The Scientific Programme of the UK Fourth Generation Light Source: 4GLS

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and

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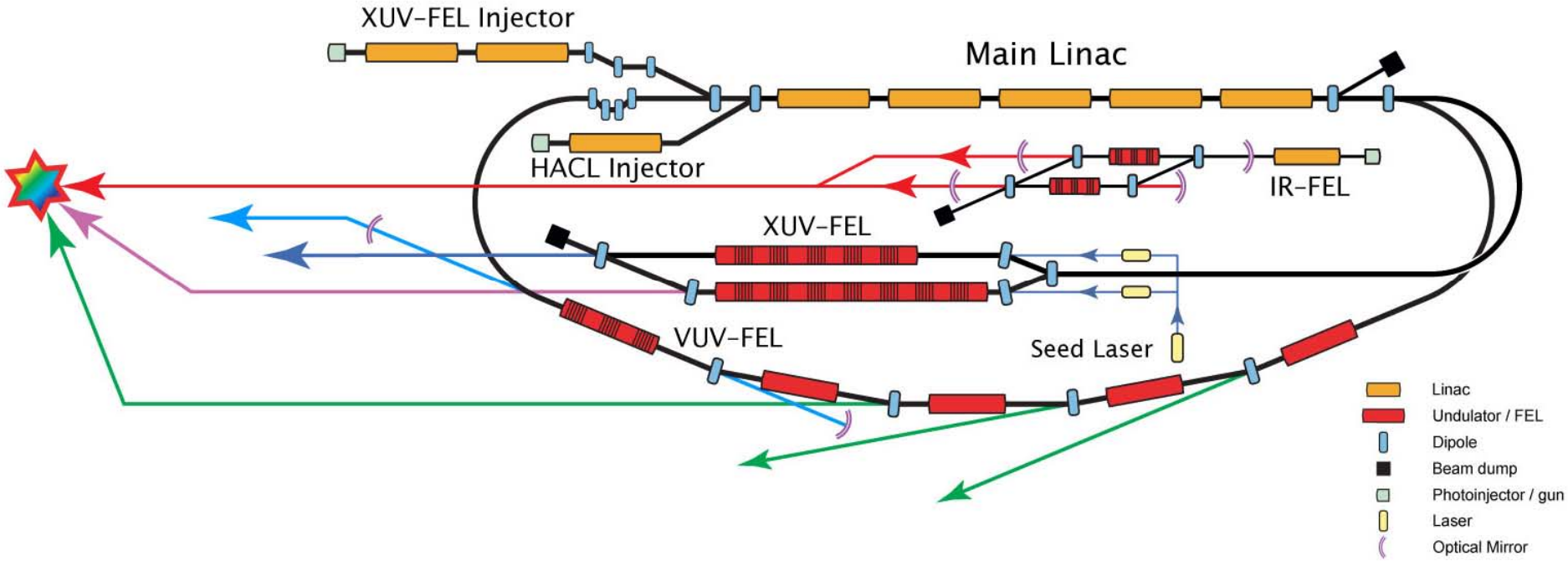
The 4GLS Design

4GLS combines superconducting ERL, SR and FEL technology in a multi-source facility

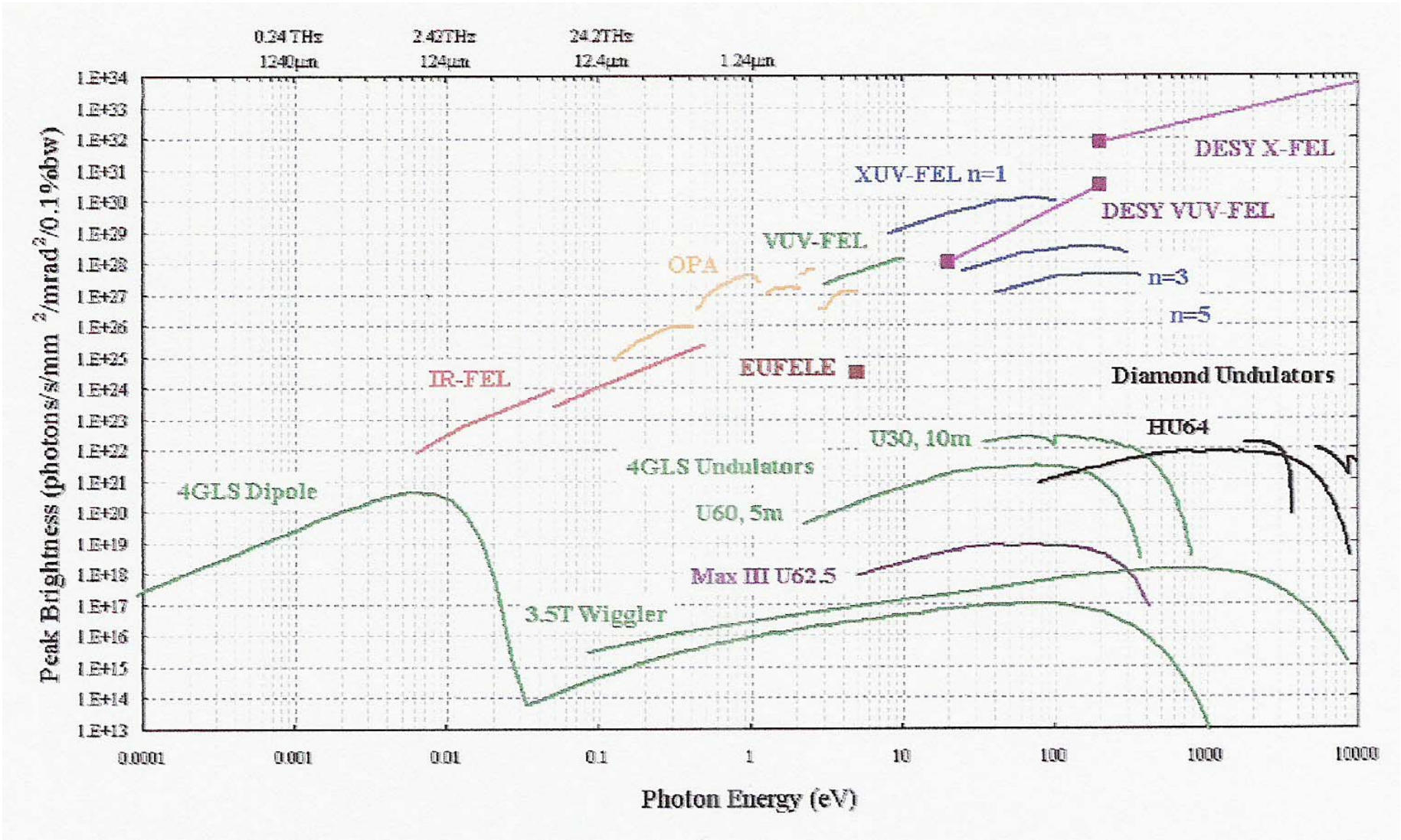
Stimulated emission sources: free electron lasers
Spontaneous emission sources: undulators and bending magnets
Combinations of sources: internal or with conventional lasers



750 MeV, 100 mA emittance < 1 nm rad, bunch length 50 fs - 50 ps

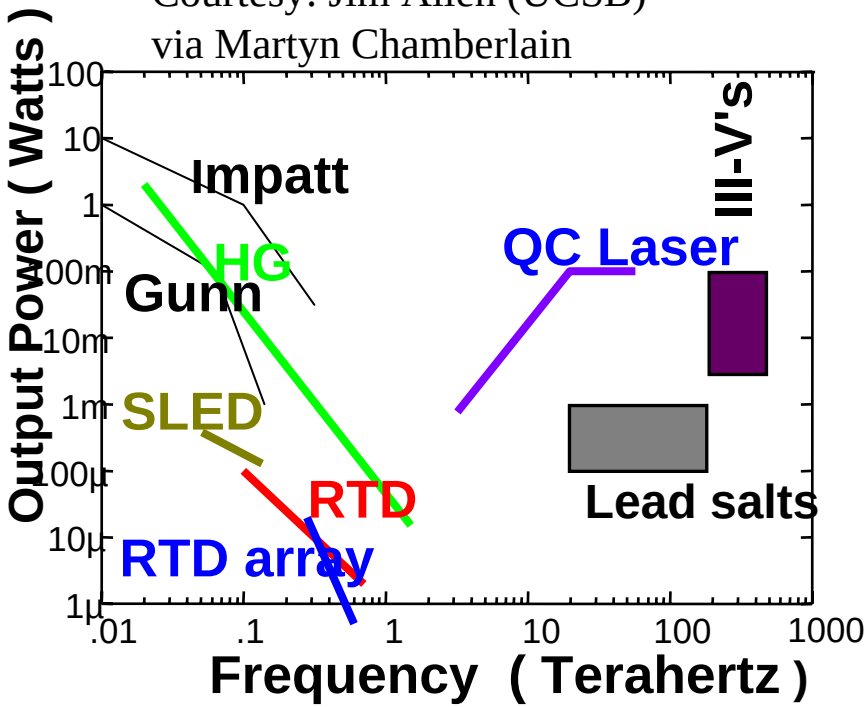
Conceptual design report available at http://www.4gls.ac.uk

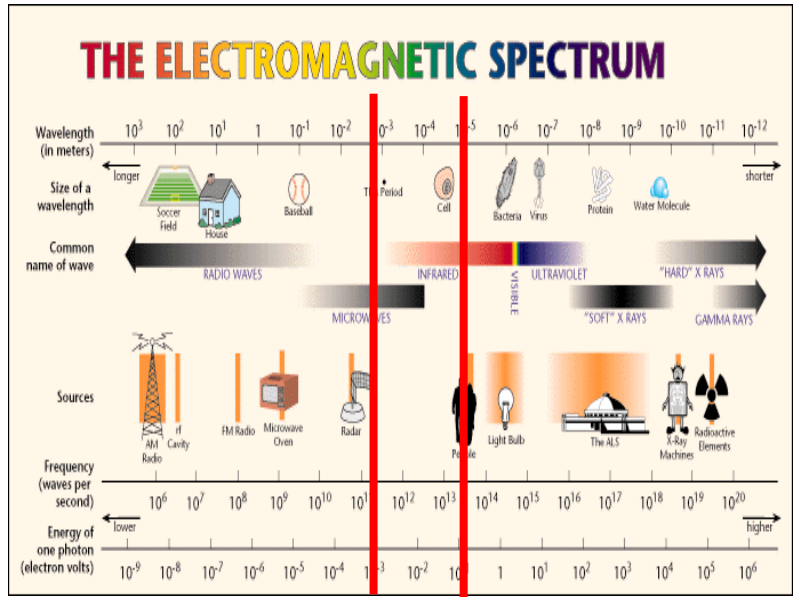
4GLS Ouput: Peak Brightness

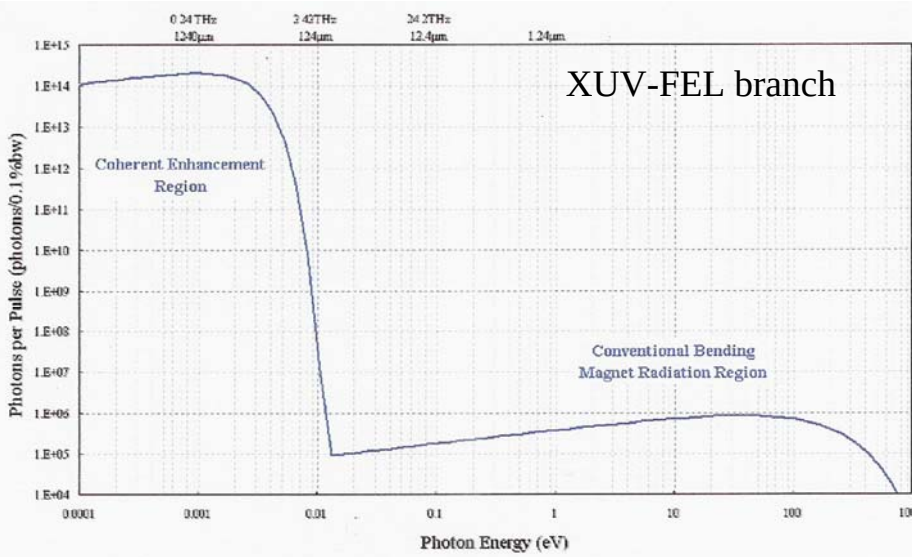


Extending Spectral Range: Terahertz

Courtesy: Jim Allen (UCSB)
via Martyn Chamberlain







4GLS: Fills the Terahertz Gap

Maximum Flux per pulse	**2×10^{14} photons**
RMS bunch length	**266 fsec**
Repetition rate	**1 kHz**
Average power	**0.09 W**
Peak power	**100 MW**

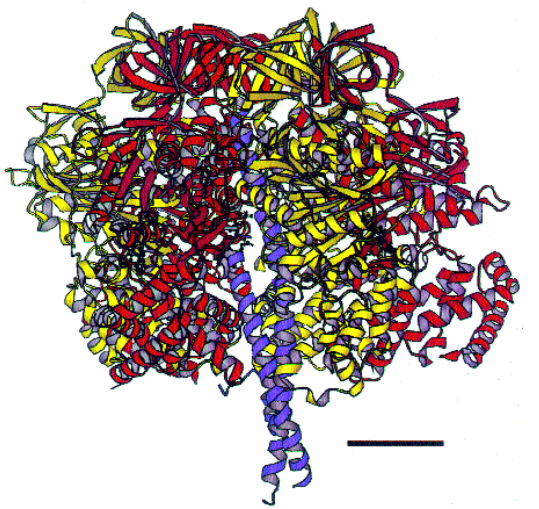
4GLS Complements the Diamond Synchrotron

Frances Crick "If you want to understand function study form"

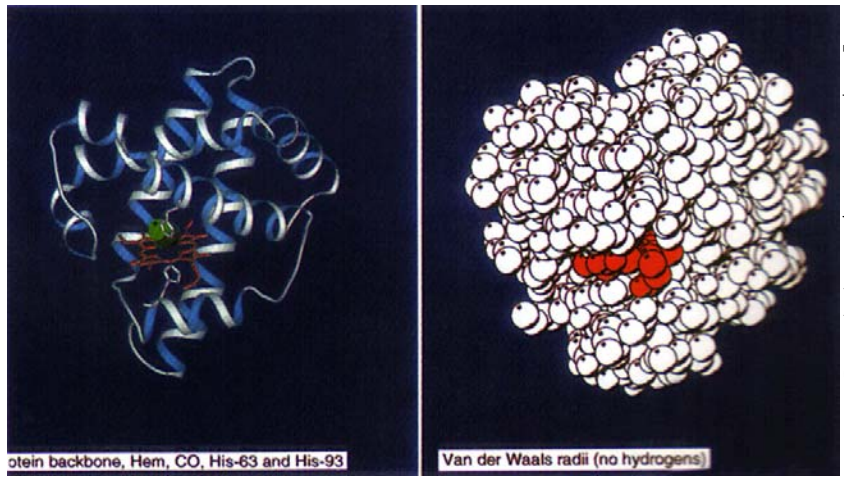
Sometimes structure gives insight into function DNA, ATP synthase

Often it doesn't:- Hemoglobin. How do the Fe groups interact?

Strucure of ATP synthase
from protein crystallography



Structure of Myoglobin
from protein crystallography



The structure must
be dynamic.

Where are the channels?

How do they open and close?

Over what timescales?

4GLS will provide insight into function directly

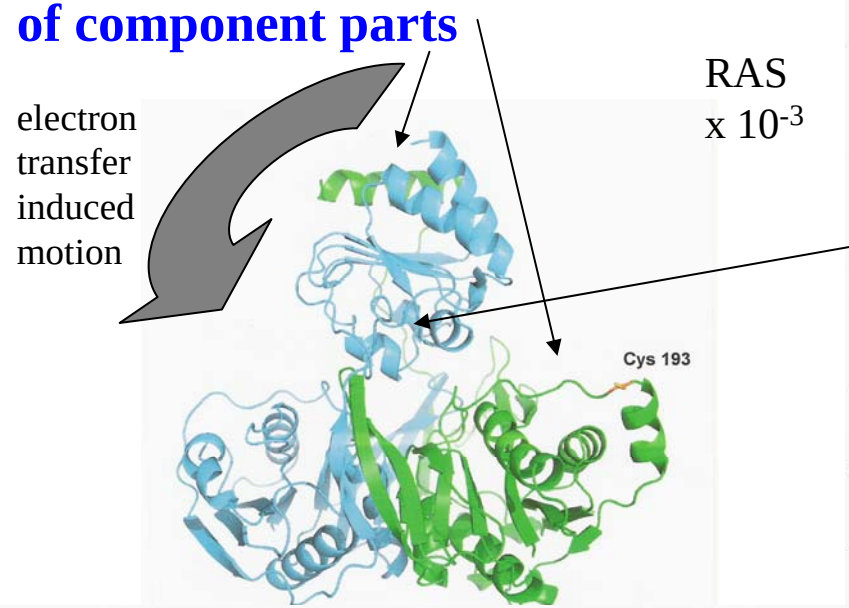
From fast spectroscopy and sub-cellular imaging.

Particularly useful for studies of membrane proteins: difficult to crystallise

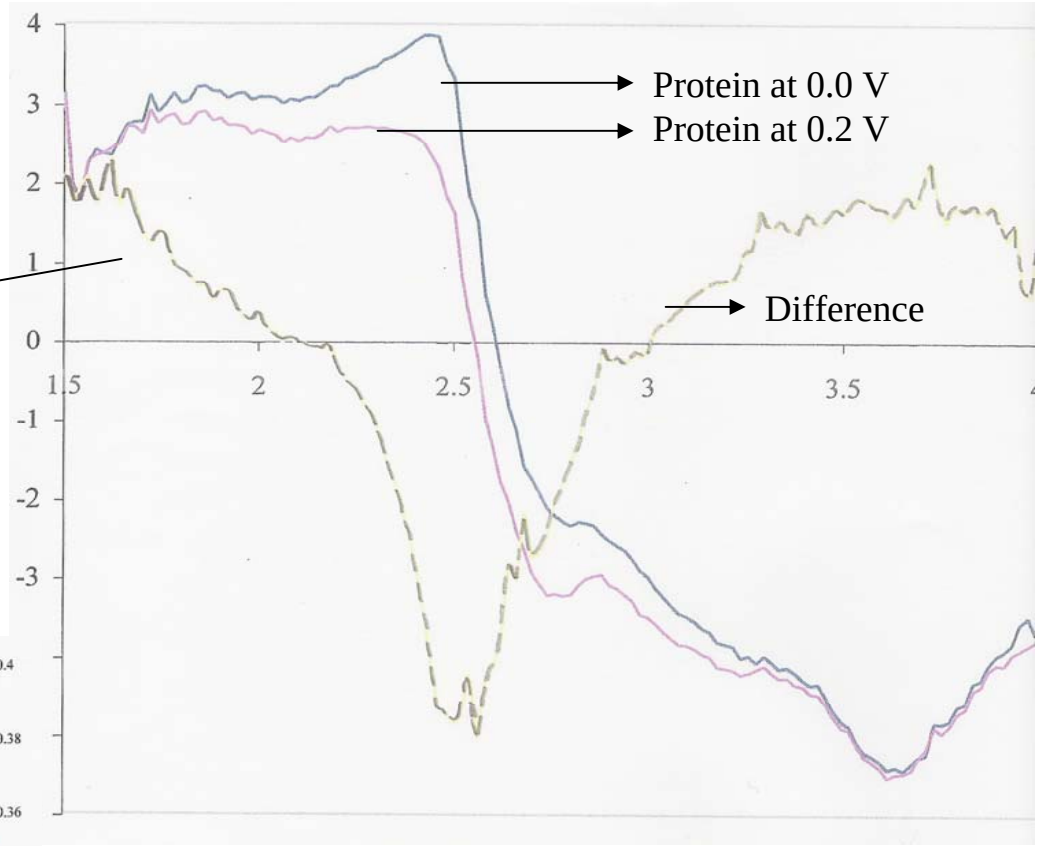
Reflection Anisotropy Spectroscopy: A monitor of protein dynamics

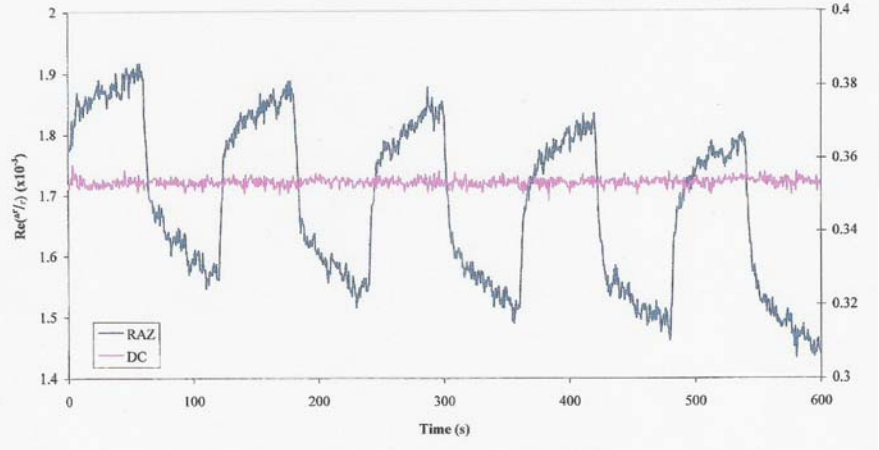
Flavoprotein

Good structural data from protein crystallography of component parts



Anchor protein to Au(110)/liquid interface through S on Cys 193: forms ordered structure





C.I. Smith, H. Messiha, N. Scrutton, P. Weightman 2007

4GLS: THz pump -- RAS probe experiments

Recent work on the potential of reflection anisotropy spectroscopy (RAS)

Can determine the 3D orientation of a molecule at a metal/liquid interface

Weightman et al Phys. Rev. Lett. **96** 86103 (2006)

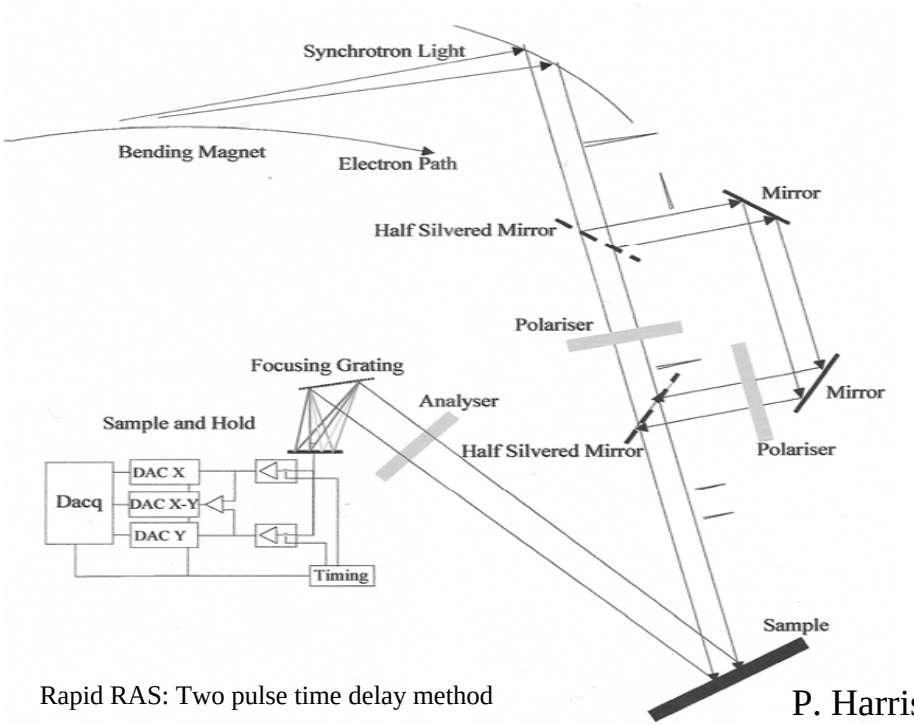
Can distinguish between single and double stranded DNA at metal/liquid interfaces

C. Cuquerella et al Langmuir:Langmuir **23** 2078 (2007)

Can monitor molecular interactions in real time LeParc et al Langmuir **22** 341 (2006)

Can monitor for the study of peptide-membrane dynamics

4GLS --> Rapid RAS in the UV at < 1 nsec, 250,000 faster than laboratory work.

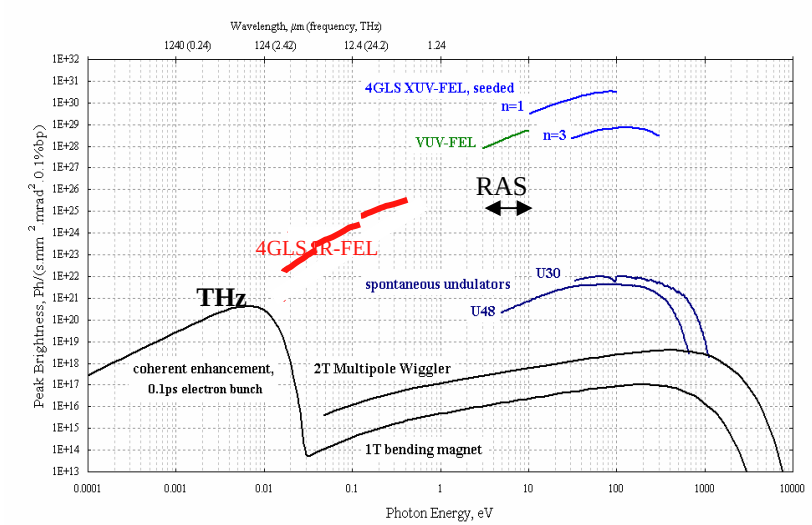


Rapid RAS: Two pulse time delay method

P. Harrison 2006

THz Pump, RAS probe

Does peptide enter membrane?

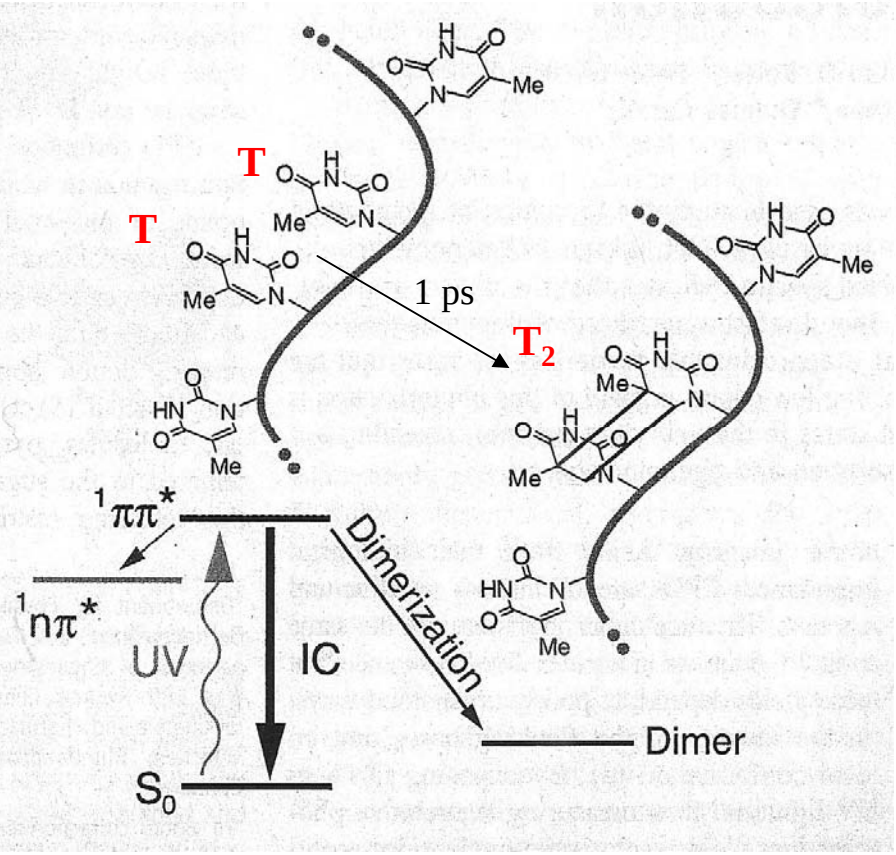


4GLS: Potential of RAS on VUV FEL

1 Extended Range: VUV FEL Range 3 eV to 10 eV

2 Increased intensity: Rapid RAS in the UV at ~ p sec to f sec

THz pump -- RAS probe on VUV FEL

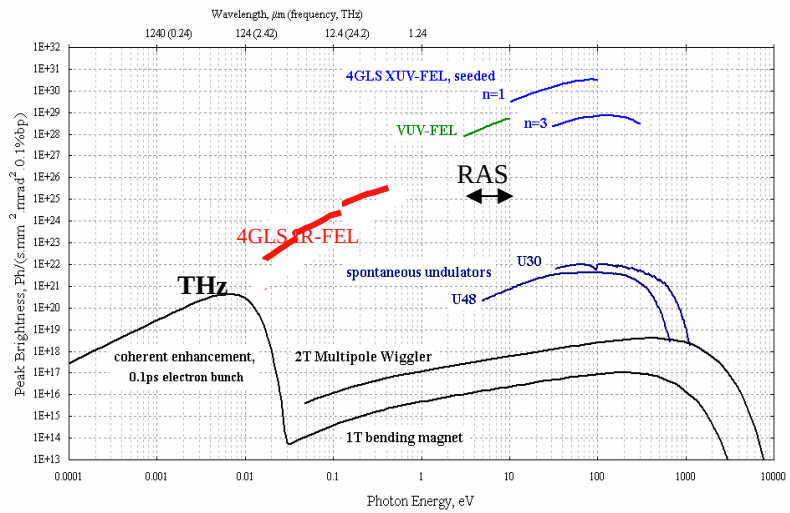


Thymine Dimerization in DNA Is an Ultrafast Photoreaction

Wolfgang J. Schreier,[1] Tobias E. Schrader,[1] Florian O. Koller,[1] Peter Gilch,[1] Carlos E. Crespo-Hernández,[2] Vijay N. Swaminathan,[3] Thomas Carell,[3] Wolfgang Zinth,[1]* Bern Kohler[2]*

SCIENCE **315** 625 (2007)

Femtosecond time-resolved infrared spectroscopy was used to study the formation of cyclobutane dimers in the all-thymine oligodeoxynucleotide $(dT)_{18}$ by ultraviolet light at 272 nanometers. The appearance of marker bands in the time-resolved spectra indicates that the dimers are fully formed ~1 picosecond after ultraviolet excitation. The ultrafast appearance of this mutagenic photolesion points to an excited-state reaction that is approximately barrierless for bases that are properly oriented at the instant of light absorption. The low quantum yield of this photoreaction is proposed to result from infrequent conformational states in the unexcited polymer, revealing a strong link between conformation before light absorption and photodamage.



4GLS Flagship Proposals

1 Origins (M. McCoustra, University of Heriot Watt)

2 Spintronics (S. Thompson, University of York))

3 Nanocomposites (B. Hamilton, University of Manchester)

4 Quantum chemical control (I. Powis, University of Nottingham)

5 High field physics (L. Frasinski, University of Reading)

6 Molecular assemblies in extra-cellular matrix and cell signaling (D. Fernig, University of Liverpool)

7 Biocatalysis, photosynthesis and membrane proteins (N. Scrutton, University of Manchester)

8 Protein structure and dynamics (D. Klug, Imperial College)

9 Cell and tissue imaging (P. O'Shea, University of Nottingham)

10 Catalysis (R. Catlow, UCL)

11 Nuclear astrophysics (R. Herzberg, University of Liverpool)

Summary: "4GLS Science Landscapes" available at http://www.4gls.ac.uk

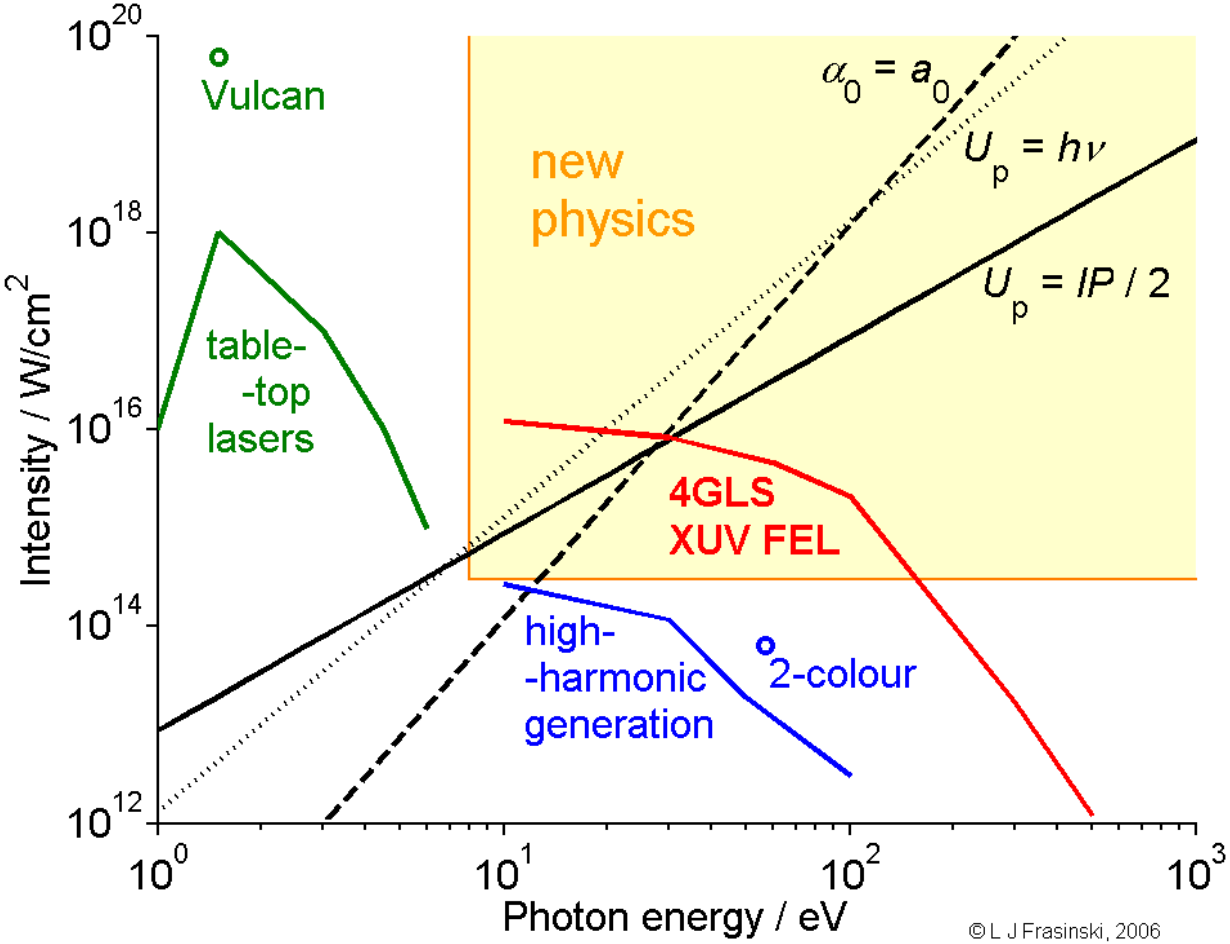
4GLS Flagship Proposals

High Field Physics

Leszek Frasinski

4GLS: Potential for Major Advances: New Physics

Uncharted Territory of Strong Field Science at High Frequencies



α_0 amplitude of electron quiver motion

U_p ponderomotive potential

Aims:

- **Molecular structure and dynamics can be probed with an unprecedented resolution on ångström spatial and attosecond temporal scales.**
- **Quantum-state tomography can reveal the fundamentals of chemical reactions.**
- **Unique parameter regime enables intense-field interactions with atoms and molecules.**

Ångström structural resolution with *attosecond* temporal resolution

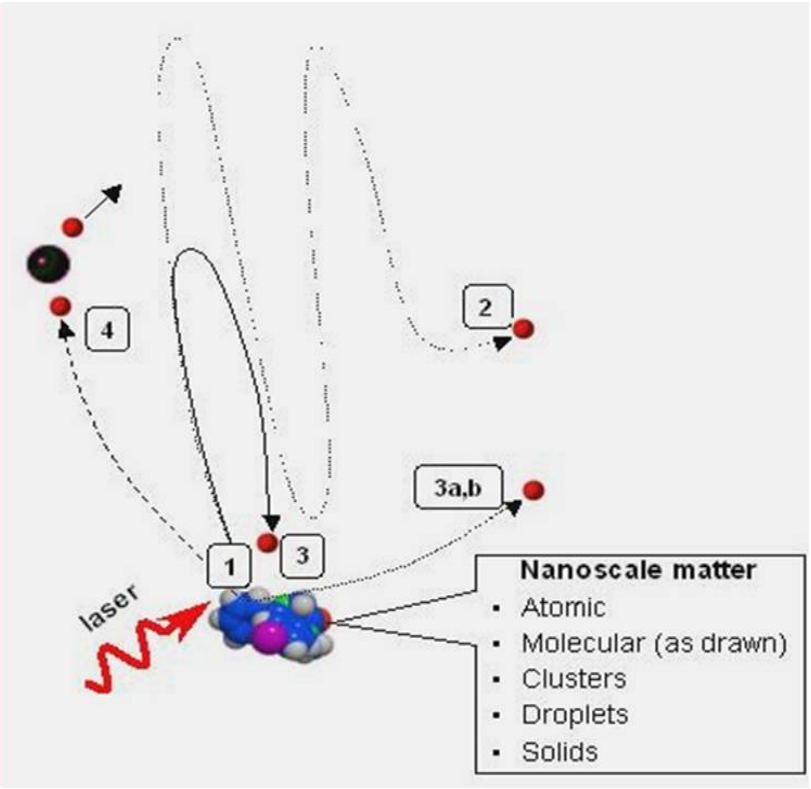
Reaction dynamics is probed through tomographic imaging of molecular orbitals.

Recollision-induced processes in a molecular sample.

Following ionisation (1) the electron may be driven away (2) or recollide (3) with the molecule depending on the field phase at the instant of ionisation.

If recollision occurs the electron can
(a) recombine – with the emission of a higher energy photon,
(b) scatter elastically or inelastically from the molecule.

In a dense sample the outgoing electron may collide with neighbouring atoms or molecules (4).



The interpretation is testing the limits of quantum mechanics

Ångström structural resolution with *attosecond* temporal resolution

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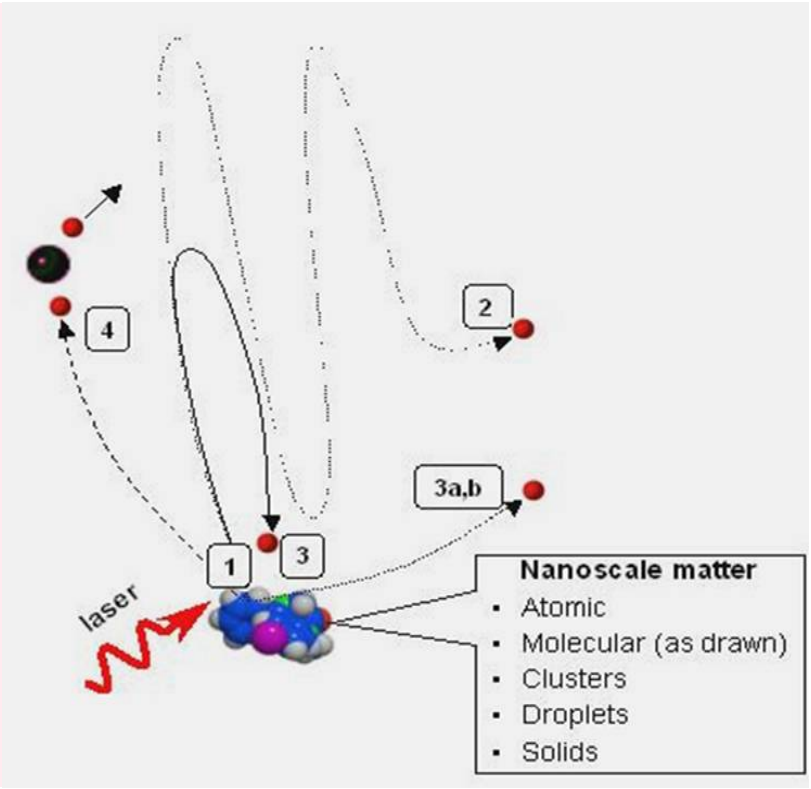


The interpretation is testing the limits of quantum mechanics

"In this meaninglessness one finds usefulness"

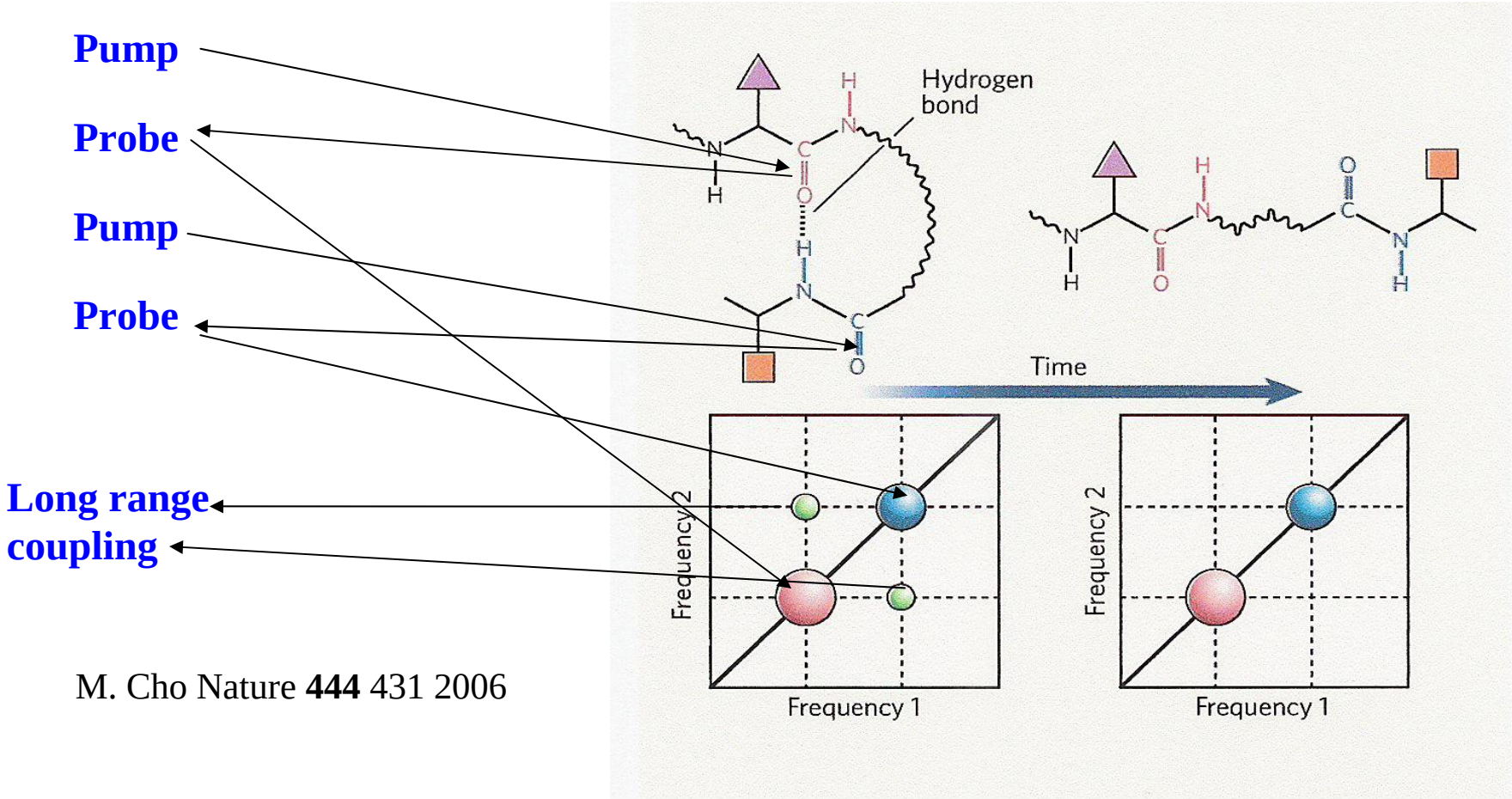
Leszek Frasiński

Protein Structure and Dynamics

David Klug

Principle of 2D IR

2D IR: A pump probe experiment: H bond between amino acids



M. Cho Nature **444** 431 2006

As the Hydrogen bond breaks and the protein changes conformation the long range coupling between the local modes weakens

Example of 2D IR

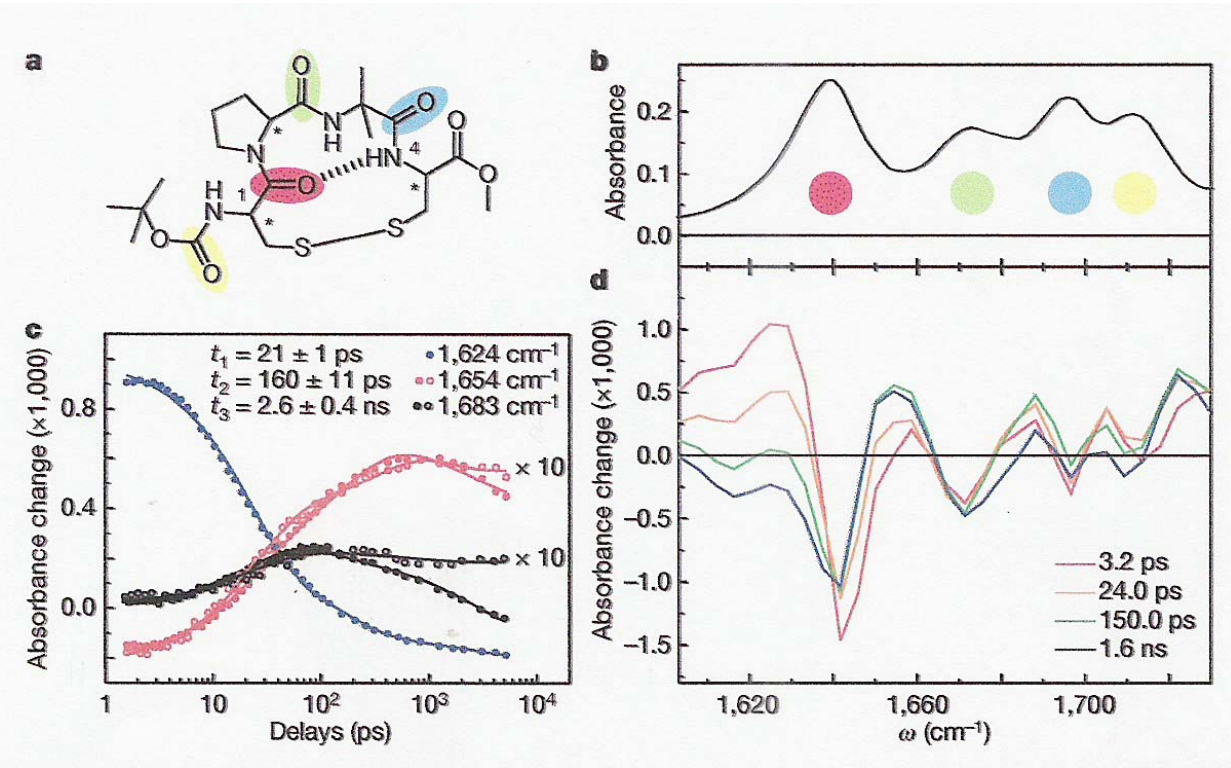
2D IR: Watching H bond dynamics in a β turn

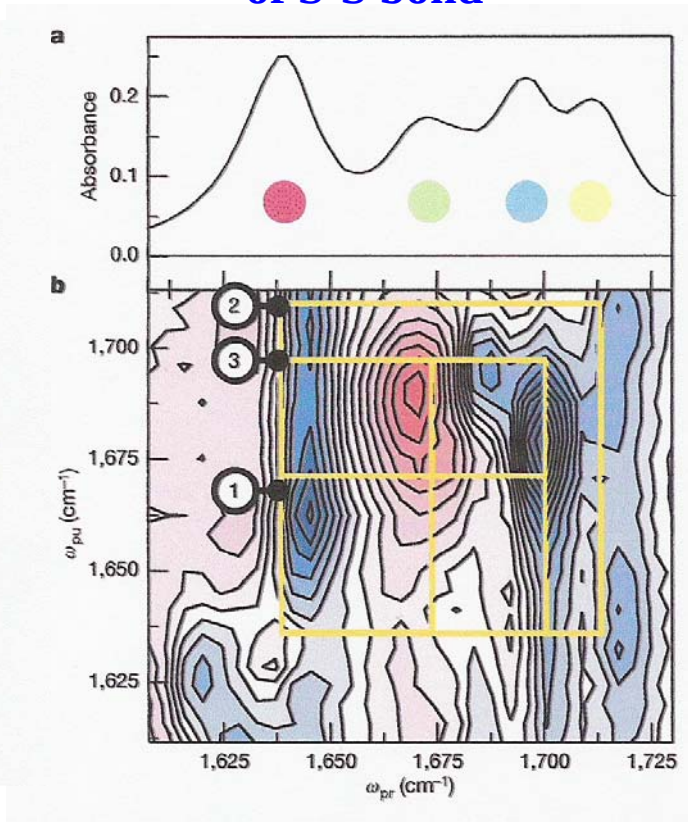
Small amino acid sequence forming a β turn linked by a S-S bond

Boc-Cys-Pr-Aib-Cys-Ome

Time dependence of IR spectrum following breaking of S - S bond by UV pulse

2D IR spectrum following breaking of S-S bond

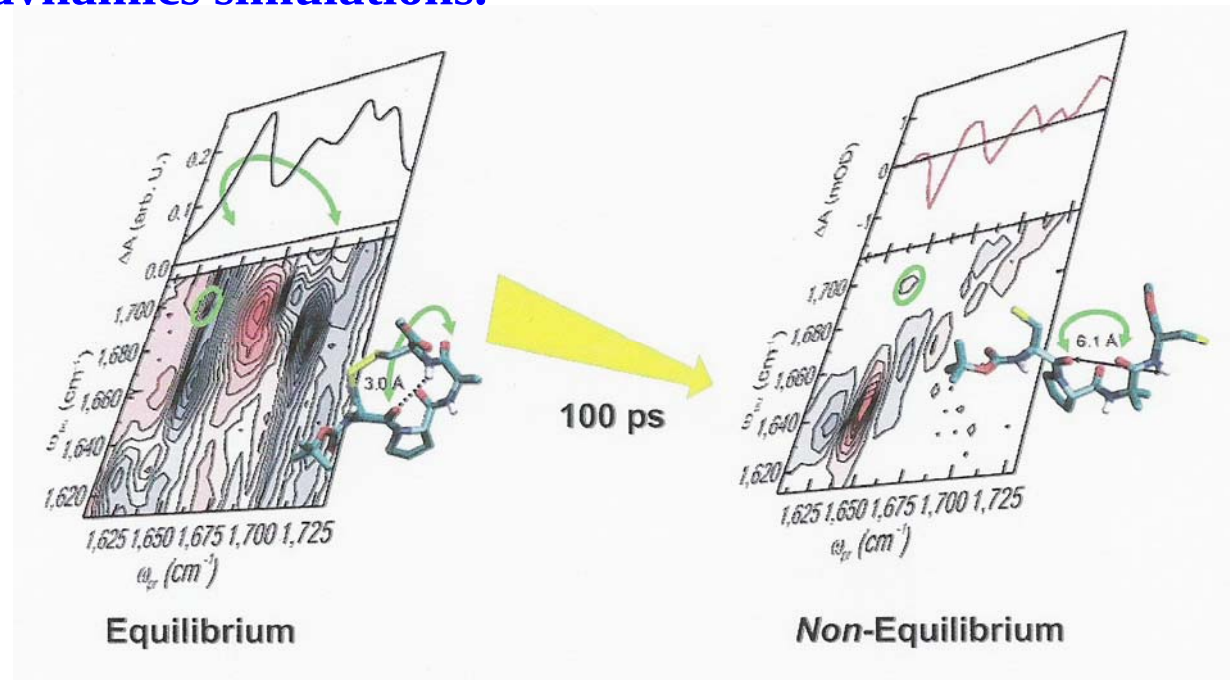




C. Kolano, J. Belbing, M. Kozinski, W. Sander and P. Hamm Nature **444** 469 2006

Example of 2D IR: Conclusion

The hydrogen bond separates at a rate that is two orders of magnitude faster than the "folding speed limit" between protein side chains given by molecular dynamics simulations.

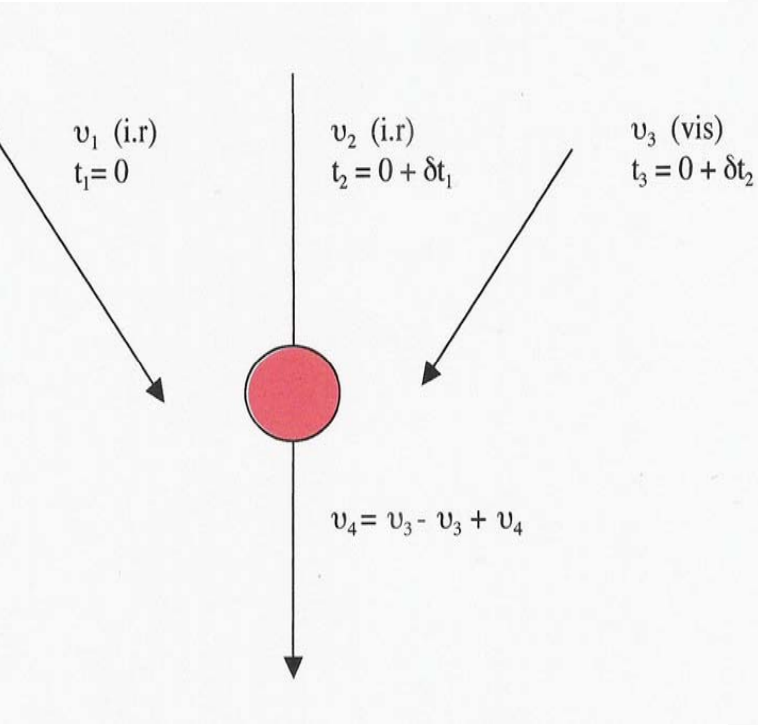


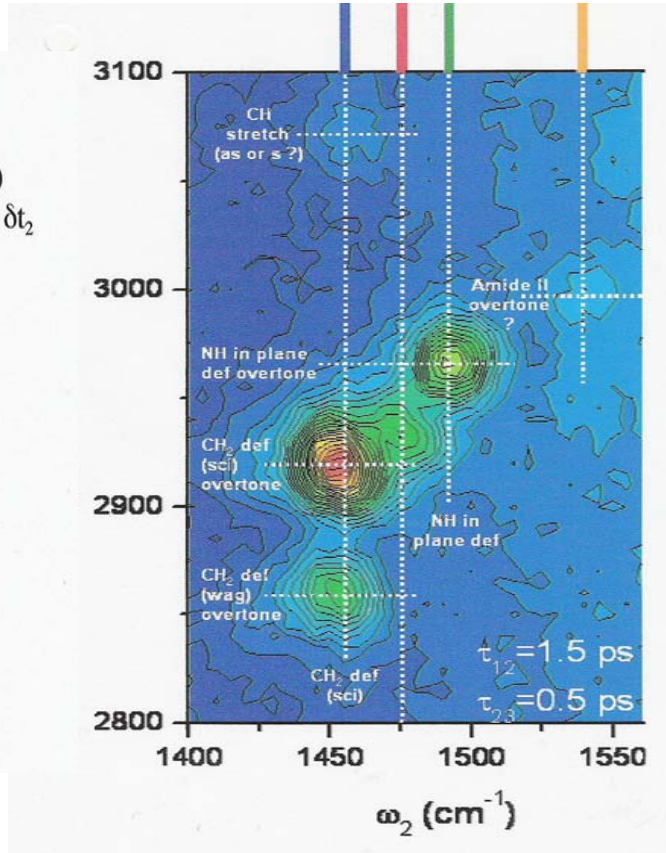
Following rupture of S-S bond system evolves on time scales of 20 ps, 160 ps and 2.6 ns

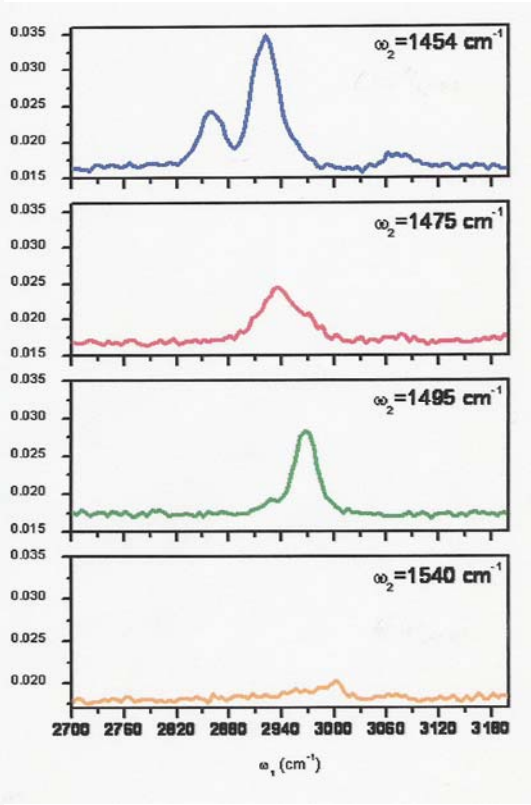
UV pulse to cleave S-S bond: 2 experiments with UV on and with UV off
Variable delay after UV pulse before starting 2D IR experiment
Vary delay between pump and probe IR pulses: 3 ps, 25 ps, 100 ps: 2D maps
Parallel and perpendicular polarisations of pump and probe pulse to enhance cross peaks
2D map is limited by signal to noise

DOVE-FWM: Double Vibrationally Enhanced Four Wave Mixing

: vibration-vibration coupling in polyhistidine (Courtesy David Klug)







δt_1 and δt_2 vary from 0 to 20 psec.

beam overlaps to > 2% on 0.1 mm

υ_1 and υ_2 are varied independently

υ_1, υ_2 and υ_3 impinge collinearly onto specimen

υ_1 and υ_2 line widths of 10 to 40 cm^{-1}

Scanning υ_4 gives a 2D map of 100 x100 pixels

4GLS: Potential for Major Advances: Protein Function: 2D IR

Mid IR FEL 0.5 eV to 0.05 eV Far IR FEL 0.05 eV to 0.005 eV THz 0.005 eV to 0.0001 eV

4GLS will open a spectral "area" 10 x greater than currently explored with 2D IR

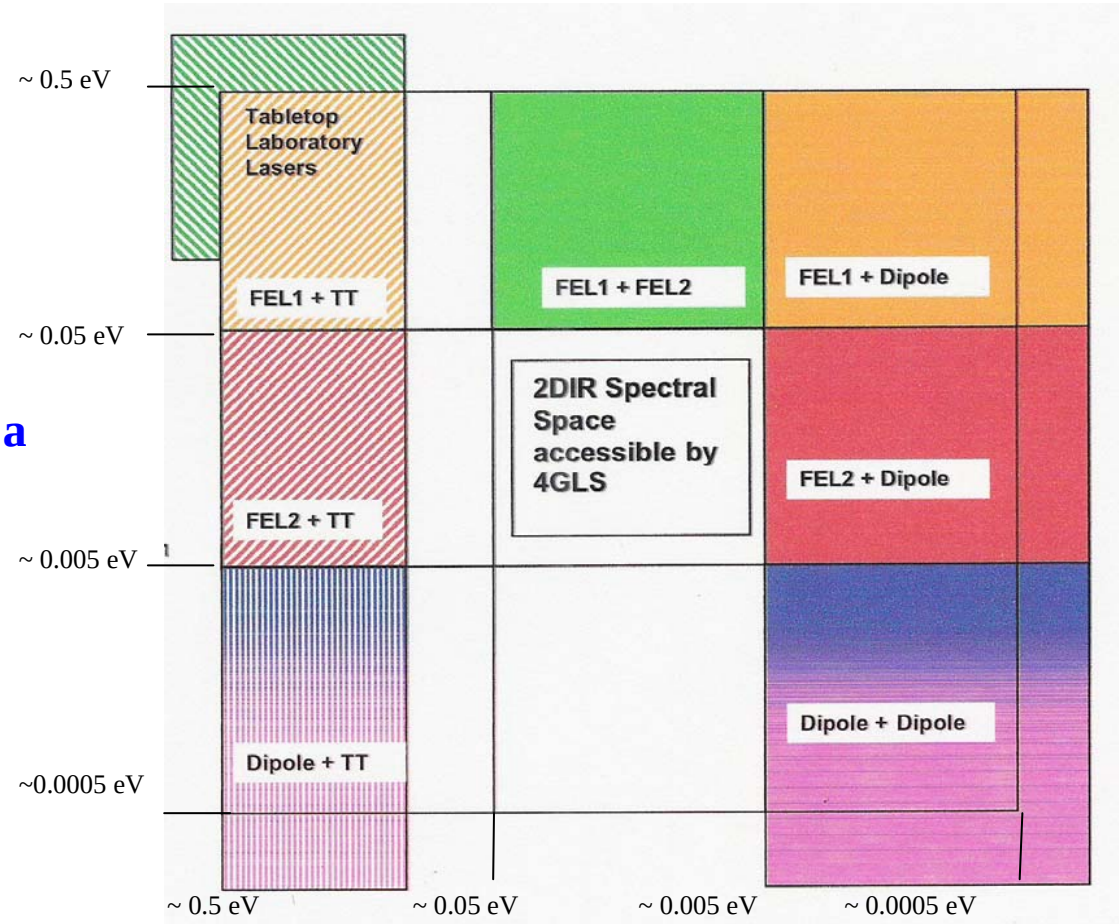
Nine tenths of the structural-dynamics elements of a protein will remain hidden without 2D IR on 4GLS

Potential for fast through put
Protein analysis ~ 10^4 faster than with laboratory 2D IR instruments

Complete proteome of a cell line in a few minutes

Screen 10^6 potential drug molecules against 10^3 proteins in 6 weeks

Equivalent cost with laboratory instruments £ 5 billion



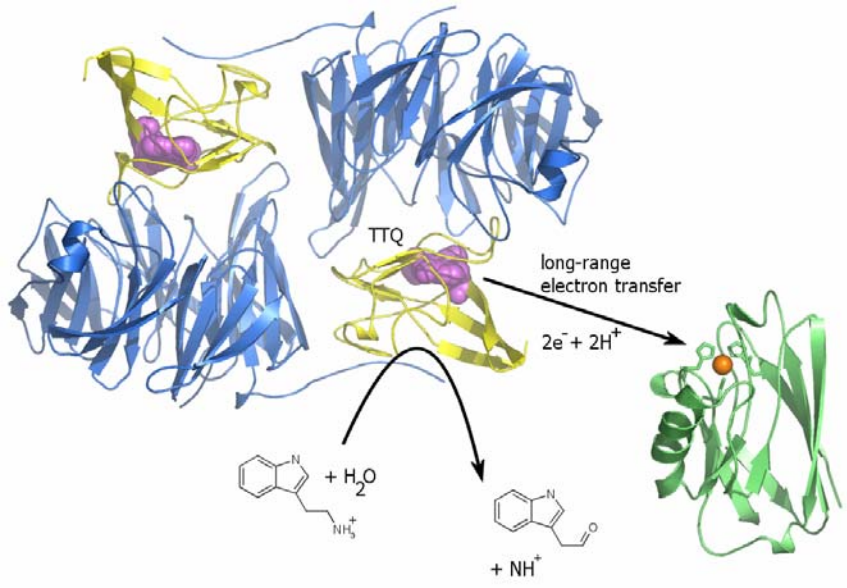
4GLS Flagship Proposals

Enzyme Catalysis

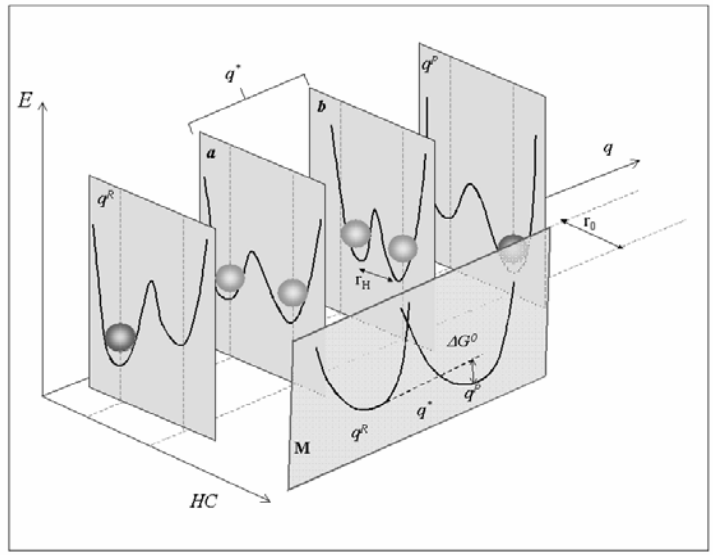
Nigel Scrutton

Fast tunnelling models for enzyme catalysis: H and electron-transfer

- **New theory emerging that fundamentally challenges TST for enzymes**
- **Protein motion (millisecond to sub picosecond) modulates barrier properties (*i.e.* 'squeezing') to facilitate tunnelling**
- **Fast (sub-picosecond) small-scale promoting vibrations/motions promote H-transfer and electron transfer by quantum tunnelling mechanisms.**
- **Large-scale motion also narrows the barrier in electron transfer**



Courtesy Nigel Scrutton



Masgrau *et al.*, *Science* in press

Leys, Sutcliffe & Scrutton *Nature Struct. Biol.* (2003)

Extra-Cellular Matrix

David Fernig

4GLS and the Extra-Cellular Matrix

Consists of molecular assemblies of proteins and polysaccharides (glycosaminoglycans)

A key regulator of cell function, and hence organ and organism function

The Central Problem

How does the structure of glycosaminoglycans drive their functional interactions with other molecules of the extracellular matrix and the cell surface to regulate cell activity?

Medical Relevance

Cancer eg. FGF, VEGF and angiogenesis in carcinomas.
Neurodegeneration eg. BACE in Alzheimer's and PrP in CJD.
Inflammation eg. cytokines in RA, asthma, skin.
Congenital disorders eg. craniosynotoses, dwarfism, EXTs, SGB.
Pathogens eg. HIV, herpes, malaria, chlamydia.

Macromolecular assemblies in the matrix

Macromolecular concentration:
~400 mg/mL

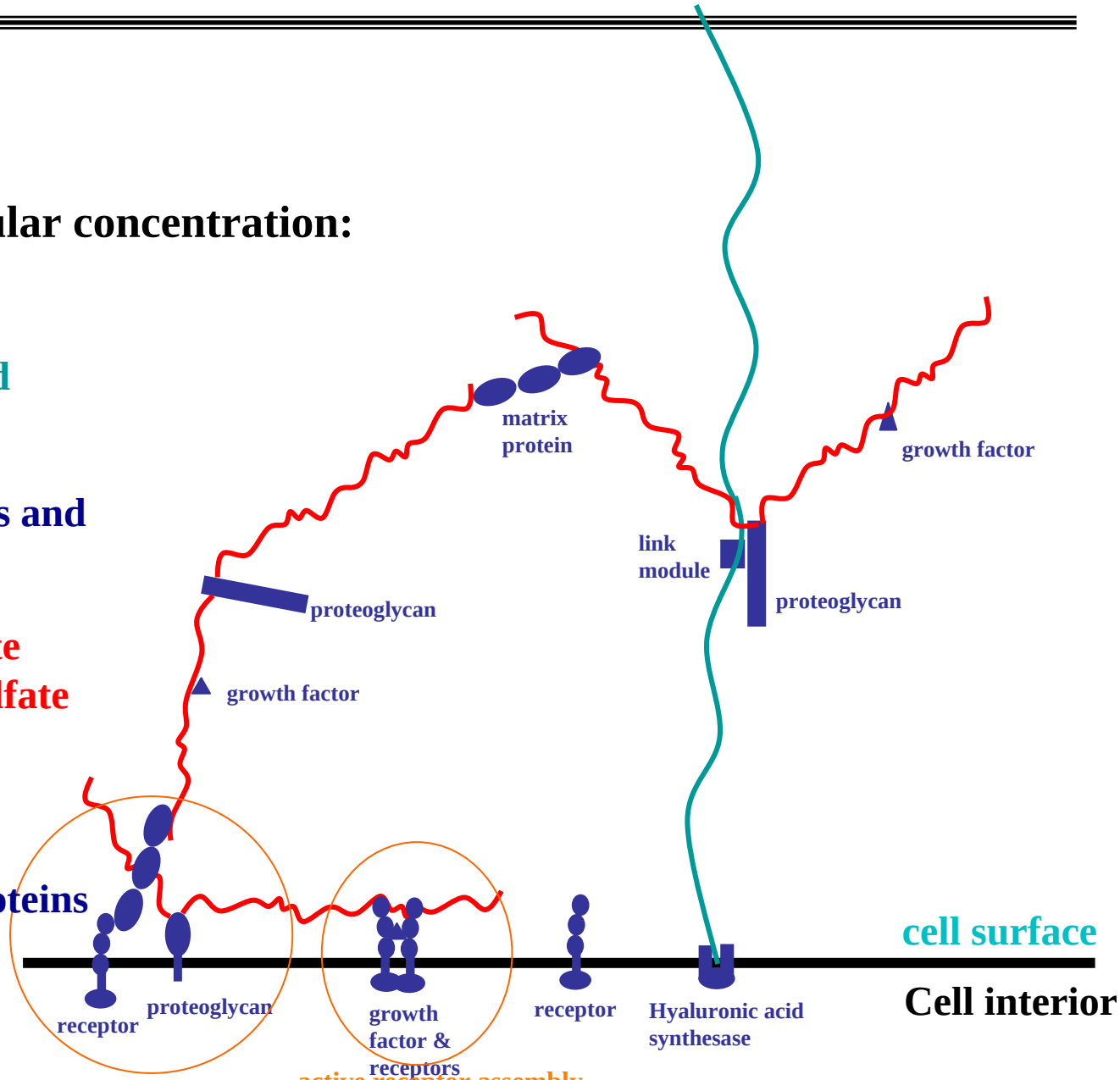
hyaluronic acid

matrix proteins and growth factors

heparan sulfate
chondroitin sulfate

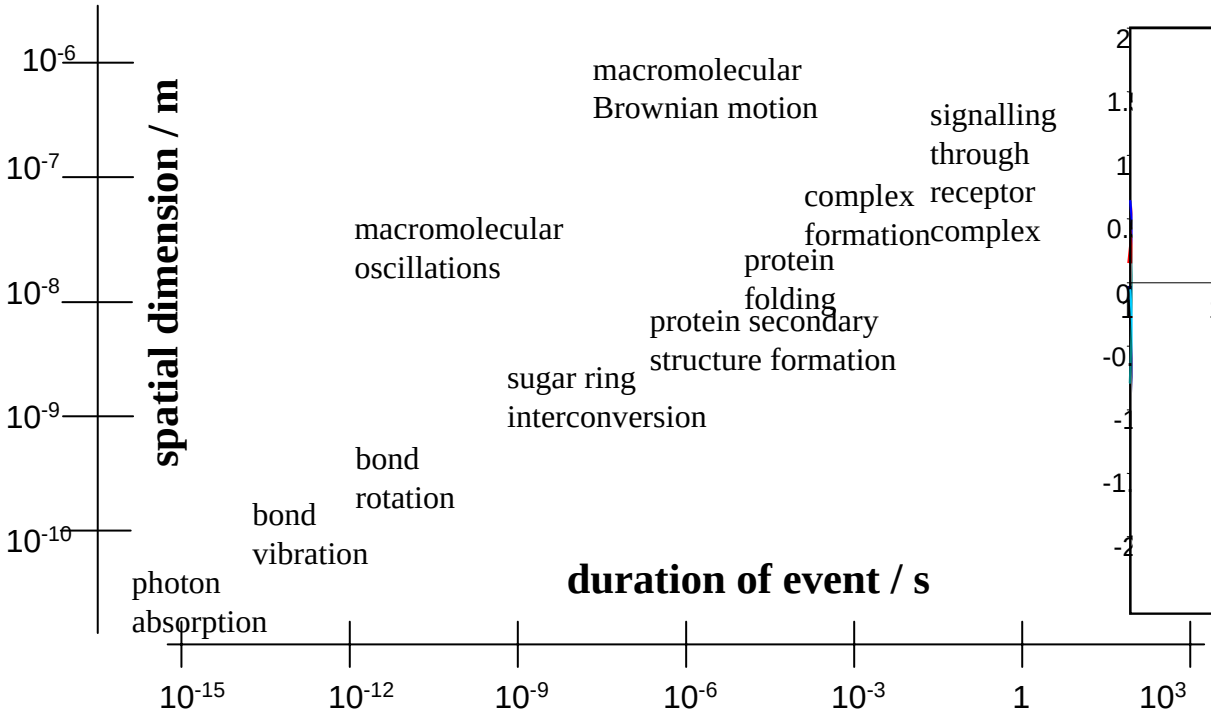
cell surface proteins

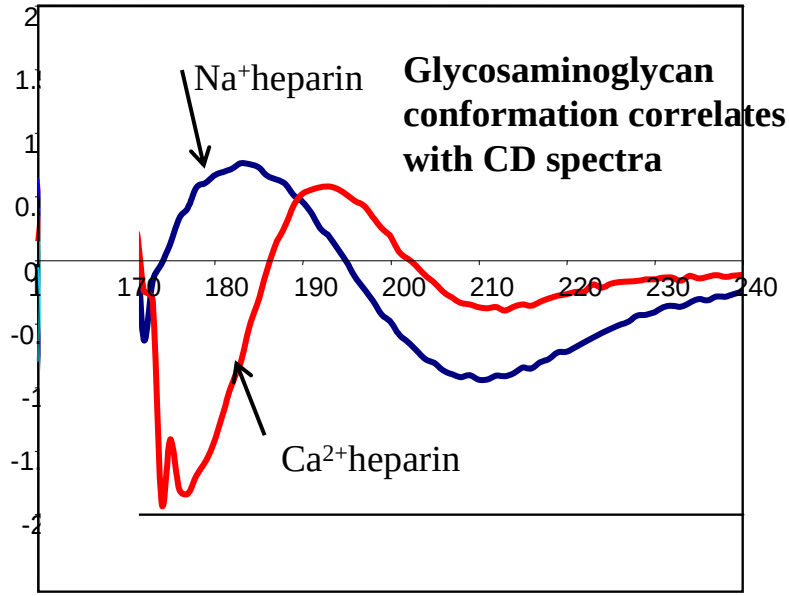
membrane



David Fernig

Spatial and temporal dimensions of events at the molecular level





Examples of Science Need

CD studies in THz, IR, Visible at low concentration:

- **VCD - bench top instrument needs 100 mg/ml,**
- **4GLS = µg/ml --> selectively study protein in presence of GAGs (GAG invisible)**

2D IR on fast timescales

Pump probe THz UV on fast timescales

Strategy for resolving glycosaminoglycan function with 4GLS

Localised structural perturbations by electromagnetic pumping and spectroscopic monitoring:

- **TeraHertz: domains and solvent structure.**
- **Infrared: selective chemical bonds and protein secondary structure.**
- **UV and visible: electronic states.**
- **Far IR and THz: bound water.**

Chemical perturbations of biological function:

- **amino acid mutations of proteins**
- **chemical modification of GAG chains**
- **selective labelling of complex components with fluorophores**
- **mass labels, eg. D_2O to bandshift**

Biology is chiral: CD in the IR and THz domains

Combine spectroscopies: including UV/THz absorption in the fast time domain

Non-linear techniques:

- **2D-spectroscopy, for coherently coupled interactions providing 3D/dynamic information.**

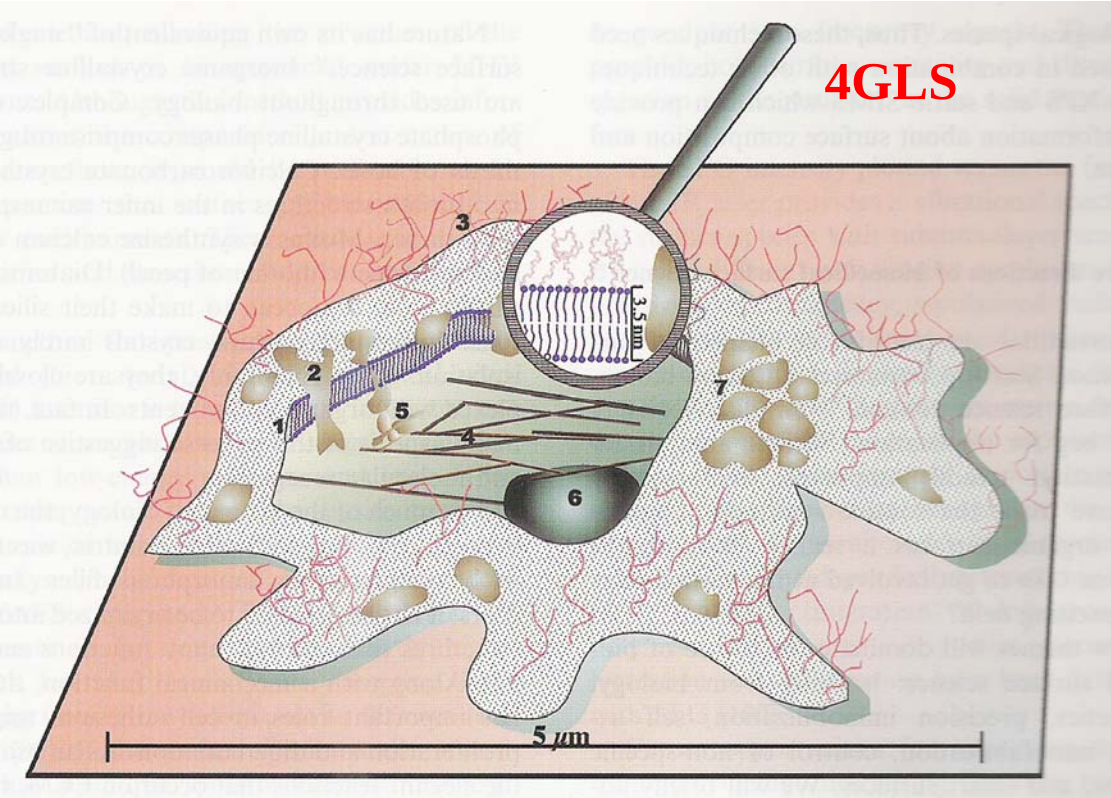
4GLS Flagship Proposals

Cell and Tissue Imaging

(membranes)

Paul O'Shea and Mike Somekh

4GLS: Membrane Analysis and Dynamics



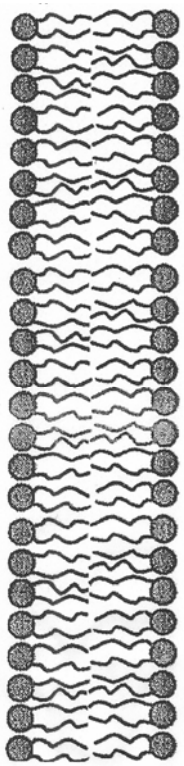
Cell Surface

1 lipid bilayer
2 embedded proteins
3 saccharide chain
4 cell cytoskeleton
5 small proteins
6 cell nucleus
7 exposed proteins

Membrane proteins are important and difficult to crystallise

Study their function directly by fast spectroscopy and imaging

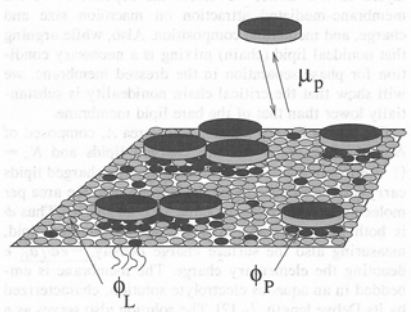
The Problem of Membrane Fusion



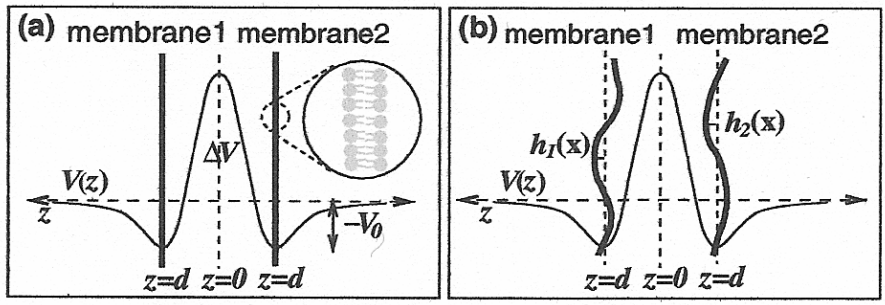
Virus and cell are surrounded by a phospholipid bilayer

While the structures of the virus, its coating and its cellular membrane target are important the dynamic interaction between them is the key to understanding how the virus and cellular membranes can fuse together and allow the virus DNA/RNA to enter the cell.

Theory:
Low frequency vibrations mediated by the environment are crucial to membrane fusion and repair.
Natural membrane frequency ~ 10^{11} Hz



Membrane Interactions: Due to presence of counter ions in solution oppositely charged membranes do not always attract, similarly charged membranes do not always repel
Membrane Fusion is important in:-
viral infection, gene therapy and intracellular trafficking
Membrane Rafts are important in cell signaling and cell interactions. May be mediated by variations in membrane dipole across cell surfaces. Interaction with H_2O a key factor.



4GLS: Potential for Major Advances: Virus cell interactions

How does the Aids virus enter a cell? **Virus and cell surrounded by a phospholipid bilayer**

The structures of the virus and cell membranes are important but the dynamic interaction between them is the key to understanding how the membranes fuse together for the virus DNA/RNA to enter the cell.

Membrane Rafts: Area ~ 50 nm are important in cell signaling and cell interactions. The membrane dipole varies spatially across cell surfaces and variations in dipole field and interaction with H_2O are key factors.

4GLS Key Contributions

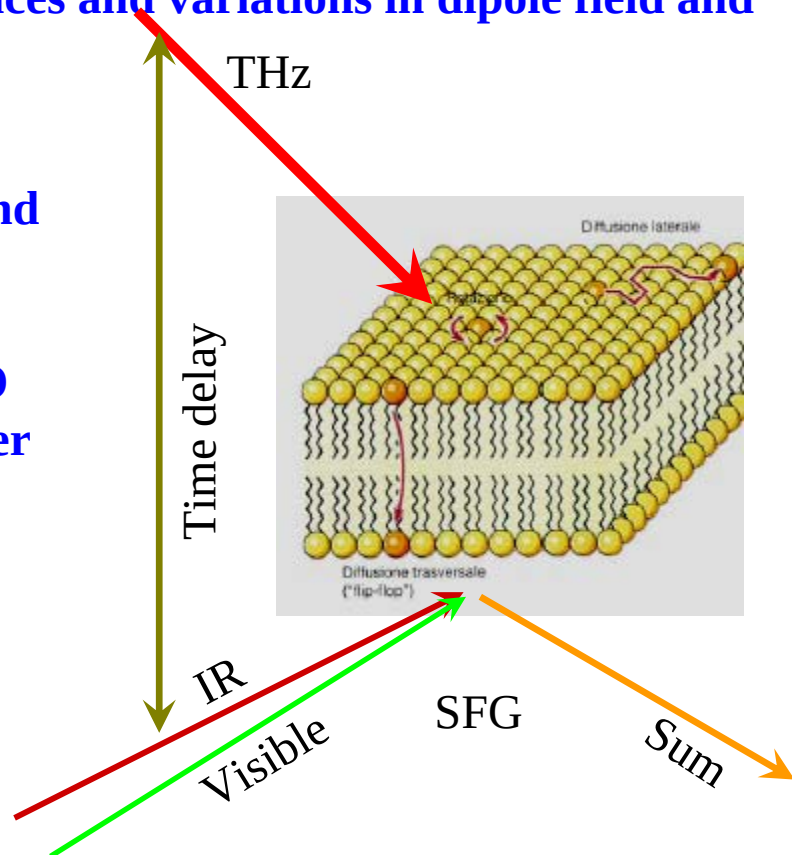
High intensity THz: Near field sub-cellular imaging and Spectroscopy of live cells.

Pump probe: IR, Visible, THz, SFG

Monitor fluorescence markers while scanning the H_2O THz spectrum. Modulation of raft dipole - bound water Interactions changes activity of membrane proteins involved in signaling

Explore Novel Therapies

Based on use of THz to modify cell behaviour Eliminating drug treatments for some neurological conditions



THz Near Field Imaging of Live Neuronal Cells

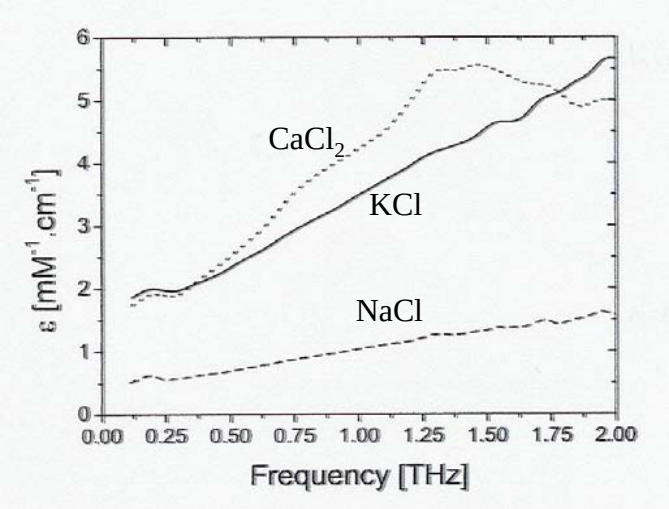
Neuronal activity results from the precise control of transient variations in ionic conductance and water exchange between the extracellular matrix and the intra-axonal compartment.

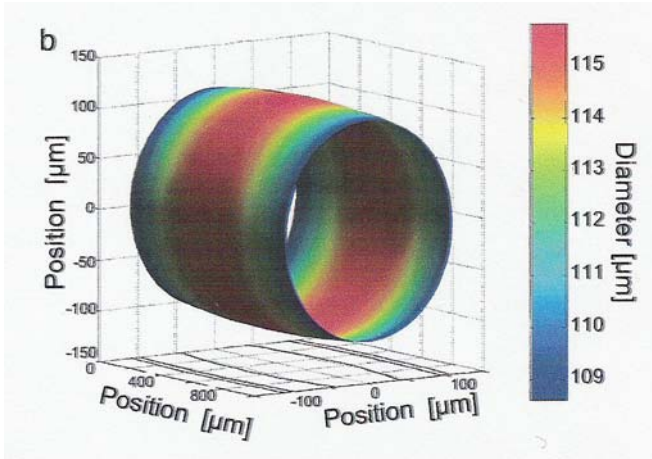
Experiment

The absorption of THz by Na and K solutions is very different and can be used as a contrast mechanism in transmission near field THz measurements of neurons.

Near field THz imaging of live functioning neuronal cells in Na and K ionic solutions. Provides quantative measurements of the ionic concentration in both the intercellular and extra cellular compartments of the neuron.

A series of of 2D scans can be used to build up a 3D image of the axon





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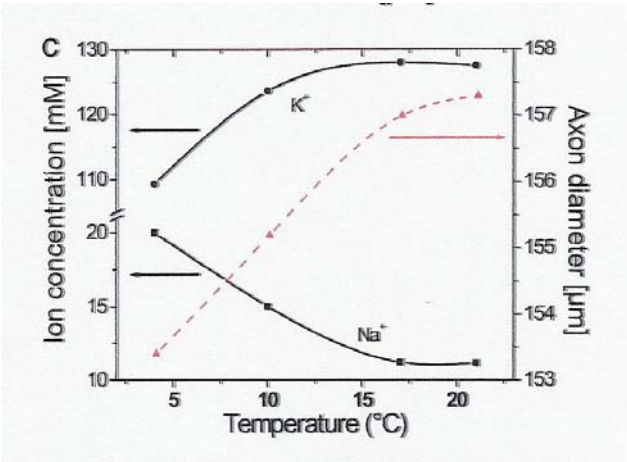
THz Near Field Imaging of Live Neuronal Cells

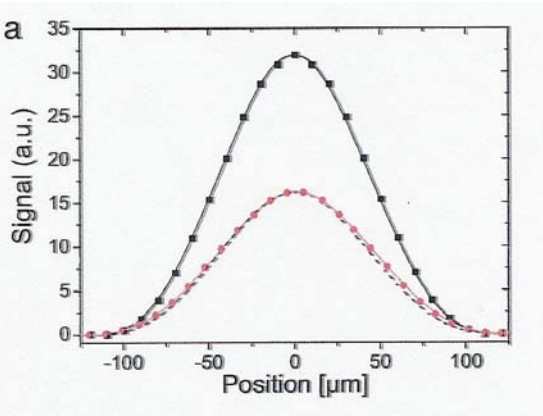
The shape of the axon is shown to vary with

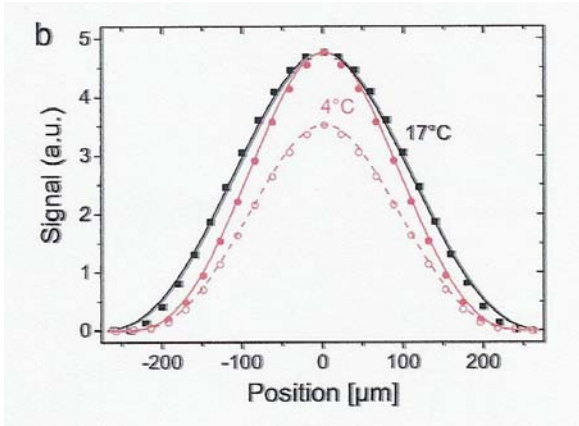
a) Introduction of veratridine, a toxin that activates Na channels in the membrane

b) Temperature

c) Concentration of K in the physiological solution surrounding the neurons







Can be used for direct non-invasive imaging of neurons during electrical, toxin or thermal stress

Results

Direct observation of neuron swelling induced by Temperature change or neurotoxin poisoning

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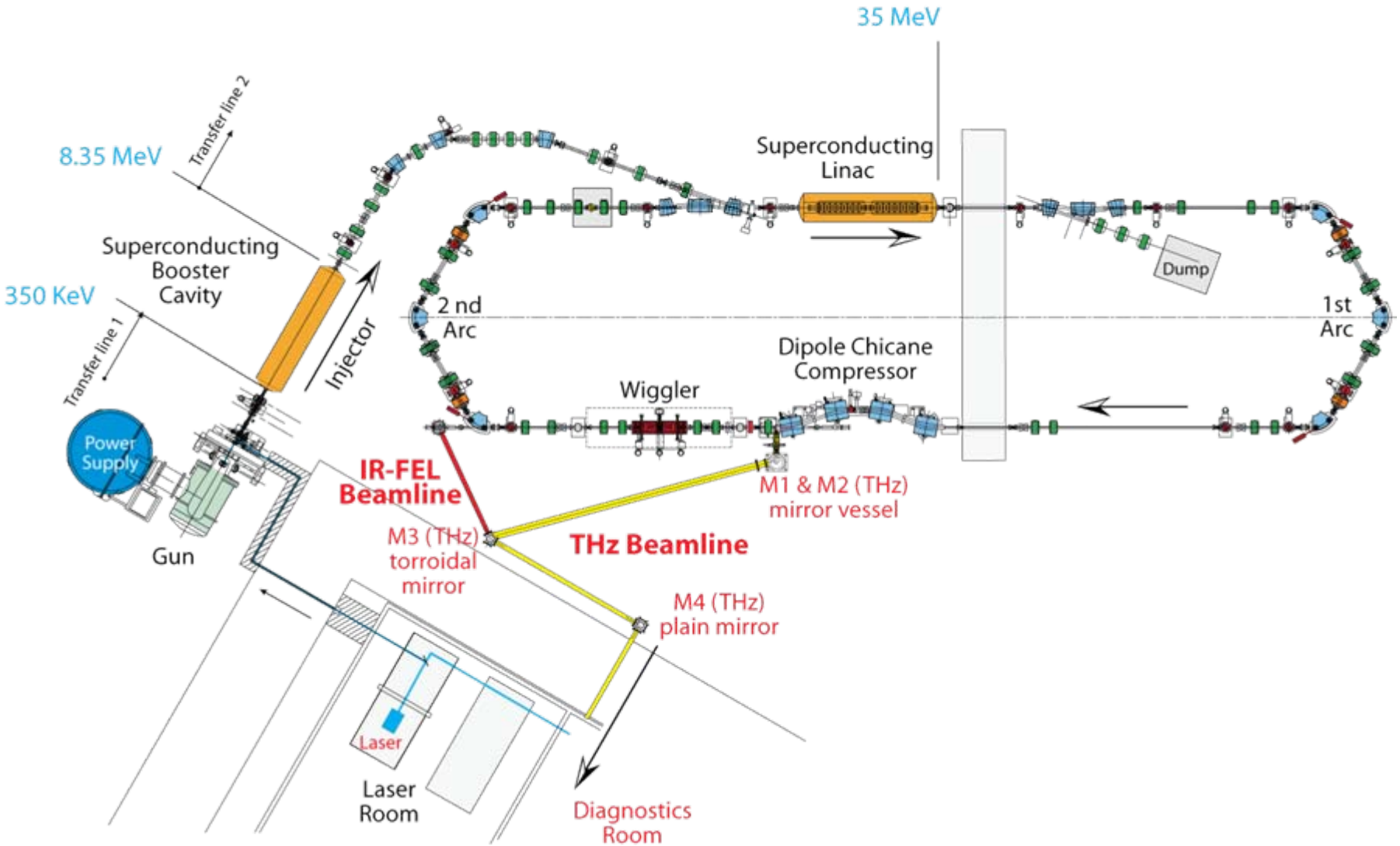
4GLS Energy Recovery Linac Prototype (ERLP)

ERL Prototype Layout



NW Science Fund: £2.9M 3 years

Exploiting ERLP: X-rays: Compton Back Scattering

Time resolved X-ray diffraction studies aimed at probing the mechanisms of shock compression of matter on sub picosecond (ps) timescales.

Exploiting ERLP: THz

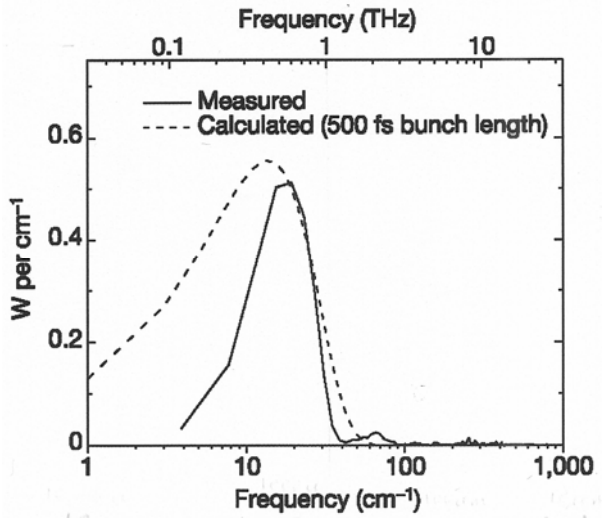
THz beamline and a tissue culture facility. Allow the ultrahigh intensity, broadband THz radiation to be utilised for the study of biological systems. In collaboration with Physics Department University of Liverpool

Laser-SR synergy: Synchronisation of SR from the SRS with a table-top fs laser system. In collaboration with the Photon Science Institute (PSI) of the University of Manchester.

NW Science Fund: Exploiting ERLP THz Radiation

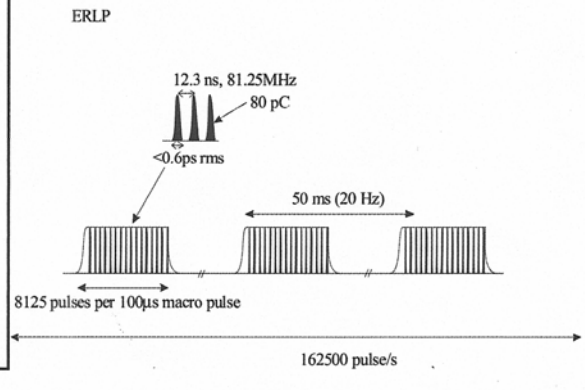
1 Construct a THz beamline on ERLP

Based on Carr et al Nature **420** 153 (2002)



Electron Beam Parameters	
Operating Mode	
long pulse	←
Electron Energy	35 MeV
Gamma Factor	68.49
Charge per Bunch	80 pC
Bunch Repetition Rate	81.25 MHz
Train Length	100 us
Train Repetition Rate	20 Hz
Number of Electrons per Bunch	5.0E+08
Bunch Spacing	12.31 ns
Train Spacing	49.90 ms
Duty Factor	0.002
Bunches per Train	8125
Bunches per second	162500
Average Current	13.0000 uA

Average power ~ 20 mW



2 Establish a Tissue Culture Facility to GLP Standard

grow and maintain live tissue

3 THz beamline into Tissue Culture Facility

4 Exposure experiments on:-

live tissue

model membrane systems

model DNA sequences

Acknowledgements

- **The 4GLS Team**
- **The 4GLS International Advisory Committee**
- **The 4GLS Steering Committee**
- **National and international scientific community**
- **Funding: OST/DTI, CCLRC, NWDA and EU**

information http://www.4gls.ac.uk