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Motif Search in Electron Tomography

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1. INTRODUCTION

Cryoelectron tomography aims to act as an interface between two levels of 3D imaging: *in vivo* cell imaging and techniques achieving atomic resolution (e.g., X-ray crystallography). This most likely will happen through a computational motif search by mapping structures with atomic resolution

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into lower-resolution tomograms of cells and organelles. There exist a large variety of pattern recognition techniques in engineering, which can perform different types of motif search. This chapter will focus on cross-correlation techniques, which aim to identify a motif within a noisy 3D image (the tomogram or the 3D reconstruction). Generally, the success of the cross-correlation approach depends on the resolution of the tomograms, the degree of corruption of the motif by noise as well as the fidelity with which the template matches the motif. For maximal detection signal, the template should have the same impulse response as the motif, which in this case is the macromolecule sought. Since the noise in the tomogram cannot be significantly decreased after data recording, the task of designing an accurate template reduces to the determination of the precise parameters of the image recording conditions, so that the searched motifs may be modeled as accurately as possible.

The range of algorithms available in electron microscopy for the computational search of different motifs is still significantly wider for 2D than for 3D images. The obvious reason is that only lately the quality of the tomograms has improved to a resolution where such a search is becoming sensible. A variety of these motif search algorithms, which were developed for high-throughput needs of single-particle cryoelectron microscopy, were compared, and their performance was assessed comprehensively (Zhu *et al*., 2004). Among those 2D pattern recognition techniques, the locally normalized cross-correlation approach proved to be the most robust and reliable technique (Roseman, 2004).

The feasibility of these cross-correlation based motif search techniques has also been demonstrated on 3D data and led to the unambiguous detection of known macromolecular structures encapsulated in vesicles (Frangakis *et al*., 2002). Furthermore, it has been demonstrated that template-matching techniques also perform reasonably well on tomograms of organelles, as shown in the localization of ryanodine receptors attached to the membrane of sarcoplasmic reticulum vesicles (Rath *et al*., 2003). However, there is still a large need and potential for improvements to develop good, quantitative detection schemes that will allow a comprehensive evaluation and cross-validation of the results.

In this chapter, a short overview of the cross-correlation techniques will be given, followed by feasibility studies with synthetic data. Some applications on real data will be presented, followed by a brief discussion on the potential and perspectives of the motif search approaches.

2. CREATION OF TEMPLATES

The generation of the templates is a difficult task, since ideally they should look as similar as possible to the motif contained in the tomogram. High-resolution structures derived from various techniques can be modi-