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Quantum Dots and Their Applications

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Abstract
Quantum dots are small semiconducting crystals with quantum mechanical properties. When the radius on a semiconducting sphere becomes small enough such that the Bohr radius of the charge carrier becomes larger than the sphere, the sphere experiences what is known as quantum confinement. This leads to various properties that differ from other semiconducting crystals. These properties make quantum dots valuable in several applications, such as biomedical assays and imaging. Their usefulness is assays is a direct result of their broad fluorescence range. Due to their long-lived fluorescence, quantum dots are also useful in the imaging of single molecule systems. However, while quantum dots are able to overcome limitations of traditional fluorophores, they come with limitations of their own. The large size, effectiveness of delivery into cells, and the multivalency of quantum dots precludes aspects of their usefulness in the lab. Thus, further development is necessary before quantum dots can be in widespread use in biological applications

1 Introduction

Quantum dots are small, semiconducting nanoparticles that exhibit unique quantum properties, which make them useful for a wide variety of applications. Quantum dots exhibit the phenomena of quantum confinement in three dimensions. This occurs when the Bohr radius of the charge carrier becomes larger than the crystal itself, leading to a transition from continuous to discrete, or quantized, energies. This is a direct result of the discrete bands of energy that form in solids. If the solid consists of too many atoms, the discrete energy bands merge into one continuous spectrum of energy. Thus, while there are many semiconducting crystals, quantum dots are usually classified as nanoparticles approximately 2-10 nm in size.[1–3]

The most useful aspect of quantum dots is the fact that they are band gap tunable. By changing the size and composition of a particle, one is able to adjust the band gap, or the spacing between energy bands which form in a solid. This allows one to fine tune other properties such as photonic emission. This makes quantum dots especially useful as fluorophores in biological applications.

A fluorophore is a fluorescent chemical that can re-emit light upon excitation. The light makes them useful in biological imaging to locate and quantify certain biological molecules. Traditionally, organic fluorophores have been used for this purpose, however they come with certain limitations: they cannot fluoresce continuously for long periods of time, are sensitive to photobleaching, and are not optimized for multicolor applications. In contrast, quantum dots are not sensitive to photobleaching in the same manner, and because they can absorb light in a wide spectrum while emitting in a narrow range, are much better suited for multicolor applications.[4]

In this paper, we will begin by providing a quantum mechanical background detailing the unique chemical properties of the semiconducting quantum dot. We will then discuss the various biological applications in

which quantum dots are useful, and finally, discuss some potential limitations in their use.

2 Theory

2.1 Chemical Bonding

Semiconductors are materials comprised of many atoms bonded together. Thus, it may be useful to define what a chemical bond is. Any chemical bond involves the sharing of one or more electrons between two atoms. There are many different models we can use to mathematically describe these bonds, and these quickly become complicated enough to require the use of a computer. We will begin with a simple particle in a box model, and from there extrapolate how a more complex approximation may work.

2.1.1 Particle in a Box Model

Let us model the bond between two hydrogen atoms. The derivation presented here follows those described in McIntyre[2] and Simon.[3] We begin by modeling each hydrogen as a box of width *L* containing an electron. For the sake of bonding, we let the electron be in the ground state. If we want to form a bond between two hydrogen atoms, we can imagine pushing two potential energy wells together to get something like Figure 2.1. Here, we have two "hydrogen atoms," modeled by the wells, joined together in a way such that their electrons are free to hop between the two wells. This is a good starting point for modeling a covalent bond like the one in H_2, which involves the sharing of electron density between atoms.

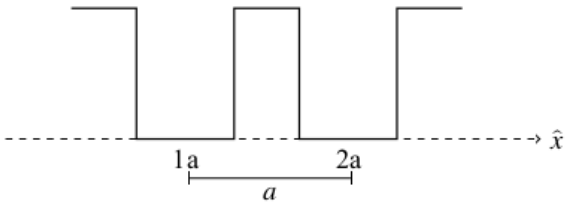


Figure 2.1: A two well system composed of finite square wells. Each well represents an atom. We have defined the coordinate of each well in terms of a so that we are able to define the interatomic spacing between them as a.

To understand this new molecular system, we want to find the eigenstates and energies of the system. For a system as simple as this one, it is possible to set up and solve the Schrödinger equation exactly, but we will instead use an approximation technique. This approach extends better to more complex systems, and so will be more illustrative for our purposes. In either case, the exact solution is no more enlightening than our approximation. We will use the linear combination of molecular orbitals (LCAO) method. This approach assumes that the eigenstates of a molecule can be constructed from the eigenstates of the single elements, or atoms, comprising it. Thus, we begin with the assumption that our molecular state as shown in Figure 2.1 is a linear combination of two states such that

$$|\rangle = c1|1\rangle + c2|2\rangle, \quad (2.1)$$

where $|1\rangle$ and $|2\rangle$ represent the ground states of the two wells. These ground states are identical, save a displacement of a from each other. We can therefore write them as

$$|1\rangle = 1x\text{-}1a \quad (2.2)$$
$$|2\rangle = 1x\text{-}2a, \quad (2.3)$$

where 1 is the ground state wavefunction for a particle-in-a-box. Since we already know the eigenstates of our atomic system, and the molecular system is simply a linear combination of those, we can use the atomic eigenstates as our basis. This allows us to solve the Schrödinger using the matrix approach rather than the differential equation approach.

For a two-well system, we have a 22 matrix representing our Hamiltonian operator. Since both wells are identical, our system is also

symmetrical. We therefore get the matrix elements

$$=H11=H22=\langle 1H1\rangle=\langle 2H2\rangle \quad (2.4)$$
$$=H12=H21=\langle 1H2\rangle=\langle 2H1\rangle. \quad (2.5)$$

The parameter α is approximately equal to the energy of the atomic state, while β is defined as the so-called "hopping term," which is the probability of an electron to move between two adjacent wells. Both terms are relatively simple to calculate in this case, but are not required for us to understand this system, so we will not do so here.

We now have the Schrödinger equation

$$* \ c1\ c2 = Ec1\ c2 \ . \quad (2.6)$$

To find the eigenstates and energies of this system we simply diagonalize the Hamiltonian to obtain

$$|\rangle=1\sqrt{2}[|1\rangle+|2\rangle], \quad (2.7)$$
$$E=\alpha\pm. \quad (2.8)$$

We see that for the two atomic orbitals we started with, we end up with two molecular orbitals (Figure 2.2). Since α was approximately our atomic energy, we can say the energies of the molecular orbitals are displaced from the original energy by an energy β. The sign of β, which depends on the structure and potential of the atomic orbitals, determines which state has the higher energy. For this two square well chain, $\beta < 0$. The lower energy state is referred to as the bonding orbital, while the higher energy state is referred to as the anti-bonding orbital.

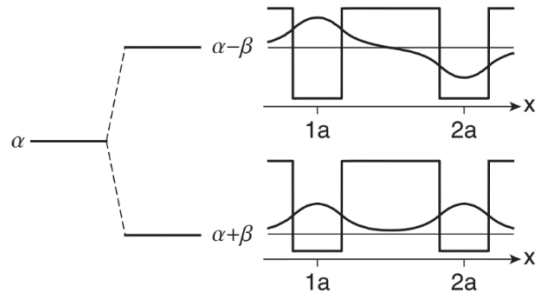


Figure 2.2: Two atomic states combine to form two molecular states.[2] The resulting molecular states exhibit a splitting effect and are displaced from the original energy, α, by a new energy, β. For this two square well chain, $\beta < 0$.

2.1.2 Molecular Orbital Theory

For more accurate models, we can use basis sets for our molecular eigenstates that better approximate the atomic orbital. One relatively simple example is that of the hydrogen-like, or hydrogenic, orbitals. This model consists of atoms with a central nucleus bound to one electron, like Hydrogen, hence the name. These atomic orbitals make use of the Born-Oppenheimer Approximation, which fixes the nucleus in space and leaves the electron free to move around it. Since the nucleus is much larger than the electron, it will have a relatively small momentum compared to the electron, making this a valid approximation. We then have an electron free to move around in a sphere with a fixed potential at the center. The electron then experiences a Coulombic potential dependent on its distance from the nucleus.[1]

This model is simple enough to allow some analytical solutions, and the derivation follows almost directly from that of a particle-on-a-sphere, though we will not repeat it here. Despite its relative simplicity, however, using this as our basis set allows us to use LCAO-MO theory, more commonly seen as Molecular Orbital (MO) theory, to accurately describe many small molecules. For example, MO theory correctly predicts that diatomic helium does not exist, and that diatomic oxygen is paramagnetic.[5]

For larger, more complex molecules, we can get better approximations by using more involved techniques to obtain the atomic orbitals we use as our starting point. For example, SCF-LCAO-MO (SCF: Self-consistent field) theory uses Slater-type orbitals as the basis rather than the hydrogen-

like orbitals. The Slater-type orbitals account for the partial shielding of the nuclear charge by electrons in multi-electron atoms.[1] For many-body systems such as proteins or other large polymers, density functional theory is often employed. These methods both require complicated calculations typically carried out by a computer, and so are beyond the scope of this paper.

2.1.3 Periodic systems of N-atoms

We can now discuss how to model the molecular orbitals of a large molecule, such as a quantum dot. Just any large molecule can be difficult to describe. Luckily, we are able to simplify our model here by only considering N-atom chains which are periodic. This works well for quantum dots, as they are crystals. Crystals are molecules with translational symmetry. This means we can consider one lattice in the entire structure and extend the subsequent model to the entire structure by recognizing that the lattice repeats with some periodicity. These periodic systems have symmetry, just like our two well state in Section 2.1.1, which helps to simplify the math. The derivation presented here follows those described in McIntyre[2] and Simon.[3]

Consider an atom, n, with a single orbital which we will denote $|n\rangle$. Then we have a wavefunction

$$|\rangle=ncn|n\rangle. \quad (2.9)$$

We again use an approximation technique rather than solving this system exactly. We start with the energy eigenvalue equation and take a complete set of our basis $I=m|m\rangle\langle m|$. We apply this to the left hand side of our energy eigenvalue equation:

$$\begin{aligned} H|\rangle=HI|\rangle=Hm|m\rangle\langle m||\rangle \\ =Hm|m\rangle\langle\rangle \\ =Hm|m\rangle cm. \end{aligned}$$

Then we can say

$$Hm|m\rangle cm=E|\psi\rangle. \quad (2.10)$$

Left multiplying both sides by $|n\rangle$ yields

$$n,mHnmcm=Ecn, \quad (2.11)$$

where $Hnm=\langle nHm\rangle$ is the matrix element of the Hamiltonian.

Another assumption we make is that the electrons are tightly bound to their respective atoms, and thus do not travel very far from them. This means the "hopping" elements of the Hamiltonian, β, will be equal to zero unless the two wells are adjacent. In other words,

$$Hnm=\langle n|H|m\rangle=\{\alpha, \quad m=n \quad (2.12)$$
$$\beta, \quad m=n\pm1 \; 0, \quad \text{else}.$$

Based on this definition and Equation 2.11, we have that for any given cn

$$cn-1+cn+cn+1=Ecn. \quad (2.13)$$

This is not true for the boundaries, but we will focus on solving this equation for now. We then find that due to the periodicity of the system, the endpoints can be dealt with in much the same way.

We propose a guess for the coefficients

$$cn=einkaN, \quad (2.14)$$

where k is the wave vector and a is the interatomic distance. The denominator accounts for normalization of the system when there are N atoms. Plugging this back into Equation 2.13 with some rearranging yields

$$ein-1kaN+-EeinkaN+ein+1kaN=0.$$

Simplifying this allows us to solve for the energies:

$$E=+2\cos ka. \quad (2.15)$$

This is known as a dispersion relation. Note that E depends on k, so here, k is denoting the molecular eigenstate. Given that k is referring to a distinct eigenstate, we might expect that k can only take on discrete values. However, for large N, we can take k to be a continuous variable. This occurs because the more atoms we have, the more atomic orbitals we are beginning with. Thus, for N number of

atomic orbitals, we must have N number of molecular orbitals. Their energy remains bounded by $\alpha \pm 2\beta$, however, so the energy gap between each molecular orbital eigenstate must get smaller to fit in the bounds. Thus, for large N, we end up with a continuous band of energy bounded above by $\alpha - 2\beta$ and below by $\alpha + 2\beta$ (Figure 2.3).

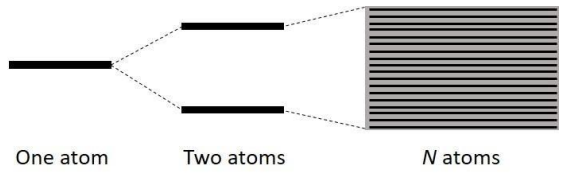


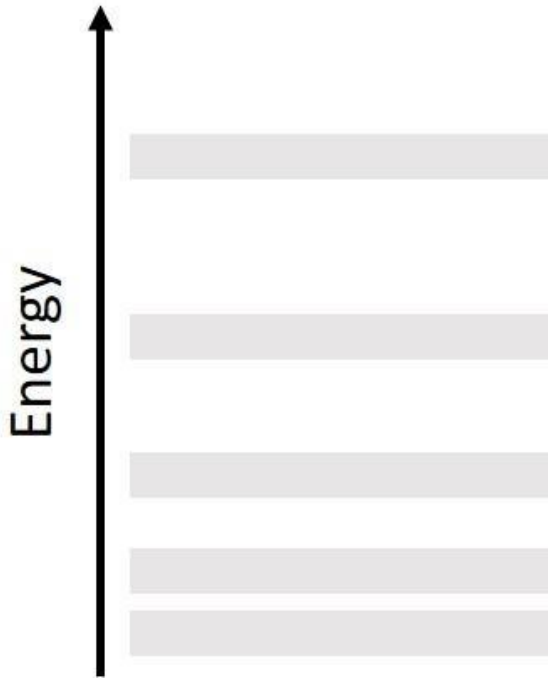
Figure 2.3: The development of a band of energies from discrete energy levels as the number of atoms increases. As individual eigenstates increase in number and become closer in energy, they form a continuous band, shown in grey.

Thus far, we have been considering only one orbital to be participating in bonding. If we extend our model to include other orbitals as well, we may obtain a picture of energy something like Figure 2.4, where the gaps between the bands are forbidden regions the electrons cannot occupy.

2.2 Electronic Band Gaps

As we have seen, in solids, it is more beneficial to discuss energy bands rather than discrete energy levels. The separation between the lowest filled band (valence band) and the highest unoccupied band (conduction band), where there are no allowed energy levels, is known as the band gap. When electrons are excited from the valence band to the conduction band, an electric current is created.[3]

Semiconductors such as quantum dots are characterized by a band gap of relatively small energy, less than 4 eV.[3] This allows some electrons to jump from the valence to the conduction band at normal temperatures, creating holes. Other electrons from lower levels are now free to jump up and occupy this hole. They then leave behind their own holes which even more electrons can move into. In this way, the hole behaves like a positive charge that can conduct electricity on its own as a positive charge carrier.



Band gaps can be engineered by combining multiple semiconducting materials to create heterogeneous structures. A simple example is a device made by combining layers of GaAs and $Al_xGa_{1-x}As$. By creating this alloyed structure, one can create any desired band gap just by tuning the composition of the alloy and thickness of the individual layers.[2,3] Consider, for example, the structure shown in Figure 2.5. Let us direct our focus to the schematic of the well structure in Figure 2.5(b). Here, the Vcx line depicts the potential of the conduction band, while the Vvx line depicts the potential of the valence band. The space between them is the band gap. Note the difference in band gap that occurs as we move from the AlGaAs layer to the GaAs layer. We see that for this structure, the band gap of GaAs is smaller than the band gap of AlGaAs. These changes in band

energy can be thought of as a potential that an electron (or hole) would feel. Thus, an electron in the conduction band, or a hole in the valence band, can be trapped in the GaAs region. This gives rise to discrete energy eigenstates similar to those from confinement of a particle-in-a-box.

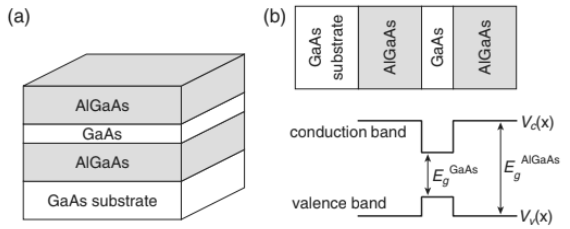


Figure 2.5: (a) A semiconductor heterostructure and (b) band diagram of a GaAs quantum well.[2]

The simple structure described above exhibits confinement in one dimension. Our charge carriers are free to move in the plane of the thin well but are otherwise restricted in their movement. Further confinement can lead to quantum wires (confinement in two dimensions) and quantum dots (confinement in three dimensions). Confinement in quantum dots arises when the Bohr radius of the charge carrier exceeds the size of the crystal, leading to the formation of discrete energies.[6] The size and composition of the dot determines the confinement size, not unlike how in our one dimensional case, the size and composition of the layers in the semiconductor heterostructure allowed us to fine tune the band gap. This in turn allows us to fine tune the wavelength of light emitted upon excitation of the charge carrier.

The process by which an electron jumps from the conduction to the valence band is not unlike the transition electrons make between discrete atomic orbitals in atoms. For example, boron compounds burn green because when they are heated, their electrons absorb a certain amount of heat energy that causes them to jump to higher energy levels. As the electrons come back down from that excited state, they release energy in the form of light. The wavelength of light varies based on the amount of energy released, and the amount of energy released depends on the difference in energy between the ground and excited state. In the same way, when electrons in a quantum dot absorb energy, they jump from the valence to the conduction band, and as they come back down, release energy in the form of light. The wavelength here is thus governed by the band gap. Therefore, by adjusting the band gap, one can design different dots which can emit different wavelengths of light upon excitation (Figure 2.6).

Figure 2.6: Photoluminescence of alloyed CdS_xSe_{1-x}/ZnS quantum dots of 6nm diameter.[7] As the composition of the CdS_xSe_{1-x} alloy is changed, so is the photonic emission of the dot.

3 Applications

The unique optical and chemical properties of quantum dots make them ideal fluorophores for use in fluorescent imaging. Traditionally, organic fluorophores such as genetically encoded fluorescent proteins or chemically synthesized fluorescent dyes have been commonly used. These, however, have some significant limitations: they cannot fluoresce continuously for long periods of time, are sensitive to photobleaching, and are not optimized for multicolor applications. Organic fluorophores absorb and emit light in a very narrow spectrum.[4] Therefore, if we want to image multiple molecules, multiple excitation sources must be used. In contrast, quantum dots are not sensitive to

photobleaching in the same manner and absorb light in a broad spectrum but emit in a narrow range. This makes them highly desirable in many biological applications that commonly use fluorescence. Quantum dots can be utilized in two main biological applications: biosensing and biological imaging.

3.1 Biosensing

Various biological assays, or tests, involved in the detection and quantification of DNA, RNA, and protein levels involve fluorescent imaging. In these applications, quantum dots can be particularly useful. Quantum dots differ from organic fluorophores in that bioconjugation with other molecules does not affect their fluorescent properties.[6] Thus, one can conjugate various molecules to the quantum dot surface to aid in small molecule detection. For example, immunoassays, which involve the use of highly specific antibodies to detect protein or DNA levels, make use of fluorophores in detection and quantification. Commonly used quantum dots for this purpose are CdSe/ZnS dots, where the CdSe is the semiconducting core, and the ZnS is a stabilizing coating.

Another assay in which quantum dots prove useful are microarrays. A microarray test can be used to measure differences in relative gene expression levels between two samples, usually an experimental and control sample. A different colored fluorescent probe is used for each sample. The two samples are mixed together and imaged. Relative expression is based on which color appears more once the samples are imaged. Thus, we can see why quantum dots may be particularly useful in this application. The use of multiple colors makes quantum dots preferable since they only require one excitation energy as compared to traditional fluorophores which would require two.

3.2 Biological Imaging

The high resolution and long-term stability of quantum dots makes them excellent for in vivo and in vitro cellular imaging. In this way, quantum dots can be used to study molecular mechanisms.

To understand the molecular mechanisms of protein binding, signaling, and regulation, it can be useful to study single molecule systems. Quantum dots can be used as a fluorescent tag for single protein tracking, thus providing insight into molecular mechanisms in systems biology. The protein of interest can be conjugated to a quantum dot and time-series fluorescent imaging can be used to track its trajectory. Various statistical analyses of the trajectories can then be used to determine dynamic properties of the proteins. The first quantum dot based single molecule tracking was performed by Dahan and colleagues in 2003,[8] and involved tracking the lateral movement of glycine receptors in the cellular plasma membrane of neuronal cells. Using antibody-conjugated quantum dots, the authors were able to track this movement and reveal that the dynamics of this movement varied across the different domains of spinal neurons.

Another example of the biological usefulness of quantum dots is in identifying in vivo protein-protein interactions. In this way, quantum dots can be used to shed light on the mechanisms underlying cellular signaling. Lidke and colleagues[9] used bioconjugated quantum dots to target two key proteins often dysregulated in cancer, receptors erbB1 and erbB2. From this experiment, they were able to elucidate protein-protein interactions between quantum dot-bound erbB1 and erbB2 receptors. This revealed the active role the erbB2 receptor plays in conferring higher aggressiveness to breast cancer.

3.3 Limitations

While there exist a wide variety of biological applications for quantum dots, there remain some limitations associated with their use.

One of the main impediments to their use is effective delivery into cells. Note that the in vivo examples described above involved study of membrane proteins, but not intracellular molecules. This is due to the difficulty associated with the cellular uptake of quantum dots. Quantum dots are inherently hydrophobic; thus, they must be made hydrophilic before they can pass through the lipid bilayer of the cell membrane. Many different strategies have been implemented in order to facilitate the hydrophilicity of quantum dots, however these modifications decrease both the stability and quantum yield. Furthermore, the colloidal nature of quantum dots in aqueous environments makes them sensitive to aggregation as a result of changes in pH or temperature. [4] These are not conditions that can be controlled in a live cell; thus quantum dots must be modified such that they are inert to their environments before use in live cells.

Another limitation of quantum dots is their size. Unlike organic dyes, which are small molecules, quantum dots are more comparable in size to a large protein - making them almost 2000 times bigger. While the semiconducting core itself ranges from 2-10 nm, the stabilizing coating and further surface conjugation of specific proteins or antibodies quickly increases their size. This massive size further raises concerns about effects of quantum dot conjugation in protein mobility and functionality. One way to overcome this limitation would be to use less molecules, or molecules which are smaller in size for bioconjugation.[4]

Furthermore, multivalency of quantum dots precludes their usefulness in labeling only a single molecule in live cells. The large surface area to volume ratio of a biocompatible quantum dot enables conjugation of multiple copies of various biomolecules. For proper detection, one would want a single quantum dot to bind to only one target biomolecule. Furthermore, these multivalent interactions of a quantum dot with a target cell surface protein can lead to protein cross-linking and consequently activate signaling pathways as well as significantly impair surface protein mobility. Wang and colleagues[10] found that nanoparticles conjugated with transferrin receptor (TfR) antibodies lead to programmed cell death in cancer cells in a bioconjugation density-dependent manner.

4 Conclusion

Semiconducting quantum dots are small nanoparticles ranging from 2-10 nm in size that exhibit quantum confinement in three dimensions. This is a direct result of the discrete bands of energy that form in solids. The band gap of these solids can be tailored by changes in composition and size, thus changing the confinement effect. This tunability of the band gap allows one to control what wavelength of light is emitted from the particle upon excitation. This, and other properties, make quantum dots useful in a variety of biological applications.

In addition to band gap tunability allowing researchers to tune which wavelength of light is emitted upon excitation, quantum dots are also not sensitive to photobleaching like traditional organic fluorophores are. Furthermore, the wide absorption range of quantum dots coupled with their narrow emission range makes these nanoparticles ideal for multicolor application. By coating the semiconducting core in a stabilizing layer and conjugating the surface with various biomolecules, highly specific and stable fluorophores can be created. These can be used in immunoassays, protein and DNA detection, as well as single molecule tracking and study of cell signaling pathways.

Though these molecules have many advantages over traditional fluorophores, they come with their own limitations. Their sensitivity to environmental changes makes

them unsuitable for intracellular live cell tracking. Furthermore, their large size may hinder protein mobility and functionality, thus casting doubts on any functional results obtained from quantum dot conjugation methods. Finally, their multivalency precludes their usefulness in labeling only a single molecule in live cells and may even lead to a significant increase in their cytotoxicity. Further development is necessary before quantum dots can be in as widespread use as organic fluorophores.

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