Monte Carlo track structure simulation for radiation microdosimetry and targeted alpha therapy

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Outline

- Introduction / Context
- Overview of Monte Carlo track-structure codes
- The *TILDA-V* Monte Carlo code
    - Processes
    - Description of media
    - Theoretical supports for the description of the inelastic processes
    - Stopping power and range for protons
- Ongoing work: cellular dosimetry
    - Interest for targeted alpha therapy
    - Previous studies for electron emitters
- Summary and conclusions

Context

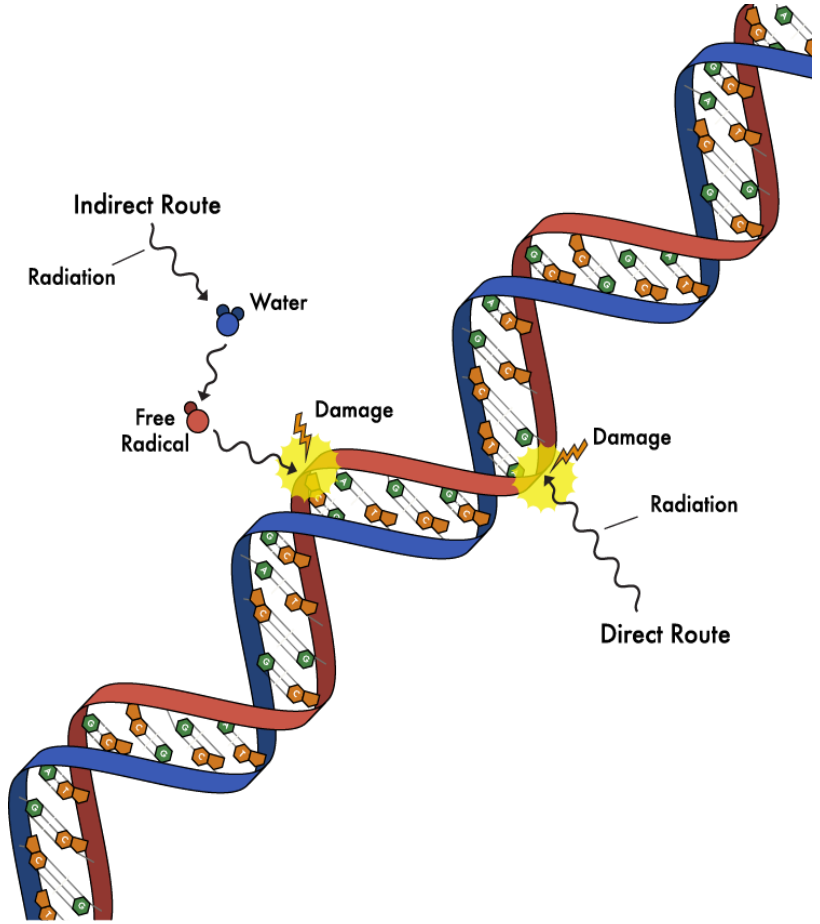
- A detailed understanding of the radiation induced interactions in living matter at the finest scale is of great importance

  - in **radiobiology**: to identify the DNA critical lesions

  - in **radiotherapy**: to adapt/improve the treatment protocols

- Monte Carlo (MC) simulations are powerful tools to describe the slowing-down of charged particles in biological media

- Among existing MC codes, only the so called **"track-structure"** approaches are appropriate for microdosimetry because they describe the history collision by collision



Source: https://sites.duke.edu/missiontomars/the-mission/cancer/what-is-cancer/

Monte Carlo track-structure codes

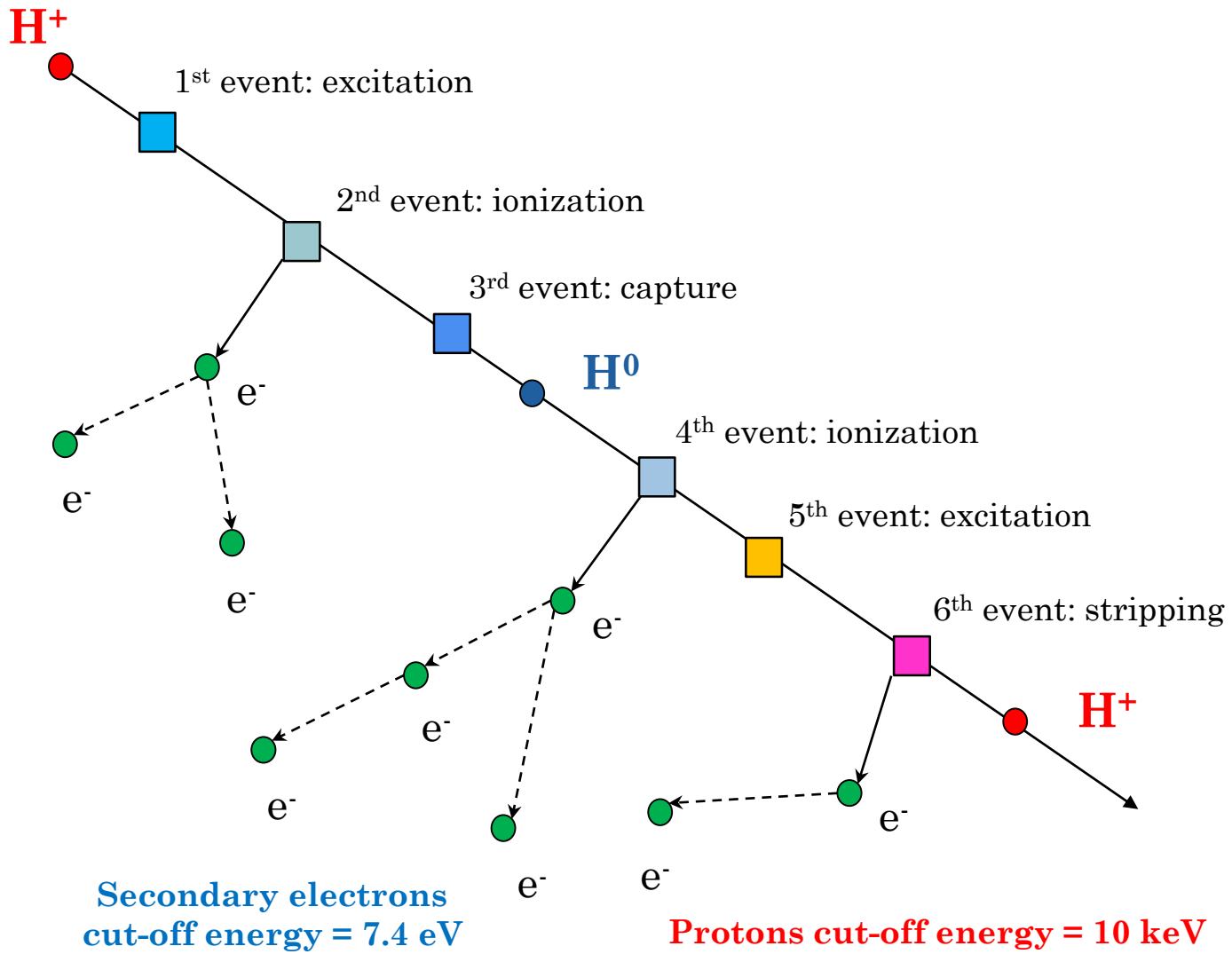
Code	Particle	Energy range	Cross-section database[a]	Reference
CPA100[b,c]	e^-	$\geqslant$10 eV–100 eV e^-	Wat. (l)	Terrissol and Beaudre, 1990
DELTA[c]	e^-	$\geqslant$10 eV–10 keV e^-	Wat. (v)	Zaider et al. (1983)
ETRACK[c]	e^-, p, α	$\geqslant$10 eV–10 keV e^-	Wat. (v)	Ito (1987)
KURBUC[c]	e^-	$\geqslant$10 eV–10 MeV e^-	Wat. (v)	Uehara et al. (1993)
LEEPS	e^-, e^+	0.1–100 keV	Many materials	Fernandez-Varea et al. (1996)
LEPHIST[c]	p	$\geqslant$1 keV–1 MeV	Wat. (v)	Uehara et al. (1993)
LEAHIST[c]	α	$\geqslant$1 keV/u–2 MeV/u	Wat. (v)	Uehara and Nikjoo (2002a)
MC4	e^-, ions	$\geqslant$10 eV e^-, ions $\geqslant$0.3 MeV/u	Wat. (v,l)	Emfietzoglou et al. (2003)
NOTRE DAME[c]	e^-, ions	$\geqslant$10 eV e^-, ions $\geqslant$0.3 MeV/u	Wat. (v,l)	Pimblott et al. (1990)
OREC[c]	e^-, ions	$\geqslant$10 eV e^-, ions $\geqslant$0.3 MeV/u	Wat. (v,l)	Turner et al. (1983)
PARTRAC[b,c]	e^-, ions	$\geqslant$10 eV e^-, ions $\geqslant$0.3 MeV/u	Wat. (v,l)	Friedland et al. (2003)
PITS04[b]	e^-, ions	$\geqslant$10 eV e^-, ions $\geqslant$0.3 MeV/u	Wat. (l)	Wilson et al. (2004)
PITS99[c]	e^-, ions	$\geqslant$10 eV e^-, ions $\geqslant$0.3 MeV/u	Wat. (v)	Wilson and Nikjoo (1999)
SHERBROOKE[c]	e^-, ions	$\geqslant$10 eV e^-, ions $\geqslant$0.3 MeV/u	Wat. (v,l)	Cobut et al. (2004)
STBRGEN[c]	e^-, ions	$\geqslant$10 eV e^-, ions $\geqslant$0.3 MeV/u	Wat. (v,l)	Chatterjee and Holley (1993)
TRION	e^-, ions	$\geqslant$10 eV e^-, ions $\geqslant$0.3 MeV/u	Wat. (v,l)	Lappa et al. (1993)
TRACEL[c]	e^-, ions	$\geqslant$10 eV e^-, ions $\geqslant$0.3 MeV/u	Wat. (v,l)	Tomita et al. (1997)

*Taken from H. Nikjoo et al., Radiation Measurements **41**, 1052–1074 (2006)*

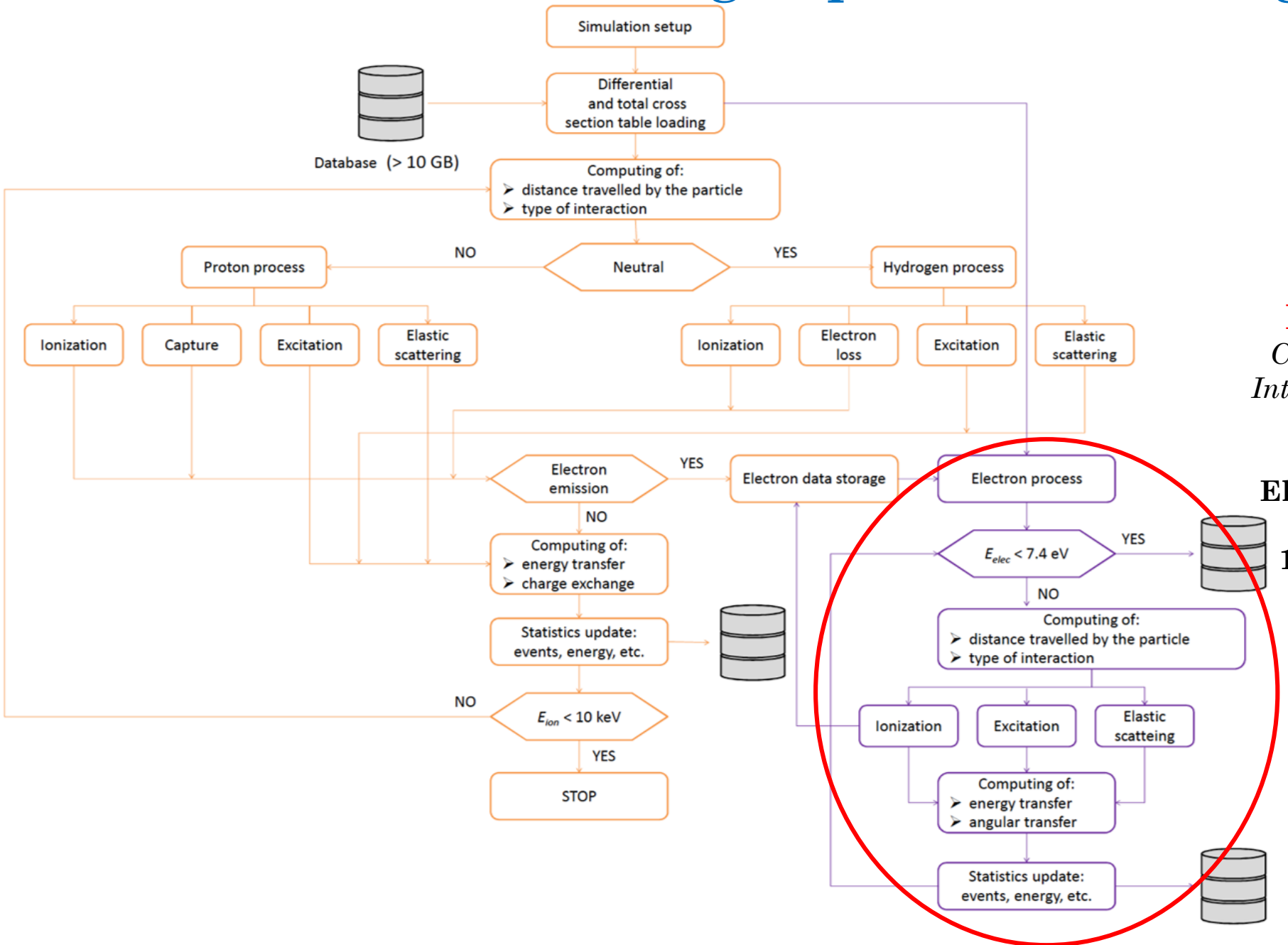
- In these codes the reliability of the results strongly depends on the cross sections given as input and describing each physical process.

TILDA-V: Transport d'Ions Lourds Dans l'Aqua & Vivo

- Monte Carlo track-structure code based on **quantum-mechanical** and **semi-empirical** models
- Includes a complete set of **multiple-differential** and **total** cross sections
- Describes all the physical processes induced by electrons, protons, hydrogen and alpha particles in the energy range from 10 keV to 100 MeV
- Water and DNA molecules as targets



TILDA-V: Details of the charged particle tracking



EPOTRAN
Champion et al., Int. J. Radiat. Biol. (2012)

Electron energy range: 10 eV – 1 MeV

TILDA-V: List of processes in the current version

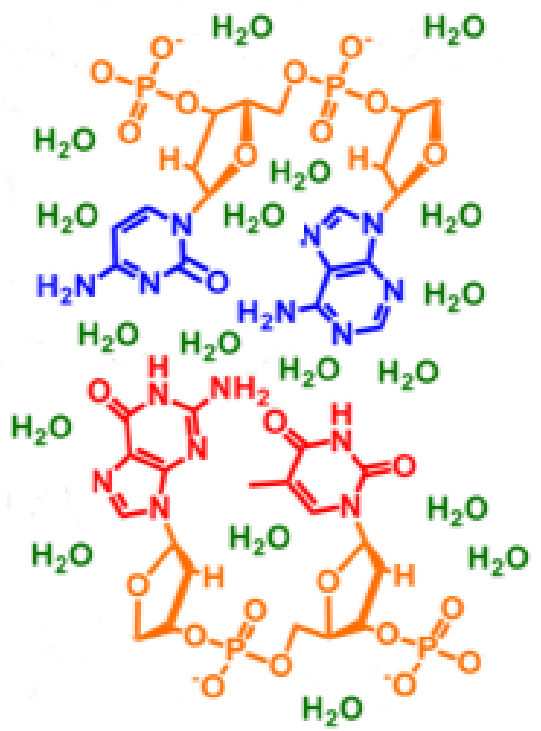
Water vapor	DNA components
Proton	
Ionization: *prior* CDW-EIS, FBA-CB1 Rudd, Rutherford, HKS, Miller and Green	**Ionization:** *prior* CDW-EIS, FBA-CB1 Rudd, HKS
Capture: *prior* CDW-EIS, CDW Rudd, Dingfelder, Green and McNeal, Miller and Green	**Capture:** *prior* CDW-EIS, CDW
Excitation: Miller and Green	**Excitation:** Miller and Green
Neutral hydrogen	
Ionization: *prior* CDW-EIS, FBA-CB1 Green and McNeal	**Ionization :** *prior* CDW-EIS
Excitation: Miller and Green	**Excitation:** curve fitting
Electron loss: Dingfelder, Miller and Green	**Electron loss:** curve fitting
Electron	
Ionization: DWBA, BEB	**Ionization:** DWBA, BEB
Excitation: Olivero	**Excitation:** fitting of experimental data
Elastic scattering: partial wave formalism	**Elastic scattering:** partial wave formalism
He^{2+}, He^{+},He^{0} (future developments)	
Ionization: *prior* CDW-EIS, FBA-CB1	**Ionization:** *prior* CDW-EIS, FBA-CB1
Capture: *prior* CDW-EIS, CDW2	**Capture:** *prior* CDW-EIS, CDW2

TILDA-V: Description of the biological media

- DNA: two nucleotides (nucleobases (A-T or C-G) and two sugar phosphate groups)
  (de Vera *et al.*, 2013)

- DNA : 58% (Adenine + Thymine) + 42% (Cytosine - Guanine)

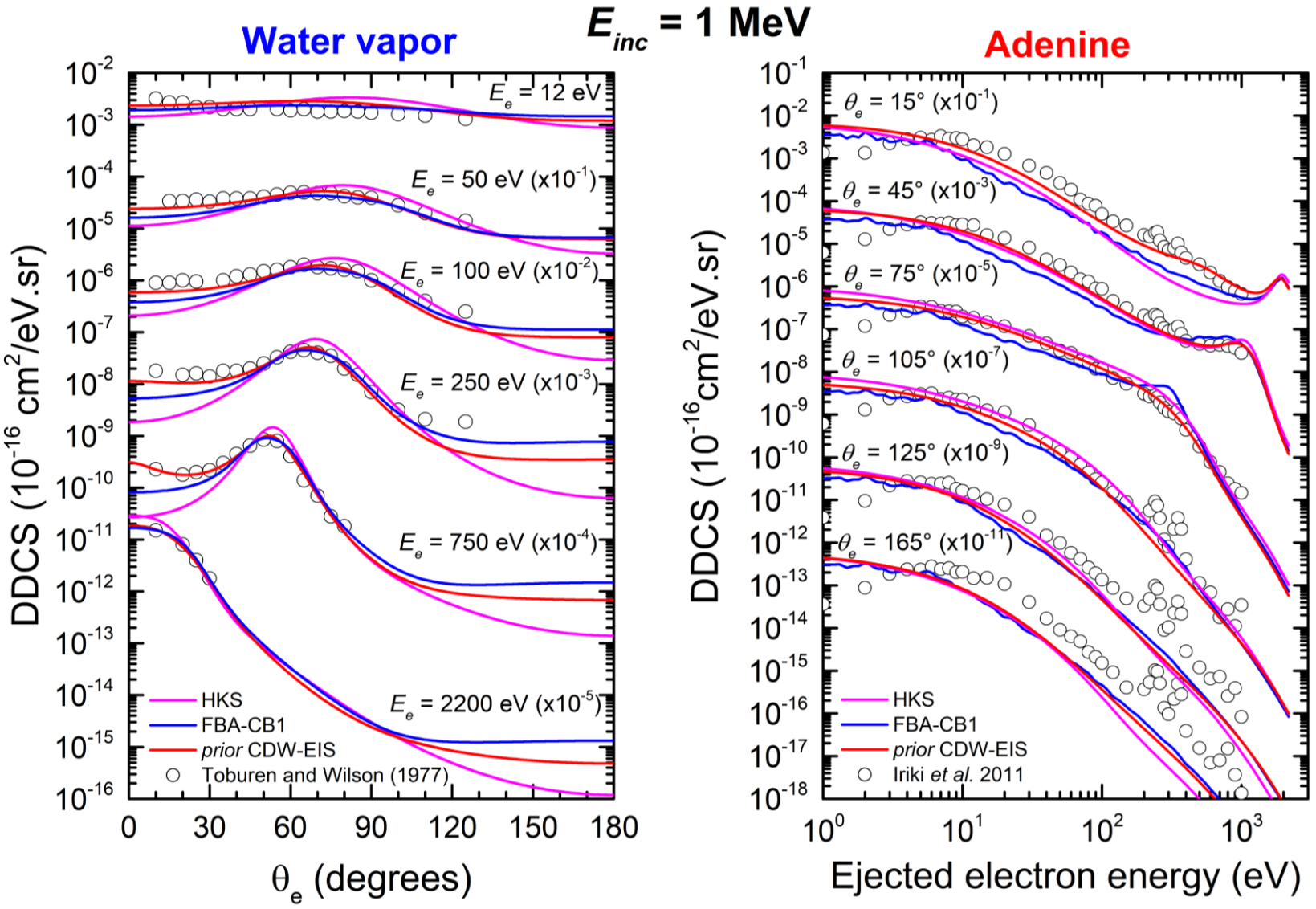
  (*Tan et al., Nucl. Instr. and Meth. in Phys. Res. B* ***248*** *(2006)*)



Dry DNA: 58% (Adenine + Thymine) + 42% (Cytosine - Guanine) + 2 sugar phosphate groups
ρ = 1.407 g cm^{-3}

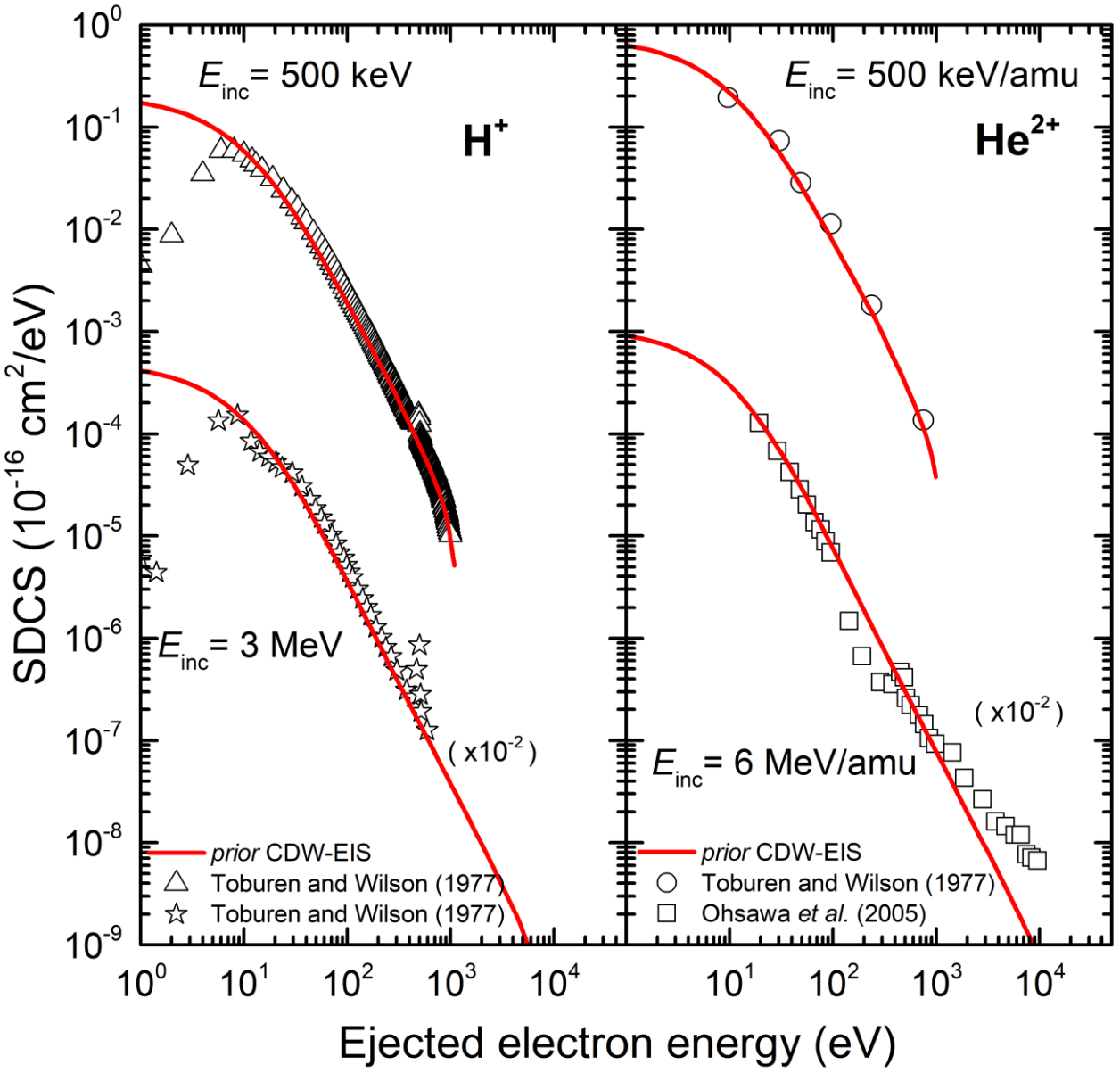
Hydrated DNA: 58% (Adenine + Thymine) + 42% (Cytosine - Guanine) + 2 sugar phosphate groups **+ 18 H_2O molecules**
(*Birnie et al., Biochim. Biophys. Acta 331,* ***283*** *(1973)*)
ρ = 1.29 g cm^{-3}

TILDA-V: Theoretical support for the proton-induced ionization: **DDCS**



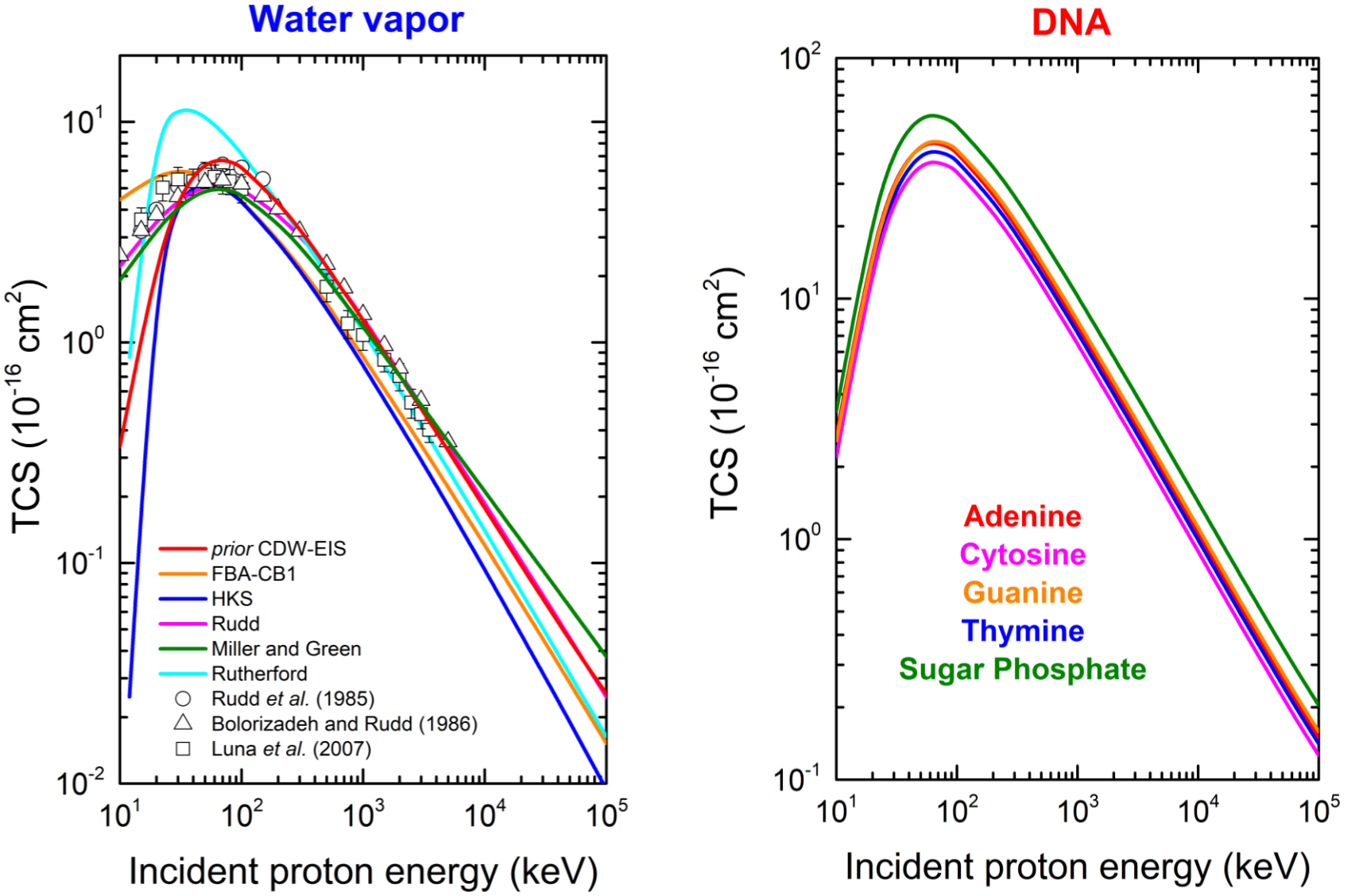
Galassi et al. Phys. Med. Biol. ***57,*** *2081 (2012)*

TILDA-V: Theoretical support for the proton- and α particle-induced ionization: **SDCS**



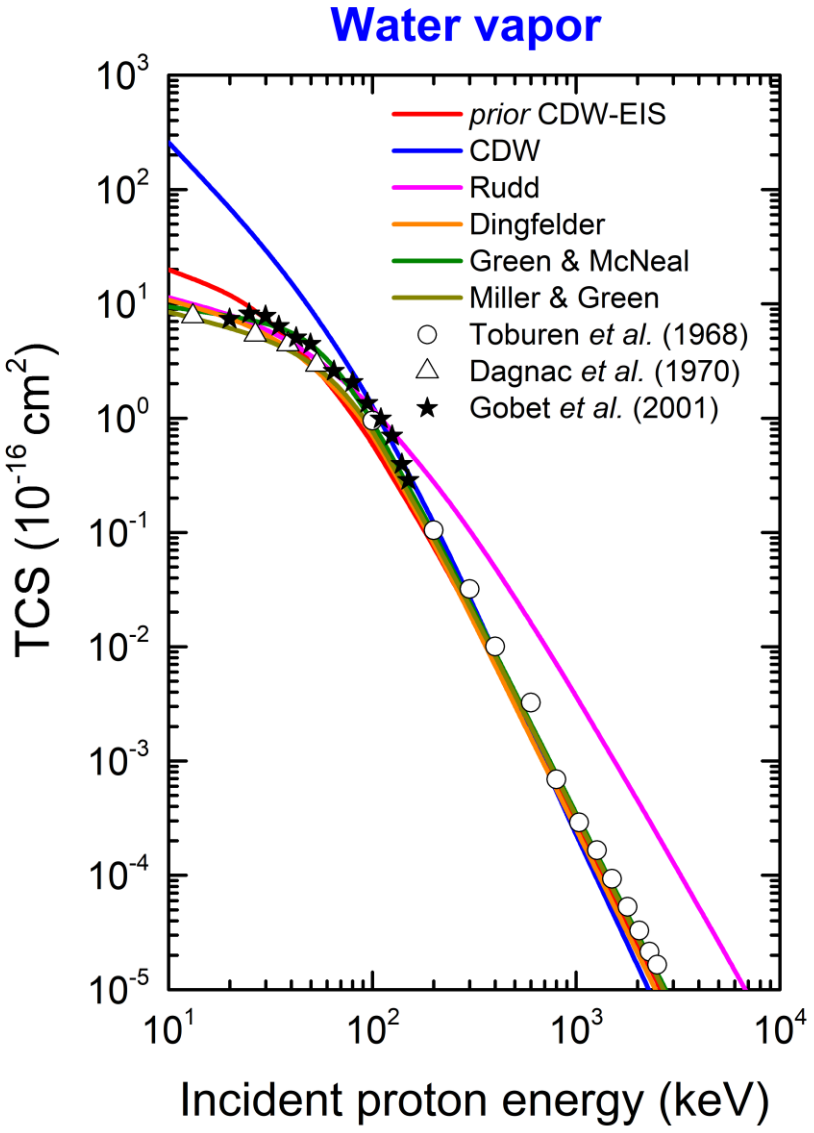
Quinto et al. Eur Phys J D ***71****, 35 (2017)*

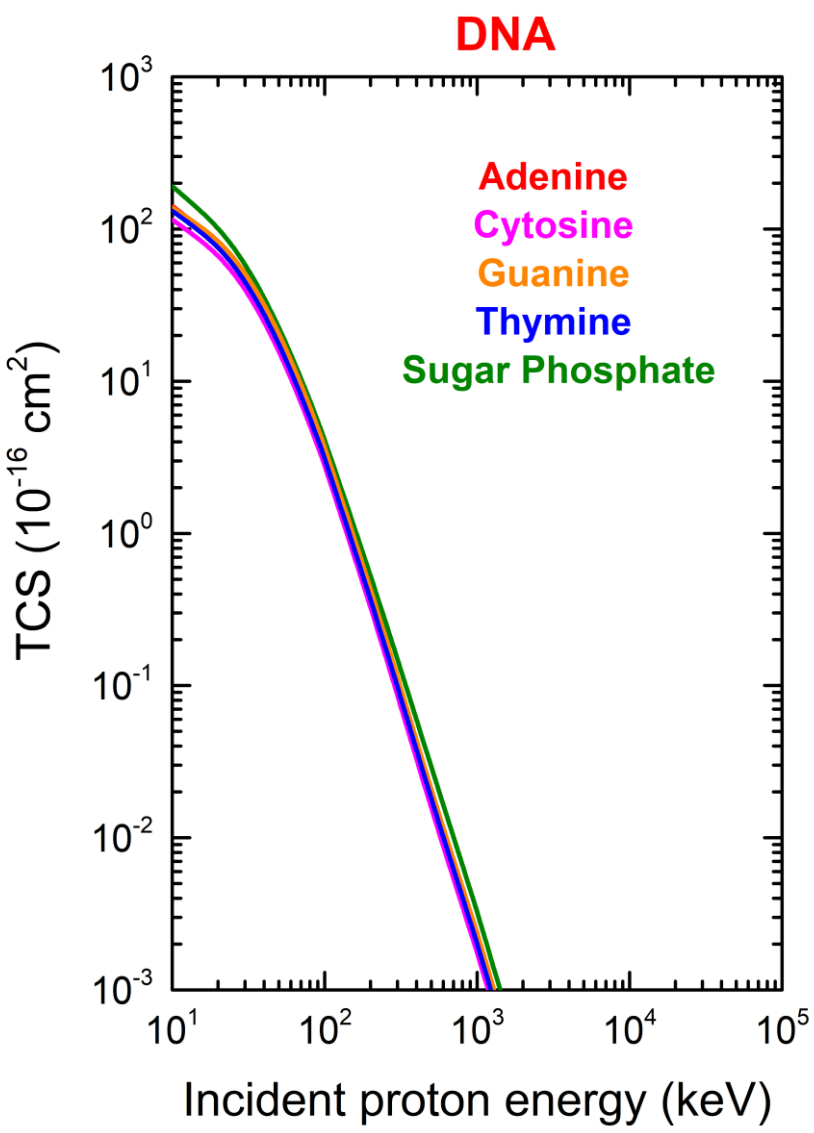
TILDA-V: Theoretical support for the proton-induced ionization: **TCS**



Champion et al., Phys. Med. Biol. ***60,*** *7805 (2015)*

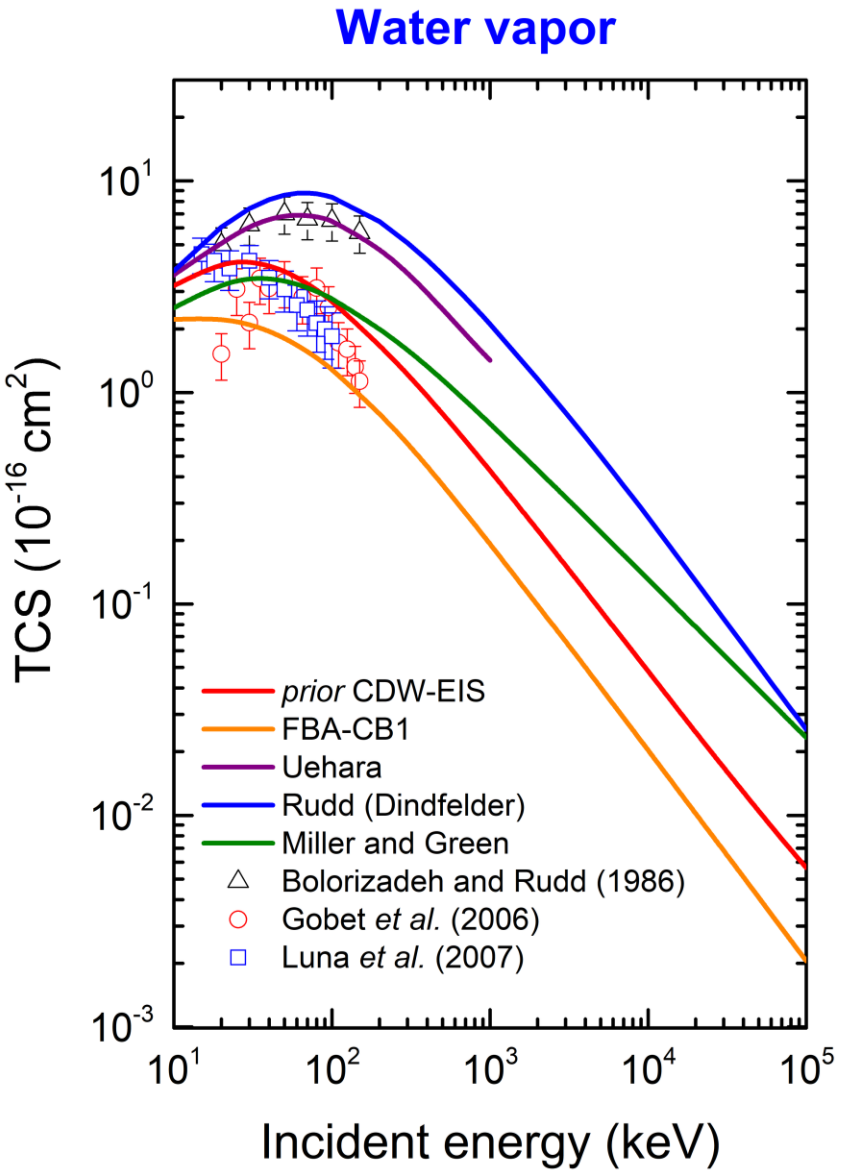
TILDA-V: Theoretical support for the proton-induced electron capture: **TCS**

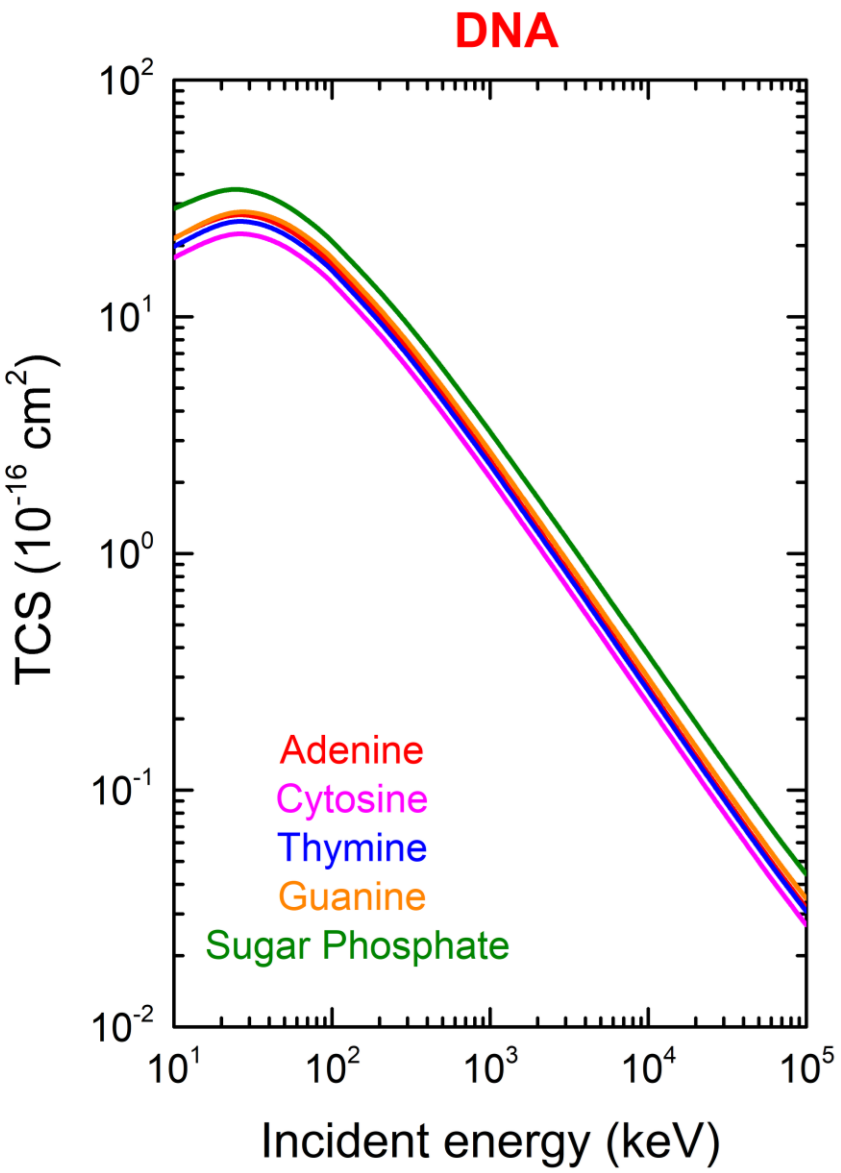




Quinto et al., Eur Phys J D ***71****, 130 (2017)*

TILDA-V: Theoretical support for the hydrogen-induced ionization: **TCS**

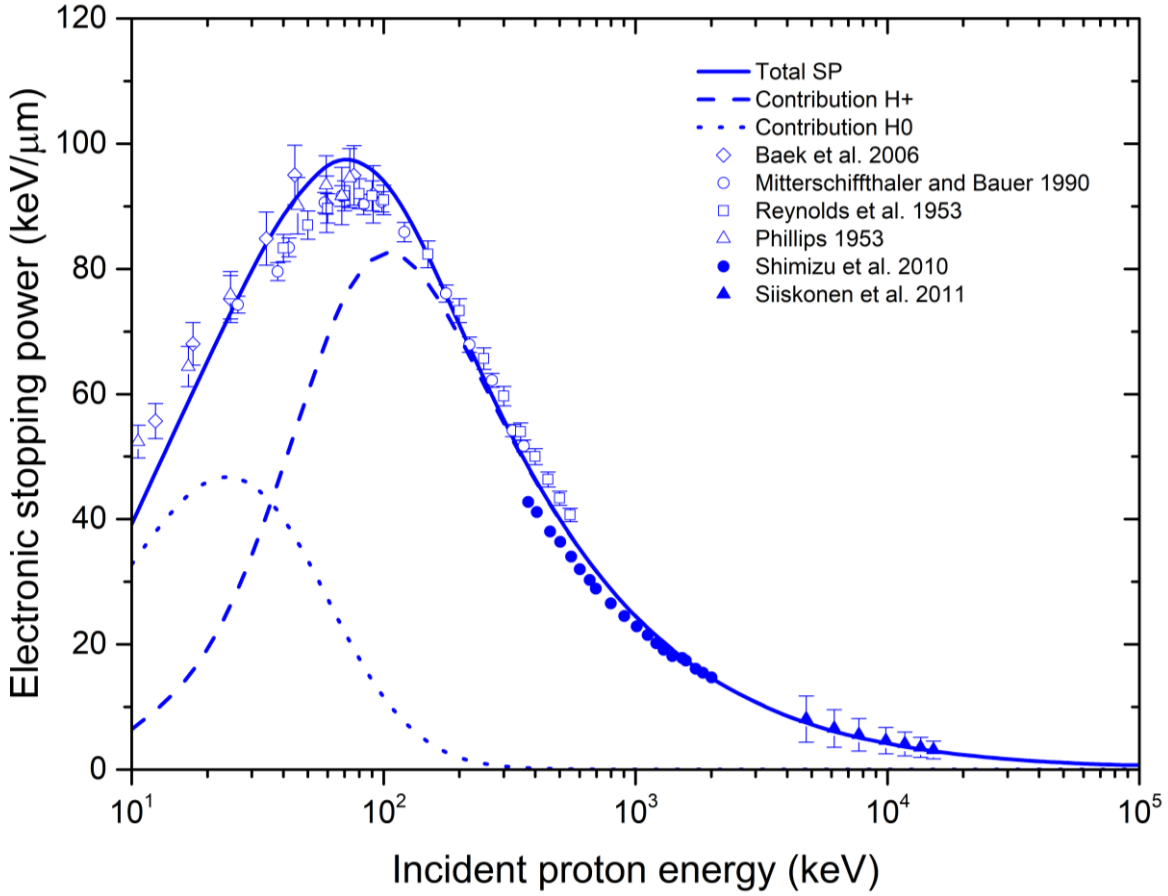




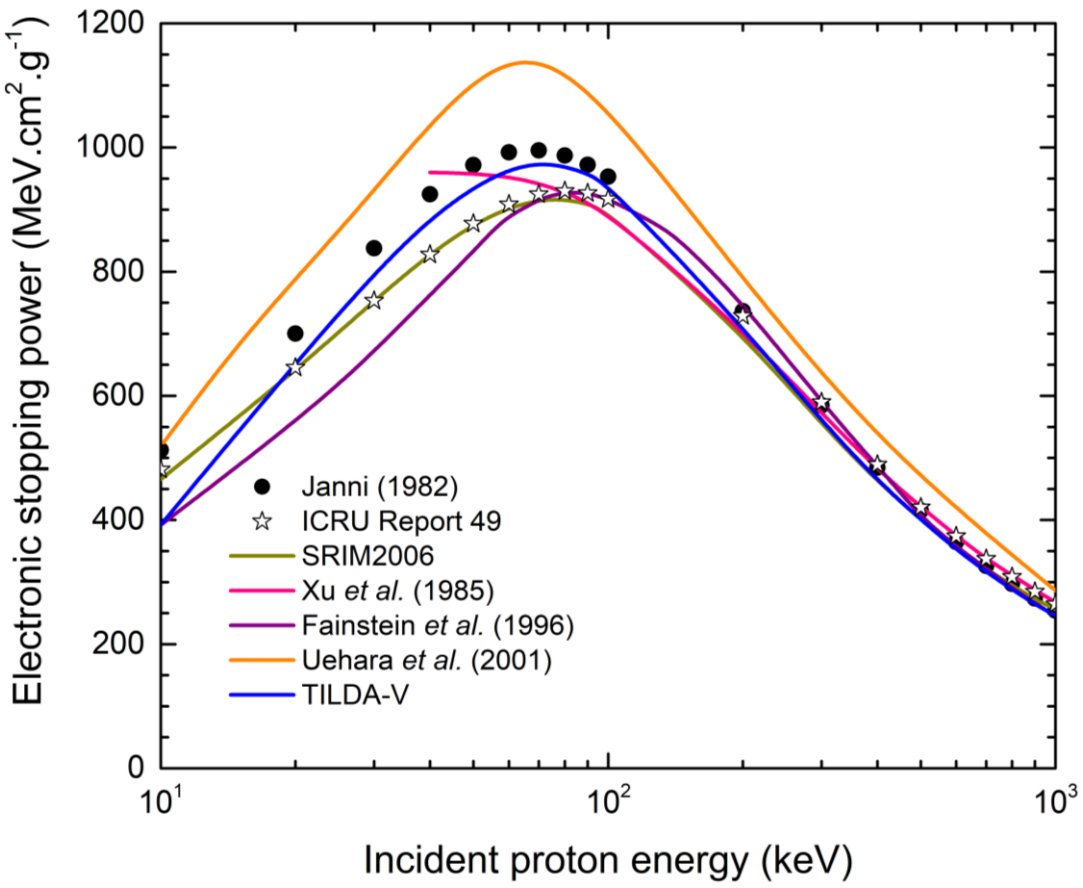
Quinto et al., Eur Phys J D ***71****, 130 (2017)*

TILDA-V: Stopping power of protons in water vapor

Comparison with experimental data



Comparison with theoretical data and other Monte Carlo codes

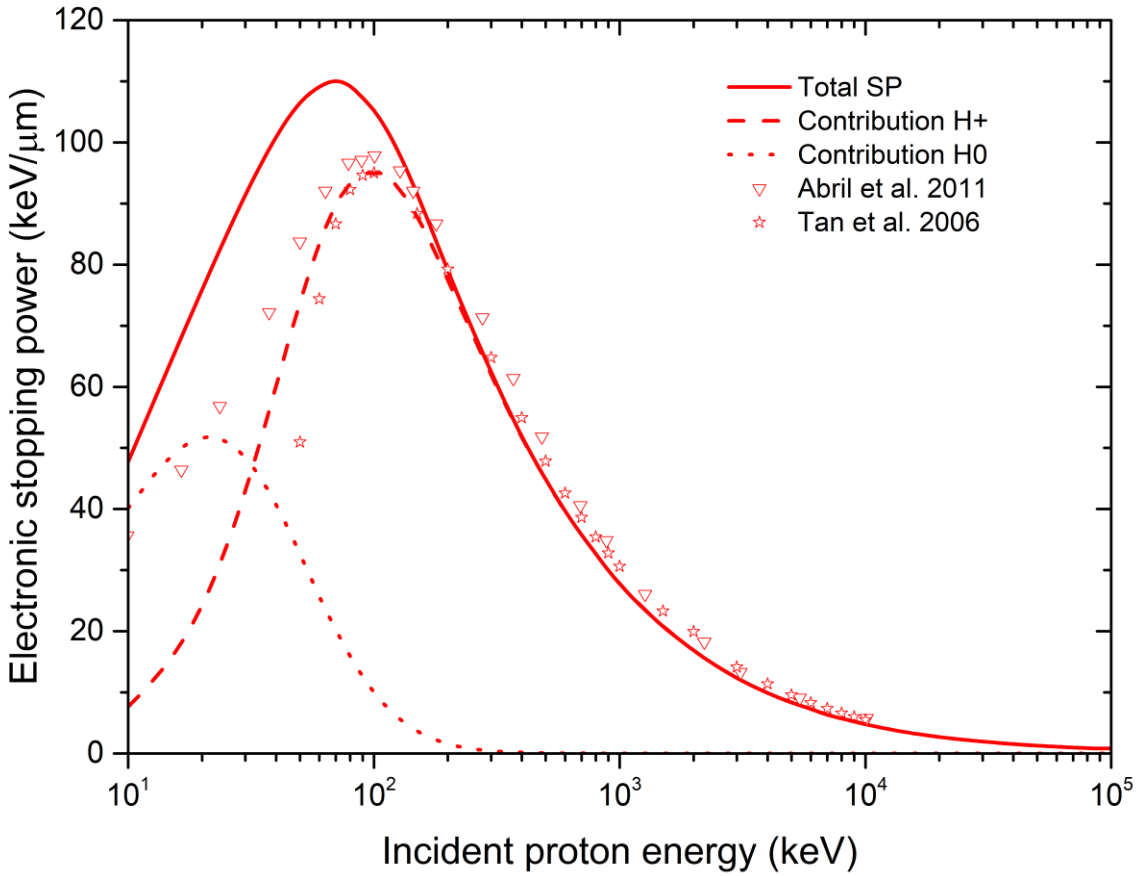


Quinto et al., Eur Phys J D ***71,*** *130 (2017)*

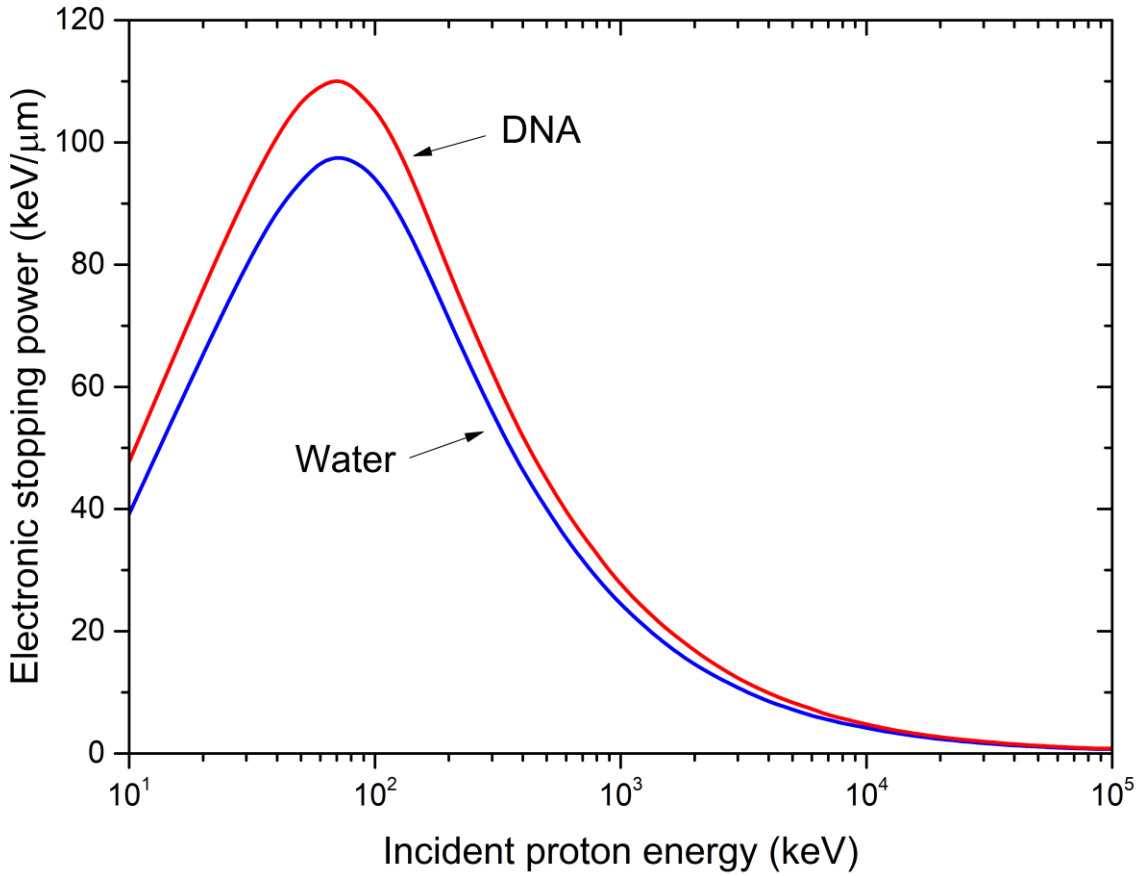
➡ **GOOD AGREEMENT WITH EXISTING DATA**

TILDA-V: Stopping power of protons in hydrated DNA

Comparison with other calculations

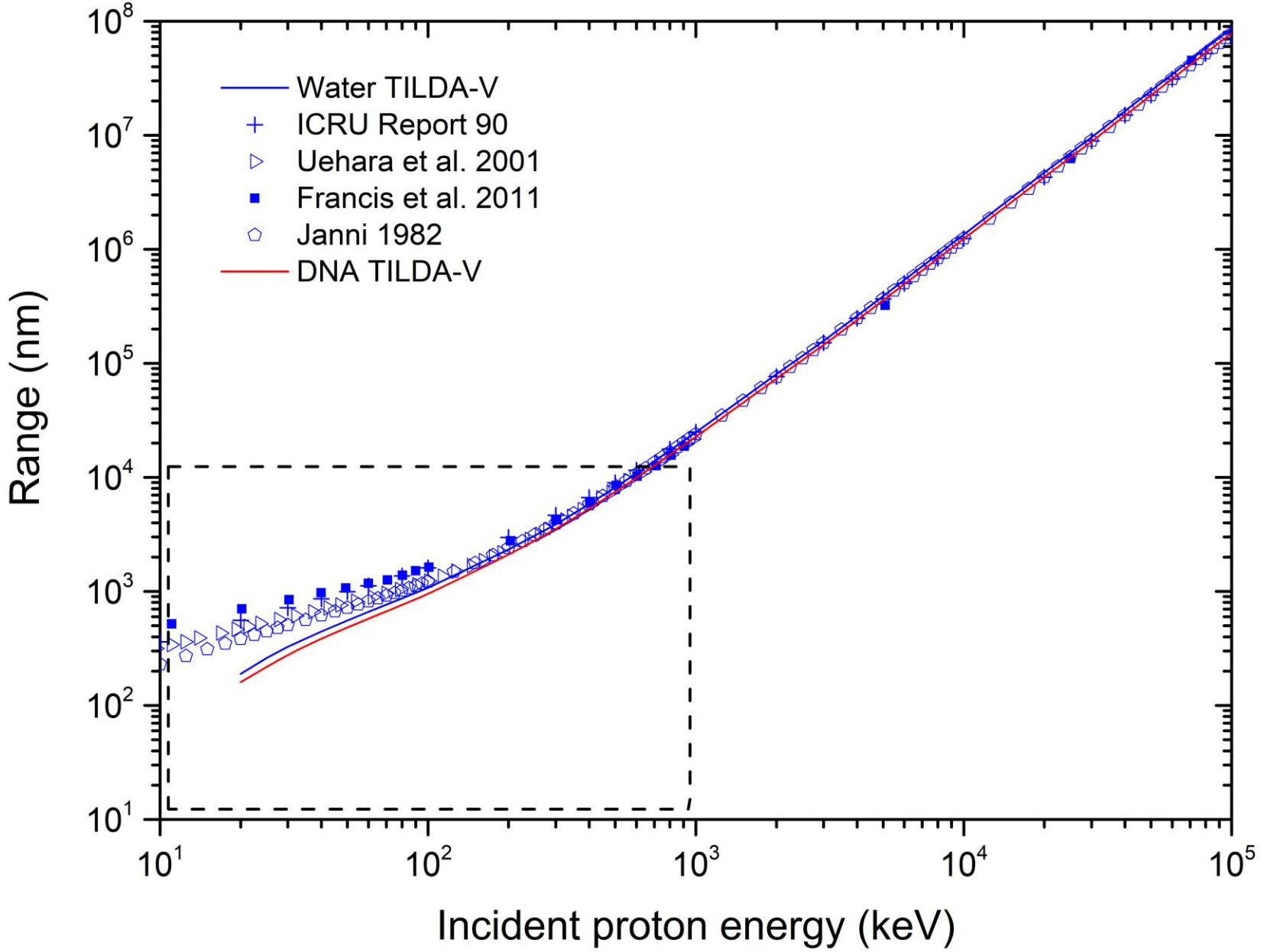


DNA *vs* water vapor

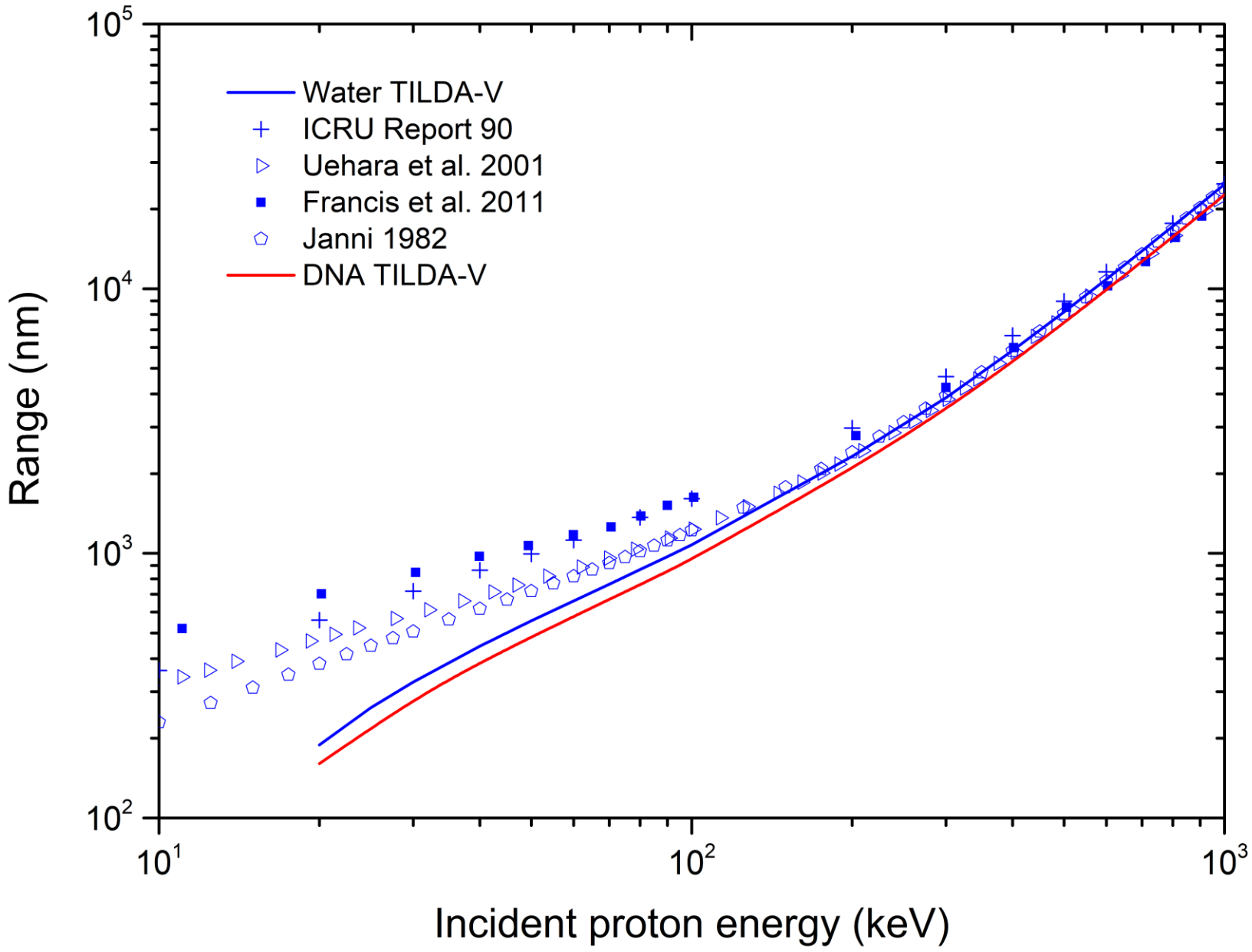


Quinto et al., Eur Phys J D ***71****, 130 (2017)*

TILDA-V: Range of protons in water and DNA



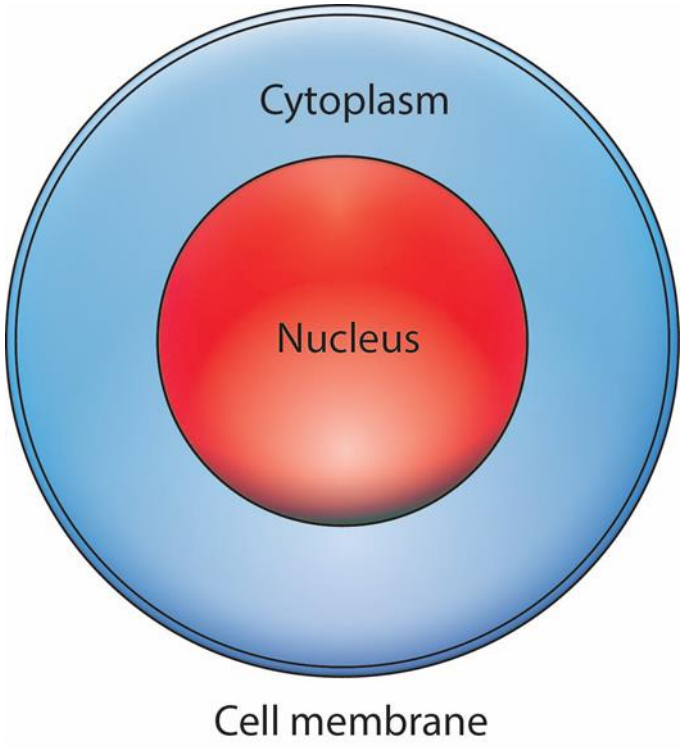
TILDA-V: Range of protons in water and DNA

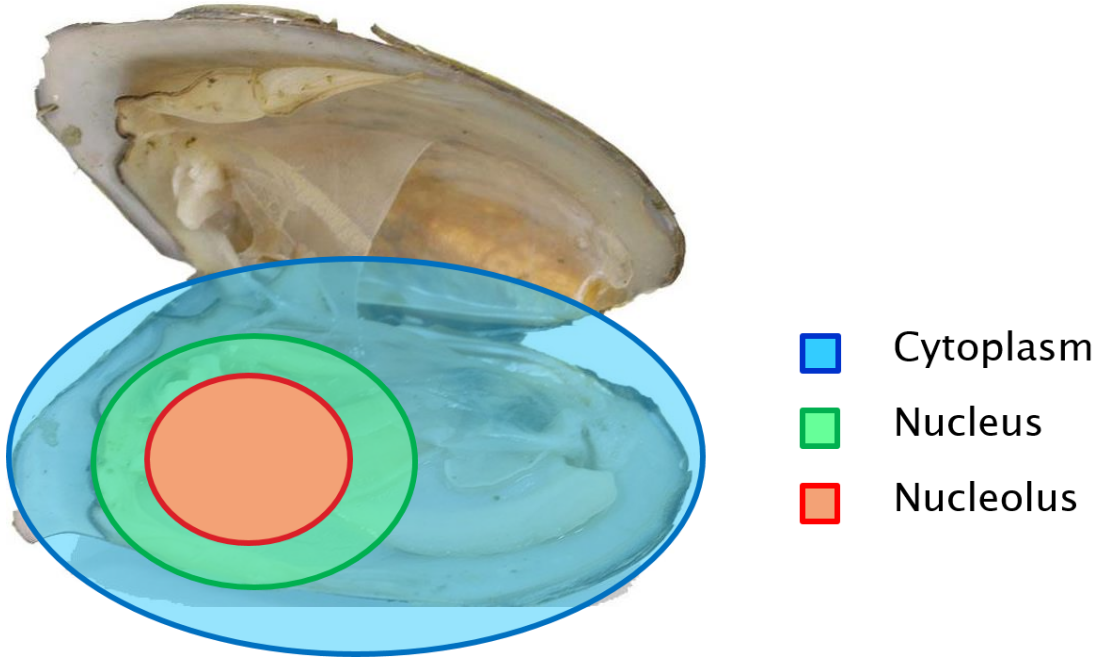


Ongoing work: cellular dosimetry

- **Protons and alpha particles**

  Dose calculation for single cells considering:
  - ✓various geometries (spherical/ellipsoidal)
  - ✓various heterogeneities
  - ✓specific initial localization of the source (cell compartments)





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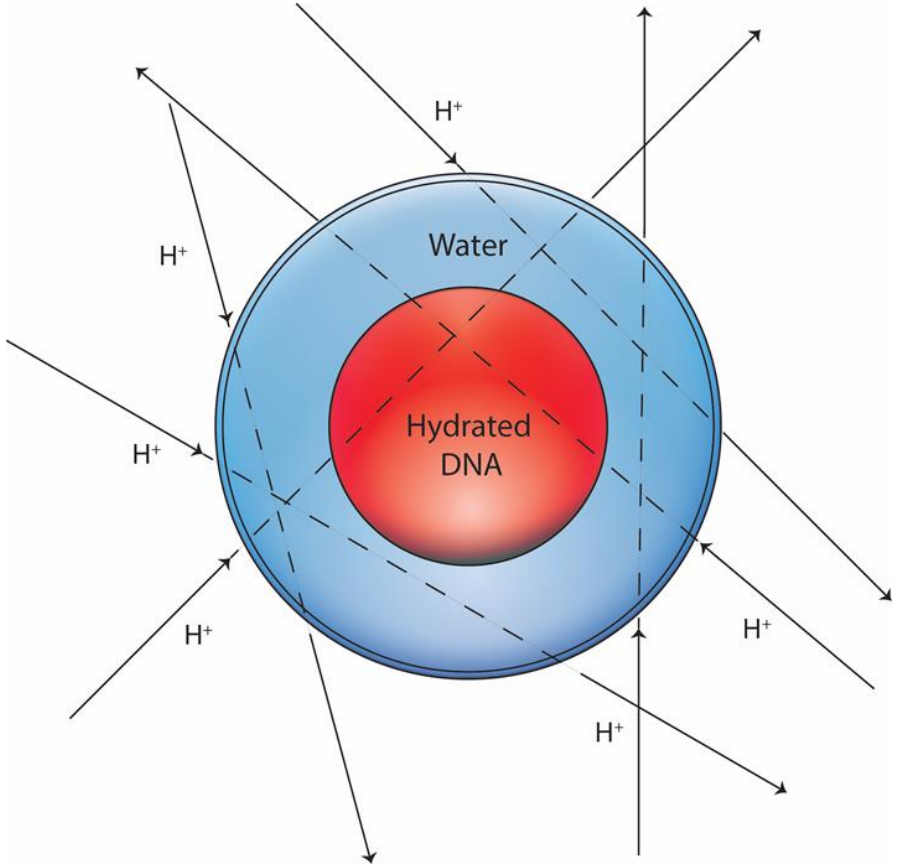
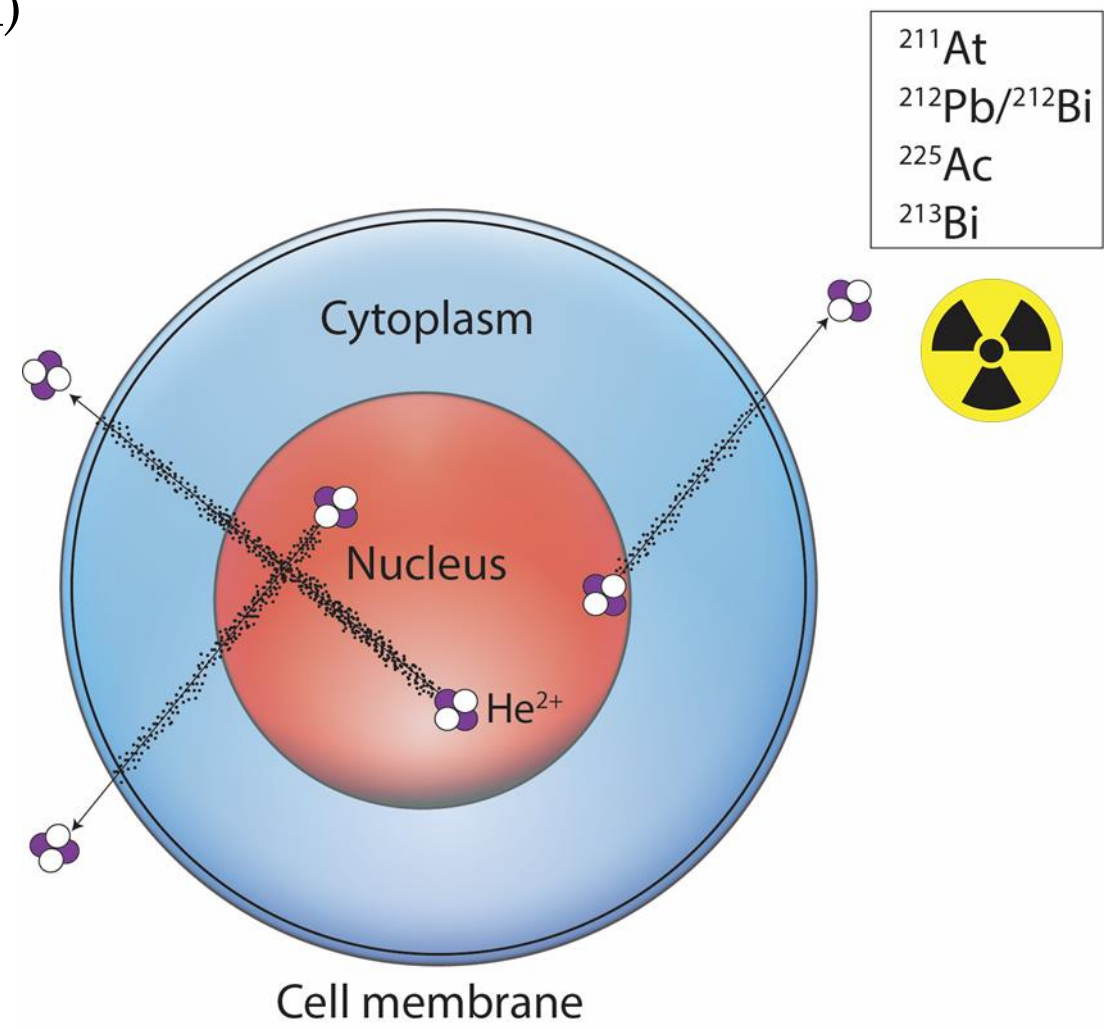
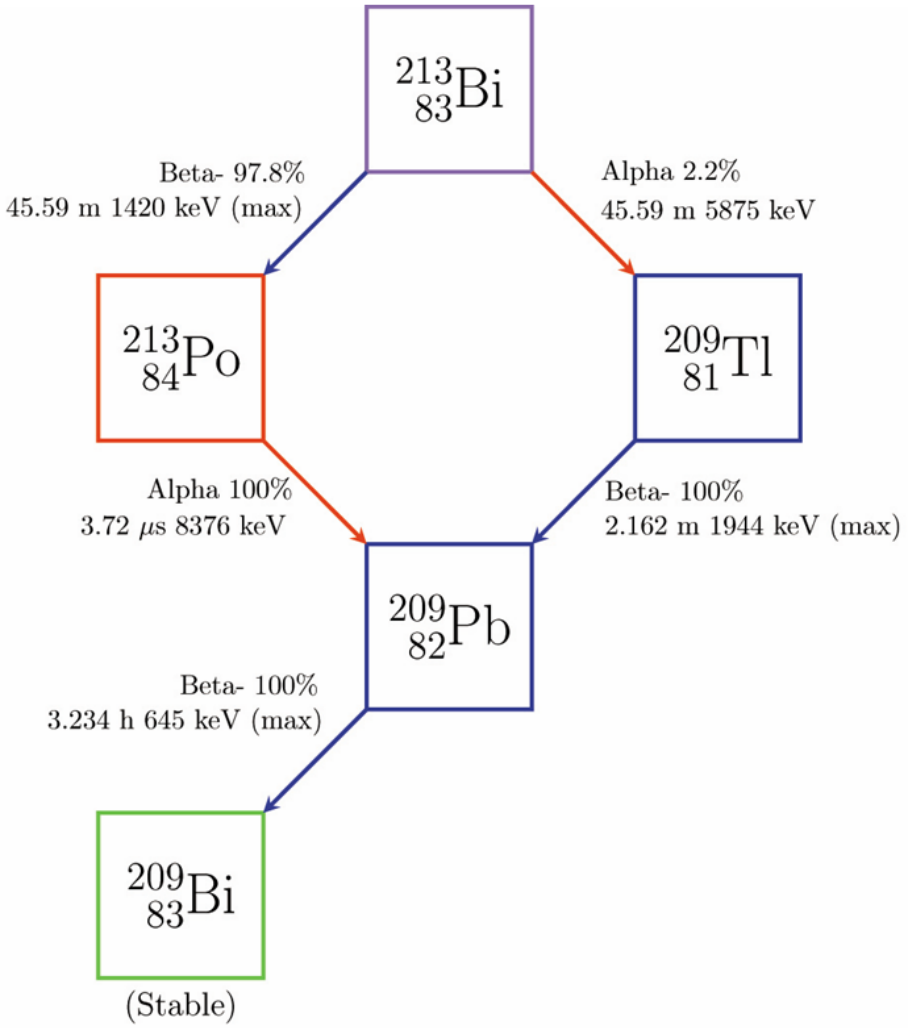




Targeted alpha therapy (TAT)

- TAT is the use of alpha emitting radionuclides to kill cancer cells
- Alpha particles have a **very short range** in matter and are **high LET** radiation, i.e., they can effectively destroy malignant cells without compromising surrounding healthy tissue
- Considered an appropriate technique to fight **micrometastases** and residual disease
- Only a few alpha emitters are currently being considered for TAT because of constraints mainly related to half-life and production costs: **^{223}Ra**, **^{211}At**, **^{212}Pb/^{212}Bi**, **^{225}Ac**, **^{213}Bi**

*The capabilities of TILDA-V to simulate the transport of alpha particles will be exploited to compare the **potential therapeutical advantages** of several alpha-emitting radionuclides.*

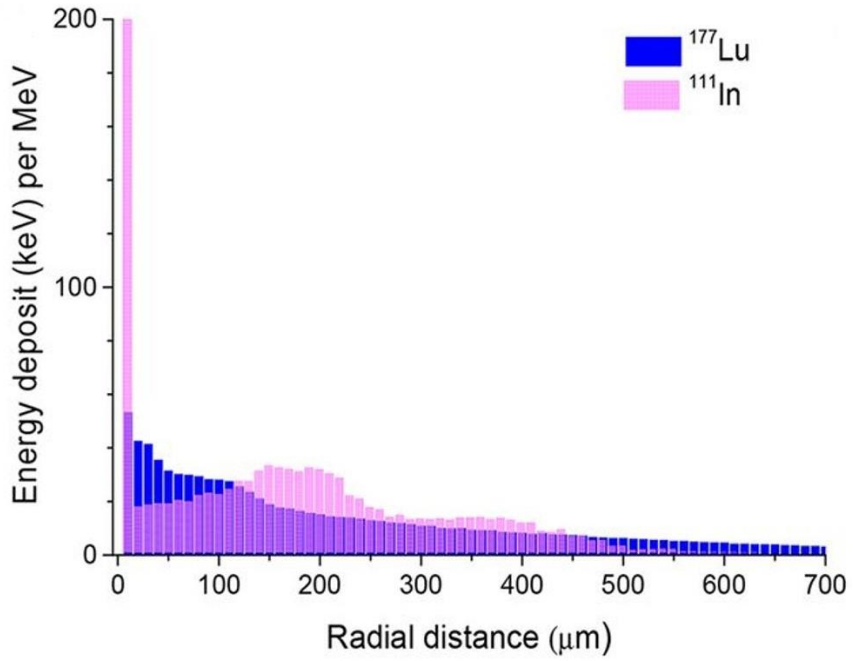


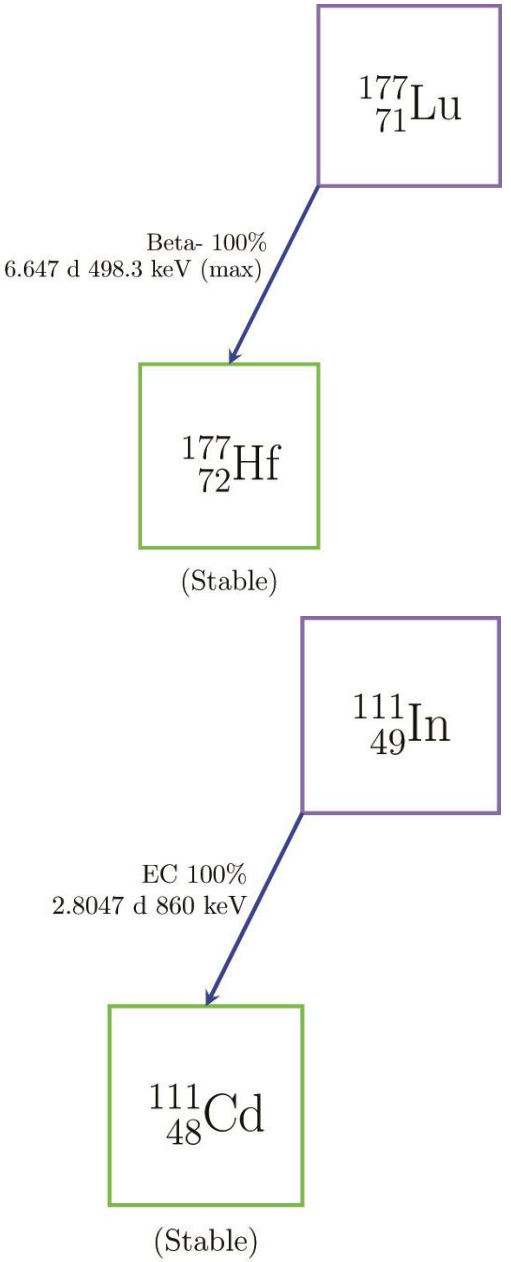
Radionuclide	Properties	Production routes	Potential applications	Current status	Drawbacks
^{223}Ra	Half-life of 11.4 days. ≈ 28 MeV of total energy per decay with ≈ 96% released as alpha particles.	Obtained from a ^{227}Ac generator. ^{227}Ac decays to either ^{227}Th or ^{223}Fr, which in turn decay to ^{223}Ra.	Castration-resistant prostate cancer with symptomatic bone metastases but no visceral disease	Approved since 2013 by the U.S. FDA and currently approved in over 40 countries. Ongoing trials to determine how to combine it with chemotherapy.	Its use is limited to the treatment of bone metastases.
^{211}At	Half-life of 7.2 hours. One alpha particle per decay of E ≈ 7.5 MeV	$^{209}Bi(\alpha, 2n)^{211}At$ reaction at a cyclotron.	Ovarian cancer, brain tumors, breast cancer.	Two clinical trials (phases I & II) have been completed. Further clinical evaluation is warranted.	Limited availability. Poor knowledge of the chemical behavior of astatine.
$^{212}Pb/^{212}Bi$	Half-lives: ^{212}Pb 10.6 h; ^{212}Bi 60 min. $E_\alpha \approx 8.8$ MeV	$^{228}Th/^{224}Ra$ generator, via the decay chain: $^{228}Th \rightarrow ^{224}Ra \rightarrow ^{220}Rn \rightarrow ^{216}Po \rightarrow ^{212}Pb$	Ovarian cancer with peritoneal metastases.	Ongoing research. A phase I clinical trial involving the intraperitoneal infusion of ^{212}Pb-TCMC-trastuzumab has been carried out with encouraging results.	Radiation safety concerns due to the high-energy (2.6 MeV) γ-ray emitted by ^{208}Tl, one of the daughters of ^{212}Bi.
^{225}Ac	Half-life of ≈10 days. 4 alpha particles per decay with a total energy of 28 MeV	Obtained through the decay of long-lived ^{229}Th ($T_{1/2}$ = 7880 years). Alternative production by means of the high-energy proton irradiation of ^{232}Th.	Castration-resistant prostate cancer; leukemia.	Ongoing research. A phase I/II clinical trial of ^{225}Ac-lintuzumab in older patients with acute myeloid leukemia is under way.	Only 3 main sources worldwide of ^{229}Th to produce relevant quantities of ^{225}Ac. Toxicity issues due to the recoil energy of the daughters.
^{213}Bi	Half-life of 46 min. One alpha particle per decay of E ≈ 8.3 MeV	$^{225}Ac/^{213}Bi$ generator.	Ovarian cancer, brain tumors, melanomas, non-Hodgkin lymphoma and leukemia.	A phase I/II clinical trial has been carried out with ^{213}Bi-lintuzumab in patients with leukemia, concluding it may help to reduce small-volume disease.	Its very short physical half-life does not allow infusion into tumors. Low availability and high cost, since it is obtained from ^{225}Ac

Beta and Auger electron emitters

Sphere diameter (μm)	Dose per decay (S value) (Gy)				Dose for 1 decay per μm³ (Gy)				Dose for 1 MeV released per μm³ (Gy)			
	^{90}Y	^{177}Lu	^{111}In	^{161}Tb	^{90}Y	^{177}Lu	^{111}In	^{161}Tb	^{90}Y	^{177}Lu	^{111}In	^{161}Tb
10,000	1.72×10^{-10}	4.30×10^{-11}	1.01×10^{-11}	5.82×10^{-11}	90.1	22.5	5.31	30.5	96.5	152	153	152
5,000	8.50×10^{-10}	3.29×10^{-10}	7.88×10^{-11}	4.47×10^{-10}	55.6	21.6	5.16	29.3	59.5	145	148	146
2,000	5.80×10^{-9}	4.54×10^{-9}	1.13×10^{-9}	6.22×10^{-9}	24.3	19.0	4.74	26.0	26.0	128	136	129
1,000	2.37×10^{-8}	2.94×10^{-8}	7.86×10^{-9}	4.14×10^{-8}	12.4	15.4	4.12	21.7	13.3	104	118	108
500	9.59×10^{-8}	1.69×10^{-7}	4.75×10^{-8}	2.54×10^{-7}	6.27	11.1	3.11	16.6	6.71	74.8	89.3	82.7
200	6.03×10^{-7}	1.48×10^{-6}	4.28×10^{-7}	2.76×10^{-6}	2.53	6.18	1.79	11.6	2.70	41.8	51.5	57.6
100	2.42×10^{-6}	6.93×10^{-6}	2.58×10^{-6}	1.71×10^{-5}	1.27	3.63	1.35	8.95	1.36	24.5	38.9	44.5
50	9.58×10^{-6}	3.18×10^{-5}	1.75×10^{-5}	1.02×10^{-4}	0.63	2.08	1.14	6.67	0.67	14.1	32.9	33.3
20	5.95×10^{-5}	2.33×10^{-4}	2.28×10^{-4}	9.70×10^{-4}	0.25	0.98	0.95	4.06	0.27	6.61	27.4	20.2
10	2.37×10^{-4}	1.11×10^{-3}	1.52×10^{-3}	5.41×10^{-3}	0.12	0.58	0.79	2.83	0.13	3.92	22.8	14.1

Point sources:



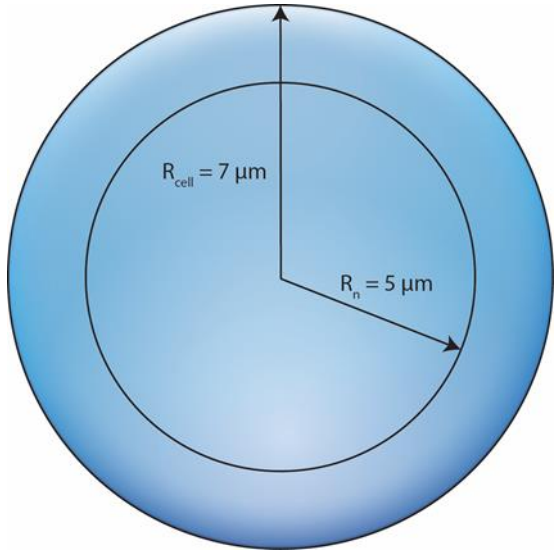


Hindié et al., J Nucl Med ***57(5), 759-64 (2016)***

Beta and Auger electron emitters

- Calculation of intracellular S-values (R_c = 7 µm and R_n = 5 µm)
- Results for some radionuclides and comparison with *Goddu et al., J Nucl Med 35:303-316 (1994)* (all values are in Gy/(Bq·s)):

	Nucleus ← Nucleus		Nucleus ← Cytoplasm		Nucleus ← Cell surface		Cell ← Cell surface		Cell ← Cell	
Radionuclide	Our value	Goddu et al.	Our value	Goddu et al.	Our value	Goddu et al.	Our value	Goddu et al.	Our value	Goddu et al.
^{125}I	3.65E-003	3.51E-003	3.18E-004	2.58E-004	2.01E-004	1.49E-004	7.88E-004	7.43E-004	1.45E-003	1.37E-003
^{67}Ga	2.05E-003	1.86E-003	1.81E-004	1.94E-004	5.06E-005	4.48E-005	4.24E-004	3.87E-004	7.96E-004	7.25E-004
^{123}I	1.57E-003	1.56E-003	1.60E-004	1.28E-004	1.08E-004	8.00E-005	3.49E-004	3.38E-004	6.31E-004	6.19E-004
^{201}Tl	4.37E-003	4.24E-003	4.47E-004	4.68E-004	1.77E-004	1.75E-004	9.14E-004	8.94E-004	1.71E-003	1.67E-003
^{111}In	1.53E-003	1.47E-003	1.83E-004	1.55E-004	1.12E-004	1.00E-004	3.35E-004	3.25E-004	6.13E-004	5.91E-004



Summary and conclusions

- *TILDA-V* is a Monte Carlo track-structure code implementing quantum-mechanical models to describe charged particles interactions in both water and DNA
- The implemented cross sections are in good agreement with the available experimental data
- *TILDA-V* is being benchmarked against other Monte Carlo codes as well as deterministic codes
- *TILDA-V* introduces a more realistic modelling of the biological matter by including the DNA nucleobases and the sugar phosphate backbone
- *TILDA-V* is being applied in radiation microdosimetry studies (for cell dosimetry calculations) and will soon be applied to DNA damage quantification/identification

Thank you for your attention

Merci pour votre attention