

# Free energy reaction profile of the desuccinylaiton catalyzed by Sirtuin 5

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Human sirtuin 5 is an NAD<sup>+</sup> dependent desuccinylase [1,2]. Deregulation of this activity is connected to several human disorders, therefore, it is important to gain in depth knowledge of its reactivity [2]. One major problem is that most techniques to characterize enzymatic reactions, especially non-dynamic schemes, strongly depended on the chosen educt conformation. A start-frame, necessary for all approaches, is usually chosen from an MM-MD simulation. Since not all educt conformations are reactive, one has to identify suitable periods within the MM-MD simulation to obtain a realistic estimate of a reaction mechanism, before applying cost intensive QM/MM methods [3]. Thus, we utilized machine learning to distinguish suitable start-frames and to discover relevant structural features for the initial step of the desuccinylation. Subsequent umbrella sampling [4] and the weighted histogram analysis method [5,6] were employed to compute the free energy reaction profile. The computational investigation lead to the conclusion that the nicotinamide cleavage, the first step of the desuccinylation, shows a SN2 type reaction mechanism.

## References

1. T. Nakagawa and L. Guarente, *J. Cell Sci.* **124** (2011), 833–838.
2. J. Du, Y. Zhou, X. Su, J. J. Yu, S. Khan, H. Jiang, J. Kim, J. Woo, J. H. Kim, B. H. Choi, B. He, W. Chen, S. Zhang, R. A. Cerione, J. Auwerx, Q. Hao, and H. Lin, *Science* **334** (2011), 806–809.
3. S. K. Sadiq and P. V. Coveney, *J. Chem. Theory Comput.* **11** (2015), 316–324.
4. G. M. Torrie and J. P. Valleau, *J. Chem. Phys.* **23** (1977), 187–199.
5. S. Kumar, J. M. Rosenberg, D. Bouzida, R. H. Swendsen, and P. A. Kollman, *J. Comput. Chem.* **13** (1992), 1011–1021.
6. F. Zhu and G. Hummer, *J. Comput. Chem.* **33** (2012), 453–465.