Supporting Information

Force field to describe breakable disulfide bond

In order to mimic the breakable behavior of disulfide bond, the CHARMM force field is modified by an additional cutoff to allow for bond breaking. The bond energy of disulfide bonds is varied to account for different chemical environments. In the classical CHARMM force field, the disulfide bond is an "unbreakable" covalent bond as the potential energy is described as a harmonic function, $E = k(r - r_0)^2$. The numerical values of r_0 and k in the harmonic bond potential of disulfide bond are 2.029Å and 173 kcal/mol, respectively. In experimental measurements, the dissociation energies of disulfide bond in reducing and oxidizing environments ranges from 7.17 to 51 kcal/mol [1-3], respectively. In our extended CHARMM force field, a cutoff of 2.23 Å introduced in the harmonic function represent an extreme case of disulfide bond in a reducing environment. The corresponding energy barrier to the cutoff is 7.17 kcal/mol. The disulfide bond force is described as:

$$F(r) = -\partial E(r)/\partial r, \tag{S1}$$

where

$$\frac{\partial E(r)}{\partial r} = \begin{cases} 2k(r - r_0), & r < r_{cut} \\ 0, & r \geq r_{cut} \end{cases} \tag{S2}$$

As depicted in **Figure S1**, we consider a system with two sulfur atoms to illustrate the behavior. As the bond length exceeds the cutoff, the bond force drops to zero, indicating that the bond breaks. This change is implemented in a revised version of the LAMMPS simulation code.

Supporting references

1. Wiita, A.P., et al., 2006 *Force-dependent chemical kinetics of disulfide bond reduction observed with single-molecule techniques.* Proceedings of the National Academy of Sciences of the United States of America, **103**(19): p. 7222-7227.
2. Wiita, A.P., et al., 2007 *Probing the chemistry of thioredoxin catalysis with force.* Nature, **450**(7166): p. 124-127.
3. Fernandes, P.A. and M.J. Ramos, 2004 *Theoretical insights into the mechanism for thiol/disulfide exchange.* Chemistry-a European Journal, **10**(1): p. 257-266.
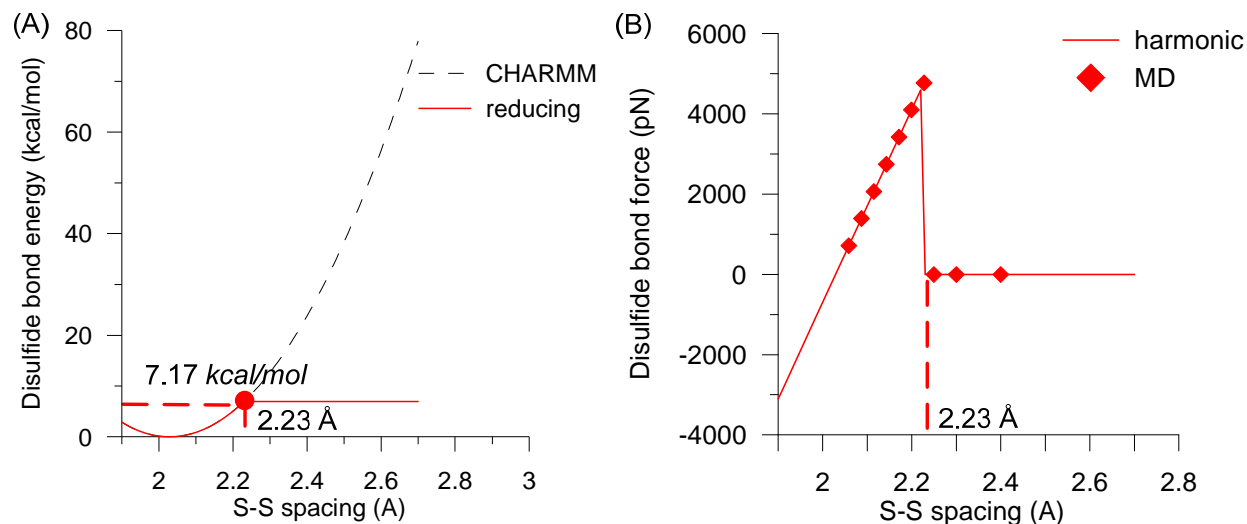
FIGURE S1 | Illustration of modified harmonic bond energy of disulfide bond in reducing microenvironments. (A) Disulfide bond energy over two sulfur atoms spacing in reducing and oxidizing environments. The disulfide bond potential energy is described by a harmonic function, $E = k(r - r_0)^2$, in the CHARMM force field. The numerical values of r_0 and k in the harmonic bond potential of disulfide bond are 2.029Å and 173 kcal/mol, respectively. A breaking distance of 2.23 Å introduced in the harmonic function represent an extreme case of disulfide bond in reducing environment. As the bond length exceeds the cutoff, the bond force drops to zero, which means the bond breaks. (B) Comparison of disulfide bond forces, calculated using the harmonic function (prediction) and Molecular Dynamics simulation (verification), for a case of two connected sulfur atoms in a reducing environment.