

Modeling Immune Response to Influenza A Infection by Integrating Quantitative/Computational Technologies

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Outline

- **Introduction**
- **Mathematical Models**
- **Statistical Methods for Model Identification**
- **User-Friendly Computer Software Development**
- **Discussion and Conclusion**

Introduction: Modeling Biological Processes

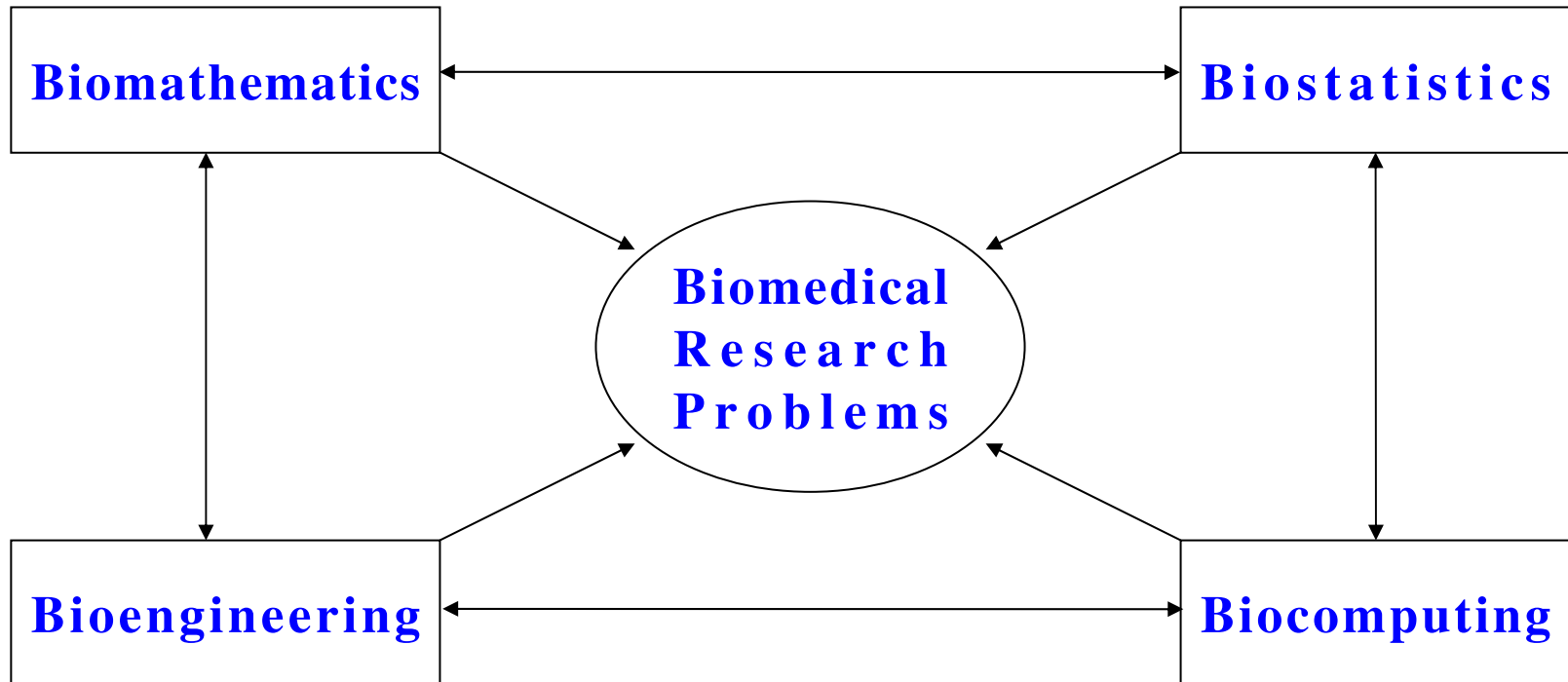
- A multi-disciplinary business
- No model is correct, but some models are useful
- Different purposes need different models
- Different models need different experimental data
- A model that does not fit the data well is not a good model, but a model that fits the data well is not necessarily a correct model
- Develop a useful model for your purpose

Interdisciplinary Biometric Sciences

Integrating quantitative/computational methods and techniques for biomedical research:

- **Biomathematics: Mathematical Biology, Theoretical Biology**
- **Biostatistics**
- **Biocomputing: Computational Biology, Bioinformatics, Biomedical Informatics, Health Informatics**
- **Bioengineering or Biophysics**

Interdisciplinary Interplay



Division of Biomedical Modeling and Informatics

Founded at the Dept of Biostatistics & Computational Biology, University of Rochester in 2004

- **Biomedical Problems:** HIV/AIDS Treatment, influenza virus infection, and immunology
- **Biomathematics/Bioengineering/Biophysics:** 2 faculty, 1 postdoc
- **Biostatistics:** 4 faculty, 1 postdoc, 4 PhD students
- **Biocomputing/Bioinformatics:** 3 faculty, 6 software developers, 1 postdoc

Funded Projects

- AIDS Clinical Trial Modeling and Simulations (NIH R01 AI 055290, **PI: Dr. Hulin Wu**)
- Nonparametric Modeling of Long-Term HIV/Cell Dynamics (NIH R01 AI 52765, **PI: Dr. Hulin Wu**)
- Center for Biodefense Immune Modeling (NIH N01 AI 50020, **PI: Dr. Hulin Wu**, Bioinformatics Core Director: **Dr. Ma**, Biocomputing Core Director: **Dr. Warnes**, Biostatistics Core Director: **Dr. Liang**)
- The Biomedical Informatics (BI) Key Function, the University of Rochester's Clinical and Translational Science Institute (CTSI) (NIH UL1 RR024160, **Co-PIs: Drs. Dongwen Wang, David Krusch and Hulin Wu**)
- Centers of Excellence for Influenza Research (Informatics Core Director: **Dr. Jingming Ma**; Biostatistics Core Director: **Dr. Hulin Wu**)

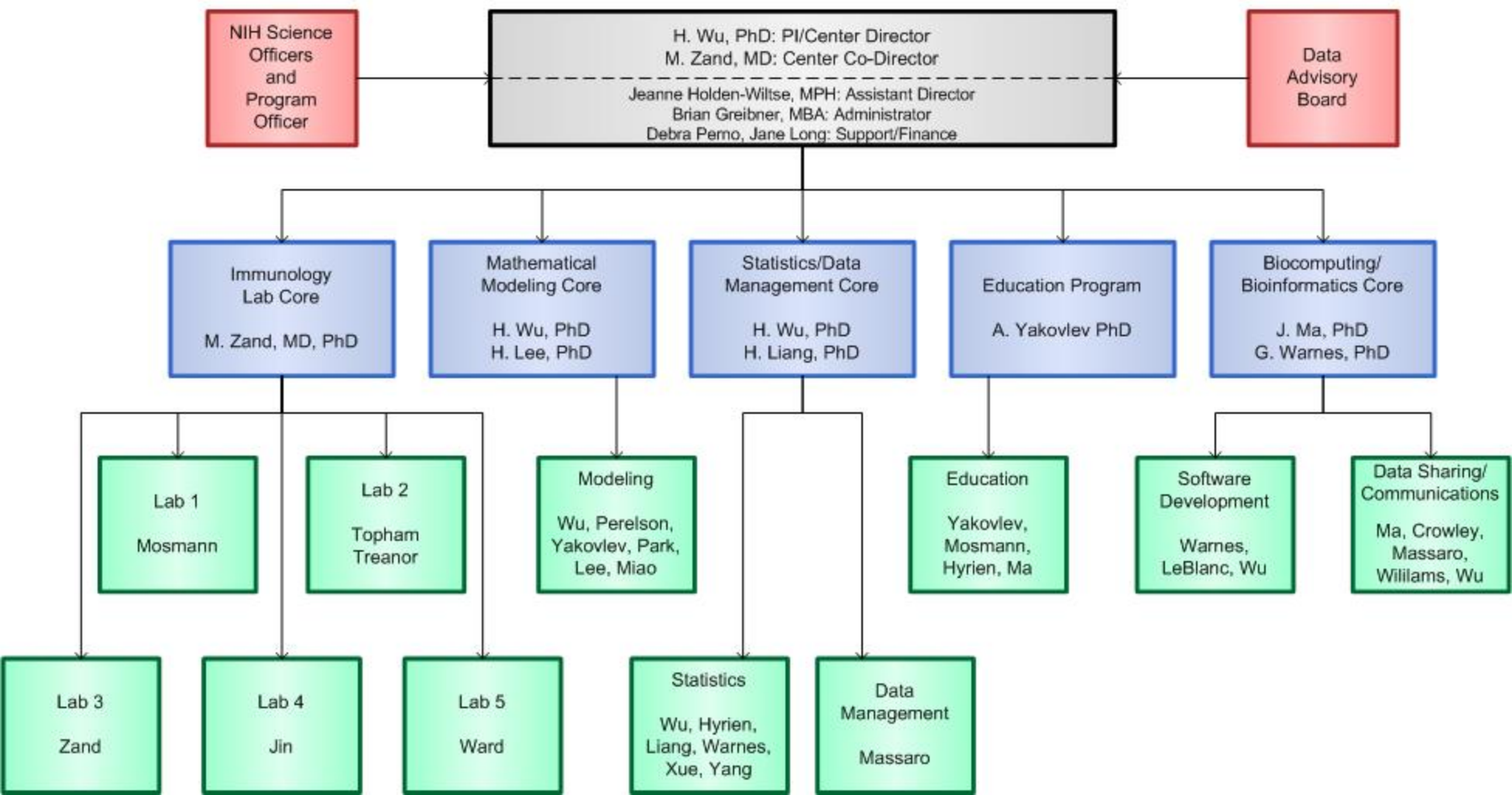
- Center grant: Immune Function and Biodefense in Children, Elderly and Immunocompromised Populations, (NIH N01 AI 50029, Informatics Core Director: **Dr. Jingming Ma**)
- Analysis of AIDS Data by Using Semiparametrical Models (NIH R01 AI 62247, **PI: Dr. Hua Liang**)
- Generalized Varying-Coefficient Partially Linear Models (NIH R01 AI 59773, **PI: Dr. Hua Liang**)
- Other collaboration grants

Center for Biodefense Immune Modeling University of Rochester

Objectives:

- Develop mathematical/computational models to simulate immune responses to influenza A virus
- Design and conduct experiments to identify, measure and validate the immune response models
- Develop statistical methods for model identifications and predictions
- Develop user-friendly database and software tools for modeling and simulating immune responses to influenza A virus
- Develop an education program to foster the next generation of researchers with multi-disciplinary expertise in mathematical modeling and immunology
- Investigate the feasibility to extend the models for other pathogens

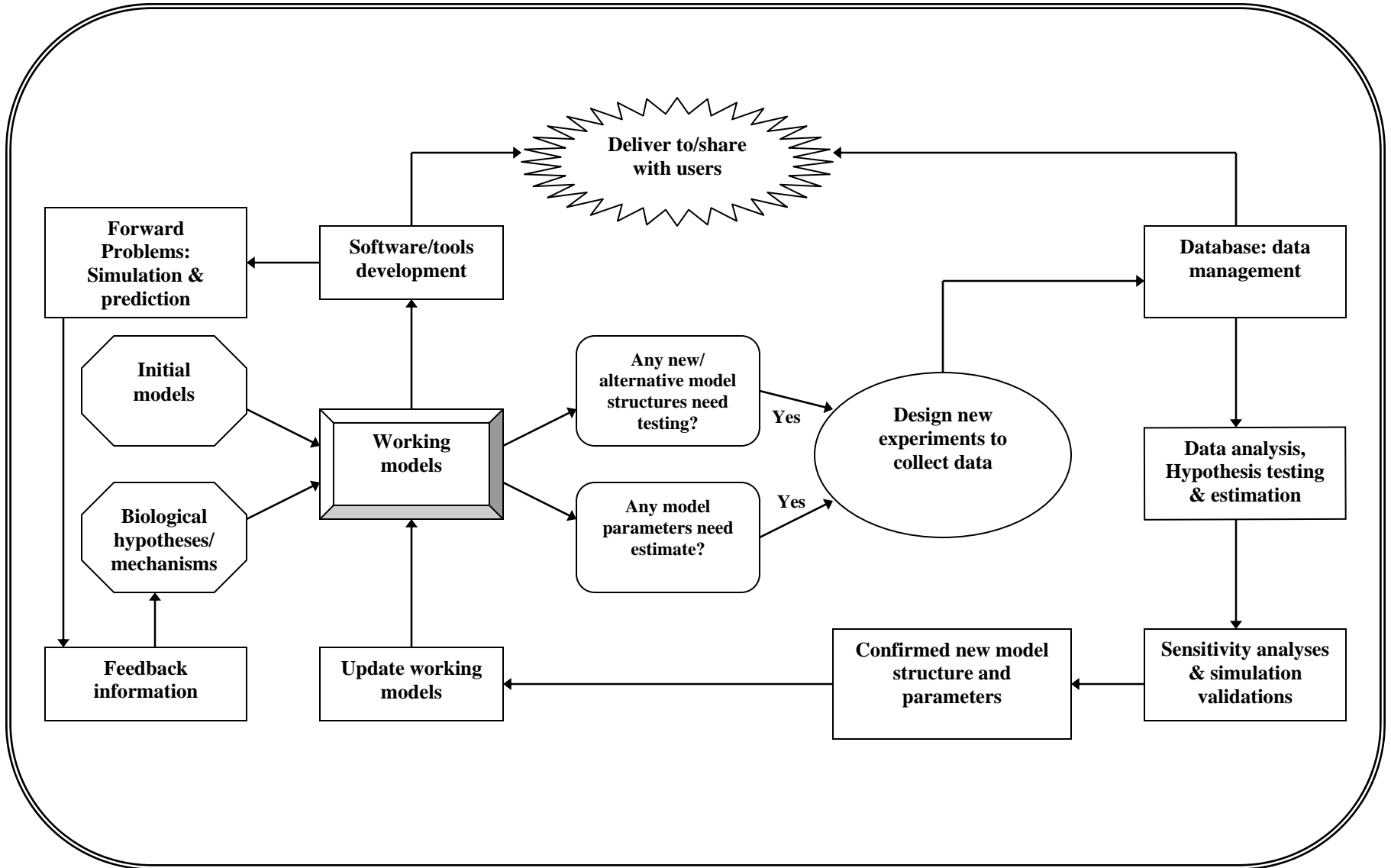
CBIM Organization



Quantitative Sciences Components

- **Mathematical Models**
- **Statistical Methods for Model Identification**
- **Computer Software Tools**

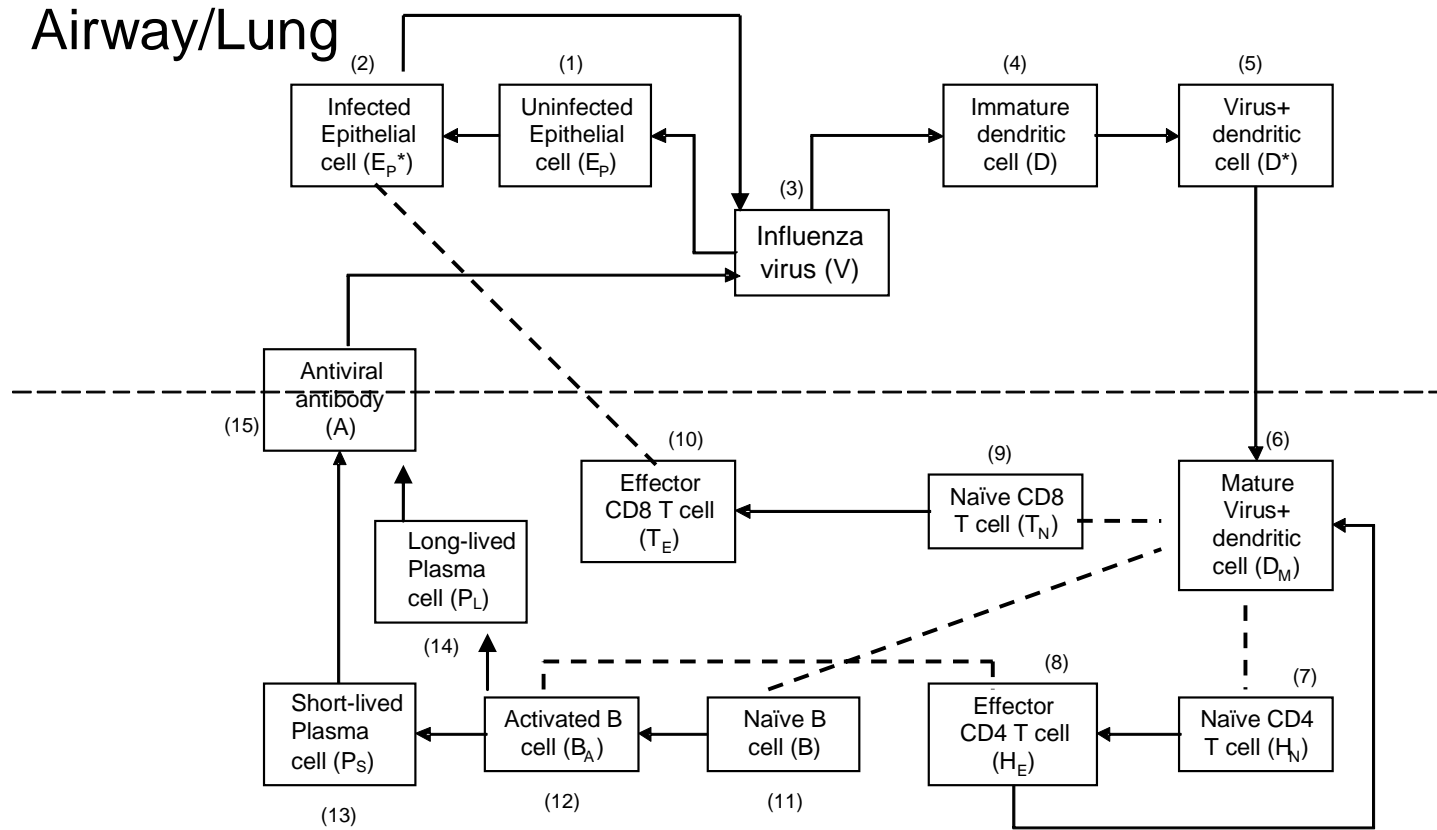
Work Flow Chart



Mechanism-Based Mathematical Models

- Close interactions between biomathematicians and influenza immunologists/virologists
- What level of details should we model?
 - Purpose of modeling
 - What can we measure in the lab?
 - Complexity and identifiability of the model from experimental data

Two Compartment Flu Model



Mathematical Models: Influenza Virus Infection

Mathematical Models: Airway/Lung Compartment

$$\begin{aligned}\frac{d}{dt}E_p &= \delta_E(E_0 - E_p) - \beta_E E_p V, \\ \frac{d}{dt}E_p^* &= \beta_E E_p V - k_E E_p^* T_E(t - \tau_T) - \delta_{E^*} E_p^*, \\ \frac{d}{dt}V &= \pi_V E_p^* - c_V V - k_V V A(t), \\ \frac{d}{dt}D &= \delta_D(D_0 - D) - \beta_D D V, \\ \frac{d}{dt}D^* &= \beta_D D V - \delta_{D^*} D^* - \gamma_{D^*} D^*\end{aligned}$$

E_p : uninfected epithelial cells

E_p^* : infected epithelial cells

V : free influenza virus

D : immature dendritic cells

D^* : virus-loaded dendritic cells

Influenza Virus Infection

Mathematical Models: Spleen/Lymph Node Compartment

$$\frac{d}{dt}D_M = k_D D^*(t - \tau_D) - \delta_{D_M} D_M,$$

$$\frac{d}{dt}H_N = \delta_{H_N}(H_{N0} - H_N) - \pi_H(D_M)H_N,$$

$$\frac{d}{dt}H_E = \pi_H(D_M)H_N + \rho_{H_E}(D_M)H_E - \delta_{H_E}(D_M)H_E,$$

$$\frac{d}{dt}T_N = \delta_{T_N}(T_{N0} - T_N) - \pi_T(D_M)T_N,$$

$$\frac{d}{dt}T_E = \pi_T(D_M)T_N + \rho_{T_E}(D_M)T_E - \delta_{T_E}(D_M)T_E,$$

$$\frac{d}{dt}B = \delta_B(B_0 - B) - \pi_B(D_M)B,$$

$$\frac{d}{dt}B_A = \pi_B(D_M)B + \rho_{B_A}(D_M + hH_E)B_A - \delta_{B_A}B_A - \pi_s B_A - \pi_L H_E B_A$$

$$\frac{d}{dt}P_s = \pi_s B_A - \delta_s P_s,$$

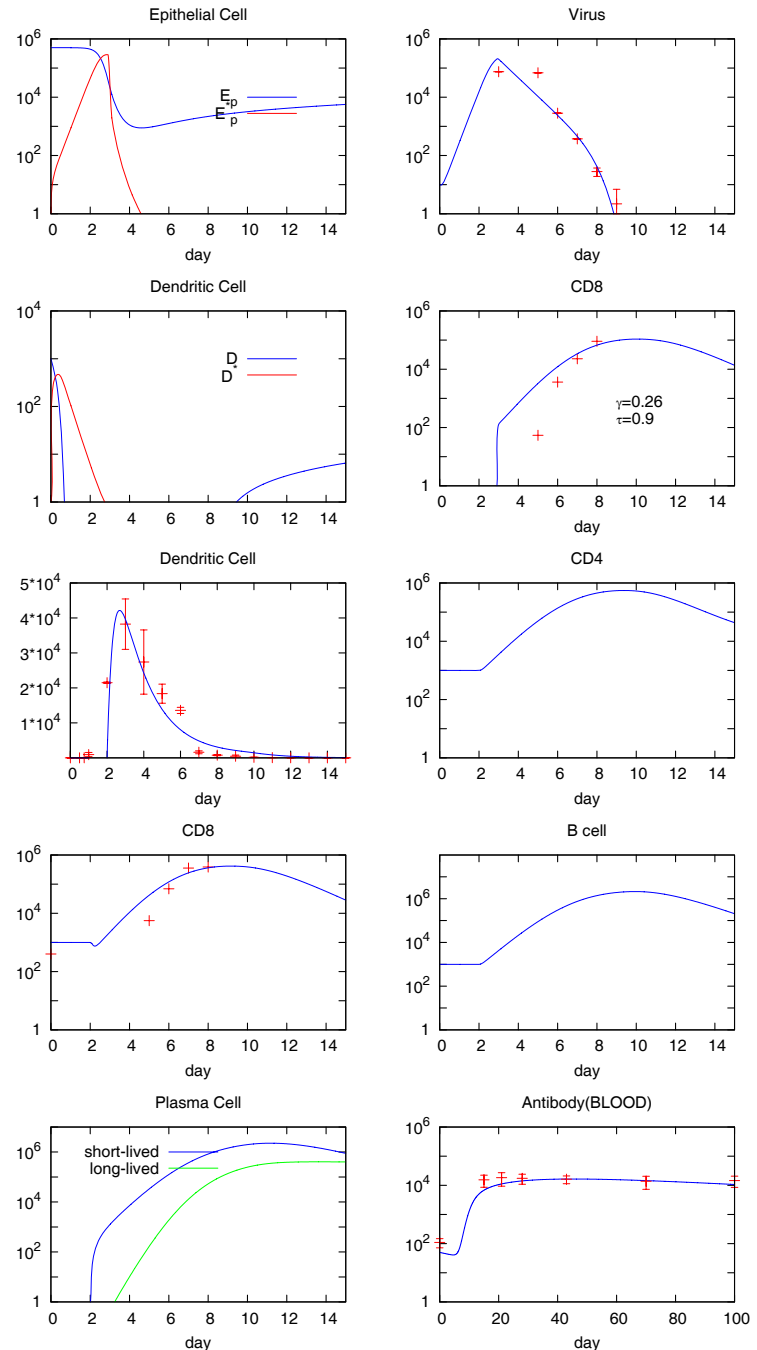
$$\frac{d}{dt}P_L = \pi_L H_E B_A - \delta_L P_L,$$

$$\frac{d}{dt}A = \pi_{AS} P_s + \pi_{AL} P_L - \delta_A A$$

Forward Problem

- X31 infection: virus cleared within 10 days since infection
- CD8+ T cells in airway/lung is approximated as $\gamma T_E(t - \tau_T)$ where $T_E(t)$ is the level of effector CD8+ T cells in spleen/lymph node
- respiratory DC migration stops around 2 days [Legge Immunity 2003]
- DC kinetics in lymph node [Belz PNAS 2004] compared with the model solution

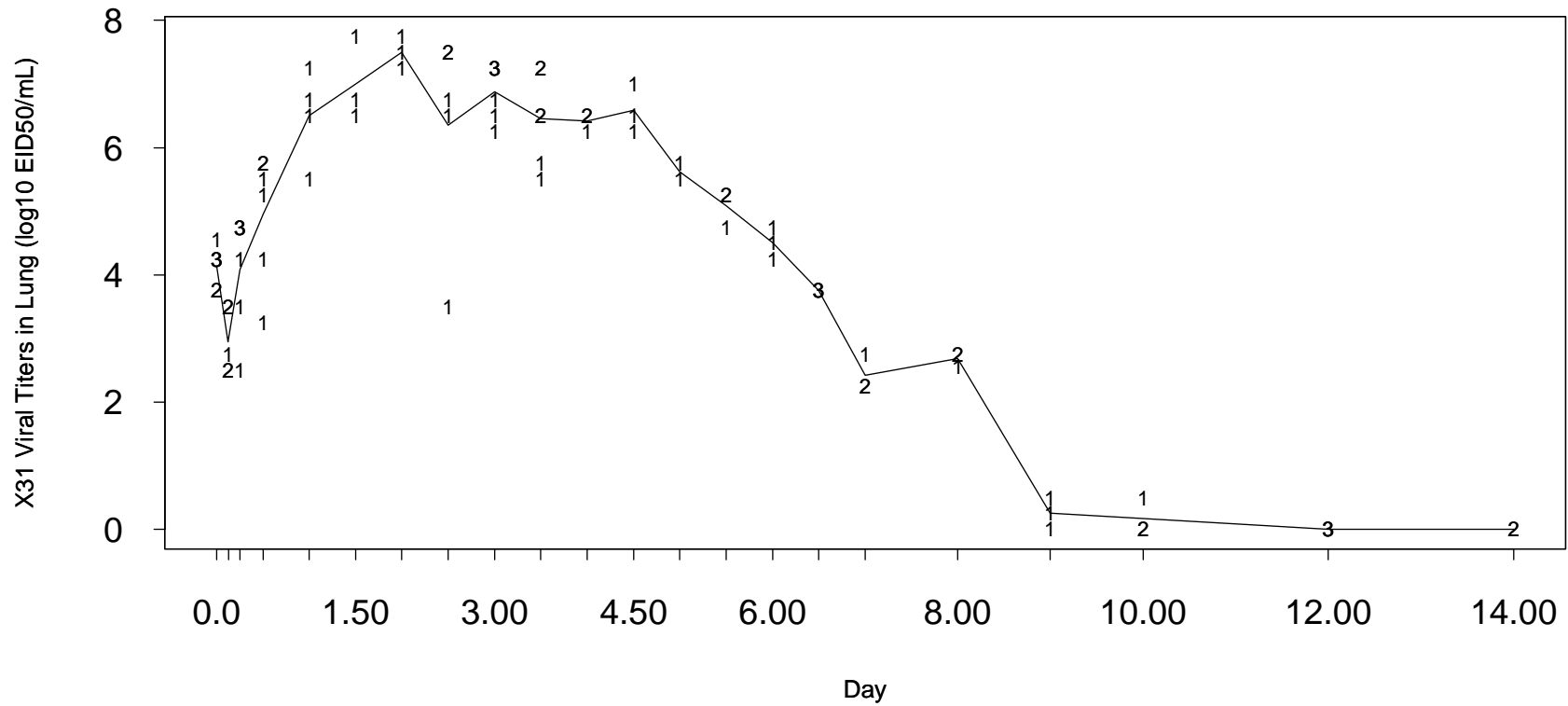
[Data provided by Topham, Belz, Heath, Randall]



Experimental Design and Statistical Methods

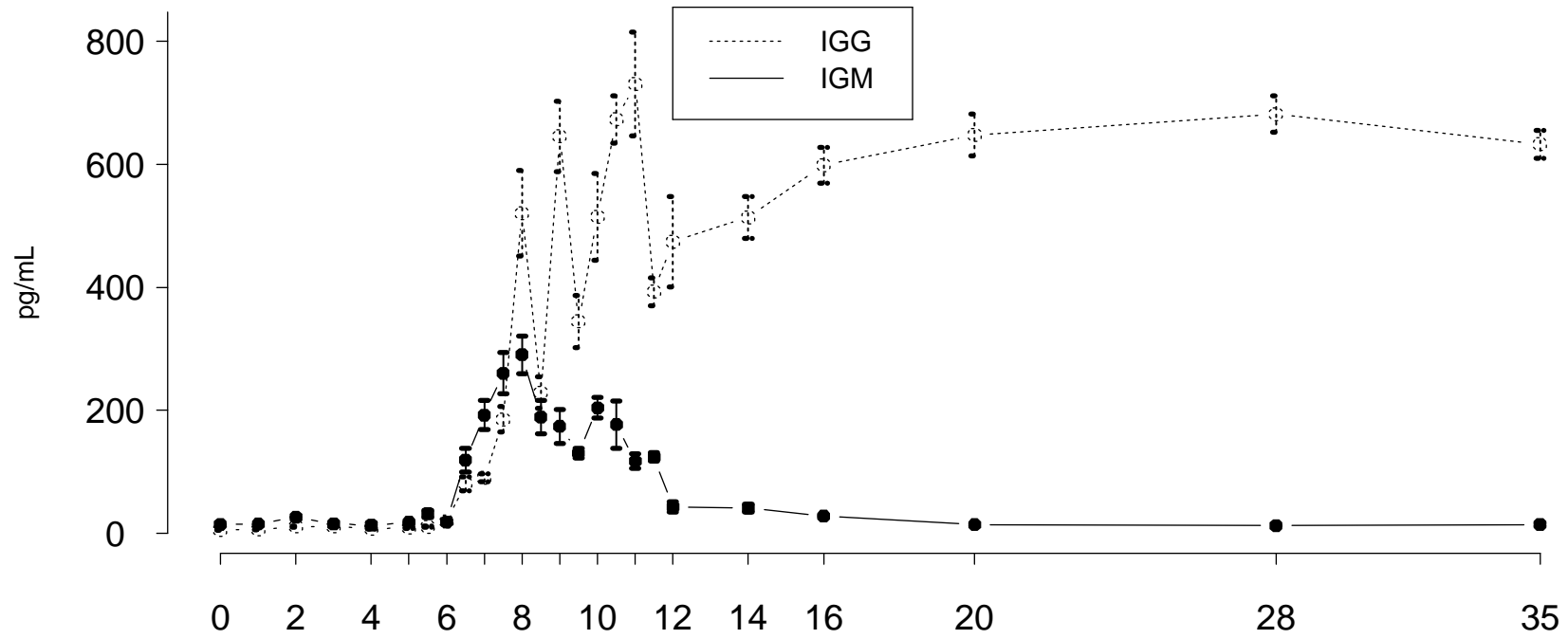
- Close interactions among statisticians, biomathematicians and influenza experimentalists
- Mathematical identifiability analysis
- Statistical identifiability analysis
- Statistical methods for parameter estimation and model validation
- Simulation-guided experimental design: what to measure and when to measure?
- Model fitting: experimental data
- Model validation and prediction

CBIM Topham Lab Haemagglutination Assay
 X31 Viral Titers in Lung (log₁₀ EID₅₀/mL)
 Pointwise Means and Individual Observations*



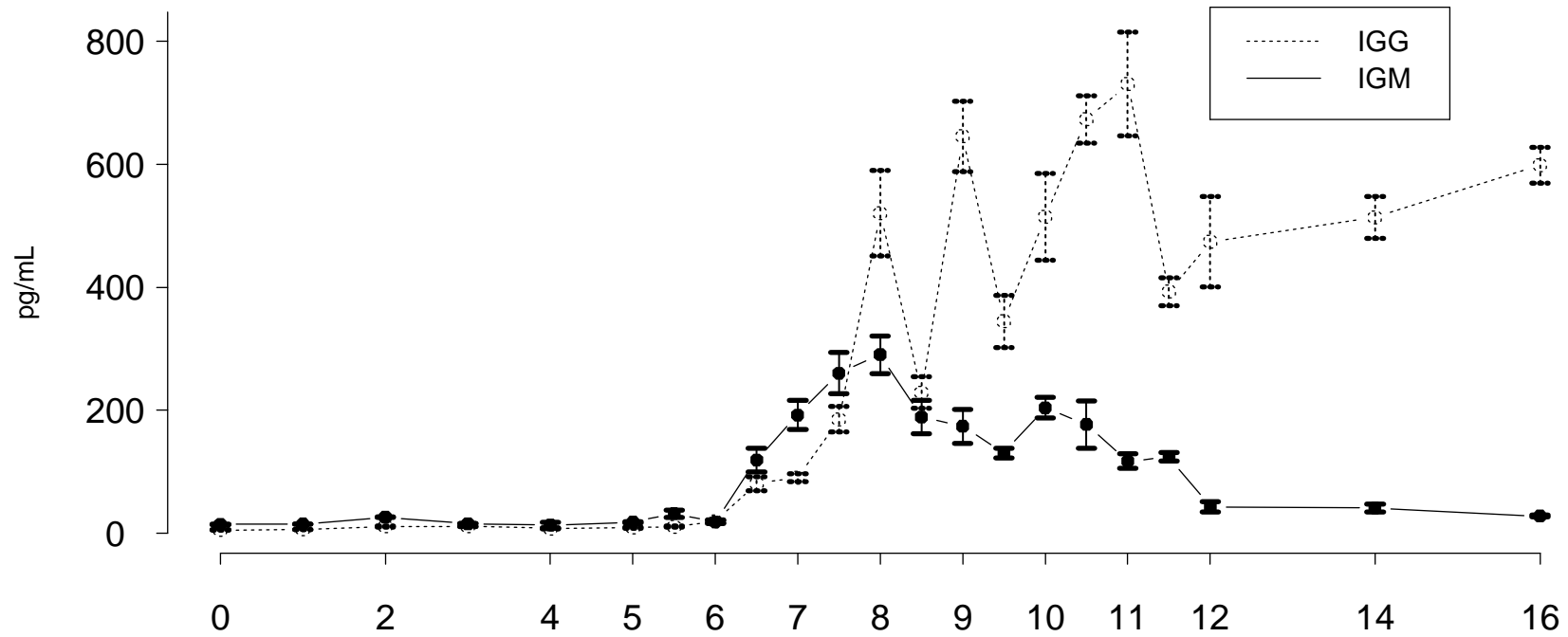
Data as of 4082008
 *=Num of Obs at each titer value

CBIM Zand Lab Elisa Results (0–35 Wks)
Serum X31–Antibody pg/mL
Pointwise Means \pm 2 Std Err



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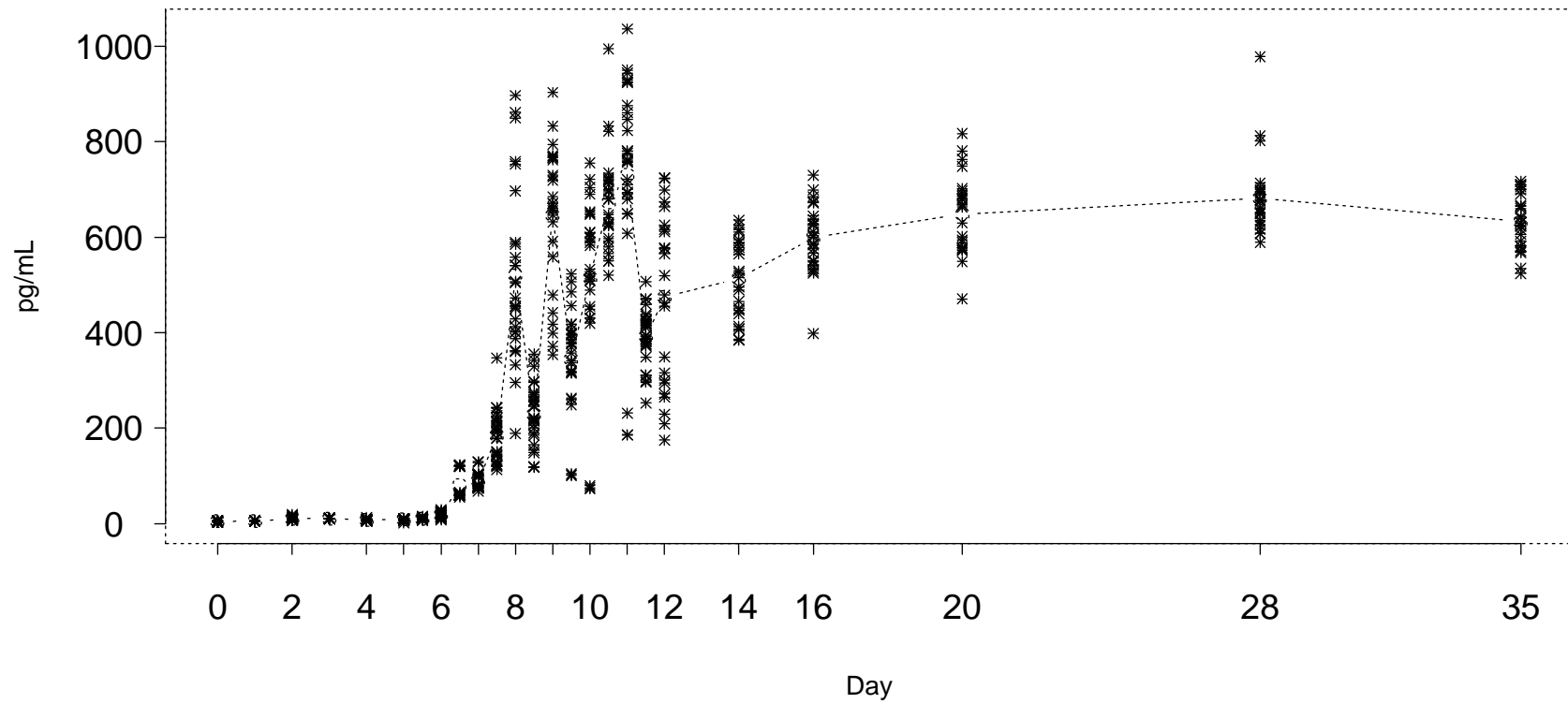
CBIM Zand Lab Elisa Results (0–16 Wks)
Serum X31–Antibody pg/mL
Pointwise Means \pm 2 Std Err



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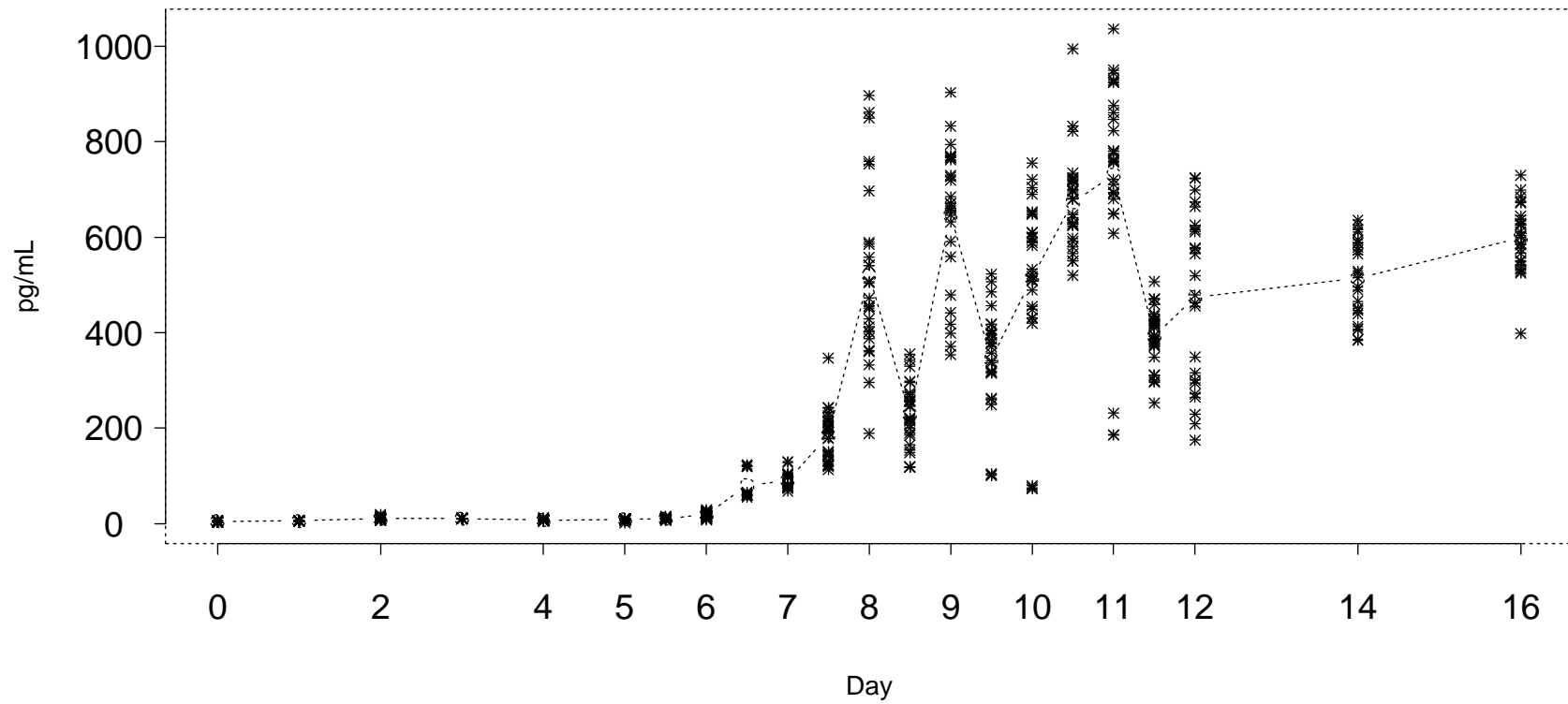
CBIM Zand Lab Elisa Results (0–35 Wks)
X31–Antibody pg/mL
Individual Replicate Observations and Pointwise Means

IGG



CBIM Zand Lab Elisa Results (0–16 Wks)
X31–Antibody pg/mL
Individual Replicate Observations and Pointwise Means

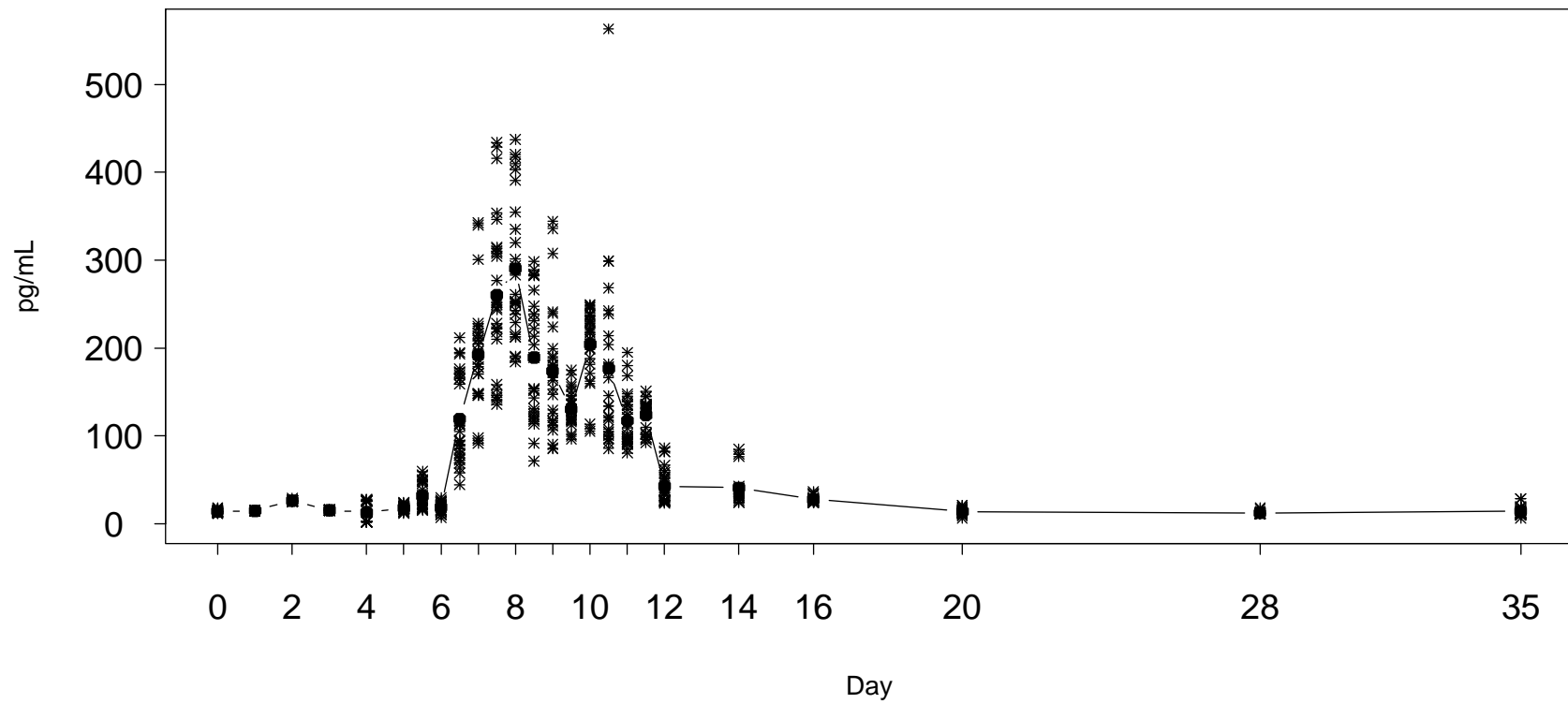
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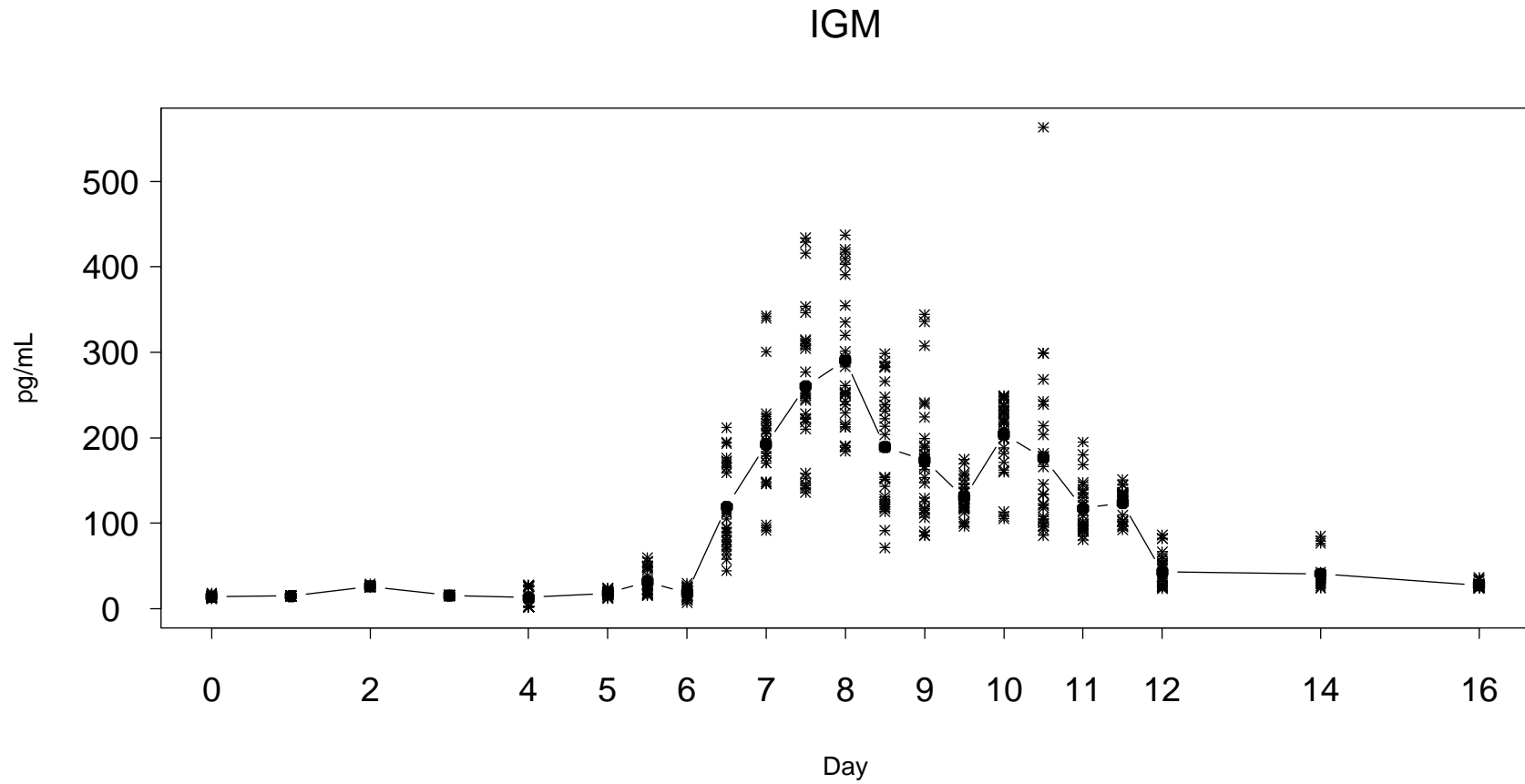
CBIM Zand Lab Elisa Results (0–35 Wks)
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Individual Replicate Observations and Pointwise Means

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Retrieved from DataTrans on Apr 7 2008

CBIM Zand Lab Elisa Results (0–16 Wks)
X31–Antibody pg/mL
Individual Replicate Observations and Pointwise Means



Retrieved from DataTrans on Apr 7 2008

Inverse Problems for ODE Models

- **Mathematical identifiability problem:** all parameters theoretical identifiable?
- **Statistical identifiability problem:** all parameters practically identifiable with presence of measurement errors
- **Statistical estimation methods:** how to identify (estimate) all identifiable parameters?

Mathematical Identifiability Problem

Under the ideal condition of noise-free observations, can all unknown parameters of the postulated model be uniquely estimated from the experimental data?

Nonlinear ODE models: difficult

- Power series expansion
- Similarity transformation
- Implicit function theorem
 - Wu, H., Zhu, H., Miao, H., and Perelson, A.S. (2008), Parameter Identifiability and Estimation of HIV/AIDS Dynamic Models, *Bulletin of Math. Biology*.
- Differential algebra methods
 - Miao, Dykes, Demeter, Wu (2008), Differential Equation Modeling of HIV Viral Fitness Experiments, *Biometrics*.
 - Miao, Dykes, Demeter, Cavanaugh, Park, Perelson, and Wu (2008), Modeling and Estimation of Kinetic Parameters and Replicative Fitness of HIV-1 from Flow-Cytometry-Based Growth Competition Experiments, *Bulletin of Math. Biology*.

Statistical Identifiability Problem

- Monte Carlo simulation approach
- Correlation matrix method

Statistical Estimation Methods for Nonlinear ODE Models

- The nonlinear least squares (NLS) principle:
 - numerically solve the ODE
 - global optimization method: necessary
 - differential evolution algorithm or scatter search method
- Bayesian methods
 - use prior to solve the identifiability problem
 - good for both cross-sectional data and longitudinal data: regression model and hierarchical model
 - computation: expensive
- Two-step smoothing approaches
 - avoid numerically solving the ODE
 - easy to implement
 - theoretical properties need to be established

The NLS Method

$$\frac{d}{dt}\mathbf{X}(t) = F[\mathbf{X}(t), \boldsymbol{\theta}], \quad \mathbf{X}(0) = \mathbf{X}_0 \quad (3)$$

$$\mathbf{Y}(t_i) = H[\mathbf{X}(t_i), \boldsymbol{\beta}] + \mathbf{e}(t_i), \quad (4)$$
$$\mathbf{e}(t_i) \sim (0, \sigma^2 \mathbf{I}), \quad i = 1, \dots, n$$

- **The NLS method:** minimizing

$$\sum_{i=1}^n \{\mathbf{Y}(t_i) - H[\mathbf{X}(t_i, \boldsymbol{\theta}), \boldsymbol{\beta}]\}^T \{\mathbf{Y}(t_i) - H[\mathbf{X}(t_i, \boldsymbol{\theta}), \boldsymbol{\beta}]\},$$

where $\mathbf{X}(t_i)$ evaluated numerically from Eq (3).

How to deal with local minima and non-convergence?

Gradient methods vs. global optimization methods.

The NLS Method: How to deal with local minima and non-convergence?

- Gradient methods: not work
- Global optimization methods: Differential evolution algorithm (Storn et al 1997).
- Mixture of stochastic global optimization method and deterministic methods: scatter search method (Rodriguez-Fernandez et al. 2006).

Bayesian Methods: Longitudinal Dynamic Model

Huang and Wu (J. of App. Stat. 2006) and Huang, Liu and Wu (Biometrics 2006).

Observation Model:

$$\mathbf{y}_i = V_i(\boldsymbol{\theta}_i) + \mathbf{e}_i, \quad [\mathbf{e}_i | \sigma^2, \boldsymbol{\theta}_i] \sim \mathcal{N}(\mathbf{0}, \sigma^2 \mathbf{I}_{m_i})$$

- $\mathbf{y}_i = (y_{i1}(t_1), \dots, y_{im_i}(t_{m_i}))^T$: measurements of V
- $V_i(\boldsymbol{\theta}_i)$: solutions to the differential equations
- $\boldsymbol{\theta}_i = (\gamma_i(t), \lambda_i, \rho_i, k_i, \delta_i, N_i, C_i)$: parameters for the i th subject
- $\mathbf{e}_i = (e_i(t_1), \dots, e_i(t_{m_i}))^T$: measurement errors

This can be written into a **nonlinear mixed-effects model**.

A Two-Step Smoothing Approach

$$\frac{d}{dt}\mathbf{X}(t) = F[\mathbf{X}(t), \boldsymbol{\theta}], \quad \mathbf{X}(0) = \mathbf{X}_0 \quad (6)$$

$$\mathbf{Y}(t_i) = \mathbf{X}(t_i) + \mathbf{e}(t_i), \quad \mathbf{e}(t_i) \sim (0, \sigma^2 \mathbf{I}), \quad (7)$$

A Two-Step Estimation Approach:

- **Step 1.** Fit model (7) to obtain the estimates of $X(t)$ and $X'(t) = dX(t)/dt$: $\hat{X}(t)$ and $\hat{X}'(t)$ using a nonparametric smoothing method.
- **Step 2.** Substitute the estimates $\hat{X}(t_i)$ and $\hat{X}'(t_i)$ in the dynamic equation (6) to obtain a regression model:

$$\hat{X}'(t_i) = F[\hat{X}(t_i), \boldsymbol{\theta}(t_i)] + e_2(t_i). \quad (8)$$

Then fit the above nonlinear regression model to estimate $\boldsymbol{\theta}$ from (8).

Statistical Estimation Methods for ODE Models: Our Publications

- Huang, Y. and Wu, H. (2006), “A Bayesian Approach for Estimating Antiviral Efficacy in HIV Dynamic Models,” *Journal of Applied Statistics*, **33**, 155-174.
- Huang, Y., Liu, D. and Wu, H. (2006), Hierarchical Bayesian Methods for Estimation of Parameters in a Longitudinal HIV Dynamic System, *Biometrics*, **62**, 413-423.
- Wu, H., Huang, Y. and Acosta, E.P. et al. (2005), Modeling Long-Term HIV Dynamics and Antiretroviral Response: Effects of Drug Potency, Pharmacokinetics, Adherence, and Drug Resistance, *JAIDS*, **39**, 272-283.
- Wu, H., Huang, Y. and Acosta, E.P. et al. (2006), Pharmacodynamics of Antiretroviral Agents in HIV-1 Infected Patients Using Viral Dynamic Models That Incorporate Drug Susceptibility and Adherence, *Journal of Pharmacokinetics and Pharmacodynamics*, **33**, 399-419.
- Chen, J. and Wu, H. (2007), Estimation of time-varying parameters in deterministic dynamic models with application to HIV infections, accepted by *Statistica Sinica*.

- **Chen, J. and Wu, H. (2007), Efficient Local Estimation for Time-varying Coefficients in Deterministic Dynamic Models with Applications to HIV-1 Dynamics, accepted by *JASA*.**
- **Wu, H., Zhu, H., Miao, H., and Perelson, A.S. (2007), Parameter Identifiability and Estimation of HIV/AIDS Dynamic Models, accepted by *Bulletin of Mathematical Biology*.**
- **Miao, H., Dykes, C., Demeter, L., Wu, H. (2008), Differential Equation Modeling of HIV Viral Fitness Experiments: Model Identification, Model Selection, and Multi-Model Inference, accepted by *Biometrics*.**
- **Miao, H., Dykes, C., Demeter, L.M., Cavanaugh, J., Park, S.Y., Perelson, A.S., and Wu, H. (2008), Modeling and Estimation of Kinetic Parameters and Replicative Fitness of HIV-1 from Flow-Cytometry-Based Growth Competition Experiments, accepted by *Bulletin of Mathematical Biology*.**
- **Liang, H., Wu, H., (2008), Parameter Estimation for Differential Equation Models Using a Framework of Measurement Error in Regression Models, invited revision for *JASA*.**

User-Friendly Software Development

- Friendly to quantitative scientists: mathematicians, statisticians and computer scientists
- Friendly to biological scientists and biomedical investigators
- Two software tools under development
 - Immunological data sharing and data management system: **DataTrans**
 - Differential equation model simulation and estimation for immunology and infectious disease modeling: **DEDiscover**

DataTrans

A web-based Data Management System for immunological experiment data

developed by the University of Rochester Medical Center - Department of Biostatistics and Computational Biology

A Comprehensive Data Management System for Immunological Research

An immunological research always involves different types of data and information, like biological samples of participating subjects, experiment raw data from immunological laboratories, processed data by computation tools, and various documents for studies. It also needs an efficient way to handle tremendous phenotype data generated by immunological assays which include flow cytometry, enzyme-linked immunosorbent assay (ELISA), and enzyme-linked immunospot (ELISPOT). In addition, researchers need a standardized tool to record all data and documents based on research workflows, an easy way to save and query data/documents from distributed locations, and an efficient platform for data sharing to the broad research community. To achieve those goals we present a comprehensive Web-based system, DataTrans, for managing data and information in the studies of immunological research.

Partial funding support from



Contract Number N01-AI-50020



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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



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April 2008						
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6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30			



Model Simulation

Parameter

delta_E: 0.0--0.01, 0.001

beta_E: 0.0--0.0010, 0.00004

k_E: 0.0--1.0, 0.04

gamma: 0.0--1.0, 0.28

tau_T: 0.0--5.0, 0.9

delta_Es: 0.0--10.0, 1

pi_V: 0.0--10.0, 1.9

c_V: 0.0--10.0, 1.9

Initial Condition

EP: 100000.0--100000..., 500,000

EPs: 0.0--0.0, 0

V: 0.0--0.0, 0

Output Control

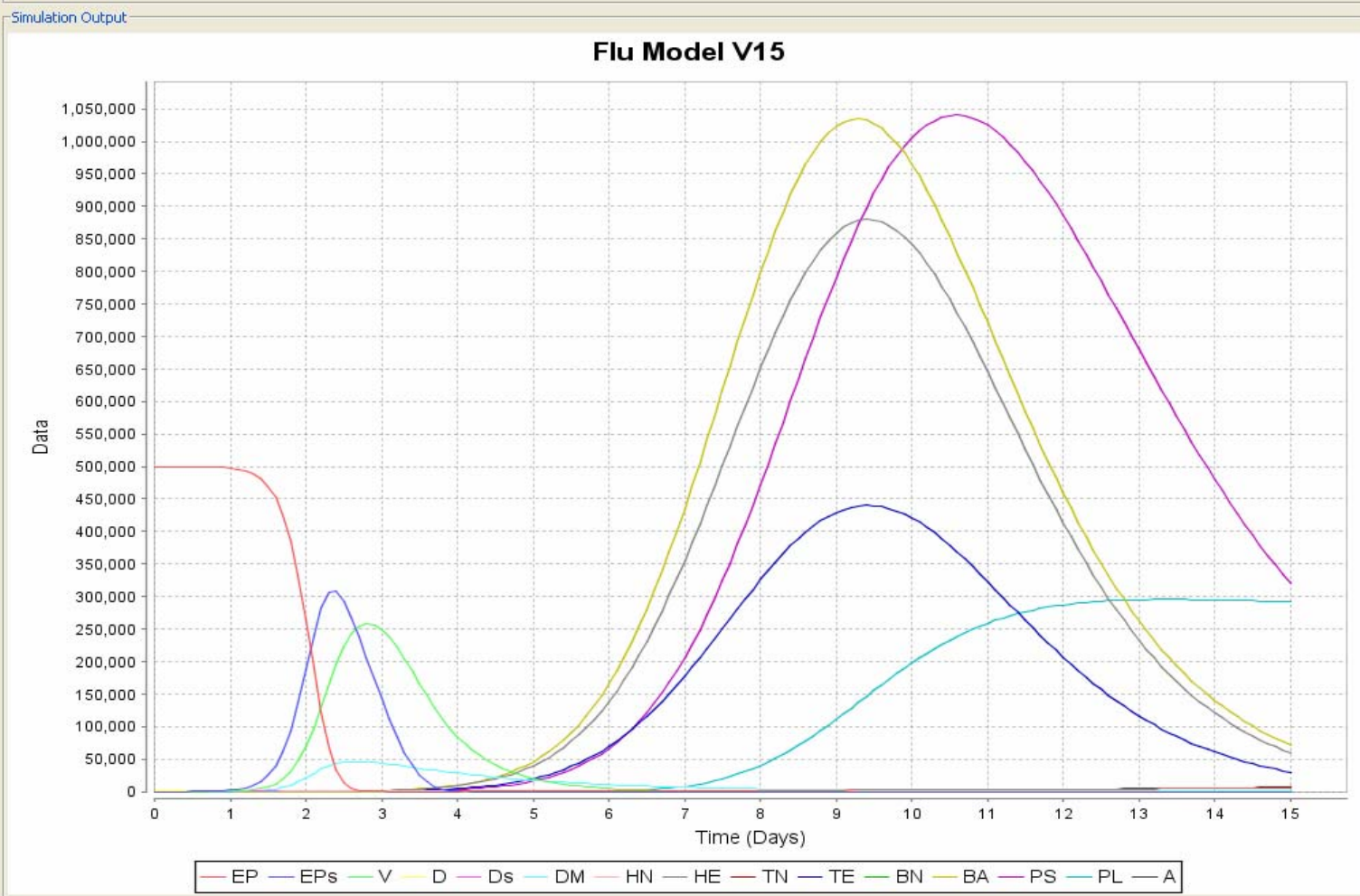
Format: Combined Individual Table

Display Variables

EP EPs V D Ds DM HN HE TN TE BN BA PS

Transformation

None Log(10) Log(e)



Discussion and Conclusion

- **Multi-discipline communication barrier**
 - Among quantitative scientists: mathematicians, statisticians, physicists, engineers and computer scientists
 - Between quantitative scientists and biological scientists
- **Management barrier**
 - Lack of leaders who have multi-disciplinary training and knowledge
 - Lack of leaders who have both management skills and research capability with long-term missions
- **Education and promotion**
 - Special training: conference, workshop, symposium, summer school
 - Regular training: education program and courses

Acknowledgment

- **Statisticians:** Drs. Yangxin Huang, Dachen Liu, Jianwei Chen, Hongqi Xue, Hua Liang
- **Math Modelers/Biophysicists:** Drs. Ha Youn Lee, Alan Perelson
- **Bioengineers:** Dr. Hongyu Miao
- **Biocomputing:** Drs. Jingming Ma, Dongwen Wang, Gregory M Warnes
- **Software/Database Developers:** Jeffrey Williams, Canglin Wu, Alain LeBlanc, Carol Crowley, Tao Wu, Stephen Massaro, Weidong Yin
- **Virologists/Immunologists:** Drs. Lisa Demeter, Xia Jin, Martin Zand, David Topham, Tim Mosmann, Brian Ward
- **Project manager:** Ms. Jeanne Holden-Wiltse

B



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- NIAID/NIH grant N01 AI50020: Center for Biodefense Immune Modeling