

Physical concepts essential to structural biology

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A general question

The object (target) to be analyzed:
Biological macromolecules or assemblies

The analysis tool:
Some particles stream

Requirements:
Interaction with the target strong enough
Provides information at the right scale

Collected information + a-priori knowledge $\leftrightarrow$ structural model

Interactions...

Force (→ interaction) nucléaire forte :

C'est celle qui cimente les nucléons dans les noyaux. Elle est portée par les gluons.

C'est elle aussi qui associe les quarks 3 par 3 à l'intérieur des nucléons et donne naissance à l'énergie nucléaire.

Elle agit sur une distance de 10^{-13} cm, elle est 100 fois plus forte que la force électromagnétique et n'agit que sur des particules massives comme le proton et le neutron d'un poids de 10^{-24} gr.

Force électromagnétique :

Cette force n'agit que sur les particules chargées.

Force gravitationnelle :

Découverte au XVII^e siècle par Isaac Newton, cette force attractive agit sur toutes masses.

La plus faible des quatre forces de la nature, mais aussi celle qui a la plus grande portée.

Force nucléaire faible :

C'est elle qui permet aux neutrons de se transformer en protons et vice versa. Bien que plus forte que la gravité, elle est 1000 fois plus faible que la force électromagnétique. Elle n'a d'influence que sur une distance de 10^{-16} cm.

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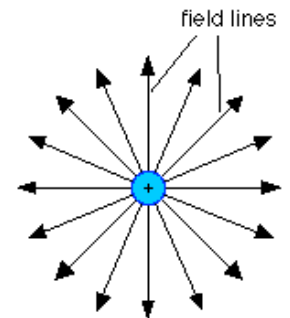
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The electromagnetic force

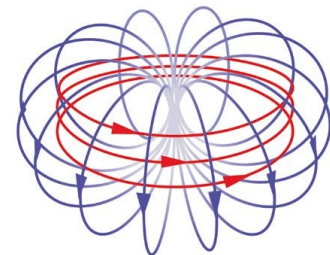
Force between 2 charged particles, carried by the photon

→ electrostatic field force from one particle to the other: $\mathbf{q} \cdot \mathbf{E}$



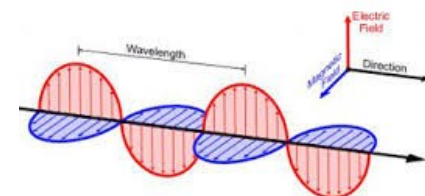
The electric field from an isolated positive charge

→ particles in motion: static electromagnetic fields $\mathbf{q} \cdot \mathbf{E}$, $\mathbf{q} \cdot \mathbf{v} \wedge \mathbf{B}$



in the general case:

- structure of the force field described by Maxwell equations
- Accounts for static fields, oscillation (waves), ...



$$\operatorname{div}(\vec{E}) = \frac{\rho}{\epsilon_0} \quad \vec{\operatorname{rot}}(\vec{E}) = -\frac{\partial \vec{B}}{\partial t}$$

(Maxwell-Gauss) (Maxwell-Faraday)

$$\nabla \cdot \mathbf{E} = \frac{\rho}{\epsilon_0}$$

$$\nabla \cdot \mathbf{B} = 0$$

$$\operatorname{div}(\vec{B}) = 0 \quad \vec{\operatorname{rot}}(\vec{B}) = \mu_0 \vec{J} + \frac{1}{c^2} \frac{\partial \vec{E}}{\partial t}$$

(Maxwell-Flux) (Maxwell-Ampère)

$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t}$$

$$\nabla \times \mathbf{B} = \mu_0 \mathbf{J} + \mu_0 \epsilon_0 \frac{\partial \mathbf{E}}{\partial t}$$

Covariance → relativité restreinte

How can we obtain structural information?



- A question of interaction between radiation and matter
- Radiations can be:
 - Photons (electro-magnetic wave: light, X-rays)
 - Electrons
 - Neutrons
- Matter
 - Your molecule under study

The output of this interaction...

Possible approaches



- “Imaging” techniques
 - Visible light microscopy
 - Electron microscopy
 - X-ray or neutron crystallography
- Localization technique
 - Super-resolution microscopy
- Spectroscopic techniques
 - NMR
 - SAXS

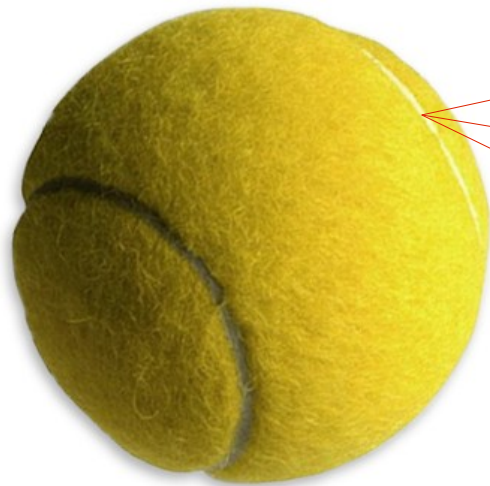
Visible light microscopy



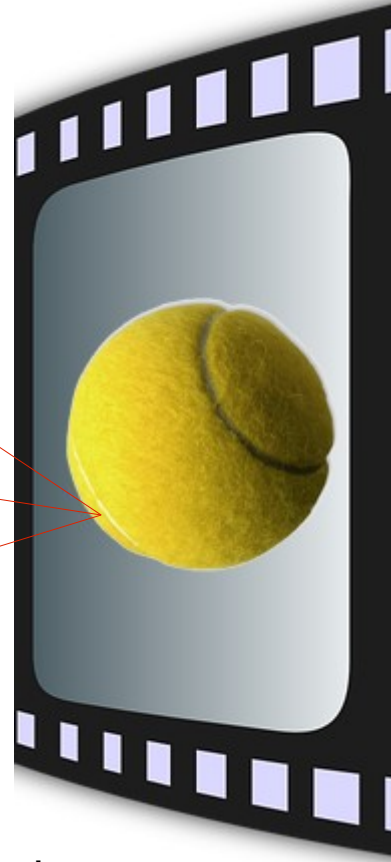
- Source light (radiation): photons or electromagnetic wave
 - Wave length: $0.3 - 0.8 \mu\text{m}$
- Object (matter): absorb and re-emit incident light in all directions
 - More or less absorption
 - some time wave length dependent (color)
- Lens: focuses light emitted by the object
 - The light emitted by one point of the object is focused on one point of the detector

A scheme to explain

Source of light



Object

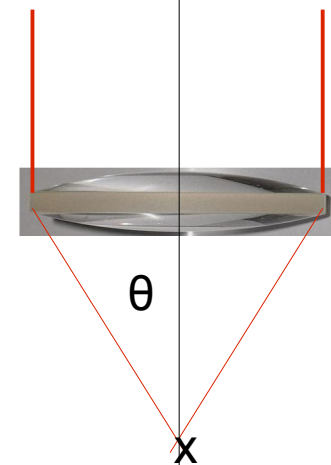
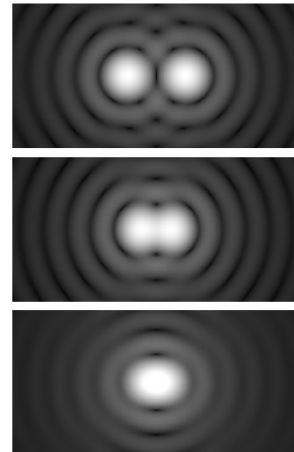


image

Why can't we see molecule with visible light?



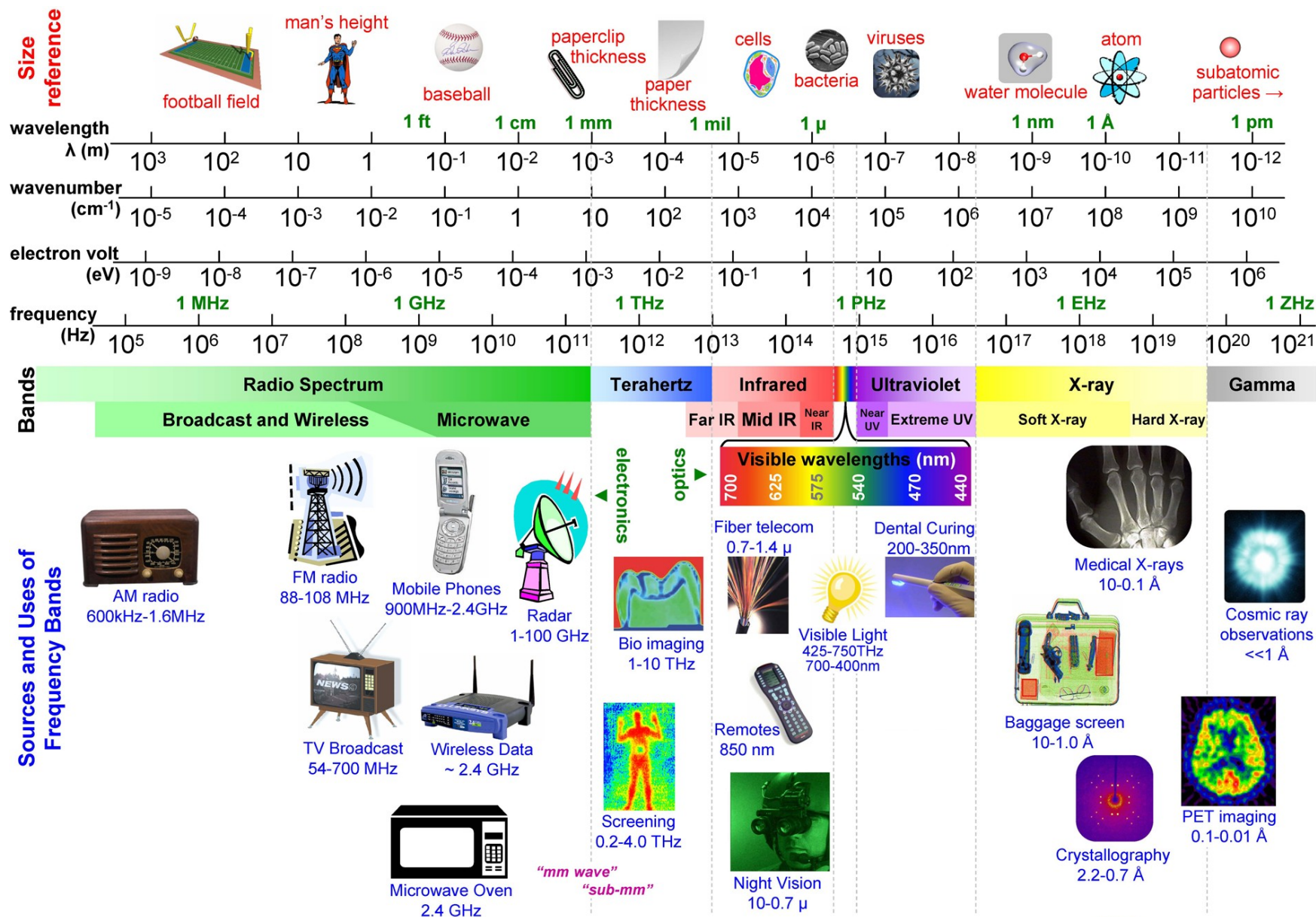
- Be because of the wave nature of light
 - Diffraction of light by a disk with limited size: each point from the object generate a diffraction pattern
- Rayleigh criterion
$$d = 1.22 \frac{\lambda}{2 n \sin \theta} \approx \frac{\lambda}{2 \sin \theta} \quad (\text{in airy})$$
 - λ is the wave length, n is the refraction index,
 - $n \cdot \sin \theta$ the numerical aperture of the lens $\rightarrow \text{Max} \approx 1.4 - 1.6$
- Maximum resolution with visible light
 - $\approx 0.25 \mu\text{m}$
 - Enough for cells
 - Not enough for molecules



How to increase resolution?

- Atomic resolution
 - $d \sim 1 \text{ \AA} \Rightarrow \lambda \leq 2 \text{ \AA}$
 - Use photons in the domain of X-rays
 - Typically: for $\lambda = 1 \text{ \AA}$, $E = h\nu = hc/\lambda \approx 12.4 \text{ keV}$

How to increase resolution?



How to increase resolution?



- Atomic resolution
 - $d \sim 1 \text{ \AA} \Rightarrow \lambda \leq 2 \text{ \AA}$
 - Use photons in the domain of X-rays
 - Typically: for $\lambda = 1 \text{ \AA}$, $E = h\nu = hc/\lambda \approx 12.4 \text{ keV}$
- Do X-rays interact with atoms?
 - Yes, X-ray photons can be elastically scattered by the electronic cloud of an atom

How a photon is scattered by an atom ?



- Elastic scattering (no loss of energy, wavelength is conserved)
 - Thomson scattering: free electrons (photon energy $\gg$ electron binding energy)
 - ♦ Carbon atom $E(1s) = -1013 \text{ eV}$, $E(2s,2p) = -36 \text{ eV}$ to be compared to 7 to 15 keV for X-ray photons
 - Photon energy should differ from element absorption edges
 - The wave description of X-ray photons (electromagnetic wave) is fine to explain the phenomenon (classical model)
 - In an electric field $\vec{E}$, a charge e feels a force: $\vec{F} = e \cdot \vec{E}$
 - ♦ Thus, the electric field of the electromagnetic wave will induce movement of nucleus and electrons
 - ♦ Due to the non-relativistic velocity of atomic electrons, the Lorentz force induced by the magnetic field of the electromagnetic wave $\vec{F} = e \cdot \vec{v} \wedge \vec{B}$ can be neglected

Ocillating dipole

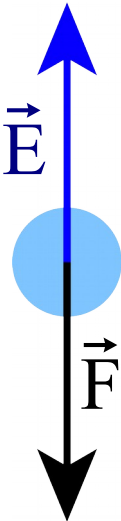
- In an electric field $\vec{E}$ a charge e feels a force: $\vec{F} = e \cdot \vec{E}$
- The force will induce an acceleration of both the electron and the nucleus
- $\vec{F} = m \cdot \vec{\gamma} \Rightarrow \vec{\gamma}_e = -e \cdot \frac{\vec{E}}{m_e}$ and $\vec{\gamma}_n = + Ze \cdot \frac{\vec{E}}{(Zm_p + (A - Z)m_n)}$

Since m_p and $m_n \gg m_e$ one can neglect the movement of the nucleus

- The dipole induced by the electric field is: $\vec{d} = Ze \cdot \vec{r}$
(with $\vec{r}$ vector between center of mass of electrons and nucleus)

$$\frac{\partial^2 \vec{d}}{\partial t^2} = -Ze \cdot \vec{\gamma}_e = Ze^2 \cdot \frac{\vec{E}}{m_e}$$

$$\underbrace{\vec{E} = \vec{E}_0 \cos[\omega t]}_{\text{ocillating electric field}} \Rightarrow \underbrace{\vec{d} = -\left(Ze^2 \frac{\vec{E}_0}{m_e \omega^2} \right) \cos[\omega t]}_{\text{ocillating dipole}}$$



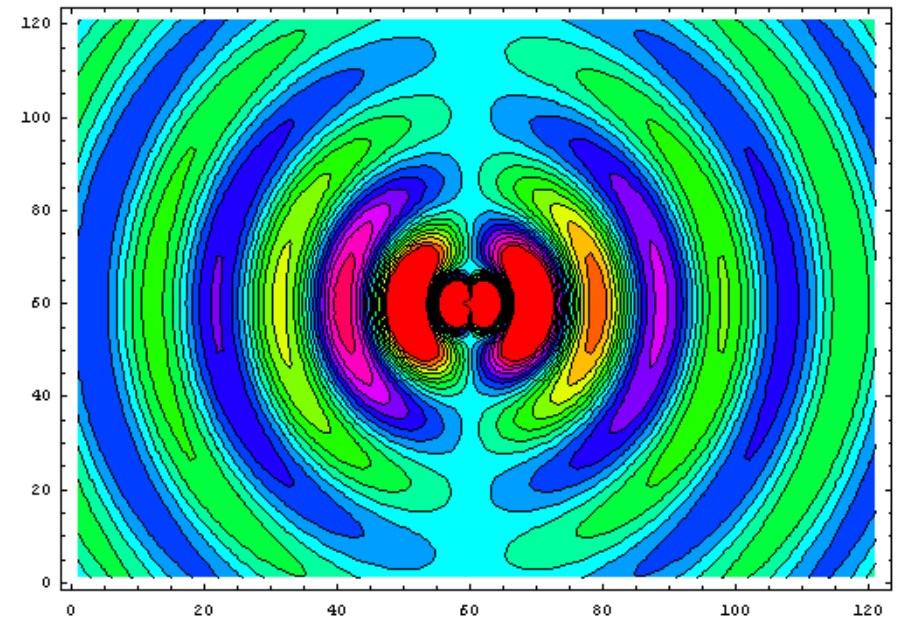
Oscillating dipole and emitted wave



$$\vec{d} = Ze \cdot (\vec{r}_n - \vec{r}_e)$$

$\vec{E}$

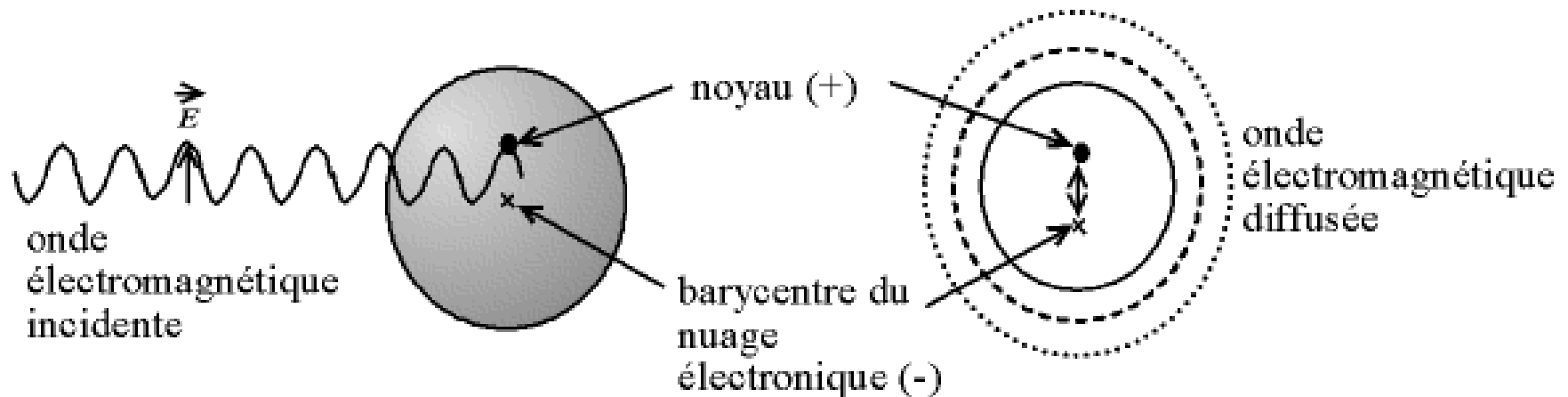
x



How a photon is scattered by an atom ?



- The incident electromagnetic wave induces the oscillation of the electronic cloud
- The negatively charged electronic cloud and the positively charged nucleus become an oscillating dipole, thus emitting a spherical electromagnetic wave of same wavelength and a phase difference of π .



- The atom becomes a source of photons, with the same wave length.

Why can't we get directly the image of the molecule with X-rays?



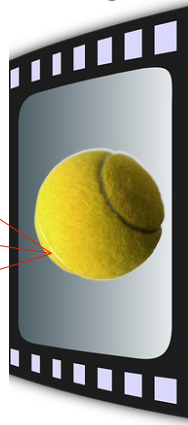
- Problem: we have no lens for X-ray photons
 - No image on the detector, but a scattering spectra
- With a lens
 - All radiation arriving on one point of the detector come from one point on the object
- Without a lens
 - Radiation arriving on one point of the detector come from all points on the object. It is the sum of waves emitted by each point of the object

Scheme for a scattering spectrum

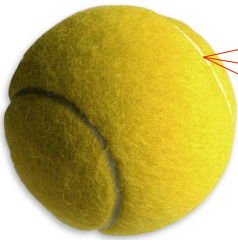
Source
of light



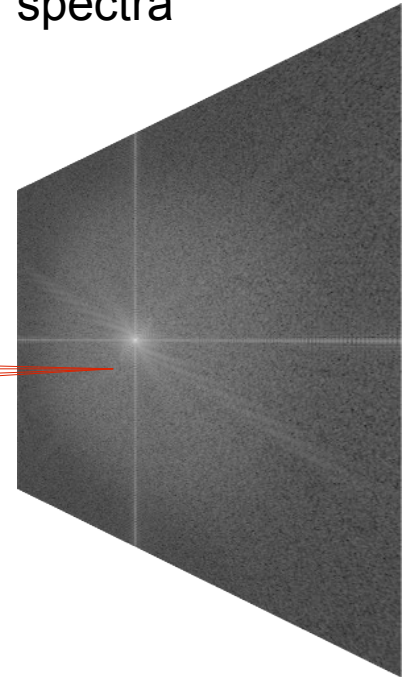
Image



Object



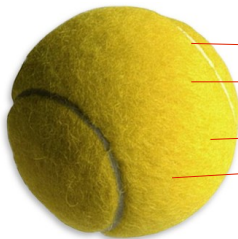
Diffusion/diffraction
spectra



Source
of light

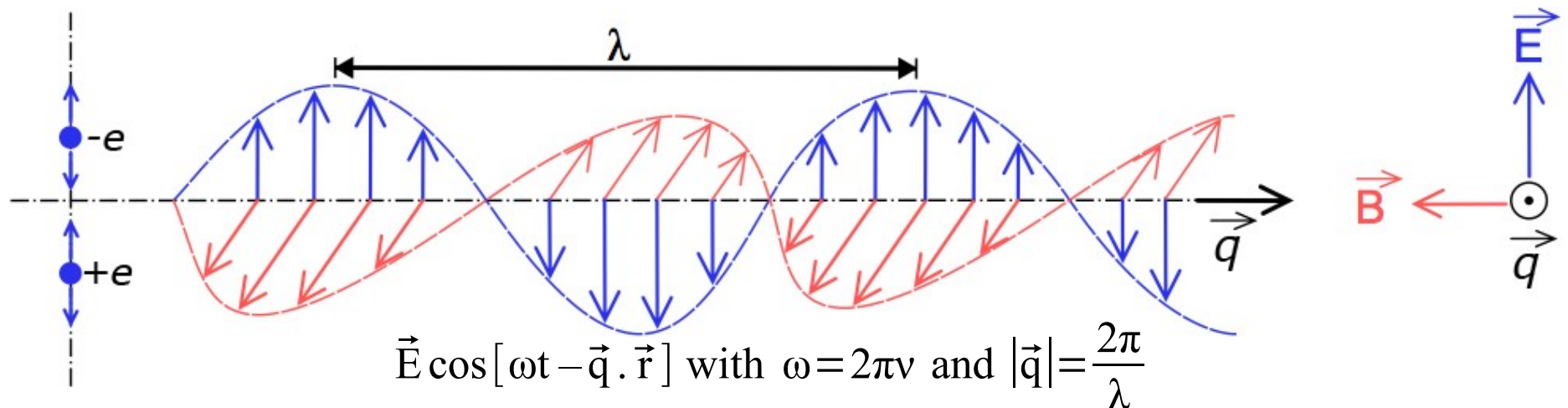


Object



What is a scattering spectra?

- What is the link between the scattering spectra and the molecule?
- Can we still get an image of the molecule?
- What is an electromagnetic wave?
 - Wave generated by an oscillating dipole

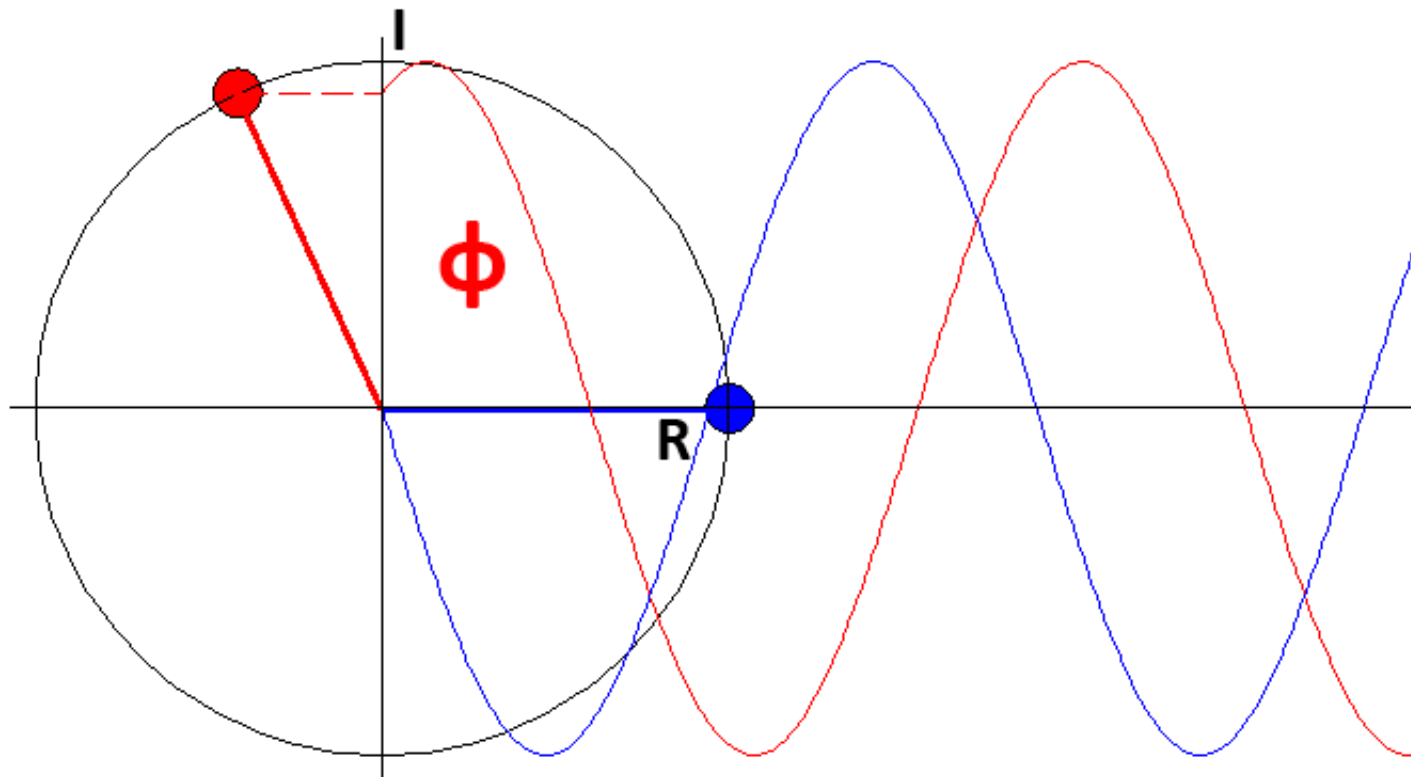


ω : angular frequency, ν : frequency, λ : wave length, $\vec{q}$: wave vector

Reminder about waves

- Fresnel representation of waves

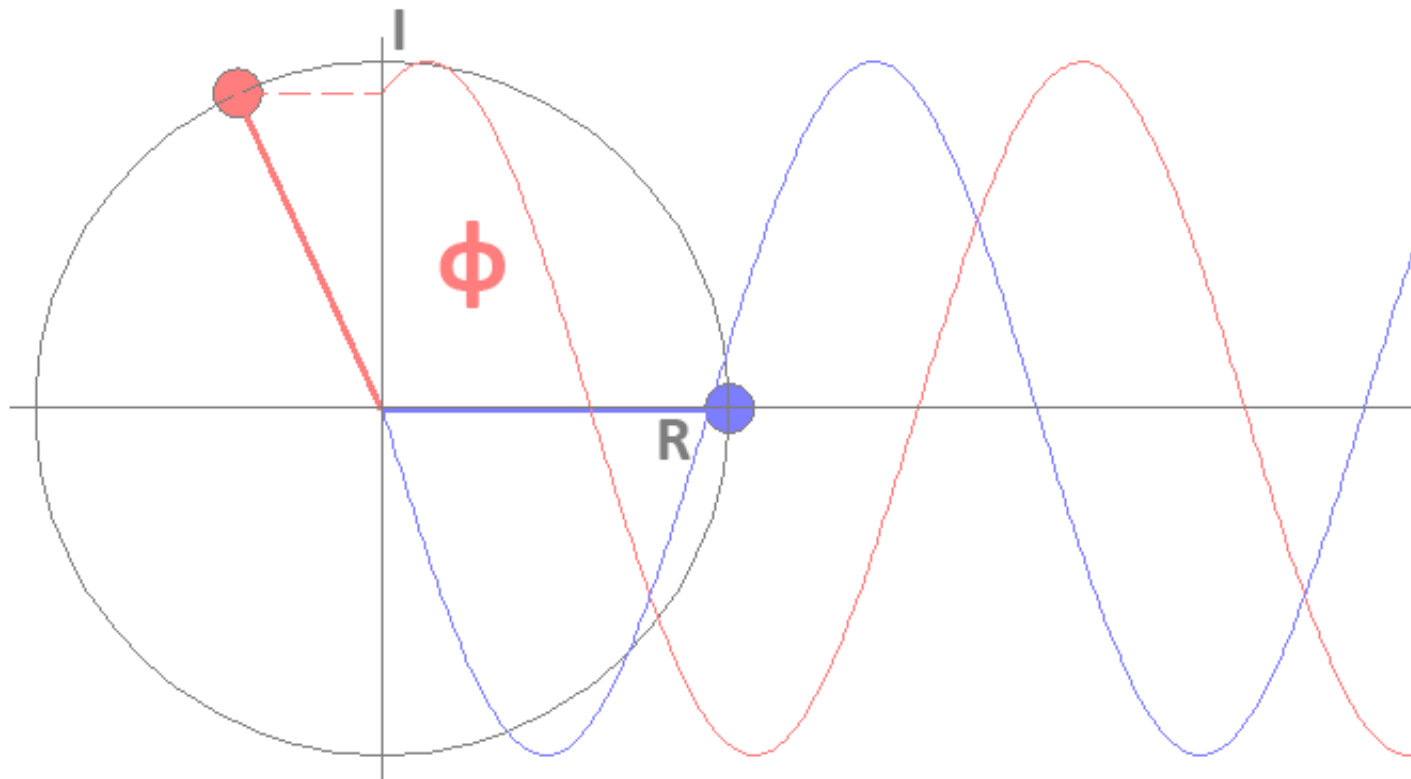
- Electric field: $\vec{E}_0 \cos[\omega t - \vec{q}_0 \cdot \vec{r}] = \vec{E}_0 \exp[i(\omega t - \vec{q}_0 \cdot \vec{r})]$
- A phase shift ϕ : $\vec{E}_0 \exp[i(\omega t - \vec{q}_0 \cdot \vec{r} + \phi)] = \vec{E}_0 \exp[i(\omega t - \vec{q}_0 \cdot \vec{r})] \cdot \exp[i\phi]$



Reminder about waves

- Fresnel representation of waves

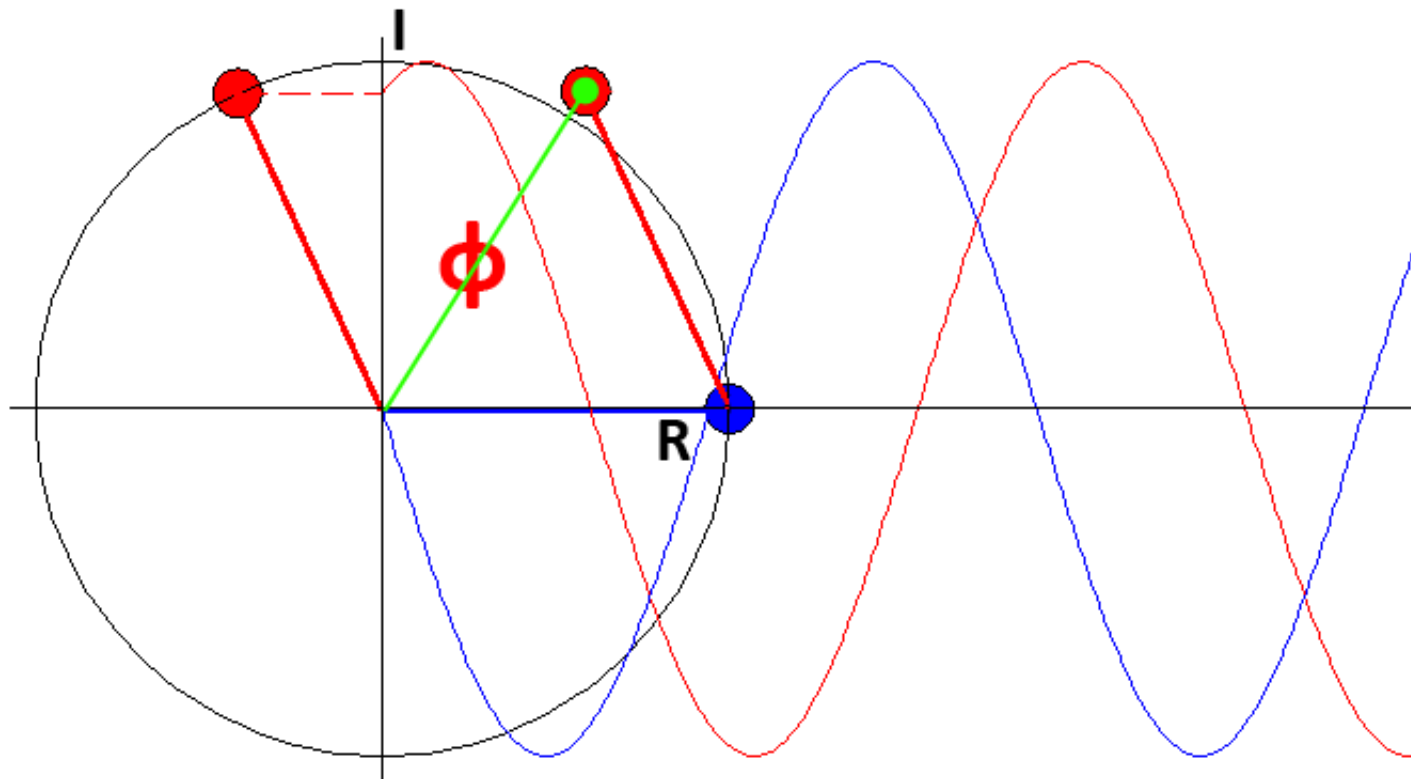
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Reminder about waves

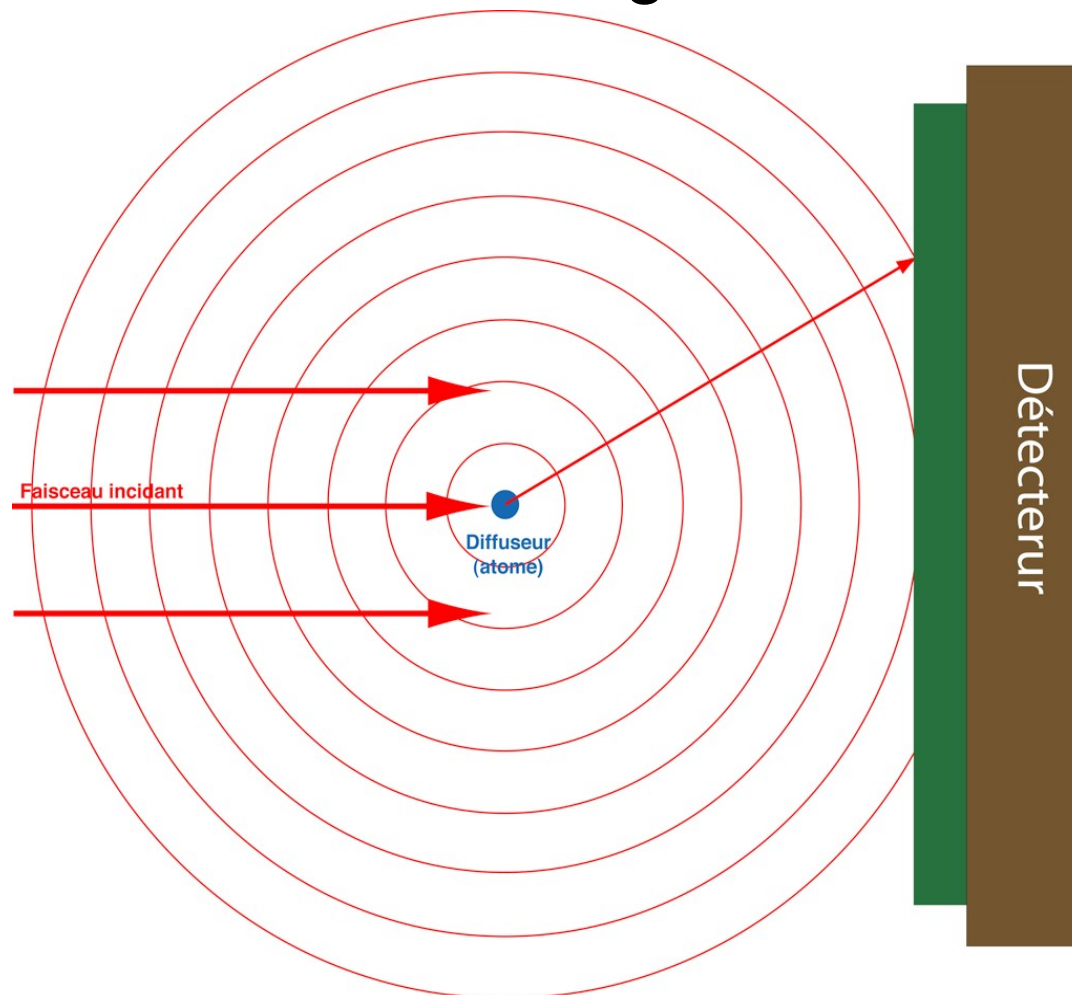
- Sum of two waves are simple to express

$$\vec{E}_0 \exp[i(\omega t - \vec{q}_0 \cdot \vec{r})] + \vec{E}_0 \exp[i(\omega t - \vec{q}_0 \cdot \vec{r})] \cdot \exp[i\phi] = \vec{E}_0 \exp[i(\omega t - \vec{q}_0 \cdot \vec{r})] \cdot (1 + \exp[i\phi])$$

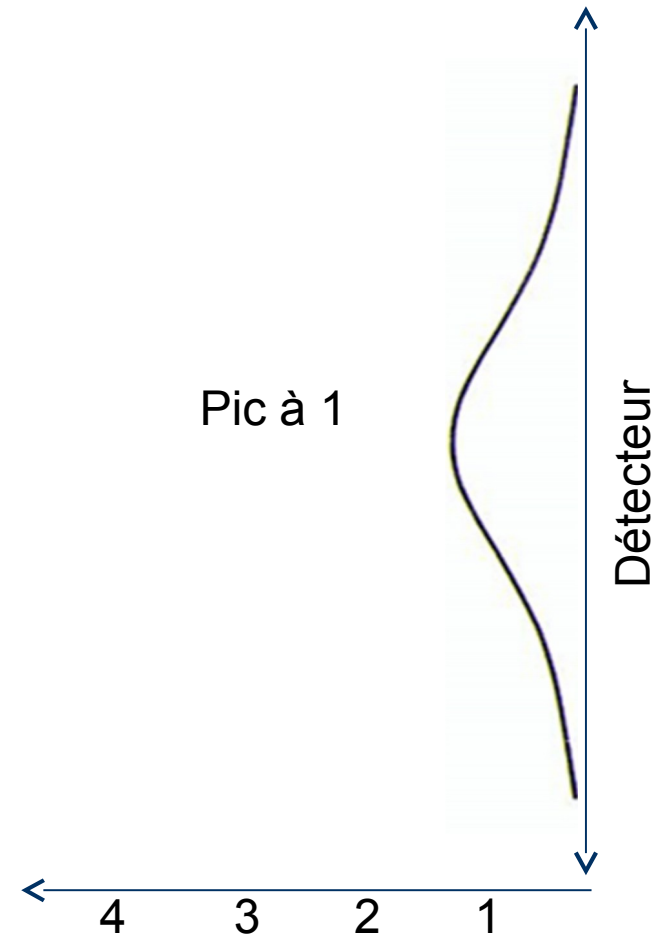
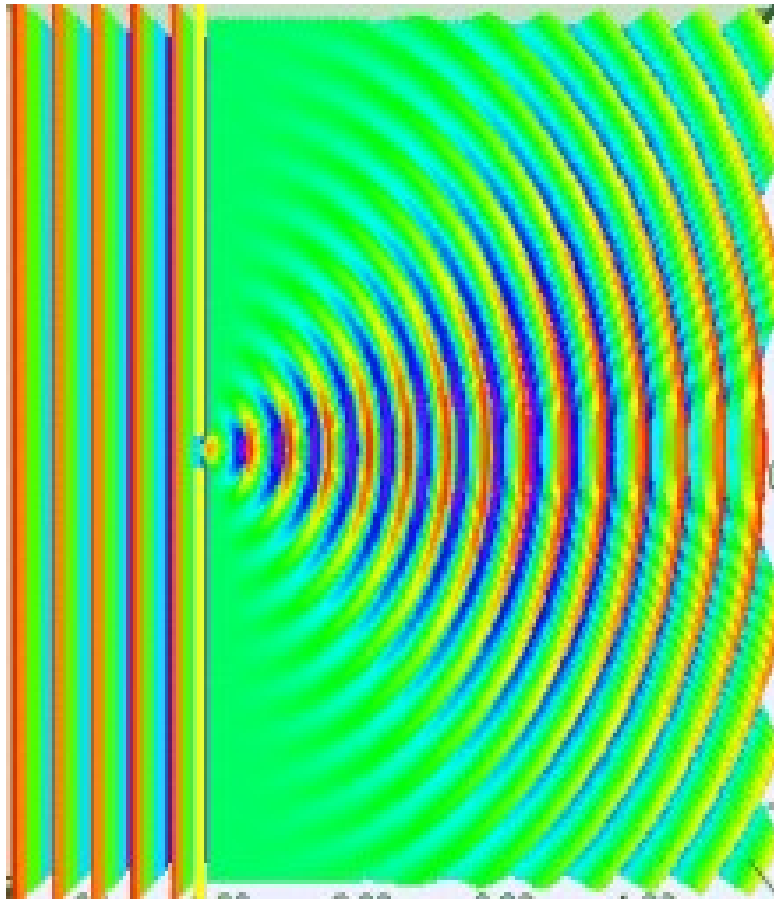


Scattering by one atom

- The planar incident wave induces the emission of a spherical wave of same wavelength and with a π phase shift

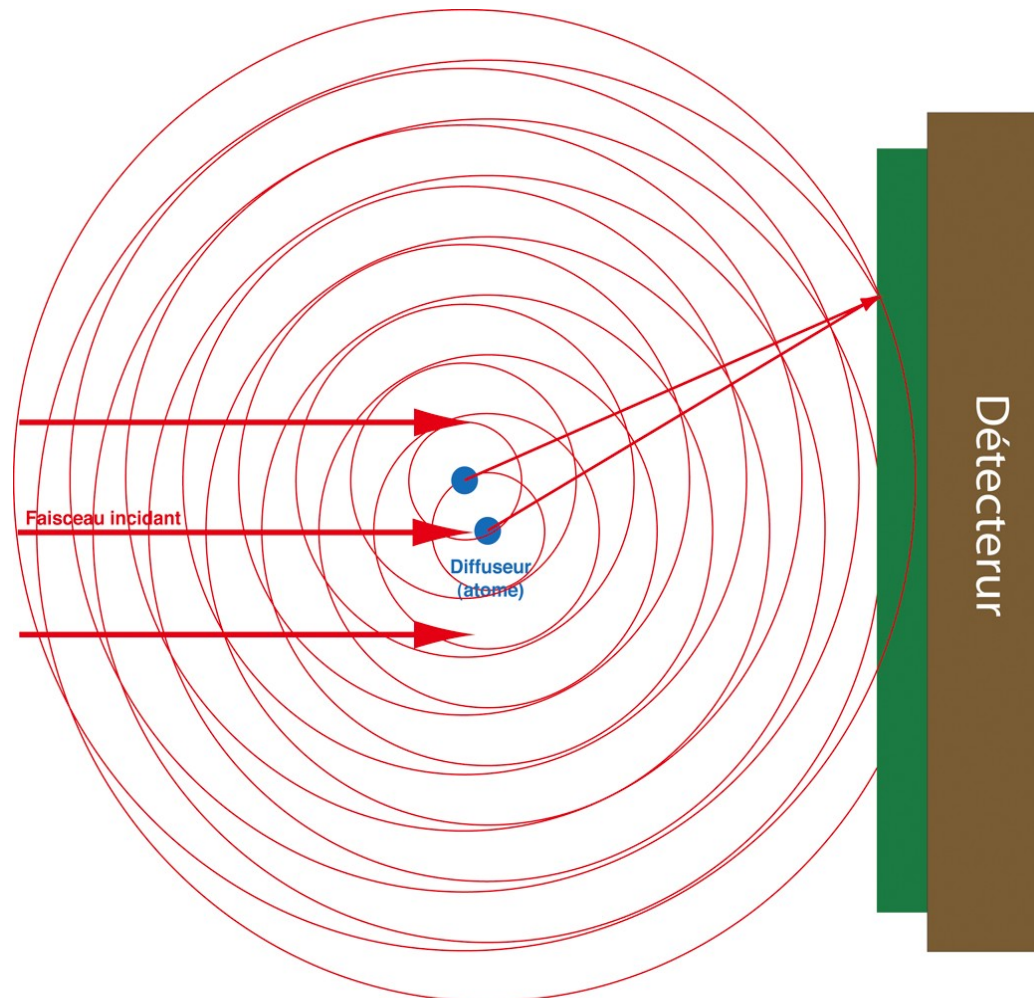


Scattering by one atom

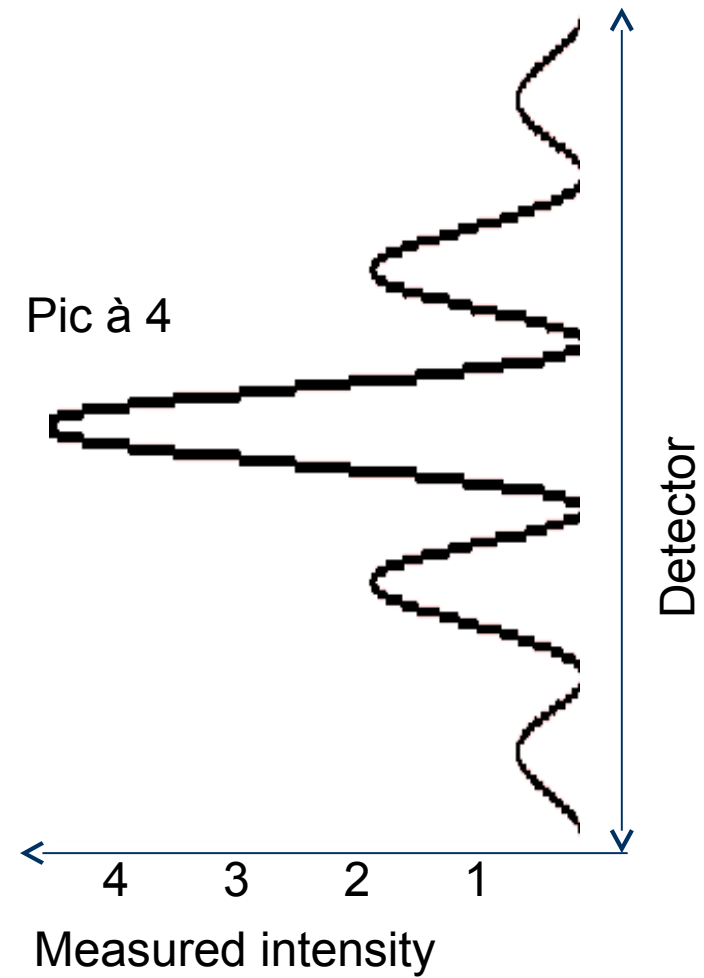
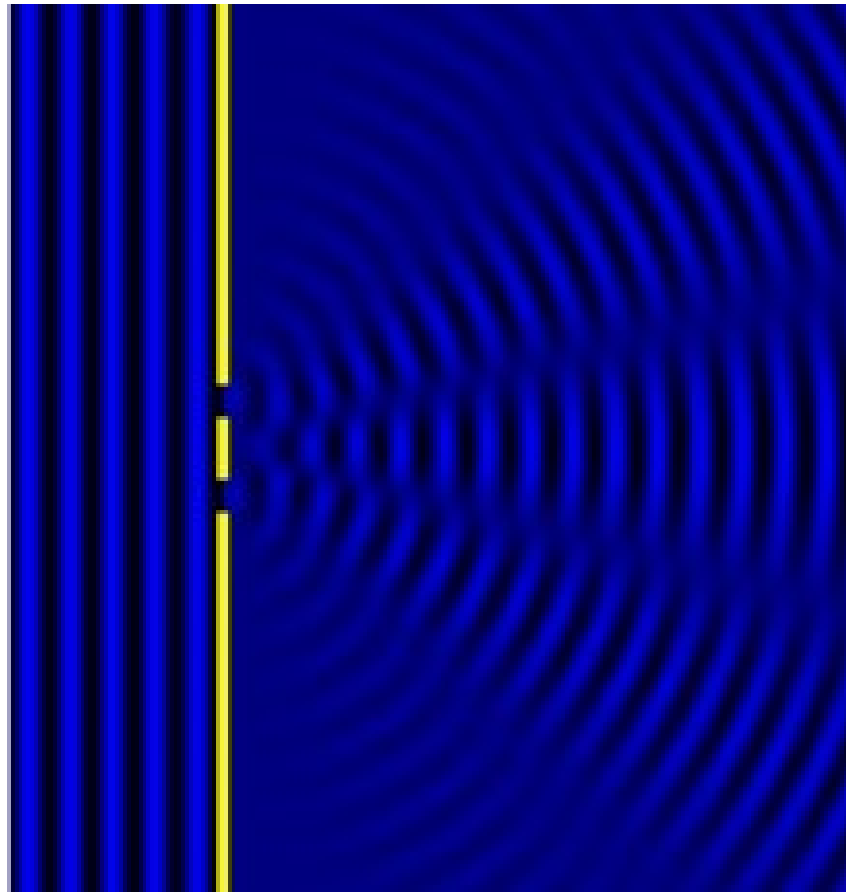


Scattering by two atoms

- The two atoms are emitting a spherical electromagnetic wave. If the two atoms are not mobile and close by, the two waves interfere

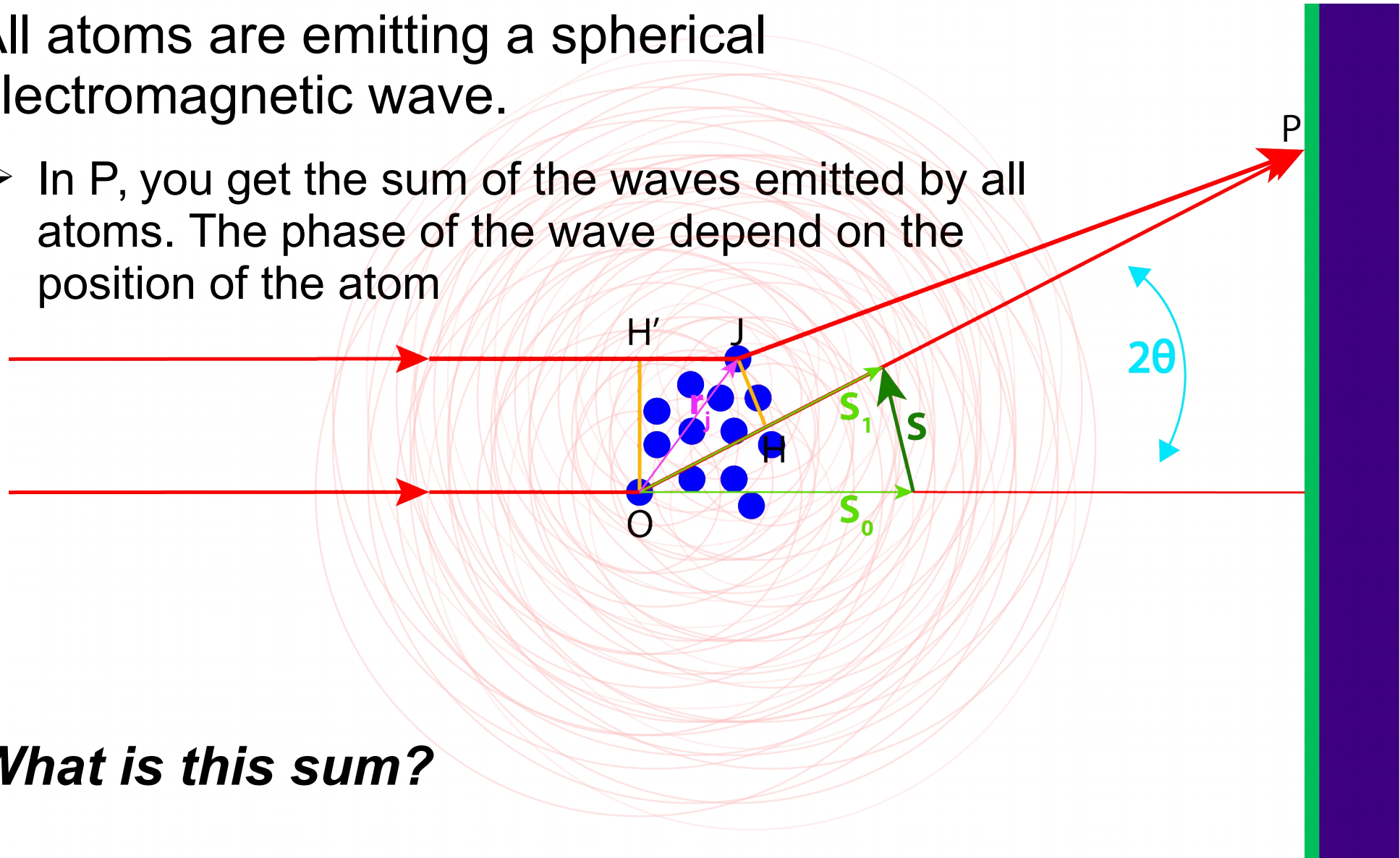


Scattering by two atoms



Scattering by numerous atoms

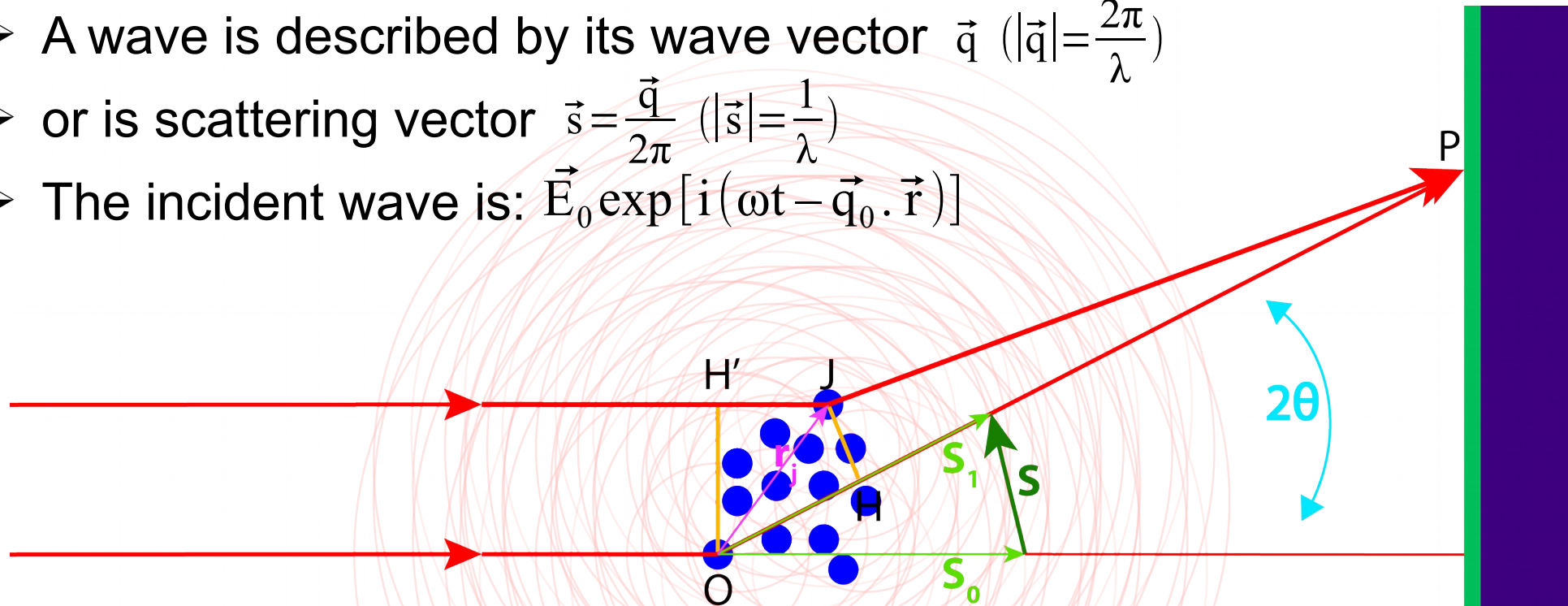
- All atoms are emitting a spherical electromagnetic wave.
 - In P, you get the sum of the waves emitted by all atoms. The phase of the wave depend on the position of the atom



- ***What is this sum?***

Scattering by numerous atoms

- A wave is described by its wave vector $\vec{q}$ ($|\vec{q}| = \frac{2\pi}{\lambda}$)
- or is scattering vector $\vec{s} = \frac{\vec{q}}{2\pi}$ ($|\vec{s}| = \frac{1}{\lambda}$)
- The incident wave is: $\vec{E}_0 \exp[i(\omega t - \vec{q}_0 \cdot \vec{r})]$



- The wave emitted by atom J in P is:

$$\underbrace{\vec{E}_0 \exp[i(\omega t - \vec{q}_0 \cdot \vec{r}_J)]}_{\text{incident wave at atom J}} \cdot \underbrace{\frac{f_J}{|\vec{r} - \vec{r}_J|}}_{\propto \text{scattering factor of atom J}} \cdot \underbrace{\exp[-\vec{q}_1 \cdot (\vec{r} - \vec{r}_J)]}_{\text{dependence with distance from atom J}} \cdot \underbrace{\exp[i\pi]}_{\pi \text{ phase shift}}$$

Scattering by numerous atoms



- The wave emitted by all atoms in P is just the sum:

$$\sum_J \vec{E}_0 \exp[i(\omega t - \vec{q}_0 \cdot \vec{r}_J)] \cdot \frac{f_J}{|\vec{r} - \vec{r}_J|} \cdot \exp[-i\vec{q}_1 \cdot (\vec{r} - \vec{r}_J)] \cdot \exp[i\pi]$$

- If sample size $\ll$ distance sample-detector it becomes:

$$\frac{\vec{E}_0}{|\vec{r} - \vec{r}_0|} \exp[i(\omega t - \vec{q}_1 \cdot \vec{r})] \cdot \exp[i\pi] \cdot \sum_J f_J \cdot \exp[i(\vec{q}_1 - \vec{q}_0) \cdot \vec{r}_J]$$

- If we define the scattering vector: $\vec{s} = \vec{s}_1 - \vec{s}_0 = \frac{1}{2\pi} \cdot (\vec{q}_1 - \vec{q}_0)$

$$\underbrace{\frac{\vec{E}_0}{|\vec{r} - \vec{r}_0|} \exp[2i\pi(\vec{s}_1 \cdot \vec{r})] \cdot \exp[i\pi]}_{\text{depend on the incident wave and position P}} \cdot \underbrace{\sum_J f_J \cdot \exp[2i\pi(\vec{s}) \cdot \vec{r}_J]}_{\text{Fourier transform of the distribution of scattering factors}}$$

depend on the incident wave and position P

Fourier transform of the distribution of scattering factors

Scattering by numerous atoms



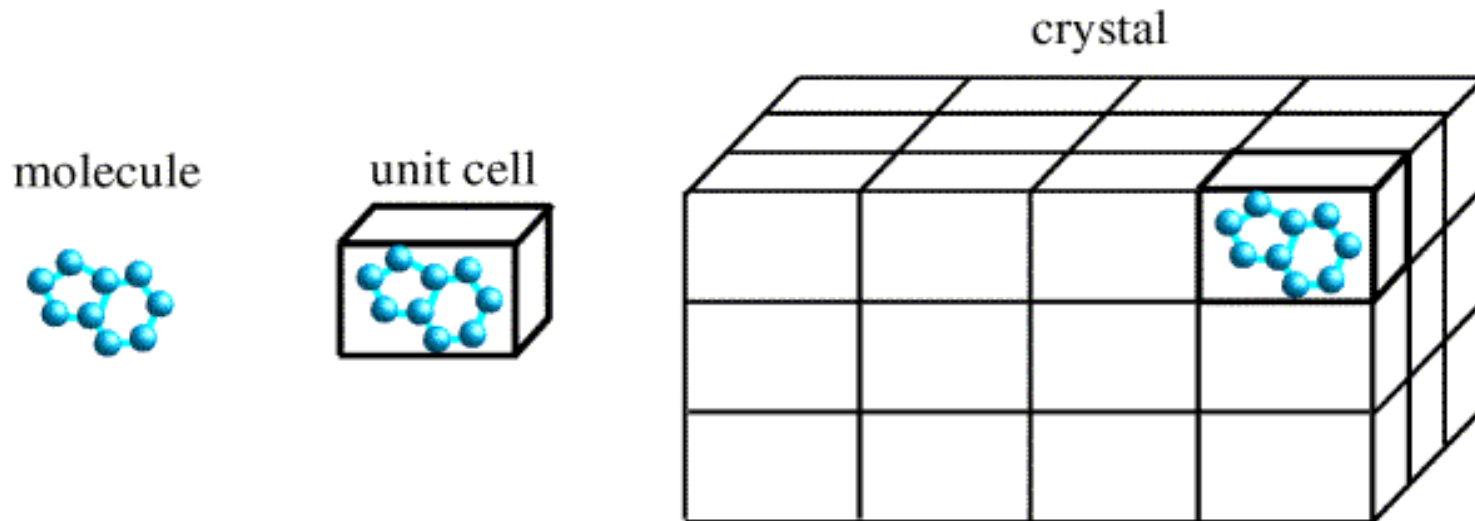
- The structure factor is $F(\vec{s}) = \sum_J f_J \cdot \exp[2i\pi(\vec{s}) \cdot \vec{r}_J]$
 - It is the Fourier transform of the distribution of electron, i.e. the electron density:
$$F(\vec{s}) = \sum_J f_J \cdot \exp[2i\pi(\vec{s}) \cdot \vec{r}_J] = \int_{\text{vol}} \rho(\vec{r}) \exp[2i\pi \vec{r} \cdot \vec{s}] \cdot d\vec{r}$$
 - It is a complex number (amplitude and phase)
- The electron density can be calculated by the reverse Fourier transform:
$$\rho(\vec{r}) = \sum_J f_J \cdot \delta(\vec{r} - \vec{r}_J) = \int_{\text{rec.vol.}} F(\vec{s}) \exp[-2i\pi \vec{r} \cdot \vec{s}] \cdot d\vec{s}$$
 - The detector measures the intensity of the scattered wave
 - This intensity is proportional to the square modulus of structure factor

$$I(\vec{s}) \propto |F(\vec{s})|^2$$

What if the sample is a crystal?



- A crystal can be described by a unit cell
 - Three vector $\vec{a}$, $\vec{b}$, $\vec{c}$ define this unit cell
- Unit cells (identical content) are piled up in the 3 directions of space



What if the sample is a crystal?



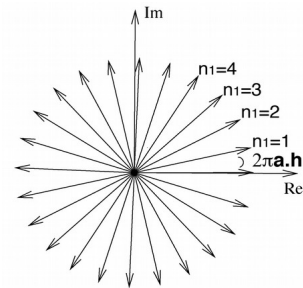
- The general form of the structure factor is:

$$F(\vec{s}) = \int_{\text{vol sample}} \rho(\vec{r}) \exp[2i\pi \vec{r} \cdot \vec{s}] \cdot d\vec{r}$$

- If the sample is a crystal, it can be described as a pile of N_{cell} unit cells

$$F(\vec{s}) = \sum_{n=1}^{N_{\text{cell}}} \int_{\text{vol cell}} \rho(\vec{r} + \vec{r}_n) \exp[2i\pi (\vec{r} + \vec{r}_n) \cdot \vec{s}] \cdot d\vec{r}$$

$$\text{with : } \vec{r}_n = n_1 \cdot \vec{a} + n_2 \cdot \vec{b} + n_3 \cdot \vec{c} \text{ and } \rho(\vec{r} + \vec{r}_n) = \rho(\vec{r})$$



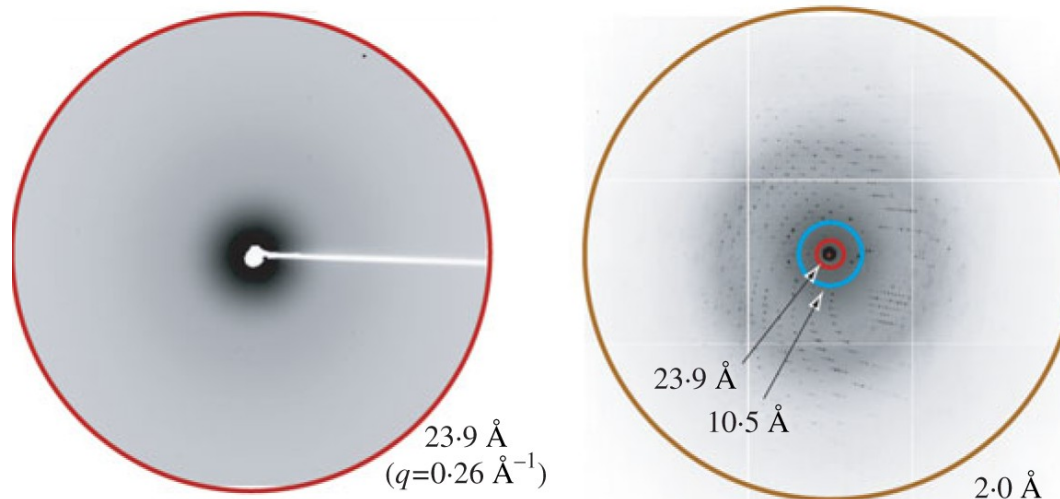
$$F(\vec{s}) = \underbrace{\sum_{n=1}^{N_{\text{cell}}} \exp[2i\pi n_1 \cdot \vec{a} \cdot \vec{s}] \exp[2i\pi n_2 \cdot \vec{b} \cdot \vec{s}] \exp[2i\pi n_3 \cdot \vec{c} \cdot \vec{s}]}_{\text{factor} \approx 0, \text{ except if } \vec{s} \text{ satisfy Laue equations : } \vec{a} \cdot \vec{s} = h, \vec{b} \cdot \vec{s} = k, \vec{c} \cdot \vec{s} = l \Rightarrow \text{factor} = N_{\text{cell}}} \cdot \underbrace{\int_{\text{vol cell}} \rho(\vec{r}) \exp[2i\pi \vec{r} \cdot \vec{s}] \cdot d\vec{r}}_{\text{Fourier transform of electron density of the unit cell}}$$

- There is significant X-ray scattering only in specific, discrete direction => diffraction phenomenon

X-ray scattering by a crystal

- In directions that satisfy Laue equation, the structure factor is the one of the unit cell, multiplied by the number of cells in the crystal.

$$F(\vec{s}) = N_{\text{cell}} \cdot \underbrace{\int_{\text{vol cell}} \rho(\vec{r}) \exp[2i\pi \vec{r} \cdot \vec{s}] \cdot d\vec{r}}_{\text{Fourier transform of electron density of the unit cell}}$$
- The crystal is a signal amplifier, in direction where you have signal: $I(\vec{s}) \propto N_{\text{cell}}^2 \cdot \left(\int_{\text{vol cell}} \rho(\vec{r}) \exp[2i\pi \vec{r} \cdot \vec{s}] \cdot d\vec{r} \right) \cdot \left(\int_{\text{vol cell}} \rho(\vec{r}) \exp[-2i\pi \vec{r} \cdot \vec{s}] \cdot d\vec{r} \right)$



How we get the "image" from a diffraction spectra



- If $\vec{s}$ satisfy the Laue equations $\vec{a} \cdot \vec{s} = h, \vec{b} \cdot \vec{s} = k, \vec{c} \cdot \vec{s} = l$
- $\vec{s}$ is a vector of the lattice, named reciprocal lattice

$$\vec{s} = h \cdot \vec{a}^* + k \cdot \vec{b}^* + l \cdot \vec{c}^* \quad \text{with} \quad \vec{a}^* = \frac{\vec{b} \wedge \vec{c}}{\vec{a} \cdot \vec{b} \wedge \vec{c}}, \quad \vec{b}^* = \frac{\vec{c} \wedge \vec{a}}{\vec{a} \cdot \vec{b} \wedge \vec{c}}, \quad \vec{c}^* = \frac{\vec{a} \wedge \vec{b}}{\vec{a} \cdot \vec{b} \wedge \vec{c}}$$

- Electronic density calculation

$$\rho(\vec{r}) = \sum_J f_J \cdot \delta(\vec{r} - \vec{r}_J) = \int_{\text{rec.vol.}} F(\vec{s}) \exp[-2i\pi \vec{r} \cdot \vec{s}] \cdot d\vec{s}$$



$$\rho(\vec{r}) = \sum_J f_J \cdot \delta(\vec{r} - \vec{r}_J) = \sum_{h,k,l} F(\vec{s}) \exp[-2i\pi \vec{r} \cdot \vec{s}]$$

- A problem ...
 - From the intensity of the wave measured, the amplitude of the structure factor can be calculated
 - The phase information is lost !
- No direct calculation of the electron density can be done from the data collected on the detector

What is a Fourier transform?

- Example of a crystal

$$\rho(\vec{r}) = \sum_J f_J \cdot \delta(\vec{r} - \vec{r}_J) = \sum_{h,k,l} F(\vec{s}) \exp[-2i\pi \vec{r} \cdot \vec{s}]$$

- The electron density is a complex function depending on the nature of your molecule
 - If the molecule is in a crystal, the electron density is periodical
- A way to describe it as a sum of well known functions
 - Sinus or cosinus
 - Discrete Fourier transform

What is the meaning of $F(s)$?



- A parallel with sound
 - The sound can be described as the acoustic pressure as a function of time
 - The Fourier transform is the analysis of the frequencies present in your sound
 - One can describe the sound as a sum of different frequencies
 - The higher frequencies, the more detailed is the sound
 - Parallel with resolution

Go back to electron density



$$\rho(\vec{r}) = \sum_{h,k,l} F(h \cdot \vec{a}^* + k \cdot \vec{b}^* + l \cdot \vec{c}^*) \exp[-2i\pi \vec{r} \cdot (h \cdot \vec{a}^* + k \cdot \vec{b}^* + l \cdot \vec{c}^*)]$$

- The reflection (h,0,0) is the coefficient for or sinusoidal function, the period of which is the a axis
- Higher indices correspond to higher spacial frequencies
- The higher you go, the highest is the resolution

Other particles...

Other particles to probe matter?



- Is photon (electromagnetic wave) the unique probe to see molecule?
- In 1924, Louis de Broglie proposed that all elementary particles can behave both as a wave and as a particle
 - Any particle can be used to probe matter if
 - the associated wave length $\lambda = \frac{h}{p}$ is appropriate
 - It interacts with matter
 - What is the wave length of an elementary particle?
 - Photon (no mass): $E = h\nu = h \frac{c}{\lambda}$, $p = \frac{h\nu}{c}$
with h (Plank constant) = $6.6257 \cdot 10^{-34}$ J.s , p : momentum , ν : frequency
 - Particle (mass $\neq 0$): $E = \frac{1}{2} mv^2$, $p = mv$, $\lambda = \frac{h}{mv}$



Energies and wave length



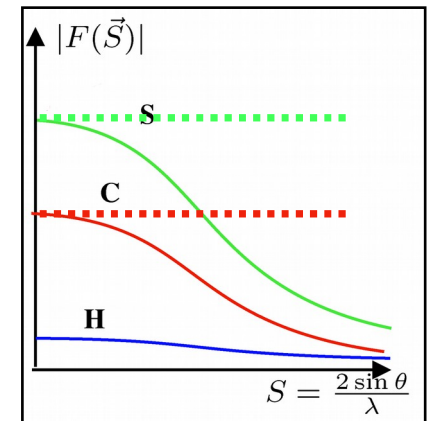
- Electromagnetic waves / photons (1901, Röntgen)
 - Photon energy: $E = h\nu = h \frac{c}{\lambda} \rightarrow 7 \text{ keV} < E < 17 \text{ keV}$ or $1.7 \text{ \AA} > \lambda > 0.7 \text{ \AA}$
- Neutrons (1932, Chadwick)
 - Neutral particle ($m_n = 1.6749 \cdot 10^{-27} \text{ kg}$)
 - $E = \frac{1}{2} m_n v^2$, $\lambda = \frac{h}{m_n v} \rightarrow \lambda = 1.5 \text{ \AA}$ for $v = 2600 \text{ m/s}$ and $E = 3.6 \cdot 10^{-2} \text{ eV}$
- Electrons (1897, Thomson)
 - Negatively charged particle ($q = 1.6 \cdot 10^{-19} \text{ C}$, $m_e = 9.1091 \cdot 10^{-31} \text{ kg}$)
 - $E = \frac{1}{2} m_e v^2$, $\lambda = \frac{h}{m_e v} \rightarrow \lambda = 1.2 \text{ \AA}$ for $v = 6000 \text{ km/s}$ and $E = 100 \text{ keV}$
in practice $100 \text{ keV} < E < 300 \text{ keV}$ and $0.004 \text{ \AA} > \lambda > 0.0009 \text{ \AA}$

- No electromagnetic interaction
 - Penetrate matter easily
- Different type of neutrons
 - Cold neutrons: $E < 0.0038 \text{ eV}$
 - Thermal neutrons: $0.0038 \text{ eV} < E < 0.5 \text{ eV} \Rightarrow$ used for diffraction and SANS experiment
 - Epithermal or resonance neutrons: $0.5 \text{ eV} < E < 100 \text{ keV}$
 - Fast neutrons: $100 \text{ keV} < E < 10 \text{ MeV}$
 - Relativistic neutrons: $E > 10 \text{ MeV}$
 - Elastic interaction with nucleus: $E < 1 \text{ MeV}$
 - Inelastic scattering by nucleus: $E > 1 \text{ MeV}$
 - Induced fission

Differences and similarities with X-rays



- Neutrons interact with nucleus
 - We observe nucleus and not electron density
 - Proton can be observed
- Nuclei are very small (10^{-15} m) compare to the wave length (10^{-10} m)
 - Quasi a point
 - Impact on the atomic form factor
 - ♦ Spherical electron density $f_{\text{at}}(\vec{s}) = f_{\text{at}}(|\vec{s}|) = 2 \int_{r=0}^{\infty} \rho(r) \sin \frac{(2\pi sr)}{s} dr$
 $f_{\text{at}}(0) = Z$
 - For neutron $f_{\text{nuc}}(s) = \sigma_{\text{scat}}$
 - No decrease with s or resolution

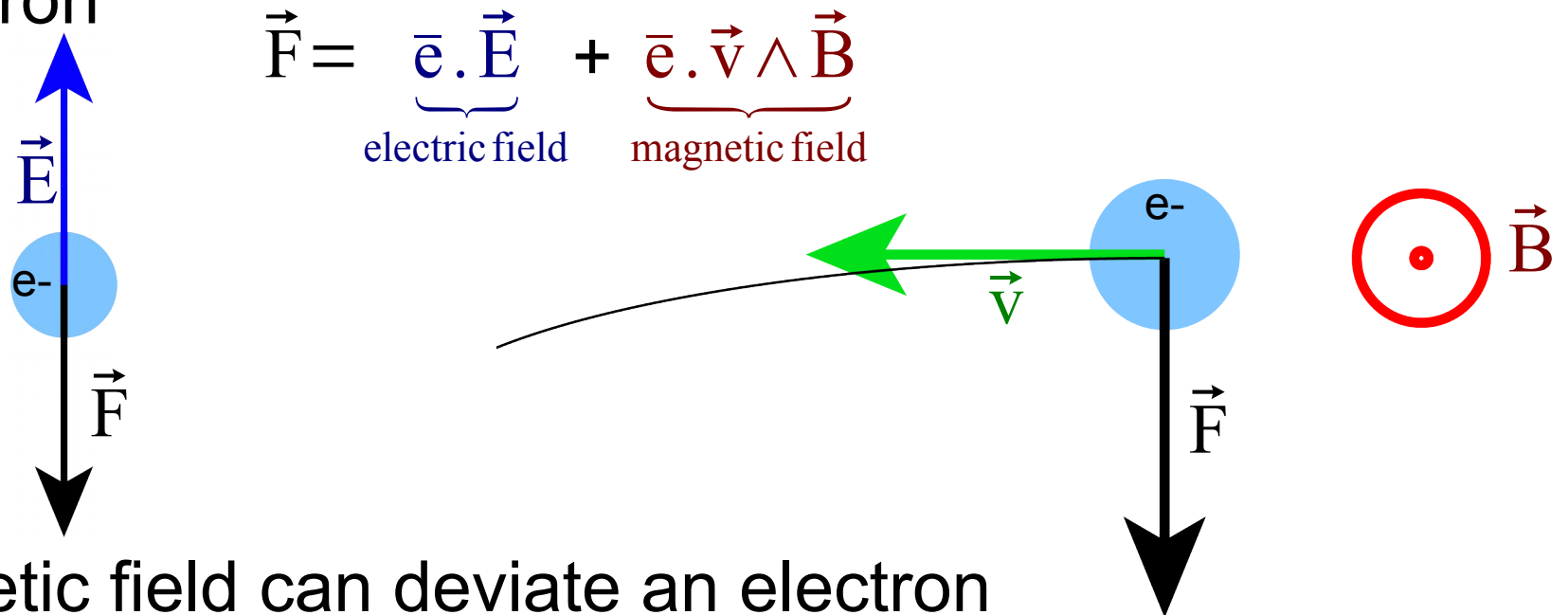


- No lens available for neutrons
 - Diffraction spectra
 - If you manage to measure the amplitude and to get the phase of the wave for each reflection on the detector
 - A Fourier transform enable to calculate the distribution of nucleus of your molecule
- $$\sum_J \sigma_J \cdot \delta(\vec{r} - \vec{r}_J) = \sum_{h,k,l} F(\vec{s}) \exp[-2i\pi \vec{r} \cdot \vec{s}]$$
- Scattering cross section for H and D are very different
 - Deuteration can be useful

- Charged particle ($q = 1.6 \cdot 10^{-19} \text{ C}$, $m_e = 9.1091 \cdot 10^{-31} \text{ kg}$)
- Strongly interact with matter
 - Elastic interaction with
 - atomic electron (small energy transfer)
 - Nucleus (Rutherford scattering)
 - “Sense” the electrostatic potential

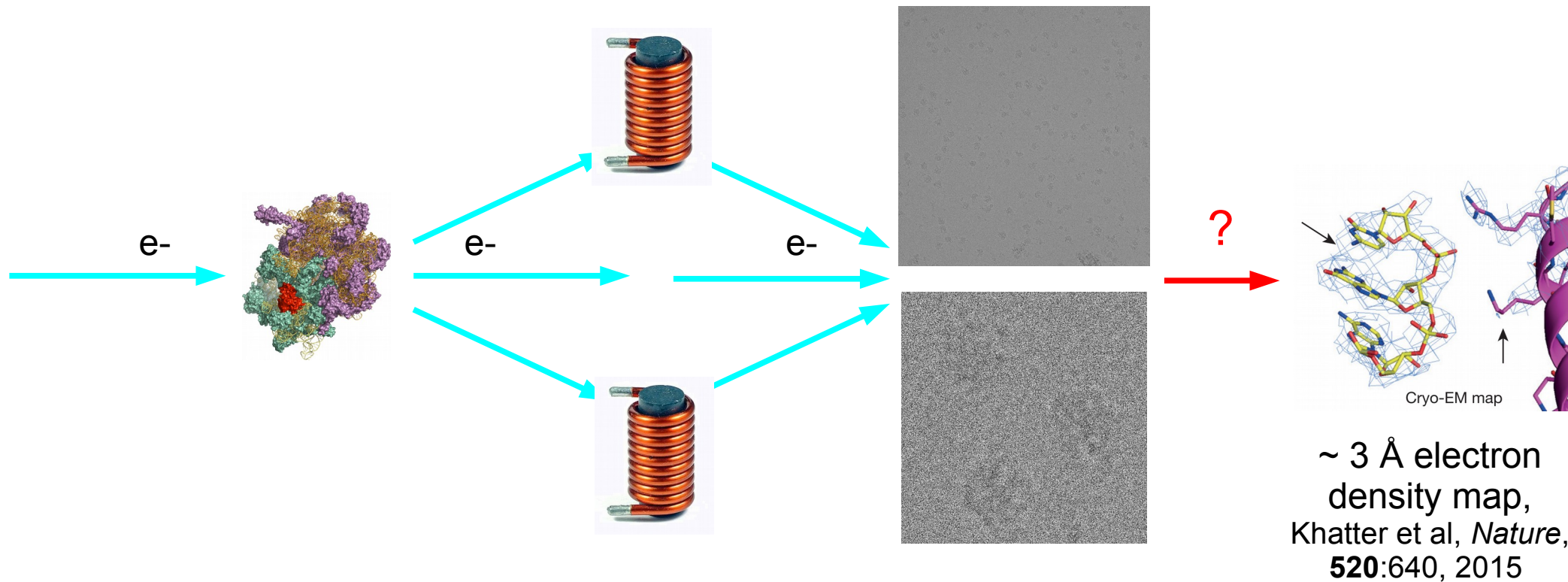
Imaging or diffraction?

- Both the electric and the magnetic field induce force on the electron



- A magnetic field can deviate an electron
- A lens can be made for electrons with electro-magnets
 - First one made in 1929 (Ruska & Knoll)

Direct imaging of the molecule



To conclude



- X-rays & Neutrons
 - Diffraction $\rightarrow F(hkl) + \varphi(hkl) \rightarrow$ electron density map
 - Small angle scattering $\Rightarrow$ ab-initio modeling (fit with scattering curve)
- Electrons
 - Direct imaging $\rightarrow$ electron density map
 - Diffraction is also possible
- NMR
 - Gather structural information (local interatomic distance, ...) $\Rightarrow$ search for models that satisfy the data.