

Magnetic Resonance in Biomedicine











OUTLINE

THE CONCEPT OF MRI

- 何謂光譜 WHAT IS SPECTROSCOPY?
- MRI的訊號從哪裡來? WHERE DOES MRI SIGNAL COME FROM?

APPLICATIONS

- 弛豫影像 **RELAXATION BASED IMAGING**
- 擴散影像 DIFFUSION BASED IMAGING
- 化學交換飽和轉移影像 CHEMICAL EXCHANGE SATURATION TRANSFER (CEST) IMAGING
- 核磁共振血管造影 MR ANGIOGRAPHY
- 功能性磁振造影 FUNCTIONAL MRI

先來了解何調光譜? WHAT IS SPECTROSCOPY?

WHAT IS SPECTROSCOPY? HUMAN'S EYE

WHY COLORED?





Think about the spectrometer you used before !!!

WHAT IS SPECTROSCOPY?

How about normal life?





What is information you get when the color of flame changes?

WHAT IS SPECTROSCOPY?

Wavelength, λ/m								
	1	10 ⁻¹ 10 ⁻² 1	0 ⁻³ 10 ⁻⁴ 10	- ⁵ 10 ⁻⁶	10 ⁻⁷ 10 ⁻⁸	10 ⁻⁹ 10 ⁻¹⁰	10 ⁻¹¹ 10 ⁻¹² 10 ⁻	⁻¹³ 10 ⁻¹⁴
	E 4	1 cm 1 mm		1 µm		1 nm	1 pm	
	Radio	Microwave	Far infrared	<mark>Near</mark> infrared Visible	<mark>Oltraviolet</mark> nltraviolet	X-ra t	iy γ-ray	y Cosmic rays
NMR & MRI		Molecular rotation Molecular vibration Electronic excitation 402			Core-electr excitation Fig	ron Nuclear excitatio 97.2	r on	



WHAT IS MAGNETIC RESONANCE?



WHAT IS MAGNETIC RESONANCE? ZEEMAN EFFECT



Higher magnetic field, larger energy gap The resonance frequency of proton nucleus at 7 Tesla= 300 MHz (Earth field=0.5 Gauss , 1 Tesla=10000 Gauss)

FARADAY'S LAW

Lenz's law: the induced current in a loop is in the direction that creates a magnetic field that opposes the change in magnetic flux through the area enclosed by the loop.

The induced current tends to keep the original magnetic flux through the circuit from changing.





NUCLEAR MAGNETIC RESONANCE



Signal: Free Induction Decay



NUCLEAR MAGNETIC RESONANCE



NUCLEAR MAGNETIC RESONANCE



INSTRUMENT 儀器設計



HOW STRONG THE MAGNET IS





NMR



Frequency = Spatial information



Anímal MRI Lab, IBMS, Academía Sínica

FROM NMR TO MRI



Paul Lauterbur

Peter Mansfield

First MRI



MR Scan of Larry Minkoff 's

10 72 STATE TIME IL 45 47 Ken out for back FUNDATURE 4:35 MM. LAW RENCE IMAGE Durin 11 second, per print 4=65 at level C13 12 13 14 15 16 17 18 19 20 21 22 2 -10 11 x = 10 11 12 13 0 0 0 **19**77 1.2 0 14 15 16 17 18 19 20 21 - 22 23 24 25 4:45AM July 3 0000 First MR Scan of The C fut.0 Port. Live Human Body 8 Completed ! õ 0.8 0 0 24 106 4



MRI NOWADAY





Contrast



THE ABILITY TO DISCRIMINATE DIFFERENT TISSUES BASED ON THEIR RELATIVE BRIGHTNESS

對比度的概念是相對的













THE IMPORTANCE OF MRI CONTRAST



分子影像 MOLECULAR IMAGING



visualization, characterization and quantification of normal / pathological biological processes at the cellular and molecular level

我們可以做哪些事?







Application-driven Research

Methodology Developments 方法開發

Clinical Application 臨床應用

Drug discovery

MRI development

Pre-Clinical Research 臨床前應用

SIZE MATTER!!




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RELAXATION BASED IMAGING

何謂弛豫? WHAT IS NMR RELAXATION?





T₁ CONTRAST AGENT (顯影劑)



w/o T_1 contras agent

w/ T₁ contras agent

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BRAIN STRUCTURE IN MRI

T2WI

Mn-enhanced



Journal of Cerebral Blood Flow & Metabolism (2011) **31,** 2009–2018;

NeuroImage, Aug. 1, 2007, pp. 82-89.



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DIFFUSION BASED IMAGING 擴散影像

DIFFUSION TENSOR MRI (DTI)

Diffusion anisotropy



Diffusion is greater in the axis parallel to the orientation of the nerve fibre



Diffusion is less in the axis perpendicular to the nerve fibre

WHAT IS THE DIFFUSION TENSOR?



TRACTOGRAPHY - OVERVIEW

- NOT ACTUALLY A MEASURE OF INDIVIDUAL AXONS, RATHER THE DATA EXTRACTED FROM THE IMAGING DATA IS USED TO INFER WHERE FIBRE TRACTS ARE
- VOXELS ARE CONNECTED BASED UPON SIMILARITIES IN THE MAXIMUM DIFFUSION DIRECTION





Johansen-Berg et al. Ann Rev. Neurosci 32:75-94 (2009)

DIFFUSION TENSOR IMAGING (DTI)





Anisotropy in cortical layer





DTI fiber tracking-Hippocampus





APPLICATIONS

CHEMICAL EXCHANGE SATURATION TRANSFER (CEST) IMAGING

OUTLINE

- What is Chemical Exchange Saturation Transfer (CEST) and Dynamic Glucose Enhanced (DGE) Imaging?
- CEST and Glucose Metabolism
- Application: Tumor Microenvironment differentiation
- Application: Tumor Immune Responses
- Application: Huntington's Disease Mice

CHEMICAL SHIFT

H nuclei on different functional group has different resonance frequency (chemical shift)

SENSITIVITY LIMITATION OF NMR/MRI



CHEMICAL EXCHANGE SATURATION TRANSFER (CEST)



Probing chemicals at Microscopic scale and show at Macroscopic MR resolution (mm)

Z-SPECTRUM OF GLUCOSE PHANTOM



DYNAMIC GLUCOSE ENHANCED (DGE) IMAGING

(Imaging the OH group on Glucose by CSET imaging)



DGE signal

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GLUCOSE METABOLISM



In vivo Magnetic Resonance Spectroscopy



GLUCOSE AND GLUTAMATE

In vivo z-spectra Analysis by CEST (15 mins after glucose injection)



Application: Tumor Microenvironment differentiation

BRUKER

Application: Tumor Microenvironment differentiation DGE Image of Mice Brain Tumor Model



Application: Tumor Microenvironment differentiation ROI Analysis of dynamic process



Application: Tumor Microenvironment differentiation Area Under Curve (AUC) Mapping

Static information

DCE imaging (0-2000 s)

DGE imaging (0-2000 s)

DGE imaging (0-4000 s)



plication: Tumor Microenvironment differentiation UC mapping of DCE image v.s. DGE



Similar BBB leakage condition but different metabolism rate

Application: Tumor Microenvironment differentiation Classification of DGE signals



Application: Tumor Microenvironment differentiation Flowchart of Signal Clustering





Application: Tumor Microenvironment differentiation Influence of Time Interval on Dynamics and Mapping Images





Application: Tumor Microenvironment differentiation SOM mapping

Colors represent different signal types



Application: Tumor Microenvironment differentiation Comparison of SOM and DESI Image



Glutamate image

0.1

0.09

0.08

0.07

0.06

0.05

0.04

0.03

0.02

0.01

0

Application: Tumor Microenvironment differentiation ROI analysis by SOM classification


Application: Tumor Microenvironment differentiation Comparison of SOM and Pathology





GLUT1

H&E

Application: Tumor Microenvironment differentiation Theoretical Model of Glucose Transportation



$$\frac{dC_o}{dt} = D(C_p - C_o) + V_{\max} \frac{C_i - C_o}{K_M + C_o + C_i + \frac{C_o C_i}{K_{ii}}}$$

$$\frac{dC_i}{dt} = V_{\max} \frac{C_o - C_i}{K_M + C_o + C_i + \frac{C_o C_i}{K_{ii}}} - R_{meta}$$



Application: Tumor Microenvironment differentiation Theoretical Simulation



Application: Tumor Microenvironment differentiation Comparison of Simulation and Pathology





Region	V _{max} /R _{meta}	$P_p: P_o: P_i$
1	0.40	3.0%:48.7%:48.3%
2	0.33	1.8%:70.0%:28.2%
3	0.34	3.0%:95.0%:2%

Difference due to the Glut1 distribution

Difference due to the Cell distribution

Wash-out Slope as An Image Biomarker

Tumor region 0.6₇ 6 DGE contralateral counterpart P<0.005 5 AUC_{300s}, %•s 0.4-4 Signal (%) Slope 3 0.2-2 1 -2 0.0--3 **Turnor** * p<=0 Magnetic Resonance in Medicine 74:1556–1563 (2015) Tumor 0 --1 1000 2000 3000 4000 0 Time (sec) * p<=0

Previous Work

BioSpec 70/20 USR

BRUKER

Application: Tumor Immune Responses

Application: Tumor Immune Responses Hot and Cold Tumor



https://blog.dana-farber.org/insight/

Application: Tumor Immune Responses The Nutritional Competition between Tumor and Immune Cells



Longzheng Xia et al., Molecular Cancer 2021

Application: Tumor Immune Responses Tumor Size of Hot and Cold Tumor

Cold tumor w/o Tamoxifen tumor







Day 16





Hot tumor

w/ Tamoxifen tumor









Application: Tumor Immune Responses Pathology of Hot and Cold Tumor



Application: Tumor Immune Responses Glucose Uptaking of Hot and Cold Tumor

Hot tumor





Application: Tumor Immune Responses Correlation Map

Allocate the tumor by AUC map



Check the correlation between the average and local DGE signal of tumor



Application: Tumor Immune Responses Correlation Map



BioSpec 70/20 USR

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Application: Huntington's Disease Mice

Application: Huntington's Disease Mice What Causes Huntington's Disease (HD)?



Application: Huntington's Disease Mice Disease Progress



Application: Huntington's Disease Mice Functional Analysis of HD Mice by DGE



Application: Huntington's Disease Mice Functional Analysis of HD Mice by DGE



4/W/4/

Connectivity Analysis

- Pearson Correlation
- Fisher z-transformation (inverse hyperbolic tangent, artanh)
- Two Sample T-Test
- Chosen brain regions: ACA, RSP, S1, S2, M1, M2, Ins, TeA, DG, Ce, CPu, Thalamus
- Data interval:
 - 21-90 mins (from post-glucose injection to end of session)
 - 21-50 mins (from post-glucose injection to 30 mins after injection)
 - 51-90 mins (from 30 mins after injection to end of session



Chuang KH, Lee HL, Li Z, et al. Evaluation of nuisance removal for functional MRI of rodent brain. Neuroimage. 2019;188:694-709. doi:10.1016/j.neuroimage.2018.12.048

Application: Huntington's Disease Mice Functional Analysis of HD Mice by DGE with Different Time Interval

DGE

Fiber photometry in neurons and astrocytes



A. Eleftheriou, L. Ravotto, M.T. Wyss et al. NeuroImage 265 (2023) 119762

Application: Huntington's Disease Mice WT (15 m.o.) v.s. zQ175 KI (15 m.o.)













Application: Huntington's Disease Mice WT (12W) v.s. R6/2 KI (12W)









APPLICATIONS

FUNCTIONAL MRI 功能性磁振造影

FUNCTIONAL MRI (FMRI, 功能性磁振造影)

Using MRI to understand the brain's responses to cognition, behavior, and other activities 利用MRI來瞭解有關大腦對於認知、行為等反應的活動區

Applications of fMRI

- Brain tumors.
- Drug abuse.
- Neuropsychiatric diseases.

- Growth and aging.
 - How it works?

By detecting Blood Oxygen Level Dependent (BOLD) contrast images, changes in brain signals are observed.

透過偵測BOLD對比的影像,來觀察大腦訊號變化

BOLD (BLOOD OXYGENATION LEVEL DEPENDENT)

- 帶氧血紅素(OXY-HEMOGLOBIN):抗磁性(DIAMAGNETISM)
- 去氧血紅素(DEOXY-HEMOGLOBIN):順磁性 (PARAMAGNETISM)

造成局部磁場不均匀 (Cause local magnet field inhomogeneity)



What is Cerebral Blood Volume fMRI?

> Application of contrast agent (iron oxide particles, T2/T2* shortening), providing better image contrast.



FUNCTIONAL MRI (FMRI, 功能性磁振造影)



Sample Data Time Series

- 64 × 64 matrix (TR=2.5 s; 130 time points per imaging run)
- Somatosensory task: 27 s "on", 27 s "rest"
- Note that this is *really* good data

-21-

pattern fitted to data



data





pattern of expected

BOLD signal

https://afni.nimh.nih.gov/class_handouts

RIGHT FINGER TAPPING











- > Gout is one of the most painful acute conditions that human can experience.
- > Gout is initiated with the deposition of monosodium urate (MSU) crystals in joints and periarticular tissues.
- > MSU crystals activate the immune system to drive inflammation.

Electrical stimulation induced CBV changes

electrical stimulation on the rat forepaw





Shih YY. et al. (2009) A new scenario for negative functional magnetic resonance imaging signals: endogenous neurotransmission. J Neurosci. 29:3036.

Experiment design



< 4.7 T scanner> TR / TE = 150 ms / 15 ms Angle = 22.5' NEX = 1 FOV / Matrix = 2.56 cm / $128x64 \rightarrow 128x128$ Slice number / thickness = 5 / 1.5 mm Repetition = 60	 1. Histological analysis a. H&E b. IHC COX-2, iNOS, IL-1 beta, CD45, CD68
3 mA 3 mA 	

Representative behavioral observation





Position Standing	Condition		
	S 0	Normal	
	S1	Complete touch of foot pads with closed fingers	Na
	S2	Partial touch of foot pads	INC
	S3	One foot stand	No
Walking	$\mathbf{W}0$	Normal	No
	W1	Slight limping	
	W2	Severe limping	No
	W 3	One foot gait	No

Brain Research, 365 (1986) 235-240

	standing	walking	Swelling
	3hr→24hr	3hr→24hr	3hr→24hr
No1	3→0	3→1	0→0
No2	3→0	3→1	0→0
No3	3→0	3→1	0→0
No4	3→0	3→0	O→X
No5	3→0	3→0	0→0
No6	3→0	3→0	O→X

Representative CBV-weighted fMRI (3-1)





Representative CBV-weighted fMRI (3-2)







averaged (n=6)
IN ADDITION TO TASK-GIVEN/STIMULATED TASK-FMRI 除了給予任務/刺激的TASK-FMRI以外...

還有一種是BASELINE狀態下的FMRI: RESTING STATE FUNCTIONAL MRI

靜息態功能性磁振造影

- BRAIN IS ALWAYS WORKING EVEN DURING REST
- → RESTING STATE ACTIVITY (SPONTANEOUS LOW FREQUENCY FLUCTUATIONS)
 - \rightarrow Ready to response to any internal or external changes
 - \rightarrow ENERGY CONSUMING !

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靜息態大腦功能性磁振造影(RESTING STATE FUNCTIONAL MRI)

- 量測原理: 一樣透過血氧濃度相依對比(BOLD CONTRAST), 分析與判斷各個腦區之間的基頻運作連結程度 (E.G. 相關性)。
- 分析目標: 低頻訊號 (LOW FREQUENCY FLUCTUATIONS) (< 0.1 HZ)





Fox MD and Greicius M. Front Syst Neurosci. 2010;4:19

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RESTING STATE FUNCTIONAL MRI

Human DMN



- RESTING STATE NETWORKS
 - DEFAULT MODE NETWORKS
 - SENSORY/MOTOR
 - VISUAL
 - BASAL GANGLIA
 - SALIENCE
 - ATTENTION

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Moussa MN et al., (2012) PLoS ONE 7(8): e44428



Liska A et al. (2015) Neurolmage 115:281–291



Liska A et al. (2015) NeuroImage 115:281-291

APPLICATIONS

MR ANGIOGRAPHY 磁振血管攝影



VASCULAR REMODELING AFTER ISCHEMIC STROKE REVEALED BY 3DAR₂ MMRA



TUMOR ANGIOGENESIS







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TAGGING – MYOCARDIAL MOVEMENT TRACKING

Grid mode

Line mode



TAGGING – MYOCARDIAL MOVEMENT TRACKING

Doxorubicin induced cardiac failure

Normal









SUMMARY

- PROVIDES A NONINVASIVE IMAGING TECHNIQUE
- PROVIDES ANATOMICAL AND FUNCTIONAL INFORMATION OF TISSUES
- IN VIVO STUDY

