Heinrich Heine University, Düsseldorf
Department of Computer Science

# Computational Systems Biology

(January 29, 2019)

**Instructor:** Deniz Sezer (PhD Physics, Cornell University)
**E-mail:** sezerd@hhu.de
**Office:** 25.02.02.25

**Lecture:** Tue 10:30-12:00 in 25.02.02.21
**Computer lab:** Tue 14:30-16:00 in 25.02.02.21

**Evaluation:**

| | | |
|---|---|---|
| Computer labs (in-class) | | 25 % |
| Midterm exam (take-home) | Nov 27 - Dec 4 | 35 % |
| Final exam (take-home) | Feb 5 - Feb 12 | 40 % |

**Course Content:**

| week | date | Lecture, Computer lab |
|---|---|---|
| | | I. Bacterial populations |
| 1 | Oct 9 | General information about the course. Cell division and exponential growth.<br>No lab this week. |
| 2 | Oct 16 | Logistic growth. Numerical solution of growth (differential) equations.<br>Lab1: Numerical analysis of exponential and logistic growth. |
| 3 | Oct 23 | Antibiotic resistance. Competition of two species.<br>Lab2: Antibiotic resistance under logistic growth. |
| | | II. Inner workings of a bacterial cell |
| 4 | Oct 30 | What is inside a cell? Chemical reaction networks.<br>Lab3: Closed, open, and enzyme-catalyzed reaction networks. |
| 5 | Nov 6 | ATP hydrolysis as a battery. "Voltage" of the ATP battery.<br>Lab4: Visualizing protein structures with VMD. |
| 6 | Nov 13 | Enzymes as "wires". Kinetic modeling of Glycolysis.<br>Lab5: Numerical analysis of the first 3 steps of Glycolysis. |
| 7 | Nov 20 | The stoichiometry matrix and its "downstream-aware" inverse.<br>Lab6: Stoichiometric modeling of reactions 4, 5, and 6 of Glycolysis. |
| 8 | Nov 27 | **Midterm exam** (take-home)<br>No lab this week. |
| | | III. Optimizing bacterial growth rate |
| 9 | Dec 4 | Cell growth rate from the marriage of stoichiometry and biochemistry.<br>Lab7: Numerical analysis of the simplest whole-cell model. |
| 10 | Dec 11 | Cellular resource allocation from optimization of the growth rate.<br>Lab8: Growth rate optimization in self-replicating cell models. |
| 11 | Dec 18 | *E. coli* eats one sugar at a time.<br>Lab9: Whole-cell model with two alternative food sources. |
| | | IV. Control of protein expression |
| 12 | Jan 8 | Regulation of protein expression: transcription factors and the *lac* operon.<br>No lab this week. |
| 13 | Jan 15 | Is bacterial growth rate optimized? A mechanism of growth-rate optimization.<br>Lab10: Optimizing growth rate through kinetics. |
| 14 | Jan 22 | Binding of transcription factors to DNA.<br>Lab11: Position energy matrix of *lac* repressor from operator sequences. |
| 15 | Jan 29 | Weighted least squares minimization. Protein sectors.<br>Lab12: Whole-genome estimate of a position energy matrix. |
| | Feb 5 | **Final exam** (take-home) |

**Reading assignments:**
(Uploaded to ILIAS.)

**Week 2** Exponential and logistic growth

- Phillips, Kondev, Theriot, Garcia, Orme, *Physical Biology of the Cell*, 2$^{\text{nd}}$ ed., Garland Science, 2013.
(Computational Exploration: Growth Curves and the Logistic Equation, pp. 103–105.)
- Hagen, Exponential growth of bacteria: Constant multiplication through division, *Am. J. Phys.*, **78**, 1290–1296 (2010). (First three sections only.)
- Ingalls, *Mathematical Modeling in Systems Biology*, MIT Press, 2013.
(Sec. 2.1.4 Numerical Simulation of Differential Equations.)

**Week 3** Antibiotic resistance

- Gullberg, Cao, . . . , Andersson$^*$, Selection of resistant bacteria at very low antibiotic concentrations, *PLoS Pathogens*, **7**, e1002158 (2011).

**Week 4** What is inside a cell

- Goodsell, *The Machinery of Life*, 2$^{\text{nd}}$ ed., Springer Science+Business Media, 2009.
(Ch. 4 Molecules in Cells: *Escherichia coli*, pp. 53–68.)
- Liebermeister, Noor, Flamholz, Davidi, Bernhardt$^*$, Milo$^*$, Visual account of protein investment in cellular functions, *Proc. Natl. Acad. Sci. USA*, **111**, 8488–8493 (2014).
- Ingalls, *Mathematical Modeling in Systems Biology*, MIT Press, 2013.
(Ch. 2 Modeling of Chemical Reaction Networks, pp. 21–48.)

**Week 5** Protein structures and their visualization.

- PDB-101 Molecule of the Month: Glycolytic Enzymes (`http://pdb101.rcsb.org/motm/50`).
- VMD Tutorial (`http://www.ks.uiuc.edu/Training/Tutorials/`).
(Ch. 1 Working with a Single Molecule & Ch. 4 Working with Multiple Molecules.)

**Week 6** Kinetic modeling of Glycolysis

- Goldbeter, Computational approaches to cellular rhythms, *Nature*, **420**, 238–245 (2002).
- Gustavsson,. . . , Snoep$^*$, Sustained glycolytic oscillations in individual isolated yeast cells, *FEBS Journal*, **279**, 2837–2847 (2012).

**Week 7** Stoichiometry matrix of a reaction network

- Ingalls, *Mathematical Modeling in Systems Biology*, MIT Press, 2013.
(Sec. 5.4 Stoichiometric Network Analysis, pp. 150–165.)

**Week 8** Farming mitochondria in fluctuating environment

- Lane, *Power, Sex, Suicide*, Oxford University Press, 2006.
(Introduction. Mitochondria: Clandestine Rulers of the World)
- Zachar, Szilágyi, Szamádó, Szathmáry$^*$, Farming the mitochondrial ancestor as a model of endosymbiotic establishment by natural selection, *Proc. Natl. Acad. Sci. USA*, **115**, E1504–E1510 (2018).

**Week 9** Mitochondrial acquisition and simplest model of a whole cell

- Garg and Martin$^*$, Asking endosymbionts to do an enzyme's job, *PNAS*, **115**, E4543–E4544 (2018).
- Jong$^*$, . . . , Mathematical modelling of microbes: metabolism, gene expression and growth, *J. R. Soc. Interface*, **14**, 20170502 (2017).

**Week 10** Cell growth and resource allocation

- Scott, Gunderson, Mateescu, Zhang, Hwa*, Interdependence of cell growth and gene expression: Origins and consequences, *Science*, **330**, 1099–1102 (2010).
- Molenaar*, van Berlo, de Ridder, Teusink, Shifts in growth strategies reflect tradeoffs in cellular economics, *Molecular Systems Biology*, **5**, 323 (2009).

**Week 11** Glucose versus lactose

- Kirschner and Gerhart, *The Plausibility of Life*, Yale University Press, 2005.
  (Ch. 4: Weak Regulatory Linkage, pp. 112-121)

**Week 12** Optimality of cell growth

- Towbin, Korem, Bren, Doron, Sorek, Alon*, Optimality and sub-optimality in a bacterial growth law, *Nature Communications*, **8**, 14123 (2017).

**Week 13** Mechanism of growth-rate optimization

- Towbin, Korem, Bren, Doron, Sorek, Alon*, Optimality and sub-optimality in a bacterial growth law, *Nature Communications*, **8**, 14123 (2017).

**Week 14** Transcription factor binding to DNA sequences

- Phillips, Kondev, Theriot, Garcia, Orme, *Physical Biology of the Cell*, $2^{\text{nd}}$ ed., Garland Science, 2013.
  (Sec. 6.1.2 The Statistical Mechanics of Gene Expression: RNA Polymerase and the Promoter, pp. 244–248.)
  (Sec. 19.2 Genetic Networks: Doing the Right Thing at the Right Time, pp. 807–817.)
- Belliveaua, . . . , Phillips*, Systematic approach for dissecting the molecular mechanisms of transcriptional regulation in bacteria, *Proc. Natl. Acad. Sci. USA*, **115**, E4796–E4805 (2018).

**Week 15** Growth laws and protein sectors

- You, . . . , Hwa*, Coordination of bacterial proteome with metabolism by cyclic AMP signalling, *Nature*, 301–306 (2013).