Teaching crystallography on real data in life sciences and beyond

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Vilnius University
Life Sciences Center
Institute of Biotechnology
Sector of Crystallography and Chemical Informatics

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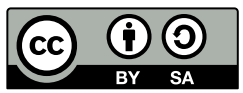


Our (teaching+research) team

Sector of Crystallography and Chemical Informatics (KICIS)

Antanas Vaitkus Algirdas Grybauskas Saulius Gražulis Andrius Merkys

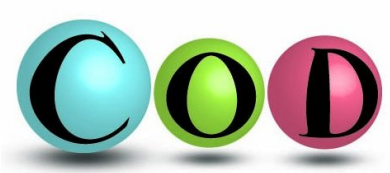
Our research interests

- Scientific databases: Crystallography Open Database
  (Gražulis et al., 2009; Gražulis et al., 2012;
  Gražulis et al., 2018)
- Applications of graph theory to cheminformatics
  (Merkys et al., 2023)
- Applications of computational geometry to bio- and cheminformatics
  (Grybauskas & Gražulis, 2023)
- Data validation using CIF ontologies and chemical perception of crystallographic data
  (Vaitkus et al., 2021; Vaitkus et al., 2023)
- Applications of group theory, topology and formal methods to crystallography, bio- and chemiformatics
  (Petrauskas et al., 2022)

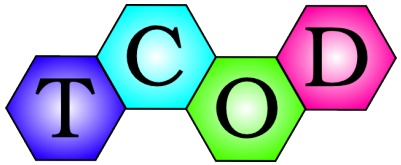
Courses that we teach

- Bionformatics (3D structure analysis)
- Programming methodologies (version control, testing, formal verification)
- Programming (Perl, Python)
- Computer architecture (for bioinformatics students)
- X-ray crystallography of biological m-molecules (elective)

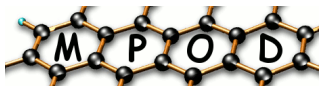
COD "sisters": 20+ years online!



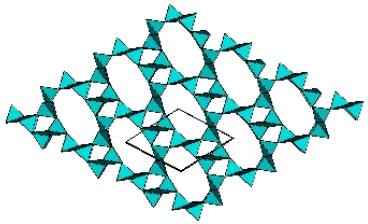
http://www.crystallography.net/cod
$>$ 500 000 entries



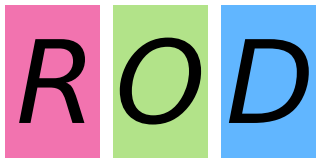
http://www.crystallography.net/tcod
$>$ 7400 entries (ready to grow to $>$ 10^7?)



http://mpod.cimav.edu.mx/
$>$ 300 entries



http://www.crystallography.net/pcod
$>$ 10^6 entries (ready to grow to $>$ 10^8?)



http://solsa.crystallography.net/rod/
$>$ 1100 entries

(Fuentes-Cobas et al., 2017; Gražulis et al., 2009; Gražulis et al., 2012; Mendili et al., 2019; Pepponi et al., 2012)

Problems with crystal structures

> *A large number of* ***incorrect crystal structures*** *is being published today. These structures are proving to be a particular problem to those of us who are interested in comparing structural moieties found in the databases in order to develop structure-property relationships.*

(Harlow, 1996)

> *Structures that* ***have been determined incorrectly****, /.../, are highly problematic because they can and do change the overall conclusions and, thus, can have an appreciable negative impact on science in general.*

(Becker & Müller, 2017)

Perils of “black boxes”

> */.../ sometimes errors do persist into the publication and the deposited model. This may be a consequence of factors such as*
> */.../ (ii) computer programs used as* ***black boxes****;*

(Kleywegt, 2000)

> *Although increased automation might result in a reduction of human errors during model building, it may equally well lead to an increase of errors if too much faith is put in results obtained with magical* ***black boxes****.*

(Kleywegt & Jones, 2002)

Perils of “black boxes” (II)

> *Despite the increasingly **“black box”** nature of these computer programs, understanding how they extract the intensities, errors, and indices from the data can make subsequent structure solution and refinement much easier.*

(Garman & Owen, 2007)

> *I also hope to impress on the casual user of crystallography that at least a qualitative understanding of the theory behind the **‘black box’** programs is essential.*

(Rupp, 2009) (cited in Helliwell (2021))

The benefits of “black boxes”

> *Those without that sort of quantitative interest will struggle to understand what is inside the **‘black box’** software but may well enjoy the symmetry (stemming from a prior core course on group theory).*

(Helliwell, 2021)

> *By itself on a web page, Jmol is just a fantastically powerful **black box**. What makes it so useful is how easy it is to turn that black box into an interactive and educational window into the beauty of the molecular world.*

(Hanson, 2010)

Our teaching aims

> *To me, you understand something only if you can program it. (You, not someone else!)*

Gregory Chaitin, “Meta Math! – The Quest for Omega Ω” //Vintage Books, A Division of Random House, Inc., New York, First edition (2006), chapter “Preface”, page xiii.

- Explicitly ***do not*** teach “pushing buttons”
- Teach students to *understand* what is going on
- Understand by *coding* a working program

“Glass box” instead of “Black Box”

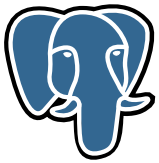
Definition

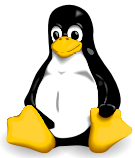
Glass box: a reusable unit of software code that can be readily analysed, understood and replaced[a].

[a] See also Wikipedia, https://en.wikipedia.org/wiki/White_box_(software_engineering)

- we reuse code where necessary to achieve efficiency;
- we analyse code of selected units and/or produce our own (improved?) version of it for learning

Tools for making “glass boxes”



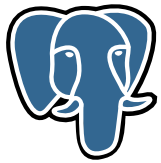


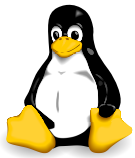
Tools for making “glass boxes”

Ada & GNU Ada toolchain





The benefits of Ada (and SPARK)

1. Durable design – first designed in 1983!
2. Modern language – latest standard is Ada 2022;
3. Mostly backwards compatible;
4. Good F/LOSS compiler available – GNAT;
5. Ada is statically very strictly typed;
6. Programs are easy to read (Level (Ada) > Level (C));
7. Ada & SPARK have a rich type system;
8. Language level concurrent programming;
9. Produces fast optimised native code, links with any language;
10. SPARK subset takes computer arithmetic into account;
11. Not controlled by any private company;

(Amiard & Hoffmann, 2022)

Why is Ada not popular (yet)?

1. The language is complex and difficult to implement;
2. No good compilers in the 1990's;
3. Procured by the DOD, used for "war fighting software";
4. Poor academic outreach in the 20th century;

(National Research Council, 1997)

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1. ~~The language is complex and difficult to implement~~;
2. The language is rich and convenient to program/design in;
3. ~~No good compilers in the 2020's;~~
4. Very nice compiler and dev. system available: `gnat`;
5. Procured by the DOD, used for "war fighting software";
6. Used for mission-critical software (avionics, spacecraft ctrl., railways, plant ctrl...)
7. Poor academic outreach in the 21st century;
8. SPARK allows formal verification of the code (!);

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Example: dihedral angle calculation

The assignment

```
Write a Perl*) program that calculates torsion angles for DNA and RNA
macromolecules. Compute the following angles: alpha, beta.

*) Note: Ada programs are acceptable; in that case all native Perl
   features mentioned in this specification SHOULD be replaced by the
   corresponding Ada features.

NB: for this particular assignment, you MAY NOT use external libraries
to read PDB files or calculate dihedral angles; these functions MUST
be implemented in the program.
```

NOTE: Students could chose a set of atoms for their individual assignment

Full assignment text: https://tinyurl.com/yp24aad4

Example: dihedral angle calculation

The vector algebra code

```
type Vector_3D is array (1 .. 3) of Long_Float;

function "-" (V, W : Vector_3D) return Vector_3D is
begin
   return (V(1) - W(1), V(2) - W(2), V(3) - W(3));
end;
```

Example given to the students

```
type Vector_3D is record
   X, Y, Z : Float;
end record;

function "-" (V1, V2 : Vector_3D) return Vector_3D is
begin
    return (V1.X - V2.X, V1.Y - V2.Y, V1.Z - V2.Z);
end;
```

Version designed by the students (Martynas Mažuolis)

Example: dihedral angle calculation

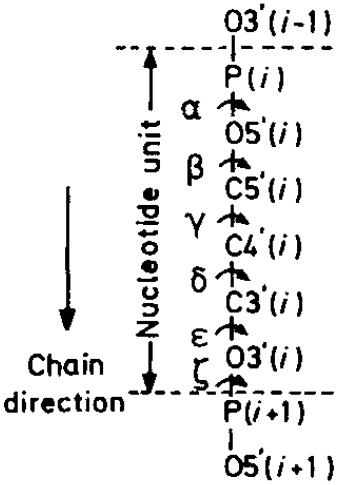
Angle definition and calculation

```
Function Dihedral_angle (Atoms: Chemical_Atom_Set) return float is
        Vector1 : Vector_3D := to_vector(Atoms.Atom_Array(1)) - to_vec..
        Vector2 : Vector_3D := to_vector(Atoms.Atom_Array(2)) - to_vec..
        Vector3 : Vector_3D := to_vector(Atoms.Atom_Array(3)) - to_vec..
        Angle1 : Bond_Angle := Angle(Vector1, Vector2);
        Angle2 : Bond_Angle := Angle(Vector2, Vector3);
        Normal1 : Vector_3D := Cross(Vector1, Vector2);
        Normal2 : Vector_3D := Cross(Vector2, Vector3);
       NX: Vector_3D := Cross(Normal1, Normal2);
        Sign : float := (if Vector2*NX >= 0.0 then 1.0 else -1.0);
        Dihedral : Float := Angle(Normal1, Normal2)*Sign;

        begin
        pragma Assert(Atoms.N>=4);
    return Dihedral;

        end;
```

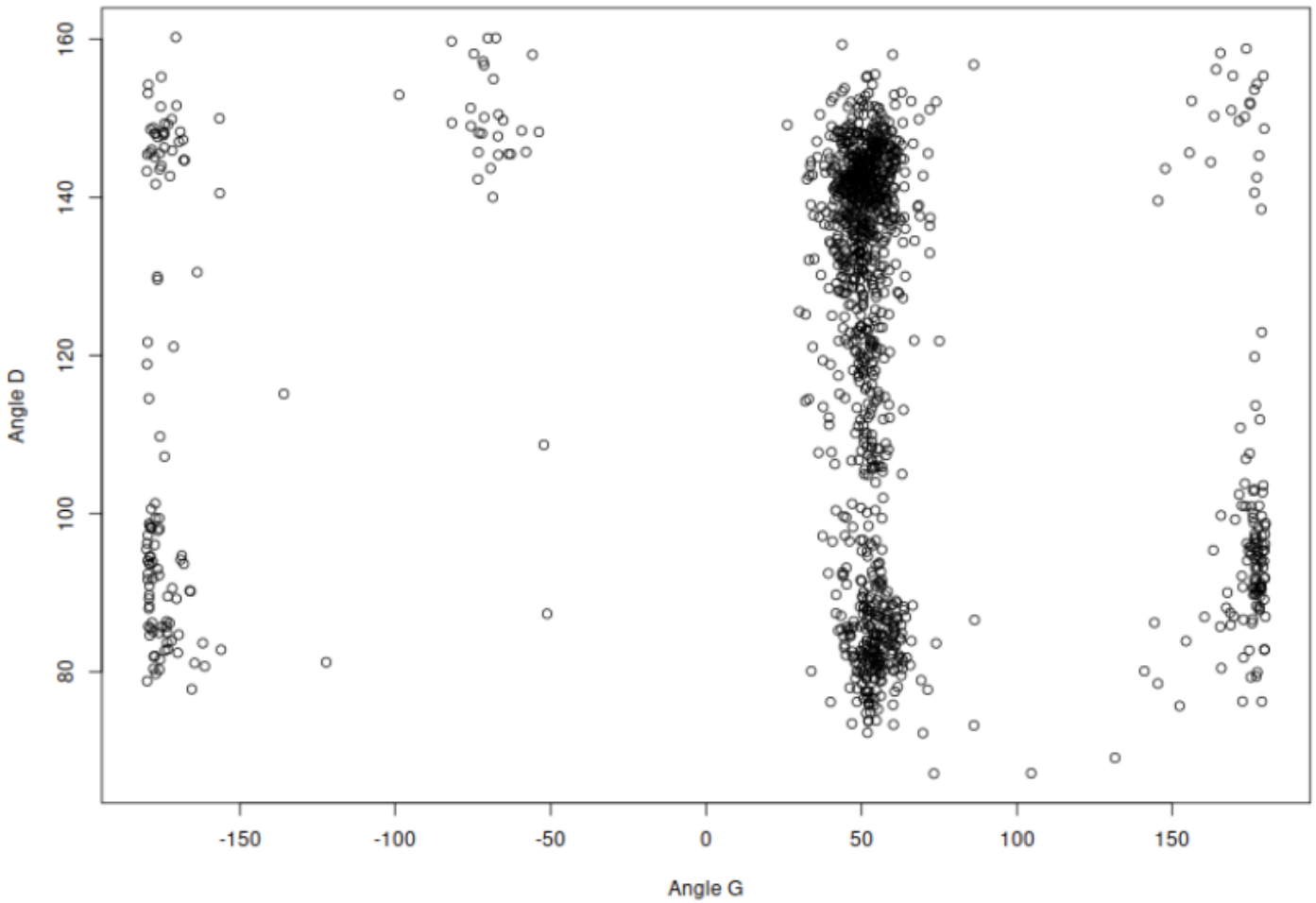
Version designed by the students (Viktorija Jugai)

Example: dihedral angle calculation

Results on the whole PDB



(IUPAC-IUB, 1983)



Result computed by Aušrinė Zeleckytė

Conclusions

- Ada is a very “learnable” language;
- Code in languages like Ada is readable and can illustrate the crystallography and bioinformatics topics;
- Students start making practically useful programs in one semester, even if they had to learn the language as a side task.

Summary

- Deep understanding of core math/algorithms is essential
- Implementation of these algorithms in HLL facilitates understanding
- There are systems (e.g. Ada) that allow implementing “glass boxes” instead of “black boxes”
- Students have successes implementing such algorithms in one semester
- Courses of Ada/SPARK or comparable systems could be beneficial for crystallography curriculum
- Comprehensive Open Access databases (PDB, COD) allow students to run “real life” investigations on crystallographic data

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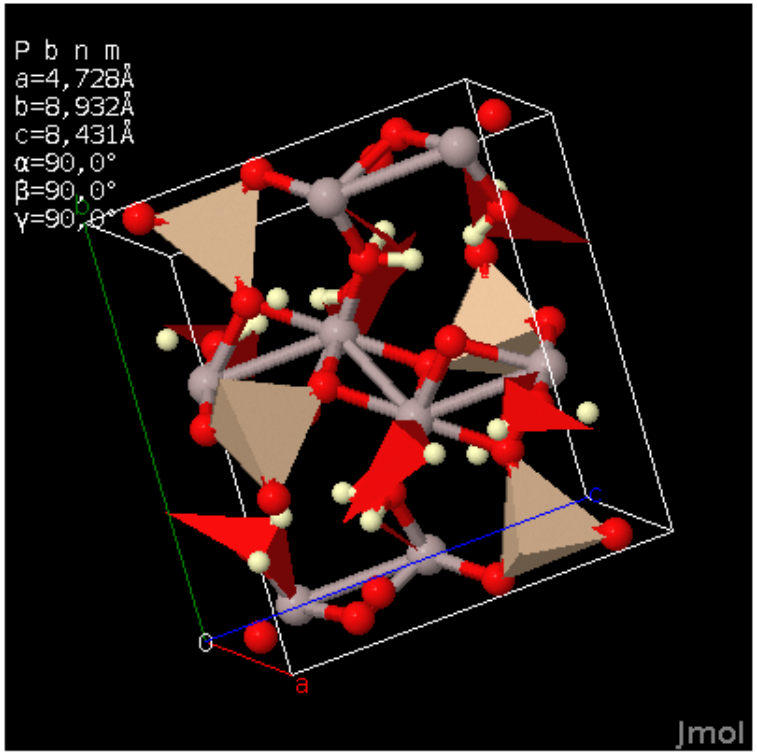
[1] Co-authors of this work

Thank you!

http://en.wikipedia.org/wiki/Topaz



Coordinates	2207377.cif
Original IUCr paper	HTML

http://www.crystallography.net/2207377.html

https://www.crystallography.net/cod/archives/2024/slides/ECM34/slides.pdf

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