Conceptual Design and Expected Performance of the Macromolecular Neutron Diffractometer (MaNDi) for the SNS

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Acknowledgment: ANL, ORAU, ORNL

Instrument Development Team (IDT)

Currently we have 55 members

Executive Committee

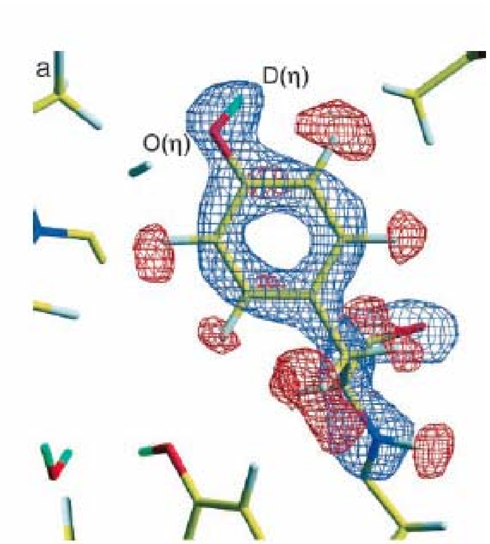
• Andrew Mesecar (Chair)	University of Illinois at Chicago
• Gerard Bunick	ORNL, University of Tennessee, Knoxville
• Chris Dealwis	University of Tennessee, Knoxville
• Martin Egli	Vanderbilt University
• Jenny Glusker	Fox Chase Cancer Center
• John Helliwell	University of Manchester, UK
• Andrzej Joachimiak	Argonne National Laboratory
• Anthony Kossiakoff	University of Chicago
• Paul Langan	Los Alamos National Laboratory
• Dean Myles	Oak Ridge National Laboratory
• Alberto Podjarny	IGBMC, France
• Arthur Schultz	Argonne National Laboratory
• P. Thiyagarajan	Argonne National Laboratory

Outline

- Motivation
- Conceptual design of MaNDi
- Accomplishments so far
- Future directions

Advantages of Neutron Diffraction for Structural Biology

- Unique Scattering cross-sections
  - H = -3.74 fm , D = 6.67 fm
- Locate hydrogens even at 2 Å resolution
  - –Complimentary to UHRMXC (~0.8 Å)
- Protonation and ionization states of atoms
  - –Yields atomic charges and pK_a's
- Orientation of polar groups, e.g., hydroxyls and amides
  - –Yields hydrogen bonding patterns
- Conformation of methyl groups and side chains
  - –Provides details on packing arrangements
- Detailed water structure
  - –Hydration at active sites and solvation shells
- Monitor Hydrogen/Deuterium (H/D) Exchange
  - –Solvent accessibility
  - –Dynamics
  - –Folding patterns, exchangeable protons



H and D atoms of the OH groups from the neutron analysis. (*a*) *F*o-*F*c omit map of Tyr-12; blue contours are positive at 3.5σ, and red contours are negative at 3.5σ. Note that the O–H bond has been deuterated but the C–H bonds have not. Also note the hole in the middle of the aromatic ring.(Rubredoxin, Kurihara et al., PNAS 101,11215,2004)

- Discriminate between metal atoms at active sites
  - Mn(25) = -3.6 fm, Fe(26) = 9.5 fm, Zn(30) = 5.6 fm

No radiation damage to crystals (room temperature structures)

Current Status of NMC

Limited facilities – but high impact science

- LADI (quasi-Laue, $\Delta\lambda$ = 0.28; λ=3.5 Å) at 58 MW reactor, France
- BIX3/BIX4 (monochromatic, $\Delta\lambda/\lambda$= 0.015; λ=2.35 Å) at JAERI, Japan
- PCS (TOF Laue, $\Delta\lambda/\lambda$= 0.01; Bandwidth = 1 - 6 Å) at 100 kW pulsed neutron source, LANL, USA

  - Unit cells >100 Å extremely difficult
  - Require large crystals (1 mm^3) (smaller if deuterated)
  - Limited in resolution for larger unit cell systems
  - Long data collection times

Opportunities on the Horizon

- Higher flux Spallation Neutron Sources (TOF Laue)
  - SNS at ORNL USA
  - JSNS at J-PARC (Japan) (BIX-P1 funded)

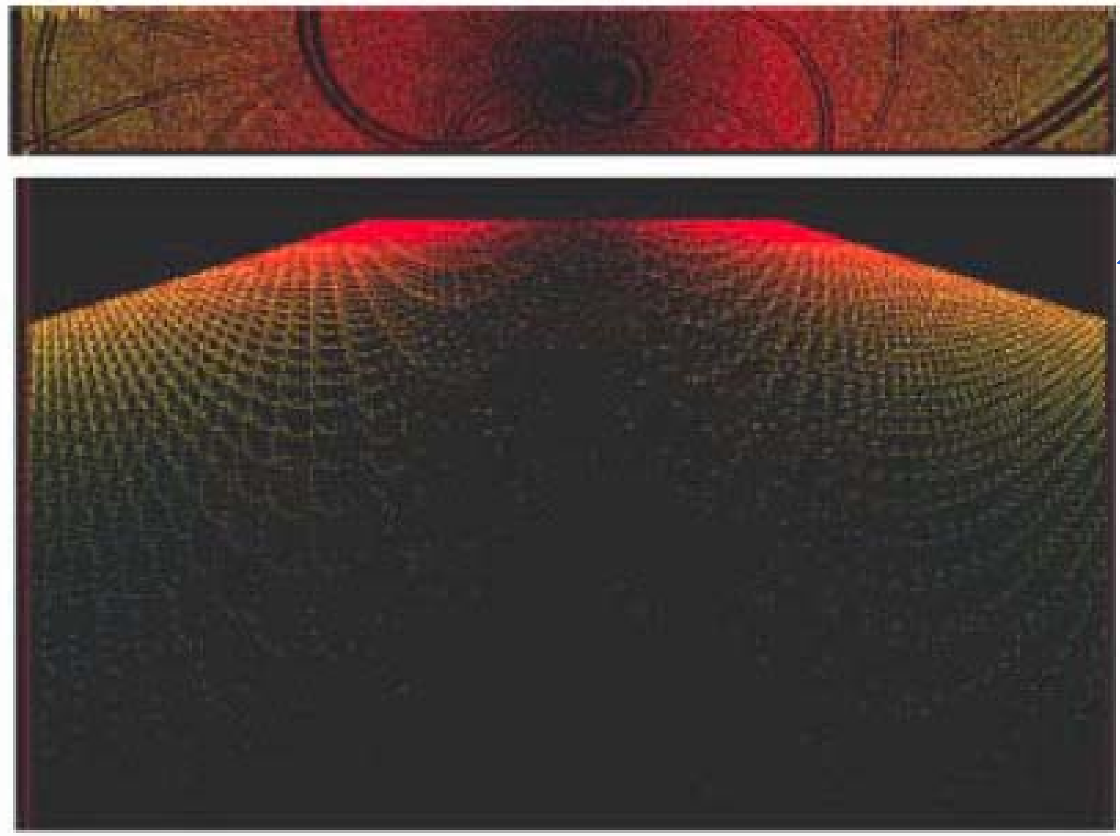
- Advanced Technologies
  - Target/moderator system
  - Neutron optics
  - Detectors

- Advancements in structural biology area
  - Protein crystal growth from Structural Genomics Projects
  - Deuteration of macromolecules
    - 3X increase in signal + 25X reduction in inc. background

      (8 to 10X net gain in data rates)

TOF-Laue Single Crystal Diffraction

Quasi-Laue
2D: (x,y)



Diffraction patterns are 3D: (x,y,λ)

Reduced reflection overlap

Reduced background

Enhanced signal-to-noise

Red-Blue: 0.6A-6A

TOF Laue

TOF direction

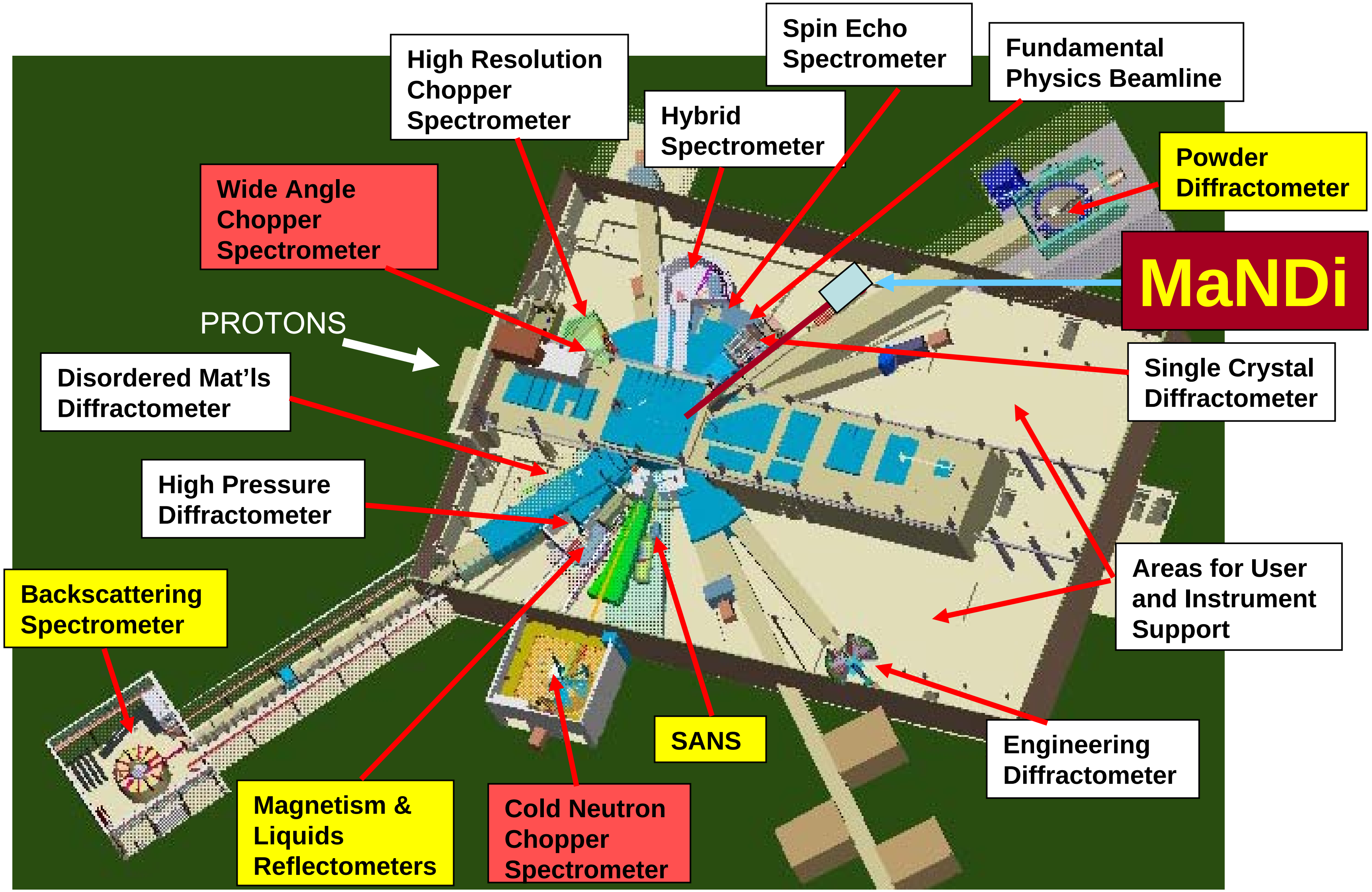
Figure 2. Wavelength resolved Laue in detector space.

Courtesy: Paul Langan, LANL

Chronology

- **December 2000**: Bunick at ORNL organized a meeting at UTK. Schultz presented a conceptual design for a NMC instrument
- **July 2002:** ACA meeting: Steering committee formed to propose MaNDi
- **October 2002**: Mesecar (UIC) presented scientific case to the SNS
  - SNS: Positive response - requested a Letter of Intent for MaNDi
- **December 2002**: Instrument design group (IDG) assembled
- **March 2003**: Schultz and Thiyagarajan presented the design of MaNDi to the SNS
  - SNS was enthusiastic on the expected performance of MaNDi
- **October 2003**: Workshop at ANL to build a stronger science case and finalize design goals and infrastructure for NMC at SNS (60 scientists)
  - Instrument Development Team (IDT) formed
  - workshop report and proposal: http://www.pns.anl.gov/instruments/mandi/mandi.html
- **July 2004**: Full Proposal on science and design of MaNDi submitted to the SNS
  - Excellent reviews from external reviewers on science and instrument design and potential impact
- **October 2004**: Response to reviewers by Mesecar, Podjarny, Schultz and Thiyagarajan
  - Beamline 11B assigned at SNS for MaNDi
- **February 15, 2005:** Presented a case at NIH to the Funding Agencies from NIH,NSF,DOE
  - July 2005 meeting to demonstrate demand from the community
  - Significant response to BioMac SIG's solicitation on identification of systems for NMC

Layout of Instruments at SNS

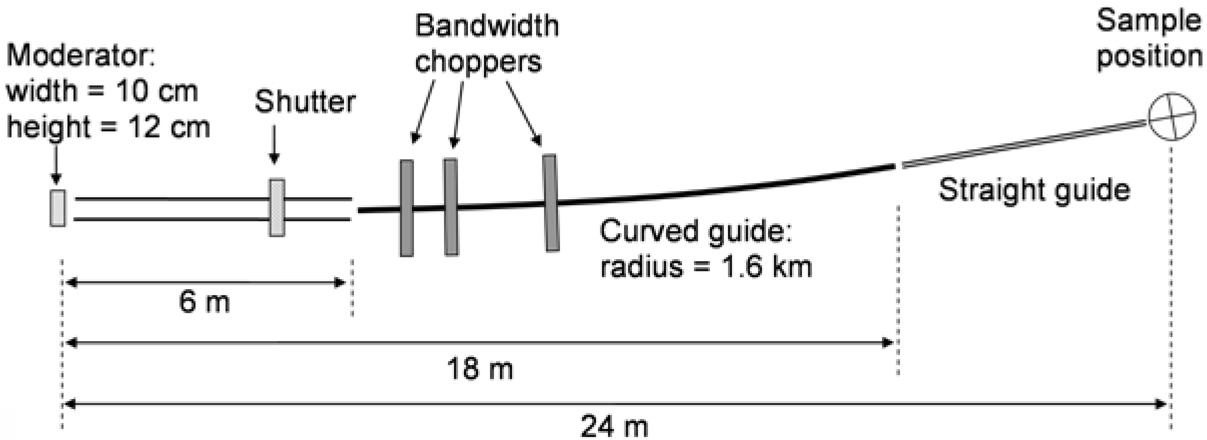


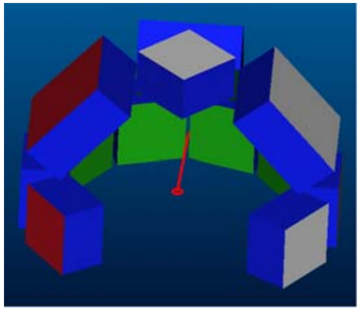
Instrument Design Features

- Measurement of Bragg data
  - d_{min} = 1.5 Å for a lattice constant of a = 150 Å ($\Delta d/d$ = 1%)
  - Fully optimized for high resolution and maximum throughput

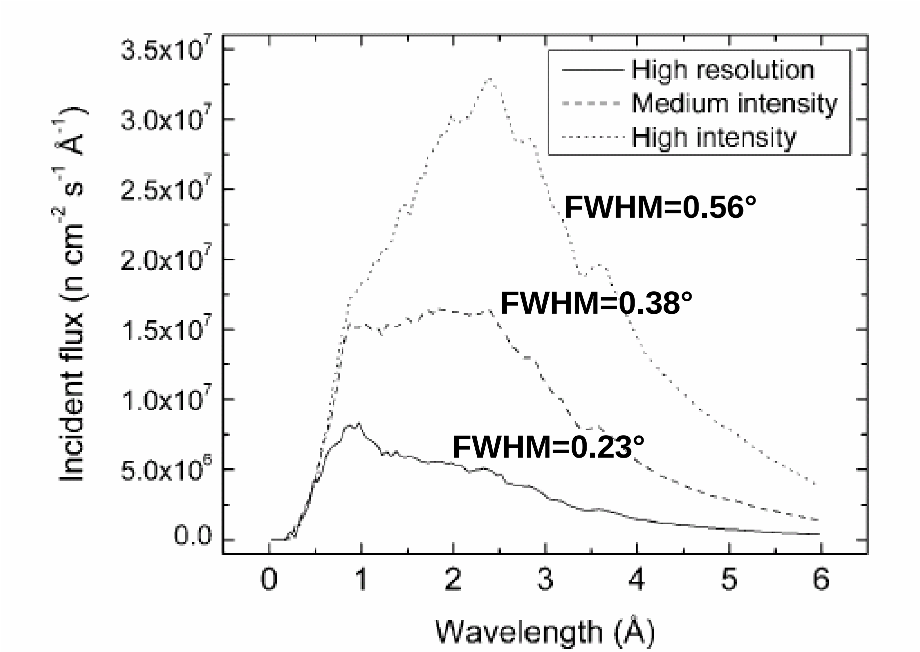
- Select Optimal moderator at the SNS
  - Decoupled hydrogen provides best combination of resolution, signal-to-noise and intensity.
- Neutron Guides
  - Curved guide – out of line of sight of source, low background.
  - Straight guide – ability to vary incident divergence and intensity.

- Maximum solid angle coverage with high resolution area detectors.

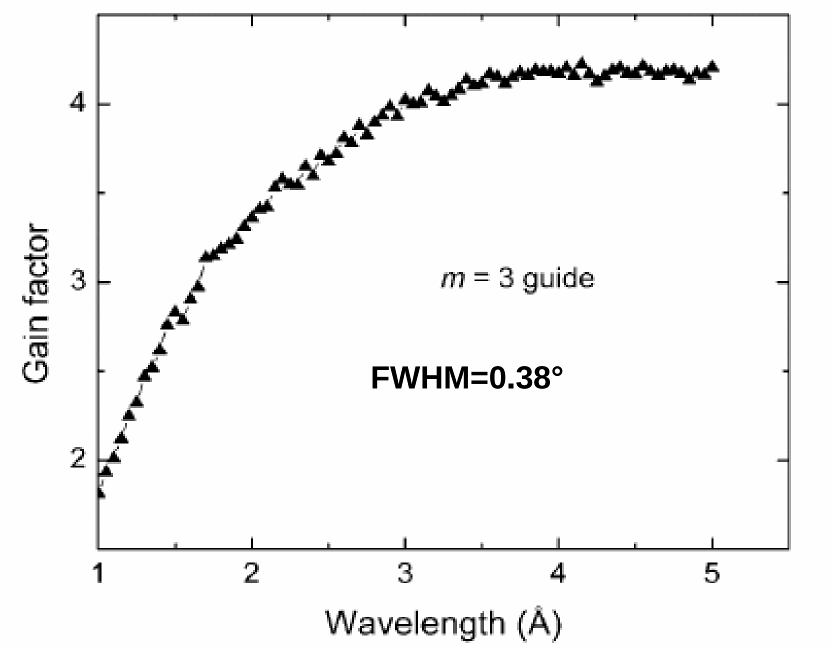




Tunable Divergence with Guides

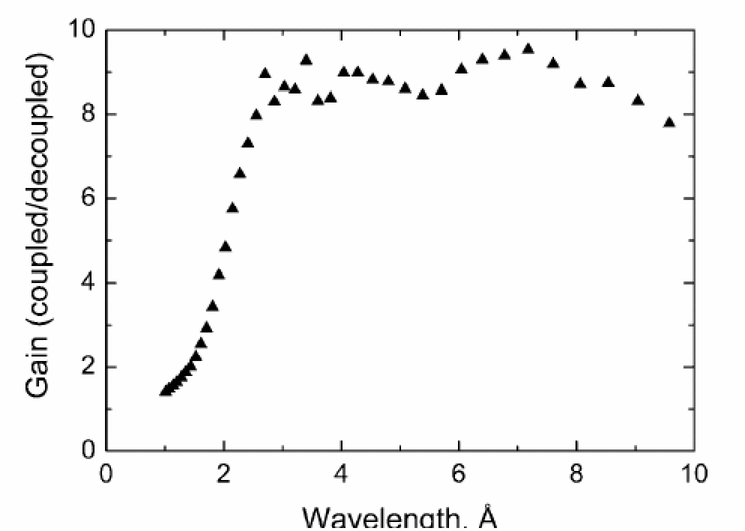


MC simulations of the incident flux at the sample position for the three guide settings Sample to guide exit (0.5m, 1.5m, 3m).



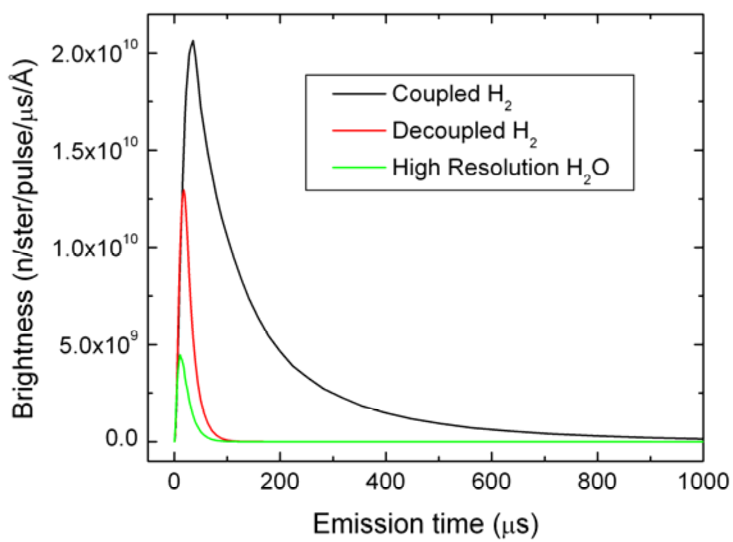
Neutron flux gain at the sample position with guides as a function of wavelength for the medium intensity configuration.

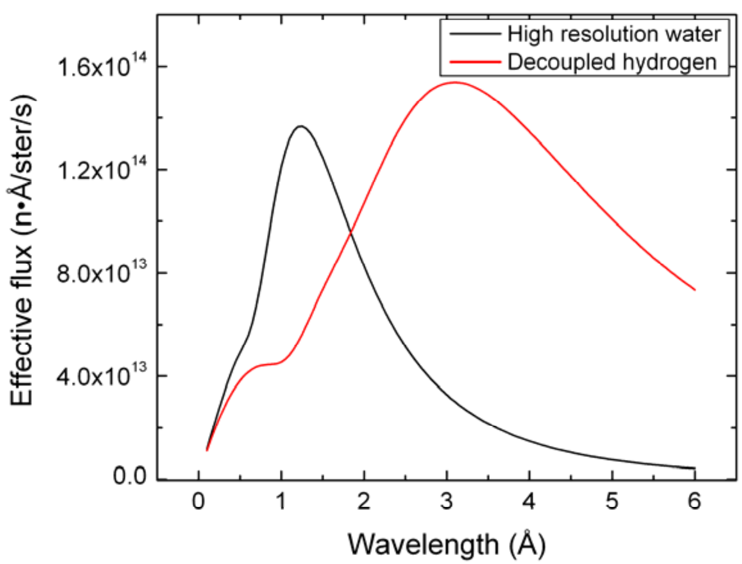
Moderator Choice for Flux and Resolution



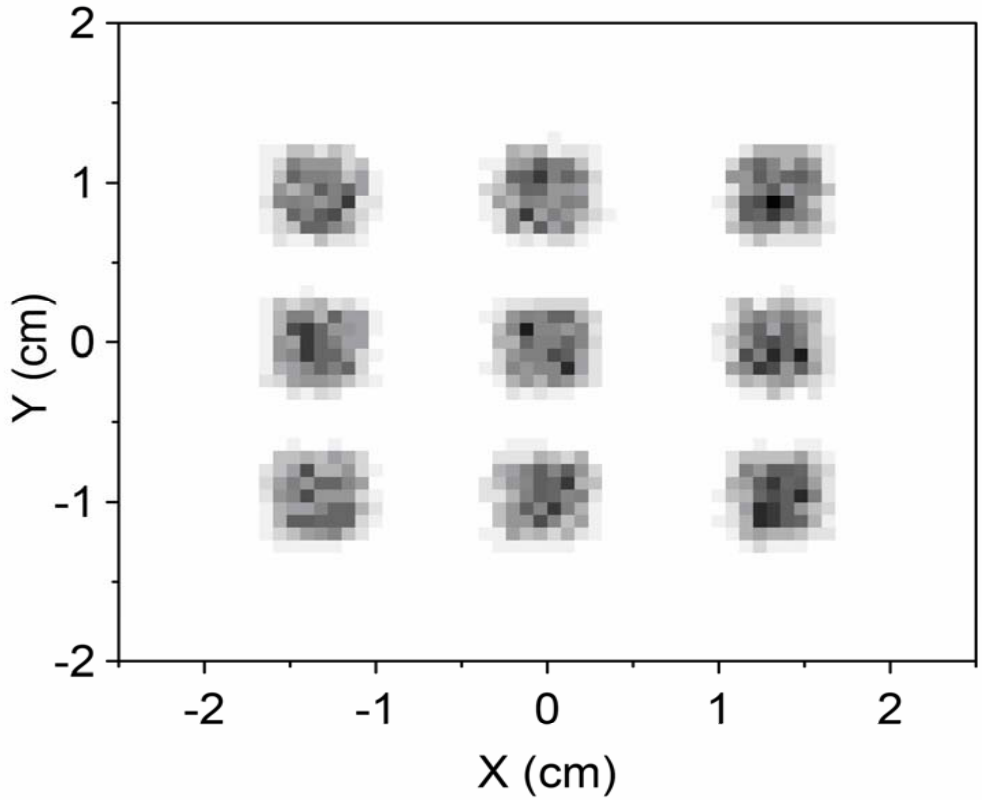
$$I_{hkl} = t\phi(\lambda)\lambda^2 A(\lambda) N_s \frac{|F_{hkl}|^2}{V_c}(2d_{hkl}^2)$$

$$R = \frac{\Delta Q}{Q} = \frac{\Delta d}{d} = \left[\left(\frac{\Delta t}{t}\right)^2 + \left(\frac{\Delta L}{L}\right)^2 + \left(\tfrac{1}{2}\Delta 2\theta \cot\theta\right)^2\right]^{1/2}$$



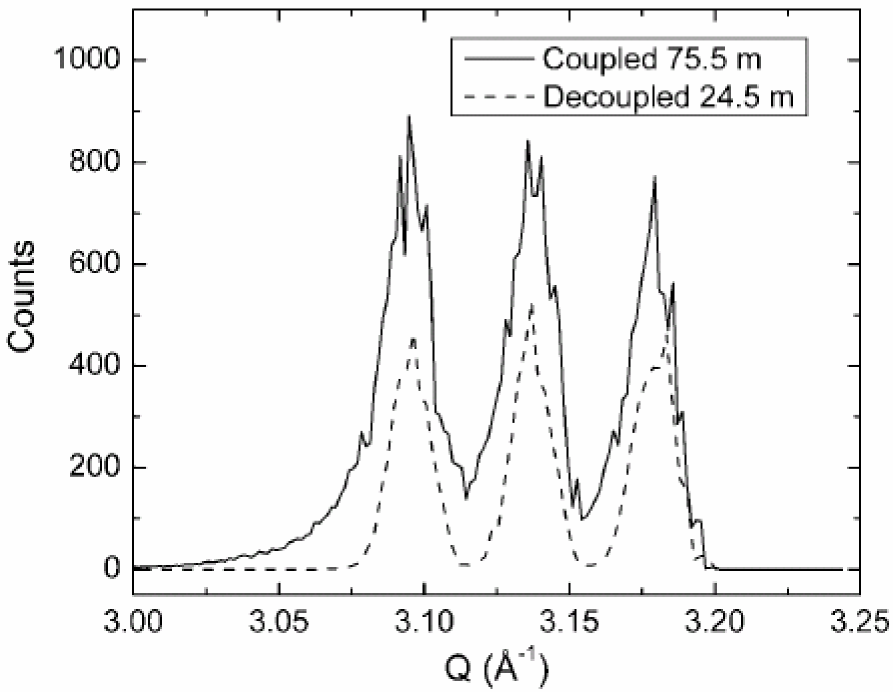


Monte-Carlo Simulation of Transverse Resolution of the Diffraction Pattern



Simulated Bragg peaks at the detector plane calculated for SNS beamline-11 (decoupled-H_2 moderator) for cubic protein crystal with a = 150 Å, detector at 2θ = 90°, d = 2.0 Å.

Resolution along the Q-vector: Peak Shapes simulated for a Single Crystal (h=74,75,76)



Calculated maximum allowed pulse full widths (derived from Eq. (8)) and ratios of the pulse full widths and intensities of the coupled and decoupled hydrogen moderators at different wavelengths for a 24.5 m instrument (a = 150 Å, d_{min} = 1.5 Å).

2θ (deg)	λ (Å)	Equation (8) FW (µsec)	Coupled FW (µsec)	Decoupled FW (µsec)	FW Ratio	Intensity Ratio
30	0.776	49	33	17	1.9	1.1
60	1.500	94	300	27	11.1	2.2
90	2.121	132	400	44	9.1	5.8
120	2.598	162	430	58	7.4	8.0
150	2.898	181	445	66	6.7	8.3

$$\Delta t_{pulse}(FW) \leq 505L(\frac{d_{min}^2}{a})\sin\theta$$

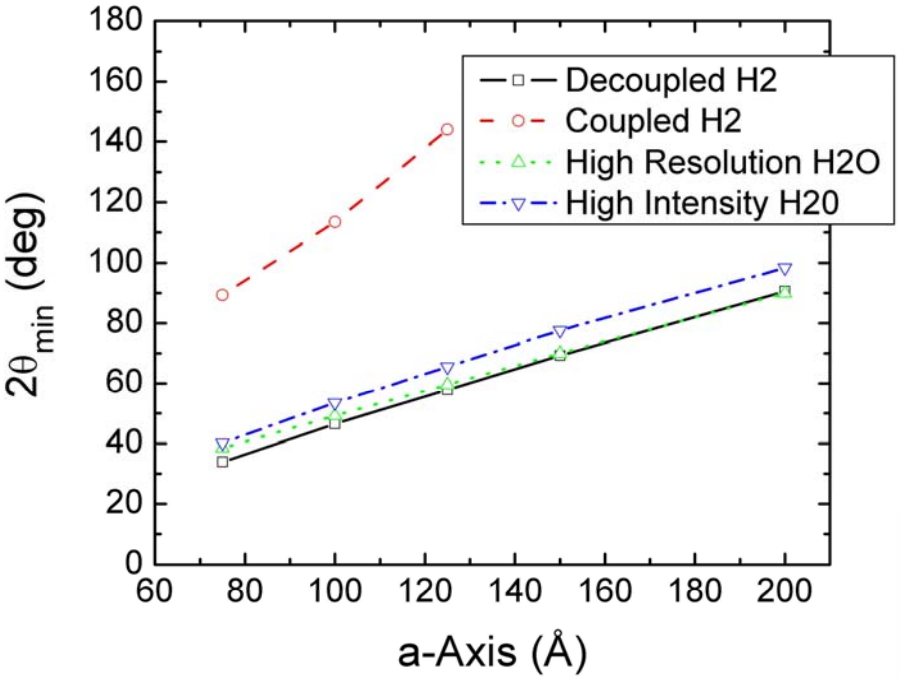
$$\Delta\lambda = 3955/(f \cdot L)$$

Peak shapes at d_{min} = 2.0 Å for a cubic unit cell of 150 Å

Coupled hydrogen moderator : flight path of 75 m (Δλ=0.87 Å)

Decoupled hydrogen moderator: flight path of 24 m (Δλ=2.69 Å)

Usable Detector Coverage based on Simulated Peak Widths ($2\theta_{max}$=165º)



Minimum usable detector angle, $2\theta_{min}$, from MC simulations to resolve Bragg peaks at d_{min} = 2 Å for four SNS moderators.

Higher $2\theta_{min}$ values leads to:

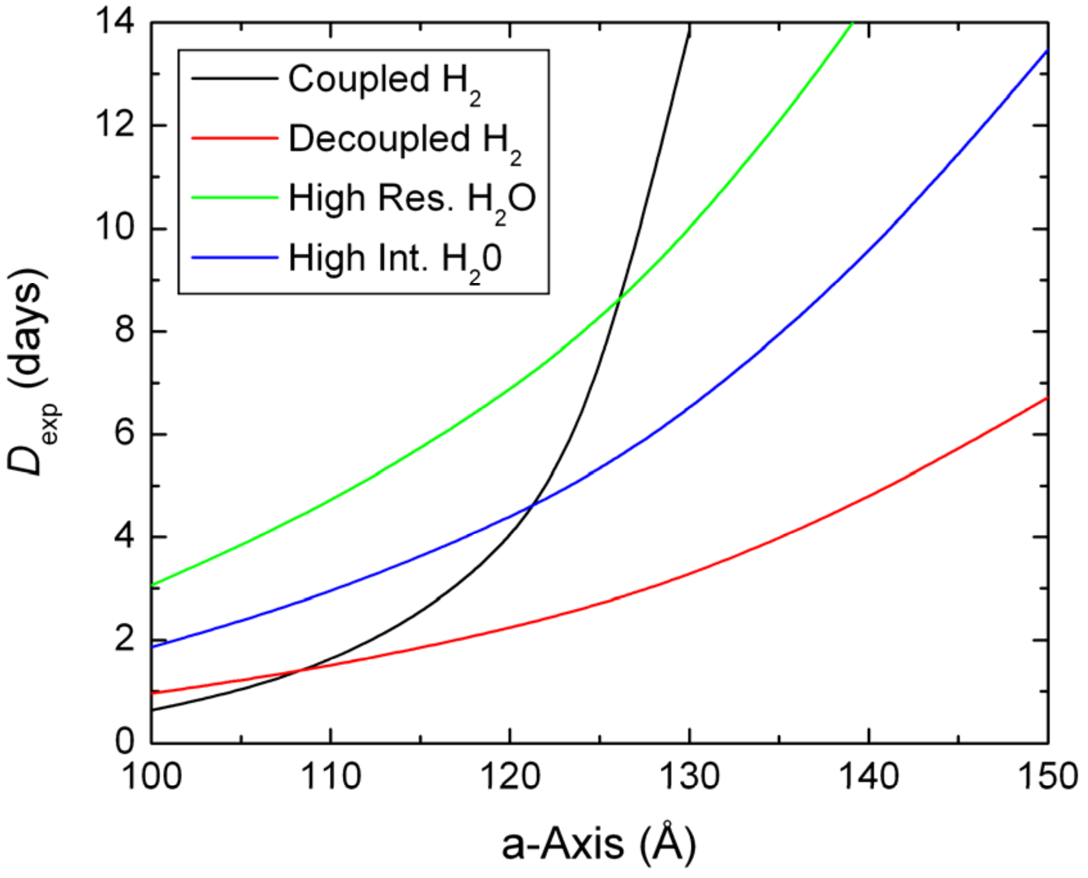
- Less detector coverage.
- More crystal settings.

Number of crystal settings

$$S = 1/(\sin\theta_{max} - \sin\theta_{min})$$

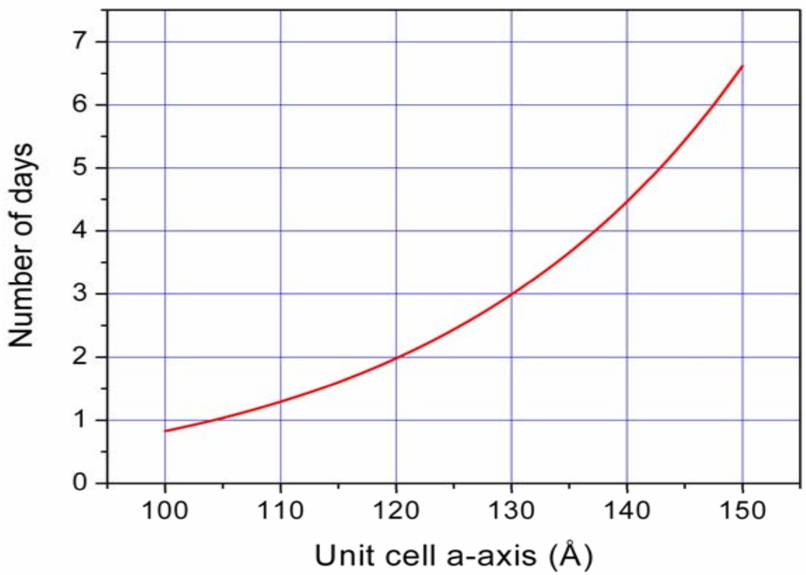
		Diffractometer (moderator, beam line)			
a (Å)	Parameter	dec-H_2 BL-11	cou-H_2 BL-5	HR-H_2O BL-8	HI-H_2O BL-17
100	*S*	3	7	3	3
	t	0.32	0.09	1.02	0.62
	D_{expt}	**1.0**	**0.6**	**3.1**	**1.9**
125	*S*	3	24	3	3
	t	0.90	0.27	2.75	1.77
	D_{expt}	**2.7**	**6.5**	**8.3**	**5.3**
130	*S*	3	40	3	3
	t	1.08	0.33	3.30	2.15
	D_{expt}	**3.2**	**13.2**	**9.9**	**6.5**
150	*S*	3	-	3	3
	t	2.24	-	6.67	4.49
	D_{expt}	**6.7**	-	**20.0**	**13.5**

Comparison of Total Experiment Beam Times for Different Moderators



Estimated experiment durations as a function of protein unit cell size for a 98% perdeuterated protein crystal of v= 0.125 mm^3, d_{min} = 2 Å.

Expected Performance of MaNDi



Data collection time vs. unit cell size for 0.125 mm^3 deuterated protein crystals at 2 Å resolution.

Comparison with Current Instruments

- Data rates 10 to 50X higher for unit cell dimensions < 100 Å at 2 Å resolution
- Unit cell size > 100 Å not possible with current instruments at higher resolution

Comparison with UHRMXC

- UHRMXC: Measurement time ~24 hrs for 0.07 mm^3 Aldose reductase crystal 49x67x47 $Å^3$ (P21) at 100 K for 0.66 Å resolution (SBC-CAT).
- NMC: Similar time at 2 Å resolution expected at MaNDi.

Revolutionize Neutron Macromolecular Crystallography applications for enzymology and structural biology research

Summary

- ➢ Conceptual Design of MaNDi shows that it will produce high resolution data in reasonable time with reasonable size crystals.
- ➢ BL-11B at SNS has been secured.

Future Direction

- Need to secure timely funding ($12M in a 3 year period)
  - Detailed instrument design, components, construction
  - Core and collaborative research in structural biology
  - Community development (workshop, training, dissemination)

For the realization of MaNDi facility at SNS

The US Macromolecular crystallography community should

- Join the Instrument Development Team (IDT).
- Develop a strong scientific case for exploiting MaNDi's performance.
- Use current facilities.
- Where applicable add NMC as a tool in addition to XMC in the funding proposals to various agencies.
- Secure timely funding for the full design and construction of MaNDi by 2006
  - actively participate in the proposal writing and planning.