

# NIAID Modeling Activities

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# NIAID - Mission

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- The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases.

# Modeling Immunity for Biodefense

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Initiative: RFP-NIH-NIAID-DAIT-BAA-05-10  
Modeling Immunity for Biodefense

Goals:

- Establish highly interactive, multi-disciplinary teams to develop innovative mathematical models of immunity to vaccines/therapeutics or infection with a focus on NIAID Category A, B, C Priority Pathogens.
- Develop “user-friendly: mathematical tools for high (whole organism or system), intermediate (tissue or organ), or fine (single cell) resolution modeling of host immune responses to infection and vaccines/therapeutics against NIAID Category A-C priority pathogens.

# Objectives

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- Centers conduct basic research for new mathematical model development or the improvement of existing models, accompanied by validation and model refinement through laboratory experimentation.
- Minimally the teams would consist of immunologists, bioinformaticians, and scientists with expertise in mathematical modeling. Additional expertise in statistics, infectious diseases, microbiology, and epidemiology could also be included as dictated by the proposal.

# Immune Modeling Centers

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- Four (4) contracts were awarded in 2005
- Duke University – DULCI
  - Duke University Laboratory for Computational Immunology
    - <https://dulci.org/>
- Mount Sinai School of Medicine – PRIME
  - Program for Research on Immune Modeling and Experimentation
    - <http://tsb.mssm.edu/primeportal/>
- University of Pittsburgh – CMPI
  - Center for Modeling Pulmonary Immunity
    - <http://cmpi.cs.pitt.edu/>
- University of Rochester – URCBIM
  - University of Rochester Center for Biodefense Immune Modeling
    - <https://cbim.urmc.rochester.edu/>

# Duke University - DULCI

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- The main goal of this program is to develop computational tools to aid in the design of vaccine adjuvants. In order to achieve this goal, the contractor is characterizing dendritic cell, B cell, and T cell function in response to various adjuvant/antigen combinations, with a focus on activation of innate immune receptors (TLRs).
- Immune cells will be examined at the site of injection, draining lymph nodes, and spleen at early time points after inoculation with anthrax recombinant Protective Antigen (rPA) mixed with one of three adjuvants (shistosome egg antigen (SEA), Alum, or LPS).
- Developing ODE-based models of the cellular population dynamics of the humoral response to rPA. The model accounts for DC activation as well as migration and has been fit to extensive flow-cytometric data. Developing a user-interface to make this model available to the immunology community.

# Duke University - DULCI

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The current version of the software has only been tested on Ubuntu 8.10. The steps below detail installation instructions for Ubuntu 8.10

Download an archive file (.zip, .gz, or .bz2) from the links to the right of msi-release-2.0 at <http://hg.dulci.org>.

Unarchive the file e.g. `tar xzf tip.tar.gz` if you downloaded the .gz archive.

Full instructions are in docs/README.pdf, but in short, just run

```
./install_script.sh
```

and give sudo password when prompted. This will install the MSI simulation software and all dependencies. See docs/README.pdf for a brief tutorial on how to run a simulation.

**Download in other formats:**

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By Edgewall Software.

Visit the Trac open source project at  
<http://trac.edgewall.org/>

<https://galen.dulci.duhs.duke.edu/msi/wiki/Software>  
<http://hg.dulci.org>

# Mt. Sinai School of Medicine - PRIME


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- The goal of this Immune Modeling Center is to develop predictive, experimentally-validated, cellular resolution models of human dendritic cell responses to category A-C viruses. Specific viral components from Influenza (NS1), Ebola (VP35), vaccinia (E3L), and Nipah (P, V, and W proteins), which alter various pathways in the interferon signaling cascade, will be evaluated for their effects on human dendritic cell function and innate immune responses.
- The contractor will attempt to identify the mechanisms of action of viral antagonists, identifying and simulating potential therapeutic strategies to overcome viral antagonism.




# Mt. Sinai School of Medicine - PRIME


Tools and Resources   Models   Education




**PRIME Database**  
A web based resource for management and sharing of public data. The PRIME Databases is powered by BioPathwise DM, which is a remotely accessible secure repository system.




**Translational Systems Biology**  
wiki




**PRIME D**  
A system that integrates microarray data from PRIME experiments, as well as several publicly accessible datasets investigating the anti-viral response in dendritic cells.




**TIDAL**  
A web interface to infer transcriptional networks that underly dynamic cellular responses, obtained from time-series of gene expression data using statistically rigorous enrichment analysis.




**CorEx**  
A web-based tool to analyze and visualize correlations within gene expression data, overlaid with annotations resulting from transcription factor enrichment analysis.



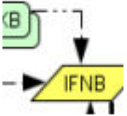
**Table of Rate Constants**  
for modeling immune response of Dendritic cells to virus infection.




**Misty Mountain Clustering**  
A fast unsupervised clustering algorithm designed for flow cytometry gating.



**PLaCA**  
A web accessible tool for inferring functional signaling networks from early gene expression data.



**BioPP**  
A web-based tool for biological pathway publishing that facilitates interactive curation and sharing of pathway knowledge-bases.



**Reagent List**  
A list of available reagents that were developed in various PRIME experiments.

<http://tsb.mssm.edu/primeportal/>

# Mt. Sinai School of Medicine - PRIME

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Tools and Resources   Models   Education

1. Agent-based model of the IFNB1-DDX58 feedback loop response to virus infection of dendritic cells
2. Immune response modeling of interferon-beta pretreated influenza virus infected human dendritic cells
3. Stochastic model of interferon transcription and enhanceosome formation leading to power laws
4. Model of shared kinase fluctuations between two enzymatic reactions
5. Stochastic gene production using transcriptional-pulsing
6. Model of Autocrine/Paracrine Signaling in Epithelial Layer
7. Input/output model for MAPK signaling
8. Enhanceosome Formation and Interferon Noisy Transcription
9. Bistability and oscillations in MAPK signaling
10. Autocrine signaling in three dimensions

<http://tsb.mssm.edu/primeportal/>

# University of Pittsburgh - CMPI

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- The main goal of this program is to develop and validate mathematical models of pulmonary innate immune responses in mice and non-human primates to three pathogens administered by the inhalation route: Influenza, *Mycobacterium tuberculosis*, and *Francisella tularensis*.
- Biological information (e.g., cytokine expression patterns) is used to train and validate the models. The majority of this biological data is obtained through analysis of innate immune responses *ex vivo* and *in vivo* in mouse and non-human primate models.
- Selected studies also will be validated through *ex vivo* analysis of human antigen presenting cell responses to influenza in cells obtained from bronchoalveolar lavage.

# University of Pittsburgh - CMPI

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## Software Tools

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by [Alexandros Labrinidis](#) — last modified 2009-10-22 12:57

List of software developed by group members:

- [Alignment, Similarity, & Database Matching for DNA Motifs \(STAMP\)](#)
  - Shaun Mahony and Takis Benos (University of Pittsburgh)
- [Short Time-series Expression Miner \(STEM\)](#)
  - Jason Ernst, Ziv Bar-Joseph (Carnegie Mellon University)
- [Analysis of Short Time-series using Rank Order preservation \(ASTRO\)](#)
  - Alain B.Tchagang, Thomas McGinnis, David Corcoran, Panayiotis V. Benos (University of Pittsburgh)
- [Energy normalized LOGOs \(enoLOGOS\)](#)
  - Workman CT, Yin Y, Corcoran DL, Ideker T, Stormo GD, Benos PV (University of Pittsburgh)
- [Energy normalized LOGOs of the C2H2 protein family \(enoLOGOS-C2H2\)](#)
  - Workman CT, Yin Y, Corcoran DL, Ideker T, Stormo GD, Benos PV (University of Pittsburgh)
- [Footer image: finding mammalian transcription factor binding sites using phylogentic footprinting \(Footer\)](#)
  - Corcoran David et al. (University of Pittsburgh)

<http://cmpi.cs.pitt.edu/software>

# University of Rochester -URCBIM

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- The project objectives are to: develop mathematical/computational models to simulate immune responses to influenza A virus; design and conduct *in vitro*, *ex vivo*, and *in vivo* experiments to identify, measure and validate the immune models; develop statistical methods and user-friendly statistical packages for immunology data analysis, model identifications and predictions; develop a web-based database and software system for modeling and simulating immune responses to influenza A virus.
- Investigate the feasibility to extend and modify influenza mathematical/computational models to vaccinia virus for immune response simulations.

# University of Rochester -URCBIM

The screenshot shows the website for the Center for Biodefense Immune Modeling (CBIM) at the University of Rochester. The header includes the university name and the center's name. A navigation menu contains links for Home, About CBIM, Links, Events, and Software. A breadcrumb trail indicates the current location: Home → Software. The main content area is titled "Software" and lists four applications: DataTrans Application, DEDiscover, Importance Measures, and MathStat. A sidebar on the right contains a search box, a "Members Only" login section with fields for Login Name and Password, and a calendar for May 2010 with the 11th highlighted. The footer includes links for Site Map, Accessibility, Contact, and CBIM Use.

UNIVERSITY OF ROCHESTER  
**Center for Biodefense Immune Modeling**  
SCHOOL OF MEDICINE AND DENTISTRY

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## Software

▲ Up one level

- DataTrans Application**  
A Comprehensive Web-Based Data Management System for Immunological Research
- DEDiscover**  
Differential Equation Modeling Solution - cross-platform tool for building and understanding differential equation models, with special attention to the features necessary for modeling the immune system and viral infection.
- Importance Measures**  
Importance Measures using analytic variance-based method in the context of global sensitivity analysis using MASAL and MARS models
- MathStat**  
MathStat is a comprehensive and general numerical algorithm package implemented mainly in C and C++. This project attends to covering up-to-date algorithms for scientific computing and data analysis. Lapack and Boost etc. are also incorporated.

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Site Map Accessibility Contact CBIM Use

<https://cbim.urmc.rochester.edu/software>

# University of Rochester -URCBIM

You are here: [Home](#) → [Software](#) → [DEDiscover](#)

## DEDiscover Overview



Overview of the features of "DEDiscover" simulation tools.



DEDiscover allows the user to enter a differential equation model or to select from a set of pre-defined models. Models may be specified as either ordinary differential equations or delay differential equations.

DEDiscover provides simulation tools and (with version 2.0) parameter estimation tools, which can be easily selected, configured and controlled using simple visual tools. Experimental data, necessary for estimation, can be loaded from standard spreadsheet formats. Simulation results are generated in real time, allowing interactive exploration of the effect of varying model parameters. Parameter estimation can be accomplished using several provided algorithms. With estimation progress displayed during computation, results are displayed in both tabular and graphical formats, and can be exported to standard file formats.

DEDiscover has been designed using a "plug-in" architecture to allow easy addition of new models, model parsers, differential equation solvers, and statistical estimation methods.

Funding provided by:



National Institutes of Health



National Institute of Allergy and Infectious Disease



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DEDiscover free trial.



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Ask and answer questions.

# Other Modeling Projects

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- Program Project: Immune Response Consortium: Integrated *In Silico*, *In Vitro*, and *In Vivo* Studies of the Immune Response to *Listeria Monocytogenes*
  - Principal Investigator: Arup Chakraborty
  - Institution: Massachusetts Institute of Technology
  - Project period: (06/15/2006 - 05/31/2011)
    - To understand how T cells detect antigen with high sensitivity and how T cell activation is regulated.
    - To develop an integrated, mechanistic understanding of how antigen presentation, T cell receptor (TCR) triggering, intracellular signaling, and migratory patterns of T cells influence the adaptive immune response to a pathogen.
    - Computational studies will be combined with in vitro and in vivo genetic and biochemical experiments to understand the adaptive immune response to *Listeria monocytogenes*. These computational studies could result in predictive algorithms that model the immune response.



# Other Modeling Projects

**IRC**

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**Sponsor:**  
National Institute of Allergy and Infectious Diseases

**Consortium Institutions:**

- Massachusetts Institute of Technology
- Los Alamos National Laboratories
- Memorial Sloan-Kettering Cancer Center
- New York University
- Stanford University
- University of California-Berkeley
- Washington University-St. Louis

## Immune Response Consortium

The adaptive immune response enables humans (and other higher organisms) to combat pathogens that they have never encountered before. In spite of many important advances over the past decades, a predictive understanding of the principles that govern the emergence of an adaptive immune response has been elusive. The **Immune Response Consortium (IRC)** aims to take steps toward the development of such predictive mechanistic principles. A specific focus is the adaptive immune response to *Listeria monocytogenes*, a class B pathogen.

The activation of the adaptive immune response is the result of cooperative dynamic processes that span molecular, cellular, and tissue scale processes. It is this hierarchically organized cooperativity with feedback that makes it difficult to intuit underlying mechanisms from experimental observations alone. The IRC aims to confront and overcome this challenge by an approach that brings together methods rooted in the biological, physical, and engineering sciences. Synergistic use is made of theoretical and computational approaches and genetic, biochemical, and imaging experiments to address the pertinent issues. The IRC is a collaboration involving scientists and engineers from MIT, Stanford University, Washington University, New York University, Memorial Sloan Kettering Cancer Center, University of California (Berkeley), and Los Alamos National Laboratory. The IRC is supported by the National Institute of Allergy and Infectious Diseases.

<http://web.mit.edu/irc/>

# Other Modeling Projects

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**IRC**

Immune Response Consortium

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**IRC Members Area**

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**IRC Research**

The [Stochastic Simulator Compiler \(SSC\)](#) is a tool for creating exact stochastic simulations of biochemical reaction networks. Its high-level syntax enables complex biochemical signaling networks to be specified without the knowledge of any formal programming languages, while direct native code generation results in very fast simulators.

<http://web.mit.edu/irc/>

# Moving Forward

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Reissued:               BAA-NIAID-DAIT-NIHAI2009074  
                              Modeling Immunity for Biodefense

Results:

- Reviewed in April 2010.
- Awards anticipated July-Aug 2010

Continue to accept and encourage individual and program project grants focused on mathematical and computational modeling of immune response and function.