TR-2008011: Contrast Transfer Function Correction in Electron Microscopy

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Contrast Transfer Function Correction in Electron Microscopy

Second Exam: Research Overview Report

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Abstract

The process of object reconstruction from its projections is widely used in many fields. One of the applications of reconstruction from projections is in electron microscopy. Various methods have been developed for correction of blurring that occurs when the projections are obtained by a real instrument. As the attainable resolution increases, new issues become apparent and need to be taken into account in the imaging model. In this review we concentrate on the contrast transfer function and its impact on the quality and usefulness of the reconstructions from images obtained by today’s electron microscopes.
1 Introduction

The process of object reconstruction from its projections is widely used in many fields. A projection of an object is a set of line integrals obtained along parallel lines going through the object that are perpendicular to a projection image plane. A collection of such projections obtained from different angles around the object is called projection data. The process of reconstruction uses this projection data to obtain an approximation of the original object.

One of the applications of reconstruction from projections is in electron microscopy. Electron microscopy uses electrons to create the image, as opposed to traditional microscopy that uses light. Electron microscopy makes possible the imaging of structures that are too small to be viewed with a light microscope. Today modern electron microscopes can reach a resolution of $1 - 2 \text{Å}$. Reconstructions from electron microscopic data are used in a wide range of natural sciences: biology, chemistry, medicine, material sciences, etc. For a brief overview of applications in different areas see Jensen and Briegel [10] and Midgley et al. [14]. General recent reviews of issues related to electron microscopic reconstruction are provided by Fernandez et al. [7], Leis et al. [13], Midgley et al. [14].

The problem of reconstruction of 3D objects imaged by an electron microscope from their 2D projections has been approached by many researchers. Some of the issues to tackle are (1) very low signal to noise ratio in obtained images, on the order of 0.1, (2) blurring that has to be estimated and then corrected and (3) non-uniformly distributed projection directions. In this

\[ 1\text{Ångström}, \text{ a unit of measurement } 1\text{Å} = 1 \times 10^{-10} \text{meter}. \]
review we discuss literature relevant only to the second of the above issues. Various methods have been developed for correction of blurring that occurs when the projections are obtained by a real instrument. See Herman et al. [9], Sorzano et al. [17] and references therein for a partial overview of some of the reconstruction methods). In Section 3 we will briefly go over just a few such methods.

As the attainable resolution increases, new issues become apparent and need to be taken into account in the imaging model. In this review we concentrate on the contrast transfer function and its impact on the quality and usefulness of the reconstructions from images obtained by today’s electron microscopes.

1.1 Definitions

An arbitrary object, \( v \), is a function of three variables with an origin centered ball as its support.

A projection operation is a mapping of \( v \) to a two dimensional array whose entries correspond to line integrals through the volume \( v \) (Figure 1). The images obtained by an electron microscope, called micrographs, are approximations of 2D ideal projections of 3D structures being imaged. We call a projection ideal if the 2D image is a collection of values of line integrals of a 3D object obtained along a set of parallel lines that are perpendicular to a projection image plane. Factors such as lens aberration, electron scattering and defocusing result in micrographs that are not representing true mathematical projections. We will refer to projections that are affected in this way
Figure 1: Projection generation process: The object is rotated by an angle $\Theta = (\theta_1, \theta_2)$ and the projection of the object is recorded on a projection plane perpendicular to the $t$-axis.

as corrupted projections. The images produced by an electron microscope resemble the convolution of the ideal projection with a point spread function (PSF). Point spread function, or blurring, is the response of an imaging system to a single point of activity. Figure 2 illustrates a single projection of a sphere. The first column shows an ideal projection (with no blurring) and the second column shows a corrupted projection that has been blurred by a point spread function whose Fourier transform is shown in the third column.
A layer of the object is defined as a flat component of the object parallel to the projection plane with some thickness.

The 3D object will be also referred to as biological object or specimen.

1.2 Mathematical notation

In this section we introduce the mathematical notation used throughout the rest of this review.

In general lower case letters in names of functions always refer to func-
tions in the spatial domain. Specifically, we use:

- \( v \) the 3D object that is being reconstructed;
- \( p_\Theta \) an ideal projection obtained from direction \( \Theta \);
- \( p \) ideal projection data - a collection of all ideal projections;
- \( g_\Theta \) a corrupted projection obtained from direction \( \Theta \);
- \( g \) corrupted projection data - a collection of all corrupted projections;
- \( h \) a point spread function.

We use upper case letters to denote Fourier transforms of the functions mentioned above. Specifically, if \( \mathcal{F} \) means application of a Fourier transform, then \( V = \mathcal{F}v, P_\Theta = \mathcal{F}p_\Theta, P = \mathcal{F}p, G_\Theta = \mathcal{F}g_\Theta, G = \mathcal{F}g, H = \mathcal{F}h \), where \( H \) has form specified by (5) in Section 2.

In the spatial domain, we use \((s_1, s_2, t)\) to denote a point of an object being reconstructed and \((s_1, s_2)\) to denote a point in a projection from a given direction. In the Fourier domain, we use \((f_1, f_2)\) to denote spatial frequency variables corresponding to \((s_1, s_2)\) and \(n\) to denote the Fourier space equivalent to the direction variable, \(\Theta\). \(f_1\) and \(f_2\) are real numbers and \(n\) is an integer.

1.3 Geometry of data collection

The projection data can be collected in several different ways for reconstruction from electron microscopic projections. The two methods relevant to the material in the rest of this review are: single axis rotation (also referred to as
the *tomographic reconstruction problem* ) and arbitrary angle (also referred
to as the *single particle reconstruction problem*), see Carazo *et al.* [2].

In *single axis rotation* a unique object is imaged and then reconstructed.
A specimen is placed on a *tilt stage* inside a microscope. The stage together
with the specimen is rotated around a single axis in small angular increments
and projections are taken for the *tilt angles* usually ranging from $-70^\circ$ to
$+70^\circ$ degrees. The projection directions are known.

In an *arbitrary angle rotation* we assume that multiple structurally identi-
cal copies of the same specimen are available. Thousands of these specimens
can be then placed on a single stage in random orientations. When projection
is taken, the images from different views are obtained. This is equivalent to
taking projections from random directions that can be thought of as points
on the 3D sphere. In this case we need two angles in order to describe any
projection direction, hence $\Theta = (\theta_1, \theta_2)$ and $n = (n_1, n_2)$, where $n_1$ and
$n_2$ are integers. The projection directions need to be determined prior to
reconstruction.

### 1.4 Image formation model in transmission electron microscopy

A single 2D ideal projection of a 3D rotated object $v_{\theta, \varphi}$ is defined by

$$p_{\Theta} (s) = p_{\theta_1, \theta_2} (s_1, s_2) = \int_{-\infty}^{+\infty} v_{\theta_1, \theta_2} (s_1, s_2, t) \, dt .$$  

(1)

The blurring of the imaging system in electron microscopy can be spec-
ified by a function \( h(s_1, s_2, t) \), referred to as the point spread function, that defines the corrupted projection as

\[
g_{\Theta}(s) = g_{\theta_1, \theta_2}(s_1, s_2) = \int_{-\infty}^{+\infty} \left[ \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} v_{\theta, \phi}(s_1', s_2', t) h(s_1 - s_1', s_2 - s_2', t) \, ds_1' \, ds_2' \right] \, dt \tag{2}
\]

### 1.5 Back-projection

One of the methods used in reconstruction from projections is back-projection. It can be thought of as smearing back collected projections.

Consider the following operators:

- \( \mathcal{P} \) a projection operator,
- \( \mathcal{B} \) a back-projection operator,
- \( \mathcal{D} \) a deblurring operator (this deblurring compensates for errors due the back-projection process).

For noiseless mathematically ideal projections, it is the case that \( v = \mathcal{DBP}v \), where \( v \) is the object being reconstructed, see Radermacher [16].

### 2 Contrast transfer function.

The contrast transfer function (CTF) is the Fourier transform, \( H_{CTF} \), of the point spread function \( h \) in (2) and it is of the form

\[
H_{CTF}(f, t) = (1 - \alpha) \sin(D(f, t)) - \alpha \cos(D(f, t)), \tag{3}
\]

\[
D(f, t) = 2\pi \lambda f^2 \left( -\frac{\Delta d(t)}{2} + \frac{\lambda^2 f^2 C_s}{4} \right) \tag{4}
\]
Figure 3: An example of the contrast transfer function: (a) pure inverse of the point spread function, $H_{CTF}(f,t)$, (b) dampened version of the CTF, $H(f,t)$.

where $\alpha$ is a fraction of the amplitude contrast, $\lambda$ is electron wavelength, and $D(s,t)$ is a phase shift produced by the lens aberration and defocusing. The graph of a 1D contrast transfer function in this form is shown in Figure 3a. In practice, this model does not represent adequately what happens during the image formation process. The additional effects of finite source size, energy spread, resolution limiting effects of the film, scanner, and drift can be described by so called *envelope functions* (see Penczek et al. [15] and references therein) which dampen the values for higher frequencies. Kazantsev et al. [12] use the following as the model of CTF that includes the effects of envelope functions:

\[
H(f,t) = H_{CTF}(f,t) \cdot E_{spat}(f,t) \cdot E_{temp}(f) 
\]  

\[
E_{spat}(f,t) = e^{-\pi^2 q_0^2 (C_s \lambda^3 f^3 - \Delta d(t) \lambda f)^2} 
\]  

\[
E_{temp}(f) = e^{-\left(\frac{1}{2} F_s \lambda f^2\right)^2} 
\]

where the parameters involved are:
\[ \alpha \] is a fraction of the amplitude contrast,

\[ f \equiv \sqrt{f_1^2 + f_2^2} \] is a spatial frequency,

\[ \lambda \] is the electron wavelength,

\[ C_s \] is the lens spherical aberration coefficient,

\[ \Delta d (t) \] is the value of the defocus, which depends on the distance of a point from the electron source,

\[ q_0 \] is the size of the electron source,

\[ F_s \] is the lens focal spread coefficient.

The graph of a contrast transfer function including the envelope function is shown in Figure 3b. From now on, we will refer to this complete model as a contrast transfer function (CTF).

A contrast transfer function alters various frequencies of the true signal by changing the sign of some frequencies, altering the amplitude of some, and setting some to zero. The high frequencies are completely removed by the dampened version of the CTF (see Figure 3b). The results of these changes in the spatial domain are inverted contrast, decreased contrast of large areas, edge enhancement and appearance of fringes along borders [4].

As long as the contrast transfer function affects each layer of an object in the same way it does not cause a problem in reconstruction since the blurring and integration commute and one can deblur the projections and then reconstruct.
Distance dependent contrast transfer function. In some applications, the contrast transfer function is distance dependent. In (4-6), $t$ depends on the distance of the point in the object from the electron source (see Figure 4). If this dependence is ignored only a single layer of the specimen is corrected exactly; others are corrected approximately. The effects of distance dependence on CTF blurring become more significant as the desired resolution of reconstructions increases and when larger specimens are imaged. As the resolution attainable by electron microscopes increases it becomes crucial that we compensate appropriately for the CTF effects rather than assume that the blurring is the same for each layer, otherwise we cannot take full advantage of the higher resolution.

The problem of distance dependence can be considered in two aspects:
1) thin specimens with large area that are imaged using single axis rotation and 2) large, thick specimens. In the first case the part of the particle closer to the electron source is blurred by a different function than the part farther away from the electron source (Figure 5 in Section 4). The projection image can be divided, though, into areas that have been affected only by a single blurring function. Hence the correction can be performed one such area after another. Examples of algorithms that attempt to solve this problem can be found in Fernandez et al. [6] and Winkler and Taylor [19]. In the second case one can think of the specimen as a collection of layers each being blurred by a different function (Figure 6 in Section 4). The projection image is the summation of all the layers and there is no way of correcting just for a single CTF. The projection has to be somehow corrected for all different CTFs that caused blurring during imaging process. Examples of algorithms that attempt to solve this problem can be found in Dubowy and Herman [4], Jensen and Kornberg [11] and Kazantsev et al. [12].

3 Current CTF correction methods

The corruption of projection data by the contrast transfer function significantly limits achievable resolution in the reconstruction of a 3D object. The issues involved in CTF elimination are estimation of parameters in the equation for CTF (see for example Fernandez et al. [6]) and then correction of collected data sets followed by a reconstruction or reconstruction that incorporates correction. In this review we concentrate on methods of CTF
correction; we do not discuss any methods for CTF determination.

Many methods have been developed for removal of the results of CTF. Some of them attempt to filter the CTF out of the projection data in order to obtain approximation of ideal projections, so that well established reconstruction algorithms from computerized tomography (CT) can be used. Frank and Penczek [8] use Wiener filtering to compensate for the effects of CTF in the data sets. Sorzano et al. [18] iterate over data with the aim of reaching projections that would have been obtained by a blur-free microscope. Fernandez et al. [6] and Winkler and Taylor [19] apply distance dependent correction to thin specimens. Dubowy and Herman [4] apply distance dependent filtering to a projection data set obtained from single axis rotation. Others incorporate the effects of CTF into reconstruction algorithms. Zubelli et al. [21] introduce effects of the CTF into reconstruction equations. Jensen and Kornberg [11] modified the weighted back-projection method to incorporate distance dependent CTF correction. A brief overview with references to different techniques is provided in the recent paper by Sorzano et al. [17]. The numerous methods of correction as well as their variety suggest that there is still no agreed upon standard for CTF correction methodology in electron microscopy.

In the remainder of this section we will briefly summarize some of the existing techniques that filter CTF ignoring its distance dependence.
3.1 Phase flipping

*Phase flipping* is a simple method of CTF correction that ensures contrast to be consistent at all spatial frequencies (see, for example, Zubelli *et al.* [21]). It involves multiplying the Fourier transform of a corrupted projection by the sign of the CTF. It corrects the collected data by making the CTF values positive at all frequencies, since one of the side effects of the CTF is to alter the sign of projection data for some frequencies. It does not correct data for invalid amplitude. It does not attempt to retrieve frequencies that have been zeroed by the CTF.

Let $G_\Theta(f)$ denote the value at frequency $f$ of the projection obtained from direction $\Theta$ and let $H_\Theta(f)$ be the value of the contrast transfer function at the same frequency. The corrected projection data is defined by

$$\bar{G}_\Theta(f) = \begin{cases} 
G_\Theta(f) & \text{if } H_\Theta(f) \geq 0 \\
-G_\Theta(f) & \text{if } H_\Theta(f) < 0 
\end{cases}$$  \hspace{1cm} (8)

This very simple method of correction is sometimes sufficient to produce biologically useful results, see Sorzano *et al.* [18].

3.2 Wiener filtering

Wiener filtering has been adapted to correction of CTF blurring by, for example, Fernandez *et al.* [6] and Frank and Penczek [8]. Wiener filtering is used in image processing for amplitude correction in such a way as to reduce the level of noise amplification. Simple multiplication of the data by
the multiplicative inverse of the CTF is not possible for two reasons: (1) The inverse does not exist at the zeros of the CTF; (2) When the signal to noise ratio is very low (in electron microscopy it can be as low as 0.1), multiplication by the inverse when CTF is very close to zero amplifies the noise. Standard application of a Wiener filter cannot retrieve frequencies for which the CTF vanishes, but it handles the cases for which CTF is near zero. It also takes care of the sign correction.

The Wiener filter is a more powerful when multiple projection sets are available, each with a different value of the contrast transfer function. In this case inverse filtering can be used to recover some of the frequencies for which at least one of the CTF’s is not zero. In the simplest case of two projection data sets we have

\[ G_1 = H_1 V + N_1 \]
\[ G_2 = H_2 V + N_2 \]

where \( G_1 \) and \( G_2 \) are the Fourier transforms of two projection sets corrupted by \( H_1 \) and \( H_2 \) respectively, \( V \) is the Fourier transform of the imaged object and \( N_1 \) and \( N_2 \) are Fourier transforms of noise in the projections. Then the Wiener-like filters proposed by Frank and Penczek [8] are

\[ H_i^+ = \frac{H_i^*}{|H_1|^2 + |H_2|^2 + S_{N_i}/S_V} \]  \( (9) \)

in which * denotes the complex conjugate of \( H_i \) and \( S_{N_i} \) and \( S_V \) are power
spectra of noise and imaged volume, respectively.

If only one projection data set is available, (9) has only one $|H|^2$ term in the denominator. In such a case the frequencies for which $H$ is zero cannot be retrieved.

3.3 Iterative methods

Chahine’s method. Chahine’s method is an iterative way of solving systems of linear equations of the form $Mx = b$, where $x, b \in \mathbb{R}^J$ and $M$ is a $J \times J$ matrix for some integer $J$. The algorithm is guaranteed to converge to a solution under some specific conditions.

Zubelli et al. [21] use the method to solve the system for which $M = BH^T\mathcal{H}\mathcal{P}$, $x = v$ and $b = BH^Tg$ where $\mathcal{P}$ and $B$ are projection and back-projection operators, $H$ is the CTF operator, $g$ is the projection data, $v$ is the imaged volume and superscript $^T$ denotes adjoint. The authors reformulate the problem of reconstruction in such a way that the Chahine’s method for solving systems of linear equations becomes applicable. The algorithm starts with an initial guess of an object and iteratively improves it, reaching an estimate of the 3D object being imaged. The authors demonstrated experimentally the advantage of their method over simple phase flipping or reconstruction with no CTF correction at all.

Iterative data refinement. The iterative data refinement family of algorithms is used widely throughout different applications in which reconstruction from projections is performed. Sorzano et al. [18] proposed an
algorithm of this kind that, given a set of CTF corrupted projections, iterates over data and refines it in each step with the ultimate goal of reaching projection data set that would be collected by an ideal device. This process approximates ideal projections that are free of CTF corruption, which then can be used in any reconstruction procedure. The well-established iterative data refinement methodology guarantees convergence under certain conditions, but even when not all of those conditions are satisfied, the iterations are known to improve the experimentally obtained data.

4 Approaches to solving the distance dependent problem

The methods described in the previous section all assume that each layer of the specimen is convolved with the same contrast transfer function. Since, in fact, the contrast transfer function is distance dependent, only a single layer of the specimen is corrected exactly; others are corrected approximately. This decreases attainable resolution of the reconstructed object.

The problem of distance dependence needs to be addressed in the reconstruction of thin, large area specimens when tilt series projections are taken. Figure 5 illustrates the blurring process in such projections. Examples of solutions to distance dependent blurring have been proposed by Winkler and Taylor [19] and Fernandez et al. [6]. The support with the specimen is tilted around a single axis of rotation and projections are taken for the tilt angles usually ranging from $-70^\circ$ to $+70^\circ$ degrees. The image that results from
Figure 5: Distance dependent CTF for tilted projections. The projection can be divided into strips parallel to the tilt axis that can be thought of as blurred by a fixed CTF.

any projection can be divided into strips parallel to the tilt axis that can be considered as blurred by a fixed CTF function. Theoretically, within each of the strips the CTF is still varying, but if the strips are narrow enough it can be considered as fixed. Each such strip can be corrected with appropriate values of the deblurring function and then reconstruction can be performed.

In the case of large, thick specimens the correction for CTF blurring is more complicated. The projection image results from integration through
many layers, each blurred by a different CTF function. Figure 6 illustrates the projection process. The correction has to be different than for thin specimens.

Two types of approaches have been taken in the literature: (1) Develop new reconstruction algorithms that can be applied directly to the projection data that has been corrupted in a distance-dependent fashion. (2) Develop correction techniques that can be applied to the corrupted projection data.
and obtain approximations to the ideal projection, and then apply established reconstruction algorithms to the corrected data.

In this section we present these approaches by discussing, for each, a paper that uses it, as well as a very recent paper that shows their mathematical equivalence in the ideal case of noiseless, infinitely many projections. We will also discuss similar problems in areas other than electron microscopy (see Section 4.4).

4.1 Defocus-gradient corrected back-projection

The defocus-gradient corrected back-projection (DGCBP) belongs to the first class of correction methods: it incorporates correction for distance dependent CTF into the reconstruction algorithm.

Jensen and Kornberg [11] suggested a modification to the weighted back-projection algorithm that is frequently used in reconstruction from electron micrographs, see Radermacher [16]. The projection data are collected from arbitrary angles. The essence of this method is to perform correction of projection images for CTF appropriate to different layers of the particle in each back-projection step. This guarantees that each layer of the reconstructed volume is corrected for the CTF appropriate for its distance from the electron source - hence we can consider this part of a reconstruction to be a valid signal. Each layer of the reconstructed volume contains also data that came from other layers and that contributes to noise in a reconstructed volume. The step by step description of this method is provided in Algorithm 1 and the schematic illustration in Figure 7.
Figure 7: Schematic explanation of the DGCBP algorithm. A particle is divided into hypothetical layers $A_1$, $A_2$, $A_3$ with the assumption that within each layer the CTF can be considered to be the same. The values of the CTF in layers $A_1$, $A_2$, $A_3$ are $C_1$, $C_2$, $C_3$ respectively. During the correction process, each projection is duplicated several times (three in the example) and each copy is corrected for CTF corresponding to one of the layers of the particle. Then layers of a back-projection body are filled with data from appropriately corrected copy of the projection.

This method assumes that superposition of corrected data and mis-corrected data enhances the appropriately corrected signal while suppressing the noise from mis-corrected layers. As the number of layers increases, the reconstruction should be more accurate. Kazantsev et al. [12] provided mathematical analysis of the DGCBP algorithm as the number of layers
Algorithm 1 DGCBP (with example referring to Figure 7)

1: for all projection directions do
2:   divide the object into hypothetical layers (three layers $A_1$, $A_2$ and $A_3$ shown) and determine the CTF appropriate for each layer (CTFs $C_1$, $C_2$ and $C_3$ shown)
3:   obtain a micrograph (it will have data corrupted by different CTFs for different layers)
4:   make as many copies of the micrograph as there are layers (3 in this example)
5:   correct each copy of the micrograph by a different CTF
6:   backproject data filling each voxel in the back-projected body with data from appropriately corrected micrograph
7: end for

goes to infinity.

4.2 Frequency distance relation

The frequency-distance relation (FDR) based method belongs to the second class of correction methods: it approximates ideal projections based on corrupted projection data sets.

The algorithm based on the frequency distance relation was introduced to electron microscopy by Dubow and Herman [4] based on a method of Xia et al. [20] proposed for a different application, to be discussed in Subsection 4.4.1. Such methods are based on a stationary phase approximation that provides a frequency distance relation for the inverse filter in the case of reconstructions of 2D objects from distance dependently blurred 1D projections, see Edholm and Lewitt [5] and Xia et al. [20]. Dubow and Herman [4] adapted this approach to 2D projections of 3D objects obtained from single axis rotation. Such an approach corrects data collected by an imper-
fect device and approximates ideal projections that would be obtained by a blur-free device. The corrected data can be used by any reconstruction algorithm.

Algorithm 2 FDR
1: Compute $G(f_1, f_2, n)$ by 3D Fourier transform of the corrupted data, $g(s_1, s_2, \Theta)$.
2: Recover an estimate of $P(f_1, f_2, n)$ based on $G(f_1, f_2, n)$ by

$$P(f_1, f_2, n) = H \left( f_1, f_2, -\frac{n}{f_1} \right) + G(f_1, f_2, n)$$

3: Compute an estimate of $p(s_1, s_2, \Theta)$ by 3D inverse Fourier transform of the estimate $P(f_1, f_2, n)$
4: Produce an estimate of the original imaged object using any reconstruction algorithm.

A single micrograph contains a projection of the 3D volume convolved with the point spread function that depends on the distance from the electron source. The objective of the FDR algorithm (see Algorithm 2) is to approximate the mathematically ideal projection data based on the set of corrupted micrographs. Recalling the image formation model in transmission electron microscopy of the ideal 3D projection data set is

$$P(f_1, f_2, n) = \frac{1}{2\pi} \int_{0}^{2\pi} \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} p(s_1, s_2, \theta) e^{-i2\pi(f_1 s_1 + f_2 s_2 + n\theta)} ds_1 ds_2 d\theta \quad (10)$$

and the Fourier transform of the corrupted projection of an impulse located at point $(s'_1, s'_2, t)$ is
Following Xia et al. [20], Dubowy and Herman [4] made use of the fact that, considered as a function of $\theta$, the real part of $e^{-i2\pi(f_1s_1+f_2s_2+n\theta)}$ oscillates rapidly except at those values for which the partial derivative with respect to $\theta$ of the function $f_1s_1 + f_2s_2 + n\theta$ is zero. These values are referred in literature as the points of stationary phase. At each stationary point the value of the $t$ coordinate is equal to $\frac{n}{f_1}$, which implies that the values of the frequencies of each coefficient are directly related to the distance from the electron source at which the points in the specimen contribute to the coefficient. The stationary phase approximation method allows for estimation of the value of the integrals of a highly oscillatory function by integration over small neighborhoods in which the stationary phase points occur. Using this principle the corrected projection data can be obtained from corrupted data by

$$P(f_1, f_2, n) \approx G(f_1, f_2, n) H^+(f_1, f_2, -\frac{n}{f_1}),$$

in which $H^+$ can be thought of as an inverse of $H$ that is well behaved at the points for which $H$ is zero, for example the one in (9).
4.3 Mathematical equivalence of DGCBP and FDR

In a very recent work, Kazantsev et al. [12] compared the two methods discussed in the previous sections. Specifically, they showed that for the subset of cases to which both approaches can be applied they produce the same reconstructions, at least in the limiting case of noiseless micrographs available in all projection directions. They compare the DGCBP algorithm in the case of single axis rotation data collection with layers of infinitesimal thickness with the FDR algorithm. In both cases the projections are noiseless and available from infinitely many angles around the axis of rotation.

Recalling the operators defined in Subsection 1.5, for noiseless mathematically ideal projections $v = DBP v$, where $v$ is the object being reconstructed, see Radermacher [16]. Let $C v$ denote the projections that are corrupted by a distance-dependent contrast transfer function. If $U$ is the operator that corrects the corrupted projections according to the FDR method described in Section 4.2 then in principle $UC v = P v$ and $DUC v = DP v$. If $V$ is the operator that reconstructs the object based on corrupted projection data according to the DGCBP method described in Section 4.1, then in principle $VC v = BP v$ and $DVC v = DBP v$. This shows that, in fact, both methods are equivalent since $DVC v = DBP v = DBUC v$.

The authors provide a detailed mathematical derivation demonstrating this equivalence.
4.4 Similar problems in other areas

4.4.1 Single photon emission computed tomography

*Single photon emission computed tomography* (SPECT) is a medical imaging procedure that produces images based on the concentration of injected radio-pharmaceuticals. The concentration has different levels that depend on the function performed by different tissues. The image is produced by photons emitted from the radio-active pharmaceutical absorbed by the tissue. A photon detector is rotated around the patient and records photons emitted from the body. The point response function of detectors depends on the distance of the detector itself to the point from which the photon is emitted. A general review of correction techniques in SPECT is provided by Bouwens *et al.* [1]. They briefly address the issue of distance-dependence in the detection system and cover mostly problems related to scatter and attenuation of photons in the body.

The problem of distance dependence for circular and elliptical detector assemblies is discussed extensively by Xia *et al.* [20]. This work is a continuation of a previous paper by Edholm and Lewitt [5]. The approach involves filtering projection data collected from all views prior to reconstruction. The filter is based on special characteristics of the Fourier coefficients of the projection data. Specifically, they noticed that the significant contribution of any given point in the object to the Fourier coefficient of the projection data at an angle $\Theta$ comes from points whose distance is $-n/f$. This is known as a frequency-distance relation for the Fourier coefficients.
The filtering mechanism used in Xia et al. [20] is based on the relation
\[ G(f, n) = P(f, n) \times H(f, -\frac{n}{J} + R) \]
where \( R \) is the distance of the detector to the center of rotation.

The CTF correction method for electron tomography using single axis rotation proposed by Dubowy and Herman [4], is based on the above relation, see Subsection 4.2.

### 4.4.2 Positron emission tomography

*Positron emission tomography* (PET) is another medical imaging procedure. In PET, the patient is injected with a radio-pharmaceutical agent and a pair of photons is emitted by a decaying radioactive tracer material accumulated in body tissues. Two photons travel in opposite directions and are detected on a cylindrical detector that surrounds the person being imaged. The cylindrical detector is composed of rings, which are subdivided into arrays of individual cells that detect radiating photons. 3D objects can be reconstructed slice by slice using a well known CT approach in which each ring of the PET detector corresponds to a single slice. This simplifies the reconstruction process to recovery of 2D objects from 1D projections. This mode of data collection and reconstruction ignores all the information coming from positrons that were emitted in directions other than the one perpendicular to the axis of the cylindrical scanner. Reconstruction methods have been developed that can utilize the extra information, but they are very time consuming in practice (see Defrise [3] and references therein).

Defrise [3] has developed a method of Fourier rebinning of the data col-
lected from arbitrary directions so that it can be assigned to a single detector ring. This allows for computationally efficient reconstruction of the object slice by slice from 1D projections. This method of rebinning uses the frequency-distance relation originally proposed by Edholm et al. [5], which we have mentioned before. It allows for determination of location along the line between two detectors from which the photons were emitted. Once this location is known, the information about the presence of the tracer material in that location can be reassigned to the detector ring that corresponds to it.

5 Summary

There are many attempts to correct the effects of contrast transfer function in reconstruction from projections obtained in electron microscopy. Most of the currently available methods assume that the entire specimen has been blurred by a single CTF. This assumptions is acceptable when the specimen are small and the resolution of reconstruction is not high. Variation in blurring within a single specimen becomes more evident as the attainable resolution of reconstructions increases. Consequently there is a need for correction methods that can account for distance dependent CTF.
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