

# Using Instanton Theory to Study Quantum Effects in Photosensitization

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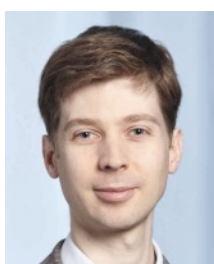
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**Abstract:** Electronic excitation is usually accomplished using light (photoexcitation) and is a key step in a vast number of important physical and biological processes. However, in instances where photoexcitation is not possible, a photosensitizer can excite the target molecule in a process called photosensitization. Unfortunately, full details of its mechanism are still unknown. This perspective gives an overview of the current understanding of photosensitization and describes how instanton theory can be used to fill the gaps, especially with regard to the importance of quantum tunnelling effects.

**Keywords:** Instanton theory · Nuclear quantum effects · Photosensitization · Singlet oxygen



Meghna A. Manae obtained her PhD in Indian Institute of Science Education and Research Pune under the supervision of Anirban Hazra in December 2019, specializing in electronic structure of excited states. This was followed by a postdoc (2020–2021) in Jawaharlal Nehru Centre for Advanced Scientific Research in the group of Umesh V. Waghmare, studying computational heterogeneous catalysis. Currently, she is a postdoc at ETH Zurich in the group of Jeremy O. Richardson, working on reaction rates and mechanisms using instanton theory.



Jeremy O. Richardson studied at Cambridge University where he also took his PhD under the supervision of Stuart Althorpe. He was a postdoc and Humboldt Research Fellow in Friedrich-Alexander University Erlangen-Nürnberg in the group of Michael Thoss and a Junior Research Fellow at Durham University. In September 2016 he became Assistant Professor at ETH Zurich and was promoted to Associate Professor in 2023. His research is focused on developing semiclassical methods for simulating molecular quantum dynamics.

## 1. Introduction

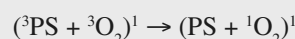
Molecular oxygen or dioxygen is unusual in that its ground state is a triplet  $^3\text{O}_2$ . Singlet  $^1\text{O}_2$  also exists but it is highly reactive, and can damage molecules like DNA by causing irreversible oxidation and other uncontrollable reactions.<sup>[1]</sup> However, this seemingly destructive entity can be harnessed for good.  $^1\text{O}_2$  is useful in chemical synthesis,<sup>[2–5]</sup> organic photovoltaics,<sup>[6]</sup> and plays a crucial role in photodynamic therapy (PDT).<sup>[7,8]</sup> PDT is used in the treatment of age-related vision deterioration, psoriasis, atherosclerosis, and malignant cancers. It is minimally invasive and circumvents the serious side-effects that typically characterize conventional cancer therapies. PDT involves four main steps (Fig. 1): (a) a photosensitizer (PS) is introduced into the affected cells and the area is irradiated with light causing its photoexcitation to an excited singlet state; (b)

this is followed by intersystem crossing (ISC) in the PS to a lower energy triplet state; (c) the triplet state then transfers its energy to an oxygen molecule present in the cell converting  $^3\text{O}_2$  to  $^1\text{O}_2$ ; and finally; (d)  $^1\text{O}_2$  causes cell death. The third step is critical to PDT and requires a PS to convert  $^3\text{O}_2$  to  $^1\text{O}_2$  since this is otherwise spin-forbidden by direct photoexcitation.

A good PS (PDT drug) is one that has a high triplet yield and a long intrinsic triplet lifetime as this translates to high efficiency of converting  $^3\text{O}_2$  to  $^1\text{O}_2$ . Owing to its importance, photosensitization has been studied extensively experimentally. Generally, experimental studies have been aimed at finding better PSs by exploring molecules with electronic and structural features similar to those of pre-existing PDT drugs.<sup>[9–11]</sup> Theoretical studies, so far, have typically focused on the second step in PDT, *i.e.* the ISC mechanism to quantify triplet yields and lifetimes.<sup>[12–15]</sup> However, few studies have focused on understanding the third step in PDT, the mechanism of photosensitization itself. The main objective of our project is to obtain a clear mechanistic understanding of photosensitization, and particularly the role of quantum nuclear effects – an aspect that has so far mostly been overlooked.

### 1.1 Current Understanding of Photosensitization

If we consider the PS– $\text{O}_2$  composite system, it is clear that spin multiplicity is conserved in the reaction.



This way, photosensitization can be viewed as being mathematically similar to electron transfer where the diabatic coupling, which is mediated by the distance between PS and  $\text{O}_2$ , is weak. This weak coupling allows photosensitization rates to be calculated using Fermi's Golden Rule (FGR). Obtaining rates from FGR requires calculating the vibrational wavefunctions, which can be very expensive, especially at higher energies and for larger molecules. In the classical limit, however, FGR reduces to Marcus theory which is easier to solve. This approach was pursued by Bai and Barbatti to estimate the rate of photosensitization of  $\text{O}_2$  by 6-aza-2-thiothymine, a substituted nucleobase, and found that it matched well with experimental rates.<sup>[16,17]</sup> A previous study by

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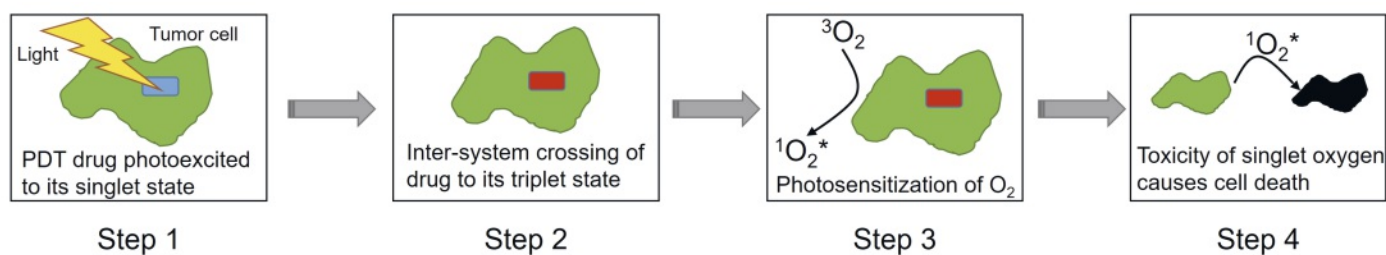


Fig. 1. Schematic representation of photodynamic therapy (PDT).

one of the authors of this article compared the rates calculated from this classical method based on Marcus theory versus a quantum approach based on FGR, albeit within the harmonic approximation.<sup>[18]</sup> The classical ( $k_{Cl}$ ) and quantum ( $k_{QM}$ ) rates were compared for the thiothymines (Fig. 2), which are known to be excellent PSs.<sup>[19]</sup> This study found that while both approaches gave similar results for 2-thiothymine, the classical rate was off by 10 and 18 orders of magnitude, respectively, for 4-thiothymine and 2,4-dithiothymine compared to the quantum rate (Fig. 2), indicating sharp differences in their electronic structure and dynamics.<sup>[20]</sup> The failure of Marcus Theory for some PSs points to the inherent quantum nature of photosensitization and the possibility of tunnelling as one of the responsible mechanisms. While the relative photosensitization rates of the thiothymines were captured correctly in this study, mechanistic questions remain unanswered. Further, the approach was implemented within the harmonic approximation, which may not be valid for large amplitude tunnelling dynamics. Instanton theory, a rate theory based on the path-integral formulation of quantum mechanics, can help fill gaps in understanding photosensitization by computing the reaction pathway from first principles.<sup>[21]</sup> It is a computationally tractable method that can capture quantum effects without a global harmonic approximation.

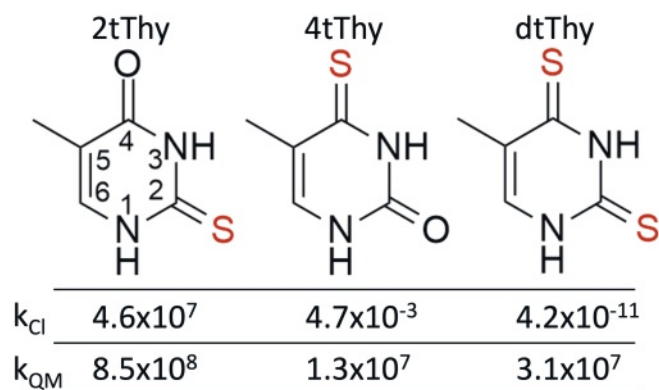


Fig. 2. The three thiothymines, 2-thiothymine (2tThy), 4-thiothymine (4tThy), and 2,4-dithiothymine (dtThy), with 2tThy showing the numbering scheme. Rate constants of  $O_2$  photosensitization in  $s^{-1}$  calculated from classical ( $k_{Cl}$ ) and quantum ( $k_{QM}$ ) approaches are given below (values taken from ref. [18]).

## 2. Instanton Theory

Instanton theory has, so far, been successfully applied to hydrogen atom abstraction reactions,<sup>[22–24]</sup> tunnelling in molecules, enzymes, clusters and surfaces,<sup>[25–30]</sup> electron transfer,<sup>[31,32]</sup> photodissociation,<sup>[33]</sup> and ISC<sup>[34,35]</sup> among other molecular processes where nuclear quantum effects play a significant role. Instanton theory offers excellent predictions of experimental rates and provides mechanistic insights. It does not require solving the vibrational wavefunctions and instead, uses a semiclassical approach based on classical-like tunnelling paths, making it computationally efficient. Consequently, molecules can be treated in full-dimensionality using *ab initio* potential energy surfaces, unlike fully quantum methods.

Transition states are typically single points on the potential energy surface which cannot account for tunnelling and are obtained by minimizing the potential energy along the path. Tunnelling, on the other hand, requires a path, not just a point, and the optimal tunnelling pathway is called the instanton. This path is obtained by optimizing the action, which includes both potential and kinetic energies. The instanton path is equivalent to an imaginary-time trajectory, which is what allows it to pass through the classically forbidden region, *i.e.* below the barrier (Fig. 3). It is a function of temperature and at high temperatures it collapses to the transition state, in accordance with the correspondence principle, and as the temperature decreases it becomes more extended and drops to lower energies to describe deep tunnelling.

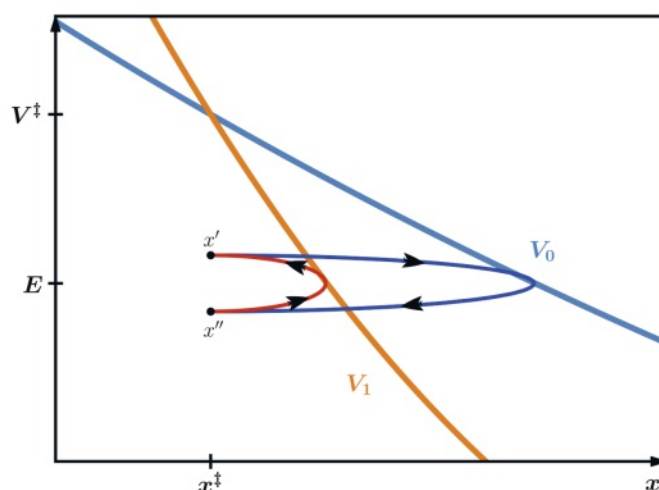


Fig. 3. Schematic of an instanton path is shown in red and blue, which corresponds to the parts of the trajectory on the reactant and product states, respectively. Figure adapted from ref. [33].

### 2.1 Adapting Instanton Theory for Photosensitization

It has been hypothesized that the mode along which ISC in a PS takes place is also responsible for photosensitization.<sup>[18]</sup> Therefore, studying the ISC mechanism in the PSs using instanton theory is the logical first step before tackling photosensitization. This would also confirm whether ISC in the PS is indeed related to photosensitization, or if it goes through an entirely different mechanism. The instanton for ISC is obtained by optimizing the path on both singlet and triplet states to minimize the total action (Fig. 3). However, the coupling, in this case the spin-orbit coupling (SOC), which drives the reaction is not considered while optimizing the instanton. This is a reasonable assumption since SOC is not very sensitive to changes in geometry. For photosensitization however, the coupling, in this case diabatic coupling, strongly depends on the distance between PS and  $O_2$ . Therefore, while optimizing the instanton, we need to minimize the action while simultaneously maximizing the diabatic coupling. To this end, we have extended the existing formulation of instanton theory to also account for geometry dependence of the coupling in a similar manner to a theory designed to treat conical intersections.<sup>[32]</sup>

We devised a simple model system to test the accuracy of the new method in the context of photosensitization. Exact rates using FGR can be calculated for the model system and compared with the rates calculated from the coupling-dependent instanton theory. The deviation of the FGR rates from classical rates (calculated using classical transition-state theory) indicates the importance of quantum effects. Our calculations found enormous tunnelling effects at room temperature and a near-perfect match between the benchmark rates and those calculated from the new method (Fig. 4) for the model system. This serves as proof of principle, and we are currently applying the method to molecules in full dimensionality. As opposed to model systems where the potentials and gradients can be calculated analytically, for molecules these properties need to be calculated on-the-fly with electronic structure methods. Due to the open-shell characters of  $^3\text{PS}$ ,  $^3\text{O}_2$  and  $^1\text{O}_2$ , multi-reference methods such as CASSCF and CASPT2 are required. This is an ongoing project. It will be interesting to see if the large tunnelling effects persist and to understand their mechanism.

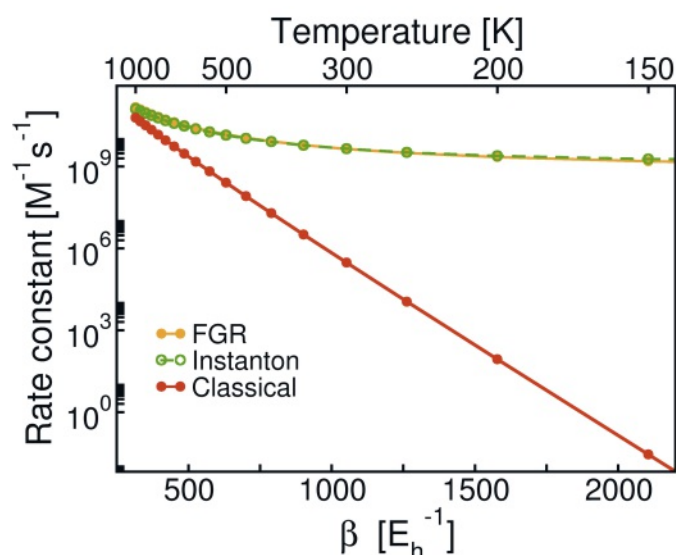


Fig. 4. Rate constants as a function of inverse temperature ( $\beta$ ) for the model system calculated using Fermi's golden rule (FGR), semiclassical instanton and classical methods.

### 3. Conclusions

We have extended instanton theory to account for distance-dependent coupling. The rate constants calculated from the methodology are in remarkable agreement with the benchmark (FGR rates) for a model system of photosensitization. Calculating rates using FGR however, is only tractable for model systems, whereas for molecules, instanton theory is the only feasible method which avoids the global harmonic approximation. While this method was developed in the context of photosensitization, it should be possible to apply it to other bimolecular nonradiative energy-transfer reactions such as singlet fission. Through this study, we hope that a thorough atomistic level understanding of the mechanism of photosensitization will guide a systematic design of better PDT drugs.

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