A Nanoscale Communication Channel with Fluorescence Resonance Energy Transfer (FRET)

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***Abstract*—In this study, a novel and physically realizable nanoscale communication paradigm is introduced based on a well-known phenomenon, Fluorescence Resonance Energy Transfer (FRET) for the first time in the literature. FRET is a non-radiative energy transfer process between fluorescent molecules based on the dipole-dipole interactions of molecules. Energy is transferred rapidly from a donor to an acceptor molecule in a close proximity such as 0 to 10 nm without radiation of a photon. Low dependency on the environmental factors, controllability of its parameters and relatively wide transfer range make FRET a promising candidate to be used for a high rate nanoscale communication channel. In this paper, the simplest form of the FRET-based molecular communication channel for a single transmitter and a single receiver nanomachine is modeled. Furthermore, using the information theoretical approach, the capacity of the point-to-point communication channel is investigated and the dependency of the capacity on some environmental and intrinsic parameters is analyzed. It is shown that the capacity can be increased by appropriately selecting the donor-acceptor pair, the medium, the intermolecular distance and the orientation of the molecules.**

I. Introduction

Nanoscale communication is a novel and quite interdisciplinary research area. In recent years, several potential approaches have been proposed in order to achieve communication in nanoscale such as electromagnetic, acoustic, nanomechanical or molecular [1]-[3]. In this paper, we introduce a novel and radically different method for the communication in the molecular scale by exploiting a well-known, physical controllable phenomenon, Fluorescence (or Förster) Resonance Energy Transfer (FRET).

FRET is a non-radiative energy transfer process between fluorescent molecules and widely used in studies of biotechnological research including fluorescence microscopy, molecular biology and optical imaging [4]-[6]. The phenomenon yields a significant amount of structural information about the donor and acceptor pair, therefore, many methods based on FRET have been developed and used in these areas. For example, using its strong dependence on distance, FRET is exploited as a spectroscopic ruler [7] while determining the intramolecular and intermolecular distances and monitoring the conformational changes of proteins [8].

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In this study, for the first time in the literature, FRET has been approached from the communication perspective and introduced as a novel molecular communication paradigm. There are many biologically inspired and theoretically modeled molecular communication techniques in the literature including the communication models devised based on intercellular calcium signaling [3], molecular motors and microtubules [9], pheromones [10], flagellated bacteria and catalytic nanomotors [11], carbon nanotubes [12], DNA and motor proteins [13], pollen and spores [10], as well as morphogenesis [14] in order to encode, transfer and decode information. FRET-based communication method is based on a physically existing phenomenon and unlike the other techniques it provides significantly higher capacity communication. The excited state energy of molecules that conveys the information is transferred in the picosecond range so that FRET-based communication is incomparably faster than the already proposed nanoscale communication techniques. Furthermore, high-level controllability of almost all of the system parameters and low dependence on the uncontrollable environmental factors make FRET-based channel much more reliable. The abundance of both theoretical and practical studies about FRET in the literature and availability of its experimental setups provide the opportunity of making improvements validating theoretical model based on experiments. Already in some studies, novel improvements on FRET technology such as multistep resonance energy transfer with sequentially located fluorophores has been achieved experimentally [15], [16]. Hence, unlike most of the existing approaches in the literature, we introduce an already analyzed and experimented, therefore, much more realistic solution to the problem of nanoscale communication.

The remainder of this paper is organized as follows. In Section II of the study, we explain the basic concepts of FRET and underline the governing physical laws and its mathematical formulation of FRET theory. In section III, we model the FRET-based communication channel with a single donor-acceptor pair. An information theoretical analysis of FRET-based channel is performed in Section IV in order to determine the closed-form expression for the capacity of the channel. In Section V, we analyze the dependence of the channel capacity on some environmental and intrinsic factors and demonstrate a selection strategy for these parameters to achieve higher communication capacity. Finally, the concluding remarks are

given in Section VI.

II. Theory of FRET

FRET is non-radiative energy transfer process observed among a wide range of fluorescent molecules including quantum dots, organic dyes and polymers [17]. This electrodynamic phenomenon is based on long-range dipole-dipole interaction between a donor fluorophore in its excited state and an acceptor molecule -not necessarily fluorophore- in its ground state and that are spatially separated in a close proximity. When the donor fluorophore is excited by an incident light, it may transfer its excited state energy to an acceptor molecule through FRET and relaxes to its ground state if certain conditions are satisfied. First of all, donor and acceptor molecules must be located in a close proximity like 0-10 nm. In addition to the proximity requirement, the spectral characteristics of donor and acceptor molecules must have significant similarity, i.e., the overlapping area of the emission spectrum of donor and the absorption spectrum of acceptor, must be large enough. Relative orientations of donor and acceptor also play an important role in the efficiency of the resonance energy transfer. Additionally, extinction coefficients of donor and acceptor, refractive index of the medium and lifetime of donor fluorophore are the other factors that affect the energy transfer efficiency and rate.

In 1948, Theodor Förster postulated the governing equations in the theory of non-radiative energy transfer in his well-known article [19] outlining the quantum-mechanical behavior of FRET. The first parameter that characterizes the donor-acceptor pairs is the Förster Radius, the distance between donor and acceptor molecules when the efficiency of the energy transfer is 50% and given by

$$R_0^6 = \frac{9000ln(10)\kappa^2 Q_D}{128\pi^5 N n^4} \int_0^\infty F_D(\lambda)\epsilon_A(\lambda)\lambda^4 \mathrm{d}\lambda \qquad (1)$$

where the κ^2 is the orientation factor, Q_D is the quantum yield of the donor fluorophore, n is the refractive index of the medium, N is the Avagadro's number. The integral part of 1 yields the degree of the overlap of the emission spectrum of the donor and the absorption spectrum of the acceptor and denoted by $J(\lambda)$,

$$J(\lambda) = \int_0^\infty F_D(\lambda)\epsilon_A(\lambda)\lambda^4 \mathrm{d}\lambda \qquad (2)$$

where $F_D(\lambda)$ is the normalized fluorescence emission intensity and $\epsilon_A(\lambda)$ is the acceptor molar absorptivity. Here, the orientation factor (κ^2) is the most problematic, i.e., with the highest uncertainty, parameter of the phenomenon given as

$$\kappa^2 = (\cos\theta_T - 3\cos\theta_D \cos\theta_A)^2 \qquad (3)$$

where θ_T is the angle between the emission transition dipole of the donor and the absorption transition dipole of the acceptor, θ_D and θ_A are the angles between these dipoles and vector joining the donor and the acceptor [20]. It is not possible to determine the exact relative orientation of donor and acceptor, i.e. the exact value of κ^2, however, it ranges between 0 and 4 [17]. $\kappa^2 = 0$ when the transition dipoles are perpendicular to each other and $\kappa^2 = 4$ when they are parallel. In most studies, donor and acceptor are supposed to randomly rotate and κ^2 is assumed to be $2/3$ [17].

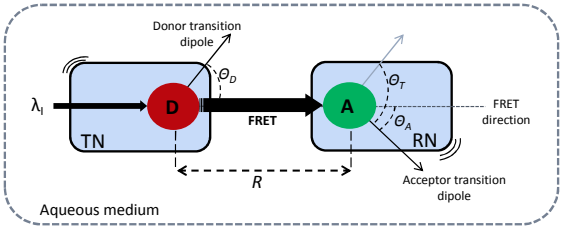

Fig. 1. Point-to-point FRET-based molecular communication channel model which a single TN communicates a single RN by transferring energy via FRET.

The efficiency of the energy transfer as a function of intermolecular distance and Förster radius, R_0 is formulated as

$$E[R] = \frac{R_0^6}{R_0^6 + R^6} \qquad (4)$$

where R is the distance between the donor and the acceptor molecules.

Consequently, the rate of the energy transfer is given by

$$k_T[R] = \frac{1}{\tau_D}\left(\frac{R_0}{R}\right)^6 \qquad (5)$$

where the τ_D is the donor lifetime, i.e., the time the donor remains in its excited state. Normally, in the absence of any non-radiative relaxation process, it is determined by only the radiative emission rate, k_R and given as

$$\tau_D = \frac{1}{k_R} \qquad (6)$$

In the case of FRET, the energy transfer to the acceptor causes a reduction in the donor's excited state lifetime and it can be formulated as

$$\tau_{DA} = \frac{1}{k_R + k_T} \qquad (7)$$

where τ_{DA} is the donor's excited state lifetime when it releases the energy through FRET.

III. FRET-Based Nanoscale Communication Channel

We constructed our communication model with a single donor molecule bound to a transmitter nanomachine (TN), and a single acceptor molecule bound to a receiver nanomachine (RN), at fixed locations separated by a reasonable distance R in an aqueous medium considering FRET as the communication channel with the system exciton being a carrier as shown in Fig. 1. Assuming the molecules are properly selected, i.e., they have sufficient spectral overlap (J_λ), in the case of a donor excitation, FRET occurs with probability of P_{FRET}. When a laser source excites the donor at a proper wavelength, there are two ways of relaxation for the donor, one is through radiative

emission and the other is through resonance energy transfer. In FRET spectroscopy, the FRET efficiency is determined by continuously exciting the donor and calculating the proportion of the number of FRET relaxations to the number of total relaxation processes in a specified time interval [21]. Therefore, for a single cycle of excitation and relaxation of the donor, the FRET efficiency can be considered as the probability of the resonance energy transfer. Thus, for a single exciton, the probability of FRET as a function of intermolecular distance can be given by

$$P_{FRET} = \frac{R_0^6}{R_0^6 + R^6} \tag{8}$$

where R_0 is the Förster radius and calculated according to (1) assuming rapid randomization of relative orientation of molecules, i.e., $\kappa^2 = 2/3$, and a refractive index of 1.3342 which is the index of water at $25\,^{\circ}\mathrm{C}$. With these constraints, for a pair consisting of Enhanced Cyan Fluorescent Protein (ECFP) as donor and Enhanced Yellow Fluorescent Protein (EYFP) as acceptor, the Förster radius is calculated as 4.92 ± 0.10 nm [22]. Both ECFP and EYFP are the variants of Green Fluorescent Protein (GFP) and widely used in various fluorescence spectroscopy applications for their photostability, high extinction coefficients and high quantum yields [23], [24]. At the same time, the pair ECFP-EYFP is a good candidate for communication purposes due to the relatively large value of R_0.

Excited state lifetime is a critical parameter determining the excitation waveform of the laser in the sense that an excited fluorophore cannot be re-excited until it relaxes to the ground state [25]. For example, the donor molecule cannot transfer the excited state energy to the acceptor through FRET if the acceptor is still in its excited state as a result of the preceding FRET process. Considering this fact, the waveform of the laser excitation consists of very short pulses (picosecond range) compared to the lifetimes of the molecules, and in the case of successive release of two pulses, the minimum interval between them, i.e., excitation period, (t_H) must be reasonably greater than the maximum of the donor's and acceptor's lifetimes that is,

$$t_H > \max\left(\tau_D, \tau_A\right) \tag{9}$$

where τ_D and τ_A are the excited state lifetimes of the donor and the acceptor, respectively. For the previously mentioned pair ECFP-EYFP, the lifetimes are measured as 2.68 ± 0.07 ns for the donor ECFP and 2.88 ± 0.05 ns for the acceptor EYFP [26]. These values are the average of many values recorded during the measurement since lifetimes of fluorophores are not constant all the time. Thus, in practice, the lifetime can be shorter or longer than the measured average value.

In the model, we implemented On-Off Keyed Modulation with two bits available as in the traditional digital communication. The excitation of the donor by the laser source at the beginning time instant of a time interval (t_H) corresponds to bit 1, and no-excitation at the beginning time instant of a time interval corresponds to bit 0. The RN checks whether the acceptor is excited through FRET or not during the corresponding time interval. If it is excited by the TN molecule, it decides that the TN transmitted bit 1 and if it is not excited it decides that the TN transmitted bit 0.

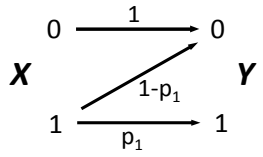

Fig. 2. Z channel transition diagram with the transition probabilities.

IV. An Information Theoretical Analysis for FRET-Based Communication

The FRET Channel is modeled similar to Z-channel with on-off keyed (OOK) modulation as in Fig. 2 disregarding the possible external noise factors such as autofluorescence materials in the environment or spectral bleed-through (SBT), i.e., direct excitation of the acceptor by the incident light and assuming that the period of excitation, i.e., t_H, is large enough so that re-excitation of previously excited molecules is prevented. Every time when the laser excites the donor at the beginning of the interval t_H, i.e., it intends to transmit bit 1 with probability P_F, the probability of FRET occurrence during that interval determines the success of transmission of bit 1. Thus, using (8), TN achieves to deliver bit 1 with probability of p_1 given in terms of intermolecular distance R as follows

$$p_1[R] = \frac{R_0^6}{R_0^6 + R^6} \tag{10}$$

Therefore, the probability of failure of transmitting bit 1 when the donor is excited is $(1 - p_1[R])$.

When the donor is not excited at the beginning of an interval, i.e., it intends to transmit bit 0 with the probability $(1 - P_F)$, the probability of FRET abstinence will give the success probability of bit 0. Assuming there is no noise factor that affects the channel like autoluminescence materials, this probability is unity, i.e., $p_0 = 1$. Therefore, in this case, the failure probability of transmitting bit 0 becomes $(1 - p_0) = 0$.

Although we disregard the external noise factors, the channel acts like a noisy channel since the probability of FRET occurrence is intrinsically not equal to 1. According to the transmission probabilities, the transition matrix of the Z-channel considering *X* as the transmitted bit by TN, and *Y* as the received bit by RN is given as

$$P(Y|X) = \begin{bmatrix} \Big(1 - P_F\Big)p_0 & \Big(1 - P_F\Big)\Big(1 - p_0\Big) \\ P_F\Big(1 - p_1[R]\Big) & P_F\ p_1[R] \end{bmatrix}$$

The simplified form of the transition matrix for $p_0 = 1$ can be given by

$$P(Y|X) = \begin{bmatrix} \Big(1 - P_F\Big) & 0 \\ P_F\Big(\frac{R^6}{R_0^6 + R^6}\Big) & P_F\Big(\frac{R_0^6}{R_0^6 + R^6}\Big) \end{bmatrix}$$

Consequently, the mutual information *I(X;Y)* between *X* and *Y* can be inferred from the transition matrix as

$$I(X;Y) = H(P_F\ p_1[R]) - P_F\ H(1 - p_1[R]), \quad (11)$$

where *H(.)* denotes the binary entropy. Therefore, the capacity of the FRET channel, C_F, can be given by maximizing the mutual information as follows

$$C_F = \max\left[I(X;Y)\right] \quad (12)$$

It is possible to increase the channel capacity that varies in accordance with some external and intrinsic parameters by selecting appropriate excitation probabilities, i.e., P_F.

V. Numerical Analysis

In this section, we present the numerical analysis performed over the mutual information expression given in (11) to show how the FRET-based communication capacity varies according to some environmental parameters and some intrinsic parameters that are specific to the employed FRET pair. The aim of this analysis is to determine the appropriate configuration of FRET-based communication parameters, which can achieve high communication capacity according to changing environmental parameters. We perform the numerical analysis using MATLAB. The simulation parameters can be seen in Table I.

TABLE I
Simulation Parameters

Donor - Acceptor pair	EBFP - DsRed ECFP - EYFP EGFP - EYFP
Intermolecular distance (R)	$3 - 6$ x $10^{-9} m$
Refractive index (n)	1 (vacuum) 1.3342 (water at 25 °C) 1.5185 (silicon oil at 25 °C)
Orientation factor (κ^2)	$2/3$ (rapid randomization) 4 (parallel dipole moments)

A. Effect of Intermolecular Distance

For the first analysis, we investigate the effect of the intermolecular distance (R) on the capacity of FRET-based communication channel. The analysis is carried out with single donor and single acceptor configuration using ECFP-EYFP as the FRET pair assembled on the nanomachines assuming rapid randomization of the relative orientation of the molecules as well as the nanomachines in a medium of water at 25 °C.

Selecting the medium and orientation parameters as specified before, the Förster radius for ECFP - EYFP pair is calculated as $R_0 = (4.92 \pm 0.10)$ x $10^{-9} m$ [22]. In Fig. 3, mutual information ($I(X;Y)$) given in (11) is shown with varying excitation probability of the donor (P_F) for different R. For higher $R = 5 - 6$ x $10^{-9} m$ compared to the Förster distance that is specific to the selected donor-acceptor pair, the probability of resonance energy transfer in the case of donor excitation, i.e., p_1, significantly decreases. As a result, the transmission of bit 1 can be erroneous when the distance between the transmitter nanomachine (TN) and the receiver nanomachine (RN) is large. Therefore, the capacity decreases for higher R. On the other hand, when the nanomachines approach to each other, i.e., the intermolecular distance is small ($R = 3 - 4$ x 10^{-9} m), and hence the probability of successfully transmitting bit 1 increases. Therefore, the capacity increases with decreasing intermolecular distance. Consequently, it is necessary to select appropriate R and P_F according to the assembled donor - acceptor pair to achieve higher communication capacity. The capacity is maximized for $R = 3\ nm$ by $P_F = 0.474$. We find $C_{max} = 0.86\ bit$. Hence, we can communicate more information by using input symbol 0 more frequently than 1 with intermolecular distance of 3 nm.

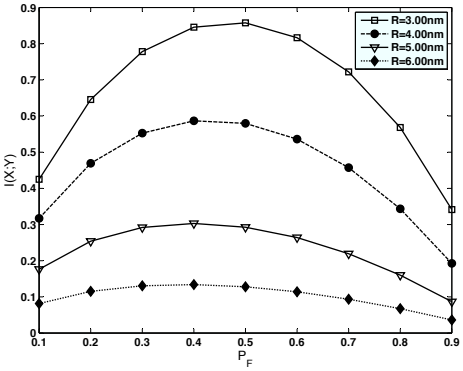

Fig. 3. $I(X;Y)$ with varying P_F for different R.

B. Effect of Medium

In this analysis, we investigate the effect of varying the refractive index of the medium on the channel capacity. The analysis is carried out with single ECFP-EYFP pair as the donor and the acceptor assembled on the transmitter and the receiver nanomachines, respectively. The nanomachines are located in different mediums and separated by a rational distance of $4nm$ assuming rapid randomization of relative orientation of the molecules and nanomachines.

For ECFP - EYFP pair, the Förster radius calculated in [22] assuming the medium as water at 25 °C changes in accordance with the medium. In Fig. 4, mutual information $I(X;Y)$ given in (11) is shown for varying excitation probability of the donor (P_F) for different media and different refractive indices. As the refractive index of the medium decreases, the Förster radius given in (1) increases. Therefore, the probability of FRET, i.e., successful transmission probability of bit 1 for the pre-specified intermolecular distance increases. As a consequence, the capacity of the channel increases with decreasing refractive index of medium. The capacity is maximized for vacuum by $P_F = 0.43$. We find $C_{max} = 0.57\ bit$.

C. Effect of Relative Orientation Factor

Here, we investigate the effect of relative orientation factor (κ^2) on the channel capacity using ECFP - EYFP as the donor - acceptor pair assembled on the nanomachines. The nanomachines are located in a medium of water at 25 °C and separated by a rational distance of 4 nm.

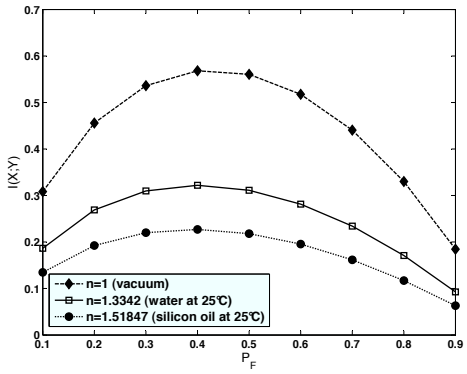

Fig. 4. $I(X;Y)$ with varying P_F for different n.

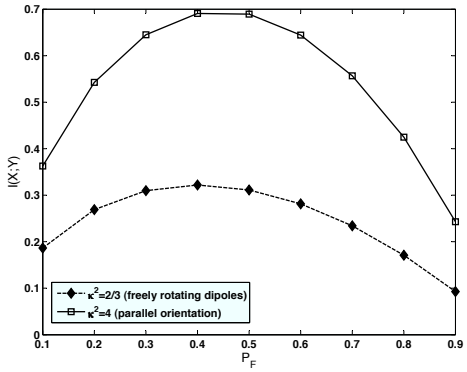

Fig. 5. $I(X;Y)$ with varying P_F for different κ^2.

Relative orientation factor is a measure of the relative orientation of the donor emission dipole moment and the acceptor absorption dipole moment. Determining the exact orientations of donor and acceptor molecules is impossible at this point. However, many of the studies in the literature about FRET assume rapid randomization of the relative orientation of the dipole moments. The orientation factor is $2/3$ in the case of rapid randomization. In addition, we investigate the mutual information when the orientation of the dipole moments of the molecules are parallel. In this case, the orientation factor reaches its maximum value, i.e., $\kappa^2 = 4$. The result of the analysis seen in Fig. 5 reveals that the parallel orientation can significantly increase the capacity of FRET-based channel compared to rapid randomization. When further advances in the nanotechnology make it possible to control the orientation of molecules, orienting the dipole moments of the donor and the acceptor molecules in parallel will be a wise strategy to achieve higher communication capacities. The capacity is maximized for parallel orientation by $P_F = 0.47$. We find $C_{max} = 0.70\ bit$.

D. Capacity Analysis for Different FRET Pairs

In the last analysis, we investigate the FRET-based molecular communication capacity for various donor - acceptor pairs with different spectral properties, assembled on the transmitter and receiver nanomachines respectively. The nanomachines are located in a medium of water at $25\,^{\circ}\mathrm{C}$ and separated by a rational distance of $4\ nm$. The molecules that constitute the FRET pairs are selected among the variants of Green Fluorescent Protein (GFP). The selected donor - acceptor pairs are commonly used in FRET studies and there is a wide variety of studies about GFP variants in the literature.

There is a direct relationship between the Förster radius as well as the resonance energy transfer efficiency, i.e., the transmission probability of bit 1 (p_1), and the overlap area of the excitation spectrum of the donor and the absorption spectrum of the acceptor. As the overlap between the spectra increases, Förster radius as well as p_1 increases. The emission and absorption spectra of the selected donor - acceptor pairs are demonstrated in Fig. 6. For the pair of Enhanced Blue Fluorescent Protein (EBFP) and Red Fluorescent Protein (DsRed), the spectral overlap is the minimum among the other selected pairs. Therefore, the Förster radius between EBFP and DsRed is the minimum and calculated as , $3.17 \pm 0.06\ nm$ in the medium of water at $25\,^{\circ}\mathrm{C}$ [22]. Conversely, the overlap between the emission spectrum of Enhanced Green Fluorescent Protein (EGFP) and the absorption spectrum of Enhanced Yellow Fluorescent Protein (EYFP) is the maximum among the others. As a result, the Förster radius of EGFP - EYFP pair is the maximum and calculated as $5.64 \pm 0.11\ nm$ in the medium of water at $25\,^{\circ}\mathrm{C}$ [22]. Although this value is one of the largest R_0 values recorded, the pair of EGFP - EYFP generally is not used due to the close proximity of absorption spectrum of the donor and the absorption spectrum of the acceptor that can result in crosstalk in FRET applications. For the remaining FRET pair of Enhanced Cyan Fluorescent Protein (ECFP) and EYFP, the Förster radius is previously given as $4.92 \pm 0.10\ nm$ [22].

Fig. 7 demonstrates the mutual information, $I(X;Y)$, given in (11) for varying excitation probability of the donor (P_F) for donor - acceptor pairs. As expected, the capacity is higher for the pair EGFP - EYFP because of the higher transmission probability of bit 1 (p_1) as the consequence of higher spectral overlap. As the spectral overlap decreases, the capacity also decreases. Therefore, for the pair EBFP - DsRed, the capacity is the minimum among the others. The selection of the donor and acceptor pair with larger spectral overlap is the key strategy in order to achieve higher communication capacity. The capacity is maximized for EGFP - EYFP by $P_F = 0.45$. We find $C_{max} = 0.74\ bit$. Hence, we can communicate more information by using input symbol 0 more frequently than 1 for EGFP - EYFP pair.

VI. Conclusions

In this study, we propose a novel molecular communication technique exploiting a well-known phenomenon FRET, for the first time in the literature. After giving the basic specifications of the phenomenon, we define a realistic communication channel model for a single transmitter-receiver pair (point-to-point) within the scope of FRET theory neglecting the environmental noises. Succeeding that, the capacity of the newborn channel is formalized information-theoretically and

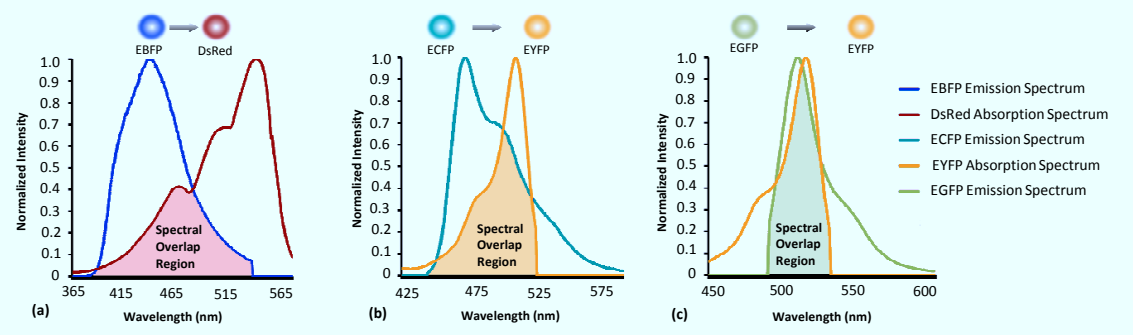

Fig. 6. Overlapping spectra for various fluorescent protein pairs [18]. a) Emission spectrum of EBFP and absorption spectrum of DsRed. b) Emission spectrum of ECFP and absorption spectrum of EYFP. c) Emission spectrum of EGFP and absorption spectrum of EYFP.

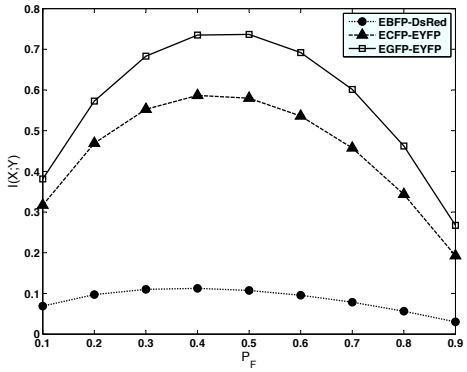

Fig. 7. $I(X;Y)$ with varying P_F for various donor - acceptor pairs.

the variation in the communication channel capacity is analyzed for different environmental and intrinsic parameters. The result of analysis reveals that the capacity of the channel can be increased significantly by appropriately choosing the parameters in accordance with each other.

Throughout the paper, we show that with the relatively low dependency on the environmental factors, high level controllability of the parameters and simplicity, FRET-based molecular communication model stands as a promising solution to high rate nanoscale communication between nanomachines. In parallel to the FRET studies in the fluorescent spectroscopy area, with further investigations over this model, longer range communication with relay nodes, broadcast communication networks with multiple receivers and new modulation techniques over these channels by the explosion of the FRET parameters are possible to be designed.

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