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Tackling photodynamic therapy oriented photosensitizes with quantum computers: AEGISS method for selecting chemically meaningful active-spaces

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Photochemistry involves light-induced chemical processes that lead to changes in the (excited-state) molecular structures and drive chemical transformations. When molecules absorb light, they can transition to excited states, leading to ensuing processes like internal conversion, Inter–System Crossing (ISC), or radiative emission (fluorescence and phosphorescence) to dissipate the excess energy.

In Photodynamic Therapy [1,2], a light-triggered targeted anticancer therapy, photons activates a Photosensitizer (PS), initiating an ISC and energy transfer to oxygen, with the ultimategoal to generate Reactive Oxygen Species (ROS) that are capable of introducing apoptosis in cancer cells. Here, a small energy gap between singlet and triplet states (ΔS1-T1) enhances ISC and reverse ISC (RISC) rates, that can lead to improved ROS production and therefore an increase in therapy eNiciency [3]. DiNerent criteria must be met to define whether a candidate molecule is a good PS: Lack of dark toxicity; Solubility in aqueous vehicle; Chemically pur;, easy to synthesize; High absorption in PDT window for deep light penetration, i.e. 700-900 nm; preferential accumulation in tumor; rapid elimination from the body; and also been able to generate suNicient singlet oxygen, even under hypoxic conditions. Some PS contains transition metals and biradicals which demand multi-configurational or strongly correlated approaches. In such cases, active space selection is vital, as it determines which orbitals are included in the description of electronic states, ensuring accurate modeling of complex structures and interactions while also controlling the computational cost. The selection of a balanced active space is therefore a critical step in multi-reference quantum chemistry calculations, particularly for systems with strong electron correlation

In this work, we present a novel approach inspired by both the AVAS [4] (Atomic Valence Active Space) and AutoCAS [5] methods. Atomic-Orbital and Entropy Guided Inference for Space Selection (AEGISS) [6] unifies orbital entropy analysis with atomic orbital projections to guide the construction of chemically and physically meaningful active spaces. This integrated scheme enables a more consistent and flexible selection of active orbitals while retaining automation and scalability. We validate our approach on a set of molecular systems relevant to photodynamic therapy, in particular a set of Ru(II)-complexes [7,8,9,10], selected to span increasing levels of electron correlation and structural complexity. These molecules serve as challenging test cases due to the presence of strong static correlation and the need for highly accurate electronic structure descriptions. Our results demonstrate that the method can reliably identify compact, chemically intuitive active spaces that capture the essential physics,making it suitable for both classical and quantum computational frameworks.

[1] 10.3390/pharmaceutics13091332
[2] 10.1063/5.0170949
[3] 10.1021/acs.chemrev.8b00211
[4] 10.1021/acs.jctc.7b00128
[5] 10.1021/acs.jctc.6b00156
[6] 10.48550/arXiv.2508.10671
[7] 10.1021/ct200640q
[8] 10.1021/acs.jctc.7b00379
[9] 10.1021/acs.chemrev.8b00211
[10] 10.1021/acs.inorgchem.6b01782

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