Evolutionary Systems Biology Modeling Introduction

3 Credit Course

Genetics 546 | 410B Wendt Commons | Fall 2018

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Office Hours
Tue 5:15pm-6:00pm
(or by appointment)

Course Times
Lecture: Tue 4:00pm-5:15pm
Lab: Thr 4:00pm-6:00pm

Cross-Listing
Genetics 546
Medical Genetics 546

Course website: https://evosysbio-course.discovery.wisc.edu/
Mailing List: genetics546-f17@lists.wisc.edu (only for EvoSysBio Students)

Goal: Teach you how to *build* your own model of a small part of biology by adopting a system's view for defining boundaries around your model, *implement* it by specifying all its parts and their actions in Evolvix (a modeling language made for simulating biological changes over time), and *analyze* it by using an EvoSysBio perspective.

Overview and Purpose

Models are the maps of modern biology. Here you will learn to read and create some of them. This course is about the bigger picture. We will build models to make connections that traverse the scale of organic life. Your interest and creativity will define the modeling possibilities, which may range from *molecules in cells* to *individuals in ecosystems* to *long-term evolution* itself.

You name it. You model it. You map it.

Evolutionary systems biology operates at the cutting edge of computational modeling, and building your own map of a small part of biology will develop your science skills like little else. By the end of the course, you will have learned much about handling certainties and uncertainties in modeling very diverse dynamic systems. Modeling skills are broadly transferable across scientific disciplines.

Official Course Description

All *Biological* organisms are *Systems* that *Evolve* in their *Biological* contexts. EvoSysBio explores this bigger picture. How do intra-organismal and trans-organismal processes interact during evolution? Accurate answers require collaborations between diverse disciplines for building robust model-ensembles, from biochemistry to ecology. Investigating biological systems of their choice, students are gently introduced to aspects of quantitative modeling, biosystems curation, and biodata science, while learning the Evolvix modeling language for running simulations to support a collaborative grant proposal presented at the end. Students actively learn to **(i)** link models to observable data they curate, **(ii)** make computational predictions and quantify their uncertainty, **(iii)** define and limit the scope of models using critical thinking, causal analysis, and independent research skills, and **(iv)** communicate across disciplinary boundaries. This course is open to all aiming to grow their modeling skills at any level. All modeling problems can be simplified, or rendered unsolvable by poor boundary choices. Thus, students from different disciplines can customize their learning. The course website is at: http://evosysbio-course.discovery.wisc.edu/

More Details in Overview

This course has no formal entry requirements, since the only technical requirement ("ability to run a CTMC model to predict time series") is rendered trivial by the Evolvix modeling language that is used in the course. It allows students to focus on problems and skills beyond low-level simulation mechanics. These 'soft skills' like drawing model boundaries or how to organize model variants are rarely taught and often require years of learning by experience. For illustration consider this car analogy: Cars (or models) can be driven (or investigated) responsibly without knowing much about engines (or stochastic and deterministic CTMC simulators that predict time series); conversely, understanding engines does not guarantee responsible driving (or meaningful model predictions, respectively). This course develops aspects of common sense in modeling, as essential for students across disciplines. This is enabled by the built-in simulation tools of Evolvix, which simplify the mechanics of transforming some key types of biological models into computable simulations. *Minimizing coding complexity frees minds for the challenges of understanding a biological system.*

Students can bring a system of their choice for modeling to this course and can develop their leadership skills by organizing its exploration. To others a system is given in a biological area of their interest. This course celebrates the diversity of different disciplines and student levels of expertise. Ideal for undergraduate and graduate students with high curiosity aiming to broaden their horizon by a fresh take on modeling. Students submitting NSF Graduate Research Fellowship proposals are encouraged to improve their proposals as part of this course.
The central role of evolutionary and population genetics in biology

Topics: A 10-slide introduction to EvoSysBio is at:
https://figshare.com/articles/EvoSysBio_in_10_Slides/1427128

Learning Outcomes

- Enhance problem-solving skills in a problem-based active learning environment
- Developing the skill to ask questions and to find an interesting research topic
- Learn how to communicate across disciplines in interdisciplinary student groups
- Learn to use *Evolvix* to describe biological models with mathematical accuracy
- Collaborate across diverse levels of experience and background and learning how to ask for and receive individual help from an expert in biological modeling

Undergraduate Students	Graduate Students
• Model a biological system and make some predictions by simulating it	• Model a bio system of choice, describe what it can predict and what it cannot by exploring its strength and weaknesses
• Learn how to explain findings to peers by writing for your ReLog in ≥5 weeks a ≥300 words and 2 ReLog peer reviews	• Hone writing skills by explaining your science in ≥7 weeks to peers in ReLogs targeting different levels (≥500 words and 2 ReLog peer reviews / week)
• Learn how to ask for and receive individual help when stuck in modeling	• Learn how to leverage an expert's experience for narrowing biologically credible intervals for unknown values
• Improve writing skills for research grant proposals by aiming to produce a well-integrated text with ≥3000 words.	• Improve writing skills for research grant proposals by producing ≥5000 words of high-quality scientific text; else submit an NSF graduate research fellowship
• Active, problem-based learning by approximately solving a small modeling problem	• Active learning by solving a slightly bigger modeling problem at a higher accuracy

Take this course if you like …

- to learn in a problem-based way by actively solving problems to which no answer is known
- to connect to new disciplines and learn how their language captures how they see things
- to get a taste of real-world research without having to redirect your career
- to think about deep connections between disparate topics as seen by few
- to hone writing abilities in order to become more skilled as a writer
(some say, it takes about 10,000 hours of practice to become really good at something, so you might as well get started in this course that emphasizes scientific writing)
- to learn a tool that helps you in modeling Continuous Time Markov Chains (CTMCs)
- to take first steps into a new field in relative privacy (taking this course is much a safer and easier way to dip toes into the vast ocean of scientific reality – compared to starting a PhD).

Do not take this course if you …

- prefer memorizing facts over learning how to ask questions and search for answers
- are uncomfortable with "the unknown" and prefer to keep it that way
- expect the instructor to always know the answer
- dislike peer reviewing and getting peer reviewed

Relationship to other courses at UW-Madison

This course does not duplicate content of any other course. It offers a starting point for exploring the fascinating world of modeling in biology at a pace that is manageable for typical 'non-computing' biology students. Adopting a 'systems' perspective from engineering, students will learn how to draw reasonable modeling boundaries around their systems and how to explore how various parts interact with each other. Students in mathematics, statistics, computer science, or engineering can learn use this course to (i) learn about and model some aspects of biology, (ii) how to collaborate with biologists, and/or (iii) identify challenging problems from their respective disciplines, which the instructor has been collecting. These problems can range from 'good challenging homework' to 'beyond the current horizon of research in the field'. Students who know what they are doing are welcome to explore these as part of their research in the course, but should not expect worked out solutions for every problem that presents itself. This course engages with problem-based learning and we use real or realistic research problems, just as in real life, where problems also do not carry a label indicating their difficulty and do not come with a guarantee that they can be solved in a reasonable way. Typical non-biological problems that are hard and reoccur in this course include aspects of concurrency, combinatorics, probability, modeling formalisms, syntax design, semantics, naming, network theory, multi-dimensional spaces, optimization, simulation, calculus, logic, or many other mathematical, statistical, computational, and data science topics. These topics are not discussed for their own sake; they are referred to as necessary, while addressing some of the diverse challenges faced when building appropriate models for simulating biological systems.

Prerequisites and Required Materials

Prerequisites

An interest in interdisciplinary approaches to modeling in biology.

This is the central prerequisite for the course! Otherwise, enrollment is open. All undergraduate and graduate students are welcome from any field related to Biology, Medicine, Chemistry, Physics, Philosophy, Math, Stats, Computer Science, or Engineering.

Perhaps you are wondering why there are no prerequisites beyond being interested. How can one class accommodate such a wide range of students? Here are some reasons:

- EvoSysBio builds on knowledge from diverse disciplines, but everything required from them will be covered in the course. EvoSysBio (and many other fields) depends on your willingness to interact with and learn from researchers in other disciplines.
  You do not need to master all disciplines to benefit from them or this course!
- Quantitative modeling is integral to EvoSysBio. In the course we will explore a very powerful standard modeling approach (known as Continuous Time Markov Chains, or ‘CTMCs’), which is not only essential to EvoSysBio but also highly relevant to many disciplines. Centrally, students learn in this course how to turn the intuitive verbal models that often result from experimental work into computable models to predict time series which can be relevant in disciplines from biochemistry to ecology.
- The Evolvix[1] modeling language used in the course is designed to provide an *easy*, user-friendly entry point for such modeling. Students can use Evolvix without needing to understand the details of its inner working, just as we can drive cars responsibly without knowing how to build them. This course will teach students how to ‘drive’ a CTMC model implemented in Evolvix to help them understand some aspects of a biological system[2].
- Biodata science and data science are becoming increasingly important for investigating diverse questions and for improving links of theoretical models to observable data. Building well-defined and well-organized collections of relevant data sets is a large part of these new fields and also a transferable skill that can be improved in this course. As with writing skills, you will need some biodata science skills for the course, and you will learn some.
- You will use previously acquired disciplinary expertise to inform the precise modeling questions chosen for your group project and the ReLog entries, both of which are integral to this course. In short, these diverse disciplinary backgrounds will make the questions, writing, and discussions in this course more interesting and analytically rigorous!

The topics and skills learned in this course are highly relevant for understanding how many models are built in biology. The basics are not difficult to learn and are immensely valuable for exploring what it may mean to propose that a certain interaction exists.

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[1] Evolvix is a model description language that is being developed by Laurence Loewe in the Evolutionary Systems Biology Group at the Laboratory of Genetics and the Wisconsin Institute for Discovery, UW-Madison. It is being designed by the course instructor for providing a reliable, research-quality platform that makes it easy to describe biological models in mathematically accurate terms. Evolvix drives a number of innovative modeling applications that are currently under development in the Loewe Lab.

[2] This course does not focus on the math, statistics, and computer science required for simulation. Students with the quantitative and formal expertise are welcome to employ their skills by extending Evolvix in a way that better meets the needs of their group project. Non-bio students are expected to learn some basic biology, just as bio students are expected to learn some basics about formal models – everyone is expected to contribute expertise to our interdisciplinary dialogue.

Required Materials

- You will need a notebook computer in class each Thursday for model development.
- You will need a computer with an operating system capable of running Evolvix models:
    - Windows 7 or 10
    - Mac OSX 10.9 – 10.11
    - Linux (RedHat, Fedora, Ubuntu)
    - See http://evolvix.org for downloads and further details; if in doubt, ask instructor.
- You must be able to:
    - Run Evolvix models on your own (at home or in the library)
    - Exchange modeling data within your research group (emails or USB stick); this will be essential during Thursday labs and to take group progress home for your own modeling work
    - Post to the group website (you will receive login information in the course)

If you anticipate difficulty meeting these material requirements, you can work with another student and bring your data on a USB stick (or use some other work around).
Please ask the instructor about your arrangement to ensure that it will work, as details may vary.
You might also consider borrowing a computer from a campus library.

Course Website

We will rely heavily on the course website

https://evosysbio-course.discovery.wisc.edu

and thus some elements require explanation before you get full access.

Login: You can only access the full website by logging in. The instructor will provide you with two user names at the beginning of the semester: (1) the "KnownName" acknowledges your identity and you will use it to post ReLog entries; (2) the "ReviewerName" is anonymous and you will use it to peer review your colleagues' written work. After establishing your user names, you will need to create two, distinct passwords. Since this site houses sensitive content, maintaining web security is essential. **Please ensure that you use https, rather than http, in the web address, and be sure that your passwords are at least 12 characters long and include at least one number and one symbol.** It is often helpful to use "passphrases" instead of passwords. For guidance on effective password creation refer to:

https://evosysbio-course.discovery.wisc.edu/how-to/choose-good-passwords

Course Tab: This page is the gateway to a series of explanations and descriptions that are more details than was possible in this syllabus. Some relevant resources include: the instructor's teaching philosophy, the course's learning goals, information on grading, expectations, and deadlines, and instructions for how to complete various course assignments. **Be sure to read and sign the Entry Agreement, which is a condition of enrollment.**

Timetable Tab: This page displays the course's progression, including deadlines.

How-To Tab: Refer to this page for assistance with the website, course assignments, and Evolvix.

Projects Tab: This is where you will develop your project proposal.

ReLogs and Feedback Tabs: These two pages are where you will develop your ReLogs and provide your peer reviews. Be sure to become acquainted with them early – much of your graded work will be developed on this page.

Evaluation and Grading

Evaluation

Evaluation in this course is intended to reflect research engagement, not memorization. What counts is the quality of:

(1) your weekly personal ReLogs, chronicling your work from the first steps into a new discipline, to an overview over a new topic, to technical progress in modeling details;
(2) your feedback to fellow students in your peer reviews of other ReLogs and proposals;
(3) your scientific, technical, literature, data, organizational, writing, editing, coordination, motivational, and other contributions to getting a high-quality group proposal done on time;
(4) your interactive participation in class and group discussions, where you think on your feet, identify problems, sketch solutions, admit errors, and ask questions *for the benefit of all*.

In your group project, you will contribute to writing and refining a research grant application by using your preliminary modeling results to propose and justify planned computational and/or experimental work to further investigate the hypotheses you described in your grant.

This course is designed to provide a taste of what is important in the life of researchers (who do not take exams and, therefore, neither do you). Instead, **your grades will be based on how well you continually engage in your research through the course's duration**.

Here are the weights associated with these activities that occur regularly throughout the course:

Undergrad. Students Evaluation Breakdown	% of Grade	**Task Description**
ReLog Entries	30%	Write (or re-write to improve substantially) an about 300 word long entry for your *ReLog* each week.
Peer Reviews	15%	Peer-review 2 *ReLog* entries each week using feedback forms
Group Project	40%	Collaborate to develop a draft and edit two revisions of a grant application delivered by the "group work" due dates given. The application's text should be in the range of 3,000-10,000 words. **Concise prose and clarity** should take precedence over length.
Participation	15%	As this course aims to foster research and collaboration beyond your disciplinary boundaries, an important part of the course is to be present at and contribute to both class and group discussions. Grades for your chosen role of group leader or group contributor carry equal weight and evaluate how you help to facilitate collegial, friendly, and efficient research group dynamics.

Graduate Students Evaluation Breakdown	% of Grade	**Task Description**
ReLog Entries	30%	Write (or re-write to improve substantially) an over 300 word long entry for your *ReLog* each week.
Peer Reviews	15%	Peer-review 2 *ReLog* entries each week using feedback forms
Group Project	40%	Collaborate to develop a draft and edit two revisions of a grant application delivered by the "group work" due dates given. The application's text should be in the range of 3,000-10,000 words. **Concise prose and clarity** should take precedence over length.
Participation	15%	As this course aims to foster research and collaboration beyond your disciplinary boundaries, an important part of the course is to be present at and contribute to both class and group discussions. Grades for your chosen role of group leader or group contributor carry equal weight and evaluate how you help to facilitate collegial, friendly, and efficient research group dynamics.

Evaluation of Participation in Class and Groups

To facilitate working beyond the boundaries of their various 'home-disciplines', this course encourages students to participate in interactive discussions that will require them to think outside of the boundaries of their own discipline. These discussions occur in the class as a whole, as well as in each individual group as students of the group work towards defining a cohesive systems model of the small part of biology they are interested in. Groups are encouraged to choose a Group Leader, all non-leader students in a group are by definition Group Contributors. Which of these roles is chosen by a student does not affect their grade, but it is evaluated, how well a student works *within the respective role* towards *facilitating the success of the whole group*. Thus:

- **If you lead**, do it well by creating an environment in which others can contribute better and do not need to worry about coordination and direction.
- **If you contribute**, focus your work on covering your area well and present **clear points of connection** for other projects. Then nobody in your group has to worry about details in your area and can efficiently use your results via the points of connection you specify. **Follow directions for coordination** from your Group Leader and clarify your tasks to improve overall group coordination.

Generally:

- **Graduate students** do not have to, but are encouraged to take a leadership role in their groups, especially if they can lead a cutting-edge project advancing their larger research goals. They can then leverage specialized background knowledge acquired in their labs to point others in their groups to interesting literature, research, and/or modeling questions.
- **Solo-projects are possible.** While not generally encouraged, these have proven useful for students who know exactly which question they want to investigate, even if no other students happen to be interested in that area.

Evaluations below are expressed as % of Participation Grade (= 10% of Overall Course Grade).

Ideal contributions in class and group reflect exceptional preparation where possible, and courageous creative smart thinking when engaging open problems. Ideas offered are substantive, provide key insights, and are presented in ways that other students can understand.
If ideas lack support, they fail in interesting ways or open up opportunities for discussing common misconceptions without judging them. Errors are corrected as soon as possible and subsequent contributions indicate corresponding adjustments in thought. There is no hesitation to question an instructor's presentation of the *status-quo* with appropriate evidence or ask for further clarification if that student's disciplinary training has not provided the background necessary for understanding a given idea. Comments are supportive and professional towards fellow students who benefit from some encouragement and help as they make their first steps towards building formal models.

Outstanding (90%-100%): Contributions as defined above are frequent and substantially add to the quality of the discussion in class and in groups.

Good Contributor (75%-90%): Contributions as defined above are regular and add to the quality of the discussion in class and in groups.

Adequate (60%-75%): Contributions as defined above are occasional or add little to the quality of the discussion in class and in groups.

Silent (40%-60%): Contributions as defined above are rare or absent or do not add to the quality of the discussion in class and in groups.

Disruptive (0% - 40%): Consistent unprofessional behavior like disrespecting contributions from students with different professional or personal backgrounds, discouraging others from learning or collaborating, unwilling to admit errors or insufficient evidence for their positions, and the like.

Group project topics

The group project is the core of this course, so choose it wisely in an area you are really interested in. If you already know your area of interest, inform the instructor as soon as possible. The aim is to help you to find a team of collaborators who share your interest. If you are unsure about your area of interest, you can always choose one of the available preselected topics or join a group led by someone who could use some help. Some project titles from previous groups:

> "*The Stag Hunt Game with Shirking: An Articulation, Analysis, and Application of a Model of Collective Action that Helps to Explain the Evolutionary Dynamics of Cooperation in Teams*"
>
> "*Modeling the Process of Switching-On Alcohol Dehydrogenase in the Human Liver*"
>
> "*Construction of a Colon Cancer Signaling Network*"
>
> "*Predicting harmful algal blooms*"

You will only have about two (2) weeks for your first pass at finding your group and your project topic, so **please start searching for your team and project options immediately**. Decisions on group composition and rough research area will need to be near final by the end of **Week 3** and are as good as locked in with the brief presentation made by you and your group at the end of **Week 4**. Bigger changes after that date need separate instructor consent, aiming to ensure that you have enough time to find and read relevant studies, build a model and analyze some simulation results before writing your part of your grant proposal. **Note that the first week can be extremely short.**

Writing help

Everything you write for this course will appear in the shared Google Drive, and these entries will be the basis for your grades. Keep in mind that your texts are only visible to others in the course. Consider taking your drafts to UW's Writing Center, where trained professionals offer free editorial services:

The Writing Center, phone (608) 263-2992, http://www.writing.wisc.edu/

With your colleagues, you will exchange peer reviews that assess the quality of written work while providing **constructive** criticism. While these assessments are part of the learning experience (both for you and the reviewers), they are not your grades and only reflect how your fellow researchers see your work. **The instructor may or may not agree, and will grade your work independently.**

Grading

Your **final course grade** will be based on the instructor's assessment of your overall performance as a researcher in your role of author, collaborator, and reviewer. Your major and previous expertise will be taken into account when evaluating the quality of your work in your main area, as well as the effort you invest into connecting to other disciplines.

Letter grades are determined as follows, where '<' means "less than, excluding equal"**:**

Undergraduate Students		Graduate Students	
A	90% - 100%	A	90% - 100%
AB	85% - <90%	AB	85% - <90%
B	75% - <85%	B	75% - <85%
BC	70% - <75%	BC	70% - <75%
C	60% - <70%	C	60% - <70%
D	50% - <60%	D	50% - <60%
F	<50%	F	<50%

If you have questions, please ask the instructor.

Attention Graduate Students

Graduate students (particularly PhD students) will be held to **higher standards**. Both your quality of work and reading loads will be greater than those of your undergraduate peers.

Extra essay on crossing disciplinary boundaries. Graduate students are required to write a ca 2000-word essay, due before the last meeting of the course. In your essay, you describe your personal observations about engaging one or more other disciplines in your research environment. Assess everything you perceive as challenge and/or strengths of research that requires more than one discipline and experiences that helped you to communicate across disciplines. At the end use your observations and your creativity to recommend strategies for overcoming challenges you have seen in your graduate research and beyond. Draw on observations in and outside of the course.

Diversity and your blind spot

Diversity is a source of strength, creativity, and innovation. While true of research in general, this is particularly true of this trans-disciplinary course. Often other disciplines than one's own have an unfamiliar culture that can be difficult to understand at first (you need to 'move' intellectually). However, once you have moved a new perspective becomes available. This perspective often helps to understand others and can hold the key to surprisingly innovative solutions to problems that might otherwise seem impossible to solve. Many have found repeatedly, that the cost of exploring new perspectives is small compared to the rewards for those who engage in this process. After some initial confusion, a new point of view opens up and it brings one of the most valuable gifts: a glimpse of what would otherwise remain well-hidden at your blind spot.

This observation can be made about various scientific disciplinary cultures, as well as other types of human cultures and perspectives, whether related to ethnic, religious, life-style, status, gender, various orientations or other.

In this class, we value the contributions of each student and respect the profound ways in which this course and the university are enriched by every student's unique identity, culture, background, experience, status, abilities, and opinion. This course is committed to integrating the diversity of its students into excellent opportunities for learning, teaching, research-project initiation, training in mental agility and outstanding communication skills.

We welcome your point of view as an important perspective on how you model the world. We strive to integrate your perspective with those of other students and relevant scientific evidence as we seek to best serve the various challenging needs of our time.

For more on the many facets of diversity see: https://stemdiversity.wisc.edu

Students with disabilities

Students that require learning support or have disabilities should contact the instructor as early as possible to explore options for reasonable accommodations. For more information regarding reasonable accommodations see: https://mcburney.wisc.edu

NSF Synergy

Students who plan to apply to the prestigious NSF Graduate Research Fellowship Program should alert the instructor early on to explore ways to integrate their research agenda in this course with their goals for the fellowship application. Doing so will take some experimenting, but students taking this course may benefit from discussions with an instructor who has some experience with NSF.

NSF Deadlines are usually in the 2nd half of October this year and depend on the discipline:

https://www.nsfgrfp.org/applicants/important_dates

NSF considers also applications from senior undergraduates. All eligible students are encouraged to consider applying and telling the instructor about such plans as early as possible to provide as much time as possible for planning how to best support a particular application.

EvoSysBio Reading Overview

Students will read a number of articles relevant to their project. **Graduate students are expected to complete a larger and/or more complex reading load than undergraduates**, reflecting their greater expertise. An important goal of the course is for students to broaden their horizon beyond areas they are already familiar with. Thus, different students modeling different systems will require different reading materials for optimally nurturing this process. Students are expected to find research papers to read on their own and can always ask the instructor for additional reading suggestions if they are looking for something specific that they cannot find. The instructor will usually find out quickly, if students are engaging with research in areas that are new to them, or whether they are simply rehashing what they already know.

The quality of work of a student and the broadening of her trans-disciplinary horizon will hinge on an earnest engagement with the scientific literature from disciplines beyond a student's horizon. Students should not mistake the freedom to read the papers they need to read for advancing their models towards the end of the course for a license to avoid difficulties posed by the unknown. They will need all the time they can get to revise their models for producing the preliminary simulation results they need to include for writing a competitive grant application before the deadline.

There is no required book, but it can be helpful to use one the recent systems biology textbooks for navigating some aspects of this course with greater ease. To explore a useful mix of topics in systems biology you may want to consider:

> *Klipp, E., et al. (2009)* ***Systems Biology: A Textbook.*** *Wiley-Blackwell-VCH.*

For a high-level overview, core definitions, and various links between disciplines that are important for EvoSysBio, this open access paper will help you to get the big picture:

> Loewe L (2016) "**Systems in Evolutionary Systems Biology**", pp. 297-318, vol. **4**, in *Encyclopedia of Evolutionary Biology*, Kliman RM (ed.), Oxford, UK, Academic Press.
> URL: http://evolutionarysystemsbiology.org/ref/Loewe-2016F-frame-EvoSysBio-Def.pdf

This paper will help you to link your own modeling work to the broader questions investigated in this course. A brief 10-slide introductory starter is here:

> URL: https://figshare.com/articles/EvoSysBio_in_10_Slides/1427128

Some shared basic expertise will need to be acquired as facilitated by the following reading plan, which details reading for all students and then additional work for graduate students or undergraduate students who know that they want to lead a group modeling a particular system.

Weekly Reading Material

Week 1:
All students: Read this syllabus, everything on the course website and the following overview:

> Loewe (2015) "**EvoSysBio in 10 Slides**" on *Figshare*
> URL: https://figshare.com/articles/EvoSysBio_in_10_Slides/1427128

Grad students: Immediately start your search for a system that you want to model if you do not have one already. Find a corresponding review article or related modeling study and read it with a view to determine if this would be a potential candidate for modeling. Make a list of all the parts in the system and of the actions they engage to the best of your knowledge. Ask instructor if this appears complicated for your model or you have difficulties finding a system of interest.

Week 2:
All students: Read the following research review and framework definition paper.

> Loewe L (2016) "**Systems in Evolutionary Systems Biology**", pp. 297-318, vol. **4**, in *Encyclopedia of Evolutionary Biology*, Kliman RM (ed.), Oxford, UK, Academic Press.
> URL: http://evolutionarysystemsbiology.org/ref/Loewe-2016F-frame-EvoSysBio-Def.pdf

Grad students: Same as week 1, only pick the next most interesting paper you can find about your system of interest. If you have not settled, pick another credible candidate system for modeling and find references. Start to write about this in your ReLogs as early as possible.

Consider, how others might contribute to developing this idea into a research grant proposal if working in a group. Settle on an interesting system as fast as reasonable, but not faster. Continue this exploratory phase in the next few weeks as needed and ask the instructor if you get stuck.

Week 3:
All students: Read the introduction to the POST system, which describes how project related data in this course is expected to be organized whenever possible. Modeling time is very limited, so it is essential to minimize unnecessary loss of time from negotiating a system for how to store research materials (or search for them in absence of a previously agreed system). The importance of shared well-organized storage increases quickly with project size and numbers of participants.

> Loewe L (2017) "**Introducing Project Organization Stabilizing Tool (POST) system ReviewedRelease v1 for evolving order and stability from innovation in chaotic environments**", see http://evolvix.org/post or pages 49-74 in Supplemental Material of **'Evolvix BEST Names for semantic reproducibility across code2brain interfaces'**. *Annal. New York Acad. Sci.* **1387**:124-144. URL: http://dx.doi.org/10.1111/nyas.13192

Grad students: See last week; continue to develop tasks for a team; ask instructor if you get stuck.

Week 4:
All students: Read the main text of the BEST Names paper referenced above and reflect in a ReLog on naming strategies and practices you are aware of. Build awareness of naming problems in preparation for naming the parts and actions in the models that are about to be built.
Grad students: See last week; continue to develop tasks for a team; ask instructor if you get stuck.

Week 5:
All students: Read the following research review on stochastic simulations:

> Gillespie, D.T. 2007. Stochastic simulation of chemical kinetics. *Annual Review of Physical Chemistry*. **58**: 35-55.

Grad students: Read in addition one of the following research reviews on stochastic simulations:

> Gillespie, D.T. 2008. Simulation Methods in Systems Biology. *Formal Methods for Computational Systems Biology*. **5016**: 125-167; (for students in math, computing, etc.)
> Gillespie, D.T., A. Hellander & L.R. Petzold. 2013. Perspective: Stochastic algorithms for chemical kinetics. *Journal of Chemical Physics*. **138**: 170901; (for students in bio, etc.)

Week 6:
All students: Read the following population genetics research on how to estimate very small changes in fitness by comparing DNA sequences sampled from two species:

> Loewe, L. & B. Charlesworth. 2006. **Inferring the distribution of mutational effects on fitness in Drosophila**. *Biology Letters* **2**: 426-430.

If previous years are any indication, by now groups will likely have formed and each will know its Group Leader (if there is one). Groups will also roughly know what they plan to model and each Group Contributor will have found some general perspective from which they can contribute.
Ask the instructor in case of problems or if you are uneasy with any of the arrangements made.

If you lead a group, your main task will be to keep the big picture together and maintain an overview of progress by identifying the most critical tasks for proposal development. You will find, integrate, and prioritize questions to research, papers to process, parameters to estimate, models to build, results to analyze, and proposal sections to be written. You will also integrate and manage all such input from Group Contributors to keep the group's focus on the most promising ideas. From this vantage point you suggest ReLog topics you consider worth exploring by other Group Contributors. You write these ideas up in your own ReLog and explain why they are important a week before Group Contributors are expected to consider them *as suggestions* for investigating related details in their ReLogs (they are *not* obliged to follow your suggestions).
Overall, it is your job to keep the group as productive as possible in order to prepare a great collection of ReLogs to draw on for writing the proposal. Thus, your group's proposal can improve by adopting details from ReLogs that already collected key references, parameter combinations, model prototypes, plots, and more - long before the first proposal draft is due. As Group Leader, you will maintain the overview of proposal writing and integration; you specify data formats in which others in the group are to prepare their contributions to simplify final integration. Unless arranged

otherwise in your group, you will also be responsible for writing the general parts of the proposal, such as overviews, introduction, background, previous work, broader relevance, and more, which provide the frame for the specific aims of the proposal (most or all of which will be delivered by other Group Contributors).

If you do not lead a group, then help your Group Leader with preselecting and prioritizing sensible research questions. As a Group Contributor, you are generally asked to consider investigating papers or questions suggested by your Group Leader, but you are not obliged to follow them if you experience technical difficulties, the task is too difficult, or you have found material that you deem more interesting and relevant for the group proposal. It is your task to let your Group Leader know about your interest and to help them to suggest tasks that are better suited for you.

Grad students: Whether you lead groups or not, you are expected to contribute more to proposals than undergraduates by leveraging your disciplinary background and research outside of class. If you agreed to be in groups led by undergraduate students, please encourage and support them in ways that benefit them and help them to learn at their respective stage. The evaluation of your contribution to the group project will be based on the research aim(s) *you* wrote, not on their texts.

Week 7:
All students: Read this investigation of how a small change in mathematical notation greatly complicated the interpretation of central concepts in ecology and evolution:

> Mallet, J. 2012 **The struggle for existence: how the notion of carrying capacity, K, obscures the links between demography, Darwinian evolution, and speciation**. *Evol. Ecol. Re*s., **14**, 627-665.

UG + Grad students: contribute to group projects (see above). *Ask instructor in case of problems.*

Week 8:
All students: Read the following EvoSysBio review and identify causes for fitness changes:

> Loewe, L. 2009. **A framework for evolutionary systems biology**. *BMC Systems Biology*. **3**: 27.
> Loewe, L. & J. Hillston. 2008. **The distribution of mutational effects on fitness in a simple circadian clock**. *Lecture Notes in Bioinformatics*. **5307**: 156-175.

UG + Grad students: contribute to group projects (see above). *Ask instructor in case of problems.*

Week 9:
All students: Read the following population genetics review and classify the fate of mutations:

> Loewe, L. & W.G. Hill. 2010. **The population genetics of mutations: good, bad and indifferent** *Phil Trans R Soc Lond B Biol Sci*. **365**: 1149-1294.

UG + Grad students: contribute to group projects (see above). *Ask instructor in case of problems.*

Week 10:
All students: For the rest of the course, gradually work through this substantial study in biodata science and draw from it ideas on how to deal with uncertainty in biological models that you build.

> Scheuer, K.S., B. Hanlon, *et al.* (2017) **FlyClockbase: Importance of BioSystems Curation for Analyzing Variability in the Circadian Clock of *Drosophila melanogaster* by Integrating Time Series from 25 Years of Research.** Freely available on *BioRxiv* URL: *BioRxiv.org*. https://doi.org/10.1101/099192

UG + Grad students: contribute to group projects (see above). *Ask instructor in case of problems.*

Week 11 – 15:
All students: Continue to read the FlyClockbase paper to learn about the challenges in biodata science that arise while building reliable models for systems beyond a certain level of complexity.
UG + Grad students: contribute to group projects (see above). *Ask instructor in case of problems.*

Fall 2018 Timetable Overview

The **"Group Work" column** specifies key events in developing your research grant application. You need to gather enough background references and preliminary simulation results to show you propose something that is new and doable. This roadmap helps you to front-load, which will likely help improve your final proposal. **Leverage your ReLogs (ResearchLogs) for your proposal.**

Deadlines are TBD, see course website. The final grant application deadline will be strict.

Week Day	Date	Topic	Group Work
1 Thur	Lect 9/6	**Course overview. Why EvoSysBio?** Why transcend disciplines? Why problem-based learning? Why is modeling important for biology?	Meet fellow students.
1 Thur	Lab 9/6	Explaining your ReLogs (peer-reviewed ResearchLogs) and group proposals. Bring your laptops each Thursday! Discussion of potential group projects starts early.	**Start to form your research group** *Many…*
2 **Tue**	Lect 9/11	**Intro to abstract populations, individuals, and actions:** from molecules in cells to organisms in ecosystems. *Reflect on the work of linking abstract math and messy biological reality by understandable names and InfoBlocks*	ReLog: explore topics for the group project; write about potential research questions.
2 Thur	Lab 9/13	Put your first ReLog on the course website. Install and run the Evolvix demo model on your laptop. In all labs: **Re-run and explore models from lectures as needed.**	**Form your research group; find topics** *…small steps…*
3 **Tue**	Lect 9/18	**Simple growing populations of bacteria** in Evolvix as 'zerodice' (deterministic) or 'manydice' (stochastic) models *Reflection on the roles of chance and necessity*.	ReLog: explore topics relevant for your group proposal
3	Lab 9/20	**All Labs: bring your computer; sit with your group.** Work on your model(s) for group project, alone or in group; ask other students or instructor for help as needed. Explain your project idea and where you need help.	**Decide to use your own or a default topic for the project?** *…very slowly…*
4 **Tue**	Lect 9/25	**Decaying population of radioactive material** recorded in Evolvix as a time series until amounts vanish. *Reflection on work with analytic and simulation models.*	**Finalize group.** ReLog on your part in the project.
4	Lab 9/27	Lab: Continue working on group project. **Today:** Groups present 2-3 min overview; adjust scope as needed after brief discussion in class.	**Present group area,** topics, rough plans. *…building on…*
5 **Tue**	Lect 10/2	**Birth, death, and extinction in cancer cell populations,** recorded by Evolvix as time series in a given time window. *Reflect on randomness and mean expectation in cancer.*	ReLog on your role in project. **Group submit title and work plan.**
5	10/4	Lab: Continue working on group project.	**Group research start!** *…top of each…*
6 **Tue**	Lect 10/9	**Reaction chains, waiting time & biopolymer synthesis,** recorded by Evolvix as time series of selected parts only. *Reflection on waiting, big data, and questions in models.*	ReLog on a question for your group's grant proposal
6	10/11	Lab: Continue working on group project.	*… other can …*
7 **Tue**	Lect 10/16	**How resource restrictions limit population sizes** in natural systems; on the unity of ecology and evolution and how to model the dynamics of natural populations over time in Evolvix by adapting the 'places model'. *Reflections on dynamic changes, differential equations and the secret language of mathematics*	ReLog on a question for your group's grant proposal
7	10/18	Lab: Continue working on group project.	*… result in …*

Week Day	Date	Topic	Group work
8 **Tue**	Lect 10/23	**How flux can stabilize populations of metabolites,** recorded in Evolvix as phase diagrams of amounts. *Reflections on dynamics, stationary flux-balance and Occam's razor.*	ReLog on a question for your group's grant proposal
8	10/25	Lab: Continue working on group project.	*... incremental ...*
9 **Tue**	Lect 10/30	**Oscillations in cell-virus, host-pathogen, predator-prey** simple systems, recorded in Evolvix as phase diagrams of fluxes, or other time series. *Reflection on the meaning of attraction and chaos in non-linear dynamics.*	ReLog on a question for your group's grant proposal
9	11/1	Lab: Continue working on group project.	*... progress ...*
10 **Tue**	Lect 11/6	**Stimulating and limiting kinetics of Michaelis & Menten** in degrading Alcohol, recorded in Evolvix as time series with varying precision. *Reflections on the differences between counts and concentrations.*	**Submit the first draft of your group's grant proposal**
10	11/8	Lab: Continue working on group project.	*... that taken ...*
11 **Tue**	Lect 11/13	**Molecular switches, Hill kinetics, and gene regulation,** recording the speed of a switch in Evolvix using time series. *Reflections on reversibility and irreversibility in biochemistry and ecology.*	**Submit the first draft of your group's grant proposal**
11	11/15	Lab: Continue working on group project.	*... together can be...*
12 **Tue**	Lect 11/20	**Summary of Continuous Time Markov Chain** (CTMC) basics as used above, reviewing Evolvix syntax for easy CTMC modeling and clear mapping to math methods. *Reflection on danger analyzing models with only a single method.*	ReLog on a question from your group work
12	11/22	Thanksgiving Break: No Lab	*... quite impressive!*
13 **Tue**	Lect 11/27	**Using CTMCs in diverse areas of biology,** including biochemistry, cell biology, physiology, epidemiology, life-history, ecology, population genetics, and phylogeny. **Directing experiments using sloppy CTMC models** despite unknown parameters with the help of ensemble approaches such as sensitivity analyses or Approximate Bayesian Computation. *Reflection on the semantics of 'nothing', 'unknown' and 'verified' in biology and math.*	ReLog on a question from your group work
13	11/29	Lab: Finalize group project.	Last bits of group work
		Deadline to be agreed upon early on.	**Submit Grant Now!**
14 **Tue**	*Talks* 12/4	**Student presentations of group projects. Discussion.**	
14 **Thur**	*Talks* 12/6	**Student presentations of group projects. Discussion.**	Submit essay on crossing disciplines
15 **Tue**	*Disc.* 12/11	**Bringing it all together**. Using fitness landscapes, CTMC models, and EvoSysBio to predict aspects of evolution. *Reflections on research, computing, reproducibility, and ways of expressing meaning in future biology.* **Debriefing from your research experience. Feedback on the course. Open Discussion.**	
		No exam. Grades are determined from your ReLogs, grant proposal, reviews, participation and presentation.	