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A micro- and nanodosimetry-based computational approach to characterize the effectiveness of a mixed radiation field

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Microdosimetry / Nanodosimetry
approaches with great potential

Radiation biological effectiveness can be ultimately traced back to
the **stochastic pattern** of **energy depositions** at the **micro**- (and **nano**-)meter level

↕

respectively, linear dimensions of structures of biological relevance as
chromosomal domains and **DNA double helix**

Potential for applications to **mixed radiation fields**
as **micro**- (and **nano**-)dosimetric quantities can both

- **characterize the field** (measurable!)
- be **correlated with the biological outcome** (RBE predictions!)

Microdosimetry / Nanodosimetry
e.g. in ion-therapy

An example (**planning**)

PAPER

On the concepts of dose-mean lineal energy, unrestricted and restricted dose-averaged LET in proton therapy

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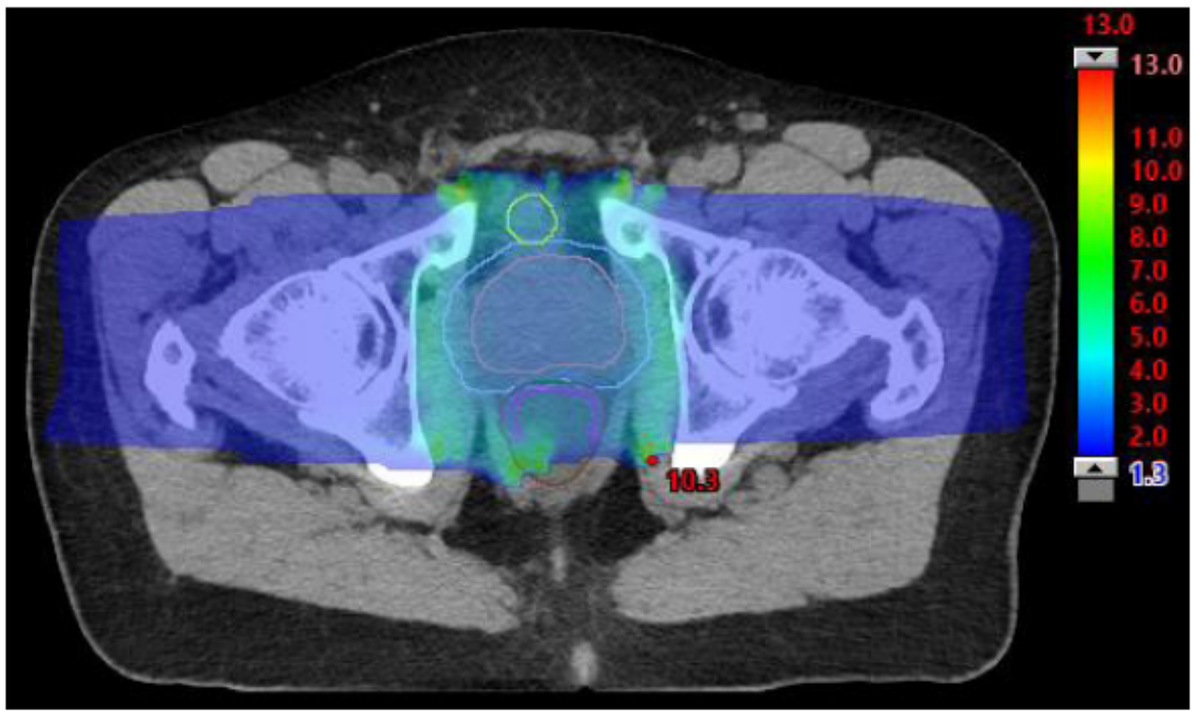


prostate cancer clinical case - y_D (1μm) in color scale
MicroCalc algorithm as a script in Eclipse - VARIAN

- **dose mean lineal energy y_D** and y_D - derived **restricted dose-average linear energy transfer LETd** can be analytically computed and compared for clinical proton plans
- calculation of y_D opens to:
    1. characterization of the clinical beam by experimental measurements ;
    2. optimization of proton treatments based on these quantities (RBE models)

Microdosimetry / Nanodosimetry
e.g. in ion-therapy

An example (**consequences**)

Radiotherapy and Oncology 121 (2016) 395–401

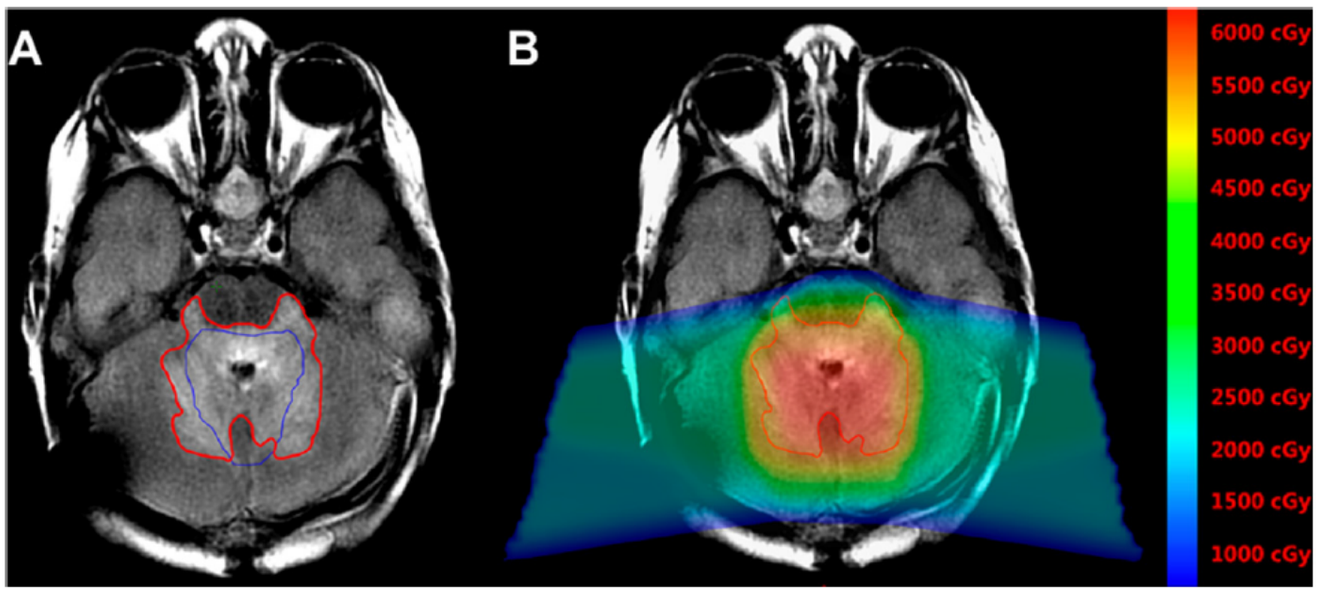
Variable proton RBE

Clinical evidence of variable proton biological effectiveness in pediatric patients treated for ependymoma

Christopher R. Peeler [a,b], Dragan Mirkovic [a], Uwe Titt [a], Pierre Blanchard [c,d], Jillian R. Gunther [c], Anita Mahajan [c], Radhe Mohan [a,1], David R. Grosshans [c,*,1]

- **RBE of a clinical proton beam set to 1.1**
  though it varies with beam penetration

- clinical evidence of correlation between high LET and changes in post-treatment MR images (a possible harbinger for severe reactions) for pediatric ependymoma proton therapy patients



(A)T2-FLAIR MR image, red hyper intense region for image change, CTV in blue.
(B) superimposed treatment plan dose

The role of biophysical modeling

- Explore **correlations of biological effects and micro- (nano)dosimetric quantities**

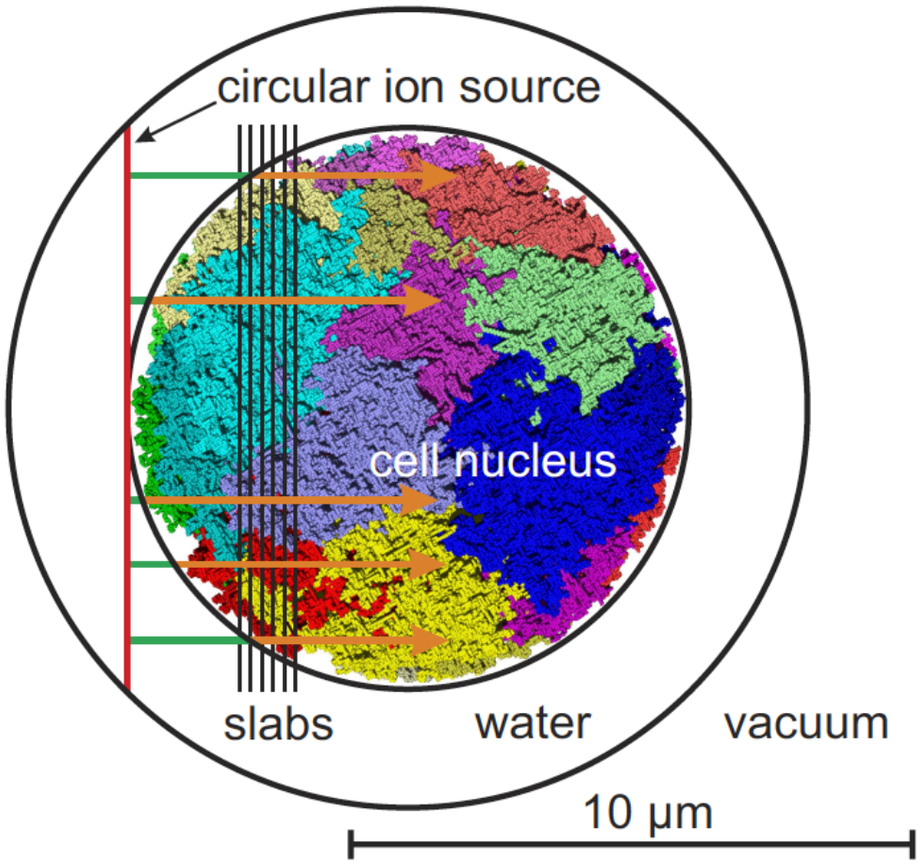
SCIENTIFIC REPORTS

Comprehensive track-structure based evaluation of DNA damage by light ions from radiotherapy-relevant energies down to stopping

W. Friedland[1], E. Schmitt[1], P. Kundrát[1], M. Dingfelder[2], G. Baiocco[3], S. Barbieri[3] & A. Ottolenghi[3]

SCIENTIFIC REPORTS | 7:45161 | DOI: 10.1038/srep45161

- biophysical code **PARTRAC**
- prediction of **different types of DNA damage** (related to **cell fate**!) by **different particles** as a function of their linear energy transfer in the **cell nucleus**



what LET are we dealing with?

$$\mathrm{LET}\,[\mathrm{keV\,\mu m^{-1}}] = 6.2415\,[\mathrm{keV\,\mu m^{-3}\,Gy^{-1}}]\,\mathrm{D}\,[\mathrm{Gy}]/\Phi\,[\mu\mathrm{m}^{-2}]$$

The role of biophysical modeling

- remembering, **in the perspective of practical implementations**, that this kind of results have to be accessed in the **quickest possible way**, *i.e.* not running full Monte Carlo simulations but taking advantage of **databases** and possibly their **analytical representation**.

SCIENTIFIC REPORTS

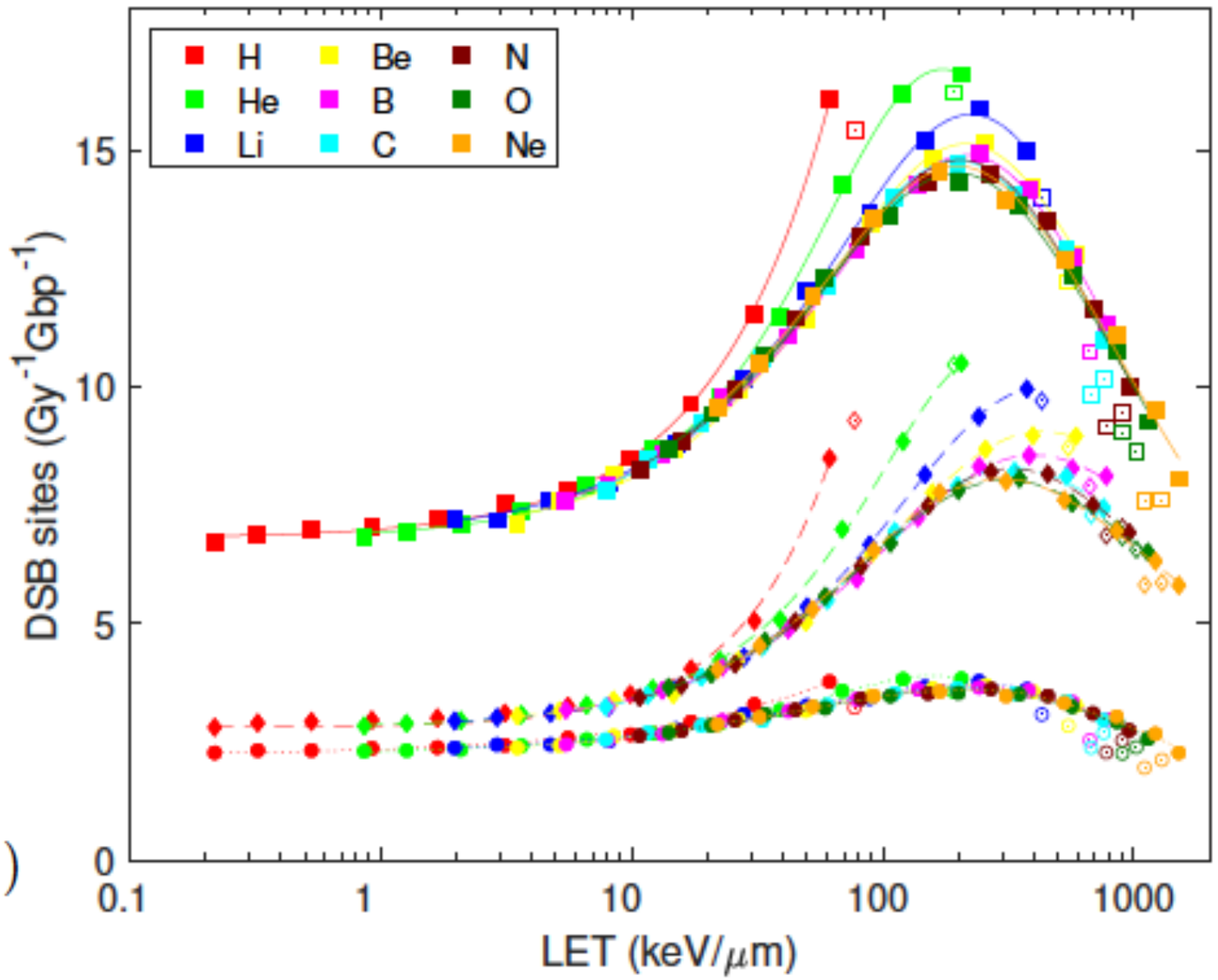
Analytical formulas representing track-structure simulations on DNA damage induced by protons and light ions at radiotherapy-relevant energies

Pavel Kundrát[1,2], Werner Friedland[1], Janine Becker[1], Markus Eidemüller[1], Andrea Ottolenghi[3] & Giorgio Baiocco[3]✉

SCIENTIFIC REPORTS | (2020) 10:15775

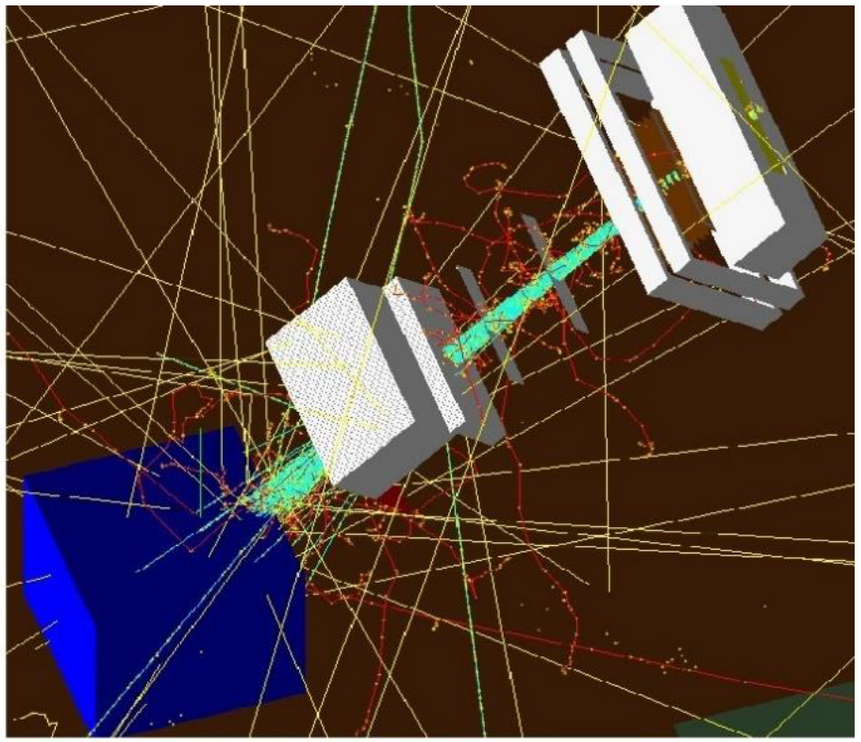
- analytical fit to a large database of **PARTRAC** results
  e.g. for DSB sites

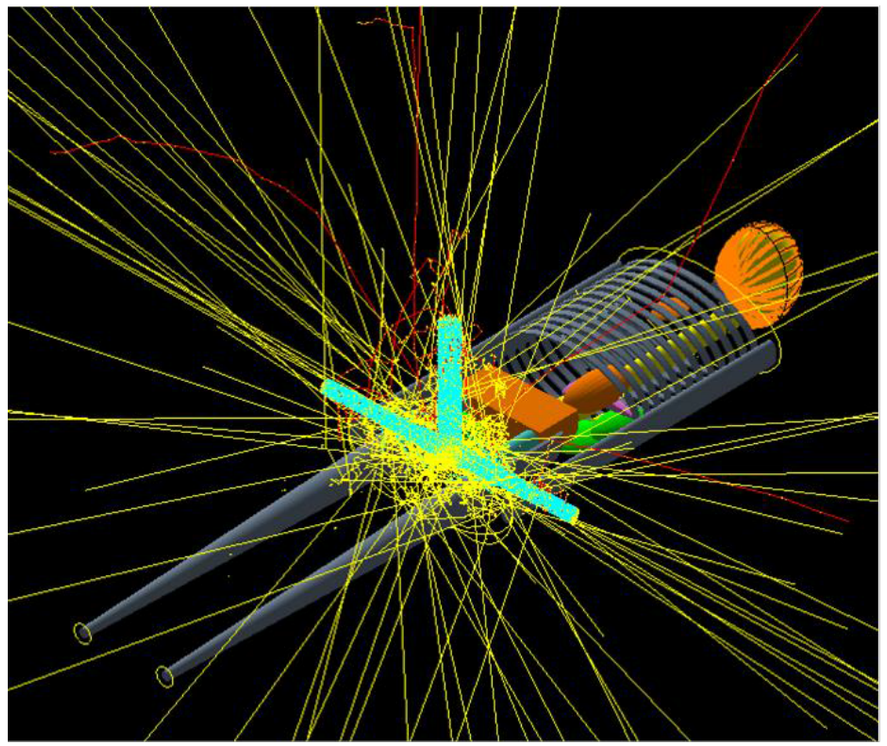
$$\text{Yield} = (p_1 + (p_2\text{LET})^{p_3})/(1 + (p_4\text{LET})^{p_5})$$

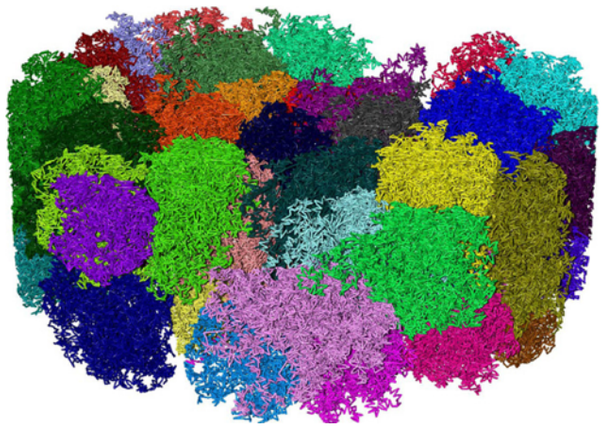


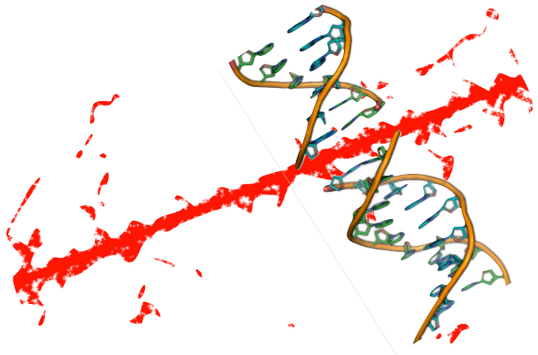
Radiation transport:
from the macro to the micro-scale

- **transport code** (as *e.g.* PHITS) can be developed to calculate **microdosimetric quantities** in **macroscopic regions**, again thanks to analytical formulas that have previously been implemented, tested to derive such quantities from full simulations of particle tracks



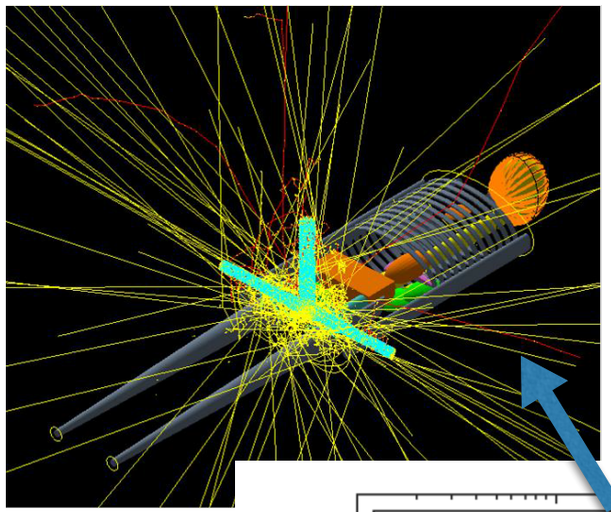






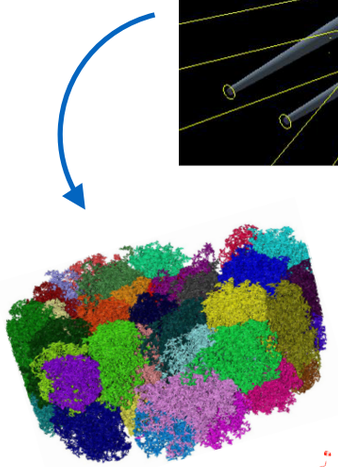
GEANT4 + PARTRAC simulations,
illustrative images for the "change" in spatial scale

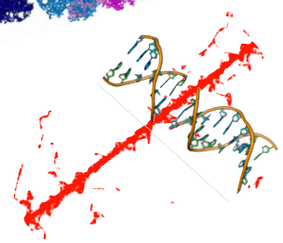
The biological effectiveness of a mixed field: general idea

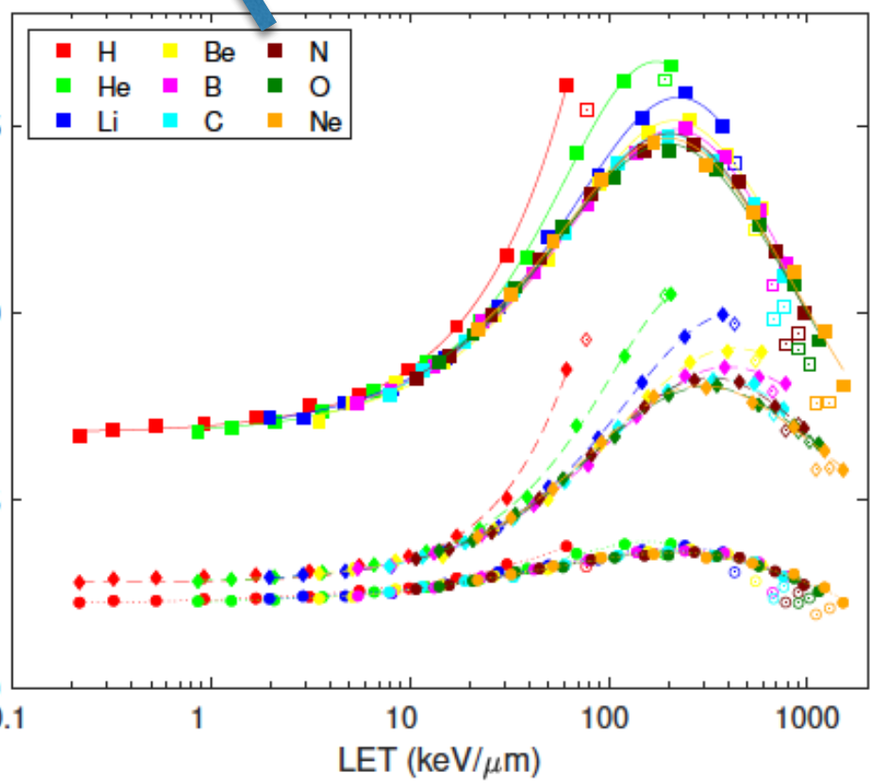


1. USE a transport code
2. derive for **ALL PARTICLES** (primary and secondaries) their
   - **relative contribution** to the **TOTAL DOSE**
   - an indicator of the spatial density of associated energy depositions at the micrometric scale, *e.g.* **DOSE MEAN LINEAL ENERGY,** y_D

   in the **macroscopic region** of interest







3. query a database/analytical functions from track-structure codes to extract **damage associated to a given particle** at its given y_D

4. weigh such damage with the corresponding **relative contribution to the total dose**

5. **sum all damages** thus obtaining **damage from the mixed field in the region of interest**

The biological effectiveness of a mixed field: the neutron case

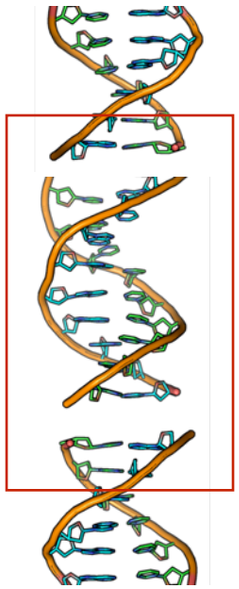
RBE for complex neutron induced DNA damage as a function of neutron energy

SCIENTIFIC REPORTS

The origin of neutron biological effectiveness as a function of energy

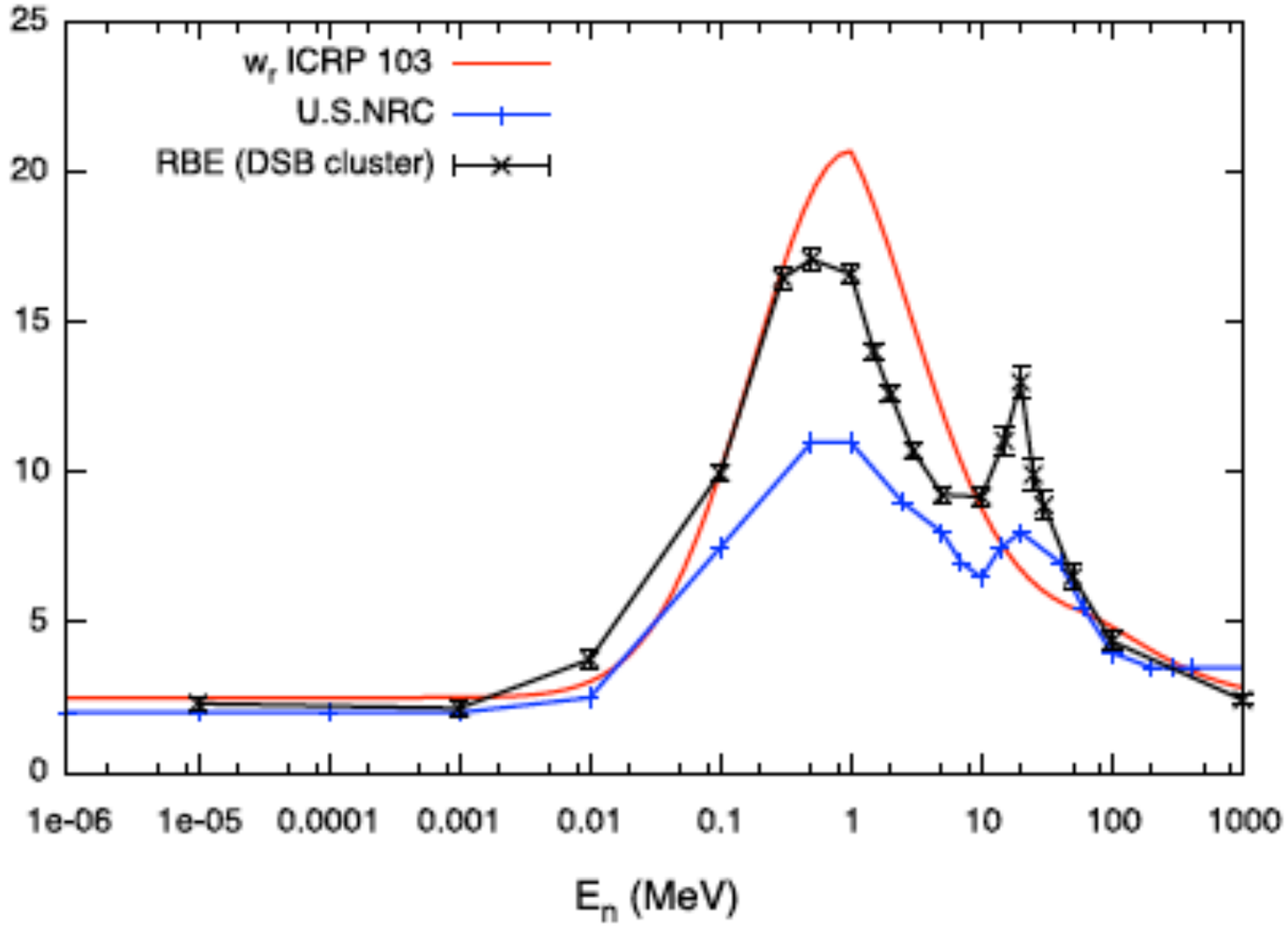
G. Baiocco[1], S. Barbieri[1], G. Babini[1], J. Morini[1], D. Alloni[2,3], W. Friedland[4], P. Kundrát[4], E. Schmitt[4], M. Puchalska[5], L. Sihver[5] & A. Ottolenghi[1]

SCIENTIFIC REPORTS | 6:34033 | DOI: 10.1038/srep34033



Comparison to experimental data "condensed" in radiation protection standards (w_R)

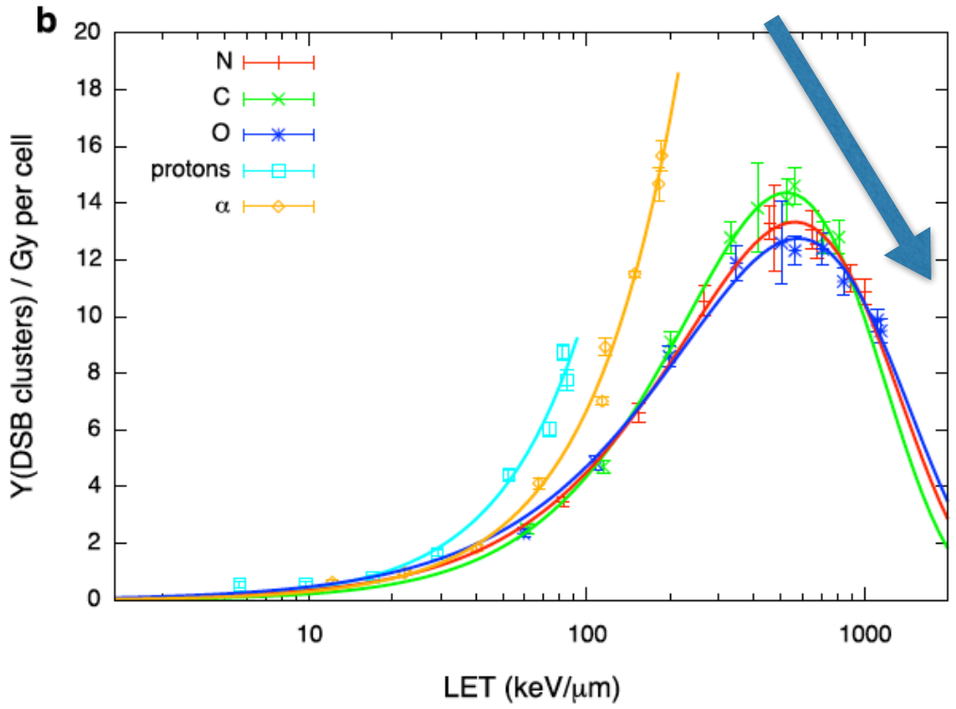
DSB cluster: complex lesion, 2 or more DNA DSBs within 25 bp

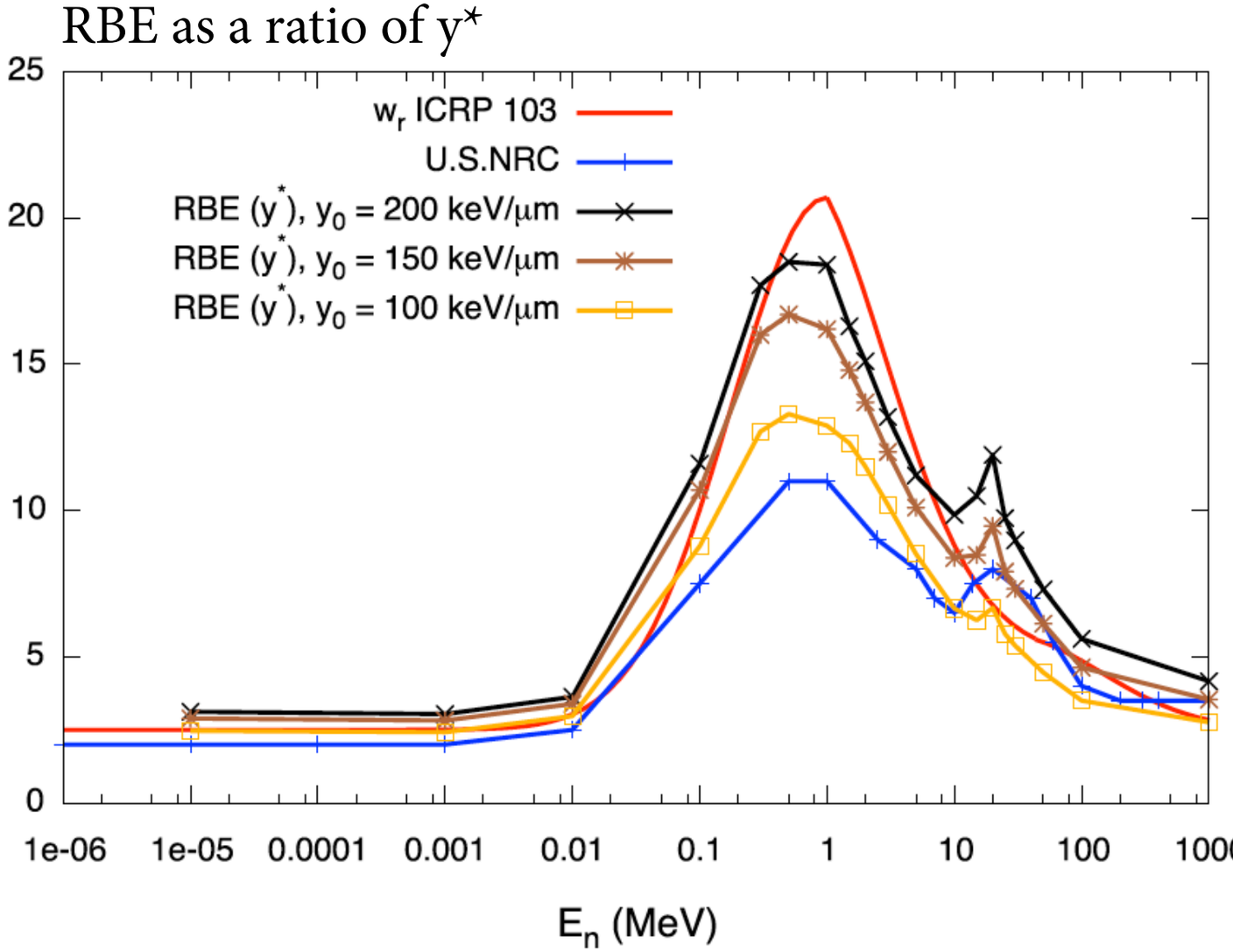


The biological effectiveness of a mixed field:
the neutron case "solved" with microdosimetry "only"

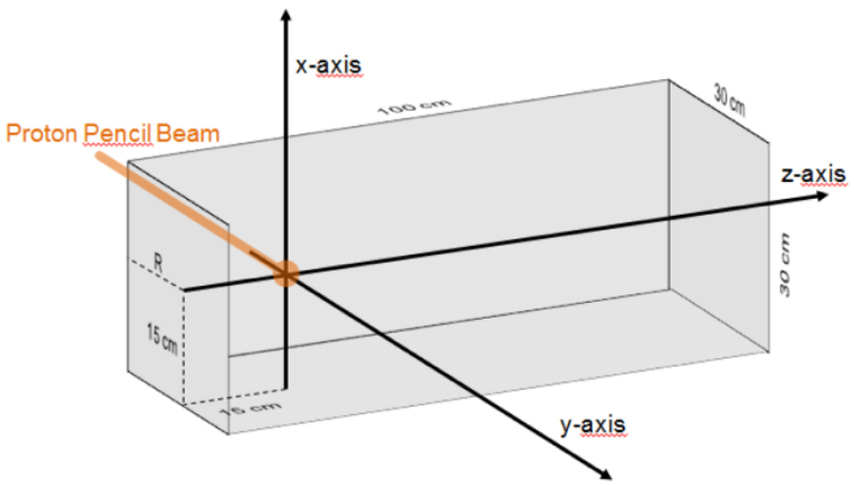
Saturation-corrected dose-mean lineal energy

$$y^* = \frac{y_0^2 \int_0^\infty \left\{1 - \exp\left[-(y/y_0)^2\right]\right\} f(y)\,dy}{\int_0^\infty y f(y)\,dy}$$





Application to treatment plans



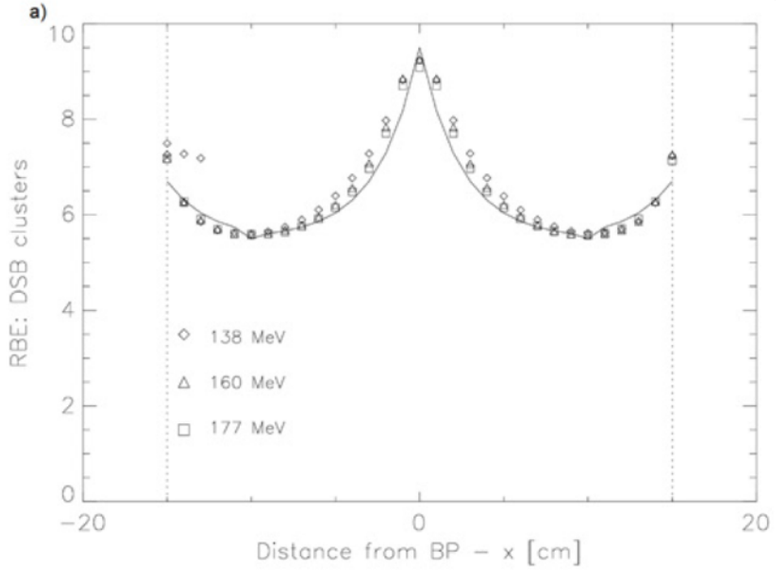
active scanning pencil proton beam @ PSI

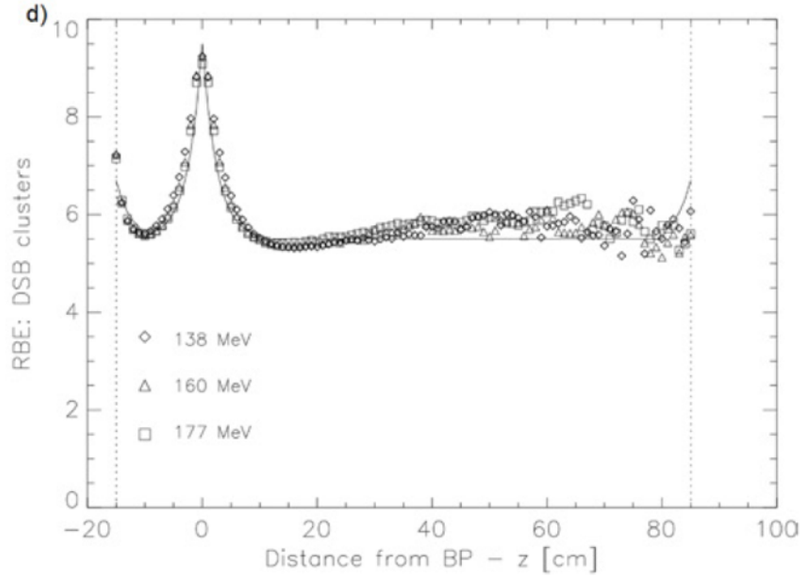
GEANT4 simulation, Gantry 1 @ PSI

voxelized water phantom

analytical parameterization of **dose, energy and secondary neutron RBE** varying beam energy

Predicted RBE for DSB cluster induction along x and z axes as a f. of distance from the Bragg peak





Neutrons in proton pencil beam scanning: parameterization of energy, quality factors and RBE Uwe Schneider[1,2], Roger A Hälg[1,2], Giorgio Baiocco[3] and Tony Lomax[4]

Phys. Med. Biol. **61** (2016) 6231–6242

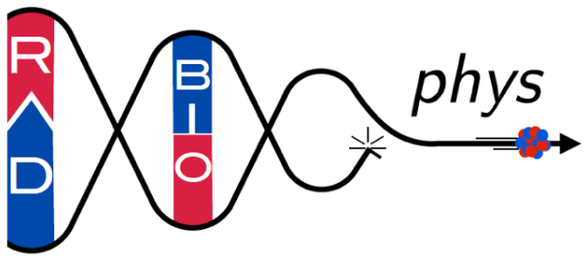
In summary

- **MICRO (and NANO)-dosimetric computational approaches** (with **full Monte Carlo simulations**) coupled to the **development of analytical formulas** (and/or large databases of results) have **great potential for applications**

- a simple methodology can be developed, by which **macroscopic radiation transport codes** can be **extended to predict biological effectiveness at the cellular/sub-cellular scale**

- **Biological effectiveness** (in absolute terms, as well as in terms of RBE) for **any mixed radiation field** can be obtained, *e.g.*:
  - the one generated by an ***ion beam in an oncological hadron therapy patient*** (including secondary ***neutrons***), thus supporting **therapy planning optimization;**
  - the one encountered by ***an astronaut in a deep-space mission***, thus contributing to **risk estimation for space radiation protection**

  …and the story is not over !



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Thanks for your attention