University of California, Merced
School of Natural Sciences/ Quantitative and Systems Biology Graduate Program

QSB 290 — FALL 2018

Current Topics in Quantitative and Systems Biology: Stochastic State Machines: a Unifying Approach

Instructors and Contact Information:
Professor David Ardell

Units, Registration, Meeting Times and Locations
QSB 290 is a 3-unit graduate-level course that may be taken for letter-grade only. The course meets from noon to 1:20 pm in CLSSRM 262, with a short break at the end of the first hour.

Course Description
QSB 290 is an introductory advanced graduate course in biology, based primarily on group discussion of classic and recent scientific literature across different disciplines and biological subdisciplines in QSB. The course advocates a unified approach to the investigation of biological systems and emphasizes universal properties of biological systems across scales of biological organization such as robustness, adaptive plasticity, and emergent individuality through cooperation in interaction networks. QSB 290 reviews how the properties of organisms and the ecology and evolution of species emerge from fundamental and universal properties of molecules and cells, and how ecological and evolutionary models and concepts such as polymorphism and genetic drift practically improve our understanding of macromolecular and cell biology.

QSB 290 adopts an *agent-based* approach to understanding complex biological systems across scale. The concept of *biological agency* itself is examined at the outset from the perspectives of computational biology (automata theory, Markov models, modularity), theoretical biology and evolution, and the philosophy of biology. Interesting, relevant and well-studied exampled biological models and model systems are examined and discussed with the aim of deepening exposure to recent advances across biology, including molecular systems biology, synthetic biology, ecology and evolutionary biology.

QSB 290 does not require prior experience with programming or statistics, nor does it teach students to program or conduct statistical work on their own data. However, it provides students the core competence and modeling literacy to collaboratively discuss the modeling of systems of interest to them, primarily through the core course concept of a *stochastic state machine* (which combines the core concepts of *state machine* from computer science and *probability distribution* from statistics). Through course readings, discussion, informal lecture and computer-based exercises, students will directly apply the *stochastic state machine* core concept to learn how computational biologists model and simulate whole macromolecules, whole cells, whole organisms, populations, and species.

QSB 290 fulfills the Systems Biology requirement for the QSB degree.

Course Format, Organization, and Assessments
QSB 290 The course is predominantly driven by discussion of literature by students and faculty. On a given day according to schedule, students may be asked to prepare written questions to help guide in-class discussion of assigned reading, work in student teams to prepare and give presentations of assigned reading and lead discussion of them, cooperate in teams to set-up and complete a small number of computer-based simulation exercises, and follow-up on discussion points independently through scholarship of literature, particularly regarding how course concepts and themes apply to biological systems of direct interest and relevance to their anticipated graduate research.

Through small number (four) of short interactive computer exercises, students will gain practical experience in running open-source software in python and work with advanced computing resources that will help build intuition and literacy in the most popular models used today in computational biology and bioinformatics. Students will be assessed through their written discussion questions, their participation in discussion, their independently completed homework exercises, their final projects consisting of eight-page white paper research proposals relating course material to student-chosen research topics, and their final project oral presentations.

Optional Supplemental Textbooks:
None of these texts are required for the course.

Systems Biology:
1. *A First Course in Systems Biology* by Eberhard Voit, Garland.
2. *Fundamentals of Systems Biology: From Synthetic Circuits to Whole-cell Models* by Markus W. Covert, CRC Press

Website: Lecture notes will be posted on CATCOURSES

Attendance: *All students are required to attend all sessions.* Attendance will be taken. More than one unexcused absence not arranged in advance (prior permission sought for standard acceptable reasons such as medical, religious or professional reasons, with documentation or permission of instructor) will cause the course grade to decrease by one level (i.e. will cause an A to become an A–, etc.) Up to two prearranged excused absences will be forgiven for the standard reasons, after the first two excused absences, each consecutive absence will be penalized in the course grade by decreasing by one level (i.e. will cause an A to become an A–, etc.).

Guest Policy:
Additional faculty guest lecturers may be invited to participate in various blocks of the course. All UC Merced faculty are invited to attend and participate in any session of the class as according to their interests.

Course Schedule DRAFT Subject to Change!

Week	Date	Topic	Readings	Instructions
Week 1	8/23/18	Course Introduction		
Week 2	8/28/18	Of what value is a unified approach to biology?	• Niklas, K. J., Owens, T. G. and Wayne, R. O. (2013) 'Unity and Disunity in Biology', *BioScience*, 63(10), pp. 811–816. doi: 10.1525/bio.2013.63.10.8.	*please have five questions about (or spurred by) this article, for group discussion in writing at the beginning of class).*
	8/30/18	What roles do theory and modeling play in biology?	• Shou, W. et al. (2015) Research: Theory, models and biology, eLife. doi: 10.7554/eLife.07158. • Voit, E. O., Martens, H. A. and Omholt, S. W. (2015) '150 Years of the Mass Action Law', *PLOS Computational Biology*, 11(1), p. e1004012. doi: 10.1371/journal.pcbi.1004012.	*Please have three questions about (or spurred by) each reading ready for group discussion in writing at the beginning of class, and be prepared to discuss any part of both readings, at least in terms of questions.*

Week	Date	Topic	Readings	Instructions
Week 3	9/4/18	How are agent-based models used in systems and synthetic biology?	• Soheilypour, M. and Mofrad, M. R. K. (2018) 'Agent-Based Modeling in Molecular Systems Biology', BioEssays, 40(7), p. 1800020. doi: 10.1002/bies.201800020. • Gorochowski, T.E. (2016). Agent-based modelling in synthetic biology. Essays Biochem 60, 325–336.	*Two teams will divide and conquer the presentation and discussion of these articles. Study Questions will be provided. Be prepared to discuss both articles, at least in terms of questions.*
	9/6/18	How are agent-based models used in evolution, ecology and engineering? *Python Exercise: Simulating agent-based models in Mesa*	• DeAngelis, D. L. and Mooij, W. M. (2005) 'Individual-Based Modeling of Ecological and Evolutionary Processes', *Annual Review of Ecology, Evolution, and Systematics*, 36(1), pp. 147–168. doi: 10.1146/annurev.ecolsys.36.102003.152644. • A.D. Semeniuk, C., Musiani, M., and Marceau, D. (2011). Integrating Spatial Behavioral Ecology in Agent-Based Models for Species Conservation. p. • Bonabeau, E., Dorigo, M., and Theraulaz, G. (2000). Inspiration for optimization from social insect behaviour. Nature *406*, 39–42.	*Three teams will divide and conquer the presentation and discussion of these articles.* *Be prepared to discuss them all, at least in terms of questions.* *Instructions for the Python-based pre-class/in-class/homework computational exercises will be given in advance*

Week	Date	Topic	Readings	Instructions
Week 4	9/11/18	What is biological agency?	• The Biological Notion of Individual (Stanford Encyclopedia of Philosophy), revision 2. Available at: https://plato.stanford.edu/entries/biology-individual/ (Accessed: 22 August 2018). • Baer, R. M. and Martinez, H. M. (1974) 'Automata and Biology', *Annual Review of Biophysics and Bioengineering*, 3(1), pp. 255–291. doi: 10.1146/annurev.bb.03.060174.001351. • Sauro, H.M. (2008). Modularity defined. Molecular Systems Biology *4*, 166.	*Please have six questions about (or spurred by) these readings* ready *for group discussion in writing at the beginning of class, and be prepared to discuss any part of both readings, at least in terms of questions.*
	9/13/18	Can automata self-reproduce? *Open-Source Software Exercise: Simulating cellular automata with Golly*	• Marchal, P. (1998). John von Neumann: the founding father of artificial life. Artif. Life *4*, 229–235.	*Please have five questions about (or spurred by) this reading* ready *for group discussion in writing at the beginning of class, and be prepared to discuss any part, at least in terms of questions.*

Week	Date	Topic	Readings	Instructions
Week 5	9/18/18	What is life?	• Eigen, M., McCaskill, J. and Schuster, P. (1988) 'Molecular quasi-species', *The Journal of Physical Chemistry*, 92(24), pp. 6881–6891. doi: 10.1021/j100335a010. • Woese, C. R. (2002) 'On the evolution of cells', *Proceedings of the National Academy of Sciences*, 99(13), pp. 8742–8747. doi: 10.1073/pnas.132266999.	*Two teams will divide and conquer the presentation and discussion of these articles. Study Questions will be provided. Be prepared to discuss both articles, at least in terms of questions.*
	9/20/18	What are minds?	• Hopfield, J. J. (1994) 'Physics, Computation, and Why Biology Looks so Different', *Journal of Theoretical Biology*, 171(1), pp. 53–60. doi: 10.1006/jtbi.1994.1211. • Smith, J. M. (1999) 'The Idea of Information in Biology', *The Quarterly Review of Biology*, 74(4), pp. 395–400.	*Two teams will divide and conquer the presentation and discussion of these articles. Study Questions will be provided. Be prepared to discuss both articles, at least in terms of questions.*
Week 6	9/25/18	Cancelled.	Prof. Ardell away at tRNA 2018	
	9/27/18	Cancelled.	Prof. Ardell away at tRNA 2018	

Week	Date	Topic	Readings	Instructions
Week 7	10/2/18	How are populations stochastic state machines? *Python Exercise: Simulating finite populations of macromolecular interaction networks in* atinflat*.*	• Sella, G. and Hirsh, A. E. (2005) 'The application of statistical physics to evolutionary biology', Proceedings of the National Academy of Sciences, 102(27), pp. 9541–9546. doi: 10.1073/pnas. 0501865102. • McCandlish, D. M. and Stoltzfus, A. (2014) 'Modeling Evolution Using the Probability of Fixation: History and Implications', The Quarterly Review of Biology, 89(3), pp. 225–252. doi: 10.1086/677571.	*Please have three questions about or spurred by each reading* ready *for group discussion in writing at the beginning of class, and be prepared to discuss any part of both readings, at least in terms of questions.* *Instructions for the python-based pre-class/in-class/ homework computational exercises will be given in advance.*
	10/4/18	How are cells stochastic state machines? *HPC Computing Exercise: Simulating Stochastic kinetics with Stochkit2*	• Székely, T., and Burrage, K. (2014). Stochastic simulation in systems biology. Computational and Structural Biotechnology Journal *12*, 14–25. • Cole, J. A. and Luthey-Schulten, Z. (2014) 'Whole Cell Modeling: From Single Cells to Colonies', *Israel Journal of Chemistry*, 54(8-9), pp. 1219–1229. doi: 10.1002/ijch.201300147	*Two teams will divide and conquer the presentation and discussion of these articles. Study Questions will be provided.* *Instructions for the Stochkit2-based pre-class/in-class/ homework computational exercises will be given in advance. Based on*

Week	Date	Topic	Readings	Instructions
Week 8	10/11/16	What is the biological significance of stochasticity in cells?	• Johnston, R. J. and Desplan, C. (2010) 'Stochastic mechanisms of cell fate specification that yield random or robust outcomes', Annual Review of Cell and Developmental Biology, 26, pp. 689–719. doi: 10.1146/annurev-cellbio-100109-104113. • Labhsetwar, P., Melo, M.C.R., Cole, J.A., and Luthey-Schulten, Z. (2017). Population FBA predicts metabolic phenotypes in yeast. PLOS Computational Biology *13*, e1005728.	*Please have three questions about or spurred by each reading* ready *for group discussion in writing at the beginning of class, and be prepared to discuss any part*
	10/18/18	How are humans and other animals stochastic state machines?	• Heitz, R.P. (2014). The speed-accuracy tradeoff: history, physiology, methodology, and behavior. Front. Neurosci. *8*.	*Please have 3-5 questions about or spurred by the reading* ready *for group discussion in writing at the beginning of class, and be prepared to discuss any part*
Week 9	10/23/18	How are macromolecules stochastic state machines?	• Tawfik, D.S. (2014). Accuracy-rate tradeoffs: how do enzymes meet demands of selectivity and catalytic efficiency? Current Opinion in Chemical Biology *21*, 73–80.	*Please have 3-5 questions about or spurred by the reading* ready *for group discussion in writing at the beginning of class, and be prepared to discuss any part*
	10/25/18	How are stochastic state machines used in bioinformatics?	• Yoon, B.-J. (2009). Hidden Markov Models and their Applications in Biological Sequence Analysis. Curr Genomics *10*, 402–415.	*Please have 3-5 questions about or spurred by the reading* ready *for group discussion in writing at the beginning of class, and be prepared to discuss any part*

Week	Date	Topic	Readings	Instructions
Week 10	10/30/18	How are stochastic state machines used in evolutionary theory?	• Galtier, N., Gascuel, O., and Jean-Marie, A. (2005). Markov Models in Molecular Evolution. In Statistical Methods in Molecular Evolution, R. Nielsen, ed. (New York, NY: Springer New York), pp. 3–24.	*Please have 3-5 questions about or spurred by the reading ready for group discussion in writing at the beginning of class, and be prepared to discuss any part*
	11/1/18	What is robustness?	• Whitacre, J.M. (2012). Biological Robustness: Paradigms, Mechanisms, and Systems Principles. Front Genet *3*.	*Please have five questions about (or spurred by) this reading ready for group discussion in writing at the beginning of class, and be prepared to discuss any part, at least in terms of questions.*
Week 11	11/6/18	What are Mutational Robustness and Survival of the Flattest?	• *C*.O. Wilke *et al.* (2001). Evolution of digital organisms at high mutation rates leads to survival of the flattest. *Nature* 412:331 • Fares, M.A. (2015). The origins of mutational robustness. Trends in Genetics *31*, 373–381.	*Please read both articles thoroughly. Prepare 3-5 questions about (or spurred by) each of these readings* ready *for group discussion in writing at the beginning of class, and be prepared to discuss any part, at least in terms of questions.*
	11/8/18	*Python Exercise: Simulating Survival of the Flattest in Quasispecies with Artificial Chemistries*	• Bull, J. J., Meyers, L. A. and Lachmann, M. (2005) 'Quasispecies Made Simple', PLOS Computational Biology, 1(6), p. e61. doi: 10.1371/journal.pcbi.0010061.	Study questions will be provided for the reading. *Instructions for the Python-based pre-class/in-class/ homework computational exercises will be given in advance.*

Week	Date	Topic	Readings	Instructions
Week 12	11/13/18	What are robustness and plasticity in folding?	• Ancel, L.W., and Fontana, W. (2000). Plasticity, evolvability, and modularity in RNA. J. Exp. Zool. *288*, 242–283.	*Study questions will be provided for the reading. Please have five questions about (or spurred by) this reading* ready *for group discussion in writing at the beginning of class, and be prepared to discuss any part, at least in terms of questions.*
	11/15/18	How do hidden internal states of proteins make cells more robust to noise?	• Wong, F., Amir, A., and Gunawardena, J. (2018). Energy-speed-accuracy relation in complex networks for biological discrimination. Phys. Rev. E *98*, 012420.	*Study questions will be provided for the reading. Please have five questions about (or spurred by) this reading* ready *for group discussion in writing at the beginning of class, and be prepared to discuss any part, at least in terms of questions.*
Week 13	11/20/18	Prof. Ardell away — Class CANCELLED		
	11/22/18	Thanksgiving Holiday — Class CANCELLED		
	11/27/18	What is developmental canalization?	• Flatt, T. (2005). The evolutionary genetics of canalization. Q Rev Biol *80*, 287–316.	*Study questions will be provided for the reading. Please have five questions about (or spurred by) this reading* ready *for group discussion in writing at the beginning of class, and be prepared to discuss any part, at least in terms of questions.*

Week	Date	Topic	Readings	Instructions
Week 14	11/29/18	What are the roles of chaperones and microRNAs in canalization and diversification of insect morphology of insects?	• Rutherford and Lundquist (1998). HSP90 as a capacitor for morphological evolution. *Nature* 396:336. • Misof, B., Liu, S., Meusemann, K., Peters, R.S., Donath, A., Mayer, C., Frandsen, P.B., Ware, J., Flouri, T., Beutel, R.G., et al. (2014). Phylogenomics resolves the timing and pattern of insect evolution. Science *346*, 763–767. • Gibson, G., and Hogness, D.S. (1996). Effect of polymorphism in the Drosophila regulatory gene Ultrabithorax on homeotic stability. Science *271*, 200–203. • Ebert, M. S. and Sharp, P. A. (2012) 'Roles for MicroRNAs in Conferring Robustness to Biological Processes', *Cell*, 149(3), pp. 515–524. doi: 10.1016/j.cell.2012.04.005.	*Two teams will divide and conquer the presentation and discussion of these articles. Study Questions will be provided.*
	12/4/18	What is adaptive developmental plasticity?	• Nettle, D., and Bateson, M. (2015). Adaptive developmental plasticity: what is it, how can we recognize it and when can it evolve? Proc. R. Soc. B *282*, 20151005.	*Please have five questions about (or spurred by) this reading* ready *for group discussion in writing at the beginning of class, and be prepared to discuss any part, at least in terms of questions.*

Week	Date	Topic	Readings	Instructions
Week 15	12/6/18	How does cooperation emerge in collectives?	• Du, Q., Kawabe, Y., Schilde, C., Chen, Z.-H., and Schaap, P. (2015). The Evolution of Aggregative Multicellularity and Cell-Cell Communication in the Dictyostelia. J. Mol. Biol. *427*, 3722–3733. • Chandra, V., Fetter-Pruneda, I., Oxley, P.R., Ritger, A.L., McKenzie, S.K., Libbrecht, R., and Kronauer, D.J.C. (2018). Social regulation of insulin signaling and the evolution of eusociality in ants. Science *361*, 398–402.	*Study questions will be provided for the reading. Please have five questions about (or spurred by) this reading* ready *for group discussion in writing at the beginning of class, and be prepared to discuss any part, at least in terms of questions.*
Final Exam	12/13/18	Proposal Presentations 8:00 a.m. – 11:00am CLSSRM 262		

<u>Program Learning Objectives (PLOs) for QSB:</u>

1. Knowledge and understanding of **quantitative** (statistical, computational, and model- dependent) and high-throughput experimental **systems** approaches to biological problems, and demonstrated ability to conceive, plan, execute and/or interpret the applications of these approaches to research questions.
2. Knowledge and understanding of **ethical standards** in proposing and executing professional scientific research.
3. Ability to effectively assist in the **teaching** of science in a classroom environment, and engage in effective **communication** of original and existing scientific inquiry and results orally and in writing.
4. Ability to undertake and demonstrate original graduate-level **scholarship** in specialized areas of biology, including integrative command of historical and current literature and broader scientific context, and identification of open research problems.
5. Ability to propose and defend a feasible **research plan** to apply scientific techniques to open research problems and execute, complete and defend original **research** that advances scientific knowledge.

<u>Course Learning Objectives and connection to PLOs:</u>

1. Knowledge and understanding of **systems biological approaches** — both conceptual and experimental — used to analyze and integrate biological systems of all kinds, and the ability to apply these to research problems (PLO 1).
2. To gain practice in rapid critical review and understanding of diverse biological systems — from macromolecules to ecosystems — including current research questions, from the unifying perspective systems and quantitative approaches (PLO 1 and 4).
3. To engage in in-depth scholarship, interpretation and synthesis of key concepts, techniques, approaches, vocabulary and literature across disciplines — including the systems biology literature — and to practice communicating these across interdisciplinary boundaries in the form of oral presentations and written reviews (as appropriate for grants and paper introductions — PLOs 3 and 4).

4. To apply systems and synthetic biology approaches to research problems in the form of a white paper research proposal (PLOs 1 and 5).

Grading Rubric for Assessments

Clarity (25%):

1. Unambiguousness and specificity of questions and answers.
2. Background provided, not assumed, on more obscure topics and references.
3. Lay definitions provided without jargon.

Significance (30%):

1. Questions and answers are framed as generally as possible
2. Questions and answers reach to the essential and deepest aspects of the work
3. Questions and answers are taken up by the group and stimulate further discussion

Creativity (25%):

1. Identification of new approaches, new papers and resources to bridge gaps and resolve questions, drawing on concepts and knowledge covered in the course.
2. Identification of future directions and implications
3. Critical assessment of feasibility and applicability of newly discovered approaches and resources to problems and questions and of future directions and implications.

Formatting and aesthetics of written work and oral presentations (20%):

1. Appropriate academic writing and presentation style (avoiding passive voice, correct use of tense)
2. Correct grammar and language
3. No typographical errors (use spell-check)
4. Appropriate formatting of content
5. Appropriate formatting of references and citations

Grading: The minimum average grade to maintain good standing for graduate courses at UCM is a "B," while a B– is the minimum passing grade. A suggested grade category breakdown is provided below with points and percentage left blank to be decided by instructors for specific courses.

	Points	**Percent of Course Grade**
Written Discussion Questions	30	30
In-class Discussion Participation	20	20
Computer Exercise Write-ups	10	10
Oral Presentations	20	20
Final Written Report	20	20
Total	**100**	**100**

The final distribution of grades in QSB 290 will depend on the overall achievement of the students in the course, but the following grades will be *guaranteed* to students achieving the indicated percentage of the total possible points in the course, listed in the chart below:

A+ 96 – 100	B+ 85 – 87.9	F 0 – 77.9
A 92 – 95.9	B 82 – 84.9	
A– 88 – 91.9	B– 78 – 81.9	

Information on grade appeals, incompletes, etc. is available from the Registrar.

Disability Services: UC Merced is committed to make our courses accessible to all students, including students with limited mobility, impaired hearing or vision, and learning disabilities. Students with special needs should contact Disability Services early in the semester so that arrangements can be made.

Cheating or Plagiarizing: We will follow the *UCM Academic Honesty, found here:* http://studentlife.ucmerced.edu/files/page/documents/academic_honesty_policy.pdf
Those who violate campus rules regarding academic misconduct are subject to disciplinary sanctions, including loss of standing in the graduate program and disqualification.

Disclaimer: This syllabus is subject to change. Any changes to syllabus will be announced in lecture.