

Fluorescent resonant energy transfer: Correlated fluctuations of donor and acceptor

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Mounting evidence suggests that in single-molecule fluorescent resonant energy transfer (FRET) measurements, correlation between fluctuations in donor and acceptor may be important. We present a general theory to describe this correlation and its effect on the FRET rate. The correlation arises from low-energy excitations (e.g., acoustic phonons) of the molecule to which a donor-acceptor pair is attached, and results in an effective interaction between local environments or baths associated with the donor and the acceptor. The correlation is found to reduce the transfer rate, in particular, at short donor-acceptor distances. The theory can quantitatively explain recent measurements of polyproline peptides. © 2007 American Institute of Physics. [DOI: 10.1063/1.2812540]

Fluorescent resonant energy transfer (FRET) is a powerful and convenient optical tool to track biological conformational changes.^{1–4} Förster showed several decades ago in his seminal work⁵ that the transfer rate k depends on the donor-acceptor distance r in a power law, $k \propto 1/r^6$, which is the scientific foundation of using FRET as a “spectroscopic ruler.”¹ Förster’s theory assumes that motions of donors and acceptors are completely decoupled,^{5,6} which may be justified in disordered systems. In a crystal, as pointed out by Soules and Duke,⁷ however, the decoupling between donor and acceptor is unlikely, since they are both coupled to the same lattice vibrational modes. Recent advancement in the FRET technology makes it possible to detect biological activity at the single-molecule level.^{3,4} Fundamentally, as the size of a system reduces to such a microscopic level, the atomic motions become less stochastic but more coherent. Since a donor-acceptor pair in most single-molecule FRET measurements is connected through a common molecule, one expects that coherent atomic motions in the molecule would translate into an undiminished correlation between fluctuations of the donor and the acceptor. Experimentally, it is shown that fluctuations in the locations of donor and acceptor are correlated in DNA.⁸ Recent single-molecule FRET experiments also indicate that when the donor-acceptor distance is short, the measured transfer rates are not well described by the Förster formula, even after possible molecular bending has been taken into account.^{9,10} Although this discrepancy may be explained by arguing that the relative orientation between the electrical dipoles of donor and acceptor is not totally random when they are close to each other,⁹ it remains unclear how the distance between them quantitatively affects the dipole orientations. On the other hand, this incomplete randomness can be viewed as correlated rotations of donor and acceptor dipoles, which, in a general sense, is a manifestation of correlated motions of donor and acceptor.

In this paper, we develop a general theory to describe correlated fluctuations of donor and acceptor in FRET and their effect on the transfer rate. This theory also provides a consistent method to describe interactions between local environments, which is fundamentally important in its own right.

The resonant energy (exciton) transfer between a donor and an acceptor has been commonly studied by a spin-boson Hamiltonian,^{7,11–14} where the exciton is coupled to two uncoupled baths associated with the donor and the acceptor,

$$H = H_e + H_b^0 + H_{e-b}, \quad (1)$$

$$H_e = \sum_{i=1,2} E_i^0 a_i^\dagger a_i + U_{12}(a_1^\dagger a_2 + a_2^\dagger a_1), \quad (2)$$

$$H_b^0 = \sum_{i\lambda} \omega_\lambda \left(b_{i\lambda}^\dagger b_{i\lambda} + \frac{1}{2} \right), \quad (3)$$

$$H_{e-b} = \sum_{i\lambda} \left(\frac{c_\lambda^2}{2\omega_\lambda} \right)^{1/2} (b_{i\lambda} + b_{i\lambda}^\dagger) a_i^\dagger a_i. \quad (4)$$

Here, a_i^\dagger (a_i) creates (annihilates) an exciton on the donor ($i=1$) or acceptor ($i=2$), E_i^0 the exciton energy, and $U_{12} \equiv \vec{\mu}_1 \cdot \nabla(\vec{\mu}_2 \cdot \vec{r}/r^3)$ the dipole-dipole interaction between the donor and the acceptor. $b_{i\lambda}^\dagger$ ($b_{i\lambda}$) creates (annihilates) a bosonic excitation at the λ th mode in the donor or acceptor bath. To capture major physics without losing generality, we consider two degenerate baths and an identical interaction between the exciton and the two baths. The exciton-bath coupling is characterized by the spectral density $J(\omega) = (\pi/2) \sum_\lambda (c_\lambda^2/\omega_\lambda) \delta(\omega - \omega_\lambda)$. The bath variables in H_{e-b} can be written as the displacement of donor or acceptor, $x_i = \sum_\lambda \sqrt{c_\lambda^2/2\omega_\lambda} (b_{i\lambda} + b_{i\lambda}^\dagger)$. Here, the exciton-bath coupling strength has been absorbed in the displacement variable. For uncorrelated baths, $\langle x_1 x_2 \rangle = 0$.

However, as illustrated in Fig. 1, a donor and an acceptor in single-molecule FRET are attached to a same molecule, or more generally, a common environment, which has low-

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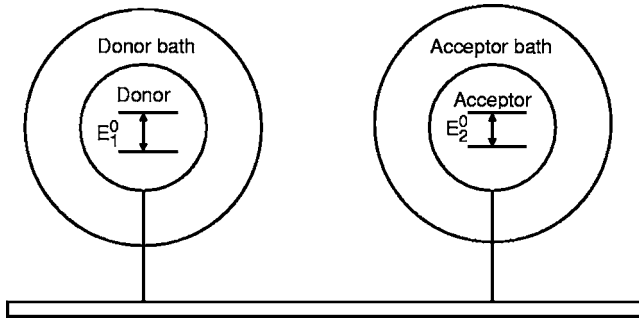


FIG. 1. Schematic diagram showing the donor-acceptor correlation and its effect on the donor and acceptor baths. The donor and the acceptor are attached to a molecule, represented by the long bar, which mediates the interaction between the two baths, represented by the two ring areas.

energy excitations with a typical dispersion $\omega_{\mathbf{q}} \propto |\mathbf{q}|$, where \mathbf{q} is the momentum and $\omega_{\mathbf{q}}$ is the frequency. Consequently, the equilibrium position x_i^0 of the displacement x_i are slowly fluctuating. For a quasi-one-dimensional (1D) long molecule, such as DNA and polyproline, where acoustic phonons are the main low-energy excitations,

$$x_i^0 \propto \sum_q \sqrt{\frac{1}{NM\omega_q}} (e^{iqR} d_q + e^{-iqR} d_q^\dagger), \quad (5)$$

where d_q^\dagger (d_q) is the creation (annihilation) operator of the acoustic phonons, N is the number of atoms in the system, and M is the atomic mass. The spatial correlation function is

$$\overline{x_1^0 x_2^0} \propto \sum_{|q| \geq \xi^{-1}} \frac{1}{NM\beta\omega_q^2} e^{iqR} \propto \int dq \frac{e^{iqR}}{\beta(q^2 + \xi^{-2})} \propto \frac{e^{-R/\xi}}{\beta},$$

where $\beta \equiv 1/k_B T$ with k_B being the Boltzmann constant and T temperature, $R = |R_1 - R_2|$ is the molecular contour length between the donor and acceptor, and $\beta\hbar\omega_q \ll 1$ has been used. Here, we have introduced a low-momentum cutoff ξ^{-1} , which is due to the finite length of a molecule. For a flexible molecule, ξ is determined by a persistence length beyond which the bending becomes significant. Correlations caused by high-energy excitations (e.g., optical phonons) are of short range and therefore less important. Defining Γ as the correlation strength, we can write

$$\overline{x_1^0 x_2^0} = \frac{\Gamma}{\beta} e^{-R/\xi}. \quad (6)$$

Since the displacement variables with respect to x_i^0 in the two baths are independent, $\langle (x_1 - x_1^0)(x_2 - x_2^0) \rangle = 0$, it follows that

$$\langle x_1 x_2 \rangle \equiv \sum_{\lambda} c_{\lambda}^2 \langle Q_{1\lambda} Q_{2\lambda} \rangle = \overline{x_1^0 x_2^0}, \quad (7)$$

where the normal coordinates $Q_{i\lambda} = \sqrt{1/2\omega_{\lambda}}(b_{i\lambda} + b_{i\lambda}^\dagger)$. Hence, a correlation between the donor and acceptor fluctuations entails an effective coupling between the two baths, $\langle Q_{1\lambda} Q_{2\lambda} \rangle \neq 0$. We emphasize that the correlations discussed here are spatial and equal time, which are distinct from the temporal correlations.¹²

To describe the interacting baths, we augment the non-interacting H_b^0 , which can be written in terms of normal coordinates, $H_b^0 = (1/2) \sum_{i\lambda} (P_{i\lambda}^2 + \omega_{\lambda}^2 Q_{i\lambda}^2)$, by a crossing term

$$H_b = H_b^0 - \sum_{\lambda} \gamma_{\lambda} \omega_{\lambda}^2 Q_{1\lambda} Q_{2\lambda}. \quad (8)$$

Under this new Hamiltonian of the baths, $\langle Q_{1\lambda} Q_{2\lambda} \rangle$ can be evaluated via

$$\langle Q_{1\lambda} Q_{2\lambda} \rangle = \int dQ_{1\lambda} dQ_{2\lambda} Q_{1\lambda} Q_{2\lambda} e^{-\beta H_b} = \frac{\gamma_{\lambda}}{\beta \omega_{\lambda}^2 (1 - \gamma_{\lambda}^2)}.$$

If we assume that γ_{λ} is independent of λ , $\gamma_{\lambda} = \gamma$, we obtain, from Eqs. (6) and (7),

$$\frac{\gamma}{1 - \gamma^2} = \frac{\Gamma}{\eta} e^{-R/\xi}, \quad (9)$$

where $\eta \equiv \int_0^{\infty} d\omega J(\omega)/\omega\pi$ is the reorganization energy. For the widely used Debye spectral density, $J_{De}(\omega) = \eta_0 \omega_c \omega / (\omega^2 + \omega_c^2)$, $\eta = \eta_0/2$. The positive definiteness of H_b requires $\gamma < 1$. Equation (9) is a major result of this paper, which relates the coupling between two baths to the correlation function in a molecule that connects them.

The crossing term in H_b means that $Q_{i\lambda}$ are no longer normal coordinates. By diagonalizing H_b , the normal coordinates and the corresponding frequencies become

$$Q_{\lambda\pm} = \frac{1}{\sqrt{2}} (Q_{1\lambda} \pm Q_{2\lambda}), \quad (10)$$

$$\omega_{\lambda\pm}^2 = \omega_{\lambda}^2 (1 \mp \gamma), \quad (11)$$

and $H_b = \sum_{\lambda\pm} \omega_{\lambda\pm} (b_{\lambda\pm}^\dagger b_{\lambda\pm} + 1/2)$, where $b_{\lambda\pm} = (1/\sqrt{2}) \times [\gamma_{\pm} (b_{1\lambda} \pm b_{2\lambda}) + \gamma'_{\pm} (b_{1\lambda}^\dagger \pm b_{2\lambda}^\dagger)]$, $\gamma_{\pm} = [(1 \mp \gamma)^{1/4} + (1 \mp \gamma)^{-1/4}]/2$, and $\gamma'_{\pm} = [(1 \mp \gamma)^{1/4} - (1 \mp \gamma)^{-1/4}]/2$. Here, we see that the coupling between the two baths splits the originally degenerate modes into two, one is in-phase, with a lower frequency, the other is out-of-phase, with a higher frequency. Accordingly, we rewrite Eq. (4) as

$$H_{e-b} = \sum_{\lambda} F_{\lambda+} (b_{\lambda+} + b_{\lambda+}^\dagger) (a_1^\dagger a_1 + a_2^\dagger a_2) + \sum_{\lambda} F_{\lambda-} (b_{\lambda-} + b_{\lambda-}^\dagger) (a_1^\dagger a_1 - a_2^\dagger a_2), \quad (12)$$

where $F_{\lambda\pm} = (c_{\lambda}^2/4\omega_{\lambda\pm})^{1/2}$.

The linear terms of $b_{\lambda\pm}$ and $b_{\lambda\pm}^\dagger$ in Eq. (12) can be eliminated by the following canonical transformation, $\tilde{H} = e^{-X} H e^X$,

$$X = \sum_{\lambda} \frac{F_{\lambda+}}{\omega_{\lambda+}} (b_{\lambda+} - b_{\lambda+}^\dagger) (a_1^\dagger a_1 + a_2^\dagger a_2) + \sum_{\lambda} \frac{F_{\lambda-}}{\omega_{\lambda-}} (b_{\lambda-} - b_{\lambda-}^\dagger) (a_1^\dagger a_1 - a_2^\dagger a_2),$$

$$\tilde{H} = \sum_i E_i a_i^\dagger a_i + \sum_{\lambda\pm} \omega_{\lambda\pm} \left(b_{\lambda\pm}^\dagger b_{\lambda\pm} + \frac{1}{2} \right) + \tilde{H}_{\text{int}}, \quad (13)$$

where E_i is the renormalized exciton energy, $E_i = E_i^0 - \sum_{\lambda\pm} F_{\lambda\pm}^2 / \omega_{\lambda\pm}$, and

$$\begin{aligned} \tilde{H}_{\text{int}} = U_{12} & \left\{ \exp \left[- \sum_{\lambda} \frac{2F_{\lambda-}}{\omega_{\lambda-}} (b_{\lambda-} - b_{\lambda-}^{\dagger}) \right] a_1^{\dagger} a_2 \right. \\ & \left. + \exp \left[\sum_{\lambda} \frac{2F_{\lambda-}}{\omega_{\lambda-}} (b_{\lambda-} - b_{\lambda-}^{\dagger}) \right] a_2^{\dagger} a_1 \right\}. \end{aligned} \quad (14)$$

From the above expression, we see that only the out-of-phase modes ($b_{\lambda-}$) contribute to exciton transfer from donor to acceptor, whereas the in-phase modes ($b_{\lambda+}$) have no effect, which is reasonable because the in-phase modes couple to donor and acceptor equally, as displayed in Eq. (12).

The rate of energy transfer due to \tilde{H}_{int} can be calculated by the standard Fermi golden rule, as discussed extensively in the literature on polarons^{7,15,16} and on electron (energy) transfer.¹⁷ In the semiclassical regime, to which most biological systems belong, the transfer rate can be written as

$$k(1 \rightarrow 2) = U_{12}^2 \frac{\sqrt{\pi}}{S} \exp[-(\Delta - W)^2/4S^2], \quad (15)$$

where $\Delta \equiv E_1 - E_2$, $S^2 = \sum_{\lambda} 2|F_{\lambda-}|^2 \coth(\beta\omega_{\lambda-}/2)$, and $W = \sum_{\lambda} 4|F_{\lambda-}|^2/\omega_{\lambda-}$. In the high-temperature (classical) approximation, $\beta\omega_{\lambda-} \ll 1$, $S^2 \approx \eta/\beta(1+\gamma)$, and $W = \beta S^2$. Thus, the transfer rate is

$$k \propto \sqrt{\frac{\beta(1+\gamma)}{\eta}} \exp \left\{ - \frac{\beta[(1+\gamma)\Delta - \eta]^2}{4\eta(1+\gamma)} \right\} \frac{1}{r^6}, \quad (16)$$

where $1/r^6$ comes from the dipole-dipole interaction U_{12} and γ is the solution to Eq. (9) for given Γ , η , and ξ . Equation (16) is another major result in this paper, which quantifies the effect of a donor-acceptor correlation on the energy transfer rate. We distinguish r , the straight-line distance, and R , the contour length, in the above expression, since they may have different values because of molecular bending. The exponential in Eq. (16) can be obtained classically by analyzing the free energies of the donor and acceptor. If we use solvent coordinate Q_1 for the donor and Q_2 for the acceptor, with a same vibrational frequency Ω , the appropriate coordinate describing energy transfer is $Q_- = (1/\sqrt{2})(Q_1 - Q_2)$ with frequency $\Omega_- = \Omega(1+\gamma)^{1/2}$. The energy potentials are $G_D(Q_-) = E_1 + (1/2)\Omega_-^2 Q_-^2 + A Q_-$ for the donor and $G_A(Q_-) = E_2 + (1/2)\Omega_-^2 Q_-^2 - A Q_-$ for the acceptor with A being the coupling between the donor/acceptor and the solvent. G_D and G_A are parabolas with minima at $X_D = -(A/2\Omega_-^2)$ and $X_A = A/2\Omega_-^2$, respectively, and the reorganization energy is then $\eta_- \equiv G_A(X_D) - G_A(X_A) = A/2\Omega_-^2 = \eta(1+\gamma)$. Classically energy transfer occurs when the energy potentials cross, $G_D(X) = G_A(X)$, or $X = -(E_1 - E_2)/A$. Hence, the transfer rate is $k \propto e^{-\beta\delta G}$ with the activation energy $\delta G = G_D(X) - G_D(X_D) = (\Delta - \eta_-)^2/4\eta_-$.

If we write the transfer rate at $\gamma=0$ as $k_0 = \tau_D^{-1}(r_0/r)^6$ with τ_D being the donor fluorescent lifetime in the absence of an acceptor, the transfer rate of Eq. (16) is $k = \Lambda(R)k_0$, where

$$\Lambda(R) = (1+\gamma)^{1/2} \exp \left\{ - \beta \frac{\gamma}{4(1+\gamma)\eta} [(1+\gamma)\Delta^2 - \eta^2] \right\}. \quad (17)$$

Consequently, the fluorescent transfer efficiency, $E \equiv 1 - \tau_D'/\tau_D$ (τ_D' is the donor fluorescent lifetimes in the presence an acceptor), as a function of R is

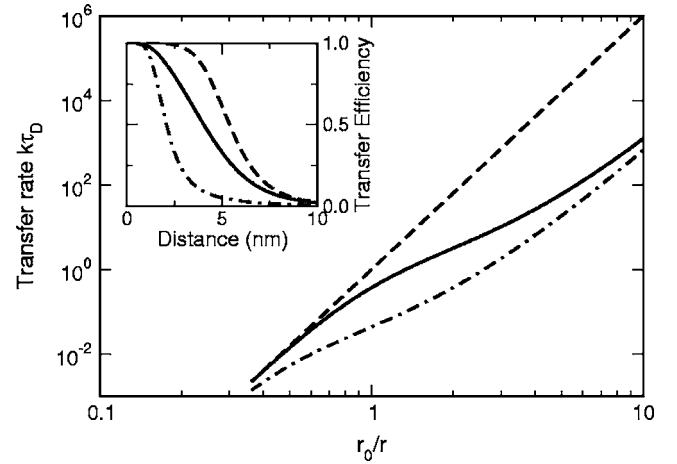


FIG. 2. Transfer rate $k\tau_D$ as a function of distance for different correlation lengths ξ . Dashed, solid, and dot-dashed lines correspond to $\xi=0$ (no correlation), 2.4 and 5 nm, respectively. The inset shows the transfer efficiency E as a function of r . Other parameters are $\Gamma=0.05$ eV, $\Delta=0.45$ eV, $\eta=0.1$ eV, and $r_0=5.4$ nm.

$$E(R) = \left[1 + \Lambda^{-1}(R) \left(\frac{r}{r_0} \right)^6 \right]^{-1}. \quad (18)$$

It is readily seen that when $\gamma=0$, $\Lambda=1$ and the above expression reduces to the Förster formula, $E = [1 + (r/r_0)^6]^{-1}$. In the case of weak correlations, where $\gamma \ll 1$, $\Lambda \propto \exp[-\beta\gamma(\Delta^2 - \eta^2)/4\eta]$, and we see that nonzero γ would reduce the transfer rate. This can be understood by noticing that the transfer is facilitated only by the out-of-phase modes, which have higher frequencies because of the couplings between the baths ($\omega_{\lambda-} > \omega_{\lambda}$) and are therefore more difficult to be excited. Figure 2 illustrates effects of the donor-acceptor correlation on the exciton transfer rate k and efficiency E in a system with representative parameters, $\Delta=0.45$ eV, $\eta=0.1$ eV, and $r_0=5.4$ nm (see below). It is also temporarily set $R=r$, i.e., the molecule is rigid. We see that at short distances, the transfer rate is reduced in the presence of the donor-acceptor correlation, compared to that from the Förster formula. This reduction decreases with the donor-acceptor distance and eventually diminishes when the distance is greater than ξ . From the transfer-efficiency plot in the inset of Fig. 2, we see that the donor-acceptor correlation leads to a smaller effective Förster radius, $r_{0e} < r_0$ [$E(r_{0e}) \equiv 1/2$], $r_{0e}=4.1$ nm for $\xi=2.4$ nm, and $r_{0e}=2.1$ nm for $\xi=5$ nm. Thus, for a given Γ , the larger ξ the smaller r_{0e} .

Now we apply the theory to a recent systematic single-molecule FRET study of 1D polyproline.⁹ Such a long molecule is susceptible to bending. We follow the works of Bresler and Frenkel¹⁸ and Landau and Lifshitz¹⁹ and consider the long molecule to be a uniform and continuous chain, whose shape at a given point is described by the curvature vector. This model is similar to but simpler than the widely used Gaussian and wormlike chain models.²⁰ The free energy associated with bending is^{18,19}

$$\Delta F = \frac{1}{2} \int \left[\alpha_1 \left(\frac{d\theta_1}{dl} \right)^2 + \alpha_2 \left(\frac{d\theta_2}{dl} \right)^2 \right] dl, \quad (19)$$

where α_1 and α_2 are the principal values of the resistance-to-bending tensor and θ_1 and θ_2 are the angles of rotations of

the tangent to the chain at $l+dl$, $\mathbf{t}_{l+\delta l}$, relative to the tangent at l , \mathbf{t}_l , in the two planes made of \mathbf{t}_l and the two principal axes of the resistance-to-bending tensor. The straight-line distance r between two points with contour length R in the chain can be obtained by minimizing the free energy,^{18,19}

$$\langle r^2 \rangle = 2\alpha^2\beta^2 \left(\frac{R}{\alpha\beta} - 1 + e^{-R/\alpha\beta} \right), \quad (20)$$

where $2\alpha^{-1} = \alpha_1^{-1} + \alpha_2^{-1}$. Substituting Eq. (20) into Eq. (18), we have

$$E(R) = \left[1 + 8\Lambda^{-1}(R) \left(\frac{l_0}{r_0} \right)^6 \left(\frac{R}{l_0} + e^{-R/l_0} - 1 \right)^3 \right]^{-1}, \quad (21)$$

where $l_0 \equiv \alpha\beta$ defines the persistence length of a flexible molecule.

In the experiment, energy transfer occurs from a green-fluorescing donor dye (488 nm or 2.54 eV) at the carboxyl terminus to a red-fluorescing acceptor dye (594 nm or 2.09 eV) at the amino terminus⁹ and, therefore, $\Delta = 2.54 - 2.09 = 0.45$ eV. Using the Förster formula, $r_0 = 5.4$ nm was obtained for this dye pair in water from the measured overlap integral of the normalized donor-emission and acceptor-absorption spectra.⁹ To retain its physical meaning and significance, we keep $r_0 = 5.4$ nm fixed because the correlation effect is expected to be weak in water, $\Lambda \approx 1$. We choose a typical value of the reorganization energy, $\eta = 0.10$ eV.¹⁷ Since the finite ξ can be caused by molecular bending, as we mentioned earlier, we set $\xi = l_0$. Now we have only two adjustable parameters, Γ and ξ , which quantify both the donor-acceptor correlation and molecular bending. Experimentally the transfer efficiency were obtained from single-molecule measurements (SMMs) and time-correlated single-photon measurements (TCSPMs). Since the latter tends to underestimate the efficiency due to a possible pileup effect, we fit our theory to the data from SMM. An excellent fit is found, as shown by the solid line in Fig. 3, for the entire experimentally measured range of R , by using $\Gamma = 0.05$ eV and $\xi = 2.4$ nm. The value of $\xi = l_0 = 2.4$ nm suggests that the molecule is fairly flexible and starts bending when the contour length is greater than 2.4 nm. If both Γ and ξ are set zero, namely, the donor-acceptor correlation is absent and the molecule is rigid, the transfer rate reduces to the well-known Förster result, as shown by the dot-dashed line in Fig. 3, which, compared to the experimental data, overestimates the transfer efficiency at shorter contour lengths (< 5 nm) and underestimates the efficiency at longer contour lengths (> 5 nm). If we neglect the correlation but allow the molecule to bend, the transfer rate is in a fairly good agreement with the experiment for contour lengths larger than 10 nm, but seriously overestimates the rate at shorter contour lengths, suggesting that the donor-acceptor correlation is particularly important at short contour lengths, where the molecular bending is weak. The strong correlation effect at short distances is also reflected in the γ versus R plot, as shown in the inset of Fig. 3, where $\gamma \geq 0.2$ for $R \leq 2.0$ nm, suggesting that the donor and acceptor baths are strongly coupled at those distances.

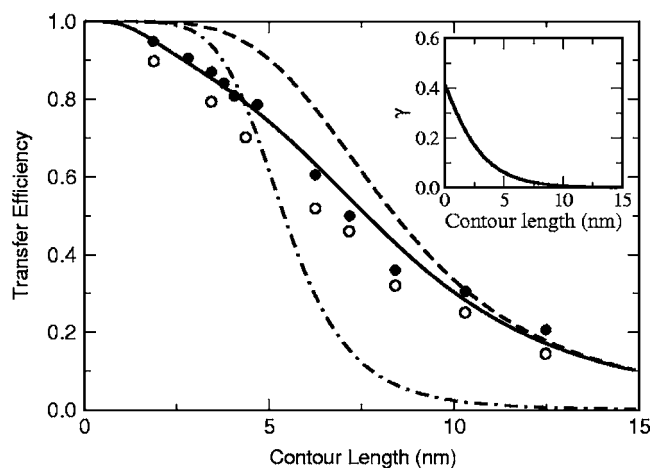


FIG. 3. Transfer efficiency E as a function of the contour length. Filled and open circles are the mean transfer efficiencies from SMM and TCSPM, respectively (Ref. 9). The lines are theoretical results from Eq. (21) with three parameter sets: (1) $\Gamma = 0.05$ eV and $\xi = l_0 = 2.4$ nm (solid); (2) $\Gamma = 0$ and $l_0 = 2.4$ nm (dashed); (3) $\Gamma = 0$ and $l_0 = \infty$ (dot-dashed). The inset shows γ as a function of the contour length. Other parameters are the same as those in Fig. 2.

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