Molecular Biophysics I
HBCG 6332

Fall Semester, 2009

Term: August 31 – December 18, 2009
Class Times: Tuesday and Thursday 1:30-3pm
Location: MRB 6.102

Course Master:
Junji Iwahara, Ph.D.

Teaching Assistant:
Debashish Sahu

Instructors:
Wlodek M. Bujalowski, Ph.D.
Robert O. Fox, Ph.D.
Alexey V. Gribenko, Ph.D.
Junji Iwahara, Ph.D.
Krishna Rajarathnam, Ph.D.
Stanley J. Watowich, Ph.D.

Course Description:
In this course, students learn thermodynamics and kinetics for biological molecules. Both theoretical and experimental aspects are covered. Students also learn the Mathematica software so that they can use it as a tool for their own research.

Syllabus:
Students use the Mathematica software **in lectures marked with an asterisk**.

<u>Part I. Fundamentals of Quantitative Analysis</u>

Lecture 1.* Error estimation
September 1 (Tue) Iwahara
- Fundamentals of Mathematica
- Sources of errors in experiments
- Error propagation based on partial derivatives

Lecture 2.* Nonlinear least-squares fitting
September 3 (Thu) Iwahara
- χ^2 function
- Confidence limit
- Model selection based on F-statistics
- Estimation of errors in fitted variables using the Monte Carlo approach

Part II. Thermodynamics

Lecture 3.* Fundamentals of thermodynamics (I)

September 8 (Tue) — Gribenko

- Enthalpy, entropy and free energy
- Reference state
- Heat capacity

Lecture 4.* Fundamentals of thermodynamics (II)

September 10 (Thu) — Gribenko

- Chemical equilibrium
- Partition function
- Chemical potential

Lecture 5.* Thermodynamics of macromolecular interactions (I)

September 15 (Tue) — Gribenko

- Association / Dissociation equilibrium (single binding site)
- Association / Dissociation equilibrium (two binding sites)
- Binding polynomial

Lecture 6.* Thermodynamics of macromolecular interactions (II)

September 17 (Thu) — Gribenko

- Cooperative binding
- Allosteric effect

Lecture 7.* Measurement of equilibrium constants (I)

September 22 (Tue) — Iwahara

- Spectroscopic methods

Lecture 8. Measurement of equilibrium constants (II)

September 29 (Tue) — Rajarathnam

- Equilibrium ultracentrifugation

Lecture 9. Thermodynamics for drug design (I)

October 1 (Thu) — Watowich

- Computation of free energy for protein-drug interactions

Lecture 10. Thermodynamics for drug design (II)

October 6 (Tue) — Watowich

- Structure-based drug design

Lecture 11. Thermodynamics of protein folding (I)

October 8 (Thu) — Fox

- Chemical Denaturation
- Denaturant Binding Model (DBM)
- Linear Extrapolation Model (LEM)

Lecture 12. Thermodynamics of protein folding (II)

October 13 (Tue) Fox

- Avg. Ex. Enthalpy, Heat Cap., dT vs. Variance, Deconvolution, Numerical vs. Analytical Differences/Differentiation, van't Hoff and Cooperativity, Calorimetric Enthalpy, Fitting DSC

Lecture 13. Thermodynamics of protein folding (III)

October 15 (Thu) Fox

- Natively Unfolded Proteins

Discussion I

October 20 (Tue) Iwahara

October 22 (Thu) - No lecture -

Part III. Kinetics

Lecture 14.* Kinetics of first-order reactions (I)

October 27 (Tue) Iwahara

- Rate equations and kinetic matrix
- Analytical and numerical solutions of rate equations
- Two-state first-order reaction
- Three-state first-order reaction (consecutive)

October 29-30. Keck Center Annual Research Conference (Students should attend)

Lecture 15.* Kinetics of first-order reactions (II)

November 3 (Tue) Iwahara

- Determination of kinetic rate constants
- Rate-limiting step in a multi-step reaction
- Steady-state approximation

Lecture 16.* Kinetics of first-order reactions (III)

November 5 (Thu) Iwahara

- Relationship between kinetics and thermodynamics
- Transition state theory
- Energy-barrier and reaction timescale

Lecture 17.* Kinetics of second-order reactions (I)

November 10 (Tue) Iwahara

- Collision theory
- Smoluchowski limit
- Diffusion- and reaction-controlled kinetics
- Macromolecular association and dissociation
- Numerical solution of rate equations for non-first-order reactions

Lecture 18.* Kinetics of second-order reactions (II)

November 12 (Thu) Iwahara

- Pseudo-first-order approximation
- Determination of association and dissociation rate constants
- Protein-DNA interactions
- Disulfide exchange reactions

Lecture 19.* Enzyme kinetics

November 17 (Tue) Iwahara

- Exact description of enzyme kinetics using rate equations
- Comparison to Michaelis-Menten formalism

Lecture 20. Stopped-flow experiments

November 19 (Thu) Bujalowski

- Principle of stopped-flow kinetics
- Kinetics of protein-DNA interactions

Lecture 21.* Kinetic analysis of a system at equilibrium

November 24 (Tue) Iwahara

- Kinetic matrix in NMR spectroscopy
- Determination of dissociation rate constants for protein-ligand interactions
- Determination of rate constants for protein translocation on DNA

November 26-27 (Thursday/Friday): Thanksgiving Day Holidays

Lecture 22.* Facilitated target location (I)

December 1 (Tue) Iwahara

- Reduced dimensionality
- Encounter complex

Lecture 23.* Facilitated target location (II)

December 3 (Thu) Iwahara

- Target search by a DNA-binding protein
- Sliding, hopping, and direct transfer

Discussion II

December 8 (Tue) Iwahara

Final Examination (in class)

December 10 (Thu)

December 15 (Tue) – No Lecture – Deadline for Take-home Final Exam

Examinations/Evaluations:

The performance of each student will be evaluated based on 1) homework assignments, 2) in-class quizzes, 3) the in-class final exam, and 4) the take-home final exam.

Homework assignments will be given five times in this course. Students must submit their answers **in Mathematica notebook (*.nb) files** to the Teach Assistant and the Course Master by email **within a week**.

Quizzes will be given in the first 15 minutes of several lectures.

Students must take the in-class final examination on December 10th at MRB 6.102. Sixty minutes are given to solve the problems. The take-home final exam will be given on December 8th. Answers in Mathematica notebook files must be submitted to the Teach Assistant and the Course Master by December 15th.

Total scores (0-100) will be calculated with the following weights:

Homework,	40%
Quizzes,	10%
In-class final exam,	20%
Take-home final exam,	30%

Absence without prior approval by the Course Master will result in reduction of 5 points per lecture from the total score.

Grades will be determined using the total scores: A, 90-100; B, 80-89; C, 70-79; and F, 69 or below.

***Student end of course evaluations are required for all A/B/C/F-graded GSBS courses. Students are required to fill out the evaluations to receive a grade in the course. If the specified evaluation form is not received, an "I" Incomplete grade will be reported to the Office of Enrollment Services. If the course requirements are not completed within 30 days, the grade automatically converts to an "F" Failure grade. The evaluations are anonymous and will be available to course directors only after grades are assigned.

Excused Absences:

Since the course is highly interactive, attendance and participation are required. Students can be excused from graded assignments without penalty to their grade if an excused letter is obtained from Dr. Sarita Sastry, Director of BMB Graduate Program or Dr. Andres Oberhauser, Director of MBET Educational Track, **in advance**. If absences are excused, appropriate make-up work will be provided for students at the discretion of the co-directors.

Important Dates:

No GSBS classes
Monday, September 7, 2009 Labor Day
Wednesday, November 11, 2009 Veteran's Day
Thursday – Friday, November 26-27, 2009 Thanksgiving Day

Last Day to Drop/Add Course
Wednesday, September 16, 2009

Recommended Books:

1) Thermodynamics and Kinetics for the Biological Sciences
by Gordon G. Hammes [Publisher, Wiley-InterScience]

2) Thermodynamics of Biochemical Reactions
by Robert A. Alberty [Publisher, Wiley-InterScience]

3) Biophysical Chemistry Part III: The Behavior of Biological Macromolecules
by Charles R. Cantor and Paul R. Schimmel [Publisher, W.H. Freeman & Company]

4) Chemical Kinetics and Catalysis
by Richard I. Masel [Publisher, Wiley-InterScience]

Books #1 and #2 are introductory and concise. The second half of Book #2 describes simulations with the Mathematica software. Books #3 and #4 are advanced and comprehensive.