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Crystallography and Physiscs: a one century old relation

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- **Modern crystallography is indebted with** :
- A) **Physics** for the theoretical fundamentals necessary to perform diffraction experiments and for starting structural crystallography.
- B) **Chemistry, Biology and Mineralogy** for the general background necessary to interpret electron density maps.
- **Chemistry, biology, physics, geosciences are indebted with crystallography** for the huge amount of information stored in the crystallographic databases, which induced a revolution in the scientific knowledge.

30 Nobel Prizes were awarded, where Crystallography has been one of the key aspects of the research,

- **of which**
- **≈1/3 physicists**
- **≈1/2 chemists ,**
- **The rest biologists and mathematicians**

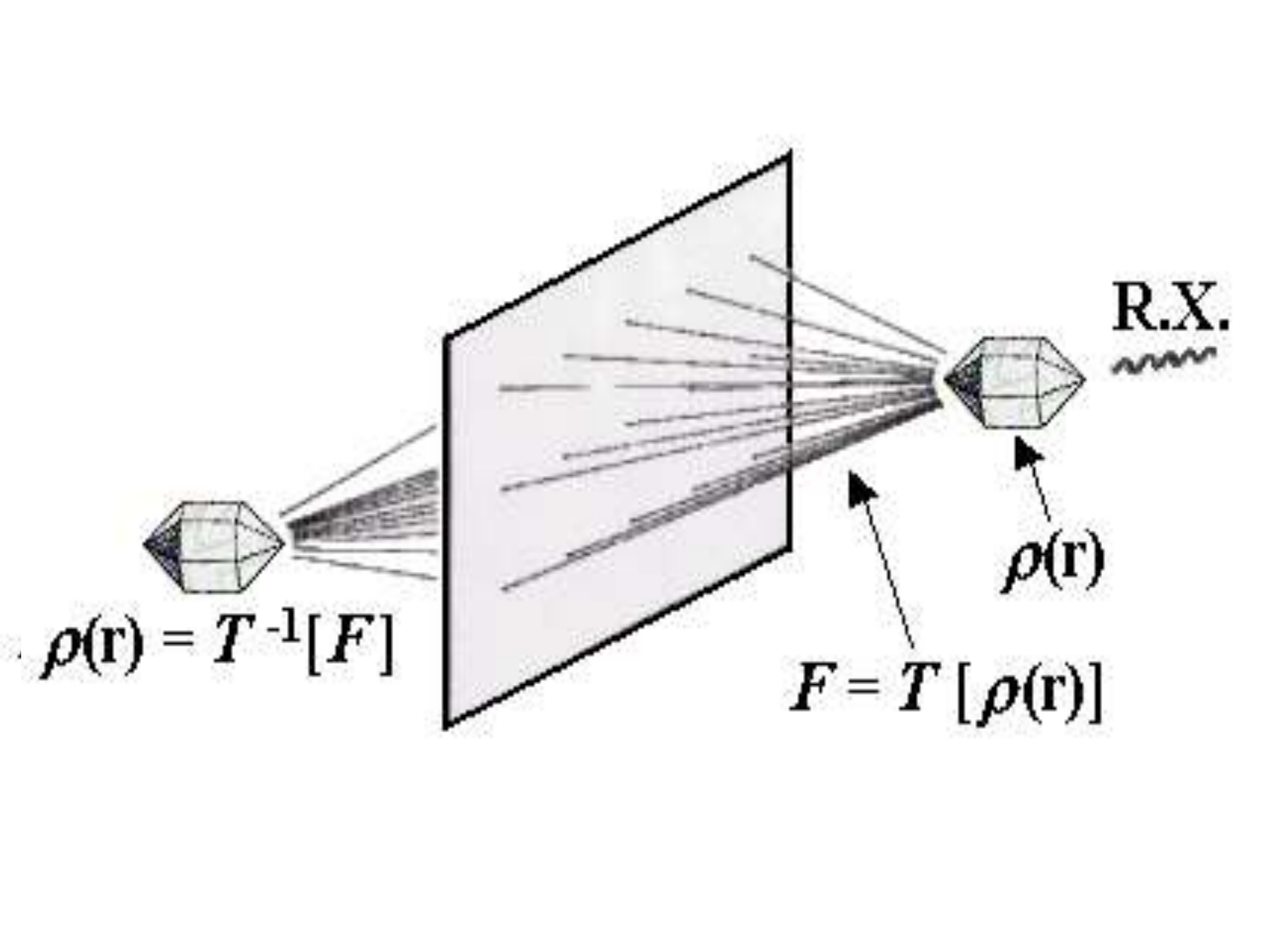
- **For brevity I will not mention** in this talk crystallographic contributions and future perspectives in the following fields:

- **liquids** , **amorphous** and in general **disordered materials (low angle scattering);**
- **powder crystallography**;
- **Modulated structures** and **quasi –crystals** ;

I will address your attention on the general problem of the **crystal structure of materials and related problems and perspectives**.

The central role of the crystal structure

- **Material properties are strictly related to the Crystal Structure.** That is true for inorganic as well as for organic or bio-compounds and in general for materials of technological interest.
- It is therefore not unexpected that, historically, the **development of methods** capable of providing the crystal structure has been a central crystallographic topic ,capable of influencing the trend in other fields .


R.X.
$\rho(\mathrm{r}) = T^{-1}[F]$
$\rho(\mathrm{r})$
$F = T[\rho(\mathrm{r})]$

Crystal structure solution is in practice an inverse problem

Indeed, $|F|^2$ **, say the observation ,** **depends on interatomic vectors**

$$|F_{\boldsymbol{h}}|^2 = \sum_{j=1}^{N} f_j \exp(2\pi i \boldsymbol{h}\boldsymbol{r}_j) \sum_{j=1}^{N} f_j \exp(-2\pi i \boldsymbol{h}\boldsymbol{r}_j)$$

$$= \sum_{i,j=1}^{N} f_i f_j \exp[2\pi i \boldsymbol{h}(\boldsymbol{r}_i - \boldsymbol{r}_j)]$$

not on the atomic positions .

The problem reduces then to :

pass from interatomic vectors to atomic positions.

PHASING and GEOSCIENCES

- The first systematic approach to structure determination started with **Patterson (1934).** Patterson techniques are very effective for structures with some heavy atoms (e.g., minerals): they perfectly answered the structural interests of the Mineralogists, one of groups more ready to exploit the new structural science.
- That is the reason why **the most active crystallographers in early times were mineralogists.**

- **PHASING and ORGANIC CHEMISTRY**
- Patterson techniques relegated to a niche by **Direct Methods**, because the last ones were also able to solve light atom structures: this detail was very important at a time in which organic chemistry was establishing strong interactions with the crystallographic community.

Phasing and Biology

- The wide capacity of the modern crystallography of solving protein crystal structures and contributing to bio-problems encouraged biologist to apply crystallography.
- Today a relevant component of the modern crystallographic community has biological roots.

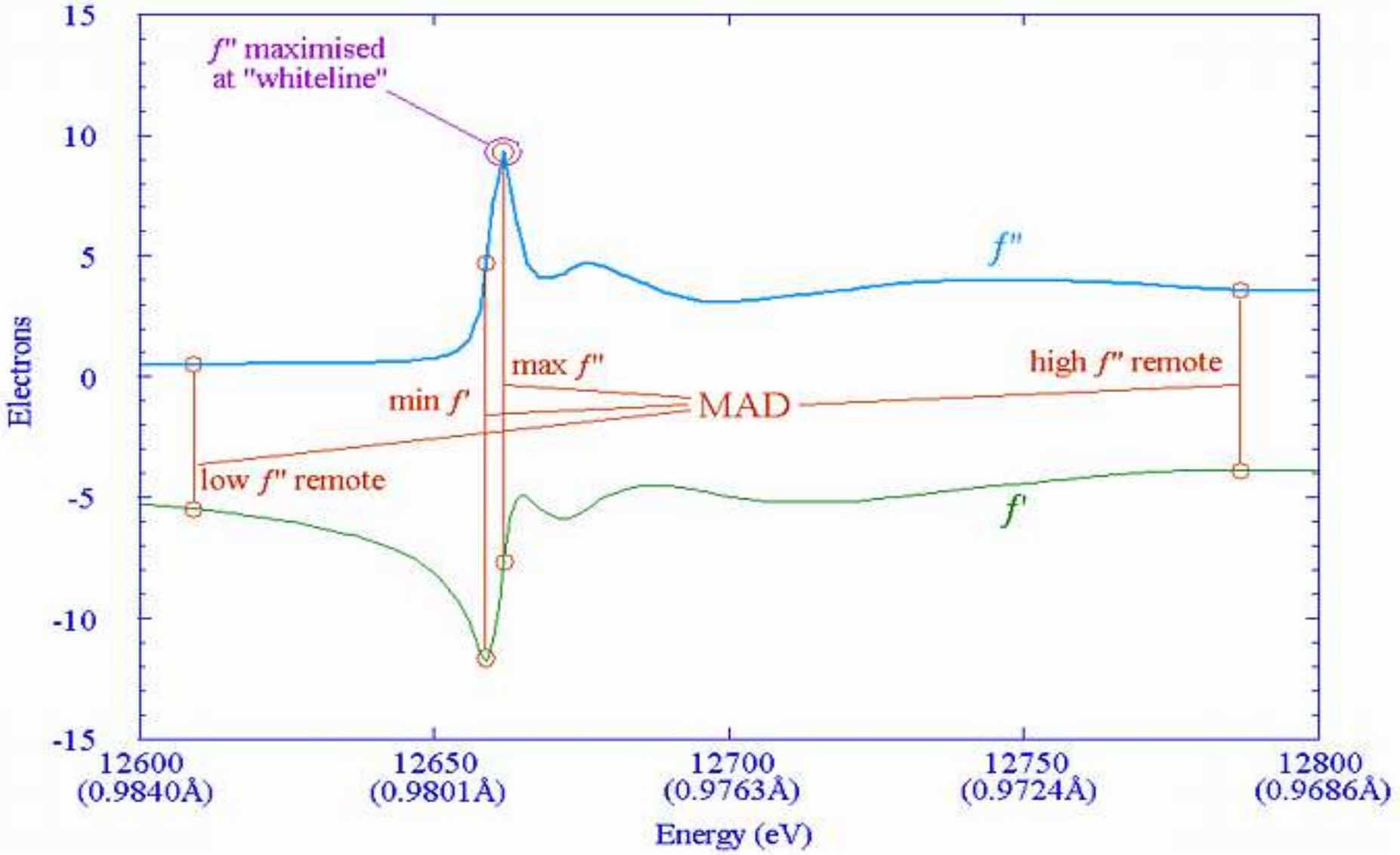
- **The small molecule Pahsing problem**

- Almost 20 years ago the **phase problem for small molecules** (say up 200 atoms in the asymmetric unit) was practically solved .
- **National Research Agencies** of the most advanced Countries recognized the great work done, considered it as conclusive, and decided not to support any more small molecule phasing.
- The small molecule methodologists moved towards proteins

PHASING and PROTEIN CRYSTALLOGRAPHY

- Macromolecule and small-molecule metodologists did not interact each other for 35 years.
- Confluence of the two groups produced great advances in the traditional macromolecular methods:
- A) **isomorphous replacement methods (SIR-MIR)**
- B) **molecular replacement**;
- C) **anomalous dispersion techniques (SAD-MAD)**
- **D) ab initio methods**

Typical dispersion curve



LIMITS AND PERSPECTIVES

- **Phasing methods today** have to face the **new challenges** of the modern research in chemistry and biology (e.g, in supramolecular chemistry, genomics, gigantic assemblies of proteins, etc.).

- **Efficiency and quickness** must be two essential qualities of the new phasing procedures. Here we quote the main problems and the **possible trends of phasing methods.**

Crystallization

- **Real bottleneck** of today's crystallography.
- **Concentration of the protein, temperature, pH, chemical additives,** etc. can affect crystallization: the appropriate combination of these conditions has to be found.
- The present situation is frustrating : samples of adequate size and quality are often very difficult to obtain in spite of the significant time and efforts spent in the crystallization step.
- The use of **robots** has mitigated the problems, but did not solve it.
- Probably **advances** in the fundamentals of crystal growth are necessary.

Resolution limits

- **In macromolecular crystallography, owing to the intrinsic low quality of the crystals,** data resolution is often too low to permit accurate crystal structure solution and refinement. Such physical limitation is very severe for ab initio methods, which, very likely, will benefit in the future by the introduction of more extended low-level information, like bond distances and angles, coordination, etc. .

Sample size

Many classes of materials (superconductor catalysts, pharmaceuticals, materials for long life batteries, etc.) are often available as **multiphase powders constituted by nanocrystals.**

Owing to the **strong interaction of electrons with matter** it is possible to obtain good diffraction patterns from 4**0 nm samples.**

Is the problem of crystal sample size and the necessity of a single chemical phase overcome?

Electron Diffraction and sample size

Electron diffraction is too **sensible to dynamical effects**: as a result the kinematical theory of diffraction is unable to dominate the phasing problem. This is essentially the reason which hindered the explosion of the electron diffraction techniques.

Recently **precession and rotation techniques** were coupled to ED , but the quality of the ED patterns is still by far inferior to that of X.R.

FEL and sample size

- FEL is an important tool for overcoming the problem of the crystal sample size : single X-ray diffraction snapshots are collected from **a stream of nanocrystals usig femtosecond pulses from a hard-Xray FEL.**
- Pulses briefer than the time scale of most damage processes are used.
- For **photosystem I** more than 3 000 000 diffraction pattern were collected, from which a 3-dimensional data set was assembled .

Single Object Structure

Recent advances in both detectors and algorithms for data analysis have recently made possible to obtain atomic models of large macromolecules without any use of crystals .

Venkatraman Ramakrishnan (Cambridge; Nobel Prize) obtained an atomic model for the large mitochondrial ribosomal subunit de novo at about 3 Å resolution.

The object was recovered by collecting thousands of projections of the single object, randomly distributed, which then were Fourier transformed and combined.

Crystallographic methods are now used to refine the model.

Single Object Structure

- Probably FEL in a next future will also able to provide **continuous diffraction images from single objects.**
- Milions of diffuse scattering patterns collected from randomly distributed samples may be combined in a 3-dimensional pattern, from which present algorithms may obtain the structure.

Prediction

- Predicting side chain conformations via minimization of energy functions (e.g. **Rosetta approach**) is probably still at an infancy stage.
- Very likely such approaches may result very useful when poor data are available and ab initio phasing is impossible. In this case diffraction data may confirm, modify or deny the predictions.

- **Why not a more strict relation between crystallography and Physics?**