Supplementary Figure S1  Coarse-grained molecular dynamics simulation trajectories of $\text{MutS}^{\text{ADP}}$ on 75 base-pairs DNA with a GC repeat sequence in the presence of 100 mM ions.
DNA base-pair mismatches are routinely generated by intrinsic factors such as DNA replication errors and oxygen species and extrinsic factors such as ultraviolet and ionizing radiation. It has been well-documented that these mismatches are corrected by the mismatch repair (MMR) pathway both in prokaryotes and eukaryotes [1,2].

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Supplementary Figure S2 Coarse-grained molecular dynamics simulation trajectories of *MutS<sub>ADP</sub>* on 75 base-pairs DNA with a AT repeat sequence in the presence of 100 mM ions.
Supplementary Figure S3  Coarse-grained molecular dynamics simulation trajectories of MutS$^{\text{ADP}}$ on 75 base-pairs DNA with a GC repeat sequence in the presence of 50 mM ions.
Introduction

DNA base-pair mismatches are routinely generated by intrinsic factors such as DNA replication errors and oxygen species and extrinsic factors such as ultraviolet and ionizing radiation. It has been well-documented that these mismatches are corrected by the mismatch repair (MMR) pathway both in prokaryotes and eukaryotes [1,2]. In *Escherichia coli* (*E. Coli*), a base-pair mismatch is searched and recognized by a MutS protein [3]. The crystal structure of MutS that recognizes a mismatch contains an adenosine diphosphate (ADP) molecule in one of the two nucleotide-binding sites [4–6]. After the mismatch recognition, the bound ADP molecule is exchanged with an adenosine triphosphate (ATP) molecule, and the other nucleotide-binding site is also occupied by ATP. The ATP binding induces a MutS conformational change, binding of MutL and MutH proteins to MutS, and release of MutS from the mismatch [7–11]. The released MutS/MutL/MutH complex diffuses along DNA to search and recognize a GATC sequence around the mismatch [12], and MutH generates a nick on the sequence [7]. Then, an exonuclease digests one strand of double-stranded DNA from the nick to the site beyond the mismatch [13]. Finally, the new strand is re-synthesized using the undigested strand as a template [13].

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Supplementary Figure S4  Coarse-grained molecular dynamics simulation trajectories of *MutS<sub>ADP</sub>* on 75 base-pairs DNA with a GC repeat sequence in the presence of 150 mM ions.
Supplementary Figure S5  Coarse-grained molecular dynamics simulation trajectories of \( \text{MutS}^{\text{ADP}} \) on 75 base-pairs DNA with a GC repeat sequence in the presence of 500 mM ions.
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**Supplementary Figure S6** Coarse-grained molecular dynamics simulation trajectories of *MutS*\(^{ADP}\) on 75 base-pairs DNA with a GC repeat sequence in the absence of electrostatic interactions between MutS and DNA.
Supplementary Figure S7 MutS\textsuperscript{ADP} position along 75 base-pair DNA with a GC repeat sequence and cumulative angle around the DNA in the presence of 100 mM ions.
Introduction

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**Supplementary Figure S8** *MutS<sub>ADP</sub>* position along 75 base-pair DNA with a GC repeat sequence and cumulative angle around the DNA in the presence of 50 mM ions.
Supplementary Figure S9  MutS\textsuperscript{ADP} position along 75 base-pair DNA with a GC repeat sequence and cumulative angle around the DNA in the presence of 150 mM ions.
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Supplementary Figure S11  MutS\textsuperscript{ADP} position along 75 base-pair DNA with a GC repeat sequence and cumulative angle around the DNA in the absence of electrostatic interactions between MutS and DNA.
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**Supplementary Figure S12** Time trajectories of a MutS\textsubscript{ADP} position on the axis orthogonal to linear lines with the slope of 10 base-pairs / 2π in the position vs cumulative angle change plots (e.g. Figure S7) in the presence of 50 mM ions.
Supplementary Figure S13  Time trajectories of a MutS\textsuperscript{ADP} position on the axis orthogonal to linear lines with the slope of 10 base-pairs / 2\pi in the position vs cumulative angle change plots (e.g. Figure S7) in the presence of 100 mM ions.
DNA base-pair mismatches are routinely generated by intrinsic factors such as DNA replication errors and oxygen species and extrinsic factors such as ultraviolet and ionizing radiation. It has been well-documented that these mismatches are corrected by the mismatch repair (MMR) pathway both in prokaryotes and eukaryotes [1,2]. In *Escherichia coli* (*E. Coli*), a base-pair mismatch is searched and recognized by a MutS protein [3]. The crystal structure of MutS that recognizes a mismatch contains an adenosine diphosphate (ADP) molecule in one of the two nucleotide-binding sites [4–6]. After the mismatch recognition, the bound ADP molecule is exchanged with an adenosine triphosphate (ATP) molecule, and the other nucleotide-binding site is also occupied by ATP. The ATP binding induces a MutS conformational change, binding of MutL and MutH proteins to MutS, and release of MutS from the mismatch [7–11]. The released MutS/MutL/MutH complex diffuses along DNA to search and recognize a GATC sequence around the mismatch [12], and MutH generates a nick on the sequence [7]. Then, an exonuclease digests one strand of double-stranded DNA from the nick to the site beyond the mismatch [13]. Finally, the new strand is re-synthesized using the undigested strand as a template [13].

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Supplementary Figure S15  Time trajectories of a MutS<sub>ADP</sub> position on the axis orthogonal to linear lines with the slope of 10 base-pairs / 2π in the position vs cumulative angle change plots (e.g. Figure S7) in the presence of 500 mM ions.
Introduction

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Supplementary Figure S17  Coarse-grained molecular dynamics simulation trajectories of the MutS\textsuperscript{ADP} clamp domain on 75 base-pairs DNA with a GC repeat sequence in the presence of 50 mM ions. Points were colored according to the location of the clamp domain: Blue when in the major groove and red when in the minor groove. Please refer to the text for the definition for the locations.
Introduction

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Supplementary Figure S18 Coarse-grained molecular dynamics simulation trajectories of the \textit{MutS}^{\text{ADP}} clamp domain on 75 base-pairs DNA with a GC repeat sequence in the presence of 100 mM ions. Points were colored according to the location of the clamp domain: Blue when in the major groove and red when in the minor groove. Please refer to the text for the definition for the locations.
Supplementary Figure S19  Coarse-grained molecular dynamics simulation trajectories of the MutS$^{\text{ADP}}$ clamp domain on 75 base-pairs DNA with a GC repeat sequence in the presence of 150 mM ions. Points were colored according to the location of the clamp domain: Blue when in the major groove and red when in the minor groove. Please refer to the text for the definition for the locations.
Introduction

DNA base-pair mismatches are routinely generated by intrinsic factors such as DNA replication errors and oxygen species and extrinsic factors such as ultraviolet and ionizing radiation. It has been well-documented that these mismatches are corrected by the mismatch repair (MMR) pathway both in prokaryotes and eukaryotes [1,2]. In *Escherichia coli* (*E. Coli*), a base-pair mismatch is searched and recognized by a MutS protein [3]. The crystal structure of MutS that recognizes a mismatch contains an adenosine diphosphate (ADP) molecule in one of the two nucleotide-binding sites [4–6]. After the mismatch recognition, the bound ADP molecule is exchanged with an adenosine triphosphate (ATP) molecule, and the other nucleotide-binding site is also occupied by ATP. The ATP binding induces a MutS conformational change, binding of MutL and MutH proteins to MutS, and release of MutS from the mismatch [7–11]. The released MutS/MutL/MutH complex diffuses along DNA to search and recognize a GATC sequence around the mismatch [12], and MutH generates a nick on the sequence [7]. Then, an exonuclease digests one strand of double-stranded DNA from the nick to the site beyond the mismatch [13]. Finally, the new strand is re-synthesized using the undigested strand as a template [13].

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Supplementary Figure S20  Coarse-grained molecular dynamics simulation trajectories of the MutS<sub>ADP</sub> clamp domain on 75 base-pairs DNA with a GC repeat sequence in the presence of 500 mM ions. Points were colored according to the location of the clamp domain: Blue when in the major groove and red when in the minor groove. Please refer to the text for the definition for the locations.
Supplementary Figure S21  Coarse-grained molecular dynamics simulation trajectories of the MutS\textsuperscript{ADP} clamp domain on 75 base-pairs DNA with a GC repeat sequence in the absence of electrostatic interactions between MutS and DNA. Points were colored according to the location of the clamp domain: Blue when in the major groove and red when in the minor groove. Please refer to the text for the definition for the locations.
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Supplementary Figure S23  Coarse-grained molecular dynamics simulation trajectories of the MutS\textsuperscript{ADP} on 75 base-pairs DNA with a GC repeat sequence in the presence of 100 mM ions. In the simulations, the same ends of two of the dsDNA strands were anchored in space.
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Supplementary Figure S25  Coarse-grained molecular dynamics simulation trajectories of the MutS_{ATP} on 75 base-pairs DNA with a GC repeat sequence in the presence of 100 mM ions.
**Supplementary Figure S26** Coarse-grained molecular dynamics simulation trajectories of the MutS$_{\text{ATP\,Closed}}$ on 75 base-pairs DNA with a GC repeat sequence in the presence of 100 mM ions.
Supplementary Figure S27  Coarse-grained molecular dynamics simulation trajectories of the MutS<sub>ADP</sub>, MutS<sub>Open</sub>, and MutS<sub>Closed</sub> simulations, respectively. For double-stranded DNA, we used two homogeneous

Inoue et al.: Molecular simulations of MutS sliding along DNA
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Supplementary Figure S29  Coarse-grained molecular dynamics simulation trajectories of the MutS<sub>ADP</sub>, MutS<sub>Open</sub>, ATP, and MutS<sub>Closed</sub> simulations, respectively. For double-stranded DNA, we used two homogeneous
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Supplementary Figure S31 MutS\textsuperscript{ATP} position along 75 base-pair DNA with a GC repeat sequence and cumulative angle around the DNA in the presence of 100 mM ions.
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Supplementary Figure S32 MutS\textsuperscript{ATP\_Closed} position along 75 base-pair DNA with a GC repeat sequence and cumulative angle around the DNA in the presence of 50 mM ions.
Supplementary Figure S33  \( \text{MutS}^{\text{ATP}}_{\text{Closed}} \) position along 75 base-pair DNA with a GC repeat sequence and cumulative angle around the DNA in the presence of 150 mM ions.
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Supplementary Figure S35  MutS\textsuperscript{ATP} \textsubscript{Closed} position along 75 base-pair DNA with a GC repeat sequence and cumulative angle around the DNA in the absence of electrostatic interactions between MutS and DNA.
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**Supplementary Figure S36** Time trajectories of a MutS<sub>ATP</sub><sup>Closed</sup> position on the axis orthogonal to linear lines with the slope of 10 base-pairs / 2π in the position vs cumulative angle change plots (e.g. Figure S7) in the presence of 50 mM ions.
Supplementary Figure S37  Time trajectories of a MutS$_{\text{ADP}}$ position on the axis orthogonal to linear lines with the slope of 10 base-pairs / $2\pi$ in the position vs cumulative angle change plots (e.g. Figure S7) in the presence of 100 mM ions.
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Supplementary Figure S38 Time trajectories of a *MutS*<sub>ATP</sub> position on the axis orthogonal to linear lines with the slope of 10 base-pairs / 2π in the position vs cumulative angle change plots (e.g. Figure S7) in the presence of 150 mM ions.
Represent the ion concentration dependency of ion screening effects. For MutS, charges were distributed on surface residue interactions [28]. It was also demonstrated that CGMD simulations that consider only electrostatic and excluded volume stated. Previous studies have shown that electrostatic interactions dominate sequence-nonspecific protein/DNA stacking pairs. The parameters were decided so that the model reproduced several types of experimental data.

Initial Structures

MutS monomer are distal to each other, and hence we name it as Open MutS, ADP, and ATP simulations, respectively. For double-stranded DNA, we used two homogeneous

Supplementary Figure S39 Time trajectories of a MutS\textsuperscript{ATP\_Closed} position on the axis orthogonal to linear lines with the slope of 10 base-pairs / 2\pi in the position vs cumulative angle change plots (e.g. Figure S7) in the presence of 500 mM ions.
Introduction

DNA base-pair mismatches are routinely generated by intrinsic factors such as DNA replication errors and oxygen species and extrinsic factors such as ultraviolet and ionizing radiation. It has been well-documented that these mismatches are corrected by the mismatch repair (MMR) pathway both in prokaryotes and eukaryotes [1,2]. In *Escherichia coli* (*E. Coli*), a base-pair mismatch is searched and recognized by a MutS protein [3]. The crystal structure of MutS that recognizes a mismatch contains an adenosine diphosphate (ADP) molecule in one of the two nucleotide-binding sites [4–6]. After the mismatch recognition, the bound ADP molecule is exchanged with an adenosine triphosphate (ATP) molecule, and the other nucleotide-binding site is also occupied by ATP. The ATP binding induces a MutS conformational change, binding of MutL and MutH proteins to MutS, and release of MutS from the mismatch [7–11]. The released MutS/MutL/MutH complex diffuses along DNA to search and recognize a GATC sequence around the mismatch [12], and MutH generates a nick on the sequence [7]. Then, an exonuclease digests one strand of double-stranded DNA from the nick to the site beyond the mismatch [13]. Finally, the new strand is re-synthesized using the undigested strand as a template [13].

The bacterial mismatch recognition protein MutS takes a homodimer consisting of 95 kDa monomers [14]. Each monomer contains the mismatch-binding, connector, lever, clamp, ATPase, and tetramerization domains from N to C terminus (Figure 1A). In the crystal structure of ADP-bound MutS that recognizes a mismatch, the mismatch binding domain in one of the dimer and the clamp domains of the dimer wrap around and attach to DNA (Figure 1B) [4,5]. The deuterium exchange mass spectrometry study suggested that similar protein/DNA contacts form on both mismatched and homo-duplex DNA, indicating that the search conformation is almost the same as the recognition conformation [15].

Previous single-molecule fluorescence microscopy [12,16–18] and fluorescence resonance energy transfer (FRET) [19,20] studies have suggested that MutS temporarily binds to DNA and one-dimensionally diffuses along it to search a base-pair mismatch. The diffusion coefficient does not depend on ion concentration, suggesting that the one-dimensional diffusion is not accompanied by microscopic dissociation and reassociation [18]. Notably, the narrow distribution of polarization of fluorescent dyes on the diffusing MutS indicated that the diffusion is coupled with the protein rotation around DNA [19]. Also, ATP binding to MutS makes the polarization distribution wider, suggesting that the diffusion after the MutS conformational change is less coupled with the protein rotation [19]. Recently, the molecular dynamics (MD) simulations of human MutS homolog, Msh2-Msh6, were performed using coarse-grained (CG) models [21]. However, structural dynamics details of bacterial MutS sliding along DNA before and after ATP binding have not been addressed yet.

The MutS structures in various conformations have been published [4–6,10,11,22]. They differ in their nucleotide state and DNA binding. We were interested in MutS sliding along DNA in three conformations. The first one is the ADP bound conformation, which recognizes a base-pair mismatch (MutS<sup>ADP</sup>) and was proposed to be relevant to the mismatch search as described above [18] (Figure 1B). We put special focus on this conformation because the previous experiment indicated that MutS in this conformation rotates around DNA long axis while diffusing along it, though the structural dynamics

**Supplementary Figure S40** Time trajectories of a MutS<sup>ATP<sub>Closed</sub></sup> position on the axis orthogonal to linear lines with the slope of 10 base-pairs / 2π in the position vs cumulative angle change plots (e.g. Figure S7) in the absence of electrostatic interactions between MutS and DNA.