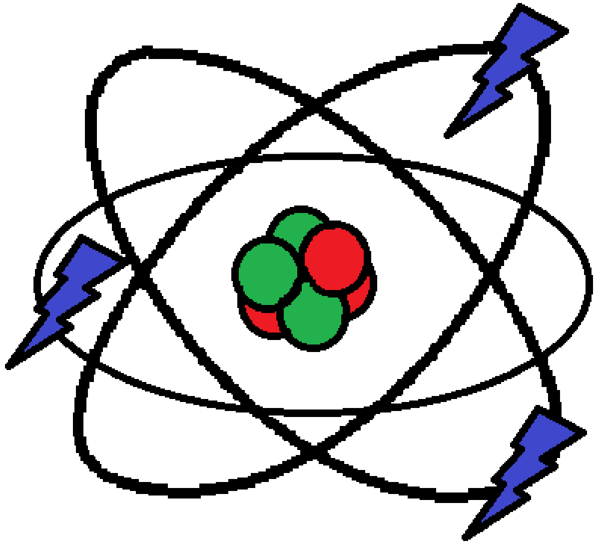
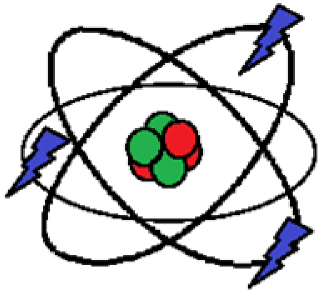




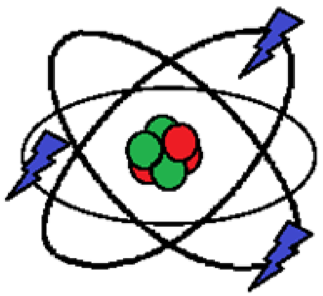
Nuclear Medicine

Dr. Michael J. Shaw

The Science Circle

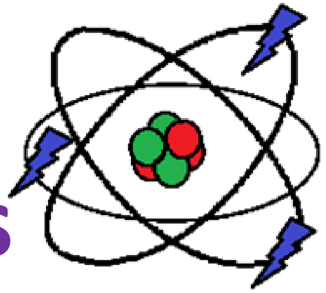
October 28, 2017

An Abstract…



Since the discovery of radioactivity, our understanding has steadily increased about how nuclear materials can be used to improve health. Individuals who worked with radioactive substances in the early decades of the 20th century were often exposed to dangerous amounts of radioactivity. Nuclear safety improved in the mid-20th century, and the application of nuclear phenomena to medicine was developed in earnest. From improved scanning techniques to tissue-specific therapies, the current state-of-the-art includes an impressive set of technologies for the diagnosis and treatment of a number of diseases.

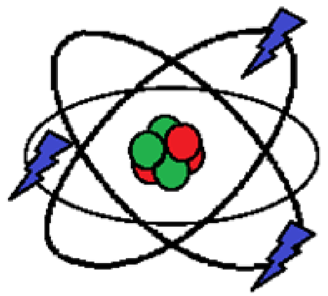
Acknowledgement: Open Education Commons



- https://www.oercommons.org/
- "OER Commons is a dynamic digital library and network. Explore open education resources and join our network of educators dedicated to curriculum improvement."

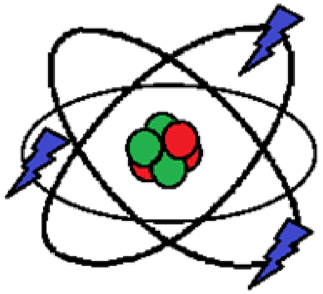
- I have identified the slides where I have used OER Commons content, including Wikibooks content.
- Good resource: https://www.oercommons.org/courses/basic-physics-of-nuclear-medicine/view

Radioactive elements have been in the public eye since their discovery…



- Marie Curie – bio from Nobel site (https://www.nobelprize.org/nobel_prizes/physics/laureates/1903/marie-curie-bio.html)
- Mark Twain… "Sold to Satan" http://www.revolutionsf.com/fiction/sold2satan/01.html has a devil made of radium (way beyond critical mass) with a polonium skin…
- "The Radium Girls" by Kate Moor. Review at http://www.npr.org/2017/04/27/525765323/the-radium-girls-is-haunted-by-glowing-ghosts

Early Days…



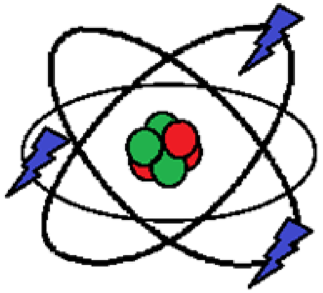
http://demoweb.physics.ucla.edu/content/60-radioactivity-and-counters

- Fiestaware! (Uranium Glaze)
- Shocking uses…
  - Quackery: The health benefits of Radium?
  - https://www.ranker.com/list/quack-medical-devices-that-contained-radium/amandasedlakhevener

Uses in Medicine?

- **IMAGING**
  - Positron Emission Tomography Scans
  - Gamma ray emission (e.g) Tc-99m
  - Nuclear Spin yields MRI
    - Can look at ^{1}H and ^{31}P, both of which are 100% abundant and which have the property of "spin"
- **THERAPY**
  - Isotopes used for research need to be delivered within compounds
  - Many Anticancer drugs:
    - Includes Boron neutron capture therapy

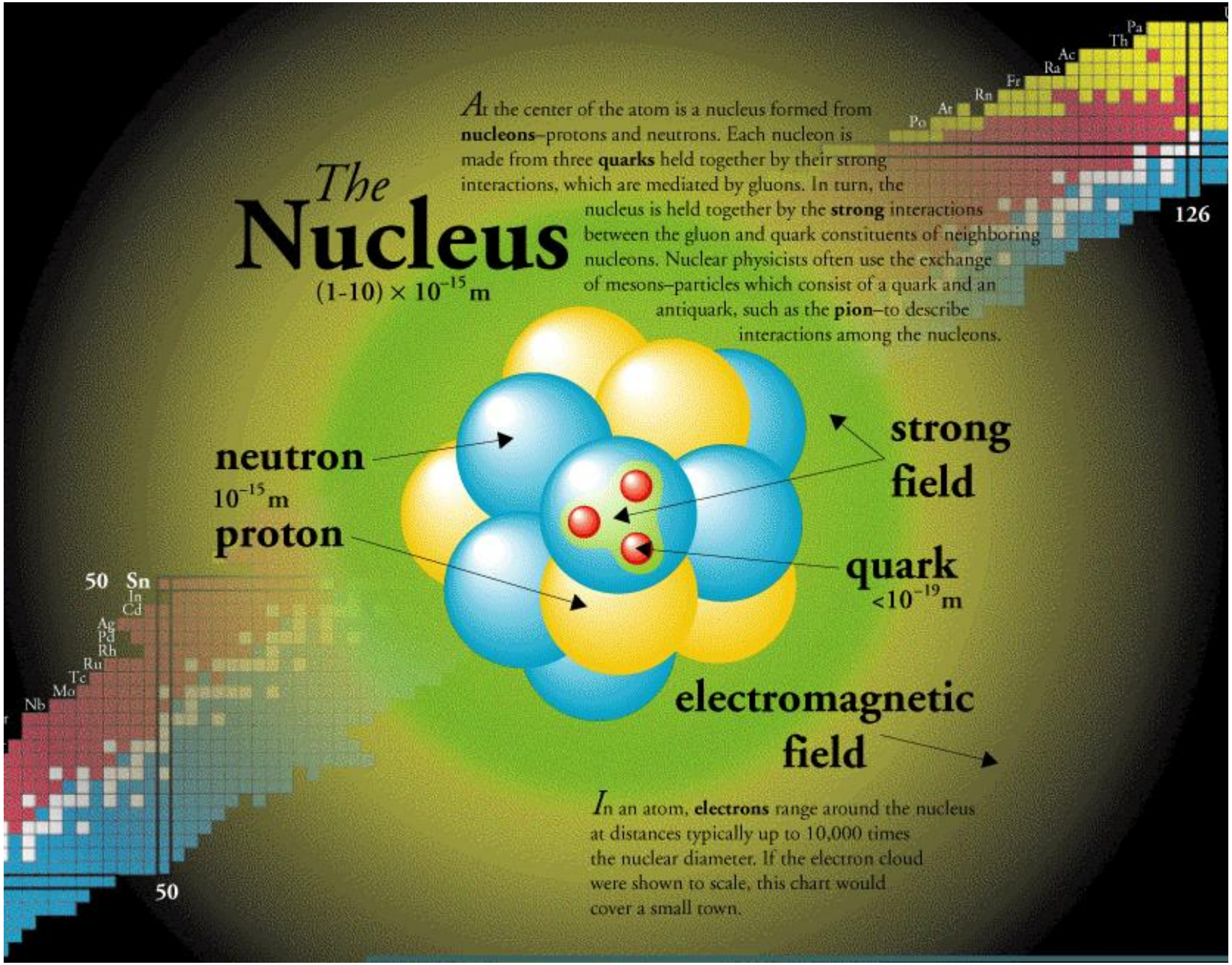
What is Nuclear Chemistry?

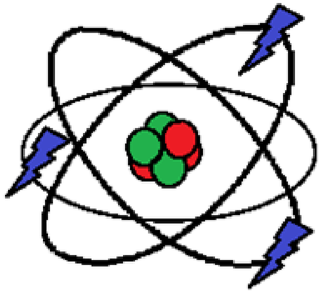


- Start with atoms
- Atoms are made of protons and neutrons in a dense core, surrounded by electrons at relatively far distances

- What type of *element* an atom is depends on how many protons there are in the nucleus.
- Which *isotope* or *nuclide* of the element, depends on # of neutrons.

For more basics see: http://www.oercommons.org/courses/abcs-of-nuclear-science-and-technology/view



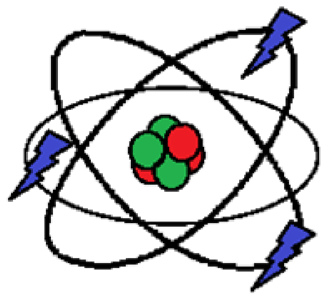


Nucleus

- See: http://www.oercommons.org/courses/abcs-of-nuclear-science-and-technology/view

  for a course and this image

Scale of Atoms:



- Electrons on outside (10^{-10} m region)
- Nucleus on inside (10^{-14} m region)
  - Protons have + charge
    - # protons determine which element
  - Neutrons have no charge
    - # neutrons helps determine overall mass
  - Both called "nucleons"
- Electrons weigh about 1/1800 of a nucleon

Long Form Periodic Table

Source: http://www.sciencegeek.net/tables/tables.shtml

1	1 H																															2 He
2	3 Li	4 Be																									5 B	6 C	7 N	8 O	9 F	10 Ne
3	11 Na	12 Mg																									13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
4	19 K	20 Ca															21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
5	37 Rb	38 Sr															39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
6	55 Cs	56 Ba	57 La	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
7	87 Fr	88 Ra	89 Ac	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No	103 Lr	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn	113 Uut	114 Uuq	115 Uup	116 Uuh	117 Uus	118 Uuo

Nh Fl Mc Lv Tn Og

*update

Alkali metals	Alkaline earth metals	Lanthanides	Actinides	Transition metals
Poor metals	Metalloids	Nonmetals	Halogens	Noble gases

State at standard tempurature and pressure

Atomic number in red: gas

Atomic number in blue: liquid

Atomic number in black: solid

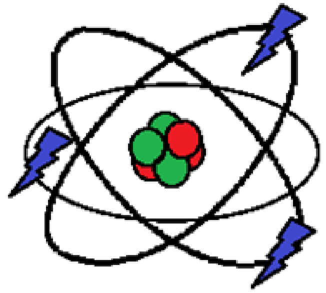
solid border: at least one isotope is older than the Earth (Primordial elements)

dashed border: at least one isotope naturally arise from decay of other chemical elements and no isotopes are older than the earth

dotted border: only artificially made isotopes (synthetic elements)

no border: undiscovered

Forces

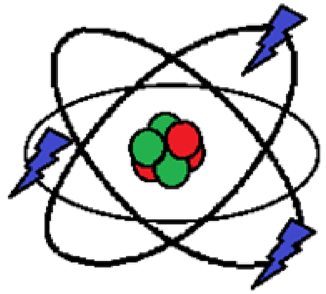


- Electromagnetic
  - Protons push each other strongly
  - Long range effect
- Strong Nuclear
  - Nucleons attract each other VERY strongly, but only if touching
- Weak Nuclear
  - Nucleons have a weak repulsion
- Gravity?
  - Not a factor with such small masses.

What you need to know:

Some atoms fall apart, giving off energy in the form of radiation

Isotopes / Nuclides



- All atoms are examples of an isotope.
- Some isotopes are stable… differ by # of neutrons

Total number of protons + neutrons “mass number”

$$^{1}_{1}\mathrm{H} \qquad ^{2}_{1}\mathrm{H} \qquad ^{3}_{1}\mathrm{H}$$

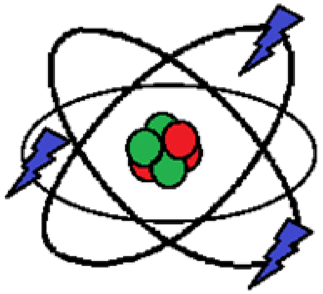
Regular hydrogen “protium”

Heavy hydrogen “deuterium”

Radioactive hydrogen “tritium”

Total number of protons “atomic number”

Nuclides or Isotopes



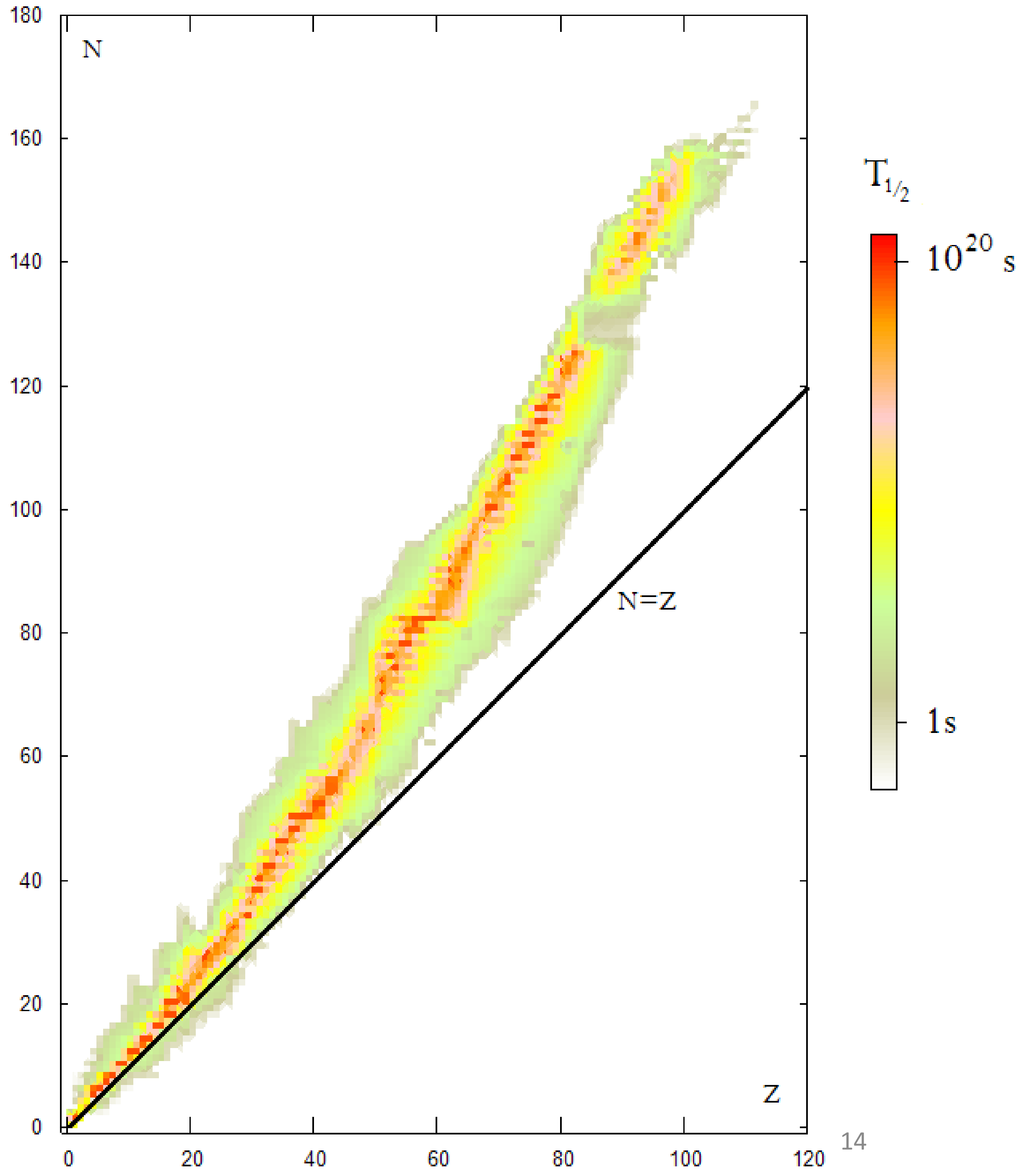
- Every element can have isotopes
- Some are stable, some aren’t
- Lighter than Ca, most stability comes from having 1:1 ratio of protons and neutrons
- Heavier than Ca, need more neutrons to hold nuclei together

Background

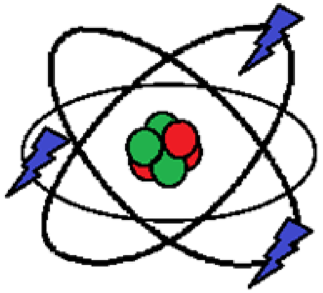
Table of Nuclides

- Color describes half-life
  - red is most stable
- X-axis is number of protons
- Y-axis is number of neutrons

- https://www.oercommons.org/courses/basic-physics-of-nuclear-medicine/view



Background… math warning!



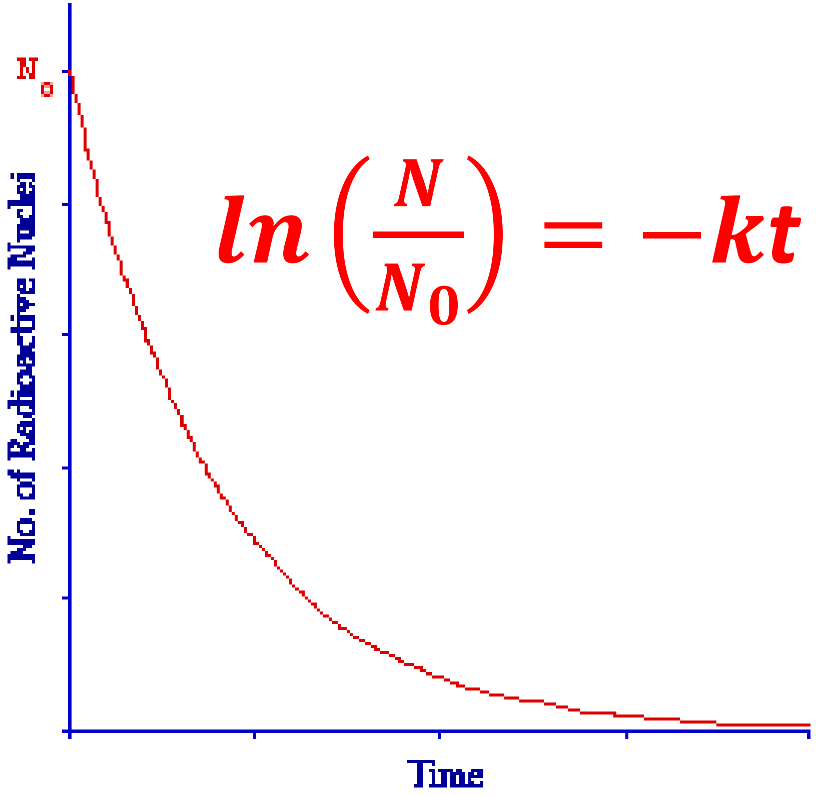
Half-life: 1st order decay

- When $N = 0.5 \times N_o$, then you're at the time it takes for half of what you started with to go away.

- "k" is a rate constant... units are s^{-1}

$\ln(0.5) = -kt_{1/2}$

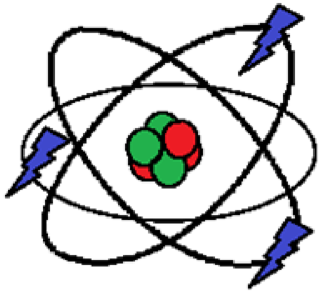
$t_{1/2} = 0.692/k$



$$\ln\left(\frac{N}{N_0}\right) = -kt$$

Image: https://upload.wikimedia.org/wikipedia/commons/0/0b/NM4_11a.gif

Stability

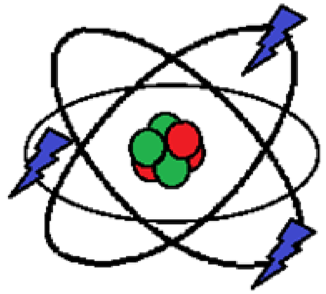


- Stable nuclei are balanced between attractive forces and repulsive forces
- Too many neutrons?
  - Eject e$^-$, turn a neutron into a proton

$$ {}^{atomic\ mass}_{atomic\ number}X \rightarrow {}^{atomic\ mass}_{atomic\ number+1}Y + {}^{0}_{-1}e^{-} $$

$$ {}^{3}_{1}H \rightarrow {}^{3}_{2}He + {}^{0}_{-1}e^{-} $$

A few too many protons?



- Eject e^+, turn proton into a neutron, or

$$^{\text{atomic mass}}_{\text{atomic number}}X \rightarrow {}^{\text{atomic mass}}_{\text{atomic number}-1}Y + {}^{0}_{1}e^{+}$$

$$^{40}_{19}K \rightarrow {}^{40}_{18}Ar + {}^{0}_{1}e^{+}$$

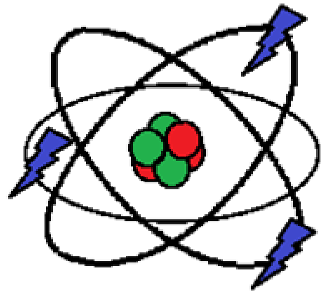
- Capture e^- from core electrons (not valence)… turn proton into neutron

$$^{\text{atomic mass}}_{\text{atomic number}}X + {}^{0}_{-1}e^{-} \rightarrow {}^{\text{atomic mass}}_{\text{atomic number}-1}Y$$

$$^{204}_{84}Po + {}^{0}_{-1}e^{-} \rightarrow {}^{204}_{83}Bi$$

Background

Way too many protons?

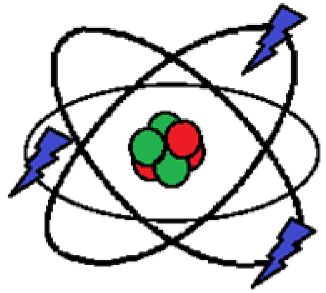


- Eject an alpha particle

$$^{\text{atomic mass}}_{\text{atomic number}}X \rightarrow {}^{\text{atomic mass}-4}_{\text{atomic number}-2}Y + {}^{4}_{2}He$$

$$^{238}_{92}U \rightarrow {}^{234}_{90}Th + {}^{4}_{2}He$$

Fission

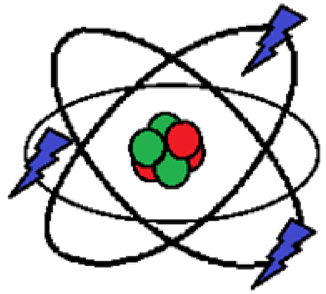


- Neutrons can cause large nuclei to break apart

$$^{235}_{92}U + {}^{1}_{0}n \rightarrow {}^{91}_{36}Kr + {}^{142}_{56}Ba + 3^{1}_{0}n$$

- The extra neutrons can break apart other U-235 nuclei
- Chain reaction modulated in nuclear reactors by boron rods… neutron capture (also carbon or water)
- Lots of energy released… not used medically, but reactors help generate starting materials!

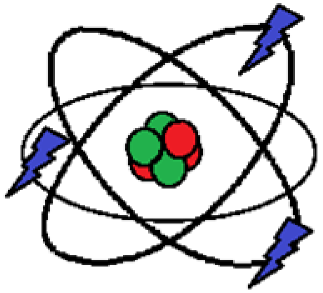
Background… but nearing end of background stuff!



Other transformations

- Positron emission and electron capture
  - have the same effect on the nucleus... a proton is transformed to a neutron
  - Accompanied by gamma rays
- Fission
  - Heavy elements can spontaneously break up into smaller nuclei and neutrons
  - Can be induced by collisions with energetic particles
- Fusion
  - Not spontaneous, no current role in medicine.
  - Light element nuclei forced together to become a new nucleus.

Fusion

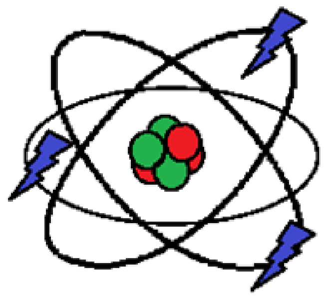


- Small nuclei come together to make bigger ones

$$^{14}_{7}N + {}^{4}_{2}He \rightarrow {}^{17}_{8}O + {}^{1}_{1}H$$

- Fusion is what makes the sun shine…
- Needs lots of energy to happen, but releases even more

Background: Hey, this has relevance to medicine!



Deliberate Reactions

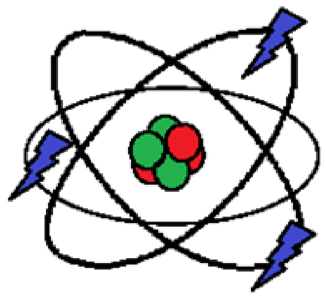
- Neutron capture

$$ {}^{\text{atomic mass}}_{\text{atomic number}}X + {}^{1}_{0}n \rightarrow {}^{\text{atomic mass}+1}_{\text{atomic number}}X \rightarrow \textit{further rxn} $$

- B-10 turns into B-11, both are stable “boron neutron capture therapy”
- C-12 turns into C-13, both are stable

- Fe-58 can capture 1 neutron, undergo positron emission to become Co-59
- Co-59 captures 1 neutron to become Co-60 (dangerous)

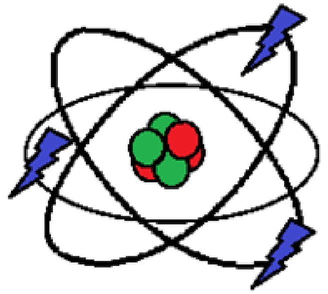
Summary: Types of radiation



- Alpha particle = helium nucleus
  - Naked positive charge can rip e^- away from any molecule… very ionizing. Dangerous internally. Not very penetrating. Can't get through paper or skin.
- Beta particle = electron
  - Not very penetrating, dangerous internally. Heavy clothing or wood blocks beta.
- Gamma ray = high energy photon
  - Penetrating, more so than X-rays. Ionizing. Very dangerous. Need thick lead to block.

Actual medicine part!

Imaging and treatment of Cancers



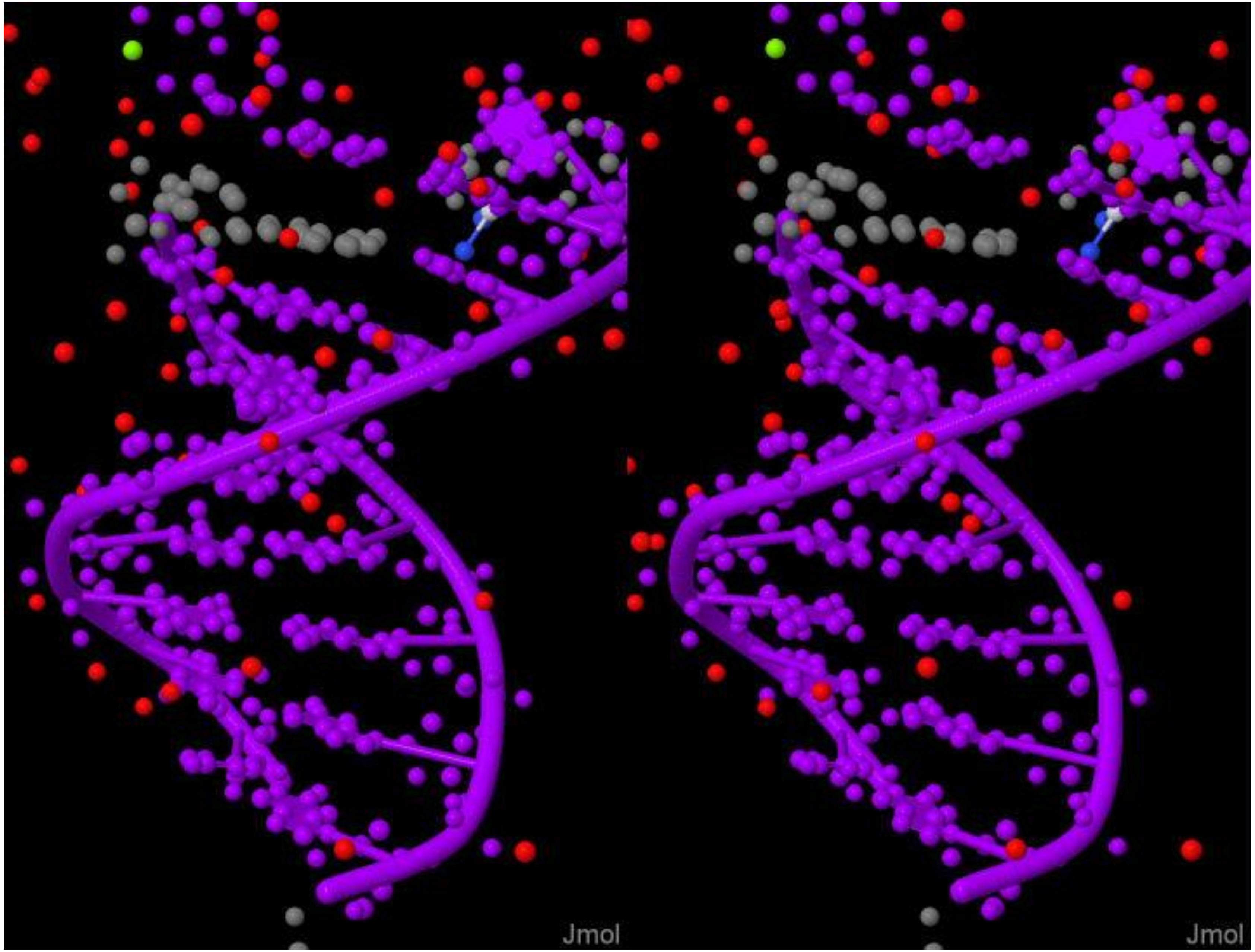
- DNA damage… can be caused by radiation in the first place!
- Next slide is an X-Ray structure of DNA polymerase wrapped around a DNA strand to which cis-platin has bound selectively btw 2 “rungs” of the DNA ladder.
- Specific binding of radioactive species allows for selective targeting.
- Goal is to damage cancer cells, leave healthy cells alone

Ajay Ummat et al , *Nature Structural & Molecular Biology* 19, 628–632 (2012), doi:10.1038/nsmb.2295.
http://www.nature.com/nsmb/journal/v19/n6/full/nsmb.2295.html

Cross-eyed stereogram of RSCB 4EEY… DNA only

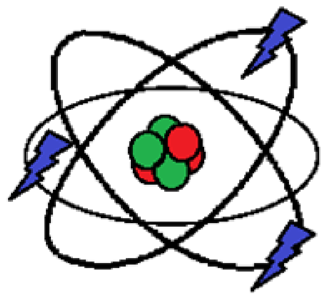
The polymerase inserts "deoxycytidine triphosphate" (grey atoms) across from Pt site… allows for rest of strand to continue without mechanical strain.

Results in tolerance for DNA damage caused by chemotherapy.



Ajay Ummat et al , *Nature Structural & Molecular Biology* 19, 628–632 (2012), doi:10.1038/nsmb.2295.
http://www.nature.com/nsmb/journal/v19/n6/full/nsmb.2295.html

Animated GIFs show various parts of this structure….

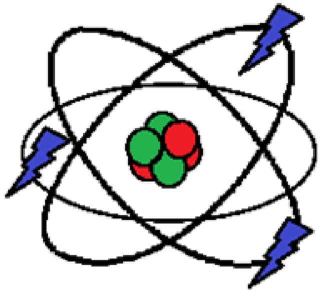


- See nearby panels
- Turn media on to see animated gifs on panels.
- If too much for your viewer and internet speed, links will be in PDF version.

Direct Links:
Complete Structure: http://dpa-llc.com/chemjs/4eey_complete.gif
DNA only: http://dpa-llc.com/chemjs/4eey_dna.gif and the $PtCl_2$ zoom: http://dpa-llc.com/chemjs/4eey_PtCl2.gif
Protein only: http://dpa-llc.com/chemjs/4eey_protein.gif

Also apk file to install hemoglobin-NO viewer on Android from last month: http://dpa-llc.com/chemjs/hemoglobin_NO.apk

Safety?

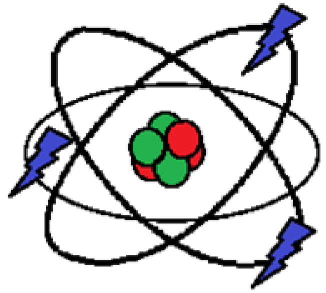


- Lesson from ^{90}Sr:
  - produced by fallout from nuclear explosions, and reactor incidents (e.g. Chernobyl)
  - Chemistry almost identical to calcium… can be incorporated into growing bones.
  - Sources include milk from cows allowed to eat contaminated grass.
  - Half life is 28.8 years. Active enough to affect a human for an entire lifetime!
  - Beta –decay inside the body can damage DNA, lead to bone cancer and related illnesses. Also have to be careful of kidney function during treatment.

Need to use isotopes that decay quickly to avoid prolonged exposure.

Hours or less for scanning, days or less for treatment

Technetium



- Element # 43. No isotopes have a half-live more than 211,000 years.

- Made by neutron bombardment of Mo targets, or separated from U-235 fission products

$$^{98}_{42}Mo + \, ^{1}_{0}n \rightarrow \, ^{99}_{42}Mo$$

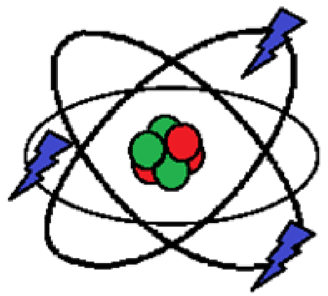
$$^{99}_{42}Mo \rightarrow \, ^{99m}_{43}Tc + \, ^{0}_{-1}e$$

$$^{99m}_{43}Tc \rightarrow \, ^{99}_{43}Tc + \, ^{0}_{0}\gamma$$

Tc containing drugs can often be adapted to ^{188}Re

Technetium

Isolated, placed in a multiuse "generator"



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$$^{99m}_{43}Tc \rightarrow {}^{99}_{43}Tc + {}^{0}_{0}\gamma$$

Used for imaging!

Generators

- Chromatographic separation
  - Responsible for huge success of ^{99m}Tc!
  - Generator can be used every few days for 6 months to make a dose of $^{99m}TcO_4^-$
  - Have to work fast to make drugs out of $^{99m}TcO_4^-$… short half-life.
  - Radiation is hard on the alumina, need very pure ^{99}Mo
  - Most common theme for generators.

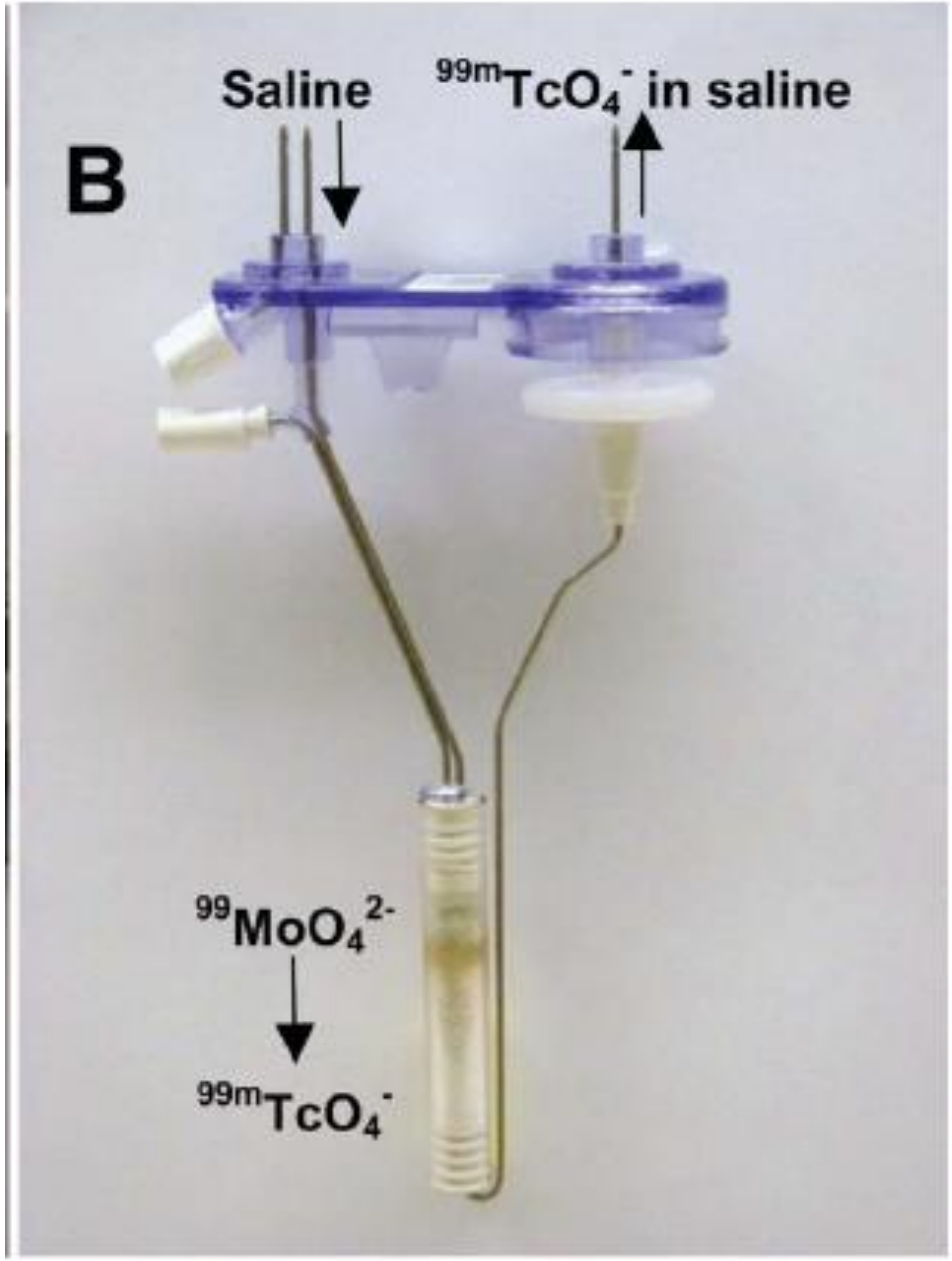
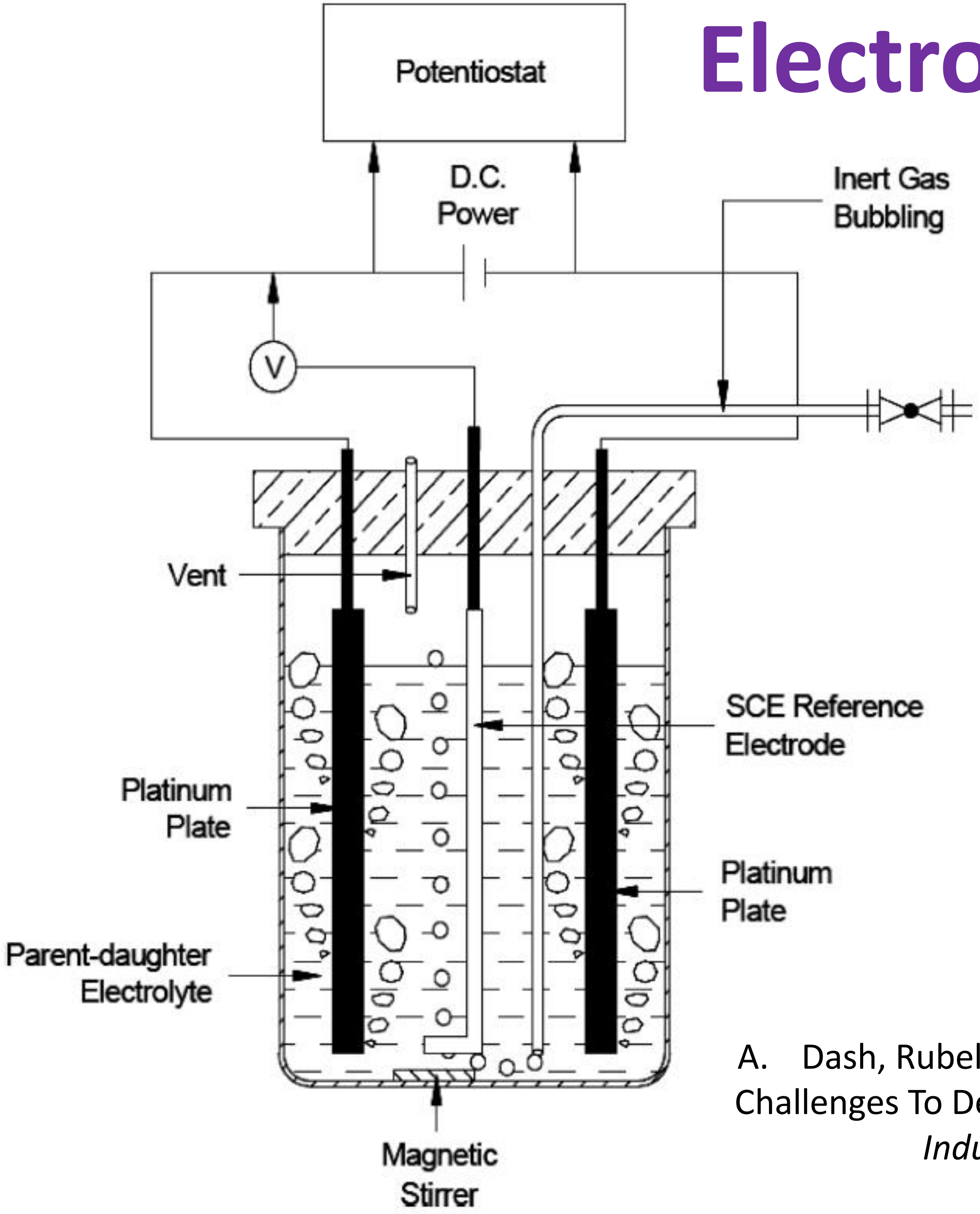
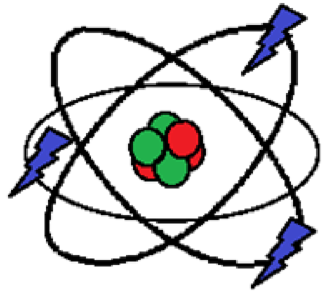


Image from S. Liu, S. Chakraborty, "^{99m}Tc-centered one-pot synthesis for preparation of ^{99m}Tc radiotracers," *Dalton Trans.*, **2011**, ***40***, 6077



Electrochemical Separation



- Rely on different E°' properties of parent and daughter nuclides
- Can "electroplate" and redissolve a couple of times quickly to get pure sample.
- Setup more robust to radiation
- Can use lower quality parent sources, makes medicine more available

A. Dash, Rubel Chakravarty "Electrochemical Separation: Promises, Opportunities, and Challenges To Develop Next-Generation Radionuclide Generators To Meet Clinical Demands," *Industrial and Engineering Chemistry Research* **2014**, *53*, 3766-3777. dx.doi.org/10.1021/ie404369y

Electrochemical Separation

- Makes ^{90}Y from ^{90}Sr, purifies so only ppm of Sr left, well within safety standards
- ^{90}Sr available b/c it is a fission product in reactors
- Makes ^{90}Y therapies available at sites which do not have reactors.

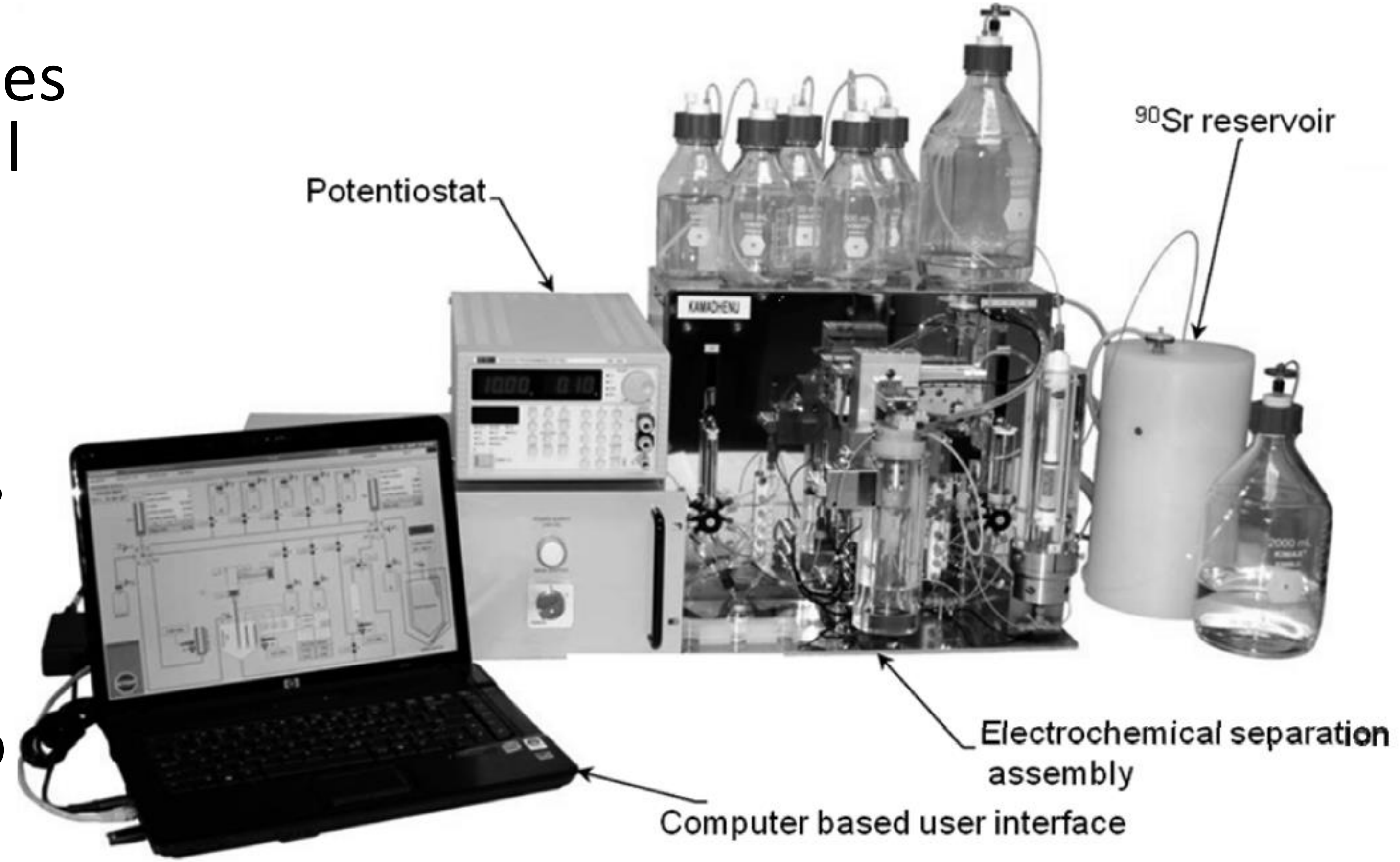
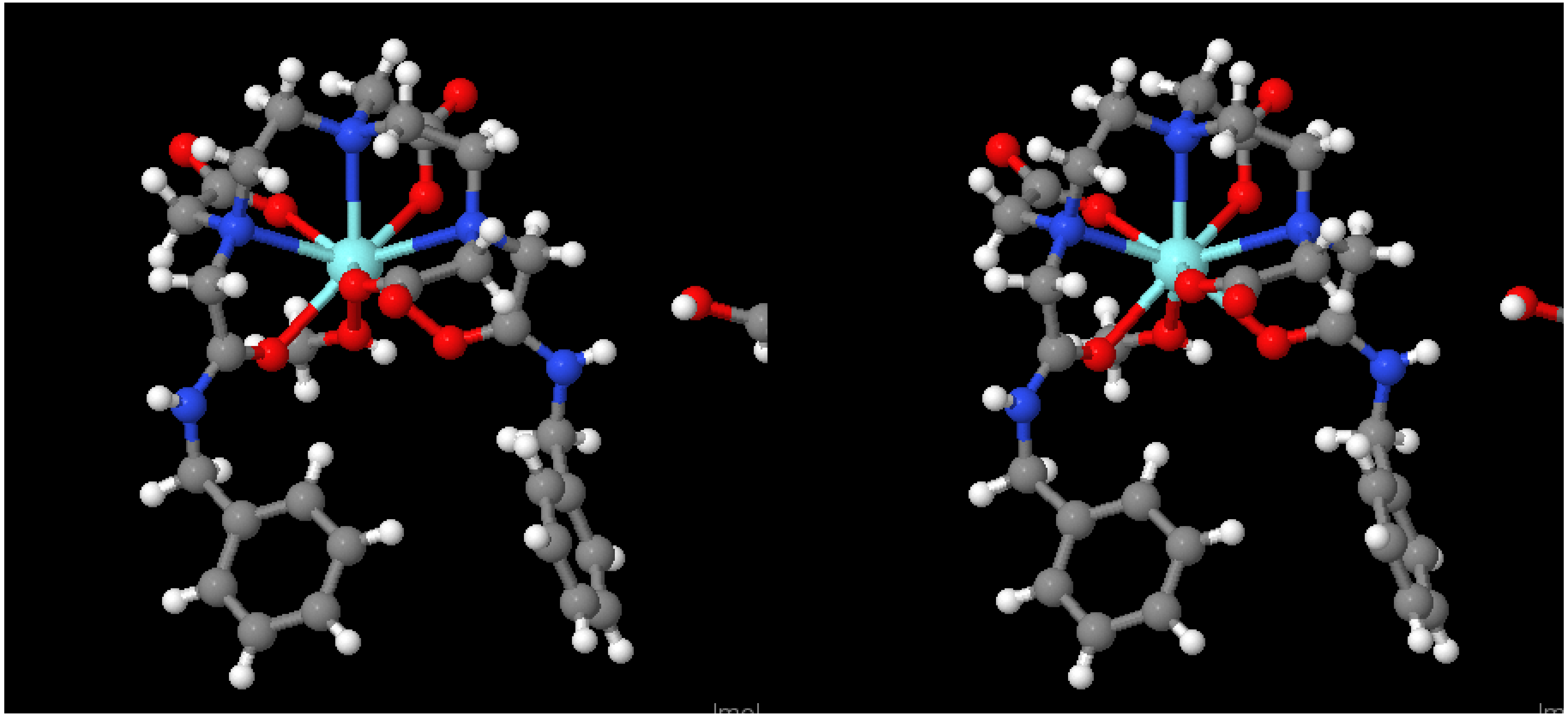


Figure 2. Fully automated $^{90}Sr/^{90}Y$ generator (Kamadhenu) commercially available from Isotope Technologies Dresden (Germany). Adapted from ref 11.

A. Dash, Rubel Chakravarty "Electrochemical Separation: Promises, Opportunities, and Challenges To Develop Next-Generation Radionuclide Generators To Meet Clinical Demands," *Industrial and Engineering Chemistry Research* **2014**, *53*, 3766-3777. dx.doi.org/10.1021/ie404369y

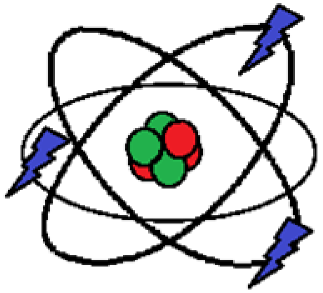
Cross-eyed stereogram rotating view: http://dpa-llc.com/chemjs/4311636.gif

Example ^{90}Y complex…



Wen-Yuan Hsieh; Shuang Liu " Synthesis, Characterization, and Structures of Indium In(DTPA-BA2) and Yttrium Y(DTPA-BA2)(CH_3OH) Complexes (BA = Benzylamine): Models for ^{111}In- and ^{90}Y-Labeled DTPA-Biomolecule Conjugates" Inorg. Chem. 2004, 43, 6006-6014.

http://www.crystallography.net/cod/4311636.html

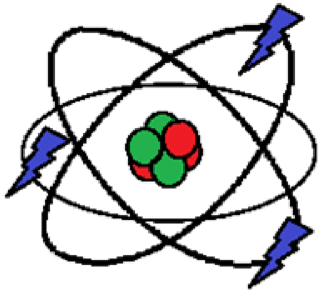


Therapeutic agents

- ^{201}Tl as chloride for myocardial imaging
- ^{33}Xe xenon gas for pulmonary ventilation studies,
- ^{131}I sodium iodide (thyroid uptake, imaging and therapy)
- ^{89}Sr or ^{153}Sm (metastatic bone palative therapy),
- ^{67}Ga gallium citrate (tumor imaging, abscess and infection),
- ^{32}P (therapy),
- ^{99m}Tc has dozens of uses… has been “go-to” substance for a long time
- https://www.radiologyinfo.org/en/info.cfm?pg=gennuclear

Information from B.S. Sekhon “Inorganics/bioinorganics: Biological, medicinal and pharmaceutical uses,” *J. Pharm. Educ. Res.* ***2011***, *2*, 1-20

More….



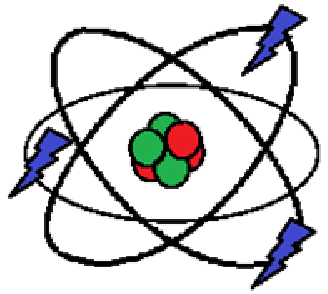
- ^{18}F in bone scanning studies as Fluorodeoxyglucose
- ^{82}Rb is a rapid cardiac blood flow tracer

- "Yttrium-90-labeled anti-CD20 monoclonal antibody is used to treat patients with non-Hodgkin's lymphoma"

- Others include ^{11}C, ^{64}Cu, ^{68}Ga, ^{72}As, ^{77}As, ^{177}Lu, ^{186}Re, ^{188}Re, ^{198}Au,

Information from B.S. Sekhon "Inorganics/bioinorganics: Biological, medicinal and pharmaceutical uses," *J. Pharm. Educ. Res.* ***2011***, *2*, 1-20

Imaging

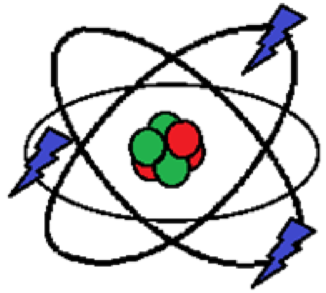


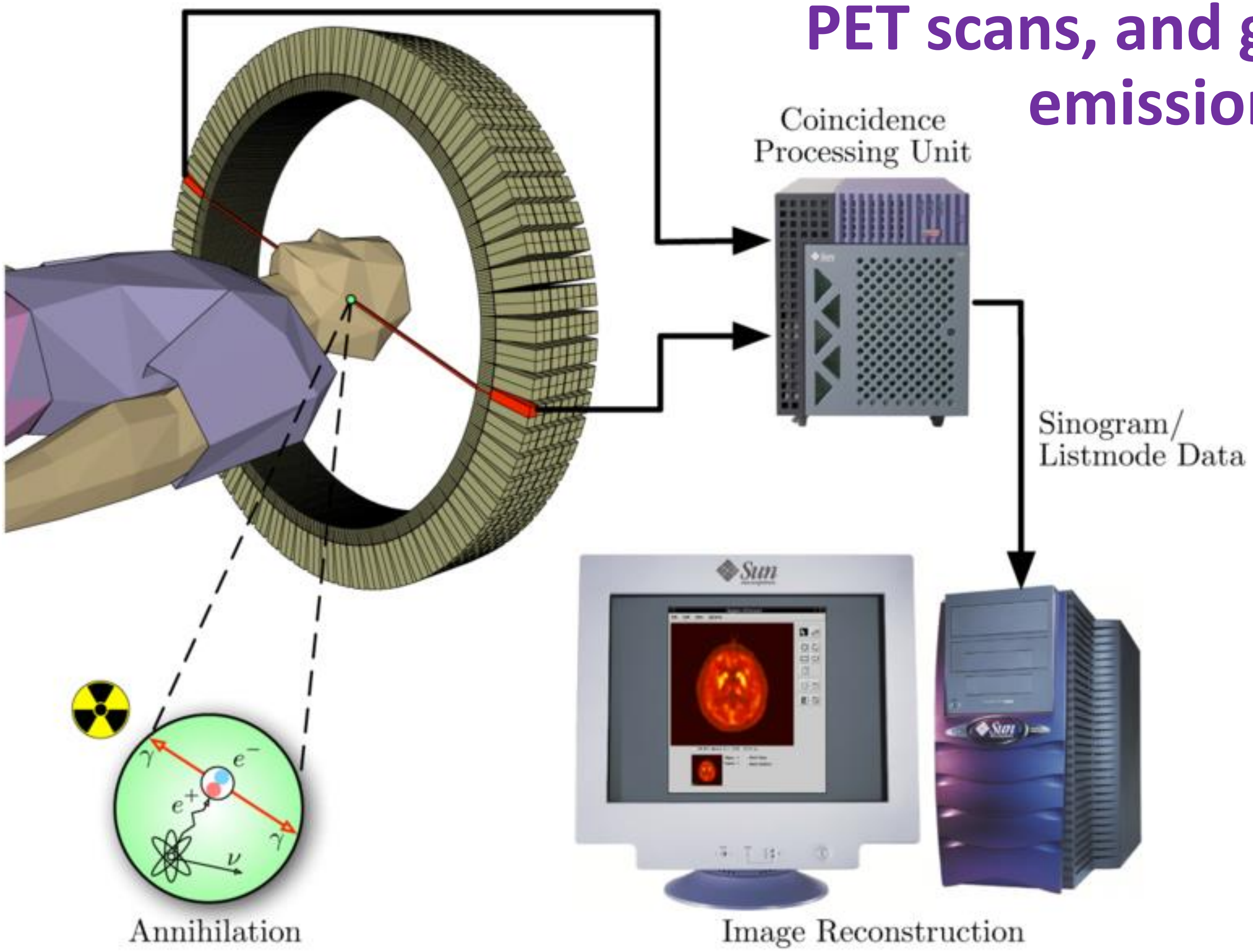
- **A couple of main types based on gamma rays, or radio waves**
- **PET:** a gamma technique.

- **MRI:** radio wave technique
- Talked about the nuclear magnetic resonance phenomenon last time… can be used for "magnetic resonance imaging" (MRI).
- MRI has nothing to do with radioactivity. Note how the word "nuclear" has been dropped to avoid confusion.

More at: https://en.wikibooks.org/wiki/Basic_Physics_of_Nuclear_Medicine/Nuclear_Medicine_Imaging_Systems

PET scans, and gamma ray emission…





- ^{99m}Tc and others…
- Processing of data allows technique ot work.
- Need to decide which gamma rays correlate with each other.

Public domain Image from Jens Maus: https://commons.wikimedia.org/wiki/File:PET-schema.png

^{99m}Tc scan of Tory

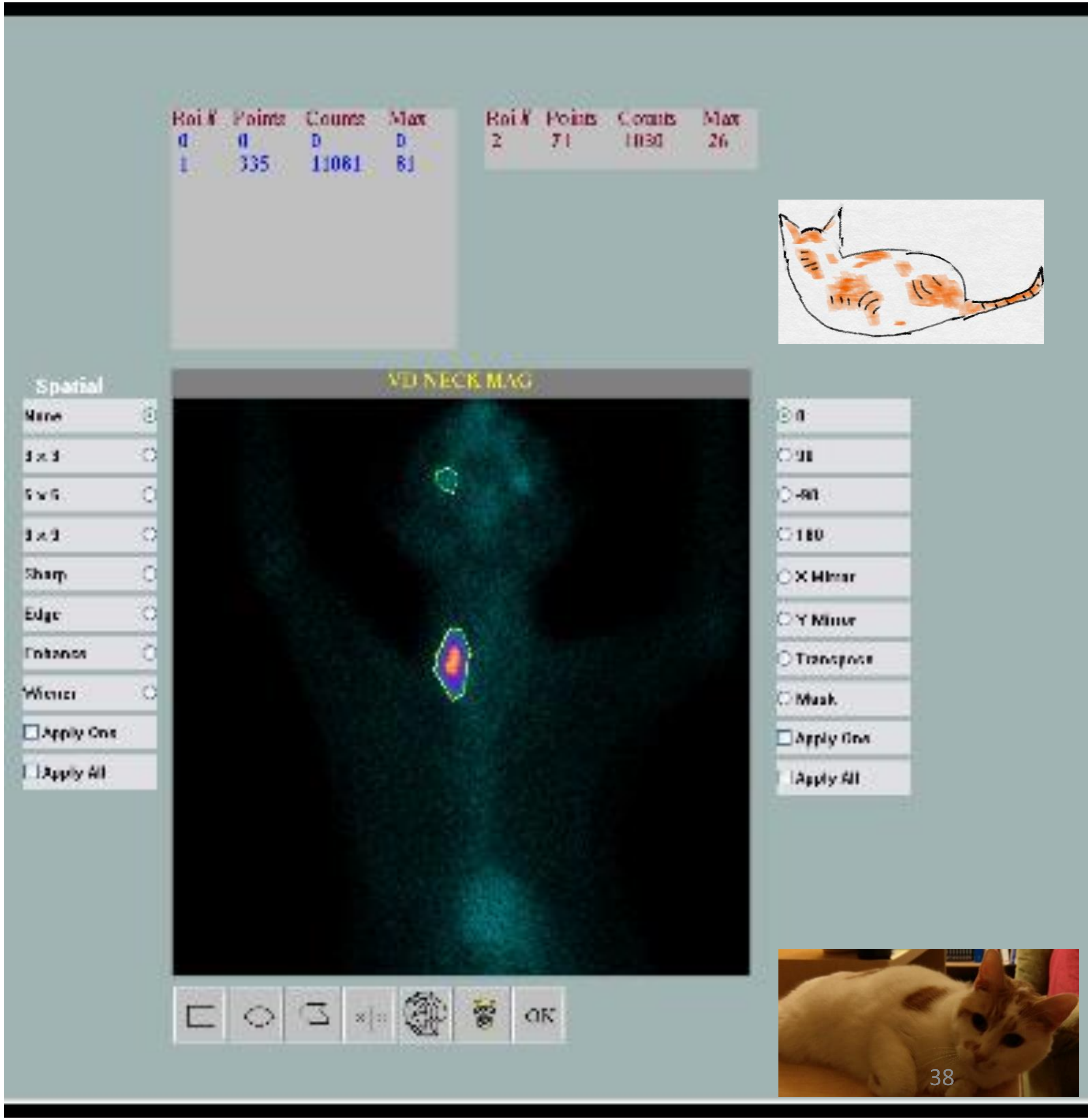
Two targets of $[^{99m}TcO_4]^-$

- Thyroid and Heart
- <eventually bladder shows up>

- ^{99m}Tc activity allows for ^{131}I dose to be calibrated
- Represents a cure for hyperthyroidism

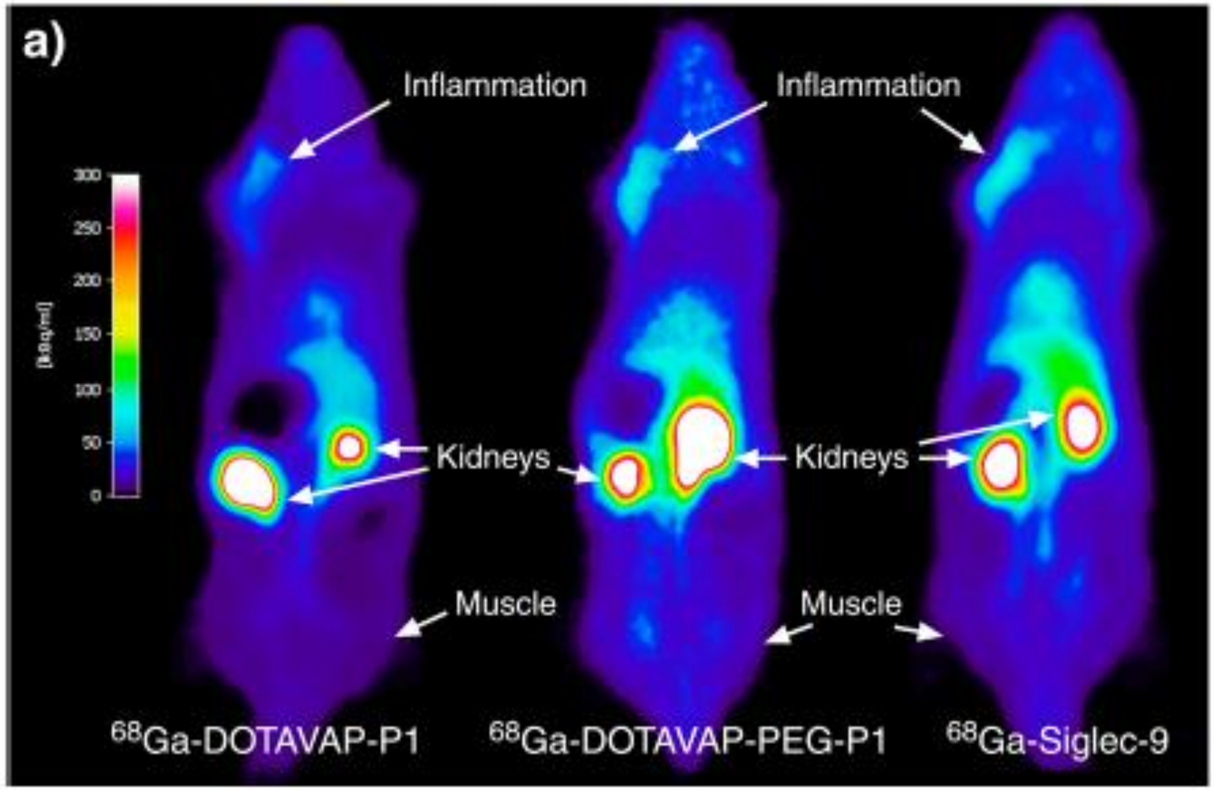
Used in people for the same purpose

Image courtesy University of Missouri Small Animal Hospital, Columbia, MO USA



Imaging examples... Inflammation

- Ongoing research:
- ^{68}Ga-labelled drug which selectively binds to a protein associated with inflammation.
- "vascular adhesion protein-1"



Inflammation in rats imaged with 3 different drugs.

Image from A. Autio, Sirpa Jalkanen, A. Roivainen, "Nuclear imaging of inflammation: homing associated molecules as targets" *EJNMMI Research* **2013**, 3:1.
http://www.ejnmmires.com/content/3/1/1 (Open Source Article, Creative Commons Attribution license)

Imaging examples ^{99m}Tc

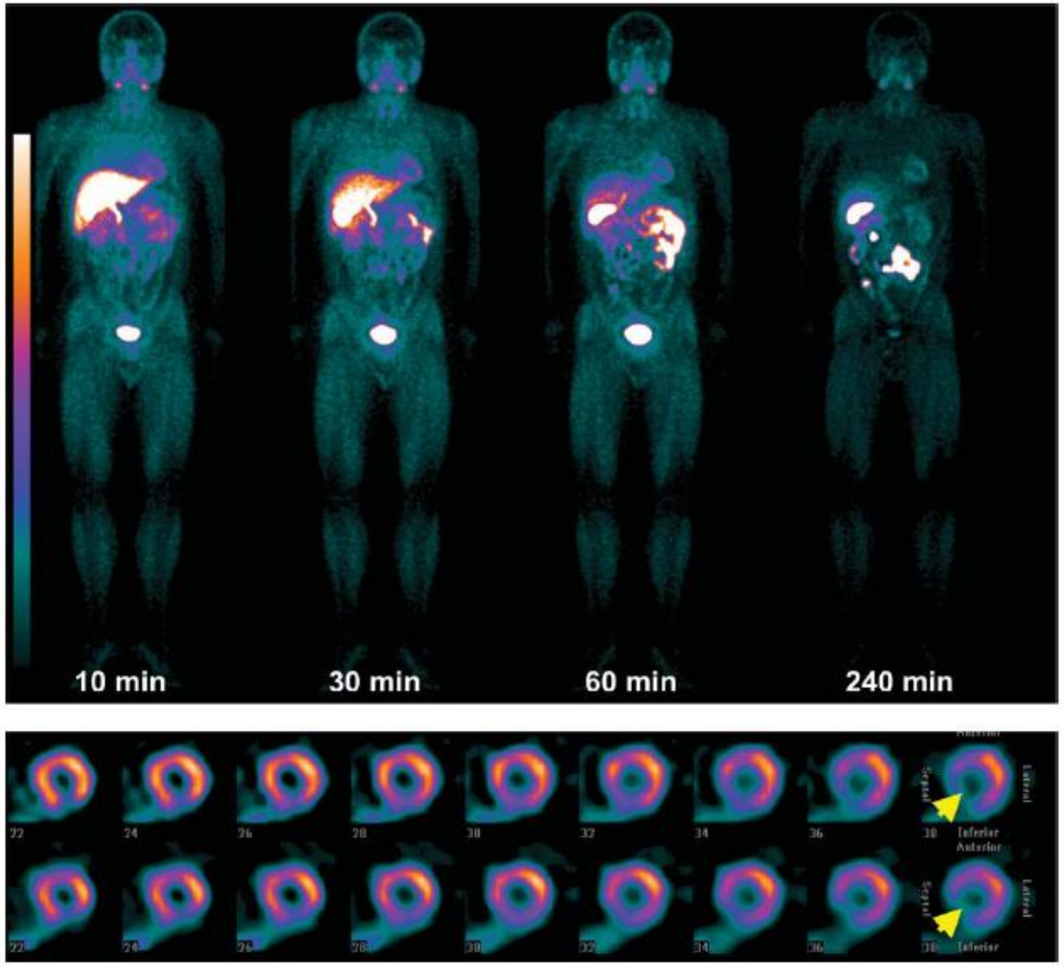
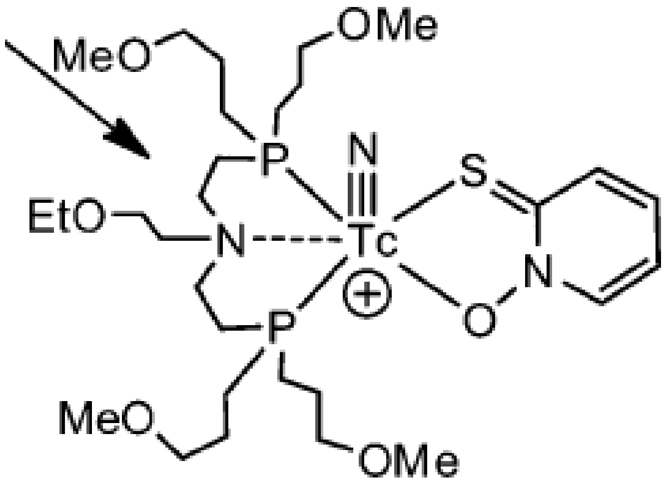


Fig. 3 Top: the whole-body images of a healthy volunteer administered with ^{99m}TcN-MPO (~25 mCi) at 10, 30, 60 and 240 min after injection. Bottom: The short axis view of 60-min SPECT images of the heart in a patient with myocardial infarction administered with ~25 mCi of ^{99m}TcN-MPO (lower panel) and ^{99m}Tc-Sestamibi (upper panel). Arrows indicate the areas of perfusion defects.

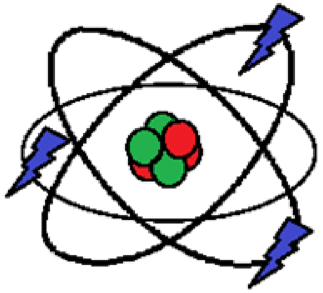


^{99m}TcN-MPO

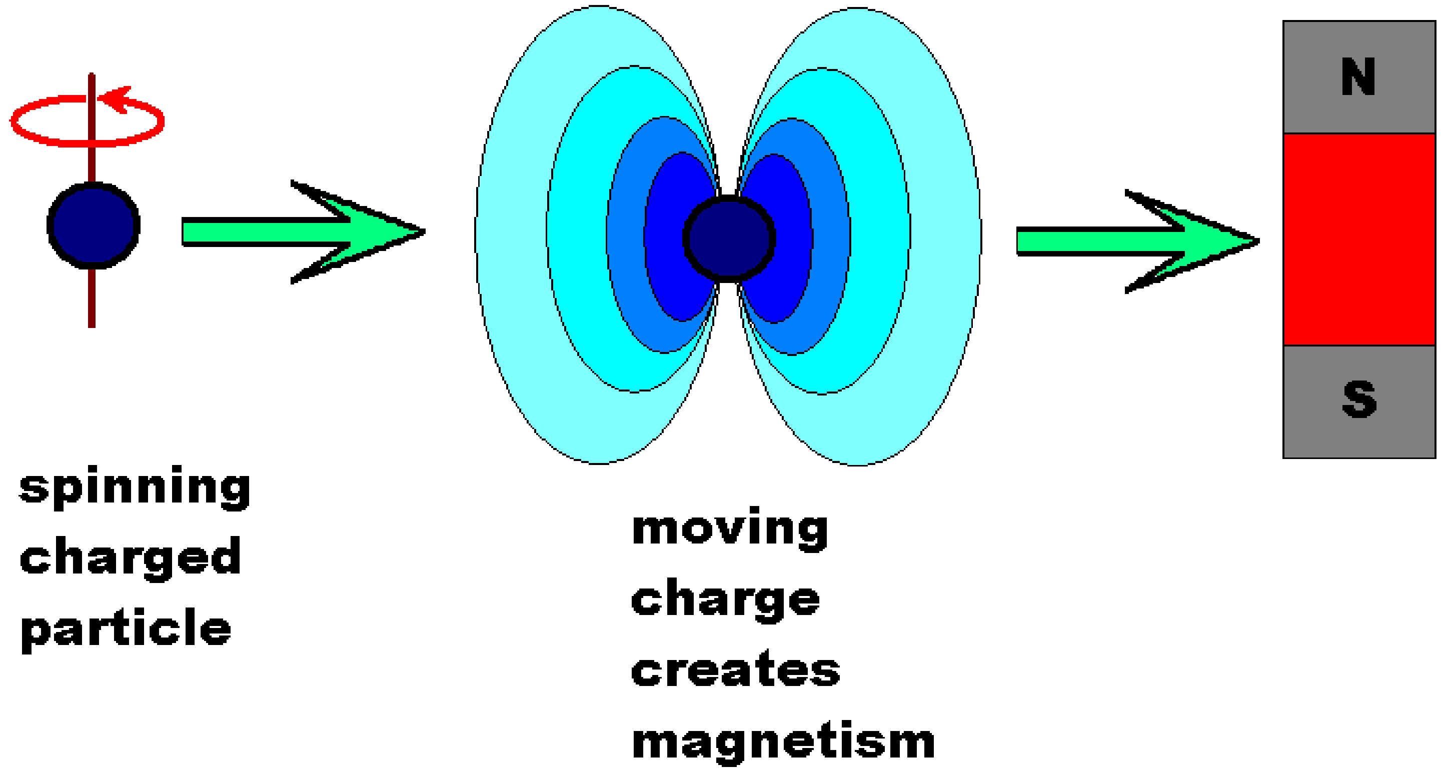
- Generator cartridges can be adapted to do derivatization "on the fly."
- This example images the heart quickly.

Image from S. Liu, S. Chakraborty, "^{99m}Tc-centered one-pot synthesis for preparation of ^{99m}Tc radiotracers," *Dalton Trans.*, **2011**, ***40***, 6077

MRI Imaging: Nuclei as magnets



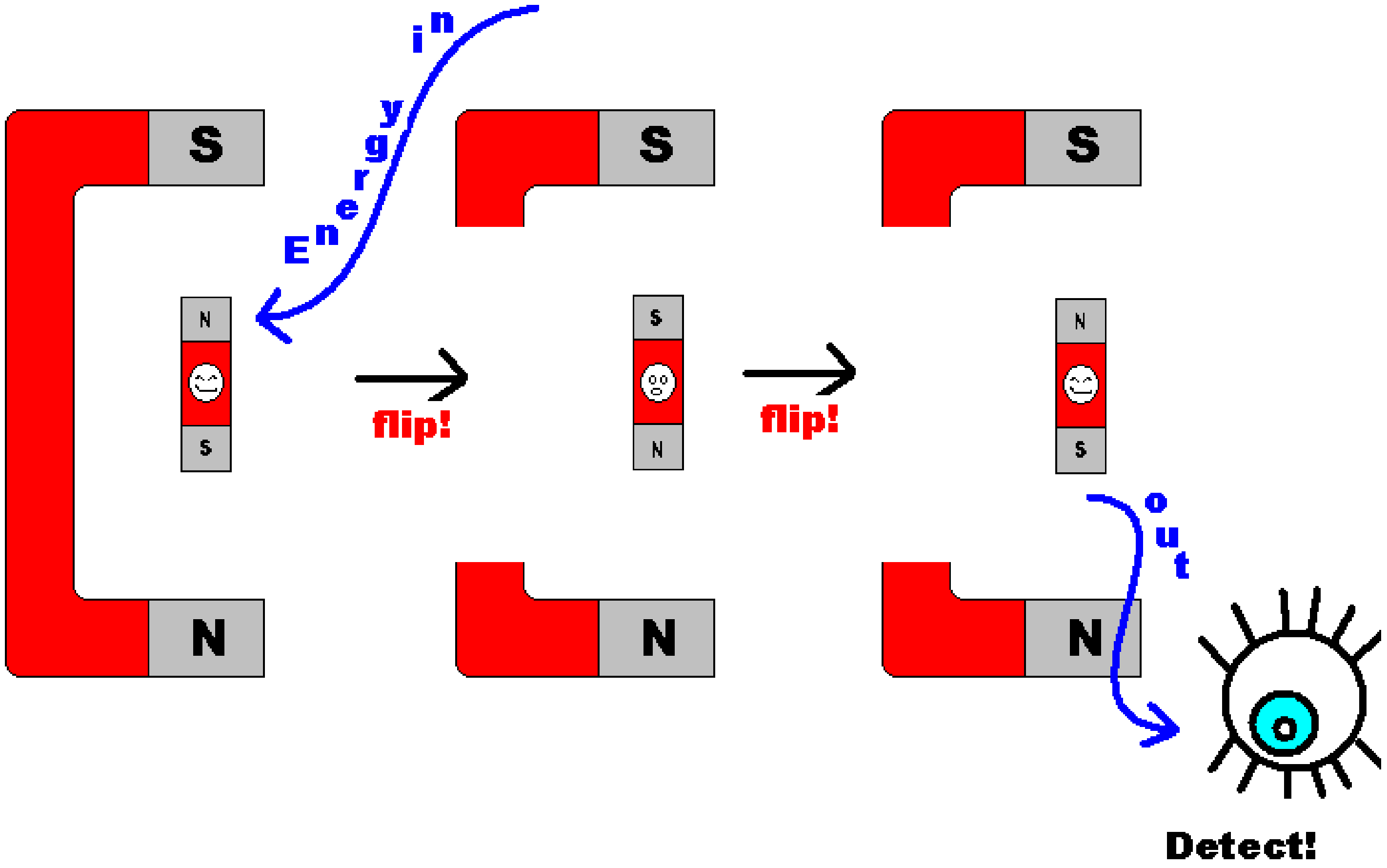
Tiny magnets tend to line up with an external field.
Takes a precise frequency of radio waves to "flip" the spin by 180°

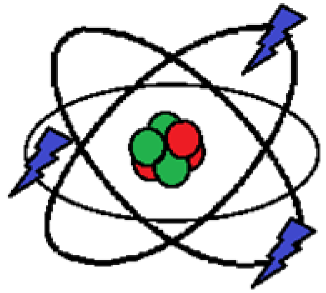


For H-atoms, the frequency depends on the EXACT magnetic field, and the identity of the rest of the molecule

Precession too! See: https://commons.wikimedia.org/wiki/File:Gyroscope_precession.gif

Simple Diagram for "Spin-Flip"





MRI looks at H in H_2O

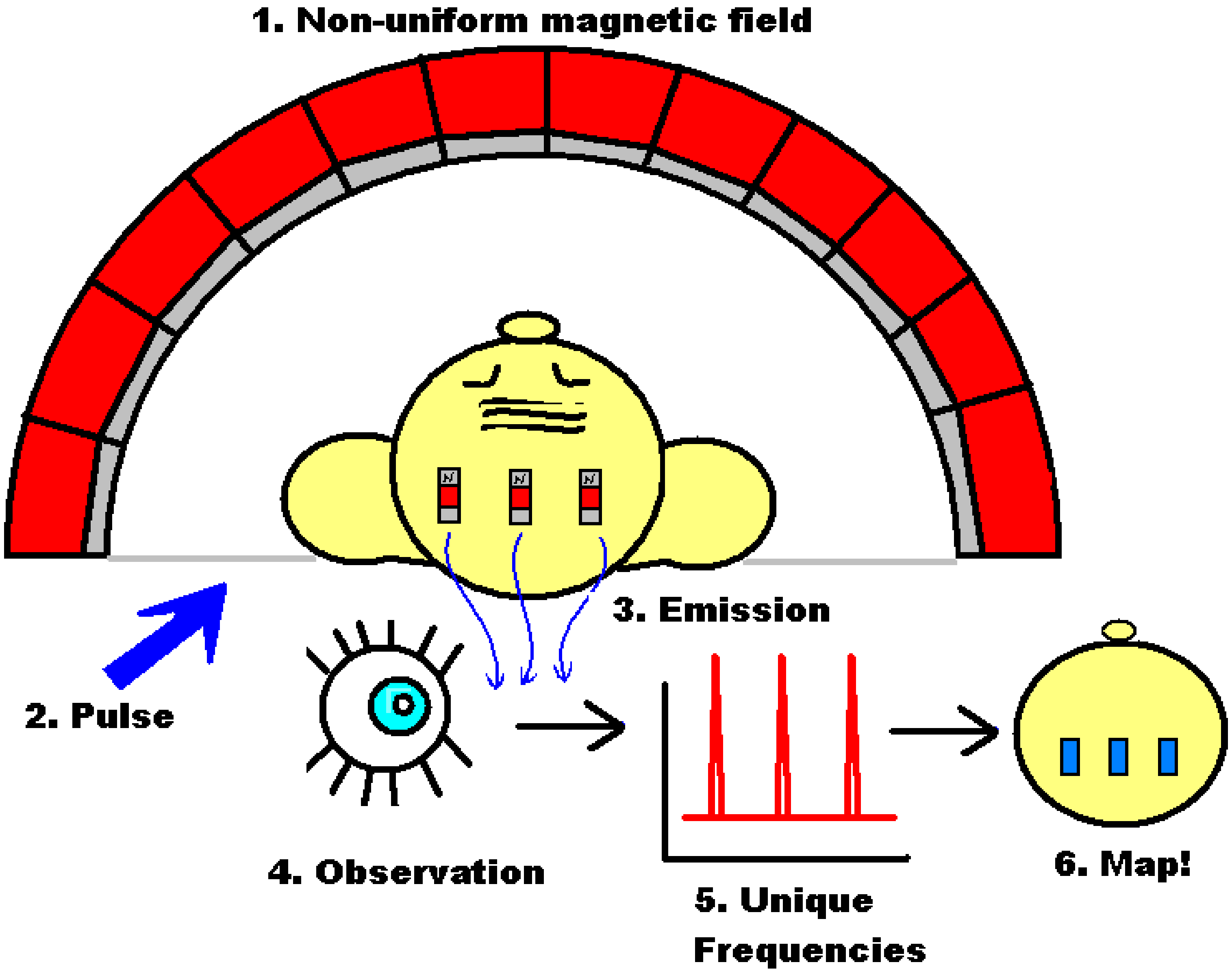
All H_2O's are identical… the only thing that can affect the frequency the H's emit is the magnetic field.

In a non-uniform magnetic field, frequency and phase info can be de-convoluted into position and intensity… i.e. a map of a slice of the "sample" (maybe a human brain!)

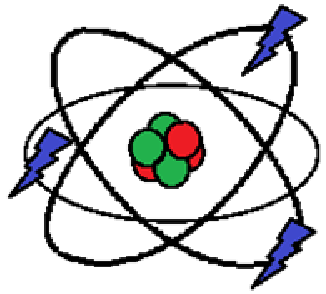
MRI basic technique

In a non-uniform magnetic field, frequency and phase info can be de-convoluted into position and intensity…

Get a map of the water distribution in a slice of the "sample"…



Contrast agents



- Make some H_2O's give up their energy faster, or by non-radiative pathways… often a lanthanide is involved, lotsa unpaired electrons

- Regions without this agent show up brighter in scans.

- Can target different tissues with different contrast agents
  - Where the contrast agent builds up, the signals in the MRI scan get weaker

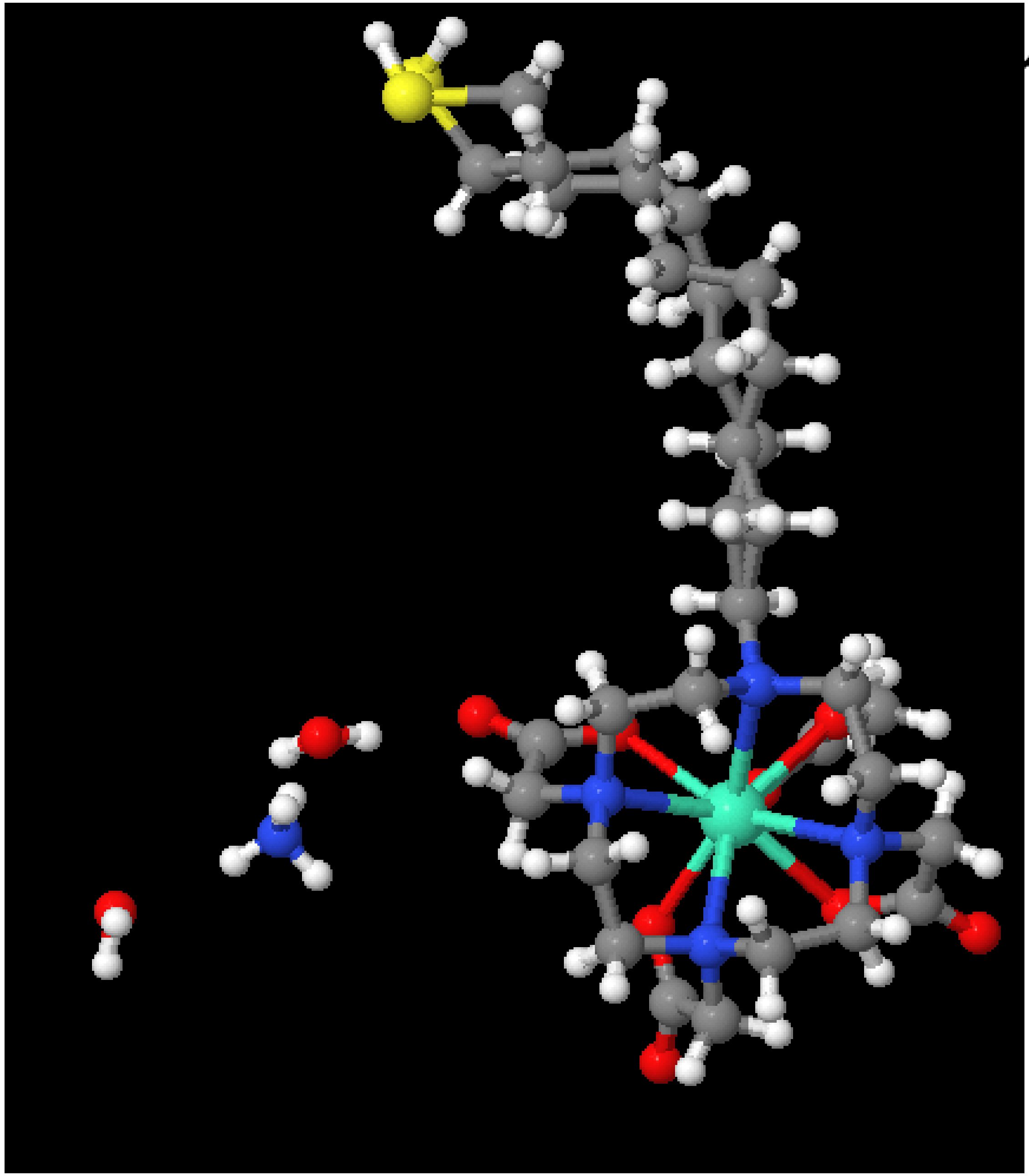
Research in contrast agents… Not Radioactive!

Rotating cross-eye stereogram at:
http://dpa-llc.com/chemjs/1502664.gif

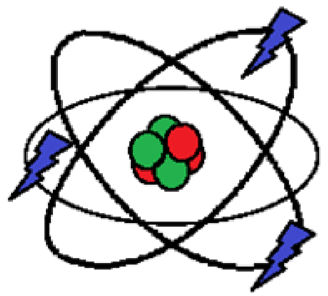
This structure is like a detergent in some ways

Note disorder in tail

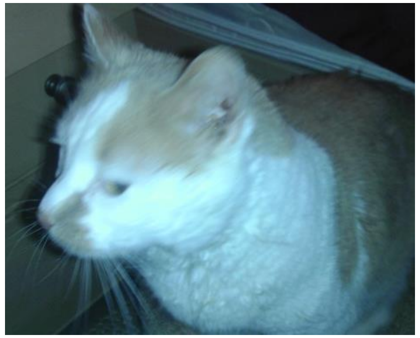
http://www.crystallography.net/cod/1502664.html
N. Raghunand et al "Design, synthesis, and evaluation of 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid derived, redox-sensitive contrast agents for magnetic resonance imaging," *Journal of medicinal chemistry*, **2010**, *53*, 6747-6757

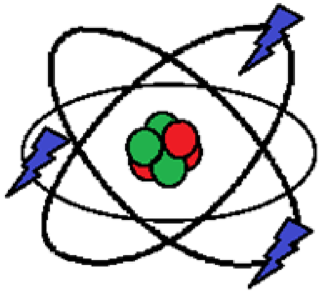


Conclusions?



- Nuclear medicine is a huge field.
- Most applications seem to be in imaging, followed by strategies for cancer treatment.
- Various Generators have brought the ability to do nuclear medicine to a more broad array of venues, since an on-site reactor is not necessary
- Safety and waste management is still a big issue!





Thanks!

- Members and Students of the Science Circle!
- Students and Faculty of Dept. of Chem., SIUE.
- Generous support of National Science Foundation for our work on heme-nitrosyl complexes, NSF-CHE 1566509
- DPA-LLC for hosting animated gifs and other files on their website
- My cats for their patience…