The physics, biology, and technology of resonance energy transfer

For these slides see: www.physics.upenn.edu/~pcn

Image courtesy Steven Haddock
I want to watch a macromolecule going about its daily business, in real time;

and

Macromolecules are at most a few nanometers in size;

but

that's way smaller than the diffraction limit; EM destroys them; purification/crystallization isn’t the normal environment; localization microscopy has its own limitations;

so

Some other method would be good.
Fluorescence

If the lifetime before reemission is long (few ns), call it fluorescence and predict a wavelength shift. (If it’s super long, minutes, instead call it “phosphorescence.”)

\[
\begin{align*}
\text{excitation photon} & \quad \text{excited-state energy } U_*(y) \\
\text{ground-state energy } U_0(y) & \quad \text{emitted photon}
\end{align*}
\]

That simpleminded model just predicted broad excitation spectrum (compared to an atom), broad emission spectrum, and redwards "Stokes shift" of the latter.
Weigert (1920) and Gaviola and Pringsheim (1924):
- When we illuminate a solution with polarized light, and if the fluorescent molecules are in a rigid environment or viscous solution so that they cannot rotate within the time of fluorescence decay, then the output is also partially polarized.
- If the fluorescent molecules act independently, the output polarization should be concentration independent. But for several dyes, the polarization was appreciably reduced when the molecules were on the average separated by about 5–8 nm, much larger than the combined radii of the molecules.
- This separation was also much greater than the distance over which the excited fluorophores could diffuse within their excited state lifetimes (especially in high viscosity solvents, or solid solutions).
- Puzzling and no obvious interpretation; later understood as indirect evidence for excitation transfer.

Cario and Franck (1922): Observed emission from thallium in a mixture of mercury vapor and thallium vapor, when the vapor mixture was excited with wavelength of 253.6 nm, which can only excite the mercury atoms. Points directly to excitation transfer.

Beutler and Josephi (1927, 1929): Showed the importance of resonance between the energy levels of the donor and the acceptor atoms.


Excitation transfer: Naive picture

Cannot explain observed high transfer efficiency when donor and acceptor are well separated – most intermediate photons will “miss.”
Dipole fields are very strong in the near-field region, potentially explaining how FRET can dominate over donor emission. The resonance idea potentially explains why the many other nearby molecules (e.g. water) don’t get excited. Together, these observations can explain the high observed transfer efficiency.

Excitation transfer

\[ \Delta U_D = \Delta U_A \]

Single-molecule conformation changes

Spectroscopic ruler

\[ E_{\text{FRET}} \]

\[ r_F \]

Orientation dependence

Efficiency of energy transfer for Cy3, Cy5-labeled DNA duplexes as a function of duplex length.

These examples motivated Jon Widom to investigated loop formation in a stripped-down form – no histone, no regulatory protein, no viral capsid. He found puzzling behavior: Too much looping according to the then-current model of DNA mechanics.
DNA looping, 2

Dissection of control circuits

Calcium reporter

The cameleon family of calcium indicators:

Similar idea:

Calcium reporter, 2

“Yellow cameleon” dye

This talk

The pictures

OK – FRET is useful. It can give real-time reporting of nanometer distances between single molecules in living cells. It can also give millisecond resolution reports on ligand concentrations inside individual living cells. Many of its features make sense, at least qualitatively, when we invoke dipole-dipole coupling.

The puzzles

(a) FRET is strongly quantum-mechanical because it deals with discrete energies and states;

but

FRET is strongly classical: Superpositions are not observed, and you can get the rate by a classical calculation.

(b) FRET follows first-order kinetics (fixed probability per time to make a one-way transition)

but

That’s not what quantum mechanics (seems to) predict.

So

What is going on?
Isolated 2-state system

We suppose that only two electronic states of the donor are relevant: the ground state \( |D_0\rangle \) and one excited state \( |D_*\rangle \). Similarly, we consider only two acceptor states \( |A_0\rangle \) and \( |A_*\rangle \). We are particularly interested in transitions between joint states of the form

\[
|1\rangle = |D_*A_0\rangle, \quad |2\rangle = |D_0A_*\rangle,
\]

whose energies are nearly equal (the resonance condition). Direct transitions between those two states, without any photon emission, are therefore compatible with energy conservation.

When the two molecules are brought near each other, they will have a coupling giving rise to a Hamiltonian operator with an off-diagonal entry in the 1, 2 basis, which we may take to be real:

\[
H = \begin{bmatrix} 0 & V \\ V & 0 \end{bmatrix}.
\]
Isolated 2-state system

\[ |1\rangle = |D_A 0\rangle, \quad |2\rangle = |D_0 A_\ast\rangle, \]

When the two atoms are brought near each other, they will have a coupling giving rise to a Hamiltonian operator with an off-diagonal entry in the 1, 2 basis, which we may take to be real:

\[ \mathbf{H} = \begin{bmatrix} 0 & V \\ V & 0 \end{bmatrix}. \]

The system’s evolving state can then be expanded as

\[ |\Psi(t)\rangle = a(t)|1\rangle + b(t)|2\rangle, \]

where the coefficient functions obey the Schrödinger equation:

\[ i\hbar \begin{bmatrix} da/dt \\ db/dt \end{bmatrix} = V \begin{bmatrix} b \\ a \end{bmatrix}. \]

Consider the solution with the initial state \( |\Psi(0)\rangle = |1\rangle \); at later times, we find that \( |b(t)|^2 = \sin^2(\Omega t/2) \), where \( \Omega = 2V/\hbar \). (Schrodinger 1927). Unfortunately, that’s not what’s seen experimentally (first-order kinetics, one-way transition).
"What we want is a story that starts with an earthquake and works its way up to a climax." — Samuel Goldwyn

Physicists love stories that are weird and upsetting but true.
An isolated 2-state resonant system sloshes back and forth between its states; and its initial transfer rate is zero; but FRET is one-way and has first-order kinetics. so What have we failed to include?

Analyze only when necessary.
Density matrix – Isolated system

A “pure” (unentangled) state $|\Psi\rangle$ is one that can be written as a simple product: $|\psi\rangle_\mathcal{S} \otimes |\phi\rangle_\mathcal{E}$. In such a state, we can express the measured value of a subsystem observable without needing to know anything about the environment $\mathcal{E}$:

$$\langle O \rangle = \mathcal{S} \langle \psi | O | \psi \rangle_\mathcal{S}. \quad \text{pure state}$$

Even if a state is not pure, we can summarize the environment. Introduce an operator $\rho$ on $\mathcal{H}_\mathcal{S}$ called the density operator, defined by constructing the dyad $|\Psi\rangle \langle \Psi|$ and taking the trace over the environment state space:

$$\rho = \text{Tr}_\mathcal{E} \left( |\Psi\rangle \langle \Psi| \right).$$

In our problem, $\rho$ can be represented by a two-by-two matrix with respect to the basis $|1\rangle$, $|2\rangle$. Then $\langle O \rangle = \text{Trace} \rho O$. 
Density matrix – Isolated system

\[ \rho = \text{Tr}_\mathcal{E} \left( |\Psi\rangle\langle\Psi| \right). \]

When \( \mathcal{S} \) is perfectly isolated from its environment, a pure (un-entangled) state remains pure:

\[ |\Psi(t)\rangle = |\psi(t)\rangle_\mathcal{S} \otimes |\phi(t)\rangle_\mathcal{E} \quad \text{for isolated subsystem} \]

\[ \rho(t) = |\psi(t)\rangle_\mathcal{S} \langle \psi(t) | \quad \text{so} \quad \rho_{ij} = \begin{bmatrix} |a(t)|^2 & a(t)b(t)^* \\ a(t)^*b(t) & |b(t)|^2 \end{bmatrix}_{ij}. \]

Note that if we change basis by a phase, the populations are unaffected, whereas the coherences pick up that phase.

The time development of \( \rho \) is determined by \( H_\mathcal{S} \), the subsystem’s Hamiltonian:

\[ \frac{d\rho}{dt} = \frac{1}{i\hbar} [H_\mathcal{S}, \rho] \quad \text{for isolated subsystem.} \]

We then recover the same oscillatory behavior as before.
Add an environment

Interactions with the environment $\varepsilon$ will destroy the product form of $|\Psi\rangle$, converting an initially pure state to one that is entangled with the environment. Although these interactions are complicated, they can be summarized by saying that the subsystem’s phase is altered by the many environmental particles that interact with it. When we perform the trace operation, the entanglement leads to the sum of many random phase factors in the off-diagonal elements of $\rho$, effectively suppressing them within some decoherence time scale $T$. The diagonal terms are unaffected, however.

Also allow for the possibility that the energies of $|1\rangle$ and $|2\rangle$ may not be exactly equal. Thus, let $H_5 = H_0 + V$, where $H_0$ is diagonal with eigenvalues $E_1$ and $E_2$ and $V$ is the off-diagonal interaction operator already introduced. The Schrödinger equation then becomes

$$
\frac{d\rho_{22}}{dt} = \frac{1}{\hbar} [V, \rho]_{22} \\
\frac{d\rho_{ij}}{dt} = \frac{1}{\hbar} ([V, \rho]_{ij} + (E_i - E_j)\rho_{ij}) - \frac{1}{T}\rho_{ij} \quad \text{for } i \neq j.
$$

The donor can also lose its excitation directly, without transfer of energy to the acceptor. We approximate this effect as a decay term in the equation for $\rho_{11}$:

$$
\frac{d\rho_{11}}{dt} = \frac{1}{\hbar} [V, \rho]_{11} - \frac{1}{\tau}\rho_{11}.
$$
Add an environment, 2

\[
\begin{align*}
\frac{d\rho_{22}}{dt} &= \frac{1}{i\hbar}[\mathbf{V}, \mathbf{\rho}]_{22} \\
\frac{d\rho_{ij}}{dt} &= \frac{1}{i\hbar} \left( [\mathbf{V}, \mathbf{\rho}]_{ij} + (E_i - E_j)\rho_{ij} \right) - \frac{1}{\tau}\rho_{ij} \quad \text{for } i \neq j. \\
\frac{d\rho_{11}}{dt} &= \frac{1}{i\hbar}[\mathbf{V}, \mathbf{\rho}]_{11} - \frac{1}{\tau}\rho_{11}.
\end{align*}
\]

These formulas are sometimes called “Pauli master equations,” or “Redfield equations.”

Clean up a bit: Let \( \Omega = 2V/\hbar \) and \( S = (E_1 - E_2)/\hbar \).

Change variables to the four real quantities \( U = \rho_{11}, W = \rho_{22}, \)
\( X = (\rho_{12} - \rho_{21})/i, \) and \( Y = \rho_{12} + \rho_{21}. \) Then the dynamical
equations take the real form

\[
\begin{align*}
\frac{dU}{dt} &= -\frac{1}{2}\Omega X - U/\tau \\
\frac{dW}{dt} &= \frac{1}{2}\Omega X \\
\frac{dX}{dt} &= \Omega(U - W) - X/T - SY \\
\frac{dY}{dt} &= -Y/T + SX.
\end{align*}
\]

This is a set of coupled linear differential equations with constant coefficients, so its solutions will be combinations of exponentials.

In FRET, both excitation transfer and the non-transfer loss are much slower than the decoherence rate: \( T \ll \Omega^{-1} \) and \( T \ll \tau. \)

V M Agranovich and M D Galanin, Electronic excitation energy transfer in condensed matter (1982).
In the limit of fast decoherence ($T \to 0$), the third and fourth equations say that $Y$ rapidly relaxes to zero, whereas the other coherence $X$ adiabatically tracks the quantity $T\Omega$. Substituting that value for $X$ into the first two equations shows that the population difference $U - W$ has a contribution to its time dependence proportional to $T\Omega^2$. In other words, fast decoherence suppresses the effects of mixed quantum states, but one coherence is constantly “pumped up” by the population difference, and feeds back negatively to it.
Stigler’s Law

Now that we’ve seen what’s going on, we can return to the full equations

\[
\begin{align*}
\frac{dU}{dt} &= -\frac{1}{2} \Omega X - \frac{U}{\tau} \\
\frac{dW}{dt} &= \frac{1}{2} \Omega X \\
\frac{dX}{dt} &= \Omega (U - W) - \frac{X}{T} - SY \\
\frac{dY}{dt} &= -\frac{Y}{T} + SX.
\end{align*}
\]

We can approach them via perturbation theory in the quantity \(\Omega T\), which is small in the situation of interest (“fast decoherence”). As we gradually turn on this small parameter, we wish to follow the eigenvalue that is initially \(-1/\tau\). The initial state starts out pure \(|1\rangle\), and hence overlaps the corresponding eigenvector, which then falls like \(e^{-\beta t}\), with \(\beta\) given by

\[
\beta = \tau^{-1} + \frac{\Omega^2 T/2}{1 + (TS)^2} = \tau^{-1} + \frac{2V^2 T}{\hbar^2 + T^2 (E_1 - E_2)^2}.
\]

That result is sometimes obtained by appeal to “Fermi’s” Golden Rule (Dirac, 1927), but it wasn’t obvious (to me) that that result is applicable: We are studying the transitions between two discrete states, not from a discrete state to a continuum. (The Golden Rule approach also leaves us helpless when we study situations where decoherence is not so dominant.)
If we prepare the initial state $Z(0) = B_0$, then strictly speaking, the initial rate of increase of $\rho_{22}$ is zero. However, after a brief transient this behavior changes: Although the time course of $\rho_{22}$ is indeed initially flat, it soon starts to increase. This gives an effective first-order rate constant describing the excitation transfer.

Similarly, although $\rho_{11}(t)$ initially starts to fall with slope $-1/\tau$, it soon starts to fall as $e^{-\beta t}$, with eigenvalue given earlier:

$$\beta = \tau^{-1} + \frac{\Omega^2 T / 2}{1 + (TS)^2} = \tau^{-1} + \frac{2V^2 T}{\hbar^2 + T^2 (E_1 - E_2)^2}.$$  

The second contribution describes FRET; we see that the transfer rate has a sharp maximum as a function of the energy difference. The area under that peak will soon be important to us, so it’s interesting to notice that it does not depend on the value of the decoherence time $T$, as long as $T$ is small enough to justify the approximations made.

This eigenvalue is real, so we don’t get oscillatory behavior – answering one of our original puzzles.

The interaction energy of two electric dipoles is proportional to the product of their electric dipole moments $d_D$ and $d_A$, and to the inverse cube of the distance between them. Specifically, in a molecular separation regime where dipole interactions dominate, $V$ is proportional to $r^{-3}\langle (d_D \cdot d_A - 3d_D \cdot \hat{r} \cdot d_A) \rangle$, yielding the famous orientation dependence of the FRET rate. The rate is also proportional to $r^{-6}$, another key feature of FRET.

- Also, as soon as transfer takes place, the acceptor begins relaxing to the conformation that minimizes energy in its excited electronic state, preventing transfer back to the acceptor.

- To understand the dominance of FRET over photon emission, note that the “near fields” of a fluctuating dipole fall off with distance as $r^{-3}$, independent of its frequency. The “radiation fields” fall off more slowly, as $r^{-1}$, and they do depend on frequency. Turning these statements around, at small distances the near fields are stronger by a factor of $(\lambda/r)^2$, where $\lambda$ is the wavelength of light corresponding to donor fluorescence. The square of this ratio can exceed $10^4$.

- Turning to the other nearby molecules, the sharply peaked form of the transfer rate also ensures that only those with a transition resonant with the donor’s emission (overlapping spectra) will have significant probability per unit time to gain energy from it.
So far, we have assumed definite (exact) values for the donor’s excited and ground state energies, and similarly for the acceptor. Actually, however, each of these energies changes over time due to molecular motions, that is, changes of the positions of the atomic nuclei. Accordingly, we now introduce realistic (that is, broad) probability distributions of these energies, and average the mean rate for energy transfer over those distributions. The sharply peaked form of the effective rate constant as a function of $E_1 - E_2$ then implies that the mean FRET rate will be proportional to the overlap integral of the two distributions, another key feature of FRET.

Chlorophyll supposedly harvests light and begins the conversion into a proton gradient; 

_ but _

Plants can utilize light at wavelengths where chlorophyll does not absorb; 

_ so _

It must be possible for some other pigment to catch a photon, then hand the excitation energy over to a chlorophyll.
Arnold’s career highlights

• “In 1926, I was given a job as research assistant to Dr S.J. Barnett who was Head of the Physics Department at UCLA and was doing research at Cal Tech on what was then called Gyromagnetic Anomaly….

• In 1930, I returned to being a full time student. There were a number of courses required for graduation which I had not taken. It proved impossible to fit them into any schedule. **Elementary Biology came at the same time as another course that was required.** My advisor in the Physics Department sent me to see Dr T.H. Morgan who was head of the Biology Department. He suggested that I take the course in Plant Physiology, which was being taught by Robert Emerson, a brand new professor in Biology. Dr Morgan said if I passed the course it would be accepted in place of Elementary Biology. I liked Emerson and I liked the course which was largely about photosynthesis….

• When I graduated in the Spring of 1931, Emerson asked me to stay on as his assistant to make a more detailed study of the effects of flashing light. **Since I had been unable to find a place to do graduate work in astronomy** I agreed to continue as his assistant **a while longer**… [see next slide for what they found]

• In 1935, I decided to go to Berkeley to **audit Robert Oppenheimer's course** in Quantum Mechanics...

• [Around 1939,] Emerson told me that he and Lewis had found, on making the action spectrum for the blue-green alga Chroococcus, that light absorbed by phycocyanin was used in photosynthesis. He asked me to see if the energy absorbed by phycocyanin was being transferred to chlorophyll or was the phycocyanin doing photosynthesis. A few simple experiments showed the energy was being transferred to chlorophyll a. **I went up to Berkeley, and told Dr Oppenheimer about the problem. He pointed out this transfer was analogous to 'internal conversion' of gamma rays**…. We agreed that I was to write a paper on the subject.

• [In 1940] I received a letter from Princeton University asking me to take part in an investigation of anti-aircraft fire. This was for the Office of Scientific Research and Development… On one of his trips to Oak Ridge, I saw Dr Oppenheimer and **he reminded me that we were writing a paper together** on energy transfer in photosynthesis. **The paper was published only in 1950.**

First quantitative puzzle: Stoichiometry

Emerson and Arnold, 1932:
A short, saturating pulse of light, which activates all chlorophyll molecules, generates very little photosynthesis, only about one oxygen per 2500 chlorophylls.
Resolve the stoichiometry puzzle

Under a blue/UV light source...

Chlorophyll solution fluoresces blood-red.

In an intact plant, chlorophylls can pass around an excitation via a FRET-like mechanism.

a: Art by David Goodsell.

Emerson and Lewis, 1942: Cyanobacteria can perform photosynthesis using only light from a part of the spectrum *not* absorbed by chlorophyll.
Resolve the action spectrum puzzle

\[ f' \text{'s} = \text{measured absorption coefficients} \]
\[ \phi' \text{'s} = \text{unknown quantum yields} \]

Proceedings of the American Physical Society
MINUTES OF THE PASADENA, CALIFORNIA, MEETING
June 18–20, 1941

2. Internal Conversion in Photosynthesis. J. R. OPPENHEIMER, California Institute of Technology.—In some chlorophyll (cpl) containing algae, light absorbed by a fluorescent dye apparently produces photosynthesis. It has been suggested that this is because the cpl absorbs the fluorescent radiation of the dye, but the calculated absorption, using the known fluorescent yield, cpl concentration $n$ and absorption coefficient $\sigma$, is far too small. We wish to point out that energy transfer from dye to cpl can be enormously enhanced by the fact that there are cpl oscillators far closer than a wave-length to the fluorescent source. This transfer gives a large scale model of the internal conversion of nuclear gamma-rays. A simple calculation gives, for the ratio of quanta transferred to cpl to those emitted in fluorescence, $n\sigma \lambda^4/d^3$, where $2\pi\lambda$ is the fluorescent wave-length in water, and $d$ the closest distance of approach of cpl and dye oscillators. With reasonable values for $d$ this can explain a very high photosynthetic yield.

Tories far closer than a wave-length to the fluorescent source. This transfer gives a large scale model of the internal conversion of nuclear gamma-rays. A simple calculation gives, for the ratio of quanta transferred to cpl to those emitted in fluorescence, $n\sigma \lambda^4/d^3$, where $2\pi\lambda$ is the fluorescent wave-length in water, and $d$ the closest distance of approach of cpl and dye oscillators. With reasonable values for $d$ this can explain a very high photosynthetic yield.

4. The Theory of Light Nuclei. Edward Gerjuoy and Julian Schwinger, University of California.—The existence of the deuteron quadrupole moment indicates the presence of tensor nuclear forces which destroy the constancy of orbital angular momentum, and thus necessitates a revision of the theory of light nuclei. In $^1H^2$, the tensor forces directly couple to the fundamental $S_1^2$ state a $D_3^2$ state, which in turn interacts with $P_3^2$ and $P_3$. To the fundamental $S_1^2$ state of $^1He^4$ is admixed a $D_3^2$ state which interacts with $P_3$. Thus all states consistent with the total angular momentum occur. These nuclei therefore constitute the simplest examples of the break-down of spin conservation laws. We have performed a variation calculation employing trial wave functions of the character $S_1^2+D_3^2$ for $H^2$ and $S_1^2+D_3^2$ for $He^4$, with simple Gaussian radial functions. Using the known force constants for rectangular well potentials, the calculations yield 40 and 50 percent of the binding energy for $H^2$ and $He^4$, respectively. A similar test calculation for $H^2$ gave 20 percent of the binding energy. The probability that these nuclei are in the $D$ state was found to be 4 percent for all three nuclei; this value is in agreement with the exact deuteron computations. Calculations with improved trial functions are in progress.
Built-in Quantum Dot Antennas in Dye-Sensitized Solar Cells

Sophia Buhbut,† Stella Itzhakov,† Elad Tauber,§ Menny Shalom,† Idan Hod,† Thomas Geiger,‡ Yuval Garini,§ Dan Oron,† and Arie Zaban†,*

†Institute of Nanotechnology and Advanced Materials, Bar Ilan University, Ramat-Gan, 52900, Israel, ‡Department of Physics of Complex Systems, Weizmann Institute of Science, Rehovot 76100, Israel, §Institute of Nanotechnology and Advanced Materials, Bar Ilan University, Ramat-Gan, 52900, Israel, and †Empa, Swiss Federal Laboratories for Materials Testing and Research Laboratory for Functional Polymers Überlandstrasse 129, 8600 Dübendorf, Switzerland

ABSTRACT A new design of dye-sensitized solar cells involves colloidal semiconductor quantum dots that serve as antennas, funneling absorbed light to the charge separating dye molecules via nonradiative energy transfer. The colloidal quantum dot donors are incorporated into the solid titania electrode resulting in high energy transfer efficiency and significant improvement of the cell stability. This design practically separates the processes of light absorption and charge carrier injection, enabling us to optimize each of these separately. Incident photon-to-current efficiency measurements show a full coverage of the visible spectrum despite the use of a red absorbing dye, limited only by the efficiency of charge injection from the dye to the titania electrode. Time resolved luminescence measurements clearly relate this to Förster resonance energy transfer from the quantum dots to the dye. The presented design introduces new degrees of freedom in the utilization of quantum dot sensitizers for photovoltaic cells. In particular, it opens the way toward the utilization of new materials whose band offsets do not allow direct charge injection.

KEYWORDS: quantum dots · semiconductor nanocrystals · Förster resonance energy transfer (FRET) · sensitized solar cells · organic dye

Harvesting energy directly from sunlight using photovoltaic technology is being increasingly recognized as an essential component of future global energy production. Dye-sensitized solar cells (DSSCs) originally introduced by Grätzel et al. are promising devices for inexpensive, large-scale solar energy conversion. Photo conversion efficiencies greater than 11% have been reported for DSSC based on nanoporous TiO₂ electrodes, dye sensitizer, and an iodide/triiodide redox system. The most successful dyes employed are ruthenium complexes, (Ru(dcbpy)₂(NCS))₂, N₃ (dcbpy = 4,4-dicarboxy-2,2'-ipyridine), or the bistratobutylammonium salt N719. In DSSCs, dye molecules absorb photons and inject electrons from their excited state into the conduction band of a mesoporous TiO₂ film where they diffuse to a transparent conducting front contact while the oxidized dye is recharged by a redox electrolyte, which transports the positive charge to a back electrode. In lower cell efficiencies compared with the standard DSSCs. A new approach recently utilizes Förster resonance energy transfer (FRET) from donor dye molecules that are adsorbed on the surface of colloidal semiconductor quantum dots.
Back to the mystery image

*Left:* Sierra Blakeley. *Right:* courtesy Steven Haddock.
Some of this material was taken from a recent book:

*From Photon to Neuron: Light, Imaging, Vision* (www.physics.upenn.edu/biophys/PtN).

Other bits are in P Nelson, *Biophys J.* 2018 (http://doi.org/10.1016/j.bpj.2018.01.010)

For these slides see: www.physics.upenn.edu/~pcn