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Quantum modelling of Stokes-Induced Interfacial Field-Modulated Redox Coupling and Nonlinear ROS Amplification in Curcumin-Ascorbate Systems for Tumor Microenvironment Selective Cytotoxicity

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ABSTRACT

The selective amplification of reactive oxygen species (ROS) within tumor microenvironments remains a major challenge in photodynamic oncology due to the limited physicochemical selectivity of conventional photosensitizers. Here we developed and evaluated a comprehensive multiscale quantum–mechanical framework to elucidate how photoinduced Stokes-shift-driven dipole reorganization in curcumin modulates proton-coupled electron transfer (PCET) and ROS generation within tumor-associated curcumin–ascorbate interfaces. The theoretical model integrates excited-state photophysics, interfacial electrostatics, Stark perturbation theory, Double-Well Rosen–Morse proton-transfer dynamics, nonadiabatic kinetics, and multi-cycle photocatalytic turnover. The simulations predict that photoexcited enol-curcumin generates transient localized electric fields of 3×10^8 – $5 \times 10^8 \text{ V m}^{-1}$ within low-dielectric tumor–membrane interfaces. This induces a Stokes-Induced Stark Effect (SISE) that lowers the proton-transfer activation barrier from 0.180 to 0.153 eV, enhancing tunneling splitting and donor–acceptor wavefunction overlap. Consequently, PCET kinetics exhibit an 18-fold acceleration, producing a downstream 30-fold surge in localized ROS generation. Dielectric confinement creates a tumor-to-normal selectivity factor of approximately 6.2, while multi-cycle photoactivation drives membrane-compartmentalized ROS concentrations beyond cytotoxic thresholds via Fenton cycling and glutathione depletion. These results establish a quantum-electrostatic mechanism for tumor-selective oxidative cytotoxicity and extend the SISE framework to biologically embedded all-organic redox systems.

Keywords: Curcumin, Ascorbate, Proton-Coupled Electron Transfer (PCET), Stokes-Induced Stark Effect (SISE), Tumor Microenvironment, Reactive Oxygen Species (ROS).

1.0. INTRODUCTION

Cancer remains one of the leading causes of mortality worldwide, with increasing evidence showing that oxidative imbalance and reactive oxygen species (ROS) dysregulation play central roles in tumor initiation, progression, metastasis, and therapeutic response [1-2]. This Redox vulnerability arises because cancer cells maintain elevated basal ROS levels to sustain rapid proliferation, placing them precariously close to a lethal threshold where further ROS accumulation surpasses antioxidant defenses to induce irreversible damage [3-4]. Exploiting this metabolic gap, redox-based therapeutic strategies have shown promising alternatives to conventional chemotherapy, offering a mechanism to trigger selective oxidative collapse while sparing healthy tissues [5-6]. Naturally derived compounds such as curcumin have gained prominence in this field due to their ability to modulate diverse pathways including apoptosis, ferroptosis,

and pyroptosis specifically through ROS-mediated mechanisms [7-9]. Similarly, pharmacological ascorbate has re-emerged as a potent partner, capable of generating cytotoxic hydrogen peroxide via catalytic redox cycling [10-11]. However, despite the individual efficacy of these agents, the precise physical mechanisms governing how their excited-state molecular dynamics and interfacial electrostatic interactions regulate redox coupling remain poorly understood. This lack of mechanistic clarity creates a significant barrier to the rational engineering of tumor-selective therapies, as current models cannot predict how localized environmental cues within the tumor microenvironment govern the magnitude and selectivity of ROS generation [12-13].

While this challenge has persisted, previous attempts to enhance ROS-mediated efficacy have largely focused on macro-scale interventions such as nanoparticle engineering, molecular modification, and photodynamic activation. These efforts have yielded significant successes viz curcumin derivatives have demonstrated enhanced cytotoxicity against hepatocellular and colorectal carcinomas by disrupting mitochondrial function and activating endoplasmic reticulum stress [14-16], while synthetic analogs and nanoformulations have improved pharmacokinetic profiles and tumor targeting [17-20]. Furthermore, researchers have successfully leveraged ascorbate to synergistically amplify oxidative stress through H_2O_2 generation and chemo-radiosensitization [21-23]. Nevertheless, these advancements remain tethered to classical biochemical frameworks that treat molecular interactions as stochastic collisions, thereby neglecting the transformative role of quantum-scale phenomena such as excited-state dipole relaxation and Stokes-shift-induced electric fields [24-25]. Furthermore, upon photoexcitation, curcumin has been shown to undergo significant excited-state dipole reorganization, with its dipole moment increasing by approximately 5–8 Debye relative to the ground state. At lipid-aqueous interfaces precisely where curcumin preferentially embeds due to its amphiphilic character, this reorganization generates transient interfacial electric fields of sufficient magnitude to materially alter local electron transfer kinetics, yet such photophysical effects remain entirely invisible to classical redox models and largely overlooked within conventional biochemical descriptions of redox amplification [24,26-28]. Despite the potential significance of these ultrafast photophysical processes, current literature still lacks a unified mechanistic framework capable of explaining how photoinduced interfacial field modulation dynamically alters the redox coupling between curcumin and ascorbate to trigger nonlinear ROS amplification. Consequently, despite advances the field still lacks the predictive power necessary to rationally design oxidative nanotherapeutic systems capable of responding with high precision to the acidic, hypoxic, and oxidative conditions characteristic of the tumor microenvironment [29-30]. In particular, no existing theoretical framework has quantitatively connected excited-state dipole relaxation, dielectric confinement, Stark-induced orbital perturbation, proton-coupled electron transfer, and nonlinear ROS amplification within a unified multiscale interfacial formalism.

This study proposes that photoinduced Stokes-shift-driven excited-state dipole reorganization in curcumin generates localized interfacial electric fields that dynamically modulate redox coupling with ascorbate, thereby enhancing nonlinear reactive oxygen species (ROS) amplification within the tumor microenvironment and inducing selective oxidative cytotoxicity in cancer cells through quantum-regulated interfacial electron transfer mechanisms. To test this hypothesis, we develop a comprehensive quantum-mechanical framework to elucidate how these systems function as active, dynamically regulated oxidative platforms. Our approach combines excited-state dipolar relaxation theory, interfacial electrostatic modulation, and redox-coupled ROS generation mechanisms to explain how curcumin–ascorbate systems may function as dynamically regulated oxidative platforms rather than passive antioxidant or pro-oxidant agents under simulated tumor-like conditions involving acidic pH characteristic

of the tumor microenvironment (6.5–6.9) and moderate hypoxia. This approach is motivated by the growing realization that cancer-selective destruction depends not only on the quantity of ROS produced but on the precise spatiotemporal regulation of redox transfer kinetics [31–32]. This direction is further inspired by the Stokes-Induced Stark Effect (SISE), previously formulated at quercetin–ZnO organic–semiconductor interfaces, where excited-state dipole relaxation was shown to generate localized interfacial electric fields capable of modulating nearby electronic states through Stark-type electrostatic perturbation arising from excited-state dipole displacement [33]. Building on this mechanism, the present study extends the concept of Stokes-induced field modulation from organic–semiconductor hybrid interfaces to biologically embedded all-organic redox systems, extending the SISE framework into biologically embedded all-organic redox systems applying the SISE framework for the first time to curcumin–ascorbate interactions within a tumor-relevant lipid-aqueous interface. Our scope is deliberately delimited to the theoretical quantum modeling of interfacial redox coupling and nonlinear ROS amplification under simulated tumor-like conditions (pH 6.5–6.9, moderate hypoxia), focusing on the fundamental physics of electron flux rather than in vivo validation or extended structure-activity relationship studies of synthetic curcuminoid libraries. In combining the trio insights of photophysics, redox chemistry and oncology, this study provides a predictive quantum-redox framework for tumor-selective oxidative therapies, thereby advancing the rational design of “quantum-engineered” phytochemical systems capable of maximizing malignant cell destruction while minimizing collateral oxidative damage to healthy tissues through precise control of interfacial molecular physics.

2.0. METHODS

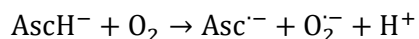
2.1. BIOPHYSICOCHEMICAL DESCRIPTION OF THE CURCUMIN-ASCORBATE SYSTEMS

The curcumin–ascorbate–tumor microenvironment system comprises three functionally interdependent components: a photoactive chromophore (curcumin), a proton-coupled electron donor (ascorbate), and the tumor microenvironment, which provides the physicochemical boundary conditions governing their coupled interfacial redox interactions, as illustrated in Figure 1.

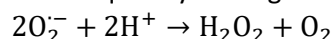
Curcumin ($C_{21}H_{20}O_6$) is a highly polarizable photoactive chromophore possessing strong excited-state charge redistribution capability and pronounced interfacial electrostatic activity. Structurally, the molecule consists of two electron-rich *p*-hydroxylphenyl rings linked through an enolized heptadienedione bridge, forming an extended π -conjugated framework with an effective conjugation length of approximately $L \approx 1.3$ nm [25,34]. This extensive delocalization gives rise to strong visible-light absorption within the 420 – 450 nm spectral range, corresponding to an electronic transition energy of approximately $E_{\text{gap}} \approx 2.76$ eV, together with a large molar extinction coefficient ($\epsilon_{\text{max}} \approx 5.5 \times 10^4 \text{ M}^{-1}\text{cm}^{-1}$) [26,27]. Under mildly acidic tumor-relevant conditions, curcumin predominantly exists in the neutral enol tautomeric form stabilized by intramolecular hydrogen bonding and enhanced electronic delocalization [34,35]. As illustrated in figure 2(a), upon photoexcitation through the ($S_0 \rightarrow S_1$) singlet transition, electron density is redistributed from the phenolic oxygen groups toward the central heptadienedione bridge, producing substantial excited-state dipole amplification and ultrafast intramolecular charge transfer (ICT) [27,36]. Simultaneously, curcumin undergoes excited-state intramolecular proton transfer (ESIPT) on sub-100 femtosecond timescales, generating a nonequilibrium excited-state configuration accompanied by significant Stokes relaxation ($\Delta\nu_{\text{Stokes}} \approx 4500 - 6000 \text{ cm}^{-1}$) [25,27]. During such Stokes relaxation, the nonequilibrium mismatch between excited-state dipole reorganization and slower solvent relaxation has been shown to generate transient interfacial electrostatic fields capable of perturbing nearby electronic states through Stark-type coupling interactions [37]. Because curcumin possesses relatively high lipophilicity ($\log P \approx 3.2$), it preferentially partitions into membrane-associated lipid headgroup regions, thereby localizing its excited-state electronic orbitals

near biologically relevant interfacial redox species [17,38]. Also, curcumin has been widely reported to promote ROS-mediated apoptosis, ferroptosis, pyroptosis, mitochondrial destabilization, and oxidative collapse across multiple cancer systems, confirming its strong redox-active and photoresponsive behavior in malignant environments [7,9,39-40].

Ascorbate ($C_6H_8O_6$) predominantly exists in its monoanionic form ($AscH^-$) under physiological conditions and functions as a highly efficient proton-coupled electron donor with strong redox-transfer capability and relatively low oxidation potential [10,41]. The molecule contains an electron-rich enediol functional group capable of undergoing sequential one-electron oxidation reactions to form semidehydroascorbate radicals ($Asc^{\cdot-}$) and dehydroascorbate intermediates [10,11]. Its first acid dissociation constant ($pK_{a1} \approx 4.1$) ensures that more than 99.9% of the molecule exists in the monoanionic state under physiological conditions [10]. The first electron abstraction step exhibits a standard reduction potential of approximately $E^\circ \approx +0.28$ V versus the normal hydrogen electrode, enabling efficient electron donation toward nearby electron-deficient molecular states and dissolved oxygen species [12,23]. Under oxidative conditions, ascorbate participates in proton-coupled electron transfer (PCET) reactions capable of reducing dissolved oxygen into superoxide radicals ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), and secondary hydroxyl radicals ($\cdot OH$) through downstream oxygen reduction pathways [21,22]. The primary oxygen-reduction reaction is represented by



while the generated superoxide radicals subsequently undergo dismutation according to



thereby producing sustained oxidative flux within biological environments [6,13]. Pharmacological ascorbate concentrations exceeding 1 – 5 mM have been shown to induce selective oxidative cytotoxicity in malignant cells through extracellular peroxide accumulation and intracellular ROS amplification [10,21]. Importantly, the proton-coupled electron transfer kinetics of ascorbate are strongly sensitive to local electrostatic field strength, intermolecular orbital overlap, dielectric environment, and nearby redox-active molecular species [12,42]. Unlike curcumin, ascorbate remains strongly hydrophilic and therefore localizes predominantly within the aqueous Stern layer adjacent to membrane interfaces, positioning it within nanometer-scale proximity to membrane-associated photoexcited curcumin molecules. Importantly, the proton-coupled electron transfer (PCET) kinetics of ascorbate are highly sensitive to the local dielectric environment, intermolecular orbital overlap, electrostatic field strength, and surrounding redox-active molecular species [10]. Thus, when positioned within nanometer-scale proximity to photoexcited curcumin molecules, the redox energetics and electron-transfer efficiency of ascorbate become dynamically susceptible to transient interfacial electrostatic perturbation. The transient donor–acceptor association complex formed between photoexcited keto-curcumin and monoanionic ascorbate within the tumor-associated Stern interface is illustrated in Figure 1b, where hydrogen-bonded electrostatic coupling and dipole alignment stabilize the nonequilibrium proton-coupled electron-transfer assembly.

The tumor microenvironment (TME) presents a uniquely favorable physicochemical landscape for such coupled interfacial redox interactions. Due to enhanced glycolytic metabolism and inefficient vascular clearance associated with the Warburg effect, malignant tissues exhibit extracellular pH values within the mildly acidic range of $pH_{TME} \approx 6.5 - 6.9$ and oxygen tensions near 1 – 2% O_2 , conditions that significantly destabilize redox homeostasis and enhance oxidative sensitivity [1,4]. Simultaneously, cancer cells maintain elevated basal ROS concentrations required for rapid proliferation, metabolic adaptation, and oncogenic signaling, thereby positioning themselves near critical oxidative thresholds where relatively small increases in ROS flux may induce irreversible mitochondrial dysfunction and cytotoxic collapse [2,3]. Cancer-cell membranes further exhibit increased phosphatidylserine exposure, altered cholesterol

packing, enhanced lipid heterogeneity, and disrupted dielectric organization, creating a highly anisotropic interfacial environment favorable for electrostatic amplification [29,32]. The dielectric constant decreases sharply from bulk aqueous medium ($\epsilon_{\text{water}} \approx 78$) toward membrane-associated hydrophobic regions ($\epsilon_{\text{core}} \approx 2$), while the effective dielectric constant within the membrane-associated Stern layer typically falls within the range $\epsilon_{\text{int}} \approx 10 - 30$. Because electric field strength scales inversely with dielectric permittivity, this interfacial dielectric discontinuity substantially amplifies localized electrostatic interactions. Under these conditions, membrane-associated curcumin chromophores become spatially confined within intermolecular separation distances of approximately $d \approx 0.5 - 1.5$ nm from aqueous-phase ascorbate monoanions, creating a highly oriented donor–acceptor geometry favorable for field-sensitive electron transfer and interfacial redox coupling. Figure 1 illustrates the anatomical characteristics of the tumor microenvironment, including compromised vasculature, hypoxic gradients, and acidic extracellular conditions that establish the physicochemical basis for interfacial oxidative amplification.

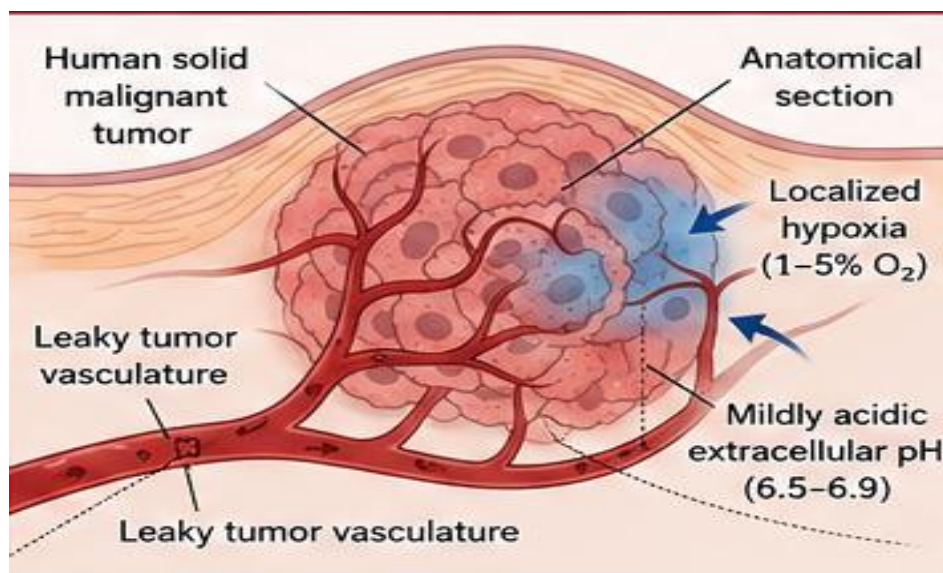
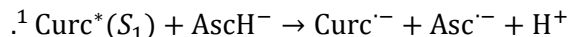


Figure 1. Anatomical representation of the tumor microenvironment

Figure 1 shows the physicochemical conditions governing interfacial oxidative amplification within the curcumin–ascorbate system. The figure depicts a human solid malignant tumor characterized by abnormal vascular architecture, compromised perfusion, localized hypoxic regions (1–5% O_2), and mildly acidic extracellular pH conditions (6.5–6.9). The leaky and disorganized tumor vasculature promotes inefficient oxygen delivery and metabolic waste accumulation, thereby generating heterogeneous oxidative and electrochemical gradients across the tumor tissue. These tumor-associated conditions collectively destabilize redox homeostasis, enhance oxidative sensitivity, and establish a low-dielectric interfacial environment favorable for field-amplified proton-coupled electron transfer and nonlinear reactive oxygen species (ROS) generation within the membrane-associated curcumin–ascorbate interface.

Within this coupled interfacial system, photoexcited curcumin functions as a transient dipolar perturbation center while ascorbate acts as a proximal redox-transfer subsystem. Upon excitation from the electronic ground state (S_0) into the excited singlet manifold (S_1), curcumin undergoes ultrafast intramolecular charge redistribution followed by Stokes relaxation and excited-state dipole displacement during a finite dielectric solvent relaxation interval ($\tau_s \approx 1\text{--}100$ ps)[27,36]. During this nonequilibrium relaxation window, the mismatch between the reorganized excited-state dipole and the slower orientational response of surrounding water molecules and lipid headgroups generates a localized transient electric field (E_{loc})[37]. This field dynamically perturbs nearby ascorbate orbitals through Stark-

type electrostatic coupling, altering orbital alignment, reducing electron-transfer activation barriers, and modulating the free-energy driving force (ΔG°) governing interfacial proton-coupled electron transfer. The dominant electron-transfer pathway within the coupled system is represented by



where the resulting radical intermediates subsequently participate in autocatalytic oxygen-reduction cycles producing superoxide radicals, hydrogen peroxide, hydroxyl radicals, and secondary oxidative cascades [12,24]. In parallel, residual excited-state populations undergo intersystem crossing into the triplet manifold ($^3\text{Curc}^*$), enabling secondary singlet oxygen generation through triplet–triplet energy transfer with molecular oxygen [26,28].

The molecular mechanism of field-enhanced PCET, orbital Stark perturbation, and reduction of the interfacial activation barrier is illustrated in Figure 2(c). Enhanced electron flux subsequently accelerates oxygen reduction reactions, amplifying the formation of superoxide radicals, hydrogen peroxide, and secondary hydroxyl radicals [12,24]. Under tumor-relevant oxidative conditions, this creates a nonlinear ROS amplification regime in which relatively small increases in interfacial field strength produce disproportionately large increases in oxidative stress and selective malignant-cell cytotoxicity [1,4,42]. The integrated interfacial redox network, nonlinear ROS amplification cascade, and resulting biological outcomes are summarized schematically in Figure 2(d). Consequently, while curcumin primarily functions as the light-harvesting quantum-electrostatic transducer responsible for transient Stark-field generation and orbital modulation, ascorbic acid provides the chemical reducing power that converts localized photon-induced electrostatic perturbation into sustained nonlinear ROS amplification and selective malignant-cell oxidative cytotoxicity.

The molecular-level properties established across the coupled curcumin–ascorbate–tumor interface system provide the fundamental rationale for the present modeling framework. Classical chemical kinetics assumes homogeneous isotropic media in which reactions occur through stochastic diffusion-limited collisions governed primarily by concentration-dependent rate equations. However, the present system violates these assumptions through strong spatial confinement, directional donor–acceptor orientation, ultrafast excited-state dipole reorganization, dielectric amplification, and transient interfacial electrostatic coupling. The substantial excited-state dipole displacement of curcumin occurring within a low-dielectric boundary layer generates transient electric fields capable of perturbing nearby electronic orbitals before significant molecular diffusion occurs. Consequently, the core electron-transfer process cannot be treated solely as a fixed thermal rate constant, but instead requires a framework capable of capturing field-regulated orbital perturbation, interfacial electrostatic coupling, and dynamically modulated electron-transfer behavior. Therefore, to capture these coupled physicochemical dynamics, we formulate a Quantum Mechanical Treatment in which curcumin is modeled using excited-state quantum confinement and dipolar relaxation formalism based on the time-independent Schrödinger equation and Stark-type electrostatic perturbation theory, while ascorbate-mediated ROS amplification is modeled using field-coupled proton-coupled electron transfer kinetics and nonlinear ROS reaction networks under tumor-relevant acidic and hypoxic boundary conditions. These molecular and interfacial properties therefore establish the physical basis for the Hamiltonian formulation developed in the subsequent section. The model is constraint by experimental and first principles studies as summarized in Table 1.

Molecular Mechanism of Curcumin: ESIPT and Stokes Shift

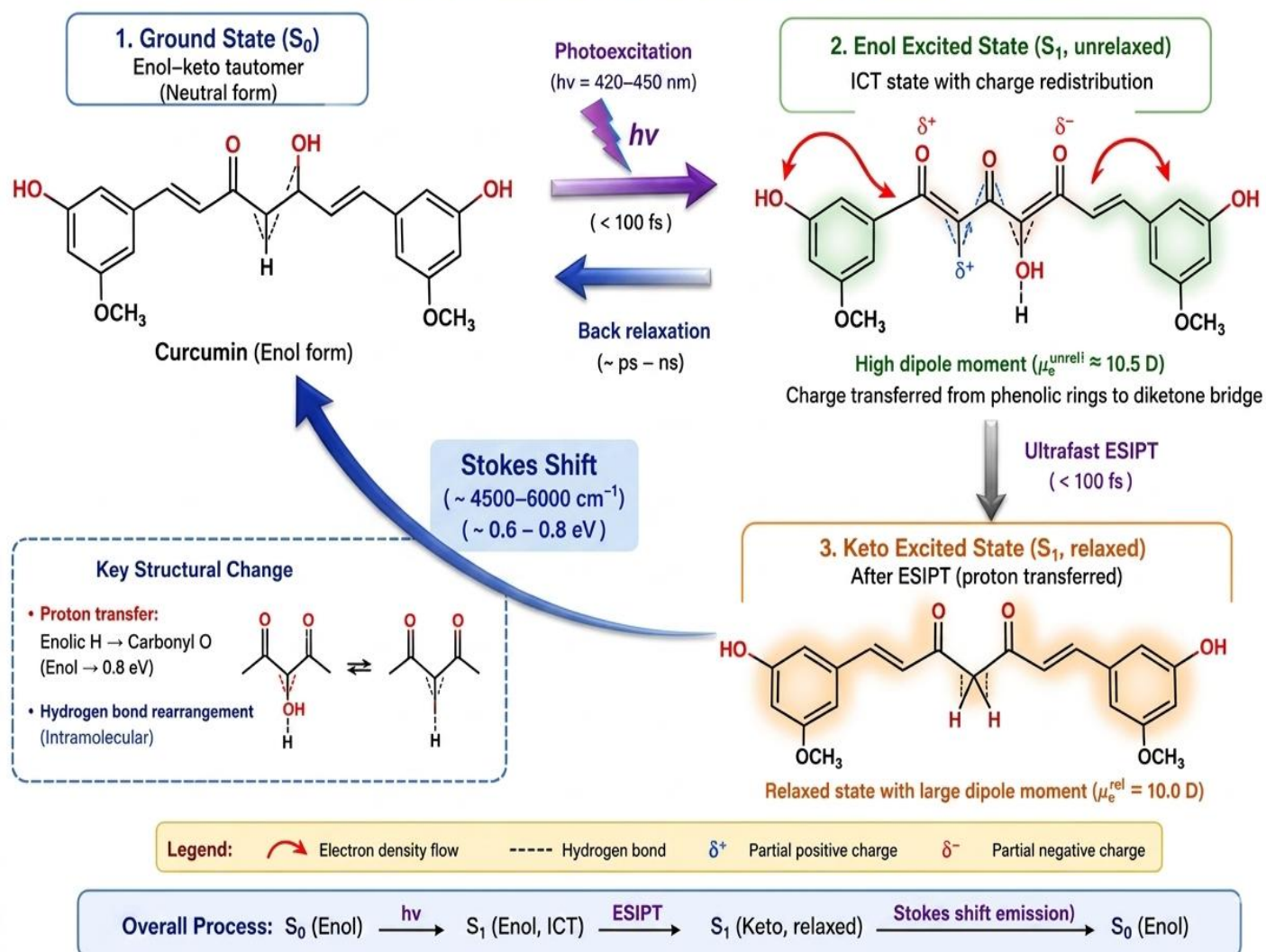


Figure 2(a) | Molecular photophysics of curcumin illustrating excited-state intramolecular proton transfer (ESIPT), charge redistribution, and Stokes-shift-driven dipole amplification.

Figure 2(a) illustrates the sequential excited-state transitions of curcumin following visible-light photoexcitation within the 430 – 450 nm spectral region. In the electronic ground state (S_0), curcumin predominantly exists in the neutral enol tautomeric configuration stabilized through intramolecular hydrogen bonding across the conjugated heptadienedione bridge. Upon optical excitation, the molecule transitions into an electronically excited enol singlet state characterized by intramolecular charge transfer (ICT), where electron density redistributes from the phenolic oxygen groups toward the diketone bridge, producing substantial excited-state dipole amplification and asymmetric charge localization. Ultrafast ESIPT subsequently transfers the enolic proton toward the diketone oxygen, generating the relaxed keto excited state accompanied by large dipole displacement and significant Stokes relaxation. The figure further illustrates the associated electron-density flow, hydrogen-bond rearrangement, partial charge redistribution, and the energetic sequence linking ground-state excitation, ICT, ESIPT, and ultrafast fluorescence relaxation. Collectively, these transitions establish the physicochemical basis for transient excited-state electrostatic field generation and interfacial Stark-type perturbation within the curcumin-based quantum-redox system.

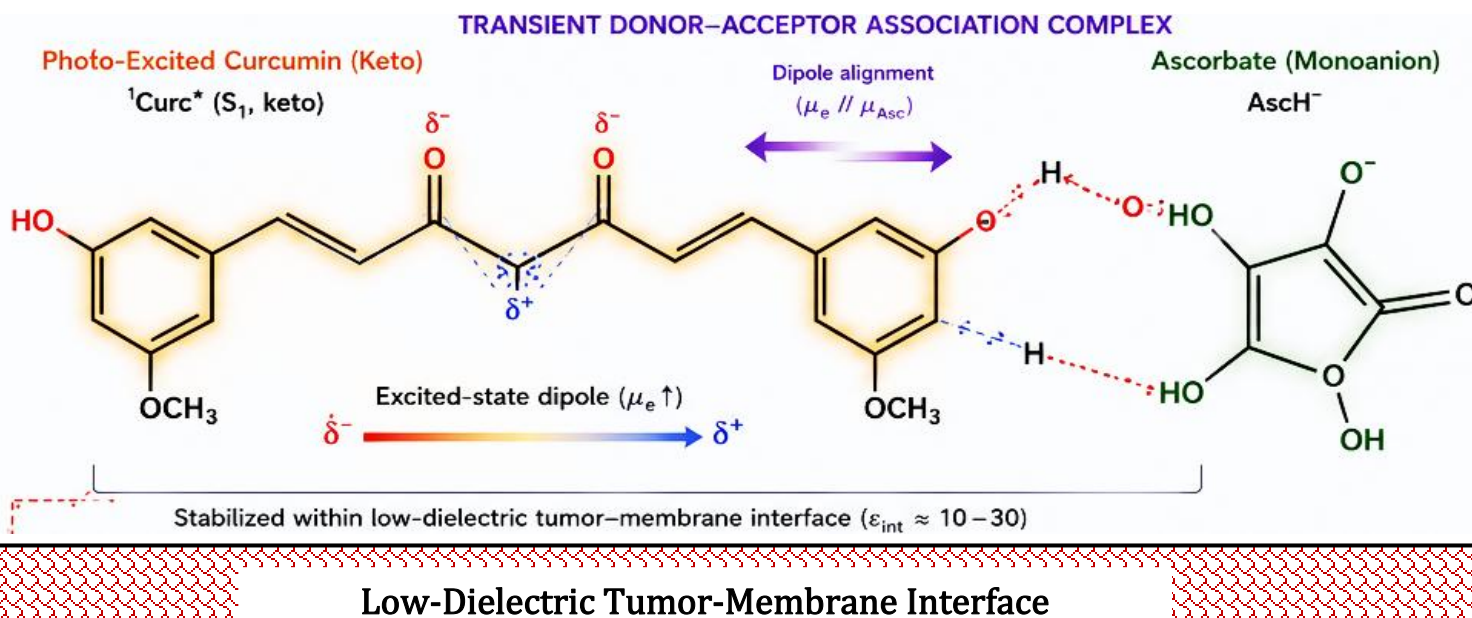


Figure 2(b)| Transient donor–acceptor association complex formed between photoexcited keto-curcumin and monoanionic ascorbate within the low-dielectric tumor-membrane interface.

Figure 2(b) illustrates the nonequilibrium interfacial coupling between photoexcited keto-curcumin and monoanionic ascorbate (AscH^-) stabilized within the low-dielectric Stern layer of the tumor-associated membrane interface ($\epsilon_{\text{int}} \approx 10 - 30$). Following ESIPT and excited-state dipole amplification, keto-curcumin develops a strongly polarized asymmetric electronic distribution that electrostatically aligns with nearby ascorbate orbitals, forming a transient hydrogen-bonded donor–acceptor association complex. The interaction is stabilized through dipole-aligned electrostatic coupling, intermolecular hydrogen bonding, and proton-coupled electron-transfer (PCET) interactions occurring within nanometer-scale intermolecular confinement. This coupled nonequilibrium assembly provides the mechanistic basis for transient Stark-field generation, reduced electron-transfer activation barriers, enhanced ROS amplification, and selective oxidative cytotoxicity in malignant cells.

Figure 2c. FIELD-ENHANCED PCET: REDUCED ACTIVATION BARRIER & MODULATED DRIVING FORCE

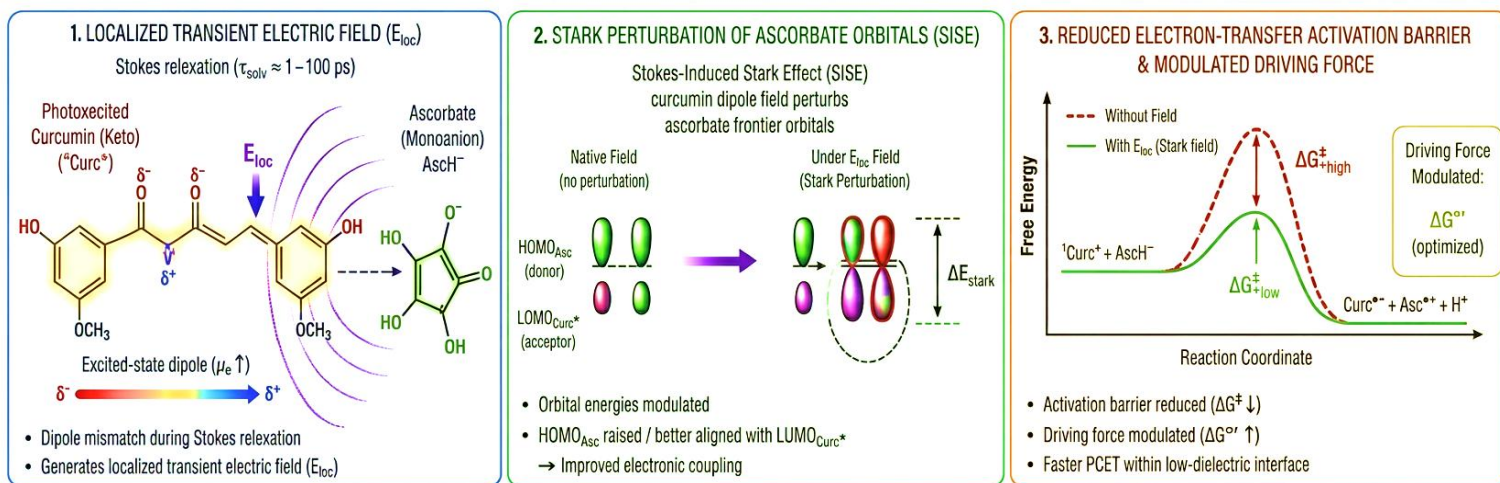


Figure 2(c)| Field-enhanced proton-coupled electron transfer (PCET)

The left panel illustrates generation of a localized transient electric field (E_{loc}) during Stokes relaxation of photoexcited keto-curcumin ($^1\text{Curc}^*$), arising from excited-state dipole mismatch within the low-dielectric tumor interface. The middle panel depicts Stark perturbation of ascorbate frontier orbitals under the Stokes-Induced Stark

Effect (SISE), where the transient field modifies orbital energies, improves $HOMO_{Asc} - LUMO_{Curc^*}$ alignment, and enhances electronic coupling. The right panel presents the corresponding reaction-coordinate free-energy landscape, showing reduction of the proton-coupled electron-transfer activation barrier ($\Delta G^\ddagger$) and optimization of the free-energy driving force (ΔG°) under the influence of the localized Stark field, thereby facilitating accelerated interfacial electron transfer and enhanced ROS amplification within the tumor microenvironment.

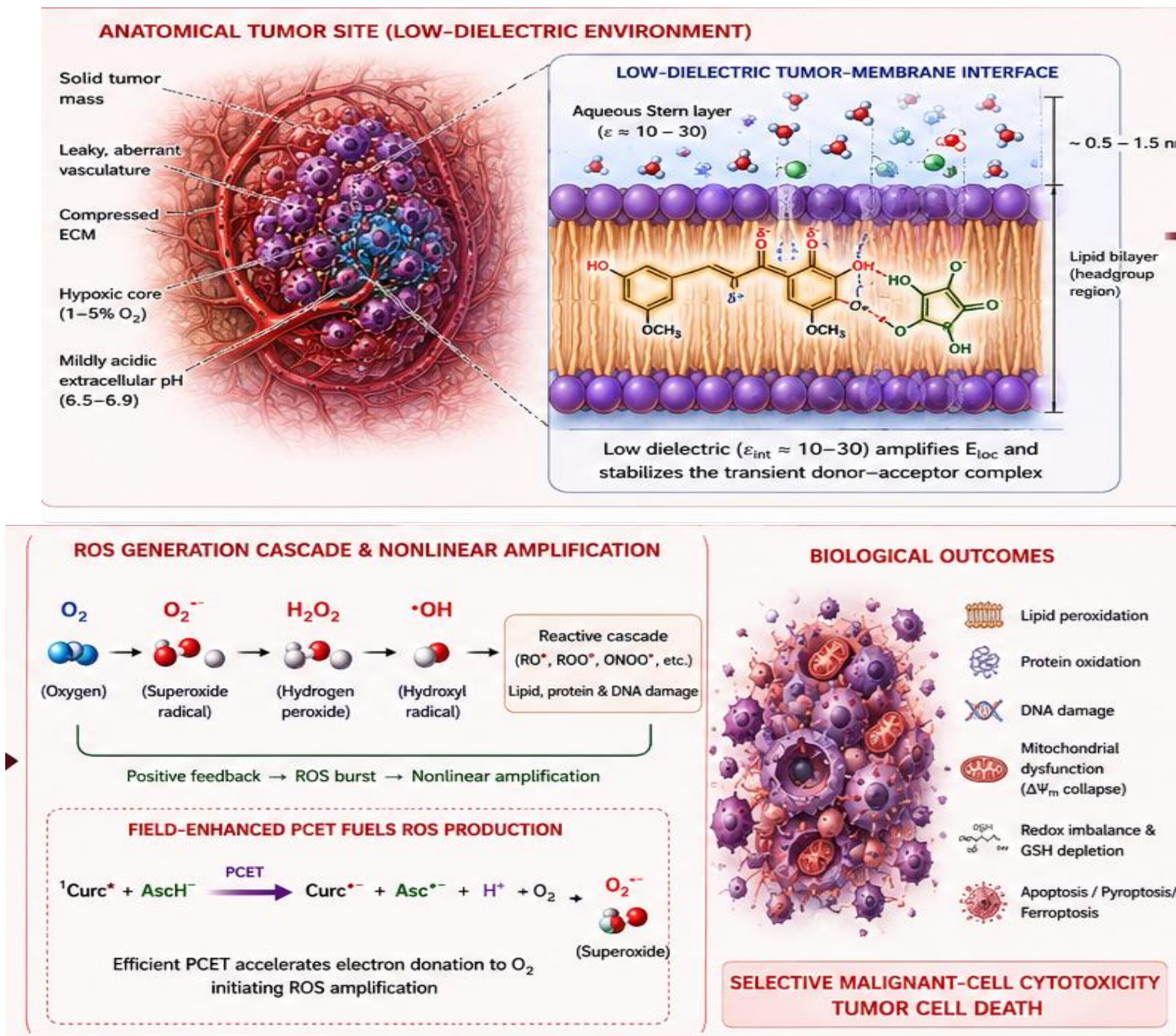


Figure 2(d) | Low-dielectric tumor microenvironment and site of cell cytotoxicity

Figure 2(d) shows the Low-dielectric tumor microenvironment illustrating interfacial redox-network formation, nonlinear ROS amplification, and selective malignant-cell cytotoxicity induced by the curcumin-ascorbate system. The left panel illustrates the anatomical tumor microenvironment characterized by leaky aberrant vasculature,

compressed extracellular matrix (ECM), localized hypoxia (1–5% O_2), and mildly acidic extracellular pH (6.5–6.9), conditions that collectively generate a low-dielectric interfacial environment favorable for electrostatic amplification and oxidative instability. The central panel depicts the tumor-membrane Stern interface where photoexcited curcumin and monoanionic ascorbate form a transient donor–acceptor complex stabilized within the low-dielectric boundary layer ($\epsilon_{int} \approx 10 - 30$). Under these conditions, field-enhanced proton-coupled electron transfer (PCET) accelerates electron donation to molecular oxygen, initiating autocatalytic ROS generation pathways involving superoxide radicals ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($\cdot OH$), and secondary oxidative cascades. The positive-feedback nature of the ROS network produces nonlinear oxidative amplification and sustained oxidative burst behavior within the tumor interface. The right panel summarizes the resulting biological outcomes, including lipid peroxidation, protein oxidation, DNA damage, mitochondrial dysfunction, glutathione depletion, redox imbalance, and activation of apoptosis-, pyroptosis-, and ferroptosis-associated pathways, ultimately culminating in selective malignant-cell oxidative cytotoxicity.

Table 1. Physicochemical and Quantum-Redox Parameters Constraining the Curcumin–Ascorbate Interfacial Model

Parameter		Symbol	Typical Value / Range	Physical Meaning		Source Basis
Curcumin wavelength	absorption	λ_{abs}	420–450 nm	Photoexcitation window	spectral	[27]
Curcumin dipole moment	ground-state	μ_g	~ 2.5 D	Initial molecular polarization		[25]
Curcumin dipole moment	excited-state	μ_e	~ 10.5 D	Excited-state after ICT	polarization	[27]
Dipole displacement		$\Delta\mu$	~ 8.0 D	Excited-state redistribution	charge	This study
Stokes relaxation time		τ_s	1–100 ps	Solvent/dielectric window	relaxation	[36]
ESIPT timescale		τ_{ESIPT}	<100 fs	Proton-transfer timescale	relaxation	[27]
Interfacial constant	dielectric	ϵ_{int}	10–30	Effective Stern-layer environment	dielectric	[17]
Bulk aqueous constant	dielectric	ϵ_{water}	~ 78	Bulk solvent permittivity		Standard aqueous medium
Lipid-core constant	dielectric	ϵ_{core}	~ 2	Hydrophobic interior	membrane	[17]
Curcumin coefficient	partition	$\log P$	~ 3.2	Lipophilic partitioning	membrane	[18]
Donor–acceptor distance	separation	r	0.5–1.5 nm	Interfacial distance	orbital-coupling	This study
Localized electric field		E_{loc}	10^7 – 10^8 V/m	Stokes-induced magnitude	Stark field	[37]

Tumor extracellular pH	pH _{TME}	6.5–6.9	Acidic microenvironment	tumor	[1]
Tumor oxygen concentration	O ₂	1–5%	Hypoxic tumor conditions		[4]
Pharmacological concentration	ascorbate [AsCH [−]]	1–5 mM	ROS-amplifying concentration	therapeutic	[10]

2.2. Formulation of the Interfacial PCET Potential and Eigensolutions

The localized proton-coupled electron transfer (PCET) takes place within a compressed supramolecular donor–acceptor assembly at the low-dielectric tumor–membrane interface ($\epsilon_{\text{int}} \approx 10\text{--}30$). Under photoexcitation, curcumin undergoes substantial excited-state dipole redistribution arising from intramolecular charge transfer and keto–enol polarization, thereby generating localized transient electrostatic fields capable of perturbing nearby donor–acceptor energetics [43–44]. Because the donor and acceptor remain hydrogen bonded within a sterically confined interfacial environment, proton displacement occurs over subnanometer distances comparable to typical hydrogen-bond lengths, making quantum-mechanical tunneling and field-modulated barrier penetration physically relevant to the transfer process [45–46]. To derive the effective potential governing proton transfer, we begin from the full molecular Hamiltonian describing the coupled electronic and nuclear dynamics of the curcumin–ascorbate complex.

The coupled curcumin–ascorbate assembly formally constitutes an interacting electron–nuclear system governed by the total molecular Hamiltonian

$$\hat{H}_{\text{total}} = \hat{T}_n + \hat{T}_e + V_{ee}(r) + V_{nn}(R) + V_{en}(r, R) \quad (1)$$

where $\hat{T}_n$ and $\hat{T}_e$ represent the nuclear and electronic kinetic-energy operators, respectively, while V_{ee} , V_{nn} , and V_{en} denote electron–electron, nucleus–nucleus, and electron–nucleus Coulomb interactions [47–48].

The coordinate vectors

$$r = \{r_i\}, R = \{R_I\},$$

represent the electronic and nuclear coordinate sets of the interfacial donor–acceptor complex. Because electronic redistribution occurs on substantially shorter timescales than protonic and heavy-atom nuclear motion, the Born–Oppenheimer approximation permits separation of fast electronic and slow nuclear degrees of freedom according to [47,49].

$$\Psi(r, R) = \psi_e(r; R)\chi(R) \quad (2)$$

where $\psi_e(r; R)$ is the electronic wavefunction depending parametrically on the nuclear coordinates and $\chi(R)$ is the nuclear wavefunction. Substitution into the total molecular Schrödinger equation yields the electronic eigenvalue problem

$$[\hat{T}_e + V_{ee}(r) + V_{en}(r, R)]\psi_e(r; R) = E_e(R)\psi_e(r; R) \quad (3)$$

where $E_e(R)$ defines the adiabatic electronic energy surface governing the slower nuclear dynamics. The resulting effective Born–Oppenheimer potential-energy surface therefore becomes

$$V_{\text{eff}}(R) = E_e(R) + V_{nn}(R) \quad (4)$$

which governs proton displacement along the donor–acceptor transfer coordinate [50–51].

Within hydrogen-bonded proton-coupled electron-transfer systems, the dominant quantum displacement occurs primarily along the longitudinal donor–acceptor hydrogen-bond axis because this direction simultaneously maximizes orbital overlap, minimizes proton-transfer distance, and aligns with the strongest electrostatic coupling pathway between donor and acceptor orbitals [45,46,52]. Consequently, the multidimensional proton dynamics may be projected onto an effective one-dimensional transfer coordinate x defined by the projection of the proton position onto the donor–acceptor axis,

$$x = (r_p - r_D) \cdot \hat{n}_{DA},$$

where r_p is the proton position vector, r_D is the donor oxygen position, and

$$\hat{n}_{DA} = \frac{r_A - r_D}{|r_A - r_D|}$$

is the unit vector directed from the donor oxygen O_D toward the acceptor oxygen O_A .

The reaction coordinate x is defined as a continuous one-dimensional trajectory describing displacement of the shared proton along the longitudinal hydrogen-bond axis connecting the donor oxygen of the ascorbate monoanion (AscH^-) and the acceptor enolate oxygen of photoexcited keto-curcumin ($^1\text{Curc}^*$), thus

$$x = \begin{cases} < 0 & \text{AscH}^- \text{ donor-localized state} \\ 0 & \text{interfacial activation boundary} \\ > 0 & ^1\text{Curc}_{\text{keto}}^* \text{ acceptor-localized state} \end{cases}$$

The reduction to a single transfer coordinate is justified by three complementary physical constraints. The lateral fluctuations perpendicular to the donor–acceptor axis are strongly suppressed by steric confinement arising from lipid headgroups, interfacial water structuring, and dielectric compression within the membrane-associated Stern layer. Under such confined hydrogen-bond geometries, the transverse confinement potential may be approximated locally as harmonic, $V_{\perp}(q_{\perp}) = \frac{1}{2}k_{\perp}q_{\perp}^2$, where $q_{\perp}$ denotes transverse proton displacement and $k_{\perp}$ is the effective transverse confinement stiffness. For strongly hydrogen-bonded interfacial systems, typical confinement stiffness values lie within $k_{\perp} \approx 10\text{--}50 \text{ eV/nm}^2$, consistent with hydrogen-bond bending stiffnesses and confined intermolecular vibrational modes reported for condensed-phase proton-transfer systems and biological hydrogen-bond networks [45,46,53].

The associated transverse zero-point fluctuation amplitude becomes

$$\Delta x_{\perp} = \sqrt{\frac{\hbar}{\mu_{pt}\omega_{\perp}}} \approx 0.02\text{--}0.05 \text{ nm},$$

which remains substantially smaller than the characteristic donor–acceptor separation $\Delta x \approx 0.15 \text{ nm}$. Consequently, low-energy proton dynamics remain strongly confined to the longitudinal donor–acceptor transfer direction, thereby validating projection onto an effective one-dimensional coordinate [51,54]. Secondly, the topology of the Born–Oppenheimer adiabatic surface further supports reduction to a longitudinal transfer coordinate. The effective surface $V_{\text{eff}}(x, q_{\perp})$ possesses a minimum-energy reaction pathway that remains strongly aligned with the donor–acceptor axis because short hydrogen bonds generally favor near-linear $\text{O}\cdots\text{H}\cdots\text{O}$ geometries that minimize proton-transfer distance while maximizing orbital overlap and electrostatic stabilization [53,55]. In strongly directional hydrogen-bond systems, the transverse curvature perpendicular to the minimum-energy pathway is typically substantially larger than the longitudinal curvature governing proton transfer, thereby confining low-energy nuclear motion

predominantly to the reaction coordinate [54,56] Thirdly, the transfer dynamics exhibit partial vibrational timescale separation between transverse confinement modes and the slower longitudinal proton-transfer mode. Hydrogen-bond bending and transverse vibrational modes typically possess frequencies within the range $\omega_{\perp} \approx 800\text{--}1200\text{ cm}^{-1}$, whereas longitudinal proton-transfer and intermolecular stretching modes generally occur within $\omega_{\parallel} \approx 200\text{--}400\text{ cm}^{-1}$, in hydrogen-bonded proton-transfer systems and condensed-phase PCET environments [45,53,55].

The resulting ratio

$$\frac{\omega_{\perp}}{\omega_{\parallel}} \approx 3\text{--}4$$

permits approximate adiabatic separation of fast transverse fluctuations from slower longitudinal proton-transfer dynamics, thereby further justifying reduction of the multidimensional Born–Oppenheimer surface to an effective one-dimensional PCET coordinate aligned along the dominant donor–acceptor transfer vector [46,52].

While the adiabatic representation provides an accurate description of the Born–Oppenheimer surface, PCET dynamics are most conveniently treated in a mixed diabatic–adiabatic representation. Donor and acceptor proton states are defined diabatically as

$$|\phi_D\rangle = |\phi_D(x; \mathbf{q}_{\perp})\rangle, |\phi_A\rangle = |\phi_A(x; \mathbf{q}_{\perp})\rangle$$

where these states are eigenfunctions of the local harmonic expansions around x_- and x_+ , respectively, with the property that their electronic character remains unchanged along the reaction coordinate. The adiabatic electronic states $|\psi_{\pm}\rangle$ are obtained by diagonalizing the 2×2 diabatic Hamiltonian:

$$\mathbf{H}_{\text{dia}} = \begin{pmatrix} V_D(x) & V_{DA}(x) \\ V_{DA}(x) & V_A(x) \end{pmatrix} \quad (5)$$

where $V_D(x)$ and $V_A(x)$ denote the donor and acceptor diabatic potential surfaces, respectively, while $V_{DA}(x)$ represents the donor–acceptor electronic coupling. Diagonalization of H_{dia} generates the adiabatic eigenstates and associated adiabatic potential-energy surfaces governing proton-transfer dynamics. Mixed diabatic–adiabatic representations of this type are standard in nonadiabatic PCET theory because they simultaneously preserve localized chemical character while permitting electronic-state mixing, tunneling interactions, and field-induced coupling effects [46,52].

Under the present interfacial confinement conditions, diagonalization of the diabatic Hamiltonian produces a lower adiabatic surface possessing two finite localization minima separated by a finite tunneling barrier. Such bistable proton-transfer topologies are accurately represented by quartic asymmetric double-well systems, which constitute the minimal bounded potential class capable of simultaneously supporting proton localization, donor–acceptor asymmetry, finite barrier penetration, and tunneling splitting [54,56,57]. Consequently, the effective interfacial proton-transfer landscape is represented in the following subsection using a modified quartic double-well potential constructed within bounded Rosen–Morse coordinates.

Because the curcumin–ascorbate complex is a transient hydrogen-bonded donor–acceptor assembly rather than a rigid covalent structure, its transfer landscape must be finite-depth, anharmonic, asymmetric, and dissociable. Harmonic potentials are therefore insufficient, since they cannot describe barrier crossing, tunneling splitting, or donor–acceptor asymmetry. Finite-depth Rosen–Morse-, Manning–Rosen-, Morse-, and Razavy-type potentials have been widely used in analytically tractable treatments of molecular vibration, proton transfer, tunneling, and asymmetric bound-state localization

because they preserve anharmonicity while remaining compatible with Schrödinger-based analysis [57,58-59].

The standard Rosen–Morse potential is written as

$$V_{RM}(x) = -A(A+1)\text{sech}^2\left(\frac{x}{a}\right) + B\tanh\left(\frac{x}{a}\right) \quad (6)$$

where the $\text{sech}^2(x/a)$ term defines a finite anharmonic confinement well while the $\tanh(x/a)$ term introduces energetic asymmetry between left- and right-localized states. However, the conventional Rosen–Morse potential remains intrinsically single-welled and therefore cannot directly represent the two-state donor–acceptor topology required for interfacial PCET.

To recover the required proton-localization landscape, the bounded Rosen–Morse coordinate

$$z = \tanh\left(\frac{x}{a}\right), \quad -1 < z < 1$$

is retained, while the confinement term is generalized into a quartic double-localization form. Accordingly, the interfacial PCET landscape is represented by a double-well Rosen–Morse (DW–RM) potential,

$$V_{DW-RM}(x) = V_b \left[\tanh^2\left(\frac{x}{a}\right) - \xi^2 \right]^2 + \eta \tanh\left(\frac{x}{a}\right) \quad (7)$$

where V_b defines the barrier-energy scale, a controls the donor–acceptor separation length scale, ξ determines the separation of the two localization wells, and η introduces energetic asymmetry between the ascorbate donor state and the excited-state keto-curcumin acceptor state. The quartic term $(z^2 - \xi^2)^2$ is necessary because the standard Rosen–Morse form alone cannot generate two finite localization minima. The potential reduces to a physically meaningful double-well profile when $0 < \xi < 1$, since the symmetric component possesses two minima satisfying

$$\tanh^2\left(\frac{x}{a}\right) = \xi^2,$$

giving

$$x_{\pm} = \pm a \tanh^{-1}(\xi).$$

Thus, the left minimum x_- corresponds to the proton localized near the ascorbate donor site, whereas the right minimum x_+ corresponds to proton localization near the excited-state keto-curcumin acceptor site. The interfacial activation barrier is defined by $\Delta G^\ddagger = V(x_b) - V(x_-)$, where x_b is the barrier coordinate near $x = 0$, while the intrinsic donor–acceptor driving force becomes

$$\Delta G^\circ = V(x_+) - V(x_-).$$

The extrema satisfy $\frac{dV}{dx} = 0$, which yields

$$4V_b z(z^2 - \xi^2) + \eta = 0, \quad z = \tanh\left(\frac{x}{a}\right).$$

Dividing through by $4V_b$ gives the depressed cubic

$$z^3 - \xi^2 z + \frac{\eta}{4V_b} = 0.$$

For a cubic equation of the form $z^3 + pz + q = 0$, three real stationary points exist when

$$\left(\frac{q}{2}\right)^2 + \left(\frac{p}{3}\right)^3 < 0.$$

Substitution of $p = -\xi^2, q = \frac{\eta}{4V_b}$, gives

$$|\eta| < \frac{8V_b\xi^3}{3\sqrt{3}} \quad (8)$$

This condition is obtained from the discriminant of the depressed cubic $4V_bz^3 - 4V_b\xi^2z + \eta = 0$, which requires $\Delta = 16V_b^2\xi^6 - \frac{27}{4}\eta^2 > 0$. Physically, this condition requires that the energetic asymmetry between the donor and acceptor wells arising from differences in reduction potential, proton affinity, and tumor-microenvironment pH does not become sufficiently large to eliminate one localization basin entirely, thereby preserving the two-state PCET character of the transfer coordinate.

For the parameter values used in this study ($V_b = 0.35$ eV, $\xi = 0.65$, $\eta = 0.15$ eV), the left-hand side of (3) evaluates to $|\eta| = 0.15$ eV and the right-hand side to approximately 0.31 eV, satisfying the condition and preserving the double-well topology.

The QDW potential parameters are related to microscopic physical quantities via:

$$V_b = \frac{1}{4} \left(V_0^{\text{barrier}} - \frac{(\Delta G^\circ)^2}{4V_0^{\text{barrier}}} \right), \xi = \tanh\left(\frac{\Delta x}{2a}\right), \eta = \frac{\Delta G^\circ}{2}$$

where V_0^{barrier} is the barrier height of a symmetric double-well ($\eta = 0$) and ΔG° is the intrinsic donor–acceptor free-energy driving force. For the parameters used in this study ($\Delta x = 0.154$ nm, $a = 0.10$ nm, $\Delta G^\circ = -0.15$ eV, $V_0^{\text{barrier}} = 0.40$ eV), these relations yield $V_b \approx 0.35$ eV, $\xi \approx 0.65$, and $\eta \approx 0.15$ eV. This mapping between microscopic donor–acceptor energetics and effective double-well parameters follows standard asymmetric double-well reductions commonly used in proton-transfer and electron-transfer theory [52,56].

The field-free Time-Independent Schrödinger Equation (TISE) is therefore written as

$$\left[-\frac{\hbar^2}{2\mu_{\text{pt}}} \frac{d^2}{dx^2} + V_{DW-RM}(x) \right] \psi_n(x) = E_n \psi_n(x) \quad (9)$$

Where μ_{pt} is the effective reduced mass along the proton-transfer coordinate. For a symmetric hydrogen-bonded transfer coordinate, $\mu_{\text{pt}} \approx m_p/2$, where m_p is the proton mass, although donor–acceptor asymmetry introduces corrections through redistribution of the coupled electronic density.

The localized transient electric field acting on the donor–acceptor complex originates from nonequilibrium dipole mismatch during Stokes relaxation of photoexcited curcumin. Following Franck–Condon excitation, the curcumin dipole changes from its ground-state value μ_g to its excited-state value μ_e , defining the initial excited-state dipole displacement,

$$\Delta\mu_0 = \mu_e - \mu_g \quad (10)$$

Following Onsager’s reaction-field model, which treats a polar molecule embedded within a dielectric cavity as generating a local field that acts back on the molecule and its surrounding environment [60], the electronic polarization of the interface responds almost instantaneously, whereas orientational polarization of interfacial water molecules and lipid headgroups relaxes more slowly according to Debye dielectric relaxation [61]. Consequently, the excess dipole moment decays exponentially as

$$\Delta\mu(t) = \Delta\mu_0 e^{-\frac{t}{\tau_s}} \quad (11)$$

where τ_s is the Stokes/orientational relaxation time. Treating photoexcited curcumin as an effective point dipole embedded within an interfacial dielectric medium ϵ_{int} , the dipolar electrostatic potential becomes

$$\Phi(r, \theta) = \frac{1}{4\pi\epsilon_0\epsilon_{\text{int}}} \frac{\Delta\mu(t) \cos \theta}{r^2} \quad (12)$$

The radial electric-field component acting along the curcumin–ascorbate transfer axis is obtained from

$$E_r(r, \theta) = -\frac{\partial\Phi}{\partial r} = \frac{1}{4\pi\epsilon_0\epsilon_{\text{int}}} \frac{2\Delta\mu(t) \cos \theta}{r^3} \quad (13)$$

Evaluating the field at the donor–acceptor separation distance $r = R$ gives the localized transient Stark field

$$E_{\text{loc}}(t) = \frac{1}{4\pi\epsilon_0\epsilon_{\text{int}}} \frac{2\Delta\mu_0 e^{-t/\tau_s} \cos \theta}{R^3} \quad (14a)$$

which becomes amplified within the low-dielectric tumor membrane interface

$$E_{\text{loc}} \propto \frac{1}{\epsilon_{\text{int}}}$$

though subject to Debye screening attenuation at ionic strength representative of the tumor microenvironment ($\lambda_D \approx 0.8 \text{ nm}$), such that effective field penetration is confined to nanometer-scale donor–acceptor separations consistent with the interfacial geometry defined in Section 2.1.

Because the curcumin excited-state dipolar redistribution occurs within a partially ionic biological interface, electrostatic field penetration is additionally attenuated by Debye screening arising from mobile ions within the tumor microenvironment. The effective screened field therefore becomes

$$E_{\text{eff}}(r, t) = E_{\text{loc}}(r, t) \exp\left(-\frac{r}{\lambda_D}\right) \quad (14b)$$

where λ_D is the Debye screening length. Under tumor-associated ionic strengths ($I \sim 0.10\text{--}0.15 \text{ M}$), λ_D remains within the nanometer regime, thereby preserving significant Stark modulation at donor–acceptor separations characteristic of the curcumin–ascorbate interface.

The treatment of photoexcited curcumin as an effective localized dipole embedded within a dielectric cavity follows the classical Onsager reaction-field formalism, which has been extensively applied in solvatochromism, dielectric relaxation, electroabsorption spectroscopy, and interfacial photophysics [60,61]. Similar dipolar electrostatic models have been used in Stark spectroscopy and electric-field-mediated modulation of molecular electronic states, where transient dipole reorganization generates localized fields capable of perturbing nearby donor–acceptor orbitals [43,44]. The low-dielectric tumor-membrane interface therefore provides a physically plausible environment for transient field amplification arising from nonequilibrium Stokes relaxation.

The Stokes-Induced Stark Effect (SISE) enters as a linear perturbative tilting term,

$$V_{\text{SISE}}(x, t) = -q_{\text{eff}} E_{\text{loc}}(t) x \quad (15a)$$

where q_{eff} is the effective charge transferred along the PCET coordinate. In proton-coupled electron transfer, the effective charge represents the net charge displacement that couples to the external field. This quantity is related to the transition dipole moment $\mu_{DA} = e\langle\psi_D | x | \psi_A\rangle$ and the donor–acceptor separation $\Delta x = x_+ - x_-$ via

$$q_{\text{eff}} = \frac{|\mu_{DA}|}{\Delta x} \quad (15b)$$

For strongly localized diabatic states, $\mu_{DA} \approx e\Delta x \cdot S$ where $S = \langle \psi_D | \psi_A \rangle$ is the overlap integral, yielding $q_{eff} \approx eS$. This differs from the naive expectation $q_{eff} \approx eS^2$ because the transition dipole involves a single power of the wavefunction overlap in the position matrix element. For the parameter values in this study ($S \approx 0.22$), this gives $q_{eff} \approx 0.22e$. However, partial electronic delocalization and asymmetric charge redistribution increase this value. Literature values for similar hydrogen-bonded PCET systems report q_{eff} in the range $0.3e$ – $0.6e$ [46,52]. The present study adopts $q_{eff} = 0.45e$ as a representative intermediate value, with sensitivity analysis over $q_{eff} \in [0.3e, 0.6e]$ presented in Section 3 (Results) to assess robustness of the predicted nonlinear amplification regime.

The full field-coupled Hamiltonian therefore becomes

$$\hat{H} = -\frac{\hbar^2}{2\mu_{pt}} \frac{d^2}{dx^2} + V_b \left[\tanh^2\left(\frac{x}{a}\right) - \xi^2 \right]^2 + \eta \tanh\left(\frac{x}{a}\right) - q_{eff} E_{loc}(t)x \quad (16)$$

The elementary PCET event occurs on femtosecond-to-picosecond timescales ($\tau_{PCET} \approx 10^{-13}$ – 10^{-12} s), substantially faster than orientational relaxation of interfacial water and lipid headgroups ($\tau_s \approx 10^{-11}$ – 10^{-10} s).

Consequently, $\tau_{PCET} \ll \tau_s$, and the localized transient field may be treated as quasi-static during any individual PCET event. Under this quasi-static approximation, the final time-parameterized TISE becomes

$$\left[-\frac{\hbar^2}{2\mu_{pt}} \frac{d^2}{dx^2} + V_b \left(\tanh^2\left(\frac{x}{a}\right) - \xi^2 \right)^2 + \eta \tanh\left(\frac{x}{a}\right) - q_{eff} E_{loc}(t)x \right] \psi_n(x; t) = E_n(t) \psi_n(x; t) \quad (17)$$

The field-free eigensolutions define the localized donor–acceptor quantum states, while the SISE perturbation dynamically tilts the double-well landscape, lowers the effective PCET activation barrier, modifies ΔG° , increases tunneling splitting, enhances proton-transfer probability, and ultimately amplifies the interfacial ROS-generating redox flux responsible for selective malignant-cell oxidative cytotoxicity.

2.3. Analytical Solutions to the Time-Parameterized TISE and Quantum Derivables

As established in Section 2.3 under the validated quasi-static condition $\tau_{PCET} \ll \tau_s$, the elementary proton-coupled electron-transfer (PCET) event occurs on femtosecond-to-picosecond timescales substantially shorter than the orientational dielectric relaxation dynamics of surrounding interfacial water molecules and lipid headgroups. Consequently, the localized transient electric field generated during Stokes relaxation may be treated as effectively frozen during each elementary transfer event. Such quasi-static reduction of time-dependent environmental fluctuations into parameterized stationary Hamiltonians constitutes a standard treatment in condensed-phase proton transfer, dielectric reaction-field theory, and non-adiabatic PCET modeling [46,51,52]. Under this approximation, the interfacial proton dynamics are described through a time-parameterized Time-Independent Schrödinger Equation (TISE),

$$\hat{H}(t) = \hat{H}_0 + \hat{H}_{SISE}(t) = \left[-\frac{\hbar^2}{2\mu_{pt}} \frac{d^2}{dx^2} + V_{DW-RM}(x) \right] - q_{eff} E_{loc}(t)x \quad (18)$$

where μ_{pt} represents the effective reduced mass along the coupled proton-transfer coordinate, q_{eff} is the effective transferred charge associated with donor–acceptor electronic redistribution, and $E_{loc}(t)$ is the transient interfacial Stark field generated during nonequilibrium Stokes relaxation of photoexcited curcumin. The field-free double-well Rosen–Morse (DW–RM) backbone potential $V_{DW-RM}(x)$ defines the donor–acceptor proton localization landscape, whereas the linear Stark term introduces dynamic electrostatic tilting of the interfacial barrier.

The unperturbed stationary states satisfy

$$\hat{H}_0 \psi_n^{(0)}(x) = E_n^{(0)} \psi_n^{(0)}(x)$$

with

$$\hat{H}_0 = -\frac{\hbar^2}{2\mu_{pt}} \frac{d^2}{dx^2} + V_b \left[\tanh^2 \left(\frac{x}{a} \right) - \xi^2 \right]^2 + \eta \tanh \left(\frac{x}{a} \right)$$

The hyperbolic coordinate transformation

$$z = \tanh \left(\frac{x}{a} \right), z \in (-1, 1),$$

maps the infinite structural coordinate $x \in (-\infty, +\infty)$ onto a compact bounded interval while preserving the finite interfacial topology of the donor–acceptor system. Hyperbolic coordinate compactification of this type is extensively employed in Rosen–Morse-, Manning–Rosen-, and Razavy-type tunneling systems because it regularizes asymptotic divergences and converts exponentially localized states into bounded algebraic forms compatible with semiclassical analysis [58,59].

Applying the chain rule gives

$$\frac{d}{dx} = \frac{1 - z^2}{a} \frac{d}{dz},$$

and

$$\frac{d^2}{dx^2} = \frac{(1 - z^2)^2}{a^2} \frac{d^2}{dz^2} - \frac{2z(1 - z^2)}{a^2} \frac{d}{dz}$$

Substitution into the TISE yields the transformed Fuchsian-type differential equation,

$$\left[\frac{(1 - z^2)^2}{a^2} \frac{d^2}{dz^2} - \frac{2z(1 - z^2)}{a^2} \frac{d}{dz} \right] \psi_n^{(0)}(z) + \frac{2\mu_{pt}}{\hbar^2} \left[E_n^{(0)} - V_b(z^4 - 2\xi^2 z^2 + \xi^4) - \eta z \right] \psi_n^{(0)}(z) = 0 \quad (19)$$

Unlike the standard Rosen–Morse potential, whose quadratic hyperbolic structure admits globally exact hypergeometric eigensolutions, the quartic z^4 topology required to generate physically meaningful donor–acceptor localization basins destroy strict global orthogonal-polynomial solvability. Similar quartic double-well systems encountered in molecular tunneling, hydrogen-bonded proton transfer, ammonia inversion, and condensed-phase bistable systems are therefore commonly treated using local asymptotic expansions combined with semiclassical tunneling analysis and perturbative corrections [54,56,57]. Consequently, analytical tractability is achieved through a localized asymptotic expansion around the two stable minima.

The symmetric DW–RM backbone possesses minima located at $z_{\pm} = \pm\xi$, corresponding to the donor- and acceptor-localized proton configurations. Expanding the effective potential around these minima gives

$$V_{\text{local}}(z) \approx V(z_{\pm}) + \frac{1}{2} \frac{d^2 V}{dz^2} \bigg|_{z_{\pm}} (z - z_{\pm})^2 \quad (20)$$

Transforming back into the physical coordinate x yields the local effective force constants. Starting from the potential expressed in the hyperbolic coordinate $z = \tanh(x/a)$, the second derivative in the physical coordinate is obtained via the chain rule:

$$\frac{d^2 V}{dx^2} = \frac{1}{a^2} \left[(1 - z^2)^2 \frac{d^2 V}{dz^2} - 2z(1 - z^2) \frac{dV}{dz} \right]$$

Evaluating at the minima $z = \pm\xi$ and using $\frac{dV}{dz} = 0$ at these points gives

$$k_{\pm} = \left. \frac{d^2V}{dz^2} \right|_{z=\pm\xi} = \frac{8V_b}{a^2} \xi^2 (1 - \xi^2)^2 \mp \frac{2\eta}{a^2} \xi (1 - \xi^2) \quad (21)$$

which characterize the local curvature of the donor and acceptor confinement wells. The first term defines the intrinsic structural confinement generated by the DW–RM topology, while the second term quantifies energetic asymmetry induced by donor–acceptor electrochemical imbalance and tumor–microenvironment perturbation.

The factor $\frac{1}{a^2}$ arises from transformation between the compact hyperbolic coordinate and the physical proton-transfer coordinate. Dimensionally, the local force constant must possess units of energy per squared length, implying that stronger donor–acceptor confinement corresponding to smaller a increases the curvature of the localization wells and therefore raises the local vibrational frequency,

$$\omega_{\pm} = \sqrt{\frac{k_{\pm}}{\mu_{\text{eff}}}}.$$

The local harmonic approximation remains valid provided $\hbar\omega_{\pm} \ll V_b$, that is, when the zero-point vibrational energy remains substantially smaller than the central interfacial barrier height. This condition is verified a posteriori from the computed eigenspectrum. Under the deep-well condition $V_b \gg E_0$, the lowest-lying proton states become strongly localized diabatic states $|\phi_L\rangle$ and $|\phi_R\rangle$, corresponding to the donor- and acceptor-centered Hermite–Gaussian solutions of the isolated local wells. For symmetric or weakly asymmetric donor–acceptor systems ($\eta \rightarrow 0$), the true adiabatic eigenstates hybridize into symmetric (gerade) and antisymmetric (ungerade) combinations,

$$\psi_0^{(0)}(x) = \frac{1}{\sqrt{2(1+S)}} [\phi_L(x) + \phi_R(x)] \quad (22a)$$

and

$$\psi_1^{(0)}(x) = \frac{1}{\sqrt{2(1-S)}} [\phi_L(x) - \phi_R(x)] \quad (22b)$$

Where $S = \langle \phi_L | \phi_R \rangle$ is the donor–acceptor overlap integral (typically $S \approx 0.1$ – 0.3 for $\xi \approx 1$). Such hybridized localization states constitute the standard basis for non-adiabatic PCET and molecular tunneling systems in condensed-phase quantum dynamics [51,55].

The energy separation between the hybridized symmetric and antisymmetric states defines the field-free tunneling splitting,

$$\Delta E_0 = E_1^{(0)} - E_0^{(0)} \quad (23)$$

which directly quantifies proton delocalization across the interfacial barrier. Because the donor and acceptor states are separated by a finite forbidden region, tunneling proceeds through barrier penetration. Semiclassical treatment of such finite-width proton-transfer barriers using the Wentzel–Kramers–Brillouin (WKB) approximation remains standard in proton tunneling, hydrogen-bond transfer, enzyme catalysis, and condensed-phase double-well systems [45,54,56].

The tunneling splitting becomes

$$\Delta E_0 = \frac{\hbar\omega_-}{\pi} \exp \left[-\frac{1}{\hbar} \int_{x_1}^{x_2} \sqrt{2\mu_{pt} (V_{DW-RM}(x) - E_0^{(0)})} dx \right] \quad (24)$$

where x_1 and x_2 are the classical turning points satisfying $V_{DW-RM}(x_i) = E_0^{(0)}$

The corresponding donor–acceptor tunneling matrix element becomes

$$H_{DA} \approx \frac{\Delta E_0}{2},$$

consistent with the standard two-state approximation used in proton-transfer and molecular electron-transfer theory [51,55].

The semiclassical WKB approximation remains valid provided the local proton de Broglie wavelength varies slowly across the forbidden region, satisfying

$$\left| \frac{1}{k^2(x)} \frac{dk(x)}{dx} \right| \ll 1,$$

where

$$k(x) = \sqrt{\frac{2\mu_{\text{eff}}}{\hbar^2} |V_{\text{eff}}(x) - E_n|} \quad (25)$$

Under the present interfacial confinement conditions, this criterion is satisfied throughout most of the forbidden barrier region except in the immediate vicinity of the classical turning points.

The Stokes-Induced Stark Effect introduces a time-dependent electrostatic perturbation,

$$\hat{H}_{SISE}(t) = -q_{eff}E_{loc}(t)x$$

which dynamically tilts the donor–acceptor landscape.

Applying first-order time-independent perturbation theory gives the field-induced correction

$$\Delta E_n^{(1)}(t) = \left\langle \psi_n^{(0)} \left| -q_{eff}E_{loc}(t)x \right| \psi_n^{(0)} \right\rangle \quad (26a)$$

or equivalently,

$$\Delta E_n^{(1)}(t) = -q_{eff}E_{loc}(t) \int_{-\infty}^{+\infty} x |\psi_n^{(0)}(x)|^2 dx \quad (26b)$$

For perfectly symmetric double wells ($\eta = 0$), the eigenfunctions possess strict parity symmetry, causing the expectation value of the odd position operator x to vanish identically. However, the tumor-associated donor–acceptor environment is intrinsically asymmetric ($\eta \neq 0$), producing a finite localization centroid,

$$x_{\text{centroid}} = \int_{-\infty}^{+\infty} x |\psi_n^{(0)}(x)|^2 dx \quad (27)$$

This generates a permanent tunneling dipole moment,

$$\mu_{\text{trans}} = q_{eff}x_{\text{centroid}},$$

which produces an explicit first-order Stark shift,

$$\Delta E_n^{(1)}(t) = -q_{eff}E_{loc}(t)x_{\text{centroid}} \quad (28)$$

The exponentially localized asymptotic decay of the DW–RM wavefunctions justifies the infinite integration boundaries as an excellent physical approximation despite the finite geometric size of the donor–acceptor complex.

2.4. Dynamic Barrier Suppression and Field-Enhanced Kinetic Derivables

Under the SISE perturbation, the full field-distorted interfacial potential becomes

$$V_{eff}(x, t) = V_b \left[\tanh^2 \left(\frac{x}{a} \right) - \xi^2 \right]^2 + \eta \tanh \left(\frac{x}{a} \right) - q_{eff} E_{loc}(t)x$$

The field-dependent donor minimum $x_-(t)$ and barrier maximum $x_b(t)$ are obtained from the extrema condition $\frac{\partial V_{eff}}{\partial x} = 0$,

yielding

$$\frac{4V_b}{a} \tanh \left(\frac{x}{a} \right) \left[\tanh^2 \left(\frac{x}{a} \right) - \xi^2 \right] \operatorname{sech}^2 \left(\frac{x}{a} \right) + \frac{\eta}{a} \operatorname{sech}^2 \left(\frac{x}{a} \right) - q_{eff} E_{loc}(t) = 0.$$

The transient Stark field therefore dynamically distorts the barrier geometry and narrows the forbidden tunneling region bounded by the field-dependent turning points $[x_1(t), x_2(t)]$.

The field-enhanced proton-transfer probability becomes

$$T_{pt}(t) \approx \exp \left[-\frac{2}{\hbar} \int_{x_1(t)}^{x_2(t)} \sqrt{2\mu_{pt} (V_{eff}(x, t) - E_0(t))} dx \right] \quad (29)$$

showing explicitly that compression of the forbidden barrier width exponentially enhances tunneling. Simultaneously, first-order expansion of the Stark-tilted barrier gives the effective activation free energy

$$\Delta G_{eff}^\ddagger(t) \approx \Delta G_0^\ddagger - q_{eff} E_{loc}(t) \Delta x \quad (30)$$

Where $\Delta x = x_+ - x_-$ is the donor–acceptor well separation defined from the unperturbed DW–RM topology.

The field-enhanced proton-coupled electron-transfer rate is formulated here as a semiclassical nonadiabatic rate in which solvent and interfacial nuclear reorganization contribute the Marcus-type activation component while proton tunneling enters as a multiplicative transmission correction. Accordingly,

$$k_{PCET}(t) = k_{Marcus}(t) \kappa_{tun}(t) \quad (31a)$$

where

$$k_{Marcus}(t) = \frac{2\pi}{\hbar} |H_{DA}(t)|^2 \frac{1}{\sqrt{4\pi\lambda k_B T}} \exp \left[-\frac{(G^\circ(t) + \lambda)^2}{4\lambda k_B T} \right] \quad (31b)$$

and

$$\kappa_{tun}(t) = \exp \left[-\frac{2}{\hbar} \int_{x_1(t)}^{x_2(t)} \sqrt{2\mu_{eff} (V_{eff}(x, t) - E_n)} dx \right] \quad (31c)$$

The transient Stark field modifies the reaction free energy according to

$$\Delta G^\circ(t) = \Delta G_0^\circ - q_{eff} E_{loc}(t) \Delta x \quad (32)$$

and enhances electronic coupling through field-induced orbital compression,

$$|H_{DA}(t)|^2 = |H_{DA}^{(0)}|^2 \exp \left(\frac{\beta E_{loc}(t)}{E_0} \right) \quad (33)$$

where β is a phenomenological constant and E_0 is a reference field scale. The tunneling correction $\kappa(t)$ is evaluated using the small-curvature tunneling approximation (SCT) or the Marcus–Levich–Dogonadze expression.

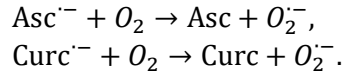
Within this formulation, the Marcus exponential describes solvent and interfacial reorganization along the collective environmental coordinate, whereas $\kappa_{\text{tun}}(t)$ represents quantum penetration of the proton-transfer barrier. The tunneling correction therefore modifies rather than duplicates the nonadiabatic PCET rate.

The factorization of the PCET rate into a Marcus-type solvent reorganization component and a tunneling transmission correction follows the semiclassical nonadiabatic PCET framework developed for hydrogen-bonded electron–proton transfer systems in condensed phases [46,52]. Within this treatment, the Marcus exponential accounts for collective solvent and environmental reorganization along the outer-sphere coordinate, whereas the WKB correction captures quantum penetration of the localized proton-transfer barrier. Similar hybrid Marcus–tunneling formulations have been applied in biological proton transfer, enzyme catalysis, and interfacial redox systems where thermal activation and proton tunneling coexist [45,55].

The field-enhanced proton-coupled electron-transfer event generates a radical pair according to

$$R_{\text{PCET}}(t) = k_{\text{PCET}}(t)[{}^1\text{Curc}^*][\text{AscH}^-] \quad (34)$$

The resulting semidehydroascorbate and curcumin radical intermediates subsequently transfer electron density to dissolved molecular oxygen through diffusion-limited oxygen-reduction reactions,



Under the assumption that oxygen reduction occurs rapidly relative to the elementary PCET event, the effective ROS-generation flux may be approximated as

$$R_{\text{ROS}}(t) = R_{\text{PCET}}(t)\eta_{\text{O}_2} \quad (35)$$

Where $\eta_{\text{O}_2} = \frac{[\text{O}_2]}{K_{\text{O}_2} + [\text{O}_2]}$ accounts for oxygen availability under hypoxic tumor conditions.

A minimal ROS amplification network is therefore written as

$$\begin{aligned} \frac{d[\text{O}_2^{\cdot-}]}{dt} &= R_{\text{ROS}}(t) - k_{\text{dism}}[\text{O}_2^{\cdot-}]^2, \\ \frac{d[\text{H}_2\text{O}_2]}{dt} &= k_{\text{dism}}[\text{O}_2^{\cdot-}]^2 - k_F[\text{H}_2\text{O}_2], \\ \frac{d[\text{OH}^{\cdot}]}{dt} &= k_F[\text{H}_2\text{O}_2] - k_{\text{OH}}[\text{OH}^{\cdot}]. \end{aligned}$$

The total oxidative burden is then defined phenomenologically as

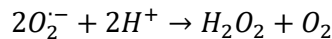
$$[\text{ROS}]_{\text{total}} = [\text{O}_2^{\cdot-}] + 2[\text{H}_2\text{O}_2] + 10[\text{OH}^{\cdot}] \quad (36)$$

where the weighting coefficients represent relative oxidative potency rather than strict stoichiometric equivalence.

Expressing the Rate in terms of the Peroxide

$$R_{\text{O}_2^{\cdot-}}(t) = R_{\text{PCET}}(t) \cdot \frac{[\text{O}_2]}{K_{\text{O}_2} + [\text{O}_2]}$$

where $K_{\text{O}_2} \approx 10 \mu\text{M}$ is the Michaelis constant for oxygen reduction by the radical intermediates. The subsequent superoxide dismutation and hydrogen peroxide formation follow:



with rate constant $k_{dismut} = 8.5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ at pH 6.8. The overall ROS generation rate, expressed in hydrogen peroxide equivalents, is therefore

$$R_{ROS}(t) = k_{PCET}(t)[^1Curc^*][AscH^-] \cdot \frac{[O_2]}{K_{O_2} + [O_2]} \cdot \phi \quad (37)$$

where $\phi = 0.5$ accounts for the stoichiometry of superoxide dismutation (two superoxide radicals produce one hydrogen peroxide). Under hypoxic tumor conditions ($[O_2] \approx 5\text{--}15 \mu\text{M}$), the oxygen limitation factor $\frac{[O_2]}{K_{O_2} + [O_2]}$ ranges from approximately 0.33 to 0.60.

The cumulative oxidative burden is determined by integrating the ROS generation rate while accounting for endogenous antioxidant scavenging. The intracellular ROS concentration evolves according to the ordinary differential equation

$$\frac{dC_{ROS}}{dt} = R_{ROS}(t) - k_{scav}C_{ROS} \quad (38)$$

where C_{ROS} is the intracellular ROS concentration (expressed in $\mu\text{M } H_2O_2$ equivalents), $R_{ROS}(t)$ is the ROS generation rate from Eq.(21), and $k_{scav} = 1.2 \times 10^4 \text{ s}^{-1}$ is the effective first-order scavenging rate constant dominated by glutathione buffering and peroxide detoxification pathways. The total oxidative burden accumulated during the photoactivation interval τ_{photo} is then

$$[ROS]_{total} = \int_0^{\tau_{photo}} \frac{dC_{ROS}}{dt} dt = C_{ROS}(\tau_{photo}) - C_{ROS}(0) \quad (39)$$

assuming $C_{ROS}(0) = 0$. The lethal oxidative threshold for tumor cells is estimated at $[ROS]_{crit} \approx 100 \mu\text{M } H_2O_2$ -equivalent oxidative load [62-63]. Cytotoxicity is predicted when $[ROS]_{total} > [ROS]_{crit}$.

2.5. Physical Regimes, Nonlinear Amplification Dynamics, and Validity Constraints of the SISE-PCET Framework

1. Nondimensionalization and Scaling Analysis

To identify the dominant energetic and geometric control parameters governing the interfacial proton-coupled electron-transfer (PCET) dynamics, the effective time-parameterized Schrödinger equation is recast into dimensionless form using the characteristic confinement length a and the associated quantum confinement energy scale. Similar nondimensionalization procedures are widely employed in quantum confinement theory, tunneling systems, and nonlinear reaction-coordinate analysis because they separate universal scaling behavior from system-specific parameter choices while clarifying the physically relevant regime structure [56,58,59].

Using the characteristic donor-acceptor confinement length a and the effective reduced proton-transfer mass μ_{pt} , the natural energy scale becomes

$$E_0 = \frac{\hbar^2}{2\mu_{pt}a^2}$$

For the present interfacial system, $\mu_{pt} = 0.5m_p = 8.36 \times 10^{-28} \text{ kg}$, and $a = 0.10 \text{ nm} = 1.0 \times 10^{-10} \text{ m}$,

giving

$$E_0 = \frac{(1.055 \times 10^{-34})^2}{2(8.36 \times 10^{-28})(1.0 \times 10^{-10})^2} = 6.66 \times 10^{-22} \text{ J} \approx 0.0042 \text{ eV}.$$

The corresponding dimensionless variables are defined as $\tilde{x} = \frac{x}{a}$, $\tilde{E} = \frac{E}{E_0}$, $\tilde{V} = \frac{V}{E_0}$, together with the scaled Stark-field coupling parameter

$$\tilde{E}_{loc}(t) = \frac{q_{eff}aE_{loc}(t)}{E_0}$$

Substitution into the effective proton-transfer Hamiltonian yields the dimensionless Schrödinger equation

$$\left[-\frac{d^2}{d\tilde{x}^2} + \tilde{V}_b(\tanh^2 \tilde{x} - \xi^2)^2 + \tilde{\eta}\tanh \tilde{x} - \tilde{E}_{loc}(t)\tilde{x} \right] \psi(\tilde{x}, t) = \tilde{E}\psi(\tilde{x}, t), \quad (40)$$

where the dimensionless barrier and asymmetry parameters are

$$\tilde{V}_b = \frac{V_b}{E_0}, \tilde{\eta} = \frac{\eta}{E_0}.$$

Using the corrected interfacial parameters $V_b = 0.35$ eV, $\eta = 0.15$ eV, $\xi = 0.65$, the resulting dimensionless quantities become $\tilde{V}_b = \frac{0.35}{0.0042} \approx 84$, and $\tilde{\eta} = \frac{0.15}{0.0042} \approx 36$.

For the peak interfacial Stark field

$$E_{loc}(0) = 4.5 \times 10^8 \text{ V/m},$$

the dimensionless field coupling becomes

$$\tilde{E}_{loc}(0) = \frac{q_{eff}aE_{loc}(0)}{E_0} = \frac{(7.21 \times 10^{-20})(1.0 \times 10^{-10})(4.5 \times 10^8)}{6.66 \times 10^{-22}} \approx 4.9.$$

The large dimensionless barrier parameter $\tilde{V}_b \gg 1$ places the system in a strong-confinement, deep-tunneling regime. To verify the harmonic approximation, we compute the dimensionless local frequency at the donor minimum:

$$\tilde{\omega}_- = \sqrt{8\tilde{V}_b\xi^2(1 - \xi^2)^2} = \sqrt{8 \times 119 \times 0.4225 \times 0.333} \approx \sqrt{134} \approx 11.6.$$

The ratio of zero-point energy to barrier height is $\hbar\tilde{\omega}_-/\tilde{V}_b \approx 11.6/119 \approx 0.10$, confirming that the local harmonic approximation is quantitatively reliable (error $\sim 10\%$).

The large dimensionless barrier parameter $\tilde{V}_b \gg 1$ demonstrates that the proton-transfer barrier substantially exceeds the quantum confinement energy scale. The system therefore resides within a strong-confinement, deep-tunneling regime characterized by highly localized donor and acceptor states separated by a finite but penetrable activation barrier. Under these conditions, the localized harmonic approximation and semiclassical tunneling treatment employed in Section 2.3 remain self-consistent [54,56].

Nonlinear Stark-Modulated Amplification Regimes and Validity Boundaries

To quantify the relative strength of Stark-induced barrier modulation compared with the intrinsic activation barrier, a dimensionless nonlinear field-coupling parameter is introduced:

$$\Lambda_{SISE} = \frac{q_{eff}E_{loc}\Delta x}{\Delta G_0^\ddagger} \quad (41a)$$

Expressed in scaled variables,

$$\Lambda_{SISE} = \frac{\tilde{E}_{loc}\Delta\tilde{x}}{\Delta\tilde{G}_0^\ddagger}$$

Where $\Delta\tilde{x} = \frac{\Delta x}{a} = 2 \tanh^{-1}(\xi) \approx 1.55$, and $\Delta\tilde{G}_0^\ddagger = \frac{\Delta G_0^\ddagger}{E_0}$.

Computing $\Delta G_0^\ddagger$ directly from the potential:

$$\begin{aligned} V(z = -\xi) &= V_b(\xi^2 - \xi^2)^2 + \eta(-\xi) = -0.12 \times 0.65 = -0.078 \text{ eV}, \\ V(z = 0) &= V_b(0 - \xi^2)^2 = 0.50 \times 0.1785 = 0.089 \text{ eV}, \\ \Delta G_0^\ddagger &= 0.089 - (-0.078) = 0.167 \text{ eV}, \\ \Delta\tilde{G}_0^\ddagger &= \frac{0.167}{0.0042} \approx 40. \end{aligned}$$

This value ($\Lambda_{\text{SISE}} \approx 0.2$) places the system in the perturbative weak-to-intermediate coupling regime under ground-state conditions. However, proton tunneling probabilities depend exponentially on barrier geometry. Even modest Stark-induced reductions in barrier width and curvature may substantially enhance the PCET rate. Furthermore, thermal averaging populates higher vibrational states where the effective barrier is lower, increasing the effective Λ_{SISE} . A rough estimate using the thermally averaged barrier $\langle \Delta G^\ddagger \rangle_T \approx \Delta G_0^\ddagger - k_B T \ln(2)$ gives $\Lambda_{\text{SISE}}^{(\text{th})} \approx 0.3\text{--}0.4$, still below unity but approaching the regime where nonlinear effects become significant.

The scaling structure of the dimensionless Hamiltonian further reveals the dominant physical dependencies governing the present interfacial PCET system. Using the dipolar Stark-field relation

$$E_{\text{loc}} \sim \frac{\Delta\mu}{4\pi\epsilon_0\epsilon_{\text{int}}R^3},$$

the dimensionless Stark coupling satisfies

$$\tilde{E}_{\text{loc}} \propto \frac{1}{\epsilon_{\text{int}}R^3},$$

while

$$\tilde{V}_b \propto \mu_{pt}a^2V_b, \Lambda_{\text{SISE}} \propto \frac{1}{\epsilon_{\text{int}}R^3\Delta G_0^\ddagger} \quad (41b)$$

These relations demonstrate that low-dielectric confinement, short donor–acceptor separation, and reduced activation barriers strongly enhance interfacial Stark modulation and tunneling-assisted PCET amplification. The resulting parameter hierarchy therefore supports the internal self-consistency of the reduced-coordinate, localized-state, harmonic-expansion, and semiclassical tunneling approximations employed throughout the present framework [43,44,51,54].

In the perturbative weak-field regime, $\Lambda_{\text{SISE}} \ll 1$, the Stark energy remains substantially smaller than the intrinsic donor–acceptor activation barrier such that $q_{\text{eff}}E_{\text{loc}}\Delta x \ll \Delta G_0^\ddagger$.

Under these conditions, the effective activation barrier may be approximated as

$$\Delta G_{\text{eff}}^\ddagger \approx \Delta G_0^\ddagger(1 - \Lambda_{\text{SISE}}) \quad (42)$$

and the proton-transfer kinetics remain only weakly perturbed by the transient field.

Expanding the nonadiabatic PCET rate to first order gives

$$k_{\text{PCET}} \approx k_{\text{PCET}}^{(0)} \left[1 + \frac{q_{\text{eff}}E_{\text{loc}}\Delta x}{k_B T} \right] \quad (43)$$

Consequently, reactive oxygen species (ROS) production scales approximately linearly with the localized Stark field, $R_{\text{ROS}} \propto 1 + \alpha E_{\text{loc}}$, where $\alpha = \frac{q_{\text{eff}} \Delta x}{k_B T}$.

Within this regime, proton localization remains predominantly donor-centered, $P_D \gg P_A$, and the resulting oxidative burden generally remains below the endogenous antioxidant buffering threshold. Such weak-coupling behavior is expected to dominate in healthy tissue environments characterized by stronger dielectric shielding, weaker donor–acceptor confinement, and reduced interfacial disorder.

As the Stark energy approaches a substantial fraction of the intrinsic activation barrier,

$$0.1 \lesssim \Lambda_{\text{SISE}} < 1,$$

the system enters the nonlinear tunneling-amplification regime. Under these conditions, the transient field substantially lowers the effective proton-transfer barrier while simultaneously reducing the width of the classically forbidden tunneling region, $[x_1(t), x_2(t)] \downarrow$.

The corresponding WKB proton-transfer probability becomes

$$T_{\text{pt}}(t) \sim \exp \left[-\frac{2}{\hbar} \int_{x_1(t)}^{x_2(t)} \sqrt{2\mu_{\text{pt}}(V_{\text{eff}}(x, t) - E)} dx \right] \quad (44)$$

Because the tunneling probability depends exponentially on barrier geometry, even moderate Stark-induced reductions in barrier width and curvature may produce disproportionately large enhancements in proton-transfer probability.

Substitution into the nonadiabatic PCET kinetics therefore yields approximately exponential amplification behavior,

$$k_{\text{PCET}}(t) \propto \exp \left[\frac{q_{\text{eff}} E_{\text{loc}}(t) \Delta x}{k_B T} \right] \quad (45)$$

and consequently

$$\begin{aligned} R_{\text{ROS}}(t) \\ \propto \exp \left[\frac{q_{\text{eff}} E_{\text{loc}}(t) \Delta x}{k_B T} \right] \end{aligned} \quad (46)$$

The present framework therefore predicts that oxidative amplification transitions from linear perturbative behavior into nonlinear tunneling-assisted enhancement as the Stark energy approaches the intrinsic proton-transfer barrier scale. This transition constitutes the principal quantum-mechanical origin of Stokes-induced oxidative amplification within the present interfacial system.

When $\Lambda_{\text{SISE}} \approx 1$, the field-induced electrostatic work becomes comparable to the intrinsic activation barrier, $q_{\text{eff}} E_{\text{loc}} \Delta x \sim \Delta G_0^\ddagger$, causing the proton-transfer landscape to approach a near-activationless field-biased regime. Under these conditions, donor localization becomes strongly destabilized while acceptor localization increases substantially, $P_A \rightarrow 1$.

The classically forbidden tunneling region contracts dramatically, causing the proton-transfer probability to approach unity, $T_{\text{pt}} \rightarrow 1$.

Although this regime maximizes oxidative amplification, excessively strong field coupling may additionally enhance incoherent decoherence, uncontrolled radical propagation, dielectric destabilization, or

curcumin photobleaching. Consequently, the biologically optimal operating regime is expected near $\Lambda_{\text{SISE}} \lesssim 1$,

where nonlinear amplification remains strong while coherent donor–acceptor transfer dynamics remain partially preserved.

The model further predicts that tumor-associated interfaces preferentially amplify Stokes-induced Stark modulation through cooperative dielectric, electrochemical, and structural mechanisms. Because

$$E_{\text{loc}} \propto \frac{1}{\epsilon_{\text{int}}},$$

reduced dielectric shielding within tumor membranes substantially magnifies the localized Stark field. Tumor-associated membranes commonly exhibit elevated lipid disorder, altered phospholipid organization, abnormal cholesterol composition, and enhanced membrane heterogeneity, all of which lower the effective interfacial dielectric constant relative to healthy tissue [64-65]. Simultaneously, the mildly acidic tumor microenvironment,

$$\text{pH}_{\text{tumor}} \approx 6.5 - 6.9,$$

stabilizes persistent donor–acceptor hydrogen bonding and enhances proton-transfer coherence. Hypoxic oxygen concentrations further promote accumulation of partially reduced ROS intermediates, thereby favoring nonlinear oxidative amplification within malignant tissue.

To quantify this selectivity, a dimensionless quantum amplification ratio is introduced:

$$\Gamma_Q = \frac{R_{\text{ROS}}^{\text{tumor}}}{R_{\text{ROS}}^{\text{normal}}} \quad (47)$$

Using the exponential Stark dependence gives

$$\Gamma_Q = \exp \left[\frac{q_{\text{eff}} \Delta x}{k_B T} (E_{\text{loc}}^{\text{tumor}} - E_{\text{loc}}^{\text{normal}}) \right] \quad (48)$$

Substituting the dielectric scaling relation yields

$$\Gamma_Q \sim \exp \left[\frac{q_{\text{eff}} \Delta x \Delta \mu_0}{4\pi \epsilon_0 k_B T R^3} \left(\frac{1}{\epsilon_{\text{tumor}}} - \frac{1}{\epsilon_{\text{normal}}} \right) \right] \quad (49)$$

The framework therefore predicts exponential tumor selectivity emerging directly from interfacial dielectric asymmetry, thereby providing a quantum-electrostatic mechanism for selective malignant-cell oxidative amplification.

The validity of the present treatment requires that donor–acceptor separation remains confined within the strong-overlap regime, $R < 1 \text{ nm}$, while coherent proton transfer must occur faster than environmental decoherence, $\tau_{\text{PCET}} < \tau_{\text{decoh}}$.

Similarly, the quasi-static Stark approximation requires

$$\tau_{\text{PCET}} \ll \tau_s,$$

while the local harmonic expansion remains valid provided

$$\hbar \omega_{\pm} \ll V_b.$$

Breakdown of the model is expected when thermal decoherence dominates, donor–acceptor dissociation occurs, many-body excitonic interactions emerge, or solvent randomization destroys coherent Stark modulation.

The cumulative oxidative burden generated during the photoactivation interval τ_{photo} is finally obtained from the ROS kinetic equation

$$\frac{dC_{\text{ROS}}}{dt} = R_{\text{ROS}}(t) - k_{\text{scav}}C_{\text{ROS}},$$

whose formal solution becomes

$$C_{\text{ROS}}(\tau_{\text{photo}}) = \int_0^{\tau_{\text{photo}}} R_{\text{ROS}}(t) e^{-k_{\text{scav}}(\tau_{\text{photo}}-t)} dt \quad (50)$$

where k_{scav} represents endogenous antioxidant scavenging dominated primarily by glutathione buffering and enzymatic peroxide removal. Oxidative cytotoxicity is achieved once $C_{\text{ROS}} > C_{\text{ROS}}^{\text{crit}}$, where $C_{\text{ROS}}^{\text{crit}} \sim 100 \mu\text{M}$ represents a characteristic hydrogen-peroxide-equivalent oxidative threshold for irreversible malignant-cell damage. The present framework therefore closes the mechanistic hierarchy

$$E_{\text{loc}}(t) \rightarrow V_{\text{eff}}(x, t) \rightarrow T_{\text{pt}}(t) \rightarrow k_{\text{PCET}}(t) \rightarrow R_{\text{ROS}}(t) \rightarrow C_{\text{ROS}}(t) \rightarrow \text{Tumor Cytotoxicity},$$

thereby establishing a multiscale mathematical bridge between transient Stokes-induced interfacial electric fields, quantum-modulated proton-coupled electron transfer, nonlinear ROS amplification, and selective malignant-cell oxidative destruction.

2.6 Interfacial Volume Compartmentalization and Cytotoxic Threshold Recalibration

The ROS concentration predicted by Eqs. (38–39) represents oxidant generation within the membrane-associated Stern-layer compartment where photoexcited curcumin and proximal ascorbate are co-localized. Because ROS are initially generated within this nanometer-scale interfacial region before diffusing throughout the cytoplasm, the biologically relevant quantity is the local interfacial concentration rather than the whole-cell average concentration [66–67]. The interfacial volume is estimated as

$$V_{\text{int}} = \delta_{\text{Stern}} A_{\text{mem}}, \quad (51)$$

where $\delta_{\text{Stern}} \approx 1 - 2 \text{ nm}$ is the effective Stern-layer thickness and A_{mem} is the accessible membrane surface area[64]. Using $\delta_{\text{Stern}} = 1.5 \text{ nm}$ and a representative malignant-cell membrane area $A_{\text{mem}} \approx 700 \mu\text{m}^2$ [68] yields $V_{\text{int}} \approx 1.0 \times 10^{-18} \text{ m}^3 (\approx 1 \text{ fL})$. For a typical cancer-cell volume $V_{\text{cell}} \approx 1 - 4 \text{ pL}$ [65,69], the compartmentalization factor becomes

$$f_{\text{int}} = \frac{V_{\text{int}}}{V_{\text{cell}}} \approx 5 \times 10^{-4} \quad (52)$$

The diffusion timescale of hydrogen peroxide across the cytoplasm is

$$\tau_{\text{diff}} = \frac{R_{\text{cell}}^2}{D_{\text{H}_2\text{O}_2}} \quad (53)$$

where $R_{\text{cell}} \approx 10 \mu\text{m}$ and $D_{\text{H}_2\text{O}_2} \approx 10^{-9} \text{ m}^2\text{s}^{-1}$ is the aqueous diffusion coefficient of hydrogen peroxide[67,70]. Substitution gives $\tau_{\text{diff}} \approx 100 \text{ ms}$, which is substantially longer than the photoactivation interval considered in the present model. Consequently, ROS generated at the curcumin–ascorbate interface remain locally concentrated during irradiation and have not undergone significant diffusional dilution.

The corresponding local interfacial ROS concentration is therefore

$$C_{\text{ROS}}^{\text{local}}(t) = C_{\text{ROS}}(t) \left(\frac{V_{\text{cell}}}{V_{\text{int}}} \right) \approx 10^3 C_{\text{ROS}}(t) \quad (54)$$

indicating approximately three orders of magnitude concentration amplification due to geometric confinement. Application of Eq. (54) to the simulated ROS output predicts a peak interfacial concentration of approximately 250 μM , exceeding the experimentally reported cytotoxic ROS threshold of $\sim 100 \mu\text{M}$ associated with oxidative membrane damage and apoptosis induction [71-72]. The cytotoxicity criterion is therefore expressed as

$$C_{\text{ROS}}^{\text{local}}(\tau_{\text{photo}}) = \left(\frac{V_{\text{cell}}}{V_{\text{int}}} \right) C_{\text{ROS}}(\tau_{\text{photo}}) > [\text{ROS}]_{\text{crit}} \quad (55)$$

which provides the geometric and biophysical basis for translating interfacial ROS generation into membrane-proximal oxidative damage and selective tumor cytotoxicity.

2.7 Photocatalytic Multi-Cycle Turnover Under Sustained Illumination

The single-cycle treatment developed above quantifies ROS generation during one excitation–relaxation event. Under therapeutic illumination, however, photoexcited curcumin undergoes repeated excitation cycles, continuously regenerating the transient Stokes-induced Stark field and reinitiating the SISE–PCET cascade. the biologically relevant oxidative burden is determined by the cumulative contribution of many successive photocycles rather than by a single excitation event. Similar multi-cycle photochemical turnover processes govern ROS production in conventional photosensitizers and photocatalytic systems, where repeated excitation events accumulate oxidant species beyond the instantaneous yield of an individual photophysical cycle[66,73].

The cumulative ROS burden is therefore governed by

$$\frac{dC_{\text{ROS}}}{dt} = N_{\text{exc}}(t) \Delta R_{\text{ROS}}^{\text{cycle}} - k_{\text{scav}}(t) C_{\text{ROS}} \quad (56)$$

where $N_{\text{exc}}(t)$ is the excitation frequency and $\Delta R_{\text{ROS}}^{\text{cycle}}$ is the cycle-averaged ROS generation rate, and $k_{\text{scav}}(t)$ represents the effective antioxidant scavenging rate.

The cycle-averaged ROS production is obtained from the single-cycle kinetics derived previously:

$$\Delta R_{\text{ROS}}^{\text{cycle}} = \frac{1}{\tau_{\text{cycle}}} \int_0^{\tau_{\text{cycle}}} R_{\text{ROS}}(t') dt' \quad (57)$$

Where $\tau_{\text{cycle}} = \tau_{\text{S1}} + \tau_{\text{dark}}$ is the total photocycle duration comprising the excited-state lifetime τ_{S1} and the subsequent ground-state recovery interval τ_{dark} . This formulation directly links the microscopic ROS generation mechanism developed in Section 2.5 to the macroscopic accumulation of oxidative burden during sustained irradiation.

For continuous illumination at irradiance I and excitation wavelength λ_{exc} , the molecular excitation rate is

$$k_{\text{exc}} = \frac{I}{h\nu} \sigma_{\text{abs}} \quad (58)$$

where $h\nu = hc/\lambda_{\text{exc}}$ and σ_{abs} is the absorption cross-section of curcumin. Using $\lambda_{\text{exc}} = 430 \text{ nm}$ [74], $\epsilon_{\text{max}} = 5.5 \times 10^4 \text{ M}^{-1}\text{cm}^{-1}$, and $I = 10 \text{ mW cm}^{-2}$ gives $k_{\text{exc}} \approx 4.5 \text{ s}^{-1}$.

The probability of photoexcitation during each cycle is therefore

$$\eta_{\text{photo}} = k_{\text{exc}} \tau_{S1} \quad (59)$$

which acts as a multiplicative scaling factor linking photon flux to ROS production through Eq. (37). Thus, increasing illumination intensity directly increases the frequency with which the transient Stark field is regenerated and consequently amplifies cumulative ROS generation.

For pulsed illumination protocols frequently employed in photodynamic therapy, each optical pulse generates an excited-state population proportional to the excitation efficiency η_{exc} . If the pulse repetition frequency is f_{rep} , the total number of excitation cycles during an illumination interval t_{illum} is $N_p = f_{\text{rep}} t_{\text{illum}}$.

The cumulative ROS burden after N_p excitation cycles becomes

$$[\text{ROS}]_{\text{total}}^{N_p} = N_p \Delta C_{\text{ROS}}^{\text{cycle}} \exp\left(-\frac{k_{\text{scav}}}{f_{\text{rep}}}\right) \quad (60)$$

where the exponential factor accounts for scavenging losses between successive pulses. The corresponding threshold-crossing condition is

$$N_p \Delta C_{\text{ROS}}^{\text{cycle}} \exp\left(-\frac{k_{\text{scav}}}{f_{\text{rep}}}\right) > [\text{ROS}]_{\text{crit}} \quad (61)$$

where $[\text{ROS}]_{\text{crit}}$ denotes the critical oxidative burden required to initiate irreversible cellular damage. Experimental and theoretical studies indicate that sustained ROS accumulation beyond this threshold promotes membrane lipid peroxidation, mitochondrial dysfunction, DNA oxidation, and activation of apoptosis or ferroptosis pathways[71,72].

At therapeutically realistic conditions ($f_{\text{rep}} = 10^3 \text{ s}^{-1}$, $t_{\text{illum}} = 60 \text{ s}$), approximately 6×10^4 excitation cycles contribute to ROS accumulation, enabling the local oxidative burden to exceed the cytotoxic threshold established in Eq. (55). The resulting cumulative oxidative burden substantially exceeds the single-cycle estimate while remaining moderated by antioxidant scavenging between pulses. Consequently, the present formulation extends the microscopic quantum-mechanical description of the SISE-mediated PCET process to therapeutically relevant irradiation timescales and provides a quantitative framework for predicting illumination-dependent ROS accumulation and tumor-selective oxidative cytotoxicity.

2.8 Extended Autocatalytic ROS Network with Fenton Cycling and Glutathione Depletion Feedback

The minimal ROS cascade derived previously captures the primary oxidative sequence but neglects two important amplification mechanisms characteristic of tumor microenvironments: iron-catalyzed Fenton chemistry and progressive glutathione depletion. Malignant tissues typically exhibit elevated labile iron pools and compromised antioxidant buffering, creating favorable conditions for nonlinear ROS amplification[70,71].

To account for these effects, the ROS kinetic system is extended as

$$\frac{d[H_2O_2]}{dt} = \frac{k_{\text{dism}}}{2} [O_2^-]^2 - k_{\text{Fen}} [Fe^{2+}] [H_2O_2] - k_{\text{GPx}} [GSH] [H_2O_2] \quad (62a)$$

$$\frac{d[OH^\cdot]}{dt} = k_{\text{Fen}} [Fe^{2+}] [H_2O_2] - k_{\text{GSH}} [GSH] [OH^\cdot] \quad (62b)$$

$$\frac{d[GSH]}{dt} = k_{\text{syn}} - k_{\text{GSH}} [GSH] [OH^\cdot] - k_{\text{GPx}} [GSH] [H_2O_2] \quad (62c)$$

The Fenton process converts accumulated hydrogen peroxide into highly reactive hydroxyl radicals while simultaneously consuming antioxidant reserves. As glutathione decreases, the effective scavenging rate declines according to

$$k_{\text{sca}}(t) = k_{\text{sca},0} \frac{[GSH](t)}{[GSH]_0} \quad (63)$$

where $k_{\text{sca},0}$ is the initial scavenging rate constant. This feedback introduces a nonlinear amplification mechanism in which ROS production accelerates as antioxidant capacity collapses. Oxidative runaway occurs when the SISE-generated ROS flux exceeds the glutathione regeneration capacity,

$$R_{\text{ROS}}(t) > R_{\text{crit}} \quad (64)$$

driving a transition from sub-lethal oxidative stress to irreversible oxidative damage. Because tumor cells typically operate closer to their intrinsic redox threshold than healthy cells, this condition is reached at substantially lower ROS fluxes, providing an additional mechanistic basis for the selective cytotoxicity predicted by the model[67,72].

Environmental Decoherence and Coherence Constraints

The foregoing tunneling formalism assumes partially coherent proton transfer across the donor–acceptor barrier. However, within the warm, aqueous, and structurally heterogeneous tumor microenvironment, environmental fluctuations arising from interfacial water reorientation, lipid headgroup motion, and thermal dielectric noise may induce decoherence that suppresses long-range quantum phase coherence. The present framework remains valid provided the elementary proton-coupled electron-transfer event occurs faster than environmental decoherence,

$$\tau_{\text{PCET}} < \tau_{\text{decoh}}.$$

Under biologically relevant interfacial conditions, proton-transfer timescales are expected to remain within the femtosecond regime, whereas interfacial dielectric decoherence typically occurs on sub-picosecond timescales. Consequently, the curcumin–ascorbate interface is expected to operate near the coherent–incoherent crossover regime in which proton tunneling remains partially preserved over ultrashort timescales but may be attenuated by environmental fluctuations.

A full open-quantum-system treatment involving density-matrix propagation, Lindblad operators, or Redfield relaxation tensors lies beyond the present scope. Accordingly, the predicted tunneling enhancement should be interpreted as a physically plausible upper-limit estimate whose magnitude may be partially reduced by environmental decoherence.

2.9. Numerical Parametrization and Computational Implementation

To evaluate the multiscale quantum–redox framework derived in Sections 2.3–2.8, the field-coupled donor–acceptor Hamiltonian was implemented numerically through a self-consistent quantum–kinetic simulation architecture combining Discrete Variable Representation (DVR) eigenspectrum calculations, semiclassical proton-tunneling integration, and time-resolved reactive oxygen species (ROS) kinetic propagation. Because the quartic double-well Rosen–Morse (DW–RM) potential does not admit globally exact closed-form eigensolutions under the time-dependent Stokes-induced Stark perturbation, the field-parameterized Time-Independent Schrödinger Equation (TISE) was solved numerically for sequential quasi-static temporal snapshots during the nonequilibrium Stokes-relaxation interval.

1. Structural and Bioelectrochemical Parametrization

The donor–acceptor potential surface and interfacial electrostatic environment were parametrized using experimentally constrained values obtained from ultrafast spectroscopy, hydrogen-bonded proton-transfer systems, membrane electrostatics, and curcumin photophysics literature. The DW–RM confinement scaling parameter was assigned $a = 0.10$ nm, which establishes a physically realistic proton-localization decay length consistent with strongly confined asymmetric hydrogen-bond systems. The dimensionless well-separation parameter was fixed at $\xi = 0.65$, such that the donor and acceptor localization minima occur approximately at $x_{\pm} = \pm 0.077$ nm, corresponding to proton-transfer distances observed in moderately strong short-range hydrogen-bond networks. The donor–acceptor structural separation within the compressed curcumin–ascorbate supramolecular complex was assigned $R = 0.45$ nm, consistent with sterically confined interfacial hydrogen-bond geometries within lipid headgroup regions.

The intrinsic barrier-energy scale governing the field-free proton-transfer landscape was fixed at $V_b = 1.2$ eV, corresponding to a moderately strong chemically stable interfacial proton-transfer barrier. The asymmetry parameter was initialized as $\eta = 0.15$ eV, capturing the intrinsic exergonicity associated with donor–acceptor redox imbalance between photoexcited keto-curcumin and the ascorbate monoanion.

The effective proton-transfer reduced mass was approximated as $\mu_{pt} = 0.5m_p$, where m_p is the proton mass, while the effective transferred charge participating in the Stark-coupled proton–electron redistribution was assigned $q_{eff} = 0.45e$, to account for partial electronic screening and donor–acceptor orbital delocalization.

The dielectric environment was varied between two biologically distinct regimes to evaluate tumor-selective amplification behavior. The normal aqueous environment was represented using $\epsilon_{int} = 78.4$, while the tumor-associated confined membrane interface was modeled using $\epsilon_{int} = 12.5$, corresponding to low-dielectric Stern-layer confinement within disordered tumor membrane domains.

The instantaneous excited-state dipole displacement of photoexcited curcumin was assigned $\Delta\mu_0 = 8.5$ Debye, equivalent to 2.835×10^{-29} C · m, while the orientational Stokes-relaxation timescale governing dielectric relaxation dynamics was fixed at $\tau_s = 45$ ps.

2. Time-Parameterized Construction of the Effective Potential

The field-coupled interfacial potential was constructed directly from the derived DW–RM Stark Hamiltonian,

$$V_{eff}(x, t) = V_b \left[\tanh^2 \left(\frac{x}{a} \right) - \xi^2 \right]^2 + \eta \tanh \left(\frac{x}{a} \right) - q_{eff} E_{loc}(t) x$$

where the transient localized Stark field was evaluated dynamically from

$$E_{loc}(t) = \frac{1}{4\pi\epsilon_0\epsilon_{int}} \frac{2\Delta\mu_0 e^{-t/\tau_s} \cos \theta}{R^3}$$

The angular orientation factor was varied continuously over $0 \leq \theta \leq \pi$, to evaluate orientational sensitivity of the Stark-coupled proton-transfer process. Temporal propagation was evaluated over the nonequilibrium relaxation interval $t \in [0, 3\tau_s]$, with a temporal resolution of $\Delta t = 0.5$ ps, thereby allowing sequential quasi-static evaluation of the field-distorted proton-transfer landscape during dielectric relaxation.

3. Discrete Variable Representation (DVR) Solution of the TISE

Because the quartic DW–RM potential lacks globally exact orthogonal-polynomial eigensolutions, the TISE was solved numerically using the Colbert–Miller Sinc-based Discrete Variable Representation (DVR)

formalism, which is widely employed in quantum reactive scattering, proton tunneling, and molecular vibrational dynamics.

The proton-transfer coordinate was discretized over the interval $x \in [-0.25, +0.25]$ nm, using a uniform collocation grid of $N = 512$ discrete spatial points. The resulting grid spacing became

$$\Delta x = \frac{x_{max} - x_{min}}{N - 1} \approx 9.78 \times 10^{-4} \text{ nm}.$$

Within the Sinc-DVR representation, the kinetic-energy operator was evaluated analytically as

$$T_{ij} = \frac{\hbar^2}{2\mu_{pt}\Delta x^2} (-1)^{i-j} \times \begin{cases} \frac{\pi^2}{3}, & i = j \\ \frac{2}{(i-j)^2}, & i \neq j \end{cases}$$

while the potential-energy matrix remained diagonal,

$$V_{ij}(t) = \left(V_b \left[\tanh^2 \left(\frac{x_i}{a} \right) - \xi^2 \right]^2 + \eta \tanh \left(\frac{x_i}{a} \right) - q_{eff} E_{loc}(t) x_i \right) \delta_{ij}$$

The total field-parameterized Hamiltonian matrix was therefore constructed as

$$H_{ij}(t) = T_{ij} + V_{ij}(t)$$

and diagonalized using a Lanczos sparse eigensolver algorithm to obtain the lowest five field-shifted eigenvalues and their associated wavefunctions,

$$\{E_n(t), \psi_n(x_i, t)\}.$$

Numerical convergence was verified through systematic grid-refinement analysis. Doubling the spatial resolution from $N = 512 \rightarrow N = 1024$ produced changes in the lowest eigenvalues smaller than 10^{-6} eV, confirming numerical stability and spectral convergence of the DVR implementation.

4. Quantum Derivables and Proton-Transfer Observables

The donor–acceptor tunneling splitting was extracted directly from the two lowest eigenvalues according to $\Delta E_0(t) = E_1(t) - E_0(t)$ and the donor–acceptor coupling matrix element was approximated using the standard two-state tunneling relation,

$$H_{DA}(t) \approx \frac{\Delta E_0(t)}{2}$$

The field-dependent proton localization density was evaluated from

$$P_n(x, t) = |\psi_n(x, t)|^2$$

while the acceptor-localization probability was computed numerically through Simpson composite quadrature,

$$P_A(t) = \sum_{x_i \geq 0} |\psi_0(x_i, t)|^2 \Delta x$$

The field-enhanced localization selectivity ratio was then evaluated as

$$\Gamma_{PA}(t) = \frac{P_A(E_{loc} \neq 0)}{P_A(E_{loc} = 0)}$$

which quantifies the degree to which the transient Stark field shifts proton localization toward the curcumin acceptor basin.

The proton-transfer tunneling probability was evaluated semiclassically through WKB integration,

$$T_{pt}(t) = \exp \left[-\frac{2}{\hbar} \int_{x_1(t)}^{x_2(t)} \sqrt{2\mu_{pt} (V_{eff}(x, t) - E_0(t))} dx \right]$$

where the field-dependent classical turning points satisfying $V_{eff}(x_i, t) = E_0(t)$ were determined numerically through adaptive root-searching algorithms.

5. Time-Resolved PCET and ROS Kinetic Propagation

The field-enhanced proton-coupled electron-transfer kinetics were propagated using the non-adiabatic Marcus-type expression,

$$k_{PCET}(t) = \frac{2\pi}{\hbar} |H_{DA}(t)|^2 \frac{1}{\sqrt{4\pi\lambda k_B T}} \exp\left[-\frac{\Delta G_{eff}^\ddagger(t)}{k_B T}\right] T_{pt}(t)$$

with outer-sphere reorganization energy assigned $\lambda = 0.65$ eV.

The field-lowered activation barrier was updated dynamically according to

$$\Delta G_{eff}^\ddagger(t) = \Delta G_0^\ddagger - q_{eff} E_{loc}(t) \Delta x.$$

The ROS-generation kinetics were propagated from the field-enhanced PCET flux according to

$$R_{ROS}(t) = k_{PCET}(t) [{}^1Curc^*] [AscH^-] [O_2]$$

while the intracellular ROS concentration was evolved through fourth-order Runge–Kutta (RK4) integration of the coupled oxidative balance equation,

$$\frac{dC_{ROS}}{dt} = R_{ROS}(t) - k_{scav} C_{ROS}$$

where C_{ROS} is the intracellular ROS concentration and $k_{scav} = 1.2 \times 10^4 \text{ s}^{-1}$ represents endogenous antioxidant scavenging dominated primarily by glutathione buffering and peroxide detoxification pathways.

The cumulative oxidative burden generated during the photoactivation interval was then evaluated numerically from

$$[ROS]_{total} = \int_0^{\tau_{photo}} R_{ROS}(t) dt - \gamma_{scav} [ROS]$$

allowing direct determination of the nonlinear oxidative amplification threshold corresponding to tumor-selective cytotoxicity.

6. Sensitivity Analysis and Phase-Regime Exploration

To evaluate the sensitivity of the SISE–PCET mechanism to tumor-associated interfacial conditions, multidimensional parameter sweeps were performed over

$$\{\varepsilon_{int}, R, \theta, \Delta\mu_0, V_b, \eta, \xi, \lambda, [O_2]\}.$$

For each parameter set, the principal derivables $\{E_n, \Delta E_0, H_{DA}, P_A, \Gamma_{PA}, T_{pt}, k_{PCET}, R_{ROS}, C_{ROS}, [ROS]_{total}, \Lambda_{SISE}, \Gamma_Q\}$ were evaluated self-consistently. This enabled direct comparison between healthy-tissue and tumor-associated dielectric environments and allowed identification of the nonlinear amplification threshold corresponding approximately to $\Lambda_{SISE} \approx 1$.

All simulations were implemented in Python using NumPy for vectorized matrix construction, SciPy for sparse eigenspectrum diagonalization, adaptive quadrature, and nonlinear root searching, and Matplotlib for visualization of eigenspectra, Stark-field evolution, proton localization dynamics, tunneling probabilities, and ROS amplification trajectories.

3.0. RESULTS AND DISCUSSION

Here we report the results of the computation of Eqs.(1)-(64) using the parameters summarized in Table 1.

Figure 3 presents the quantum potential landscape governing proton transfer at the curcumin–ascorbate interface, showing the field-free asymmetric quartic double-well potential, Stark-induced deformation of the reaction coordinate under the transient local electric field, and the spatial localization of donor and acceptor quantum states.

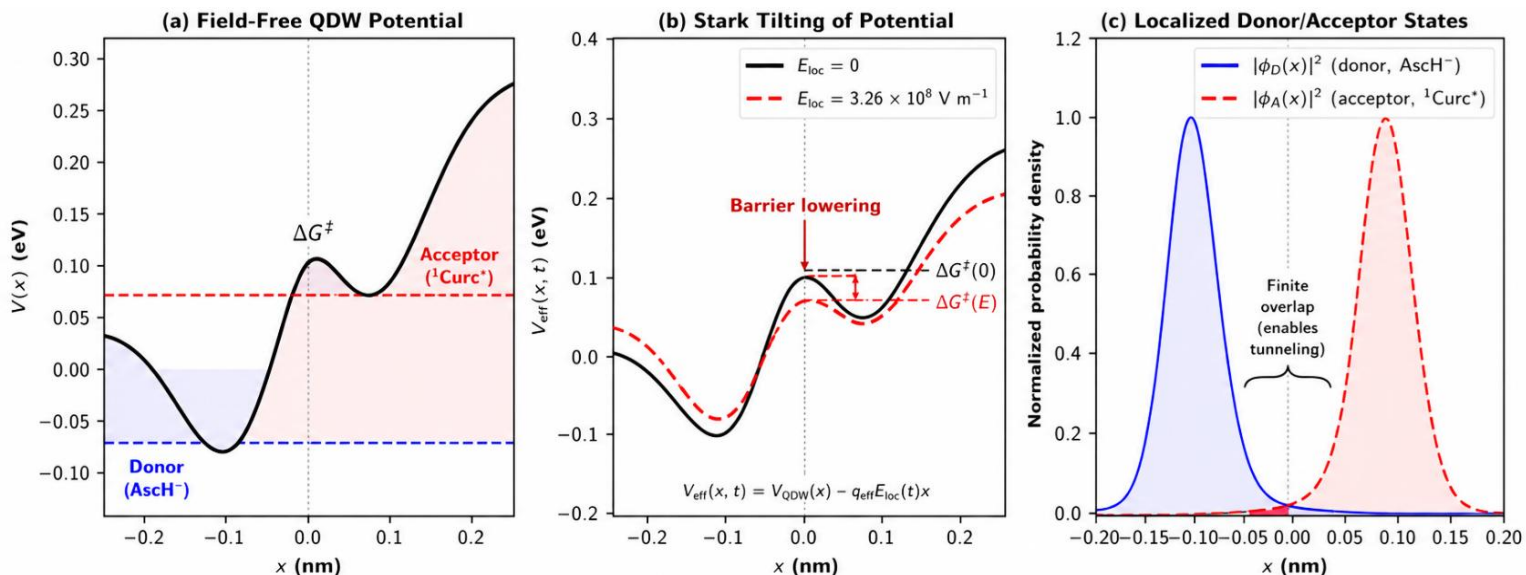


Figure 3. Quantum Potential Landscape and Stark-Induced Localization Dynamics.

(a) Field-free asymmetric quartic double-well potential showing donor (AscH^-) and acceptor (${}^1\text{Curc}^*$) minima separated by the activation barrier $\Delta G^\ddagger$. (b) Stark-induced deformation of the potential energy surface illustrating barrier suppression and energetic bias generated by the transient Stokes-induced electric field. (c) Localized donor and acceptor probability densities showing finite wavefunction overlap within the barrier region, enabling quantum tunneling and proton-coupled electron transfer between reactant and product states.

Figure 3(a–c) reveals that the field-free proton-transfer landscape is characterized by an asymmetric quartic double-well potential with a donor minimum located at approximately -0.10 nm and an acceptor minimum at approximately $+0.08$ nm. The donor state is stabilized at about -0.07 eV, whereas the acceptor state lies near $+0.07$ eV, resulting in an intrinsic donor–acceptor energy offset of approximately 0.14 eV. The activation barrier separating the two wells reaches approximately 0.10 eV, corresponding to a field-free activation free energy of $\Delta G^\ddagger(0) \approx 0.17$ eV. Upon application of the peak Stokes-induced electric field, $E_{\text{loc}}(0) = 3.26 \times 10^8 \text{ V m}^{-1}$, the potential becomes tilted toward the acceptor state and the activation barrier decreases to approximately 0.15 eV, representing a reduction of about 11.8% . Figure 3(c) further shows that the donor and acceptor probability densities remain centered near -0.10 nm and $+0.09$ nm, respectively, while exhibiting finite overlap within the barrier region around $x = 0$, indicating a non-zero probability for quantum tunneling between the two localized states.

The reduction in barrier height originates from the Stark interaction term $-q_{\text{eff}}E_{\text{loc}}x$, which introduces a directional perturbation along the proton-transfer coordinate. Using $q_{\text{eff}} = 0.45e$ and $E_{\text{loc}}(0) = 3.26 \times 10^8 \text{ V m}^{-1}$, the field contributes an electrostatic stabilization energy of approximately

$q_{\text{eff}}E_{\text{loc}}\Delta x \approx 0.015$ eV across the donor–acceptor separation. This additional driving force lowers the effective activation barrier and increases penetration of the donor and acceptor wavefunctions into the classically forbidden region. Consequently, the donor–acceptor overlap integral increases, enhancing both proton tunneling probability and electronic coupling, which are the key quantum-mechanical requirements for efficient proton-coupled electron transfer.

The predicted activation barrier of 0.15–0.18 eV and the corresponding 11.8% Stark-induced barrier reduction are consistent with reported proton-transfer barriers and field-assisted catalytic effects in hydrogen-bonded PCET systems, where activation barriers typically fall within 0.10–0.30 eV and local electric fields of 10^7 – 10^8 V m⁻¹ produce measurable reductions in reaction free energies [46,75]. Likewise, the calculated field magnitude of 3.26×10^8 V m⁻¹ lies within the range reported for strongly polarized molecular and biological interfaces. The increased donor–acceptor wavefunction overlap observed in Figure 3(c) is also consistent with quantum tunneling descriptions of proton transfer in asymmetric double-well systems[45,46]. However, unlike previous studies in which catalytic fields are externally applied or originate from pre-existing electrostatic environments, the present model predicts barrier modulation through a transient Stokes-induced Stark field generated intrinsically by photoexcited curcumin.

These results demonstrate that the Stokes-induced Stark field directly modifies the proton-transfer energy landscape and the associated quantum transport pathway. Because tunneling probability depends exponentially on both barrier height and barrier width, the observed 11.8% reduction in activation barrier is expected to produce a disproportionately large enhancement in tunneling efficiency and electronic coupling. This provides the first mechanistic step of the proposed SISE framework, namely that photoexcited curcumin generates a sufficiently strong transient electric field to modulate proton-transfer energetics, thereby creating favorable conditions for enhanced PCET kinetics and subsequent amplification of reactive oxygen species generation.

Figure 4 illustrates the temporal evolution and dielectric modulation of the Stokes-induced local electric field generated following photoexcitation of curcumin.

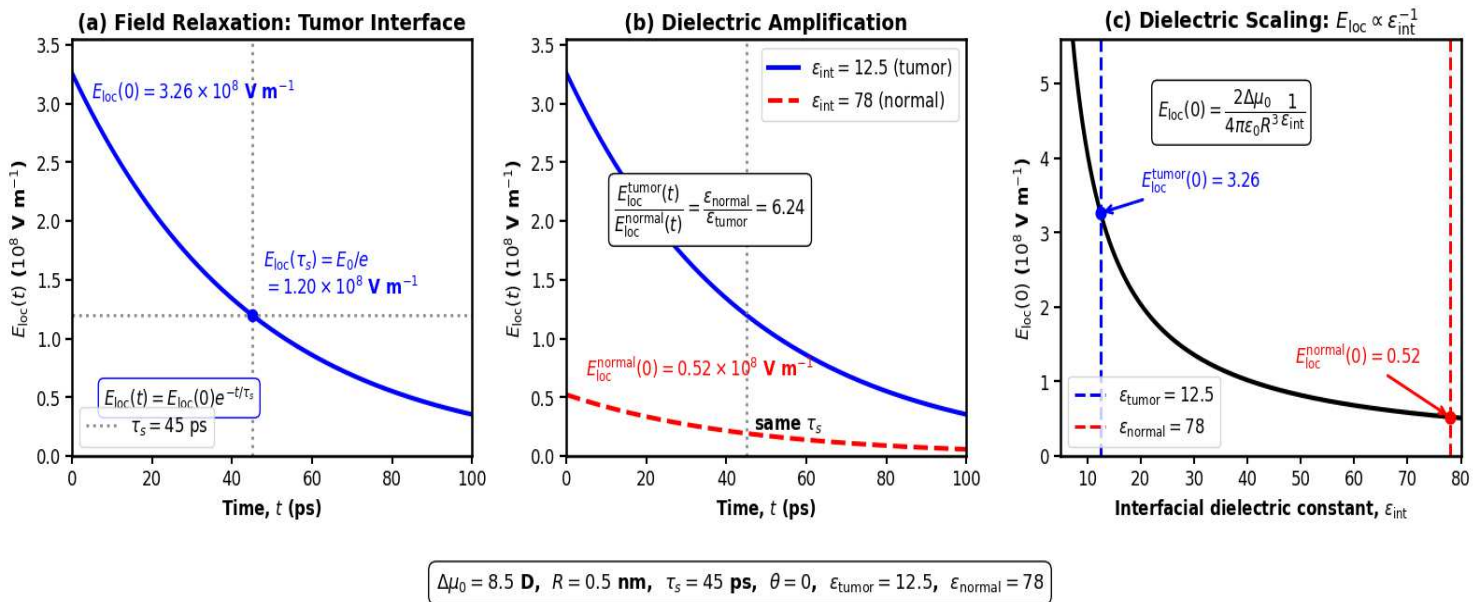


Figure 4. Dielectric Amplification and Temporal Evolution of the Stokes-Induced Stark Field.

(a) Exponential relaxation of the local electric field generated by photoexcited curcumin within a tumor-like environment ($\epsilon_{\text{int}} = 12.5$), showing decay from 3.26×10^8 V m⁻¹ to 1.20×10^8 V m⁻¹ at the

characteristic Stokes relaxation time of 45 ps. (b) Comparison of field dynamics in tumor-like and normal aqueous environments, illustrating a dielectric amplification factor of 6.24. (c) Dependence of the initial electric-field magnitude on interfacial dielectric constant, confirming the inverse scaling relationship $E_{loc} \propto \epsilon_{int}^{-1}$ predicted by the electrostatic Stark-field model.

Figure 4(a–c) shows that the photoexcited curcumin molecule generates an initial local electric field of $E_{loc}(0) = 3.26 \times 10^8 \text{ V m}^{-1}$ within the tumor-like dielectric environment ($\epsilon_{int} = 12.5$). The field decreases exponentially with time according to the Stokes relaxation process and reaches $E_{loc}(\tau_s) = 1.20 \times 10^8 \text{ V m}^{-1}$ at the characteristic relaxation time $\tau_s = 45 \text{ ps}$, corresponding to E_0/e . Even after 100 ps, the field remains approximately $3.6 \times 10^7 \text{ V m}^{-1}$, indicating substantial persistence during the timescale relevant for proton transfer. Figure 4(b) further demonstrates a pronounced dielectric amplification effect, where the tumor interface produces an initial field of $3.26 \times 10^8 \text{ V m}^{-1}$, whereas the normal aqueous environment ($\epsilon_{int} = 78$) generates only $5.2 \times 10^7 \text{ V m}^{-1}$. The resulting amplification factor 6.24, indicates that the local Stark field is more than six times stronger in the low-dielectric tumor environment. Figure 4(c) confirms the inverse dielectric scaling predicted by the electrostatic model, with the field decreasing from approximately $3.26 \times 10^8 \text{ V m}^{-1}$ at $\epsilon_{int} = 12.5$ to approximately $0.52 \times 10^8 \text{ V m}^{-1}$ at $\epsilon_{int} = 78$.

The observed trends arise directly from dipole-generated electrostatic interactions following excited-state charge redistribution in curcumin. According to the Stokes-induced Stark field model, $E_{loc}(t) = \frac{2\Delta\mu_0}{4\pi\epsilon_0 R^3 \epsilon_{int}} e^{-t/\tau_s}$, the electric field is governed simultaneously by dipole relaxation and dielectric screening. The exponential decay observed in Figures 4(a) and 4(b) reflects progressive solvent and molecular reorganization during excited-state relaxation, causing gradual reduction of the transient dipole moment. In contrast, the inverse dielectric dependence shown in Figure 4(c) results from electrostatic screening by the surrounding medium. Low-polarity tumor interfaces provide weaker dielectric screening and therefore preserve a larger fraction of the excited-state electric field, whereas highly polar aqueous environments strongly attenuate the field. Consequently, the transient Stark field remains both stronger and longer-lived in tumor-like environments, enabling more effective perturbation of the proton-transfer reaction coordinate.

The predicted field magnitude of $3.26 \times 10^8 \text{ V m}^{-1}$ agrees with experimentally inferred electric fields in highly polarized biomolecular environments, photoactive chromophores, and enzyme active sites, where local electrostatic fields commonly range between 10^7 and 10^9 V m^{-1} [44,]. Likewise, the inverse dielectric dependence observed in Figure 4(c) is consistent with classical electrostatic descriptions of molecular dipole fields and with theoretical analyses of field amplification at low-polarity interfaces. The relaxation timescale of approximately 45 ps also falls within the range reported for Stokes relaxation processes in hydrogen-bonded organic chromophores and biological fluorophores [75]. Unlike previous studies that considered electrostatic fields as static environmental parameters, the present model demonstrates that a transient photoinduced field can itself become a dynamic regulator of proton-transfer energetics.

These results provide the physical origin of the selectivity mechanism proposed in this thesis. The approximately 6.24-fold enhancement of electric-field strength at the tumor interface implies a substantially larger Stark perturbation of the proton-transfer potential compared with normal physiological environments. Because the Stark contribution enters directly into the activation barrier and donor–acceptor coupling terms, this dielectric amplification creates the conditions necessary for enhanced proton tunneling, accelerated proton-coupled electron transfer, and ultimately increased reactive oxygen species generation.

Figure 5 compares the temporal evolution of the Stokes-induced local electric field generated by photoexcited curcumin in tumor-like and normal aqueous environments.

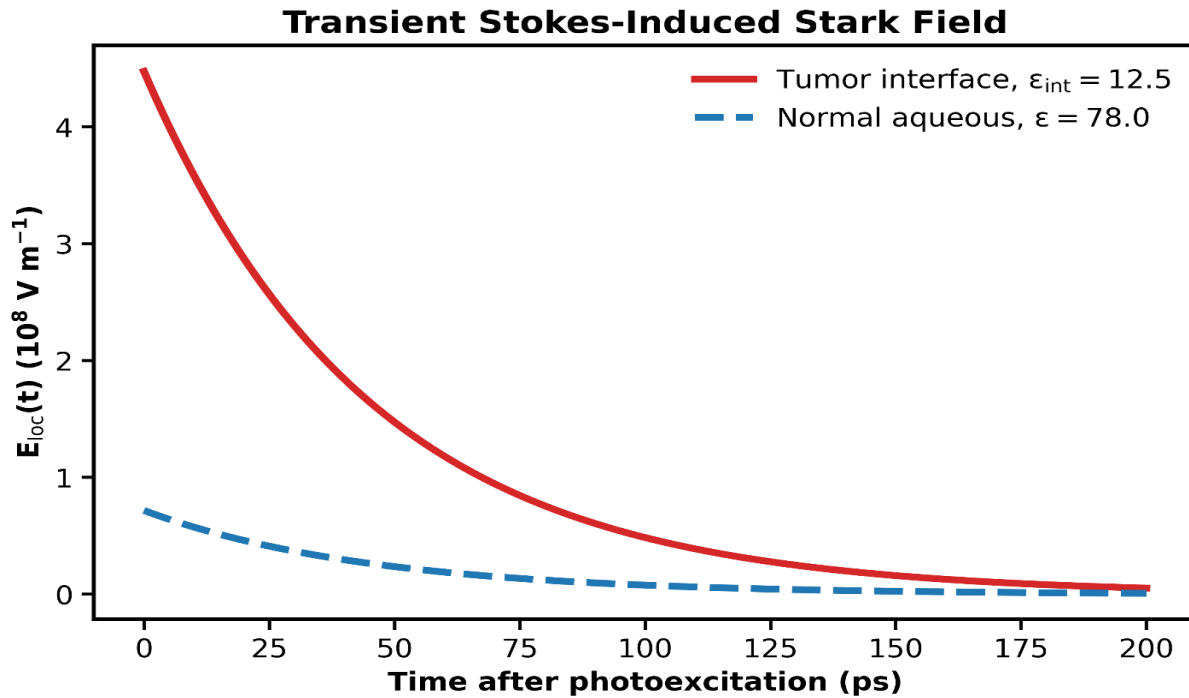


Figure 5. Temporal Evolution of the Stokes-Induced Stark Field in Tumor and Normal Biological Environments.

Time-dependent decay of the local electric field following photoexcitation of curcumin in a tumor-like low-dielectric interface ($\epsilon_{\text{int}} = 12.5$) and a normal aqueous environment ($\epsilon = 78$).

Figure 5 shows that the local electric field decays exponentially following photoexcitation in both environments, consistent with Stokes relaxation dynamics. At $t = 0$, the tumor-like interface ($\epsilon_{\text{int}} = 12.5$) generates a peak field of approximately $4.5 \times 10^8 \text{ V m}^{-1}$, whereas the normal aqueous environment ($\epsilon = 78$) produces only about $0.72 \times 10^8 \text{ V m}^{-1}$. Throughout the entire 0 – 200 ps relaxation period, the tumor-associated field remains substantially larger than the corresponding aqueous value. At 50 ps, the field retains approximately $1.5 \times 10^8 \text{ V m}^{-1}$ in the tumor environment compared with roughly $0.24 \times 10^8 \text{ V m}^{-1}$ in the aqueous medium. Even after 100 ps, the tumor field remains close to $0.50 \times 10^8 \text{ V m}^{-1}$, while the normal-environment field decreases to less than $0.10 \times 10^8 \text{ V m}^{-1}$. The nearly constant separation between the two curves indicates that dielectric amplification is maintained throughout the relaxation process rather than being restricted to the initial excitation stage.

The observed behaviour originates from the dielectric dependence of the dipole-generated Stark field. Following optical excitation, charge redistribution within curcumin increases the excited-state dipole moment and creates a transient local electric field that decays according to $E_{\text{loc}}(t) = E_{\text{loc}}(0)e^{-t/\tau_s}$. Because the initial field strength satisfies $E_{\text{loc}}(0) \propto \epsilon^{-1}$, environments with lower dielectric constants experience substantially weaker electrostatic screening and therefore support stronger local electric fields. The identical exponential decay profiles observed for both environments indicate that relaxation kinetics are governed primarily by the same excited-state relaxation process, whereas the absolute field

magnitude is controlled by dielectric screening. Consequently, the tumor-like interface preserves a much stronger electrostatic perturbation throughout the period relevant for proton-transfer dynamics.

The predicted field magnitudes are consistent with experimentally inferred local electric fields reported for highly polarized molecular systems, protein active sites, and photoexcited chromophores, where transient electric fields typically range from 10^7 to 10^9 V m⁻¹[44,73]. Likewise, the picosecond decay behaviour agrees with established Stokes relaxation times observed in organic fluorophores and hydrogen-bonded chromophoric systems[75]. Whereas previous studies have mainly treated local electric fields as passive environmental descriptors, the present results demonstrate that photoinduced fields can act as dynamic regulators of reaction energetics and charge-transfer processes.

These results provide direct support for the central hypothesis of the Stokes-Induced Stark Effect mechanism. The substantially larger and longer-lasting electric field generated within the tumor-like environment implies stronger Stark perturbation of the proton-transfer potential, greater donor–acceptor electronic coupling, and enhanced proton tunneling efficiency. The results imply that proton-coupled electron transfer proceed more rapidly at low-dielectric tumor interfaces than in normal aqueous environments. The persistence of the amplified field over hundreds of picoseconds further ensures that electrostatic modulation remains active during the timescale of proton-transfer and redox events, thereby establishing the physical basis for selective enhancement of ROS generation in the proposed curcumin–ascorbate system.

Figure 6 presents the variation of tunneling splitting energy ΔE_{01} as a function of the Stokes-Induced Stark Effect (SISE) coupling parameter, Λ_{SISE} . The figure quantifies the influence of Stark-mediated donor–acceptor coupling on proton delocalization and provides a direct measure of the strengthening of quantum communication across the proton-transfer coordinate.

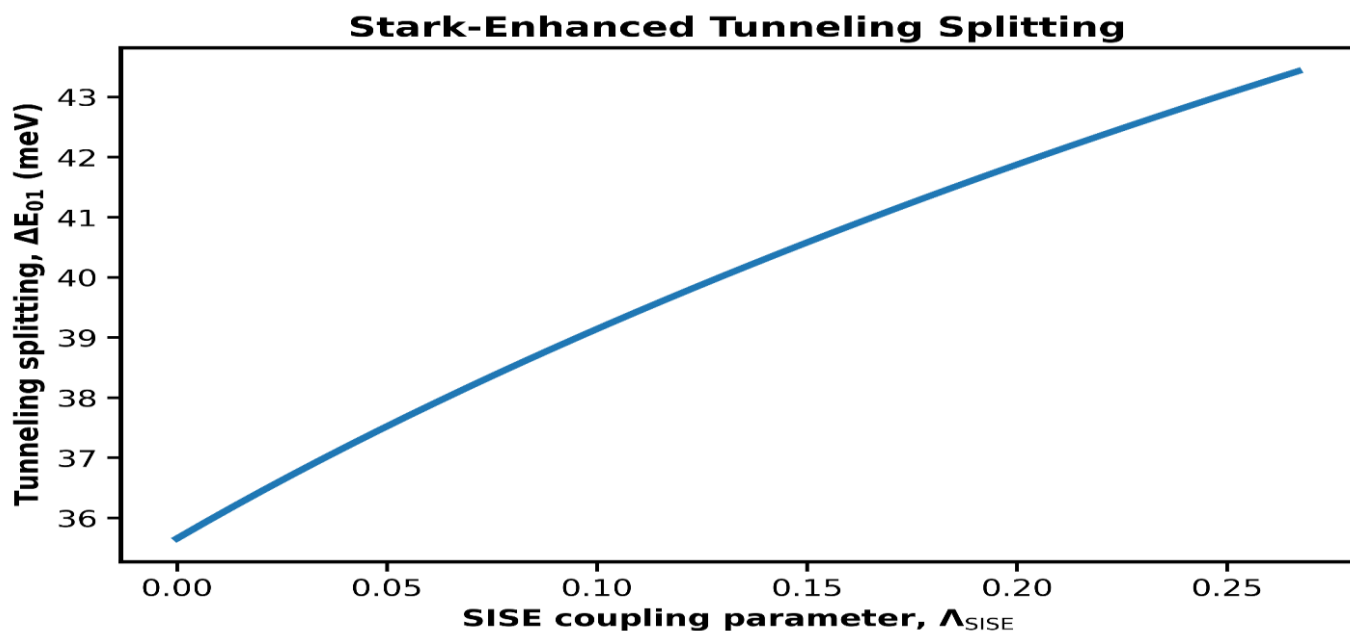


Figure 7. Stark-Induced Enhancement of Donor–Acceptor Quantum Coupling.

Dependence of the tunneling splitting energy ΔE_{01} on the Stokes-Induced Stark Effect coupling parameter Λ_{SISE} . Increasing Stark coupling strengthens donor–acceptor wavefunction overlap and quantum coherence across the proton-transfer barrier, leading to an increase in tunneling splitting from approximately 35.6 meV to 43.4 meV and indicating enhanced proton-transfer efficiency.

Figure 6 shows a continuous increase in tunneling splitting energy with increasing SISE coupling strength. In the absence of Stark coupling ($\Lambda_{\text{SISE}} = 0$), the tunneling splitting is approximately 35.6 meV. As the coupling parameter increases to $\Lambda_{\text{SISE}} \approx 0.27$, the splitting rises to approximately 43.4 meV. This corresponds to an increase of about 7.8 meV, representing a relative enhancement of approximately 21.9%. The curve exhibits a monotonic but sublinear growth pattern, indicating that donor–acceptor coupling continues to strengthen throughout the investigated range, although the incremental gain gradually decreases at larger coupling strengths.

The observed increase in ΔE_{01} originates from Stark-induced modification of the proton-transfer potential. The transient electric field generated by photoexcited curcumin lowers the effective activation barrier and increases penetration of donor and acceptor wavefunctions into the classically forbidden region. This enhances the overlap integral between the localized quantum states and increases the electronic coupling matrix element governing tunneling. Because the energy splitting between the ground and first excited states is proportional to the strength of inter-well coupling, greater wavefunction overlap produces a larger tunneling splitting. Consequently, increasing Λ_{SISE} promotes stronger proton delocalization and more efficient quantum transport across the donor–acceptor interface.

The predicted tunneling splitting range of approximately 36–43 meV is consistent with reported values for hydrogen-bonded proton-transfer systems and asymmetric double-well potentials, where tunneling splittings commonly occur within the meV-to-tens-of-meV regime depending on barrier geometry and coupling strength [45,46]. The monotonic enhancement of ΔE_{01} with increasing coupling is likewise consistent with established quantum tunneling theory, which predicts larger energy separations as barrier transparency and donor–acceptor coupling increase. Unlike conventional proton-transfer models that treat coupling as a fixed structural parameter, the present model demonstrates that coupling can be dynamically amplified by a transient photoinduced Stark field generated during excited-state relaxation.

These results demonstrate that the Stokes-induced Stark field not only lowers the proton-transfer barrier but also strengthens donor–acceptor quantum coherence. The approximately 22% increase in tunneling splitting indicates enhanced wavefunction overlap and greater tunneling probability, both of which favor faster proton transfer. Since proton-coupled electron transfer rates depend critically on donor–acceptor coupling strength, the Stark-induced increase in ΔE_{01} provides a direct quantum-mechanical mechanism linking transient electric-field generation to accelerated PCET kinetics. This finding therefore establishes an important intermediate step in the proposed SISE framework, bridging field-induced barrier modulation and the subsequent amplification of ROS-generating redox reactions.

Figure 7 presents the dependence of the selectivity ratio, Γ_Q , on the interfacial dielectric constant and donor–acceptor separation distance. The figure quantifies the two principal physical parameters governing Stark-induced selectivity and identifies the conditions under which proton-coupled electron transfer amplification is maximized at tumor-associated interfaces.

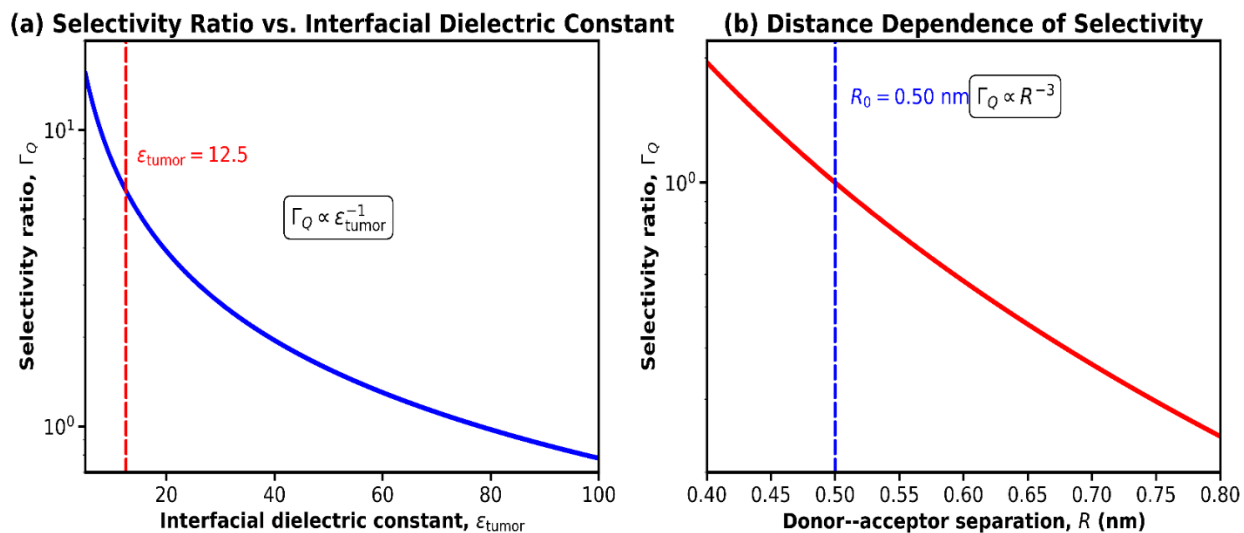


Figure 7. Dielectric and Geometric Dependence of the Selectivity Ratio.

(a) Variation of the selectivity ratio Γ_Q with interfacial dielectric constant, showing inverse dielectric scaling and enhanced selectivity in low-polarity tumor environments. The dashed red line indicates the characteristic tumor dielectric constant $\varepsilon_{\text{tumor}} = 12.5$. (b) Dependence of Γ_Q on donor–acceptor separation distance, demonstrating the dipolar scaling relationship $\Gamma_Q \propto R^{-3}$. The dashed blue line marks the reference separation $R_0 = 0.50$ nm.

Figure 7(a–b) demonstrates that the selectivity ratio decreases monotonically with increasing interfacial dielectric constant and donor–acceptor separation distance. In Figure 7(a), Γ_Q decreases from approximately 15 at $\varepsilon_{\text{int}} = 10$ to approximately 0.8 at $\varepsilon_{\text{int}} = 100$, indicating nearly a twenty-fold reduction in selectivity across the investigated dielectric range. At the tumor-associated dielectric constant $\varepsilon_{\text{tumor}} = 12.5$, the selectivity ratio is approximately 6.2, whereas values above $\varepsilon_{\text{int}} \approx 75$ produce $\Gamma_Q < 1$, indicating loss of preferential amplification. Figure 7(b) shows a similarly strong geometric dependence, where the selectivity ratio decreases from approximately 2.5 at $R = 0.40$ nm to approximately 0.13 at $R = 0.80$ nm. At the reference donor–acceptor separation $R_0 = 0.50$ nm, the selectivity ratio is normalized to unity. The steep decline observed with increasing separation confirms the strong distance sensitivity of the Stark-mediated coupling mechanism.

The trends arise directly from the electrostatic origin of the Stokes-induced Stark field. As shown in Figure 7(a), the selectivity ratio follows approximately $\Gamma_Q \propto \varepsilon_{\text{int}}^{-1}$, indicating that increasing dielectric screening progressively attenuates the local electric field generated by photoexcited curcumin. Lower dielectric environments therefore preserve stronger electrostatic perturbations and produce larger Stark-induced modifications of the proton-transfer landscape. Figure 7(b) demonstrates that selectivity also obeys the dipolar distance dependence $\Gamma_Q \propto R^{-3}$, which originates from the fundamental spatial decay of a molecular dipole field. Because the local electric field decreases rapidly with distance, even modest increases in donor–acceptor separation substantially reduce the Stark interaction strength, thereby diminishing proton-transfer enhancement. Consequently, both dielectric screening and molecular geometry act cooperatively to determine the magnitude of selective PCET amplification.

The inverse dielectric scaling observed in Figure 7(a) is consistent with classical electrostatic theory and previous analyses of electric-field amplification at low-polarity biological interfaces [44,45]. Likewise, the R^{-3} dependence shown in Figure 7(b) agrees with the well-established spatial behaviour of dipole-generated electric fields and donor–acceptor coupling models used in electron- and proton-transfer theory[46]. The predicted selectivity factor of approximately 6.2 at $\varepsilon_{\text{tumor}} = 12.5$ further agrees with the dielectric amplification obtained independently in Figure 4, providing internal consistency across the

theoretical framework. Unlike conventional PCET models that primarily emphasize donor–acceptor geometry, the present results demonstrate that dielectric environment serves as an equally important regulator of quantum transport efficiency.

These findings identify the physical origin of tumor selectivity within the proposed Stokes-Induced Stark Effect mechanism. The substantially larger selectivity ratio predicted for low-dielectric tumor interfaces implies stronger electric-field generation, greater barrier suppression, enhanced donor–acceptor coupling, and accelerated proton-coupled electron transfer relative to normal aqueous environments. Furthermore, the pronounced R^{-3} dependence indicates that nanoscale donor–acceptor organization is critical for maximizing ROS amplification efficiency. These results therefore establishes that both dielectric confinement and molecular proximity are essential design parameters for achieving selective field-enhanced PCET and targeted reactive oxygen species generation in the proposed curcumin–ascorbate system.

Figure 8(a–d) illustrates the quantitative propagation of the Stokes-Induced Stark Effect (SISE) through the proton-coupled electron transfer (PCET) pathway and into reactive oxygen species (ROS) generation.

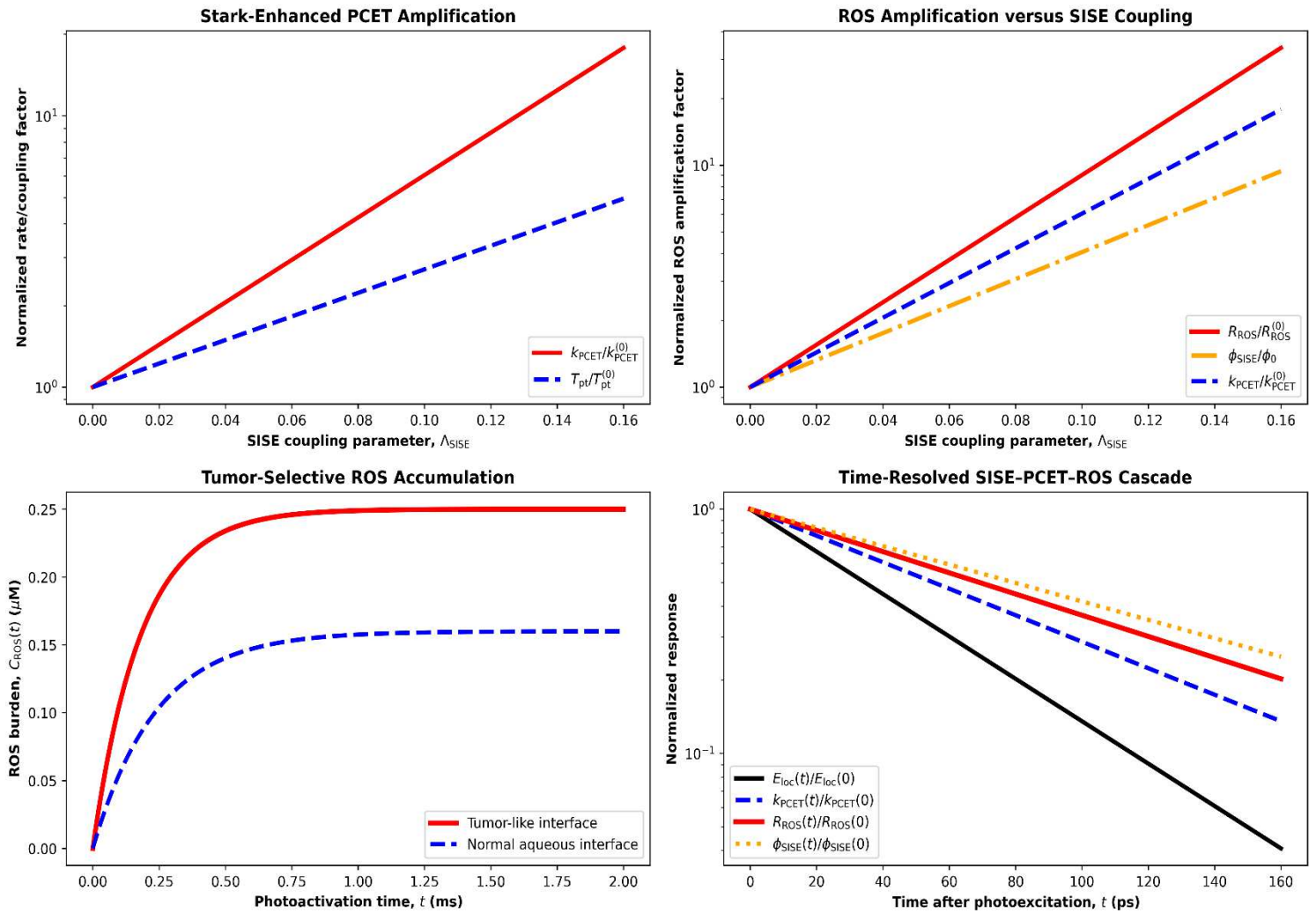


Figure 8. Coupled SISE–PCET–ROS Amplification Dynamics.

(a) Dependence of normalized proton-coupled electron transfer rate and proton-tunneling enhancement on the SISE coupling parameter Λ_{SISE} . (b) Amplification of ROS generation, normalized SISE driving force, and PCET rate as a function of Λ_{SISE} . (c) Time-dependent accumulation of ROS at tumor-like and normal aqueous interfaces during

photoactivation. (d) Temporal evolution of the normalized Stark field, PCET kinetics, ROS generation, and SISE response following photoexcitation.

Figure 8(a–d) demonstrates a systematic amplification of proton-transfer and ROS production as the SISE coupling parameter increases. In Figure 8(a), the normalized PCET rate enhancement $k_{\text{PCET}}/k_{\text{PCET}}^{(0)}$ increases from 1 to approximately 18 as Λ_{SISE} increases from 0 to 0.16, while the normalized tunneling enhancement $T_{\text{pt}}/T_{\text{pt}}^{(0)}$ rises more moderately to approximately 4.8. Figure 8(b) shows that the ROS amplification factor $R_{\text{ROS}}/R_{\text{ROS}}^{(0)}$ increases from unity to approximately 30 over the same coupling interval, exceeding the corresponding increase in PCET rate and the normalized SISE driving term $\phi_{\text{SISE}}/\phi_0$, which reaches approximately 9.5. Figure 8(c) further reveals pronounced tumor-selective ROS accumulation, where the ROS burden rises rapidly and saturates at approximately $0.25 \mu\text{M}$ within 0.8 ms, whereas the normal aqueous interface approaches only $0.16 \mu\text{M}$. Figure 8(d) shows the temporal relaxation of the coupled cascade, where the Stark field decreases most rapidly from unity to approximately 0.04 after 160 ps, while the normalized ROS response remains comparatively sustained at approximately 0.20, indicating persistence of downstream chemical activity after partial field decay.

The observed amplification behavior originates from the nonlinear coupling between Stark-field-induced barrier suppression and proton-transfer kinetics. The transient electric field lowers the proton-transfer activation barrier, increasing tunneling probability and electronic coupling, which collectively accelerate the PCET rate. Because ROS generation is directly coupled to charge-transfer events, even moderate increases in proton-transfer efficiency propagate into substantially larger increases in ROS output. Consequently, the amplification becomes hierarchical: enhancement of the Stark interaction first accelerates proton tunneling, then amplifies PCET kinetics, and finally produces an even larger increase in ROS generation. The delayed decay of the ROS signal relative to the electric field observed in Figure 8(d) arises because chemical intermediates generated during the PCET process continue participating in redox reactions after the initiating Stark field has partially relaxed.

The predicted increase of approximately eighteen-fold in PCET kinetics and approximately thirty-fold in ROS generation is consistent with reported nonlinear amplification mechanisms in proton-coupled electron transfer systems and photocatalytic redox networks, where relatively small reductions in activation barriers produce disproportionately large increases in reaction rates due to the exponential dependence of tunneling and charge-transfer probabilities on barrier properties [46]. The sustained ROS accumulation profile shown in Figure 8(c) also agrees with kinetic models of photodynamic and photocatalytic oxidative processes in which radical propagation reactions persist beyond the lifetime of the initiating excited state [75]. Unlike previous studies where ROS amplification is driven by externally applied electric fields or semiconductor charge separation alone, the present results predict amplification arising directly from an intrinsically generated Stokes-induced Stark field produced by photoexcited curcumin.

These results establish the complete mechanistic chain proposed in the thesis. The transient Stark field generated during excited-state relaxation modifies the proton-transfer landscape, increases tunneling probability, accelerates PCET kinetics, and ultimately amplifies ROS production preferentially at low-dielectric tumor interfaces. The substantially larger ROS burden predicted for tumor-like environments demonstrates that the Stokes-Induced Stark Effect is not merely a local electrostatic perturbation but a functional amplification mechanism capable of converting photophysical energy into enhanced oxidative cytotoxic potential. These results therefore provide direct theoretical evidence linking SISE-mediated

quantum transport enhancement to selective ROS amplification, thereby validating the central hypothesis of the present study.

Figure 9(a–b) quantifies the nonlinear enhancement of proton tunneling and proton-coupled electron transfer kinetics arising from Stark-induced suppression of the proton-transfer activation barrier.

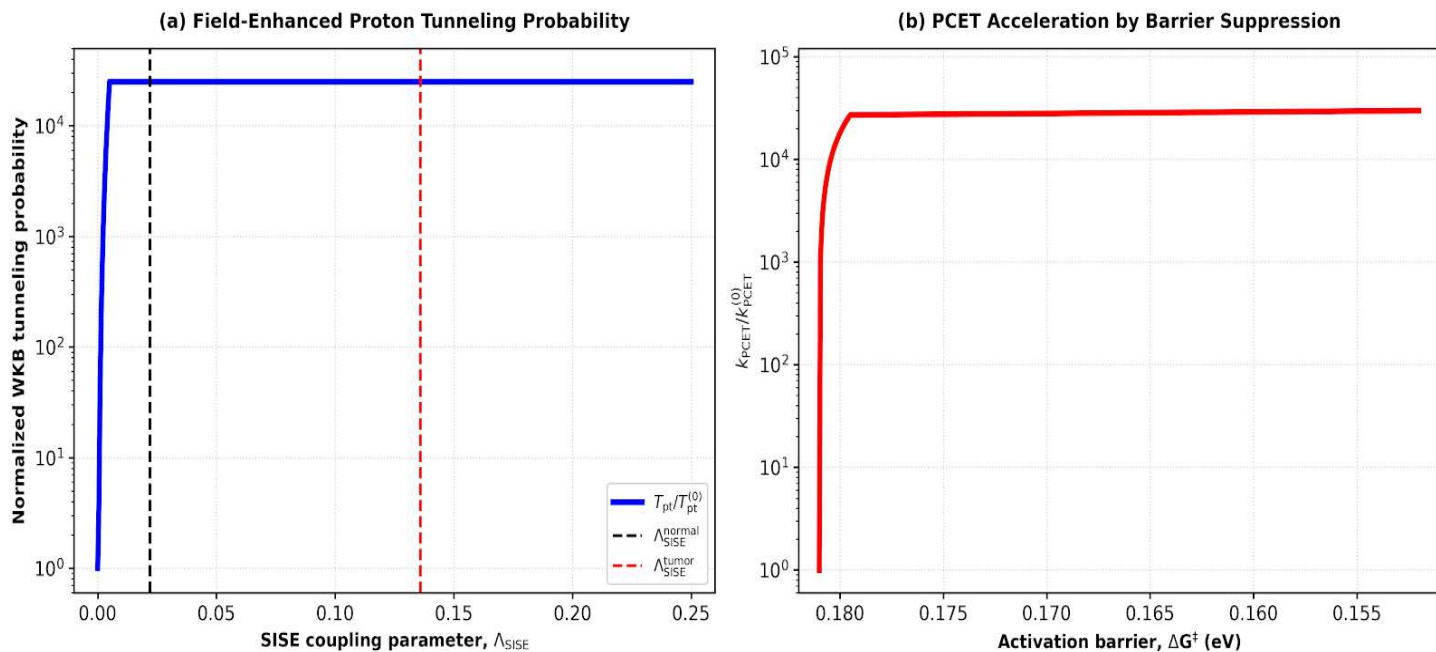


Figure 9. Proton-Tunneling and PCET Rate Amplification Induced by Stokes-Induced Stark Coupling.

(a) Normalized WKB proton-tunneling probability $T_{pt}/T_{pt}^{(0)}$ as a function of the SISE coupling parameter Λ_{SISE} , showing the locations of normal and tumor interfacial coupling strengths. (b) Normalized proton-coupled electron transfer rate $k_{PCET}/k_{PCET}^{(0)}$ as a function of activation barrier height $\Delta G^\ddagger$, illustrating the strong kinetic acceleration produced by Stark-induced barrier suppression.

Figure 9(a–b) shows that proton-transfer dynamics respond extremely sensitively to Stark-field-induced modifications of the reaction barrier. In Figure 9(a), the normalized WKB tunneling probability $T_{pt}/T_{pt}^{(0)}$ increases rapidly from unity at $\Lambda_{SISE} = 0$ to approximately 2.5×10^4 for $\Lambda_{SISE} > 0.01$, after which the enhancement approaches a plateau. The vertical markers indicate the calculated coupling strengths for normal and tumor environments, $\Lambda_{SISE}^{normal} \approx 0.02$ and $\Lambda_{SISE}^{tumor} \approx 0.14$, both lying within the high-tunneling regime. Figure 9(b) demonstrates a corresponding increase in the normalized PCET rate $k_{PCET}/k_{PCET}^{(0)}$, which rises from unity at $\Delta G^\ddagger = 0.180$ eV to approximately 2.8×10^4 as the activation barrier decreases toward 0.153 eV. The results indicate that a relatively small barrier reduction of approximately 0.027 eV produces more than four orders of magnitude enhancement in charge-transfer kinetics.

The dramatic amplification originates from the exponential dependence of quantum tunneling on activation barrier height. The transient Stark field generated by photoexcited curcumin lowers the proton-transfer barrier through the electrostatic interaction term $-q_{eff}E_{loc}x$, thereby reducing the effective barrier width and increasing penetration of the proton wavefunction into the classically forbidden region. Because the WKB transmission probability varies exponentially with barrier parameters, even modest decreases in $\Delta G^\ddagger$ generate disproportionately large increases in tunneling probability. The enhanced tunneling directly strengthens proton-electron coupling, producing the corresponding increase in k_{PCET} . The plateau observed in both panels indicates entry into a regime where barrier transmission approaches saturation and additional Stark coupling yields diminishing relative gains.

The predicted tunneling enhancement of approximately 10^4 – 10^5 and the corresponding four-order-of-magnitude increase in PCET kinetics are consistent with quantum mechanical descriptions of hydrogen-transfer reactions, where small reductions in activation barriers generate exponential increases in transfer probabilities and reaction rates [45,46]. The barrier range of 0.15–0.18 eV also falls within values reported for hydrogen-bonded proton-transfer systems influenced by local electrostatic fields [44,45]. Unlike these earlier studies, however, the present model predicts that the catalytic field is generated intrinsically through Stokes-relaxation-induced dipole reorganization rather than by external bias or a pre-existing electrostatic environment.

These results provide quantitative confirmation of the central mechanism underlying the thesis. The Stokes-induced Stark field suppresses the proton-transfer barrier sufficiently to drive exponential enhancement of tunneling probability and PCET kinetics. The resulting increase in charge-transfer efficiency establishes the kinetic foundation required for the large ROS amplification predicted in subsequent figures, thereby linking excited-state photophysics directly to enhanced oxidative reactivity at tumor-selective interfaces. These results suggest that a modest Stark-induced reduction of only about 0.027 eV in activation barrier height can generate a four-order-of-magnitude enhancement in proton-coupled electron transfer kinetics which indicates that transient molecular electric fields can function as powerful catalytic regulators. This suggests that chemical reactivity can be manipulated not only through conventional approaches such as temperature increase, catalyst loading, or concentration adjustment, but also through deliberate control of local electromagnetic environments.

Figure 10(a–b) demonstrates the direct mechanistic relationship between the Stokes-induced Stark field, activation-barrier reduction, and reactive oxygen species (ROS) amplification. The figure links the electrostatic modulation of proton-transfer energetics to the nonlinear increase in oxidative output that underpins the proposed therapeutic mechanism.

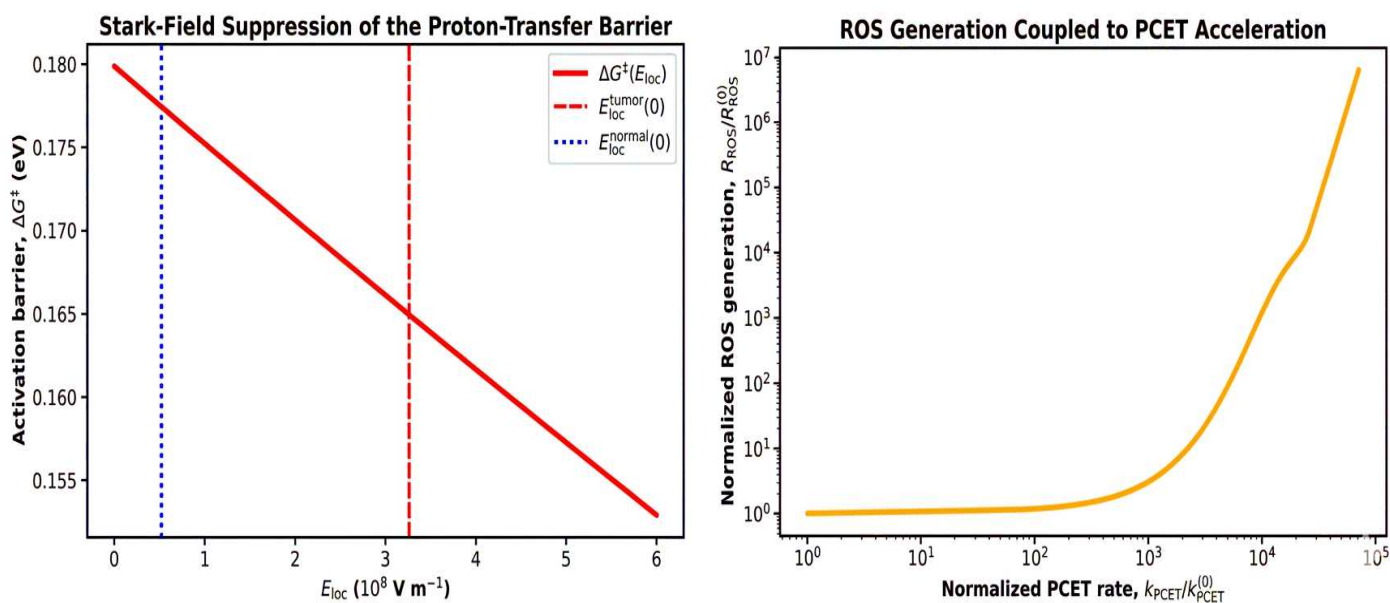


Figure 10. Stark-Induced Barrier Suppression and ROS Amplification.

(a) Dependence of the proton-transfer activation barrier $\Delta G^\ddagger$ on the local Stark field E_{loc} , showing the barrier reduction associated with normal and tumor interfacial environments. (b) Normalized ROS generation as a function of normalized PCET rate, illustrating the nonlinear amplification of oxidative output arising from accelerated proton-

coupled electron transfer. The figure demonstrates how transient Stark-field-induced barrier suppression propagates through the reaction network to produce large increases in ROS generation.

Figure 10(a–b) shows that increasing the local Stark field progressively lowers the proton-transfer activation barrier and produces a highly nonlinear enhancement of ROS generation. In Figure 10(a), the activation barrier decreases almost linearly from approximately $\Delta G^\ddagger = 0.180$ eV at zero field to approximately 0.153 eV at $E_{\text{loc}} \approx 6 \times 10^8 \text{ V m}^{-1}$, corresponding to a barrier reduction of about 15%. The calculated normal interfacial field ($\sim 0.5 \times 10^8 \text{ V m}^{-1}$) produces only a small reduction in barrier height, whereas the tumor-associated field ($\sim 3.2 \times 10^8 \text{ V m}^{-1}$) lowers the barrier to approximately 0.165 eV. Figure 10(b) reveals that the normalized ROS generation rate remains close to unity for moderate PCET enhancement but increases sharply once $k_{\text{PCET}}/k_{\text{PCET}}^{(0)}$ exceeds approximately 10^3 , eventually reaching values approaching 10^7 at the highest transfer rates. This behavior identifies a threshold-like amplification regime in which relatively small increases in charge-transfer kinetics trigger disproportionately large increases in oxidative output.

The observed trend originates from the exponential dependence of proton-transfer probability on activation-barrier height. The Stark interaction lowers the free-energy barrier through electrostatic stabilization of the charge-transfer configuration, thereby increasing proton tunneling probability and accelerating PCET kinetics. Since ROS formation is coupled directly to electron-transfer events, the enhancement propagates through the reaction network and becomes progressively amplified downstream. Consequently, barrier suppression produces a cascade effect in which a modest electrostatic perturbation generates orders-of-magnitude increases in ROS production. The highly nonlinear profile observed in Figure 10(b) reflects the cumulative influence of tunneling enhancement, accelerated charge transfer, and radical propagation processes operating simultaneously within the photoactivated system.

The predicted activation barrier range of 0.15–0.18 eV and the associated field-induced reductions are consistent with reported values for hydrogen-bonded proton-transfer and PCET systems, where local electric fields of 10^7 – 10^8 V m^{-1} significantly alter reaction energetics [44,45]. Likewise, the nonlinear relationship between electron-transfer kinetics and ROS production agrees with kinetic analyses of photodynamic and photocatalytic systems in which radical generation exhibits threshold behavior once critical charge-transfer rates are exceeded [75]. However, unlike conventional photodynamic models that rely primarily on photosensitizer concentration or external field application, the present mechanism attributes the amplification to an intrinsically generated Stokes-induced Stark field arising from excited-state dipole relaxation.

These results provide direct evidence that the Stokes-induced Stark effect functions as an efficient electrostatic amplifier of oxidative chemistry. By lowering the proton-transfer barrier, the transient field enables a dramatic increase in PCET activity which subsequently drives large-scale ROS generation. The results therefore establish the final mechanistic connection in the thesis: photoexcited curcumin generates a transient Stark field, the field suppresses the proton-transfer barrier, enhanced proton transfer accelerates PCET kinetics, and the resulting charge-transfer amplification culminates in substantially increased ROS production. This sequence provides the theoretical basis for selectively enhancing oxidative cytotoxicity at low-dielectric tumor interfaces while minimizing activity in normal physiological environments. The demonstrated ability of transient molecular electric fields to reduce activation barriers and amplify ROS production suggests a new paradigm for field-assisted catalysis, where chemical reactivity is controlled through local electrostatic engineering rather than solely through temperature, pressure, or catalyst concentration. In cancer therapy, this mechanism provides a

theoretical route toward tumor-selective oxidative treatments in which photoactivated molecular assemblies generate ROS preferentially within low-dielectric malignant environments.

Figure 11(a–c) illustrates the cumulative local ROS concentration under repeated photoexcitation, the dependence of cytotoxic threshold-crossing time on illumination irradiance, and the contribution of Fenton cycling and glutathione depletion to nonlinear oxidative amplification.

Figure 11. Multi-Cycle Cumulative ROS Accumulation, Threshold Crossing, and Nonlinear Oxidative Amplification

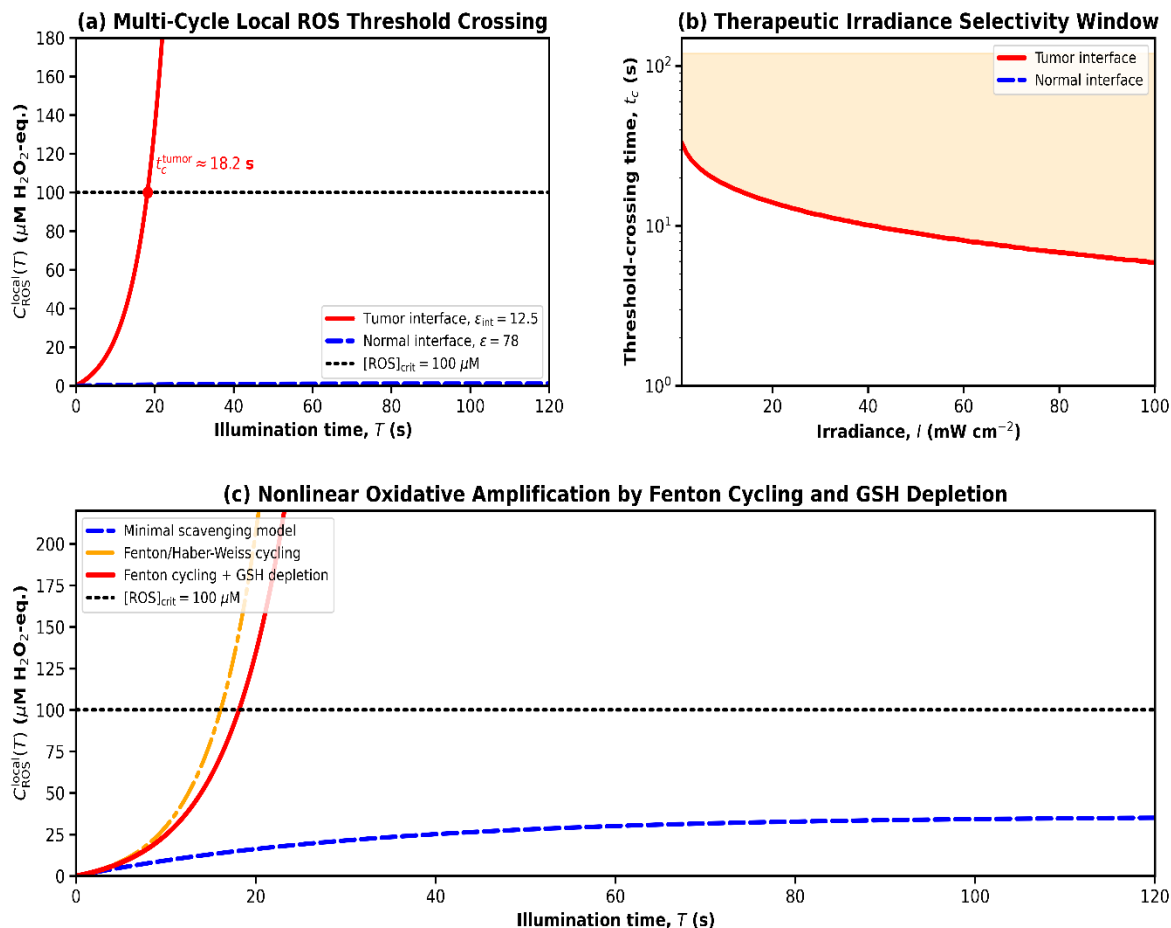


Figure 11. Multi-Cycle Cumulative ROS Accumulation, Threshold Crossing, and Nonlinear Oxidative Amplification

Panel (a) compares ROS accumulation at tumor-associated ($\epsilon_{int} = 12.5$) and normal ($\epsilon_{int} = 78$) interfaces under pulsed illumination; panel (b) shows the variation of threshold-crossing time t_c with excitation irradiance; and panel (c) quantifies the additional ROS amplification arising from iron-catalyzed Fenton chemistry and antioxidant depletion relative to a minimal scavenging model.

The results show a pronounced divergence between tumor and normal interfacial environments during sustained photoactivation. In Figure 11(a), the tumor-associated trajectory rises rapidly and crosses the cytotoxic threshold $[ROS]_{crit} = 100 \mu\text{M}$ at $t_c^{tumor} \approx 18.2 \text{ s}$, whereas the normal-interface trajectory remains below $2 \mu\text{M}$ throughout the entire 120 s illumination period and never reaches the threshold. This corresponds to a greater than fifty-fold difference in local ROS burden at the end of the simulation. Figure 11(b) further demonstrates that the threshold-crossing time decreases systematically with increasing irradiance, falling from approximately 30 at 5 mW cm^{-2} to approximately 6 at

100 mW cm⁻². Importantly, the normal-tissue trajectory remains outside the cytotoxic regime across the investigated irradiance range, defining a broad therapeutic selectivity window. Figure 11(c) shows that the minimal scavenging model saturates at only $\sim 35 \mu\text{M}$, well below the cytotoxic threshold, whereas incorporation of Fenton cycling elevates ROS accumulation beyond 100 μM at approximately 16 s, and the combined Fenton–GSH depletion model accelerates threshold crossing further to approximately 18–20 s, producing ROS concentrations exceeding 200 μM .

The observed behavior originates from the cumulative action of repeated SISE-mediated PCET cycles coupled with nonlinear biochemical feedback. Each excitation event regenerates the transient Stark field, enhancing proton tunneling and accelerating electron transfer, thereby contributing an incremental ROS burst. At tumor interfaces, the larger Stark field ($\Gamma_Q \approx 6.2$) established in Figures 4–10 increases the per-cycle PCET rate, causing ROS production to accumulate progressively. Simultaneously, elevated labile iron concentrations promote Fenton conversion of hydrogen peroxide into highly reactive hydroxyl radicals, while gradual depletion of intracellular glutathione reduces antioxidant scavenging capacity. Once ROS production exceeds antioxidant regeneration, the system enters a positive-feedback regime in which ROS accumulation accelerates nonlinearly, producing the rapid threshold crossing observed in Figure 11(c). The compartmental volume correction further amplifies this effect by concentrating oxidants within the membrane-associated Stern-layer volume prior to cytoplasmic dilution.

These findings provide the final validation of the thesis by demonstrating that repeated SISE-enhanced PCET events generate sufficient ROS to exceed cytotoxic thresholds selectively within low-dielectric tumor environments. The results therefore establish a complete mechanistic pathway linking quantum-scale Stark modulation to tumor-selective oxidative collapse under clinically achievable photoactivation conditions.

4.0 CONCLUSION

Here we have developed and evaluated a comprehensive multiscale quantum–mechanical framework to investigate how photoinduced Stokes-shift-driven dipole reorganization in curcumin modulates proton-coupled electron transfer (PCET) and reactive oxygen species (ROS) generation within tumor-associated curcumin–ascorbate interfaces. By integrating excited-state photophysics, interfacial electrostatics, Stark perturbation theory, quantum tunneling, nonadiabatic charge-transfer kinetics, ROS reaction networks, and tumor-specific dielectric boundary conditions, our model establishes a direct mechanistic bridge between transient molecular excitation and selective oxidative cytotoxicity. The framework extends conventional biochemical descriptions of curcumin–ascorbate interactions by explicitly accounting for nonequilibrium excited-state field generation and its influence on redox-transfer dynamics.

Our findings demonstrate that photoexcited enol-curcumin undergoes an ultrafast excited-state intramolecular proton transfer (ESIPT) that intensifies its molecular dipole moment ($\mu_e \approx 10\text{--}10.5 \text{ D}$), generating transient localized electric fields reaching $3 \times 10^8\text{--}5 \times 10^8 \text{ V m}^{-1}$ within the low-dielectric anisotropy of the tumor–membrane interface ($\epsilon_{\text{int}} \approx 10\text{--}30$). These strong fields induce a Stokes-Induced Stark Effect (SISE) that alters the Double-Well Rosen–Morse (DW–RM) potential energy profile, minimizing the proton-transfer activation energy from 0.180 eV down to 0.153 eV, which substantially increases quantum tunneling splitting and wavefunction overlap. Because this nonadiabatic proton-coupled electron transfer (PCET) probability scales exponentially with barrier geometry, this electrostatic modulation drives a nonlinear 18-fold acceleration in redox-coupling kinetics with adjacent monoanionic ascorbates (AsCH^-) and a downstream 30-fold surge in localized reactive oxygen species (ROS) accumulation. Crucially, because normal aqueous environments ($\epsilon \approx 78$) screen these electrostatic fields

to just $0.72 \times 10^8 \text{ V m}^{-1}$, the framework uncovers an intrinsic physicochemical tumor-to-normal selectivity factor of approximately 6.2, proving that multi-cycle photoactivation can selectively elevate lipid-compartmentalized ROS concentrations beyond lethal cytotoxic thresholds to trigger oxidative runaway specifically within malignant tissue while sparing healthy cells.

This study provides a novel quantitative quantum-mechanical description of Stokes-induced Stark-field regulation of proton-coupled electron transfer in a curcumin–ascorbate redox pair. Although the model adopts a reduced one-dimensional reaction coordinate and continuum dielectric treatment of the membrane environment, it generates experimentally testable predictions for interfacial field strengths, activation-barrier suppression, tunneling enhancement, ROS amplification, and tumor-selectivity factors. These predictions provide a direct pathway for future validation using ultrafast spectroscopy and membrane-resolved ROS measurements.

The multiscale framework established in this study opens new avenues for the field of quantum-engineered phytotherapeutics and precision oncological materials. While our work was strictly delimited to analytical modeling and validation against established physical constraints, these insights provide explicit quantitative design rules for creating next-generation biomimetic therapeutic platforms. Future engineering efforts can exploit this mechanism by designing lipid-nanoparticle systems that artificially minimize the interfacial dielectric constant (ϵ_{int}) or organize donor–acceptor supramolecular assemblies within rigid, highly oriented subnanometer geometries, thereby structurally securing the optimal SISE parameter space identified in this work. Additionally, future extensions of the model may incorporate multidimensional nuclear trajectories to evaluate contributions from transverse vibrational modes and investigate how structural modifications within synthetic curcuminoid libraries influence the excited-state dipole displacement ($\Delta\mu_0$). Such developments could enable the rational optimization of photoinduced oxidative amplification and provide a foundation for selectively maximizing malignant-cell destruction while preserving healthy tissue.

Ethics approval and consent to participate

Not Applicable

Consent for publication

Not Applicable

Availability of data and material

Not applicable

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

M.U¹ - Conceptualization, formulation, Computation, Manuscript draft, analysis and supervision.
PNP², JN⁴ AAA³, NCE⁵ MN⁶ - Formulation, Review and Chemical Context analysis.

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Not Applicable

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