# How to make periodic objects look non-periodic and how to find their structure from the diffraction pattern, using a real space method

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In the first part, I describe some methods that produce the diffraction pattern (or hologram) of a single molecule, even if it is part of a crystal.

1. Local emission and local absorption holograms.
2. Low energy electron diffraction from a crystal with a partially occupied overlayer.
3. Diffraction from a crystal that contains two closely related molecules. One example is a protein crystal where some fraction of the molecules is in some activated state.
4. Diffraction from a crystal using partially coherent X-rays.

In each one of these cases the damage is distributed over the whole crystal. Each one of the methods is sensitive only to local (short range) order. Apart from 1., the diffraction pattern has high contrast, therefore a good signal to noise ratio. The main interest is to use those methods for macromolecular imaging.

In the second part, I will introduce our real space, "holographic" method for the recovery of electron densities from diffraction patterns. The program EDEN, based on the method, is able to tackle crystallographic "phase recovery" in essentially all its manifestations. Low resolution, high resolution, "phase extension", solvent target, MIR, MAD, NCS, etc. We have used the program for the determination of accurate electron densities of Cu2O, as well as for the 5A resolution map of the ribosome, and for lots in between. The main relevance of EDEN for the conference is that the program was also used (unmodified!) for the determination of the light induced changes in the "Photoactive Yellow Protein" from its oversampled, continuous diffraction pattern (method # 3 above). Needless to say that the results were near perfect. We have a lot of practical experience with the accuracy and convergence properties of our program.