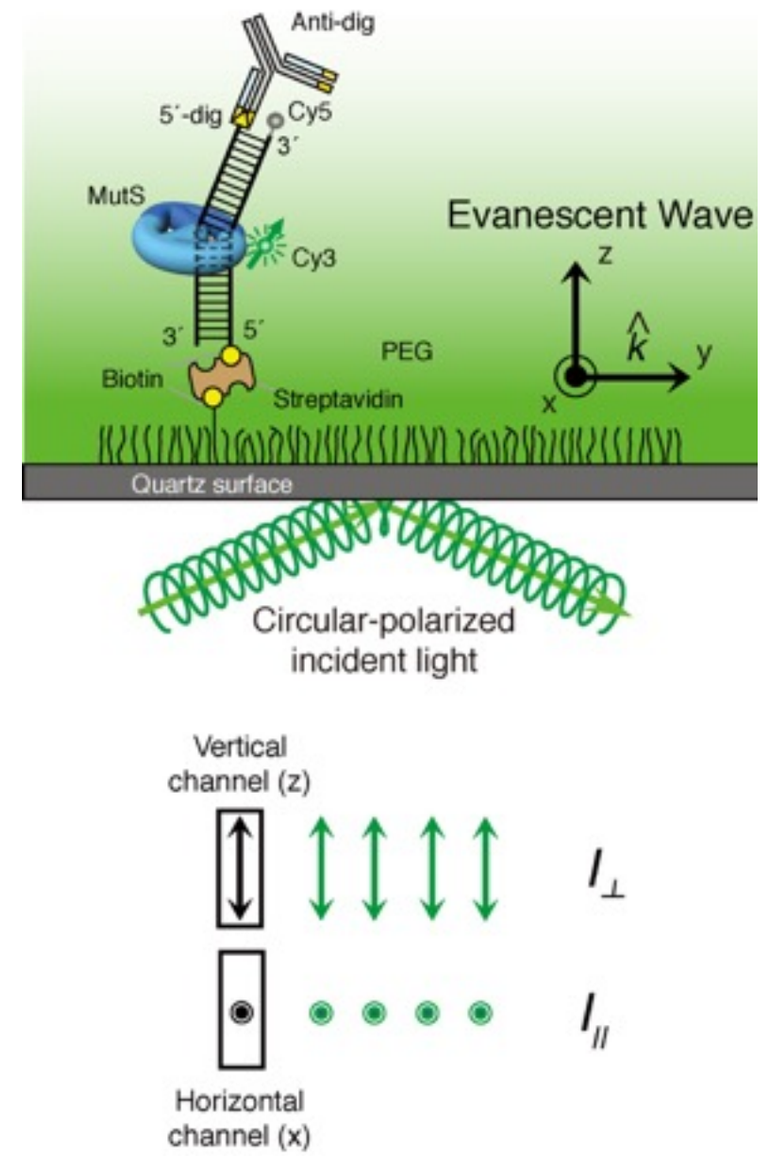
Polarization of Cy3-MutS

Photon Absorption Probability $\propto \left|\vec{E}\cdot\vec{\mu}\right|^2$ ~ Emission Intensity



Polarization-controlled photo-switching

Lee et al. PRL (2012)

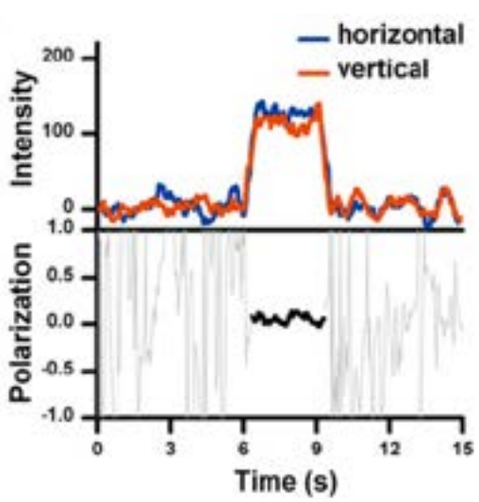


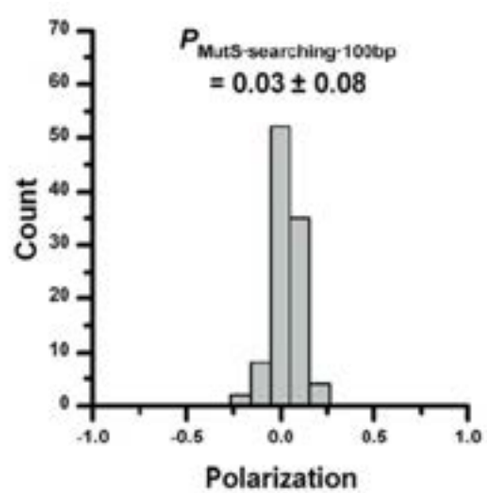
Cho et al. Structure (2012)

25 turns along a helical pitch (10.5 bp)
per 50 ms (time resolution)

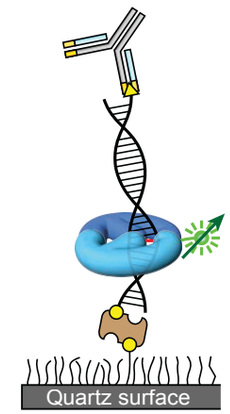
⇨ Depolarized signals

100 bp
duplex DNA
w/o mismatch

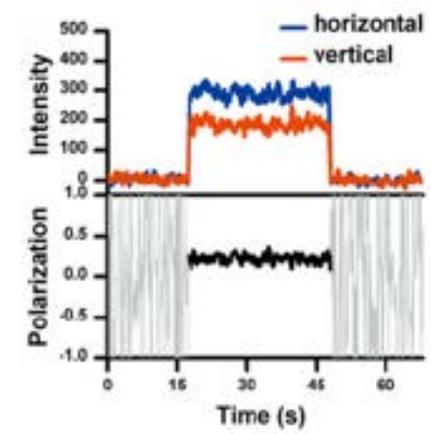


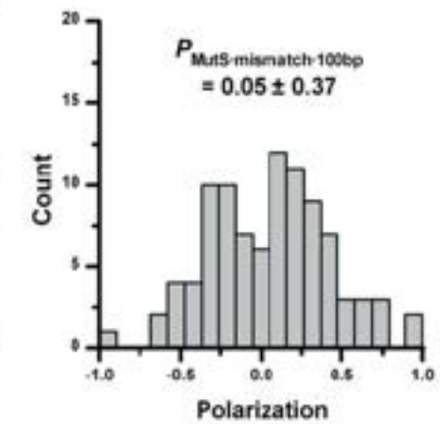


100 bp
mismatched DNA



-ATP

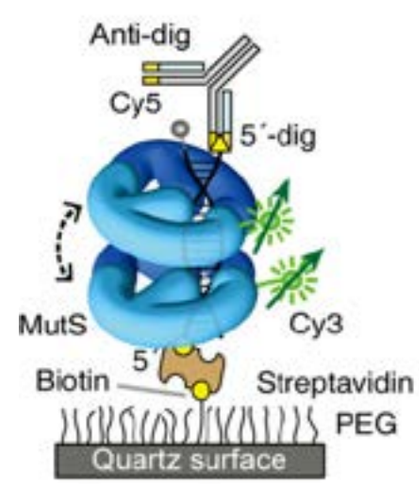


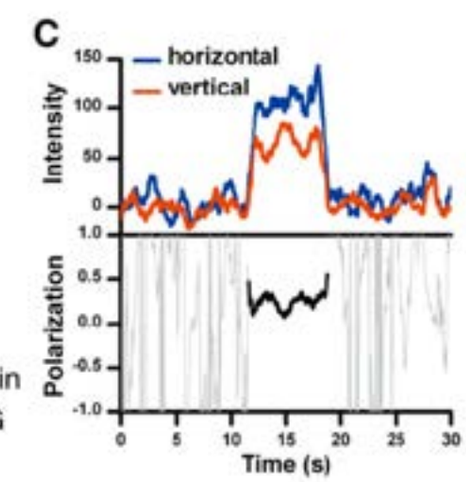


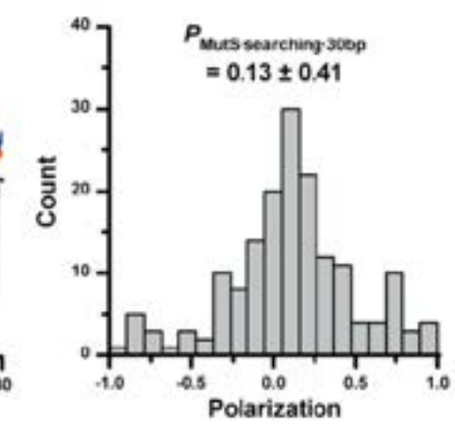
Stop the rotation at the mismatch

⇨ Polarized signals

30 bp duplex DNA
w/o mismatch

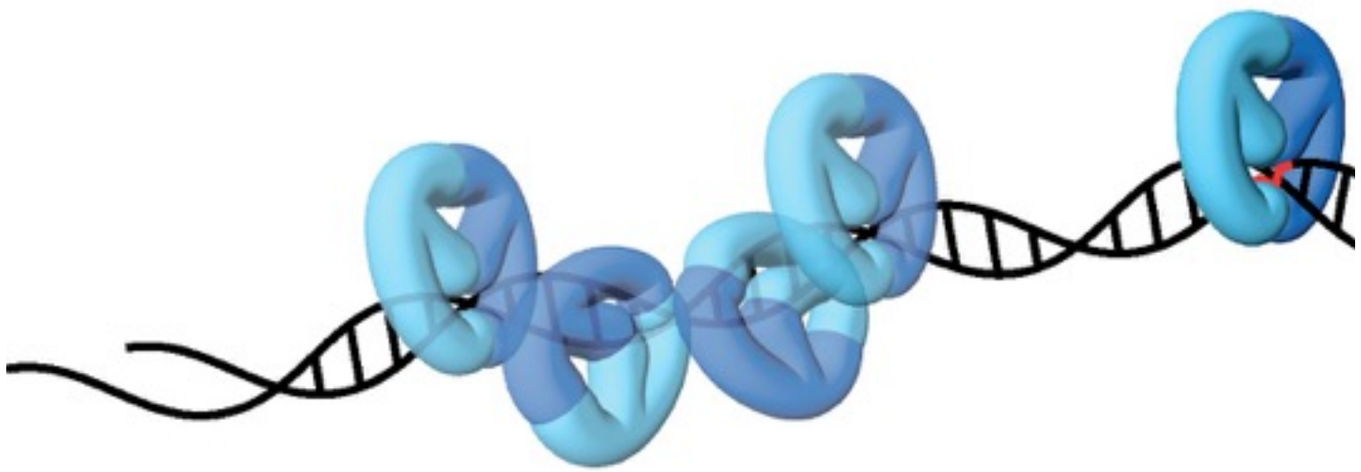






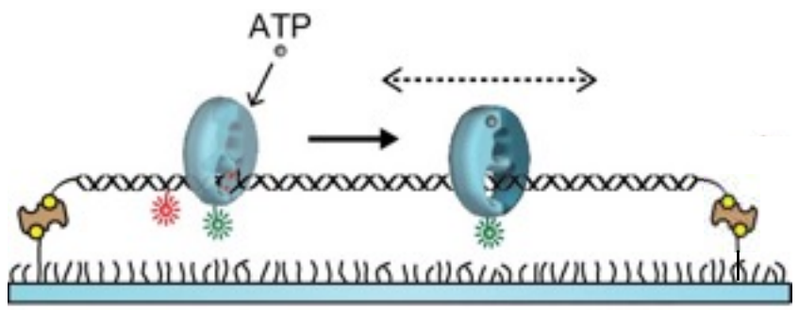
Footprint of MutS: ~ 24 bp

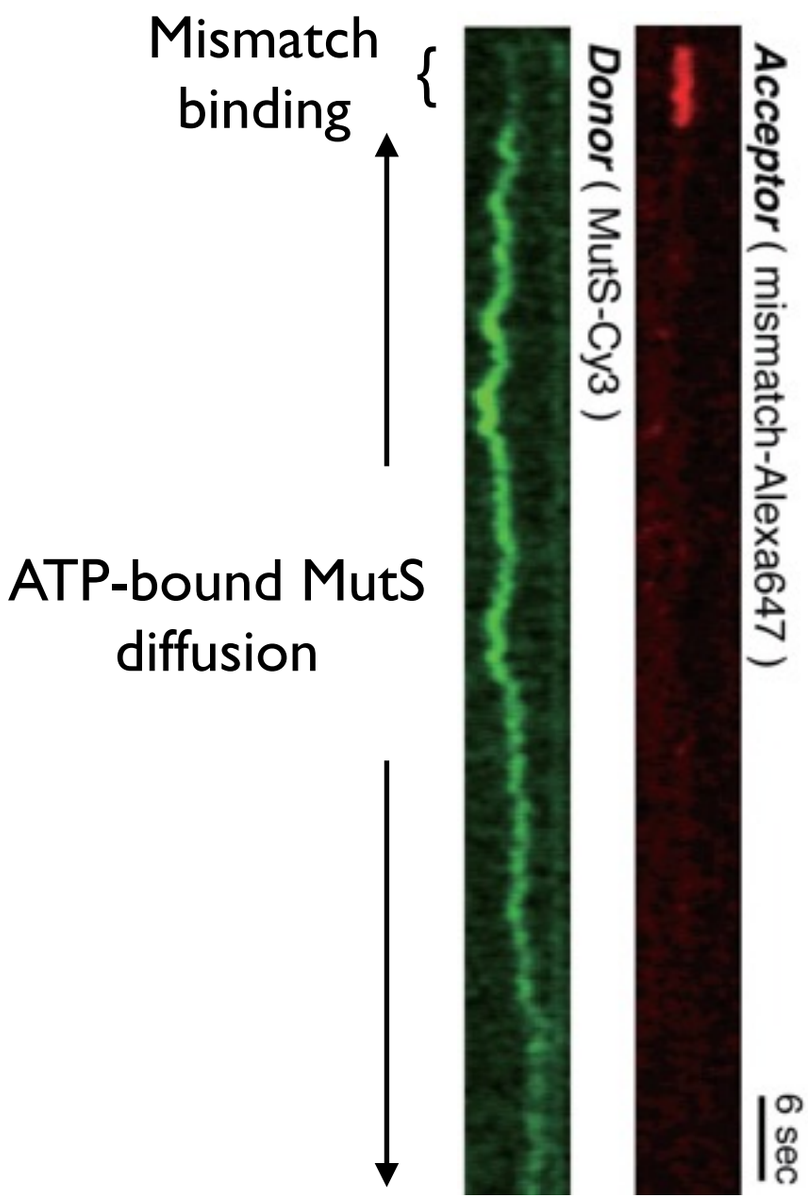
Searching a mismatch by facilitated diffusion



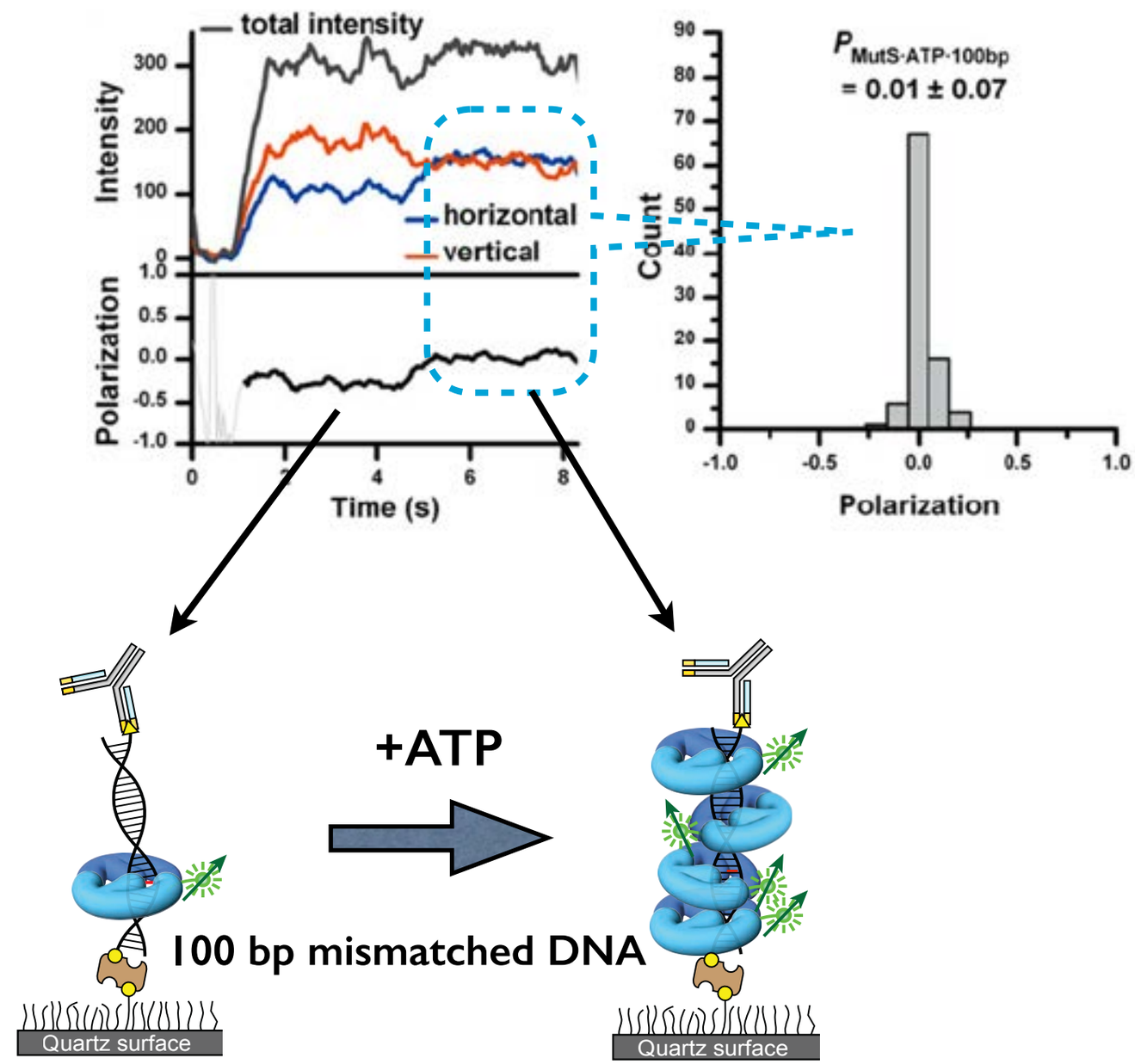
Helical Diffusion along DNA backbone

In the presence of ATP (ATPγS)





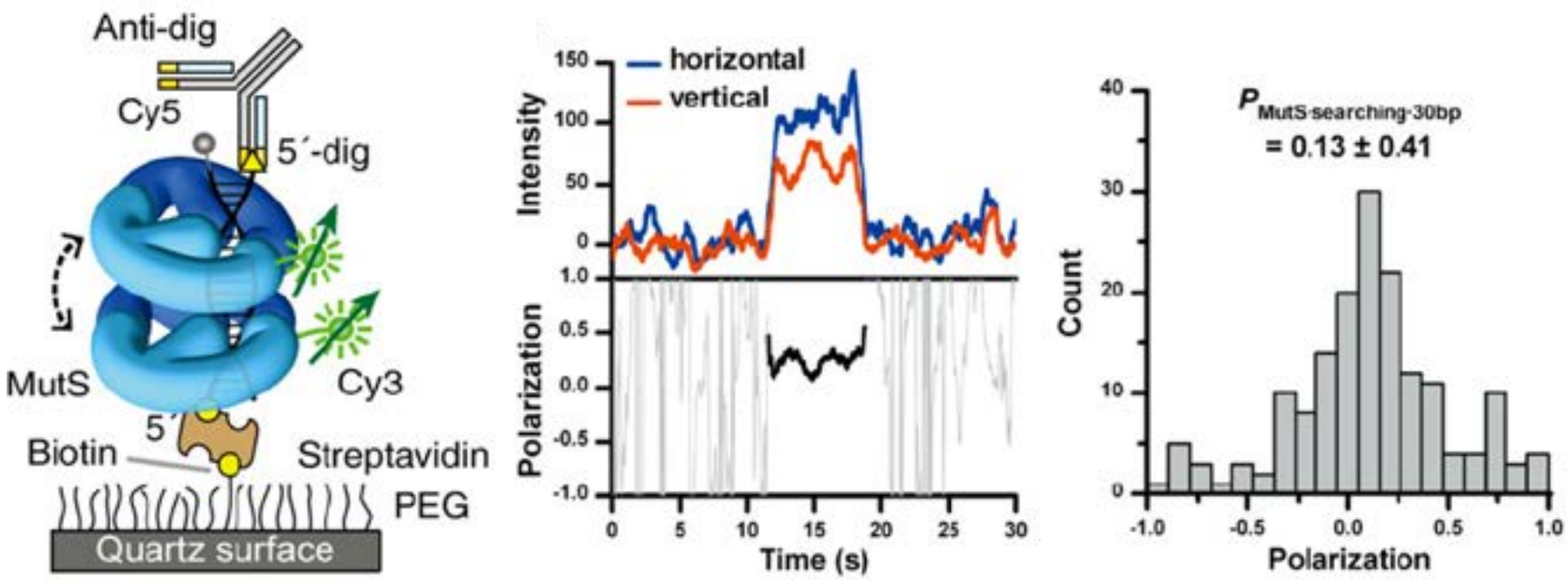
Polarization



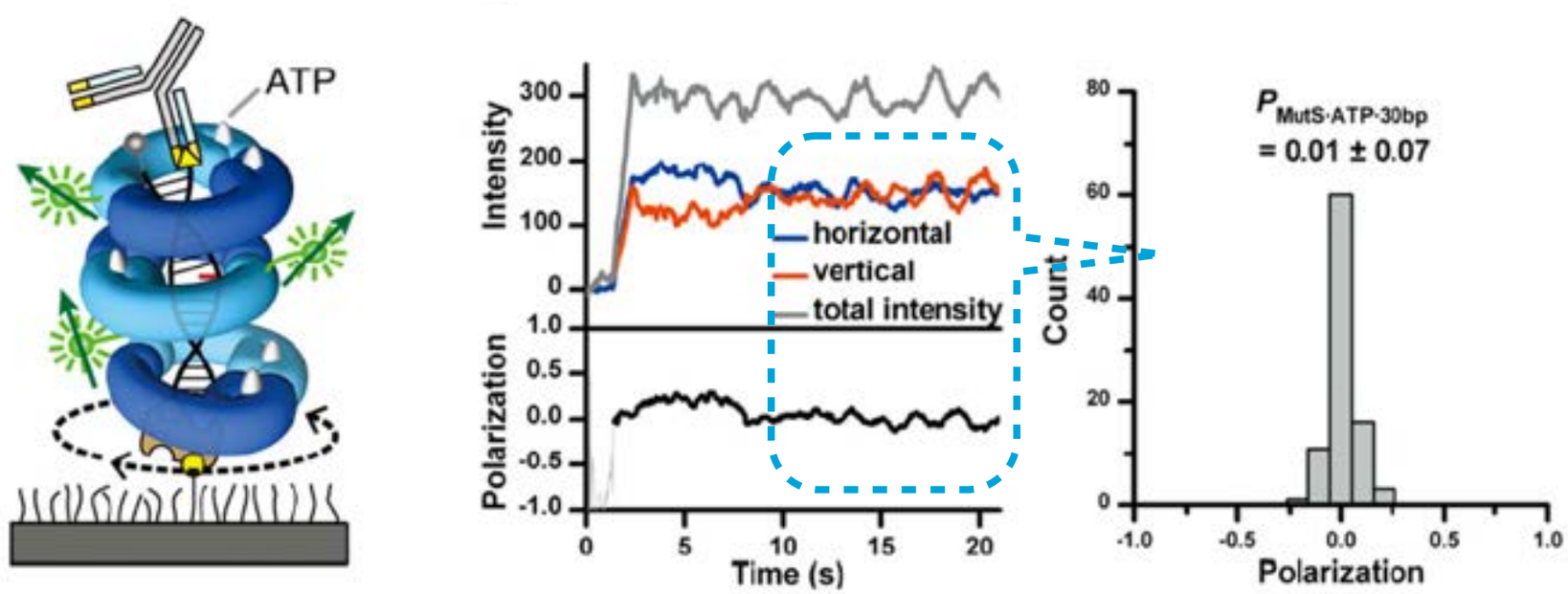
Cho et al. Structure (2012)

30 bp matched DNA

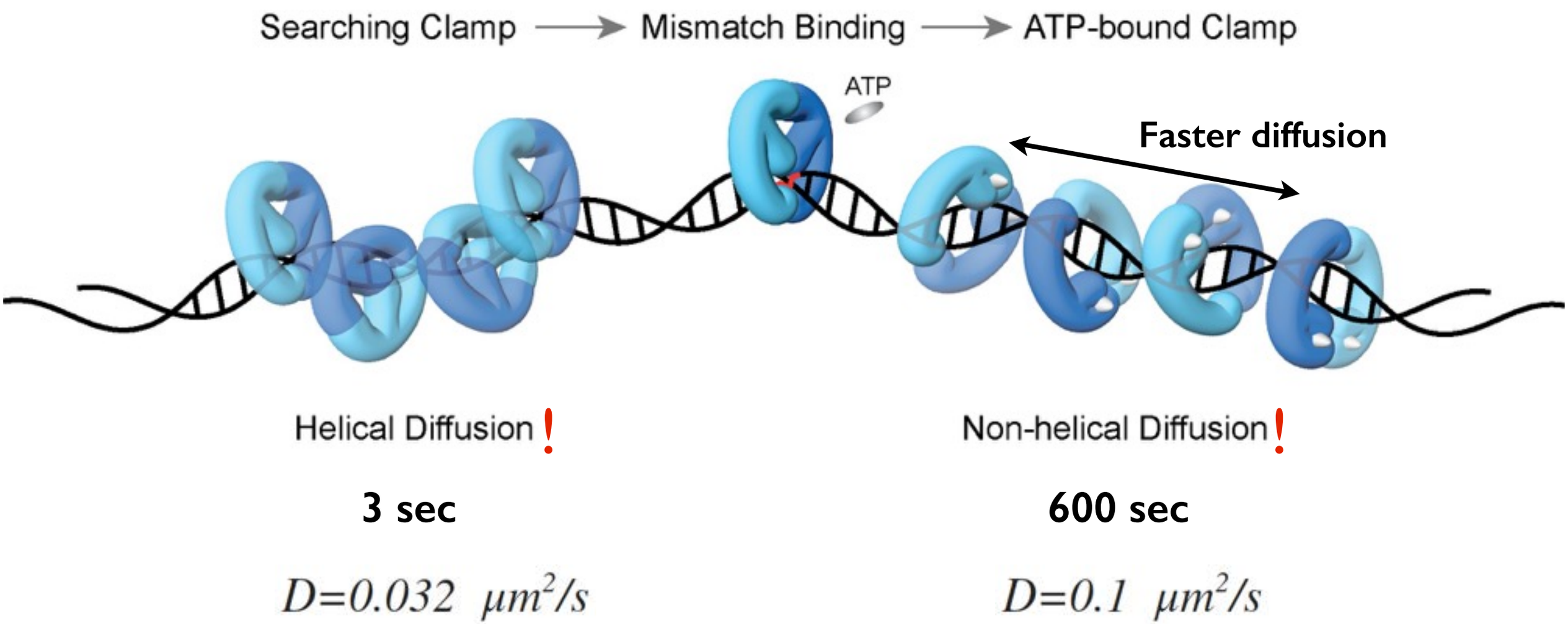
24 bp footprint



30 bp mismatched DNA



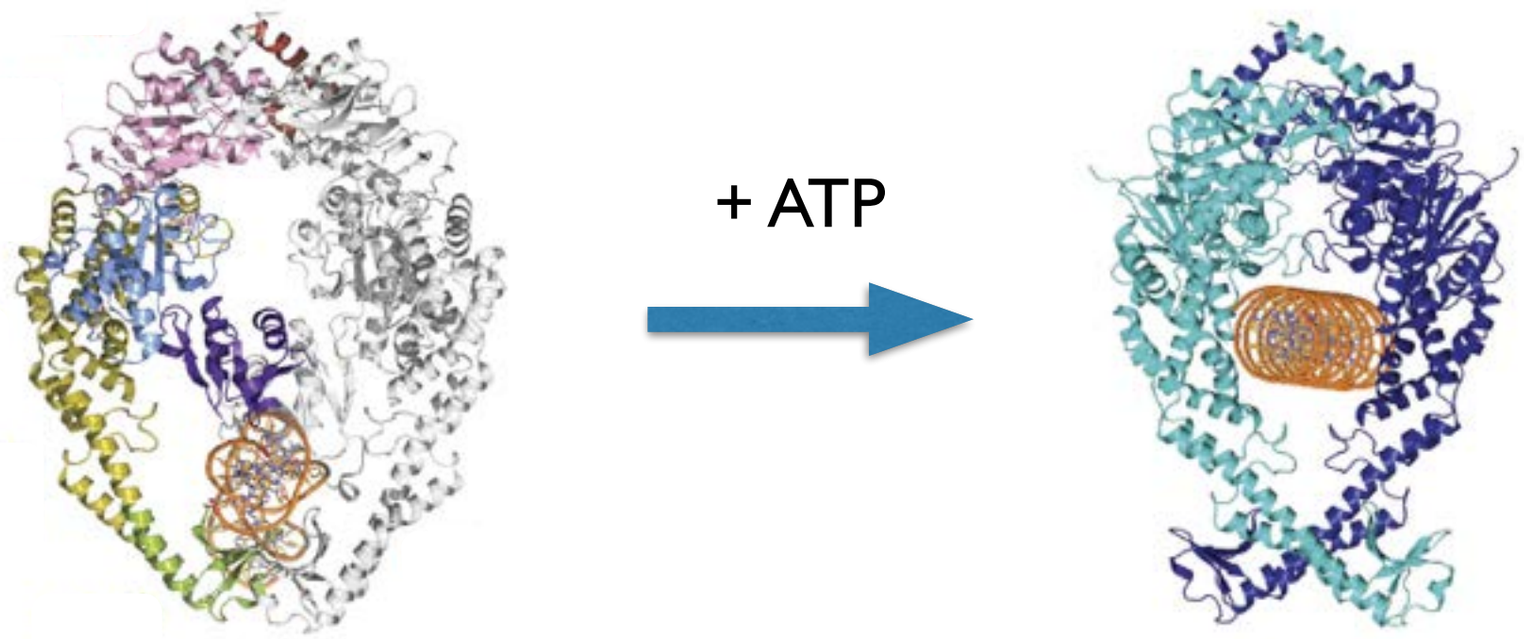
Cho et al. Structure (2012)



✓ MutS scans duplex DNA in a continuous contact with the DNA backbone to find a mismatch.

✓ ATP-bound MutS moves away from the mismatch in a non-helical diffusion.

Crystal Structure of *E. coli* ATP-bound MutS



Groothuiaen et al. eLife 2015

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