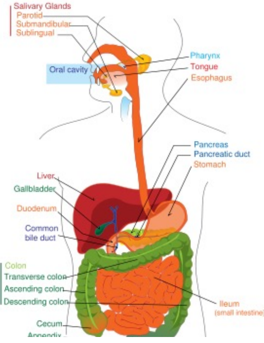
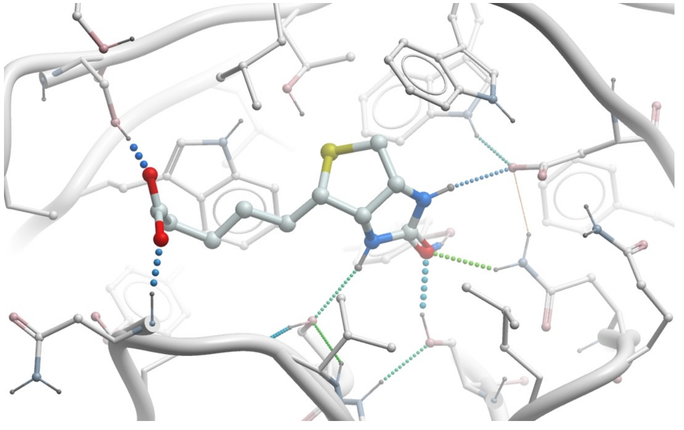
Physical Pharmacology. Molecular Structures and Drug Properties

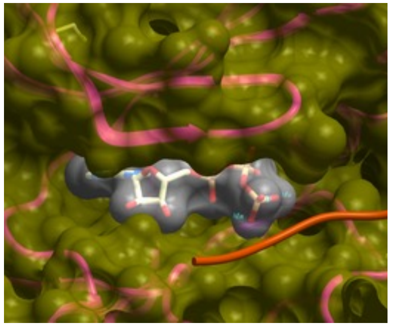
Thermodynamics: transitions, reactions, laws

$G=H-TS, \quad RT \ln K_{eq} = -\Delta G^o, \quad P_{osm}$



- **Radioactive & fluorescent drugs**
- **2D, 3D Structure and Interactions of Drugs**
- **Interaction energetics**
- **Ionization**
- **Solubility**
- **Permeability**
- **Analytical methods**





Radioactivity applications in pharmacology and medicine. Nuclear pharmacy

- Radio-pharmaceuticals : diagnostic or therapeutic agents, ^{47}Ca, ^{11}C,^{14}C, ^{57}Co,^{18}F,$^{67,68}Ga$, $^{123,124,\mathbf{131}}I$, Fe, Kr, ^{13}N,..Tc,Xe,Yt
- SPECT : single-photon, ^{99m}Tc
- Positron Emission Tomography (**PET**) radiotracers (eg ^{18}F and fluoro deoxy glucose, ^{18}F-FDG)
- Surgery assistance

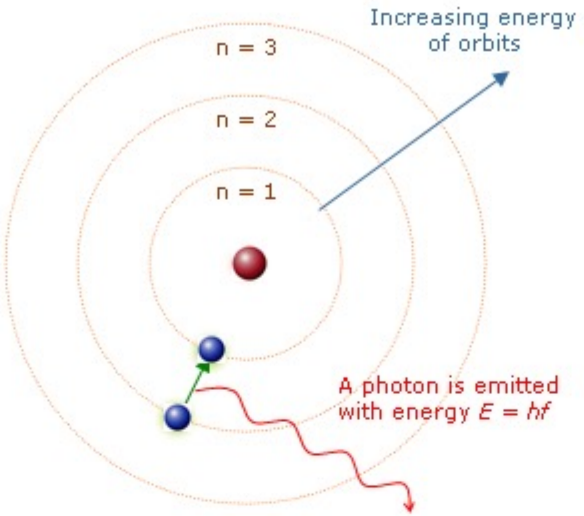
SPECT: Single Photon Emission Computed Tomography

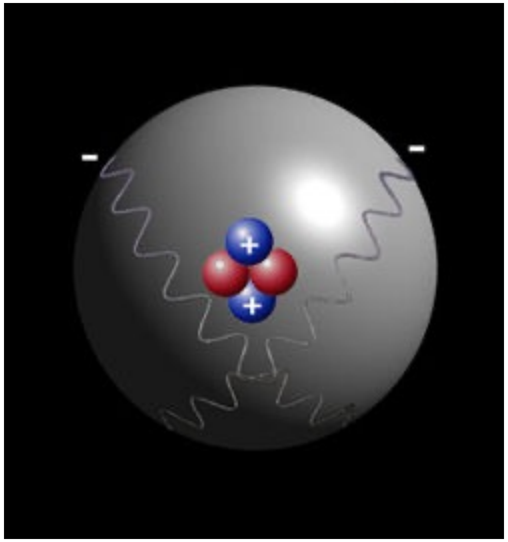
Quantum Description of Atoms and Molecules

- *Electrons* are described as probability waves around nuclei
- Electrons occupy *discrete states*: *orbitals*, one electron per state, two with opposite spins
- Transition between orbitals is associated with discrete energies and *wave frequencies*

  E =hν=ħω (ν of *f* in cycles, ω in radians)
- Reduced **Planck constant**

  $\hbar = h/2\pi \approx 10^{-34}$ J s





Schrödinger equation explains molecules, particles, nuclear reactions and transitions

- Schrödinger equation helps finding the energies $\boldsymbol{E_i}$ and shapes of the discrete orbitals (a.k.a. “wave functions” Ψ)

$$\left[-\frac{\hbar^2}{2m}\nabla^2 + U(\mathbf{r})\right]\psi(\mathbf{r}) = E\psi(\mathbf{r})$$

- All energies, electronic and vibrational properties of atoms and molecules are explained by the the equation

Erwin Schrödinger

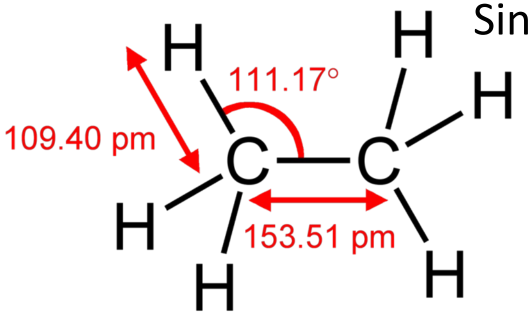
Time-dependent form

Molecular interactions: Why atoms repel each other at close distances?

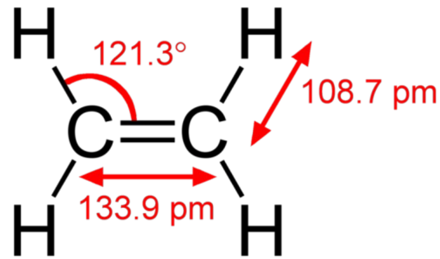
- Electrons, protons and neutrons have "half-odd-integer" angular momentum (spin): $1/2\hbar$, $3/2\hbar$,$5/2\hbar$. They are called *fermions*.
- **Sub-atomic particles** with *integer* spin are called *bosons* (e.g. photons)
- **The *Pauli exclusion principle*: Fermions (electrons, protons, neutrons) are "*stiff*": two fermions can not occupy the same quantum state.**
- That is why atoms repel each other at close distances

σ,π–bonding, bond types, transitions

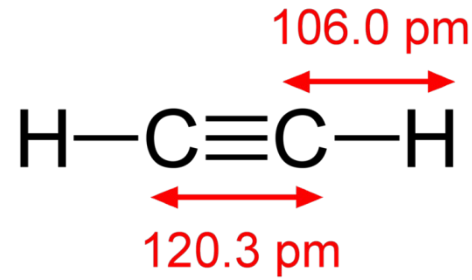
Single (σ)



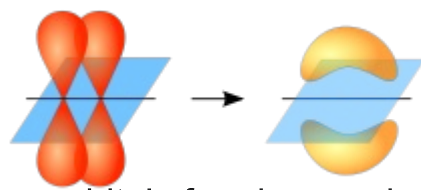
Double ($\sigma+\pi$)



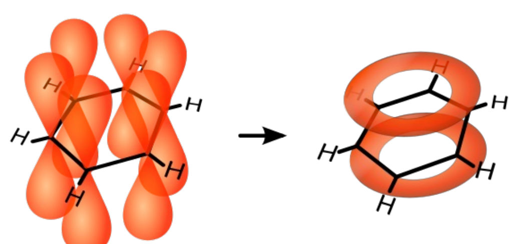
Triple ($\sigma+2\pi$)



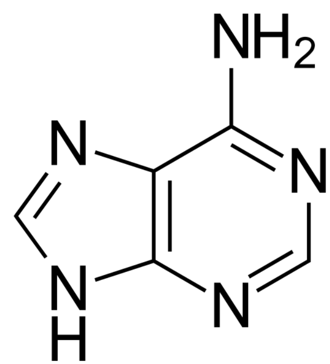
Aromatic (delocalized electrons, flat structures)



Two p-orbitals forming a π-bond.



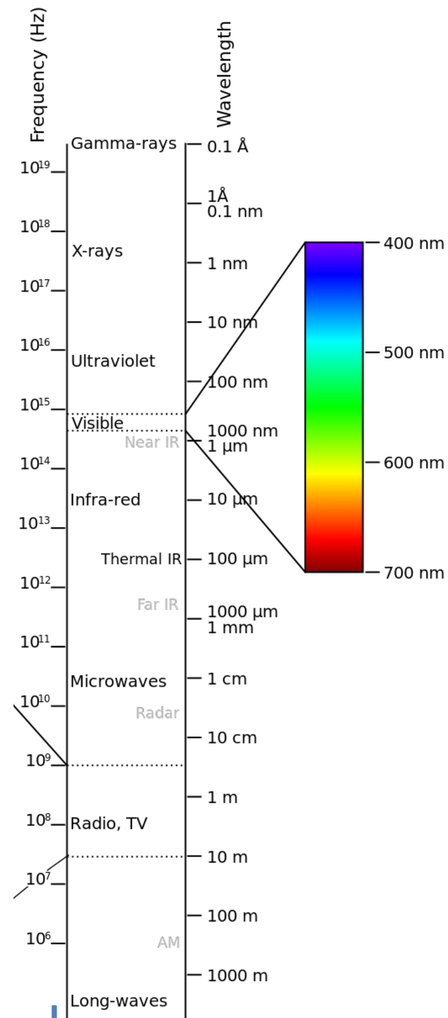
6 p-orbitals delocalized



Energies of photons, from Radioactivity to Fluorescence

Low energy transitions, drug binding

- A molecule can change its
  - *Electronic state* (excited electronic level >> RT, ΔE > 100 kJ/mol, which corresponds to ~1 eV)
  - *Vibrational state* (changes in bond lengths and bond angles, ΔE ~ 10kJ/mol)
  - Torsion and positional variables (ΔE less than 2 kJ/mol , almost *continuous spectrum* for translation)
- At physiological T (**RT≈2.5kJ/mol**), the electronic states of a non-covalent drug are typically frozen into their ground states.



High energy particles **break** multiple bonds and molecules

Radio-pharmacology: radioactive isotopes decay to make **high energy** alpha **particles**, protons, neutrons, electrons, positrons and γ rays

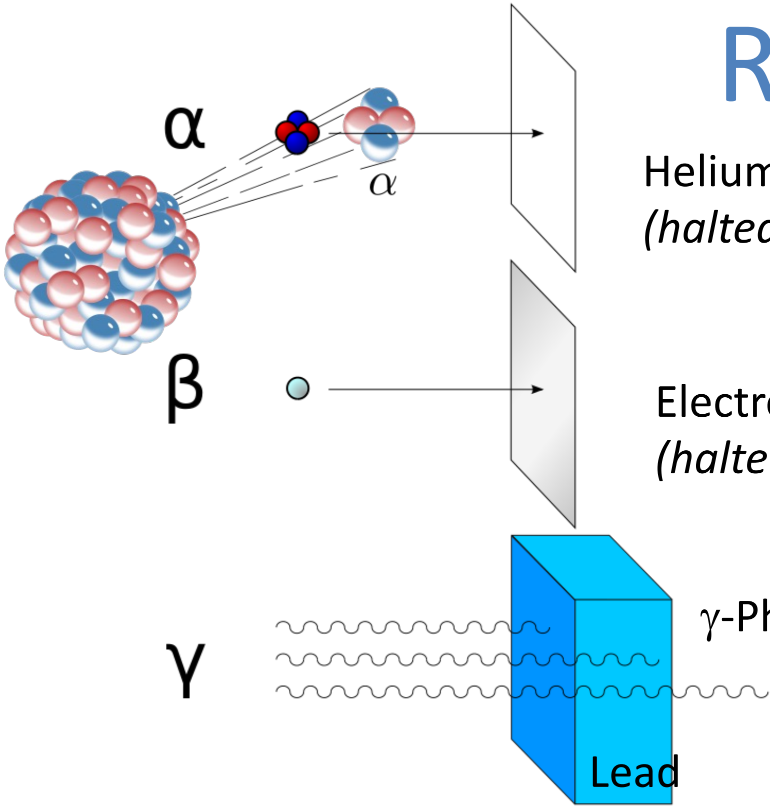
Isotopes : “same place” in Periodic table

Atoms with the **same atomic number** but different mass numbers (i.e. *different number of NEUTRONS*) are called **isotopes**.

^{12}C and ^{13}C are stable.

“Radiocarbon dating” is based on ^{14}C (half-life of ^{14}C is about 5,730 years)

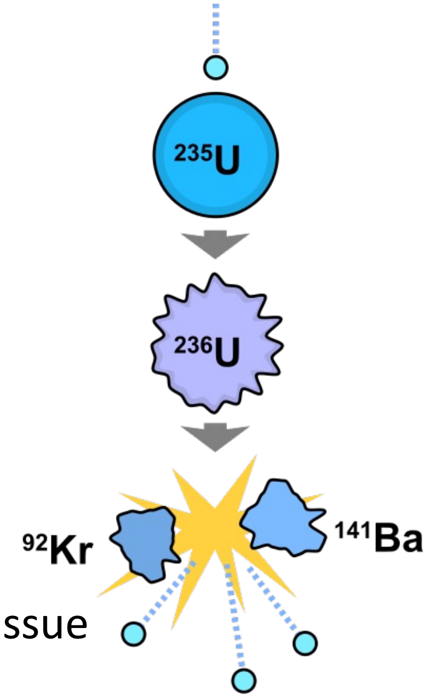
Radioactivity



Helium nuclei
(halted by paper)

Electrons and Positrons
(halted by aluminum plate)

γ-Photons pass through the biological tissue



- Decay Units: Production (Bq), Absorption (Gy)

Bq (Becquerel) = s^{-1} is the *number of decays per second*

(older: 1 **Curie** (**Ci**) = 3.7×10^{10} **Bq**)

Gy (Gray) = absorption of *one joule* of radiation energy *per kilogram* of matter

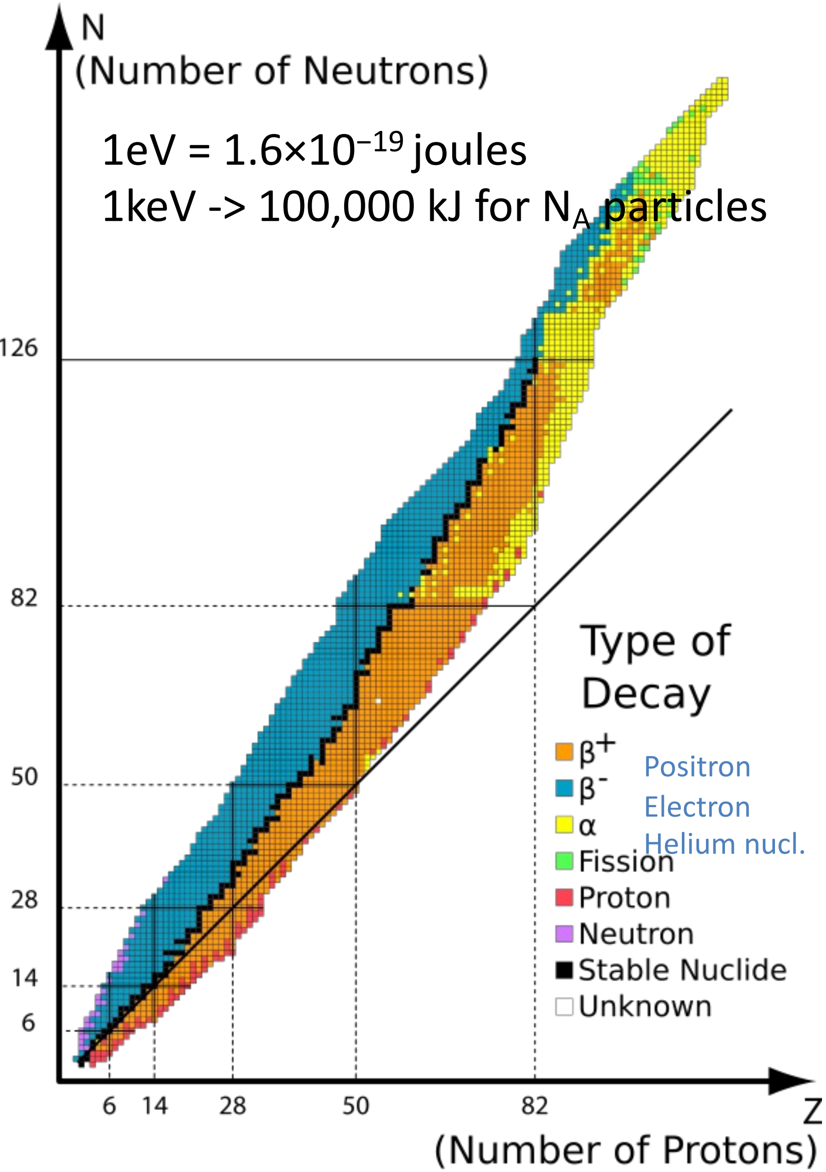
Also: **Sievert, Sv = Gy** for X-rays

$$1\ \mathrm{Gy} = 1\ \frac{\mathrm{J}}{\mathrm{kg}} = 1\ \frac{\mathrm{m}^2}{\mathrm{s}^2}$$

1 Sv = 1 joule/kilogram – a biological effect. deposit of a joule of radiation energy in a kilogram of human tissue. The equivalence to absorbed dose is denoted by Q.

Radionuclides in Medicine: destruction or imaging

1eV = 1.6×10^{-19} joules
1keV -> 100,000 kJ for N_A particles



- Unstable isotopes convert into more stable ones and produce *gamma rays* (most penetrating) and/or high energy particles α,p,n,β–,β+, γ
- Particles may destroy cells

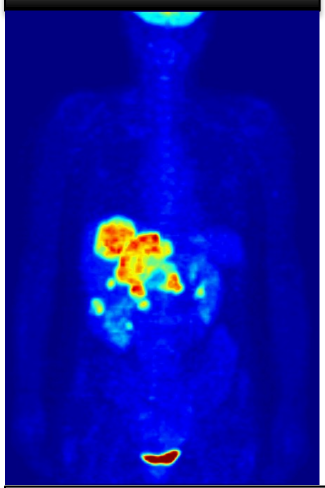
- Radio-pharmacetical is injected, distributed in the body (may be in a carrier molecule, e.g. glucose), used for **imaging** or therapy

- Examples:

Diagnostic **imaging** of colorectal cancers:
- Technetium-99m -> γ
- ^{99m}Tc **arcitumomab** <1MeV
- Fluoro deoxy glucose

Treatment of hyperthyroidism with Iodine
- I–131 (8 days) => γ+β 971 keV

Lead container for iodine-123 capsule



PET: positron-emission tomography

Medical X-ray doses in Gray units

- For a *solid epithelial tumor :* **60 to 80 Gy**, or Sv
- *Lymphomas* are treated with **20 to 40 Gy**.
- Preventive doses are typically around 45–60 Gy in 1.8–2 Gy fractions for breast, head, and neck cancers.

Diagnostic doses

- The average radiation dose from *an abdominal X-ray* is 0.7 *milli*sieverts (**0.0007 Sv**), that from an *abdominal CT scan* is **8 mSv**

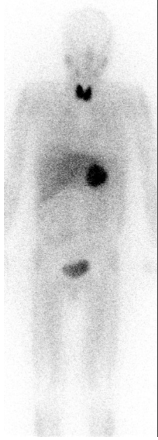
High energy photons for diagnostics

Radiation doses of common imaging procedures in milli Sievers (mSv)

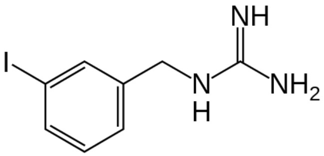
Radiation comes from either an external source or an injected/infused radioactive substance (e.g. Iodine-123, Barium-130,131 ..)

	Procedure	Approximate effective radiation dose (mSv)	Approximate comparable time of natural background radiation exposure
ABDOMINAL REGION	Computed Tomography (CT) — Abdomen and Pelvis	7.7 mSv	2.6 years
	Computed Tomography (CT) — Abdomen and Pelvis, repeated with and without contrast material	15.4 mSv	5.1 years
	Computed Tomography (CT) — Colonography	6 mSv	2 years
	Intravenous Pyelogram (IVP)	3 mSv	1 year
	Barium Enema (Lower GI X-ray)	6 mSv	2 years
	Upper GI Study With Barium	6 mSv	2 years
BONE	Lumbar Spine	1.4 mSv	6 months
	Extremity (hand, foot, etc.) X-ray	< 0.001 mSv	< 3 hours
CENTRAL NERVOUS SYSTEM	Computed Tomography (CT) — Brain	1.6 mSv	7 months
	Computed Tomography (CT) — Brain, repeated with and without contrast material	3.2 mSv	13 months
	Computed Tomography (CT) — Head and Neck	1.2 mSv	5 months
	Computed Tomography (CT) — Spine	8.8 mSv	3 years
CHEST	Computed Tomography (CT) — Chest	6.1 mSv	2 years
	Computed Tomography (CT) — Lung Cancer Screening	1.5 mSv	6 months
	Chest X-ray	0.1 mSv	10 days
DENTAL	Dental X-ray	0.005 mSv	1 day
	Panoramic X-Ray	0.025 mSv	3 days
	Cone Beam CT	0.18 mSv	22 days
HEART	Coronary Computed Tomography Angiography (CTA)	8.7 mSv	3 years
	Cardiac CT for Calcium Scoring	1.7 mSv	6 months
	Non-Cardiac Computed Tomography Angiography (CTA)	5.1 mSv	< 2 years
MEN'S IMAGING	Bone Densitometry (DEXA)	0.001 mSv	3 hours
NUCLEAR MEDICINE	Positron Emission Tomography — Computed Tomography (PET/CT) Whole body protocol	22.7 mSv	3.3 years
WOMEN'S IMAGING	Bone Densitometry (DEXA)	0.001 mSv	3 hours
	Screening Digital Mammography	0.21 mSv	26 days
	Screening Digital Breast Tomosynthesis (3-D Mammogram)	0.27 mSv	33 days

Radioactive decay: therapies



Substance	*Condition*
^{131}**I**-sodium iodide	hyperthyroidism and thyroid cancer
Yttrium-90-ibritumomab tiuxetan (Zevalin) and ^{131}**I**-tositumomab (Bexxar)	refractory lymphoma
^{131}**I**-MIBG (meta iodo benzyl guanidine)	neuroendocrine tumors
Samarium-153 or **Strontium-89**	palliative bone pain treatment



^{90}**Y** undergoes β− decay to zirconium, $T_{½}$ = 64.1 hours, E=**2.28 MeV**

^{131}**I** $T_{½}$ = 8 days (eg as potassium iodide or iodate, KI, or KIO_3)

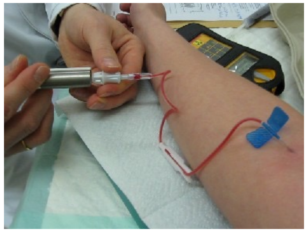
$$^{131}_{53}\mathrm{I} \longrightarrow \beta + \bar{\nu}_{\mathrm{e}} + {}^{131}_{54}\mathrm{Xe}^{*} + 606\,\mathrm{keV}$$

$$^{131}_{54}\mathrm{Xe}^{*} \longrightarrow {}^{131}_{54}\mathrm{Xe} + \gamma + 364\,\mathrm{keV}$$

- Ionizing radiation, *potential hazard*:
  - Broken molecules, cells killed, anemia/neutropenia, immunogenicity, radiation burns
  - *Mutations* in somatic or germ cells, new neoplasms

Mild Nuclear reactions for imaging

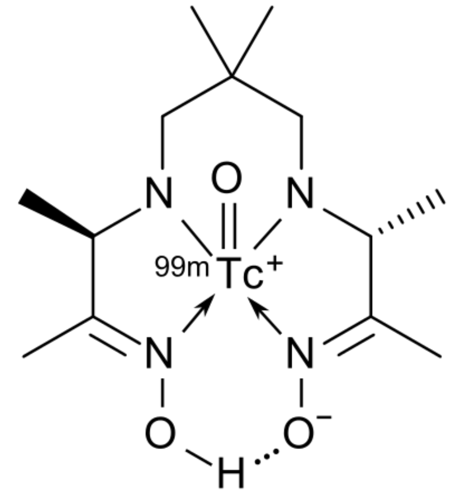
$$^{99m}Tc \rightarrow {}^{99}Tc + \gamma$$ **140 keV**



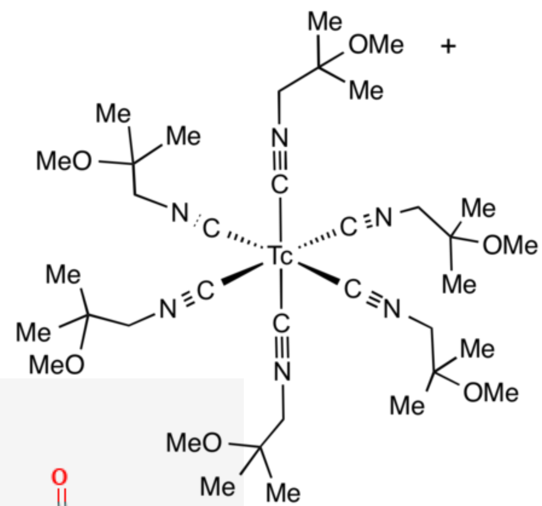
- ^{99m}Tc is a *metastable isomer* of ^{99}Tc
- ^{99m}Tc half-life is 6 hours (syringe is shielded)
- ^{99m}Tc is produced in hospitals from ^{99}Mo
- Source: ^{99}Mo ($T_{1/2}$ =66 hours) is produced in nuclear reactors from ^{235}U
- ^{99m}Tc chelators: pyrophosphate, exametazime, disofenin, oxidronate, arcitumomab, medronate, sestamibi,tetrofosmin, ...
- Unit conversion: 1eV corresponds to 96 kJ/mol, 23 kcal/mol

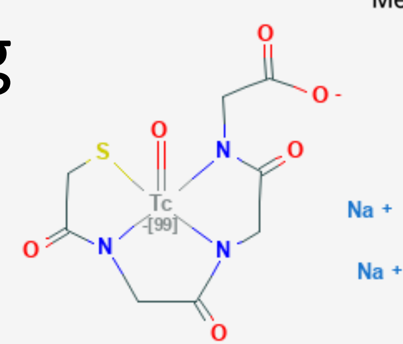
Example: ^{99m}Tc + targeting molecule to tumor-related lymph nodes
Lymphoseek: mannosylated carrier (tilmanocept) binds to macrophage CD-206 receptors

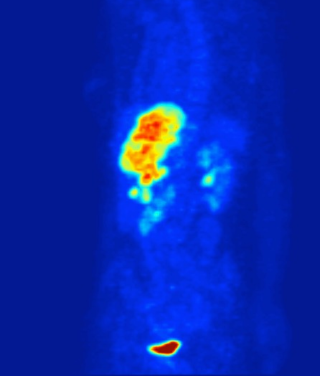
Technetium-99m carriers: target organ delivery



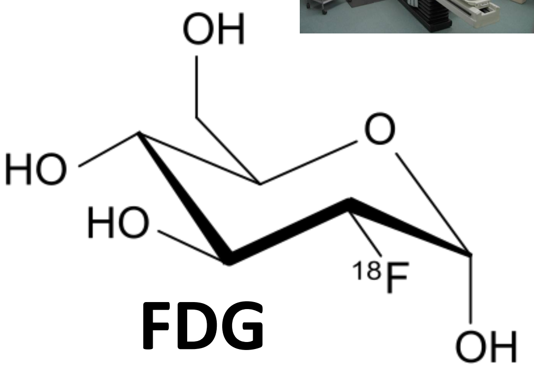
- Exametazine (Ceretec) for cerebral imaging in stoke
- Sestamibi for myocardial perfusion imaging
- Mercapto Acetyl Tri-Glycine (MAG3) for kidney imaging



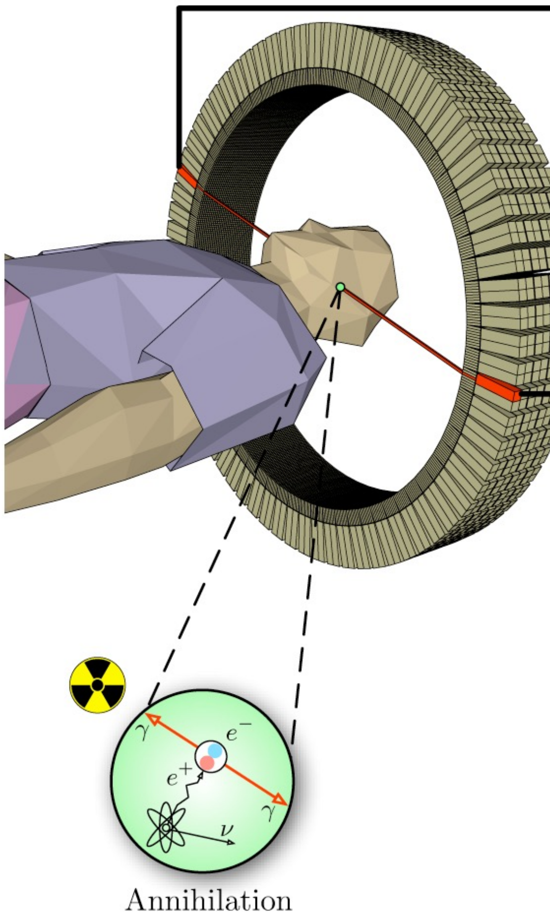




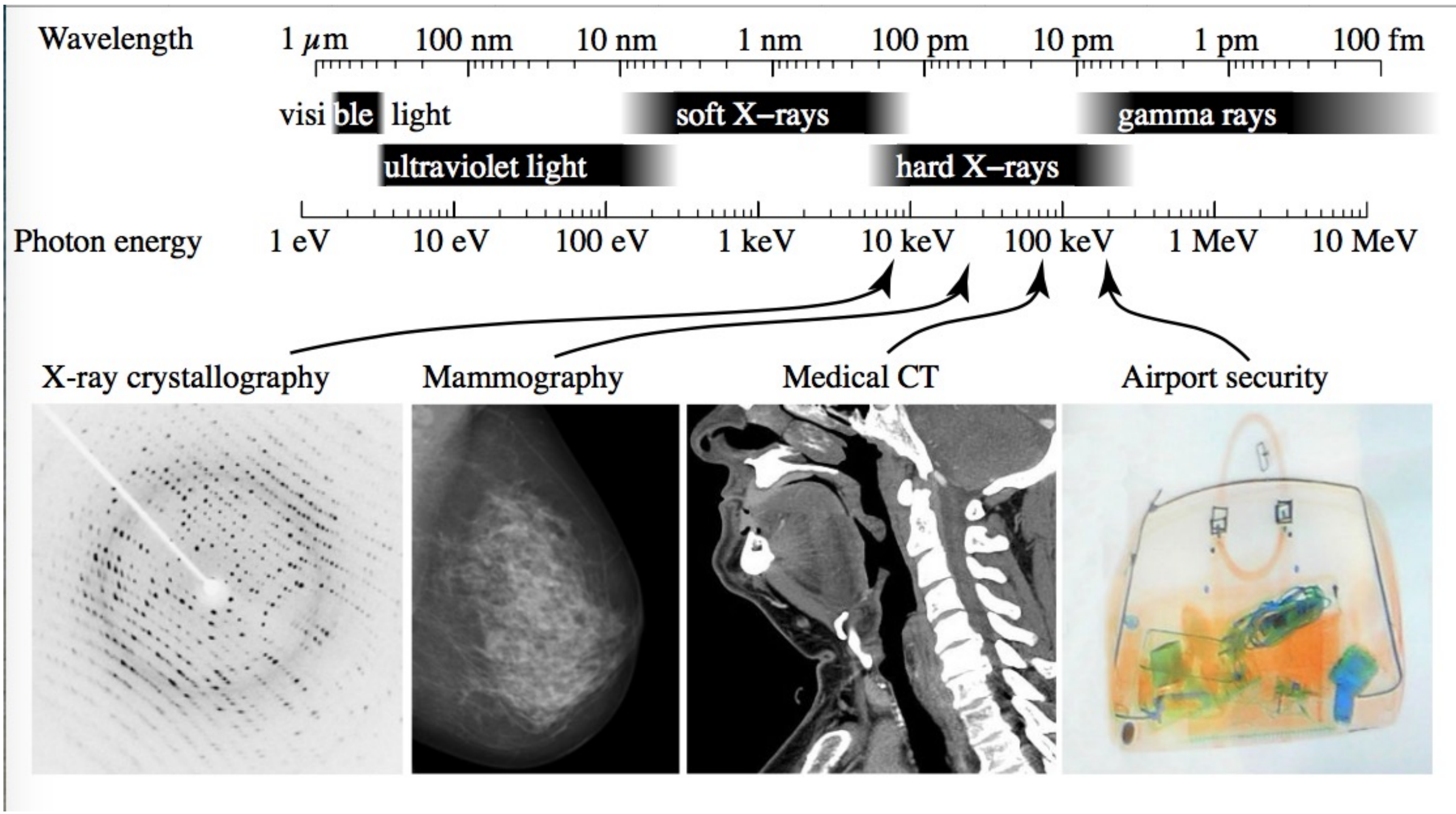
PET: Positron-Emission Tomography



- Tracer: ^{18}F in FluoroDeoxyGlucose.
  Other carriers possible for specific receptor destination
- Destination: Hungry cells eat FDG
- Reaction: ^{18}F decays by emission of a **positron e^+** ($t_{half\text{-}life}$ = 109 min).
- Annihilation: $e^+ + e^-$ → pair of 511 keV *opposite photons*; detection; computer tomography

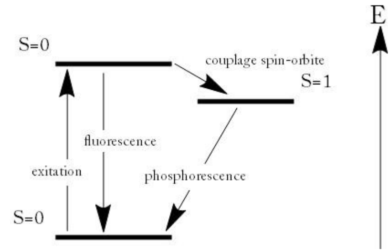


$E=h\nu \quad \lambda=c/\nu \quad c=3\cdot10^{8}$ m/s, $h=6.626\cdot10^{-34}$ J s



Luminescence is emission of light NOT from heat; a form of **cold** body radiation

- **Fluorescence**
- **Phosphorescence**



Fluorescence in Pharmacology

- **Sample**: Take a specimen (solution, semi-transparent sample, tissue, crystal) with a fluorescent drug (or inject it).
- **Excitation**: Shine light of ***higher*** frequency (can be UV or even X-ray) at the sample
- **Emission**: Observe the light of ***lower*** frequency emitted by the the drug

Why fluorescence?

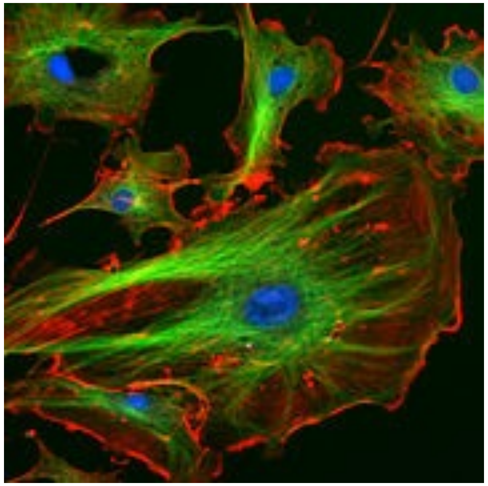
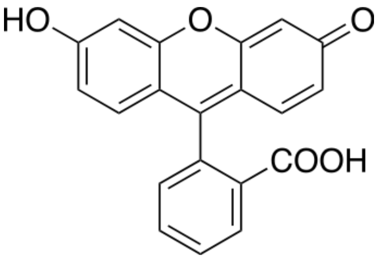


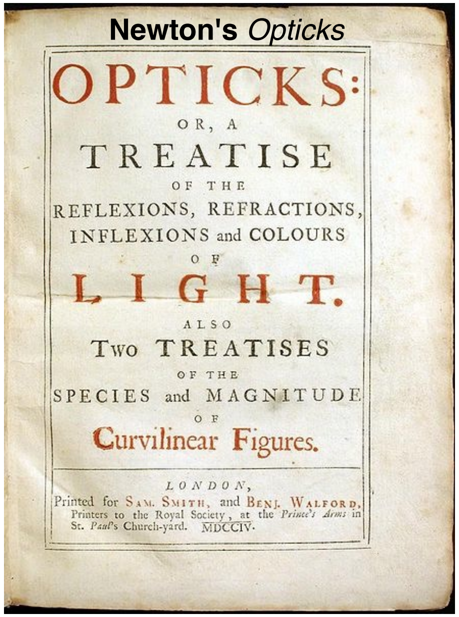
Image courtesy of Photometrics

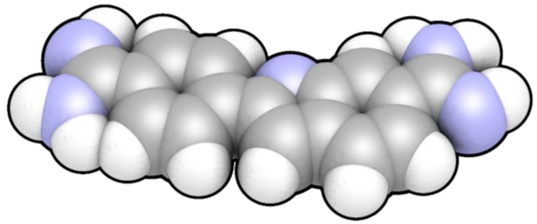
- Fluorescent microscopy
- High Contrast and Spatial resolution
- High specificity via using antibodies and specific dies
- Live cell imaging with fluorescent proteins
- Drugs for interactive cancer imaging during surgery, ophthalmology etc.
- Multiple colors
- Quantitative

Fluorescein (ocular,IV)

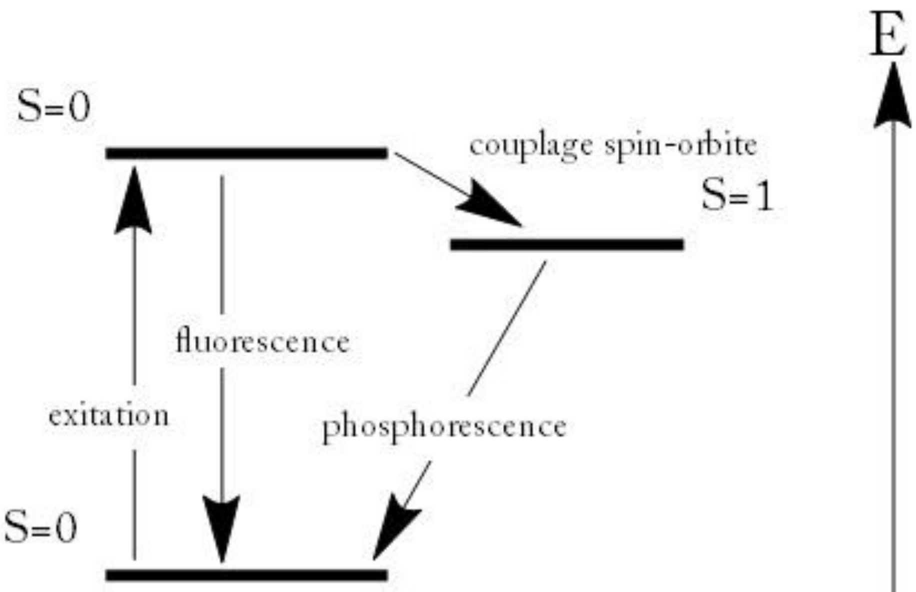


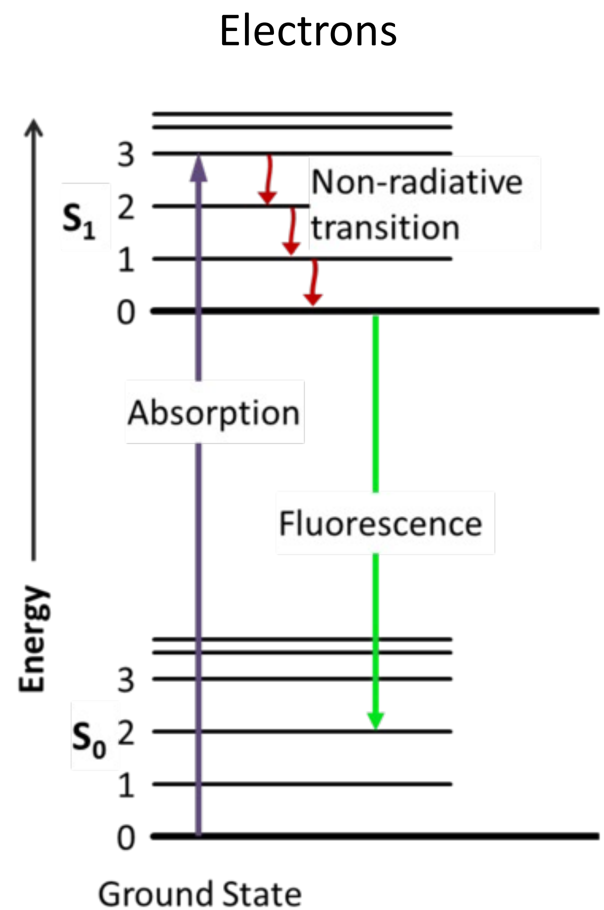
How it works





DAPI (stains DNA)





Jablonski Diagram of electronic and vibrational states.

See Nico Stuurman (UCSF) lecture: http://www.youtube.com/watch?v=iPrZ84kHH2U