生物系統模擬
Modeling and Simulation in Systems Biology

BEBI 5009

星期四 2,3,4

明達203

Contact

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- Office hour: Friday afternoon or by appointment

- Course website: https://ceiba.ntu.edu.tw/1062BEBI5009/

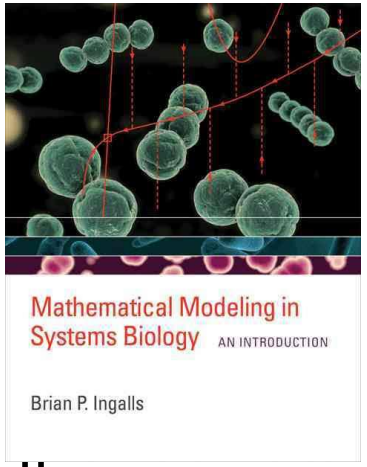
Course introduction

- System techniques are integral to current research in molecular cell biology.
- System level investigations are often accompanied by mathematical models.
- These models serves as working hypothesis.
- They help us to understand and predict the behavior of complex systems.
- This course offer an introduction to mathematical concepts and techniques needed for the construction and interpretation of models in molecular systems biology

Course objective

- Mathematical modelling is becoming an important tool for molecular and cell biology.
- Introduction to the key concepts that are needed for the construction and investigation of mathematical models in molecular systems biology
- Learning fundamental tools and modeling techniques to develop and apply quantitative models of cellular systems.
- Current topics in systems biology

TEXTBOOK & Readings



- Mathematical Modeling in Systems Biology(2013), by Brian P. Ingalls
- https://www.math.uwaterloo.ca/~bingalls/MMSB/MMSB_w_solutions.pdf
- https://www.math.uwaterloo.ca/~bingalls/MMSB/MMSB_code.xhtml

- Hard copy is in NTU library

References:

- Stochastic Modelling for Systems Biology(2011) by Darren J. Wilkinson (ebook in NTU library)

Evaluation

編號	項目	百分比	說明
1	期中考	30%	in class
2	期末報告	30%	書面 + 口頭
3	作業	40%	6-8 HW, 會需要用MATLAB來寫作業

Homework:

Homework:

- About 4-6 HWs in total, ~biweekly
- Due in 2 week after the HW is distributed. Due date and time will be TBA
- HW is due at 9am on Thursday before the class.
- Late homework will not be accepted for any circumstances.
- Matlab/Python code could be sent by email to me or upload to CEIBA

- Class Attendance:
  - Strongly Recommended
  - I don not take attendance in a regular basis

- Policy on missed exams:
  - Students who experience a serious medical condition or other emergency may be excused
  - He/She must contact the instructor BEFORE the exam (Easiest way is to send me an email)
  - He/She must VERIFY their condition by official documents
  - NO EXCEPTIONS will be made for job interviews, holiday travel, or other non-academic activities
  - No make-up exam (Grades will be adjusted based on other elements)

Academic Dishonesty

- Violations can include cheating on exams, plagiarism, reuse of assignments without permission, improper use of the Internet and electronic devices, unauthorized collaboration, alteration of graded assignments, forgery, falsification and lying.

- May result in
  - ◮ Failure on an assignment
  - ◮ Failure in a course
  - ◮ Permanent transcript notation
  - ◮ Expulsion

Tentative course outline

Date	
3月1日	Introduction
3月8日	Introduction to Matlab/Python
3月15日	Systems of differential equations , Separation of Timescales
3月22日	Enzyme kinetics , Cooperativity
3月29日	Phase plane analysis , Stability
4月5日	放假日
4月12日	Sensitivity analysis; Parameter fitting
4月19日	Review
4月26日	期中考
5月3日	Stochastic processes and simulation
5月10日	Stochastic Modeling
5月17日	Gene regulatory networks; Invited talk Dr. Wen Hao-Jui
5月24日	Signal transduction pathways
5月31日	Metabolic network
6月7日	Oral presentation
6月14日	Oral presentation
6月21日	Term project due

Ch1-4: mathematical modelling in molecular systems biology

- Chapter 1 introduces molecular systems biology and describes some basic notions of mathematical modelling, concluding with four short case-studies.
- Chapter 2 introduces dynamic mathematical models of chemical reaction networks. These are differential equation models based on mass-action rate laws. Some basic methods for analysis and simulation are described.
- Chapter 3 covers biochemical kinetics, providing rate laws for biochemical processes (i.e. enzyme-catalysed reactions and cooperative binding). The last section treats common approximation methods.
- Chapter 4 introduces techniques for analysis of differential equation models, including phase plane analysis, stability, bifurcations, and sensitivity analysis.

Ch 5-8: specific biological domain

- Chapter 5 covers modelling of metabolic networks. Sensitivity analysis plays a central role in the investigation of these models. The last section introduces stoichiometric modelling, which is often applied to large-scale metabolic networks.
- Chapter 6 addresses modelling of signal transduction pathways. The examples taken up in this chapter survey a range of information-processing tasks performed by these pathways. The last section introduces the use of frequency-response analysis for studying cellular input-output systems.
- Chapter 7 introduces modelling of gene regulatory networks. The chapter starts with a treatment of gene expression, then presents examples illustrating a range of gene-circuit functions. The final section introduces stochastic modelling in molecular systems biology.
- Chapter 8 covers modelling of electrophysiology and neuronal action potentials. One section contains a brief introduction to spatial modelling using partial differential equations.

- Essential biological concepts and mathematical fundamentals will be reviewed.
- Introduction of Python/MATLAB programming.

XPPAUT

- a freely available program that that was written specifically for dynamic modelling
- http://www.math.pitt.edu/~bard/xpp/installonwindows.html

MATLAB

- NTU App Share
- EE電二130 (or 132)，電機系大學部學生
- SciLab (free): http://www.scilab.org/
- Octave (free): https://www.gnu.org/software/octave/

- Tutorials
- https://www.mathworks.com/support/learn-with-matlab-tutorials.html
- Matlab On Ramp

Learn with MATLAB and Simulink Tutorials

Get started with the basics of MATLAB and Simulink

Learn MATLAB in Just 2 Hours

Learn MATLAB Basics

MATLAB® is the high-level language and interactive environment used by millions of engineers and scientists worldwide. It lets you visualize ideas across disciplines including signal and image processing, communications, control systems, and computational finance.

Read Documentation Basics

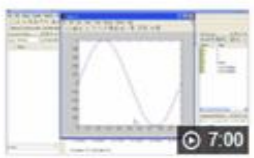
Desktop Basics: Enter commands and view results

Matrices and Arrays: Create variables that contain multiple values

Array Indexing: Access data in an array.

» See more documentation topics

Watch Introductory Videos



Getting Started with MATLAB

Image Processing Made Easy

Using Basic Plotting Functions

Learn Simulink Basics

Simulink® is a block diagram environment for multi-domain simulation and Model-Based Design. It supports simulation, automatic code generation, and continuous test and verification of embedded systems. Simulate dynamic systems leveraging graphical editors, customizable block libraries, and solvers for modeling.

Read Documentation Basics

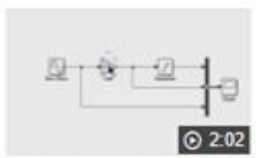
Create a Simple Model: Build and simulate a model.

Model a Dynamic System: Create a dynamic control system.

Simulate a Dynamic System: Simulate and evaluate system behavior.

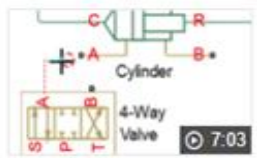
» See more documentation topics

Watch Introductory Videos



Getting Started with Simulink

Physical Modeling with Simscape



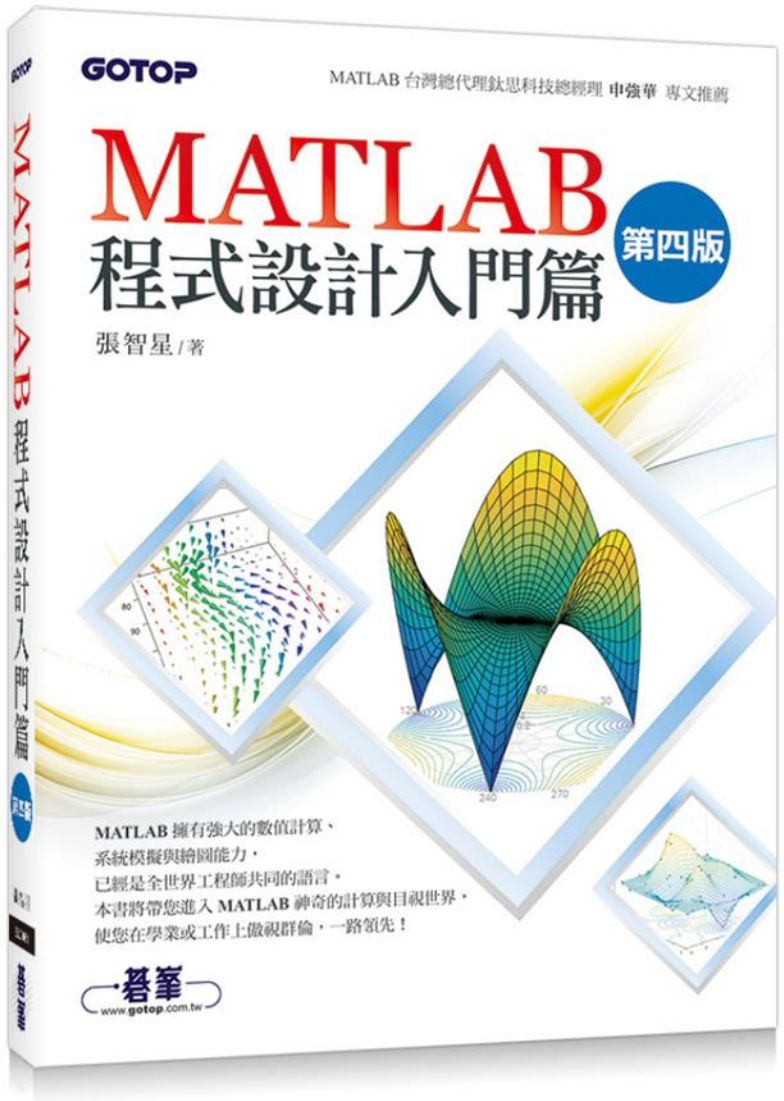
Modeling a Hydraulic Actuation System

https://www.mathworks.com/support/learn-with-matlab-tutorials.html

https://www.terasoft.com.tw/

https://www.terasoft.com.tw/event/workshops/2018/

MATLAB 程式設計 【入門篇】



MATLAB程式設計《入門篇》：投影片 & 教學影片

張智星

各章主題	投影片	教學影片
MATLAB小傳與外觀	01-MATLAB小傳與外觀.ppt	按此觀看影片
初探MATLAB	02-初探MATLAB.ppt	按此觀看影片
二維平面繪圖	03-二維平面繪圖.ppt	按此觀看影片
三維立體繪圖	04-三維立體繪圖.ppt	按此觀看影片
特殊圖形	05-特殊圖形.ppt	按此觀看影片
動畫製作	06-動畫製作.ppt	按此觀看影片
握把式圖形與 GUI 設計	07-握把式圖形與 GUI 設計.ppt	按此觀看影片
GUIDE	08-GUIDE.ppt	
矩陣的處理與運算	09-矩陣的處理與運算.ppt	按此觀看影片
字元與字串	10-字元與字串.ppt	按此觀看影片
多維陣列	11-多維陣列.ppt	按此觀看影片
異質陣列	12-異質陣列.ppt	按此觀看影片
結構陣列	13-結構陣列.ppt	按此觀看影片
MATLAB 的運算元	14-MATLAB 的運算元.ppt	
M檔案	15-M檔案.ppt	
程式流程控制	16-程式流程控制.ppt	按此觀看影片
程式除錯	17-程式除錯.ppt	按此觀看影片
檔案讀寫	18-檔案讀寫.ppt	按此觀看影片
影像顯示與讀寫	19-影像顯示與讀寫.ppt	按此觀看影片
音訊讀寫、錄製與播放	20-音訊讀寫、錄製與播放.ppt	按此觀看影片

https://mirlab.org/jang/books/matlabProgramming4beginner/slide/

MATLAB 程式設計 【入門篇】:

MATLAB程式設計：入門篇

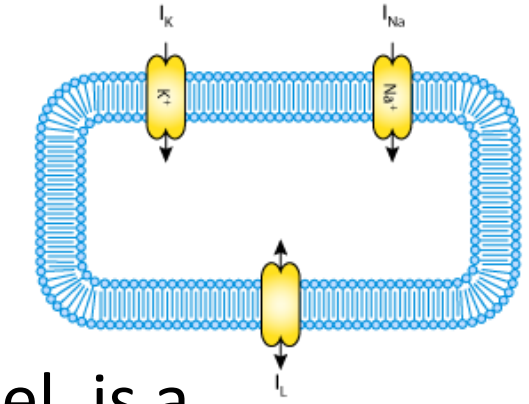
Roger Jang (張智星)

- 本線上教材已經付梓成書，請見「碁峰連結」。
- 姊妹作：MATLAB程式設計：進階篇
- Download: [all examples] [all slides]

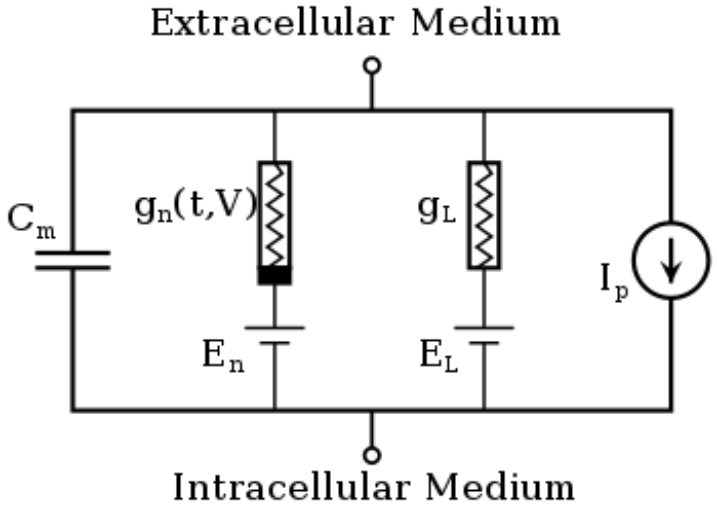
Table of Contents

http://mirlab.org/jang/books/matlabProgramming4beginner/

Hodgkin–Huxley model



- The Hodgkin–Huxley model, or conductance-based model, is a mathematical model that describes how action potentials in neurons are initiated and propagated. It is a set of nonlinear differential equations that approximates the electrical characteristics of excitable cells such as neurons and cardiac myocytes.



Mathematically, the current flowing through the lipid bilayer is written as

$$I_c = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t}$$

and the current through a given ion channel is the product

$$I_i = g_n(V_m - V_i)$$

where V_i is the reversal potential of the *i*-th ion channel. Thus, for a cell with sodium and potassium channels, the total current through the membrane is given by:

$$I = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t} + g_K(V_m - V_K) + g_{Na}(V_m - V_{Na}) + g_l(V_m - V_l)$$

https://en.wikipedia.org/wiki/Hodgkin%E2%80%93Huxley_model

Hodgkin-Huxley Model

https://models.cellml.org/e/e1/tutorial

ophysical mechanism for the generation of action potentials.

Potassium current

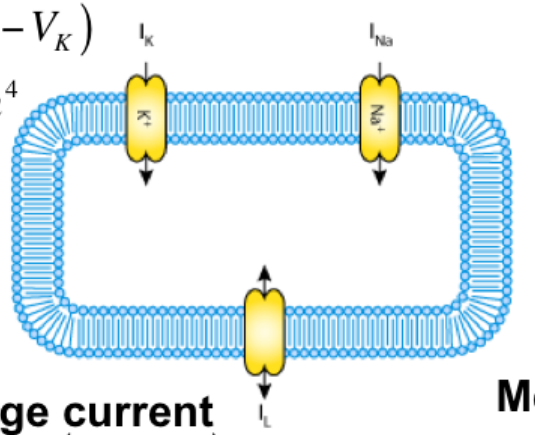
$$I_K = g_K (V - V_K)$$

$$g_K = g_{K_{max}} n^4$$

Sodium current

$$I_{Na} = g_{Na} (V - V_{Na})$$

$$g_{Na} = g_{Na_{max}} m^3 h$$



Gates (n,m,h)

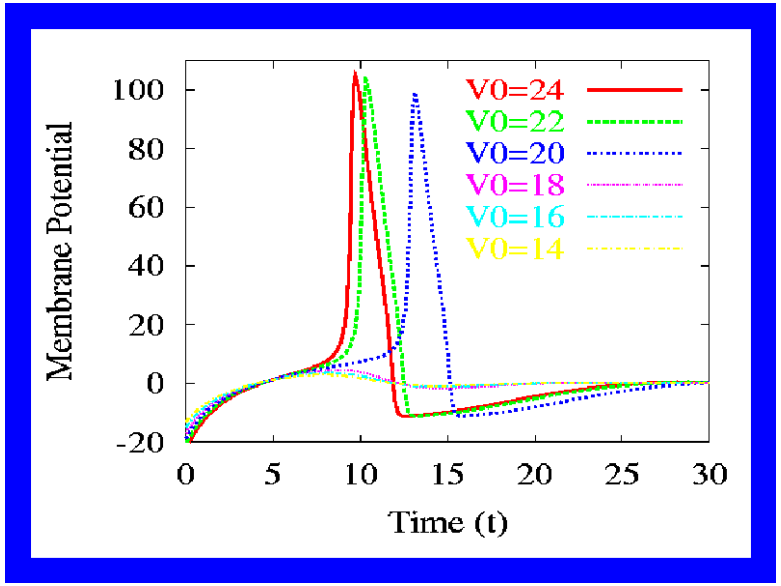
$$\frac{dX}{dt} = \alpha_X (1 - X) - \beta_X X$$

Leakage current

$$I_{leak} = g_{leak_{max}} (V - V_{leak})$$

Membrane potential

$$\frac{dV}{dt} = \frac{I_{stim} - (I_K + I_{Na} + I_{leak})}{C_m}$$



Probabilities of Channel Openning

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h$$

Membrane as a Capacitor

$$C_m \frac{dV}{dt} = I(t)$$

$$I(t) = I_{Na^+} + I_{K^+} - I_L$$

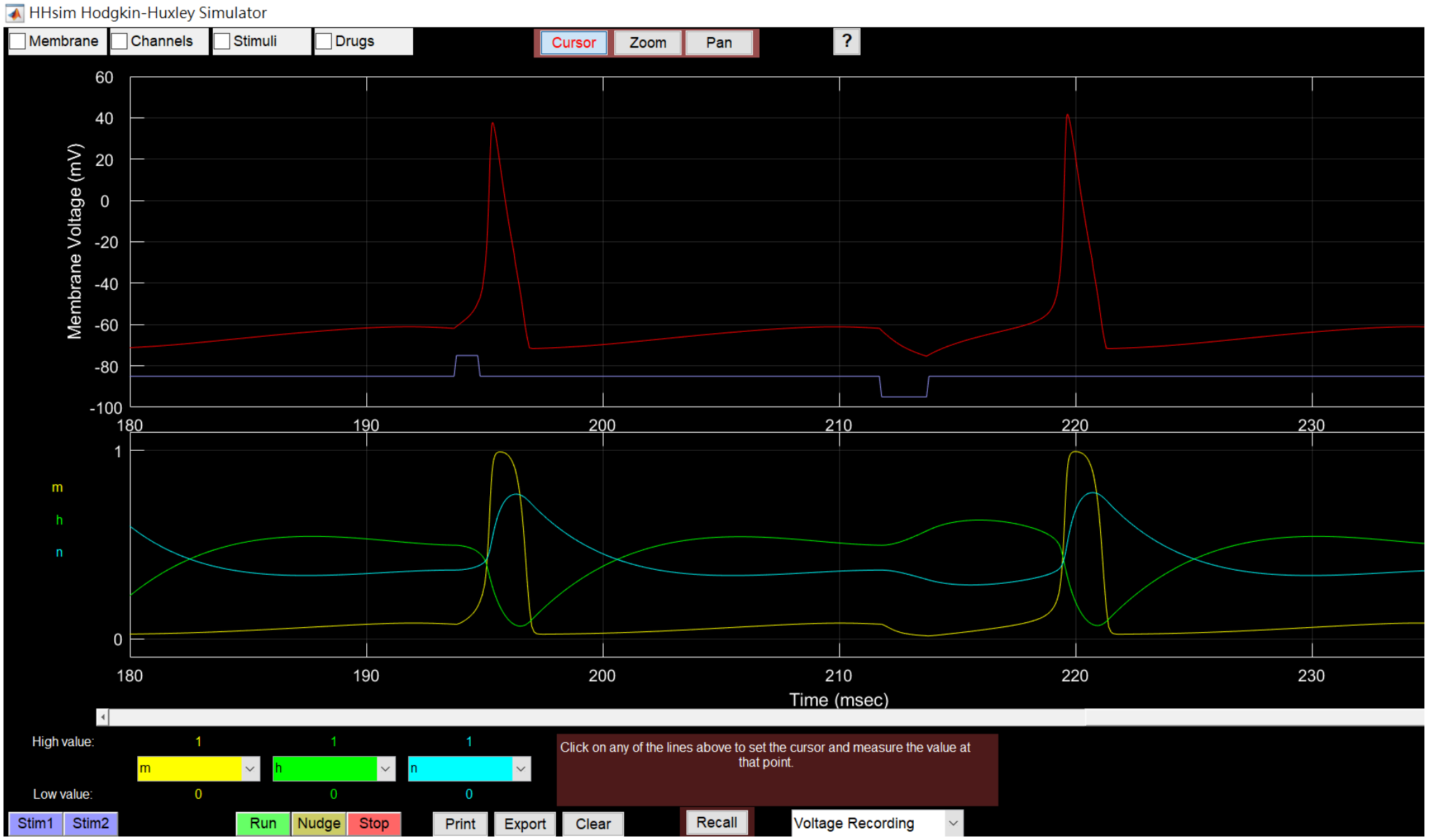
$$I_{K^+} = \bar{g}_K n^4 (V - V_K)$$

$$I_{Na^+} = \bar{g}_{Na} m^3 h (V - V_{Na})$$

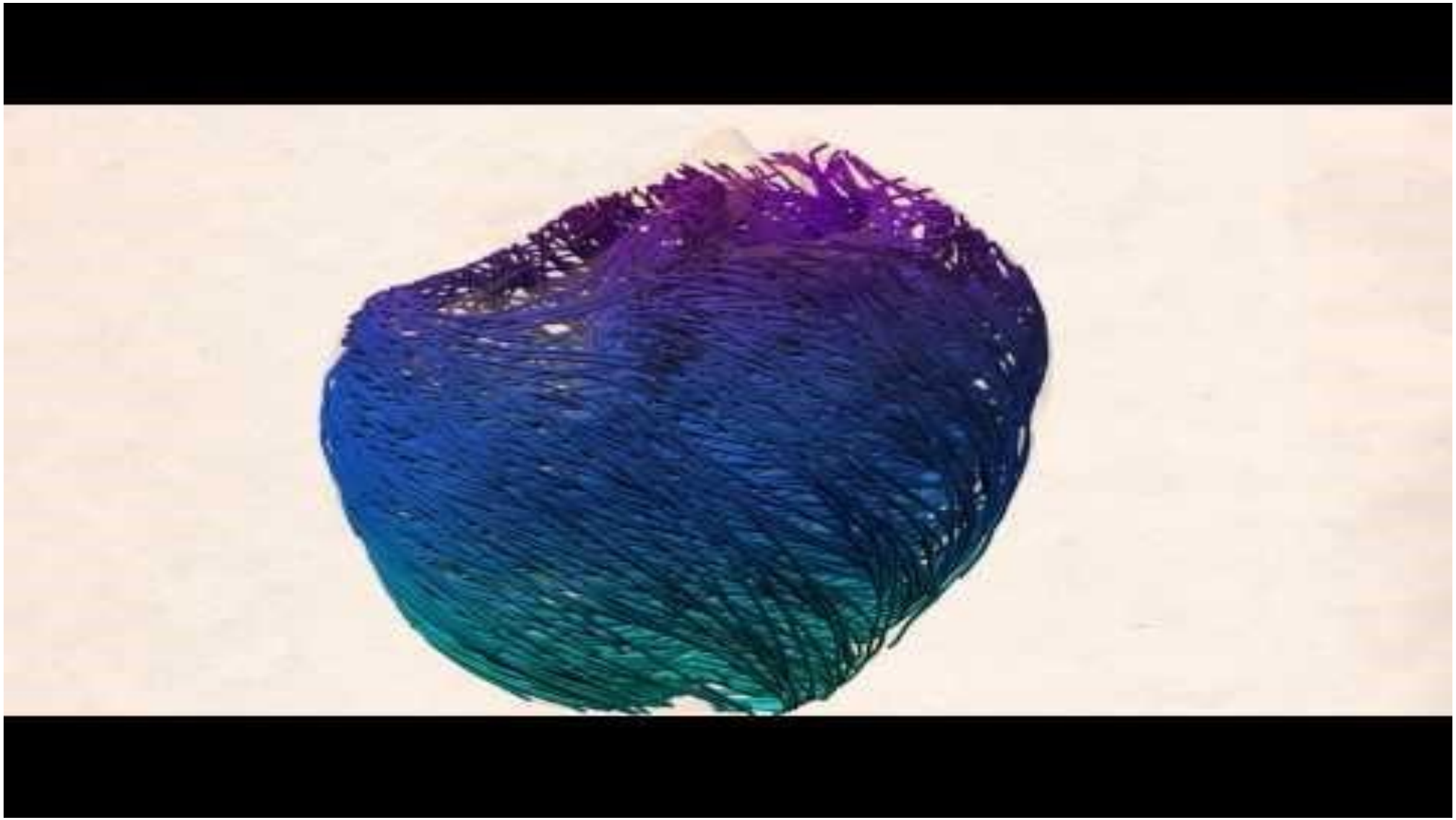
$$I_L = \bar{g}_L (V - V_L)$$

http://www.amath.washington.edu/~qian/talks/talk5/

HHsim


HHsim Hodgkin-Huxley Simulator
Membrane
Channels
Stimuli
Drugs
Cursor
Zoom
Pan
?
Membrane Voltage (mV)
60
40
20
0
-20
-40
-60
-80
-100
180
190
200
210
220
230
m
h
n
1
0
Time (msec)
High value:
Low value:
1
1
1
0
0
0
m
h
n
Click on any of the lines above to set the cursor and measure the value at that point.
Stim1
Stim2
Run
Nudge
Stop
Print
Export
Clear
Recall
Voltage Recording

Alya Red: A Computational heart



https://www.youtube.com/watch?v=hiKgDOXlPfk

Python

- Python is an interpreted high-level programming language for general-purpose programming. Created by Guido van Rossum and first released in 1991, Python has a design philosophy that emphasizes code readability, and a syntax that allows programmers to express concepts in fewer lines of code, notably using significant whitespace. It provides constructs that enable clear programming on both small and large scales.
- Python features a dynamic type system and automatic memory management. It supports multiple programming paradigms, including object-oriented, imperative, functional and procedural, and has a large and comprehensive standard library.

https://zh.wikipedia.org/wiki/Python

Pre-Class Survey

- Self introduction
- your major, which year
- Research interest, whose lab you are from
- Why do you take this class?
- What’s your expectation of the class?

TA Time

Python