学校编码：10384　　　　　　　　　　　　分类号________密级________
学号：33120130154211　　　　　　　　　　　　　　UDC________

厦门大学

博　士　学　位　论　文

不均匀磁场下高分辨二维核磁共振谱新技术

High-Resolution Two-dimensional NMR Spectroscopy in Inhomogeneous Magnetic Fields

陈浩

指导教师姓名：蔡淑惠 教授

专 业 名 称：物理电子学

论文提交日期：2017 年 4 月

论文答辩时间：2017 年 5 月

学位授予日期：2017 年　月

答辩委员会主席：__________

评　　阅　　人：__________

2017 年　月

厦门大学学位论文原创性声明

本人呈交的学位论文是本人在导师指导下,独立完成的研究成果。本人在论文写作中参考其他个人或集体已经发表的研究成果，均在文中以适当方式明确标明，并符合法律规范和《厦门大学研究生学术活动规范（试行）》。

另外,该学位论文为(　　　　　　　　　　　　　　)课题(组)的研究成果，获得（　　　　　　　　　）课题（组）经费或实验室的资助，在（　　　　　　　　）实验室完成。（请在以上括号内填写课题或课题组负责人或实验室名称，未有此项声明内容的，可以不作特别声明。）

声明人（签名）:

年　　月　　日

厦门大学学位论文著作权使用声明

本人同意厦门大学根据《中华人民共和国学位条例暂行实施办法》等规定保留和使用此学位论文，并向主管部门或其指定机构送交学位论文（包括纸质版和电子版），允许学位论文进入厦门大学图书馆及其数据库被查阅、借阅。本人同意厦门大学将学位论文加入全国博士、硕士学位论文共建单位数据库进行检索，将学位论文的标题和摘要汇编出版，采用影印、缩印或者其它方式合理复制学位论文。

本学位论文属于：

（　　）1.经厦门大学保密委员会审查核定的保密学位论文，于　　年　　月　　日解密，解密后适用上述授权。

（　　）2.不保密，适用上述授权。

（请在以上相应括号内打"√"或填上相应内容。保密学位论文应是已经厦门大学保密委员会审定过的学位论文，未经厦门大学保密委员会审定的学位论文均为公开学位论文。此声明栏不填写的，默认为公开学位论文，均适用上述授权。）

声明人（签名）：

年　　月　　日

专用缩写词英汉对照表

1D = One-Dimensional	一维
2D = Two-Dimensional	二维
3D = Three-Dimensional	三维
COSY = COrrelated SpectroscopY	相关波谱
CPMG = Carr-Purcell-Meiboom-Gill	CPMG 序列
DDF = Distant Dipole Field	远程偶极场
DMSO = DiMethyl SulphOxide	二甲基亚砜
DNP = Dynamic Nuclear Polarization	动态核极化
DQF = Double-Quantum Filtered	双量子滤波
EPI = Echo-Planar Imaging	平面回波成像
EPSI = Echo-Planar Spectroscopic Imaging	平面回波波谱成像
FT = Fourier Transform	傅立叶变换
GABA = γ-Aminobutyric acid	γ-氨基丁酸
HMBC = Heteronuclear Multiple Bond Correlation Spectroscopy	异核多键偶合相关谱
HMQC = Heteronuclear Multiple Quantum Correlation Spectroscopy	异核多量子相关谱
HOMOGENIZED = HOMOGeneity ENhancement by Intermolecular ZEroquantum Detection	分子间零量子检测的均匀性增强
HSQC = Heteronuclear Single Quantum Correlation Spectroscopy	异核单量子相关谱
iDQC = intermolecular Double-Quantum Coherence	分子间双量子相干
iDQF = intermolecular Double-Quantum Filter	分子间二量子滤波
iMQC = intermolecular Multiple-Quantum Coherence	分子间多量子相干
iSQC = intermolecular Single-Quantum Coherence	分子间单量子相干

iZQC = intermolecular Zero-Quantum Coherence	分子间零量子相干
IR = Inversion Recovery	反转恢复
JRES = J resovled	J 分解
mD = Multi-Dimensional	多维
MRI = Magnetic Resonance Imaging	磁共振成像
MRS = Magnetic Resonance Spectroscopy	磁共振波谱
NMR = Nuclear Magnetic Resonance	核磁共振
NOE = Nuclear Overhauser Effect	核 Overhauser 效应
RF = Radio Frequency	射频
SE = Spin Echo	自旋回波
SNR = Signal Noise Ratio	信噪比
SPEN = SPatiotemporal Encoding	时空编码
TOCSY = TOtal Coherence SpectroscopY	全自旋相干转移回波谱
TR = Time of Repetition	扫描重复等待时间
WURST = Wide Uniform Rate and Smooth Truncation	宽带均匀速率与平滑截断

目录

Contents

作者姓名：陈 浩

论文题目：不均匀磁场下高分辨二维核磁共振谱新技术

作者简介：陈浩，男，1989 年 3 月出生，2011 年 9 月师从于厦门大学蔡淑惠教授，于　　年　月获博士学位。

中 文 摘 要

核磁共振（Nuclear Magnetic Resonance，NMR）波谱作为一种无损伤的非侵入性检测技术，业已成为物理、化学、生命科学以及医学等领域研究中一种必不可少的检测手段。高分辨二维谱及多维谱方法可以有效缓解常规一维谱中谱峰拥挤等问题，并获得更多的相关信息，已经成为有机小分子检测以及大分子结构研究中重要的分析工具。然而，高分辨谱图的获取需要有高均匀度的磁场，其空间变化率一般要低于 1 ppb/cm^3。但受到外磁场不均匀或样品内在磁化率差异等条件的限制，常常无法获得高度均匀的磁场。另外，较长的实验时间也限制了二维谱方法的应用。本论文采用分子间多量子相干技术，并结合时空编码方法，设计了几种新的脉冲序列，能够在不均匀磁场下快速获取高分辨二维谱信息。论文的主要研究成果如下：

一、研究了基于同核分子间多量子相干的高分辨方法中选择性脉冲在不均匀磁场中的激发效率。针对选择性脉冲可能诱发多个远程偶极场引起谱峰归属困难，提出了基于异核分子间零量子相干的新方法。结合时空编码和相干转移技术，利用锁场试剂中的氘自旋产生远程偶极场，可以在不均匀磁场下快速获取高分辨二维 J 分解谱。对氘自旋进行提前激发，能使氘自旋充分编码，序列可以在不均匀度较大的磁场下获取高分辨二维 J 谱。

二、通过分子间零量子相干和 J 调制采样方法，在不均匀磁场中获取高分辨三维 J 分解相关谱。分子间零量子相干能有效消除磁场不均匀所引起的相位畸变，使谱线在三个维度均不会出现展宽。新序列采用了时空编码技术，能够在常规二维谱的实验时间内完成三维谱的采样。经过投影可以同时得到高分辨二维 J 分解谱和化学位移相关谱（COSY）。变换序列中的相干转移模块，还可以获得全

相关谱（TOCSY），用以区分化合物的偶合网络，展现了方法的灵活性。

三、在磁场强度不均匀的情况下，核磁共振氢谱谱线增宽，使谱峰相互重叠、无法辨识归属，也无法准确测量对应基团质子的纵向弛豫时间（T_1）。本文提出了利用分子间二量子相干方法,通过时空编码超快速二维采样方式,仅需单次扫描就能在不均匀磁场下获取高分辨一维氢谱，以区分归属谱峰的化学位移。结合反转恢复法，实现对各基团质子纵向弛豫时间的准确测量。并将新方法测得的 T_1 时间应用于 T_1 加权实验，抑制强信号，也验证了新测量方法的准确性。

关键词： 核磁共振二维谱；不均匀磁场；高分辨

High-Resolution Two-dimensional NMR Spectroscopy in Inhomogeneous Magnetic Fields

Hao Chen

ABSTRACT

With the features of non-invasive and non-destructive, nuclear magnetic resonance (NMR) has become an indispensable analytical tool widely used in many disciplines, from physics and chemistry to biology and medicine. High-resolution two-dimensional (2D) NMR can alleviate the jam or even overlapping of resonances in conventional one-dimensional (1D) spectra, and release correlation information. In turn, 2D NMR has become a routine analytical tool for the elucidation of small organic molecules and study of macromolecular structures. However, the acquisition of high-resolution spectroscopy relies on the highly homogeneous external magnetic fields, which are inaccessible in many cases, such as poorly shimmed fields or intrinsic heterogeneity of magnetic susceptibility in samples. In addition, the long experiment time hinders further applications of 2D NMR. In this dissertation, based on intermolecular multiple-quantum coherences (iMQC), associated spatiotemporal encoding technique, novel methods are developed to retrieve high-resolution 2D spectra in inhomogeneous fields. The related contents can be summarized as follows:

1. The efficiency of selective pulses used in homonuclear iMQC methods, is investigated in inhomogeneous fields. Selective pulses may induce more than one distant dipolar field (DDF), and split the resonances into several groups, leading to difficulties in spectral assignment. In order to circumvent this influence, a new method based heteronuclear intermolecular zero-quantum coherence (iZQC) is proposed. Associated with spatiotemporal encoding and coherence transfer technique, the new method can obtain high-resolution 2D J-resolved spectra in inhomogeneous fields via the DDF originated from ^{2}H spins of deuterium agent. With ^{2}H spins excited in advance,

the new method can encode ^2H spins sufficiently and achieve high-resolution 2D J-resolved spectra in severe inhomogeneous fields.

2. High-resolution three-dimensional (3D) J-resolved correlation spectra are achieved in inhomogeneous fields via intermolecular zero-quantum coherence (iZQC) and J modulation detection method. The dephasing induced by field inhomogeneity can be removed by iZQC, thus the spectrum is free of the influence of line broadening in all three dimensions. Associated with spatiotemporal encoding technique, the acquisition of 3D spectrum can be accomplished within the time for a conventional 2D NMR experiment. A COSY spectrum and J-resolved spectrum can be simultaneous obtained after 2D projection. Furthermore, as TOCSY can be attained by changing the coherence transfer module, the coupling networks of compounds are accessible in inhomogeneous fields.

3. The spin-lattice relaxation time (T_1) plays a critical role in the study of spin dynamics, signal optimization and data quantification. However, the measurement of chemical shifts specific T_1 constants is hampered by the magnetic field inhomogeneity due to poorly shimmed external magnetic field or intrinsic magnetic susceptibility heterogeneity in biological tissues. A new protocol is designed to determine chemical shift specific T_1 constants in inhomogeneous fields. Based on intermolecular double-quantum coherences, the new method can resolve overlapped peaks in inhomogeneous fields. The measurement results are in consistent with the measurements in homogeneous fields using conventional method. Since spatial encoding technique is involved, the experimental time for the new method is same to the conventional method. With the aid of T_1 knowledge, some concealed information can be exploited by T_1 weighting experiment.

Keywords: 2D NMR; Inhomogeneous magnetic fields; High-resolution