NMRbox: Toward Reproducible Computation for Bio-NMR

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Overview

- What is NMR?
- Biomedical applications
- Computation in NMR
- Challenges, especially reproducibility
- Application of virtualization and clouds
- Challenges awaiting solutions

The mission of the Center is to

- Simplify the development, discovery, maintenance, and use of bio-NMR software
- Facilitate optimal and reproducible workflows
- Provide access to advanced training and computational resources
- Serve as a test bed for applying emerging computing technologies to bio-NMR
- *Foster reproducibility of bio-NMR analyses*

People

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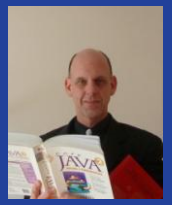

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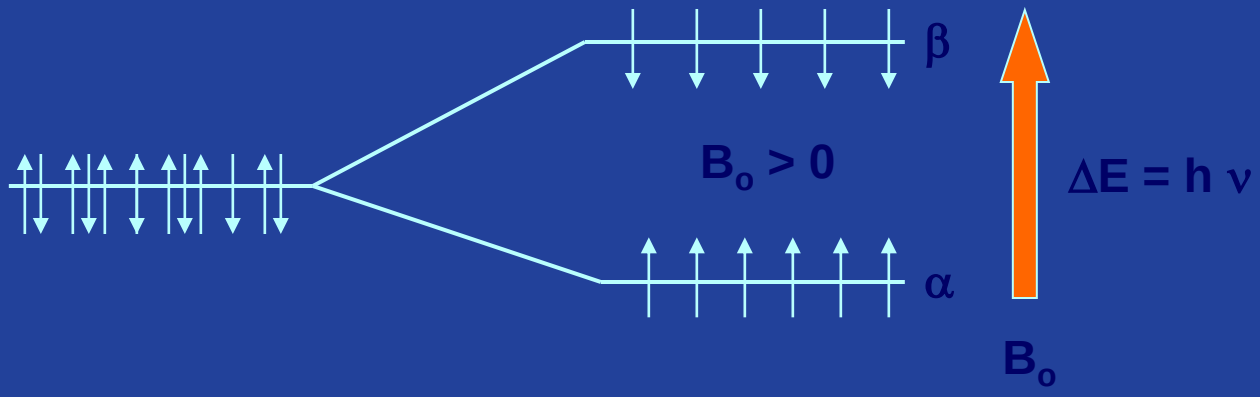
What is NMR?

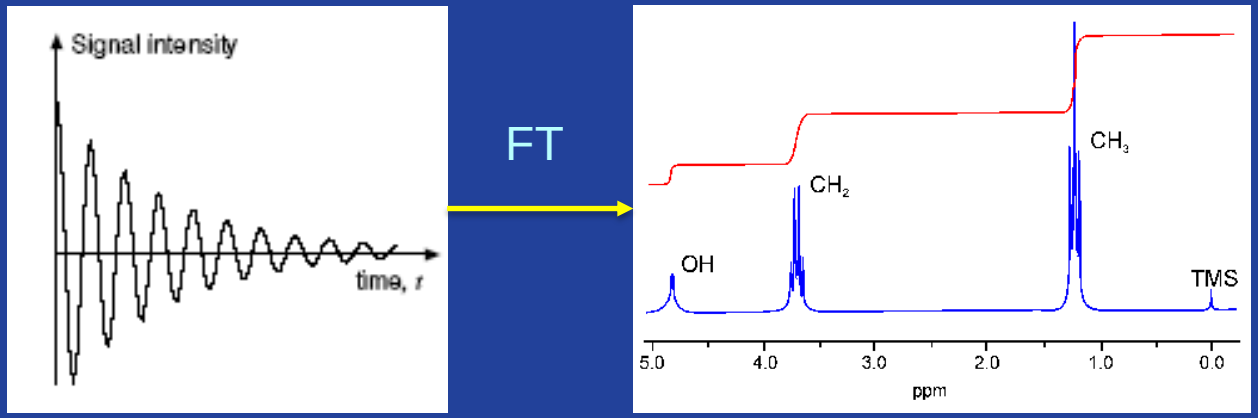
Nuclear magnetic resonance is a *quantum mechanical* property of magnetic nuclei when placed in a strong magnetic field



In a complex molecule, each nucleus experiences a slightly different magnetic field due to local interactions. It is thus possible to detect individual nuclei by measuring the frequency of the energy emitted when a nucleus relaxes from the high energy state to the low energy state

How NMR is measured

Excite all the nuclei in the molecule with a powerful RF pulse, then record the response



Fourier transformation of the response yields the frequency (energy) spectrum.

Very intense magnetic fields are required, produced by superconducting magnets

NMR is a versatile analytic method

Many biomolecular applications of NMR:

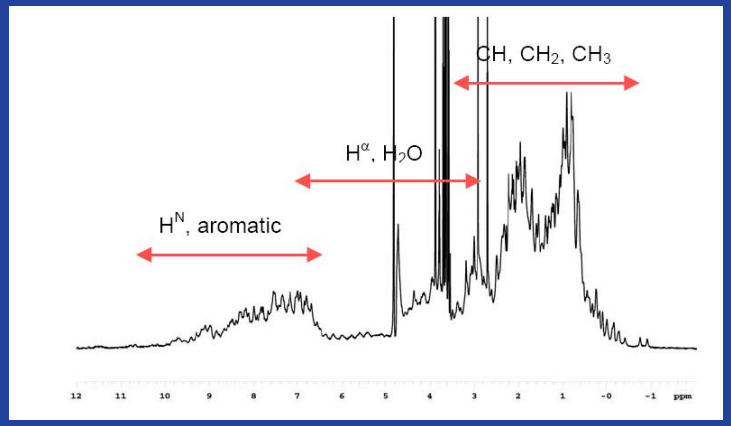
- Structural biology
- Rate processes (dynamics, kinetics)
- Metabolomics
- Drug discovery

This versatility is reflected in the broad range of computer software for NMR

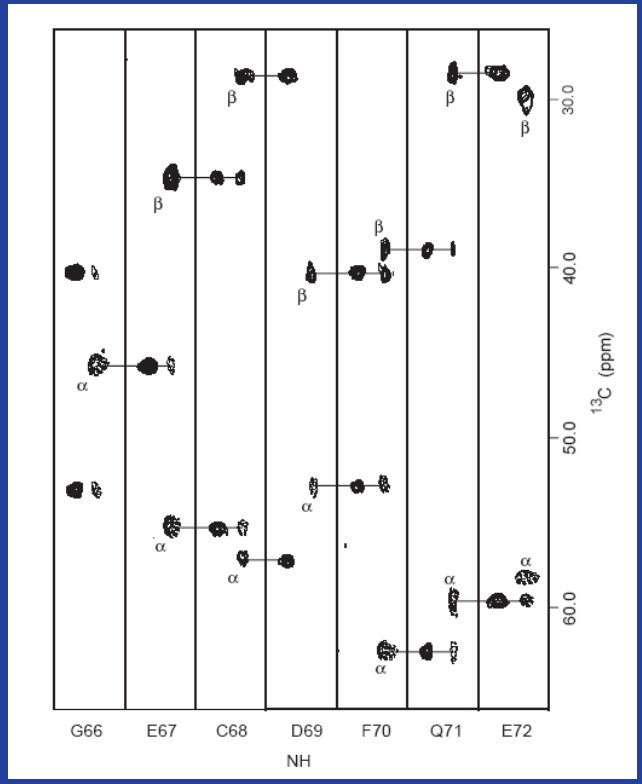
BioMagResBank depositions cite >100 software packages

NMR of proteins: spectral assignment

- Many hundreds to thousands of atoms
- Multidimensional NMR experiments are needed to resolve separate signals for individual atoms



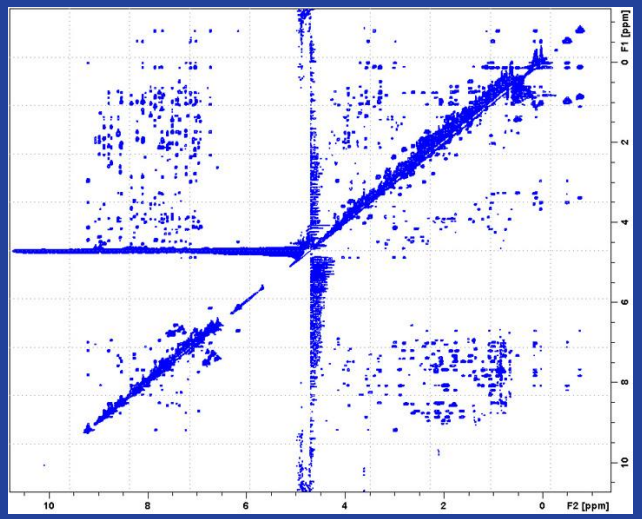
Correlation of the $C\alpha^{i}$ & $C\alpha^{i-1}$ and $C\beta^{i}$ & $C\beta^{i-1}$ sequentially aligns each pair of NHs in the protein's sequence.



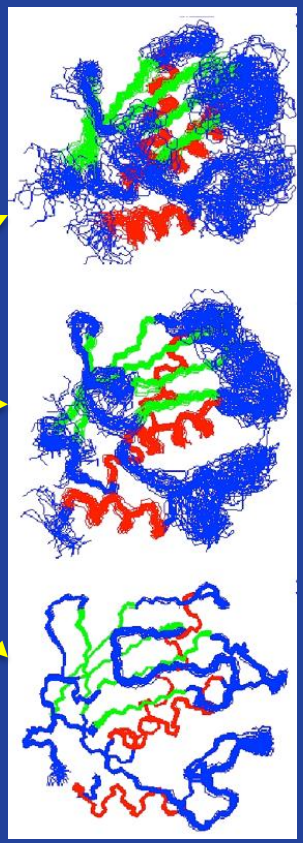
- It is possible to sequentially assign signals to specific amino acids in the protein

NMR of proteins: structure determination

- Short-range distances between atoms can be determined from nuclear Overhauser effect measurements
- Using many of these distances, the protein structure can be determined

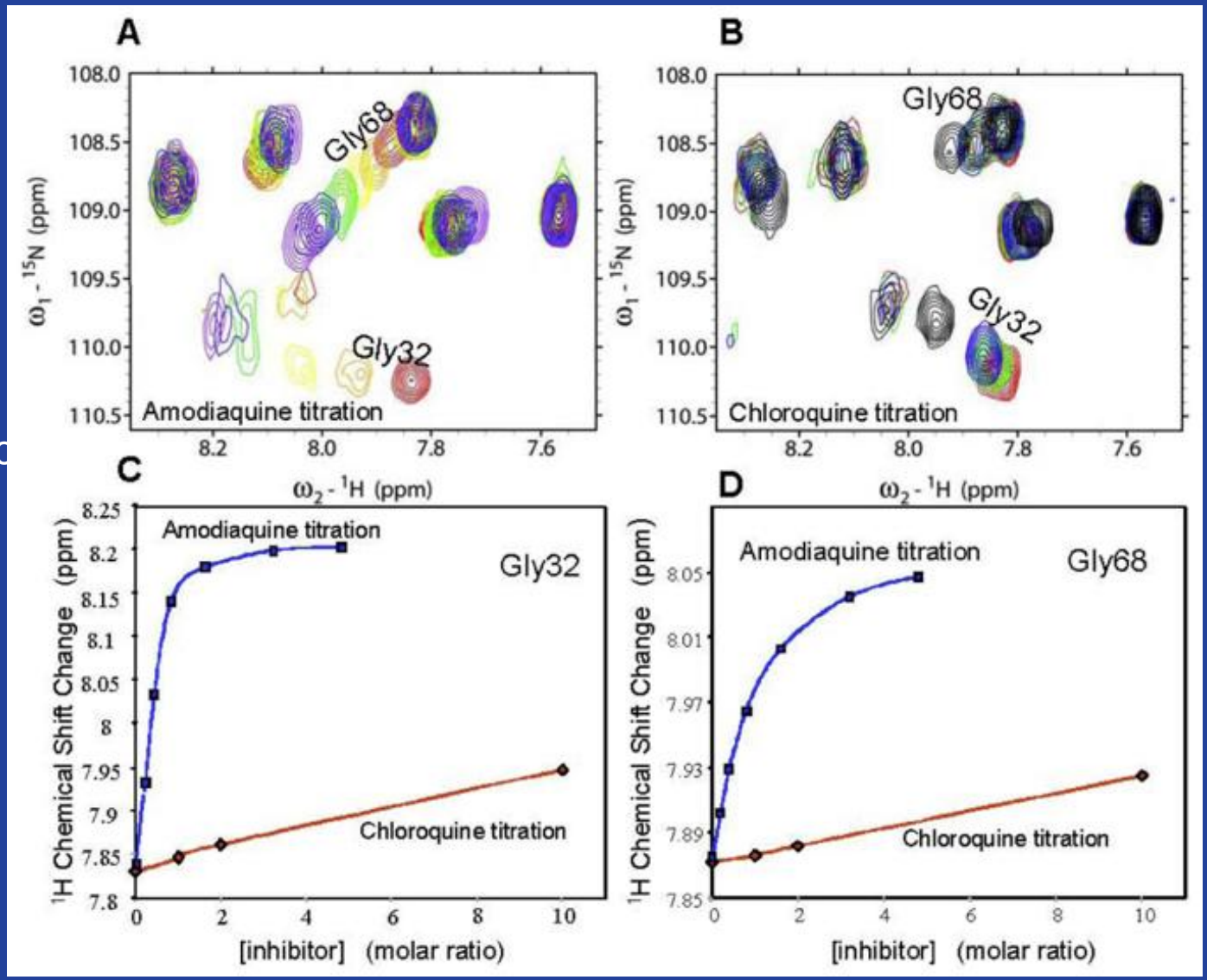


Iterative cycle of refinement as additional peaks are assigned



NMR in drug discovery

NMR rapidly distinguishes specific and non-specific inhibitors



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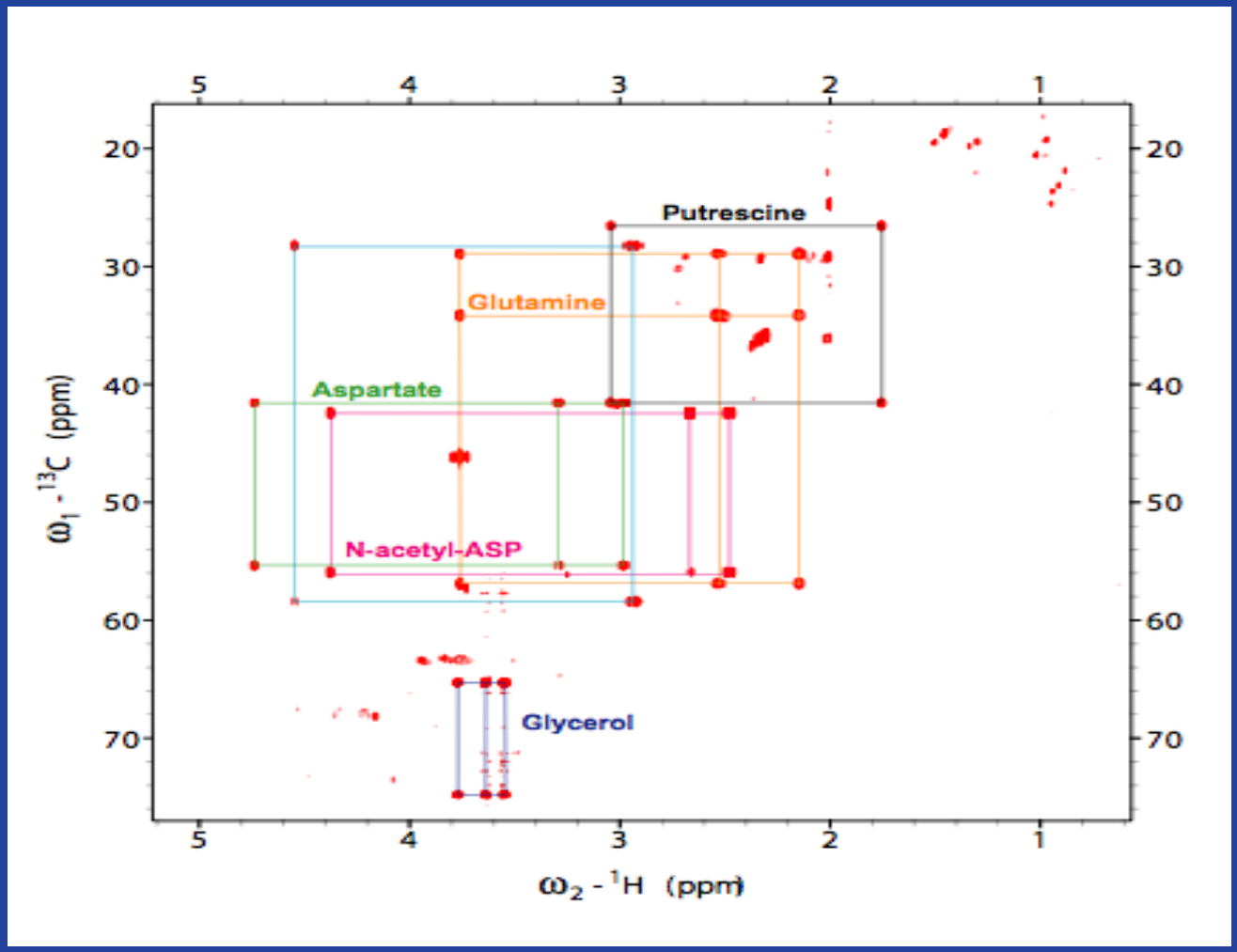
NMR metabolomics

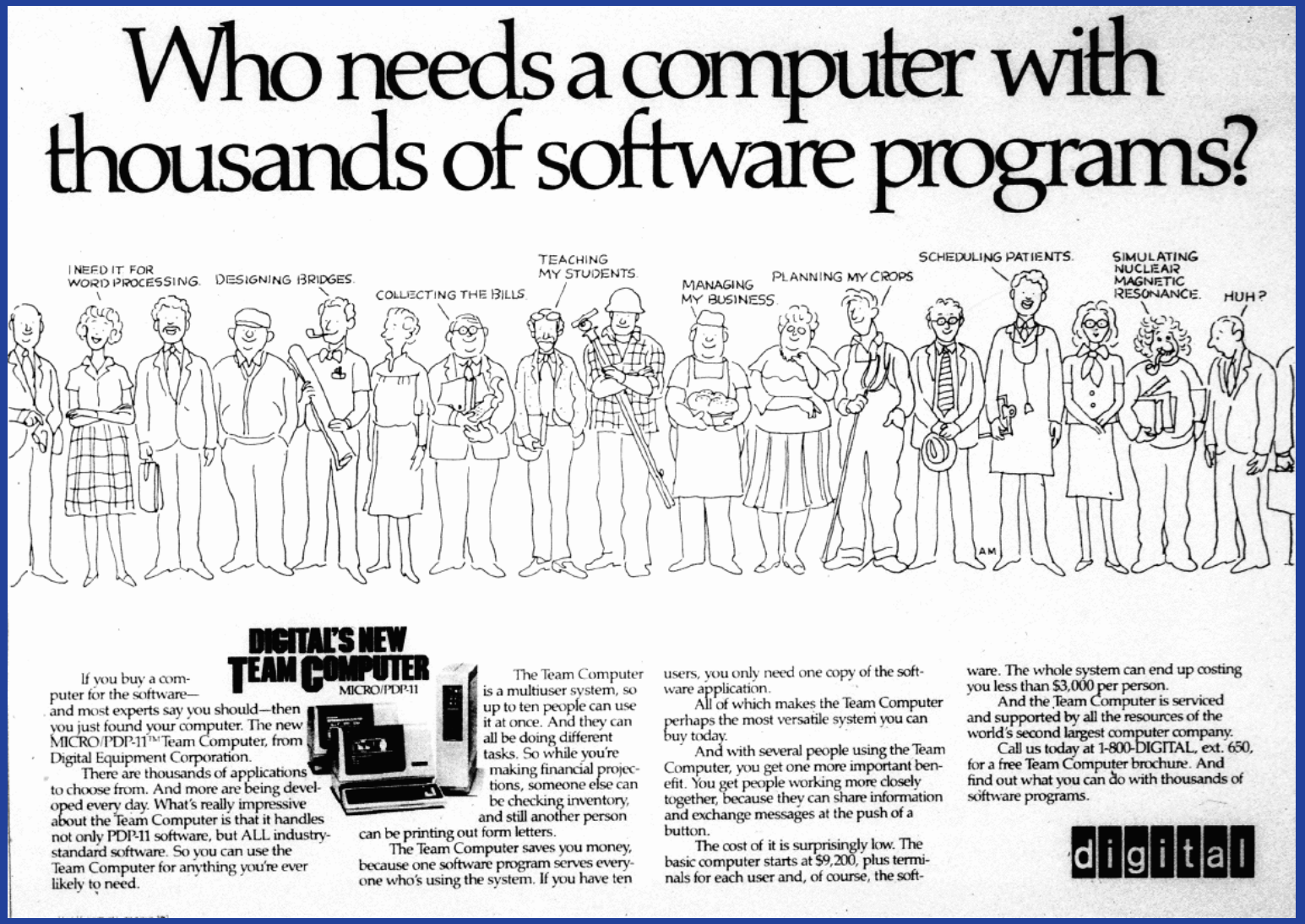
Concentration of all the metabolites in a cell is a direct readout of the cell state

NMR spectrum of E.coli grown on ^{13}C-labelled nutrient

NMR can be used for living cells, organisms (MRI)



A pervasive problem



Who needs a computer with thousands of software programs?

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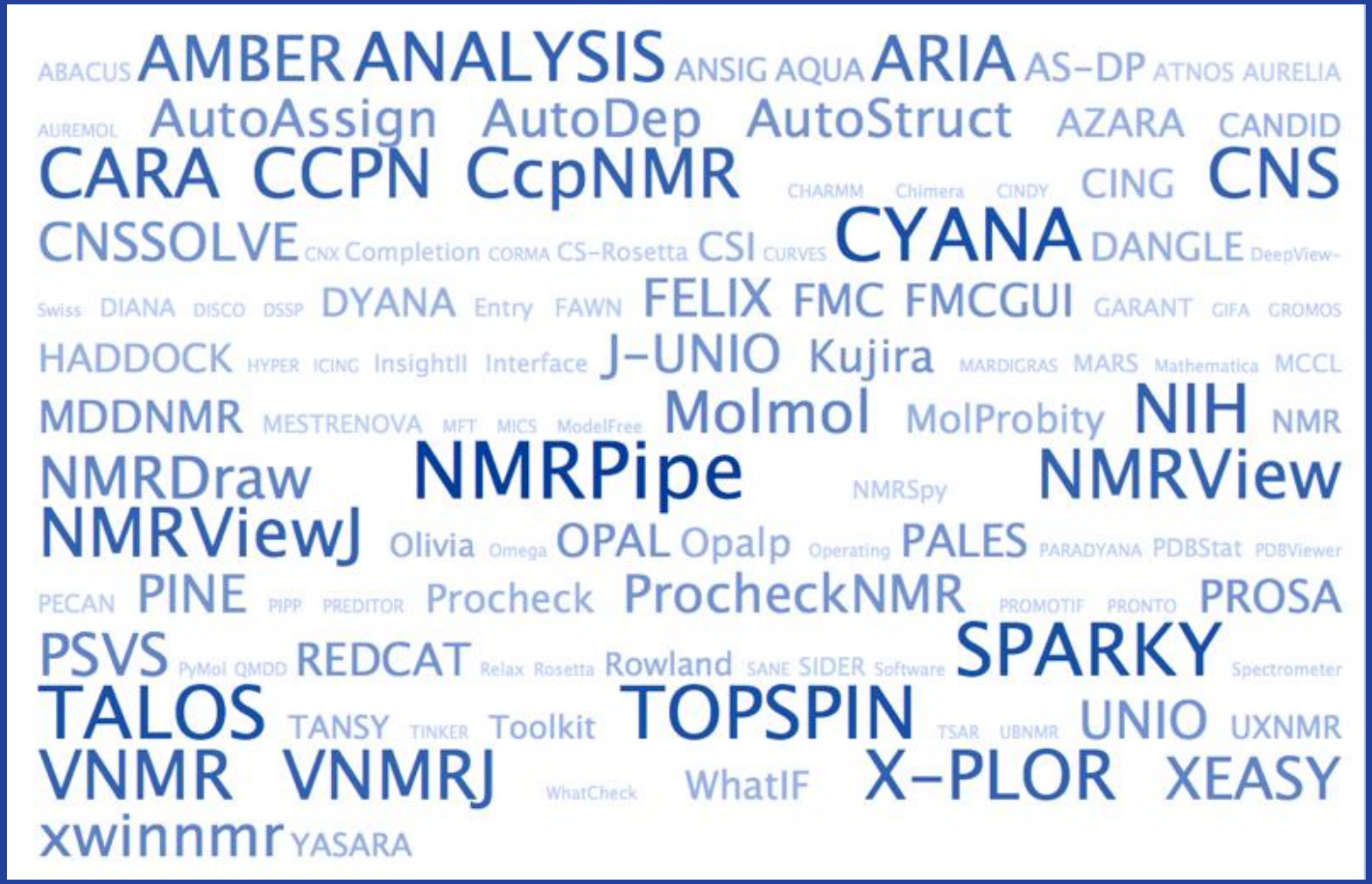
Advertisement from *Newseek* in 1981

Software abundance

>100 packages cited in BioMagResBank depositions



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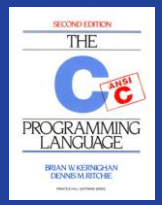
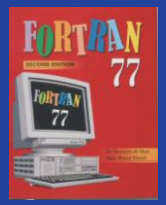
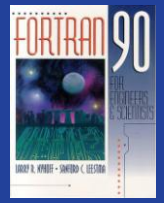
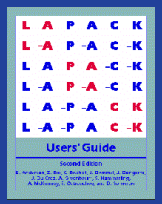
Fragmentation

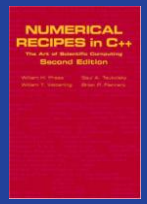
Operating systems, languages, libraries









BLAS

Motivation

- Complex, dynamic software environment
  - Many hundreds of software packages
  - Users: difficult to set up, manage
    (e.g. asynchronous updates, conflicts)
  - Developers: difficult to support (fragmentation)
  - Meta-software ascendant
- Challenges to reproducibility
  - Lack of standards for scripted workflows
  - Lack of annotation for manual steps
  - Poor software persistence

Reproducibility

Seminal paper by Ioannidis, 2005

PLOS | MEDICINE

Essay

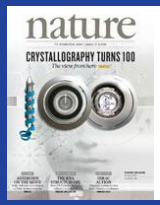
Why Most Published Research Findings Are False

Pharma concerns

MERCK Be well

NOVARTIS

NIH concerns



Policy: NIH plans to enhance reproducibility

Francis S. Collins & Lawrence A. Tabak

27 January 2014

Francis S. Collins and Lawrence A. Tabak discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.

>70% of published studies on putative drug targets are not reproducible

Obstacles to reproducibility

A computational study is reproducible when it provides the "complete software environment needed to reproduce the figures" (D. Donoho, Stanford)

- Missing primary data
- Missing meta-data
- Missing software (scripts, programs)
- Non-persistence of software
- Manual interventions

Persistence

Why NMR software isn't persistent

Developers graduate

Platforms become obsolete

Grants end

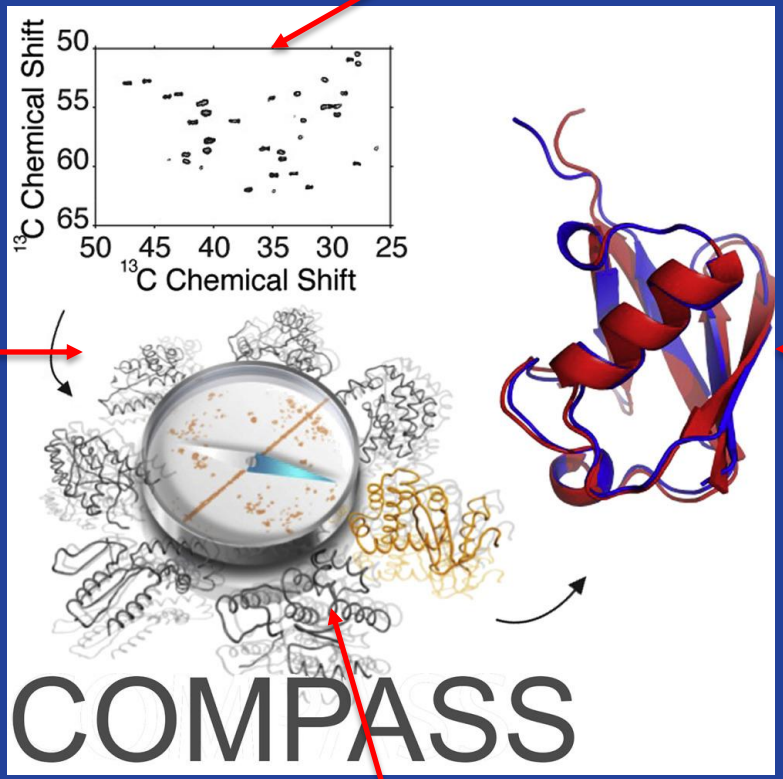
Examples: Sparky, MARDIGRAS, MOLMOL, XEASY, ANTIOPE,…

Meta-software

Experimental Protein Structure Verification by Scoring with a Single, Unassigned NMR Spectrum. Courtney, Rienstra et al. , 2015

Sparky

SHIFTX/X2



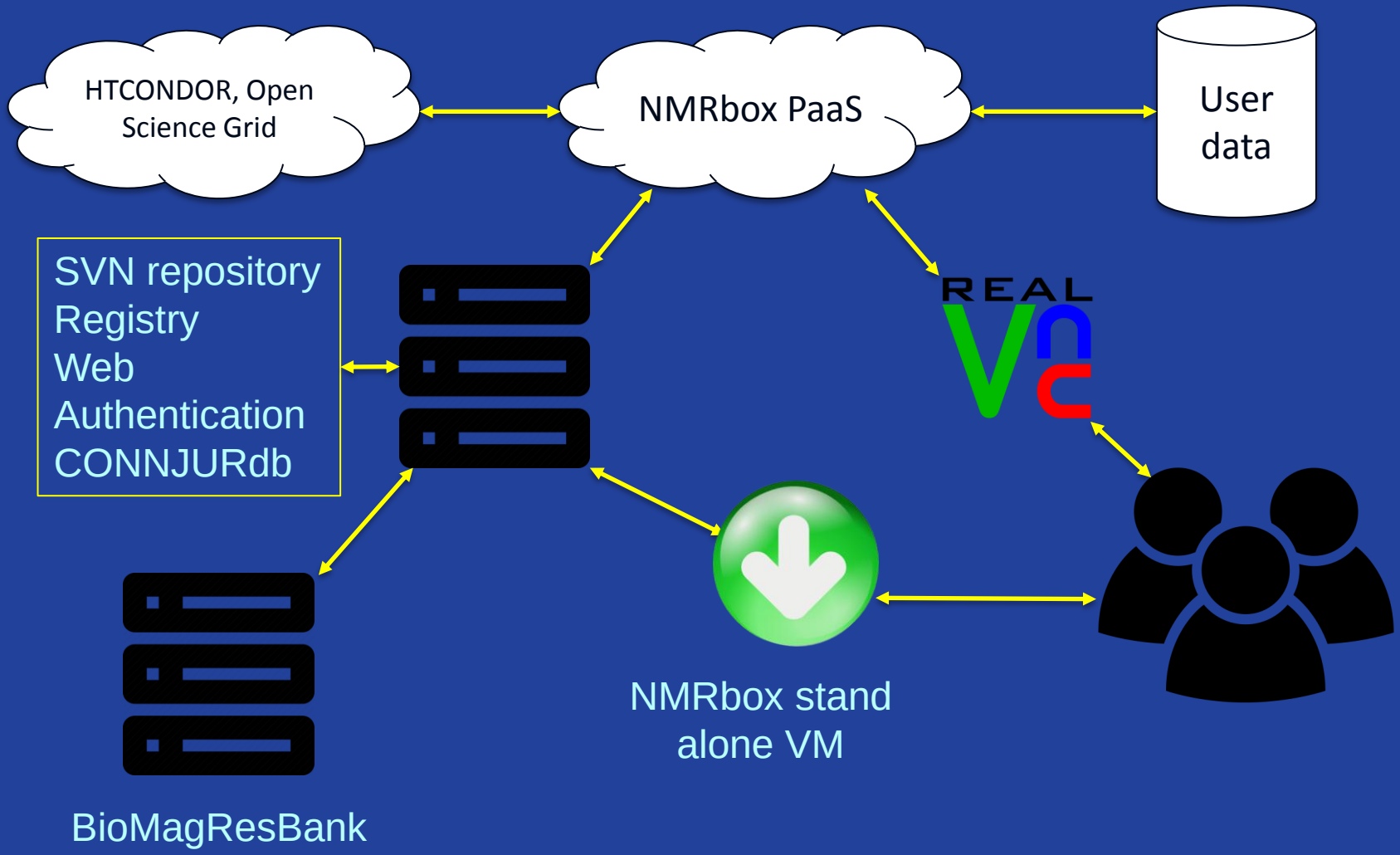
Rosetta

MODELLER

NMRbox approach

- Capture the complex, evolving NMR software environment
  - Delivery via pre-configured, fully provisioned VMs
  - Agnostic: provision with all available software
  - Archive VMs at regular intervals
  - Software registry for discovery
- RDB for workflows (CONNJUR)
  - Regularization
  - Annotation
  - Interoperability
  - Preferred/recommended workflows
- Robust inference
  - Bayesian tools for users
  - API for developers

Functional overview



Registry

NMRbox ENC Workshop Documentation Downloads Registry

Software Registry

GUARDD

guardd
Graphical User-friendly Analysis of Relaxation Dispersion Data

Principal citations:

GUARDD: user-friendly MATLAB software for rigorous analysis of CPMG RD NMR data.
Kleckner IR, Foster MP.
J Biomol NMR. 2012 Jan;52(1):11-22. doi: 10.1007/s10858-011-9589-y. Epub 2011 Dec 11.
PMID: 22160811

Synopsis

GUARDD is a flexible, user-friendly package for analysis of relaxation data built on the power of Matlab. Features include

- Accurate site-specific fits to two-state exchange model at any timescale
- Refinement of best fit for maximum accuracy
- Examine dynamic motion of entire molecule
- Optimization and education with RD Simulator

Keywords

Relaxation analysis, CPMG, Relaxation dispersion

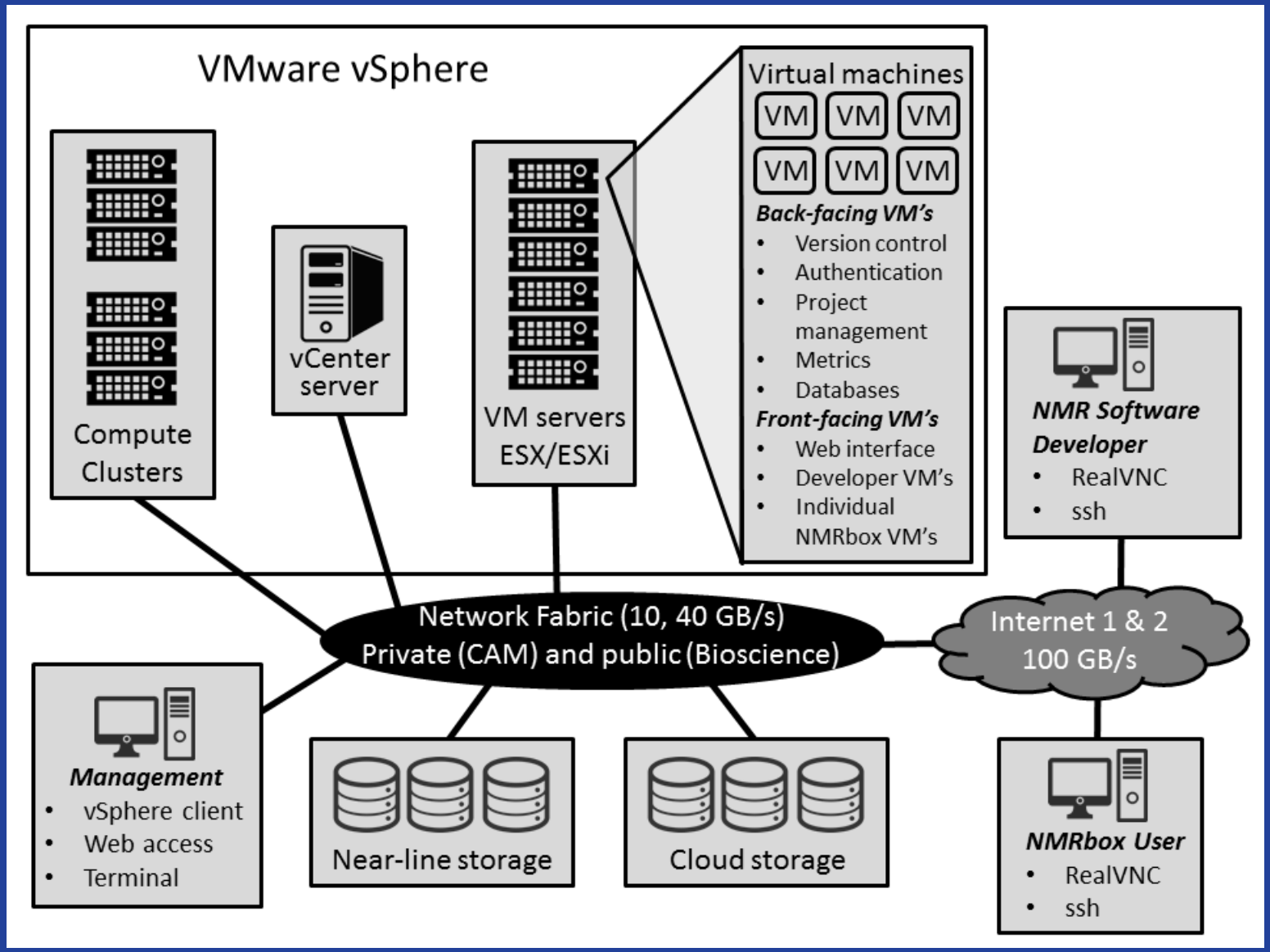
Documentation GUARDD

Related software

DASHA
FAST ModelFree
ModelFree
Relax

BMRB entries citing GUARDD

Infrastructure



Broader Impacts

- NMRbox can serve as a platform for software delivery in other, related domains: X-ray, simulation, thermodynamics
- VMs can serve as a platform for reproducible research in other domains
- Reducing software administration burden allows scientists to spend more time on science
- Reducing hardware requirements allows scientists to spend more $$$$ on science

Unmet challenges

Executable codes with built-in vulnerabilities

- Time “bombs”
- External services
- Hardware dependencies (GPUs, graphic cards)

Making web services persistent and reproducible

- Requires development and acceptance of standards
  - Versioning
  - Mirror
  - Repository (escrow, conditional)

Finding a harmonious solution…

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