**Exploring native amorphous-crystalline silk structures and molecular binding behavior in response to pH**

*Description*

*Bombyx mori* silk fibroin is a remarkable biopolymer for biomedical applications such as drug delivery. Our previous experimental studies showed the potential of silk nanoparticles for anticancer drug delivery including doxorubicin loading/release behavior. However, silk structures and the interaction mechanism between silk and doxorubicin are still unknown at the molecular level. Here, we generated a 300 amino acid silk fragment containing amorphous and crystalline regions and exploited the advanced sampling technique called well-tempered (WT) metadynamics simulations to examine the molecular conformations of amorphous-crystalline silk in water system. The selected silk structures and the N-terminal domain were investigated pH-dependent interaction (at pH 4 and pH 7.4) towards model drug doxorubicin using classical molecular dynamics simulations.

*Modelling software:*

1. GROMACS 5.0.4 packages
2. PLUMED 2.1.1
3. AMBER 12 packages

*Analysis software:*

1. Discovery Studio (DS)
2. Visual Molecular Dynamics (VMD)
3. OriginPro 9.2 Software
4. Gaussian 09W package
5. AnteChamber PYthon Parser interface (ACPYPE)
6. GraphPad Prism 7 Software

The dataset was saved in four separated folders as listed below:

1. Multidomain silk structure folder containing
   1. Input files
   2. All initial structures
   3. 16 equilibrated silk structures
   4. Phi-psi angles of 16 equilibrated silk structures
2. WT-metadynamics folder containing all raw data from WT-metadynamics simulations
3. Protonation by Discovery Studio folder containing Pka and silk structure with protonation states
4. Molecular dynamics\_Silk-Dox interactions folder containing raw data from molecular dynamics simulations with different optimised silk structure towards doxorubicin.
   1. The most stable structure of silk with doxorubicin at pH 4 and 7.4 (folder named 2018\_02\_07\_Silk\_dox\_pH4 and 2018\_02\_07\_Silk\_dox\_pH7.4).
   2. The N-terminus of silk with doxorubicin at pH 4 and 7.4 (folder named 2018\_02\_11\_3UA0\_pH4 and 2018\_02\_11\_3UA0\_pH7.4).
   3. The highest amount of beta-sheet in silk structure with doxorubicin at pH 4 and 7.4 (folder named 2018\_02\_14\_Silk\_highbetasheet\_pH4 and 2018\_02\_14\_Silk\_highbetasheet\_pH7.4).
   4. The highest amount of amorphous in silk structure with doxorubicin at pH 4 and 7.4 (folder named 2018\_02\_15\_silk\_highamourphous\_pH4 and 2018\_02\_15\_silk\_highamourphous\_pH7.4).
   5. Doxorubicin structure
5. Figuresforpaper folder containing images of each figure
6. Amber force field parameter files (amber12sb.ff.tar)
7. ACPYPE software (acpype-master.zip)