PhD school SAT – Physics and astrophysics

XXIV cycle

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Beam modeling and biological dose optimization for the INFN TPS project

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Outline

- ***Introduction:***
  - What are hadrontherapy and Treatment Planning Systems (TPS).
  - The Italian INFN TPS project and the collaboration with the Belgian IBA company for the development of a validated carbon ion TPS to be commercialized.
- ***Biological dose optimization:***
  - The general (inverse) problem.
  - Our work in Torino: Research on biological cost function, algorithms, start vector dependence. Implementation and tests of the former mentioned. Results with basic example CG method on a small tumor volume.
- ***Beam modeling:***
  - Why it is needed for forward planning and database (biological and physical).
  - Implementation and test of a beam line transfer function (BTF) method for carbon and proton data. Results with a basic carbon ion ripple filter simulation for the longitudinal part.
- ***Summary of the years 2009-2010:***
  - Work done within the TPS project. Presented work on conferences and publications.

Introduction:

Cancer and radiotherapy

- **Problem cancer:**
  - In Italy every year ca. 280.000 new cancer cases, in Germany ca. 436.000 (~0.5 % of the population). **Cancer is the second cause of death directly after heart diseases.**
- **Radiotherapy:**
  - About 70% of the patients with cancer would need a treatment with radiotherapy. **Radiotherapy is the second most commonly used cancer therapy directly after surgery and even before chemotherapy.**
  - The technical developments in radiotherapy and the always greater knowledge in radiobiology makes it convenient to use more and more.
- **Treatment Planning:**
  - The most important aspect for the radiotherapy is to **find the best mode for the dose distribution, maximizing the dose on the tumors while preserving normal healthy tissues, for each patient.**

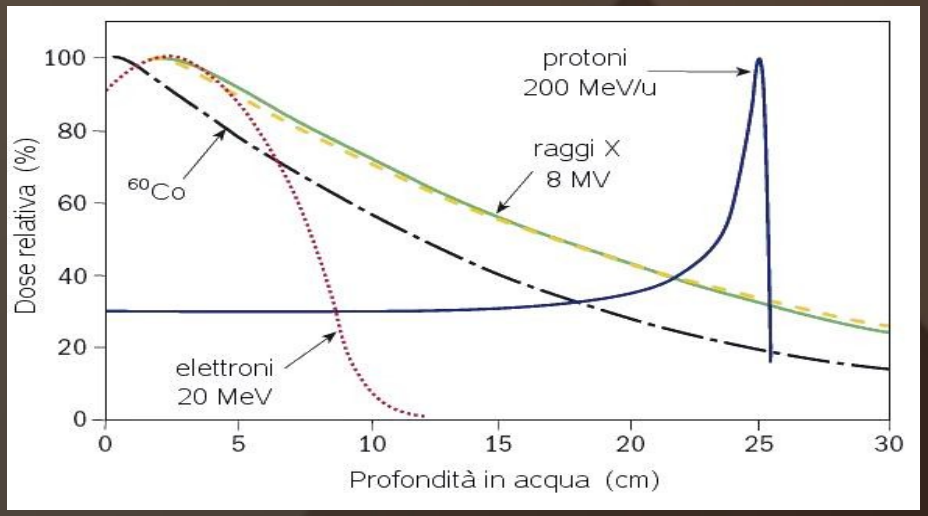
$$dose = \frac{energy_{released}}{mass}$$

  - Need of **prediction methods for the cell survival (radiobiological models and forward planning) and optimization methods of the delivered biological dose (inverse planning).**

Introduction:
Hadrontherapy

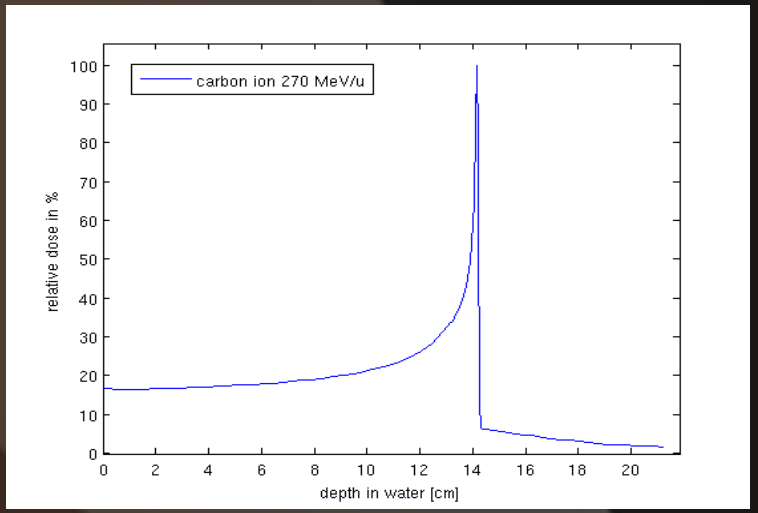
- **In modern cancer therapy the use of charged hadrons (protons, carbon ions, …) is favored due to the advantages over traditional radiotherapy (X-rays):**

  - better radial and depth localization properties (for protons and even more for carbon ions) → sparing of organs at risk (OAR)
  - adjustable depth of dose deposition → treatment of deep seated tumors
  - higher relative biological effectiveness (RBE) for carbon ions → kills radio resistant tumors



Dose distribution curves for different conventional radiation sources:

x-rays (γ) electrons (β) protons (α)



Dose distribution curve:

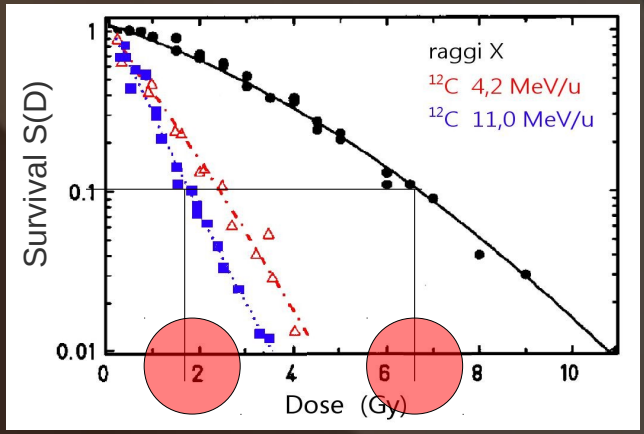
carbon ions (α)

Introduction:
TPS and RBE

- For the treatment planning with active delivery system a complex software, called ***Treatment Planning System (TPS)***, is both used
  - to optimize the biological dose delivered to the patient (inverse planning) and
  - to compute the related physical dose (forward planning).
- This has to be done in a **general way** so that the TPS can be easily adapted for every specific beam line of ion therapy centers.
- The optimization has to include the ***relative biological effectiveness (RBE)***.

$$RBE = \frac{D_{x-ray}}{D_{radiation}}$$

$RBE_{proton} \approx 1.1$ $RBE_{carbon} \approx 3$



Survival curves X-rays and carbon ions

Introduction:

Radiobiological model

- The cell survival S(D) is modeled by the **biological parameters α and β** and the **physical dose D** through the ***Linear Quadratic (LQ) model***

$$S(D) = \exp(-\alpha \cdot D - \beta \cdot D^2)$$

  - Limits of the model: It does not refer to a real structure of the cell and its parameters depend for example on the type of tissue, temperature, presence of oxygen, cell cycle...
  - **α-component:** Corresponds to **irreparable damage** (DSB, Double Strand Breaking) on the DNA. It is dominant for cell lines with low repair capacity and for high LET. It is quasi not affected by splitting of the given dose.
  - **β-component:** Corresponds to **reparable damage** (SSB, Single Strand Breaking) on the DNA. It is dominant for cell lines with high reparation capacity. It is much affected by splitting of the given dose.
- The **biological parameters α and β** are obtained by cell experiments or (in case of **ions**) can be also predicted using the ***Local Effect Model (LEM)***, developed by the Biophysics group at GSI.
  - For carbon ions or protons we have a **mixed field** of N beams:

$$\alpha = \frac{\sum_{j=1}^{N} \alpha_j D_j}{\sum_{j=1}^{N} D_j} \qquad \beta = \left(\frac{\sum_{j=1}^{N} \sqrt{\beta_j} D_j}{\sum_{j=1}^{N} D_j} \right)^2$$

Introduction:
The INFN TPS project

The Italian INFN TPS is a multidisciplinary project involving many different research areas and sections of the INFN.

- **Major research is underway both on nuclear physics and radiobiology.**

- ***Carbon ion therapy is not yet clinically proved as the proton therapy but one expects better results due to the larger RBE.***
- So far **world-wide about 50 000 patients treated with protons** (since late 1950s first in Berkeley, USA) and circa **3000 with carbon ions** (since late 1990s, first in Chiba, Japan).
- **World-wide proton centers ~ 35, carbon ion centers** (operative or under construction) **~5**:
- ***NIRS-HIMAC and Hyogo Hadrontherapy center in Japan.***
- ***GSI and HIT in Germany.***
- ***CNAO in Italy.***
- ***The scope of the TPS project is to create with all this experiences a fully functional Ion Treatment Planning system which is needed for the hadrontherapy (specially for carbon ions).***
- Since 2009 the INFN has an industrial cooperation with the Belgian IBA company.

INFN TPS collaboration:
Catania (LNS), Frascati (LNF), Legnaro (LNL), Milano, Napoli, Pisa, Roma3, Sassari, Torino

The general inverse problem

- ***Find the minimum of the biological cost function***

Penalty function

$$\chi^2(N) = \sum_{x \in target} (D_p(x) - D_a(x,N))^2 + \sum_{x \notin target} (D_p(x) - D_a(x,N))^2 * \theta(D_p(x) - D_a(x,N))$$

with respect to the number of particles N (or the ***fluence***).

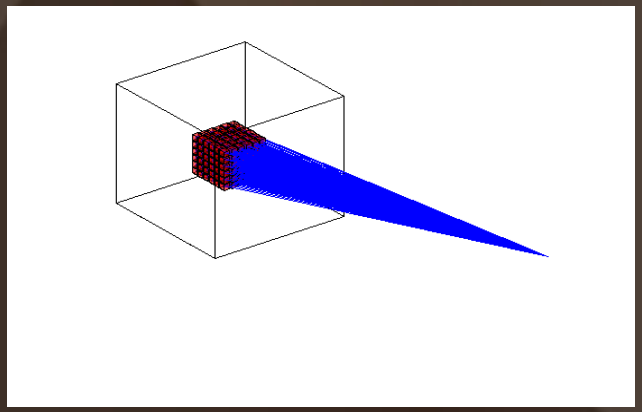
- Hereby $D_p(x)$ is the **dose in unit Gray [Gy] prescribed** by the physician for the voxel x and $D_a(x, N)$ is the **actual dose** at the voxel x (depending on the fluence).
- Optimization is a complex process due to the **nonlinearity and to the great number of variables up to 10^5**. → Needs advanced optimization methods and/or good start vectors.
- **Prescription of the physician** is in biological dose that means Gy corresponding to X-ray radiation! → **Problem with carbon**: RBE changes along the beam propagation.

Activities and current status

- ***Modeling of the biological cost function***
- ***Implementation with open source packages for the non-linear optimization***
- ***Optimization algorithms***
- ***Research on start vector dependence***
- I have implemented a **basic biological cost function and nonlinear optimization** (PCG method for $\sim 10^3$ variables) **in Matlab**.
- Furthermore we have implemented also in **Matlab a program to simulate a tumor together with the prescription and the corresponding physical dose matrix.** This was obtained by MC simulations starting from the CNAO beam line, the carbon ion beams were then ray traced within the full volume.
- I am currently implementing the Matlab model with gsl library (open source).

Basic tests on a small tumor volume

- To **test the performance of different local optimization methods** and of the start vector dependence I used
  - a **small rectangular treatment volume of 31x31x101 voxels** (each of size 2 mm)
  - with an **tumor of dimension 6x6x14 voxels (12x12x28mm), located roughly in the center of the treatment volume**.
- The **calculation grid** was set equal to the **voxel grid**.
- The **spot grid** was set automatic in distances according to the beam sigmas in x, y and z (about 4.71mm in x, y and 5.10 mm in z) and in positions such to cover the tumor.



Treatment volume example with tumor and beam

Basic tests on small tumor volume

Dose matrix D0

- From MC simulation, depending on target (tumor, OAR)
- Matrix dimension: 31x31x101x175 (in evaluation grid)
- Position of gun: x=y=0, z=-6 m
- Tumor size and position: 12x12x28 mm, placed in the center of the whole volume of 62x62x202 mm
- Number of beams: 175 (in spot grid)

$$D = \sum_j D0_j \phi_j$$

Biological matrices α and β

- From cell experiments or LEM simulations or constant values
- Matrix dimension: 31x31x101x175 (in voxel or translated in evaluation grid)
- *Basic case:* X-ray values (α_c = 0.18, β_c=0.028) constant over all the volume **or** *Advanced case:* different values varying per tissue (tumor and OAR) and beam

$$S(D) = exp(-\alpha_c D - \beta_c D^2)$$

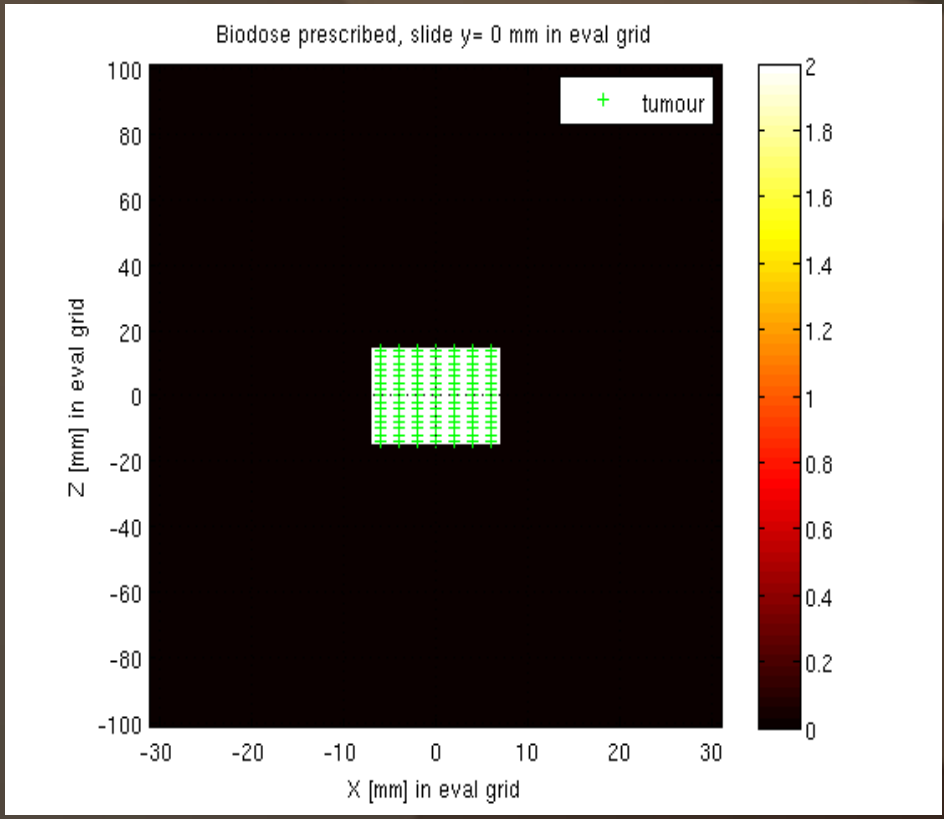
Remember: Prescription D_{pres} is referring to biological dose in X-ray (with α_x and β_x). We have to transfer this to the survival in carbon domain (with α_c and β_c), where we perform the optimization, and to re-transfer to compare with the original prescription.

$$S(D) = exp(-\alpha_x D - \beta_x D^2)$$

$$N_x = \alpha_x D_{pres} + \beta_x D_{pres}^2 =! N_c = \alpha_c D_{opt} + \beta_c D_{opt}^2$$

$$D_x = \frac{\sqrt{\alpha_x^2 + (2\beta_x)^2 N_c/\beta_x} - \alpha_x}{2\beta_x}$$

Basic tests on small tumor volume



Example slice (for fixed central y) of dose prescription in voxel grid (or already translated in evaluation grid)

Prescription biological Dose D_{pres}

- From physician
- Example: Tumor 2 Gy, OAR 0 Gy

$$S(D) = exp(-\alpha_x D - \beta_x D^2)$$

$\alpha_x = 0.18$ $\beta_x = 0.028$

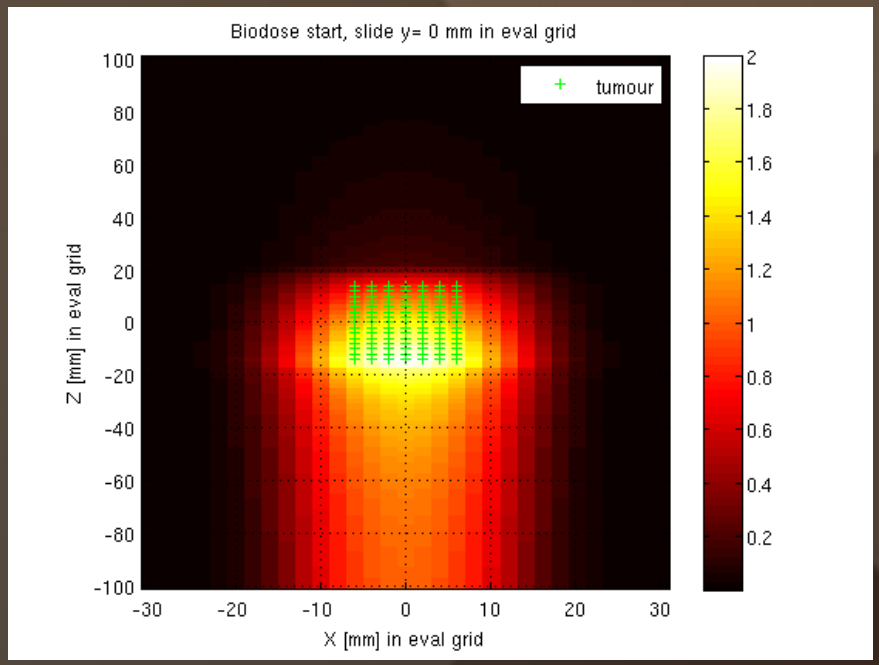
Prescription weights

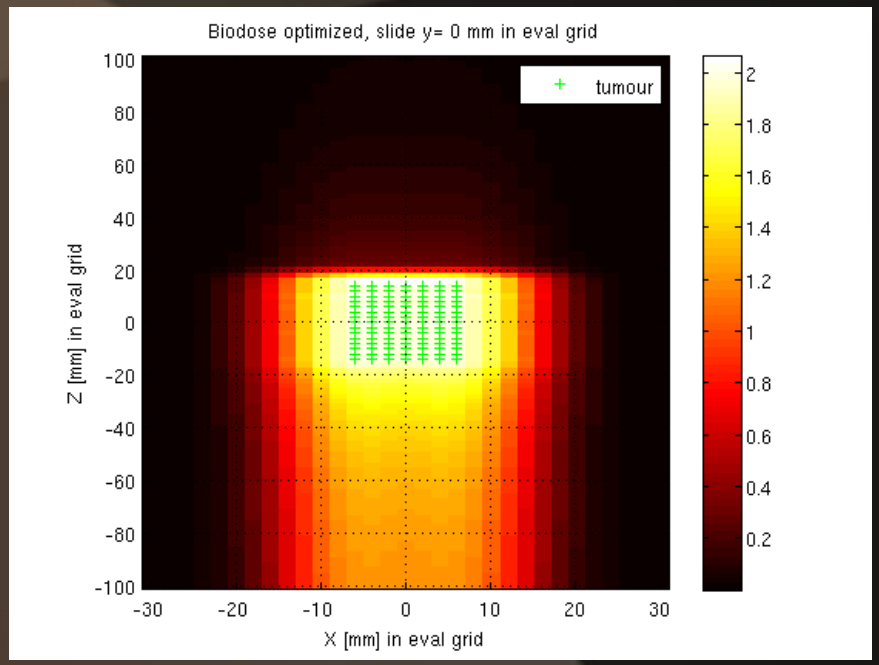
- From physician
- *Basic case:* Tumor 1, OAR 0 **or** *Advanced case:* with 0<OAR <1

Biological dose optimization

Results basic tests on small tumor volume

Dose optimization example (CG) with α, β constant X-ray and weights 1 on tumor, 0 on OAR and start vector all 1*normalization factor. ***Dose optimization is of great importance for carbon ion treatments because the dose gradient is much steeper than for normal radiotherapy and a bad optimization can lead to a big underdosage of the tumor and overdosage of the OAR.***





Start biological Dose

- From dose at start fluence
- Matrix dimension: 31x31x101 (evaluation grid)
- Depends on D_0, fluence and α, β
- X^2 in carbon domain= $9.59*10^{45}$

Obtained biological Dose

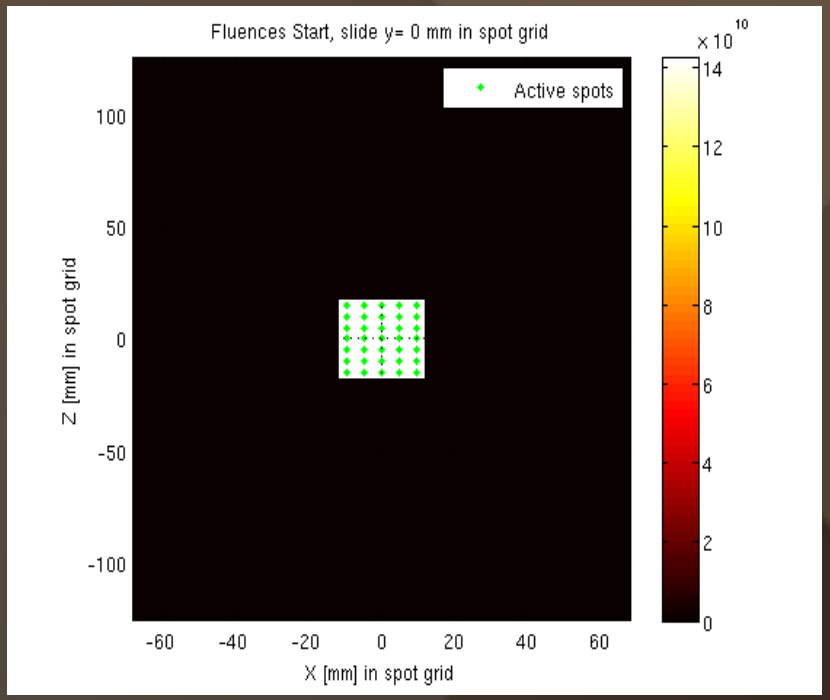
- From dose optimization of fluence (CG)
- Matrix dimension: 31x31x101 (evaluation grid)
- X^2 in carbon domain=71.61

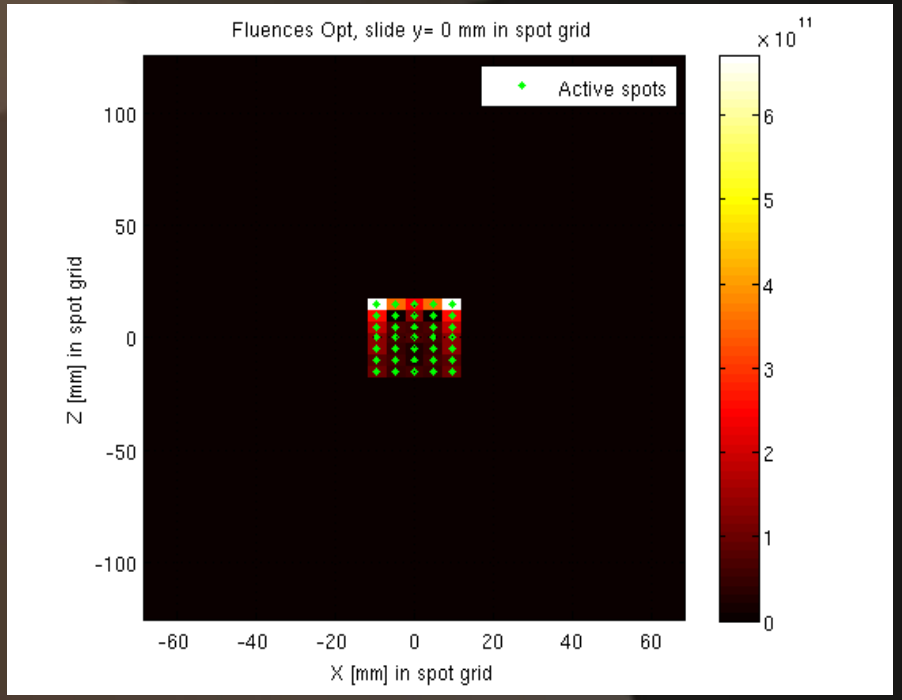
Iterations: 8

Biological dose optimization

Results basic tests on small tumor volume

Dose optimization example (CG) with α, β constant X-ray and weights 1 on tumor, 0 on OAR and start vector all 1*normalization factor





Start fluence

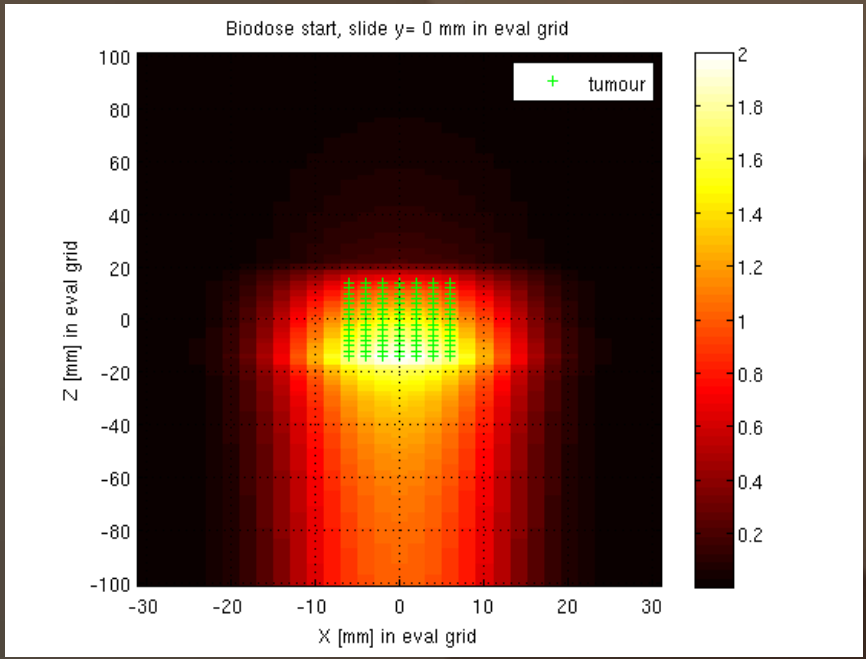
- Decided start fluence for all 175 beams is all 1*normalization factor
- Number and position of beams (in spot grid) depends on tumor and beam sigma

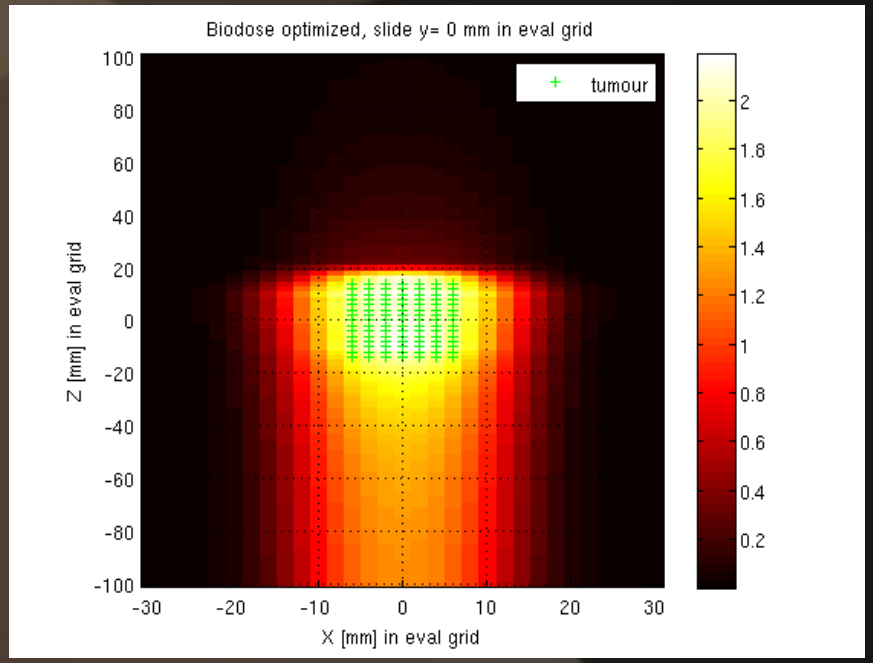
Obtained optimized fluence

- From dose optimization of fluence in evaluation grid (CG)
- 175 active beam spots (in spot grid)
- Fluence distribution ok?

Results basic tests on small tumor volume

Dose optimization example (CG) with α, β const X-ray and **weights 1 on tumor, 0.1 on OAR** and start vector all 1*normalization factor





Start biological Dose

- From dose at start fluence
- Matrix dimension: 31x31x101 (Evaluation grid)
- Depends on D_0, fluence and α, β
- X^2 in carbon domain= $9.8*10^4$

Obtained biological Dose

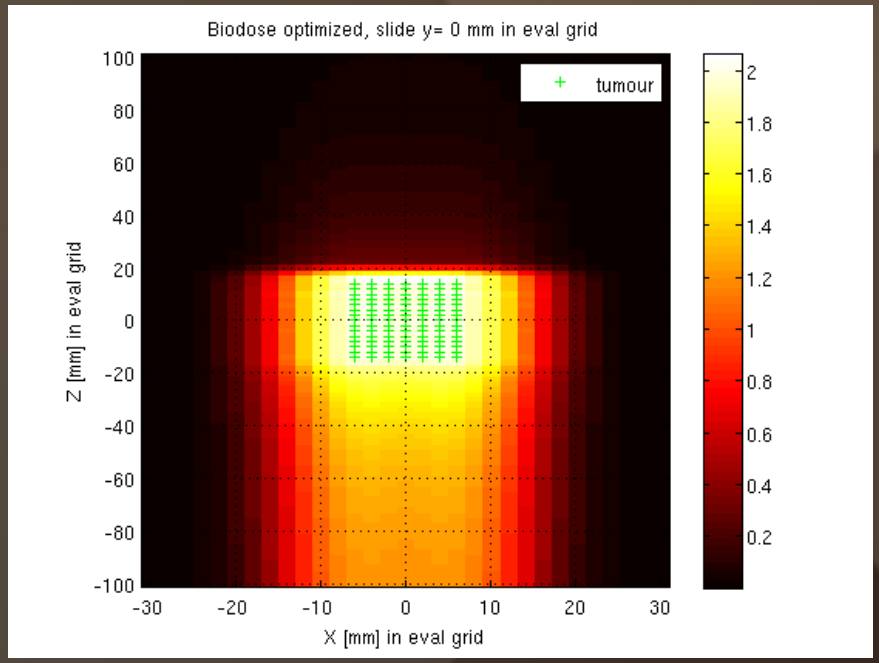
- From dose optimization of fluence
- Matrix dimension: 31x31x101 (Evaluation grid)
- X^2 in carbon domain= 6.1825

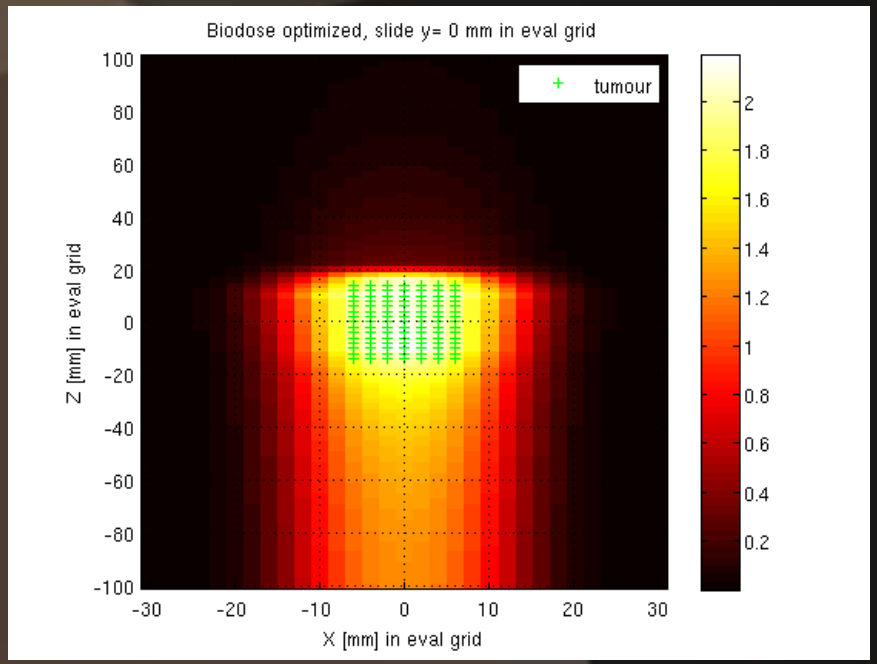
Iterations: 39

Biological dose optimization

Results basic tests on small tumor volume

Dose optimization example (CG) with α, β const x-ray and weights 1 on tumor, 0.1 on OAR and **start vector from optimization without OAR**





Start biological Dose

- From dose at start fluence
- Matrix dimension: 31x31x101 (evaluation grid)
- Depends on D_0, fluence and α, β
- X^2 in carbon domain=$3.9*10^{45}$

Obtained biological Dose

- From dose optimization of fluence
- Matrix dimension: 31x31x101 (evaluation grid)
- X^2 in carbon domain=6.2351

Iterations: 15

Biological dose optimization

Conclusions and outlook

- The optimization based on the Matlab model with CG method is basically working (also tested with non constant α and β values).
  - **Some care has to be taken in deciding the optimization starting vector.**
  - **The optimization can lead to results that are optimized but the fluence distribution suffers of large gradients. The effect has to be avoided with further constraints on the fluence distribution.**
  - **We plan to implement and test** also the local first order **SD (Steepest Descent)** and second order **QN (Quasi Newton)** method as both are (beside CG) the referred standard methods in dose optimization. Therefore we need to compute the (continous) derivatives of the cost function.
  - I have started a test on the self-implemented **SD method with optimal step size computation** where I forced the fluence to positive values. The first and second derivatives were analytically computed and added in the code. This work is still not completely satisfying, in particular the step size needs to be optimized.
  - **We need some realistic data (bigger volume D0, OARS, α and β for tissues and beams variable) to test more precisely the performance of the different optimization algorithms.**
- **The best method(s) will be inserted in the final C++ TPS** with the actual model of the cost function and the beams setting dose engine (using for the common algorithms an open source optimization library).

Beam line transfer function (BTF)

- **Problem:**

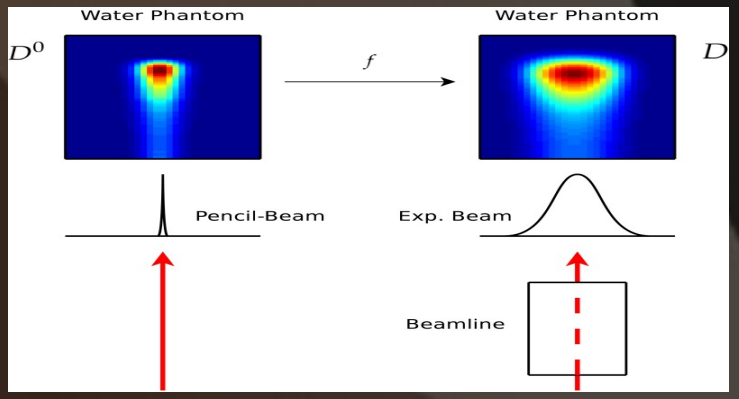
- **Physical dose D(x, y, z, E) can be measured relatively easy** in experiments or simulated by MC methods **but the radiobiological effects can be determined only by not trivial** (time consuming, statistics) cell survival experiments or biological simulations (with LEM).

- **Also the dose deposition D(x, y, z, E) differs as a function of the beam line**, thus each beam line has to be described individually.

- **Idea:**

- **The he biological parameters α and β could be calculated by applying a *beam line transfer function (BTF) f* to the parameters α_0 and β_0 which correspond to the LEM simulations of a pencil beam D^0 without the effects of the beam line.** $\alpha = f * [\alpha^0 \cdot D^0]/D$ $\beta = (f * [\sqrt{\beta^0} \cdot D^0]/D)^2$

- Additionally also the physical dose D of the beam line could be calculated by applying a BTF to the pencil beam MC simulation. $D = f * D^0$



Beam line transfer function (BTF)

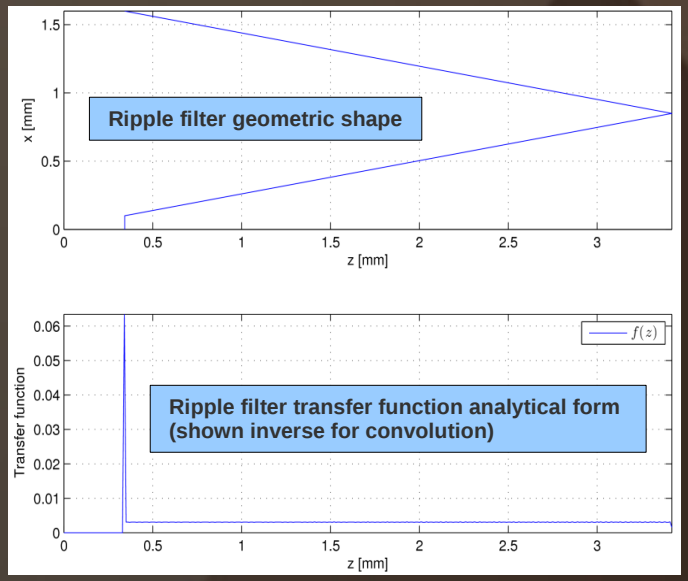
- **Most important issues:**
  - How to determine the BTF? (And is it unique?)
  - How well does the BTF model the physical and biological dose distribution?
- **Solution for the first issue:**
  - **The biological BTF should be obtained by the physical dose distribution D_0 and D**, where D_0 is the dose distribution of an ideal ***pencil beam*** (that means a beam which is along a line, each particle generated at x=0, y=0) as obtained with a simulation and D is the actual dose distribution that can be measured (or simulated) for a real beam line, with a beam perturbated by several detectors, etc...
  - **The 3-dimensional BTF can be factorized in a longitudinal part along the beam line z and a radial part in the x, y-plane.** For practical reasons we are treating them separately.

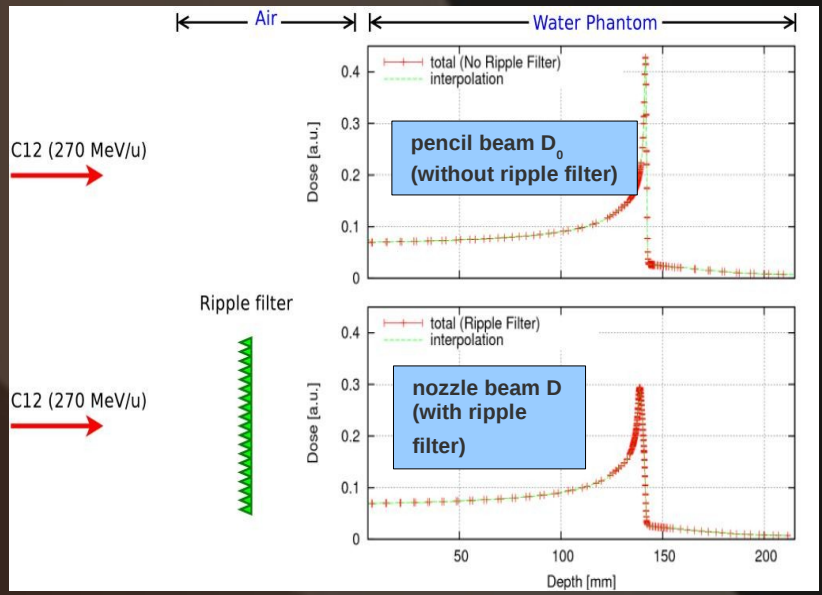
Basic example: carbon ion with ripple filter

- In the following we show for ***carbon ions of 270 MeV/u*** the physical dose distribution of a ***pencil beam*** $\mathbf{D_0}$ along z and an example of a beam which has been perturbated (hereafter called nozzle ***nozzle beam***) **D.** The ***ripple filter*** is a device used to flaten the dose distribution.

- To test the procedure we perturbate the beam using a ***ripple filter*** which basically affects the beam in a way that can be described analytically. In other ways we know the analytical form of f.

- The connection between pencil beam D_0 and nozzle beam D is given through the **unknown *beam line transfer function f*** (which we want to determine and to compare with the analytical form). $f(D_0) = D$





Basic example: carbon ion with ripple filter

A: Discrete Fourier Transform method

- We try to find the transfer function f(z) as a kind of **linear filter**.
  - Therefore we write the problem as **convolution**

$$D(z) = f(z) * D_0(z)$$

and de-convolute via (inverse) **Fourier transform *F***

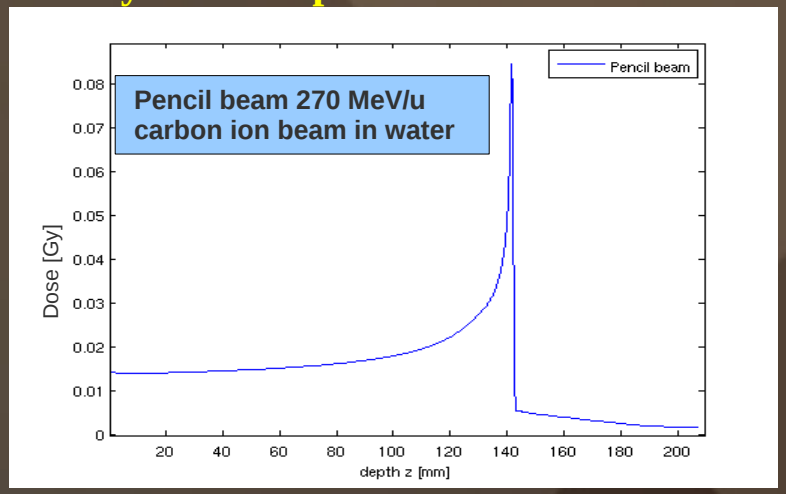
$$f(z) = F^{-1}\left(\frac{F(D)}{F(D_0)}\right)$$

- **Results:**
  - **Finds a unique filter (which reproduces only qualitatively the analytical transfer function).**
  - **Performs well on the physical and biological data.**
  - **Problems:** Needs smoothing through pre-conditioning with Gaussian due to missing tails, needs low-pass filtering in frequency domain due to noise, needs to be cut and re-normalized in frequency (fluence) domain to fulfill the positiveness condition given by physical reasons.

Basic example: carbon ion with ripple filter

A: Discrete Fourier Transform method

- **The application of the transfer function to the pencil beam saves time and memory and performs very well compared with the MC nozzle beam:**



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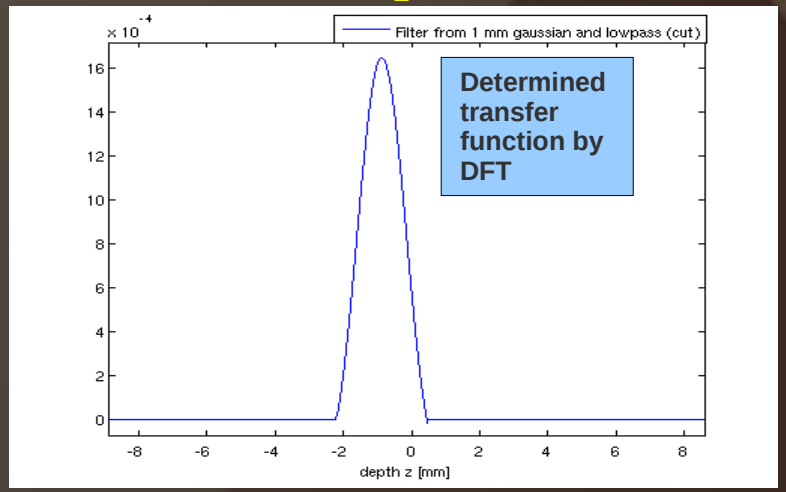

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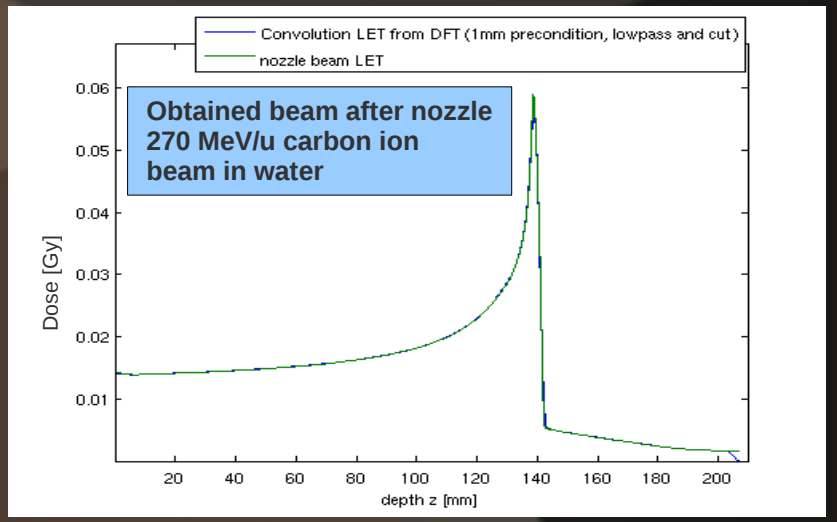
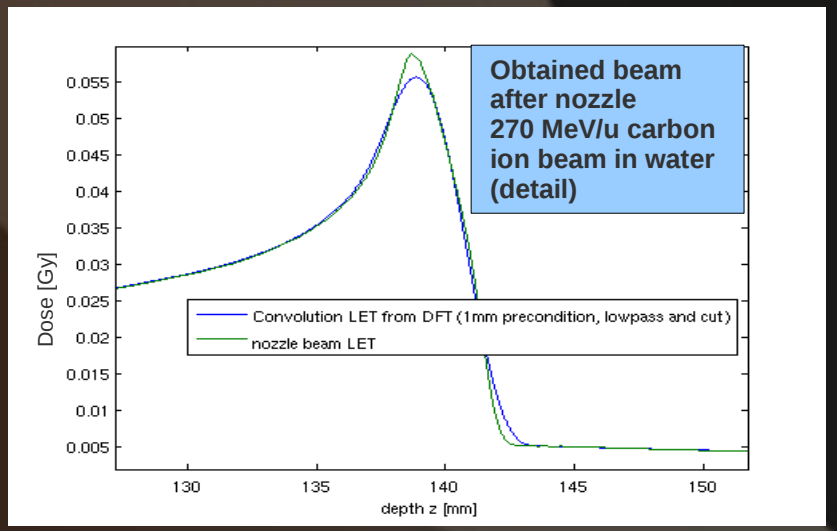
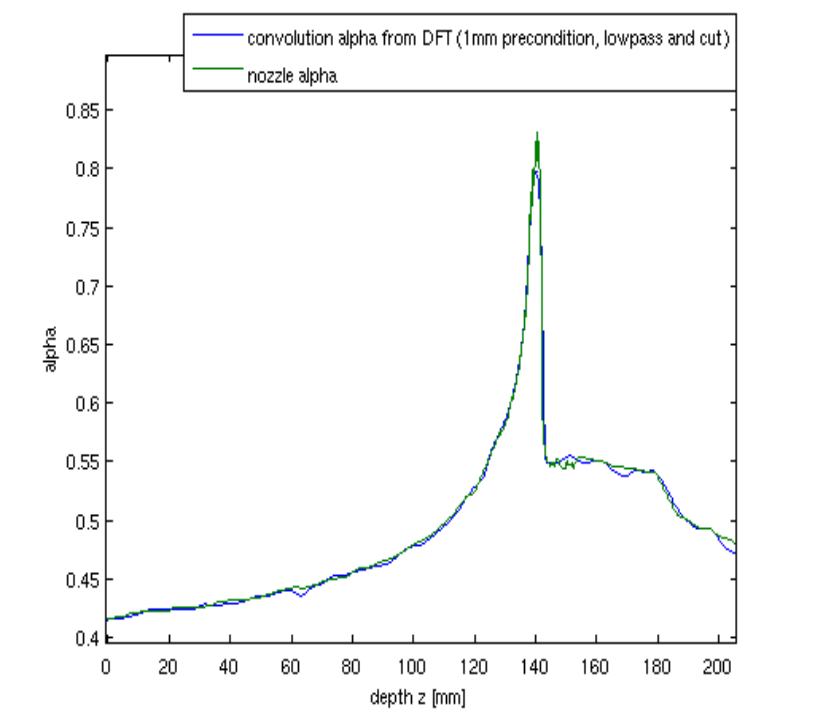




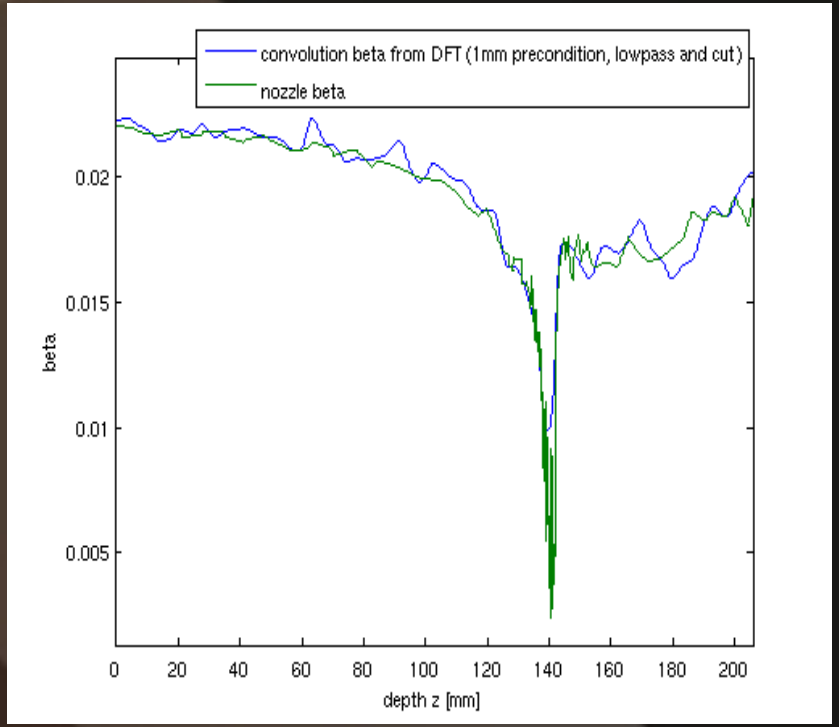
Basic example: carbon ion with ripple filter

A: Discrete Fourier Transform method

- **Again the application of the transfer function to the biological pencil data saves time and memory and compares very well to the full LEM simulation of the biological nozzle:**



Obtained alpha after nozzle from 270 MeV/u carbon ions compared with full LEM



Obtained beta after nozzle from 270 MeV/u carbon ions compared with full LEM

Basic example: carbon ion with ripple filter

B: Weight optimization method

- The problem is seen as a **superposition of different beam energies** E_i with the unknown **weight function** $w(E_i)$:

$$D(z) = \sum_i w(E_i) \cdot D_0(E_i, z)$$

  - We **approximate** the different energy curves through the E=270 MeV **curve shifted** with certain steps $z_i = i \cdot \Delta z$ within a certain range so that $D_0(E_i, z) \approx D_0(z - i \cdot \Delta z)$
  - We **solve the linear system**

$$D(z) = \sum_i w_i \cdot D_0(z - z_i)$$

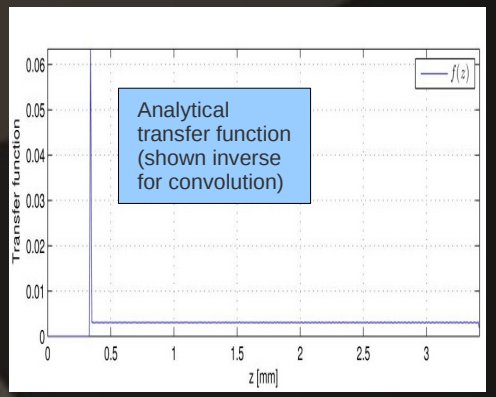
    for the weight function *w* with the **conjugate gradient method (CG)**.

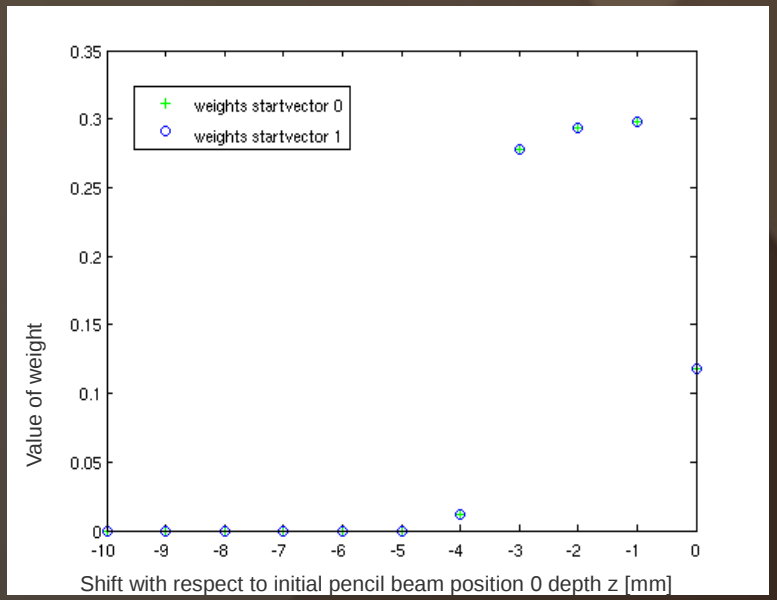
- **Results:**
  - **Does not find a unique solution**. Weight function **reproduces only qualitatively the analytical filter.**
  - **Performs well on the physical and biological data** (already for few beams and 1 mm steps).
  - **Advantages:** It is not affected by noise. It is always positive.

Basic example: carbon ion with ripple filter

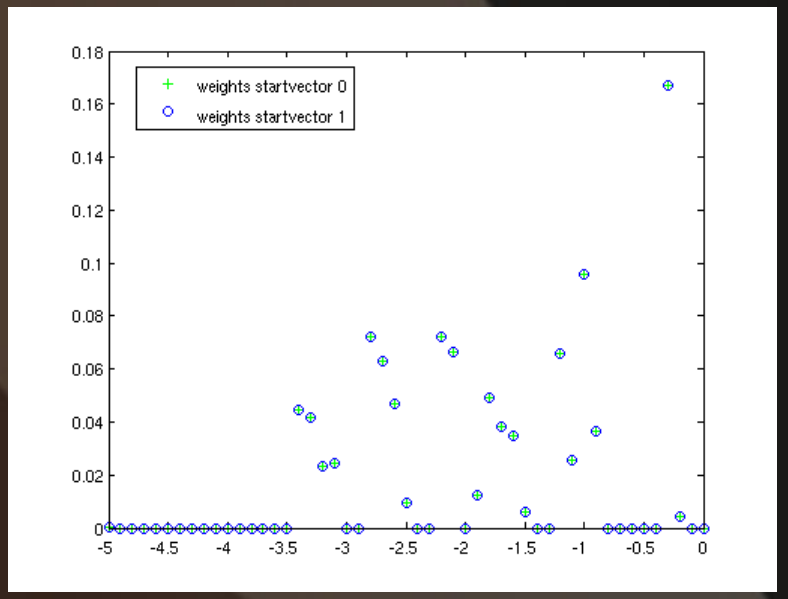
B: Weight optimization method

- To test the method (each with start vector 0 and 1) we chose
  - 10 translated beams with 1 mm steps and
  - 50 translated beams with 0.1 mm steps.





Weight function obtained from CG with 10 translations of 1 mm step

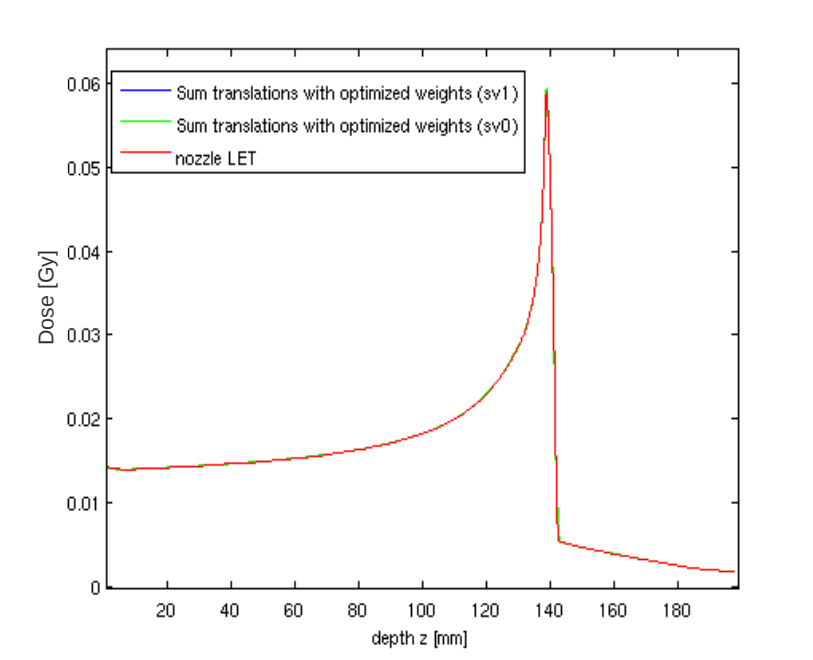


Weight function obtained from CG with 50 translations of 0.1 mm step

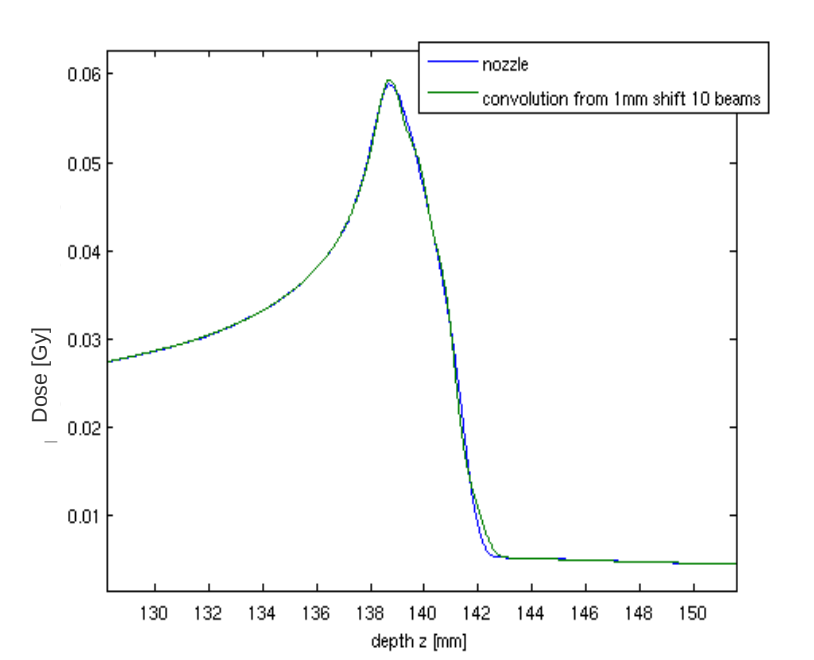
Basic example: carbon ion with ripple filter

B: Weight optimization method

- **Again the application of the transfer function to the pencil beam compares very well with the MC nozzle beam while the algorithm saves as before time and memory** (as already few beams were sufficient to obtain a good result we show only the first example)**:**



Sum of translations with weight function obtained from CG optimization with 10 translations of 1 mm step compared to original beam after nozzle

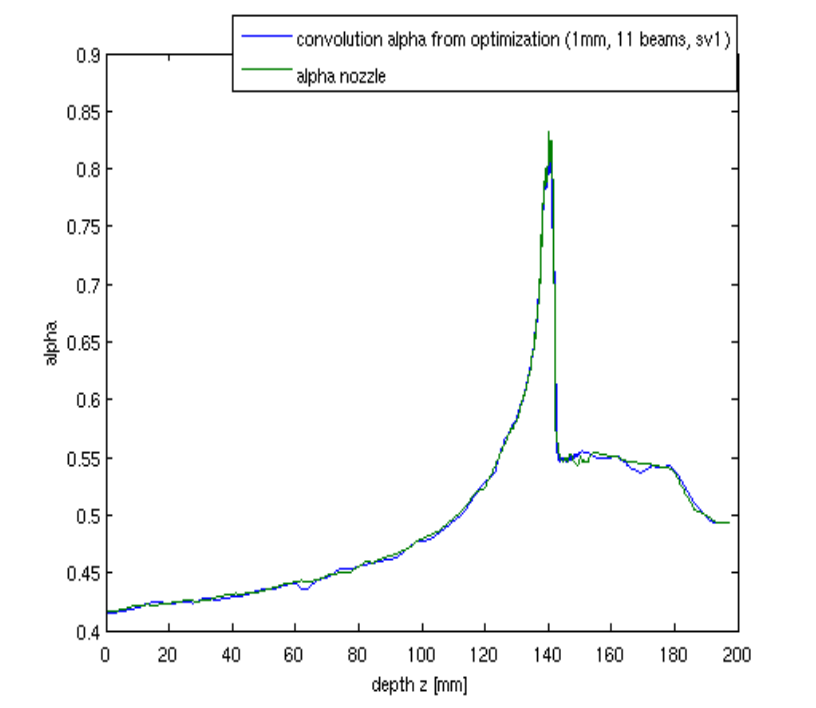


Sum of translations with weight function obtained from CG optimization with 10 translations of 1 mm step (detail) compared to original beam after nozzle

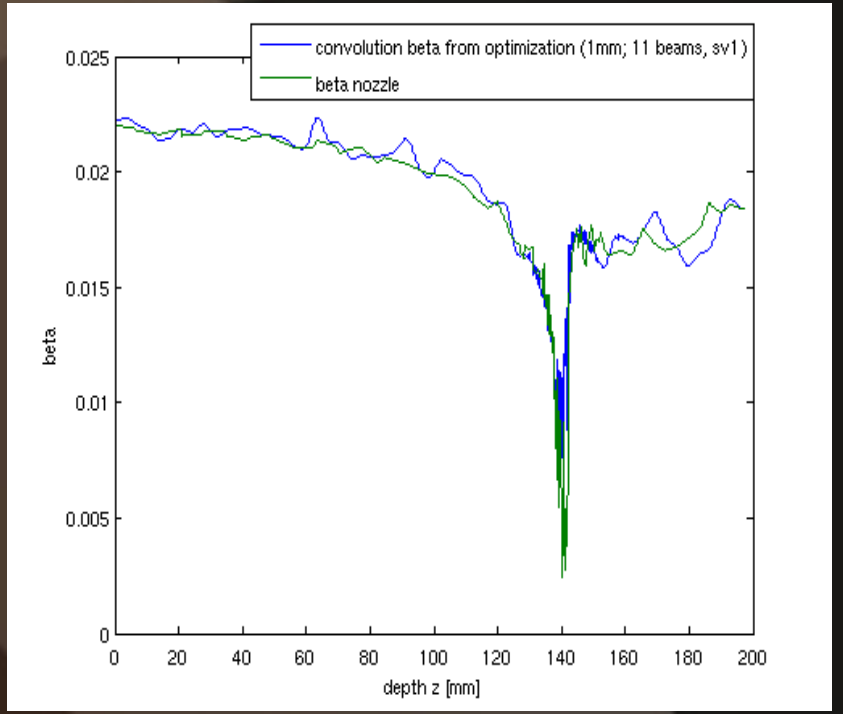
Basic example: carbon ion with ripple filter

B: Weight optimization method

- **Again the application of the transfer function also to the biological pencil data** to check its performance with respect to the full LEM simulation of the biological nozzle:



Obtained alpha after nozzle from 270 MeV/u carbon ions with CG 10 beams and 1 mm step compared to full LEM.



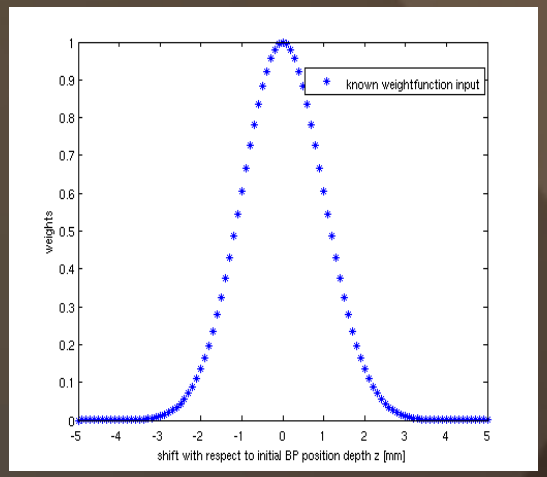
Obtained beta after nozzle from 270 MeV/u carbon ions with CG 10 beams and 1 mm step compared to full LEM

Weight optimization method: Modifications and checks

- **Algorithms for solving the determination of the beam weights** used so far:
  - **Preconditioned conjugate Gradients (PCG)** with constraints of non-negative weights (lsqlin Matlab) and
  - Active set algorithm (uses LG multipliers) which forces automatically nonnegative weights (lsqnonneg Matlab).
- **Relative simple system** (linear and few variables $\sim 10\text{-}10^2$) to solve, but **convergence can depend on**
  - ***start vector and***
  - ***data noise*** (not so much for our carbon simulation but larger for a set of proton data we have analyzed).

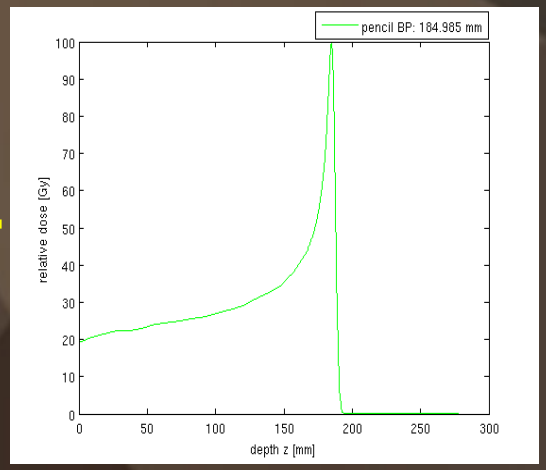
Optimization method: Modifications and checks

We explored several shapes in input and proceeded as follows:



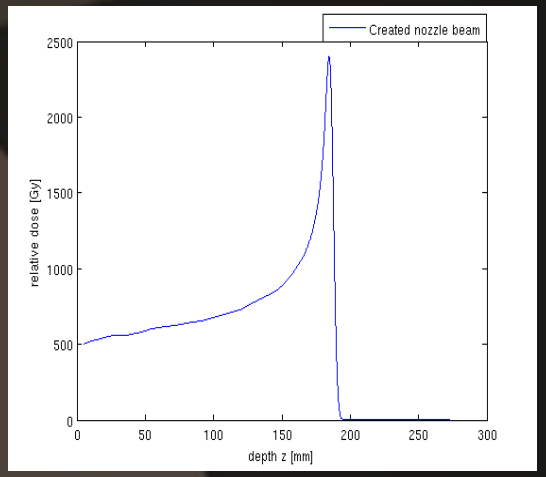
Input: weights

+



Input: pencil beam

=



Output: nozzle beam

Compare!

Optimization

Output: weights

=

Input: pencil beam

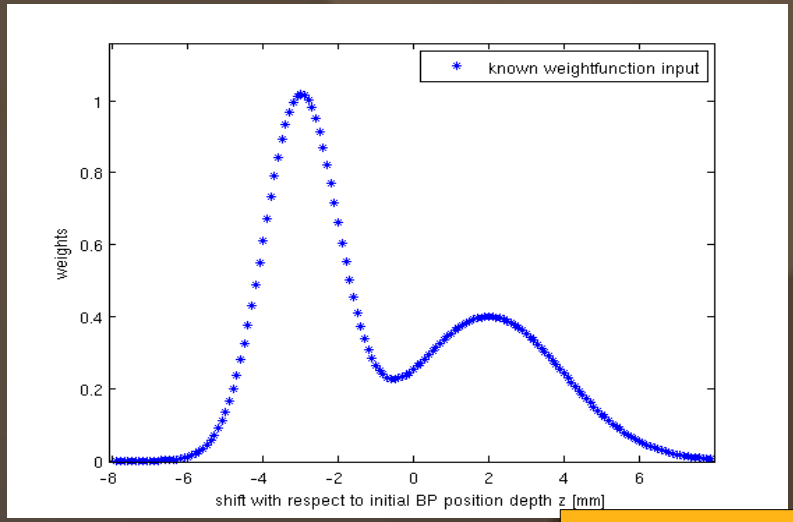
+

Input: nozzle beam

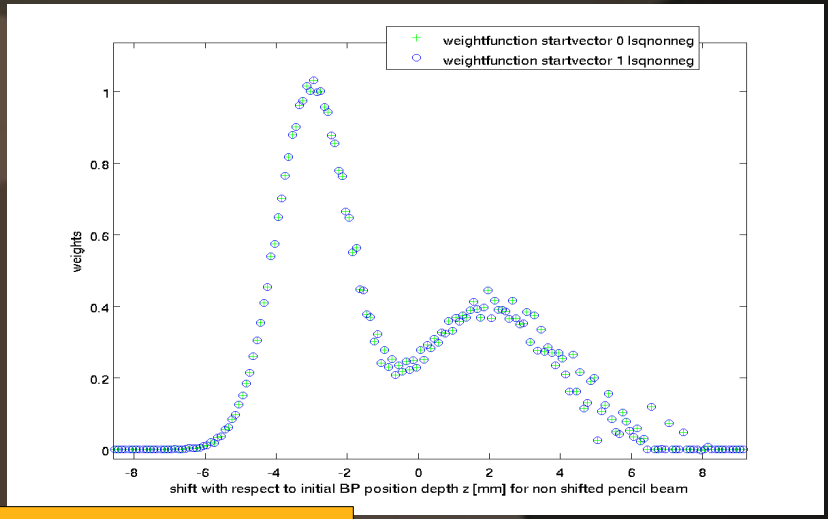
Optimization method: Modifications and checks

Example 1: Double Gaussian unbalanced in height and width

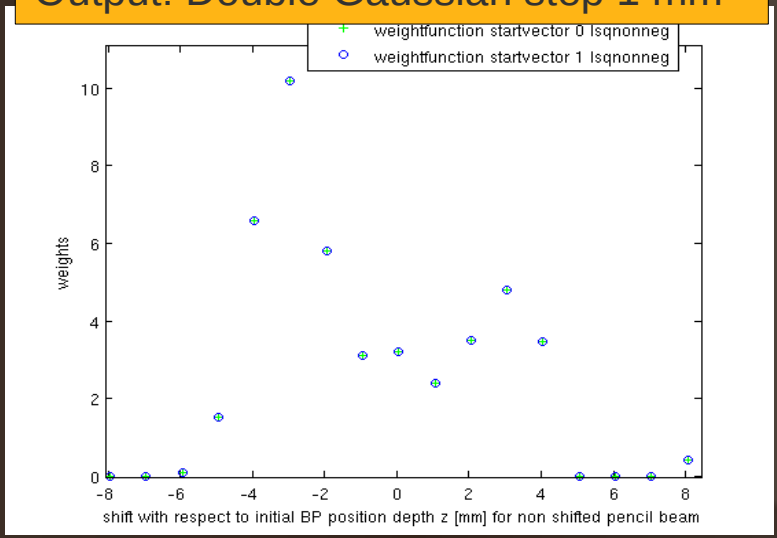
Input: Double Gaussian step 0.1 mm



Output: Double gaussian step 0.1 mm



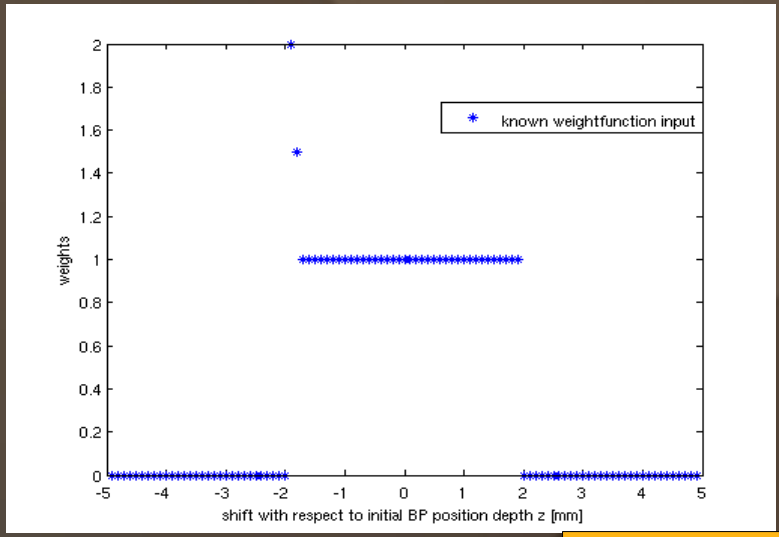
Output: Double Gaussian step 1 mm



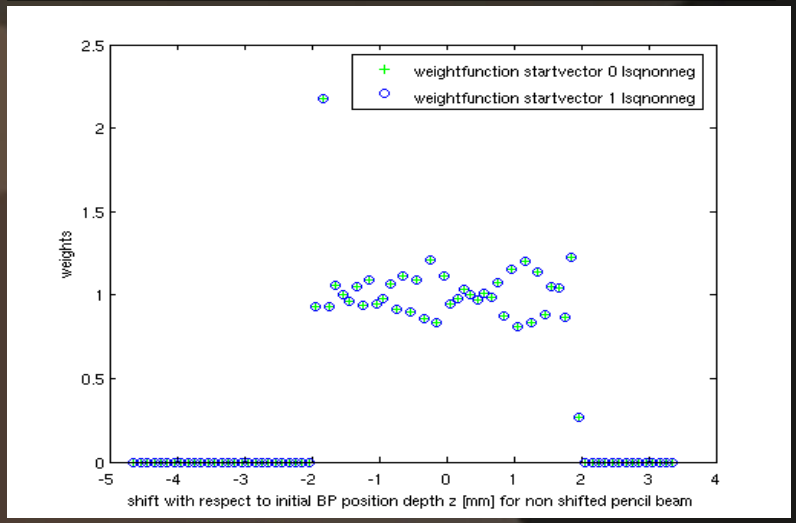
Optimization method: Modifications and checks

Example 2: Ripple filter

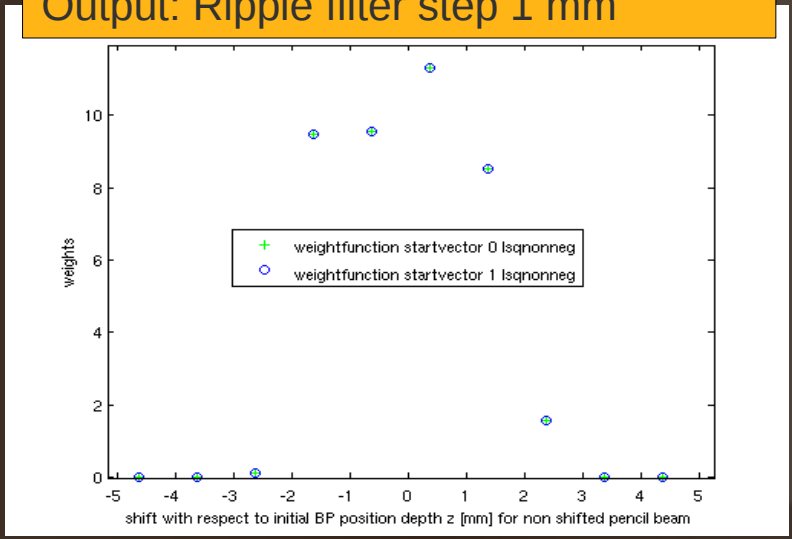
Input: Ripple filter step 0.1 mm



Output: Ripple filter step 0.1 mm



Output: Ripple filter step 1 mm



Conclusions and outlook

- **The longitudinal nozzle beam dose deposition can be modeled** by a pencil beam convoluted with a transfer function (DFT method) or by the superposition of many pencil beams (weight optimization method).
  - Both algorithms (DFT and optimization method) are technically working well: **test on physical and biological carbon ion simulations of ripple filter successfully done, test on physical experimental proton data done**.
  - **For practical reasons we decided from now on to concentrate on the modified optimization method approach.**
- **The radial nozzle beam dose deposition can be modeled** by two independent Gaussians with variable sigma.
  - **Analysis done for experimental proton data.**
  - We have to **implement and to test the transfer function for the radial part.**
- **Factorization of the 3-D transfer function.**
  - **We have to integrate the procedures for the longitudinal and for the radial part of the transfer function in one program and to test the factorization** (Matlab prototype and C++).

Summary 2009 - 2010

Done and future work on TPS project

- ***Biological dose optimization:***

✓ ***Done 2010:*** First implementation and test of the biological dose optimization with basic cost function and optimization method (CG) on a small volume in Matlab.

→ ***To do in 2011:*** Implementation and test of other optimization methods (SD, QN, …) on realistic treatment volume in Matlab. Integration in TPS kernel (translated in C++ and with gsl or other appropriate optimization library). Research on and implementation and test of start vector methods. Modeling of advanced cost function and its derivatives.

- ***Beam modeling:***

✓ ***Done 2009-2010:*** First implementation and test of the beam line transfer function (BTF) method for the longitudinal part for physical (on carbon ion ripple filter simulation and proton data) and for biological dose (only carbon) in Matlab. First implementation and test on interpolated BTF method on proton data.

→ ***To do in 2011:*** Complete implementation in 3-D of the BTF method (normal and interpolated) and test on realistic carbon data or simulation (for physical and biological dose). Integration in TPS kernel (translated in C++ with gsl library).

Summary 2009 – 2010
Work presented on conferences and publications

- ***INFN TPS collaboration meetings:***
  - **TPS Napoli 2009, TPS Torino 2009, TPS Milano 2010, TPS Legnaro 2010, TPS Frascati 2010** (all with talks, also some with referees from INFN and invited guests of IBA, GSI).
- ***Conferences:***
  - **XCV Congresso Nazionale SIF Bari 2009** (with talk), **XCVI Congresso Nazionale SIF Bologna 2010** (with talk), **XLIX International Winter Meeting on Nuclear Physics Bormio 2011** (with presented poster).
- ***Publications:***
  - ***Bourhaleb F., Attili A., Russo G., Schmitt E., Cirio R., Giordanengo S., Marchetto F., Monaco V., Peroni C., Sacchi R.:* "Biological Modeling of the Beam Delivery Line Components for Active Scan Irradiation Technique in Heavy-Ion Radiotherapy"** *Med. Phys., vol. 36, issue 6, p. 2639 (2009)*
  - ***G. Russo, A. Attili, F. Bourhaleb, F. Marchetto, C. Peroni, E. Schmitt, D. Bertrand:* "Analysis of the reliability of the Local Effect Model for the use in carbon ion treatment planning systems"** *Journal of Radiation Protection Dosimetry, doi:10.1093/rpd/ncq407*
  - ***E. Schmitt, A. Attili, G. Russo, F. Marchetto, V. Monaco, C. Peroni:* "Treatment Planning System (TPS) for Carbon Ion Therapy: The INFN TPS project"** *will be submitted to the refereed conference proceedings of the XLIX International Winter Meeting on Nuclear Physics* (2011)

Thank you!

And see you again for the final PhD presentation in one year... ;-)

INFN TPS project:
http://totlxl.to.infn.it/mediawiki/index.php/Main_Page

Hadrontherapy group of University and INFN Turin:
http://totlxl.to.infn.it/NewSite/introduction.html