Andreas Handel
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January 22, 2008

Computational Biophysics Search Committee
Department of Physics and Astronomy
The University of Georgia
Athens, GA 30602-2451

Dear Members of the Search Committee,

I am writing to apply for a tenure-track faculty position in computational biophysics at the University of Georgia.

I obtained my Ph. D. in Physics from the Georgia Institute of Technology in 2004. Since then I have been a postdoctoral researcher in the Biology Department at Emory University. Currently, I am the Principal Investigator of an NIH K25 grant ($365,000), which was awarded to me in May 2007.

In my research, I use mathematical and computational approaches to study the processes that drive pathogen dynamics on different spatial and temporal scales. I am especially interested in the complex interactions between pathogens, drugs and the immune system. My work involves several biological and biomedical fields, such as immunology, microbiology, pharmacology, ecology, epidemiology, and evolutionary biology. The tools I use come mostly from the areas of applied mathematics, physics, scientific computation and statistics.

My background in Physics provides me with familiarity of the coursework and the field. In addition, the research performed during my Ph. D., and even more so my current work, have taught me how to work and collaborate effectively across disciplines. I believe that the combination of my background and my research makes me well suited to significantly contribute to both research and teaching within the department, to help grow the biophysics program and the Center for Simulational Physics, to facilitate close interdisciplinary collaborations with other departments and research units at UGA and to contribute towards UGA's continued development as a nationally and internationally renowned institution.

I have asked four of my current collaborators, namely Professors Rustom Antia, Ira Longini, Bruce Levin and Sergei Pilyugin, to provide letters of recommendation. I would be happy to provide additional recommendation letters from former or current colleagues and mentors.

For further information about myself and my research, as well as a brief teaching statement, please see the enclosed documents.

Thank you for your consideration of my application and I look forward to hearing from you.

Sincerely,

Andreas Handel

## CURRENT RESEARCH FOCUS

I use mathematical and computational approaches to investigate the dynamics of pathogens on different spatial and temporal scales. I am especially interested in the complex interactions between pathogens, drugs and the immune system.

## EDUCATION

| | | |
|---|---|---|
| 7/2004 | Ph. D. in Physics with minor in Mathematics | Center for Nonlinear Sciences and School of Physics, Georgia Institute of Technology, Atlanta, GA<br>Thesis Topic: "Limits of localized control in extended nonlinear systems", Advisor: Dr. Roman Grigoriev |
| 7/1999 | B. S. equivalent in Physics | Department of Physics, University of Stuttgart, Germany |

## RESEARCH EXPERIENCE

8/2004 – present Postdoctoral researcher, Emory University, Atlanta, GA

- Analyzed the dynamics of pathogens and their interactions with drugs and the immune response.

8/2001 – 7/2004 Graduate Research Assistant, Georgia Institute of Technology, Atlanta, GA

- Performed analytical and computational research at the intersection of nonlinear dynamics, fluid mechanics and control theory.

## TEACHING EXPERIENCE

8/2004 – present Substitute Lecturer, Emory University, Atlanta, GA

- Occasionally lectured undergraduate and graduate classes in immunology and mathematical biology.

1/2000 – 7/2001 Graduate Teaching Assistant, Georgia Institute of Technology, Atlanta, GA

- Taught and graded undergraduate and graduate physics courses and laboratories.

10/1998 – 7/1999 Undergraduate Teaching Assistant, University of Stuttgart, Germany

- Taught and graded undergraduate physics laboratories.

## SELECTED GRANTS AND AWARDS

| | | |
|---|---|---|
| 5/2007 – present | NIAID/NIH K25 Career Award Grant (PI) | $365,000 |
| 9/2005 – 12/2005 | Emerson Center Visiting Fellow Grant | $4,800 |
| 6/2005 – 7/2005 | IAS/PCMI Conference on Mathematical Biology Travel Grant | $2,500 |
| 8/1999 – 1/2000 | World Student Fund Scholarship | $7,500 |

**PROFESSIONAL AFFILIATIONS**

- American Physical Society
- American Society for Microbiology
- International Society for Computational Biology
- Society for Mathematical Biology

**CONFERENCE PARTICIPATION**

- Viral Paradigms: Molecules, Populations, Ecosystems and Infectious Disease, 1/14-1/16/2008, Atlanta, GA
- Immunobiology of Influenza Virus Infection: Approaches for an Emerging Zoonotic Disease, 7/29 - 7/31/2007, Athens, GA
- Symposium on Vaccine-Induced Immunity, 3/22/2007, Atlanta, GA
- 4th Annual Conference on Ecology and Evolution of Infectious Diseases, 5/18 - 5/20/2006, State College, PA
- Institute for Advanced Study & Park City Mathematics Institute, Summer Conference on Mathematical Biology, 6/26 - 7/16/2005, Park City, UT
- 3rd Annual Conference on Ecology and Evolution of Infectious Diseases, 5/16 - 5/21/2005, Fort Collins, CO
- MIDAS Consultation on Pandemic Influenza, 10/27 – 10/28/2004, Atlanta, GA
- American Association of Immunology Introductory Course in Immunology, 6/25 - 7/1/2004, Philadelphia, PA
- American Physical Society Topical Conference: Opportunities in Biology for Physicists, 1/30 - 2/1/2004, San Diego, CA
- Dynamics Days 2004, 1/2 - 1/5/2004, Chapel Hill, NC
- Dynamics Days 2002, 1/4 - 1/7/2002, Baltimore, MD
- Dynamics Days Europe 2001, 6/5 - 6/8/2001, Dresden, Germany
- Dynamics Days 2001, 1/3 - 1/6/2001, Chapel Hill, NC

**REVIEWER FOR THESE JOURNALS**

- Chaos, Evolution, Journal of Theoretical Biology, Journal of Virology, Physical Review E, PLoS Computational Biology, PLoS Pathogens, Proceedings of the Royal Society B, Theoretical Population Biology, Trends in Immunology

**ADDITIONAL INFORMATION**

German Citizen, U.S. permanent resident

Published or in press

- Rozen DE, Habets MGJL, Handel A, de Visser AGM (in press) "Heterogeneous adaptive trajectories of small populations on complex fitness landscapes" PLoS One
- Handel A, Longini IM, Antia R (2007) "Neuraminidase Inhibitor Resistance in Influenza: Assessing the Danger of its Generation and Spread", PLoS Computational Biology 3(12): e240
- Handel A, Yates A, Pilyugin SS, Antia R (2007) "Gap junction mediated antigen transport in immune responses", Trends in Immunology 28 (11), 463-466
- Grigoriev RO, Handel A (2007) "Localized Control of Spatiotemporal Chaos", Handbook of Chaos Control, Chapter 8, Wiley-VCH
- Handel A, Longini IM, Antia R (2007) "What is the best control strategy for multiple infectious disease outbreaks?", Proceedings of the Royal Society B 274, 833-837
- Handel A, Regoes RR, Antia R (2006) "The Role of Compensatory Mutations in the Emergence of Drug Resistance", PLoS Computational Biology 2(10): e137
- Viboud C, Tam T, Fleming D, Handel A, Miller MA, Simonsen L (2006) "Transmissibility and mortality impact of epidemic and pandemic influenza, with emphasis on the unusually deadly 1951 epidemic", Vaccine 24, 6701
- Handel A, Grigoriev RO (2006) "Transient dynamics and nonlinear stability of spatially extended systems", Physical Review E 74, 036302
- Handel A, Grigoriev RO (2005) "Pattern selection and control via localized feedback", Physical Review E 72, 066208
- Handel A (2004) "Limits of localized control in extended nonlinear systems", Ph. D. Thesis, School of Physics, Georgia Institute of Technology
- Grigoriev RO, Handel A (2002) "Spectral theory for the failure of linear control in a nonlinear stochastic system", Physical Review E 66, 065301(R)
- Grigoriev RO, Handel A (2002) "Non-normality and the localized control of extended systems", Physical Review E 66, 067201

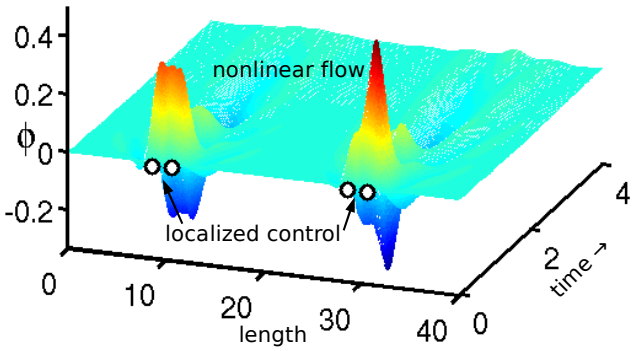
Submitted or in preparation

- Handel A, Margolis E, Levin BR, "The contribution of the immune response in preventing the emergence of resistance during the course of antibiotic treatment"
- Handel A, Yates A, Pilyugin SS, Antia R, "Gap junction mediated antigen transport and CTL responses during viral infections"
- Handel A, Longini IM, Antia R, "Comparing models for influenza A infection in mice"
- Handel A, Longini IM, Antia R, "Emergence of Neuraminidase Inhibitor resistant influenza through compensatory mutations "
- Handel A, Antia R, "How sticky should a virus be? - The balance between Hemaglutinin and Neuraminidase during influenza infections"
- Handel A, Rozen DE, "The impact of population size on the evolution of microbial populations on rugged fitness landscapes"
- Handel A, Bennett MR, "Bottlenecks, transmission mutants, and the evolution of microbial populations"
- Handel A, Masopust D, "Resource competition during CD8 T-cell expansion"

Andreas Handel, Department of Biology, Emory University, ahandel@emory.edu, 404-727-1765

## Previous research

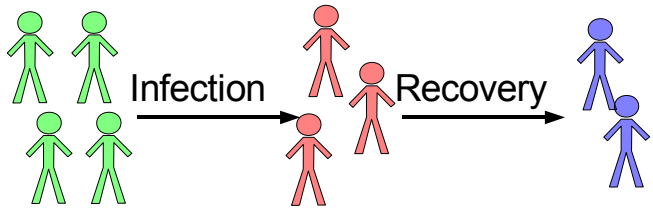
**Localized control of nonlinear systems.** The air flow around cars and planes, and the flow of fluids in industrial plants are examples of spatially extended, nonlinear systems. It is often desirable to control such systems with few localized controllers. For the research leading up to my Ph. D., I used a combination of analytical computations and numerical simulations to study the limits of such localized control. This research combined elements from fluid mechanics, applied mathematics, dynamical systems theory and control theory. I was able to derive general criteria for the minimum number of controllers needed to control a large class of nonlinear dynamical systems.

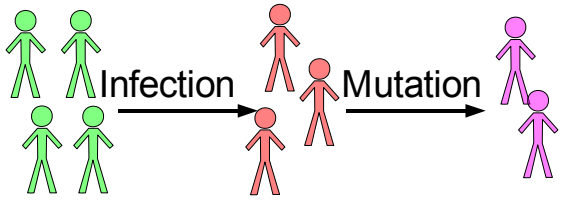



## Current research

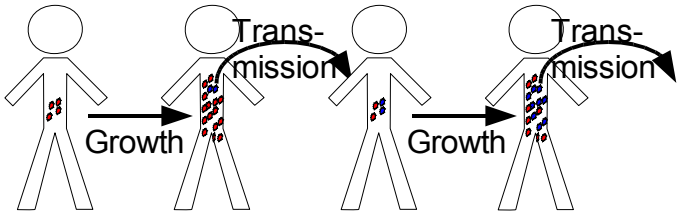
In my current research, I use mathematical models and numerical simulations, combined with experimental data, to obtain a comprehensive understanding of the processes that drive pathogen dynamics on different spatial and temporal scales. The following sections describe some of my recent and ongoing projects.

**Epidemiological models of pathogen spread.** In epidemiological models, the spread of pathogens through a host population is usually described by changes in host status. For instance in a simple model, the host changes from uninfected (green) to infected (red) to recovered (blue). I have applied this modeling approach to study the spread and possible control of pandemic influenza. Previous studies have evaluated control strategies to minimize the potentially devastating impact of a *single* pandemic outbreak. However, during the pandemic spread of a novel influenza strain, *multiple* outbreaks in a single location are likely. I investigated possible intervention strategies for such a situation. The results from this study, done in collaboration with Rustom Antia (Emory U) and Ira Longini (U Washington), show that a control strategy that strongly reduces the number of infected during the first outbreak might in fact be suboptimal. These findings should be helpful towards improving pandemic influenza preparedness plans.

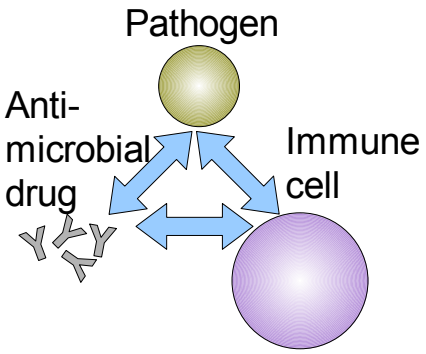


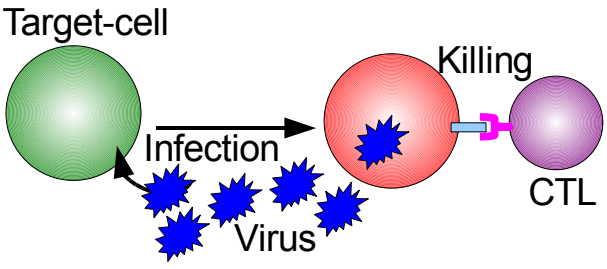

**Epidemiological models of pathogen evolution.** Most epidemiological models focus on short-term dynamics and ignore evolutionary processes. However, many pathogens have a short generation time and high mutation rate. This can lead to the rapid evolution of mutants (pink). An important example of pathogen evolution is the emergence of drug resistance, which is increasingly causing public health problems. Mutations that lead to drug resistance often reduce the fitness of the pathogen, but subsequent compensatory mutations have been shown to restore fitness. I investigated how drug use and compensatory mutations interact to affect the spread of drug resistant *Neisseria gonorrhoeae* mutants in a population. This work, done in collaboration with Rustom Antia and Roland Regoes (ETH Zurich), demonstrated that the ability of the resistant mutants to spread depends in a nonlinear fashion on the amount of drug use. This has important implications for public health; as even small increases in the level of drug use can significantly shorten the time for resistance emergence.




**Dynamics of pathogens on the population level.** The epidemiological framework described in the previous sections focuses on the dynamics of the hosts. A complementary approach focuses instead on the dynamics of pathogen populations. This approach has been used successfully in the study of microbial evolution. For instance models and experiments of repeated growth and dilution cycles of microbes represent a simplified version of the life cycle of many pathogens. Therefore, studying the evolution of microbial populations in such simple systems can provide insights towards the dynamics of pathogens. In a collaboration with Matthew Bennett (UC San Diego), I have investigated how transmission bottlenecks influence the ability of pathogens to evolve. The results suggest that mutants with an improved ability to survive transmission have a significant chance of evolving. In an independent collaboration with Daniel Rozen (U of Manchester) we used a combination of experiments and simulations to investigate how population size impacts the ability of *Escherichia coli* populations to evolve. We showed that – counter to the prevalent view – small populations of microbes can increase their fitness beyond that of large populations.

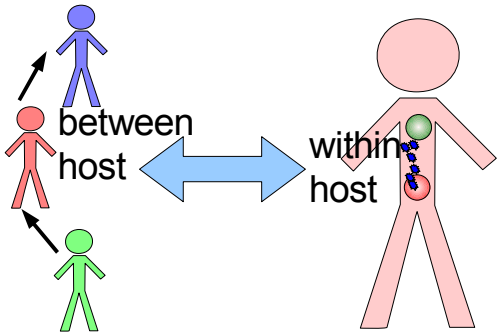



**Interactions of pathogens, drugs and immune response.** The approaches described in the previous sections focus on pathogen dynamics at the between-host level. It is equally important to understand the details of pathogen dynamics during an infection within a host. In a recent study, I analyzed several conceptual models that considered interactions between bacterial pathogens and both the immune response and antimicrobial drugs, something that is not widely studied. This work, done in collaboration with Bruce Levin and Elisa Margolis (Emory U), showed that the detailed mechanisms governing the immune response can have a profound impact on the emergence of antimicrobial drug resistance during infections. We have completed a theoretical study, and follow-up studies are planned to test some of our predictions in a mouse model of *Staphylococcus aureus* infection.

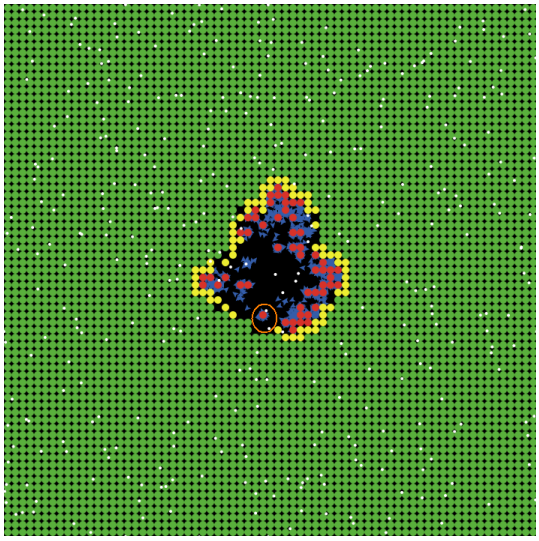


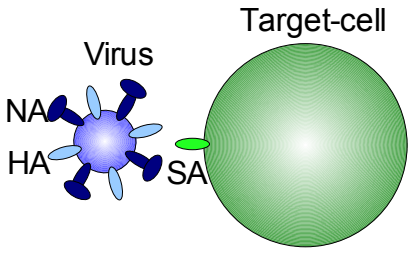

**Immune responses during viral infections.** During viral infections, cytotoxic T lymphocytes (CTL, also known as killer T-cells) are one of the most important components of the immune response and therefore an important driver of within-host pathogen dynamics. The signals that control the CTL response after infection are not yet fully known. To address this question, I started a collaboration with David Masopust (U of Minnesota). We combined computer simulations with an experimental model of *Lymphocytic choriomeningitis virus* infections in mice to test how the administration of immune response stimulating adjuvants affects the CTL response. Interestingly, our preliminary results suggest that these adjuvants can both increase and decrease the CTL response.

**Combining within-host and between-host modeling approaches.** One of the crucial components of a comprehensive, systems biology approach is an integration of results across different scales. While many studies deal with pathogen dynamics on either the within-host or between-host level as described in the previous sections, studies that connect the two levels are still rare. I recently devised a framework that bridges the within-host dynamics of influenza infections in response to antiviral drugs with the epidemiological approach described above. This work lead to a novel way of estimating the danger posed by influenza resistant to Neuraminidase Inhibitors (NI), currently the most potent antiviral drug against influenza. The ability to obtain such estimates is a crucial step that will help us to further improve predictive modeling of novel infectious disease outbreaks.




**Spatial models of infections.** The within-host dynamics of infections is usually modeled with ordinary differential equations or their stochastic counterparts. While these approaches have often been very successful, they ignore spatial structure. For many infections, spatial structures such as biofilms, granulomas, or organ geometry, likely play an important role. It is therefore important to study spatially explicit models. In recent work with Andrew Yates (Emory U), Sergei Pilyugin (U of Florida) and Rustom Antia, I considered localized viral infections with special focus on the spatial effects. We studied a specific mechanism, whereby infected cells (red) transport viral antigen through gap-junctions – small channels that can connect adjacent cells - to uninfected cells (green), turning these cells in bystander cells (yellow). These bystander cells, as well as the infected cells, can be killed by CTL (white). This killing can increase the distance a virion (blue) has to diffuse to reach the next target cell (see orange ellipse), making it more likely that it is cleared. We found that the impact of gap junctions depends strongly on inherently spatial features, such as the structure of the infection site and the diffusion speed of the virus.






**Molecular aspects of infections.** At the smallest scale, the dynamics of pathogens is driven by changes on the molecular level. I recently started to investigate how molecular changes in some of the envelope proteins of influenza impact the infection dynamics. The viral protein hemaglutinin (HA) binds to a sialic acid (SA) receptor on the target cell, thereby allowing the virus to attach and enter the cell. To allow exit of newly created progenitor virions, another protein, neuraminidase (NA), cleaves the target-cell receptors. A number of experimental studies have shown that optimal virus replication requires a balance between binding strength of the HA and ability to cleave of the NA. I am currently investigating this trade-of between optimal cell entry and optimal cell exit. Preliminary findings suggest that, again, spatial structure is important. In addition, the study suggests that antiviral drugs, which disturb the balance between HA and NA activities, can significantly affect the evolution of virus fitness and virulence.

**Future Research**

For my future research, I will continue to use analytical and computational methods to study the dynamics of pathogens on the multiple levels described above. A comprehensive understanding of pathogen dynamics and the interactions between pathogens, the immune system, and drugs will require bridging several, historically divided disciplines. To do so successfully, I intend to continue my current collaborations and establish new ones. I plan to collaborate especially closely with experimentalists, to achieve a synergistic combination of data and theory, which will be crucial for the future progress in biology on a systems level. I intend to pursue the following specific topics for the near future:

- **The dynamics of influenza.** Influenza remains a threat to the health of both humans and animals. Despite being one of the best studied viruses, much remains to be understood. A significant problem is our lack of *quantitative* knowledge of what drives the dynamics of this virus. This is especially true for individual infections, and to a lesser part for the population-wide spread and evolution of the virus. As described in the previous sections, I currently investigate a number of aspects of influenza dynamics, ranging from the molecular to the population level. I plan to continue and extend this work for some time to come. I anticipate to continue my collaborations with Ira Longini and Rustom Antia. Additionally, Dr. Rafi Ahmed's group at Emory University and Dr. Cecil Czerkinsky at the International Vaccine Institute in Seoul are likely to join as experimental collaborators for the within-host dynamics studies. I hope to establish further collaborations with both experimentalists and theorists who work on influenza.
- **Interactions of pathogens, drugs and the immune response.** One specific topic is my ongoing study of the interactions between influenza, the Neuraminidase Inhibitor antiviral drugs and the immune response. Additionally, through the work with Dr. Levin, I have become interested in bacterial infections, especially *Staphylococcus aureus* and its interactions with drugs and neutrophils. I plan to follow up on a recent theoretical study with additional theoretical modeling work, as well as collaborations with experimentalists. I intend to eventually extend this work towards other pathogens, with the final goal of obtaining a comprehensive, *quantitative* understanding of the dynamical interactions between specific pathogens, drugs and the immune response, from the molecular level to the evolution and spread of the pathogen.
- **The dynamics and evolution of microbial populations.** I plan to further address fundamental questions of microbial evolution by using theoretical approaches as well as data from model organisms. Specific topics, which I expect to study soon with my collaborators Dr. Rozen and Dr. Bennett, are peak-shifts/host-jumps during evolution and the impact of migrations between populations on the evolutionary dynamics of microbes. I consider this approach of studying fundamental mechanisms and processes of pathogen evolution as a complement to my other studies that focus on specific pathogens.
- **Interactions of pathogens with the cytotoxic T-cell component of the immune response.** The immune response is an important driver of pathogen dynamics. In the context of viral infections, cytotoxic T-lymphocytes (CTL) play a crucial role. I intend to continue my work on the interactions of pathogens with the immune response, and especially the CTL component during viral infections, both with respect to specific pathogens (mostly influenza) and to understand general mechanisms of pathogen-immune response interactions. This work is currently funded by my NIH K25 Career Award. I have started to investigate the mechanisms that lead to immunodominance of T-cells during influenza infections, as well as the connection between T-cell avidity and expansion during immune responses. I expect my collaboration with David Masopust to continue, with additional experimental collaborators in Rafi Ahmed's group also getting involved.

**Funding Sources**

I have identified several potential funding sources for my future work:

- For the between-host dynamics of influenza, a possible funding source is the NIGMS/NIH MIDAS program, through which I was previously supported. An alternative source is the NSF program on Ecology of Infectious Diseases (NSF 07-513). For studies on the within-host dynamics of influenza I expect to obtain funding from the NIH, either in response to NIH program announcements (for instance RFA-AI-08-002, PAR-07-376 or similar) or through the R01 mechanism as unsolicited application.
- For research on the interactions between drugs, immune responses and pathogens, funding could for instance come from the NSF (for instance NSF 08-513), NIH (for instance future RFAs similar to RFA-AI-07-025) or the BWF program of Pathogenesis of Infectious Disease.
- For the work on microbial evolution, funding can potentially be obtained from NIH (for instance PA-07-130) or NSF, as well as European funding agencies or the Human Frontier Science Program through the collaboration with Dr. Rozen in Manchester.
- Work on the interactions between pathogens and cytotoxic T lymphocytes is currently supported by my NIAID/NIH K25 grant. I expect to obtain further funding for this line of work through NIH R01 grants.

I am certain that additional funding sources exist and I am confident that I can obtain funding for my research.

**Summary**

My research focuses on developing and using analytical and computational approaches to solve biological problems. The research performed during my Ph. D., and even more so my current studies, have taught me how to work effectively across disciplines. I believe that the future of biological research lies in a systems biology approach, where theoretical models and experiments are combined to address a problem on multiple scales simultaneously. My ideal research environment is one where I can: 1) attract students with strong quantitative and problem solving skills who are interested in applying these skills to biological problems; 2) interact with colleagues who solve problems using approaches and tools that are very similar to my own; 3) establish strong collaborations with experimentalists who work on interesting biological problems. The department of Physics and Astronomy's quantitative and computational strengths, combined with the University of Georgia's overall strength in biomedical research, appears to be such an ideal environment. In turn, my Physics background, combined with my ability to work closely with theoretical and experimental collaborators, puts me in the perfect position to significantly contribute to both research and teaching within the department, to help grow the biophysics program and the Center for Simulational Physics, to facilitate interactions and close interdisciplinary collaborations with other departments and research units at UGA and to contribute towards UGA's continued development as a nationally and internationally renowned institution.

## Teaching Philosophy

As an undergraduate and graduate student, I taught classes and laboratories in physics. As a postdoctoral fellow, I occasionally lectured mathematical biology and immunology classes. From these experiences, I have learned several important lessons about what it takes to be a successful teacher:

- Students learn better if they are interested in the topic. I found that students usually become interested in a topic once they perceive it as meaningful to their own lives. From my experience, it is possible to connect even the most abstract concepts to students' everyday experiences, thereby increasing their interest and subsequent ability to learn and remember the material.
- Students retain information better if they are actively involved in the learning process. While a passive lecturing style is sometimes necessary to provide a basis of knowledge, I try to use approaches that involve students in the learning process as often as possible. Such approaches can take on many forms, for instance lively discussions during lectures, homework that is designed to engage students with the material, group projects, and hands-on experiences through experimental or computational labs.
- Students often get lost in the details. While detail knowledge is important, I try to ensure that the details are connected to the bigger picture, thereby providing students with a comprehensive view. This is especially important for complex scientific topics. Additionally, the increasingly interdisciplinary nature of most work, not only in academia but also in industry, requires big-picture thinking coupled with mastering the details.
- Students need to learn critical thinking. I have often experienced that students report results without critical reflection. This lead to claims that a lab cart weighs several thousand pounds and travels at a speed of thousand miles per hour. To prevent such obvious mistakes, I find it important to stress careful and critical thinking. This applies to the students own work and to any facts claimed by someone else, be that a journal article, a textbook or a teacher. It is my goal to not only teach students the course material, but also to help them develop their ability to 'think scientifically'. I believe the ability to think critically is vital for success in today's complex, fast-changing world.

## Teaching at the University of Georgia

My familiarity with the Physics curriculum would allow me to teach a variety of courses in Physics. Additionally, I am very interested in developing and teaching courses that combine quantitative methods and approaches from physics with biological topics. This could encompass different types of courses, such as:

- A course for students in the biomedical sciences who are not too quantitatively inclined but want to gain a basic understanding of quantitative approaches.
- A course for students who want to learn quantitative methods in the context of biomedical problems.
- A course for students who already have a strong mathematical/computational background and want to learn how to apply quantitative approaches to biological problems.

Depending on specific student needs, I would design such courses to either cover a wide variety of quantitative approaches and biological topics, or alternatively discuss in-depth either a specific approach (e.g. dynamical systems theory, computational methods, stochastic processes) or a specific biological topic (e.g. epidemiology, immunology, population genetics/evolution).

Andreas Handel, Department of Biology, Emory University, ahandel@emory.edu, 404-727-1765