

Radiation-bombs in amyloids

Internees: Hannah Scharff, Maria Rebouta

Supervisors: Lia Pereira, Carina Coelho, and
Pamela Teubig

LIP Summer Internships 2022

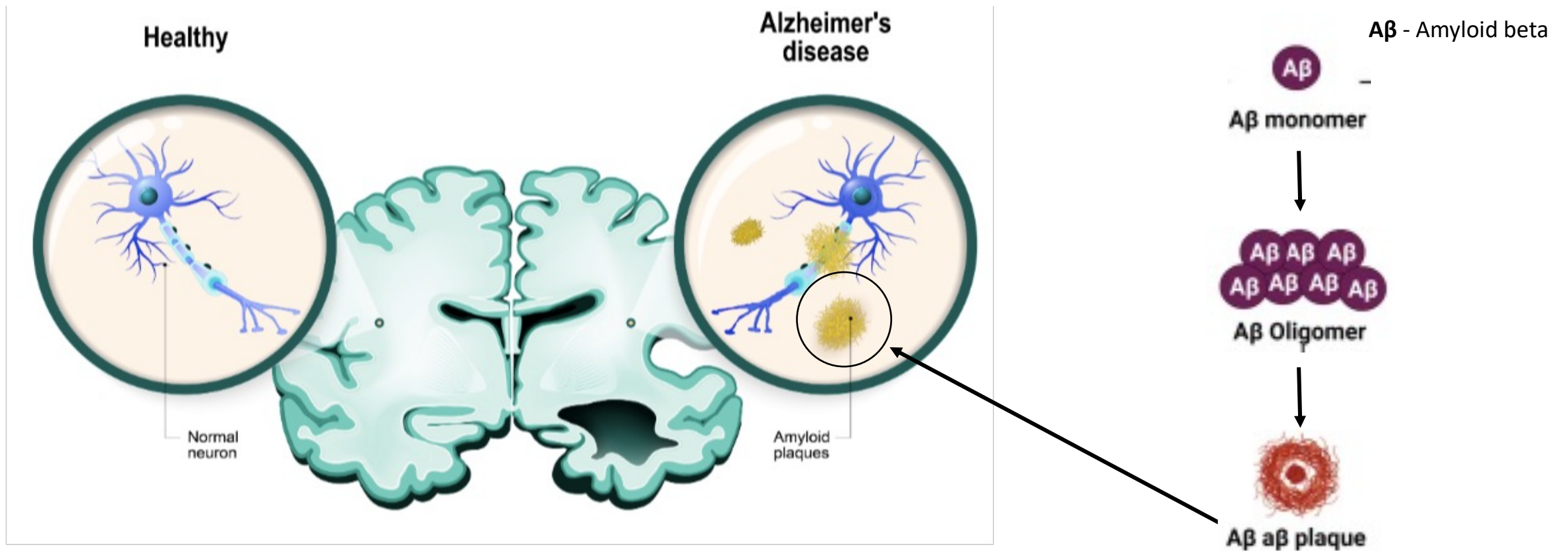


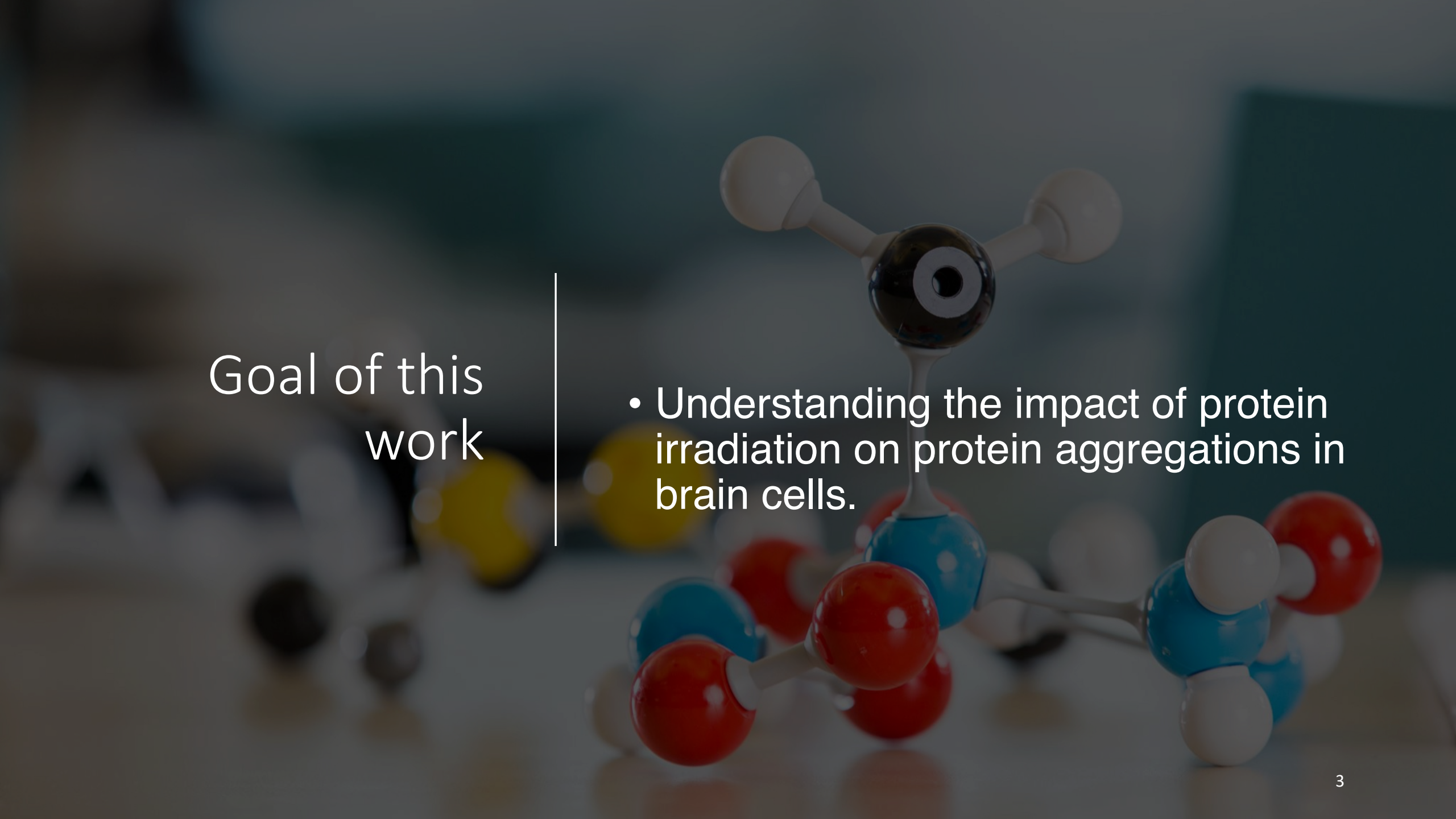
LABORATÓRIO DE INSTRUMENTAÇÃO
E FÍSICA EXPERIMENTAL DE PARTÍCULAS



Ciências
ULisboa

Motivation



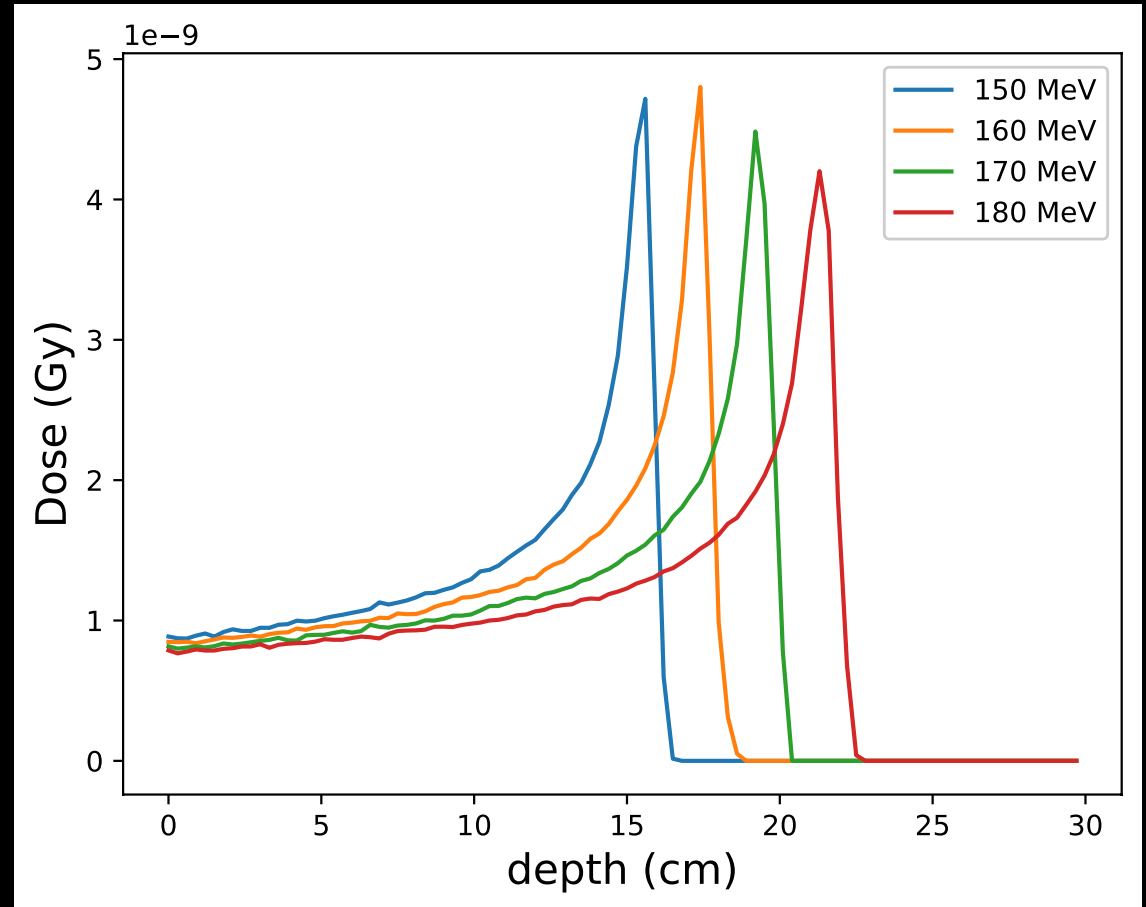
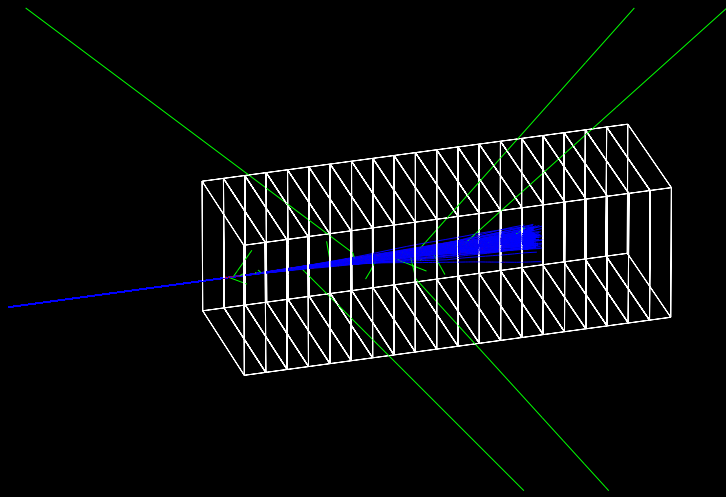


Goal of this work

- Understanding the impact of protein irradiation on protein aggregations in brain cells.

Bragg Peak

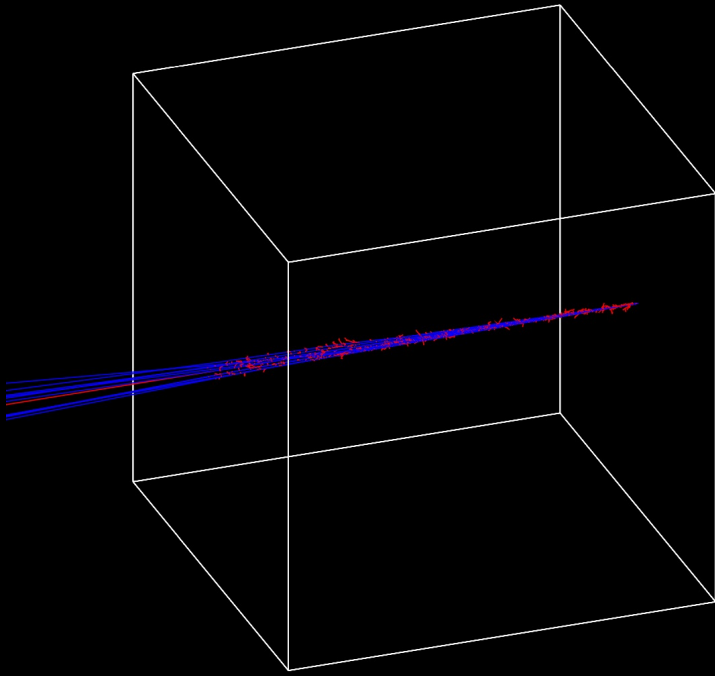
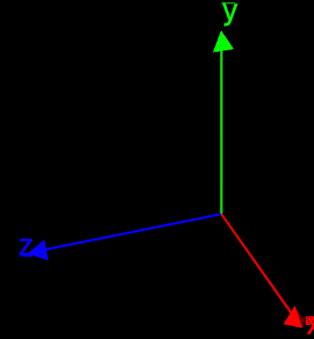
Number of events: 10^2 .



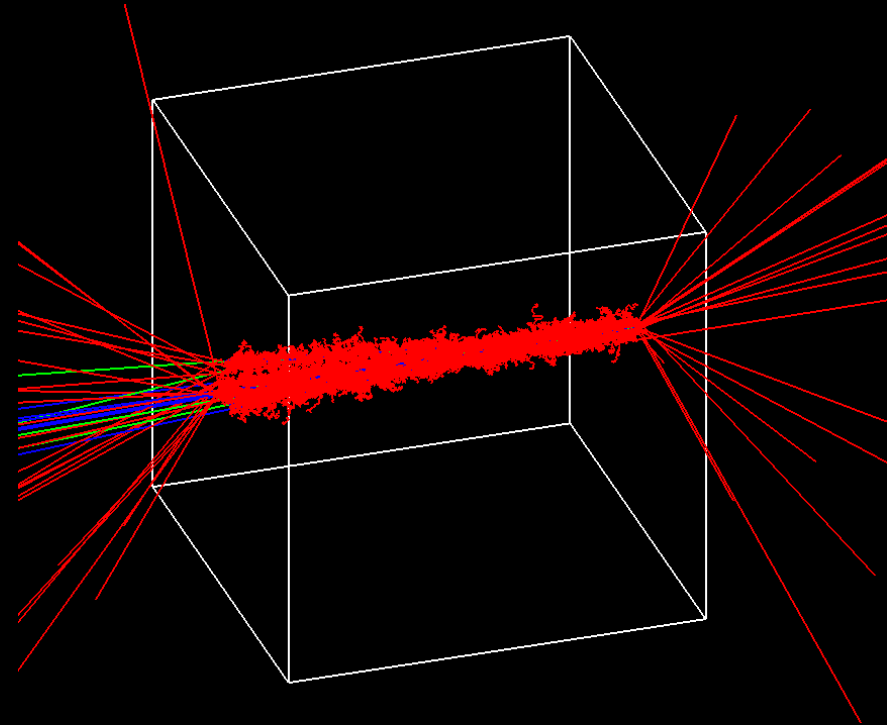
First Step: water box

Proton Beam Energy: 100 keV

Box dimensions: $HLX^* = HLZ^* = HLY^* = 1000 \text{ \AA}$



"g4em-standard_opt4"



"g4em-dna"

*HL = half length

Second Step:
add amyloid

Will irradiation induce
damage in amyloids?

TOPAS nBio

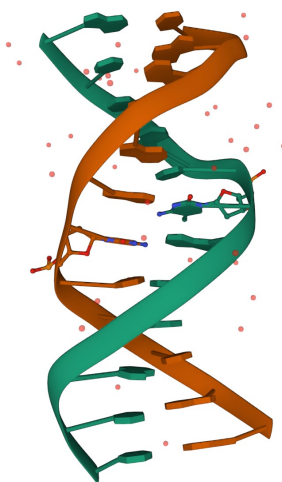
- Overview Diagram

PDB File of DNA molecule structure

```

ATOM      1  O5'  DA  A   1   -26.661  23.211  11.200  1.00  42.04
ATOM      2  O5'  DA  A   2    10.000  10.000  10.000  1.00  45.85
ATOM      3  O5'  DA  A   3    10.000  10.000  10.000  1.00  44.02
ATOM      4  O5'  DA  A   4    10.000  10.000  10.000  1.00  46.13
ATOM      5  O5'  DA  A   5    10.000  10.000  10.000  1.00  43.51
ATOM      6  O5'  DA  A   6    10.000  10.000  10.000  1.00  44.92
ATOM      7  O5'  DA  A   7    10.000  10.000  10.000  1.00  41.37
ATOM      8  O5'  DA  A   8    10.000  10.000  10.000  1.00  38.84
ATOM      9  O5'  DA  A   9    10.000  10.000  10.000  1.00  30.88
ATOM     10  O5'  DA  A  10    10.000  10.000  10.000  1.00  26.31
ATOM     11  O5'  DA  A  11    10.000  10.000  10.000  1.00  22.41
ATOM     12  O5'  DA  A  12    10.000  10.000  10.000  1.00  22.64
ATOM     13  O5'  DA  A  13    10.000  10.000  10.000  1.00  21.21
ATOM     14  O5'  DA  A  14    10.000  10.000  10.000  1.00  20.36
ATOM     15  O5'  DA  A  15    10.000  10.000  10.000  1.00  18.03
ATOM     16  O5'  DA  A  16    10.000  10.000  10.000  1.00  20.49
ATOM     17  O5'  DA  A  17    10.000  10.000  10.000  1.00  19.59
ATOM     18  O5'  DA  A  18    10.000  10.000  10.000  1.00  24.71
ATOM     19  O5'  DA  A  19    10.000  10.000  10.000  1.00  50.53
ATOM     20  O5'  DA  A  20    10.000  10.000  10.000  1.00  44.77
ATOM     21  O5'  DA  A  21    10.000  10.000  10.000  1.00  58.98
-----

```

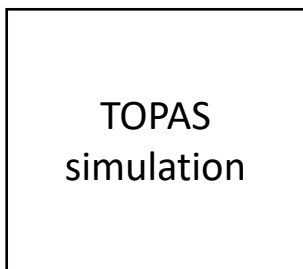


```

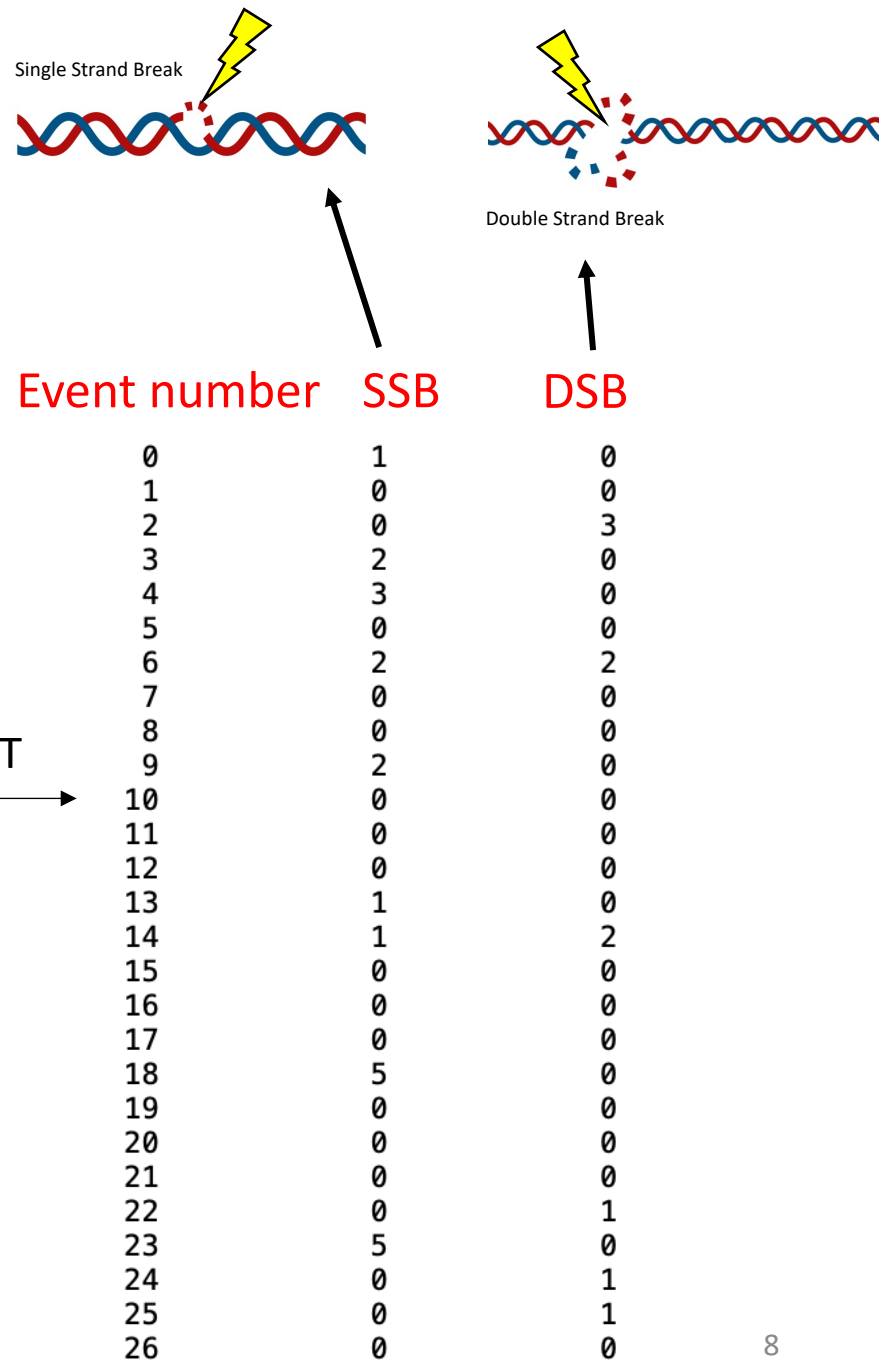
O
C
C
O
C
C
O
C
C
N
C
N
C
C
N
N
C
N
C
P
O
O
-

```

INPUT



OUTPUT



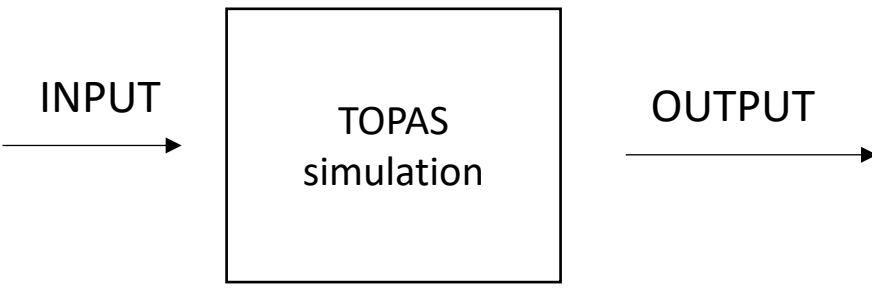
What we want to simulate:

PDB File of Amyloid molecule structure

```
ATOM      1  N   ASP A  1   -14.439 -56.597 103.986  1.00  0.00
ATOM      2  CA  ASP A  1   -15.582 -56.020 104.745  1.00  0.00
ATOM      3  C   ASP A  1   -15.885 -54.629 104.195  1.00  0.00
ATOM      4  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM      5  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM      6  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM      7  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM      8  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM      9  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     10  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     11  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     12  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     13  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     14  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     15  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     16  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     17  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     18  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     19  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     20  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     21  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     22  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     23  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     24  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     25  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
ATOM     26  O   ASP A  1    15.222  54.219 102.100  1.00  0.00
```



```
N
C
C
O
C
C
O
O1-
H
H
H
H
H
H
N
C
C
O
```



Event number	Breaks
0	1
1	0
2	0
3	0
4	0
5	0
6	0
7	0
8	0
9	0
10	0
11	0
12	0
13	0
14	0
15	1
16	0
17	0
18	0
19	0
20	0
21	1
22	0
23	0
24	0
25	0
26	0

Structure Summary

3D View

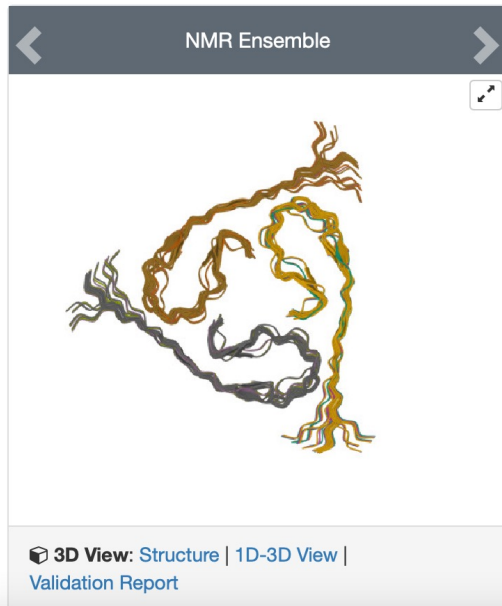
Annotations

Experiment

Sequence

Genome

Versions



2M4J

40-residue beta-amyloid fibril derived from Alzheimer's disease brain

PDB DOI: [10.2210/pdb2M4J/pdb](https://doi.org/10.2210/pdb2M4J/pdb) BMRB: 19009

Classification: **PROTEIN FIBRIL**

Organism(s): **Homo sapiens**

Mutation(s): No

Deposited: 2013-02-05 Released: 2013-09-25

Deposition Author(s): [Lu, J.](#), [Qiang, W.](#), [Meredith, S.C.](#), [Yau, W.](#), [Schweeters, C.D.](#), [Tycko, R.](#)

Experimental Data Snapshot

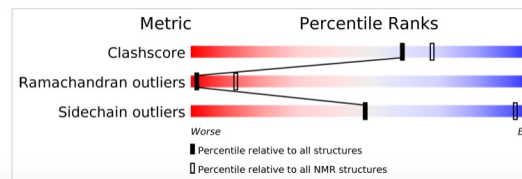
Method: SOLID-STATE NMR

Conformers Calculated: 600

Conformers Submitted: 20

Selection Criteria: no violations, low restraint energy, and maximum structural diversity

wwPDB Validation



Display Files Download Files

```

HEADER      PROTEIN FIBRIL                                05-FEB-13   2M4J
TITLE      40-RESIDUE BETA-AMYLOID FIBRIL DERIVED FROM ALZHEIMER'S DISEASE BRAIN
COMPND     MOL_ID: 1;
COMPND     2 MOLECULE: AMYLOID BETA A4 PROTEIN;
COMPND     3 CHAIN: A, B, C, D, E, F, G, H, I;
COMPND     4 FRAGMENT: UNP RESIDUES 672-711;
COMPND     5 SYNONYM: ABPP, APPI, APP, ALZHEIMER DISEASE AMYLOID PROTEIN, CEREBRAL
COMPND     6 VASCULAR AMYLOID PEPTIDE, CVAP, PREA4, PROTEASE NEXIN-II, PN-II, N-
COMPND     7 APP, SOLUBLE APP-ALPHA, S-APP-ALPHA, SOLUBLE APP-BETA, S-APP-BETA,
COMPND     8 C99, BETA-AMYLOID PROTEIN 42, BETA-APP42, BETA-AMYLOID PROTEIN 40,
COMPND     9 BETA-APP40, C83, P3(42), P3(40), C80, GAMMA-SECRETASE C-TERMINAL
COMPND    10 FRAGMENT 59, AMYLOID INTRACELLULAR DOMAIN 59, AICD-59, AID(59),
COMPND    11 GAMMA-CTF(59), GAMMA-SECRETASE C-TERMINAL FRAGMENT 57, AMYLOID
COMPND    12 INTRACELLULAR DOMAIN 57, AICD-57, AID(57), GAMMA-CTF(57), GAMMA-
COMPND    13 SECRETASE C-TERMINAL FRAGMENT 50, AMYLOID INTRACELLULAR DOMAIN 50,
COMPND    14 AICD-50, AID(50), GAMMA-CTF(50), C31
SOURCE     MOL_ID: 1;
SOURCE     2 ORGANISM_SCIENTIFIC: HOMO SAPIENS;
SOURCE     3 ORGANISM_COMMON: HUMAN;
SOURCE     4 ORGANISM_TAXID: 9606
KEYWDS     AMYLOID, ALZHEIMER'S DISEASE, SOLID STATE NMR, PROTEIN FIBRIL
EXPDTA     SOLID-STATE NMR
NUMMDL     20
AUTHOR     J.LU,W.QIANG,S.C.MEREDITH,W.YAU,C.D.SCHWEITERS,R.TYCKO
REVDAT     3   05-FEB-14  2M4J   1
REVDAT     2   02-OCT-13  2M4J   1      JRNL
REVDAT     1   25-SEP-13  2M4J   0
JRNL       AUTH   J.X.LU,W.QIANG,W.M.YAU,C.D.SCHWIETERS,S.C.MEREDITH,R.TYCKO
JRNL       TITL   MOLECULAR STRUCTURE OF BETA-AMYLOID FIBRILS IN ALZHEIMER'S
JRNL       TITL   2 DISEASE BRAIN TISSUE.
JRNL       REF    CELL(CAMBRIDGE,MASS.)          V. 154  1257  2013
JRNL       REFN   ISSN 0092-8674
JRNL       PMID   24034249
JRNL       DOI    10.1016/J.CELL.2013.08.035
REMARK     2
REMARK     2 RESOLUTION. NOT APPLICABLE.
REMARK     3
REMARK     3 REFINEMENT.
REMARK     3 PROGRAM      : X-PLOR_NIH
REMARK     3 AUTHORS      : SCHWIETERS, KUSZEWSKI, TJANDRA AND CLORE
REMARK     3
REMARK     3 OTHER REFINEMENT REMARKS: INCLUDES "NON-CRYSTALLOGRAPHIC"
REMARK     3 SYMMETRY, 3-FOLD ROTATIONAL SYMMETRY, AND TRANSLATIONAL SYMMETRY
REMARK     3 RESTRAINTS. THREE STAGES OF ANNEALING, STARTING WITH RANDOM
REMARK     3 CONFIGURATION OF NINE BETA-AMYLOID PEPTIDE MOLECULES. SEE
REMARK     3 PUBLICATION FOR FULL DETAILS.
  
```

Amyloid Input File

	ATOM NUMBER		RESIDUE NAME		RESIDUE NUMBER		X		Y		Z
ATOM	12	HA	ASP A	1	-16.453	-56.650	104.617				
ATOM	13	HB2	ASP A	1	-14.338	-55.317	106.360				
ATOM	14	HB3	ASP A	1	-16.035	-55.525	106.796				
ATOM	15	N	ALA A	2	-16.786	-53.907	104.869				
ATOM	16	CA	ALA A	2	-17.170	-52.557	104.446				
ATOM	17	C	ALA A	2	-16.079	-51.557	104.834				

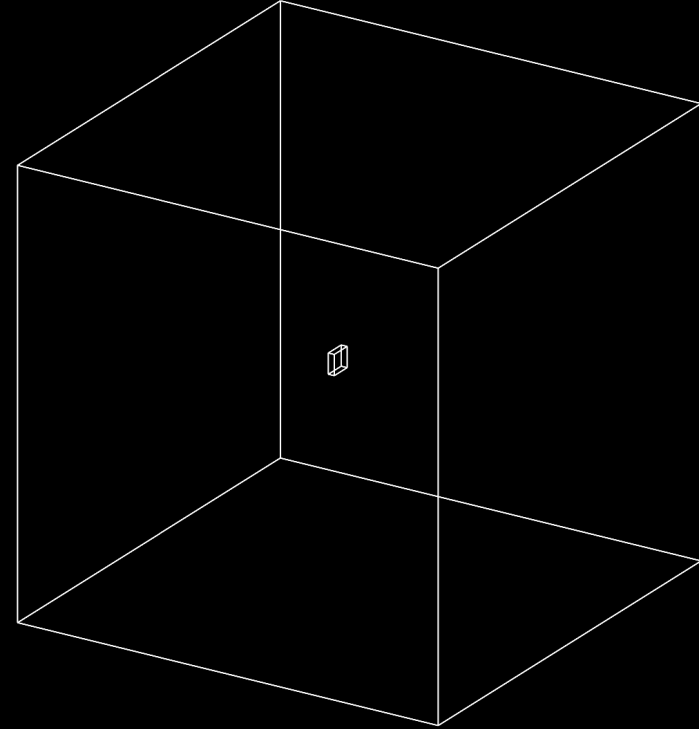
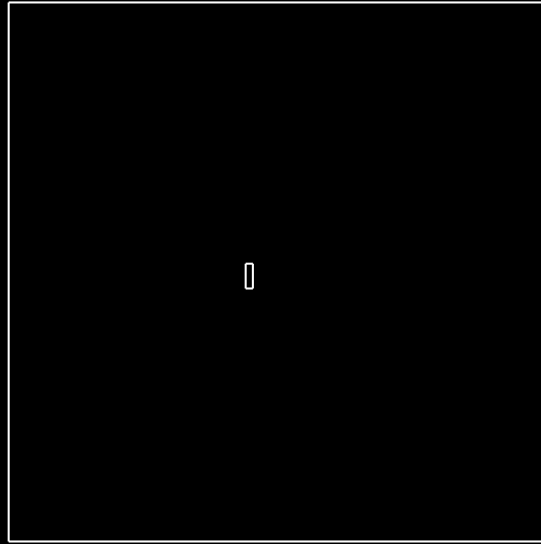
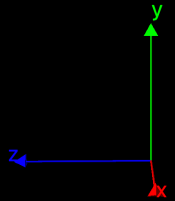
ELEMENT

MOLECULE CHAIN

COORDINATES

Second Step: add amyloid

Simulation Geometry



Box dimensions: 1000 Å x 1000 Å x 1000 Å

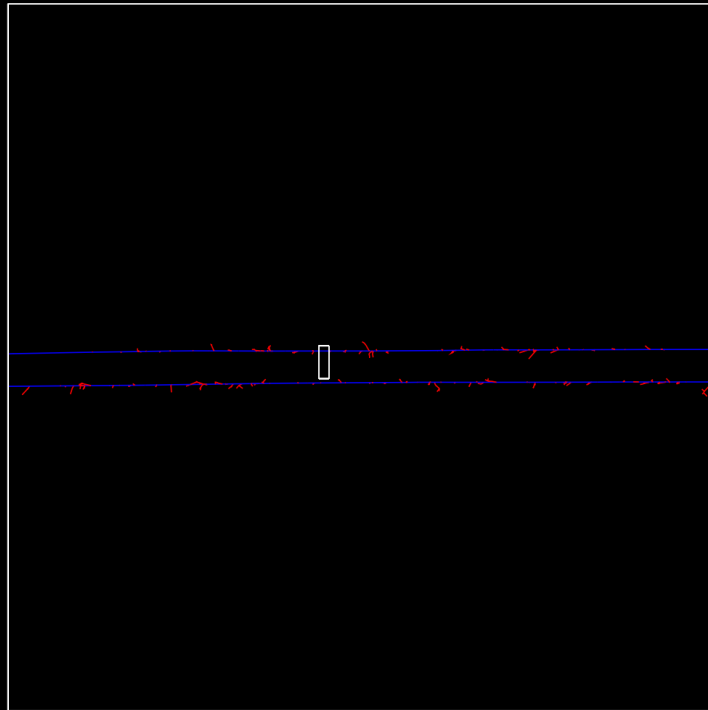
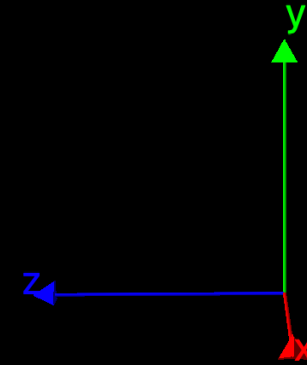
Amyloid dimensions: 50 Å x 50 Å x 14 Å

Second Step: add amyloid

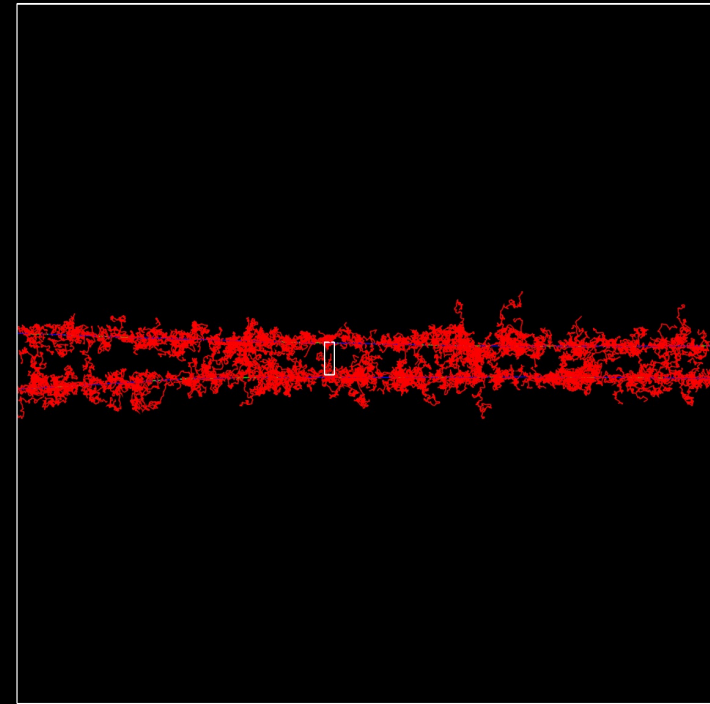
Proton Beam Energy: 100 keV

Box dimensions: 1000 Å x 1000 Å x 1000 Å

Amyloid dimensions: 50 Å x 50 Å x 14 Å



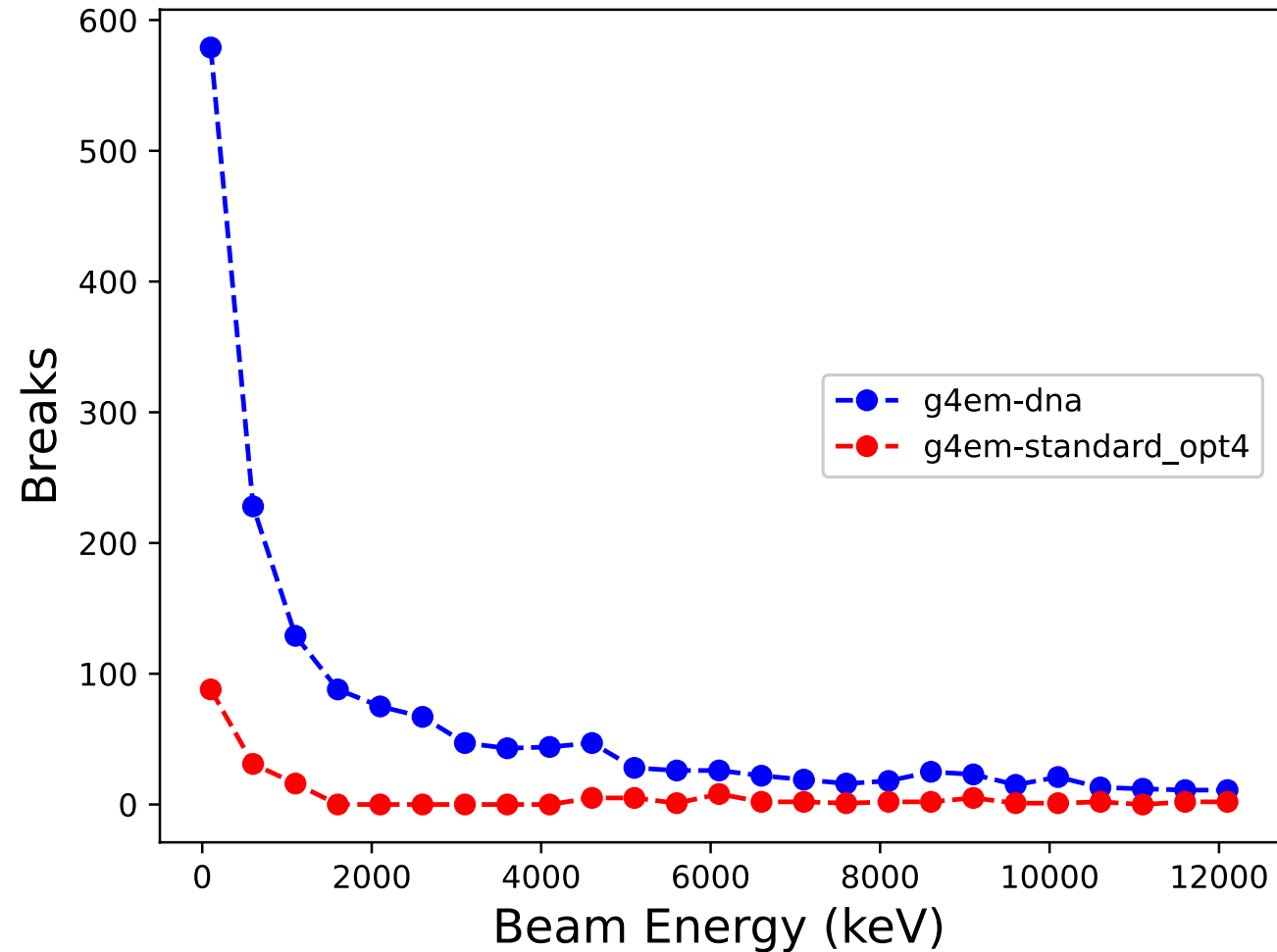
"g4em-standard_opt4"



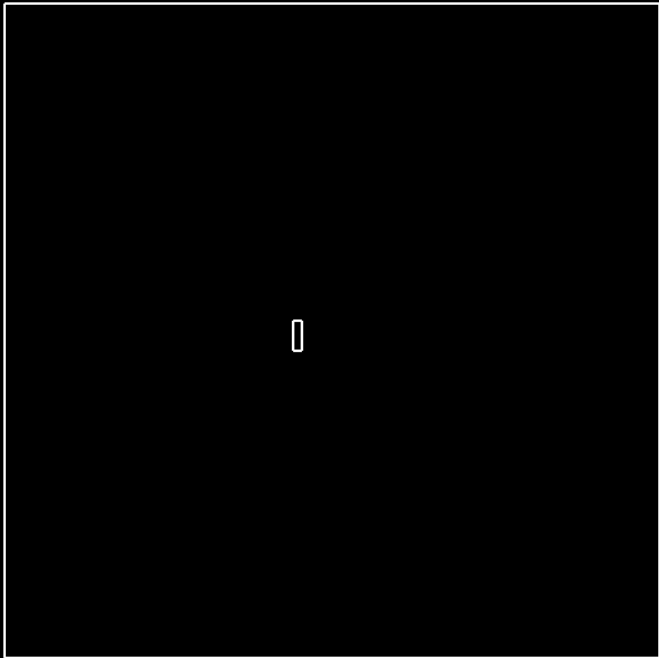
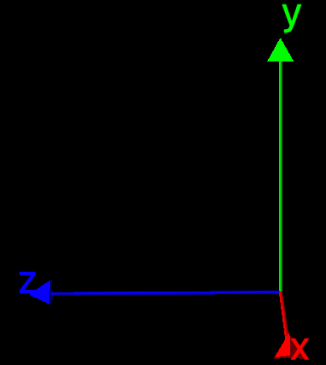
"g4em-dna"

Second Step: add amyloid

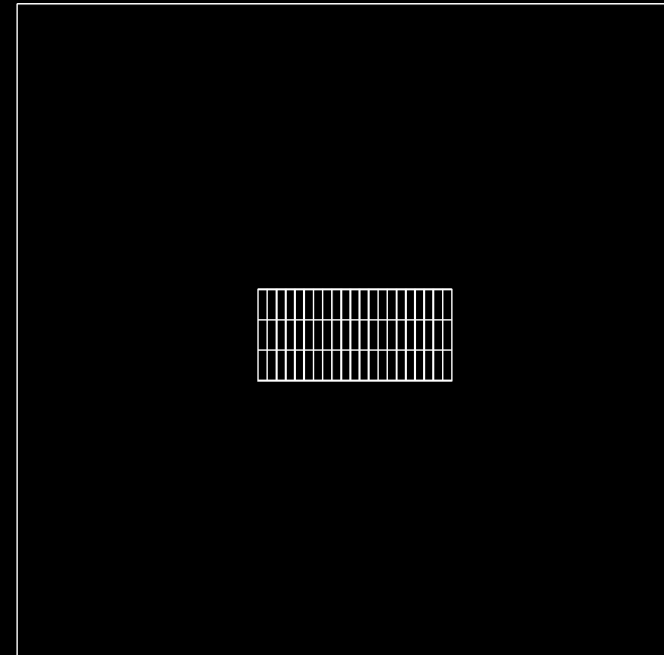
Total number of strand breaks on the amyloid induced by a proton beam. Number of events: 10^4 .



Third Step: increase amyloid size



Box/Amyloid volume ratio: 30 000



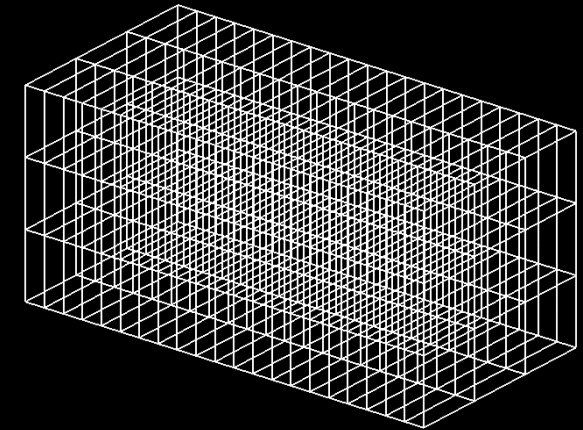
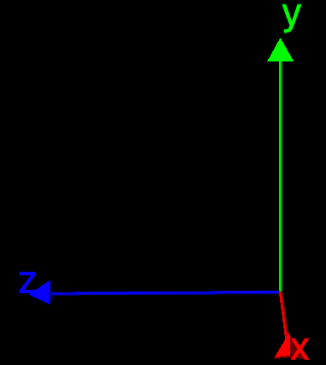
Box/Amyloid volume ratio: 150

Third Step: increase amyloid size

- How?
- Change coordinates on pdb file!

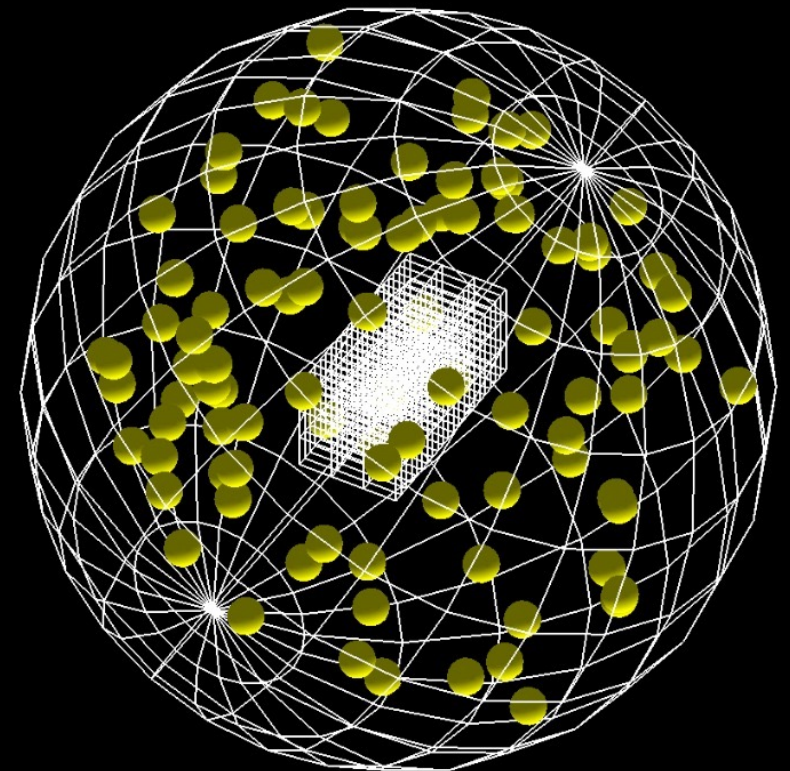
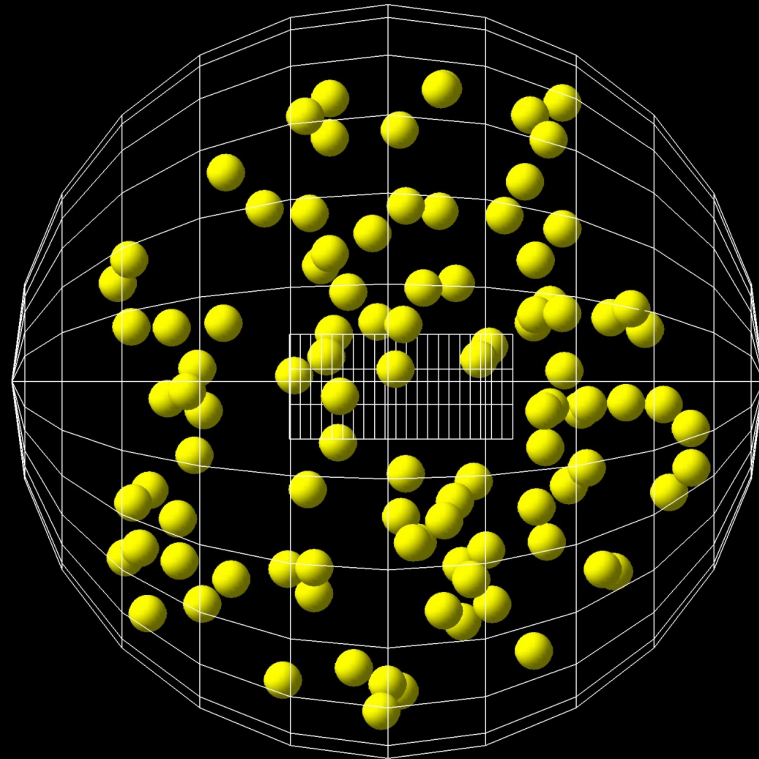
						X	Y	Z
ATOM	12	HA	ASP	A	1	-16.453	-56.650	104.617
ATOM	13	HB2	ASP	A	1	-14.338	-55.317	106.360
ATOM	14	HB3	ASP	A	1	-16.035	-55.525	106.796
ATOM	15	N	ALA	A	2	-16.786	-53.907	104.869
ATOM	16	CA	ALA	A	2	-17.170	-52.557	104.446
ATOM	17	C	ALA	A	2	-16.079	-51.557	104.834

COORDINATES



Fourth step: add gold nanoparticles

Radiation bombs simulation geometry



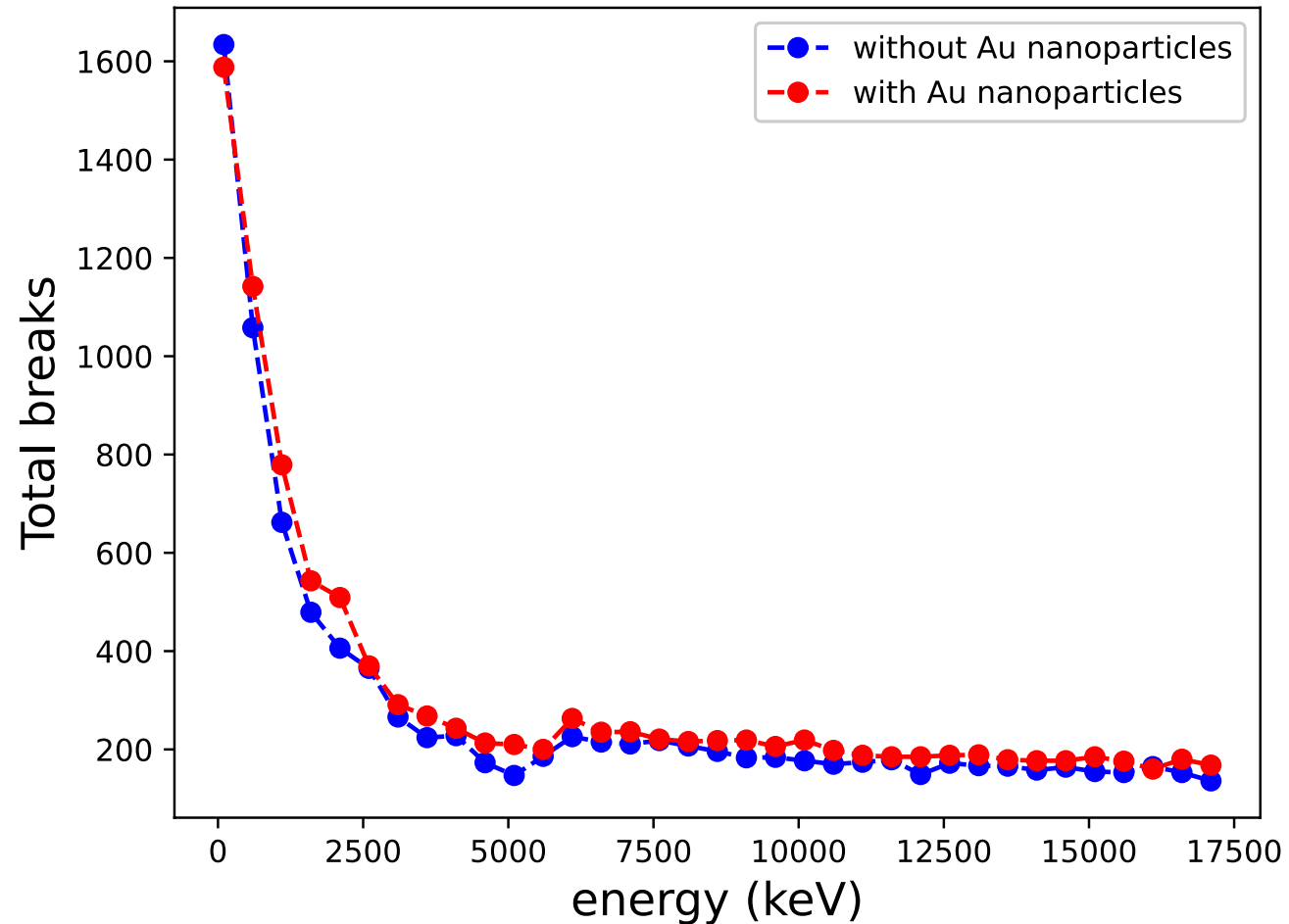
Sphere radius: 1000 Å

Amyloid dimensions: 150 Å x 150 Å x 300 Å

Gold nanoparticles radius: 50 Å

Fourth step: add gold nanoparticles

Total number of strand breaks on the amyloid induced by a proton beam. Number of events: 10^5



Future Work...



Thank you!

Hannah Scharff: diazscharffha@gmail.com

Maria Rebouta: mariatrebouta@gmail.com