Charges and boundary terms: easy ways to spoil your QM/MM(MD) results

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Hybrid quantum mechanical/molecular mechanical (QM/MM) simulations are a staple of modern computational biochemistry. A small portion of the molecular system is modeled with a more accurate QM approach, while everything else is kept under a much computationally cheaper MM description. To saturate open valencies on QM atoms when the subsystem is passed to the QM engine, capping hydrogen atoms are added. These atoms are called link atoms (LA) and are invisible to the MM engine. LA placed along a bond to a sizably charged MM atom will be heavily influenced by it. This results in artifacts called hyperpolarization, which bring a setup that does not bear much chemical sense. A number of elaborate schemes to correct the issue were proposed. However, they have got limited traction in popular QM/MM software.

In our recent work, we showed that neglecting the hyperpolarization correction while placing a LA on bond to the polar MM atom produced incorrect results [1]. In a case of subtilisin Carlsberg, we demonstrated that incorrect LA setup produces surprising outcomes that may be erroneously interpreted as groundbreaking results with regards to enzymatic mechanisms.

We then focused on how well different intra-backbone partitions reproduce backbone dynamics, a feature crucial to QM/MM MD. Here, a consideration of which MM terms are kept or deleted turned out to play the main role. Even with hyperpolarization correction schemes, only three intra-backbone boundaries produced correct results in dynamics when the classical scheme to omit angular and dihedral terms with only one MM atom was used. When these terms were retained (as in Amber suite), five out of six boundaries were mostly correct.

In our newest and yet unpublished work, we continue this study to investigate how well the sidechain dynamics is recapitulated in sidechain-only QM systems. Such a setup is very common in computational enzymology. We show that both classical and Amber schemes distort the rotation along $\chi 1$ and $\chi 2$ angles. We then propose an updated scheme that may be of interest to the broad biomolecular modeling community.

[1] A. Zlobin, J. Beliaeva, A. Golovin, *Journal of Chemical Information and Modeling*, **2023**, *63*, 546-560.