课程大纲
COURSE SYLLABUS

1.	**课程代码/名称 Course Code/Title**	电子显微学在生物学中的应用/The Application of Electron Microscope In Biology
2.	**课程性质 Compulsory/Elective**	Elective
3.	**课程学分/学时 Course Credit/Hours**	3/48
4.	**授课语言 Teaching Language**	Bilingual (English and Chinese)
5.	**授课教师 Instructor(s)**	刘忠民 （Zhongmin Liu）
6.	**是否面向本科生开放 Open to undergraduates or not**	not
7.	**先修要求 Pre-requisites**	（如面向本科生开放，请注明区分内容。 If the course is open to undergraduates, please indicate the difference.） Cell Biology, Biochemistry

8. 教学目标 Course Objectives

（如面向本科生开放，请注明区分内容。 If the course is open to undergraduates, please indicate the difference.）

冷冻电子显微学是现今结构生物学领域中发展最快、应用最广的前沿交叉学科。本课程的目标是为生物学各专业的学生传授电子显微学的基本原理和实验方法。通过课程的理论和实验紧密结合的学习方式，让学生能够基本理解冷冻电子显微学的研究对象、研究方法和研究思路，并最终学会了解应用电子显微学来解析生物大分子的三维结构，解决生物医学中的问题。

As one of the fastest growing frontier discipline, cryo-Electron Microscope （cryo-EM） has been emerging as the most powerful tool in determining the high resolution structures of bio-macromolecules. Our aim is to teach the basic principles and methods in cryo-Electron Microscope, especially Single Particle Analysis. With this course, we will present the basic knowledge of the Single Particle Analysis, the principle of negative staining Electron Microscope and cryo-EM sample preparation, to teach students to apply the knowledges and skills to solve biomolecular structures and biomedical problems.

9. 教学方法 Teaching Methods

（如面向本科生开放，请注明区分内容。 If the course is open to undergraduates, please indicate the difference.）

通过本课程的学习，学生可以

1、 了解电子显微学的发展史；

2、 初步掌握生物大分子冷冻电镜的原理以及冷冻电镜样本的制备过程；

3、 初步掌握解决生物样本冷冻电镜应用中的常见问题；

4、 了解单颗粒冷冻电子显微学的基本原理和应用。

At the end of the course, students should be able to

1. Understand the history of electron microscope development;
2. Grasp the knowledge of cryo-EM and cryo-EM sample preparation;
3. Fix common problems in biological EM;
4. Preliminarily understand the principle of Single Particle Analysis.

10. 教学内容
Course Contents
（如面向本科生开放，请注明区分内容。 If the course is open to undergraduates, please indicate the difference.）

Section 1	**Introduction (4 hrs)** **The historical background of the development of electron microscopy** **Hardware breakthrough** **The development of EM sample preparation** **Algorithm in processing EM images** **Classification of EM** **The future of TEM in biology**
Section 2	**Basic anatomy of the TEM (3 hrs)** **Electron gun** **Column** **Condenser** **Vacuum** **Camera**
Section 3	**Fourier transforms and reciprocal space for the beginner (2hrs)**
Section 4	**Image Formation (2hrs)**

Section 5	**Fundamental challenges in biological EM (6 hs)** **Preservation of the native structure of biological sample** **Radiation damage** **Beam induced motions of EM samples** **Low contrast** **Heterogeneity of biological samples** **Low dose cryo-EM mode** **Fast camera** **Signalling in EM images**
Student Presentation I: tackling the problems in biological EM (2 hs)	
Section 6	**Sample preparation for TEM (4 hs)** **Sample preparation pathways** **Grid preparation** **Negative staining EM sample preparation** **Cryo-EM sample preparation** **Cryo-negative-staining** **Substrates for cryo-EM**
Section 7	**How to operate a TEM in checking biological sample (2 hs)** **Basic operations of TEM** **Basic microscope alignment** **Negative staining EM** **Cryo-EM low dose mode setup**
Section 8	**Single-particle analysis (10 hs)** **Basic principle of single particle analysis** **Workflow of a typical structure determination** **Limitations of single-particle analysis** **Biological sample preparation for single-particle analysis** **Grid screening and evaluation** **Common troubles in vitrifying single-particle samples** **Application examples of single-particle analysis** **Application of Alphafold in single-particle analysis**

	Student Presentation II: Single particle cryo-EM applications in Biology (2 hs)	
	Section 9	**Introduction of cryo-Electron tomography (4 hs)** **Correlative light electron microscopy** **Basic principle of cryo-Electron tomography** **Brief introduction of sub-tomography** **Applications of cryo-ET in cell biology** **Challenges in cryo-electron tomography** **Brief introduction of electron crystallography (1 hs)** **Brief introduction of electron crystallography** **Application examples of electron crystallography**
	Section 10	**Labelling technology in biological EM (2 hs)** **In situ labelling** **Labelling in single particle analysis**
	Section 11	**Application of EM in studying Covid-19 virus (2 hs)** **EM in virus** **Application of single particle analysis in studying Covid-19** **Application of Cryo-electron tomography in studying Covid-19** **Application of sub-tomography in studying Covid-19**
	Section12	**Model building, refinement and validation(2 hs)**

11. 课程考核
Course Assessment

（①考核形式 Form of examination；②.分数构成 grading policy；③如面向本科生开放，请注明区分内容。If the course is open to undergraduates, please indicate the difference.）

Assignments and quiz 35%

Discussion and presentation 45%

Attendance 20%

12. 教材及其它参考资料
Textbook and Supplementary Readings

Books:

《Three-Dimensional Electron Microscopy of Macromolecular Assemblies》by Joachim Frank

《Diffraction Physics》Third Revised Edition by John M.Cowley

《电子衍射物理教程》 by 王蓉

《电子晶体学与图像处理》by 李方华

《薄晶体电子显微学》by P. Hirsch

《生命科学中的电子显微镜技术》by 丁明孝等主编

Video：

冷冻电子显微镜（Cryo-EM）入门 by 加州理工学院 Grant J.Jensen
链接：https://www.coursera.org/learn/cryo-em

MRC Lectures:

ftp://ftp.mrc-lmb.cam.ac.uk/pub/scheres/EM-course

Advances in Cryo-EM related book

Cryo-EM Part A-C & Recent advances in cryo-EM (Methods in Enzymology)

http://www.sciencedirect.com/science/bookseries/00766879/481

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http://www.sciencedirect.com/science/bookseries/00766879/483

http://www.sciencedirect.com/science/bookseries/00766879/579