MIRD Techniques for Internal Dosimetry

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Outline

- MIRD Schema
  - Simplified MIRD schema
  - Full equations
  - Dose reciprocity theorem
  - Cumulated activity & residence time
  - Voxelized MIRD Shema
- Examples :
  - Internal Organ Dosimetry (Zubal Phantom)
  - Radionuclide Synovectomy
  - P-32 Drug eluting stent

Introduction

- Medical Internal Radiation Dosimetry (MIRD)
  - Calculation of absorbed dose to internal organs
  - Ingredients:
    - Physical property of the radionuclide
    - Biological data distributions
  - Calculations:
    - Conversion of activity into energy emitted
    - Conversion to energy absorbed per unit mass (S-factors)
  - Voxel method extends application to any size and shapes in homogeneous medium

MIRD Schema (simplified)

Mean dose to target organ per unit administered activity:

$$\overline{D}/A_0 = \tau\, S$$

τ : residence time

S : dose to target from unit cumulated activity in source organ (S-factor)

Radiopharmaceuticals of major interests in nuclear medicine :

- **electron emitters**
- **photon emitters**

E = mean energy per particle

n = number of particles emitted per transition

n E = mean energy emitted per transition

A = activity (nuclear transition rate)

$\tilde{A}$ **= activity accumulated over a time interval**

$$\tilde{A}\ n\ E$$

is the <u>radiation energy emitted</u> by the activity in the source during the time interval

A fraction ϕ of the energy emitted will be absorbed,

$$\tilde{A}\ n\ E\ \phi$$

is the <u>energy absorbed</u> (imparted to) the target during the time interval of interest.

The <u>mean absorbed dose</u> to the target is,

$$\overline{D} = \tilde{A}\ n\ E\ \phi/m$$

where *m* is the mass of the target.

In more convenient form:

Mean energy emitted per nuclear transition:

$$\Delta = n E$$

Specific absorbed fraction,

$$\Phi = \phi/m$$

The S-factor is defined by,

$$S = \Delta \Phi$$

Mean absorbed dose to the target,

$$\overline{D} = \tilde{A} S$$

Define the residence time,

$$\tau = \tilde{A}/A_0$$

where A_0 is the administered activity.

Mean absorbed dose to the target,

$$\overline{D}/A_0 = \tau S$$

MIRD Schema (full equations)

Mean dose to target organ per unit administered activity due to a single source:

$$\overline{D}/A_0 = \tau S$$

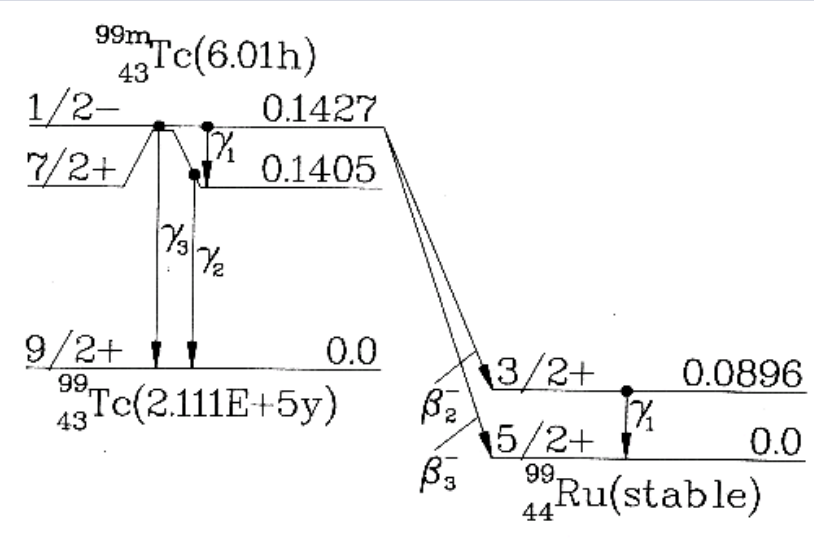
For multiple sources,

$$\overline{D}/A_0 = \sum \tau S$$

where the summation is over all sources (type of radiation, locations).

Radiopharmaceutical emits several kinds of radiation.

(Example: Tc-99m)



43-TECHNETIUM-99M

HALF-LIFE = 6.01 HOURS
DECAY MODE(S): β^-, IT

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RADIATION	PARTICLES/ TRANSITION n(i)	ENERGY/ PARTICLE E(i) MeV	ENERGY/TRANSITION Δ(i) rad g/μCi h	Δ(i) Gy kg/Bq s
ce-M, γ 1	9.16E-01	1.748E-03†	3.41E-03	2.56E-16
ce-N+, γ 1	7.58E-02	2.173E-03†	3.51E-04	2.64E-17
γ 2	8.91E-01	1.405E-01	2.67E-01	2.00E-14
ce-K, γ 2	8.84E-02	1.195E-01	2.25E-02	1.70E-15
ce-L1, γ 2	9.72E-03	1.375E-01	2.85E-03	2.15E-16
ce-L2, γ 2	6.32E-04	1.377E-01	1.85E-04	1.40E-17
ce-L3, γ 2	3.29E-04	1.378E-01	9.66E-05	7.26E-18
ce-M, γ 2	1.94E-03	1.401E-01†	5.79E-04	4.36E-17
ce-N+, γ 2	3.74E-04	1.405E-01†	1.12E-04	8.43E-18
ce-K, γ 3	5.53E-03	1.216E-01	1.43E-03	1.08E-16
ce-L1, γ 3	9.34E-04	1.396E-01	2.78E-04	2.08E-17
ce-L2, γ 3	1.94E-04	1.398E-01	5.78E-05	4.34E-18
ce-L3, γ 3	5.92E-04	1.400E-01	1.77E-04	1.33E-17
ce-M, γ 3	3.35E-04	1.422E-01†	1.02E-04	7.64E-18
Kα1 x-ray	3.99E-02	1.837E-02	1.56E-03	1.17E-16
Kα2 x-ray	2.10E-02	1.825E-02	8.17E-04	6.14E-17
Kβ1 x-ray	6.82E-03	2.062E-02	3.00E-04	2.26E-17
Auger-KL1L1	1.23E-03	1.487E-02	3.90E-05	2.95E-18
Auger-KL1L2	2.14E-03	1.512E-02	6.90E-05	5.17E-18
Auger-KL1L3	1.64E-03	1.524E-02	5.33E-05	4.00E-18
Auger-KL2L3	6.44E-03	1.547E-02	2.12E-04	1.60E-17
Auger-KL3L3	2.43E-03	1.559E-02	8.07E-05	6.07E-18
Auger-KL1X	1.80E-03	1.755E-02†	6.73E-05	5.05E-18
Auger-KL2X	1.42E-03	1.780E-02†	5.39E-05	4.05E-18
Auger-KL3X	2.49E-03	1.792E-02†	9.51E-05	7.13E-18
Auger-L2MM	1.98E-02	2.125E-03†	8.97E-05	6.74E-18
Auger-L2MX	8.37E-03	2.538E-03†	4.53E-05	3.40E-18
Auger-L3MM	4.81E-02	2.009E-03†	2.06E-04	1.55E-17
Auger-L3MX	2.07E-02	2.422E-03†	1.07E-04	8.03E-18
Auger-MXY	1.11E+00	4.092E-04†	9.68E-04	7.27E-17
Listed x,γ and γ± radiations			2.69E-01	2.02E-14
Omitted x,γ and γ± radiations‡			3.22E-04	2.42E-17
Listed β,ce and Auger radiations			3.43E-02	2.58E-15
Omitted β,ce and Auger radiations‡			1.22E-04	9.20E-18
Listed radiations			3.03E-01	2.27E-14
Omitted radiations‡			4.45E-04	3.35E-17

† Average energy
‡ Each omitted transition contributes <0.100% to ΣΔ(i) in its category.
RUTHENIUM-99 daughter, yield 3.70E-05, is stable.
TECHNETIUM-99 daughter, yield 9.9996E-01, is radioactive.

The mean energy of the i-type radiation is,

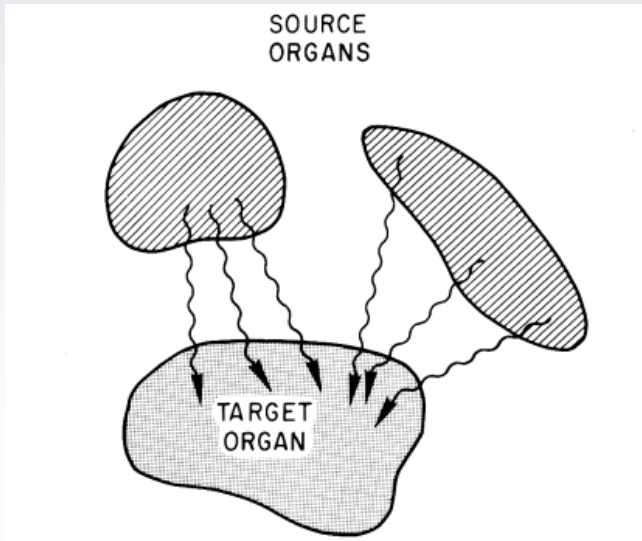
$$\Delta_i = K\, n_i\, E_i$$

where K is a constant (units).

Several sources organs may contribute to the target organ,

The absorbed fraction in target organ r_k from source organ r_h is:

$$\phi_i(r_k \leftarrow r_h)$$



$$\phi_i(r_k \leftarrow r_h) = \frac{\text{i-type radiation energy emitted in source } r_h \text{ and absorbed in target } r_k}{\text{i-type radiation energy emitted in } r_h}$$

Depends on:

- type and energy of the radiation

- size, shape and composition of the source and target

Value lies between 0 and 1,

$$0 \leqslant \phi_i\,(r_k \leftarrow r_h) \leqslant 1$$

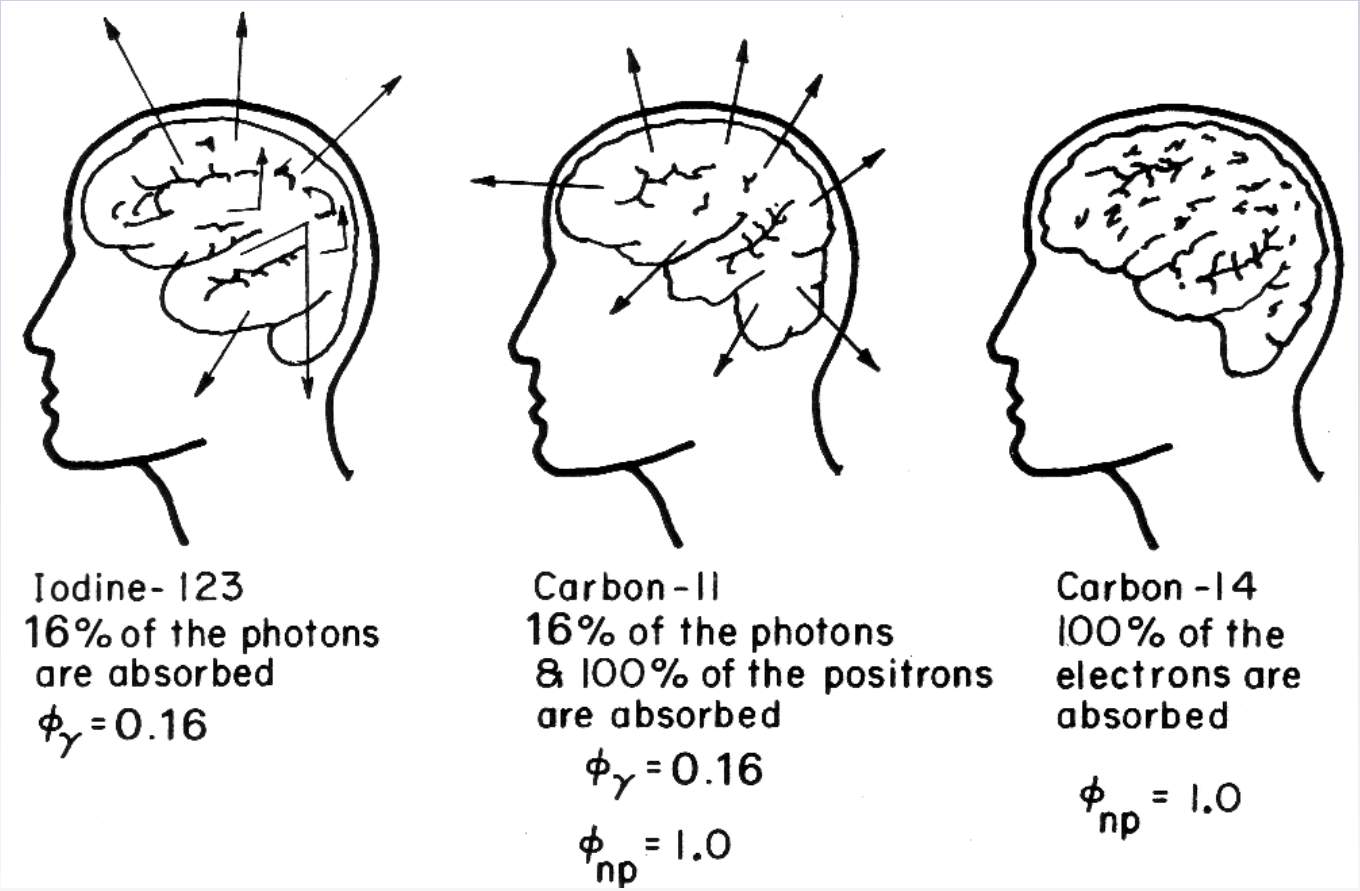
Non-penetrating (np) radiation:

$$\phi_{np}(r_h \leftarrow r_h) = 1;$$

$$\phi_{np}(r_k \leftarrow r_h) = 0,\ k \neq h$$

i.e., the source organ is the only target organ.

Beta particles, electrons and low energy photons (< 20 keV) can be considered non penetrating for internal organ dosimetry.



γ(159 keV) + low energy electrons

$\beta^+ + \gamma$ (511 keV)

β^- (E_{max}=156 keV)

The specific absorbed fraction in target r_k from source r_h for i-type radiation is,

$$\Phi_i(r_k \leftarrow r_h) = \phi_i(r_k \leftarrow r_h)/m_k$$

where m_k is the mass of the target organ.

The mean absorbed dose per unit cumulated activity is for i-type radiation is,

$$S_i(r_k \leftarrow r_h) = \Delta_i \, \Phi_i(r_k \leftarrow r_h)$$

S values have been tabulated for monoenergetic electrons and photons and for different source and target organs.

S values are also tabulated for specific isotopes for different sources and target organs

$$S(r_k \leftarrow r_h) = \sum_i S_i(r_k \leftarrow r_h)$$

MIRDOSE (PC program no longer available)
Replaced by OLINDA

http://www.doseinfo-radar.com/RADARphan.html

Mean absorbed dose in target r_k from source r_h,

$$\overline{D}(r_k \leftarrow r_h) = \tilde{A}_h \sum_i \Delta_i \, \phi_i(r_k \leftarrow r_h)/m_k$$

$$= \tilde{A}_h \sum_i \Delta_i \, \Phi_i(r_k \leftarrow r_h)$$

$$= \tilde{A}_h \, S(r_k \leftarrow r_h)$$

Total dose in target r_k (summed over all sources) ,

$$\overline{D}(r_k) = \sum_h \overline{D}(r_k \leftarrow r_h)$$

Using the residence time,

$$\tau_h = \tilde{A}_h / A_0$$

the total dose in target r_k (summed over all sources) is ,

$$\overline{D}(r_k)/A_0 = \sum_h \tau_h \, S(r_k \leftarrow r_h)$$

In simplest form,

$$\overline{D}/A_0 = \sum \tau S$$

Dose Reciprocity theorem

Specific absorbed fraction,

$$\Phi = \phi / m_t$$

= radiation emitted by the source organ that is absorbed by the target organ.

<u>Dose reciprocity theorem</u>

$$\phi(r_h \leftarrow r_k)/m_h = \phi(r_k \leftarrow r_h)/m_k$$

or,

$$\Phi(r_k \leftarrow r_h) = \Phi(r_h \leftarrow r_k)$$

i.e., energy absorbed per gram is the same for radiation traveling from r_k to r_h vs from r_h to r_k.

S, Absorbed Dose per Unit Cumulative Activity (rad/μCi · hr) for ^{131}I

	Source Organs									
			Intestinal Tract							
Target Organs	*Adrenals*	*Bladder Contents*	*Stomach Contents*	*SI Contents*	*ULI Contents*	*LLI Contents*	*Kidneys*	*Liver*	*Lungs*	*Other Tissue (Muscle)*
Adrenals	3.1E-02	6.1E-07	6.3E-06	3.9E-06	2.7E-06	1.4E-06	3.2E-05	1.4E-05	6.9E-06	4.2E-06
Bladder wall	3.3E-07	1.2E-03	1.0E-06	8.5E-06	5.6E-06	1.7E-05	1.0E-06	7.4E-07	1.8E-07	5.0E-06
Bone (total)	4.1E-06	1.8E-06	1.8E-06	2.5E-06	2.2E-06	3.2E-06	3.0E-06	2.3E-06	3.0E-06	3.0E-06
GI (Stom. wall)	8.2E-06	8.8E-07	9.7E-04	9.9E-06	1.0E-05	5.0E-06	9.4E-06	5.4E-06	5.2E-06	3.9E-06
GI (SI)	2.6E-06	7.6E-06	7.3E-06	6.0E-04	4.6E-05	2.6E-05	7.8E-06	4.6E-06	6.9E-07	4.4E-06
GI (ULI wall)	2.8E-06	6.6E-06	9.5E-06	6.5E-05	1.1E-03	1.2E-05	8.1E-06	7.0E-06	9.1E-07	4.6E-06
GI (LLI wall)	8.4E-07	2.0E-05	3.6E-06	1.9E-05	8.4E-06	1.7E-03	2.4E-06	8.1E-07	2.6E-07	4.8E-06
Kidneys	3.2E-05	9.6E-07	9.5E-06	8.7E-06	7.7E-06	2.5E-06	1.5E-03	1.1E-05	2.7E-06	4.0E-06
Liver	1.4E-05	7.2E-07	5.6E-06	5.1E-06	7.1E-06	9.0E-07	1.1E-05	3.0E-04	6.8E-06	3.1E-06
Lungs	6.7E-06	1.1E-07	5.0E-06	8.5E-07	8.9E-07	2.8E-07	2.5E-06	6.8E-06	4.5E-04	3.7E-06
Marrow (red)	7.5E-06	4.1E-06	3.2E-06	7.9E-06	6.9E-06	9.7E-06	7.6E-06	3.3E-06	3.8E-06	4.1E-06
Other tissue (muscle)	4.2E-06	5.0E-06	3.9E-06	4.4E-06	4.1E-06	4.8E-06	4.0E-06	3.1E-06	3.7E-06	1.9E-05
Ovaries	1.6E-06	1.9E-05	1.4E-06	2.7E-05	3.4E-05	5.0E-05	3.4E-06	9.6E-07	4.0E-07	5.6E-06
Pancreas	2.4E-05	7.9E-07	5.0E-05	5.8E-06	5.8E-06	2.0E-06	1.8E-05	1.2E-05	7.5E-06	5.0E-06
Skin	1.8E-06	1.7E-06	1.5E-06	1.4E-06	1.4E-06	1.6E-06	1.8E-06	1.6E-06	1.8E-06	2.4E-06
Spleen	1.8E-05	5.6E-07	2.7E-05	4.4E-06	3.7E-06	2.5E-06	2.4E-05	2.7E-06	6.2E-06	4.1E-06
Testes	1.7E-07	1.4E-05	1.3E-07	1.0E-06	1.2E-06	5.7E-06	3.9E-07	3.0E-07	5.7E-08	3.4E-06
Thyroid	5.2E-07	2.1E-08	3.9E-07	9.5E-08	1.0E-07	4.1E-08	2.4E-07	5.7E-07	3.0E-06	3.8E-06
Uterus (nongravid)	3.4E-06	4.3E-05	2.4E-06	2.5E-05	1.3E-05	1.7E-05	2.6E-06	1.2E-06	2.7E-07	5.9E-06
Total body	1.1E-05	5.9E-06	6.7E-06	1.0E-05	8.2E-06	8.8E-06	1.1E-05	1.1E-05	9.9E-06	9.8E-06

$$S(r_k \leftarrow r_h) = \sum_i \Delta_i \, \Phi_i(r_k \leftarrow r_h)$$

Cumulated Activity and Residence time

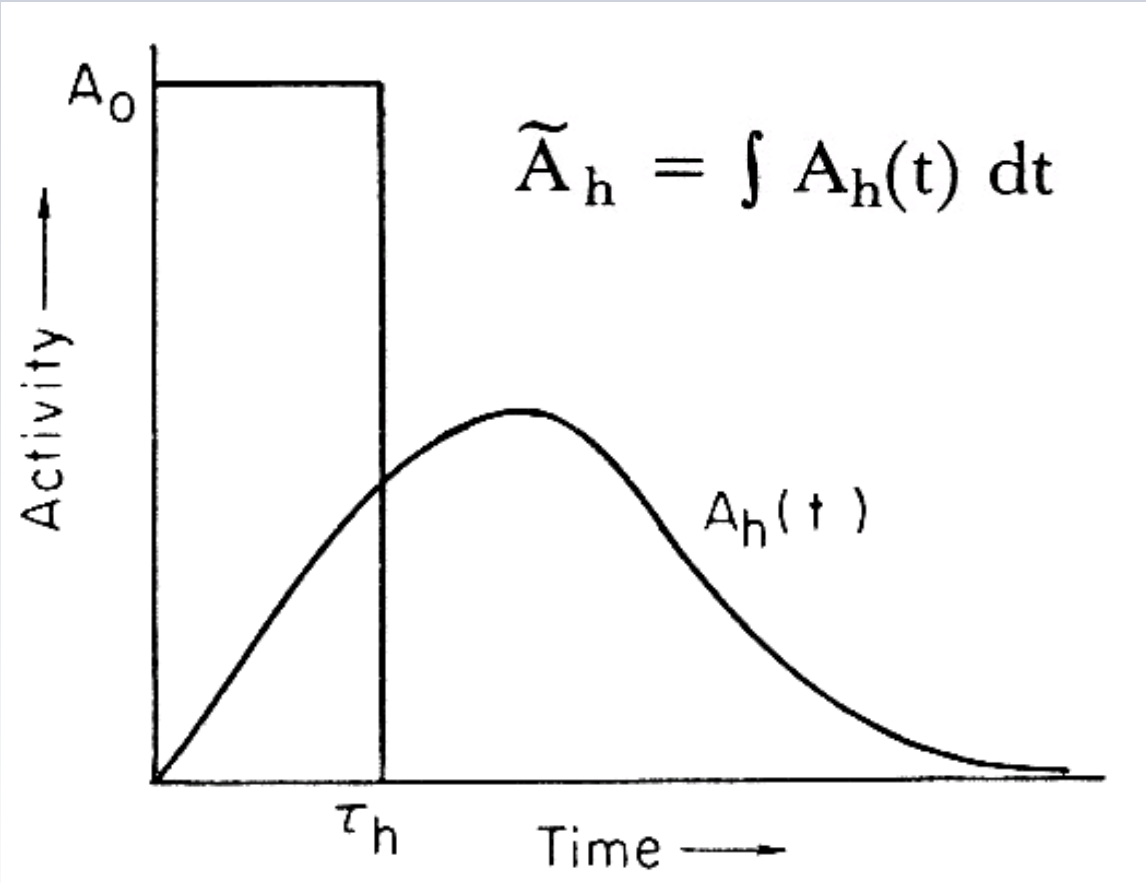
Mean absorbed dose in target r_k from source r_h,

$$\overline{D}(r_k \leftarrow r_h) = \tilde{A}_h \, S(r_k \leftarrow r_h)$$

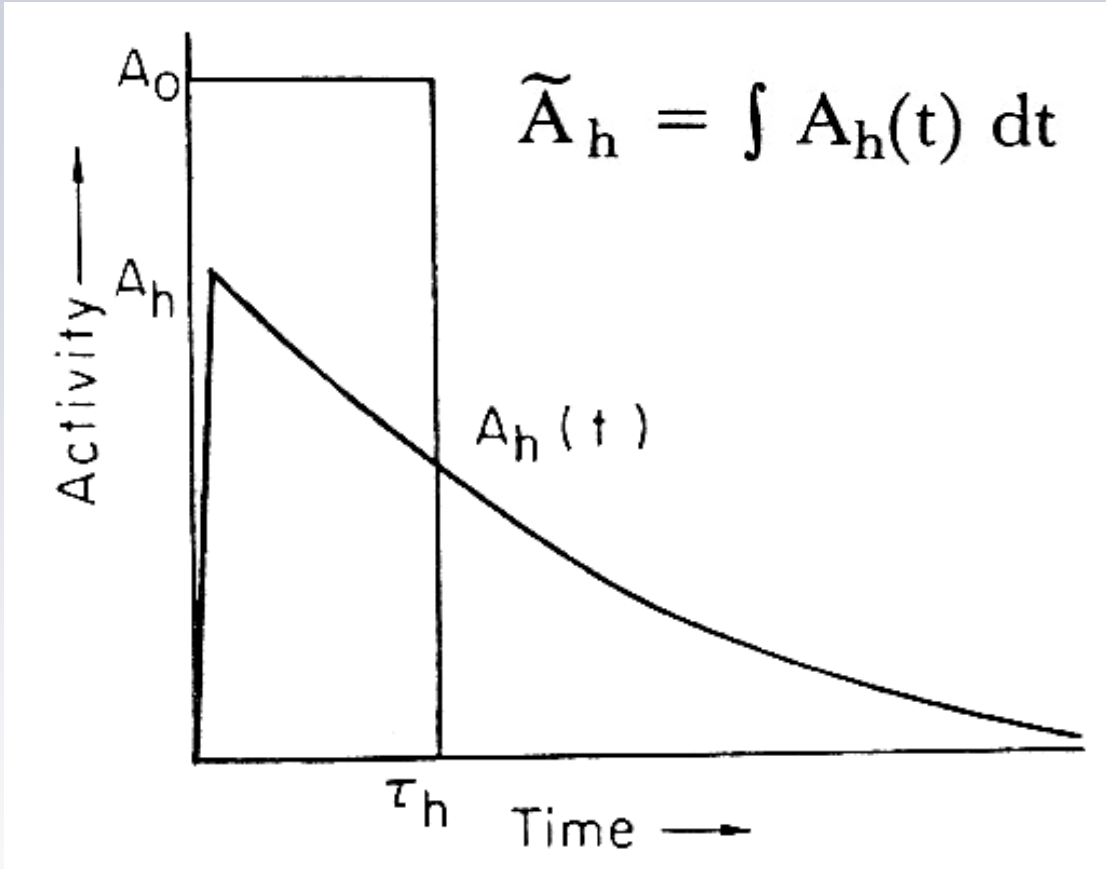
$\tilde{A}_h$ **= activity accumulated over a time interval**

$\tau_h = \tilde{A}_h / A_0$ **= residence time**

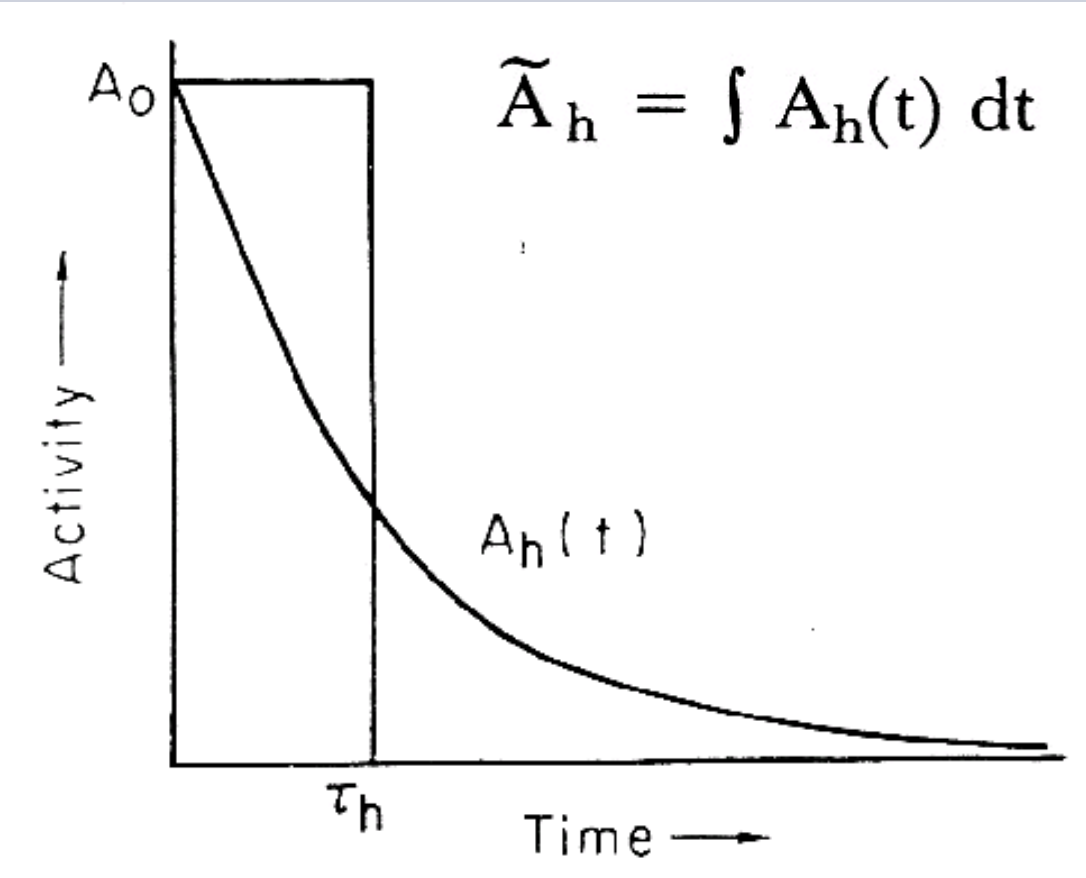
$$\overline{D}(r_k)/A_0 = \sum_h \tau_h \, S(r_k \leftarrow r_h)$$



The concept of residence time (τ_h) for an organ that has no activity at time t = 0. The area under $A_h(t)$ equals the area of the rectangle.



The concept of residence time (τ_h) for an organ that has no activity at time t = 0, with an uptake that is rapid compared to decay and removal rates. The area under $A_h(t)$ equals the area of the rectangle.



The concept of residence time (τ_h) for the organ into which the activity A_0 is administered at time t = 0. The area under $A_h(t)$ equals the area of the rectangle.

Simple exponential decay

$$\lambda = \ln(2)/T_{1/2} \qquad \text{(physical half-life)}$$

$$\lambda_h = \ln(2)/T_h \qquad \text{(biological half-life)}$$

$$\begin{aligned}\tilde{A}_h &= \int_0^\infty A_h\, e^{-(\lambda + \lambda_h)t}\, dt \\ &= A_h/(\lambda + \lambda_h) \\ &= 1.443\,(T_h)_{eff}\, A_h\end{aligned}$$

$$\frac{1}{T_{eff}} = \frac{1}{T_{1/2}} + \frac{1}{T_h}$$

$$(\lambda_h)_{eff} = \lambda + \lambda_h$$

$$(\lambda_h)_{eff} = \frac{\ln(2)}{(T_h)_{eff}} = \frac{1}{1.443\,(T_h)_{eff}}$$

$$\begin{aligned}\tau_h &= \tilde{A}_h/A_0 \\ &= 1.443\,(T_h)_{eff}\,\frac{A_h}{A_0}\end{aligned}$$

Example:

Tc-99m ($T_{1/2}$ = 6.02h) sulfur colloid (liver imaging) is injected to a patient.
Assume 85% is uniformly deposited in the liver with no biologic removal.

- Find the residence time
- calculate self-dose to the liver (S = 4.6e-5 rad/μCi h) for 1 mCi injected activity

$$\tau_h = \tilde{A}_h / A_0 \qquad \tilde{A}_h = A_h \int_0^\infty e^{-\lambda t}\, dt = \frac{A_h}{\lambda}$$

$$\lambda = \frac{\ell n\, 2}{T} = \frac{0.693}{6.02\ h} = 0.115\ h^{-1}$$

$$\tau = \frac{\tilde{A}_h}{A_0} = \frac{A_h}{A_0}\frac{1}{\lambda} = \frac{0.85}{0.115\ h^{-1}} = 7.39\ h$$

A_0 = 1mCi =1000μCi

$$\bar{D} = A_0 \tau S$$ = 1000 μCi x 7.39h x 4.6e-5 rad/μCi h

= 0.332 rad = 3.32 mSv

Limitations of the Standard MIRD Schema

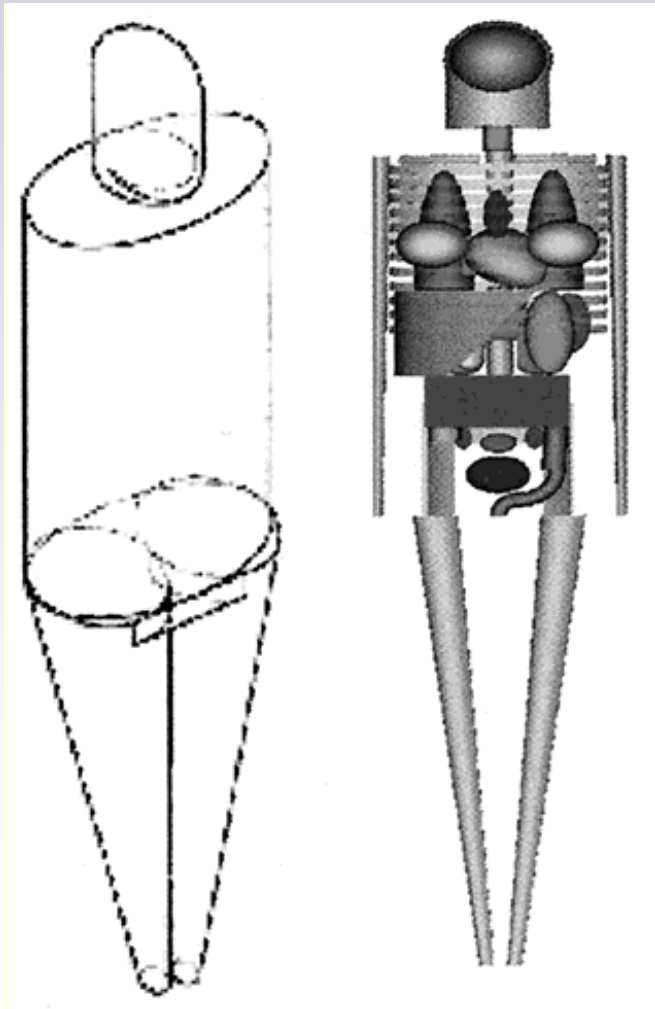
S-factors are defined for "standard" antropomorphic phantoms.

Assumes distribution in organs are uniform

Does not allow for "patient specific" characteristics

S-factors not tabulated for distributions other than organs

Large uncertainties for specific patients

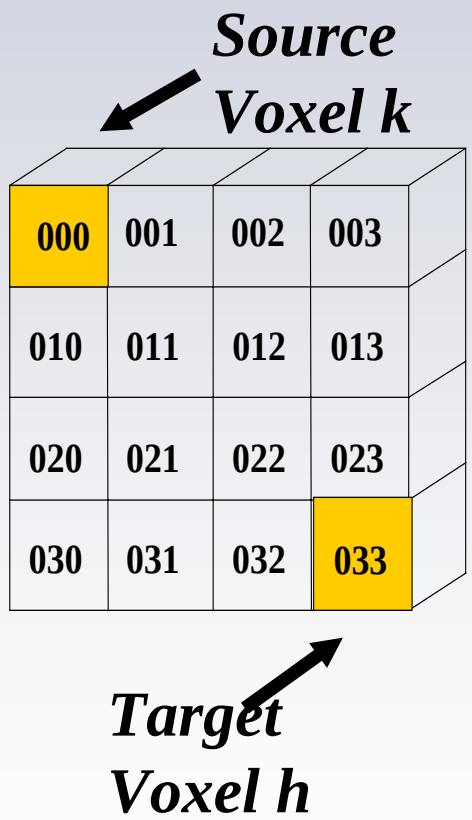


The Voxel S value approach

Sources and targets are defined as "voxels"

$$\bar{D}(\text{voxel}_k) = \sum_{h=0}^{N} \tilde{A}_{\text{voxel}_h} \cdot S(\text{voxel}_k \leftarrow \text{voxel}_h).$$

$$S(\text{voxel}_k \leftarrow \text{voxel}_h) = \sum_i \Delta_i \cdot \frac{\phi_i(\text{voxel}_k \leftarrow \text{voxel}_h)}{m_{\text{voxel}_k}}$$



Ref: MIRD Pamphlet No.17, JNM Vol. 40, No.1, 1999

The Voxel S value approach

Advantages:

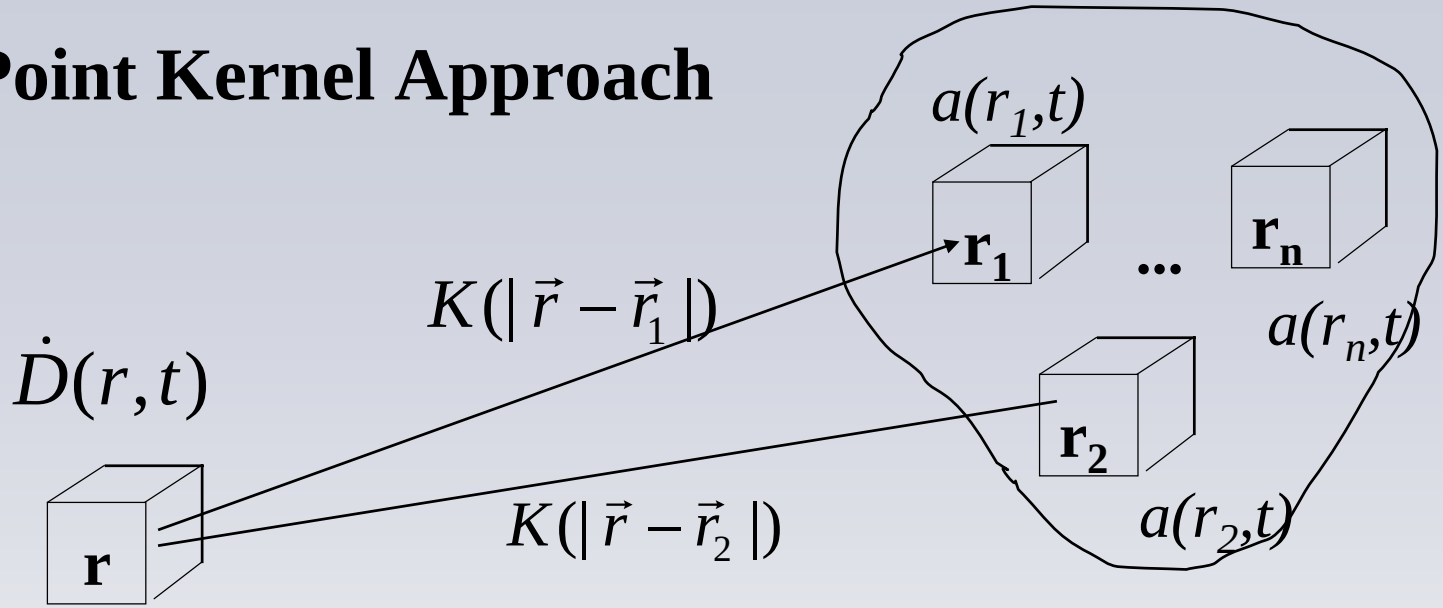
Allows for non-uniform distributions
Can be adapted to any geometry
Allows Patient specific dosimetry
Calculation engine for a "treatment planning system"

Disadvantages:

S-tables not available for all isotopes and voxel sizes
Requires computer calculations to model organs

Treatment planning systems are not commercially available

Dose Point Kernel Approach



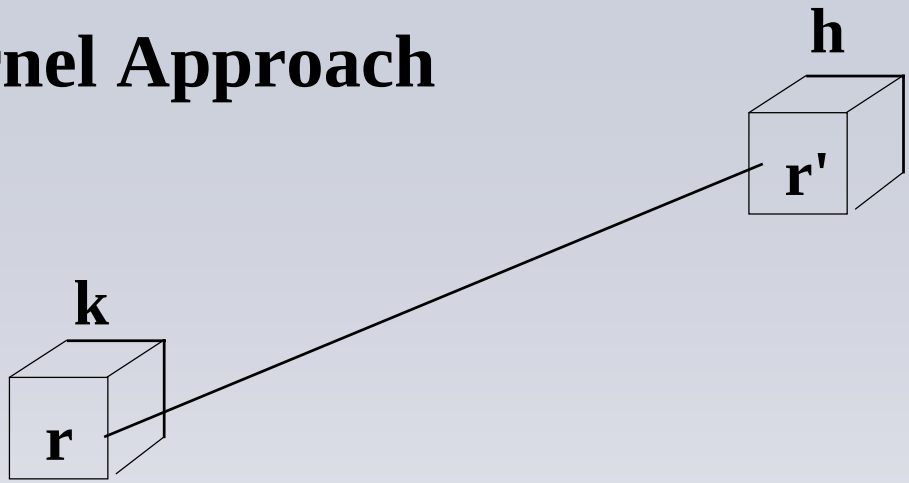
$a(r',t)$ = Activity density (e.g. Bq/cm^3) at r' at time t.

$K(|\vec{r}-\vec{r}'|)$: Dose rate at **r** due to a "Point Source" at **r'** (e.g. mGy/MBq-h).
Depends only on distance $|r - r'|$ if medium is homogeneous.
== "Dose Point Kernel"

The dose rate at point **r** is,

$$\dot{D}(\vec{r},t) = \int a(\vec{r}',t) \times K(|\vec{r}-\vec{r}'|) d^3r'$$

Dose Point Kernel Approach



Consider 2 voxels h and k. The dose rate at a point **r** in voxel k due to a uniform activity a_h in voxel h is,

$$\dot{D}(\vec{r},t) = a_h(t) \times \int_h K(|\vec{r} - \vec{r}'|)\, dV_h$$

The <u>average dose rate</u> in voxel k is (using $a(t) = A(t)/\Delta V$ with A(t) the activity),

$$\dot{D}_k(t) = A_h(t) \times \frac{1}{\Delta V_h \Delta V_k} \int_k \int_h K(|\vec{r} - \vec{r}'|)\, dV_h\, dV_k$$

Dose Point Kernel Approach vs MIRD Shema

$$\dot{D}_k(t) = A_h(t) \times \frac{1}{\Delta V_h \Delta V_k} \int_k \int_h K(|\vec{r} - \vec{r}'|)\, dV_h\, dV_k$$

Integrating over *dt*, we obtain

$$D_{k \leftarrow h}(t) = \tilde{A}_h(t)\, S_{k \leftarrow h}$$

with,

$$\tilde{A}_h(t) = \int_0^t A_h(t) dt$$

$$S_{k \leftarrow h} = \frac{1}{\Delta V_k\, \Delta V_h} \iint_{h\,k} K(|\vec{r} - \vec{r}'|) dV_h dV_k$$

Dose Point Kernel Approach vs MIRD Shema

The total dose in voxel k is obtained by summing over all voxels h,

$$D_k = \sum_h \tilde{A}_h S_{k \leftarrow h}$$

This is a "convolution" formula and can be calculated using FFTs.

The S-factors can be calculated using numerical integration of the Dose-Point-Kernel functions over voxel volume ΔV_k and ΔV_h,

$$S_{k \leftarrow h} = \frac{1}{\Delta V_k \, \Delta V_h} \iint_{h\,k} K(|\vec{r} - \vec{r}'|) dV_h dV_k$$

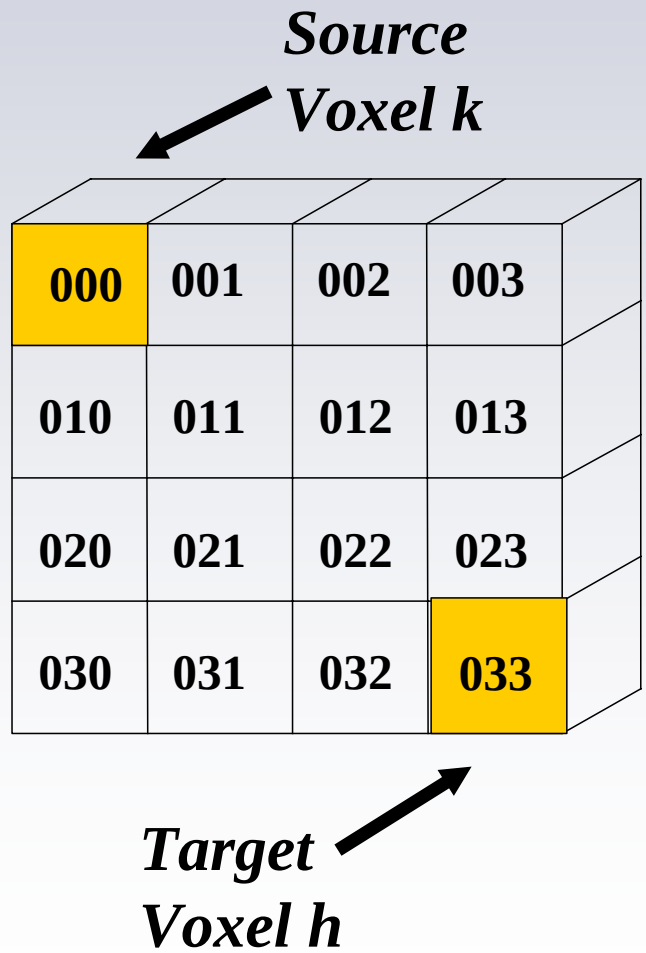
S-factors at the Voxel Level

$S_{k \leftarrow h}$ at voxel level can be calculated using numerical integration of the DPK :

$$S_{k \leftarrow h} = \frac{1}{\Delta V_k \, \Delta V_h} \iint_{h\,k} K(|\vec{r} - \vec{r}'|) dV_h dV_k$$

$$\approx K(|\vec{r} - \vec{r}'|) \text{ at large distances}$$

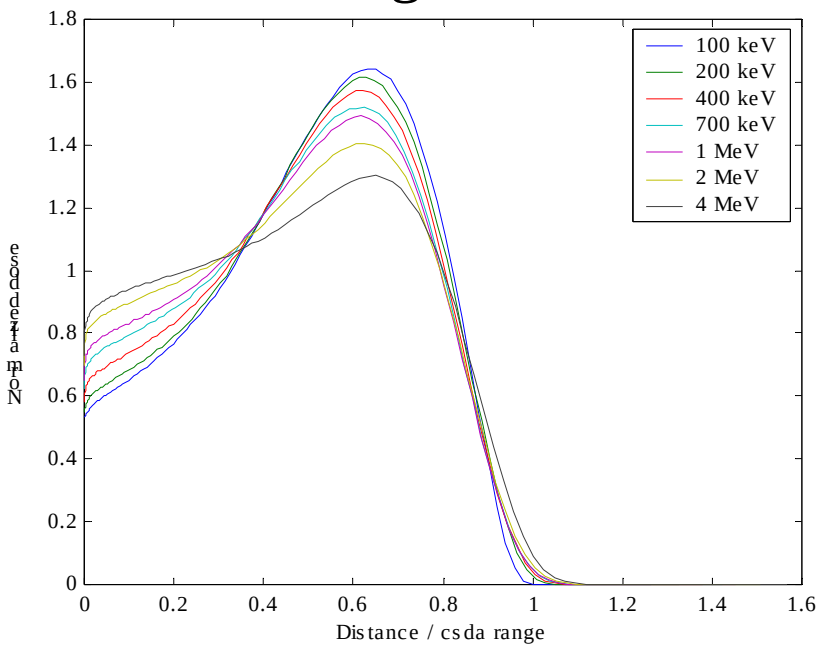
⇨ **Convolution Kernel**



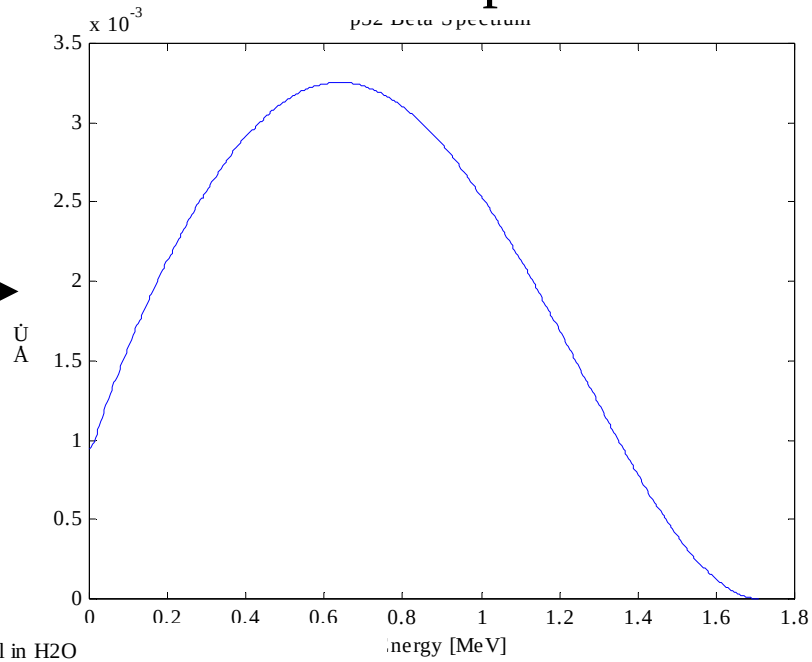
S-factors at the Voxel Level

- MIRD Pamphlet-17 gives tables for P-32, Sr-89, Y-90, Tc-99m and I-131 for cubic voxels sizes of 3 - 6 mm and 0.1 mm (I-131)
- For other isotopes or voxel sizes (cubic or non-cubic), no data is available
- This work :
  - Develop a kernel convolution software to calculate the S-factors for any voxel sizes (cubic and non-cubic)
  - Used 6-D numerical integration method to voxelize K(r)
  - Use EGSnrc generated Kernels for beta emitters
  - Gamma emitters calculated using build-up factors from MIRD-2
  - Use ICRP-38 and/or MIRD database (RSIC DLC-172)

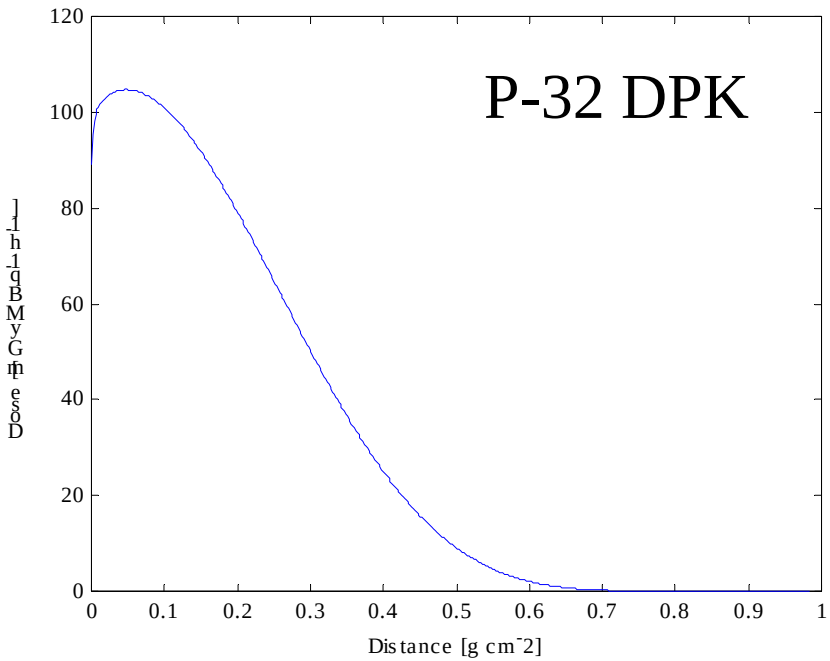
Monoenergetic DPK's



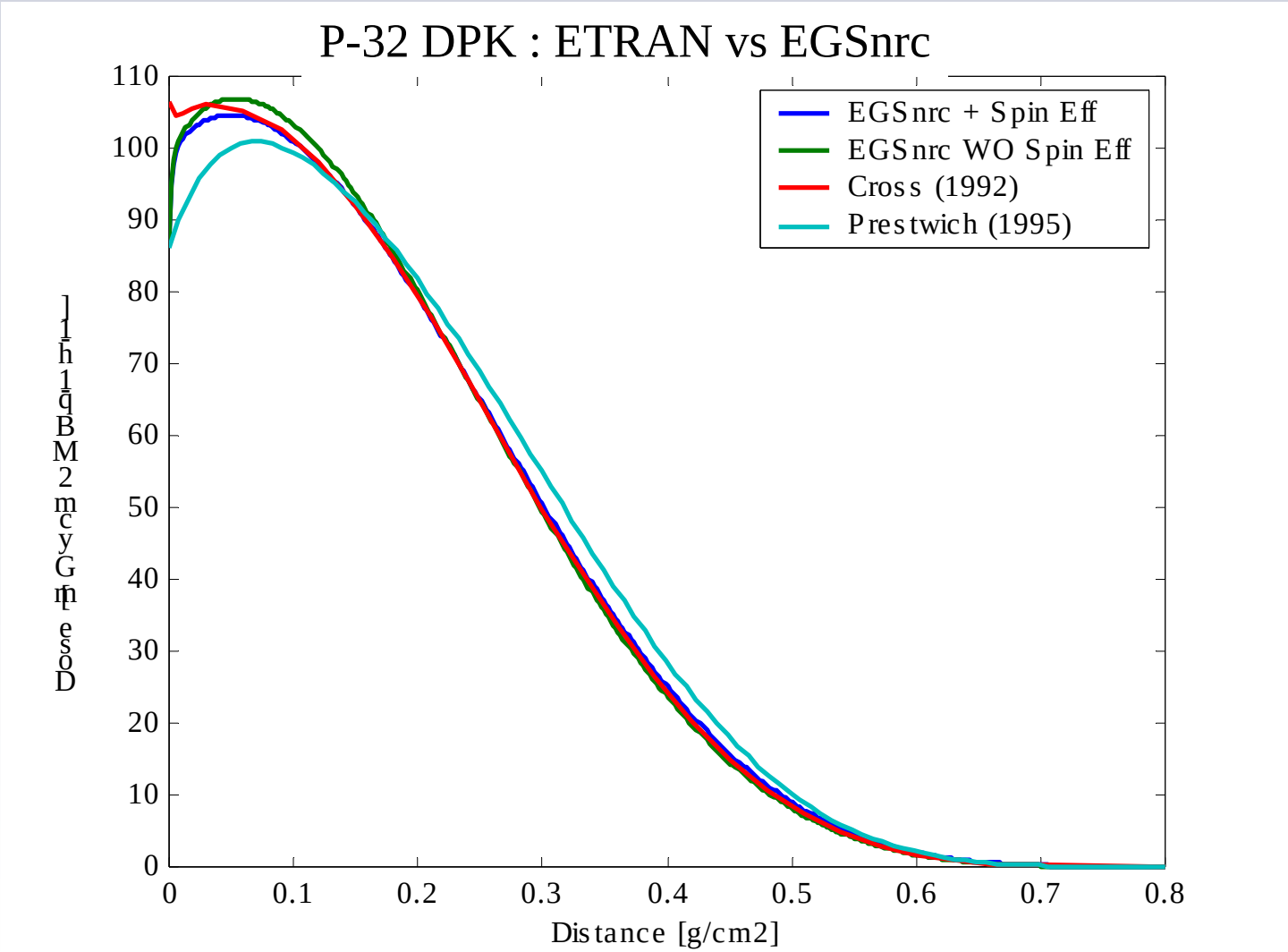
P-32 beta spectrum



P-32 DPK



P-32 Dose-Point-Kernel

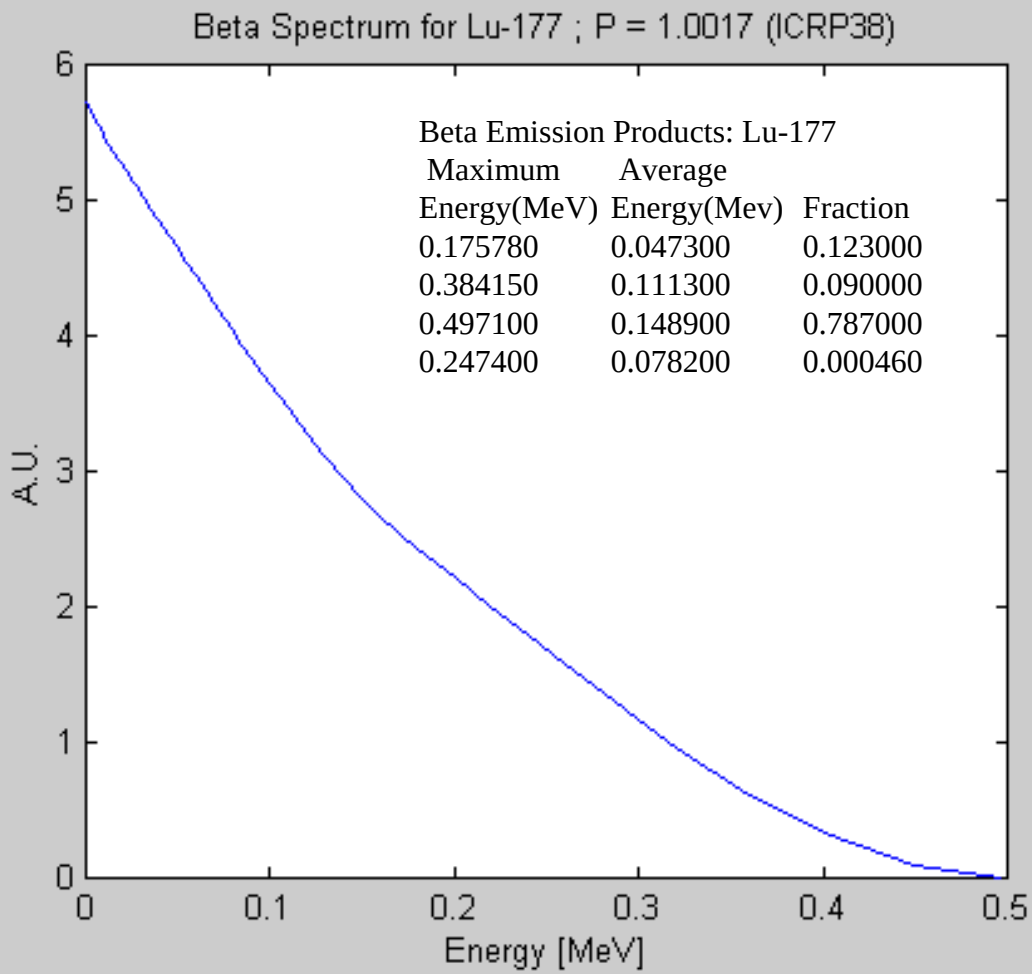


Beta Kernel Calculation

Press RETURN to Continue ...

ICRP 38 MIRD

Isotope Lu-177 Al-28 Calculate Kernel SAVE EXIT

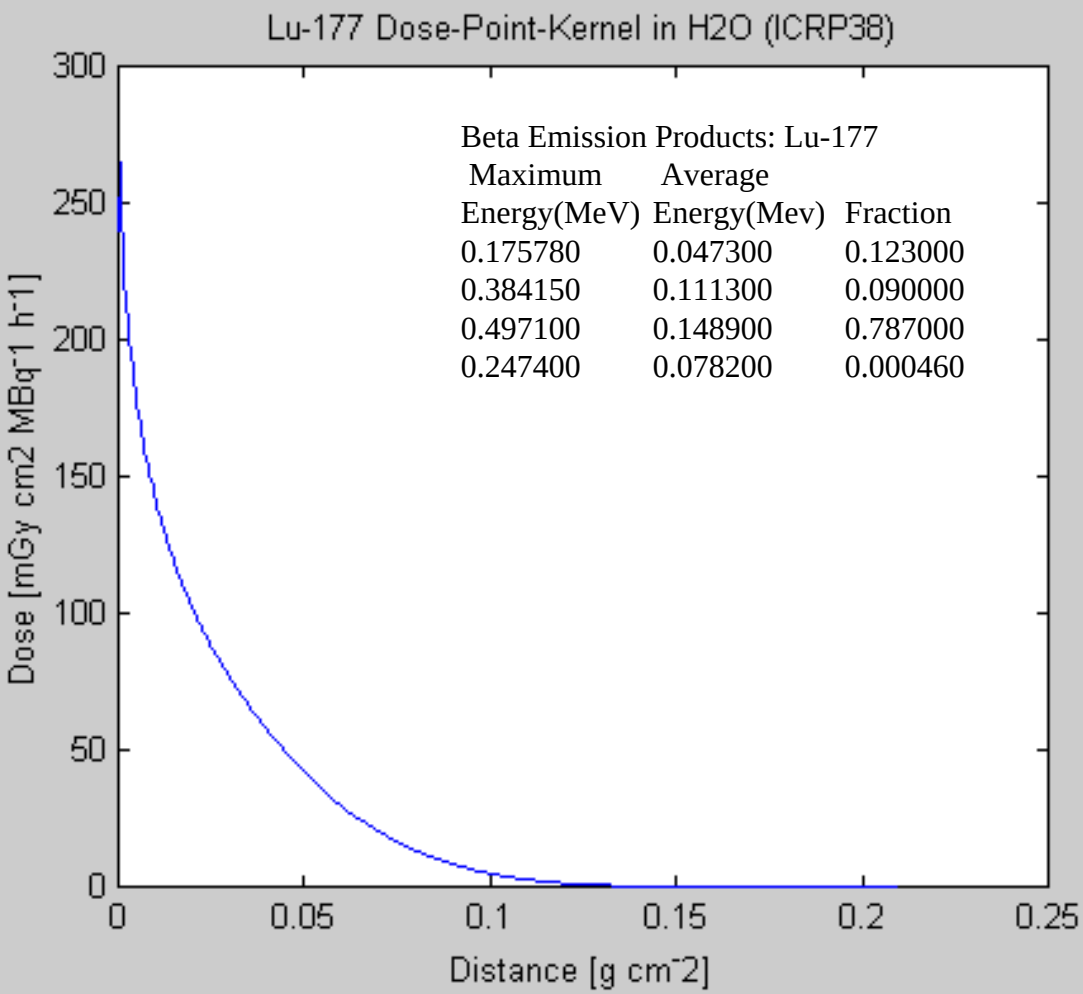


Beta Kernel Calculation

Click to SAVE KLu177_ICRP38.dat

ICRP 38 MIRD

Isotope Lu-177 Al-28 Calculate Kernel SAVE EXIT



Beta Emission Products: Lu-177

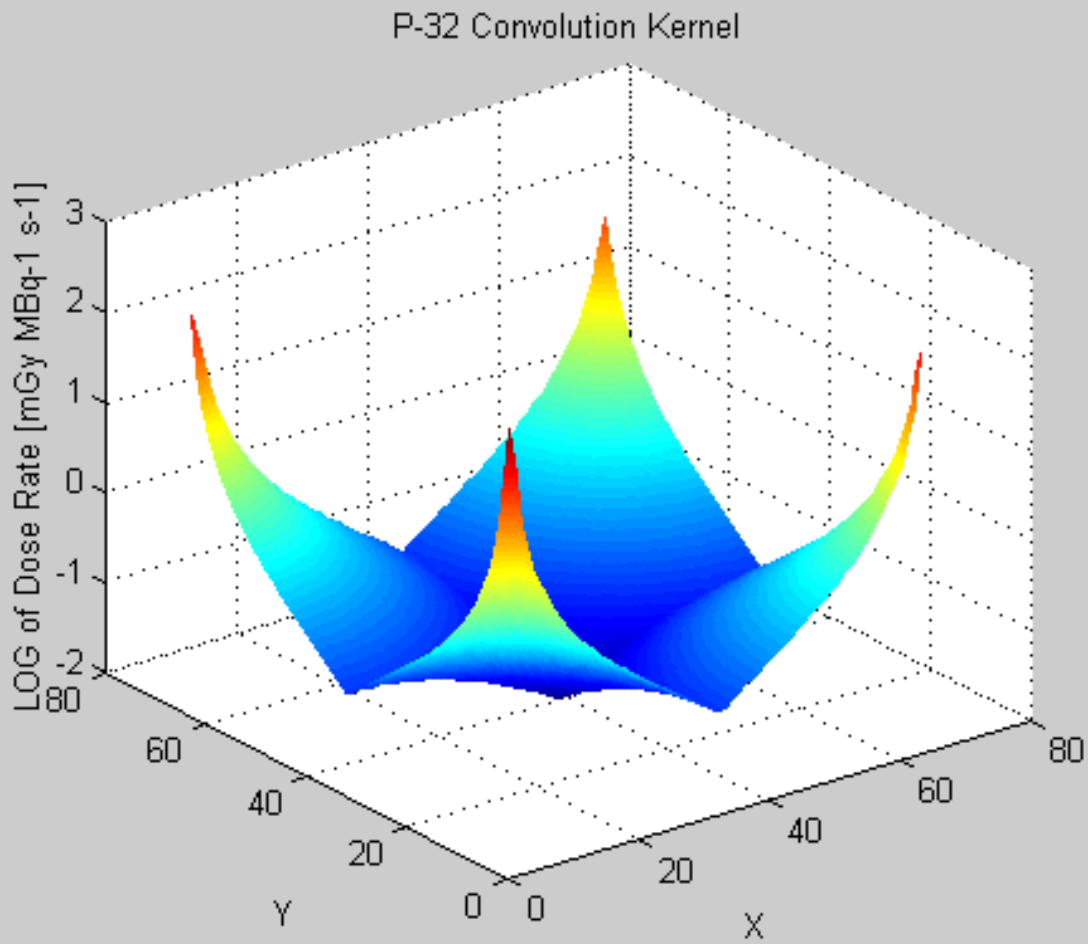
Maximum Energy(MeV)	Average Energy(Mev)	Fraction
0.175780	0.047300	0.123000
0.384150	0.111300	0.090000
0.497100	0.148900	0.787000
0.247400	0.078200	0.000460

S-Voxel Kernel Calculation

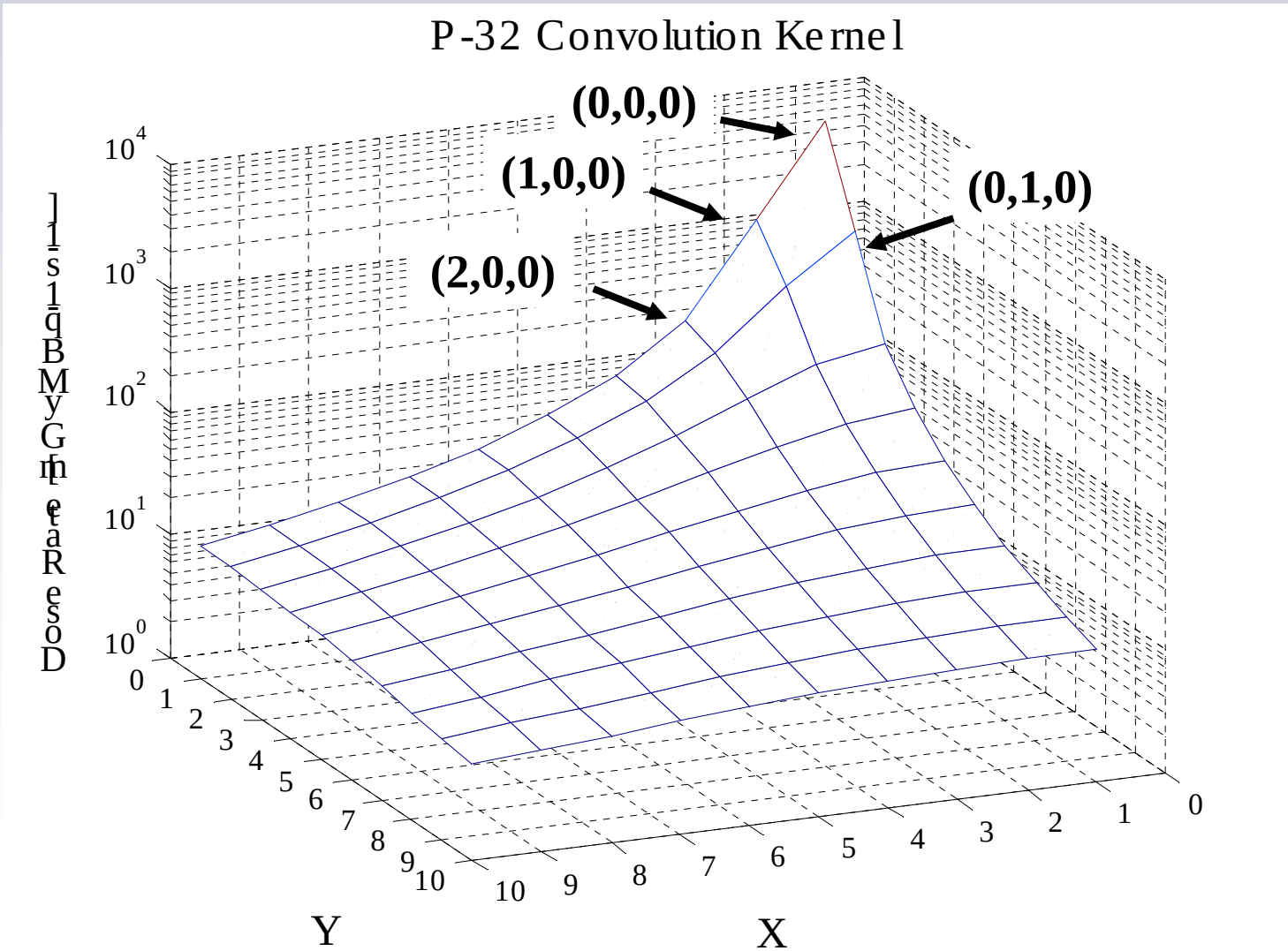
	X	Y	Z
Grid Size	64	64	64
Pizel size (cm)	0.01	0.01	0.02

Isotope: P-32

Calculate S-voxels

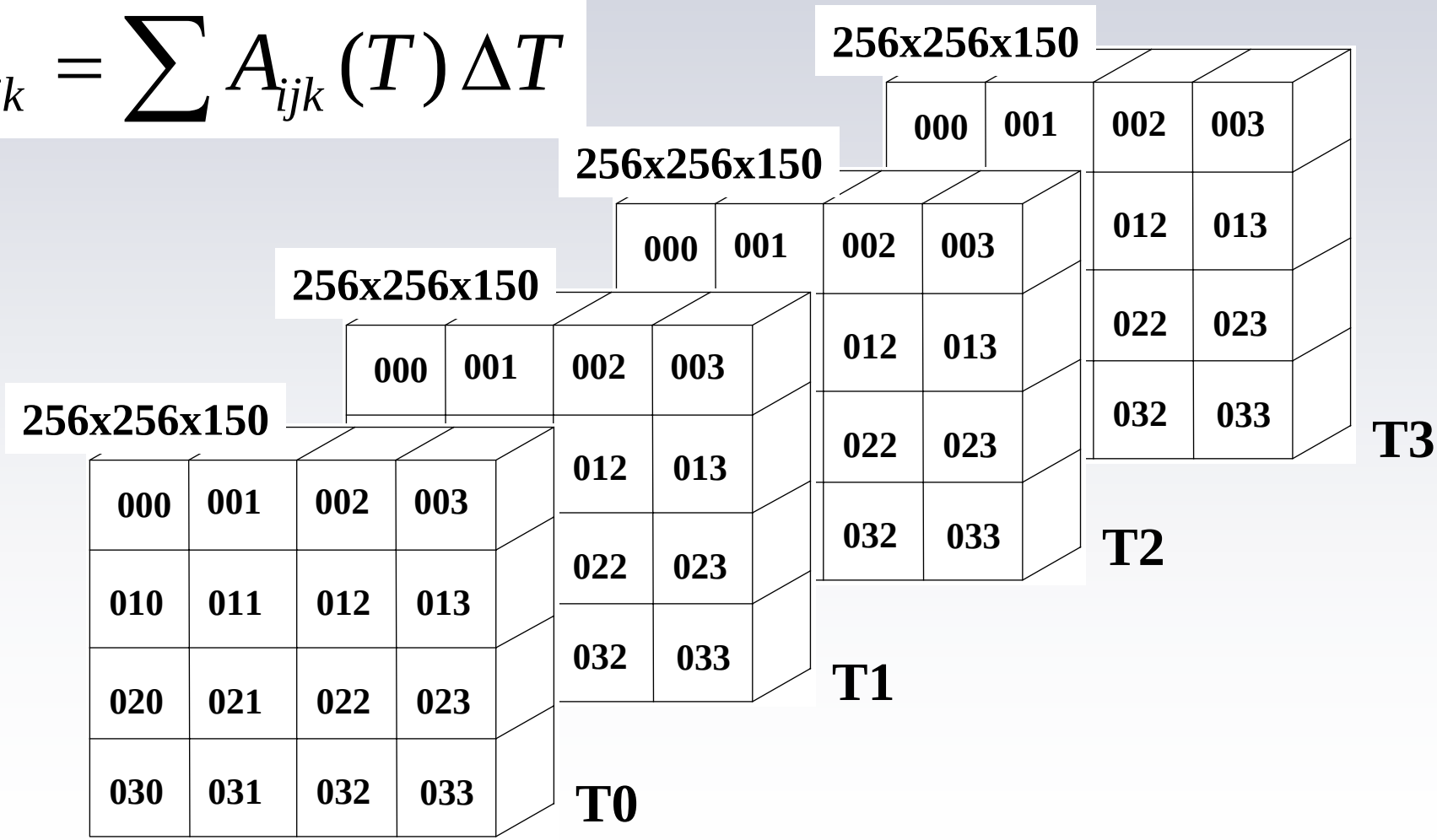


Voxel based P-32 Convolution Kernel S_{ijk}

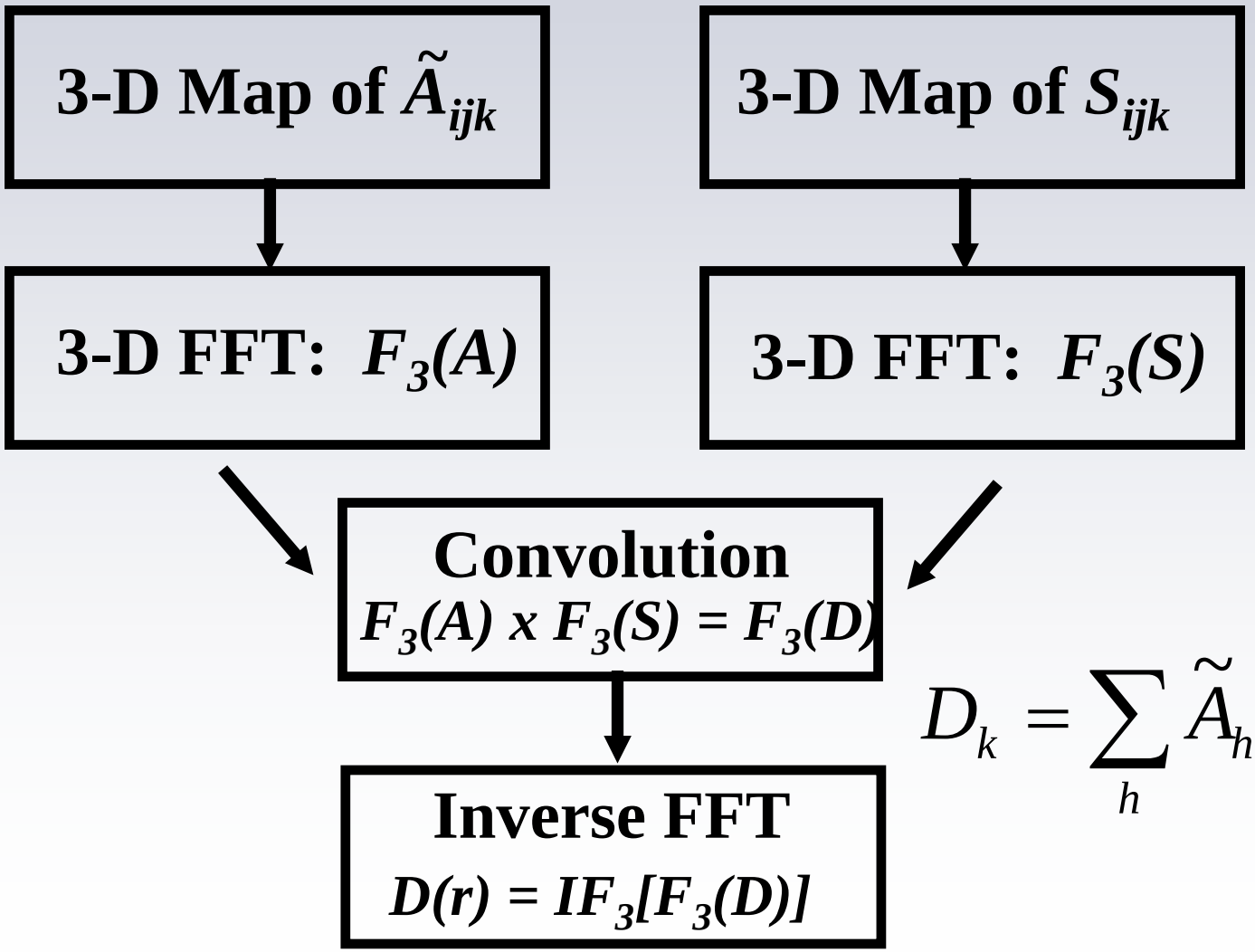


TAC at the Voxel Level

$$\tilde{A}_{ijk} = \sum A_{ijk}(T)\,\Delta T$$

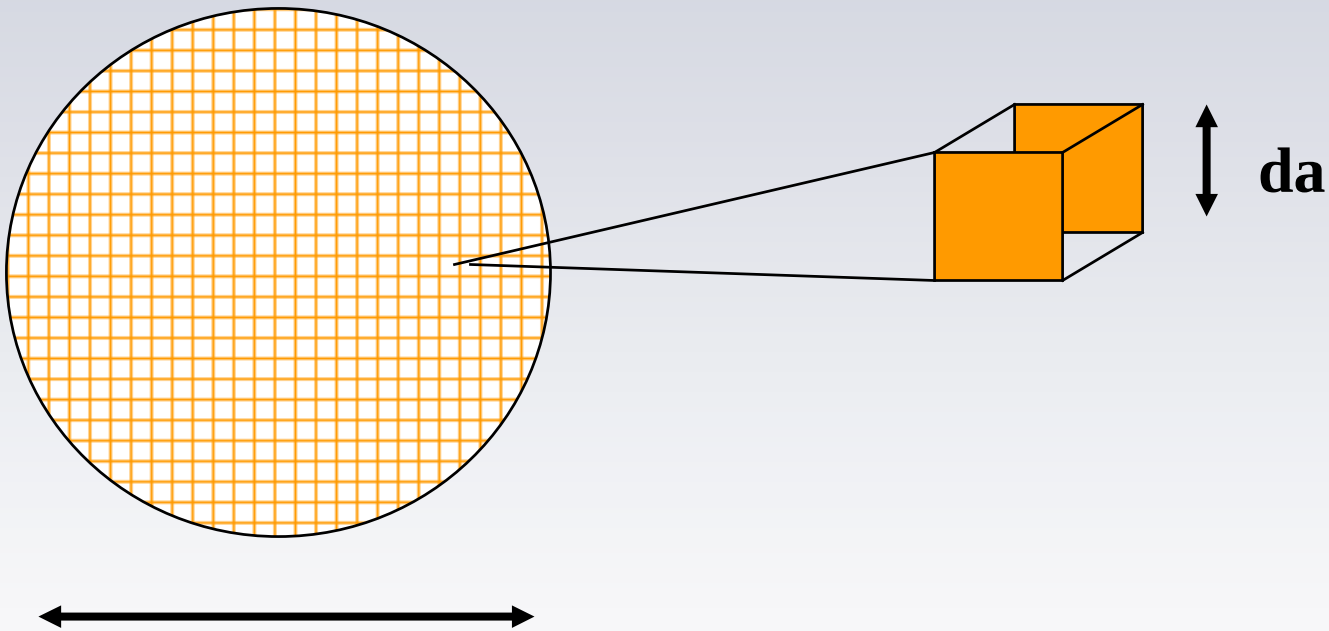


Dose-Point-Kernel Convolution using FFTs



$$D_k = \sum_h \tilde{A}_h \, S_{k \leftarrow h}$$

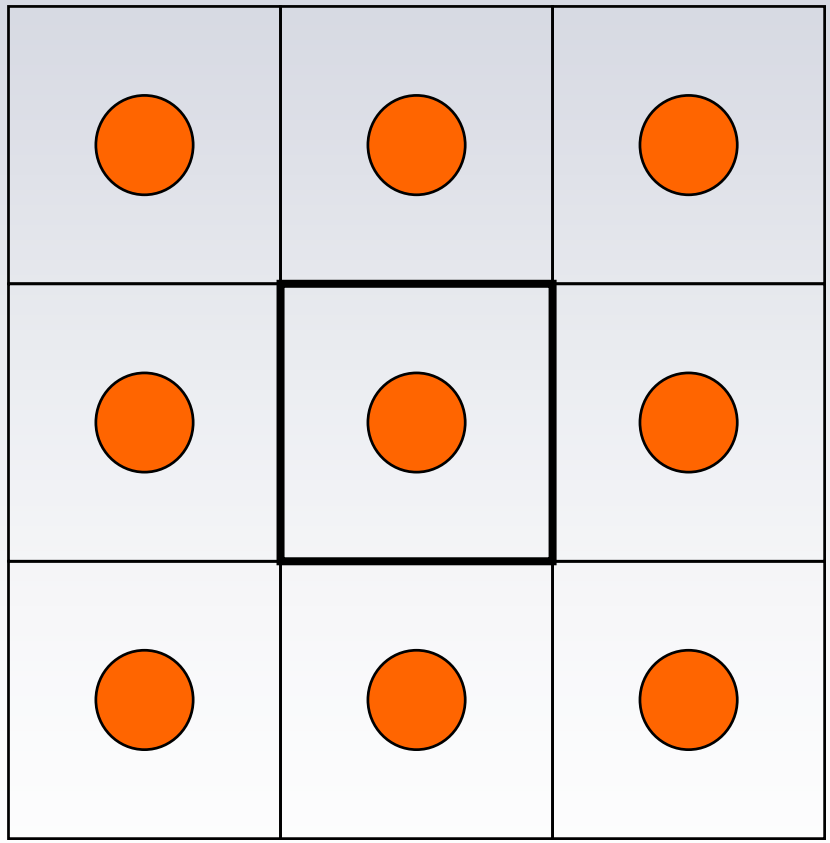
Dose from a Small Sphere



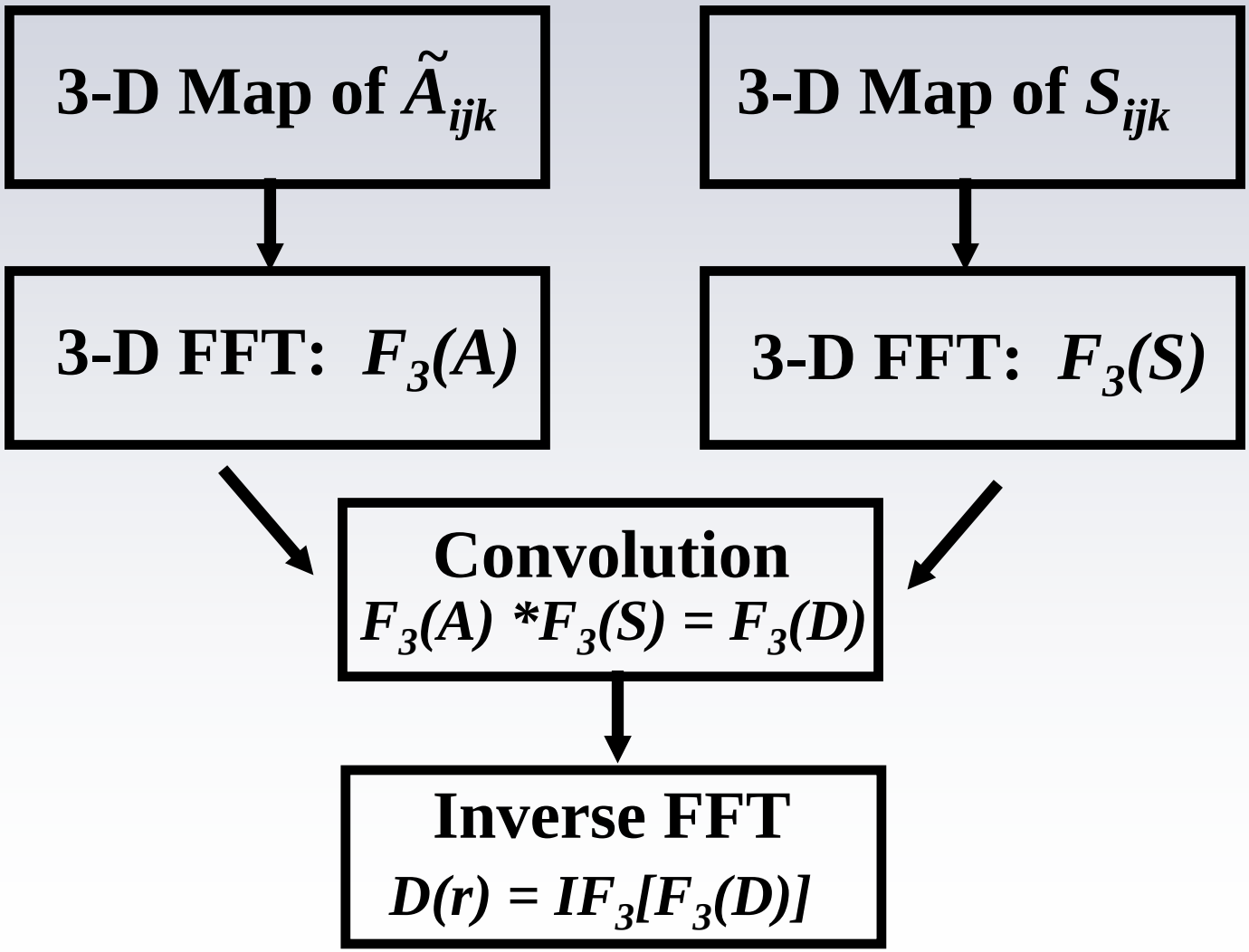
- **Sphere diameter is changed by varying the "voxel size"**
- **Activity can be defined for each voxel (non-uniform)**

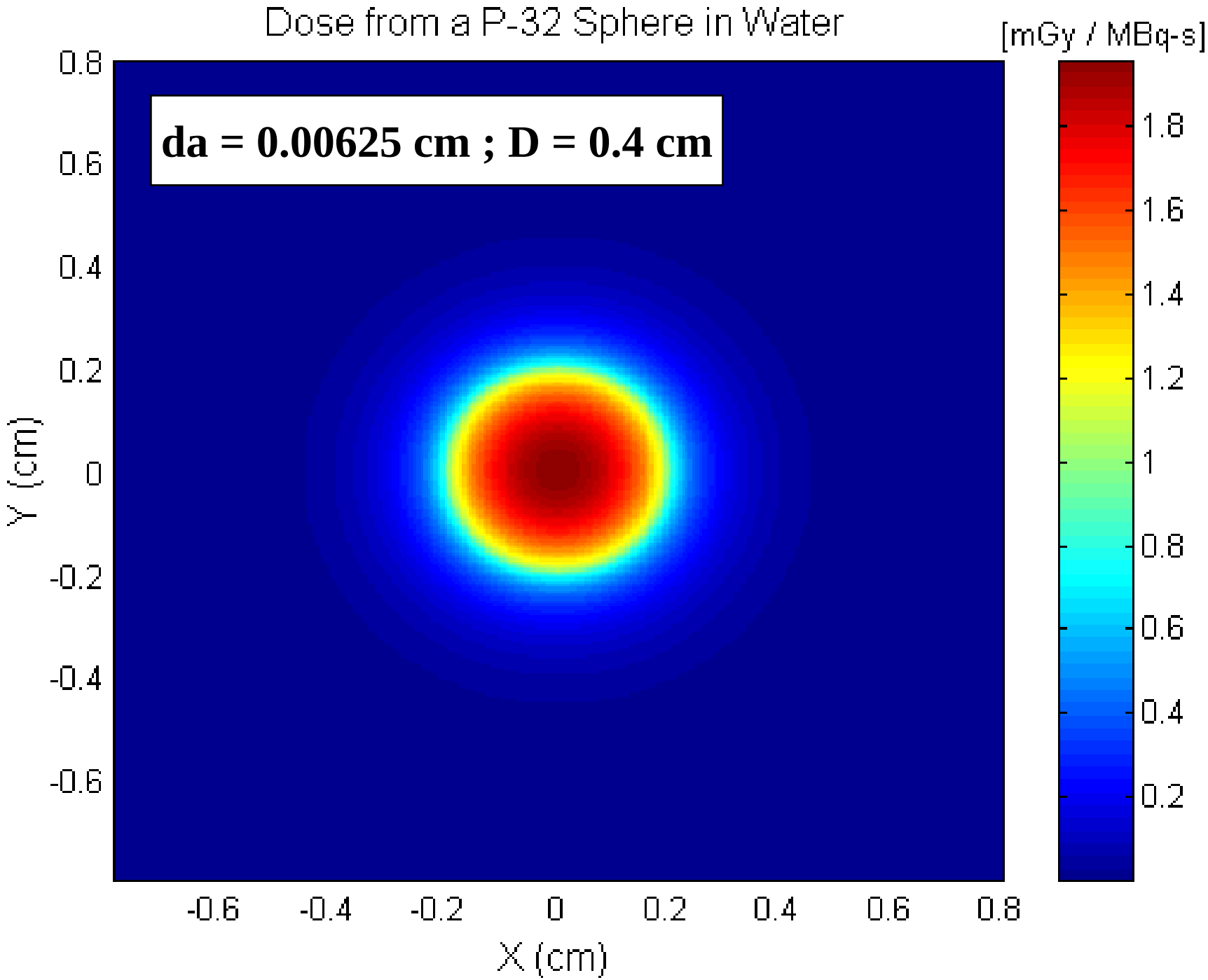
FFT Cyclic Convolution

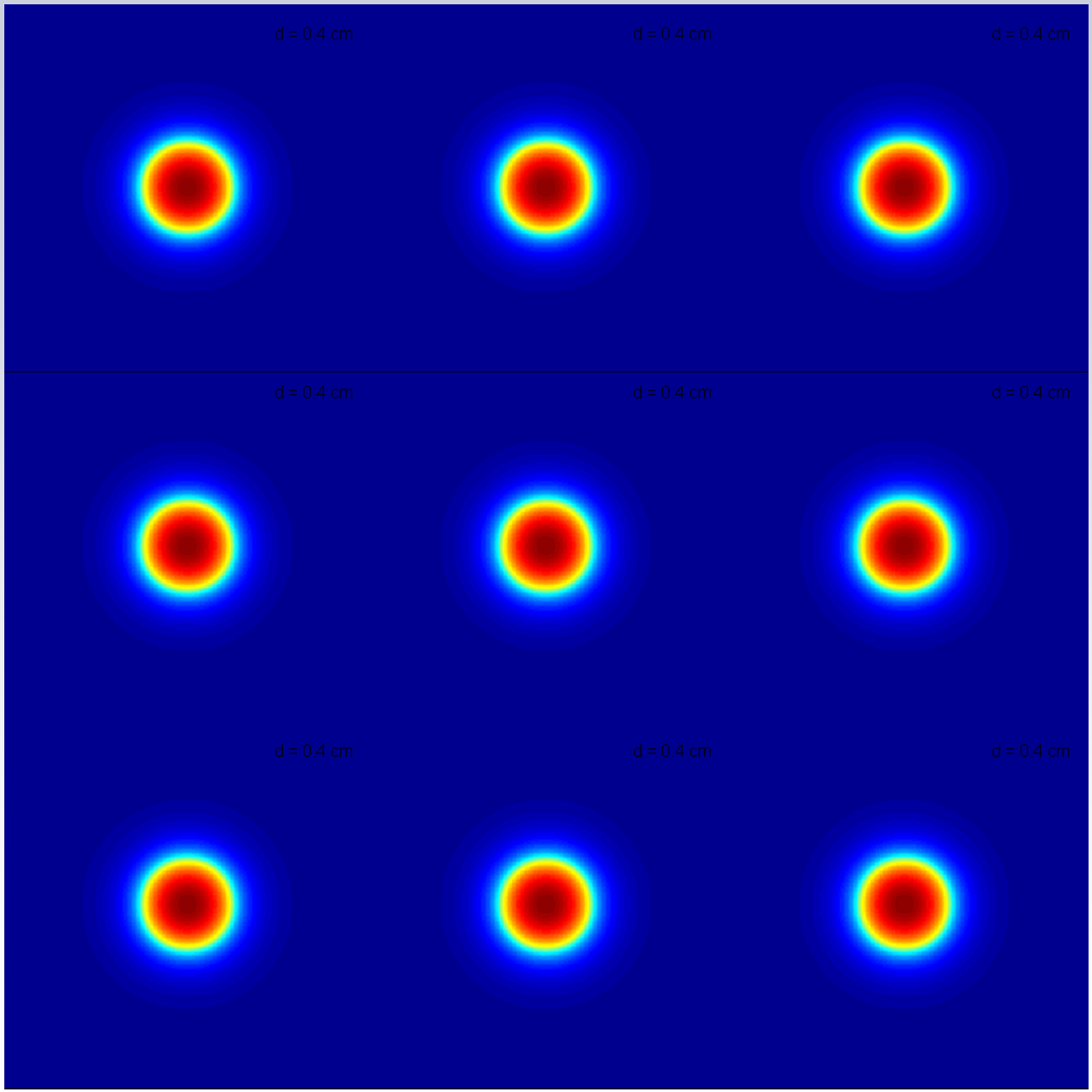
- **Discrete FT makes object "periodic" in space**
- **Dose from virtual sources can be important**
- **Need to chose box size to avoid overlapping effects**

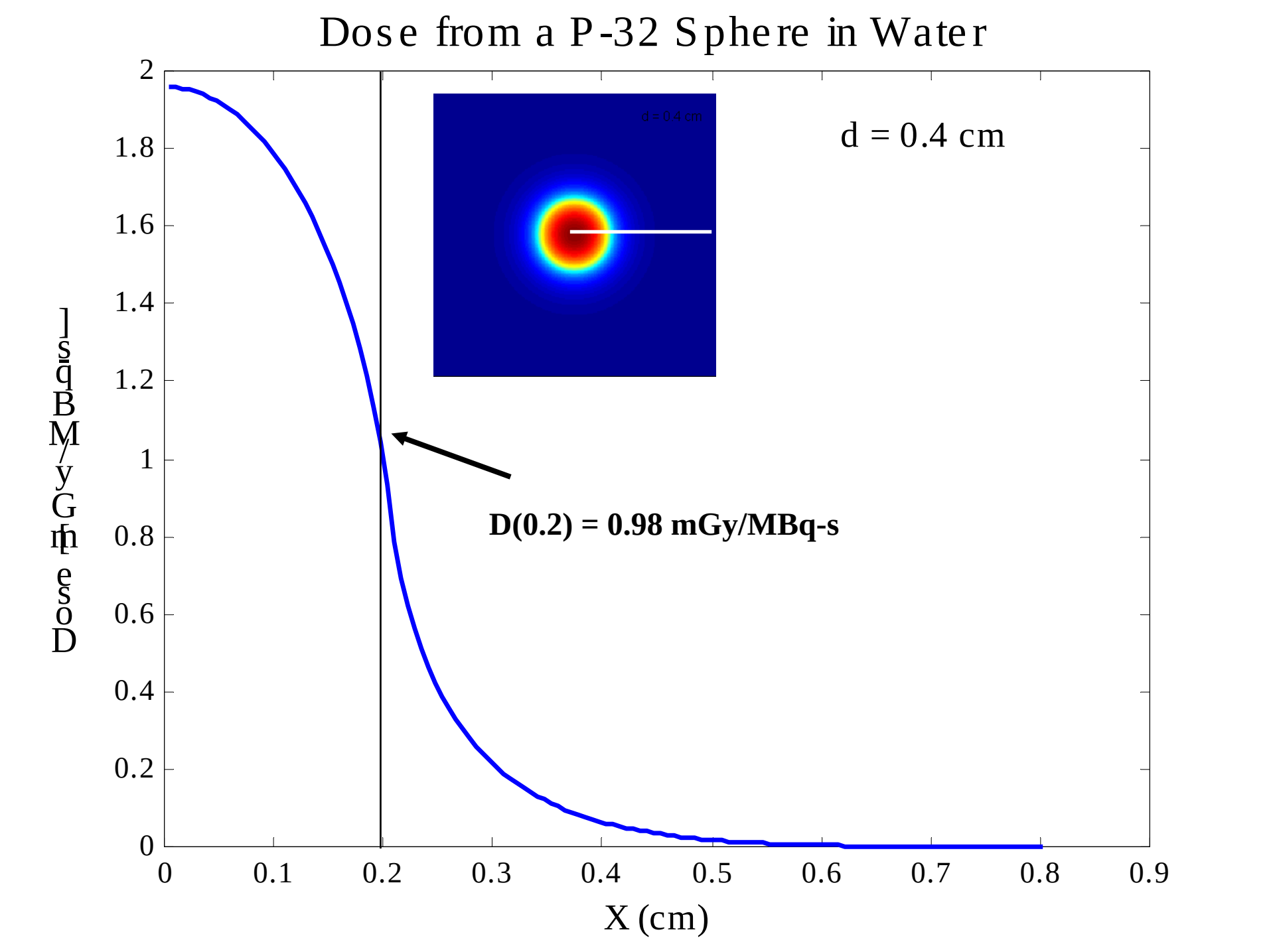


DPK Convolution using FFTs

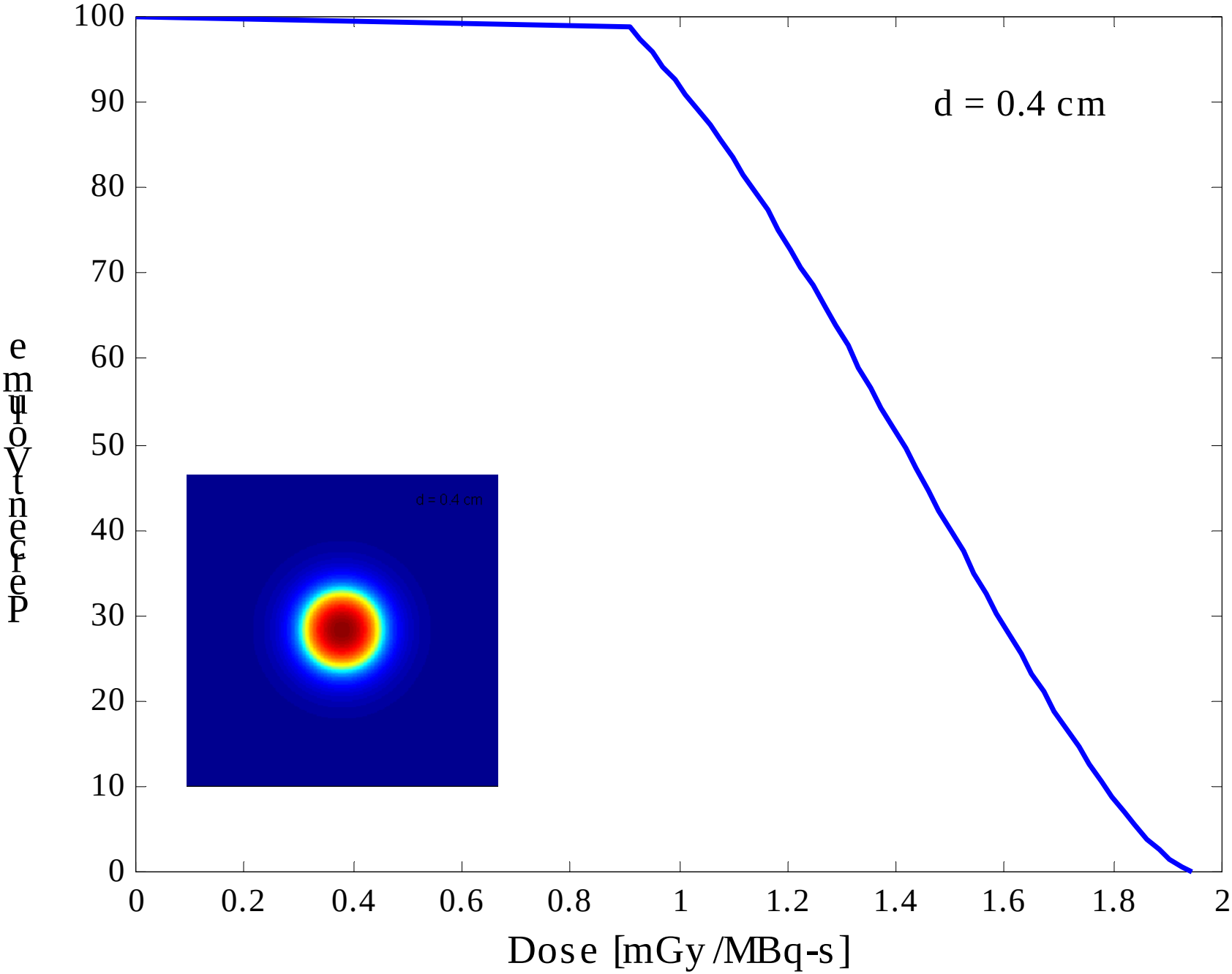



Dose from a P-32 Sphere in Water
[mGy / MBq-s]
da = 0.00625 cm ; D = 0.4 cm
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
Y (cm)
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
X (cm)
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2


d = 0.4 cm
d = 0.4 cm
d = 0.4 cm
d = 0.4 cm
d = 0.4 cm
d = 0.4 cm
d = 0.4 cm
d = 0.4 cm
d = 0.4 cm


Dose from a P-32 Sphere in Water
d = 0.4 cm
d = 0.4 cm
D(0.2) = 0.98 mGy/MBq-s
Dose mGy/MBq-s
X (cm)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9

Dose Volume Histogram : P32 Sphere



P-32 Colloid treatment for cystic tumors :

Cyst Diameter (cm)	Cyst Volume (ml)	**Taasan 1985 *** Act (μCi)	Loevinger, Eq.(9) Act (μCi)	DPK Model Act (μCi)	EGSnrc * Act (μCi)
0.2	0.0042	**0.220**	0.713	0.719	0.721
0.4	0.0335	**2.050**	3.448	3.298	3.280
0.6	0.1131	**7.110**	9.032	8.953	8.843
0.8	0.2681	**17.660**	19.732	19.142	18.942
1.0	0.5236	34.010	35.792	35.229	34.968
1.2	0.9048	58.820	60.205	58.597	58.128
1.4	1.4368	91.990	92.957	90.631	90.385
1.6	2.1447	135.14	135.76	132.69	132.37
1.8	3.0536	189.13	189.51	186.17	184.65
2.0	4.1888	255.78	256.01	252.42	249.65
2.2	5.5753	339.12	339.26	332.82	334.04
2.4	7.2382	437.10	437.19	428.73	428.88
2.6	9.2028	553.01	553.07	541.52	539.88
2.8	11.494	686.75	686.75	672.58	668.45
3.0	14.137	840.75	840.75	823.26	825.66
3.2	17.157	1009.40	1009.40	994.95	993.09
3.4	20.580	1202.80	1202.80	1189.00	1186.30
3.6	24.429	1421.80	1421.80	1406.90	1401.40
3.8	28.731	1672.10	1672.10	1649.80	1632.80
4.0	33.510	1937.40	1937.40	1919.30	1912.40
4.2	38.792	2233.90	2233.90	2216.70	2214.50
4.4	44.602	2552.40	2552.40	2543.40	2537.50
4.6	50.965	2917.00	2917.00	2900.70	2888.50
4.8	57.906	3300.40	3300.40	3289.90	3294.10
5.0	65.450	3707.00	3707.00	3712.60	3719.20

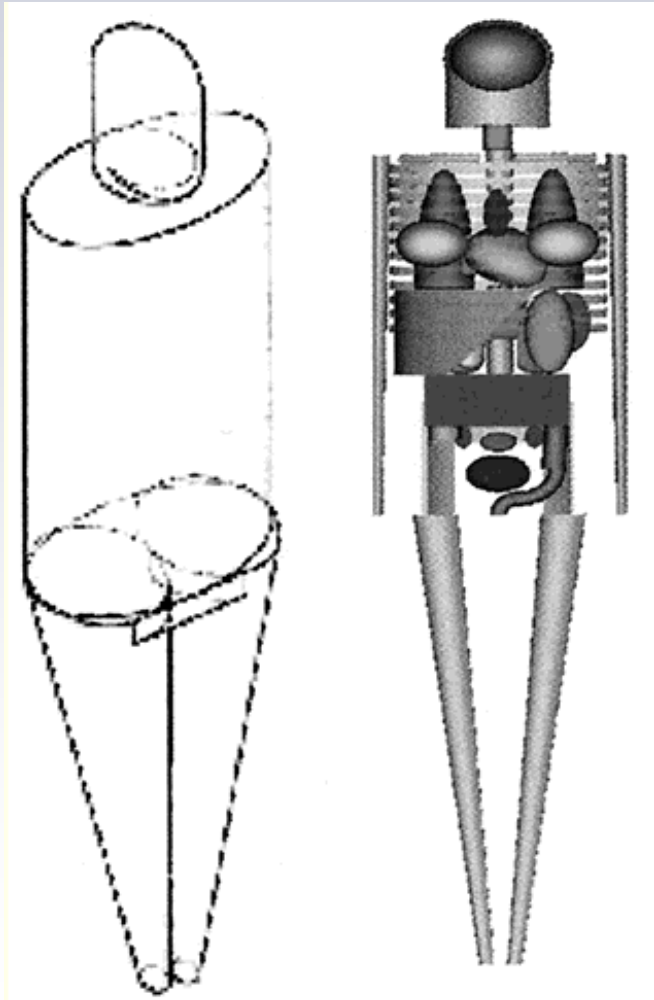
***Taasan V, Shapiro B, Taren JA, et al : J Nucl Med 26: 1335-1338, 1985**
Shapiro B, Figs LM, Cross MD, Q J Nucl Med 43: 367-374, 1999.

Standard Man Dosimetry

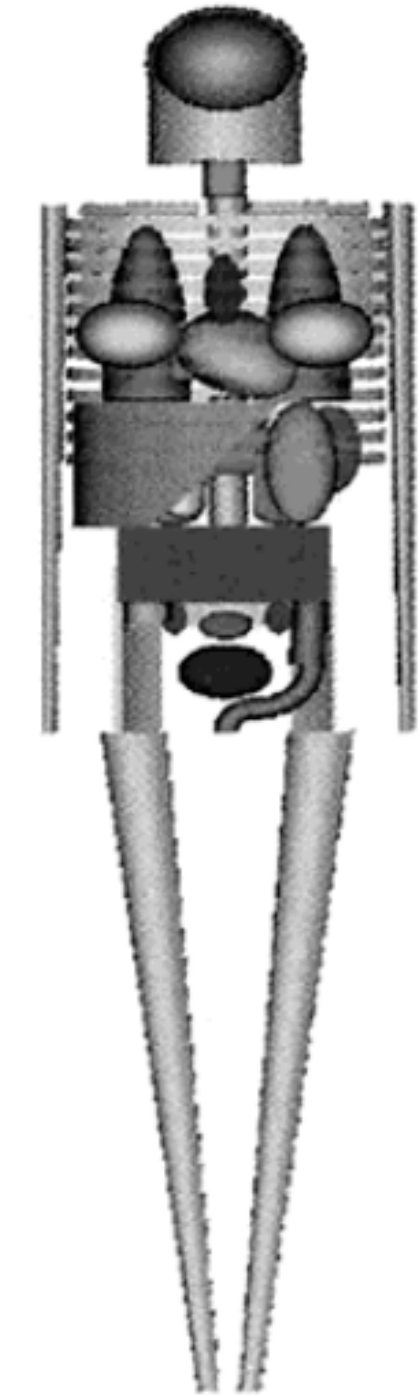
- Organ dose usually estimated using the "standard man"
- MIRDOSE3 is a popular program based on the standard MIRD formalism
  - Used recently for the dosimetry of Zevalin (1st FDA approved radiopharmaceutical to treat Non-Hodgkin's lymphoma)
- MIRDOSE3 gives only an "average dose" for an "average man" or population
- **Voxel-based MIRD** can be used for "**patient specific dosimetry**"

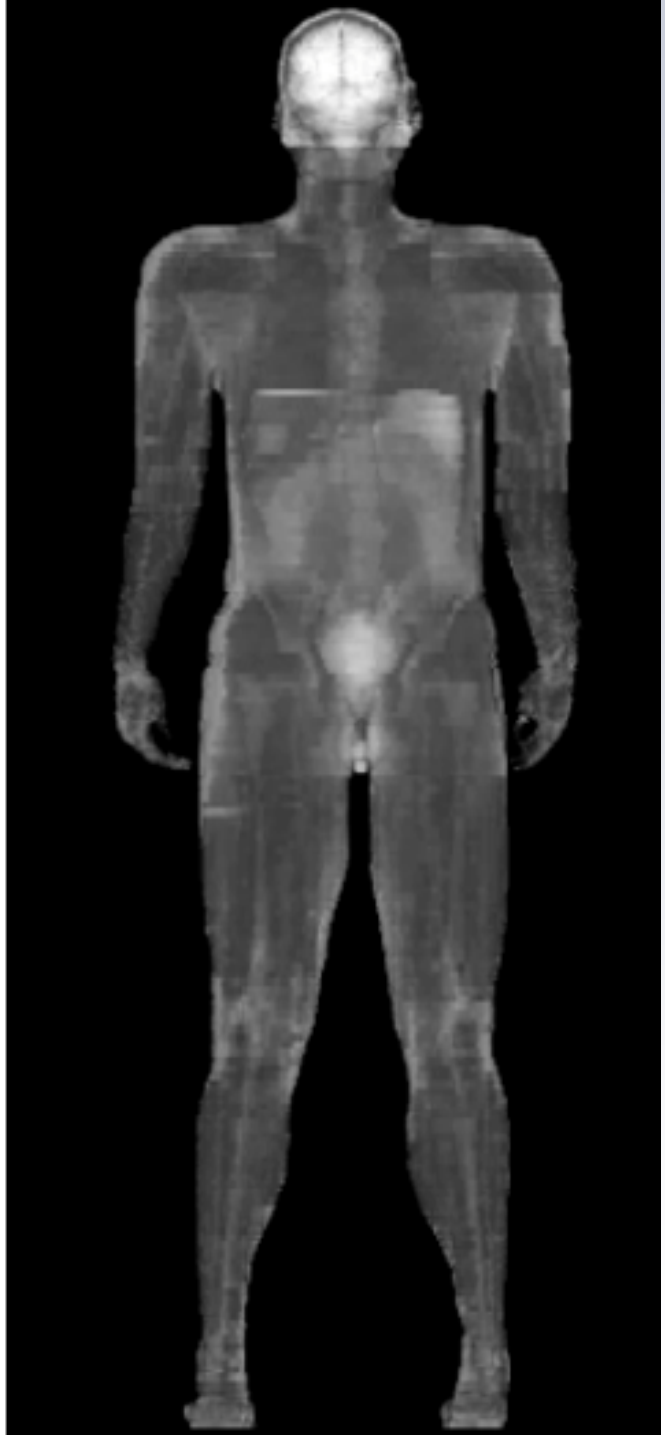
Standard Man

- Originally defined as a 20-30 y-old Caucasian, 70 Kg, 170 cm height
  - Elliptical cylinder and cones used to define Arm, Torso, Hips, Legs, Feet, Head & Neck
  - > 40 organs & tissue specified
  - 3 media : bone, tissue, lungs
- Family of phantom (both sex) at various ages also constructed*



*** Cristy and Eckerman, ORNL/TM-8381/VI; 1987.**





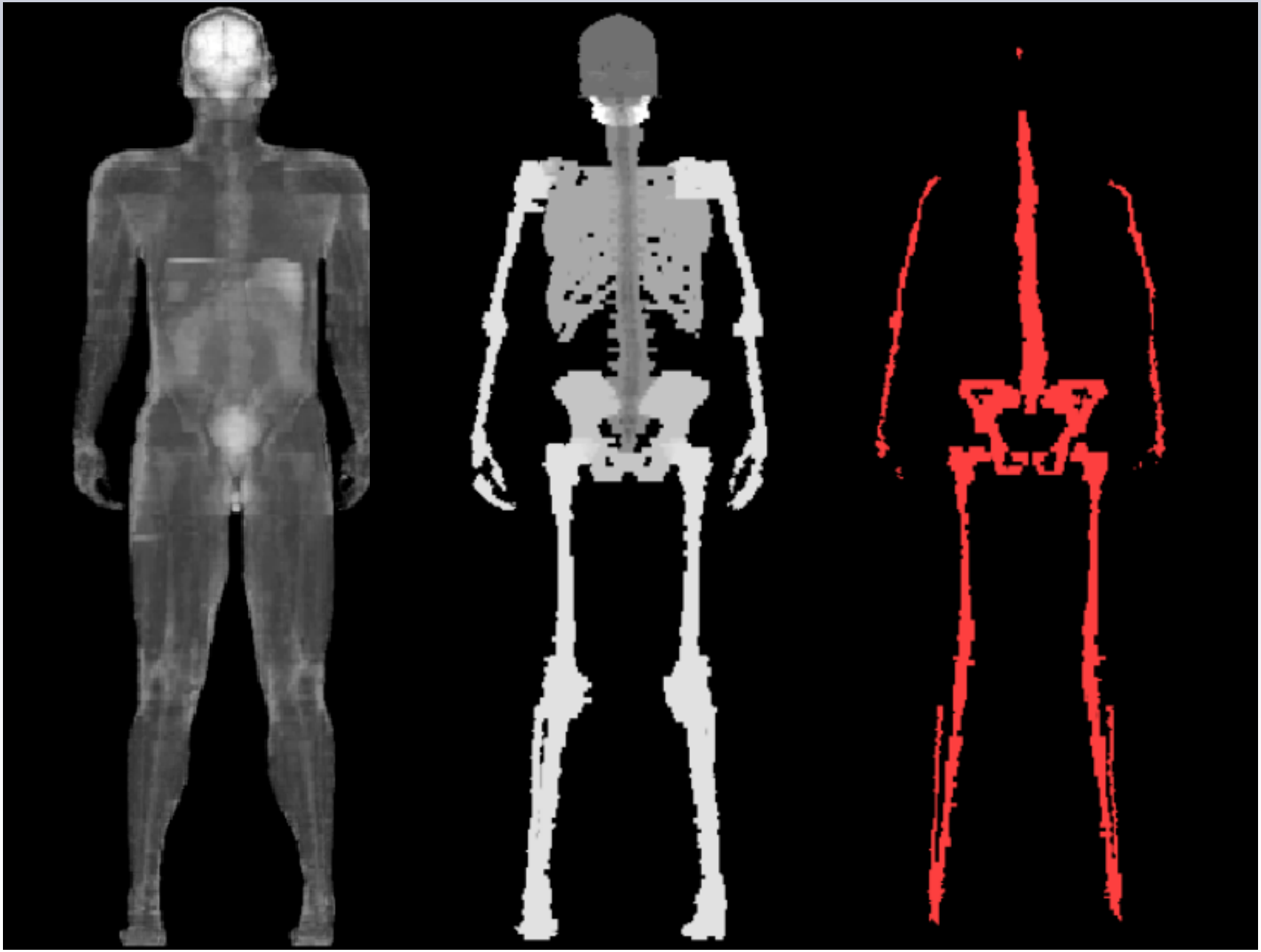
Yale IPAG

Zubal Phantom

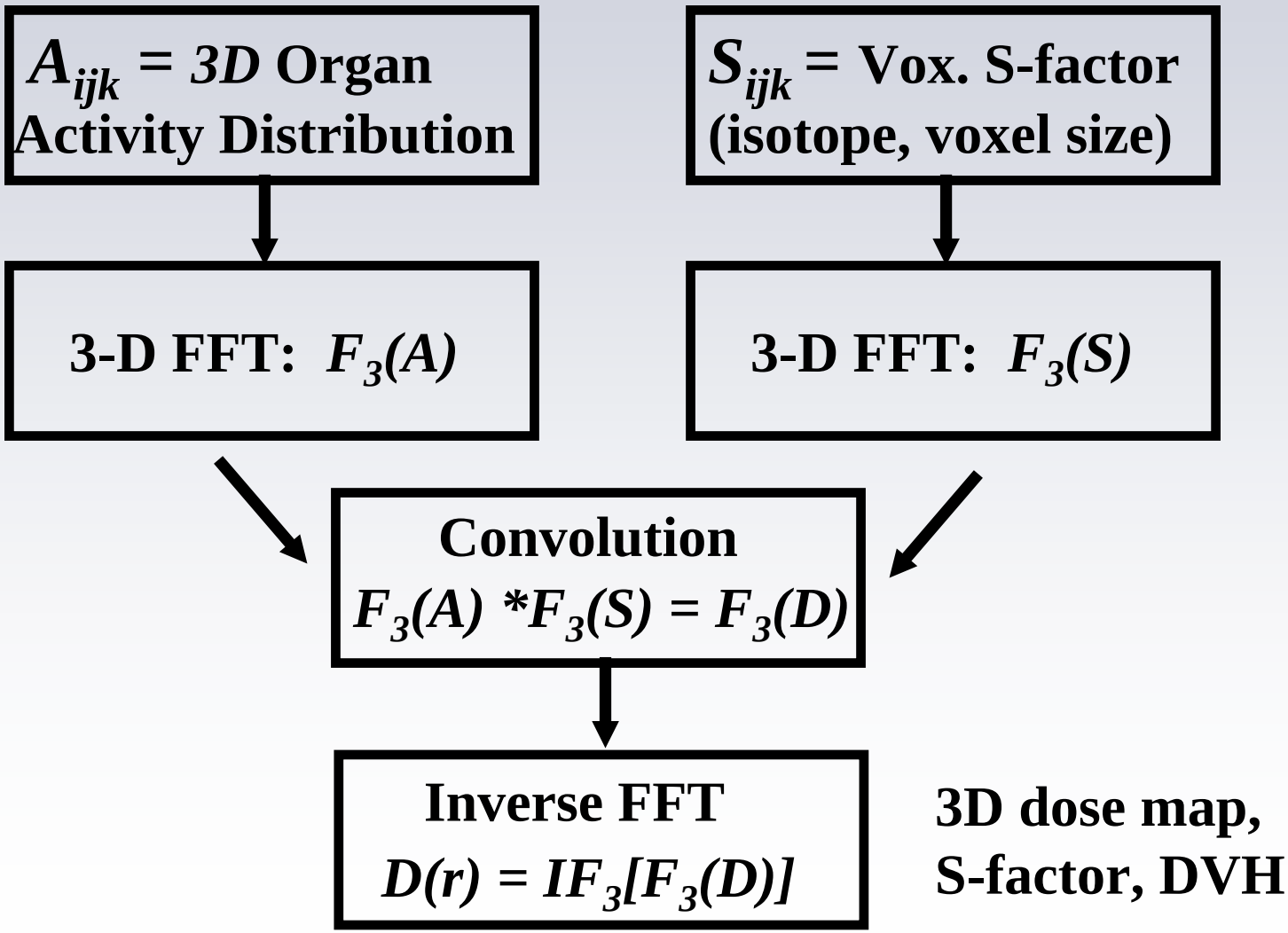
voxel (cm)	Mass (Kg) with Fat	Mass (Kg) w/o Fat
0.32	58.2	47.5
0.33	63.9	52.1
0.34	69.8	57.0
0.35	76.2	62.1
0.36	82.9	67.6
0.37	**90.0**	**73.4**
0.38	97.5	79.5
0.39	105.4	86.0
0.40	113.7	92.7
0.41	122.5	99.9
0.42	131.7	107.4
0.43	141.3	115.2
0.44	151.4	123.4
0.45	161.9	132.1

(192 x 96 x 498) x 1 byte

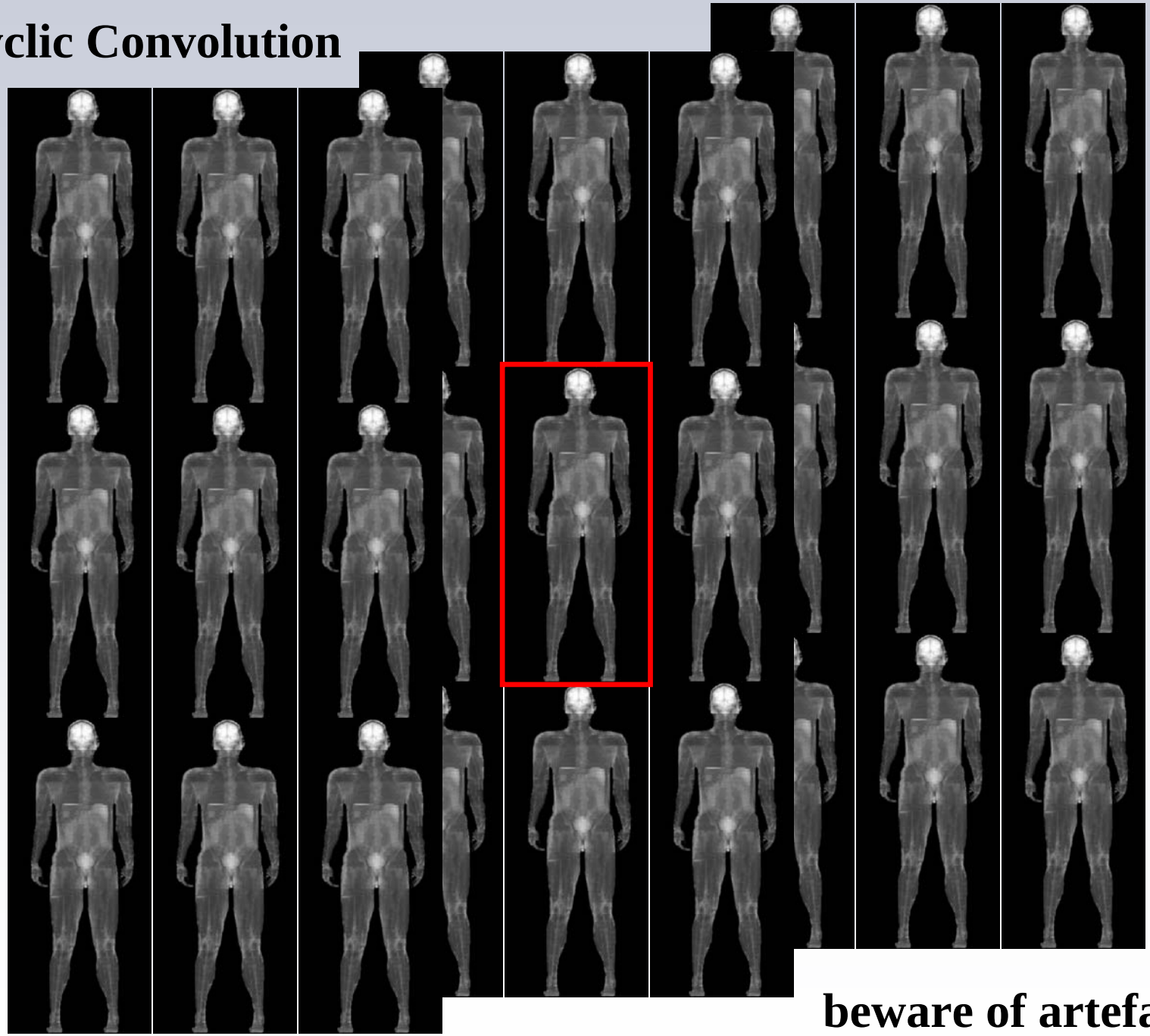
~ 9 MB



Kernel Convolution for Organ Dose using FFTs



FFT Cyclic Convolution



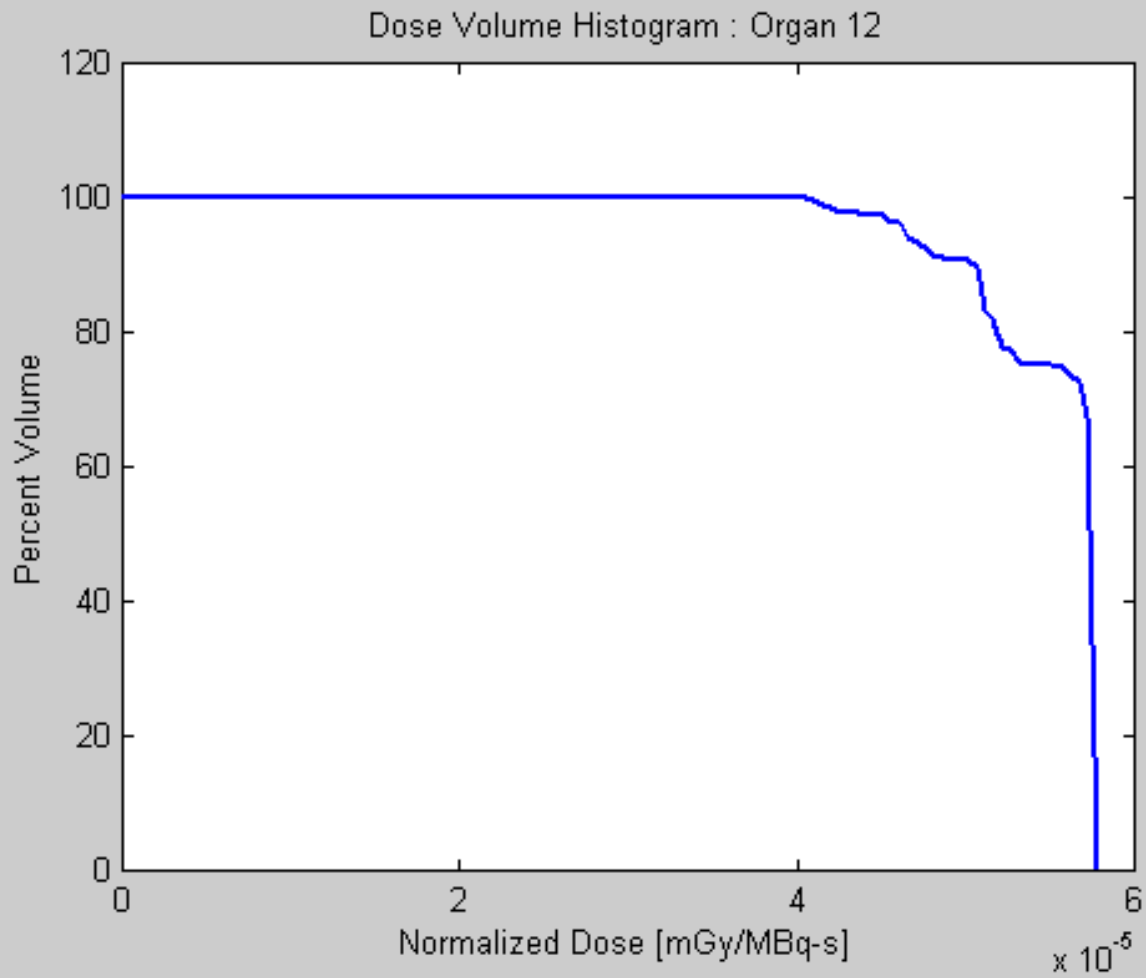
beware of artefact !

VIRTUAL MAN ORGAN DOSE CALCULATOR

Isotope	Weight (Kg) :	Source Organ	Target Organ
P-32	93	Liver	Liver

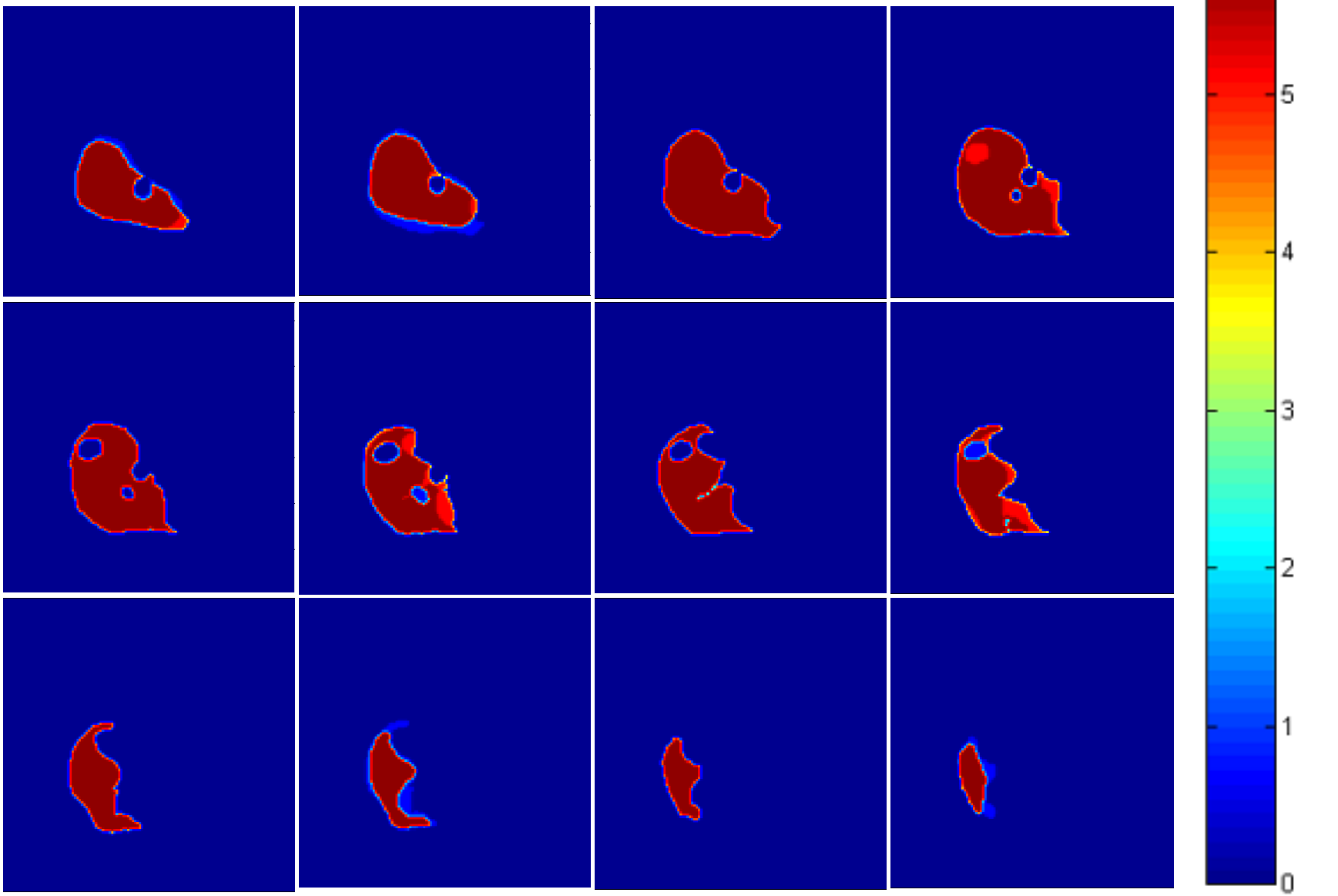
S-factor [mGy/MBq-s]

Average	Min	Max
5.58e-5	3.26e-5	5.80e-5



[mGy/MBq-s]

Self-Dose to Liver for 93 Kg Zubal Phantom (P-32)



Radiation Synovectomy

- Used to treat rheumatoid arthritis (RA)
- Treatment : drugs, surgery
- **RS** consists in injection of beta-active radionuclide in joint capsule to destroy diseased tissue lining
- Regenerated tissue free of symptoms for ~2-5 y reducing pain and swelling

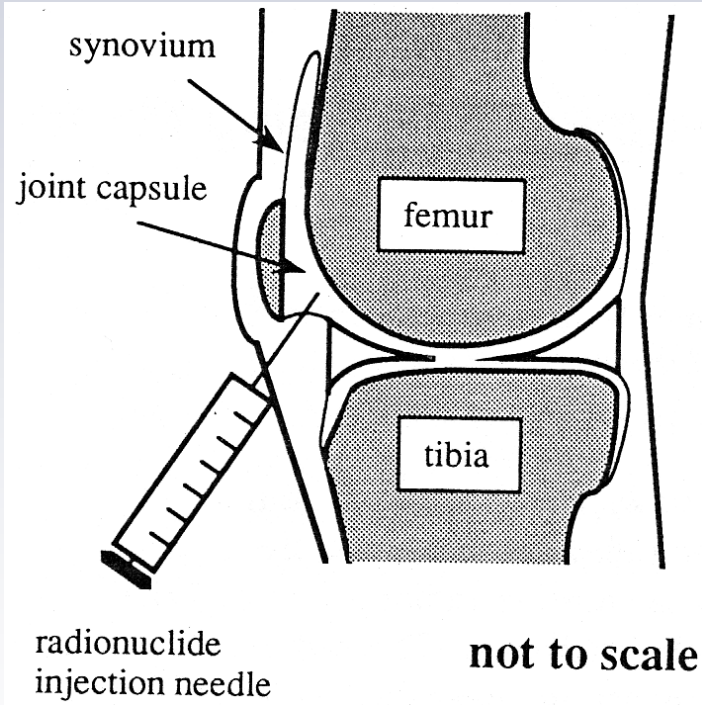


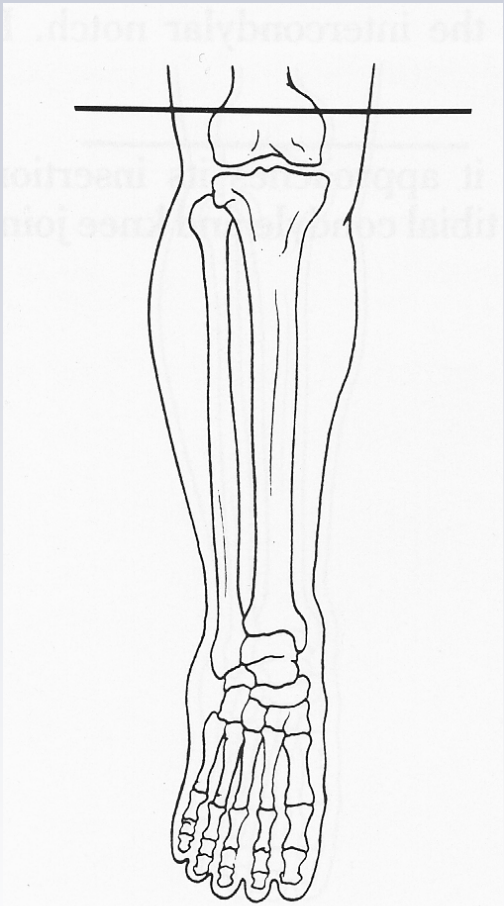
Figure from Johnson, L.S., et al., *Beta-particle dosimetry in radiation synovectomy.* Eur J Nucl Med, 1995. **22**(9): p. 977-88.

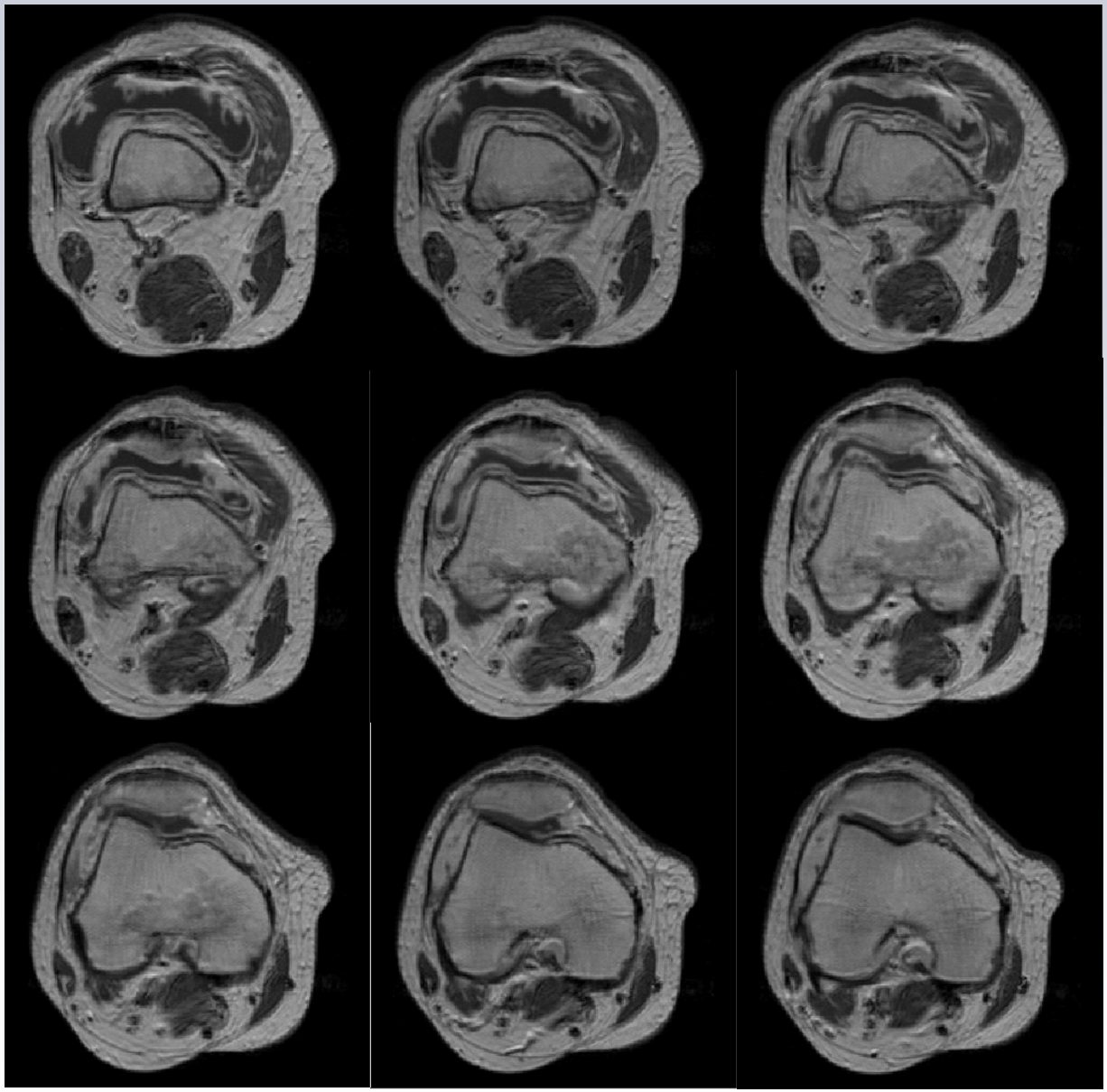
Collaborator: George Mawko
Queen Elizabeth II health Center, Halifax, Canada

RS Dosimetry

- Therapeutic dose to synovium not clearly established
- Absorbed dose depends on
  - Radionuclide (P-32, Y-90, Au-198)
  - Injected activity (mCi range)
  - Final distribution of radioactivity (shape + volume)
- Monte-Carlo (EGS4) model have been developed for specific geometry (source thickness 0.74 mm)*
- Inadequate for patient specific studies
- **This Work : Develop a treatment planning system based on MRI imaging & segmentation of joint capsule**

*Johnson, L.S., et al., Eur J Nucl Med, 1995. **22**(9): p. 977-88.

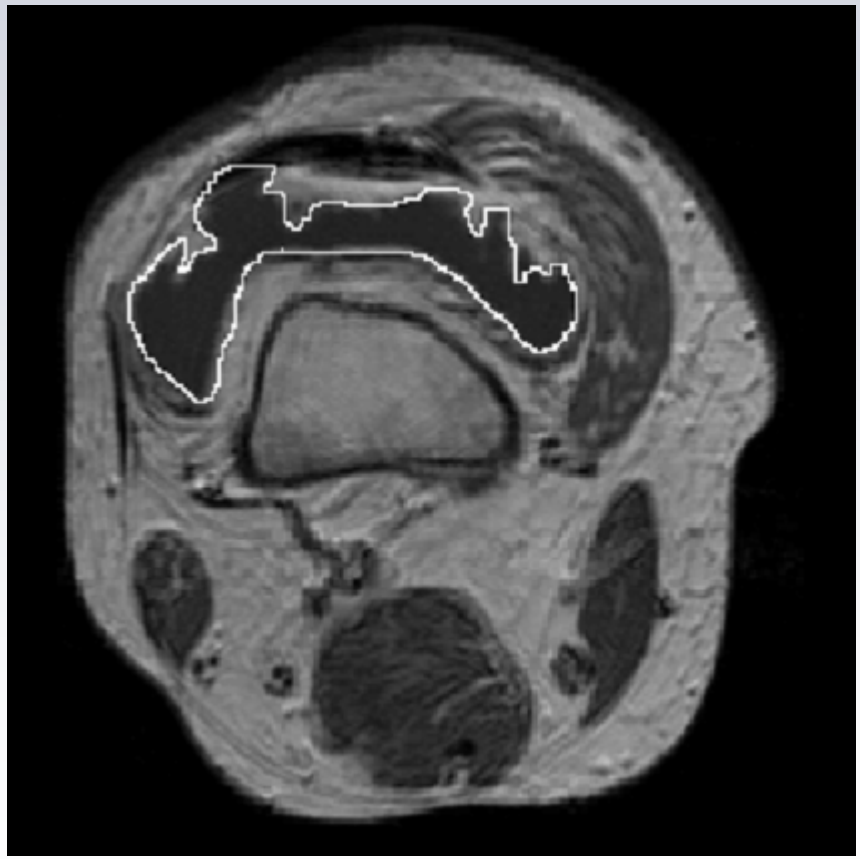




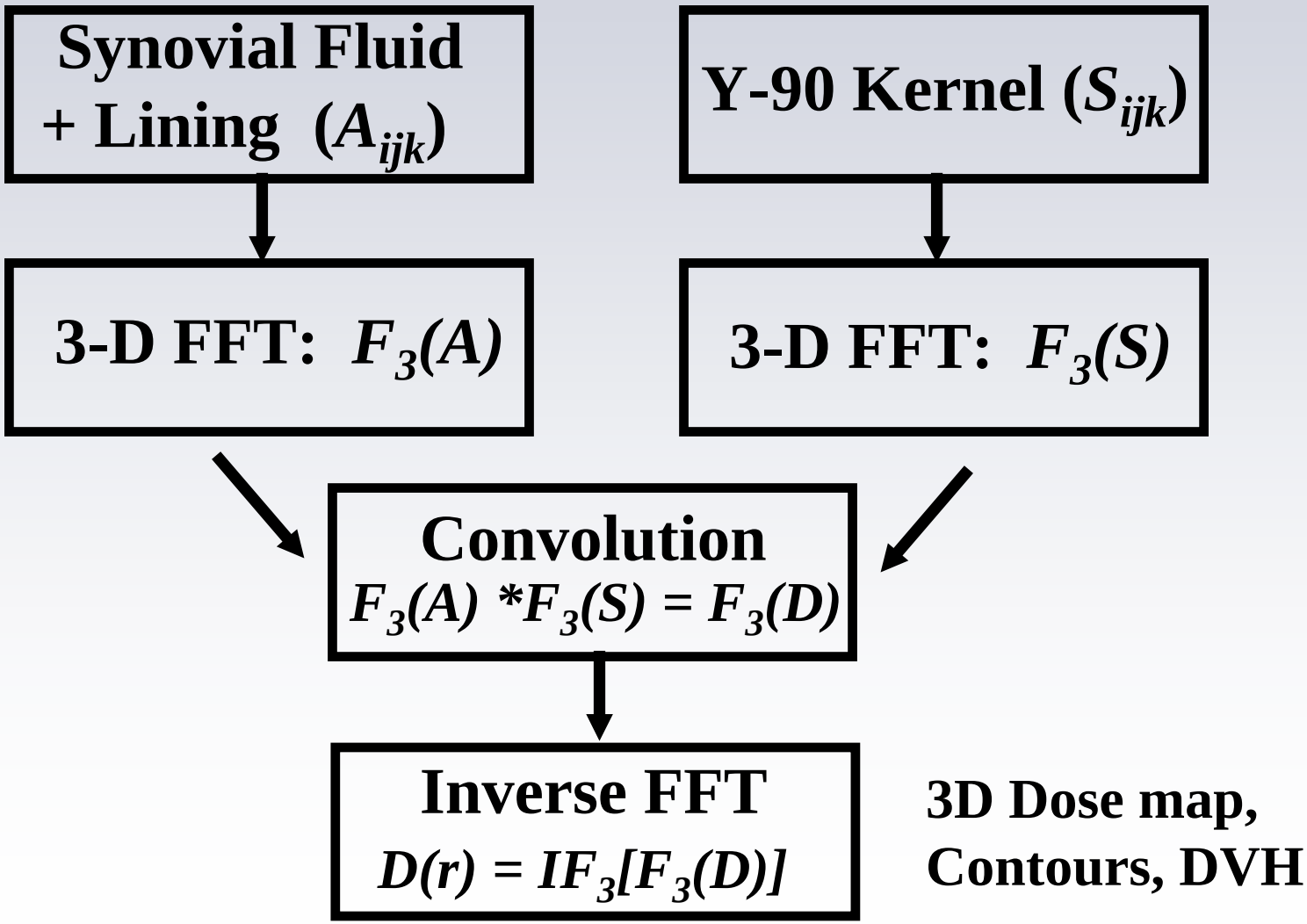
Axial T1 image above the knee shows synovial space distended with fluid

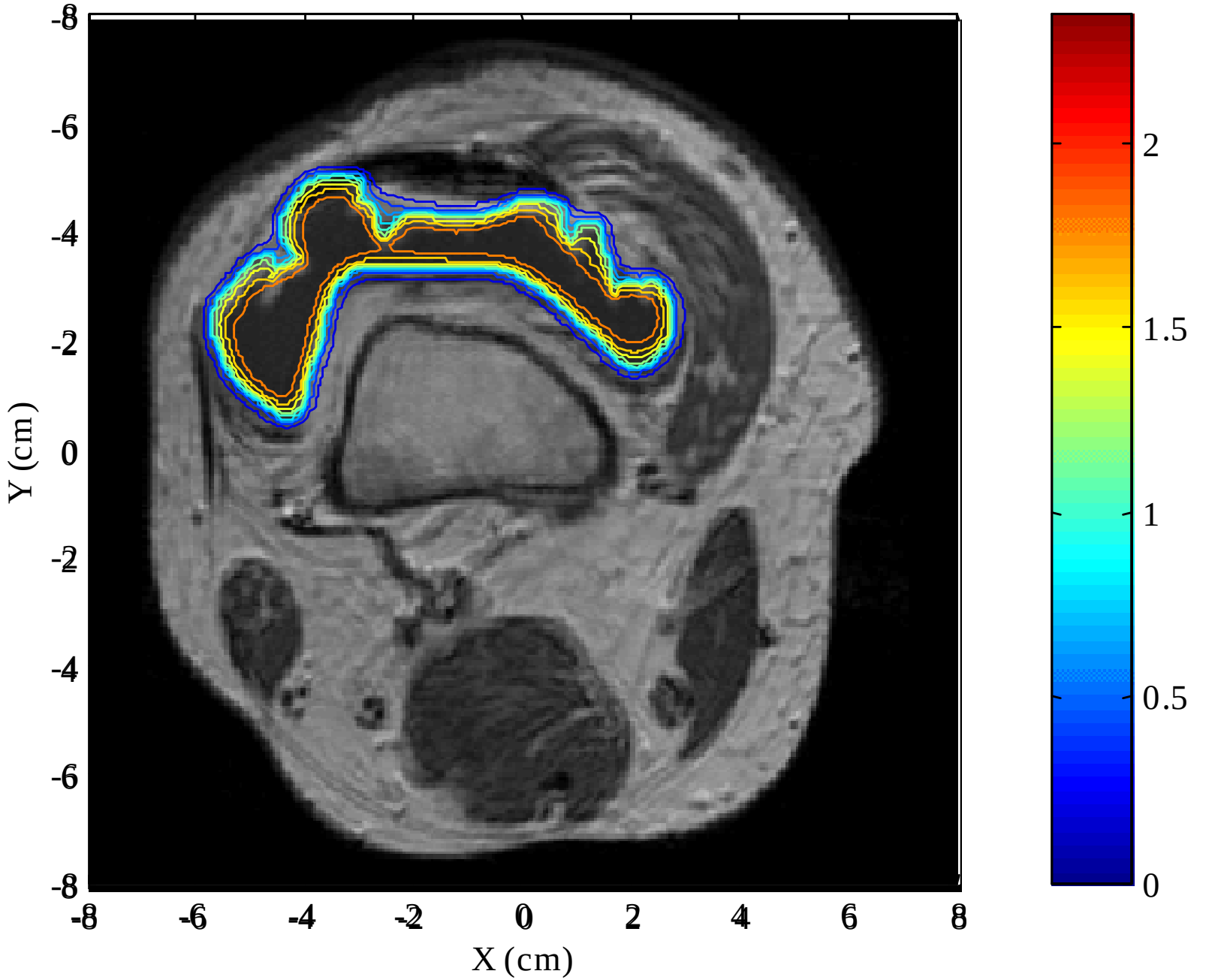
RS Dosimetry

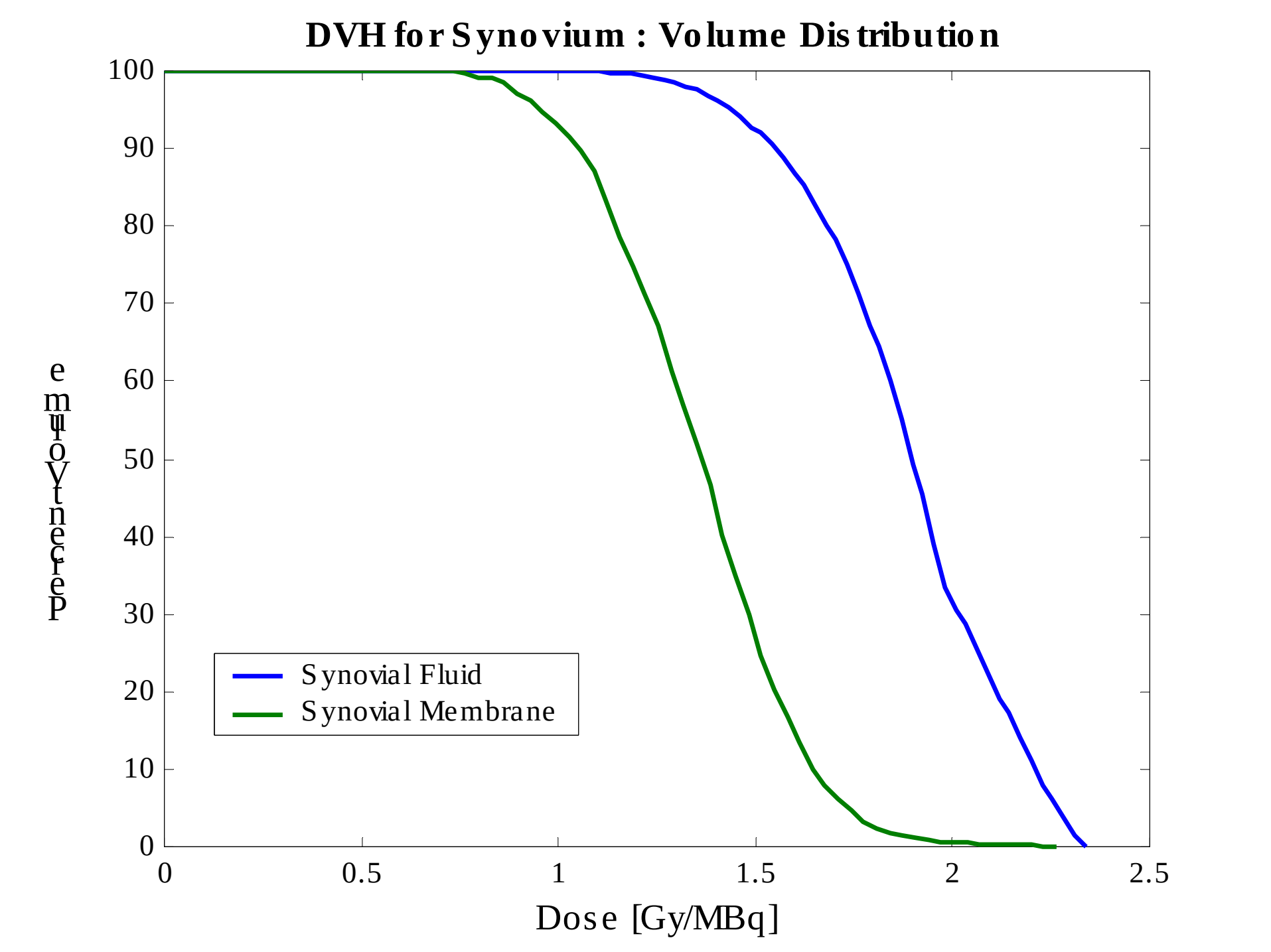
- Use ROI techniques to determine volume of joint cavity + lining
- Assume uniform activity distribution in volume + lining
- Use Voxelized MIRD techniques to calculate dose to lining



Kernel Convolution for Synovium using FFTs




Dose [Gy/MBq] from Y-90 colloid : Frame 1
[Gy/MBq]
Y (cm)
X (cm)
-8
-6
-4
-2
0
2
4
6
8
2
1.5
1
0.5
0


DVH for Synovium : Volume Distribution
Percent Volume
100
90
80
70
60
50
40
30
20
10
0
0
0.5
1
1.5
2
2.5
Dose [Gy/MBq]
Synovial Fluid
Synovial Membrane

Radiolabeled Drug Eluting Stent for Restenosis

Collaborators :

Chao-Wei Hwang, Elazer Edelman

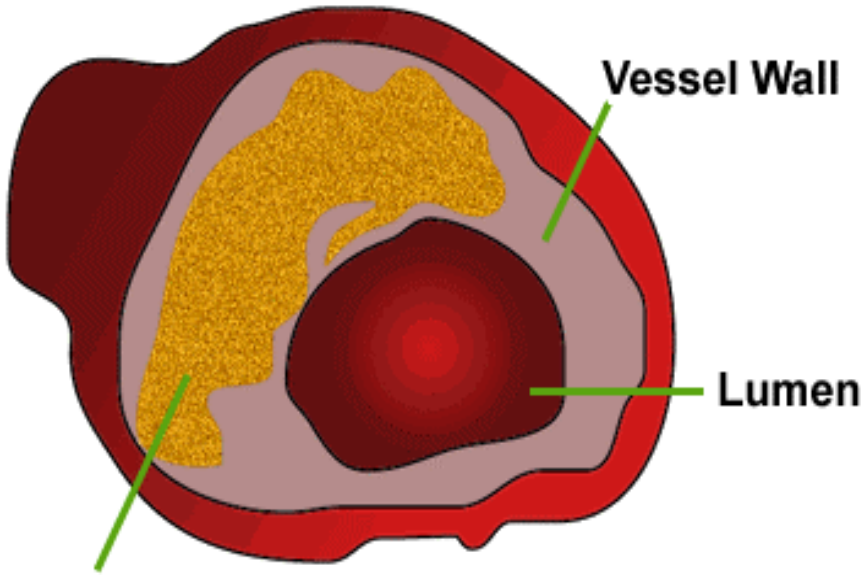
Harvard-MIT Biomedical Engineering Center

Atherosclerosis

- Degeneration of the vessel wall due to **fatty plaque** and **scar tissue** accumulation
- Limits blood circulation
- Predisposes to angina pectoris or heart attack

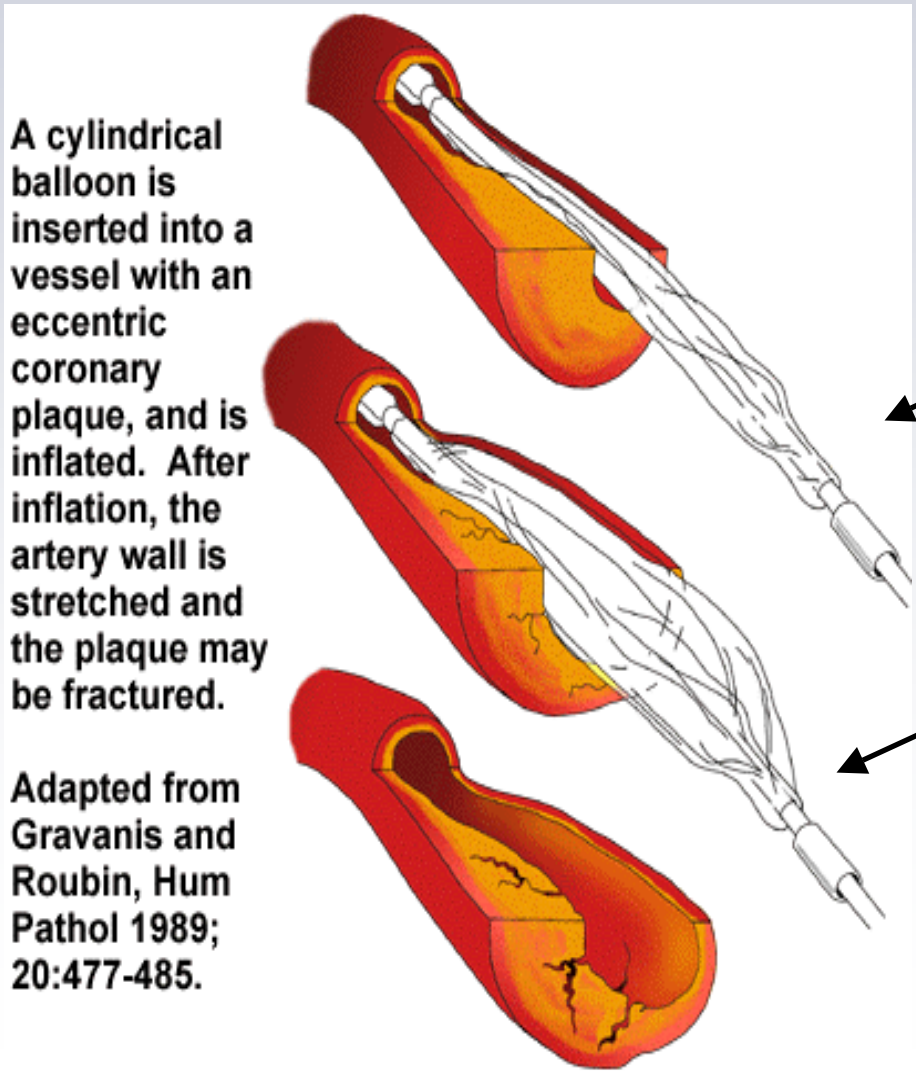
Causes :

Diet rich in animal fat (cholesterol), cigarette smoking obesity, inactivity ...



Cross-section of a coronary artery.
Adapted from Kimura et al.,
Am Heart J 1995; 130:386-96.

Percutaneous Transluminal Coronary Angioplasty (PTCA)



A cylindrical balloon is inserted into a vessel with an eccentric coronary plaque, and is inflated. After inflation, the artery wall is stretched and the plaque may be fractured.

Adapted from Gravanis and Roubin, Hum Pathol 1989; 20:477-485.

Catheter monted balloon introduced through the illiac artery

Balloon is inflated to high pressure (> 10 atm.)

PTCA and Stenting

Stent is crimped to the balloon and inserted at the injured site

Balloon is inflated and stent is expanded

Balloon is retracted. Stent is deployed permanently

Restenosis

- During PTCA, the **arterial wall is stretched** causing injury
- **Repair process is initiated** (cell proliferation and migration, fibrosis)
- Formation of **proliferative neointima**
- **Remodeling** (wound contraction) due to adventitial fibrosis
- In **~40% cases**, **restenosis** occurs and sometimes results in more narrowing of the lumen than was resolved by angioplasty

Intravascular Radiation Therapy (IVB)

- Beta and gamma **radiation** successful in reducing **restenosis** in numerous clinical trials
- Radiation responsible for **inhibition of cell proliferation** (media, adventitia) into the lumen
- Only **approved** therapy for this disease (in-stent restenosis)
- Therapeutic dose is in the range between **10-50 Gy** typical
  - < 10 Gy may lead to stimulatory response
  - > 50 Gy may be associated to aneurysm formation

IVB Devices

FDA Approved catheter based system :

- **Cordis** Checkmate IRT system (Ir-192 ribbon)
- **Novoste** Beta-Cath System (Sr/Y-90 ribbon)
- **Guidant** GALILEO (P-32 wire + spiral centering balloon)

Under development or abandoned systems :

- **Isostent** (P-32 stents, gamma stents)
- **Angiorad**/US surgical system (Ir-192 wire)
- **Boston Scientific**/Schneider IR System (Y-90 wire)
- **Columbia University**/Re-188 liquid filled balloon
- **Angiogene** (Local Injection of P-32 labeled 15-mer ODN)

Local Drug Injection (LDI)

- **Intramural Injection** of radio-labeled substances (Tc-99m Liposomes, P-32 ODNs) proposed to reduce restenosis (Waksman, 1999; Fareh *et al.* 2000)
- Use **infiltrating catheter** (*Infiltrator™, Boston Scientific/Interventional Technologies*) to deliver the drug directly into arterial wall
- **Drug Eluting Stent** also proposed as a delivery device for P-32 ODNs (Gobeil *et al.,* 2001)
- **Potential difficulties**
  - **Delivery Efficacy and Variability (biological factors)**
  - **Systemic fraction and dose to organs**

IVB vs LDI

- IVB uses "**sealed sources**"
- **Physical parameters** affecting dosimetry
  - Source Isotope
  - Source activity
  - Source geometry
  - Source position
  - Dwell time

system design

Treatment planning

- **Accurate dosimetry** is possible with control of the **source position** and **dwell time** (physical parameters)

IVB vs LDI

- LDI uses "**unsealed sources**"
- **Physical & Biological** parameters affecting dosimetry
  - drug labeling isotope
  - Injected activity

  } **Physical factors**

  - Target Tissue uptake
  - Target geometry
  - Residence time

  } **Biological factors**
- Only the **injected activity** can be controlled at the time of treatment
- **Can we predict the dose to target accurately ?**
- **What is the dose to organs ? Is it safe ?**

Error in the Delivered Dose to the Arterial Wall

Total activity Injected into Patient (PLANNING) :

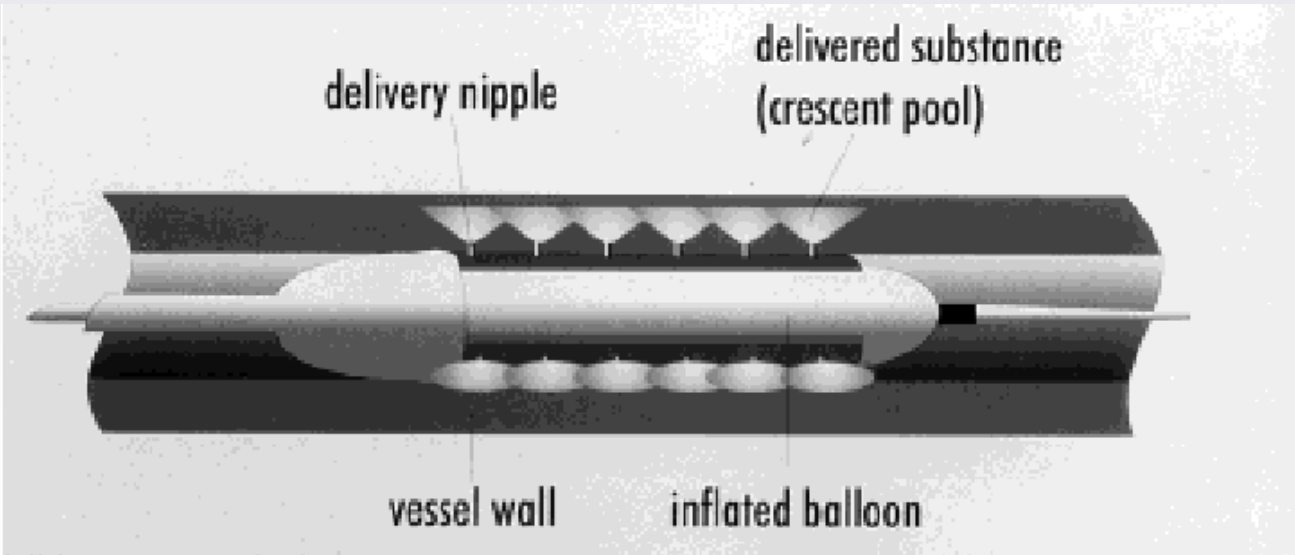
$$A_{TOT} = \frac{D}{E \times \tau \times S(w)}$$

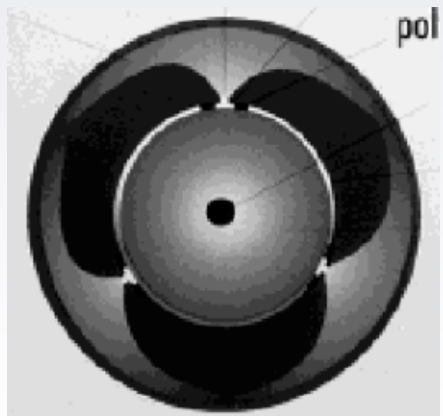
Uncertainty in the prescribed **dose to artery** :

$$\frac{\delta D}{D} \cong \left[\underbrace{\left(\frac{\delta E}{E}\right)^2 + \left(\frac{\delta \tau}{\tau}\right)^2 + \left(\frac{\delta w}{w}\right)^2}_{\text{Biological}} + \underbrace{\left(\frac{\delta A_{TOT}}{A_{TOT}}\right)^2 + \left(\frac{\delta S}{S}\right)^2}_{\text{Physical}} \right]^{1/2}_{w}$$

Infiltrator™ Angioplasty Balloon Catheter

Infiltrator™ Angioplasty Balloon Catheter or IABC (*Boston Scientific/IVT*) with **three longitudinal strips of seven injection needles**, which on inflation stands 0.01 inch (~0.25 mm) high





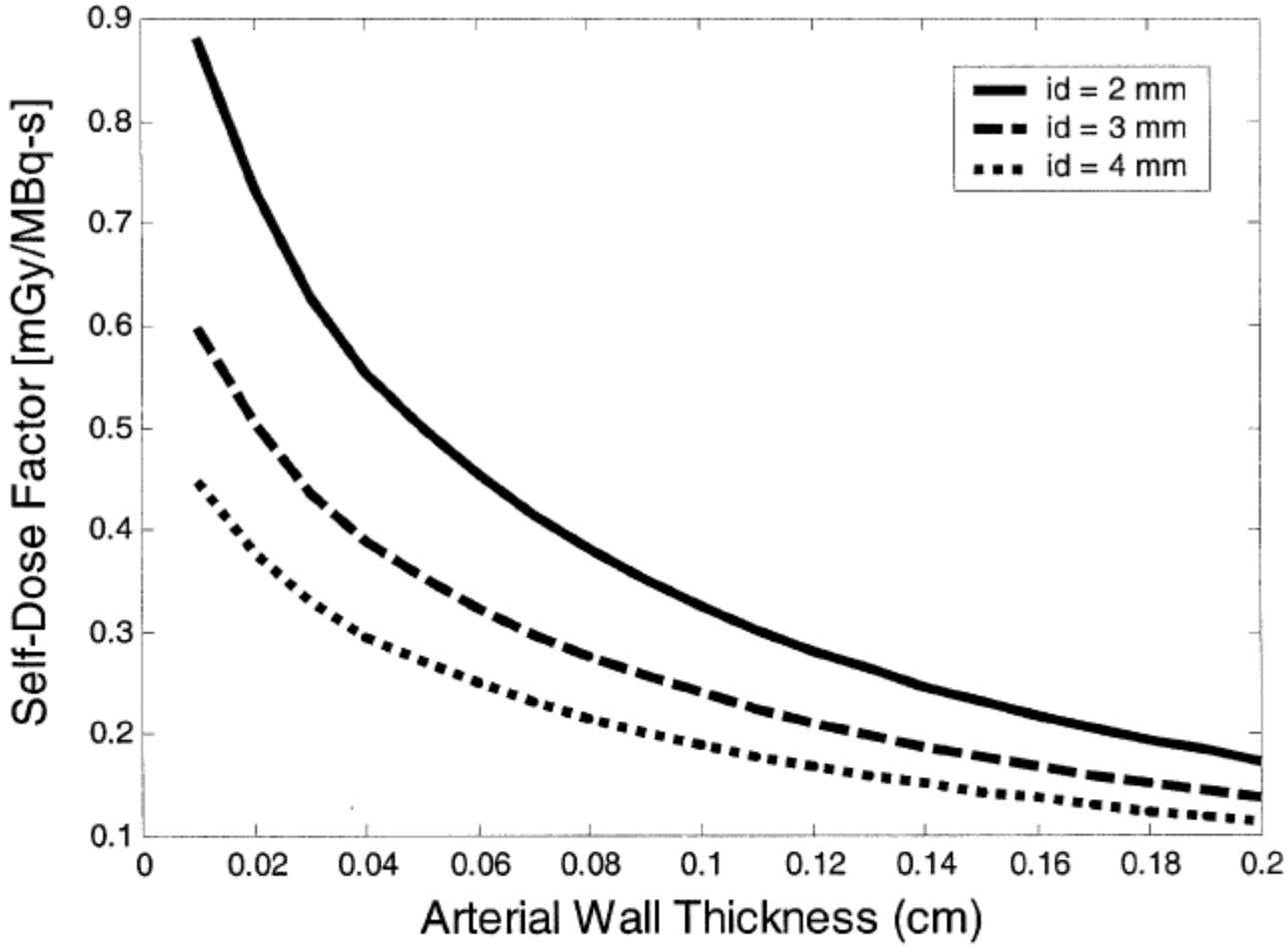


Fig. 1. Self-dose factor *S* in [mGy/MBq-s] to the arterial wall assuming uniform distribution of a P-32 labeled ODN inside the target volume. The *S*-factors are plotted for a wall thickness varying between 0.1 and 2 mm and inside lumen diameters (id) of 2, 3 and 4 mm.

Infiltrator-P-32 ODN Experiment

- *Le Bail et al., 44th COMP Meeting, London, Canada, 1998 (Abstract) :*
  - τ **= 18h**
  - ***D*** **~ 1 Gy/μCi**

  } arterial wall

- Consistent with MCNP model (this work) for ***w*** **~ 0.6 mm**

A_{TOT} **~ 1 mCi** of **P-32**

- for **D ~ 10-50 Gy** to the artery assuming ***E =*** **1-5%**

- Angiogene Phase I/II trial:
  - 6 Patients injected with P-32 labeled ODN with activities in the range of 1 mCi in 2001-2002 (Montreal)
  - Experiments discontinued in late 2003 ?!

Dose to Organs for P-32 ODN Experiment

- Pharmacokinetic In-111 ODN published **independently** by Dewanjee (JNM, 1994)
- Methodology :

1 - Data (% injected dose) scaled from **mouse model** to **humans**

2 - Exponential fit of TAC => λ_{biol} for each organ

3 - (1) and (2) yields the residence time (τ) for the P-32 labeled ODN for each organs

4 - *S-factors* (MIRD) yields dose to organs per unit activity administered in "standard man"

Animal Studies

- Radiopharmaceutical administered to an animal model (mouse, rat, pig, ...)
- Animal sacrificed at different times
- Organs harvested and counted (imaged) for activity
- Decay correction yields % of injected activity per organs
- Results are extrapolated to humans

Scaling to Humans

- Extrapolation to humans **NOT an exact science**
- May or may not work
- Useful for INITIAL dose assessment
- Validation on human subjects required (using small dosage)

$$\left(\frac{\%}{organ}\right)_H = \left(\frac{\%}{organ}\right)_A \times \left(\frac{kg_{TB\ weight}}{g_{organ}}\right)_A \times \left(\frac{g_{organ}}{kg_{TB\ weight}}\right)_H$$

Kirschner *et al.*, J Nucl Med 16(3):248-249; 1975.

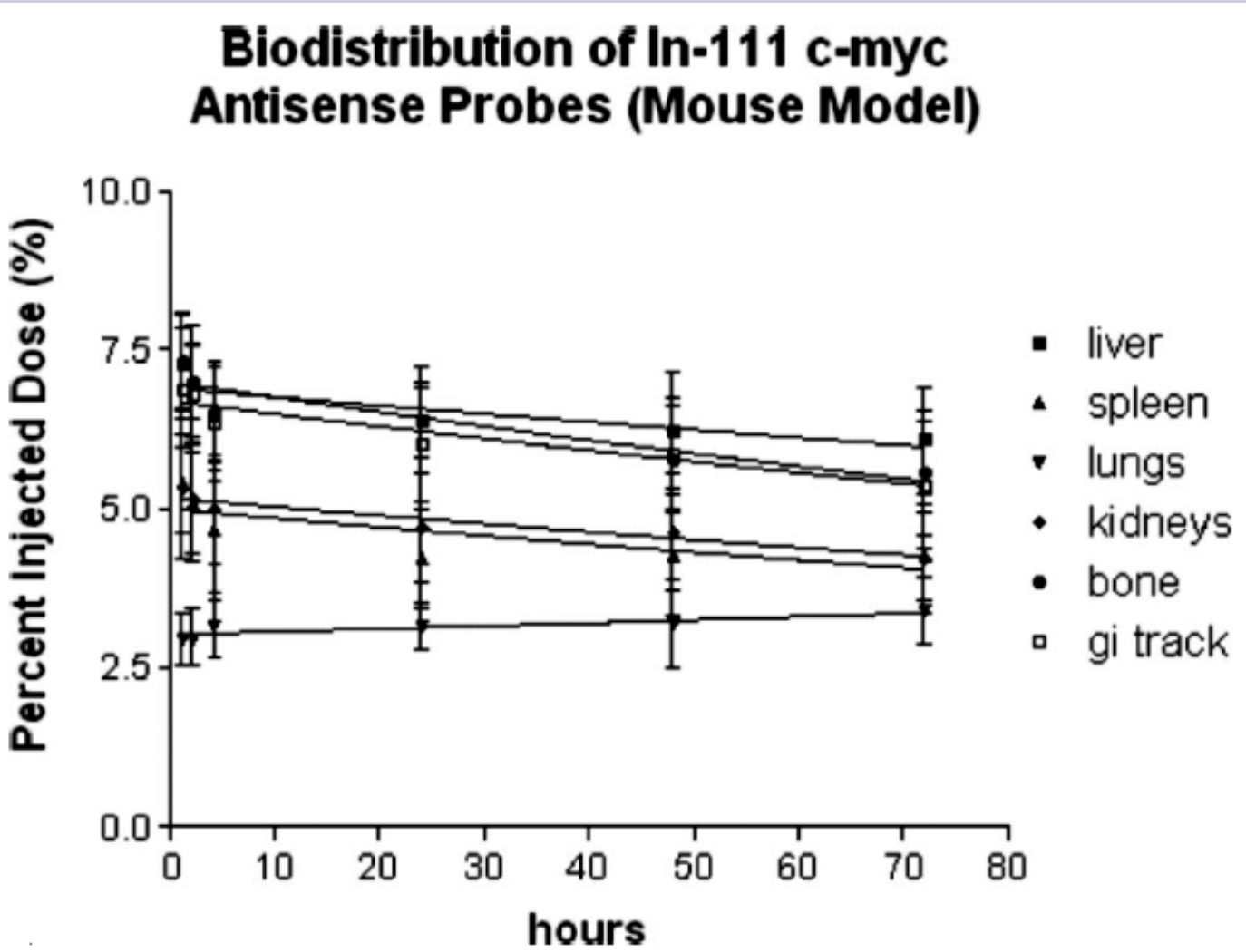
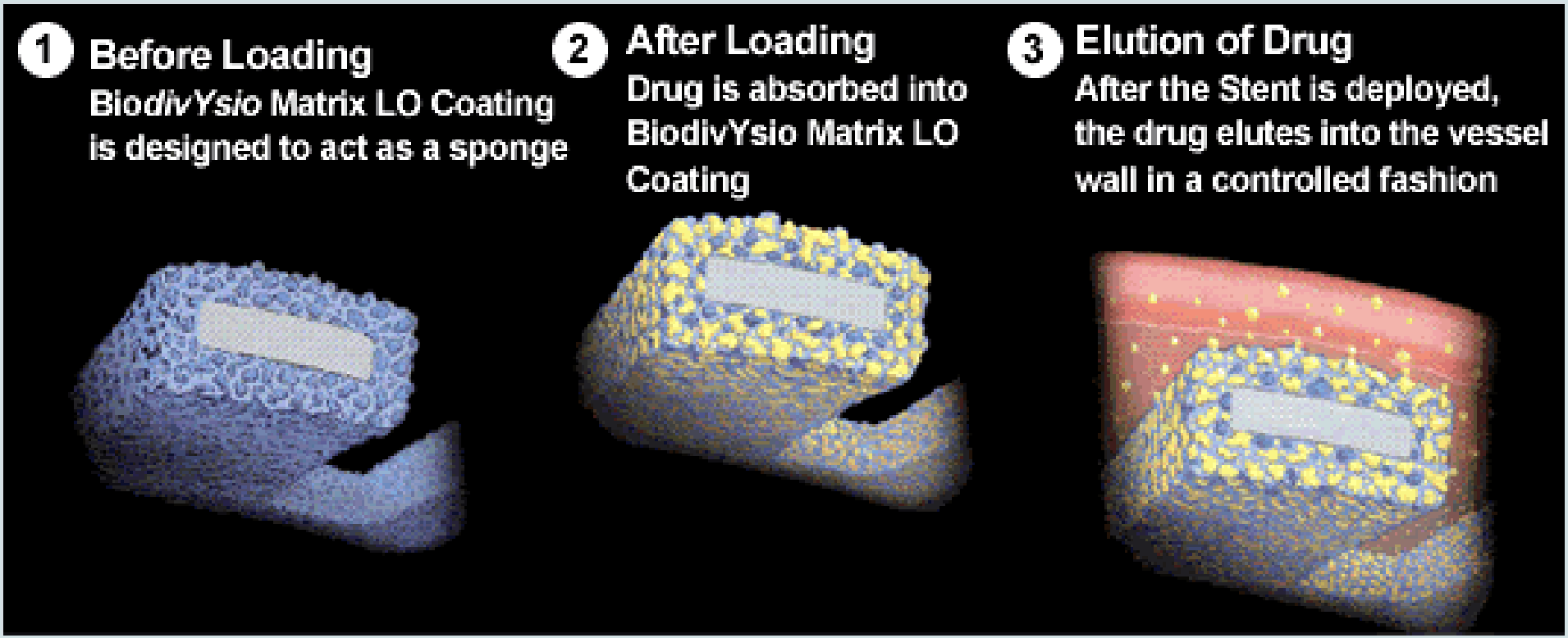


FIG. 8. Pharmacokinetic for the c-myc 15-mer phosphorothioate oligonucleotide in the mouse model. The data are decay corrected and scaled to humans to yield the TAC and the cumulated activities A for the P-32 ODN in organs [adapted from Dewanjee *et al.*, (1994)].

Organs (human)	$A0$ (%/organ)	τ (h)	S [mGy/MBq s]	D [mGy/MBq]
Liver	4.62	181–488	$5.83E-05$	1.80–4.75
Spleen	3.03	128–495	$5.88E-04$	8.21–31.8
Kidneys	1.74	172–320	$3.62E-04$	3.89–7.25
Lungs	5.60	465–495	$1.11E-04$	10.4–11.1
Bone	2.50	117–495	$4.42E-05$	0.47–1.97
GI track	1.47	155–320	$1.32E-04$	1.09–2.23

TABLE I. Dose to organs from a P-32 labeled c-myc antisens ODN (15-mer phosphorothioate) per MBq injected. A is the percent of total injectate per organs (scaled to humans) and τ is the residence time (min, max range for 95% confidence interval) for the P-32 ODN, using the biological half-life determine by curve fitting the results of Fig. 6. The S factors are for the 70 kg standard man and D is the dose (min, max range) in mGy/MBq.

"Radiolabeled" Drug Eluting Stent (P-32 ODN)



Adapted from www.biocompatibles.co.uk

P-32 ODN Eluting Stent

- Proposed by Gobeil et al (2001)*
- 32 PC-coated stent implanted in 32 adult farm pigs
- animals sacrificed at time points (T) between 0 - 672 h
- Artery segments harvested, homogenized and radioactivity level measurements performed
- Initial pre-implantation balloon-stent activity was **167±6 uCi**
- Claims that total dose delivered was **25 Gy** mostly within 72h

***Canadian Cardiovascular Congress 2001**

Ref. : http://www.ccs.ca/society/congress2001/abstracts/abs/a499.htm

Dosimetry for drug eluting stent (non-uniform model)

- Dose at P in the target tissue evaluated at the voxel level

$$\tilde{A}_{wall}\, S_{wall} \Rightarrow \sum_j \tilde{A}_j S_{i \leftarrow j}$$

$\tilde{A}_j =$ *TAC in voxel j (obtained from 3D diffusion-convection model)*

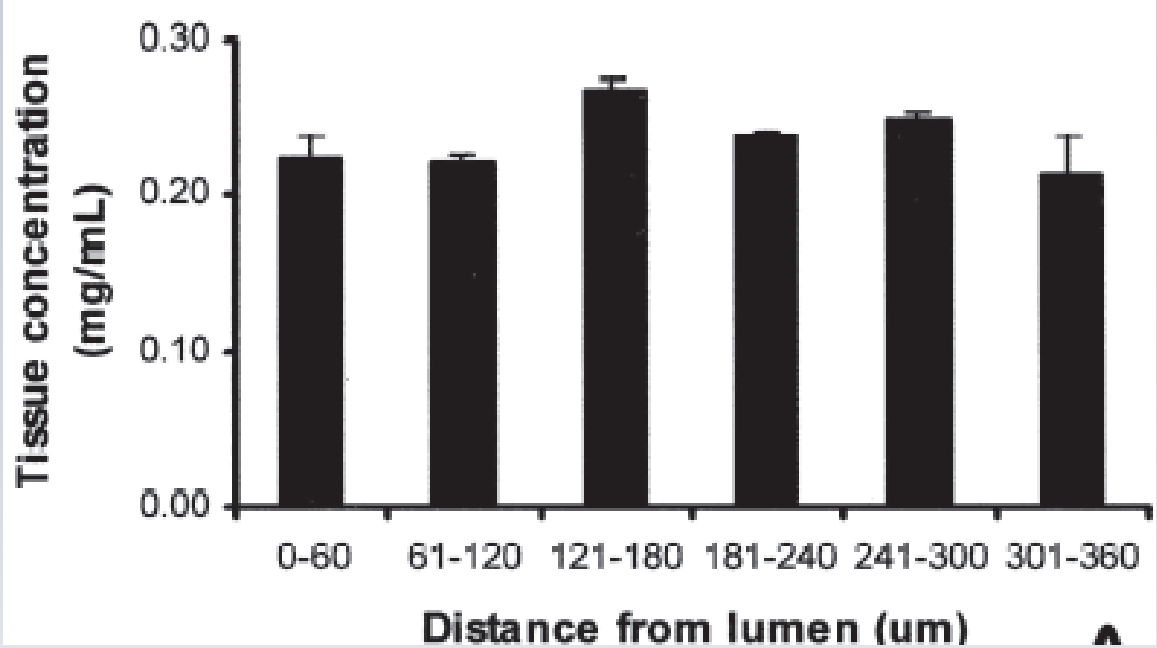
$S_{i \leftarrow j} =$ *S factor for dose in voxel i from activity in voxel j (obtained from DPK or Monte Carlo)*

Dosimetry for drug eluting stent (uniform elution model)

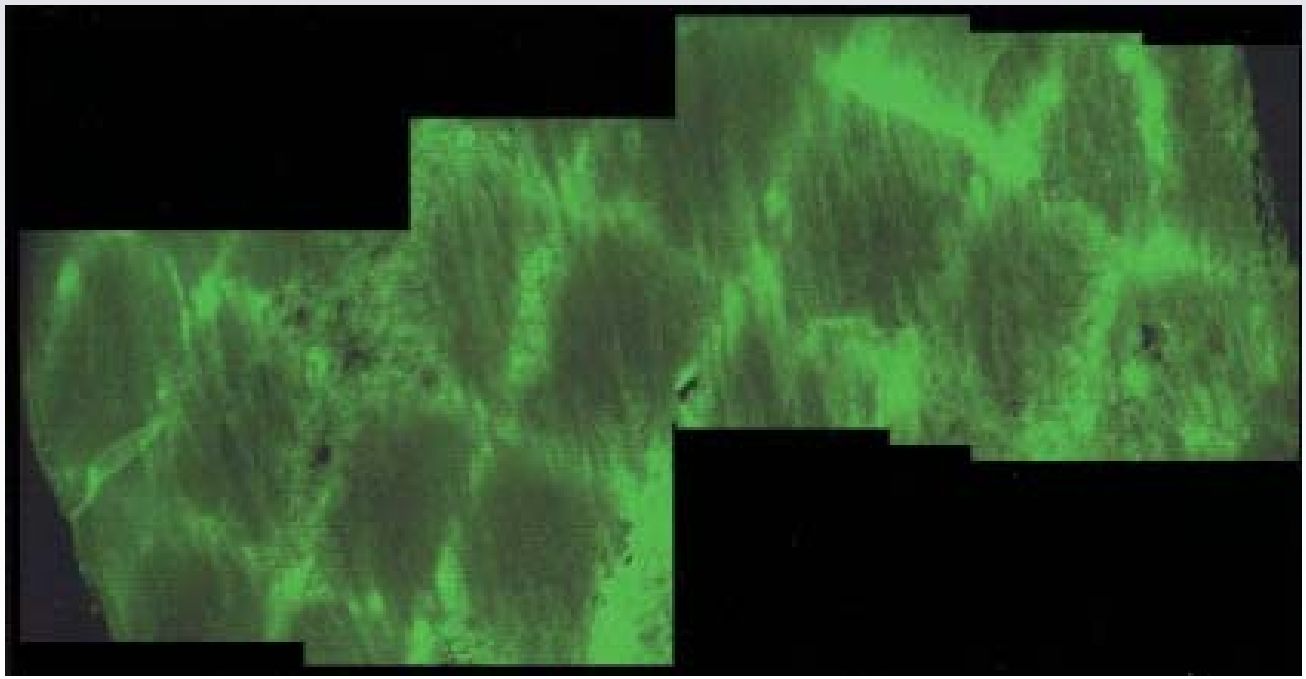
- Dose at P in the target tissue will be the sum of 2 contributions
  - Self-dose from drug within target wall (eluted fraction + TAC) : S_{wall}
  - Dose in target wall from activity residing on the stent surface : $S_{wall<-stent}$

$$D_{wall} = \tilde{A}_{wall}\ S_{wall} + \tilde{A}_{stent}\ S_{wall \leftarrow stent}$$

*Concentration profile from **bulk elution** of serial en face sections*



Fluorescein distribution @ 200 μm from luminal surface of bovine carotid artery



Hwang CW, Wu D, Edelman E, Circulation, 2001;104:600-605

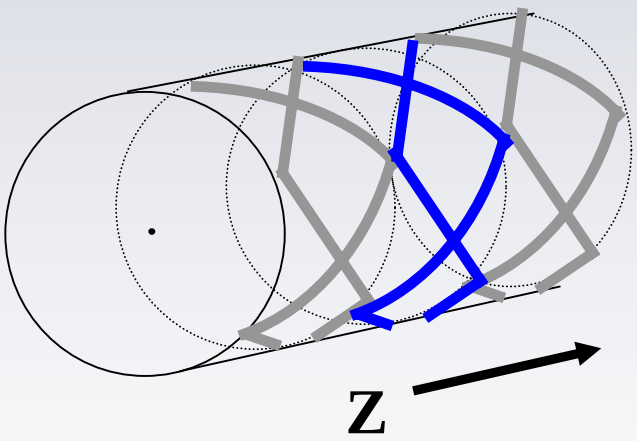
Drug elution from stent and cumulated activity A_{ijk}

- Use simple wire mesh stent model coated with Heparin
  - Stent dimensions : D=4.78 mm, L = 3 mm
- Use 3D diffusion-convection model* to simulate drug elution in tissues
  - Use experimentally measured diffusion coefficients
  - Assume 7 day half-life for source term decay

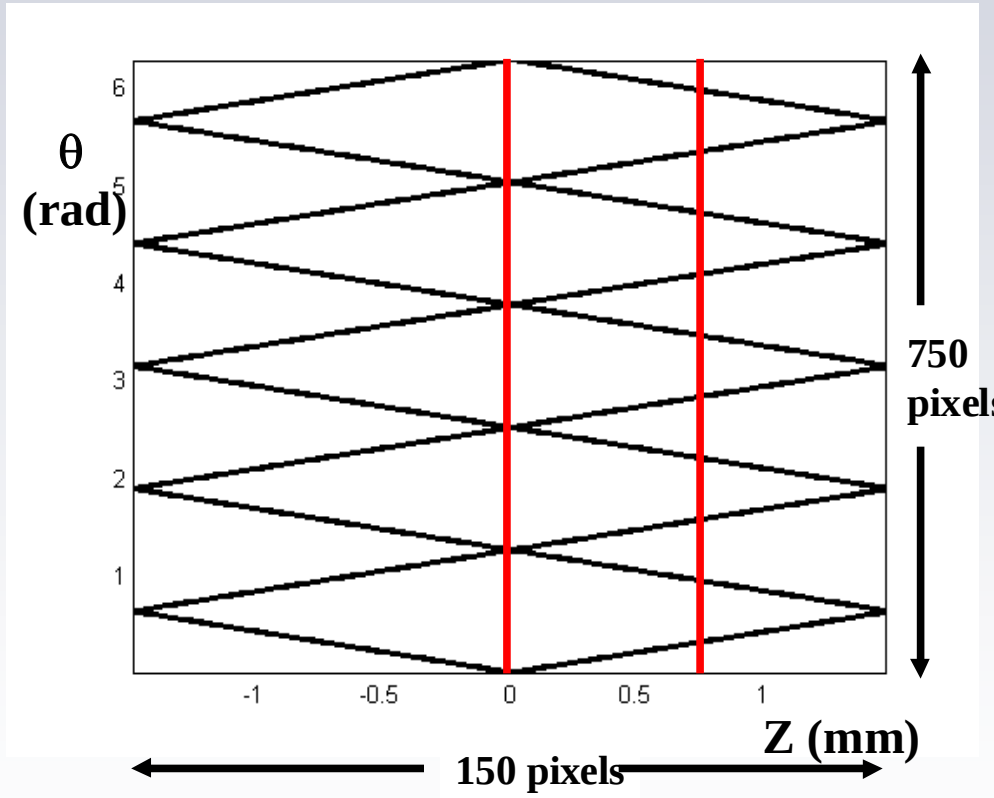
Hwang CW, Wu D, Edelman E, Circulation, 2001;104:600-605

Stent Model: D=4.776 mm ; L=3 mm

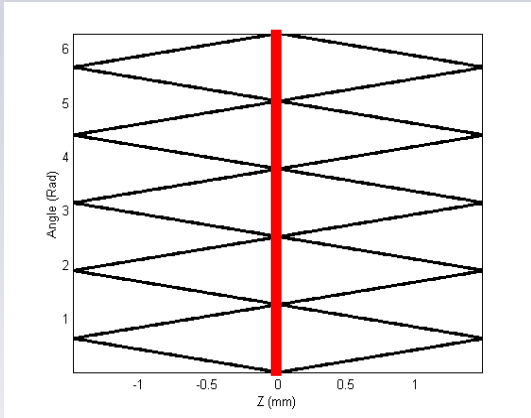
Diamond shape is periodic in Z and θ



unroll



Diffusion of Heparin from Stent



Z position

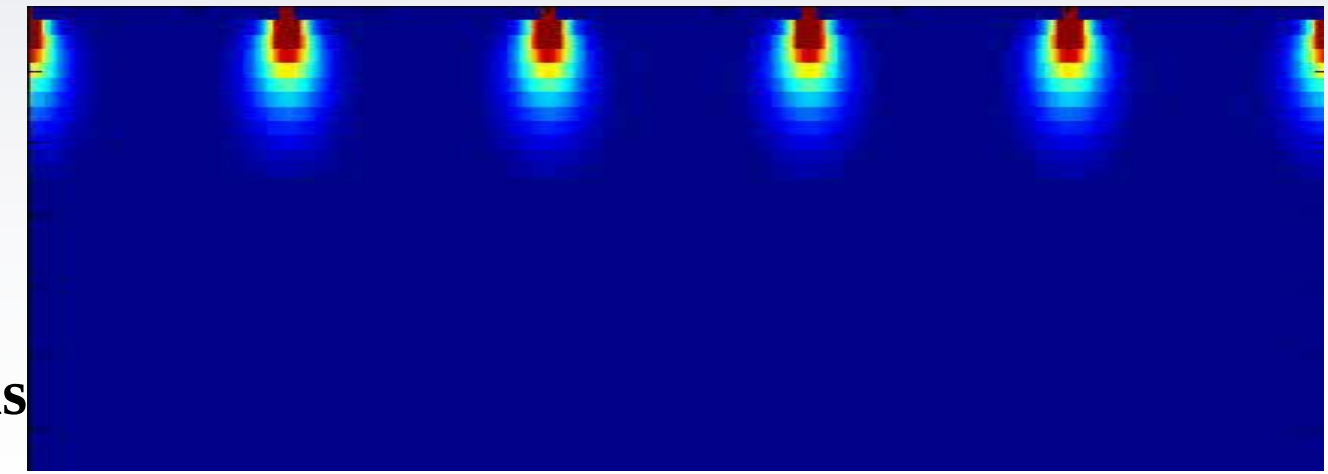
x 150

θ (rad) → **750 pixels**

Depth

↓

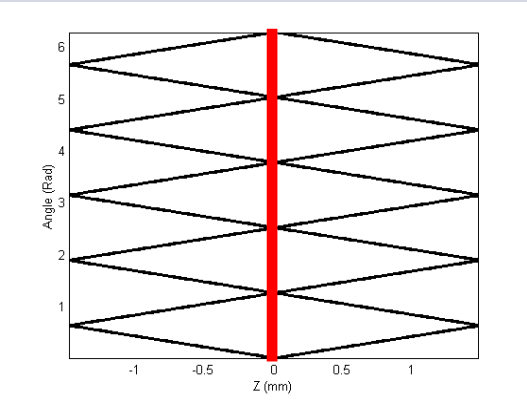
31 pixels



0 mm

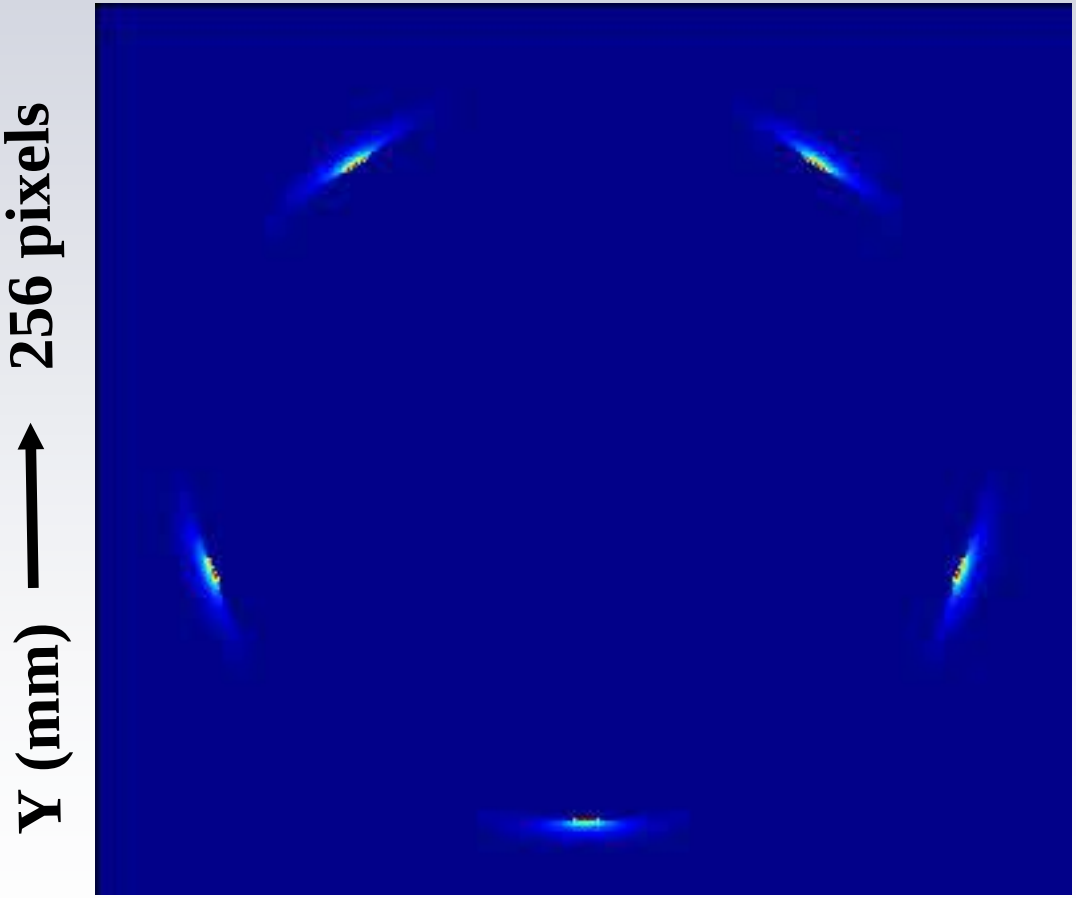
0.620 mm

Diffusion of Heparin from Stent



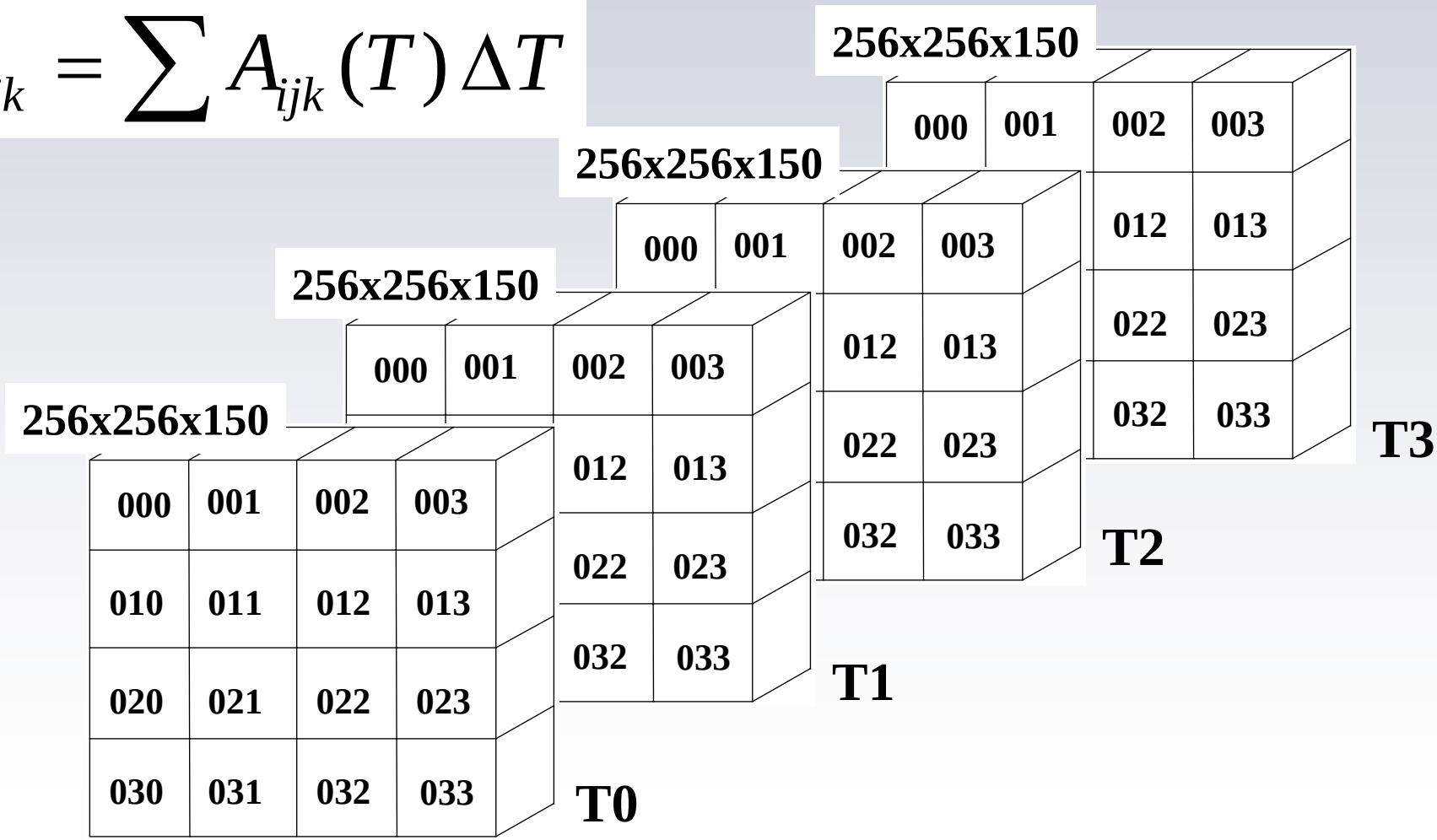
Transform to cartesian coordinates (X,Y,Z)

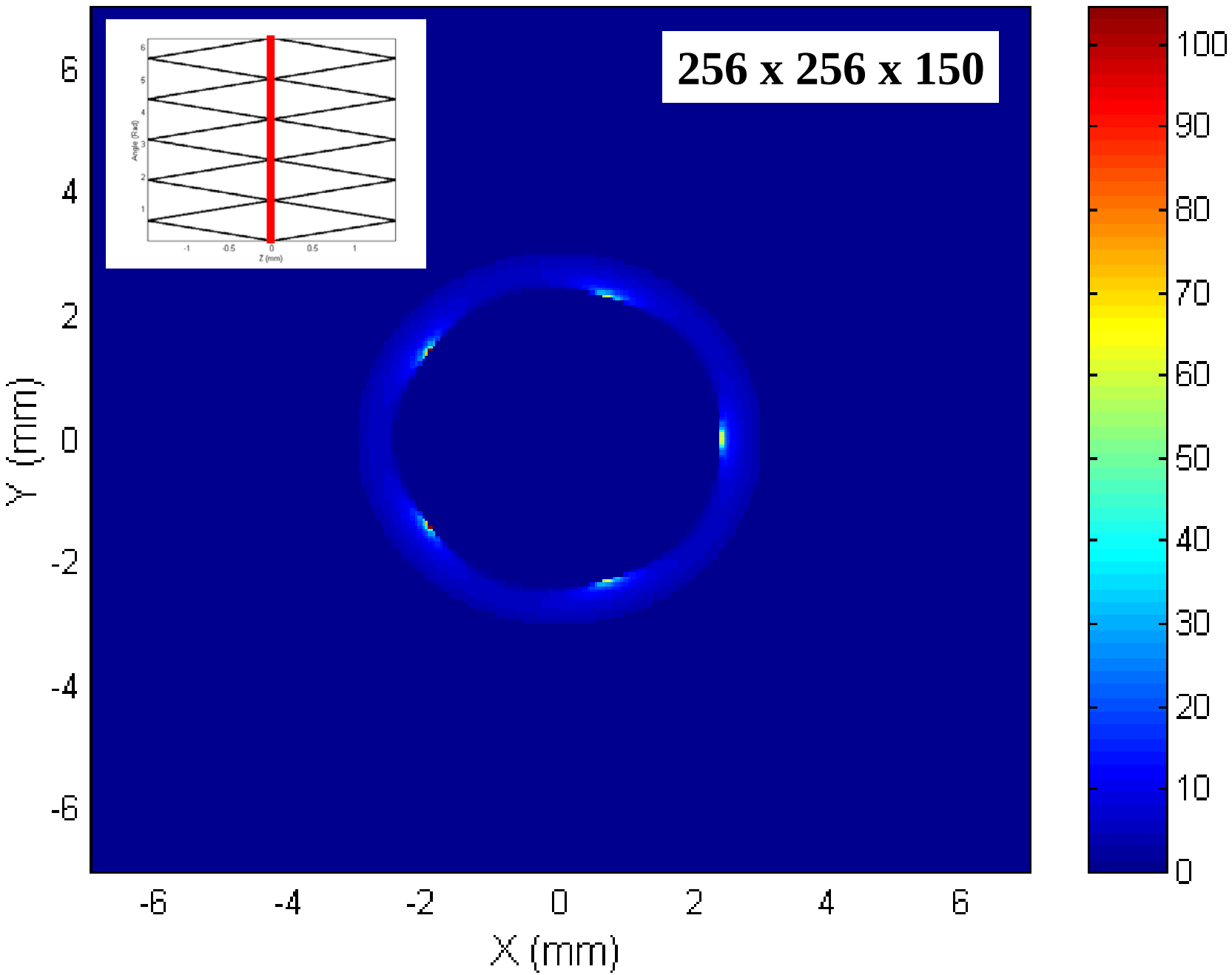
256 x 256 x 150



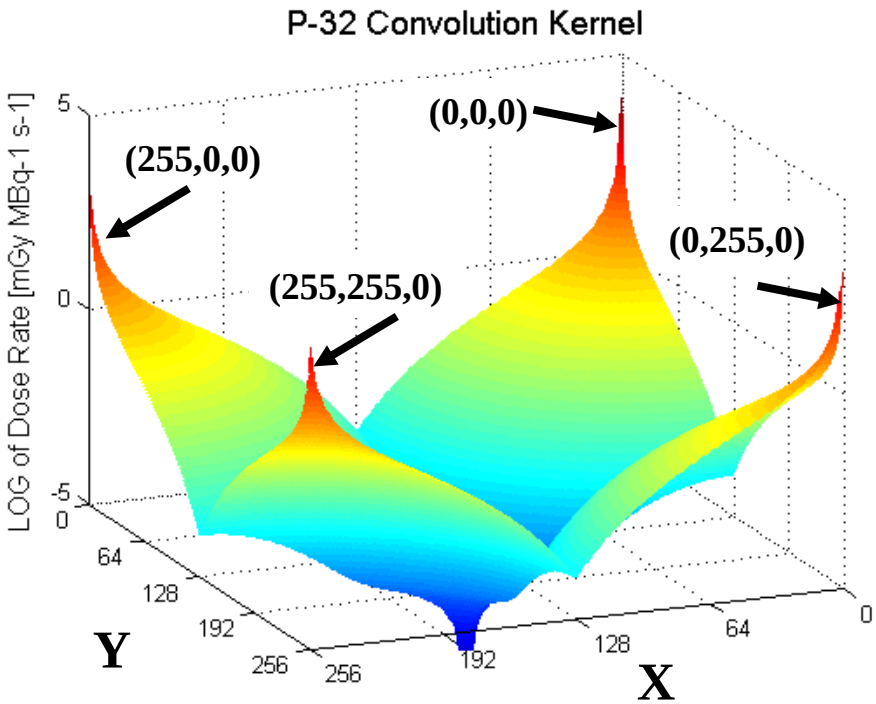
TAC at the Voxel Level

$$\tilde{A}_{ijk} = \sum A_{ijk}(T)\,\Delta T$$

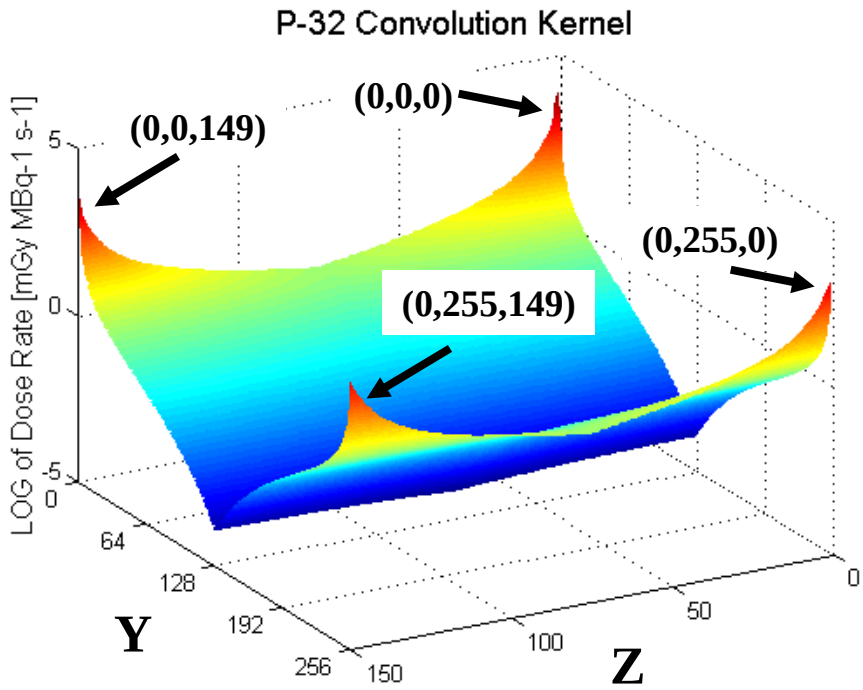



Cumulated Activity @ 7 days : Z = 0 mm
256 x 256 x 150
Y (mm)
X (mm)
-6
-4
-2
0
2
4
6
100
90
80
70
60
50
40
30
20
10
0

P-32 Convolution Kernel S_{ijk}

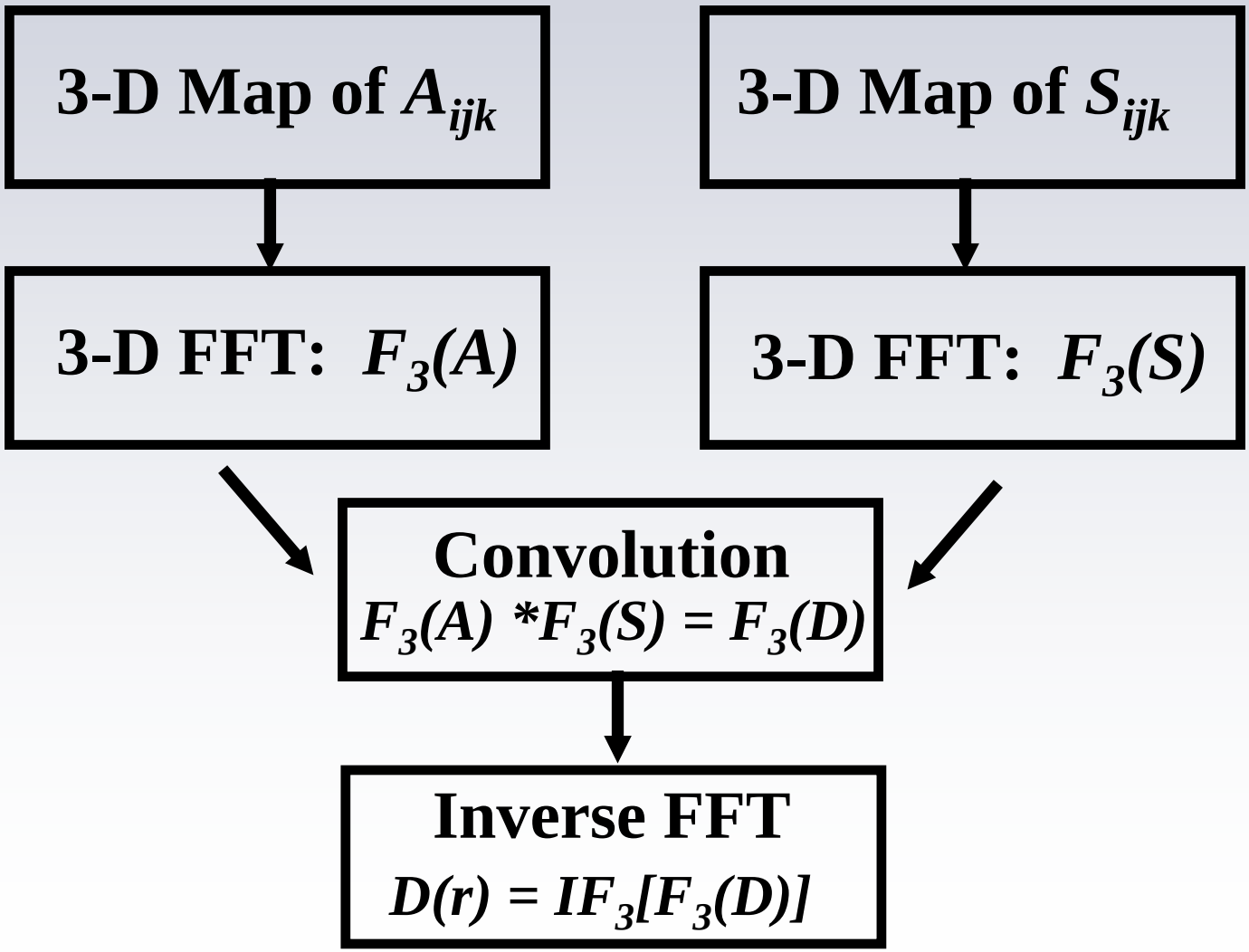


X-Y Plane (Z=0)



Y-Z Plane (X=0)

Dose-Point-Kernel Convolution using FFTs

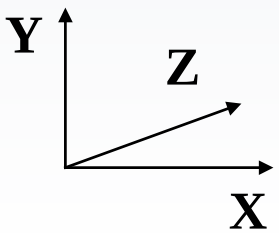


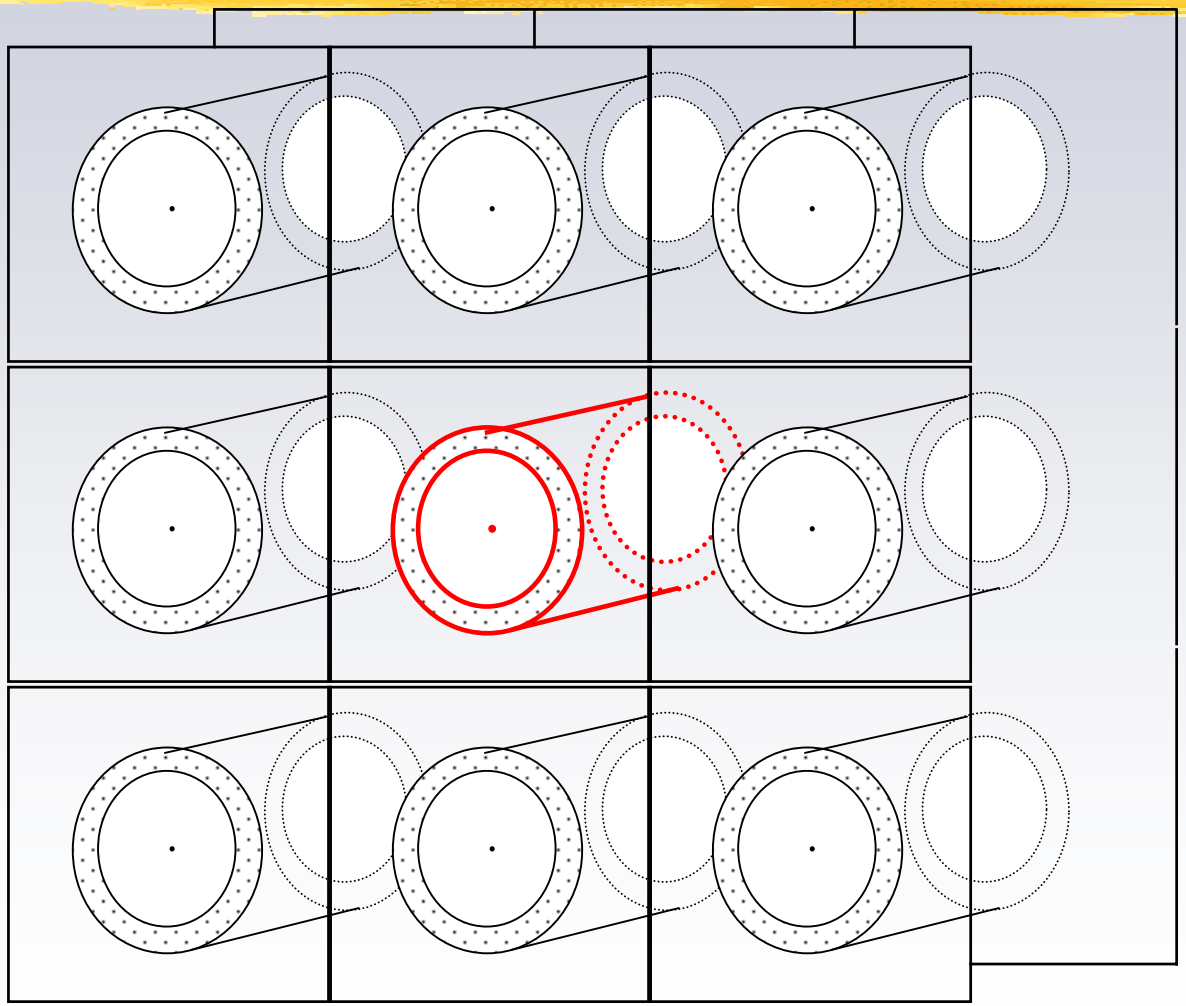
Dose-Point-Kernel Convolution

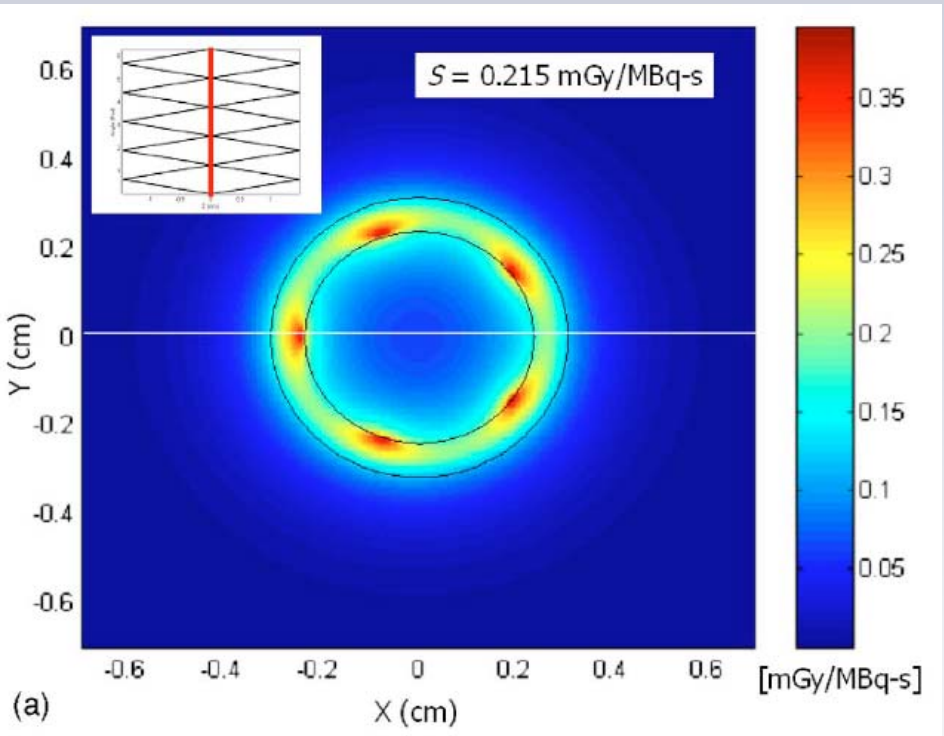
FFT Convolution
⇨ periodicity

Set X-Y large enough to minimize aliasing

Keep periodicity in Z to model an infinite long stent







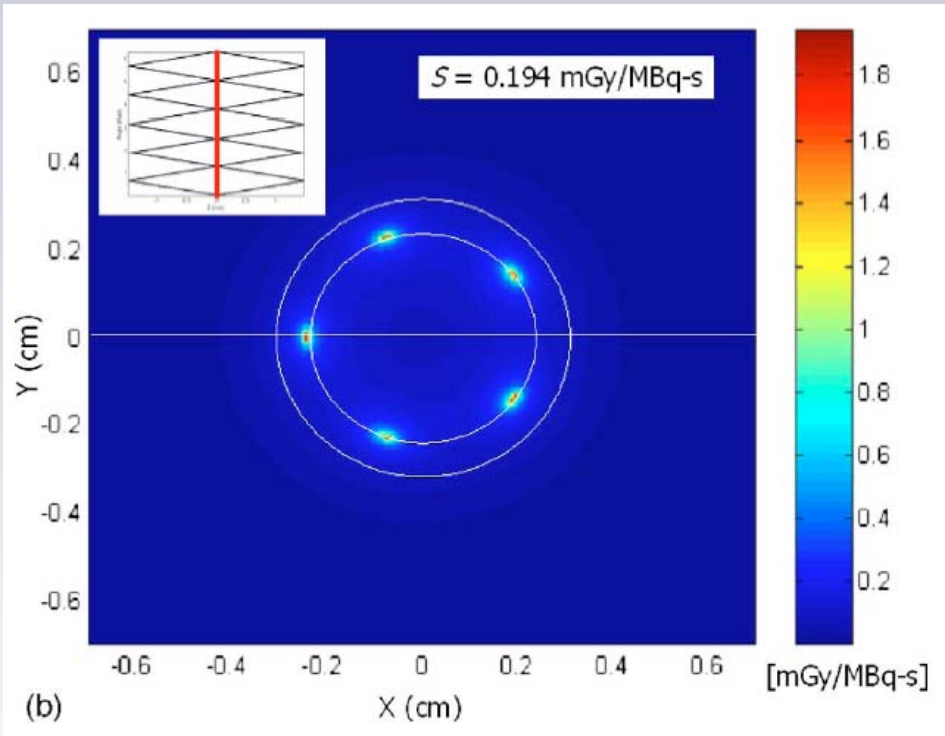
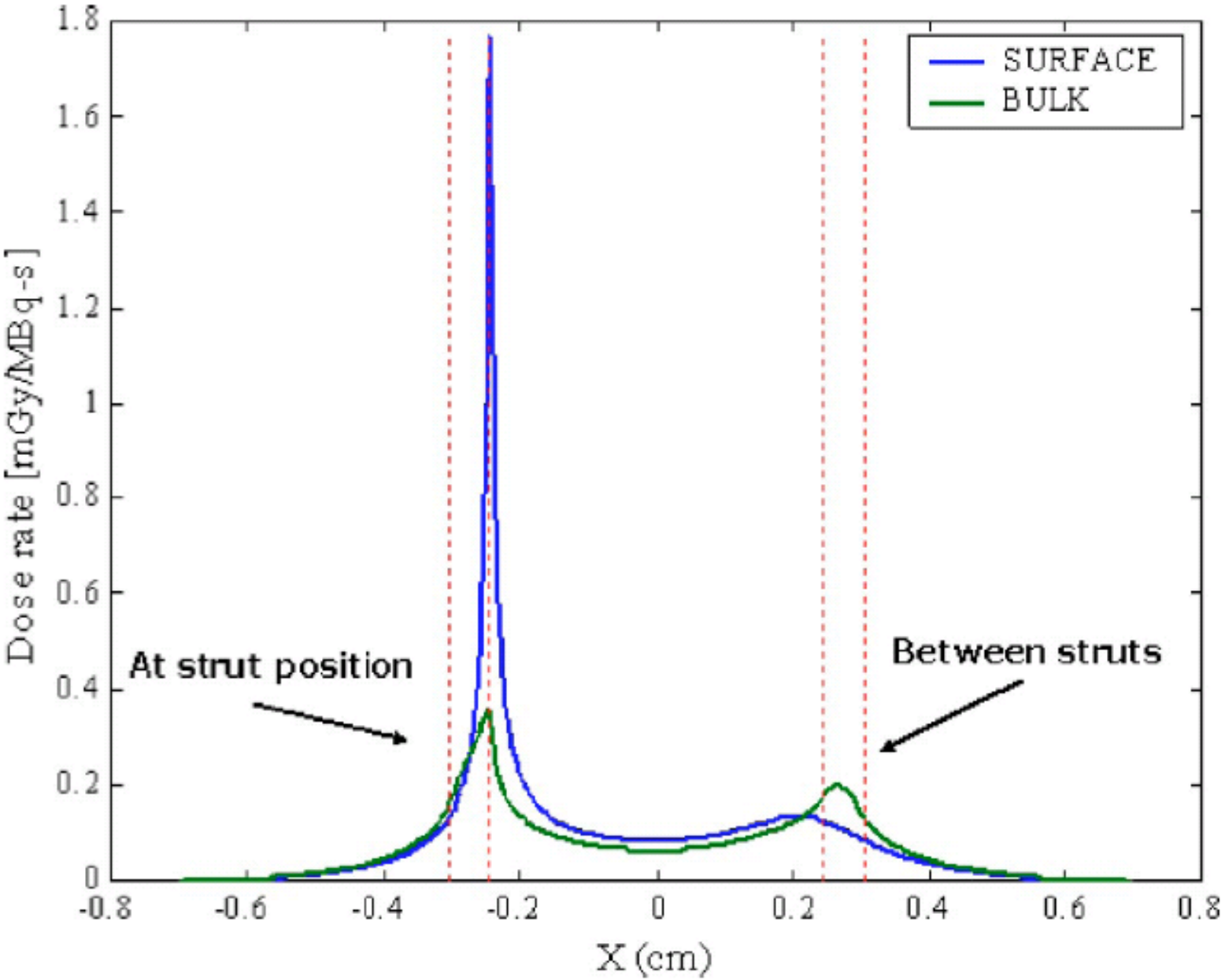
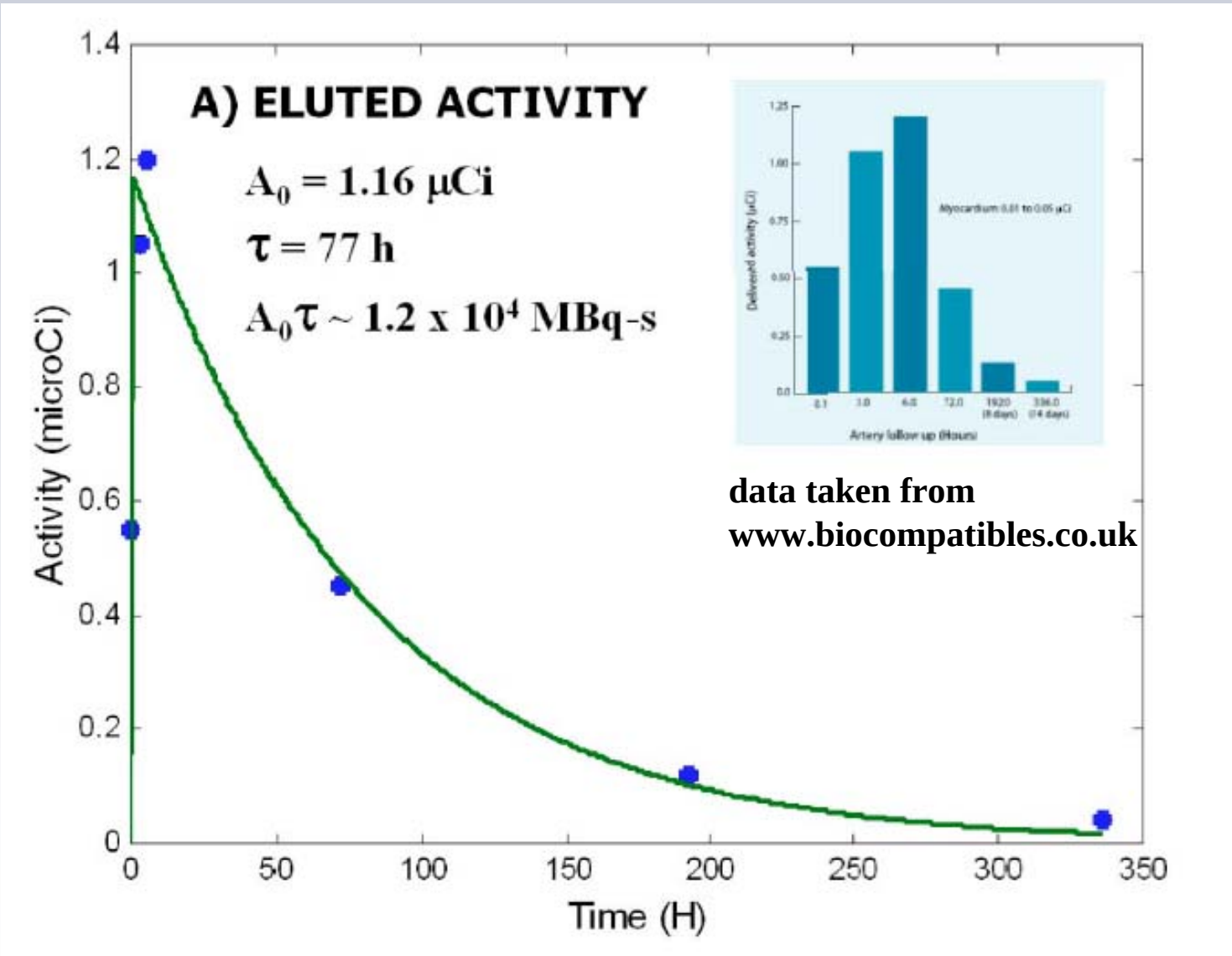
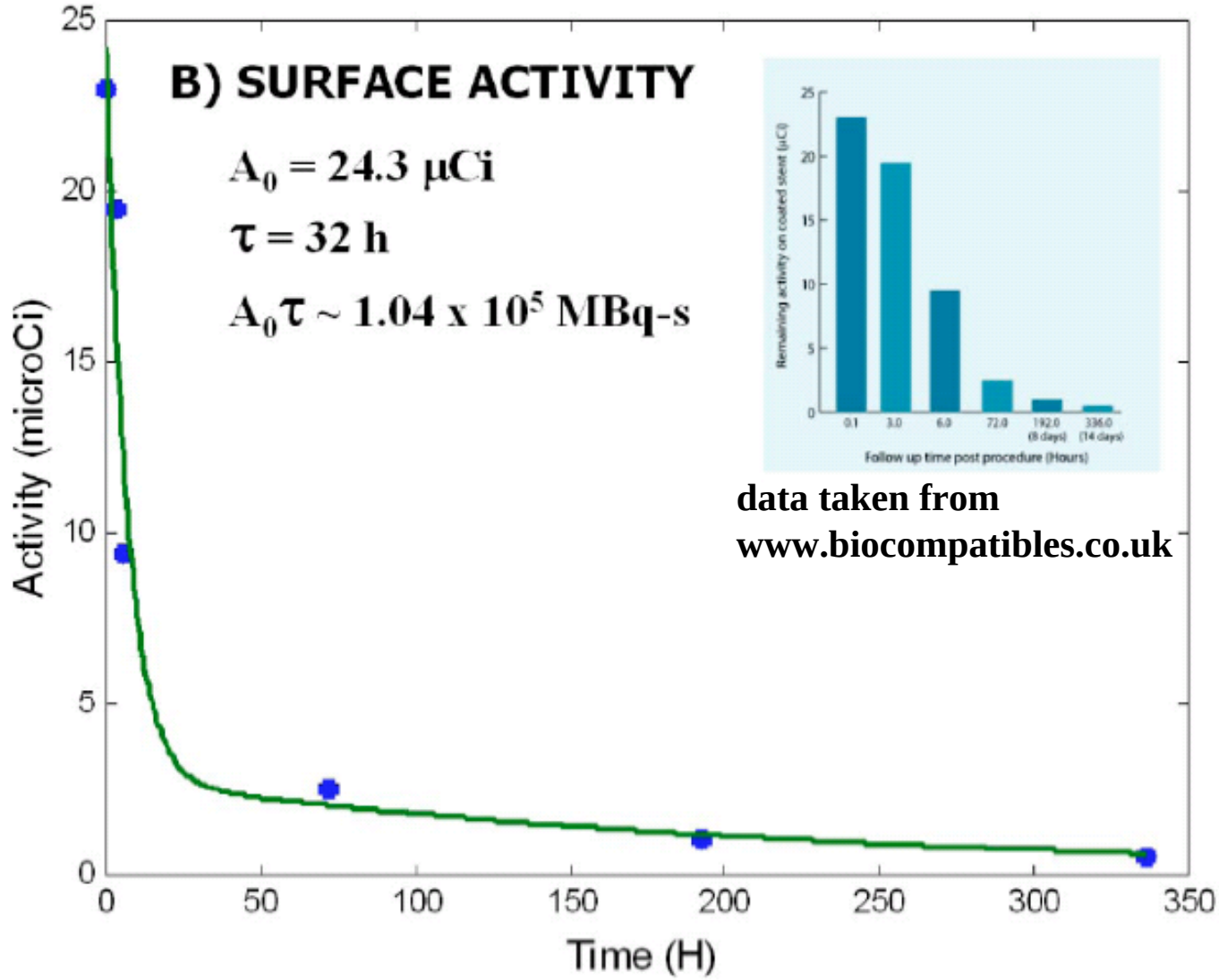


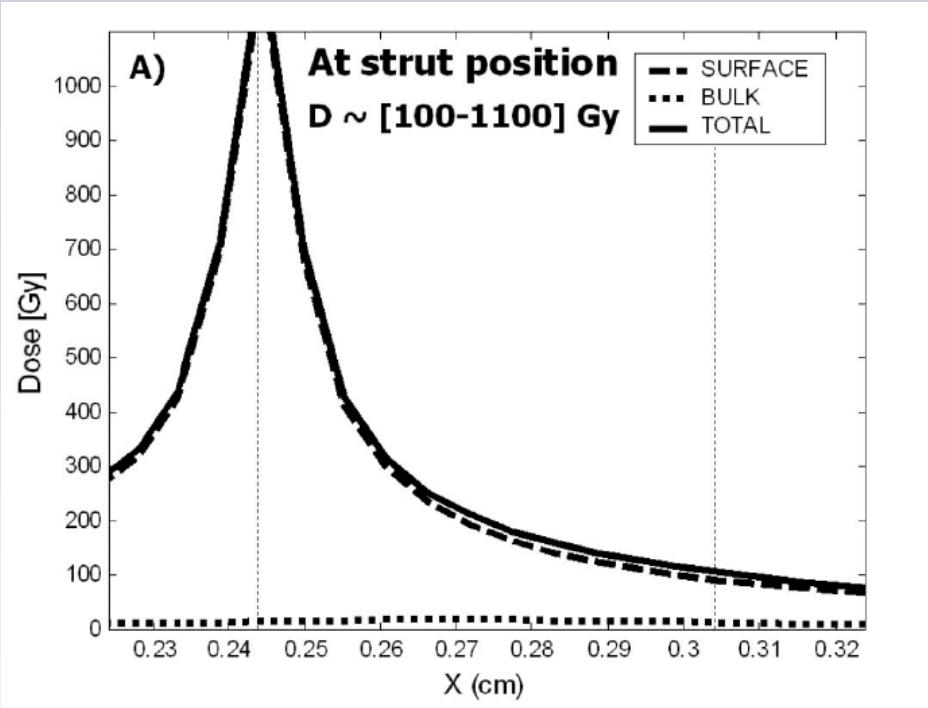
FIG. 3. Dose distribution through the middle plane of the 3 mm stent section due to (a) the P-32 ODN drug eluted from the stent into the arterial wall and (b) the drug activity at the surface of the stent. The doses are normalized per MBq s of cumulated activity for the respective sources. The average *S* factors to the target media for the eluted drug and the surface drug distributions are 0.21 and 0.19 [mGy/MBq s], respectively.


SURFACE
BULK
Dose rate [mGy/MBq-s]
X (cm)
At strut position
Between struts
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8


A) ELUTED ACTIVITY
$A_0 = 1.16\ \mu Ci$
$\tau = 77\ h$
$A_0\tau \sim 1.2 \times 10^4\ MBq\text{-}s$
Activity (microCi)
Time (H)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
0
50
100
150
200
250
300
350
data taken from
www.biocompatibles.co.uk



data taken from www.biocompatibles.co.uk



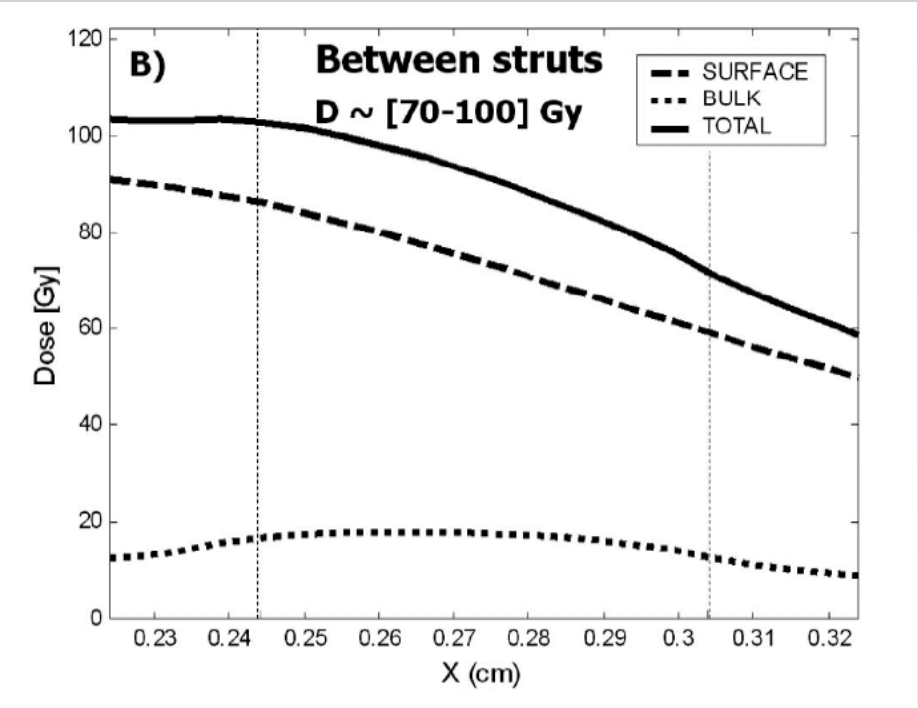


FIG. 6. Radial dose profile at 14 days for a 6.1 MBq (165 μCi) P-32 ODN with non-uniform drug elution (transport model) (a) at the strut position and (b) between the stent struts (see Fig. 3). The target media is delimited by the dotted lines. The dose from the eluted drug (BULK) contributes to less than 15% of the total dose throughout the media.

P-32 ODN Eluting Stent

- Low Delivery Efficiency (Typically < 5%)
- Biological residence time in artery comparable to washout time from stent surface (77h vs 25h)
- Dose to arterial wall @ 0.5mm is due mainly to activity **residing at surface of stent**
- Dose enhancement from drug elution is minimal (less than ~10%)
- Dose to organs is of concern (P-32 washout is ~80% after 24h)

Infiltrator™ Angioplasty Balloon Catheter

- **Variables which may affect the Infiltrator's intramural delivery efficiency * :**
  - All InjectorPorts (IP) embedded in the target tissue (penetrating IEL)
  - No InjectorPorts in side branch vessels
  - Sufficient pressure during delivery to force injectate through all IP
  - Sufficient time is allowed for the drug delivery lumen to reach equilibrium pressure post injectate delivery
- **Assuming the above scenario, fluid delivery efficiency can be ~ 90% ***
- **Quantity taken up by the target tissue is function of the properties of the injectate* (~ 1-5% at most**)**

**SC Thornbury (Boston Scientific/IVT), personnal communication, 2002.*

***N Kipshidse (Lennox Hill, NY), personal communication, 2002.*

nm/mird PAMPHLET NO. 5, REVISED

ESTIMATES OF SPECIFIC ABSORBED FRACTIONS FOR PHOTON SOURCES UNIFORMLY DISTRIBUTED IN VARIOUS ORGANS OF A HETEROGENEOUS PHANTOM

Walter S. Snyder, Mary R. Ford, and Gordon G. Warner

Health Physics Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37830

http://interactive.snm.org/index.cfm?PageID=2199&RPID=1372