Inverse problems in mathematical imaging sciences and applications to the health care sector

Ozan Öktem
ozan@kth.se

Department of Mathematics
KTH – Royal Institute of Technology, Stockholm, Sweden

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Promote mathematics in industry and serve as an interface between academia and industry.

Membership open to all active in the field of industrial and applied mathematics.

Project gallery at http://eu-maths-in.se/category/projects/
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Content of presentation

- Example 1: Microlocal analysis in imaging
- Example 2: Optimisation in radiotherapy
- Experiences and thoughts related to industrial mathematics
Example 1: Microlocal analysis in imaging
The industrial problem
Use 3D electron microscope techniques to visualize interaction of proteins and other macromolecular assemblies in specimens relevant for drug discovery and/or development.

Productive sector
- Pharmaceutical industry
- Scientific and Technical Instruments

Involved companies
- Sidec Technologies
- FEI Company (now part of Thermo Fisher Scientific)

H2020 Societal Challenge
Health, demographic change and wellbeing

Principal investigator: Assoc. Prof. Ozan Öktem, Department of Mathematics, KTH.

Duration of collaboration: 2003–2008
The societal challenge

Main challenge in drug discovery/development

There are an unacceptable number of failures in late phases, mainly due to lack of predictability of current preclinical tools.
Main challenge in drug discovery/development

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The societal challenge

Main challenge in drug discovery/development

There are an unacceptable number of failures in late phases, mainly due to lack of predictability of current preclinical tools.

Desired impact:

- Less failures in late phases
- Increased predictability of current preclinical tools
- Improved molecular understanding of the biological phenomena

In biomedical research, including drug discovery/development, the target biological system is often treated as a “black box” due to a lack of proper understanding.

To avoid high failure rates requires a better understanding, often at molecular level, of the target biological system.
Addressing the scientific challenge
How can one look into the “box”? 

Difficulties in understanding the target biological system roughly boils down to the following:

- Understand interaction between the involved proteins, which often translates into studying their structure.
- The same protein can have many different interactions, therefore one needs to understand the structural dynamics.

Hence, one needs to study the structure of individual proteins in their natural environment.

The structure determination problem
Recover the 3D structure of an individual molecule (e.g., a protein or a macromolecular assembly) at highest possible resolution in situ (in their cellular environment) or in vitro (in aqueous environment).
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Recover the 3D structure of an individual molecule (e.g., a protein or a macromolecular assembly) at highest possible resolution in situ (in their cellular environment) or in vitro (in aqueous environment).
Overview of methods used for investigating protein structures (in this case membrane proteins). Resolution figure for each method is stated below and ranges from best to typical (lower is better).
Addressing the scientific challenge
Imaging technologies for structural studies

Difficult to produce membrane proteins in sufficient quantities, to isolate and purify them, and to grow well-diffracting crystals. For crystallization in 3D, membrane proteins have to be solubilised with detergents, which takes them out of their native membrane context. For functional studies it is often necessary to reconstitute the isolated proteins into a lipid bilayer. By similar methods, many membrane proteins form two-dimensional (2D) crystals, which can then be studied by electron crystallography. 2D crystals often grow more easily than 3D crystals, and because the protein is in a quasi-native lipid environment, it tends to be more stable. However, 2D crystals are rarely suitable for high-resolution structure determination, because of limited size and intrinsic disorder. To date, only very few membrane protein structures at better than 4 Å resolution have been determined by electron crystallography ([9, 10, 13]).

The method is however well suited to studying membrane proteins under different conditions. Examples are pH-induced conformational changes in sodium-proton antiporters NhaA and NhaP ([2, 22]), which would be difficult with 3D crystals. 3D maps at 6–8 Å resolution can usually be obtained by crystallographic image processing. At this resolution, membrane-spanning alpha-helices are clearly visible, [Fig. 9.1]

### Summary of methods used for investigating membrane protein structure, with resolution ranges (best to typical) given below

- **Electron tomography**
  - Allows structural studies of individual macromolecular assemblies in their natural environment (no crystallisation and/or averaging).

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**3D crystal**

**2D crystals**

**single particles**

**3D crystal**

**2D crystals**

**single particles**

**organelle suspension**

- **X-ray crystallography** provides atomic detail
  - **electrocrystallography** shows membrane context
  - **single-particle EM** shows large complexes

- **1.3 - 3.5 Å**
- **1.8 - 8 Å**
- **3.3 - 15 Å**
- **30 - 70 Å**

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Addressing the scientific challenge
Electron tomography

Tomographic phase contrast imaging
Addressing the scientific challenge
Electron tomography

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Addressing the scientific challenge
Electron tomography

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Addressing the scientific challenge
Electron tomography

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Electron tomography

Challenge 1: Data is highly noisy

A single 2D projection image (left).
Addressing the scientific challenge
Electron tomography

Challenge 1: Data is highly noisy

A single 2D projection image (left). Corresponding high-dose image (right). Typical dose in a single image is about 5–50 e⁻/pixel.
Addressing the scientific challenge

Electron tomography

**Challenge 2:** Tomographic inverse problem is severely ill-posed.

- Limited angle data, leads to severe instability.
- Local tomography data, leads to formal non-uniqueness.

**Challenge 3:** Large scale problem.

Typical size of 3D region is $1024 \times 1024 \times 100$ voxels and larger regions frequently occur.
Summary of challenges

Severely ill-posed large scale tomographic inverse problem with highly noisy data!

Solution proposed by mathematics

Reconstruct only some information about the specimen that can be stably retrieved, in our case the singularities of the scattering potential, i.e., the boundaries/edges of the molecules in the specimen.
Microlocal analysis in imaging

Mathematical research topics:

- Define the notion of an “edge”.
- Understand artefacts (their nature and how/why they arise).
- Reconstruct edges.
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Notion of an “edge”

**Practical viewpoint:** Edges are boundaries between regions in the image where the contrast makes “quick” changes.
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Notion of an “edge”

Practical viewpoint: Edges are boundaries between regions in the image where the contrast makes “quick” changes.

Mathematical viewpoint: Assume the (non-digitized) image is represented by a real-valued function \( f : \Omega \rightarrow \mathbb{R} \) for fix domain \( \Omega \subset \mathbb{R}^n \). Then, the edges are the “singularities” of \( f \).
Edges of an image $f$ are where $f$ is not smooth. Use Fourier characterisation of smoothness:

\[ f \text{ is smooth if and only if its Fourier transform decays rapidly at infinity, i.e, } \left| \hat{f}(\xi) \right| \text{ decays faster than any power of } 1/|\xi| \text{ as } |\xi| \to \infty. \]
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1. Smoothness is a local property, so the singular support describes where edges are located.
2. Location of edges is not enough to understand how they transform. Need to describe the directions of the high frequencies causing the singularities.
3. Capturing these directions requires a further localisation, micro-localisation, in the directions where we lack smoothness. Leads to the notion of the wavefront set $WF(f)$. 
Example of the wavefront set
Let $\Gamma \subset \mathbb{R}^n$ be a smooth hyper-surface and assume that $f$ has a jump discontinuity along $\Gamma$. Then $WF(f)$ consists of $(x, \xi)$ where $x \in \Gamma$ and $\xi$ is normal to $\Gamma$.

Technical note: $\xi$ is actually not an element in the same space as $x$, it is a cotangent vector.
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Understand artefacts and reconstruct edges

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Main microlocal principle in inverse problems

Let $f : \Omega \to \mathbb{R}$ for some $\Omega \subset \mathbb{R}^n$ and assume $g := \mathcal{A}(f)$. Then, for a fairly large class of operators $\mathcal{A}$, one can relate $WF(g)$ to $WF(f)$. 

Answer: Fourier integral operators.

Answer: Through the phase function and symbol of $\mathcal{A}$. 

Usage in tomographic imaging:

Reconstruct edges in image $f$ from the data $\mathcal{A}(f)$.

Determine those edges in $f$ that are possible to recover and the degree of ill-posedness in the recovery.
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- What class of operators $A$?
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- What class of operators \( A \)?
  
  **Answer:** Fourier integral operators.

- How exactly does one relate \( \text{WF}(g) \) to \( \text{WF}(f) \)?
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Usage in tomographic imaging:
- Reconstruct edges in image \( f \) from the data \( A(f) \).
- Determine those edges in \( f \) that are possible to recover and the degree of ill-posedness in the recovery.
Most forward operators in imaging are Fourier integral operators.

- $k$-plane transforms (includes Radon and ray transforms)
- Weighted Radon and ray transforms
- Generalized Radon and ray transforms (integration over curved sub-manifolds)
- Solution operator for the radiative transport equation
- Forward operator arising in several wave-based imaging modalities (seismic prospecting, phase contrast imaging, inverse scattering, radar, ...)
- The filtered back projection reconstruction operator
$f$ is the characteristic function of the unit ball.
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**Electron tomography**

A single 2D projection image
$f$ is the characteristic function of the unit ball.

Electron tomography

Beam direction (z-axis)

Tilt-axis (x-axis)

Corresponding high-dose image
\( f \) is the characteristic function of the unit ball.

Electron tomography

3D reconstruction
Reconstruction (left) using established methods of an in situ specimen and reconstruction using microlocal analysis (right).
The forward problem in many imaging problems is a Fourier integral operator.

Inhomogeneities of a medium can be modeled as singularities.

Singularities – Wavefront set (location and orientation).

Fourier integral operators propagate wavefront sets in specific ways that can be described. In particular, pseudodifferential operators do not move singularities.

Microlocal analysis can be used to determine the parts of the wavefront set that can be recovered (visible singularities) and also reconstruction operators for the recovery.
Variational reconstruction with microlocal edge priors.

Multi-channel image reconstruction where edges across channels may coincide.

Need a quantitative version of the wavefront set:
- To define a notion of “resolution” of edges, and
- Apply to forward operators that include a smoothing, like convolution.

Numerical representation of the wavefront set (shearlets, curvelets, . . . ).
Variational reconstruction with microlocal edge priors: Reconstruct image from data $g$ with forward operator $\mathcal{A}$ by solving

$$\min_{f} \left[ \lambda S_p(f) + \|\mathcal{A}(f) - g\|_2^2 \right] \quad \text{with} \quad S_p := \int_{\Omega} |\nabla f(x)|^{p(x)} \, dx.$$ 

Here $p : \Omega \to [1, 2]$ is a microlocal edge prior. Note that $p \equiv 1$ is total variation and $p \equiv 2$ is Dirichlet energy.

Example from tomography: Ground truth (left), total variation reconstruction (middle), and reconstruction using variable $L^p$-regularisation with microlocal edge prior (right).
Results & benefits to the company

Results

- Algorithms for tomographic reconstruction applicable to ET that outperform established approaches regarding both performance and image quality.
- Edge reconstruction from limited angle and local tomographic data is only mildly ill-posed, i.e., comparable to usual reconstruction from complete data.
- Possible to characterize a priori which edges that are possible to reconstruct (visible singularities).
- Inspiration for new mathematics research.

Benefits for the company

- Possible to do 3D reconstruction on large scale ET problems.
- Short step from fundamental research to implementation in company’s imaging pipeline.
- Access to expertise within mathematical sciences.
- Scientific legitimacy from peer-reviewed publications.
Example 2: Optimisation in radiotherapy
The industrial problem
Use optimization techniques to improve performance of radiation therapy.

Productive sector
- Medical Technology
- Scientific and Technical Instruments

Involved companies
- RaySearch Laboratories

H2020 Societal Challenge
Health, demographic change and wellbeing

Principal investigator: Prof. Anders Forsgren, Department of Mathematics, KTH.

Duration of collaboration: 2003–
Project data

Pursued with industrial PhD students

- First project 2003–2008
  Fredrik Carlsson.

- Second project 2008–2013
  Rasmus Bokrantz and Albin Fredriksson.

- Third project 2013–
  Michelle Böck and Lovisa Engberg.

- Students employed by RaySearch Laboratories with academic supervisor at KTH.

- Reference group with representatives from KTH and RaySearch Laboratories.

- Partial financial support from the Swedish Research Council (first and second).

- Studies of fundamentally important problems.
The societal challenge

- Treatment of cancer is a very important task
- Radiation therapy is one of the most powerful methods of treatment. It is often used in conjunction with other therapies, such as chemotherapy or tumor-removal surgery. In Sweden 30% of the cancer patients are treated with radiation therapy.
- Radiation therapy also damages surrounding tissue so treatment often results in side effects that are costly to manage for society.
The scientific challenge

Improve performance of radiation therapy, more precisely give a treatment with a desirable dose distribution in the patient.

- High dose in the tumor cells, and low dose in other cells.
- Certain organs (e.g., the spine) are very sensitive to radiation and must have a low dose.
Addressing the scientific challenge

- **Radiation treatment technology**: Generate modulated high energetic photon beams and/or use other particles (protons, ions, ...).
  - Intensity-modulated radiation therapy (IMRT)
  - Intensity-modulated proton therapy (IMPT)

Involves mostly physics and engineering sciences.

- **Mathematics**:
  - Forward planning: Simulate outcome of a given treatment plan (dose distribution). Uses Monte Carlo simulation techniques.
  - Inverse planning: Reconstruct a treatment plan (dose distribution) fulfilling a priori specified requirements. Uses optimization techniques.

Need to combine technology with mathematics.
Radiation treatment technology

Treatment plan

Segment shaped to match target projection

Fluence plane with discretized fluence

Transversal slice

Isocenter

Target

80 Gy
70 Gy
60 Gy
50 Gy
40 Gy
30 Gy
20 Gy
Delivery. Ionizing radiation field generated by a linear accelerator equipped with a rotating gantry.

Fluence modulation. Superposition in time of collimated fields with uniform intensity.

Treatment goal. Deliver a highly conformal dose to the tumor volume while sparing surrounding healthy tissues.

Five-field treatment of head-and-neck cancer case.
Intensity-modulated proton therapy (IMPT)

As IMRT but using proton beams instead of photons.

- Protons interact with impeding particles.
- The dose depositions increase as the protons slow down.
- Bragg peaks and depth modulation allow for conformal dose.
- Steep beam dose gradients and stopping power sensitivity make IMPT sensitive to errors.
Inverse treatment planning problem

Find the treatment plan in terms of machine parameters that best achieve the treatment goals within the limitations of the delivery method.

The research deals with two particular areas:

- **Multi-objective formulation**: Provide means for planner is to balance contradictory objectives, e.g., tumor control against organ-at-risk protection.

- **Handling uncertainties**: Many sources of uncertainties, e.g., patient setup position, geometric outline of critical organs and tumor, delivery errors, etc. introducing models for uncertainties in the optimisation.
Focus on understanding and formulation of fundamental optimization problems.

- Based on quadratic penalty functions.
- Explanation of the excellent performance of quasi-Newton sequential quadratic programming methods.
- Closely related to fundamental behavior of the method of conjugate gradients.
Focus on multiobjective optimization.

- Inherently conflicting treatment goals.
- Traditionally handled by weighted sum of optimization functions.
- Explicit handling of multiobjective aspects.
- Modelling challenges and computational challenges.
- Gives a framework for managing tradeoffs in treatment planning.
Focus on robust optimization.

- Handling of model error is of utmost importance for treatment quality.
- Particularly important for ion therapy, e.g., protons.
- Inclusion of robustness in the modeling.
- Gives a framework for handling uncertainties in different ways, ranging from expected value to worst case.
Focus on adaptive radiation therapy.

- Traditionally fractionation is used, i.e., identical treatment each time.
- Adaptation gives a tool for individual treatment each time.
- Conceptual study on a one-dimensional phantom patient.
- Optimal control approach.
Focus on automated treatment planning.

- Common evaluation criteria is dose-at-volume, which is mathematically intractable.
- Explicit and convex optimization of plan quality measures is used.
- Computationally tractable models that correlate well with desired criteria.
Results & benefits to the company

Results

- Algorithms for inverse treatment planning.
- Mathematical understanding of uncertainties in inverse treatment planning.
- Novel treatment options thanks to new algorithms.
- Inspiration for new mathematics research.

Benefits for the company

- A very rewarding research cooperation for both sides.
- Company has gained an understanding of the importance of mathematics research in their activities.
- Recruitment: Company has grown from approximately 20 employees in 2003 to approximately 200 in 2016.
- Short step from fundamental research to implementation in company’s treatment planning system.
- Scientific legitimacy from peer-reviewed publications.
RaySearch Laboratories are currently in the process of expanding the scope of research by launching two new industrial PhD student projects joint with KTH. The scope is widened:

- Optimization of the treatment clinic’s resources.
- Automated planning by machine learning.
Experiences and thoughts related to collaboration with industry
Mathematics and computation: Mathematics is relevant in both how and what to compute. The latter often involves pure mathematics.
Mathematical research in industry

General thoughts

- Mathematics and computation: Mathematics is relevant in both how and what to compute. The latter often involves pure mathematics.
- Industrial mathematics in relation to applied mathematics:

  Area within applied mathematics focusing on solving industrial problems, which includes addressing issues like cost efficiency and implementability.
Mathematical research in industry

General thoughts

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- Industrial mathematics in relation to applied mathematics:

  *Area within applied mathematics focusing on solving industrial problems, which includes addressing issues like cost efficiency and implementability.*

Not a useful characterisation since industrial problems often involve multiple subject areas within mathematical sciences, including some considered as pure mathematics. More relevant to focus on the skill set of an *industrial mathematician* rather than subject areas.
Mathematics and computation: Mathematics is relevant in both how and what to compute. The latter often involves pure mathematics.

Industrial mathematics in relation to applied mathematics:

An industrial mathematician is a person with expertise in the mathematical sciences and an interest towards solving problems within industry, including issues like cost efficiency and implementability.
Do we really need new mathematics or can most problems be solved using existing mathematics?

- New sensor and detector technologies coupled with large scale ICT infrastructure provide an increasing capacity to gather and store data (big data).
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- New sensor and detector technologies coupled with large scale ICT infrastructure provide an increasing capacity to gather and store data (big data).
- Many systems and phenomena of interest are complex and first principles based modelling is not applicable. This is especially the case in life and social sciences.
Mathematical research in industry
Is mathematical research needed?

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- Inverse problems are often severely ill-posed (underdetermined, incomplete data, . . .) despite access to huge amounts of data.
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- Inverse problems are often severely ill-posed (underdetermined, incomplete data, . . . ) despite access to huge amounts of data.

Many of the above challenges are not only computational but also conceptual, i.e., determining what to compute. This requires new mathematical theory.
Mathematicians

- Accept losing control over the problem formulation. Don’t reformulate the problem so that it fits your methods, look instead for methods that fits the problem.
Mathematical research in industry
Important factors for successful collaboration

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- Ensure access to software developer resources and whenever possible/suitable, work with software components used by industrial partner.
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- Try to enter into to cooperative collaborations that are not too large.
Industrial partner

- Mathematicians often want to understand all aspects of the problem so they often question fundamental assumptions. Don’t see this as an annoyance, it is rather an honest attempt at understanding the problem.
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- Keep in mind that mathematics is not only about computations, conceptual issues are surprisingly important.

- Whenever relevant, try to provide a continuum (non-digitised) formulation of your problem.

- Try to make precise what you really need from a solution, don’t ask for too much.
Industrial partner

- Mathematicians often want to understand all aspects of the problem so they often question fundamental assumptions. Don’t see this as an annoyance, it is rather an honest attempt at understanding the problem.
- Try to allow for intellectual exchange in both directions.
- Keep in mind that mathematics is not only about computations, conceptual issues are surprisingly important.
- Whenever relevant, try to provide a continuum (non-digitised) formulation of your problem.
- Try to make precise what you really need from a solution, don’t ask for too much.
- Even though you don’t care about the mathematics, don’t explicitly say that. It may have a demoralising effect.
Mathematical research in industry
Common challenges

- **Sustainability**: Academy-industry contacts are very person dependent, becomes problematic at re-organisations.
- **Dissemination**: Experiences and knowledge generated within a collaborative project have limited dissemination at both the academic and industrial partner.
- **Time horizon**: Industry can rarely wait several years to address an important problem whereas academic research often operates under long time horizons.
- **Benefit**: Access to an expert network often more important than specific results in a collaborative project.
- **Scope**: Unnecessary and erroneous focusing on specific areas, like numerical analysis, optimisation or statistics. Challenging problems, especially those from outside the physical and engineering sciences, require combining methods from a wide range of fields within mathematical sciences.
Mathematical research in industry
Common challenges

- **Internal competition**: Collaboration often thwarted by internal research and development units.

- **Problem formulation**: Difficult to collaborate in projects that are of key importance, collaboration often deals with projects that address “good to know” type of problems rather than “must know”. Also difficult for companies to discuss important problems they cannot solve.

- **Software development**: Importance of access to software developers is often underestimated, becomes a problem when mathematical methods are to be implemented.

- **Management**: Project management non-existent and/or inadequately performed, hard to handle uncertainty in research using a management model designed for development.
Institutionalize contacts with industry by establishing an infrastructure for collaboration where research expertise in mathematical sciences meet problems from industry.

Have a concentration of resources of industrial mathematicians with broad expertise from computer science and mathematical sciences.

Better academic collaboration between computer science and mathematical sciences.

Improve mobility between academia and industry.

Increase the academic prestige in industrial mathematics research.