Preparing North Carolina for a New Era in Biology :
A Program for Undergraduate Training in Quantitative Biology at UNC

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Summary

The mission of our University is to educate our students in preparation for the challenges and demands of future careers and intellectual pursuits, both in our home state and around the world. Many of our undergraduates choose to be educated in the field of biology due to exciting advances in the treatment of human disease, leaps in our understanding of basic biological processes, and a desire to improve the lives of others through a career in medicine, ecology, or the environment. Biology is consistently among the top three majors chosen by our students, with over 800 juniors and seniors currently enrolled as Biology majors. As we move into the 21st century, substantial training in mathematics, statistics, and computer science will be required to meet modern challenges in the biological sciences. We propose a new track within the Biology department at UNC in Quantitative Biology (hereafter Qbio) to provide our students with these skills. To support further development of Qbio at UNC, we propose a directed faculty recruitment in Biology of 8 total new faculty, several of whom we suggest should be jointly hired with the Carolina Center for Genome Sciences.

Motivation

Biology is undergoing a rapid change from a qualitative field to one in which quantitative approaches play a critical role. Contributions to biological research from computer science, mathematics and statistics are now integral not only to traditionally model-intensive subfields (e.g. evolutionary and population biology) but also to an increasing number of investigations at the molecular and cellular levels.

Over the past 15 years, progress in genetics, structural biology, biophysics and computational modeling have led to an enormous shift in how scientists approach biological problems from scales of nanometers to kilometers. At one end of this spectrum, the shift has been accelerated by the emergence of whole-genome DNA sequences of hundreds of microbial isolates and hundreds of multicellular organisms, including humans. The vast amount of information and complexity inherent in each genome, in the proteins each genome encodes, and in the cells and organisms each genome specifies, has driven advances in technology that allow the storage and manipulation of increasingly precise and comprehensive data sets. At the opposite end of the scale spectrum, time resolved remote sensing technologies across many environments, and the application of genomics tools to entire communities of organisms in diverse environments, has driven a similar expansion of quantitative applications in metagenomics (NRC, 2007). Data thus generated has spawned new research areas that are almost exclusively quantitative in nature (e.g. systems biology). The accumulation of data has been paralleled by a tremendous growth in computing power, which has opened the door to whole new classes of computationally-intensive methods that would not have been possible a decade ago. In addition to these technological advances, there is a growing awareness that mathematical models can provide general insights into the behavior of a wide variety of biological phenomena. Predictions from these models are increasingly being tested in the laboratory and the field. In sum, increased quantitative skills are mandated across the biological sciences.

It is important to stress that this is not an ephemeral trend. A real change has occurred, one that has moved out of the laboratory and into society. For example, modern quantitative approaches involving complex computer simulations and specialized statistics that handle huge arrays of data are having a practical impact on policy decisions concerning climate and the environment, and are influencing how doctors treat their patients in the clinic. Our academic mission obligates the Biology department to respond to this shift in a way that provides our undergraduates with the educational opportunities available at several of our peer institutions (see below). The Qbio track in Biology will provide those opportunities and establish a foundation for a future comprehensive quantitative biology program.

Clear recognition of a need to incorporate the curricular changes noted above has been addressed in the scientific and education literature over the past ten years. There is growing recognition that future researchers in biology must be prepared with more rigorous mathematical and computational training than most now receive (NRC, 2003; Bialek and Botstein, 2004). The problem is not the lack of talented students, but rather in the lack of an integrated inter-disciplinary approach. One motivation of the Qbio track is to begin building bridges between the traditionally quantitative subjects, Math, Statistics, Computer Science and Physics, and Biology. Mathematics is the universal language of science, and the QBio track aims to integrate that language more deeply into the study of biology.

Many practitioners of Qbio were trained in fields other than biology, but all want to answer important questions in the biological sciences. As noted by the Burroughs-Wellcome Foundation, Qbio researchers utilize "…approaches including, but not limited to, physical measurement or manipulation of biological phenomena, computer simulation of complex processes in physiological systems, mathematical modeling of self-organizing behavior, building of probabilistic tools, developing novel imaging tools or biosensors, applying nanotechnology to manipulate cellular systems, predicting cellular responses to topological clues and mechanical forces, and developing a new conceptual understanding of the complexity of living organisms." Examples of publications that derive from the kinds of collaborations we anticipate to be born from this enterprise, and that cover the breadth of Biology at UNC, can be found at on the departmental server BIOARK:

\\BioArk.bio.unc.edu\FacultyShare\ in a folder titled Qbio LIT examples.

The Current Situation at UNC Chapel Hill

While UNC, particularly the Department of Biology and the Carolina Center for Genome Sciences (CCGS), have incorporated this scientific transformation into faculty hiring decisions and graduate education, our undergraduate curriculum has largely been left behind. The current undergraduate curriculum in Biology has not been substantially modified in almost 20 years. As one example, biology students are required to take Math 231, "Calculus of Functions of One Variable". This is the first course in a sequence of three classes that cover basic calculus. Topics covered in Math 231 are limits, derivatives and integrals of functions of one variable. The course is taught in the traditional style of definitions and proofs with very few real-world applications. In fact, exponentials and logarithms, both concepts underlying many biological processes, are not discussed in this class. In response to the increased appreciation for the emergence of Qbio, the UNC Math department has developed Math 241, introductory calculus that is geared toward biologists. The pilot section was successful and this course will be included as an option in the Qbio track. Similarly, Physics 405 (Biological Physics) explores biologically relevant questions from a physics perspective and is cross listed in Biology already. Yet realignment of the core courses from Chemistry, Physics, and indeed, Biology has not yet been deeply discussed across the College. We feel that the ultimate development of an integrated Qbio core will depend on the hiring of a cadre of faculty trained adequately to lead a revamping of core curricula, at least in Biology, and should be a medium term (3-5 years) goal of both this particular initiative and our departmental hiring process.

Future Development

We propose to develop a Q-bio track that will empower students with the tools to integrate mathematics, biology, physics and chemistry. The QBio track will not be a diluted path for biologists, rather a rigorous route for dedicated biology students. We expect that the track will evolve, over the first few years as we add faculty, make adjustments to new advances, and respond to student feedback. For example, while the Math 241 course mentioned above is a useful starts, one could envision a year-long course on mathematics and statistics for biologists that would probably be more appropriate. Such a class might integrate the two subjects in a coherent way, with all mathematical and statistical techniques motivated by applications to biology. This course would not just cover calculus, but also introduce the students to important aspects of linear algebra, difference and ordinary differential equations, and possibly some numerical methods. The class would have a computer laboratory, and would also prepare students to take upper level math classes if they become interested mathematical and computational biology.

In the long term, taking our department and University beyond our peer institutions will require fundamental shifts in the way education in biology is approached and organized. It will require cooperation between departments, particularly the departments of chemistry, physics, mathematics, computer science, statistics, and biology. Significant inroads have been made, as individual faculty across these departments are collaborative and are cognizant of the need for reform. Importantly, guiding, maintaining and further developing the QBio track will require strong leadership and vision. As detailed below, we feel this role would be most successfully filled by at least one senior faculty level hire that shares our vision and has the drive and intellectual credentials to reorganize the College’s academic efforts in this area.

Our Peers

While many of our peer institutions have established Qbio based graduate programs (as has UNC), efforts to bring the paradigm shift in Biology to undergraduate education have been slower. A few institutions, such as Princeton, have created dramatically novel curricula that first establish a basic education in quantitative skills, such as mathematics, statistics, and computer programming. Subsequently, undergraduates are trained in the basic principles of biology. Students are then exposed to the vast array of conceptual and empirical challenges confronting Q-bio. Princeton’s innovations were made possible in part by the Lewis-Sigler Institute for Integrative Genomics, which is a federally and privately funded research Institute at Princeton, and a very small entering class size.

In contrast to Princeton, undergraduate Q-Bio programs at most other universities are limited to a few courses (Cambridge, University of Reading, University of Ottawa, Carleton University, CUNY). UMass-Amherst took this approach further, and defined a suite of four inter-related “systems biology” courses. East Tennessee State University has developed a summer curriculum specifically for Q-bio training. Ohio University, in contrast, folded its quantitative biology program into the highly flexible curriculum of its Honors degree program.

Among the UNC Institutional peer group that have implemented some form of Q-bio program (Table 1), only UCLA has developed a strong program oriented at undergraduate training. This program is detailed below along with the programs at Case-Western University and University of California Davis.

Institution	**Program Description**	**Target**
University of Arizona	Quantitative Biology Consortium	Graduate Students, Post-doctoral fellows
UC –Berkeley	Living Systems and Q-bio	Faculty
UCLA	Computational and Systems Biology	Undergraduate (see below)
University of Illinois Urbana-Champaign	n/a	Some undergraduate and graduate courses
University of Iowa	n/a	Graduate courses
University of Michigan	In Engineering	Some courses
University of Oregon	n/a	n/a
University of Washington & FHCRC	Computational Molecular Biology	Graduate

<u>UCLA: Computational and Systems Biology major for undergraduates</u>. This program requires seven (*quarter system*) courses of mathematics; five of chemistry, including organic chemistry; 3 of physics; 3 of Biology; and 8 in computer science prior to admission to the Major during the junior year. After admission to the Major, students choose a concentration in Systems Biology, Bioinformatics, Neurosystems, Biomedical Systems, or Computer Systems and then select from a broad range of “approved” courses taught in a variety of departments.

<u>Systems Biology Bachelors of Science at Case Western Reserve University</u>. The curriculum at Case Western is less prescribed and more biology oriented than UCLA. Also, in contrast to UCLA, there are no areas of concentration, although there are several recommended course combinations recommended for students with particular interests. Again, these are more biology focused than UCLA as the track choices are all sub-disciplines of biology—e.g. neuroscience, genetics and evolutionary biology. A capstone research project is required the senior year.

As a final example, UC Davis has created a minor for undergraduates in biology or mathematics wishing to bridge the two fields, although it is open to all majors. Nor surprisingly, the minor is much less demanding than the majors at either Case-Western University or UCLA. Three core courses teach the basics of programming, mathematically modeling in Biology, and basic bioinformatics. Additional courses in data structures, mathematics and statistics are required. After these are completed two to three more classes are selected from a broad array of existing courses (taught in a wide range of departments) that are approved for completion of the minor.

Interestingly, UC-Davis also offers an intensive third year program, “collaborative learning at the interface of mathematics and biology—CLIMB”, that combines research with course work and seminars to rapidly train undergraduates.

The Proposed Qbio Track in Biology at UNC

Majoring in Biology: Bachelor of Science, Quantitative Track

This program is designed for students with a strong interest in a multi-disciplinary approach to biological problems in preparation for graduate study in biological or health sciences. A foundation in mathematics, encompassing calculus, statistics, and computer programming prepares students for advanced courses in the quantitative biology curriculum. Courses offered as quantitative electives allow students to tailor their course of study to their individual interests. Students completing this degree will have an enhanced knowledge of mathematical modeling and statistical methods in the analysis of biological systems. Students must fulfill all General Education requirements with these restrictions and additions (see also Appended Tables):

1. Foundation Foreign language: Through level 4. Level 4 may be taken P/D/fail unless placement level.

2. Foundations Quantitative Reasoning:
   Math 231 or Math 241 (Biocalculus I)

3. Approaches: Physical and Life Sciences:
   Chem 101-101L
   Biol 101-101L with a grade C or better.

4. Approaches Quantitative Intensive:
   Math 232 or 283 (Biocalculus II)

5. In addition students must complete the following:
   Chem 102-102L
   Chem 261 (Organic)
   Comp 116 (Programming)
   Math 233 (Multivariate Calculus)
   Phys 104 and 105 **OR** 116 and 117
   Stor 155 (Statistics)

6. Biol 201, 202, and 205 (Core courses for Biology majors)

7. Two lab courses. One must be a Quantitative lab chosen from:
   Biol 452 (Mathematical and Computational Models in Biology)
   OR Biol 526 (Computational Genetics)

The other can be any Biology lab course, including two semesters of Biology 395.

8. A choice of three Biology electives, of which at least two Quantitative electives must be chosen from:
   Biol 454 (Evolutionary Genetics)
   Biol 562 (Statistics for Environmental Scientists)
   Biol 542 (Light Microscopy)
   Biol 405 (Phys 405) (Biological Physics)
   Biol 551(Comparative Biomechanics)
   Biol 642 (Quantitative Cell Biology)
   Biol 452* (Mathematical and Computational Models in Biology) (Quantitative lab)
   OR Biol 526* (Computational Genetics) (Quantitative lab)
   *this selection cannot count as both a Quantitative lab and Quantitative elective.

9. A choice of two Allied Sciences electives or additional biology courses. Pre-meds are encouraged to take:
   Chem 241-241L (analytical) and Chem 262-262L (organic).

A Proposed Qbio Faculty Hiring Plan

UNC has an opportunity to build on a solid core of active faculty researchers in quantitative biology and become a world leader in this field. But the current core faculty group is insufficient to both grow the Qbio training that we propose and coalesce broad collaborative research across the College and life sciences across campus.

Three Guiding Principles

1. A focus on cross-cutting research areas

We foresee new hires in quantitative biology that will enrich research programs covering the much of breadth of biological sciences at UNC. Key to this will be the recruitment of faculty who study mathematical approaches applicable to different areas of biology. While it is advisable to keep the search process very open in order to recruit the very best candidates on the market, an important criterion should be the ability of the individual to tackle problems that transcend the peculiarities of any one biological problem, study system, or given level of biological organization. We provide some examples of cross-cutting issues in quantitative biology below.

2. Fostering a culture of interdisciplinary collaboration

An infusion of quantitative biological approaches throughout the research enterprise at UNC will come about through everyday interactions and collaborations between quantitative biology faculty and biologists who can provide the experimental testing of mathematical approaches and models. Hence, it will be critical to foster a close environment supportive of interdisciplinary research. We feel strongly that the academic home for these new hires should be one in which the biological question they address remain paramount. At the same time, it is important not to isolate these individuals from other potential colleagues on campus. We thus propose the primary home for the Qbio positions be within the College of Arts and Sciences, and specifically within the Department of Biology, but that secondary appointments be explored with other units on campus for some or all of the positions. Furthermore, because much of the current and emerging systems biology / Qbio research arena is genomics-driven, we anticipate that many of the individuals hired will be associated with the CCGS. In this regard, the expectation of close collaboration between “wet lab” experimental and “dry lab” quantitative biology is a key design feature of the Genome Science Building, providing a focal point for quantitative biology activities on campus. Indeed, we further anticipate that several of the faculty hired under this initiative may require both wet and dry lab space.

3. Early recruitment of leadership

For the last several years, there has been a great deal of conversation across many different units on campus about how to jumpstart a formal Qbio program at UNC. However, the effort has lacked grassroots leadership, in large part because the majority of quantitative biologists within the College are, or were until recently, junior faculty. We thus strongly feel that UNC should recruit, very soon, a tenured quantitative biologist of growing or established international reputation as a first step to putting UNC on the map in Qbio. This individual would be expected to provide leadership across the College of more comprehensive curricular reform, to act as a liason with the BCB Graduate Program and CCGS in terms of attracting center and training grants, and to participate in the further hiring of Qbio faculty over the coming years.

Scale of Qbio Faculty Hiring Initiative and Timeline

We propose that the College allocate for 5 tenure track faculty FTEs in Qbio within the next one to five years. Because a major driving force for the establishment of Qbio at UNC is genomics-driven, we further strongly urge the Provost to allocate 3 additional tenure track Qbio faculty FTEs to the CCGS, explicitly to be split with Biology, in the same time frame. There are already models for CCGS/Biology joint faculty that have served Biology, the College, and CCGS extremely well in the recent past.

Hence, we advocate a final hiring of 8 new faculty, 6 or whom would be interested in quantitative aspects of genomics-based research, broadly defined. We further advocate that recruitment start with one to two junior positions and one open-rank position to be recruited in 2008-2009. Finally, we would hope that the advertisement for these first positions would be explicitly worded to make it abundantly clear that these were the first of eight positions at UNC. This strategy was very successful in the early hiring for Biology/CCGS positions.

The numbers are justified by several considerations. First, the breadth of coverage necessary is very wide—Qbio approaches to biological problems need to span scales covering at least 12 orders of magnitude of biological organization from genomes to metagenomes of organisms interacting in complex communities, and from cellular nanomachines to ecosystems. Another consideration is that a growing number of federal research dollars in the life sciences are directed to interdisciplinary teams that include applied mathematicians, statisticians and computer scientists (e.g. the NIH Roadmap; NSF Plant Genome; NSF IGERT; NSF FIBRE etc.). Thus, recruitment of a critical mass of new Qbio will increase UNC's competitiveness in attaining collaborative grants. Finally, while the proposed Qbio track within the Biology major rests upon existing courses, additional faculty are needed to regularly teach existing offerings and to develop new courses, both for students within the track, as well as traditional biology majors and students from outside the department.

A cross-cutting research agenda

Quantitative biology rests on the direct integration of mathematical approaches with biological phenomena. The extent to which Qbio can permeate the biological sciences at UNC depends on recruiting individuals who work on problems that cut across multiple areas of study and span the organizational scales of biology. In many cases, these individuals may have received their primary training in non-biological fields (e.g., math or physics). But in all cases, we see these future hires as biologists who are actively engaged in the pursuit of biological questions, either through collaboration with other faculty in the biology department, or through their own empirical work. At the same time, we aim to identify those individuals who are at the forefront of generating new quantitative frameworks that inform our understanding of biological processes.

Common mathematical principles may be relevant to biological phenomena that, at first glance, seem to be quite disparate. Several authors have reviewed the common mathematical challenges posed by many different biological systems (Murray 2003a,b, Cohen 2004, Hastings et al 2005). Below, we describe some of these areas, highlighting their potential impact for biological research.

Nonlinear stochastic models

Hastings et al (2005) note that “mathematics has been well developed to deal with nonlinear models that are deterministic, or with linear models that include stochasticity. Future advances will require the use and analysis of nonlinear stochastic models”. Such models can be expected to show novel behaviors of great mathematical interest. A quantitative biologist with this expertise might apply it to models of neural networks, population demographics, or gene expression.

Spatial and temporal heterogeneity at multiple scales

To effectively model biological systems of interest, it is often necessary to consider interacting processes that operate on different temporal and/or spatial scales. Studies of simple heterogeneous processes have a long pedigree. For example, reaction diffusion equations have been applied in many different biological contexts, from obvious ones such as the kinetics of biochemical processes to the formation of patterns in development (Turing 1952) and the spread of novel genetic variants within populations (Kimura 1955). However, many open mathematical challenges remain for systems with a multitude of spatial and temporal scales. These could involve behavior of cells in organisms, or organisms in environments, for example.

Network dynamics

Many biological processes can be understood as networks. Two examples are the complex cascades of transcription factors controlling early development and the interplay between different trophic levels in metacommunites. Applications of network theory to biological networks are driving new advances in both graph theory and our understanding of basic biological processes. Current theory works well for networks with a limited number of nodes, or a very large number of nodes. But biological systems analyzed to date are largely summarized by networks featuring node numbers where current theory is very poor. Statistical methods to infer the structure of a network from observations on individuals are in their infancy, and static observations may be insufficient to infer the structure of evolving networks.

Modelling complex processes

Efforts to model complex biological systems in fields such as Neuromechanics, Biomechanics, and Biophysics often involve integrating several of the analytical approaches described above. Neuromechanics, for instance, brings together network theory and temporal and spatial heterogeneity to build experimentally testable models of neuromuscular development. Similarly, biophysical models of cellular processes such as the chromosome dynamics bring together network dynamics with both linear and non-linear stochastic models. Models such as these rely heavily on parameters observed from living systems and as a result these research areas often involve teams of investigators with different areas of expertise.

Computational analysis of large datasets

Many sub-disciplines of biology are awash with large data sets. Ecologists are increasingly using remote sensing data to shifts in species diversity accompanying climate change. Geneticists and cell biologists have developed high throughput screens for identifying genes, proteins, or chemicals affecting cell growth, movement, and diversification. These screens often generate enormous amounts of data—far more than can be analyze by an individual. Moreover, these data sets have significant error rates, which are often unknown. Data such as these typically needs to be “compressed” to be understandable by an investigator (such as the use of Gene Ontology in genomics). This need has led to advances in methods of categorizing and “self-organizing” of data. For example, recently developed self-organizing map methods have been used to identify and classify clusters of co-expressing genes in microarray data from tumor tissues.

In sum, it is our opinion that an aggressive recruitment of quantitative biologists with strong interests in cross-cutting areas of applied mathematics could have a profound and positive impact across the biology research enterprise at UNC.

References

[See also examples of research papers and reviews posted at: \\BioArk.bio.unc.edu\FacultyShare\ in a folder titled Qbio LIT examples.]

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Students must fulfill the **General Education Requirements**, with some restrictions and additions (see full description of requirements), including
Quantitative Reasoning: Math 231 (Calculus of Functions of One Variable I) OR Math 241 (BioCalculus I) AND
Quantitative Intensive: Math 232 (Calculus of Functions of One Variable II) OR Math 283 (BioCalculus II)

Biology (7)		**Other Requirements (7)**		**Allied Sciences (2)**	
1. Biology Core	Biol 201: Ecology & Population Biology	1. Physics	Phys 104: General Physics OR Phys 116: Mechanics	1. Allied Science or Biology Elective	**
2. Biology Core	Biol 202: Molecular Biology & Genetics	2. Physics	Phys 105: General Physics OR Phys 117: Electromagnetism & Optics	2. Allied Science or Biology Elective	**
3. Biology Core	Biol 205: Cellular & Developmental Biology	3. Chemistry	Chem 102(L): General Descriptive Chemistry (Lab)	**Premed students are encouraged to take: Chem 241-241L (Analytical Chemistry) Chem 262-262L (Organic Chemistry)	
4. Biology Lab	Biology course (above 201) with lab, excluding 213, 291, 292, 293, 295, 296, 396, and 692. Can include two semesters of 395. Other restrictions apply (see full description of requirements).	4. Chemistry	Chem 261: Introduction to Organic Chemistry		
5. Q-Bio Lab	Biol 452: Mathematical & Computational Biology OR Biol 526: Computational Genetics	5. Computer Science	Comp 116: Introduction to Programming		
6. Q-Bio Elective	Biol 405 (Phys 361): Biological Physics Biol 454: Evolutionary Genetics *Biol 452: Mathematical & Computational Biology *Biol 526: Computational Genetics Biol 542: Light Microscopy for the Biol Sciences Biol 551: Comparative Biomechanics Biol 562: Statistics for Environmental Sciences Biol 642: Quantitative Cell Biology	6. Mathematics	Math 233: Multivariate Calculus		
7. Q-Bio Elective		7. Statistics	Stor 155: Introduction to Statistics		
Optional 3rd Qbio Elective		*Optional* (could count as Allied sciences)	Stor 435: Intro to Probability		
	*Cannot count as both Q-Bio Lab and Q-Bio Elective				

Requirement	BA	BS	Qbio BS
Foundations: Foreign language	through level 3 unless plasced in to level 4	through level 4	through level 4
Foundations: Quantitative Reasoning	1 of MATH 130, 152, 231; COMP 101, 161; STOR 155, 215	MATH 231	MATH 231 or 241
Approaches: Natural Sciences	CHEM 101L, BIOL 101L	CHEM 101L, BIOL 101L	CHEM 101L, BIOL 101L
Connections: Quantitative Intensive	none	1 of MATH 232; COMP 101, 161; STOR 155, 215	MATH 232 or 283
Connections: Communication Intensive	satisfied by BIOL101L	satisfied by BIOL101L	satisfied by BIOL101L
Physics	none	(104 and 105) or (116 and 117)	(104 and 105) or (116 and 117)
Chemistry	102 and 102L	102,102L, 241,241L, 261, 262,262L	102L, 261
Biology core	201, 202, 205	201, 202, 205	201, 202, 205
Laboratory & diversity	1 organismal laboratory course	1 organismal laboratory course	1 quantitative laboratory (BIOL 452 or 526)
Biology electives	3, including 1 w/a lab and 1 above 400	4, including 2 w/ lab, and 2 above 400	4, including 1 w/lab, and 2 from a menu of 9 eligible Qbio courses
Natural science or math electives	4 courses	2 courses	2 courses
Computer Science	none	none	COMP 116
Statistics	none	none	STOR 155
Mathematics	none	none	MATH 233
Academic hours	120 minimum	123 minimum	127 Minimum