Advances in Large Field and High Resolution Electron Tomography

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Credits

- *Software Development*
  - Sebastien Phan
  - Rajvikram Singh
  - Alex Kulungowski
- *Instrumentation*
  - James Bouwer
- *Technical Support*
  - Masako Terada

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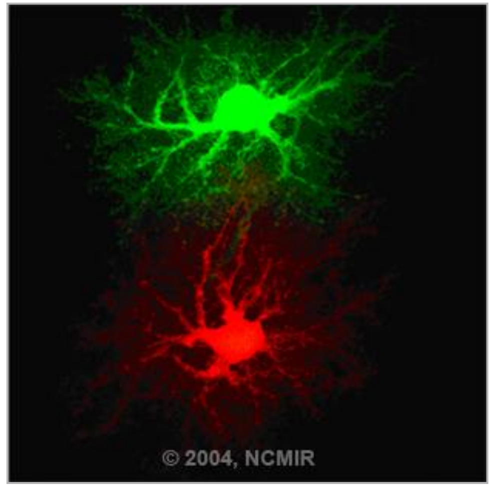
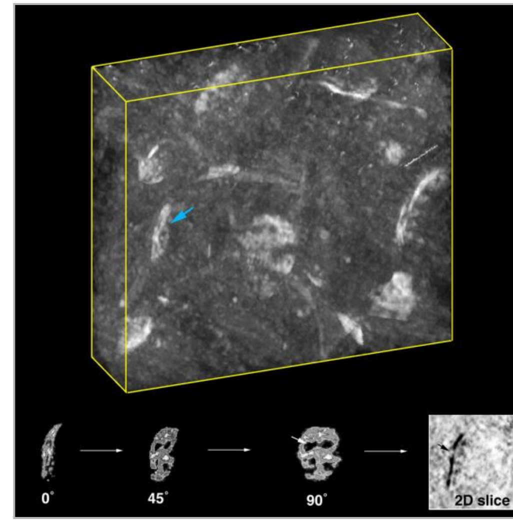
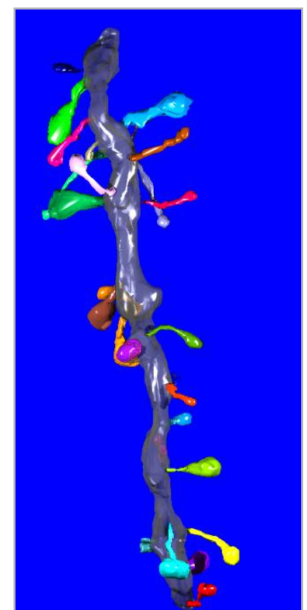
Supporting Clinical and Basic Biological Research

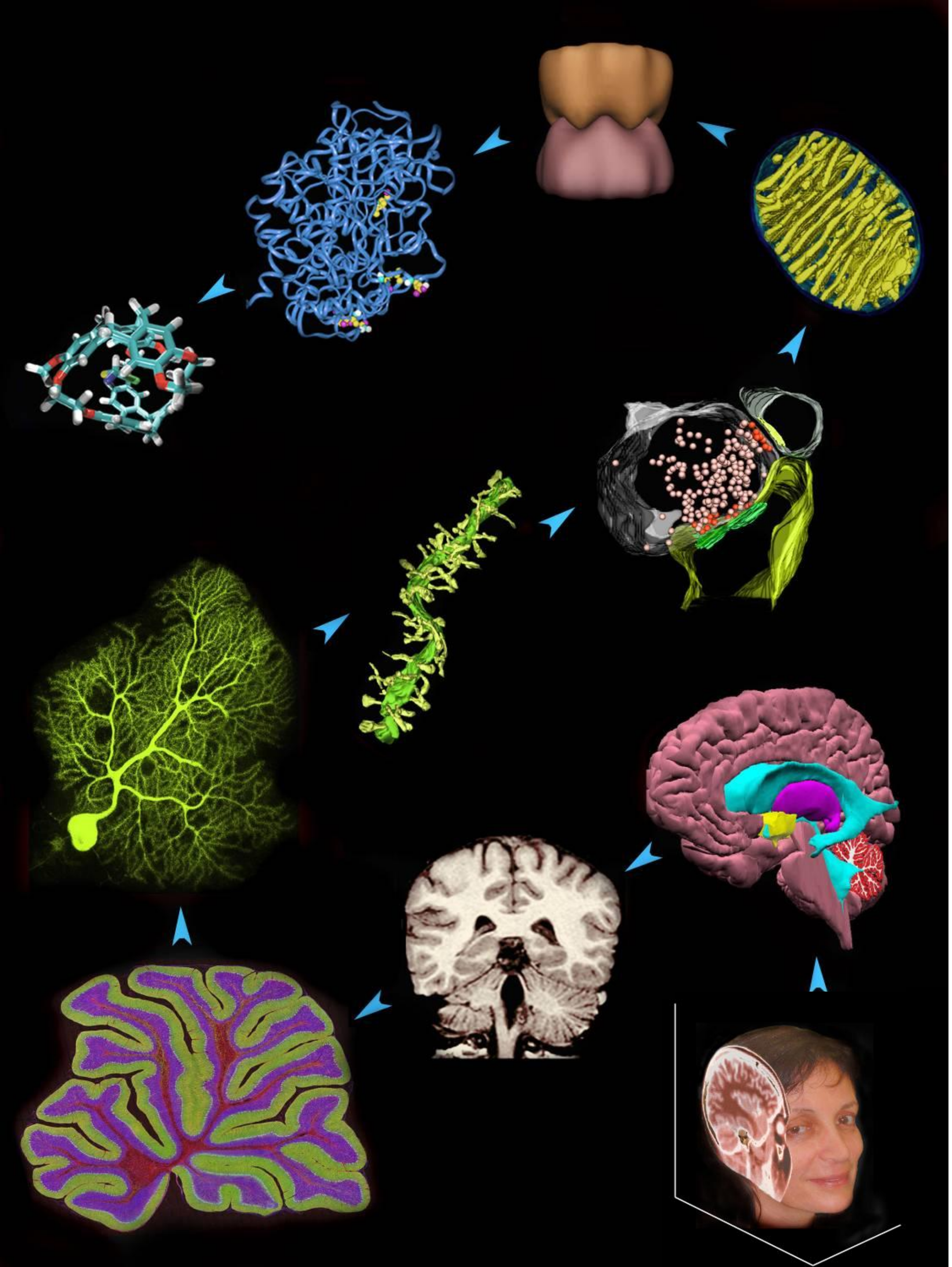
- **Major activities in clinical Research:**
  - –Neurodegenerative disease
  - –Cardiomyopathy
  - –Diabetes
  - –Stroke
  - –Mental retardation
  - –Cancer
  - –Addiction
  - –Autism





- **Basic research:**
  - –Astrocyte structure
  - –Computational modeling of synaptic function
  - –Function of the node of Ranvier
  - –Macromolecular and organellar dynamics
  - –Structure and function of mitochondria
  - –Adult neurogenesis
- **Imaging sciences**
- **Instrumentation**
- **Computational sciences**





The National Center for Microscopy and Imaging Research

Develop and deploy technologies to determine and reveal supramolecular details in their cellular and tissue contexts.

- Focus on the ‘Meso-scale’ - ~0.5nm to > 100um

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NATIONAL CENTER for MICROSCOPY and IMAGING RESEARCH
at San Diego, an NIH supported resource center

Computational Challenges in the Biosciences

- Life is organized on many spatial scales
- Biochemistry is exceedingly complex
- Representations of physical structure grow exponentially in complexity as range of spatial scale widens
- Flood of data from microscopes challenges the capabilities of digital computers
- Three dimensional reconstruction of physical structure is already a supercomputer problem
- Subsequent modeling of dynamics even more so

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Petascale Biology?

•From EM to light microscopy:
•Scale Change: 100K
•Volume Change: 1 X 10^15
•Tremendous amplification factor in biological processes

•Which details are important?
•Which become statistical?
•Which become irrelevant?

•Biology is largely a descriptive science. We have to put together realistic structural descriptions before tackling the dynamics.

•Merely piecing together a structural description is a daunting computational task.

•Google Brain? A map of the brain down to molecular details—and in 3D.

Outline

- Large-field tomography—quick overview
- Instrument characteristics
- Inverse problems
- Ray transforms
- The reconstruction process
- TxBR
- New mathematical developments

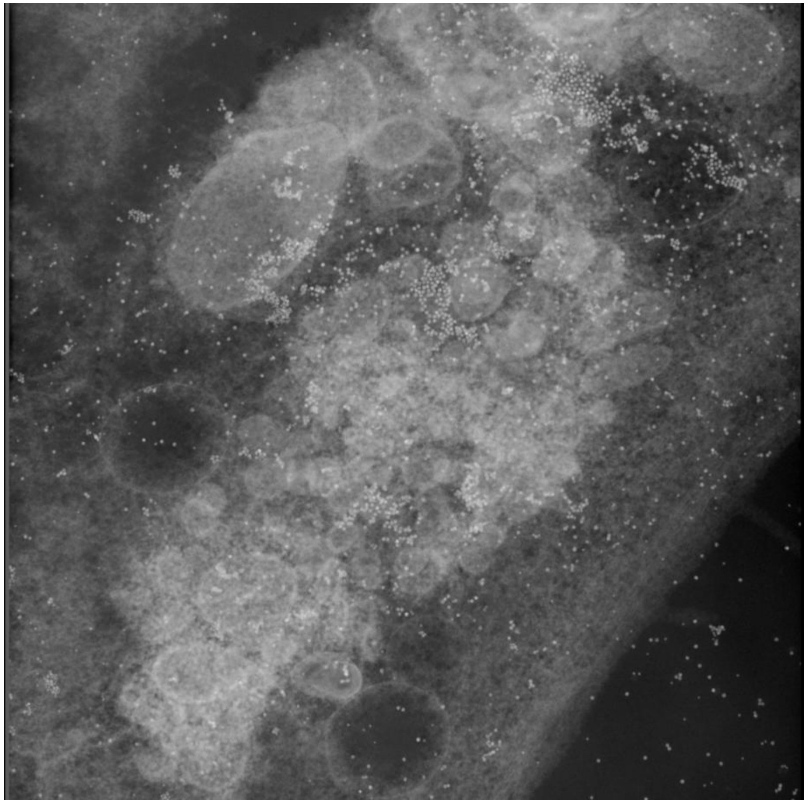
Why Do EM Tomography?

- Eliminate shadowing effects

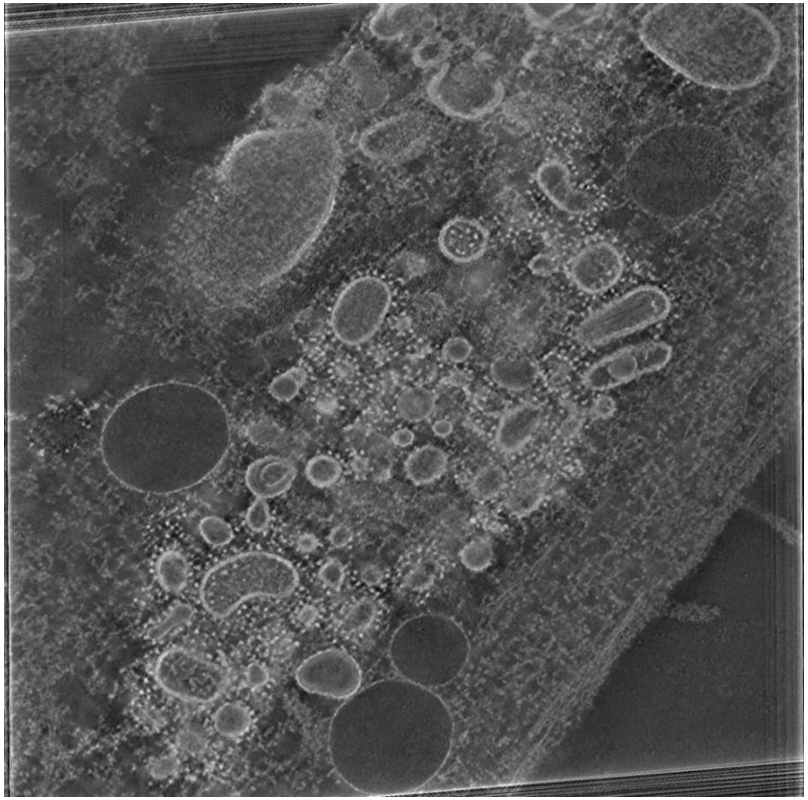
- Elucidate 3D structure

- Connect supramolecular structure with light microscopy

Electron Microscope Tomography



Electron Microscope Image

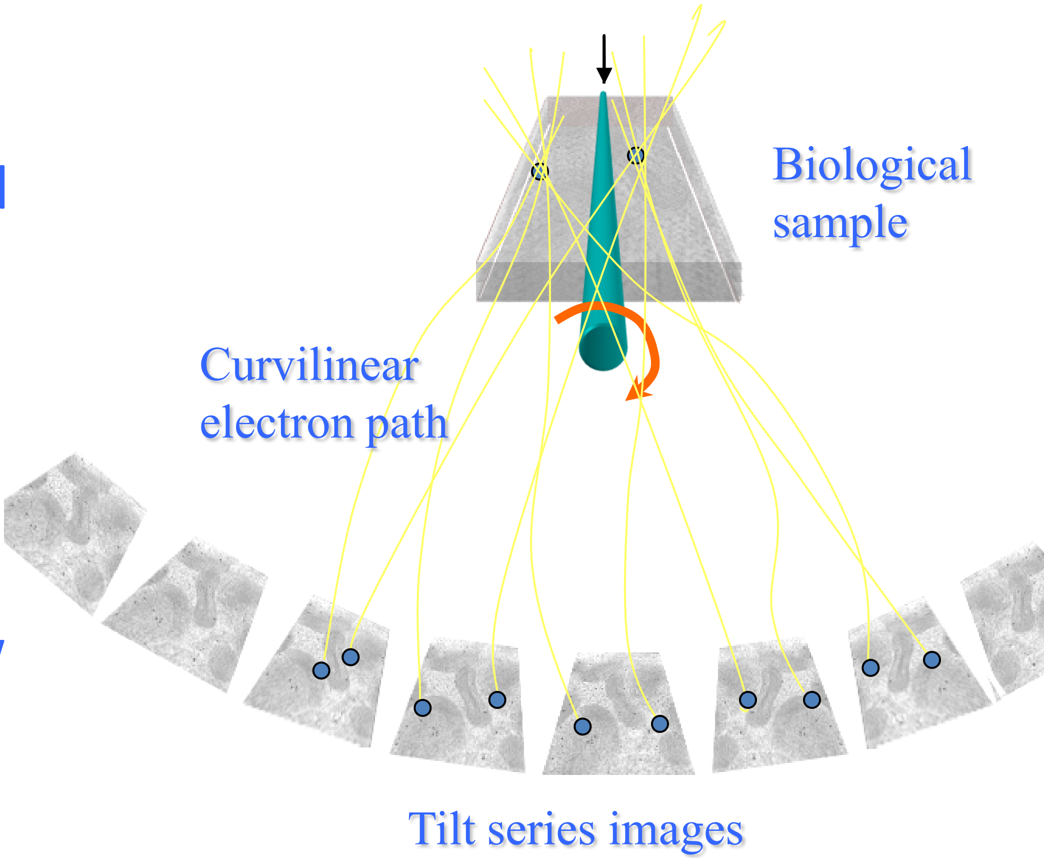


Section of Reconstruction

https://www.nbcr.net/pub/wiki/index.php?title=Tomography_Day_2008

Electron Microscopic Tomography at a Glance

- Used for constructing 3D views of sectioned biological samples
- Sample is rotated around an axis and images are acquired for each ‘tilt’ angle
- Electron tomography enables high resolution views of cellular and neuronal structures.
- 3D reconstruction is a complex problem due to low signal-to-noise ratio, curvilinear electron path, sample deformation, scattering, magnetic lens aberrations…



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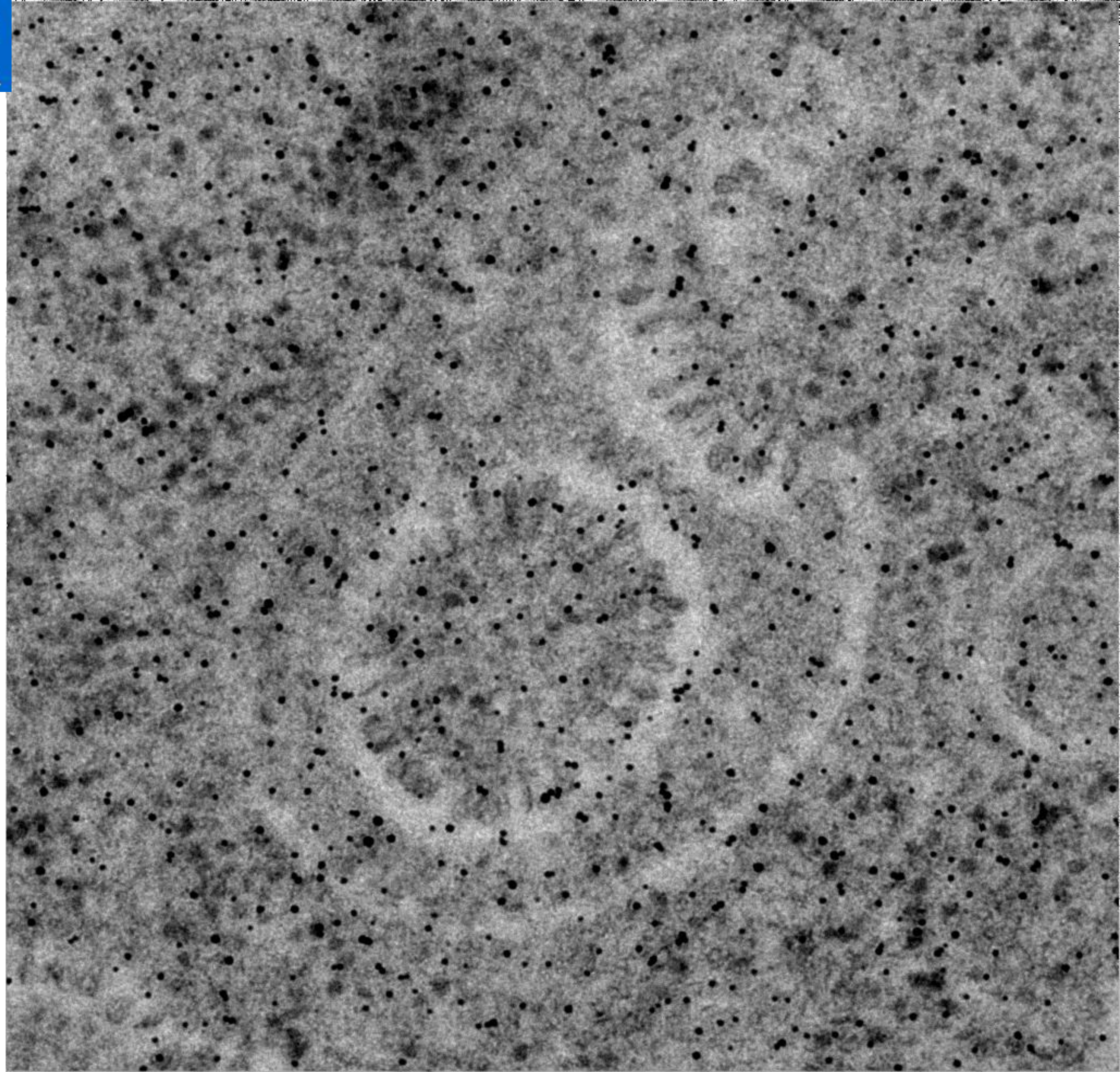


Flock House Virus

4.1Kx
Magnification

12.2 Å /pixel

995 frames

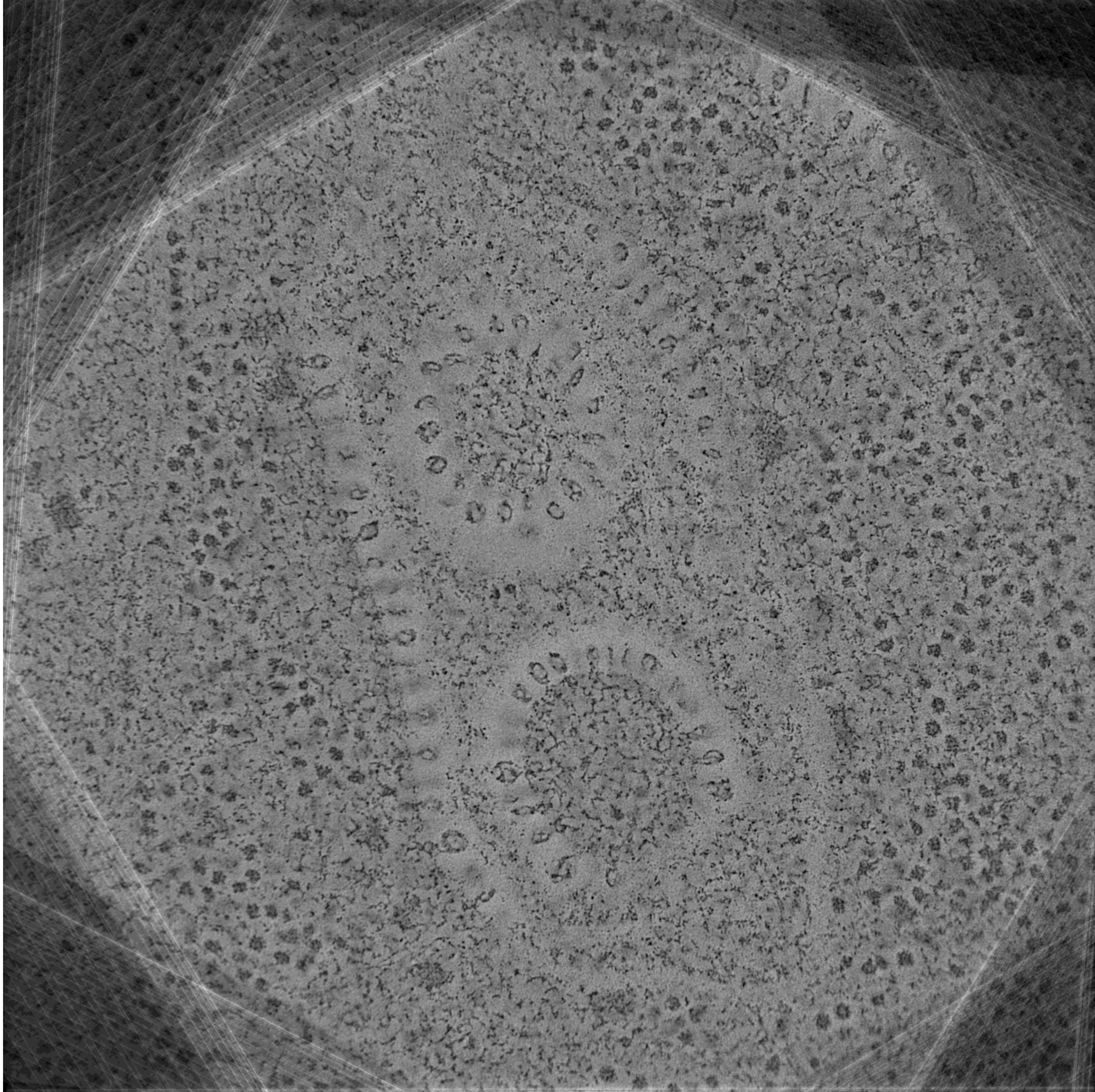
Flock House Virus

4.1Kx Magnification

12.2 Å /pixel

Six Fold Tilt Series Reconstruction

Single Z Section of Reconstruction



Tomography in Context

- Tomography, in practice, requires many steps
  - Sample preparation
  - Data collection
  - Feature isolation and tracking
  - Image alignment
  - Image filtering
  - Volume reconstruction
  - Object segmentation
- Each step carries it's own set of problems
- Choice of methods on one step affects subsequent steps

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Technical Problems in EM Tomography

- Noise. Imaging is through electrons scattering out from beam.
- Limited data. Exponential decrease of flux thru sample at high angles.
- Positioning accuracy. Sub micron information required.
- Magnetic lenses. Electrons travel in helical paths in focusing fields.
- High energy electrons, Structure degradation. Number of angles exposure-limited.
- Sample mass loss. Sample warping.
- Imperfect lenses. Aberrations. Image distortion.

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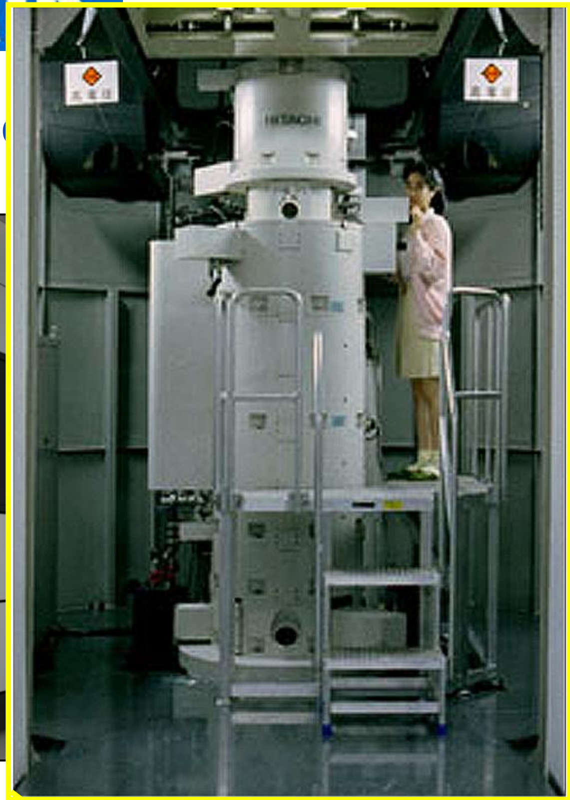
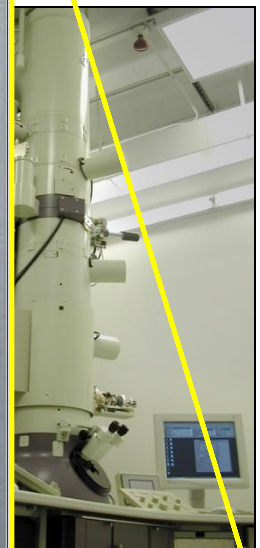
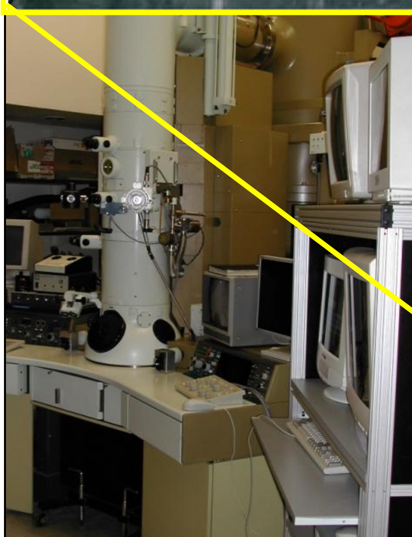
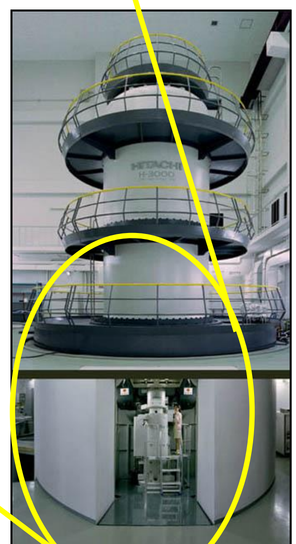
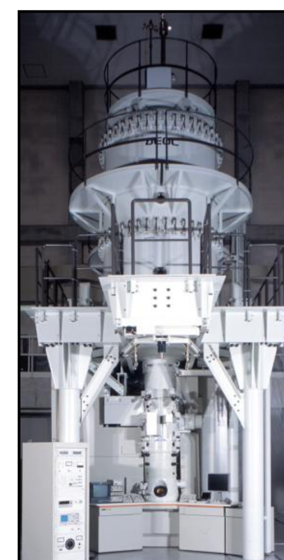
Interm Microscope Resources











Derivation from First Principles

- Dirac Equation
- Schrodinger Equation
- Paraxial Schrodinger Equation
- Paraxial Image Formation
- Classical Paraxial Equation
- Higher Order Corrections

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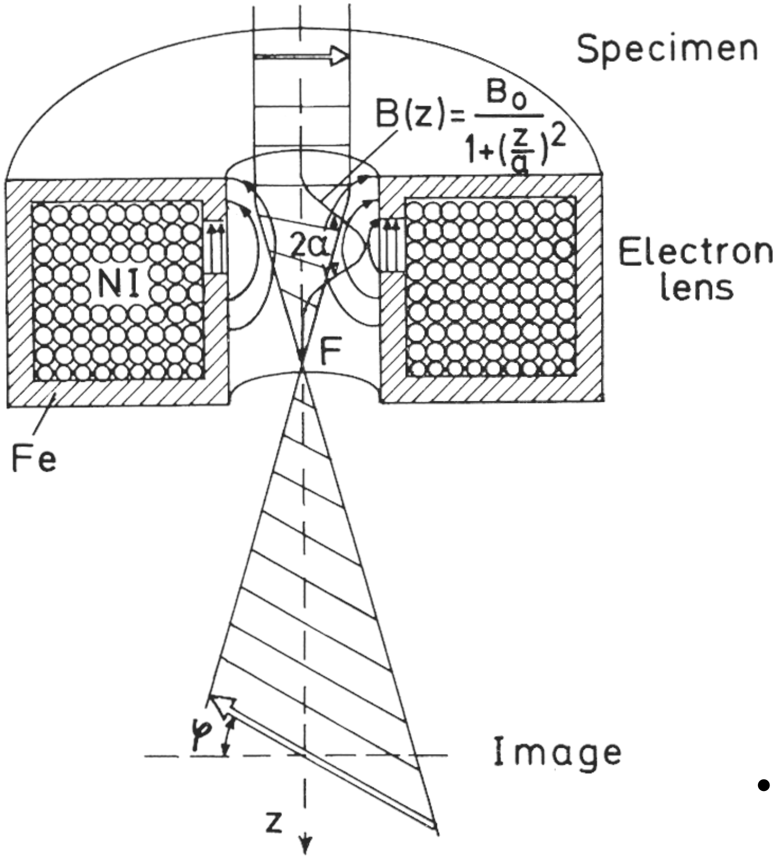
Paraxial Equation

- Light waves in homogeneous media
- Classical charged particle in electromagnetic field
- Quantum mechanical electron in electromagnetic field

$$\psi_{|xx} + \psi_{|yy} + \frac{2i}{\hbar} g(z)\psi_{|z} - \frac{g^2 r^2}{\hbar^2} F(z)\psi(x, y, z) = 0$$

- This does not account for lens aberrations and diffraction effects.

Physics of Electron Lensing



Can be solved analytically through separation of variables in cylindrical coordinates to produce the equations of motion for the imaging electrons

$$\omega_L = \frac{e}{2m_e} B_z(r,\theta,z)$$

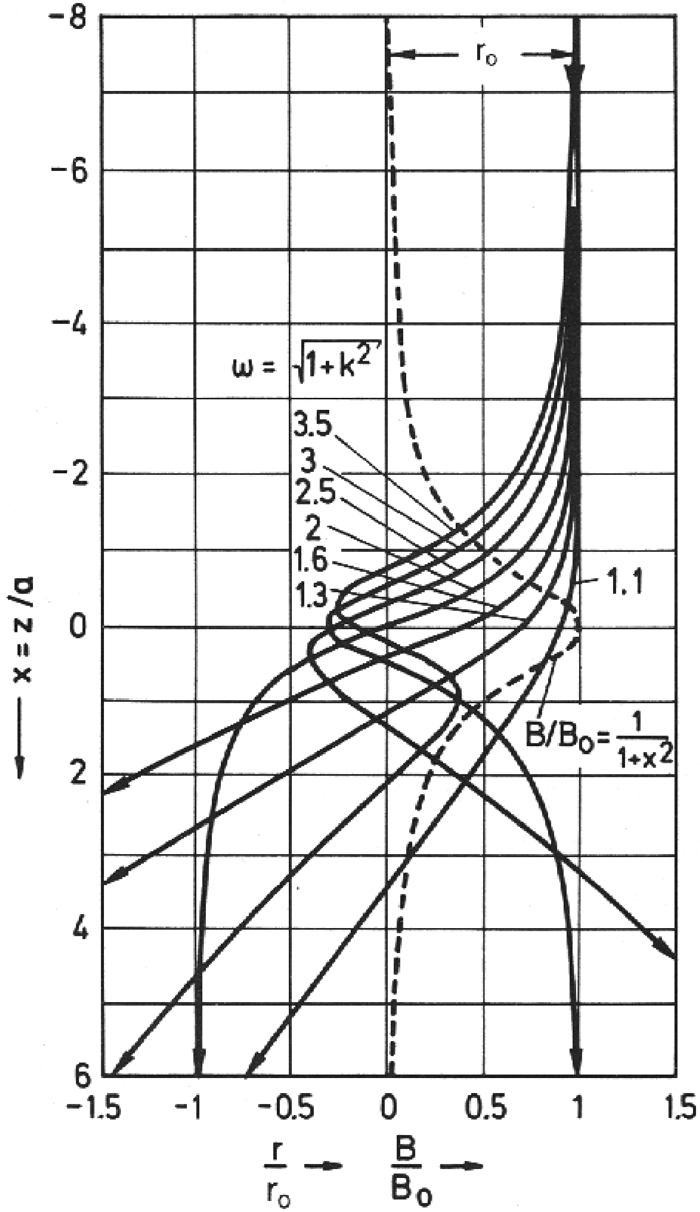
Bell Shaped Field:

$$B_z = \frac{B_0}{1+(z/a)^2}$$

- B_z = z-component of the magnetic field
- ω_L = Larmor frequency
- e = charge of an electron
- m_e = rest mass of an electron

* Image from L. Reimer, TEM 1993

Real Electron Trajectories in Rotating Reference Frame



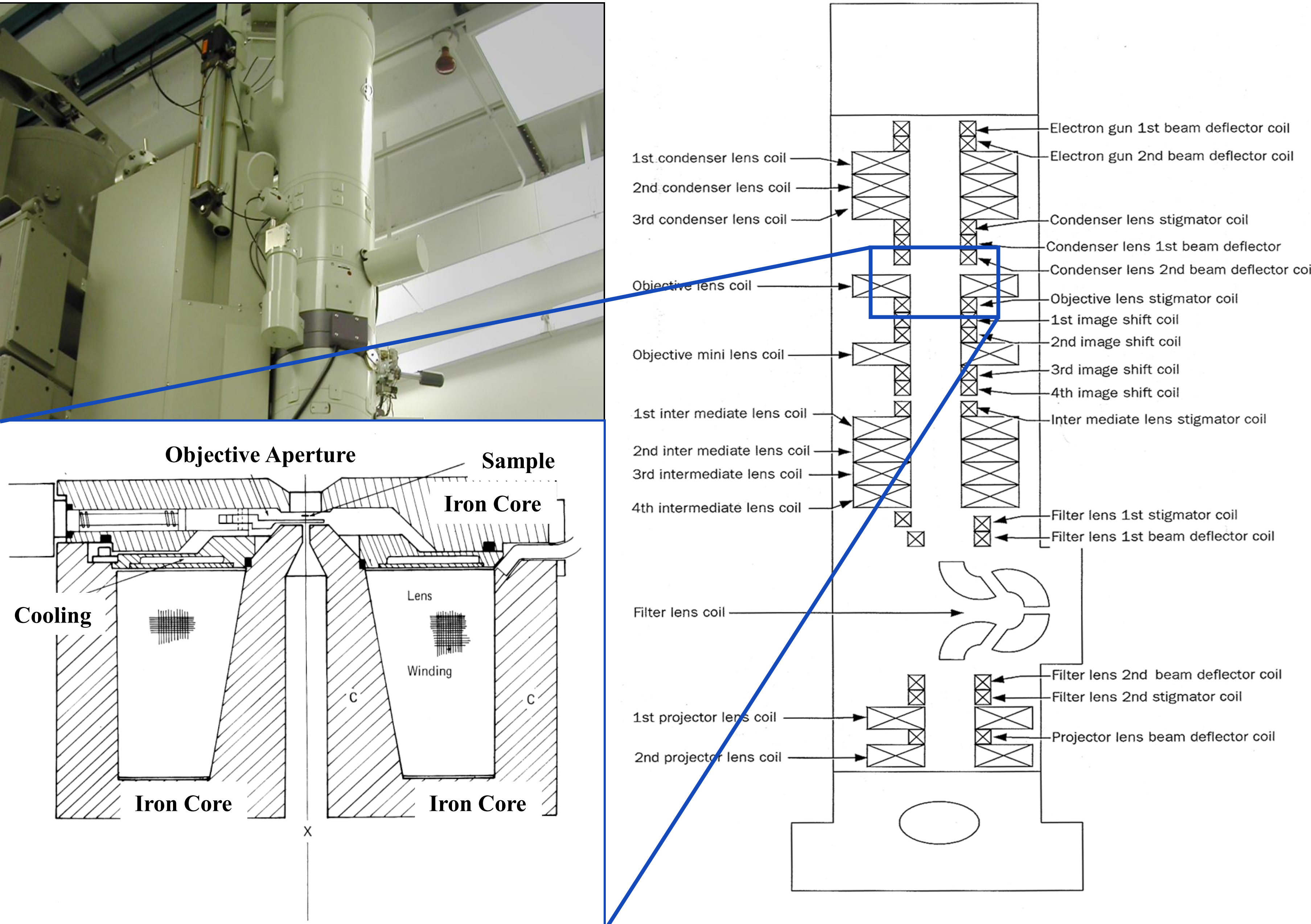
Electron trajectories for electrons incident parallel to the optical axis for various B-field strengths

$$k^2 = \frac{eB_0^2 a^2}{8 m_0 U}$$

$$\omega = \sqrt{1 + k^2}$$

* Image from L. Reimer, TEM 1993

The Electron Microscope



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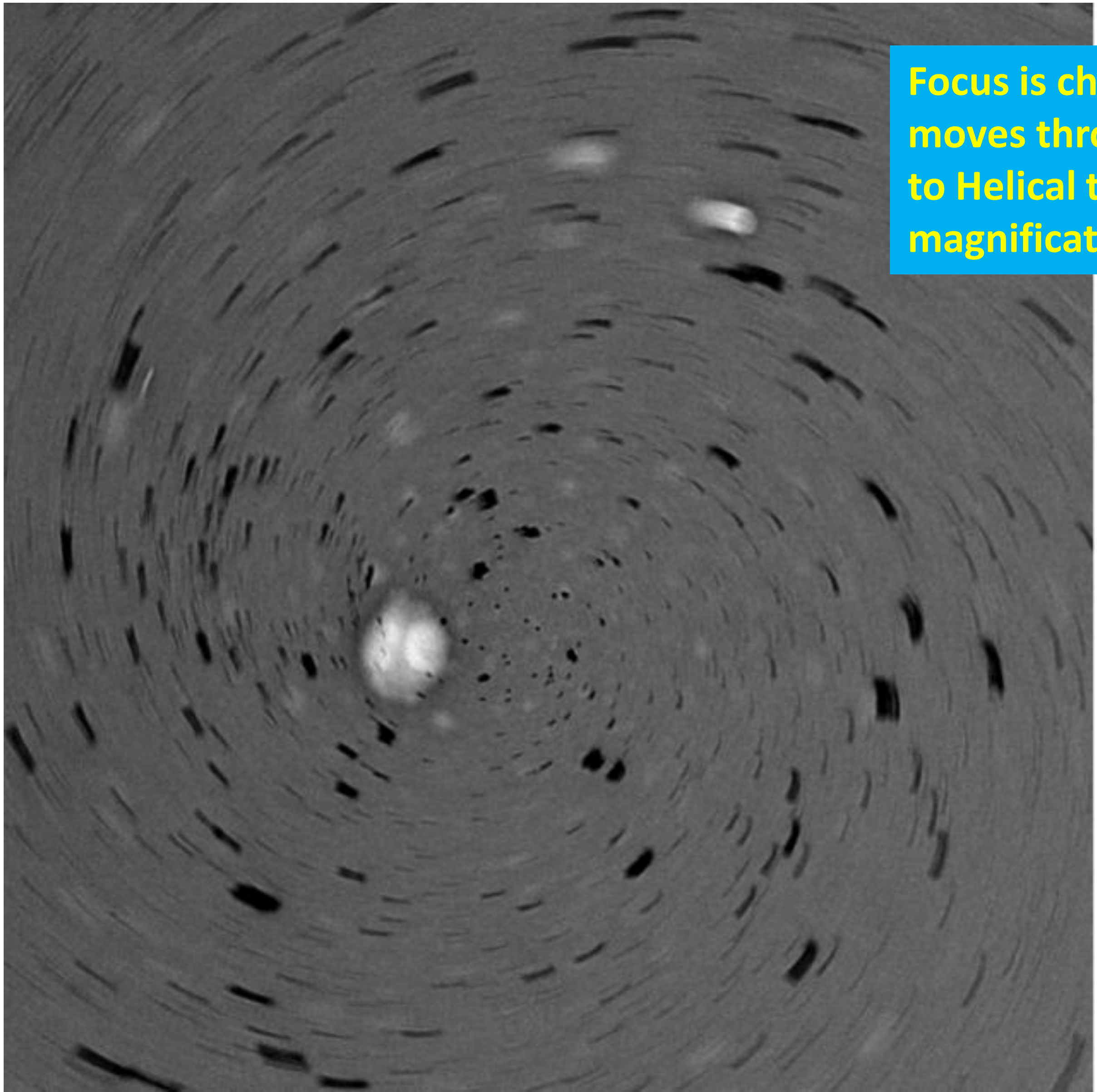
Helical Distortions



Focus is changed in steps so focal plane moves through object. Note effects due to Helical trajectories and differential magnification.

The Contrast Transfer Function (CTF)

$$I(k) = O(k)CTF(k)$$

where:

I(k) = Image

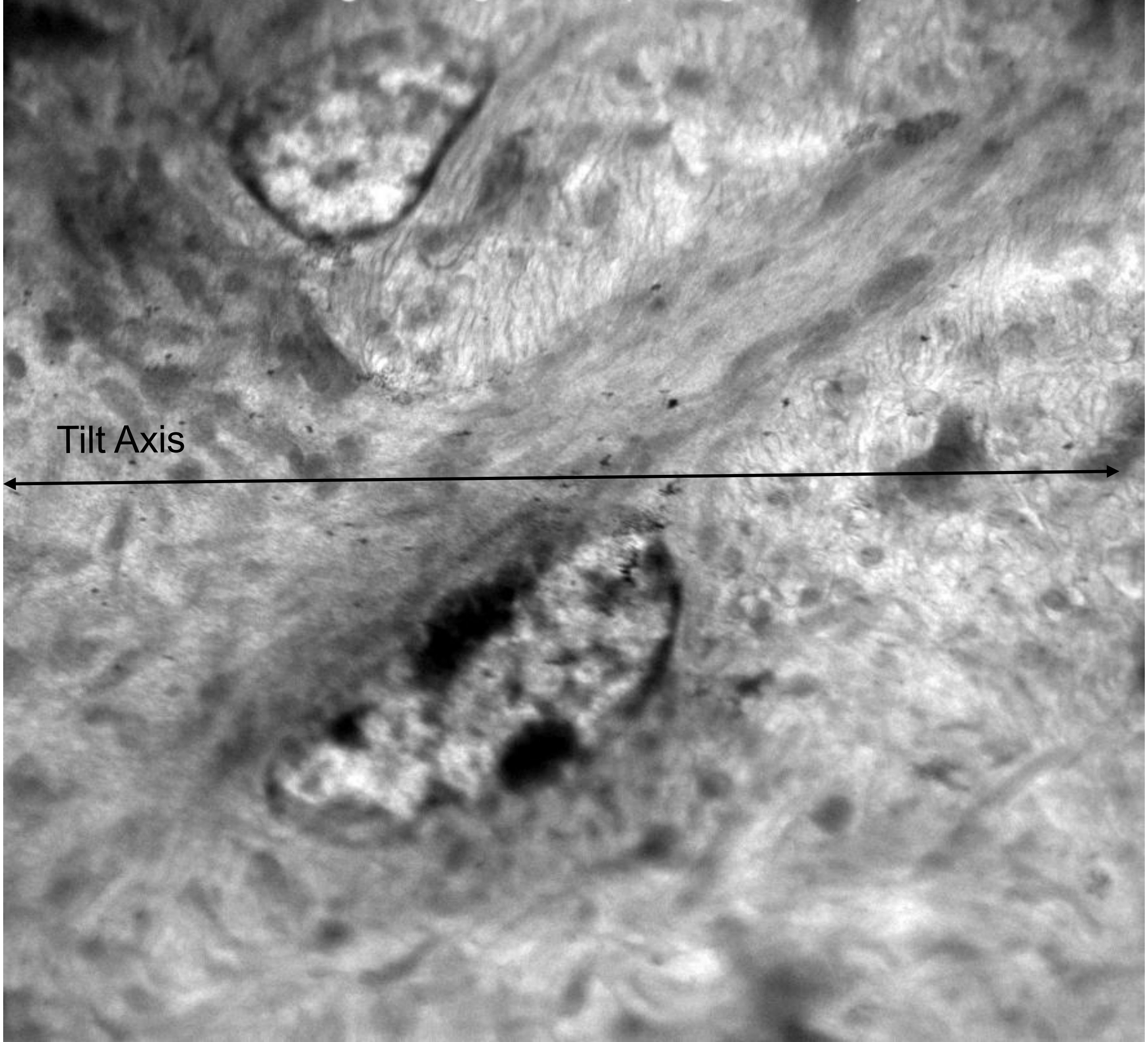
O(k) = Object

k = spatial frequency

and

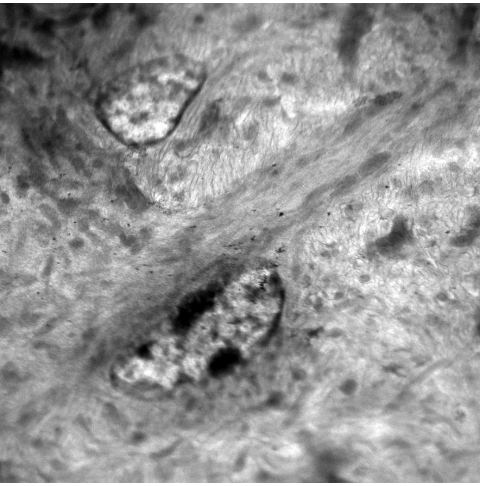
CTF is also a function of position along optical axis

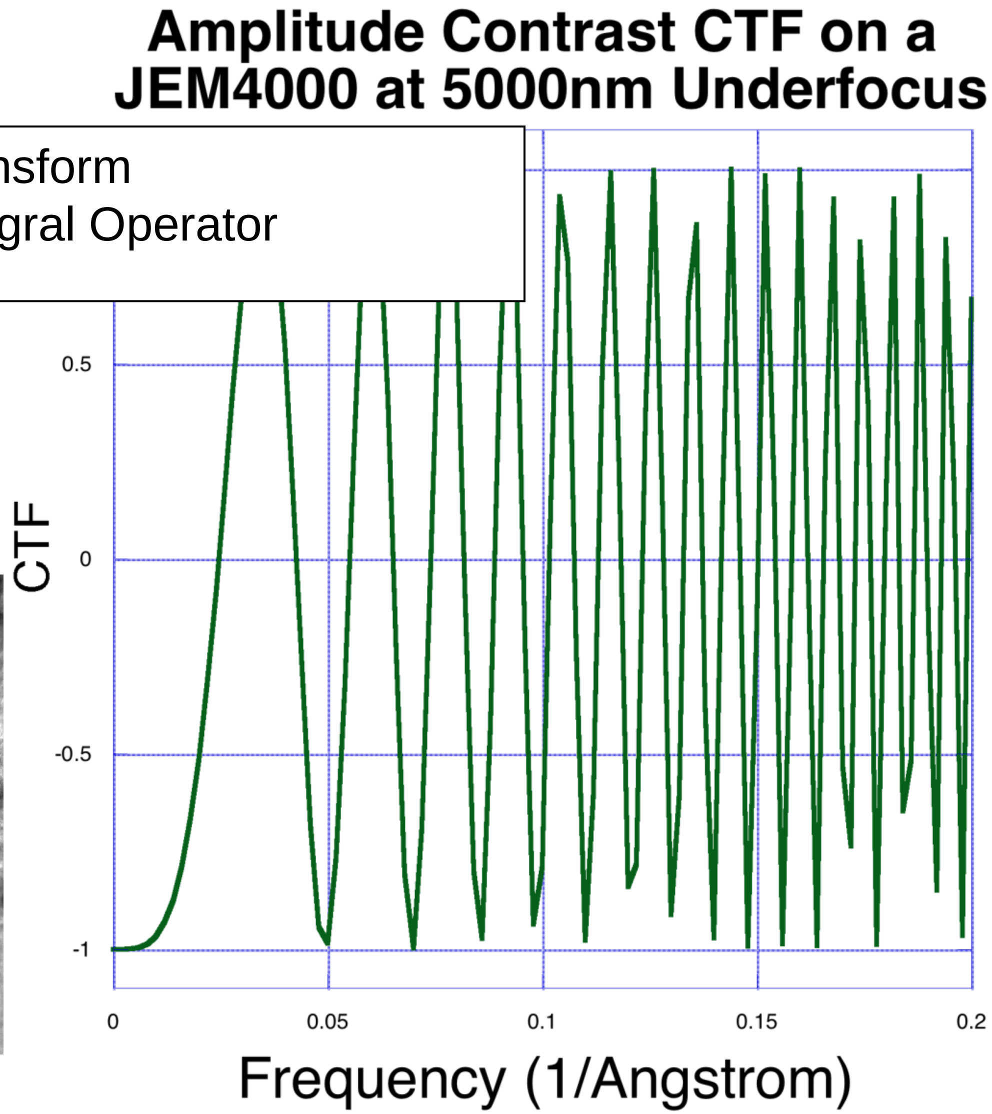
Wide-field Images of 60 degree tilted sample show a strong focus gradient (CTF gradient)



Large Field of View Requires CTF Reconstruction from a Thru Focus Series

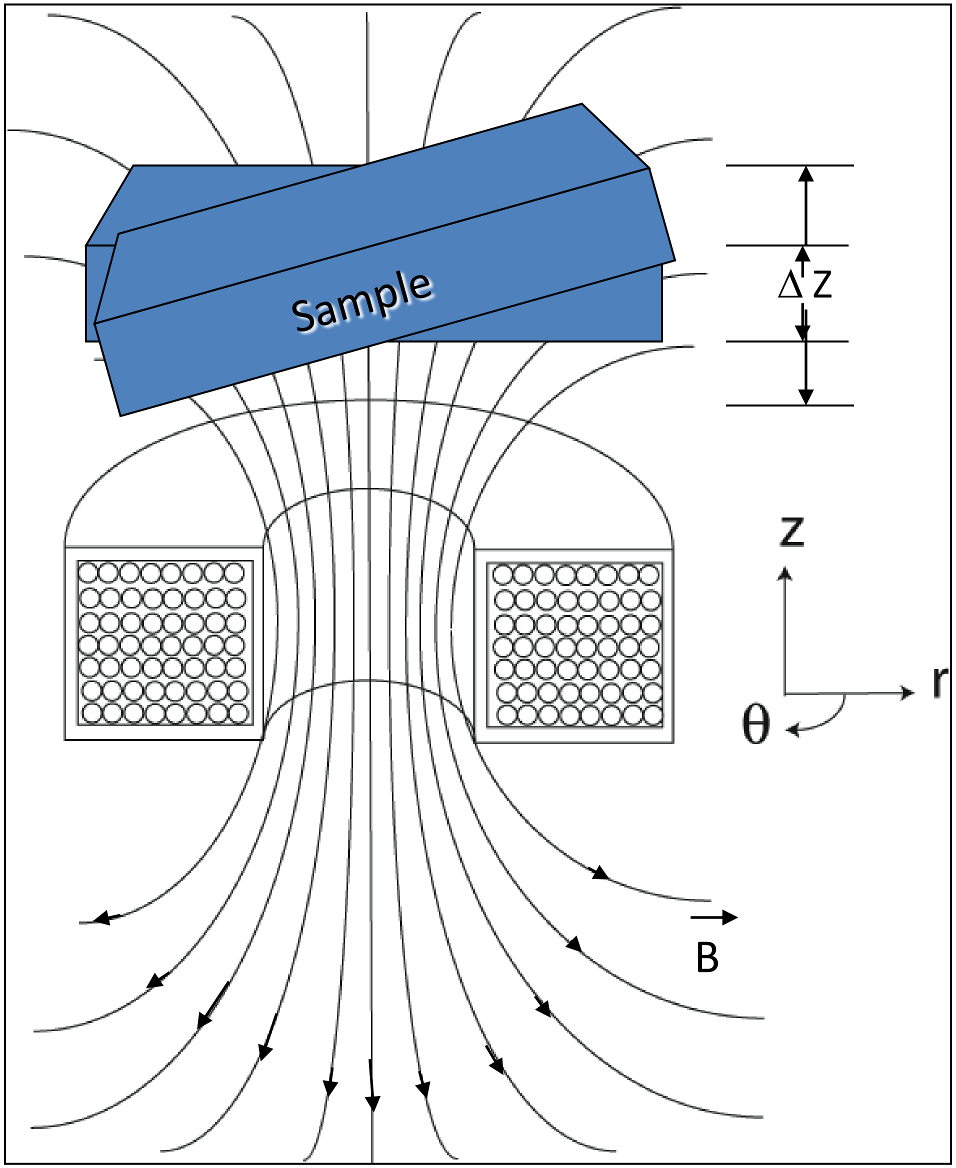
2D => Fourier Transform
3D => Fourier Integral Operator





* Generated with CTF generator written by Wen Jiang and Wah Chiu

Fringing Fields Affect Image Formation

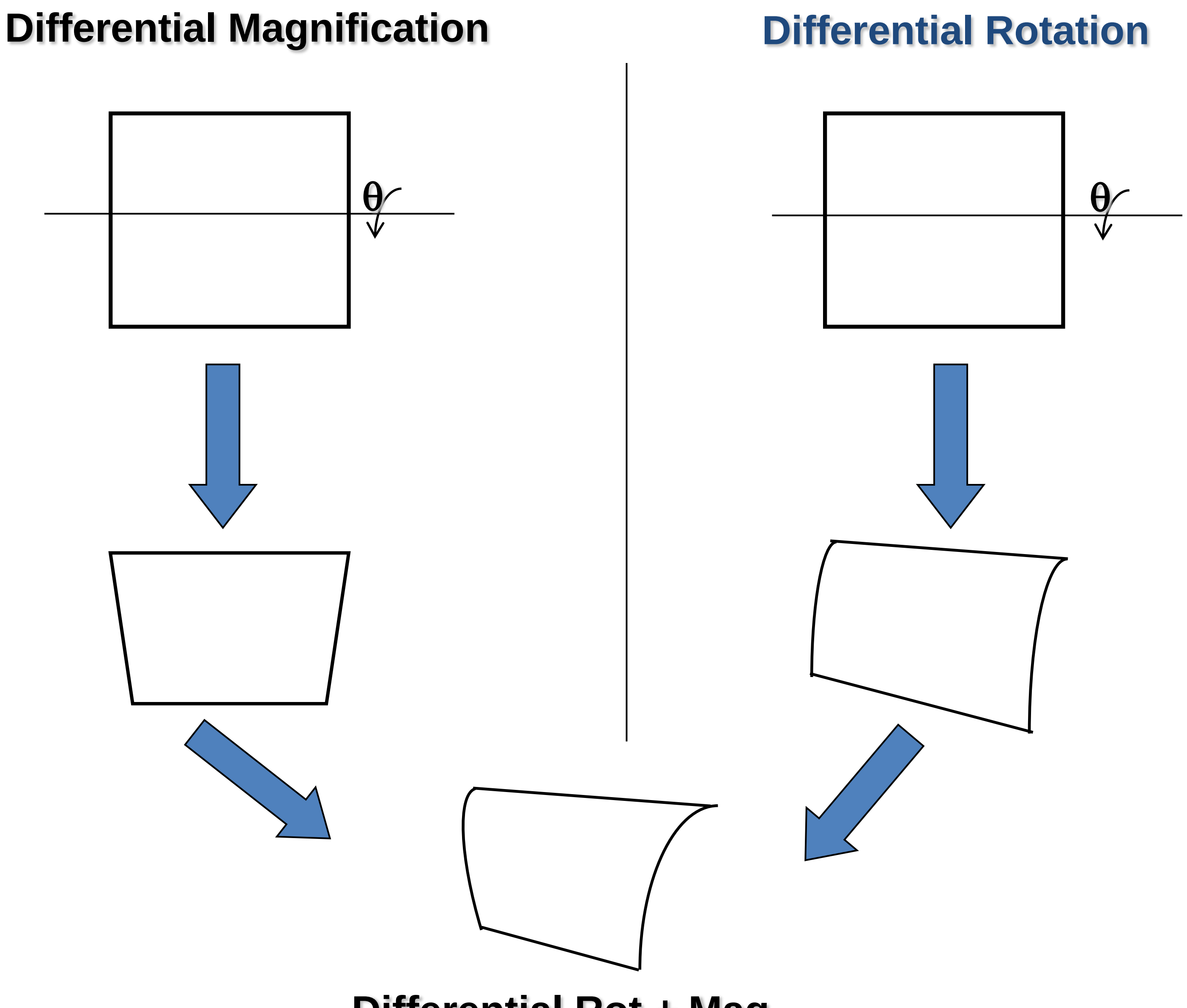


- Differential magnification
- Differential rotation
- More pronounced for large format images
- Rotation and magnification are troublesome for tomography

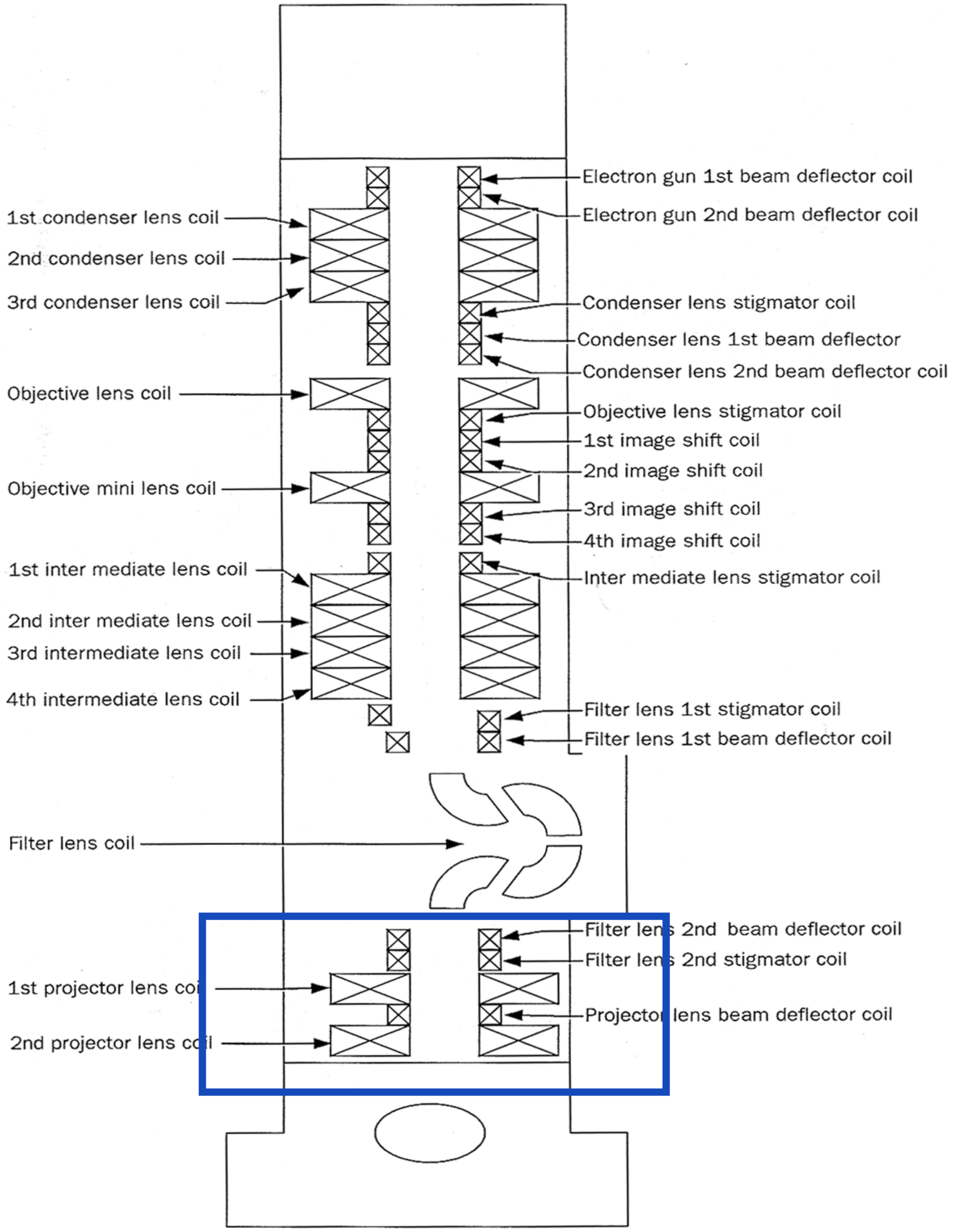
$$\theta_L \propto B_z(r,z)$$ (rotation)

$$\frac{\Delta M_{ag}}{M_{ag}} = \frac{\Delta z}{f}$$ (magnification)

Tilt Geometry Distortions



Projector Lens Aberrations



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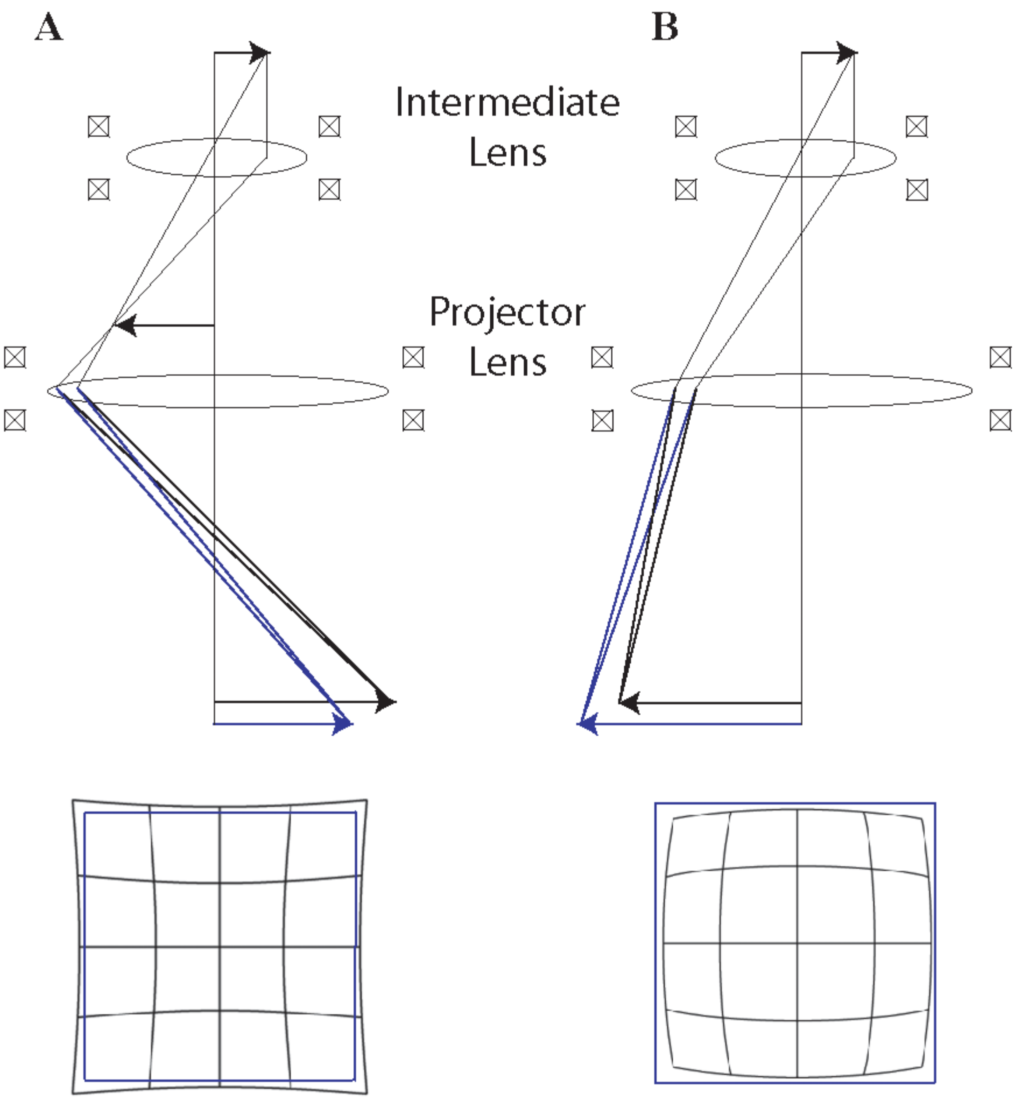
Spherical Aberration Produces Spatial Distortion

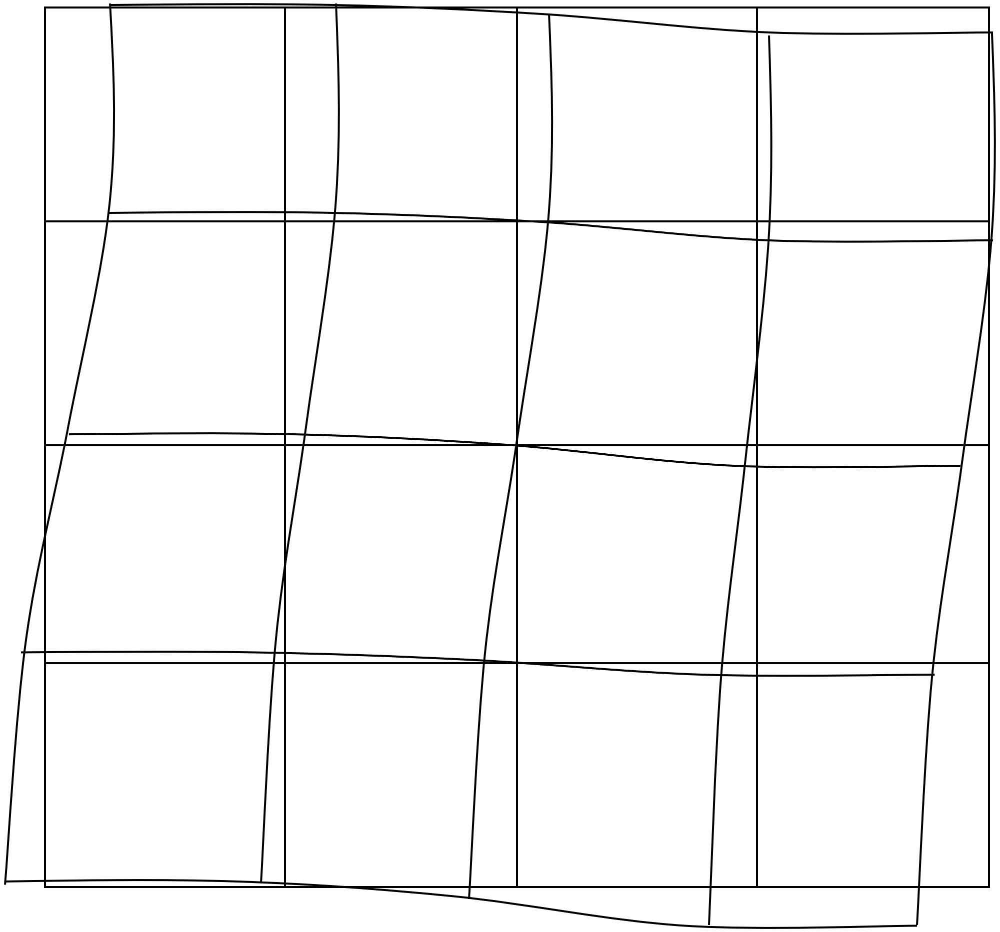


Spherical aberration results from a change in focus in center vs outer edge of lens

Virtual image produces barrel distortion

Real image at projection produces pincushion distortion

Largest Spatial Aberrations are S-type Distortions in the Projector Lens Optics



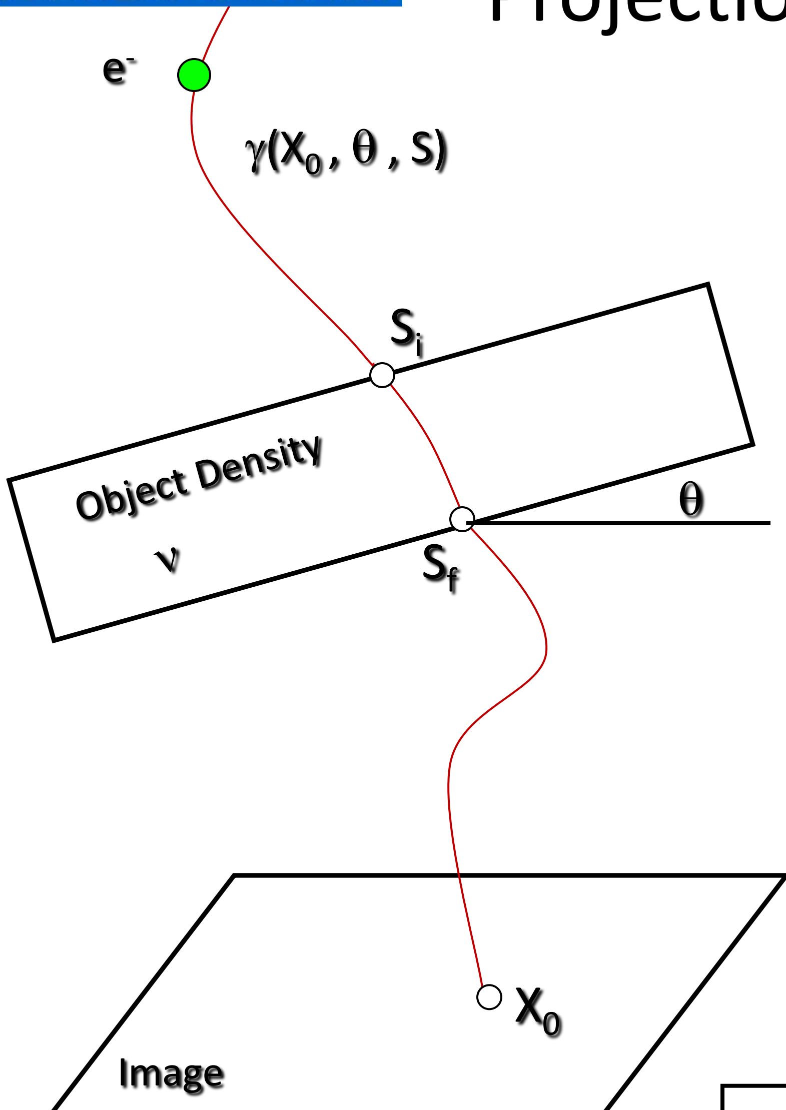
EM manufacturer Specs:

Δ < 1.5% @ r = 5cm

For a 4k x 4k detector 6cm diameter
Δ~ 40 pixels

For a 8k x 8k detector 10cm diameter
Δ ~ 80 pixels

Projection in Electron Microscope



γ = electron path

S_i = point of entrance

S_f = point of exit

θ = tilt angle

$X_0 = (x, y)_{image}$

$X = (x,y,z)$

ν = object density fxn

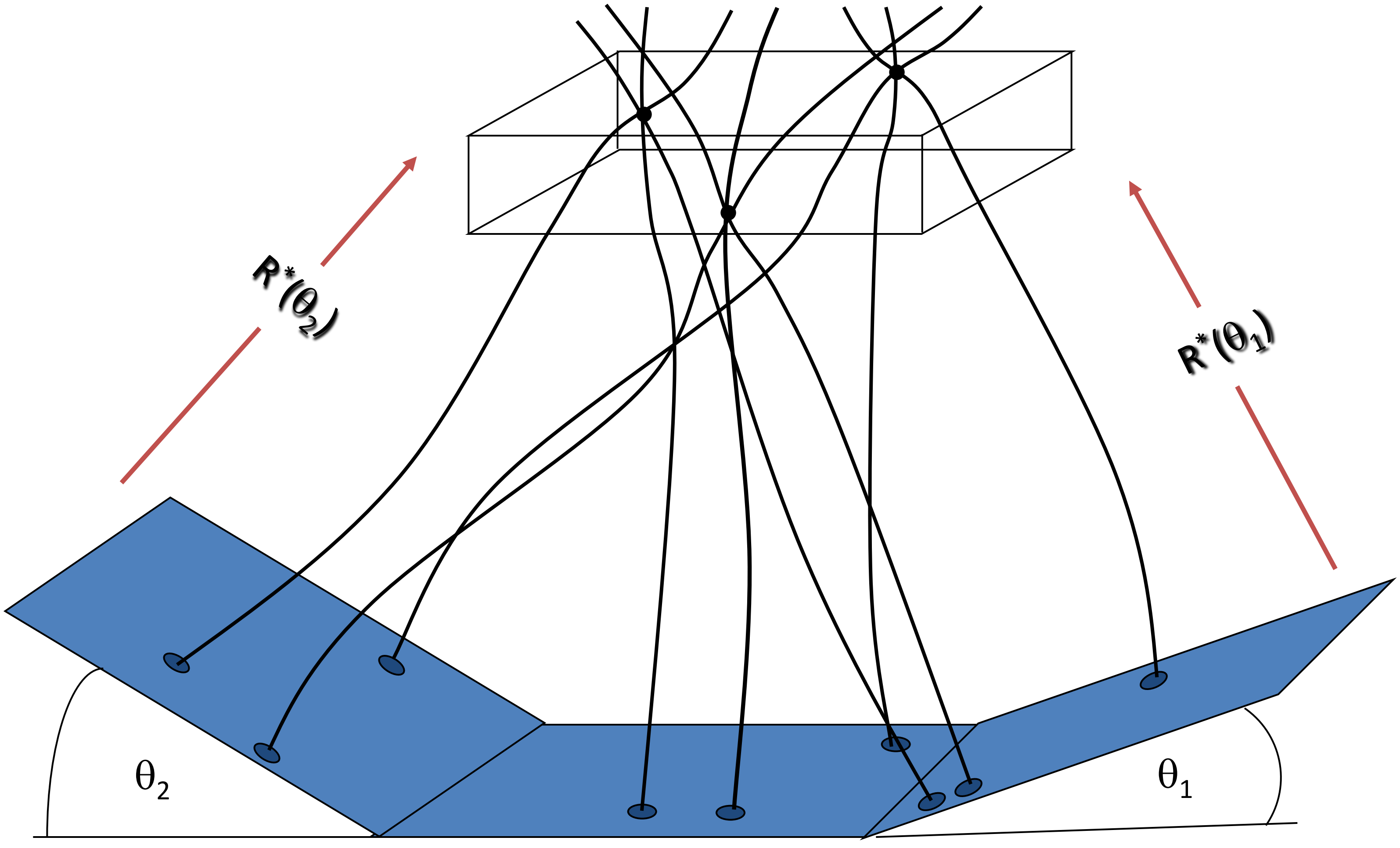
$\hat{u}$ = image intensity

Linear "single scattering model"

$$\hat{u}(\theta; X_0) = u_0 \cdot e^{-\int_{S_i}^{S_f} \nu(\gamma(\theta; X_0, s))\,ds}$$

$$u = \ln(\hat{u}(\theta; X_0)) = -\int_{S_i}^{S_f} \nu(\gamma(\theta; X_0, s))\,ds$$

Backprojection Along Curvilinear Trajectories



Mathematical Model

$$\Gamma = \{\gamma_{(\theta;x,y)}\}$$

Family of trajectories
Indexed by image point
and sample angle.

$$R_\Gamma u(\theta;x,y) = \int_{s=s_i}^{s=s_f} u(\gamma_{(\theta;x,y)}(s))ds$$

Transform defined by
integration of density
along trajectories

$$R_\Gamma^* v(x,y,z) = \int_{\gamma_{(\theta;x,y)}(s)=(x,y,z)} R_\Gamma u(\theta;x,y)d\theta$$

Adjoint transform
defined by integration over
sample orientations

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Operator Theory for Filters

$$u + Tu = R_\Gamma^{\ *} F R_\Gamma u = R_\Gamma^{\ *} F v$$

• In general, filtered backprojection works only up to an error term. For some special cases $T \to 0$.

$$\Psi = R_\Gamma^{\ *} R_\Gamma$$

• A well-known theorem states that the composition of a ray transform with its adjoint is an elliptic pseudo-differential operator.

$$u = \Psi^{-1} R_\Gamma^{\ *} v$$

• Heuristically, we would like to invert the operator, and compose with the adjoint ray transform.

Setting Up the Transform as a Fourier Integral Operator

Electron trajectories define coordinate transform

Inverse transforms

Constant beam model

FIO as coordinate transform

$$\Omega_\theta : (X,Y,Z) \to \gamma_{\theta;X,Y}(Z)$$

$$\Pi_\theta{}^{aug}(X,Y,Z) = (\Pi_\theta(X,Y),Z)$$

$$\Omega_\theta \Pi_\theta{}^{aug} = I$$

$$A_\theta(X,Y,Z) = {\Pi_\theta^{aug}}^{-1}\Omega_0(\Pi_\theta^{aug}(X,Y,Z),Z)$$

$$\overline{R_\Gamma u}(\omega) = I_\Gamma \bar{u}(\omega) =$$

$$\frac{1}{(2\pi)^3}\iint e^{i(x\cdot\xi - \omega\cdot A_\theta^{-1}(x))}\det(A_\theta^{-1}(x))\bar{u}(\xi)\,dx\,d\xi$$

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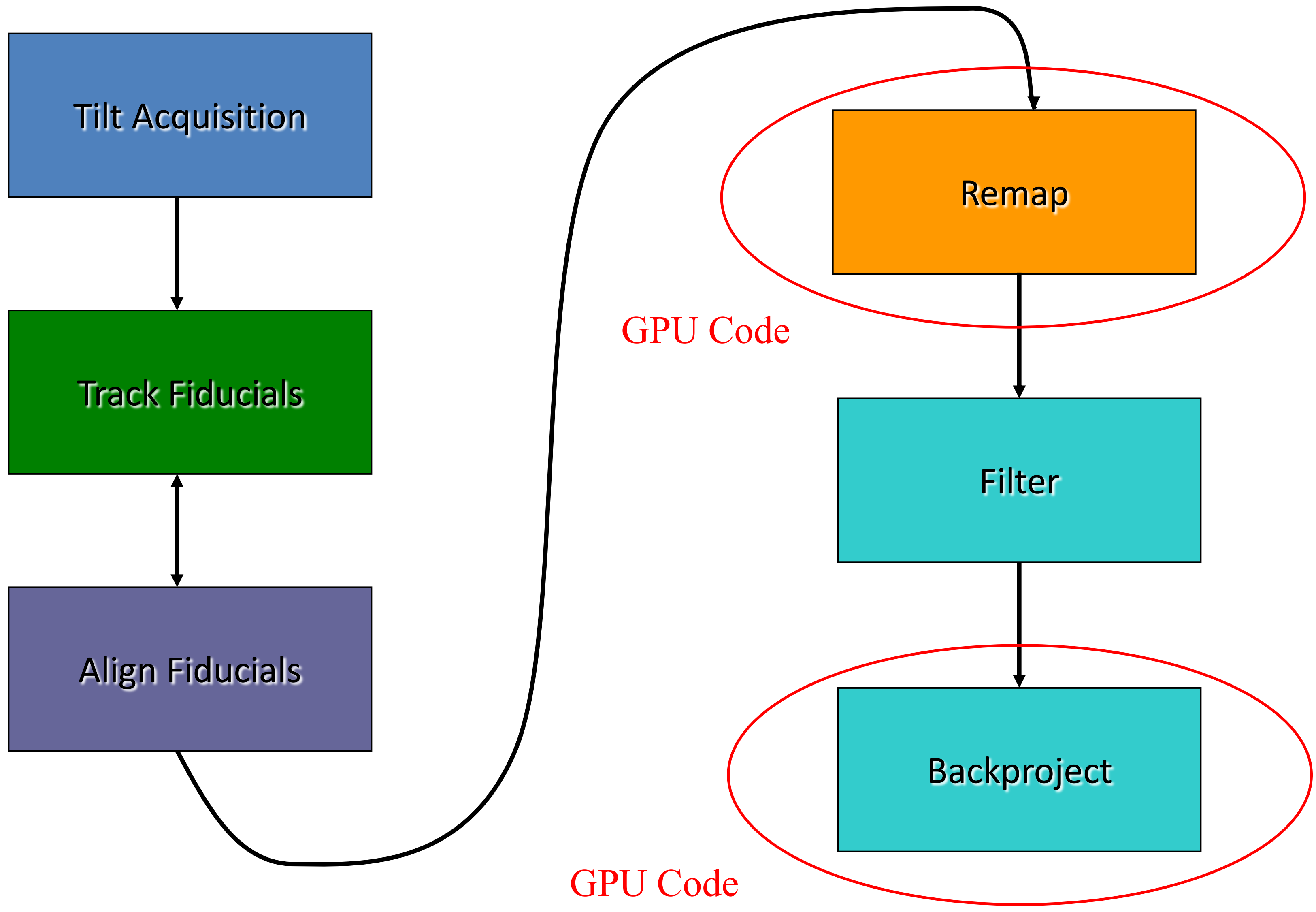
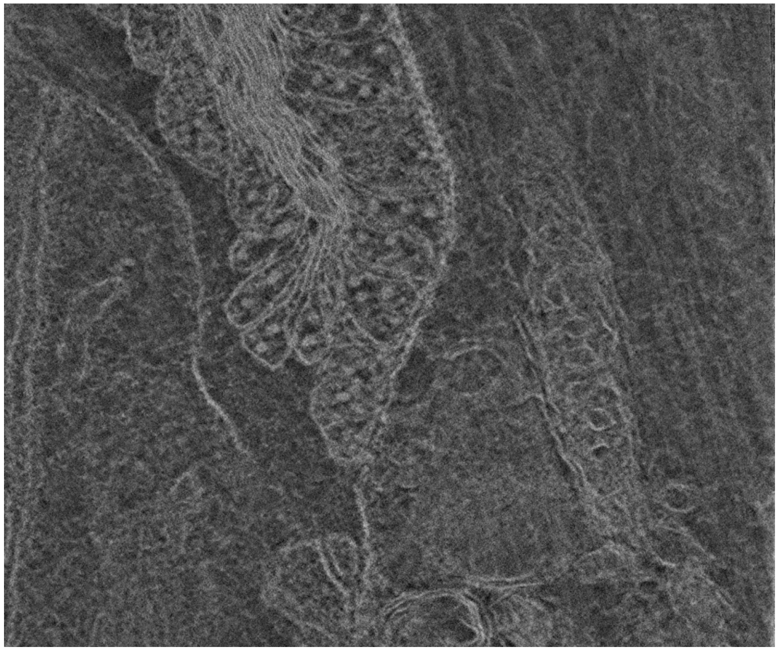
Tomography Workflow



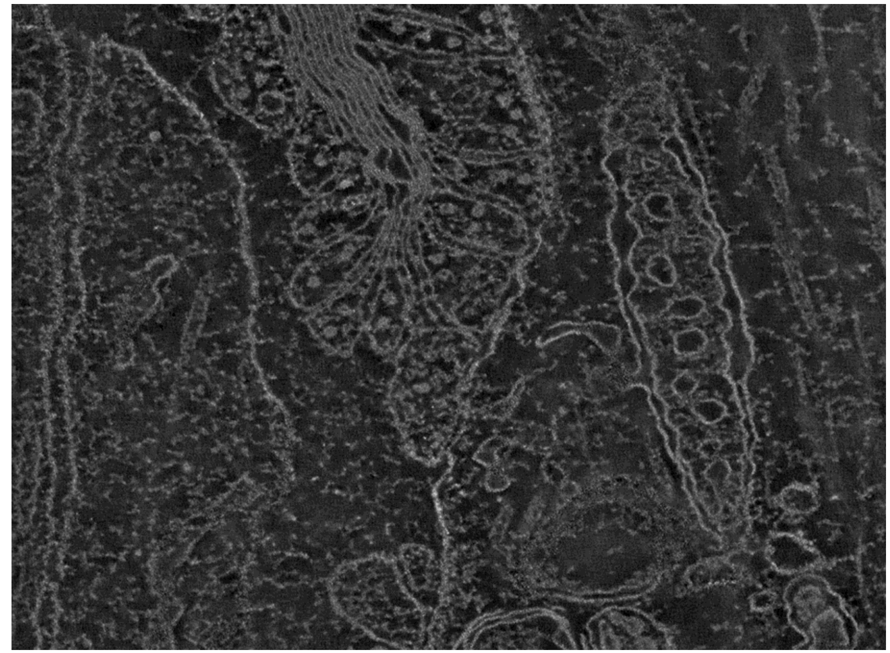
Transform-based Tracking, Bundle adjustment and Reconstruction

- Tracks gold particles deposited on surface of sample through tilt series images.
- Accepts general set of sample orientations.
- Constructs series of geometrically nonlinear projections simultaneously with 3D model of gold particle positions via generalized bundle adjustment.
- Corrects projection maps to 9th order polynomials.
- Remaps (warp) tilt series images to align tracks to run orthogonally to projected tilt axis.
- Applies one of the common r-weighted filters to tilt series images.
- Backprojects via adjoint of curvilinear projection calculated in the bundle adjustment.
- Utilizes fast recursion, MPI code for backprojection.

Curvelet Noise Reduction and Quality Enhancement



Reconstruction from Original Tilt Series

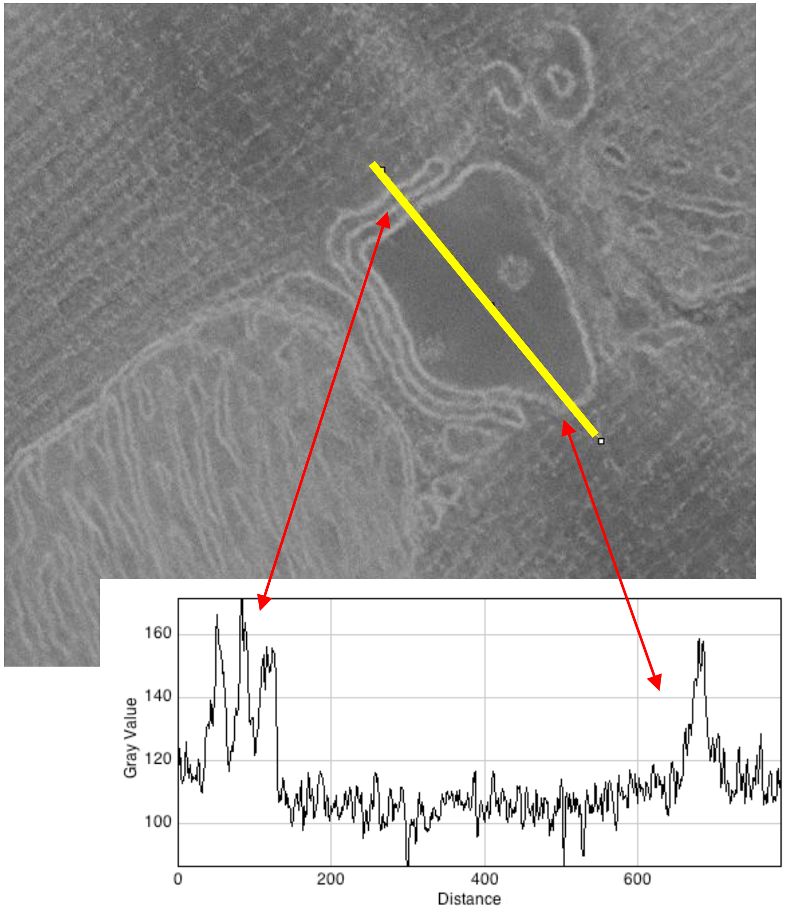


Reconstruction after Curvelet Denoising of Tilt Series

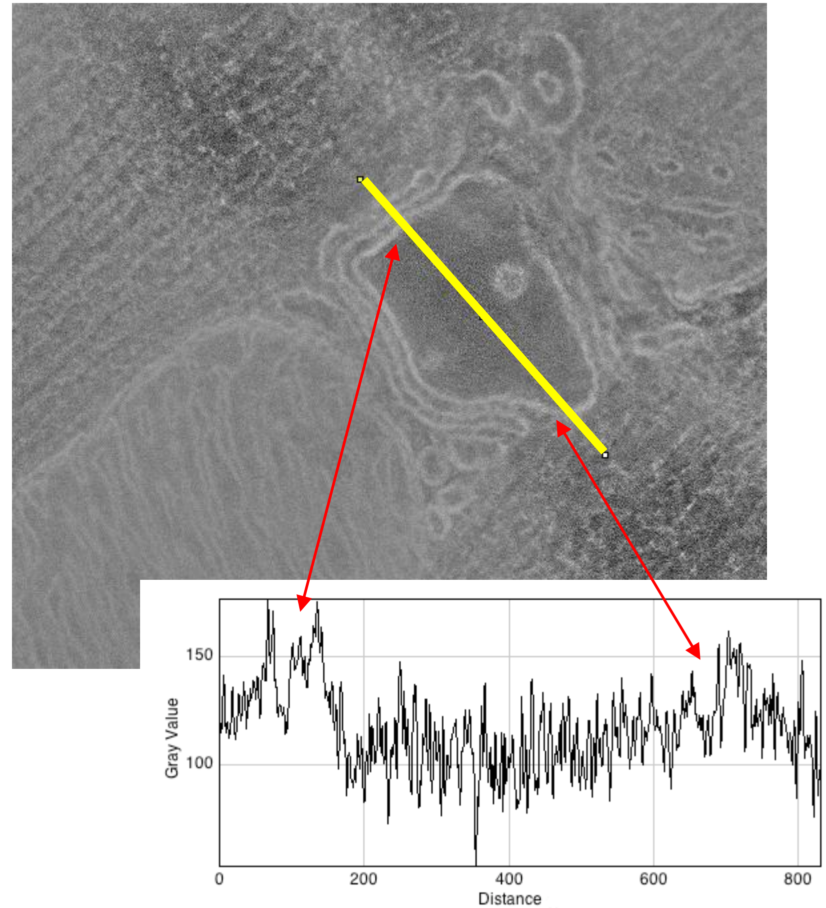
- Curvelet algorithms are computationally costly
- Noise reduction is not always succesful
- More research is needed—Combine with regularization?

Which is Better for Automatic Segmentation?

TxBR



IMOD

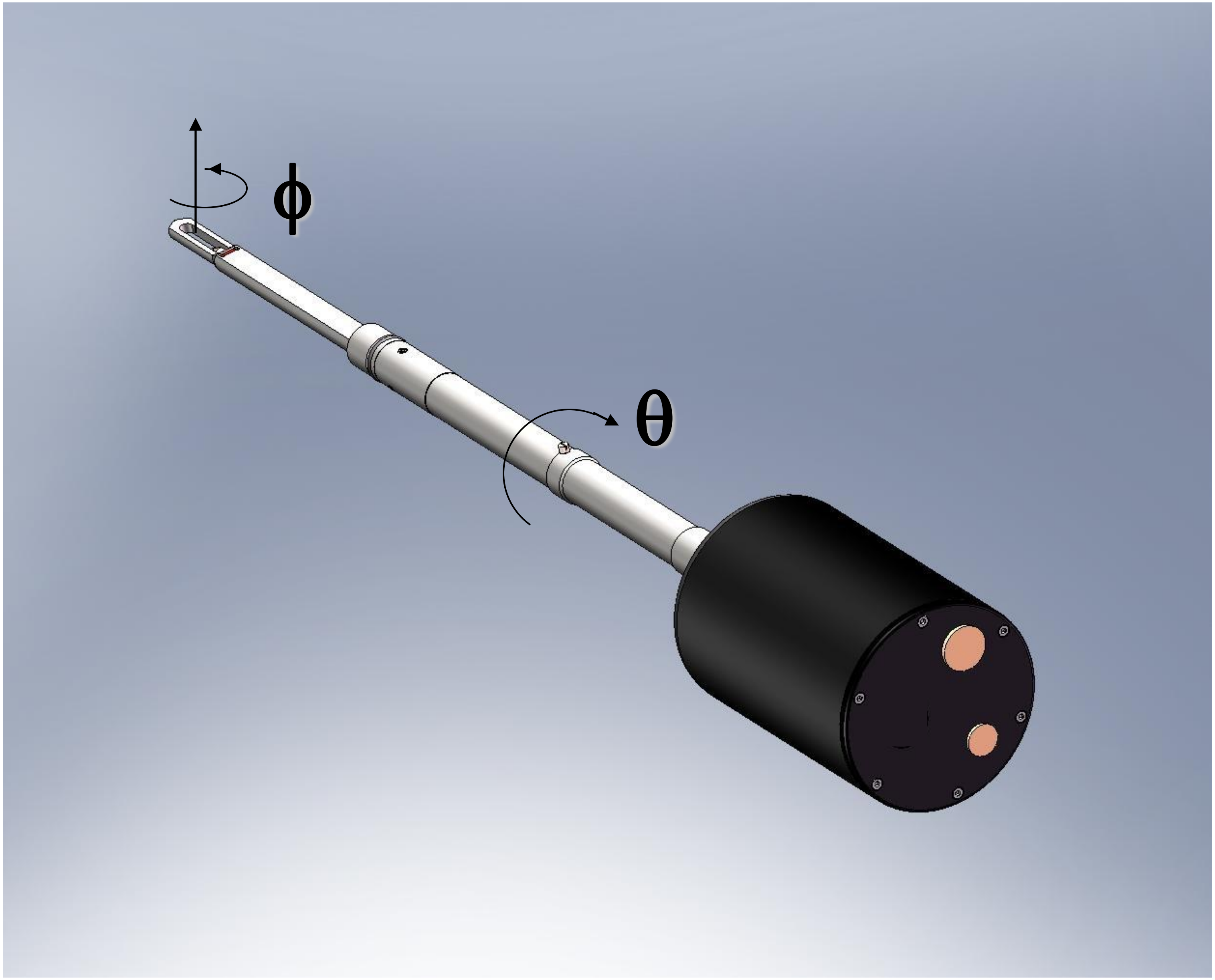


Cardiac tissue reconstruction sections

Tracking

- Correlation-based
- Marker based
- Feature based
- Extended structures

Multiple Axis Tomography



Alignment

- Electron trajectories are curvilinear
- This makes the alignment problem three dimensional
- Feature positions in object are calculated from tracks in images
- Feature positions and projection maps must be consistent with markers in images
- Intrinsic trajectory equations

$$P_\omega(\gamma^1_{x,\omega}(t), \gamma^2_{x,\omega}(t), \gamma^3_{x,\omega}(t)) = (x_1, x_2)$$

- Projection maps

$$P_\omega(X_1, X_2, X_3) = (x_1, x_2)$$

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Alignment Models

- Projective model

$$\lambda_{\omega}(X_1, X_2, X_3)\begin{bmatrix} x_1 \\ x_2 \\ 1 \end{bmatrix} = P_{orth}\left(\left[G_{\omega} \mid t_{\omega}\right]\begin{bmatrix} X_1 \\ X_2 \\ X_3 \\ 1 \end{bmatrix}\right)$$

$$\lambda_{\omega}\left(X_1, X_2, X_3\right) = 1 + \sum_i \lambda_{\omega}^i X_i \qquad \left[G_{\omega} \mid t_{\omega}\right] = \begin{bmatrix} b_{\omega}^{11} & b_{\omega}^{12} & b_{\omega}^{13} & t_{\omega}^{1} \\ b_{\omega}^{21} & b_{\omega}^{22} & b_{\omega}^{23} & t_{\omega}^{2} \\ b_{\omega}^{31} & b_{\omega}^{32} & b_{\omega}^{33} & t_{\omega}^{3} \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

- Note that “projection” and “projective” are used in two different senses

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General Alignment Model

- Projection model with features, projections, markers and tracks

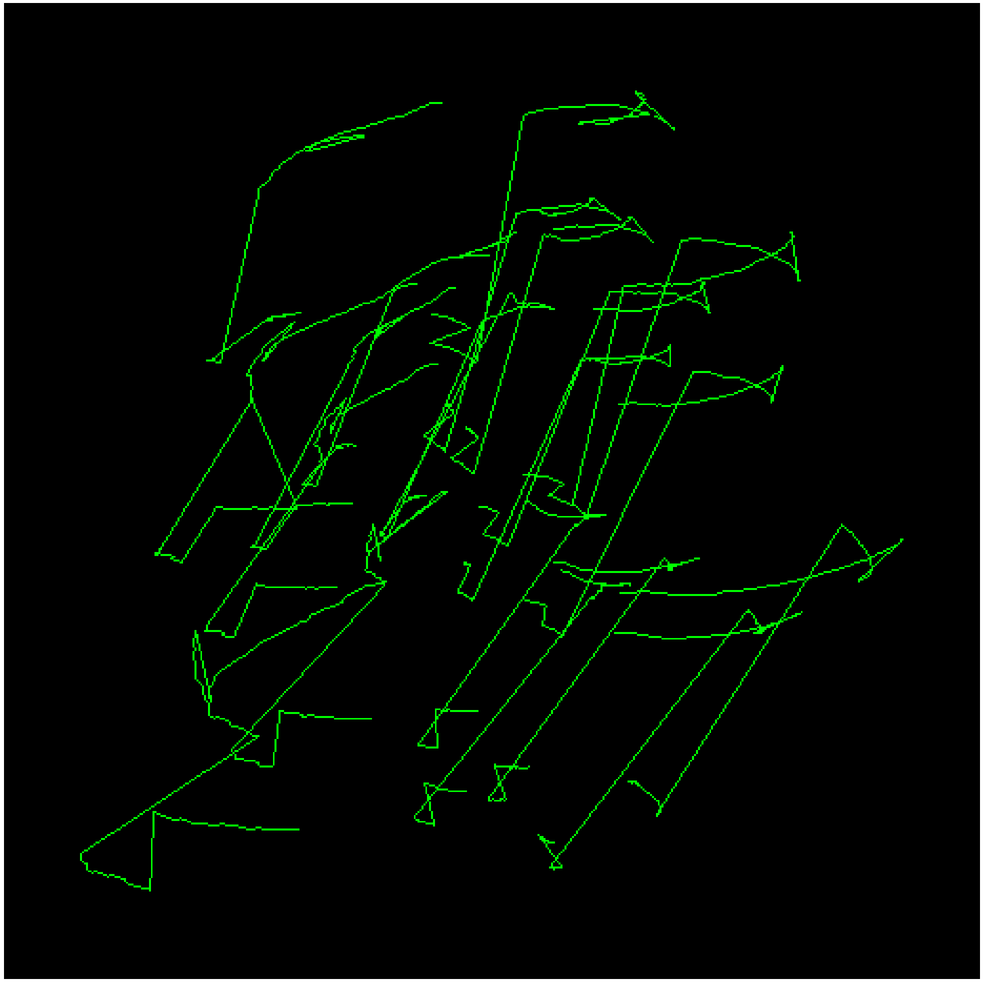
$$P_{\omega} = P_{proj,\omega} + P_{nonlin,\omega}$$

$$T_{\omega\rho} = \left\{ \left(x_{\omega\rho 1}, x_{\omega\rho 2} \right) \middle| \omega \in \left\{ \omega_1, \omega_2, \cdots, \omega_N \right\}, P_{\omega} \overline{X}_{\rho} = \overline{x}_{\omega\rho} \right\}$$

- Error term for conjugate gradient optimization

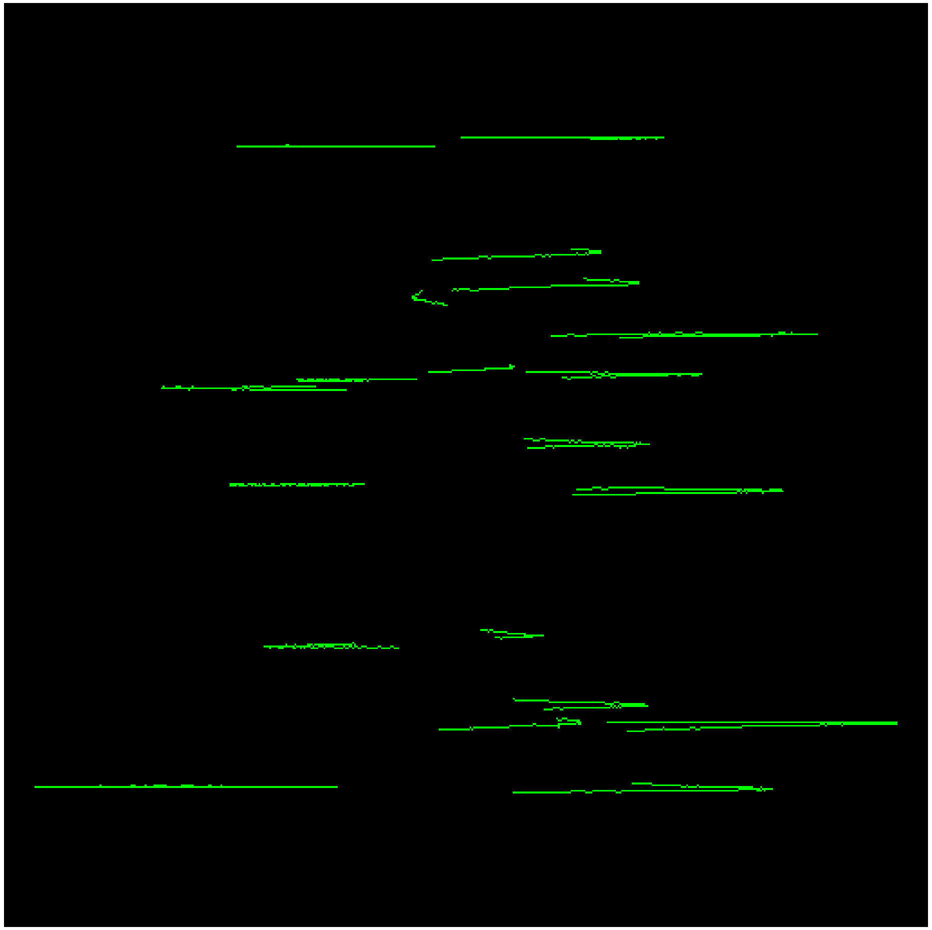
$$E = \sum_{\omega,\rho} \left\| P_{\omega}\left(\overline{X_{\rho}} \right) - \overline{x_{\omega\rho}} \right\|^2$$

Fiducial Marker Tracking



“Remap the images so that the tracks are level”
A. Lawrence - The Tao of TxBR

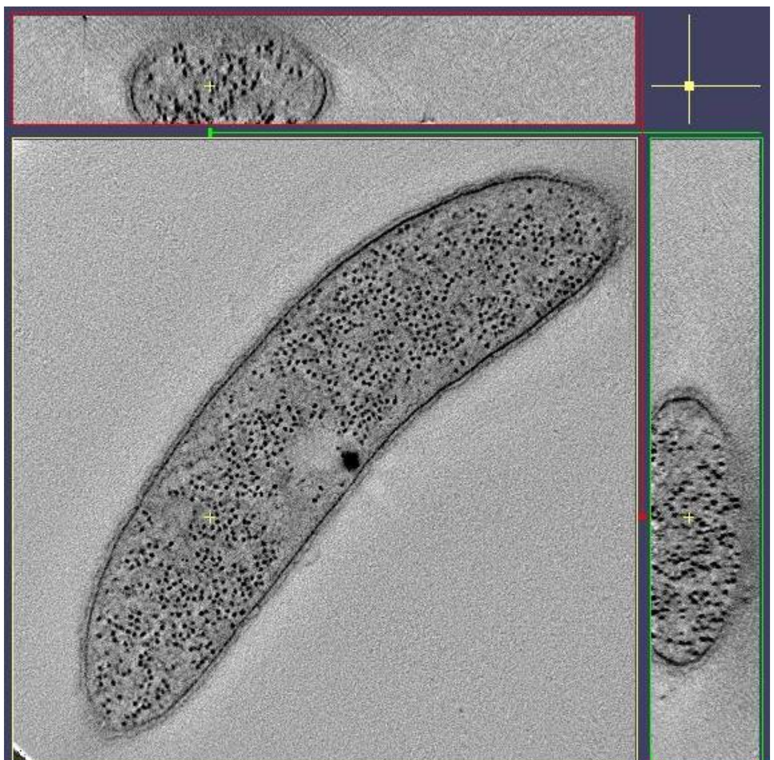
Image Remapping Pre-alignment



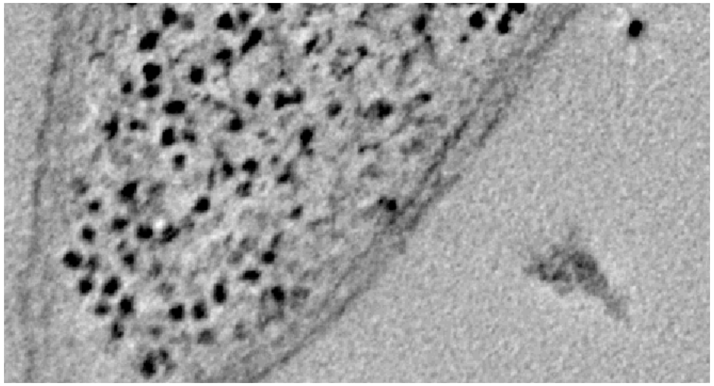
Remaped Particle Tracks

TxBR Reconstruction for Curvilinear Electron Paths

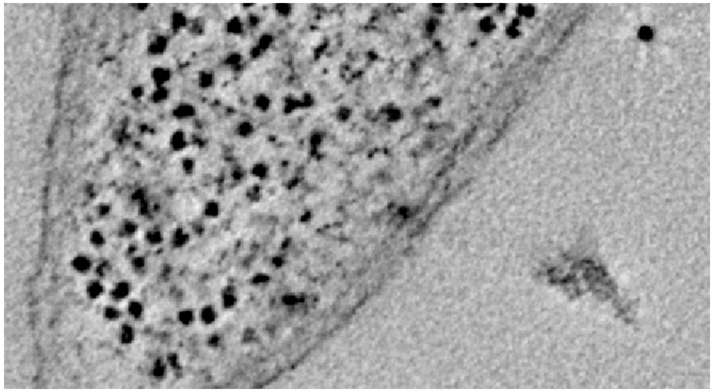
3D TxBR Reconstruction of a Caulobacter Crescentus from 2kx2k electron micrograph



order 1: Reproj. Err.~0.95px



order 3: Reproj. Err.~0.3px



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Transform-based Tracking, Bundle Adjustment and Reconstruction (TxBR-09)

- Aligns on surface contours, fibers and point features; reconstructs surfaces as during alignment process
- Dewarping of objects distorted by mass loss
- Backprojection code runs on GPU boards
- Cross validation for elimination of limited angle artifact, discretization artifact and sampling bias.

Contour Alignment

- Spreading gold markers on the surface is a random process.
- No gold markers within a plastic section.
- Gold particles bring artifacts in the reconstructed volume.
- Living cells contain extensive membrane structures.
- Staining generally occurs along surfaces.
- Surfaces project to contours in images.

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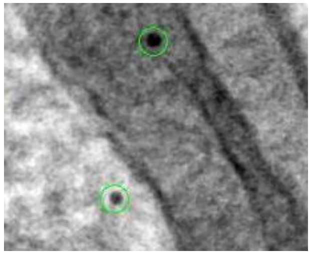
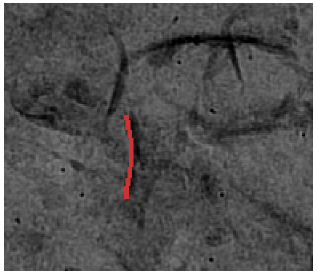
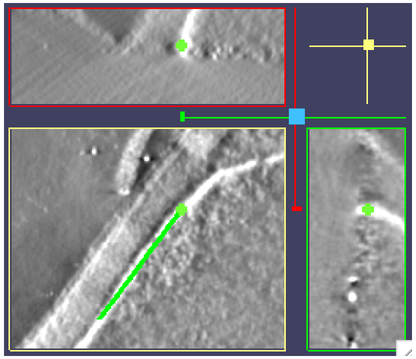
Possible Alignment Markers in Electron Tomography

- Point-like Markers (gold particle, ribosome…)

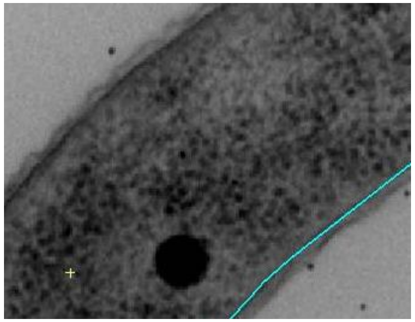


- Linear Markers (fibers, structure edges…)





- Surface Markers (membranes,…)



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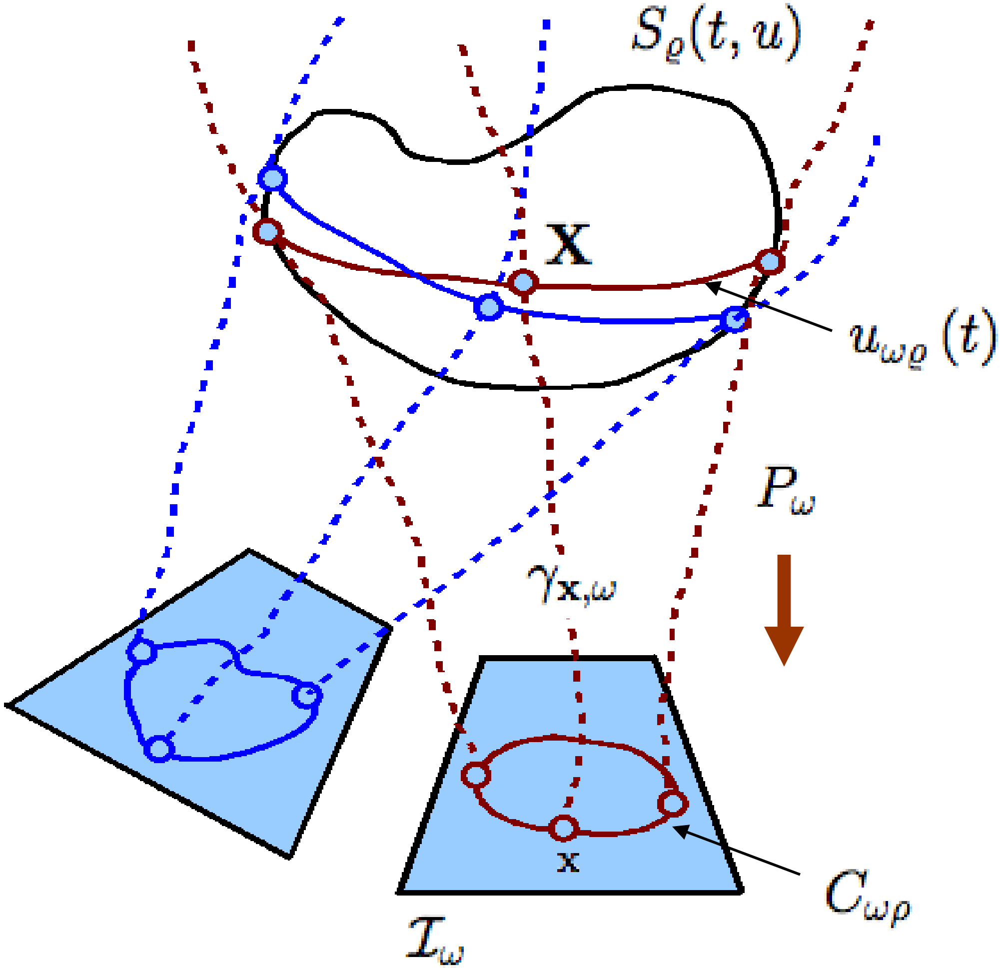
Projection Along Rays



- **Surface S_ρ of a 3D object ρ is parameterized with (*t*,*u*).**
- **We restrict S_ρ to be small patches. Use of polynomial expressions for S_ρ (*t*,*u*).**
- **Curvilinear rays tangent to surface. Use of a polynomial expression for the projection map P_ω. Index ω represents a sample orientation.**
- **Contour in surface where $u_{\omega\rho}(t)$ projects to contour $C_{\omega\rho}$ in image I_ω.**

Contour Alignment Model

- Contour Tracks:

$$C_{\omega\rho} = (x_{\omega\varrho 1}(t), x_{\omega\varrho 2}(t)) \qquad x_{\omega\varrho i}(t) = \sum_{k=0,\cdots,N_1} c_{\omega\varrho ik} t^k$$

- Projection Map:

$$P_\omega (X_1, X_2, X_3) = (P_{\omega 1} (X_1, X_2, X_3), P_{\omega 2} (X_1, X_2, X_3))$$

$$P_{\omega i} (X_1, X_2, X_3) = \sum_{N_2 \geq j,k,l \geq 0} b_{\omega ijkl} X_1^j X_2^k X_3^l$$

- Structure Patches:

$$S_\varrho(t, u) = (S_{\varrho 1} (t, u), S_{\varrho 2} (t, u), S_{\varrho 3} (t, u))$$

$$S_{\varrho i}(t, u) = \sum_{N_3 \geq kl \geq 0} a_{\varrho ikl} t^k u^l$$

- Surface Contours:

$$u_{\omega\varrho} (t) \cong \sum_{k=0,\cdots,N_4} d_{\omega\varrho k} t^k$$

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A Generalized Bundle Adjustment

Two Error Terms to minimize:

- A Projection Error: $P_\omega S_\varrho\left(t, u_{\omega i}\left(t\right)\right) = C^{(r)}_{\omega\varrho}(t)$

$$E^P_{\omega\varrho} = \int_{t_0}^{t_1} \left\|P_\omega S_\varrho\left(t, u_{\omega\varrho}\left(t\right)\right) - C_{\omega\varrho}(t)\right\|^2 dt$$

- A Tangency Error:

$$P_{\omega i}\left(\gamma^1_{\mathbf{x},\omega}(t), \gamma^2_{\mathbf{x},\omega}(t), \gamma^3_{\mathbf{x},\omega}(t)\right) = x_i \qquad \nabla P_{\omega i} \cdot \dot{\gamma}_{\mathbf{x},\omega} = 0$$

$$E^T_{\omega\varrho} = \int_{t_0}^{t_1} \left\|\nabla P_{\omega 1} \times \nabla P_{\omega 2} \cdot \left(\frac{\partial S_\varrho}{\partial t} \times \frac{\partial S_\varrho}{\partial u}\right)\right\|^2 dt$$

Symbolic Calculation / Optimization

- Error functions are expanded and integration on contours performed prior to optimization.
- Symbolic calculation is implemented with GiNaC (GiNaC is Not a CAS). Use of the swiginac interface. Python libraries sympy and sympycore are too slow for calculations needed in the bundle adjustment process.
- Coefficients $a_{\varrho ikl}, b_{\omega ijkl}, c_{\omega\varrho ik}, d_{\omega\varrho k}$ are treated in a symmetric way. Code is built so it is easy to free or freeze variables during minimization, and also to easily add new variables.
- A linear combination of $E^P_{\omega\varrho}$ and $E^T_{\omega\varrho}$ is minimized with a Line-search Newton Conjugate Gradient algorithm

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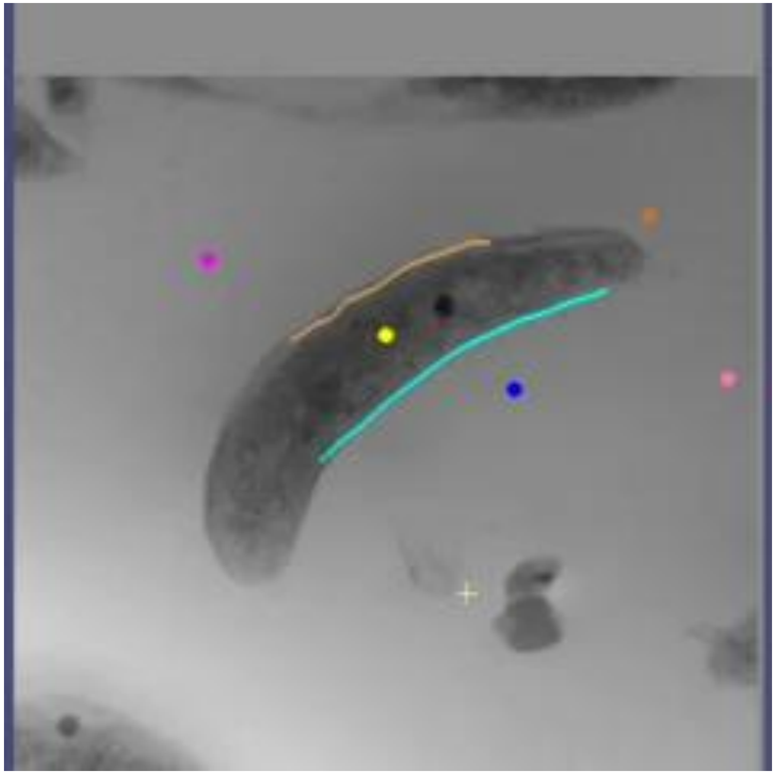
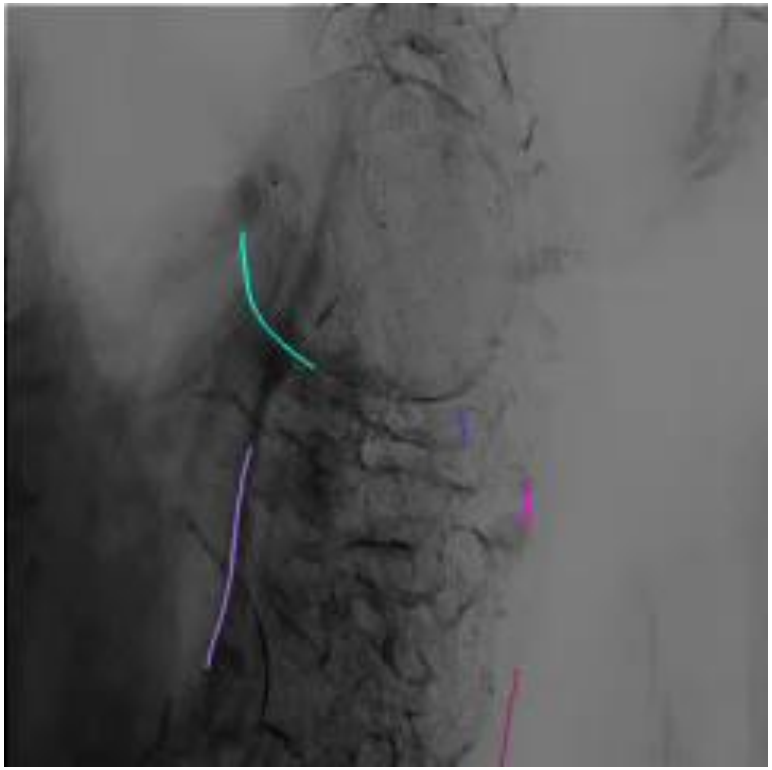
Structure Segmentation



Caulobacter Crescentus



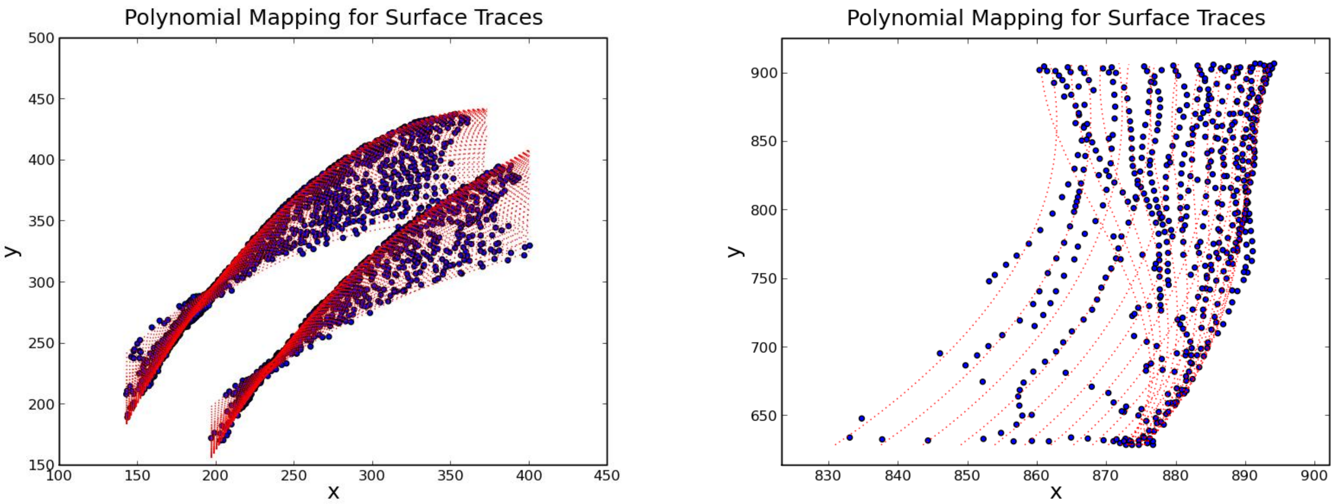
Gia

Parameterization of the contours

What choice? For a tilt series:

- t parameterizes the projection of a surface point onto the camera plane.
- u parameterizes the tilt index

Simultaneous parameterization of tracks allows to assess optimal patch order to describe an object.



⇒ Minimization is then implemented with independent parameterization for each contours.

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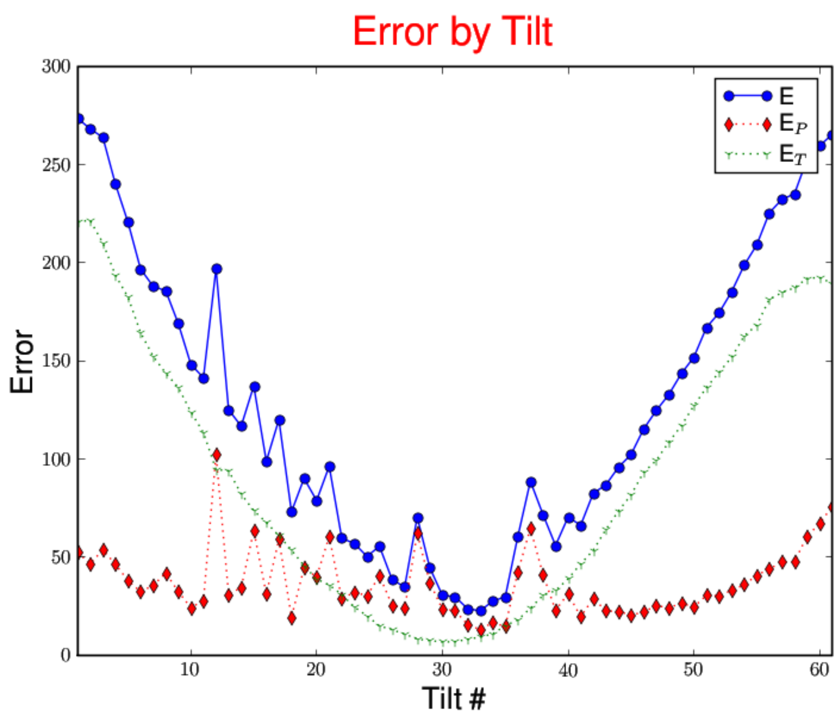
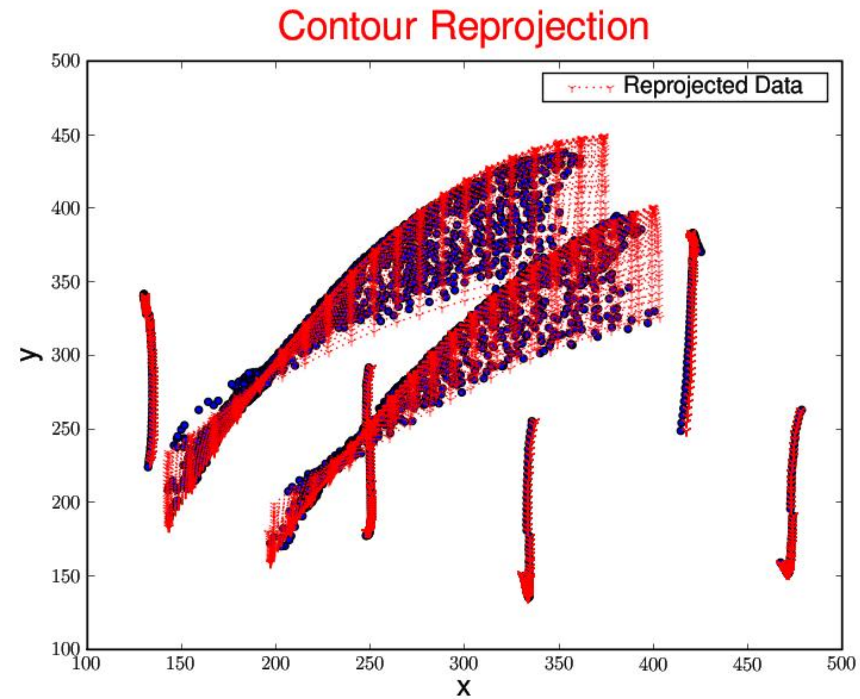
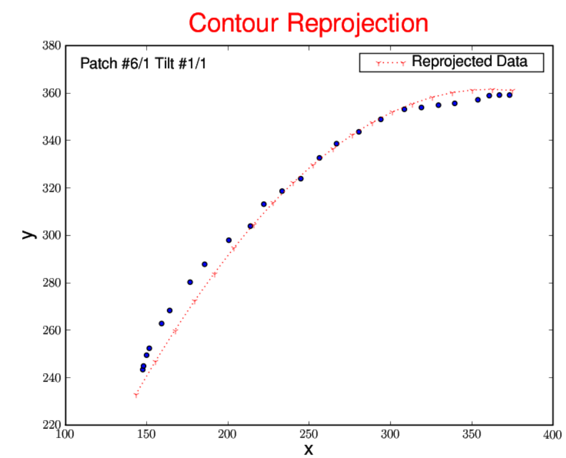
Re-projection Error at Minimum

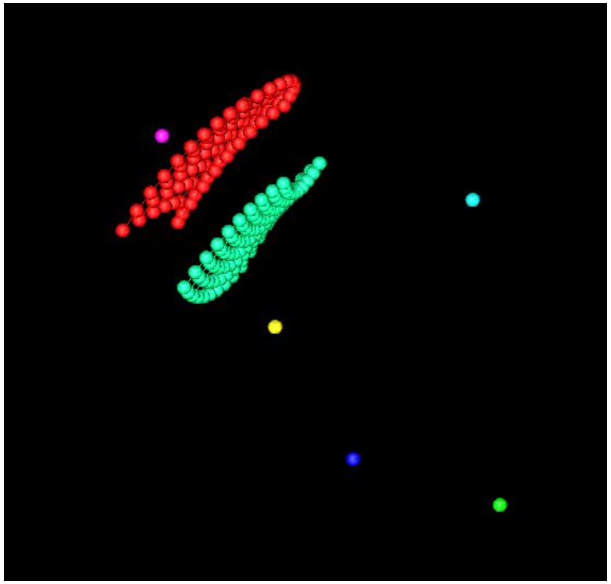
Bundle adjustment applied on Caulobacter Crescentus dataset (500ptsx500pts) with parabolic patches

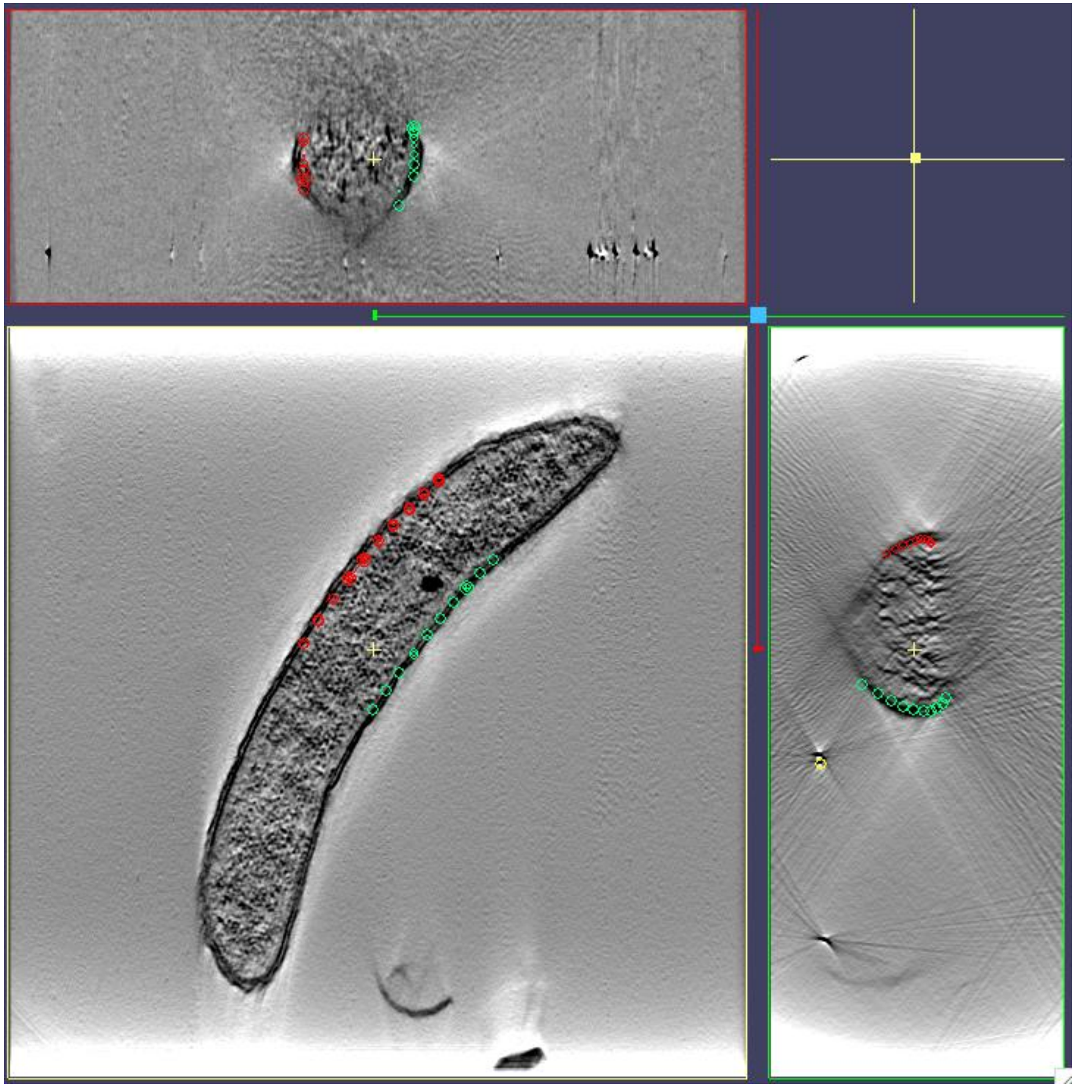






Volume and Patch Reconstruction





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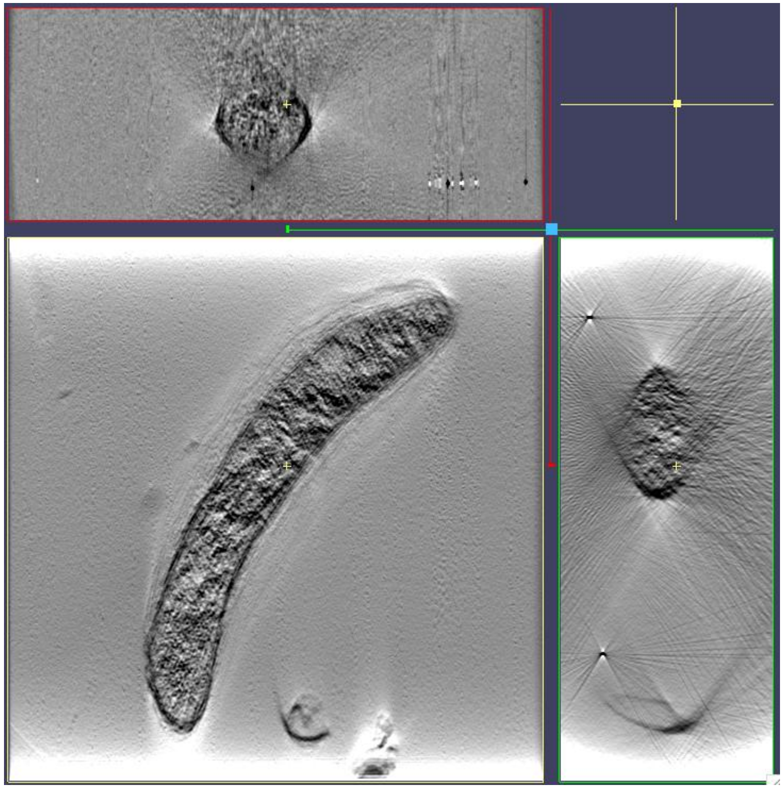
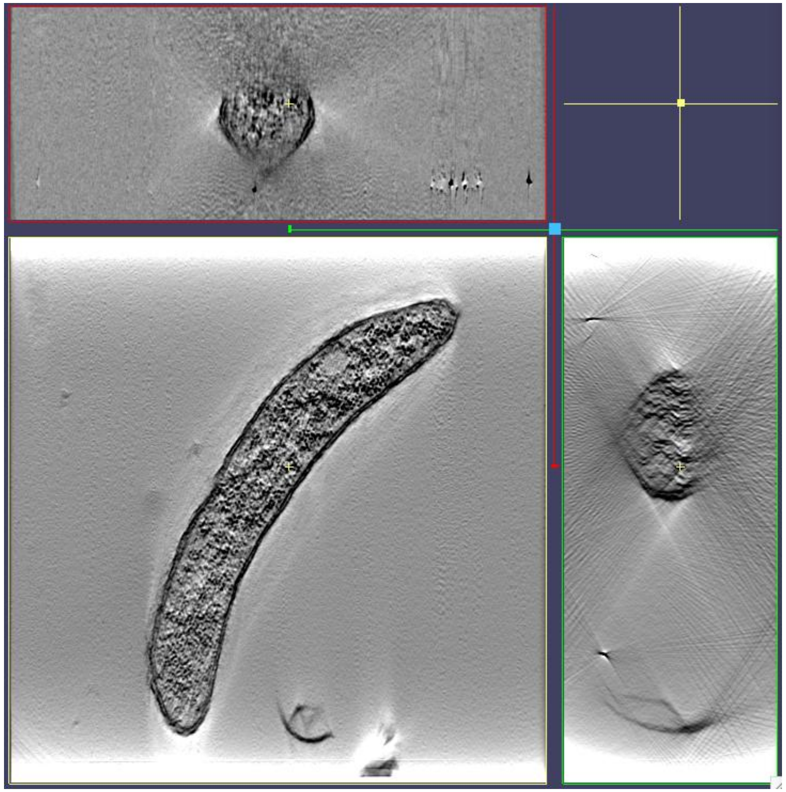
Pure Gold Markers case *vs* Combination of Gold and Surface Tracks case

91 Gold Markers



5 Gold Markers and 2 patches.



(X=262,Y=297,Z=110)

Gold markers only on one side of the specimen.

Linear General Model - No other (orthogonal...) constraint.

Backprojection

- Backprojection requires evaluation of polynomial at each position of object

$$x_{\omega i} = P_{\omega i}\left(X_1, X_2, X_3\right) = \sum_{n \geq i, j, k \geq 0} b_{\omega jkl} X_1^{j} X_2^{k} X_3^{l}$$

- This implies hundreds of calculations at each point for each summand in the backprojection

Recursion Scheme

- Along a line polynomial projection reduces to single variable

$$q(X) = P_{\omega i}(X, N_1, N_2)$$

- Set up recursion scheme to evaluate polynomials

$$q_0^n = q(n), q_1^n = q_0^n - q_0^{n-1}, q_2^n = q_1^n - q_1^{n-1}, etc$$

- If polynomial is of nth degree nth differences are constant

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Implementing Recursion

- Reverse procedure which gives higher-order differences

$$q_m^{n+1} = q_m^n + q_{m+1}^{n+1}$$

- Polynomial can be calculated from initial segment of difference table and nth order differences
- Evaluation of polynomial is reduced to a few additions at each point, linear increase of computations with increase of degree

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Graphics Processing Unit (GPU)

- Development driven by the multi-billion dollar game industry
  - Bigger than Hollywood
- Need for physics, AI and complex lighting models
- Impressive Flops / dollar performance
  - Hardware has to be affordable
- Evolution speed surpasses Moore's law
  - Performance doubling approximately 6 months

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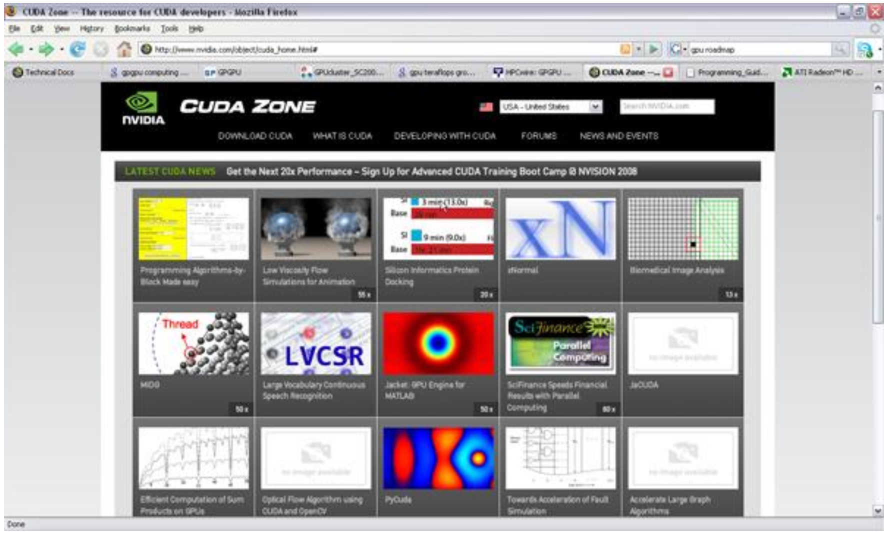
GPGPUs (General Purpose GPUs)

- A natural evolution of GPUs to support a wider range of applications
- Widely accepted by the scientific community
- Cheap high-performance GPGPUs are now available
  - Its possible to buy a $500 card which can provide a TeraFlop of computing.



What Does it Mean for the Scientist?

- Desktop supercomputers are possible
  - No sharing
  - No network latency. Good for real-time applications
- Very efficient
  - Approx 200 Watts / Teraflop
- Turnaround time can be cut down by magnitudes.
  - Simulations can take several days

GPU Hardware

- Highly parallel architecture
  - SIMD
- Designed initially for efficient matrix operations and pixel manipulations pipelines
- Computing core is lot simpler
  - No memory management support
  - 32-bit native cores
  - Little or no cache
  - Largely single-precision support.

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TxBR Backprojection Speedup vs Polynomial Order of Approximation and Image Size

	Order 1	Order 3	Order 5
1K x 1K	3.7 X	4.6X	16.23 X
2K x 2K	4.57 X	6.16 X	44.9 X
4K x 4K	4.18 X	5.08 X	31.8 X
8K x 8K	4.78 X	6.84 X	45.64 X

- Fast recursion algorithm
- One thread per pixel row
- No modification of original MPI code

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Some Cautions

- C-like language support
  - Missing support for function pointers, recursion, double precision not very accurate, no direct access to I/O
  - Cannot pass structures, unions
- Code has to be fairly simple and free of dependencies
  - Completely self contained in terms of data and variables.
- Speedups depend on efficient code
  - Programmers have to code the parallelism.
    - No magic spells available for download
  - Combining CPU and GPU code might be better in cases

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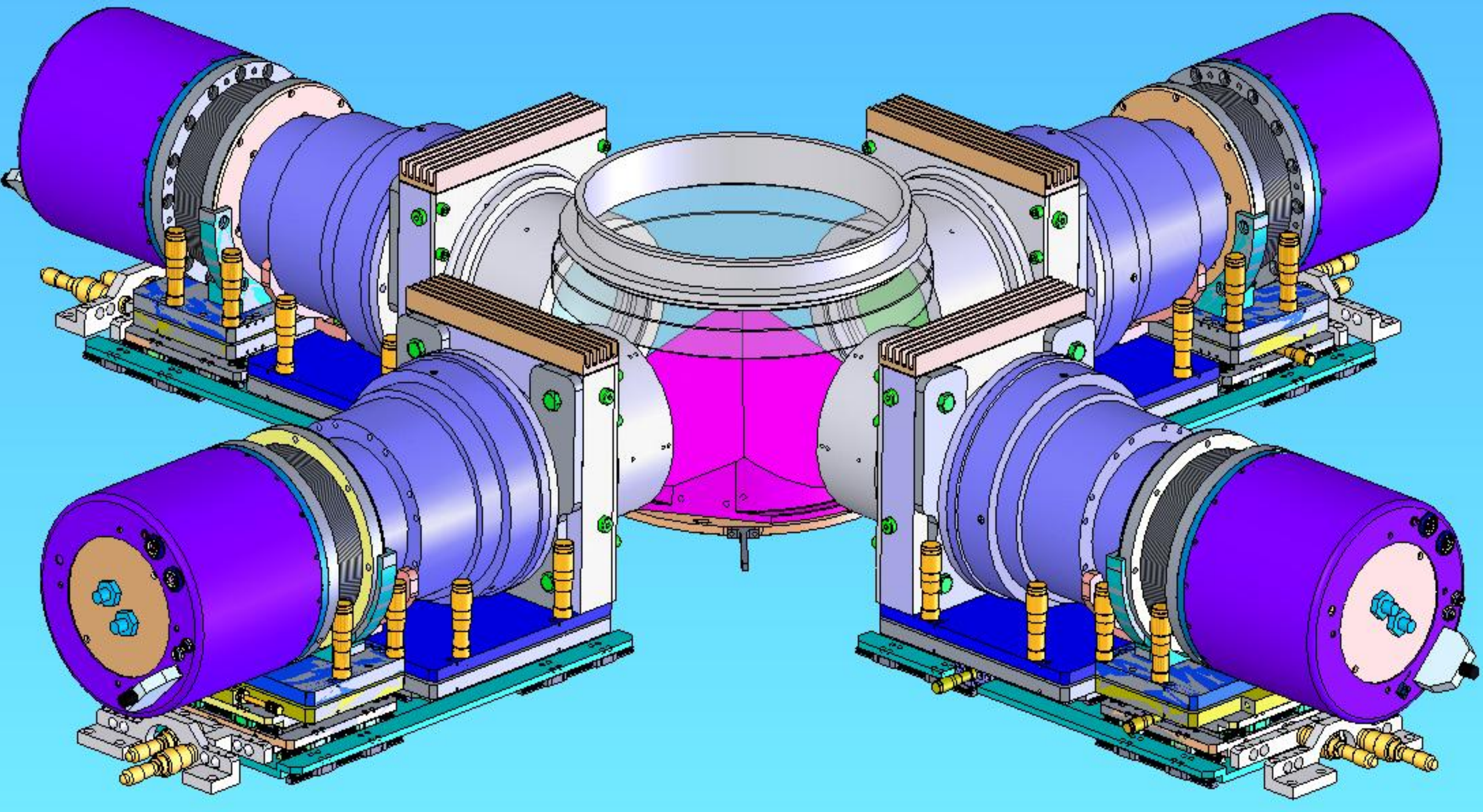
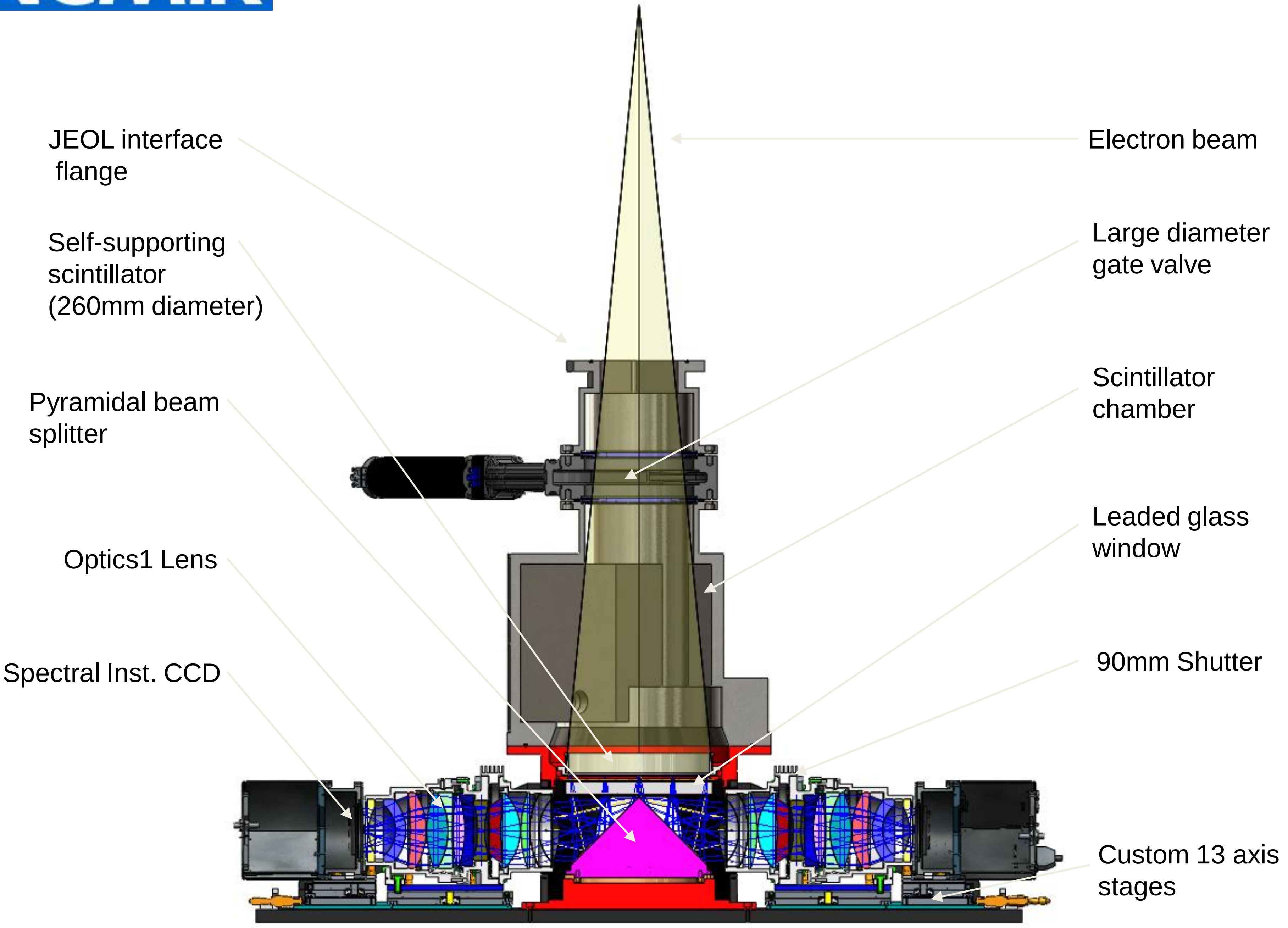
And More Cons …

- Performance is best for computation intensive apps.
  - Data intensive apps can be tricky.
- Bank conflicts hurt performance
- It’s a black-box with little support for runtime debugging.
- BUT…
- The technology is progressing rapidly
- Wider range of applications, and easier programming in the future

A 64 Mega Pixel Digital Detector for TEM



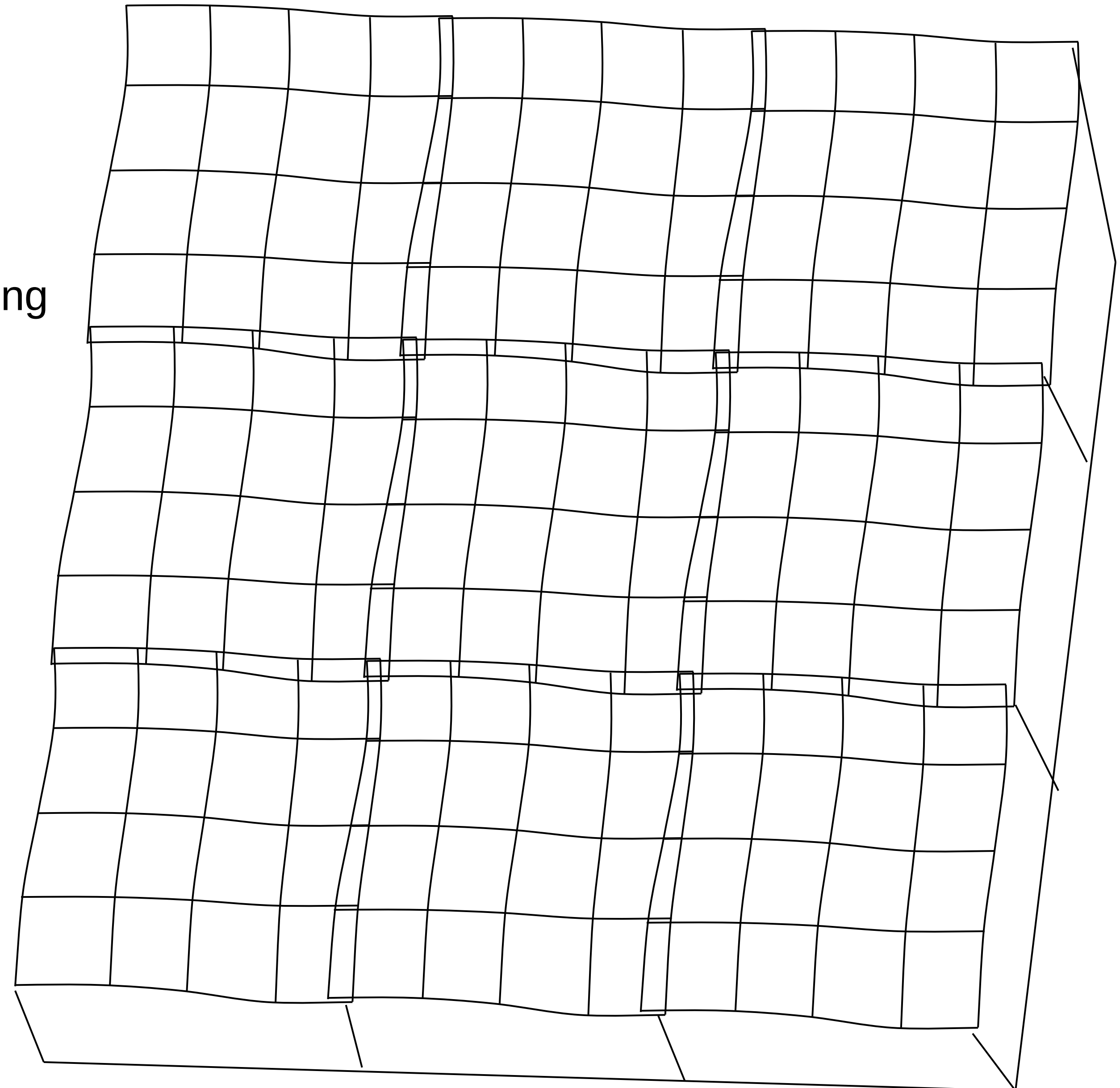
SupraCam in Cross-Section



Montage Tomography

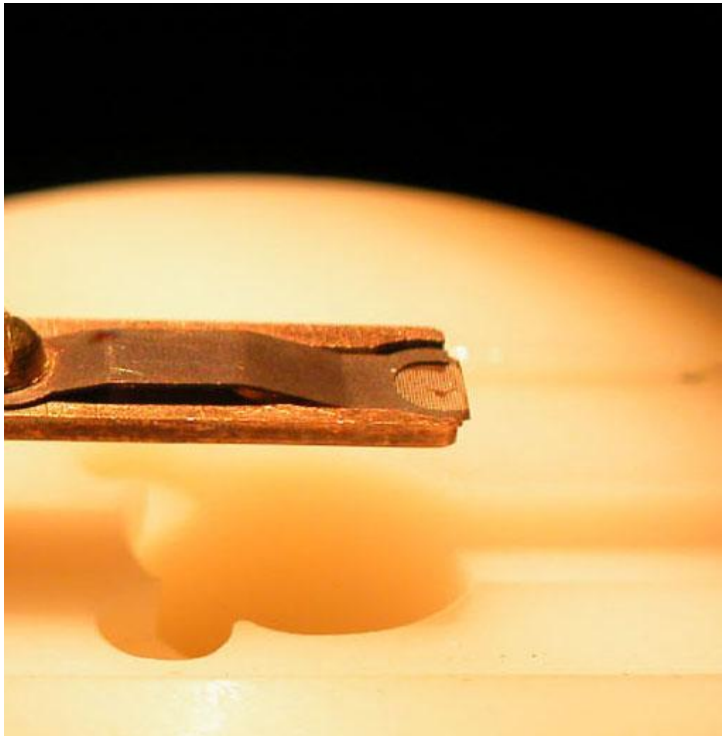
-stage montaging

-image shift montaging

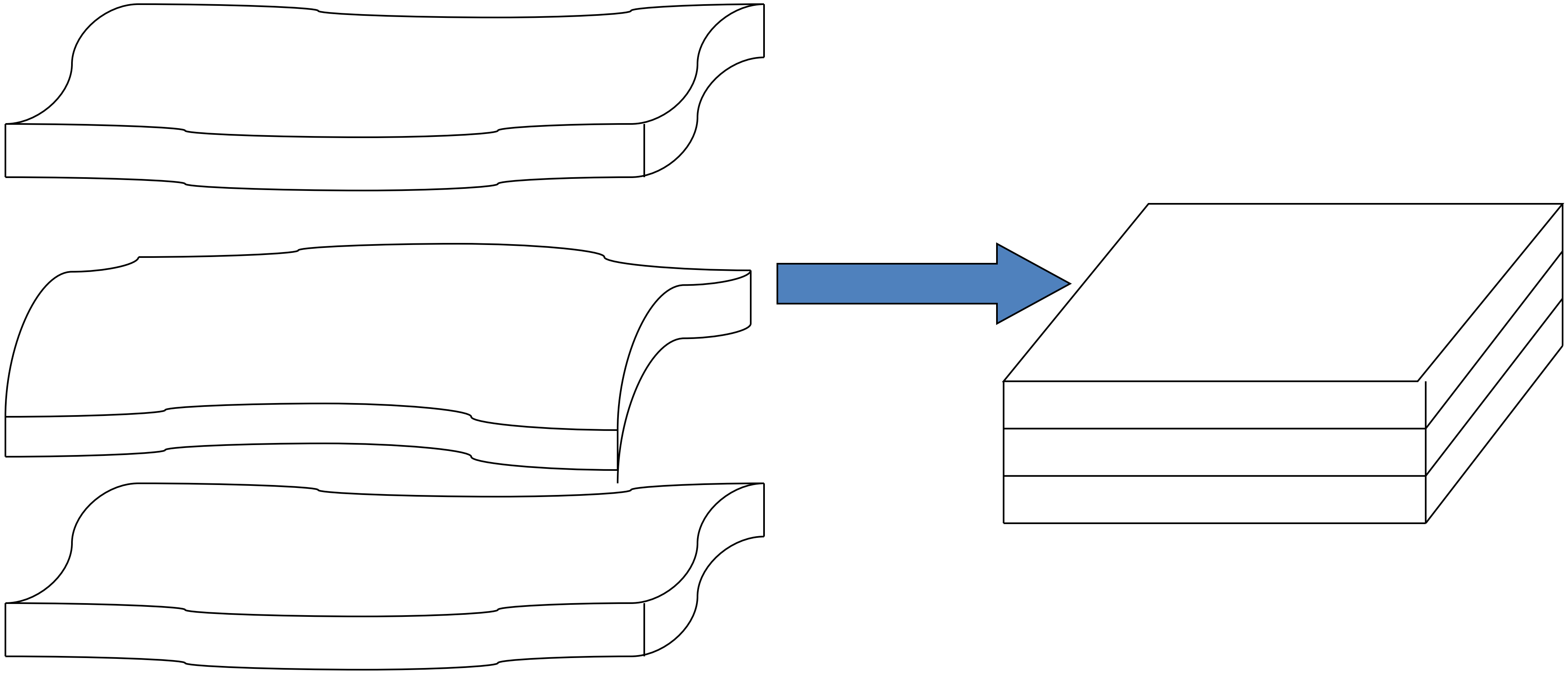


Montaging Problem

- Thin slices become warped during sample sectioning, handling and data acquisition (beam induced mass loss and lens distortions)
- Difficulty in stacking volumes in a serial tomography



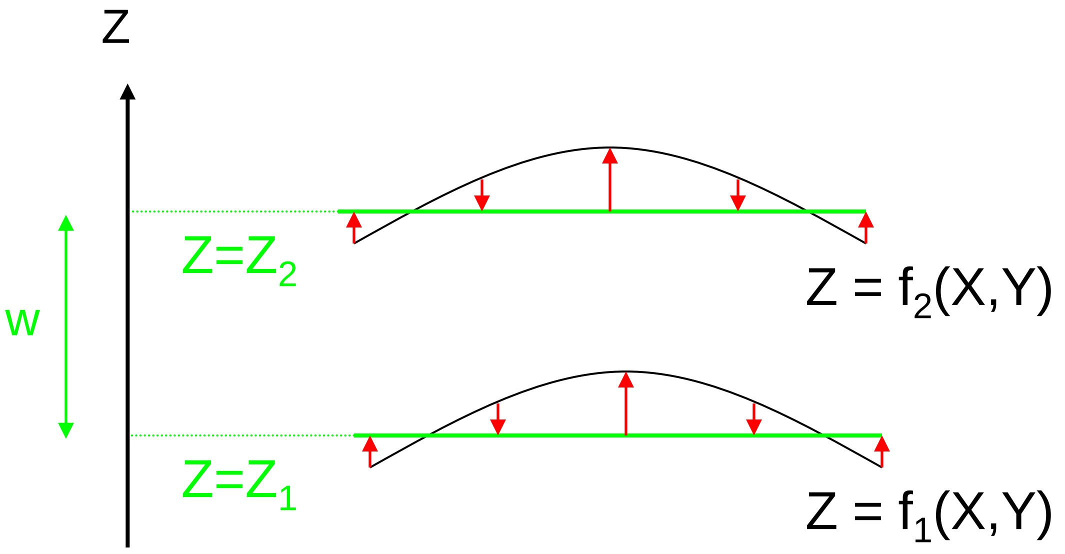
Serial Section Tomography



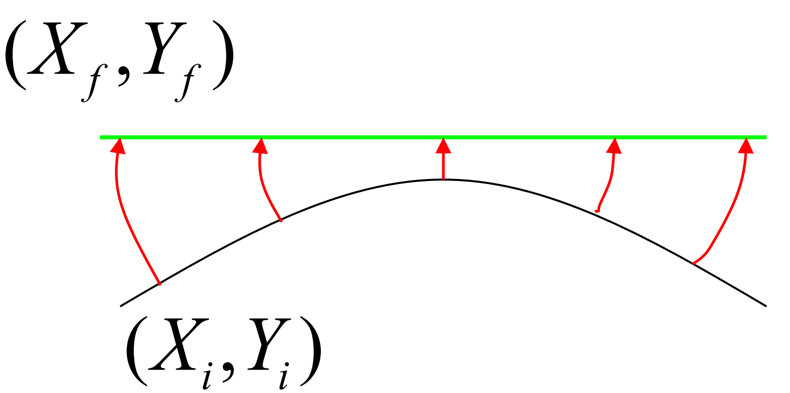
Two Possible Approaches

- Transform an already reconstructed volume
- Modify the projection maps during the bundle adjustment procedure

A shear based warping transformation

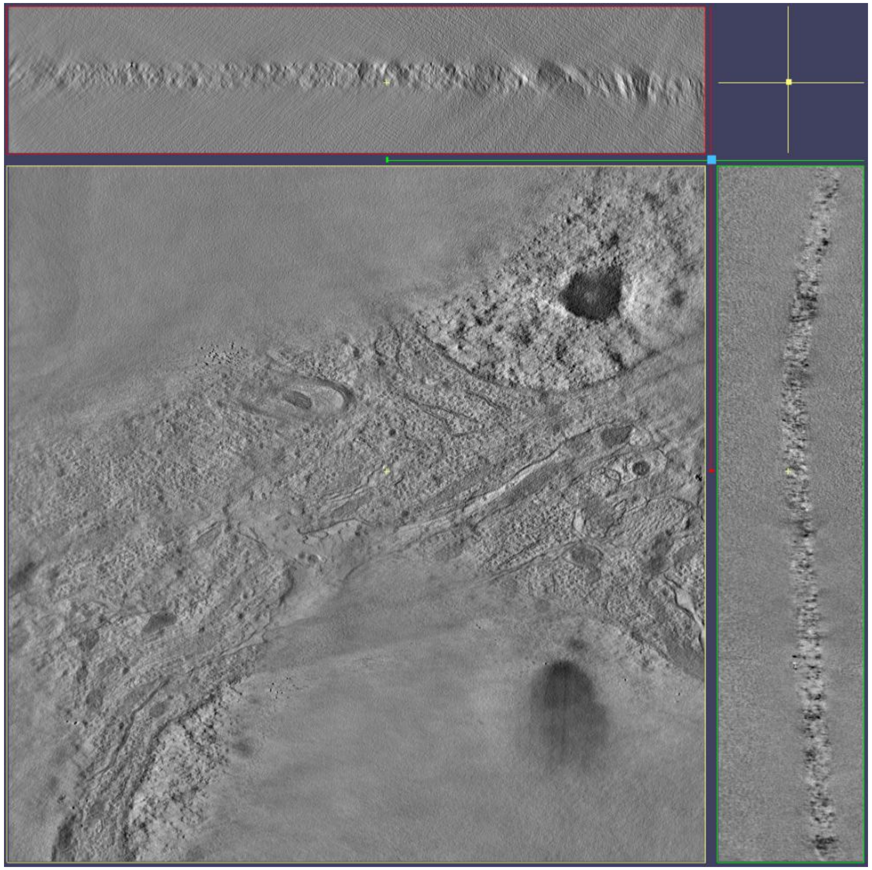


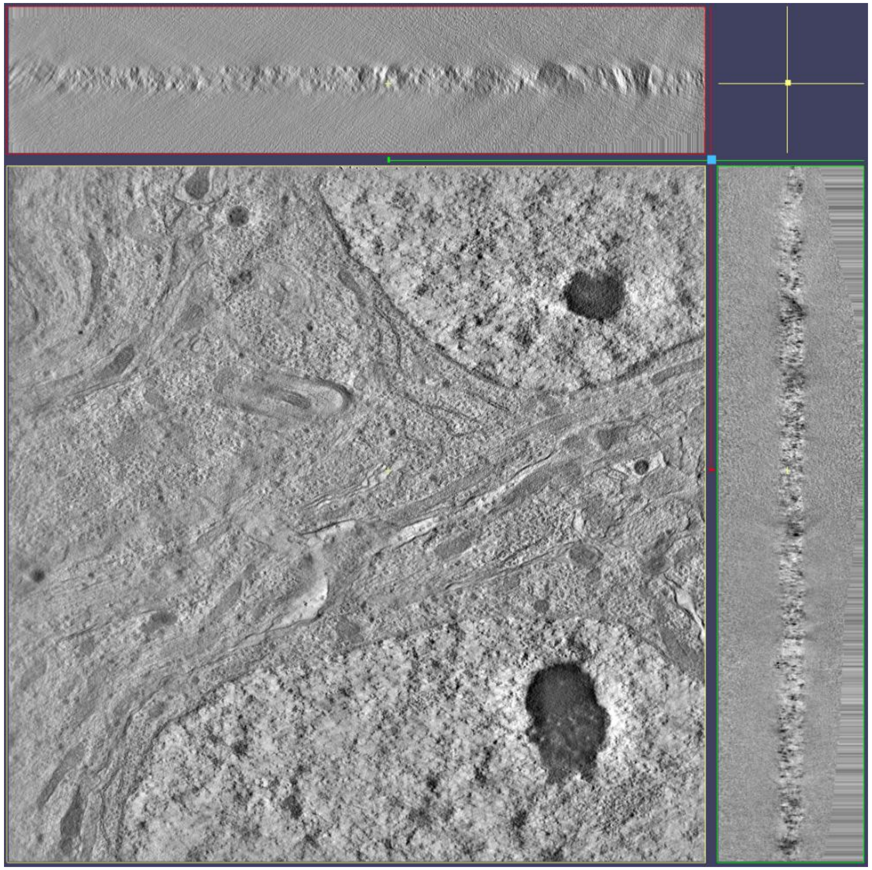
Orthogonal warping transformation



work by: Sebastien Phan, NCMIR-UCSD

Neuron Specimen

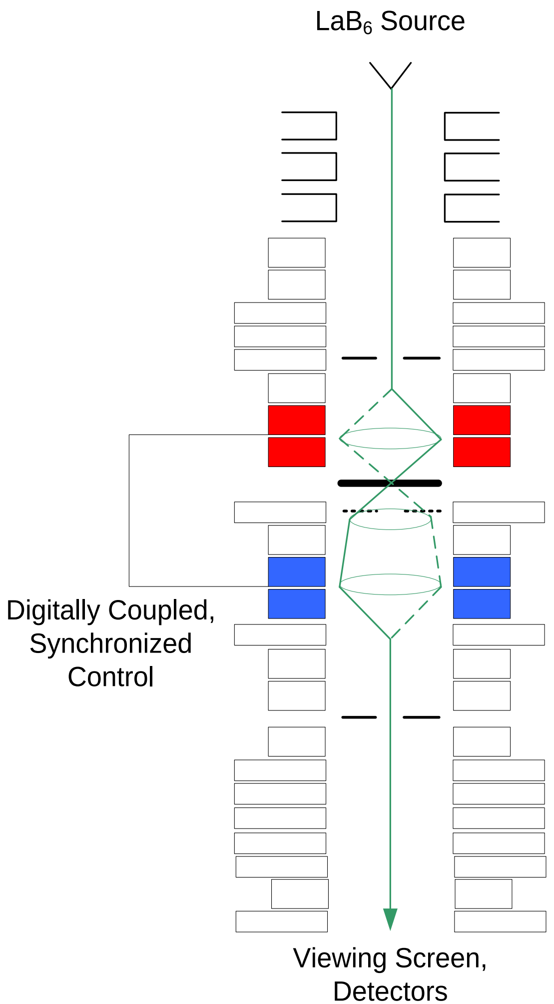


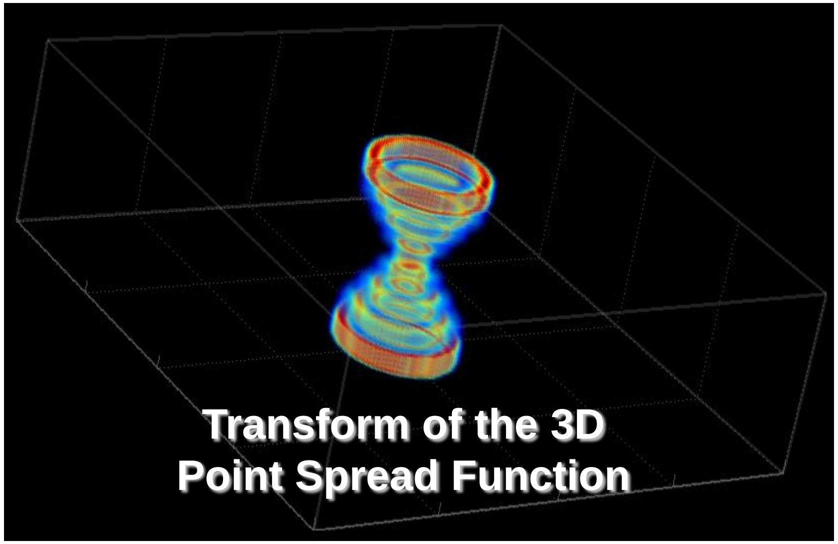


Shear based transformation

Naoko3A7

Continued Progress in Electron Optical Sectioning





- Collecting data to building accurate point-spread function models
- Working on techniques to deconvolve the sections
- Working with Angus Kirkland to explore techniques for controlling the stigmator coils to reduce aberrations

Dev Team: J. Bouwer, T. Molina, G. Yang, B. Smith, Y. Hakozaki

A Final Change of Topic

- Connecting with the physics
- Mathematics and electron microscopy
- Some research objectives
- Connections with hard analysis

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A Physicist Looks at Image Processing

"A glance at any image processing textbook reveals immediately that such works are more like cookery books than scientific treatises and that the vocabulary of the subject is quite different in the widely separated areas of application (microscopy, astronomy, medicine, geology, forensic science,…). In an attempt to harmonize all this work and to put it on a sound mathematical footing, an image algebra has been created, in terms of which the various image processing algorithms can be written compactly…

… But why should we stop there? It would be very satisfying if we could express the whole chain – image formation plus image processing – in terms of this algebra …"

Peter Hawkes, **Recent advances in electron optics and electron microscopy, 2004.**

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Some Long-Term Objectives

- **Automated tomography, with tracking, alignment, rebinning, filtering and reconstruction done while data is collected**

- **Explicit treatment of instrument physics and beam-sample interactions in tomographic reconstruction algorithms**

- **Advancement of mathematical treatment in algorithm development**

- **The biggest problem is the AI**