Hands-On on geometries

« pdb4dna »

Emmanuel Delage

Yann Perrot

(Sébastien Incerti)

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pdb4dna

- We are going to study the pdb4dna extended example which shows how to implement

  Protein Data Bank (PDB) geometries for direct DNA damage quantification in realistic geometries of macro-molecules

- This is an extended example and it is located in
  $G4INSTALL/examples/extended/electromagnetic/dna

- Developed by Emmanuel Delage and Yann Perrot, LPC Clermont-Ferrand, France

1) Scope of « pdb4dna »

Protein Data Bank

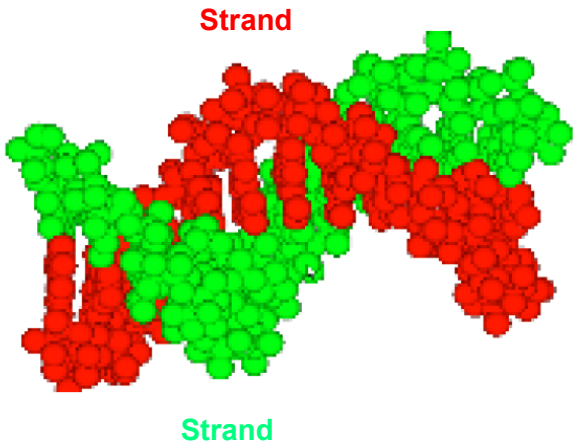
http://www.rcsb.org/

- Protein Data Bank files
  - A way to store and exchange polyatomic structures (proteins, DNA)
  - File describing the 3D structural information of molecules
  - A worlwide free access to files obtained experimentally by crystallography techniques or computed with geometry optimization codes:

- File format
  - ASCII file '.pdb'
  - We mainly extract information from ATOM keyword

```
HEADER                    TRANSFERASE 19-APR-13 4BJP
TITLE   CRYSTAL STRUCTURE OF E. COLI PENICILLIN BINDING PROTEIN 3
...
JRNL    DOI 10.1371/JOURNAL.PONE.0098042
...
REMARK 200 EXPERIMENT TYPE : X-RAY DIFFRACTION
...
ATOM    265  C   ASP  A   149   -38.902  78.078  31.778 C
ATOM    266  O   ASP  A   149   -39.587  78.804  32.500 O
ATOM    267  CB  ASP  A   149   -36.407  78.326  31.747 C
...
TER     3106 ALA A 567
...
END
```

10 base pairs: two whole DNA strands




```
HEADER    DNA                          10BP EXAMPLE
...
MODEL     1
ATOM      1  O5'  A   1      9.256  -9.769   4.573  O
ATOM      2  C5'  A   1     10.679  -9.579   4.526  C
...
ATOM     33  OP1  A   2     12.795  -8.381   9.736  O
...
ATOM     65  P    A   3     11.850  -2.418  12.300  P
...
ATOM    445  O5'  A  10      1.100   5.570  32.583  O
TER     445       A  10
ATOM    446  O5'  B  14     -9.356  10.980  33.794  O
...
ATOM    688  C4   B  20      2.805   3.343   8.223  C
TER     688       B  20
ENDMDL
```

This file encodes DNA molecule

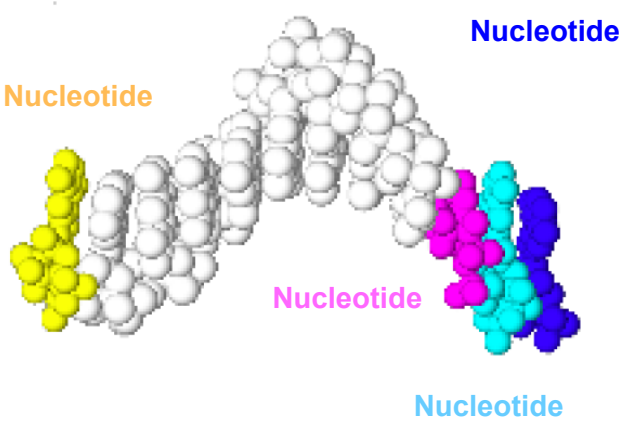
Start molecule

Atom coordinates – first strand (A)

Atom coordinates – second strand (B)

End molecule

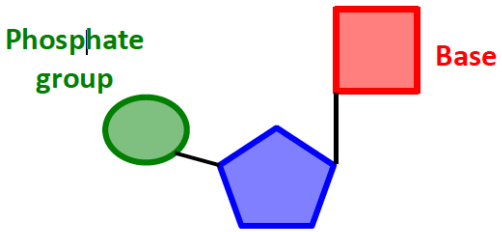
10 base pairs: individual nucleotides

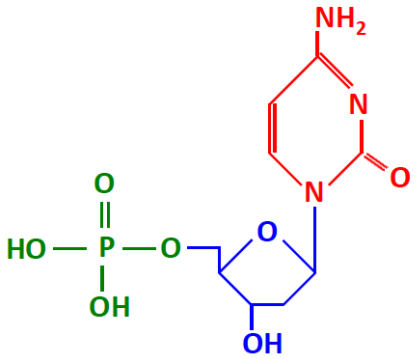



```
HEADER    DNA                          10BP EXAMPLE
...

MODEL     1

ATOM      1  O5'  A  1     9.256  -9.769   4.573  O
ATOM      2  C5'  A  1    10.679  -9.579   4.526  C
...
ATOM     33  OP1  A  2    12.795  -8.381   9.736  O
...
ATOM     65  P    A  3    11.850  -2.418  12.300  P
...
ATOM    445  O5'  A 10     1.100   5.570  32.583  O
TER     445       A 10

ATOM    446  O5'  B 14    -9.356  10.980  33.794  O
...
ATOM    688  C4   B 20     2.805   3.343   8.223  C
TER     688       B 20

ENDMDL
```

10 base pairs: atomistic content of nucleotides

Nucleotide structure





Cytosine nucleotide

HEADER DNA 10BP EXAMPLE

...

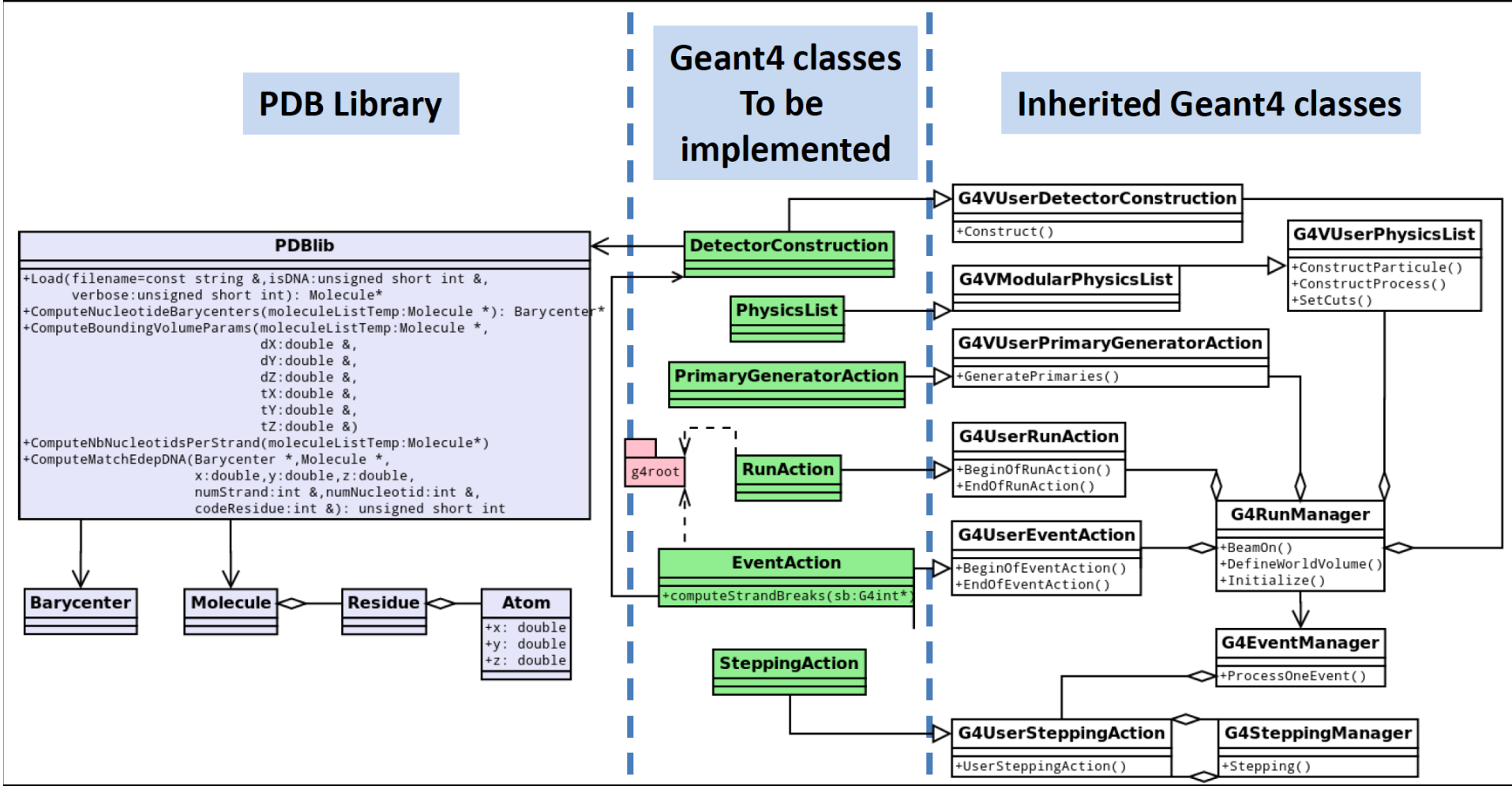
ATOM	65	P	DC	A	3	11.850	-2.418	12.300	P
ATOM	66	OP1	DC	A	3	15.242	-2.080	12.670	O
ATOM	67	OP2	DC	A	3	11.107	-3.437	11.073	O
ATOM	68	O5'	DC	A	3	12.981	-1.059	12.299	O
ATOM	69	C5'	DC	A	3	11.563	0.189	11.896	C
ATOM	70	C4'	DC	A	3	12.527	1.314	11.875	C
ATOM	71	O4'	DC	A	3	11.455	0.915	11.029	O
ATOM	72	C3'	DC	A	3	11.954	1.427	11.278	C
ATOM	73	O3'	DC	A	3	12.405	2.645	11.894	O
ATOM	74	C2'	DC	A	3	10.453	1.552	11.042	C
ATOM	75	C1'	DC	A	3	10.249	1.499	11.527	C
ATOM	76	N1	DC	A	3	9.058	0.693	11.174	N
ATOM	77	C2	DC	A	3	7.998	1.341	10.557	C
ATOM	78	O2	DC	A	3	8.060	2.547	10.316	O
ATOM	79	N3	DC	A	3	6.897	0.610	10.230	N
ATOM	80	C4	DC	A	3	6.836	-0.699	10.496	C
ATOM	81	N4	DC	A	3	5.745	-1.381	10.158	N
ATOM	82	C5	DC	A	3	7.924	-1.372	11.112	C
ATOM	83	C6	DC	A	3	9.008	-0.643	11.454	C

Phosphate group

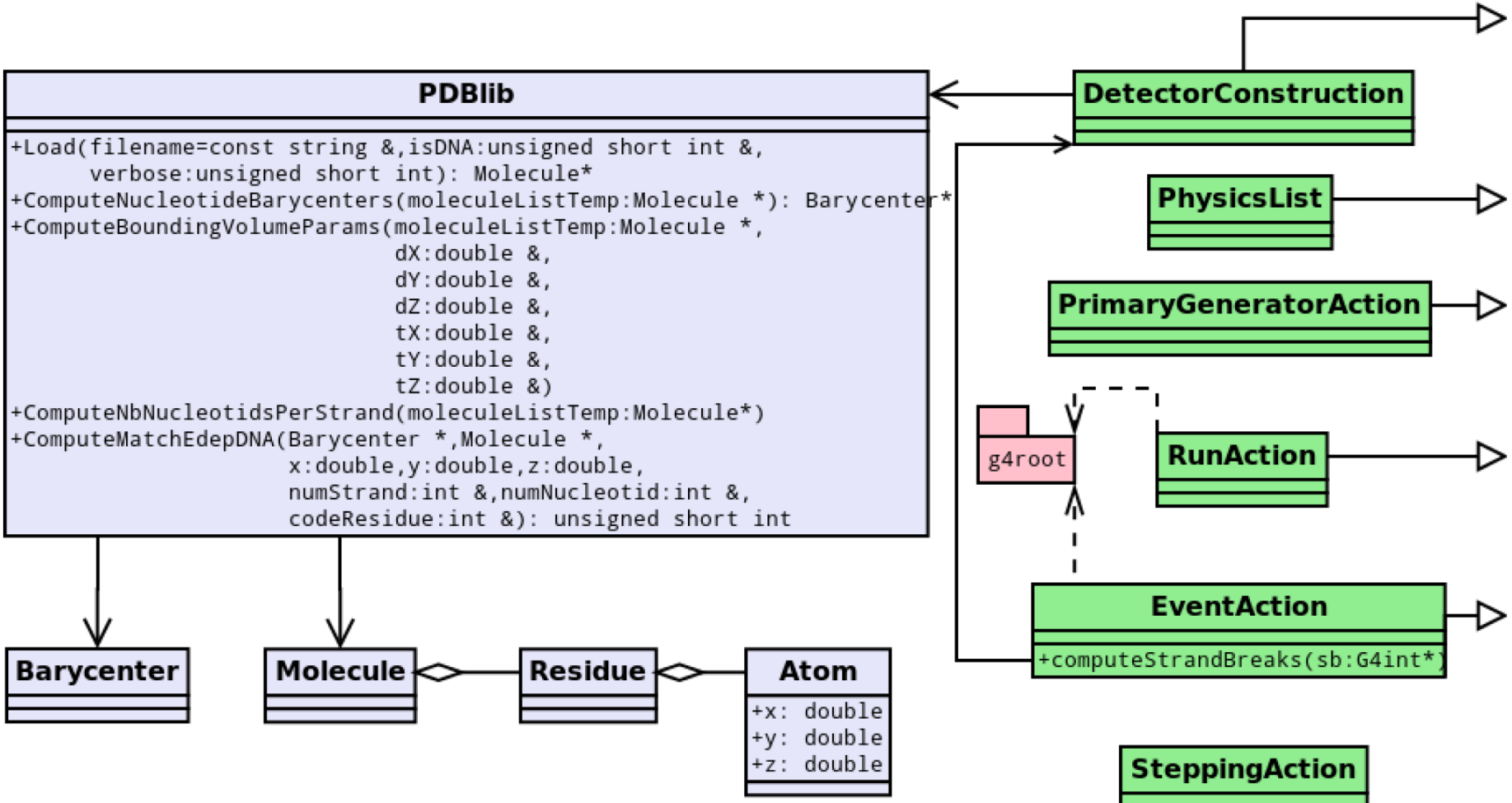
Sugar

Base

Integration into Geant4 (1/2)



Integration into Geant4 (2/2)



- **DetectorConstruction** call PDBlib to construct molecule geometry
- **EventAction** compute match between Edep and DNA via Detector construction

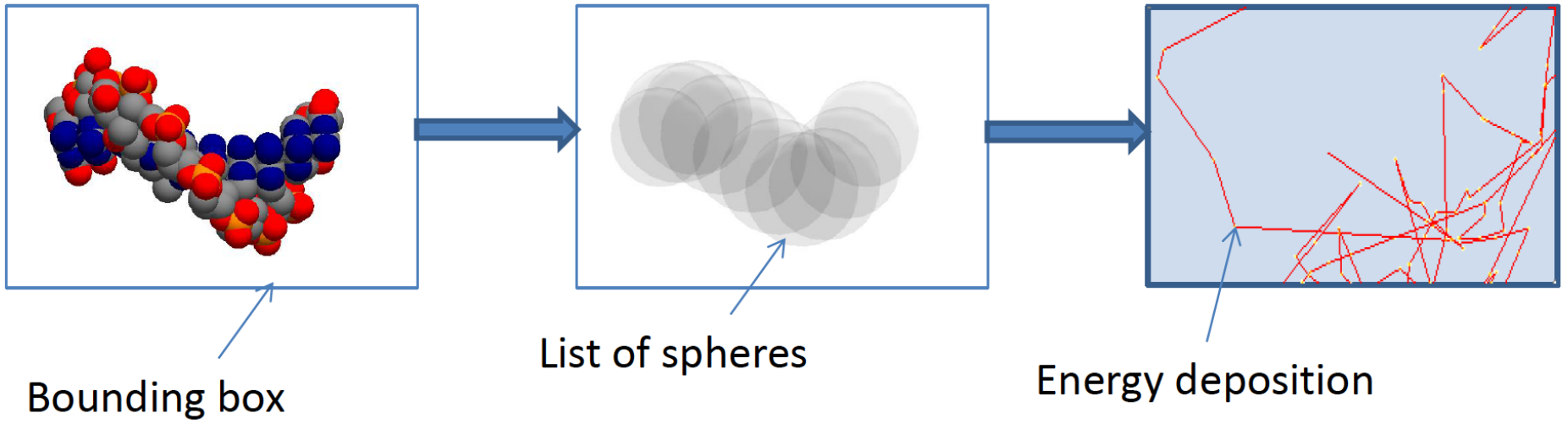
Algorithm to find the closest atom (1/2)

GOAL : allocate energy depositions to a geometrical element

[sugar, phosphate, base] of nucleotides and then deduce SSB and DSB

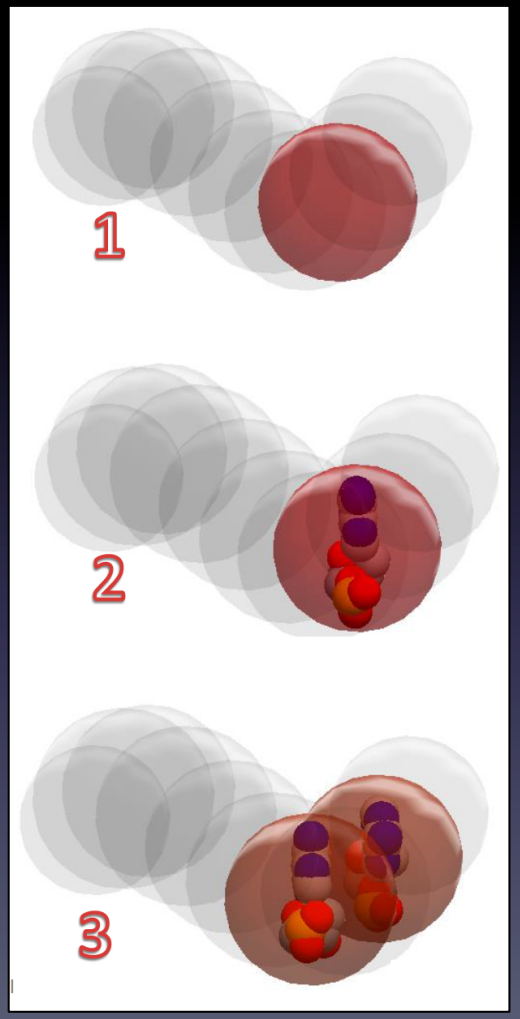
- A bounding box is calculated with atoms coordinates
- No other Geant4 solid is needed for simulation
- We consider that a sphere is a good approximation to englobe a nucleotide.

  A list of spheres representing nucleotides is calculated
- DNA specific



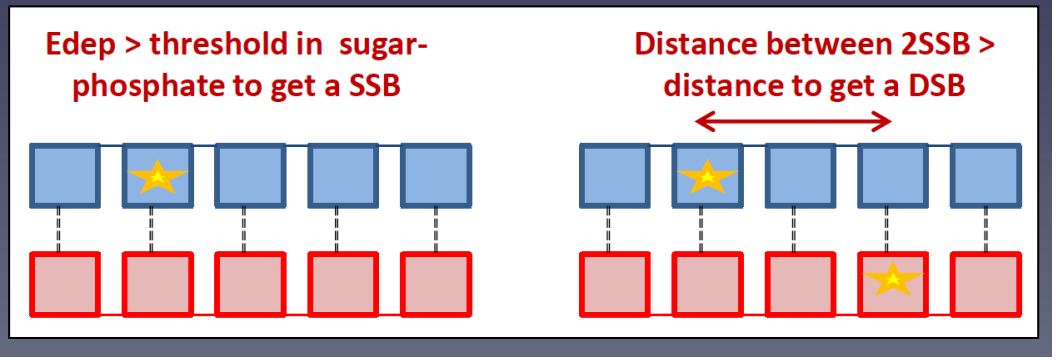
Algorithm to find the closest atom (2/2)

1. Find the closest nucleotide from the energy deposition inside the two strands
2. Find the closest atom from the energy deposition
   - atom by atom inside the selected nucleotide
   - considering Van der Waals radii
3. Due to sphere overlapping, find a better match in the next two nucleotides in the list
4. Return algorithm response:
   - No DNA hit
   - or DNA hit, return nucleotide ID, DNA strand, group type (sugar, phosphate or base)



Strand breaks

- Begin of Event
  - A map for each strand is created to store nucleotide ID and associated energy deposition
- For each step
  - If the step is in the bounding volume, increment energy deposition per event
  - Ask to PDBlib to check the step position
    - If the step is in a sugar or a phosphate: get nucleotide ID, strand number, energy deposit, update the map (ID, Edep+=StepEdep)
- End of Event
  - Compute and store strand breaks
  - Store energy deposit in the bounding volume



2) « pdb4dna » hands-on

Directory content

```
ll $G4EXAMPLES/extended/medical/dna/pdb4dna/
```

```
2266137 Jun 26 12:11 1ZBB.pdb
   1380 Jun 26 12:11 analysis.C
   2222 Jun 26 12:11 CMakeLists.txt
    420 Jun 26 12:11 GNUmakefile
   1819 Jun 26 12:11 gui.mac
   2197 Jun 26 12:11 History
   4096 Jun 29 09:16 include/
    201 Jun 26 12:11 init.mac
    197 Jun 26 12:11 init_vis.mac
   8202 Jun 26 12:11 pdb4dna.cc
    341 Jun 26 12:11 pdb4dna.in
  11786 Jun 26 12:11 pdb4dna.out
   4744 Jun 26 12:11 README
    274 Jun 26 12:11 runInGUI.mac
   4096 Jun 29 09:16 src/
   2722 Jun 26 12:11 vis.mac
```

PDB file

ROOT macro file

Macro to run in batch mode

```
Jun 26 12:11 ActionInitialization.hh
Jun 26 12:11 Analysis.hh
Jun 26 12:11 CommandLineParser.hh
Jun 26 12:11 DetectorConstruction.hh
Jun 26 12:11 DetectorMessenger.hh
Jun 26 12:11 EventAction.hh
Jun 26 12:11 EventActionMessenger.hh
Jun 26 12:11 PDBatom.hh
Jun 26 12:11 PDBbarycenter.hh
Jun 26 12:11 PDBlib.hh
Jun 26 12:11 PDBmolecule.hh
Jun 26 12:11 PDBresidue.hh
Jun 26 12:11 PhysicsList.hh
Jun 26 12:11 PrimaryGeneratorAction.hh
Jun 26 12:11 RunAction.hh
Jun 26 12:11 RunInitObserver.hh
Jun 26 12:11 SteppingAction.hh
```

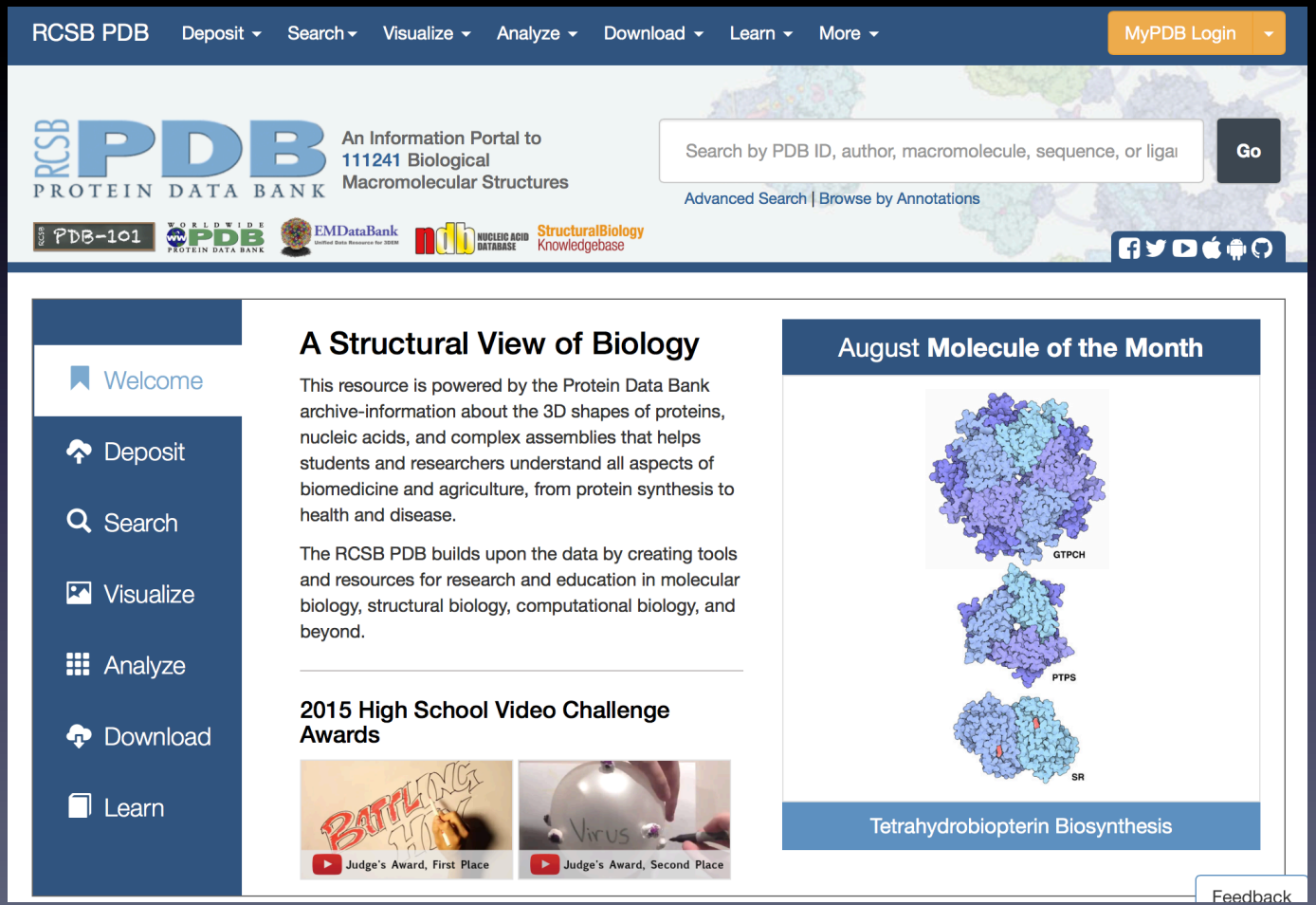
Compile the application

```
cd
cp -R $G4EXAMPLES/extended/medical/dna/pdb4dna/ .
mkdir build-pdb4dna
cd build-pdb4dna
cmake ../pdb4dna
make –j2
```

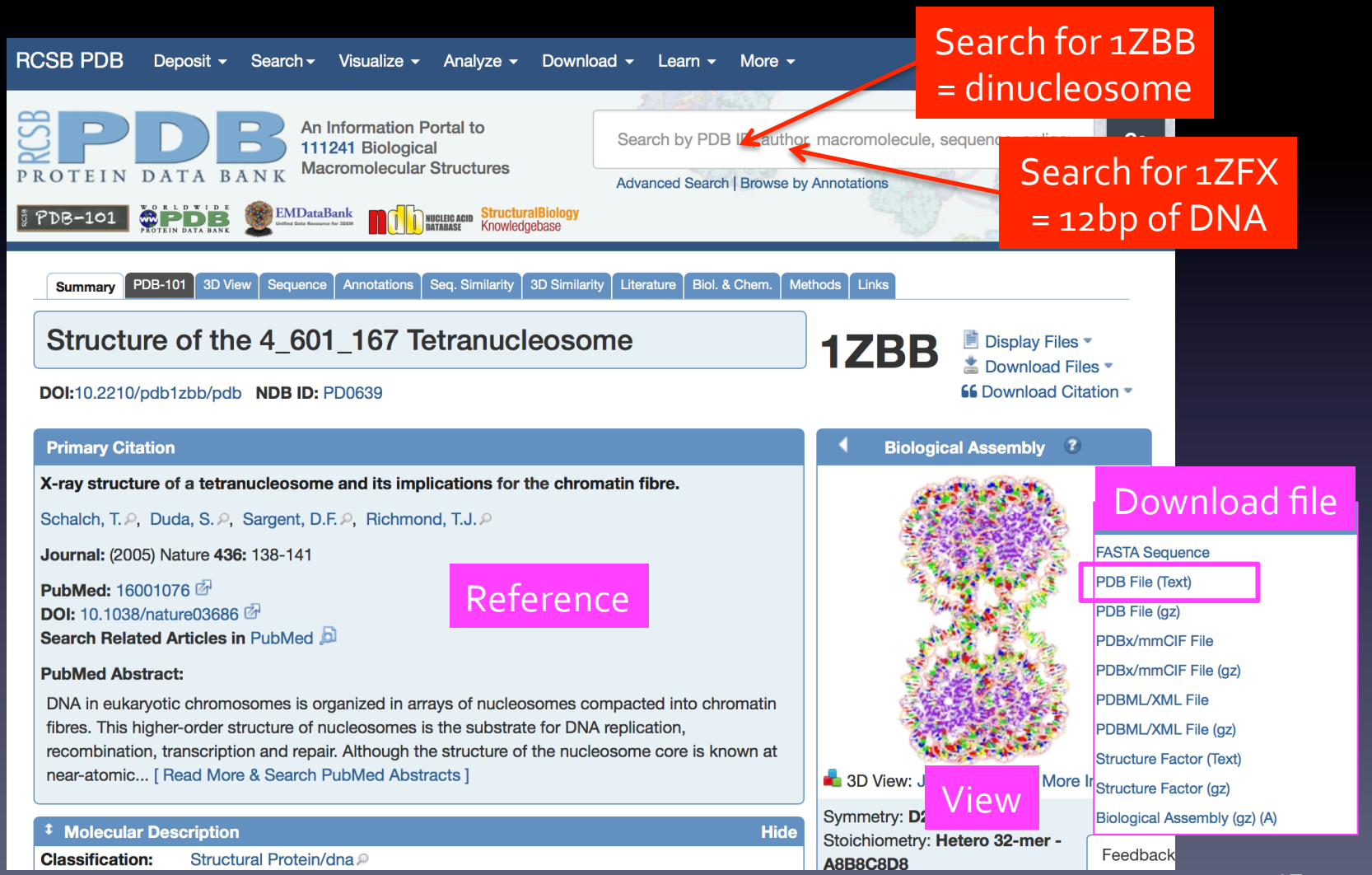
```
localhost.localdomain:/build-pdb4dna < 482 >make -j2
Scanning dependencies of target pdb4dna
[  5%] [ 11%] Building CXX object CMakeFiles/pdb4dna.dir/pdb4dna.cc.o
Building CXX object CMakeFiles/pdb4dna.dir/src/RunInitObserver.cc.o
[ 17%] Building CXX object CMakeFiles/pdb4dna.dir/src/ActionInitialization.cc.o
[ 23%] Building CXX object CMakeFiles/pdb4dna.dir/src/PDBmolecule.cc.o
[ 29%] Building CXX object CMakeFiles/pdb4dna.dir/src/PDBatom.cc.o
[ 35%] Building CXX object CMakeFiles/pdb4dna.dir/src/CommandLineParser.cc.o
[ 41%] Building CXX object CMakeFiles/pdb4dna.dir/src/PrimaryGeneratorAction.cc.o
[ 47%] Building CXX object CMakeFiles/pdb4dna.dir/src/DetectorMessenger.cc.o
[ 52%] Building CXX object CMakeFiles/pdb4dna.dir/src/SteppingAction.cc.o
[ 58%] Building CXX object CMakeFiles/pdb4dna.dir/src/PhysicsList.cc.o
[ 64%] Building CXX object CMakeFiles/pdb4dna.dir/src/PDBresidue.cc.o
[ 70%] Building CXX object CMakeFiles/pdb4dna.dir/src/RunAction.cc.o
[ 76%] Building CXX object CMakeFiles/pdb4dna.dir/src/PDBbarycenter.cc.o
[ 82%] Building CXX object CMakeFiles/pdb4dna.dir/src/DetectorConstruction.cc.o
[ 88%] Building CXX object CMakeFiles/pdb4dna.dir/src/EventActionMessenger.cc.o
[ 94%] Building CXX object CMakeFiles/pdb4dna.dir/src/EventAction.cc.o
[100%] Building CXX object CMakeFiles/pdb4dna.dir/src/PDBlib.cc.o
Linking CXX executable pdb4dna
[100%] Built target pdb4dna
localhost.localdomain:/build-pdb4dna < 483 >
```

Preparation before run (1/2)

Visit PDB web site **http://www.rcsb.org**



Preparation before run (2/2)



Running with GUI

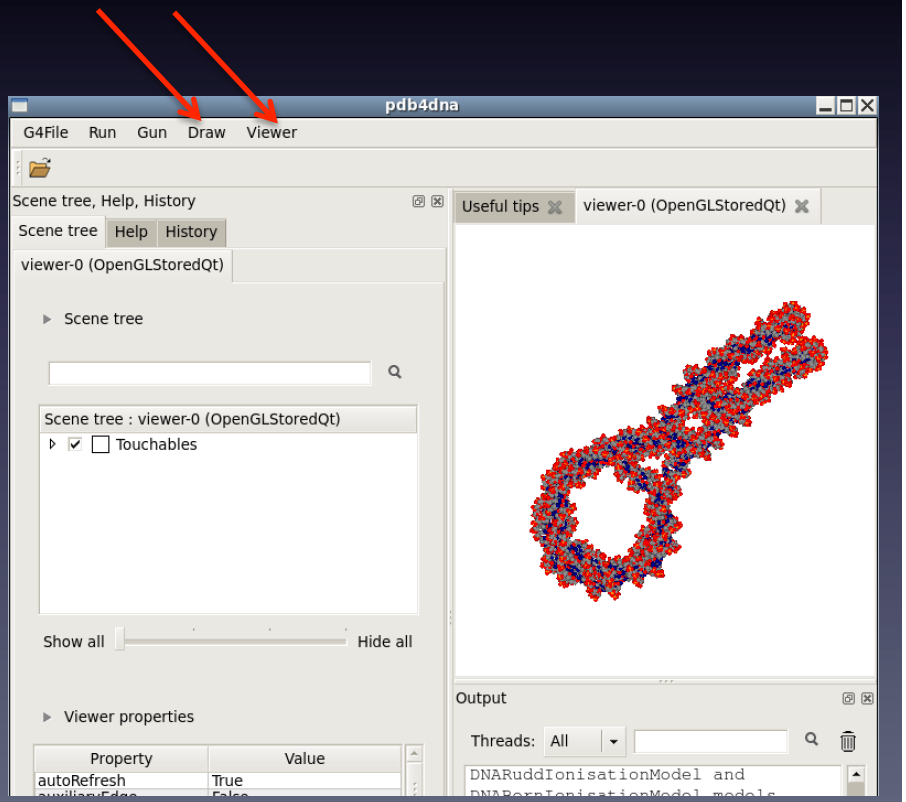
- Rename your PDB file (extension « pdb ») as a macro file (« mac » extension)

```
mv 1ZBB.pdb 1ZBB.mac
```

- Open GUI

```
./pdb4dna -gui
```

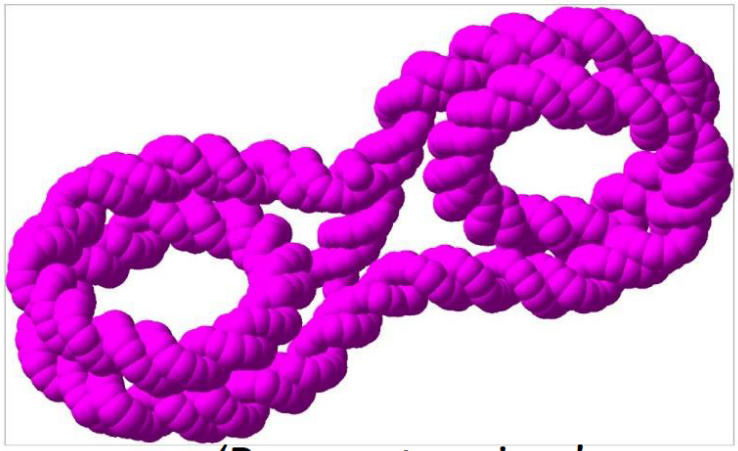
- Open the 1ZBB.mac file
- Click on Viewer → Set style surface
- Click on Draw and try different options…



3 visualizations

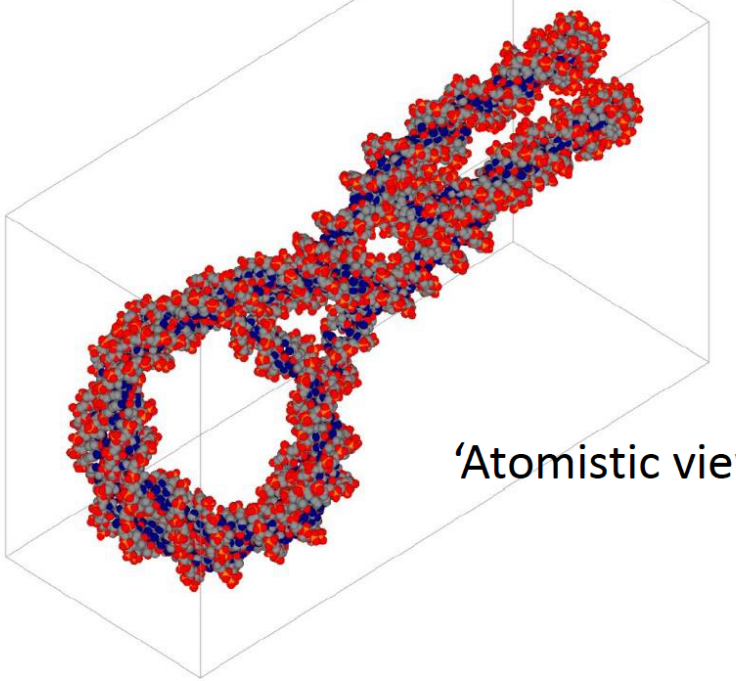
- Base → blue sphere,
- Sugar → yellow sphere,
- Phosphate → red sphere.

'Residue view'



'Barycenter view'

CPK coloring
- Hydrogen(H) → white sphere,
- Carbon(C) → gray sphere,
- Oxygen(O) → red sphere,
- Nitrogen(N) → dark blue sphere,
- Sulfur(S) → yellow sphere,
- Phosphorus(P) → orange sphere,
- others/undefined → pink sphere

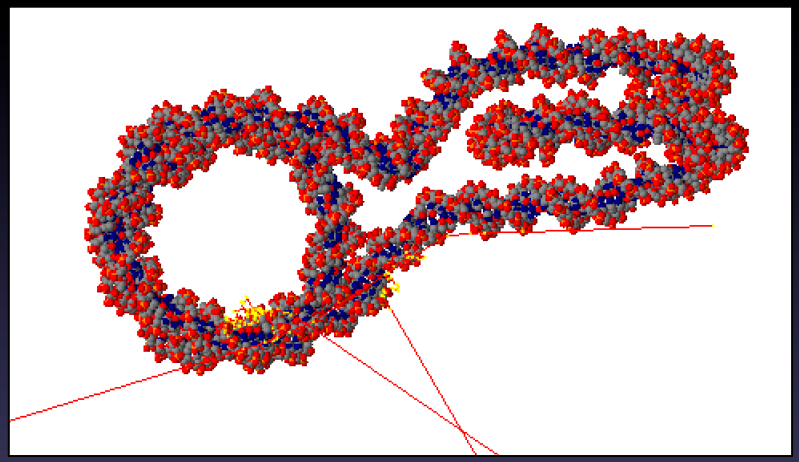


'Atomistic view'

Running with GUI

- Once you have loaded your PDB file, go to the Session window and enter:

```
/gun/particle e-
/gun/energy 1 keV
/run/initialize
/run/beamOn 1
```



- Might be a bit slow with visualization
- Nice for visualization, but swtich to batch mode for energy deposition scoring…

Running in batch mode (1/2)

1. Prepare your macro file using an editor (nedit, geany)
   - You can alternatively use pdb4dna.in

```
localhost.localdomain:/build-pdb4dna < 540 >more pdb4dna.in
#/control/execute vis.mac

/run/initialize

/tracking/verbose 0

/PDB4DNA/det/loadPDB 1ZBB.pdb
/PDB4DNA/det/buildBoundingV

/PDB4DNA/event/setEnergyThres 8.22 eV #default value: 8.22 eV
/PDB4DNA/event/setDistanceThres 10    #default value: 10

/gun/particle e-
/gun/energy 100 keV

/run/initialize

/run/printProgress 100

/run/beamOn 10000
localhost.localdomain:/build-pdb4dna < 541 >
```

Select your PDB file

Construct bounding volume

Set thresholds for strand breaks: energy, distance

Primaries

Run control

Running in batch mode (2/2)

2. Run the simulation

```
./pdb4dna –mac pdb4dna.in –mt 2
```

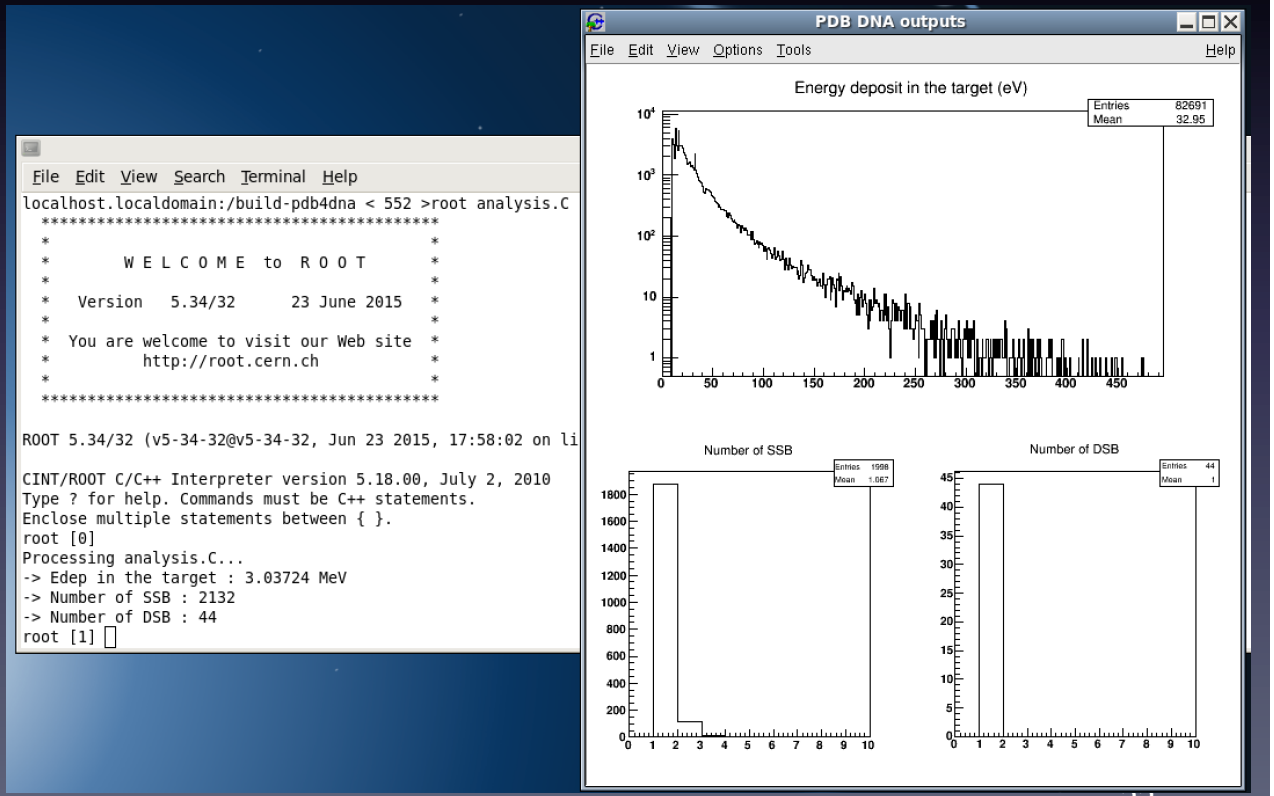
Macro file

Number of threads

Analysis of results

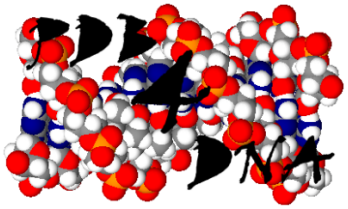
- All results are stores in the file pdb4dna_output.root
- A ROOT macro file is provided for easy analysis: 3 histograms
  - For each event
    - energy deposits in the bounding volume
    - # SSB
    - # DSB
- Do

```
root analysis.C
```



http://pdb4dna.in2p3.fr

Dedicated web site



Geant 4

Last update : December 8, 2014
Examples & tutorials from Geant4-DNA

The **pdb4dna** example can be found in 'extended/medical/dna' Geant4 10.1 example directory.
It simulates energy deposits in a target volume generated from a PDB file representing DNA geometry.
Position of energy deposits are used to compute strand breaks in the DNA geometry.
Geant4-DNA physical processes and models are used.

Authors: Emmanuel Delage, Yann Perrot, Quang Trung Pham.

- Download the package here or preferably with whole Geant4 package,
- PDB4DNA: Implementation of DNA geometry from the Protein Data Bank (PDB) description for Geant4-DNA Monte-Carlo simulations Computer Physics Communications,
- Limitations: this example works only with Geant4.10.0 and later,
- Download whole Geant4 package including pdb4dna.
- License: Geant4.

~~PDBlib~~

HOT SPOT
Geant4 DNA
tutorial
ESA/ESTEC
November 2014

MENU
PDB4DNA example
PDBlib
Geometry and visualization
Simulation analysis
1ZBB with GLmol

LINKS
Geant4
Geant4-DNA
PDB @ RCSB

Questions ?

delage@clermont.in2p3.fr

perrot@clermont.in2p3.fr