Representation Theoretic Patterns in Three-Dimensional Cryo-Electron Microscopy II—The Class Averaging Problem

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Abstract In this paper we study the formal algebraic structure underlying the intrinsic classification algorithm, recently introduced in Singer et al. (SIAM J. Imaging Sci. 2011, accepted), for classifying noisy projection images of similar viewing directions in three-dimensional cryo-electron microscopy (cryo-EM). This preliminary classification is of fundamental importance in determining the three-dimensional structure of macromolecules from cryo-EM images. Inspecting this algebraic structure we obtain a conceptual explanation for the admissibility (correctness) of the algorithm and a proof of its numerical stability. The proof relies on studying the spectral properties of an integral operator of geometric origin on the two-dimensional sphere, called the localized parallel transport operator. Along the way, we continue to develop the representation theoretic set-up for three-dimensional cryo-EM that was initiated in Hadani and Singer (Ann. Math. 2010, accepted).

Keywords Representation theory · Differential geometry · Spectral theory · Optimization theory · Mathematical biology · 3D cryo-electron microscopy

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1 Introduction

The goal in cryo-EM is to determine the three-dimensional structure of a molecule from noisy projection images taken at unknown random orientations by an electron microscope, i.e., a random Computational Tomography (CT). Determining three-dimensional structures of large biological molecules remains vitally important, as witnessed, for example, by the 2003 Chemistry Nobel Prize, co-awarded to R. MacKinnon for resolving the three-dimensional structure of the Shaker K+ channel protein [1, 4], and by the 2009 Chemistry Nobel Prize, awarded to V. Ramakrishnan, T. Steitz and A. Yonath for studies of the structure and function of the ribosome. The standard procedure for structure determination of large molecules is X-ray crystallography. The challenge in this method is often more in the crystallization itself than in the interpretation of the X-ray results, since many large molecules, including various types of proteins, have so far withstood all attempts to crystallize them.

Cryo-EM is an alternative approach to X-ray crystallography. In this approach, samples of identical molecules are rapidly immobilized in a thin layer of vitreous ice (this is an ice without crystals). The cryo-EM imaging process produces a large collection of tomographic projections, corresponding to many copies of the same molecule, each immobilized in a different and unknown orientation. The intensity of the pixels in a given projection image is correlated, [5], with the line integrals of the electric potential induced by the molecule along the path of the imaging electrons (see Fig. 1). The goal is to reconstruct the three-dimensional structure of the molecule from such a collection of projection images. The main problem is that the highly intense electron beam damages the molecule and, therefore, it is problematic to take projection images of the same molecule at known different directions as in the case of classical CT1. In other words, a single molecule is imaged only once, rendering an extremely low signal-to-noise ratio (SNR), mostly due to shot noise induced by the maximal allowed electron dose.

1.1 Mathematical Model

Instead of thinking of a multitude of molecules immobilized in various orientations and observed by an electron microscope held in a fixed position, it is more convenient to think of a single molecule, observed by an electron microscope from various orientations. Thus, an orientation describes a configuration of the microscope instead of that of the molecule.

Let \((V, (\cdot, \cdot))\) be an oriented three-dimensional Euclidean vector space. The reader can take \(V\) to be \(\mathbb{R}^3\) and \((\cdot, \cdot)\) to be the standard inner product. Let \(X = \text{Fr}(V)\) be the oriented frame manifold associated to \(V\); a point \(x \in X\) is an orthonormal basis \(x = (e_1, e_2, e_3)\) of \(V\) compatible with the orientation. The third vector \(e_3\) is distinguished, denoted by \(\pi(x)\) and called the viewing direction. More concretely, if we identify \(V\)

1We remark that there are other methods like single-or multi-axis tilt EM tomography, where several lower dose/higher noise images of a single molecule are taken from known directions. These methods are used for example when one has an organic object in vitro or a collection of different objects in the sample. There is a rich literature for this field starting with the work of Crowther, DeRosier and Klug in the early 1960s.