Multiscale approach to the physics of ion beam cancer therapy

Andrey Solov‘yov

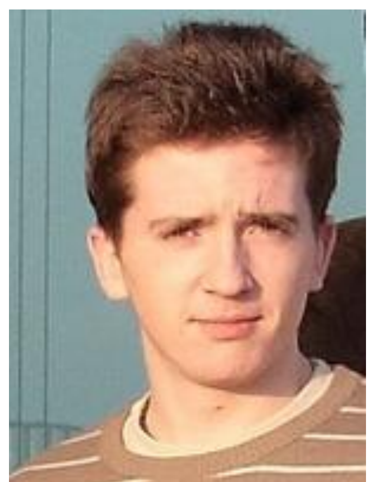
FIAS-EMMI Day, FIAS, Frankfurt am Main, Tuesday 11 January 2011

Acknowledgements

Research group:

Andrey V. Solov‘yov
Emanuele Scifoni
Andrey V Korol
Andiy Kostyuk
Adilah Hussein
Stephanie Lo
Maneesh Mathew
Veronika V. Dick
Dorin Poenaru
Alexander V. Yakubovich
Ilia A. Solov‘yov

Eugene Surdutovich
Oakland University, Rochester, MI, USA



Alexander V. Yakubovich

Emanuele Scifoni

Outline

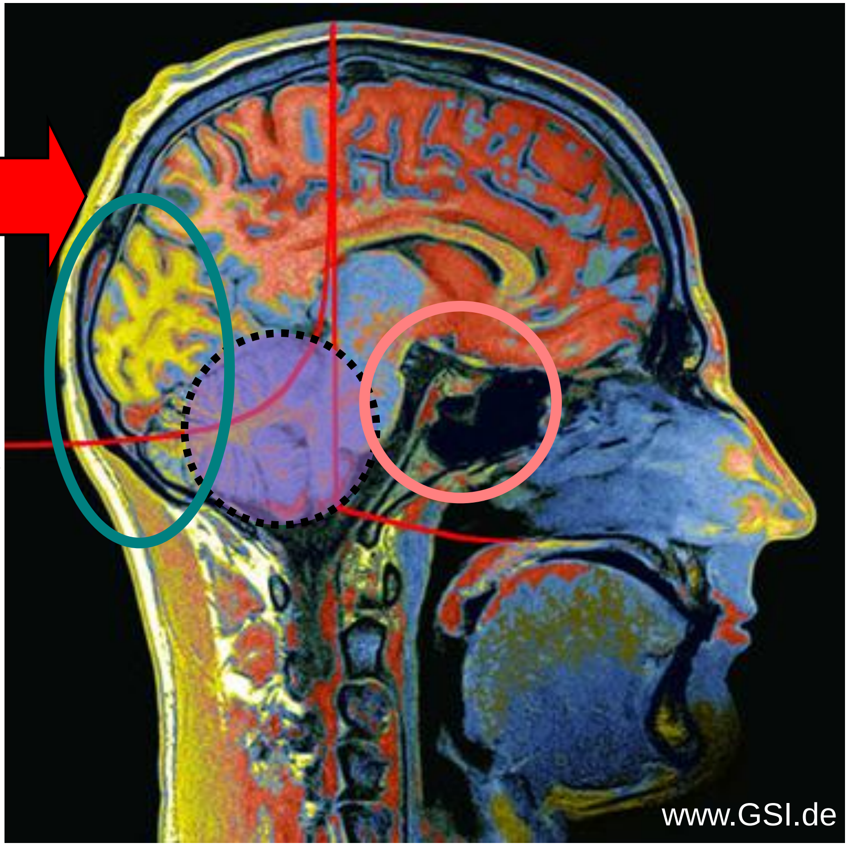
MesoBioNano Science

- Introduction to the problem of radiation biodamage by ions and ion-beam cancer therapy
- Multiscale approach: current status and perspectives
  - Propagation of ions
  - Primary ionization in the medium
  - Propagation of secondary electrons, holes and free radicals
  - Mechanisms of DNA degradation
  - Radiobiological scale effects
- Conclusions and outlook

Ion beam cancer therapy principles in brief

- Fundamental properties of propagation of charged particles: - dE/dx (LET) ~ Z_{eff}^2 /E
- Bragg peak in Linear Energy Transfer (LET) closer to the end of the ion's track
- Beams easily manipulated, better focusing

^{12}C beam



1992-2007

Technical development

Kraft et al. Rep.Mod.Phys. (2007)

Nov.2009 - now

Clinical treatment

www.hit-centrum.de

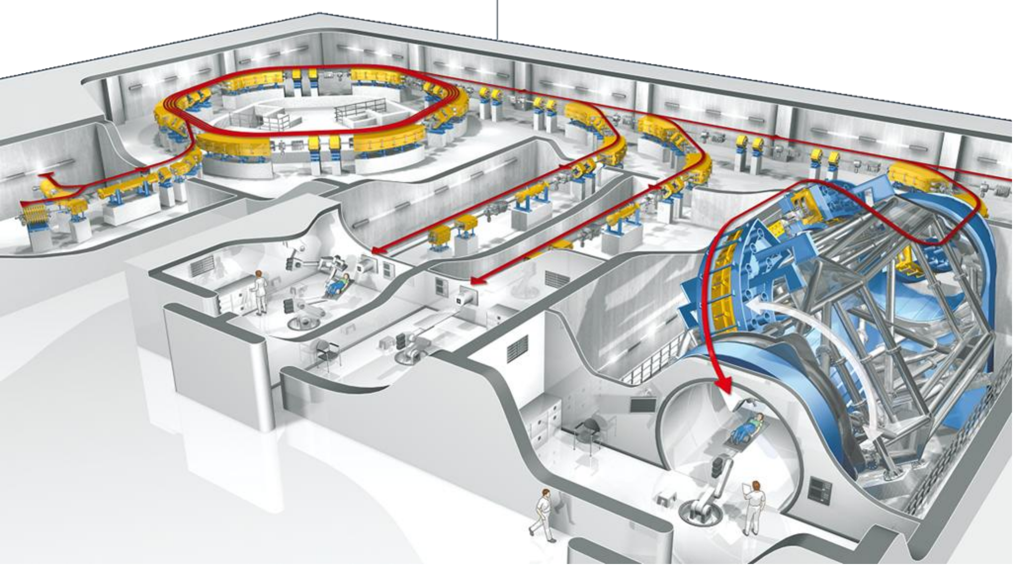
COST Action Nano-IBCT 2010- 2014

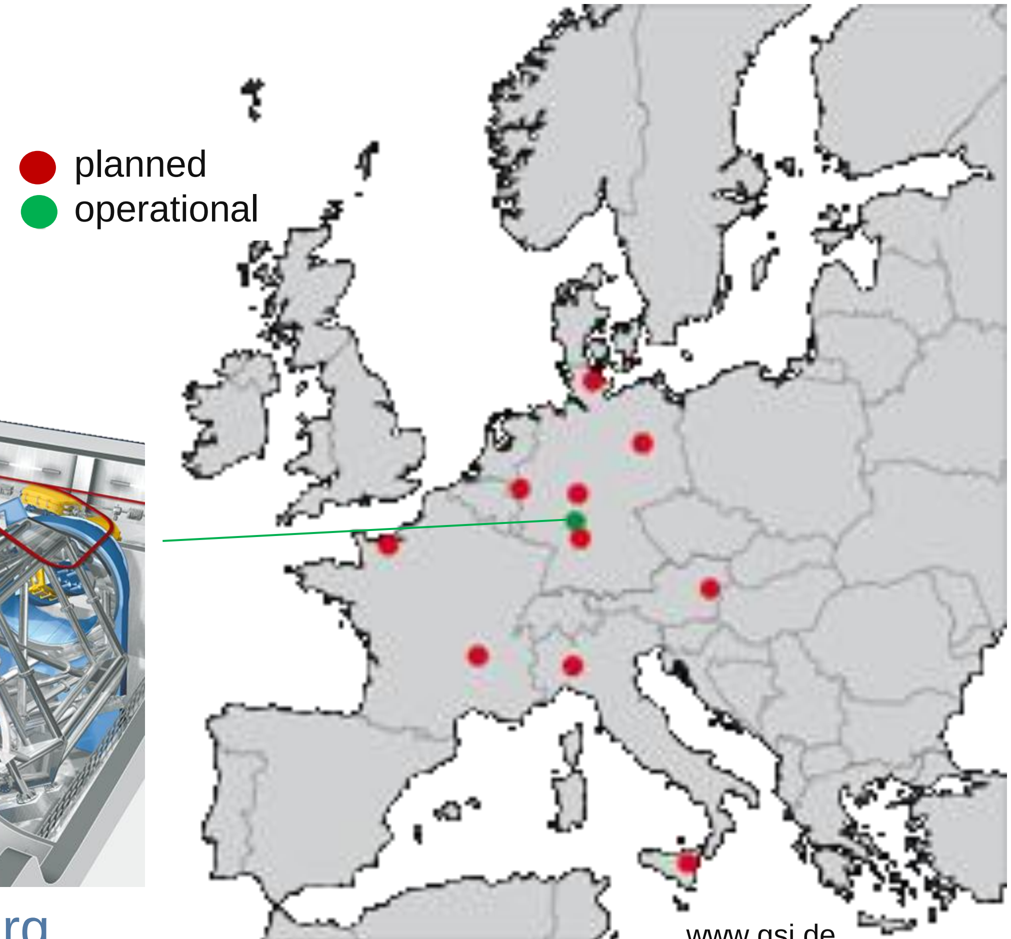
Nanoscale insights

E. Surdutovich, E. Scifoni, A.V. Solov'yov,
Mutation Research- Reviews, v.704, p.206-212 (2010)

Present and future of IBCT in Europe

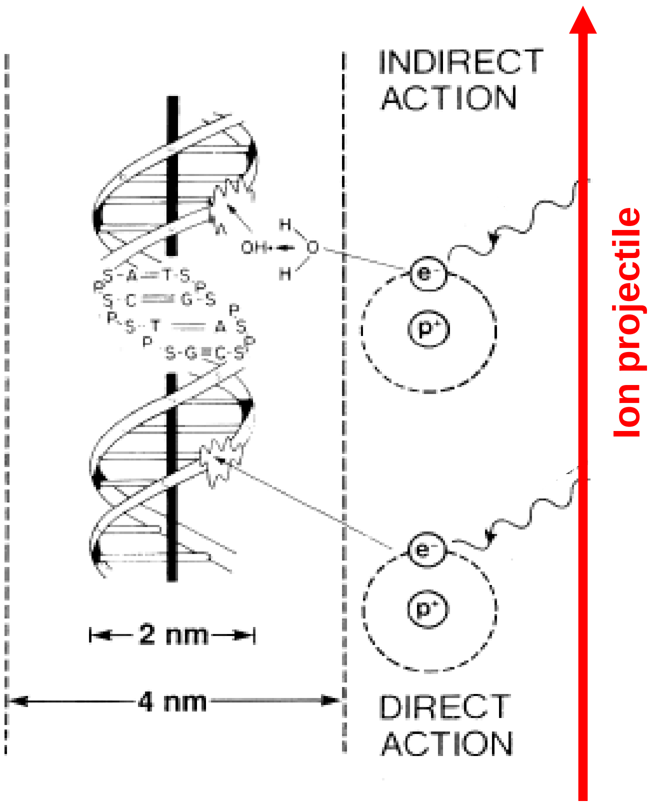
- Heidelberg operational from November 2009, using carbon ions
- 1300 patients to be treated per year …
- Full clinical integration
- Raster scanning world-wide first scanning ion gantry





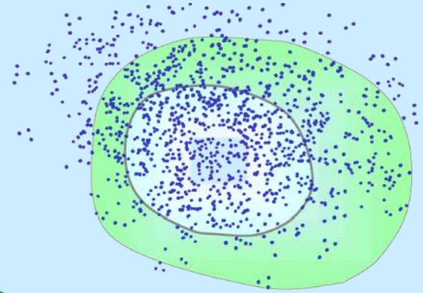
- In construction: Pavia, Kiel, Marburg, Lyon, Vienna, Catania, Maastricht…

Lack of understanding of molecular and nanoscale mechanisms of biodamage

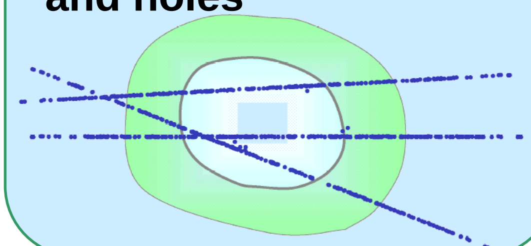


Single Strand Break - **SSB**
Double Strand Break - **DSB**

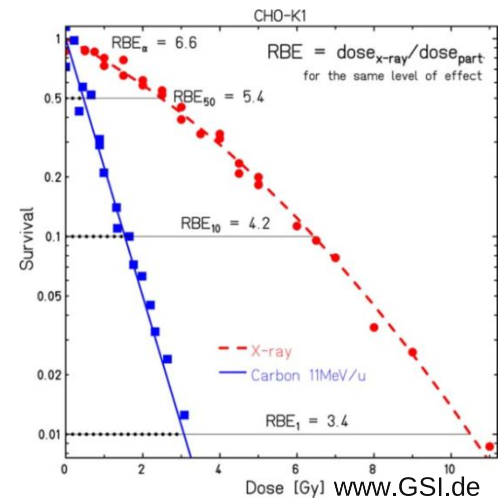
Low LET: indirect action **OH attack**



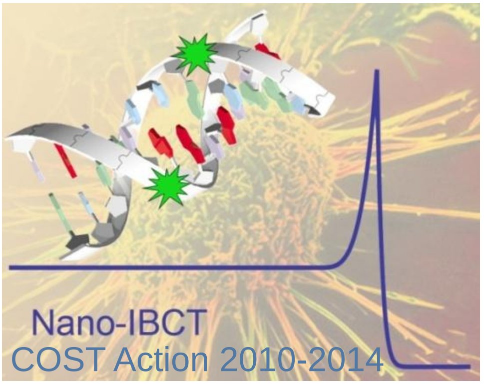
High LET: direct action **secondary electrons and holes**



Relative Biological Effectiveness (RBE): enhanced cell killing at the same dose



www.GSI.de



DSB's – the most pernicious DNA damage…

What processes on a microscopic level cause DSBs'?

Multiscale approach to the physics of ion beam cancer therapy

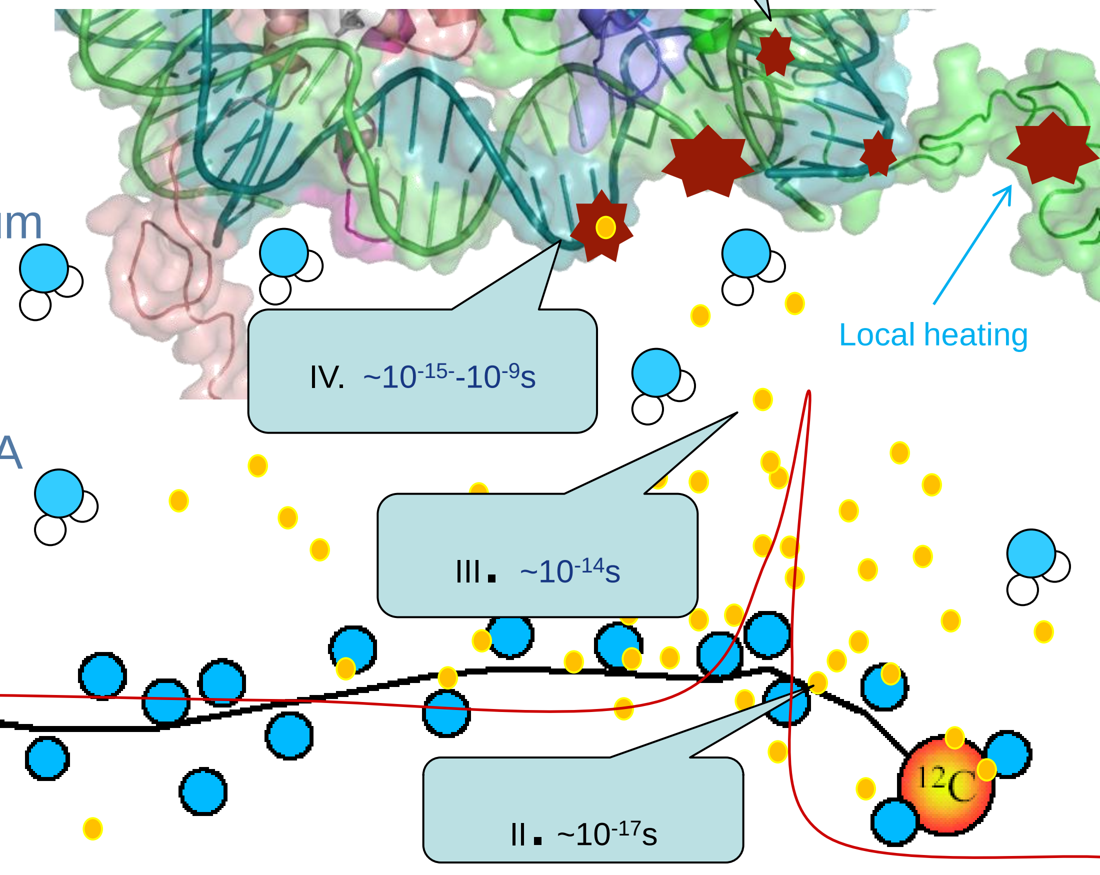
MesoBioNano Science

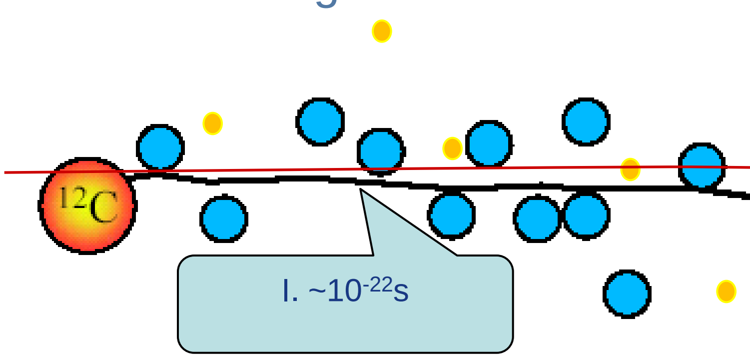
Elucidation of the key processes leading to biodamage on the nanoscale within a single physical scenario

E. Surdutovich , A.V. Solov'yov et al, Europhysics News (2009); Phys. Rev. E (2009), Mutation Research- Reviews (2010), European Physical Journal D , v.60, n.1 (2010)

Different STAGES:

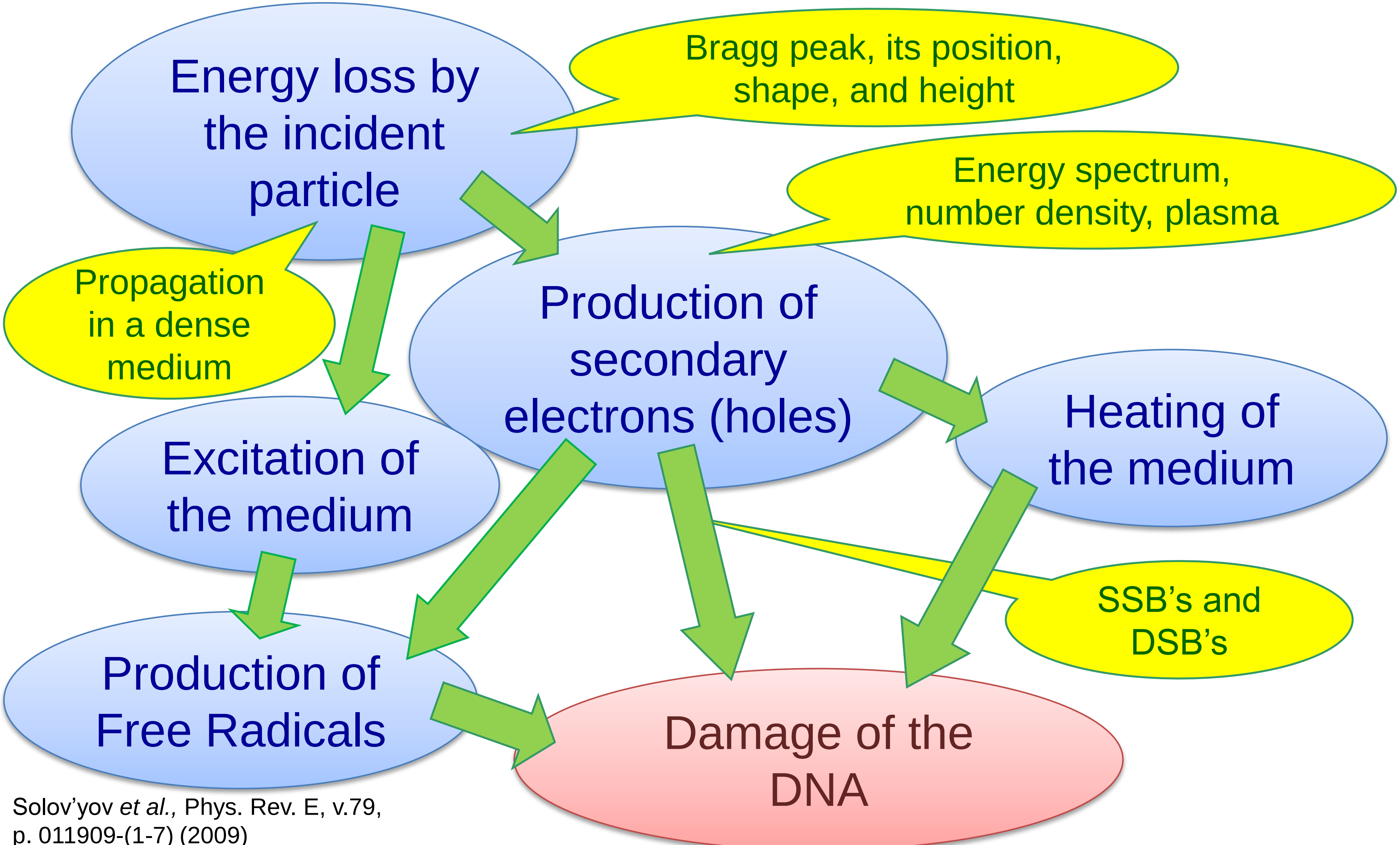
I. Propagation of ions
II. Primary ionization of the medium
III. Propagation of secondary electrons, holes and radicals
IV. Electron, hole, radical, thermo-mechanical degradation of DNA
V. Radiobiological scale effects





Multi-scale approach to DNA damage in ion-beam cancer therapy

MesoBioNano Science



Solov'yov *et al.*, Phys. Rev. E, v.79, p. 011909-(1-7) (2009)
Europhysicsnews, v.40, n.2, p.21-24 (2009)

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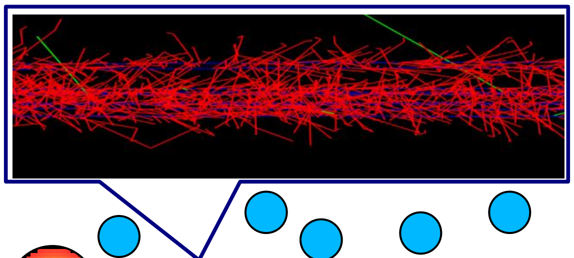
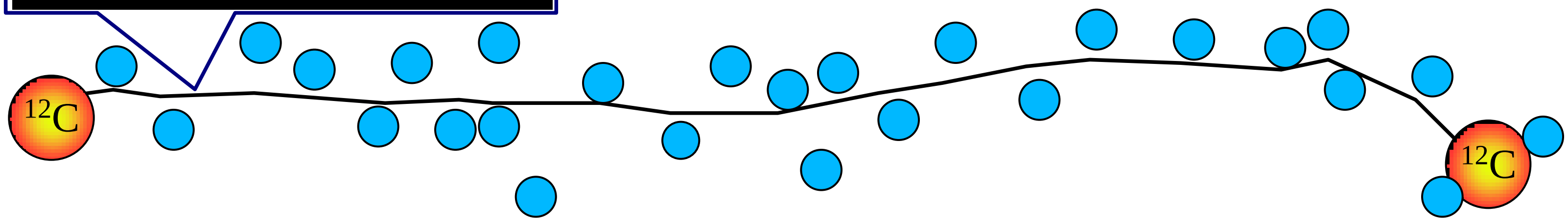
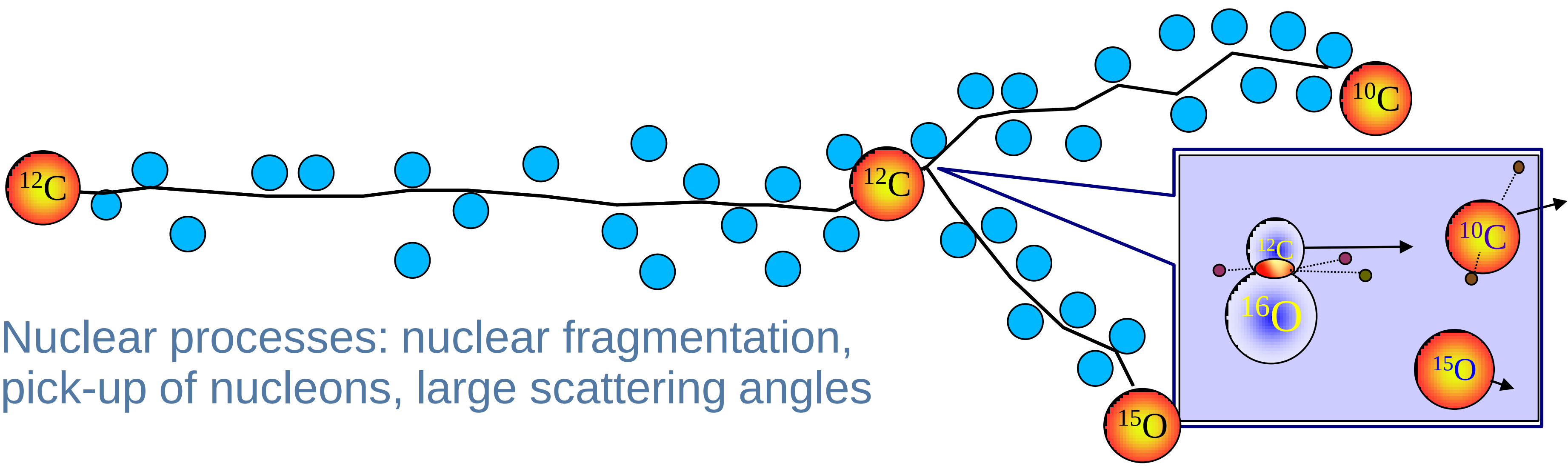
Transport of ions in target medium

$$-dE/dx \sim 1/\beta^2 \sim 1/E$$

Atomic processes: elastic scattering, scattering with excitation, ionization, multiple Coulomb scattering, small scattering angles





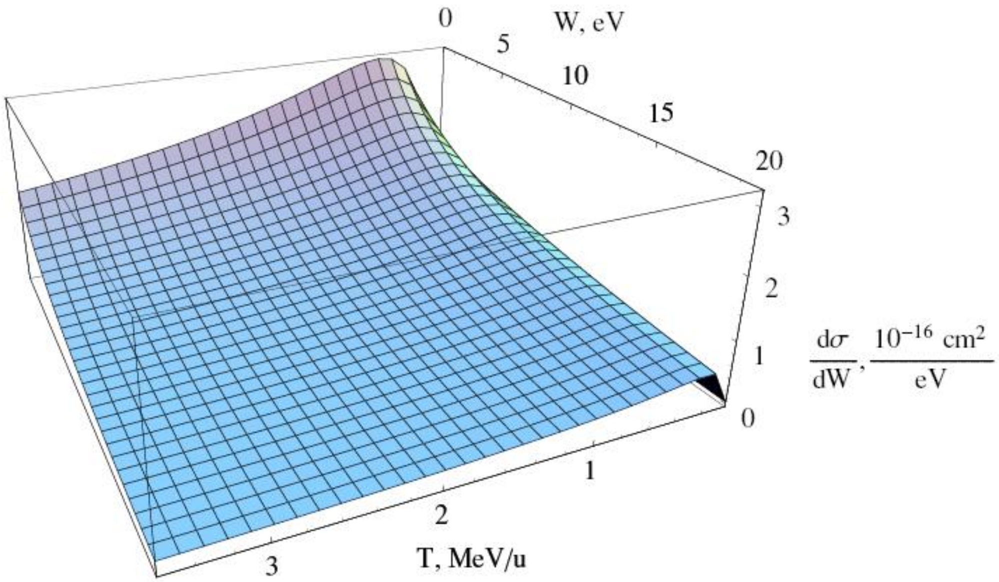


Nuclear processes: nuclear fragmentation, pick-up of nucleons, large scattering angles

Ion stopping in the medium

Ionization cross section (ICS) is the key quantity in modeling of ion energy loss and abundance of secondary electrons

I CS for water by A.V. Solov'yov et al NIMB 266,1623(2008); E. Surdutovich et al EPJD, v.51, p.63-71 (2009)



Rudd's semi-empirical model

$$\frac{d\sigma}{dW} = \sum_i \frac{N_i}{I_i^2} z^2 f\left(\frac{W}{I_i}, \sqrt{\frac{m}{M}\frac{T}{I_i}}\right)$$

M.E. Rudd et al. Rev. of Mod. Phys., 64, 1992

Beyond Rudd's semi-empirical model

- Relativistic effects (γ up to 1.5) – relativization of the Rudd model

$$v^2 \to c^2\beta^2; \ \ln\left(1+v^2\right) \to \ln\left(\frac{1+v^2}{1-\beta^2}\right) - \beta^2$$

Correct asymptote with relativistic Bethe-Bloch formula for energy loss;
Surdutovich, Scifoni, Solov'yov et al. EPJD , v.51, p.63-71 (2009)

Critical for the position of the Bragg peak

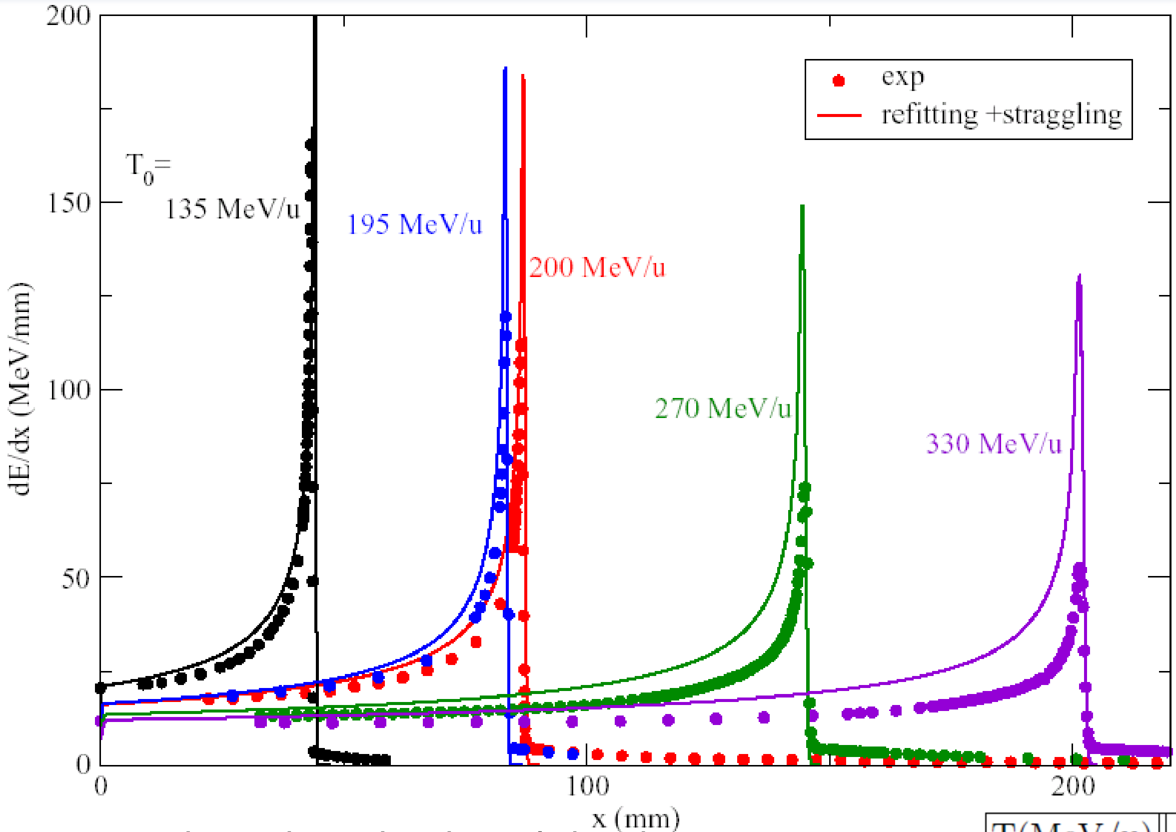
- Charge transfer

$$z_{eff} = z(1 - \exp(-125\beta z^{-2/3}))$$

Barkas H.W., 1963

Critical for the correct height of the Bragg peak

Tuning on the Bragg Peak for carbon ions



Experiment by Schardt et al. (GSI) 2000

Good agreement with experimental positions of Bragg peak for a large range of initial energies T_0

$$\sigma_{str}(x_0) = 0.012 x_0^{0.951} / \sqrt{A}$$

x_0= *max penetration depth*
A=ion mass

Deviation<0.5mm, i.e. within therapeutic tolerance

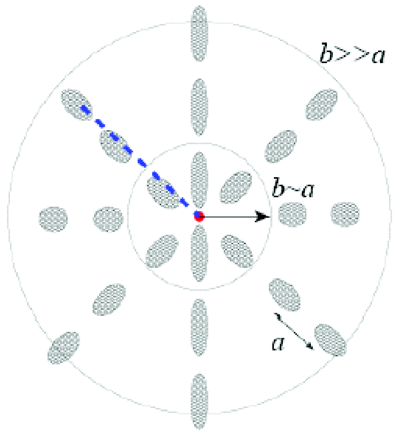
E.Scifoni, E.Surdutovich, A.V. Solov'yov *PRE, v.81, p.021903-(1-7) (2010)*

T(MeV/u)	Bragg peak position (mm)			
	us (single ion)	us (straggling)	Schardt	MCHIT
400	275.75	275.01	274.72	274.53
330	201.81	201.30	201.42	200.52
270	144.78	144.42	144.82	143.78
200	87.19	86.94	86.46	86.90
195	83.49	83.26	83.39	
135	44.20	44.05	43.34	43.73

Liquid water: ionization in the medium

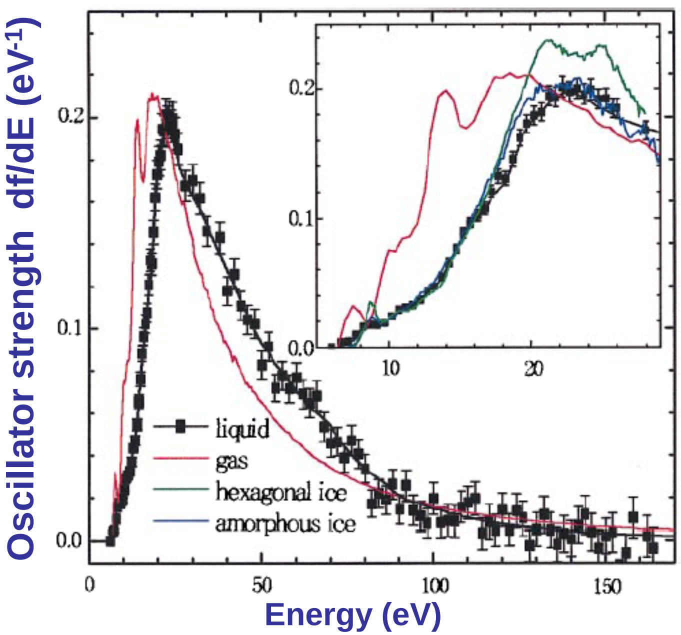
MesoBioNano Science

- Polarization and screening of the medium become important for **distant** collisions, with a net effect of suppression of these ionizations



- Optical experiments may provide a key quantity: the **generalized oscillator strength** *df/dE(E,q) at q→0,* the co-called optical limit

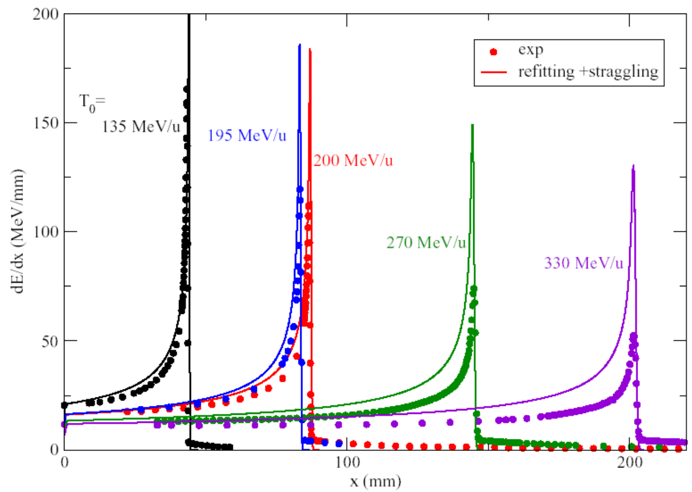
X ray water spectrum
Hayashi,Watanabe 2000



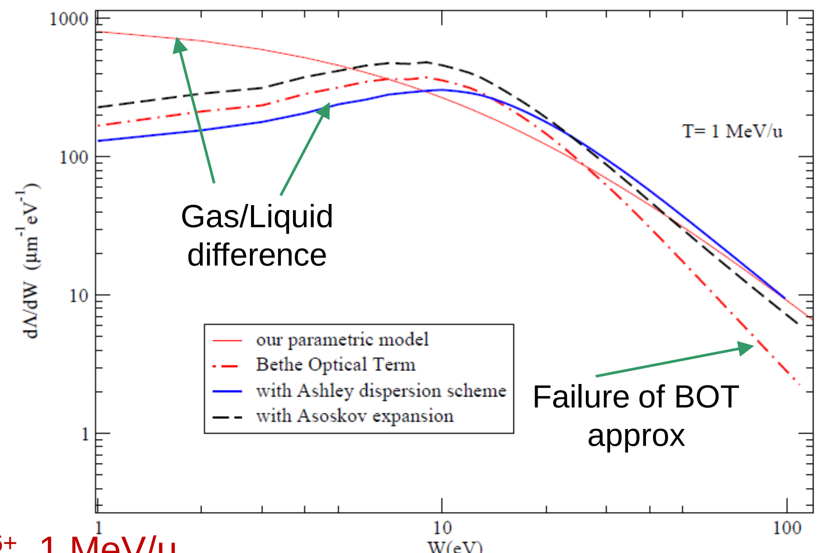
- Description of the collision process depends on the energy range of the projectile:
  - » Fast ions T>0.2 MeV/u, Born approx. (BA) is valid
  - » Slow ions T<0.2 MeV/u, BA not fully valid

Secondary electrons production in liquid H_2O

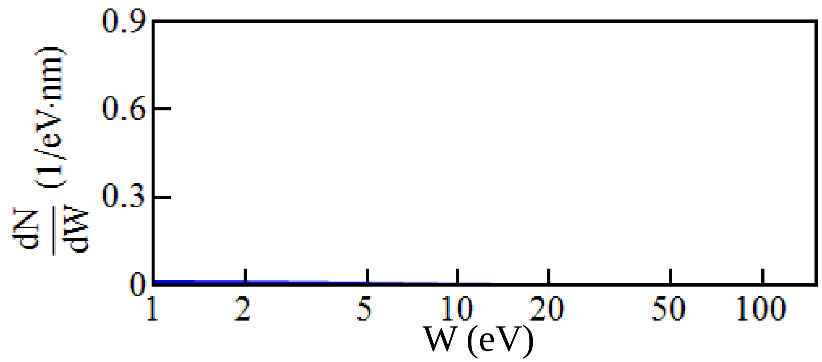
MesoBioNano Science

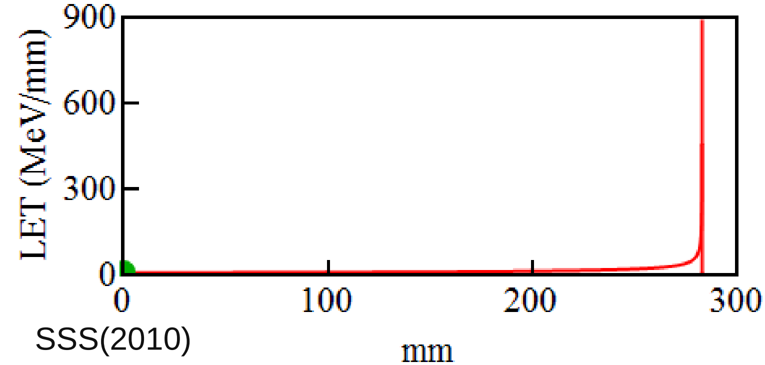


Scifoni, Surdutovich, Solov'yov *PRE,v.81, p.021903-(1-7) (2010);*
A.V. Solov'yov et al., NIMB 266,1623(2008)



C^{6+}, 1 MeV/u





SSS(2010)

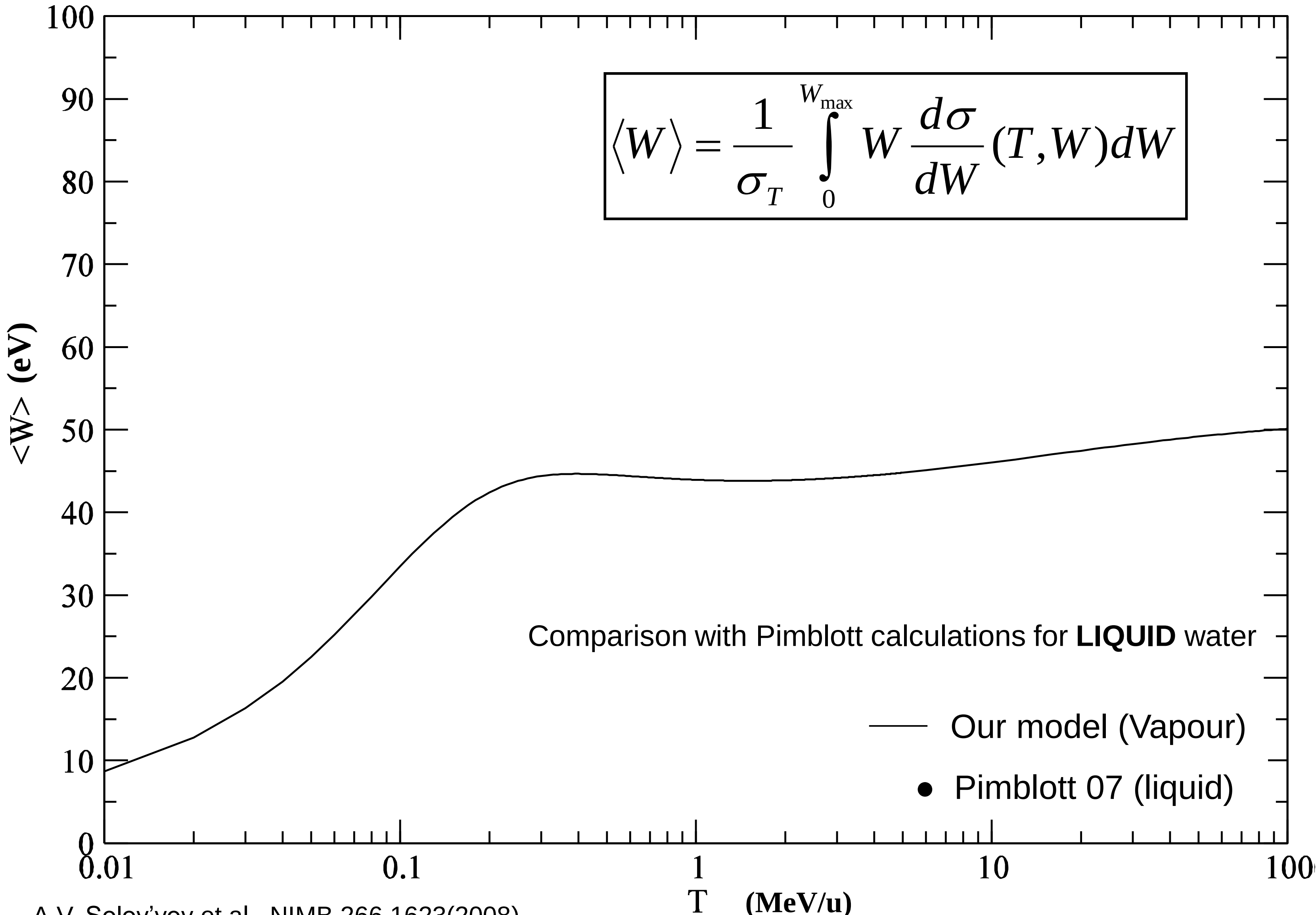
Parametric model

$$\frac{dN}{dW} = n z_{eff}^2(T)\sum_i f\left(\frac{W}{I_i},\frac{T}{I_i}\right)$$

Dielectric function approach

$$\frac{dN}{dW} = \frac{z_{eff}^2(T)}{\pi a_0 T}\int_{k_{min}}^{k_{max}} \eta_2(E,k)\frac{dk}{k} \; .$$

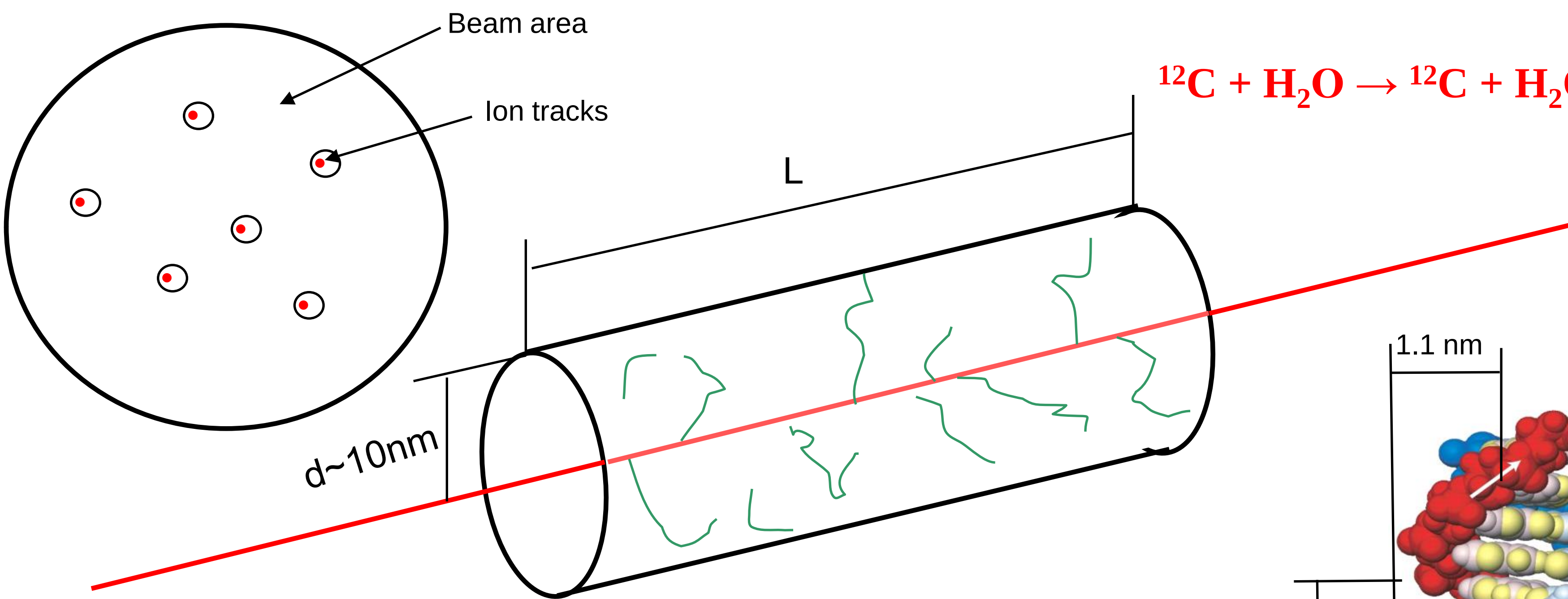
Average energy of secondary electrons

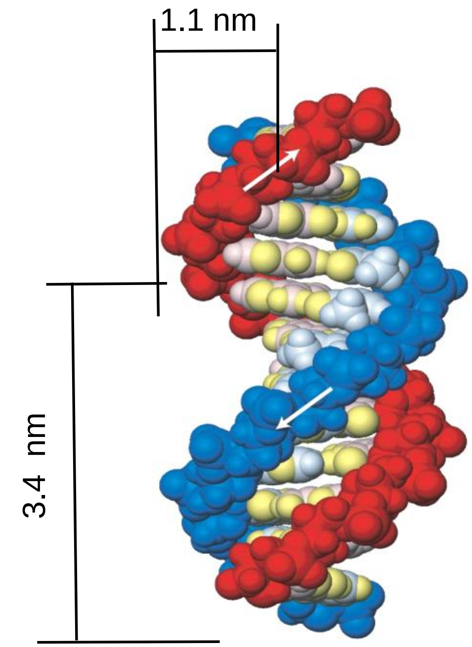


A.V. Solov'yov et al., NIMB 266,1623(2008)

Electron plasma along a heavy ion track

$$^{12}C + H_2O \rightarrow {}^{12}C + H_2O^+ + e^-$$





$$\sigma_T\left(0.1\ \mathrm{MeV}\right) \approx 0.4\mathrm{nm}^2$$

$$n_{water} = 33.4\mathrm{nm}^{-3}$$

$$\text{Number of } e^- / \mathrm{nm} = n_{water}\sigma_T \approx 13/\mathrm{nm}$$

$$e^-\text{plasma density} \approx 13/\pi d^2 = 0.04\mathrm{nm}^{-3} = 4\times10^{19}\mathrm{cm}^{-3}$$

$$\text{Number of } e^- / \text{DNA conv.} = V_{\text{DNA conv}} n_{e^-} = 0.5$$

$$V_{\text{DNA conv}} = 13\mathrm{nm}^3$$

E. Surdutovich, O. I. Obolensky, E. Scifoni, I. Pshenichnov, I. Mishustin, A. V. Solov'yov and W. Greiner, EPJD , v.51, p.63-71 (2009)

Targeting DNA with secondary electrons

MesoBioNano Science

$$N_{SSB} = \Gamma_{SSB}(W)\sum_{k}\int d\zeta\, d\vec{A}\cdot D\nabla\left[P\left(k,\ |\vec{r}|\right)\varepsilon\left(k,\ W\right)\frac{dN(\zeta,W)}{d\zeta}\right]$$

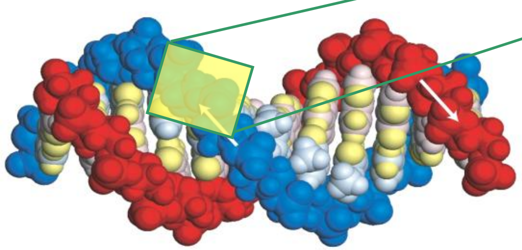
Probability of SSB by e$^-$ with energy W

Element of the DNA's surface

Probability of random walk @ ***r***

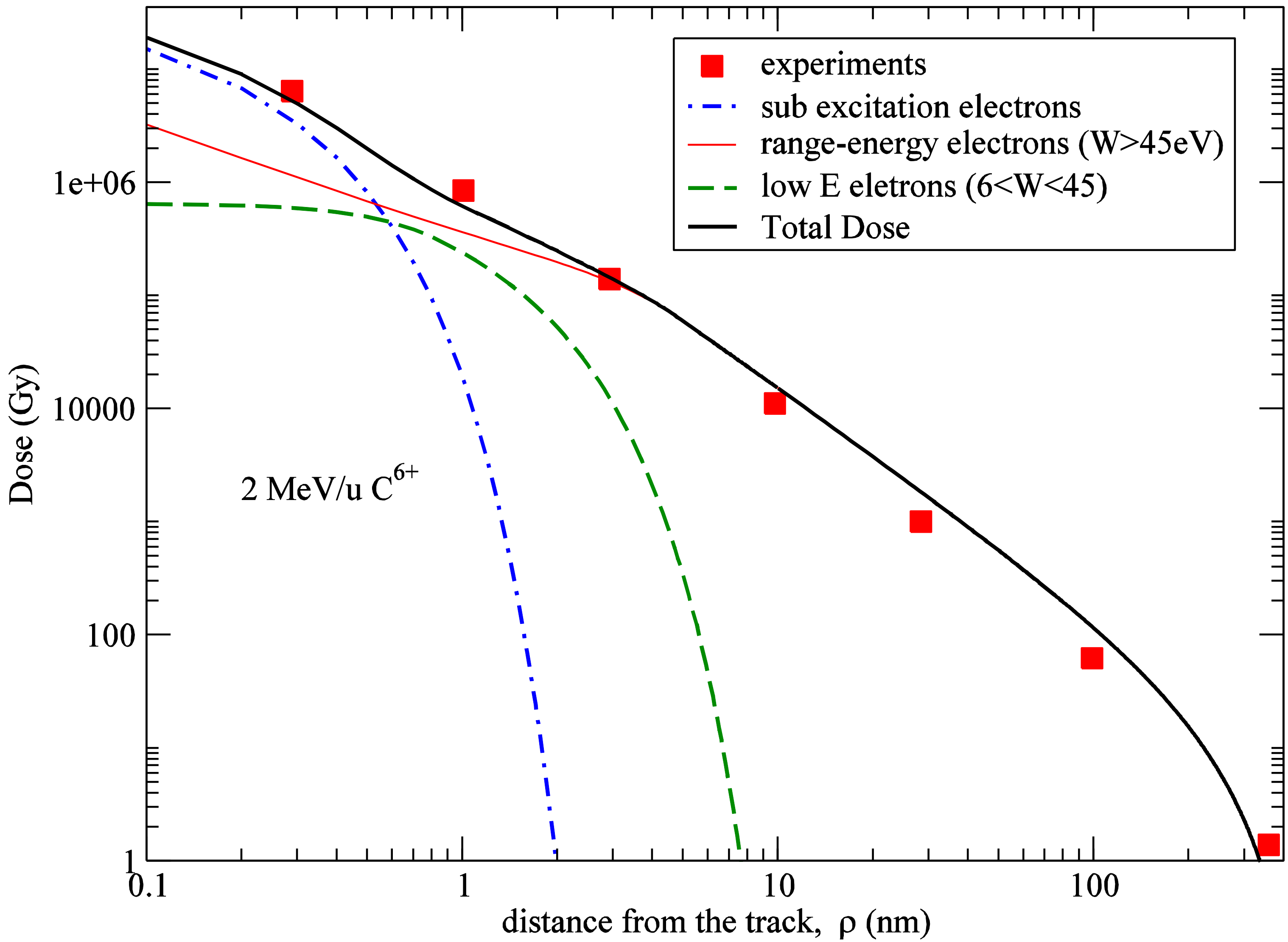
Attenuation due to inelastic collisions

Number of secondary electrons with kinetic energy *W* produced at a given segment of projectile's trajectory



Solov'yov *et al.*, Phys. Rev. E, v.79, p. 011909-(1-7) (2009)

Radial Dose



E. Scifoni , A.V. Solov'yov, E. Surdutovich, EPJD, v.60, p.115–119 (2010)

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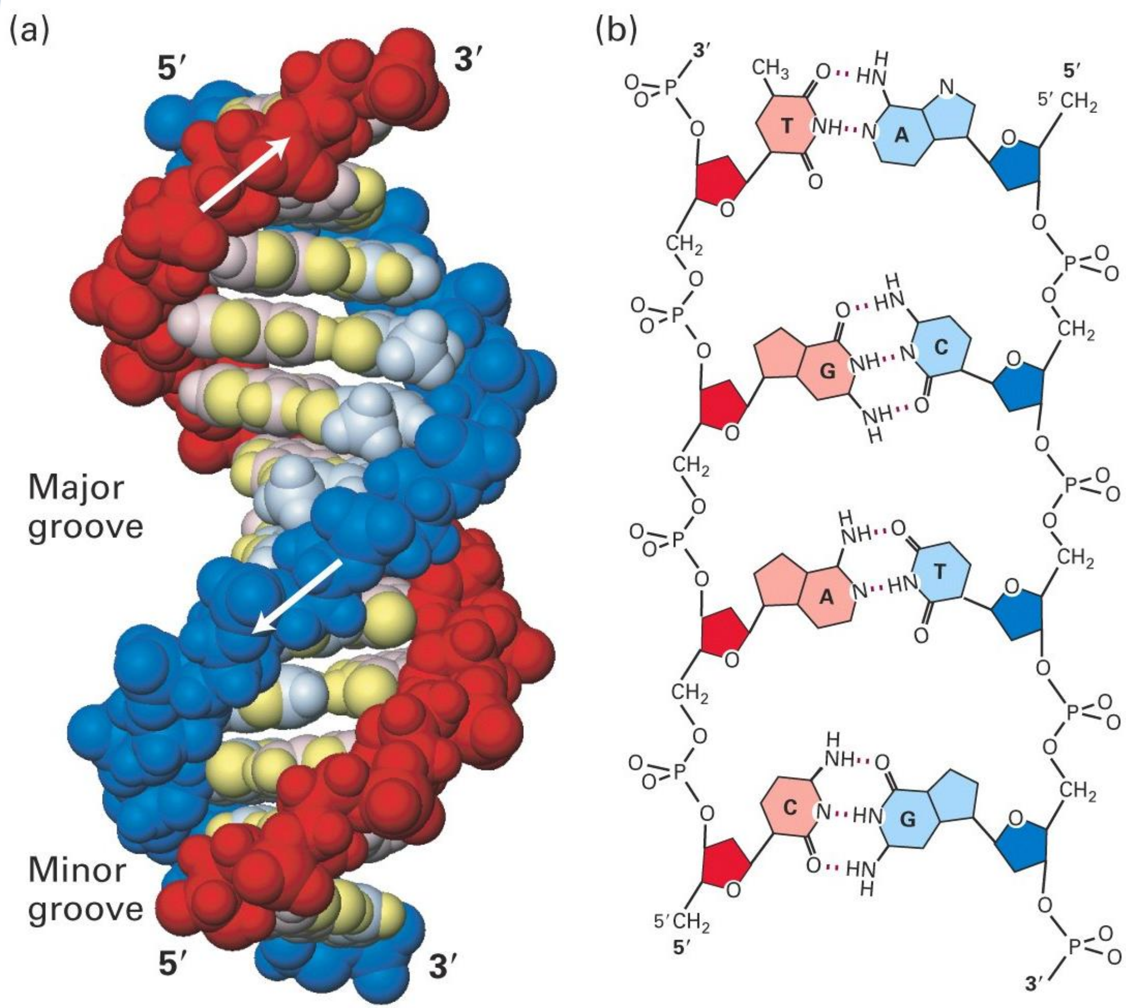
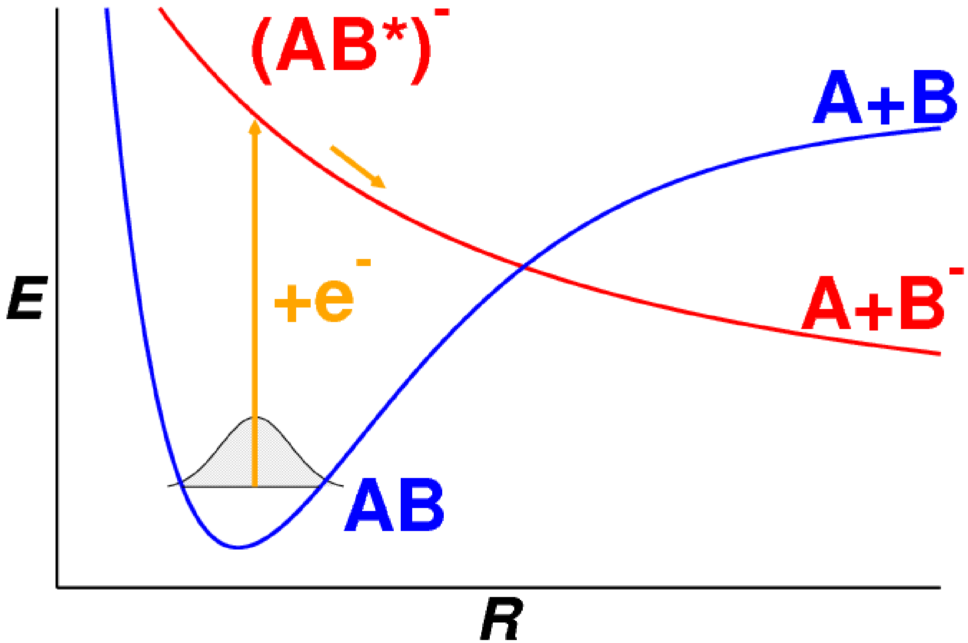
DNA structure

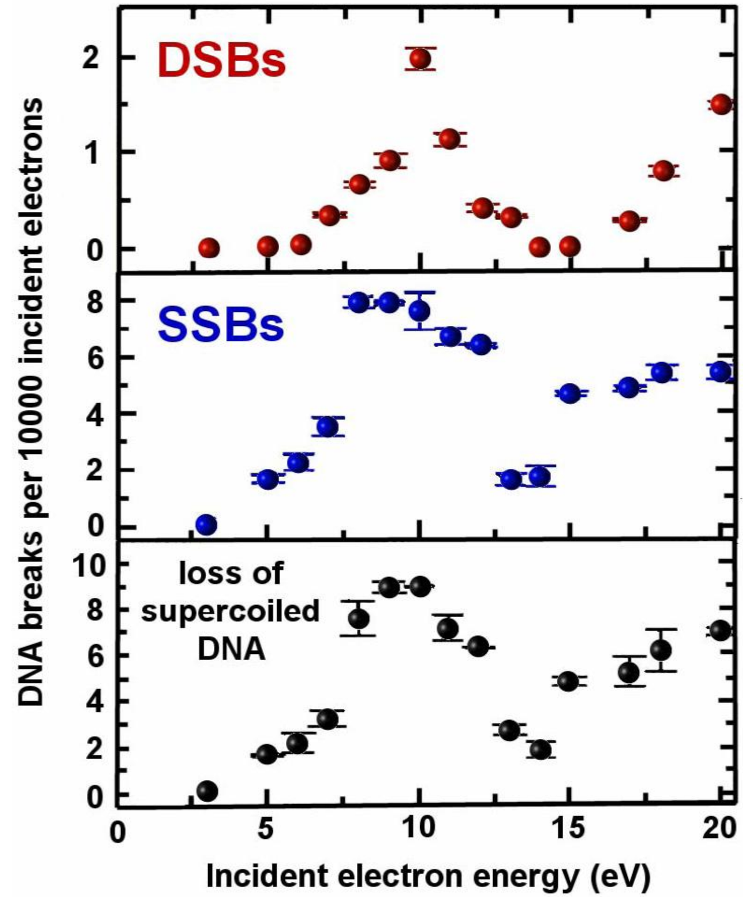


DNA’s backbone is made of sugars and phosphate groups joined by ester bonds. Attached to each sugar is one of four types of molecules called bases. Each type of base on one strand forms a bond with just one type of base on the other strand. This is called complementary base pairing. A bonds only to T, and C bonds only to G.

Low energy dissociative electron attachment



$$AB + e^- \rightarrow (AB^*)^- \rightarrow A + B^-$$



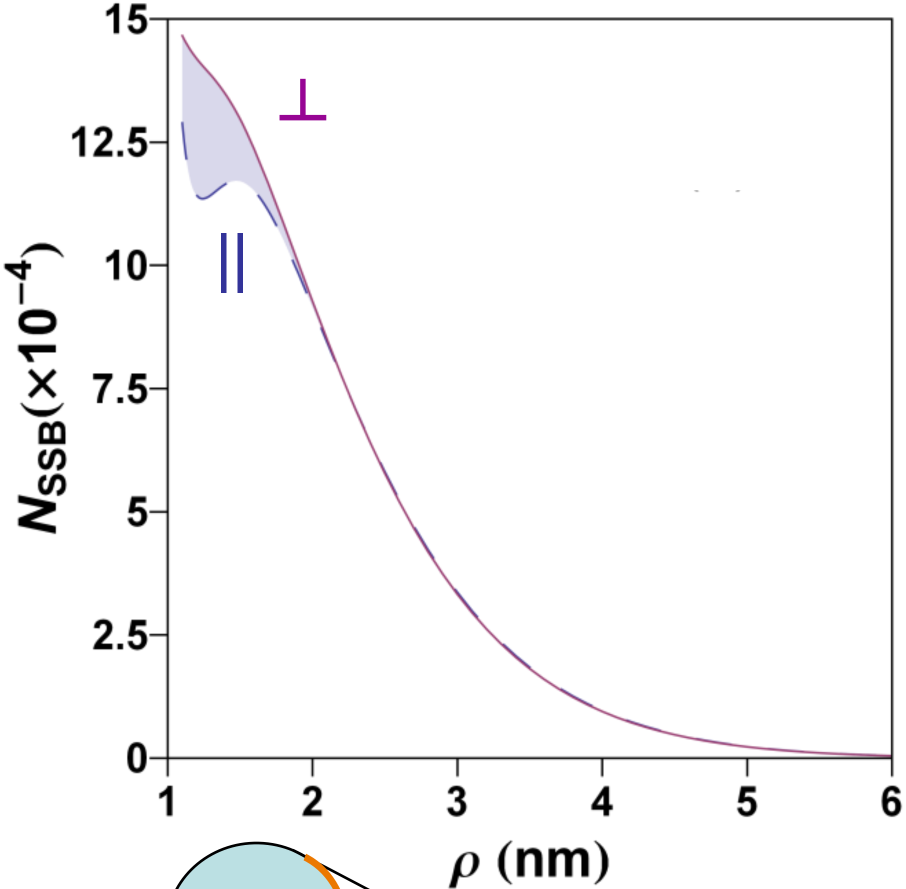
Many experiments (**Sanche**) and quantum calculations on the selected DNA components (**Gianturco, Greene**) confirm the presence of these resonances at low energy.

The resonant mechanism has **comparable** effect to higher energy mechanism

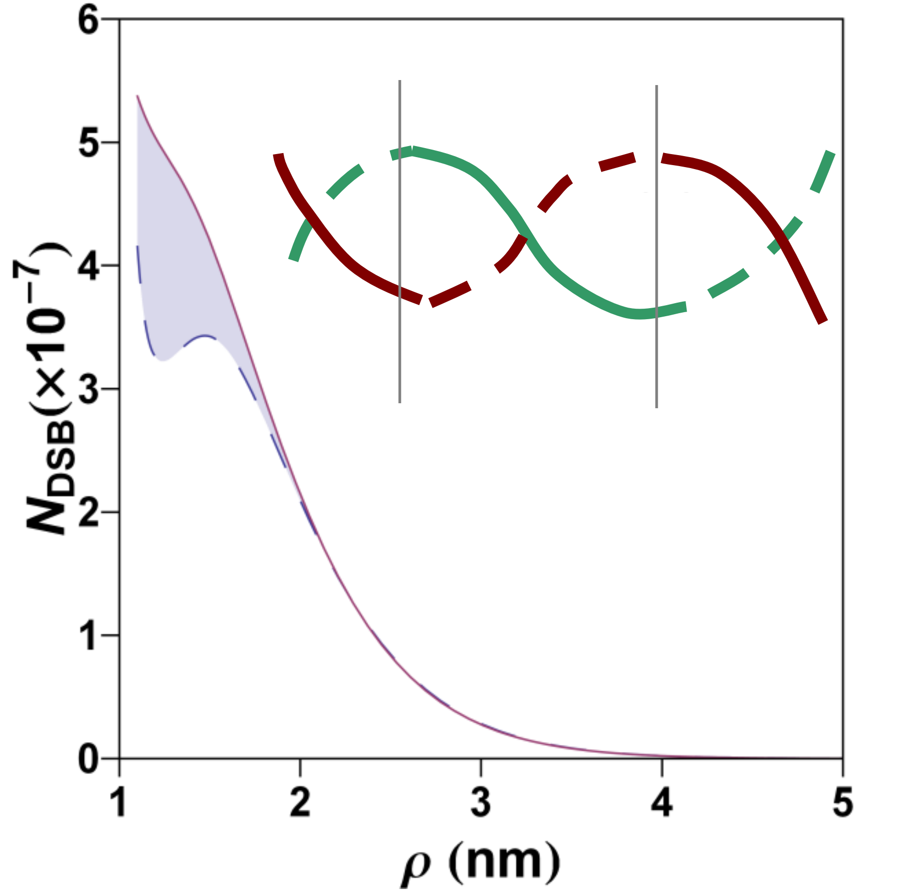
M.A. Huels, B. Bouda¨ıffa, P. Cloutier, D. Hunting, L. Sanche, J. Am. Chem. Soc. 125, 4467 (2003)

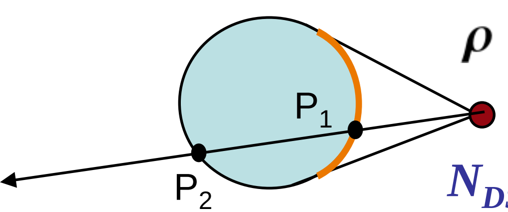
DNA double strand breaks

Overall SSB



Overall DSB's due to separate e⁻

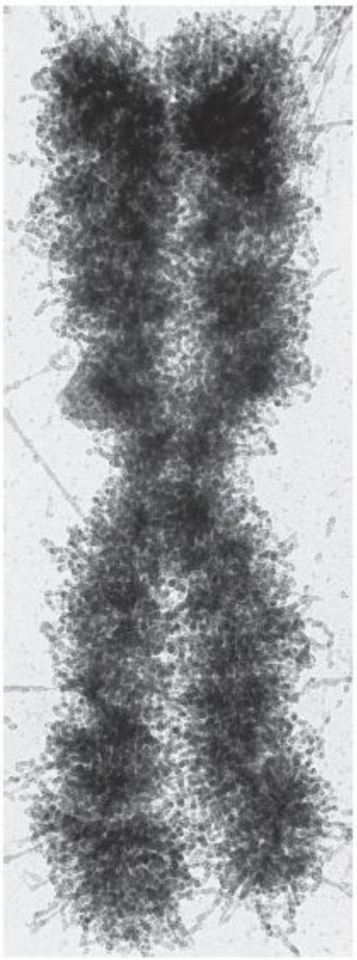


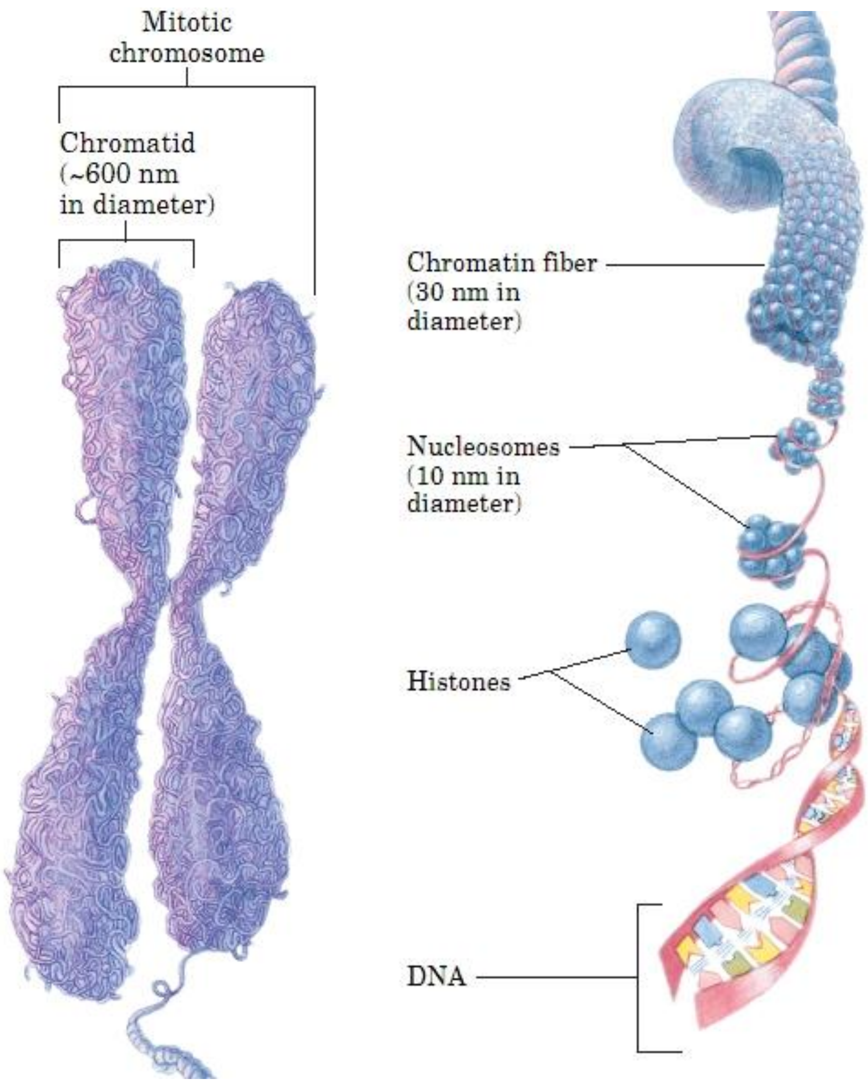


$$N_{DSB} = \frac{1}{4}(N^2_{SSB,face} + N^2_{SSB,back}) + \frac{1}{2}N_{SSB,face}N_{SSB,back}$$

Solov'yov *et al.*, Phys. Rev. E, v.79, p. 011909-(1-7) (2009)

Generalization for macromolecular targets: packing in histons, chromatid and chromosome





Averaging over orientations of a decamer all along the chain by introducing a distribution function for decamer orientations

Preliminary estimates on cell damage

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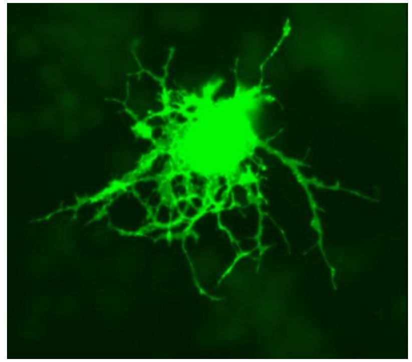
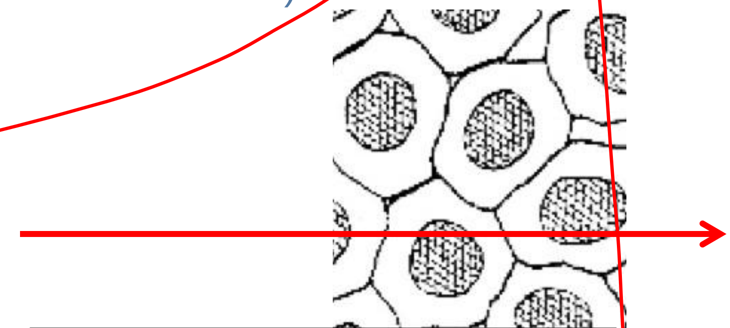
An example:
Glial cells comprise 90% of brain cells



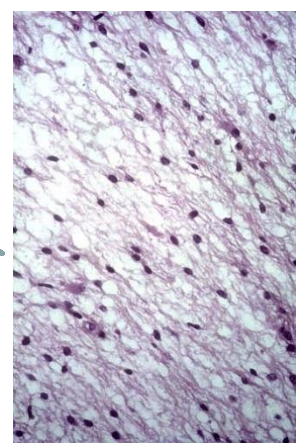
How many cells may be affected by a single ion near Bragg peak?

The Bragg peak width of a single **C-**ion, *d*=1mm
(LET>100 MeV/mm)



$$N_{cells} \approx n_{cells}^{1/3} d = 75$$

With how many nuclei will this ion interact ?

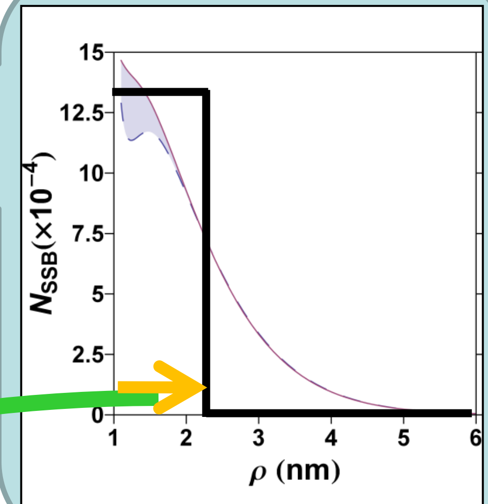


$$N_{nucl} \approx \frac{\sigma_n}{\sigma_c} N_{cell} = 12$$

Solov'yov *et al.*, Phys. Rev. E, v.79, p. 011909-(1-7) (2009)

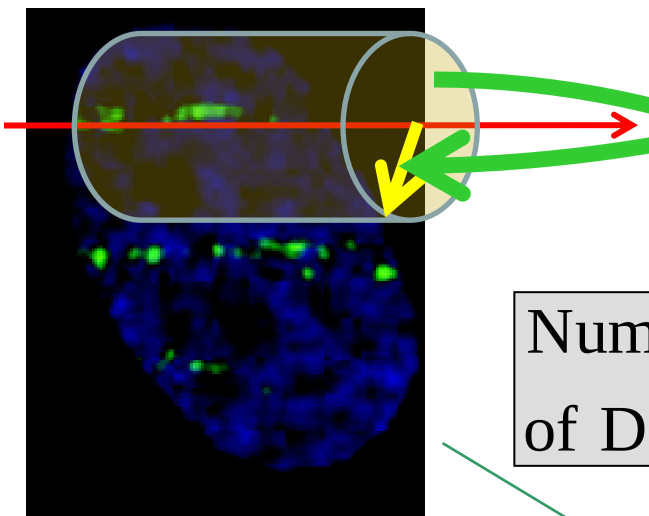
Number of DSB's per nucleus

1. Probability of a DSB vs. distance between the track and a convolution
2. Account for larger ionization cross sections inside the nucleus
3. Distribution of convolutions: uniform inside the nucleus for cells in interphase



$$n_{conv} \approx 4.3\times10^{6}\,\mu m^{-3}$$

Solov'yov *et al.*, Phys. Rev. E, (2008)



$$\text{Number of DSB's} = \bigcirc \times P_{DSB} \times n_{conv} \approx 3.5\,\mu m^{-1} \approx 18 \text{ per nucleus}$$

No experiments for glial cells; for **human fibroblasts, GSI** reports **2.6** DSBs/μm

Jakob, Splinter and Taucher-Scholz., Rad. Res. **171**, 405 (2009).

Heat transfer from the ion track: thermal spike model

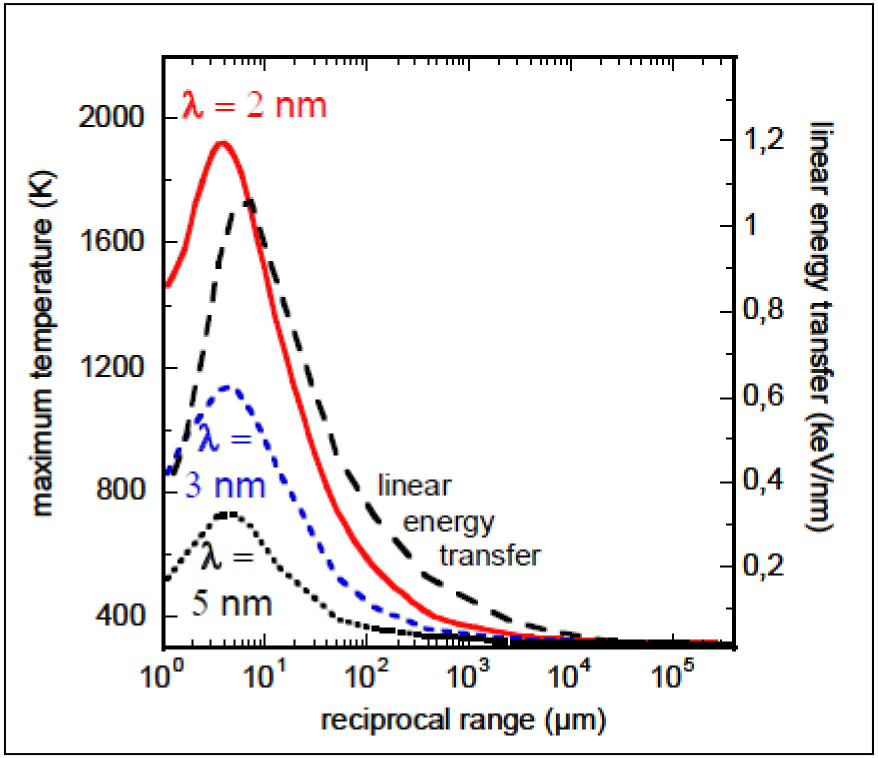
MesoBioNano Science

Coupled thermal conductivity equations for electron and lattice components

$$C_e \frac{\partial T_e}{\partial t} = \nabla \cdot (K_e \nabla T_e) - g(T_e - T) + B(r,t)$$

$$\rho C \frac{\partial T}{\partial t} = \nabla \cdot (K \nabla T) + g(T_e - T)$$

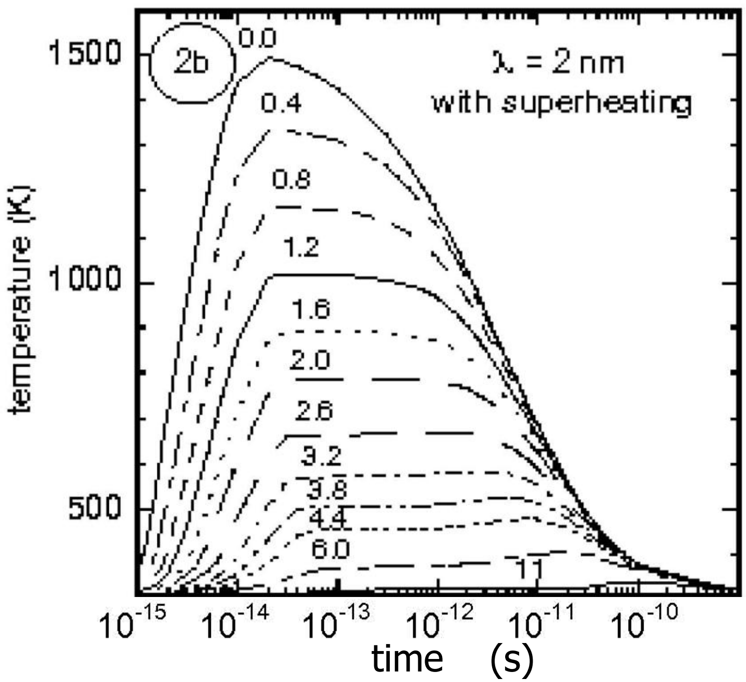
- *B(r, t)* is the energy density supplied by the incident ion to the electronic system by ballistic collisions at a distance *r* from the track at time *t.*
- *g* – electron-phonon coupling
- λ –electron-phonon mean free path



M. Toulemonde, E. Surdutovich and A.V. Solov‘yov , Phys. Rev.E, v.80, p. 031913 (2009).

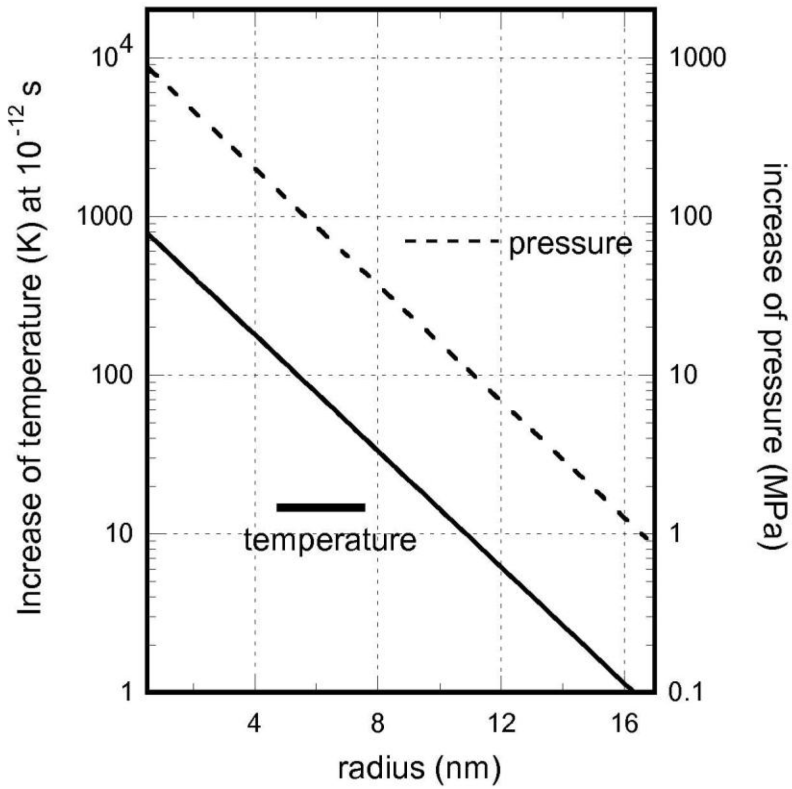
Thermal and pressure spikes: mechanical mechanism of DNA damage?

MesoBioNano Science



Temperature dependence on time in the vicinity of Bragg peak for C ions at different distances from the ion track

Temperature and pressure vs. distance from the ion track

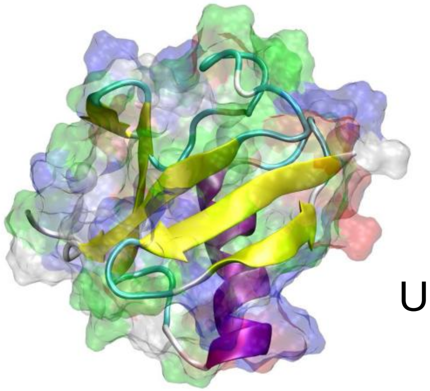


Estimated forces acting on sections of DNA are over 100 pN.

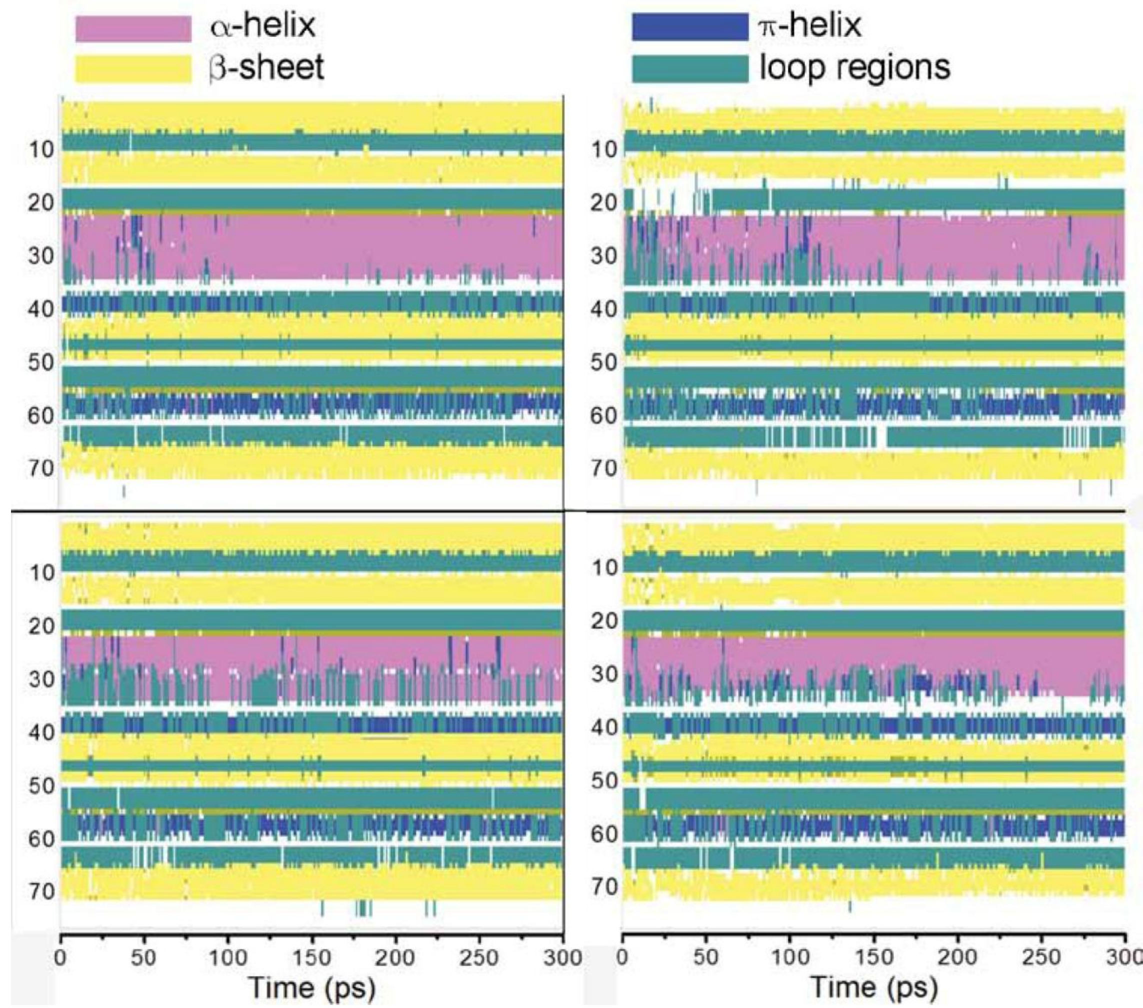
Can this cause strand breaks?

M. Toulemonde, E. Surdutovich and A.V. Solov'yov , Phys. Rev.E, v.80, p. 031913 (2009).

Effects of thermal spikes on biomolecules



Ubiquitin



- Explore molecular dynamics at the conditions of a thermal spike
- Explore effects of the corresponding temperature and pressure dependences on biomolecules and other molecules
- Consider the consequences of residual temperature increase

E. Surdutovich, A.V. Yakubovich and A.V. Solov'yov , Topical Issue on Biodamage, EPJD , v.60, n.1 (2010)

Energy deposition: geometry and pressure

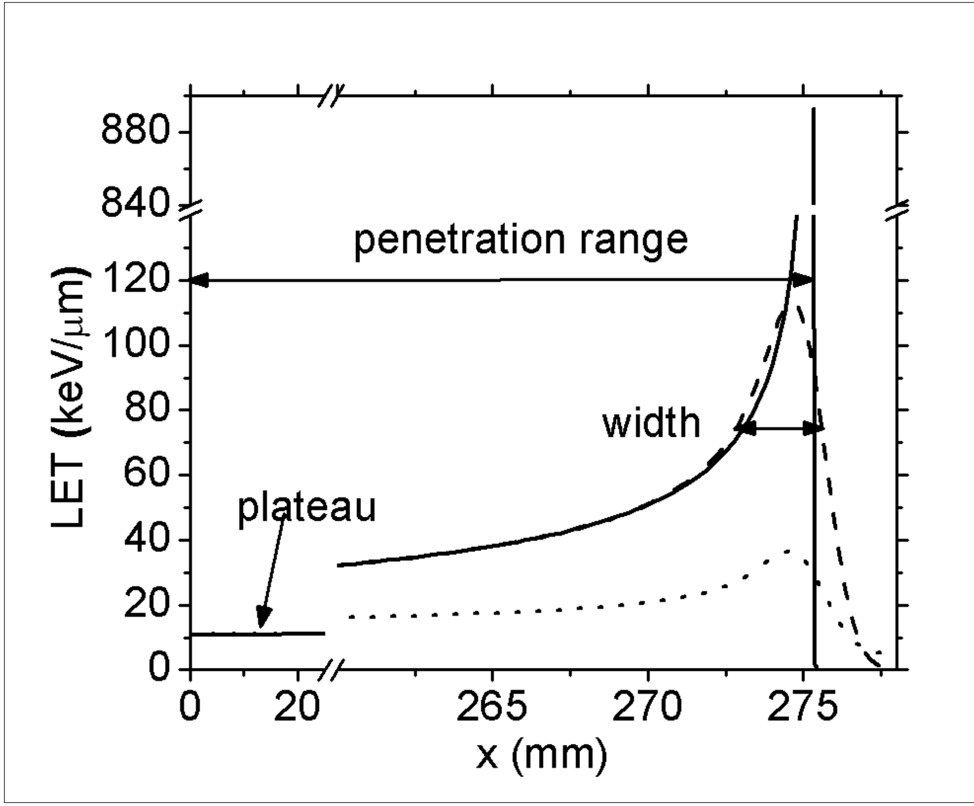
MesoBioNano Science

Goal: model the environment following the thermal spike

- LET on the length of the Bragg peak =0.9keV/nm; determines the energy loss by an ion/nm

- Characteristic sizes:
  - •Characteristic time (1000 electron collisions) is 0.1ps.
  - •C-ion's energy =0.3 MeV/u
  - •Per 0.1ps, it passes 0.8μm
  - •Secondary electrons wander within 1nm radius

- Strength of the explosion:
  - •Pressure inside the cylinder is higher than 10^3 MPa
  - •Pressure outside the cylinder is 0.1 MPa



$$\frac{P_{in}}{P_{out}} \gg \frac{\gamma+1}{\gamma-1} = 10, \gamma = \frac{Cp}{Cv} = 1.22$$

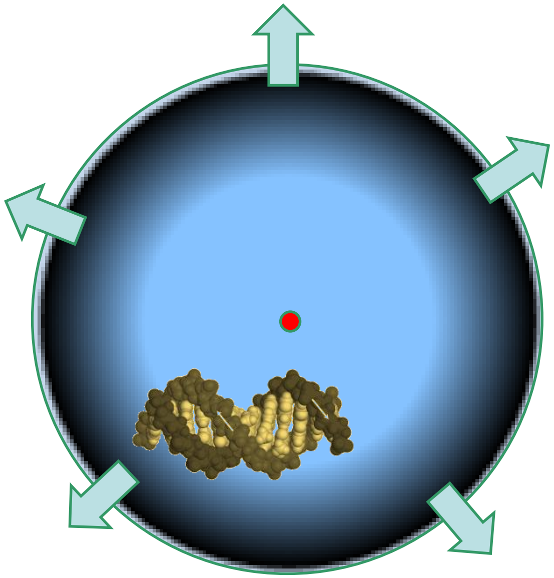
Holds up to t=1ns;

E. Surdutovich and A.V. Solov'yov, PRE 82, 051915 (2010)

Hydrodynamics: strong explosion

L. I. Sedov (1946) and
J. von Neumann (1947)

Cylindrical shockwave



$$\frac{\partial\rho}{\partial t}+\frac{\partial\rho v}{\partial r}+\frac{\rho v}{r}=0$$
$$\frac{\partial v}{\partial t}+v\frac{\partial v}{\partial r}=-\frac{1}{\rho}\frac{\partial P}{\partial r}$$
$$(\frac{\partial}{\partial t}+v\frac{\partial}{\partial r})\ln\frac{P}{\rho^\gamma}=0$$

Hydrodynamic equations

$$\xi=\frac{r}{\beta\sqrt{t}}\left[\frac{\rho_1}{\varepsilon}\right]^{1/4}$$

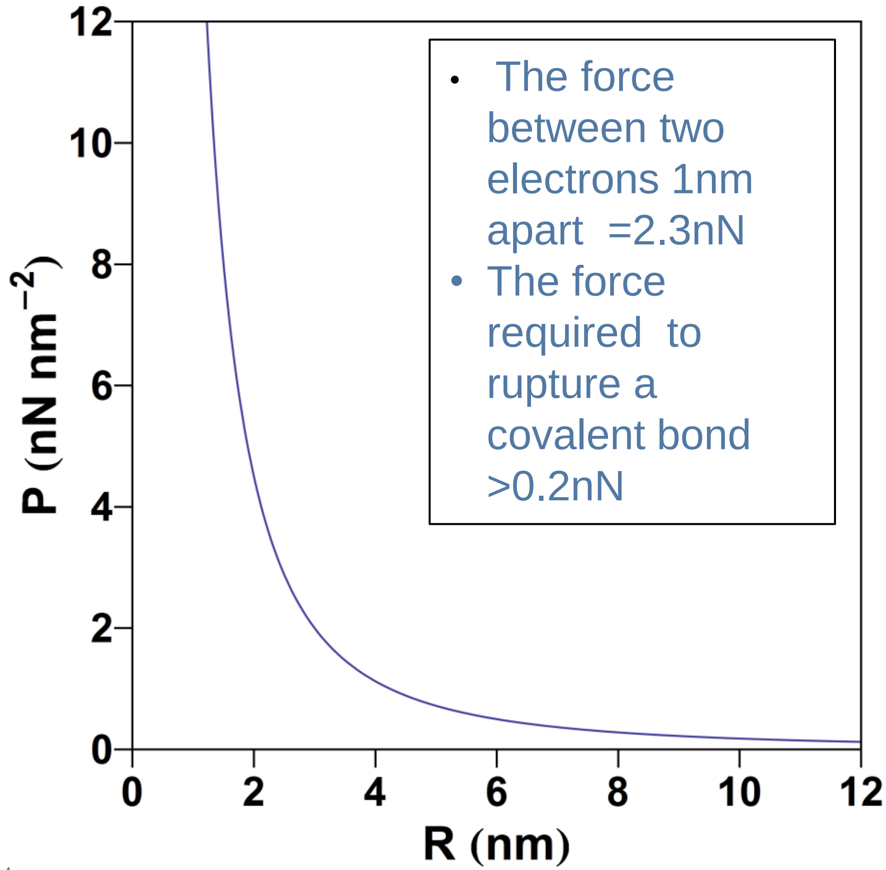
Self-similar flow

Explore the conditions on the wave front and in the wake

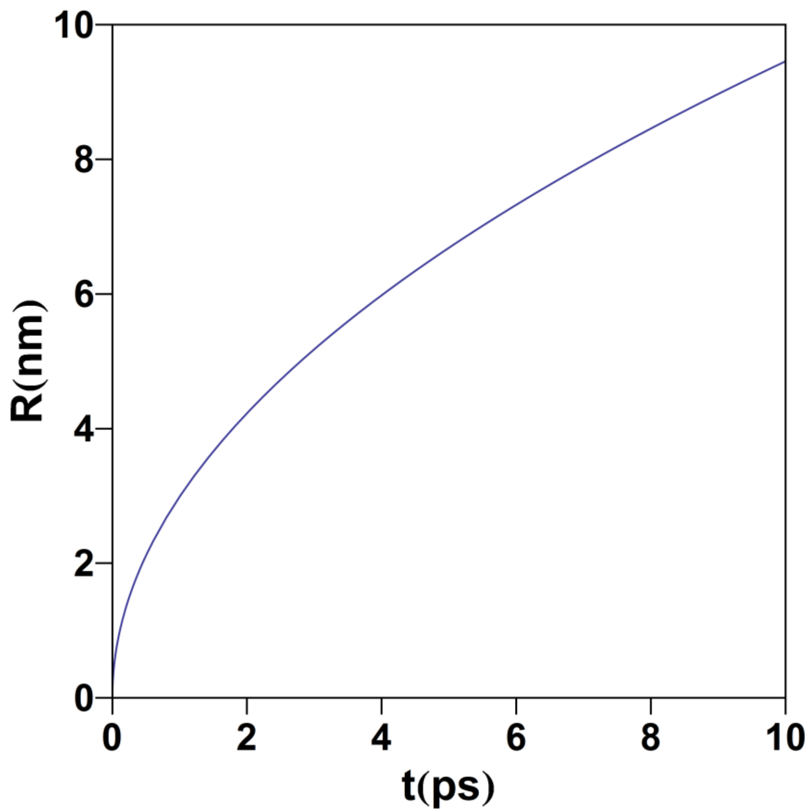
E. Surdutovich and A.V. Solov'yov, PRE 82, 051915 (2010)

On the front of shockwave

Dependence of pressure on the shockwave front on the front radius



- The force between two electrons 1nm apart =2.3nN
- The force required to rupture a covalent bond >0.2nN

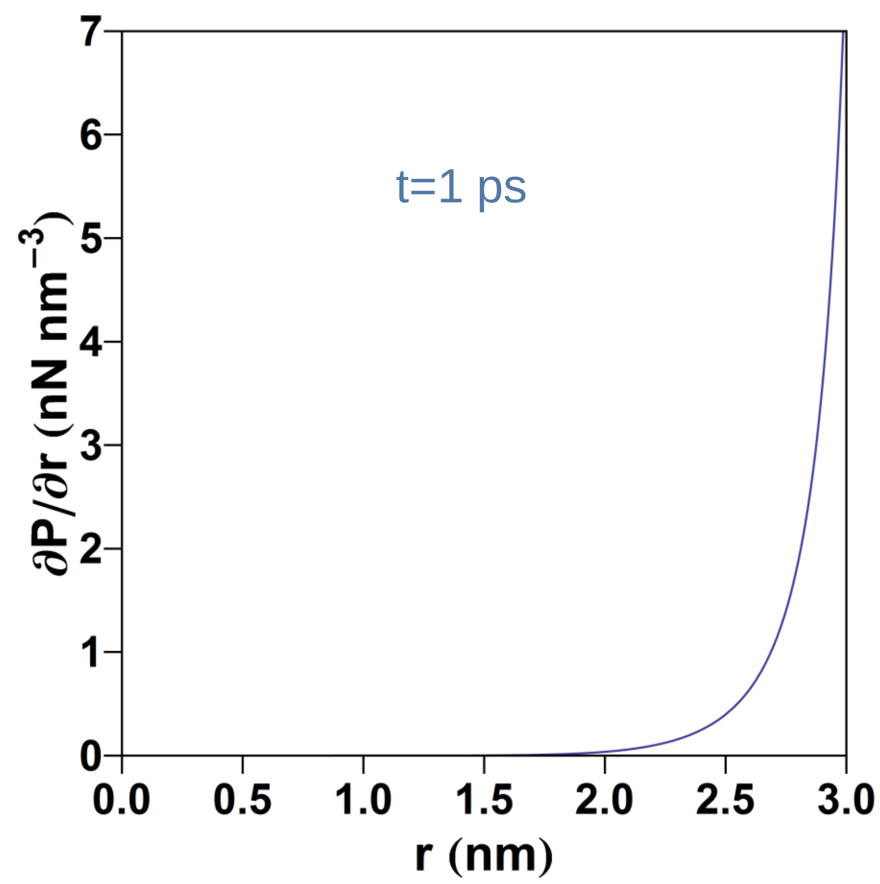


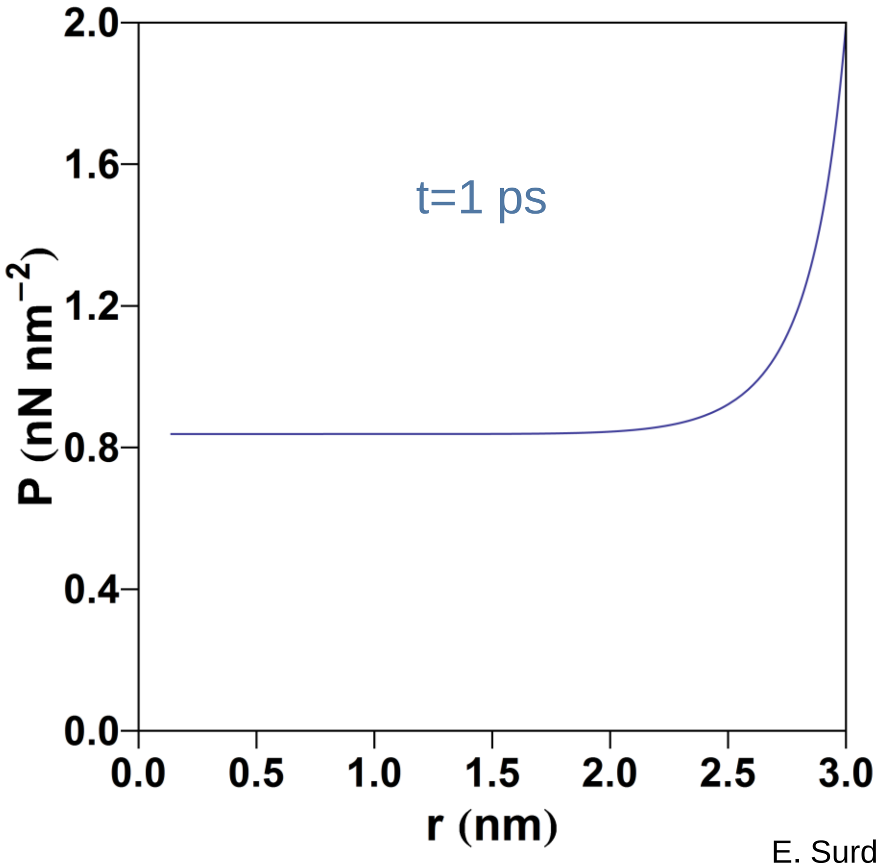
Propagation of shockwave's front on time

E. Surdutovich and A.V. Solov'yov, PRE 82, 051915 (2010)

In the wake of shockwave

Dependence of pressure gradient in the wake of shockwave

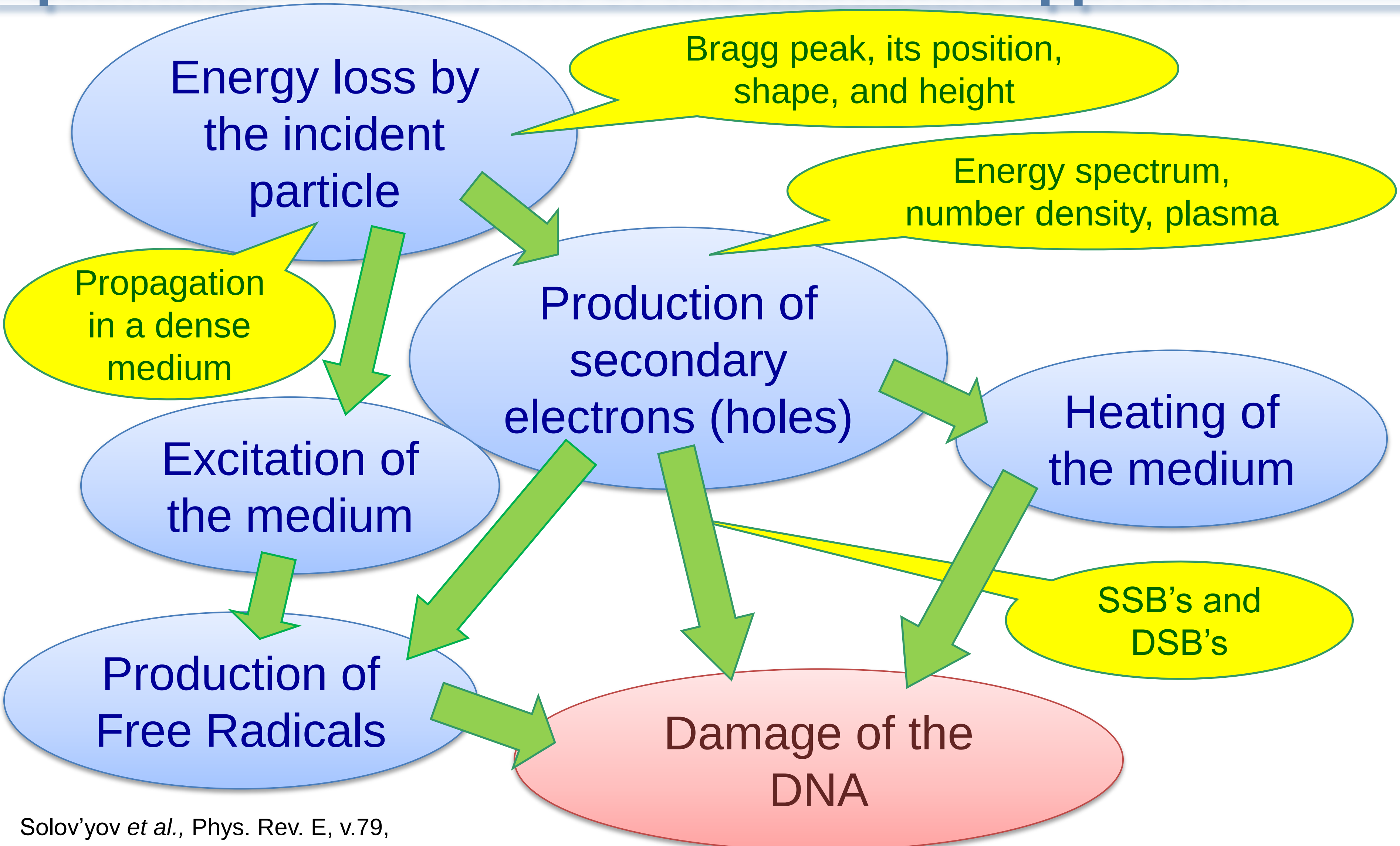




Dependence of pressure in the wake of shockwave

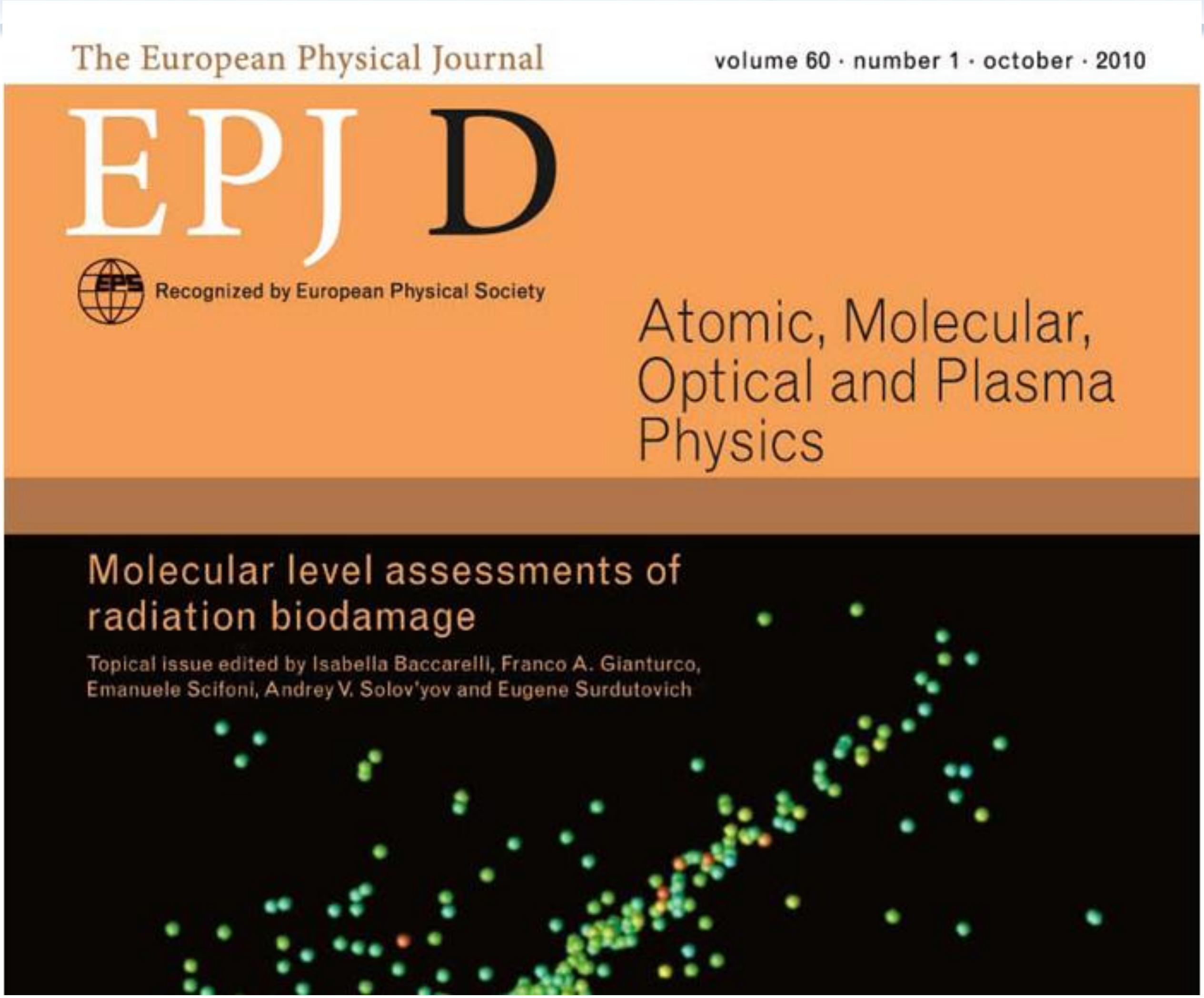
E. Surdutovich and A.V. Solov'yov, PRE 82, 051915 (2010)

Conclusion I: radiation biodamage can be quantified on the basis of the multiscale approach

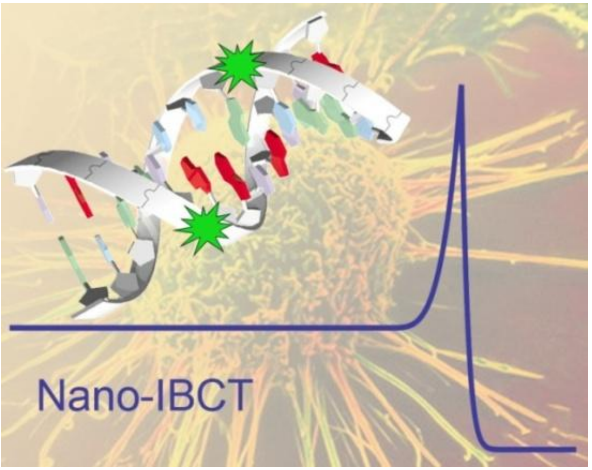


Solov'yov *et al.*, Phys. Rev. E, v.79, p. 011909-(1-7) (2009)
Europhysicsnews, v.40, n.2, p.21-24 (2009)

Conclustion II: quantification of biodamage on the cellular scale require further research efforts



COST Action Nano-IBCT ‘Nanoscale insights into ion beam cancer therapy



Memorandum of Understanding (MoU)
http://www.cost.esf.org/domains_actions/mpns/Actions/nano-ibct/%28glossary%29/off

MoU has been signed by 17 EU countries:
Austria, Belgium, Czech Republik, Denmark, Finland, France, Germany, Hungary, Italy Ireland,Netherlands, Portugal, Serbia, Slovakia, Spain, Sweden, Greatbritain;
other 4 EU countries are expected to sign

Australia, USA andJapan will join the COST Action

Thank you for your attention!