Understanding the Immune System Using Optimization and Control

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Advanced Methods and Perspectives in nonlinear Optimization and Control.
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Part I: Control & Optimization in Critical Care Medicine (w/ Pinsky & Hravnak)

- Small dimensional system – complex dynamics

Part II: Understanding The Immune System in Infectious Diseases (CMPI)

- Huge dimensional system – simple dynamics

Shock

A physiological state with significant, systemic reduction in tissue perfusion → tissue injury.

Four Profiles

Hypovolemic: Decreased preload->small ventricular end-diastolic volumes -> inadequate cardiac generation of pressure and flow

Septic: release of inflammatory mediators

Cardiogenic: Intrinsic abnormality of heart -> inability to deliver blood into the vasculature with adequate power

Neurogenic :Loss of autonomic innervation of the cardiovascular system

Hemodynamic Profiles

	PCWP	CVP	CO/CI	SVR/I
Hypovolemic	Low	Low	Low	High
Cardiogenic	High	High	Low	High
Inflammatory	Low / N	Low/N	High	Low
Neurogenic	Low	Low	Low	Low

PCWP: Pulmonary capillary wedge pressure -indirect estimate of left atrial pressure
CVP: Central Venus pressure- a good approximation of right atrial pressure
CO/CI: Cardiac Output, Cardiac Index
SVR/I: Systemic Vascular Resistance, Systemic Vascular Resistance Index

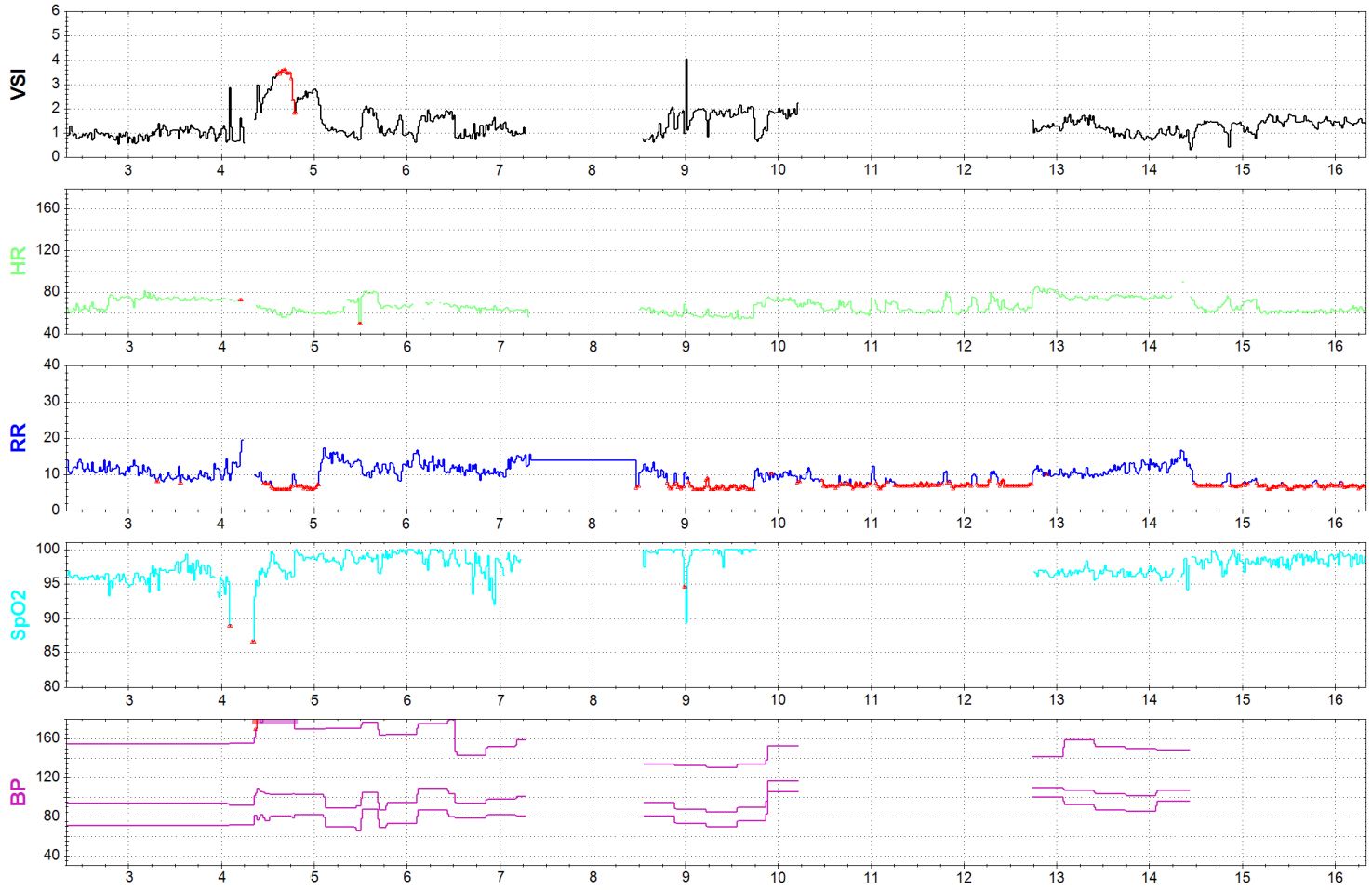
The four profiles represent different regions in phase space with possibly attractors of different shapes

Medical Issues

- Assessment of severity
- Stratifying the risk for complications
- Gauging the adequacy of therapy
- Estimating improved predictions if additional measurements were supplied

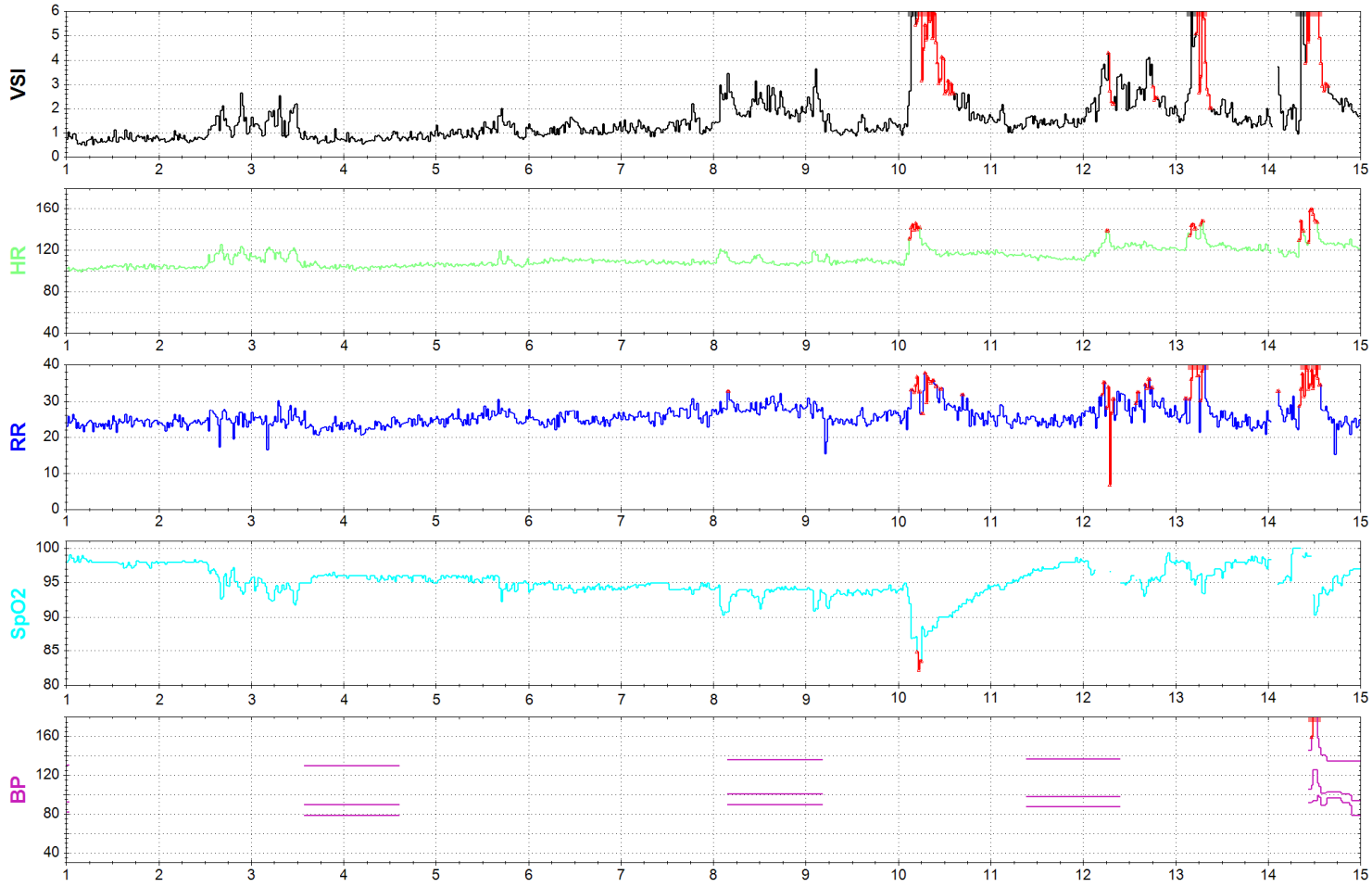
- Need to develop metrics to assess these challenges

Chaotic Dynamics



Mild changes in the attractor over time. Data: Hravnak & Pinsky

Chaotic Dynamics cont.



Significant changes in the attractor over time. Data: Hravnak & Pinsky

Mathematical Modeling

ODE $$dX/dt = V(X, \alpha) \quad X(t) \in \mathbb{R}^n$$

Basic model : X(t) - physiological measurements,
α - model parameters

Attractor is rough → Add noise to smooth it.
Noise may also be biologically relevant

SDE $$dX_t = V(X_t, \alpha)dt + \sqrt{2\sigma}dW_t$$

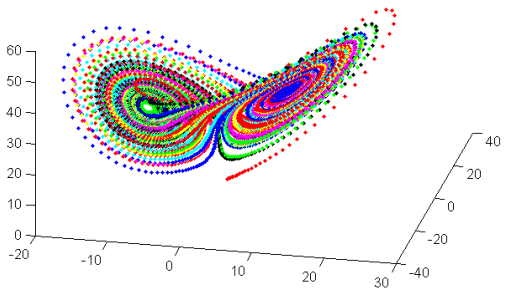
- **The attractor is stable under perturbation**
- **Trajectories are sensitive to perturbation**

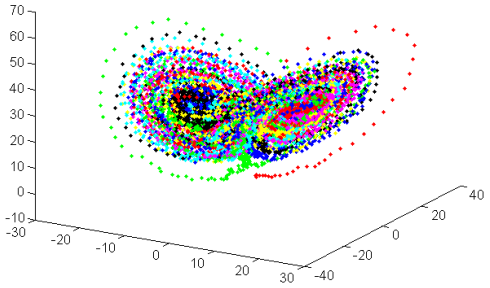
The Attractor and its Measure

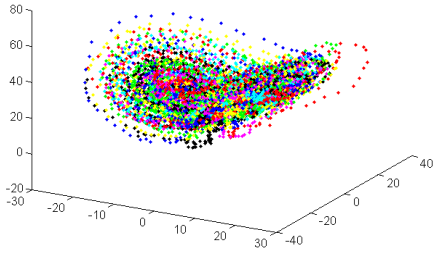
The biologically significant quantity is the measure satisfying the equation

$$div(V(x,\alpha)\rho) - \sigma\triangle\rho = 0$$

$\rho(x)dx$ represent the fraction of time the trajectory spend in a small volume around x







Modeling a Patient – System Identification

- Find a model for the chaotic dynamics, i.e, V(x,a), using data ρ_d
- Define a distance $E(\alpha) = d^2(\rho(\alpha), \rho_d)$
- SysID problem

$$Min_{\,\alpha}\ E(\alpha) \qquad \text{subject to}$$

$$div(V(x,\alpha)\rho(x,\alpha)) - \sigma\triangle\rho(x,\alpha) = 0$$

The Choice of Distance

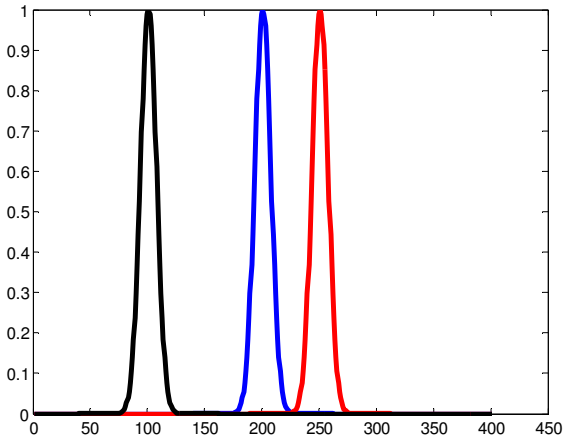
- Example

$$E(\alpha) = d^2(\rho(\alpha), \rho^*) = \|\rho(\alpha) - \rho^*\|_2^2$$

Not a good optimization problem: Functional is flat when the support of the two measures are far apart.

Dist(red, black) ~ Dist(red, blue)

Functional has flat regions!!



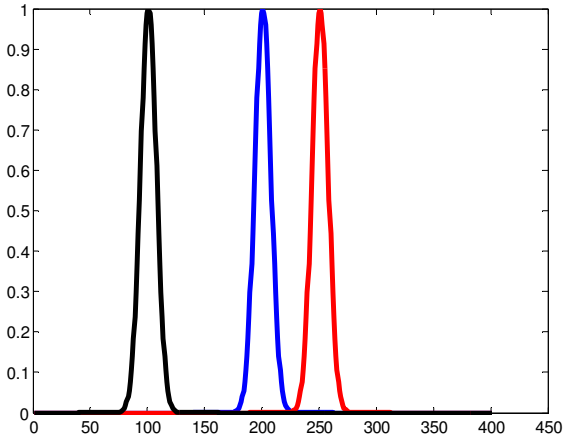
Choice of Distance cont.

- Example II:

$$E(\alpha) = d_W^2(\rho, \bar{\rho}) \quad \text{2-Wasserstein Distance}$$

- A natural distance between measures.

- Functional is sensitive to changes in the measures even when their supports are far apart.
  Dist(red, black) ~ 3 Dist(red,blue)



2-Wasserstein Distance

absolutely continuous case

$$d_W^2(\rho,\bar{\rho}) = \min_{\phi_\# \rho = \bar{\rho}} \int |\phi(x) - x|^2 \rho(x) dx$$

Or

$$d_W^2(\rho,\bar{\rho}) = \min_{U,W} \int U(x)\rho(x) + \int W(y)\bar{\rho}(y)dy + const.$$
$$U(x) + W(y) \leq x \cdot y$$

Optimality conditions

$$U(x) + W(y) = x \cdot y \quad \text{for} \quad \mu(x,y) > 0$$
$$\int \mu(x,y)dy = \rho(x) \qquad \int \mu(x,y)dx = \bar{\rho}(y) \quad \mu(x,y) \geq 0$$

Calculating Gradients

Cost function $E(\alpha) = d_W^2(\rho, \rho^*)$

Optimization Problem

$$Min_{\alpha}\ E(\alpha) \qquad \text{subject to}$$

$$div(V(x,\alpha)\rho(x,\alpha)) - \sigma\triangle\rho(x,\alpha) = 0$$

Perturbations:

$\alpha \to \alpha + \epsilon\tilde{\alpha}$

$V \to V + \epsilon V_\alpha \tilde{\alpha}$

$\rho \to \rho + \epsilon\tilde{\rho}$

$$div(\tilde{V}\rho) + div(V\tilde{\rho}) - \sigma\triangle\tilde{\rho} = 0$$

Gradients Cont.

Lagrangian

$$\mathcal{L}(\rho, \lambda, \alpha) = d_W^2(\rho, \rho^*) + \int \lambda(div(V\rho) - \sigma\triangle\rho)dx$$

$$\frac{d}{d\epsilon} d_W^2(\rho + \epsilon\tilde{\rho}, \rho^*)|_{\epsilon=0} = \int U(x)\tilde{\rho}(x)dx$$

$$-div(V\lambda) - \sigma\triangle\lambda = U$$ **Adjoint equation**

$$\nabla_\alpha E(\alpha) = -\int \rho V_\alpha \nabla\lambda dx$$ **The Gradient**

Implementation Details

- Approximating V(x,α)

$$V(x,\alpha) = \alpha_0 + \alpha_1 x + \alpha_2\, xx^T$$

Multigrid Solver

- Variables: $\rho^h, \lambda^h, U^h, W^h, \alpha$
- FAS transfers between levels.
- Optimizing for α on coarsest levels, pointwise relations for $\rho^h, \lambda^h, U^h, W^h$

Primal-Dual Formulation

$$\min_{\alpha, U^h, W^h} \int U^h(x)\rho^h(x)dx + \int W^h(y)\bar{\rho}^h(y)dy \quad \text{subject to}$$

$$div_h(V(\alpha)\rho^h) - \sigma\triangle_h\rho^h = 0 \qquad \int \rho^h dx = \int \bar{\rho}^h dx$$

$$U^h(x) + W^h(y) \leq x \cdot y$$

Optimality conditions

$$div_h(V(\alpha)\rho^h) - \sigma\triangle_h\rho^h = 0 \qquad \int \rho^h dx = \int \bar{\rho}^h dx$$

$$-div_h(V\lambda^h) - \sigma\triangle_h\lambda^h = U \qquad \int \rho^h V_\alpha \nabla_h \lambda^h dx = 0$$

$$U^h(x) + W^h(y) = x \cdot y \quad \text{for} \quad \mu^h(x,y) > 0$$

$$\int \mu^h(x,y)dy = \rho^h(x) \qquad \int \mu^h(x,y)dx = \bar{\rho}^h(y) \quad \mu^h(x,y) \geq 0$$

Designing Treatment Using Control Theory

Medicine tells us that some ρ^* are 'good'.

They characterize healthy people. Or that some regions in the phase space are 'bad' (Four profiles)

Biological parameters are implicit in $V(x, \alpha)$

A control problem: $E(\alpha) = d_W^2(\rho(\alpha), \rho^*)$

Treatment Design

$$Min_{\,\alpha}\ E(\alpha) \qquad \text{subject to}$$

$$div(V(x,\alpha)\rho(x,\alpha)) - \sigma\triangle\rho(x,\alpha) = 0$$

Additional Functions

The probability that we are in a 'bad' region A $\int_A \rho(x)dx$

Recall the four profiles (Hypovolemic, Cardiogenic Inflammatory, Neurogenic) - 'bad' regions of the phase space

Enforcing constraints $\int_A \rho(x)dx \leq \eta$

Or modifying cost function

$$E(\alpha) = d_W^2(\rho(\alpha), \bar{\rho}) + \beta \int_A \rho(x)dx$$

Relating Physiological Measurements and Model Coefficients

Treatment affects dynamics parameters α.

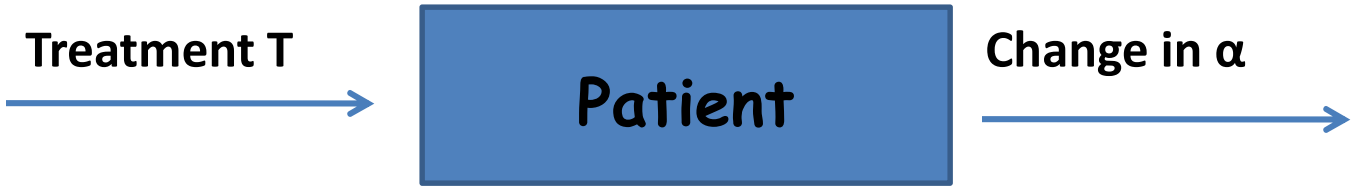
Hypovolemic : ABCs, IVF (crystalloid), Transfusion Stem ongoing Blood Loss

Septic: ABCs, IVF, Blood cx, ABX, Drainage, pressors

Cardiogenic : *CHF*– diuretics & vasodilators +/- pressors.
LV failure – pressors, intra aortic balloon pump & ventricular assist device.

Neurogenic: IVF, vasoactive medications if refractory

Need: α sensitivities with respect to all treatments



Medical Challenges and Mathematical Formulations

- Assessment of severity
  - W-distance from 'healthy' attractors
- Stratifying the risk for complications
  - Probability to be in certain regions of phase space
- Gauging the adequacy of therapy
  - Change of cost function with treatment
- Estimating Improved Predictions if additional measurements were supplied
  - Comparing higher dimensional models (more measurements) with lower dimensional ones

Understanding The Immune System in Infectious Diseases

NIH Biodefense

Center for Modeling Pulmonary Immunity

University of Pittsburgh

Carnegie Mellon

University of Michigan

Experiments

Penny Morel, PI

Jerry Nau

Ted Ross

Russ Salter

Joanne Flynn

Math Modeling

Shlomo Ta'asan, co-PI

Emrah Diril

Ziv Bar-Joseph

Benoit Morel

Jason Ernst

Denise Kirschner

Simeone Marino

Statistical Analysis

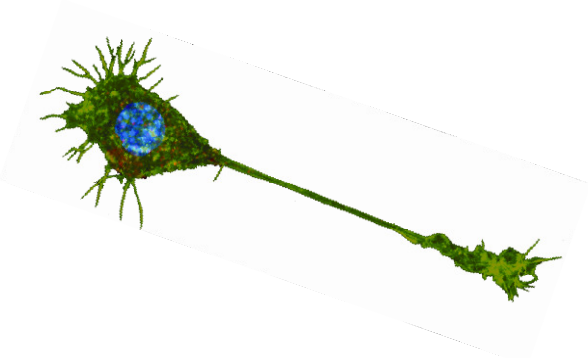
Takis Benos

Shaun Mahony

Bioinformatics

Panos Chrysanthis

Alex Labrinidis



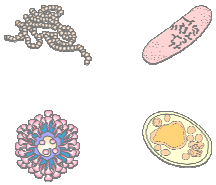
The Immune System

- **The Players:**

  Organs (handful), cells (~2 dozen), molecules (~2000), genes

- **The Pathogens**

  Viruses, Bacteria, Parasites, Fungi



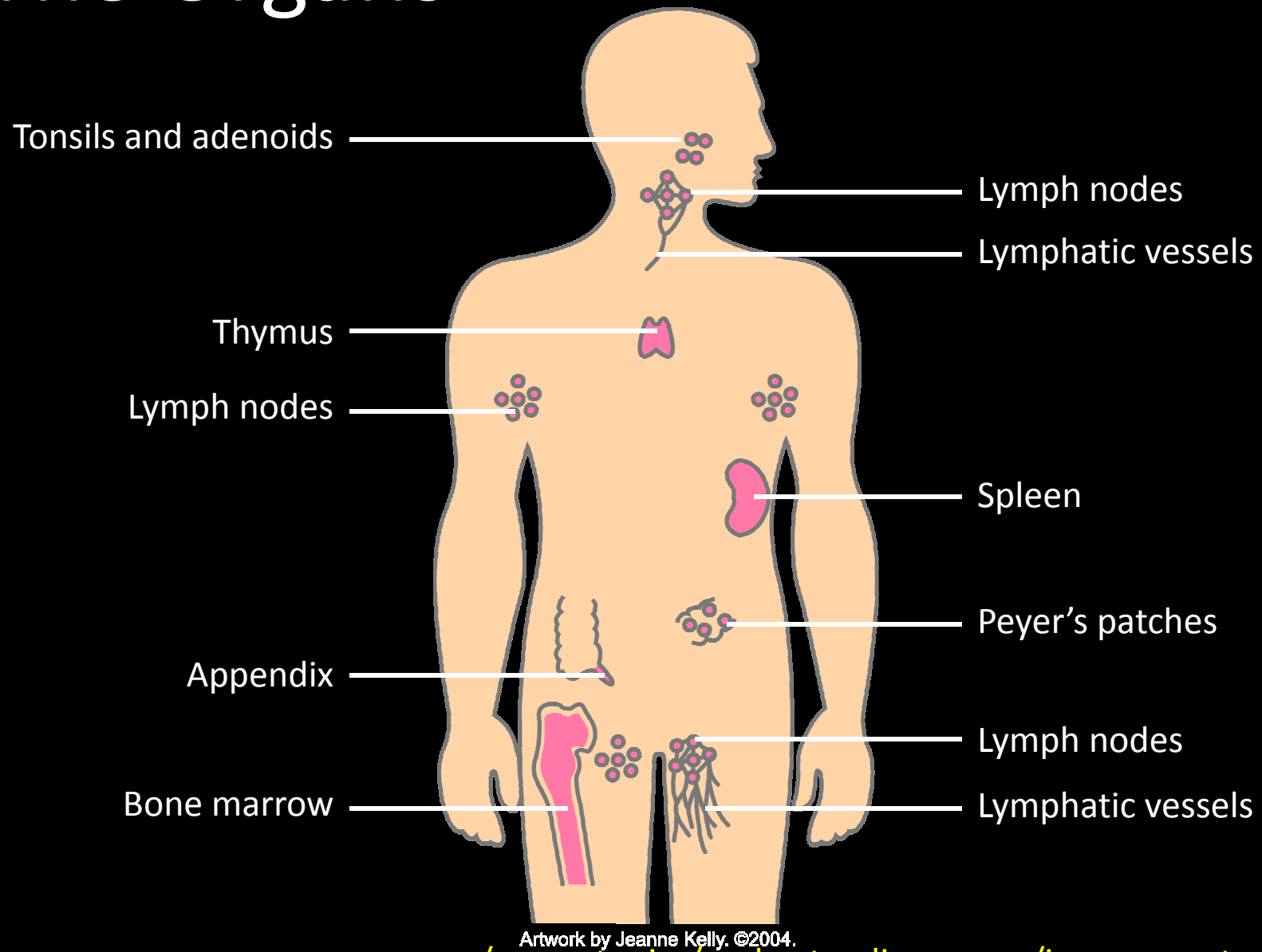
- **The State of the System:**

  High dimension

- **Its Purpose**

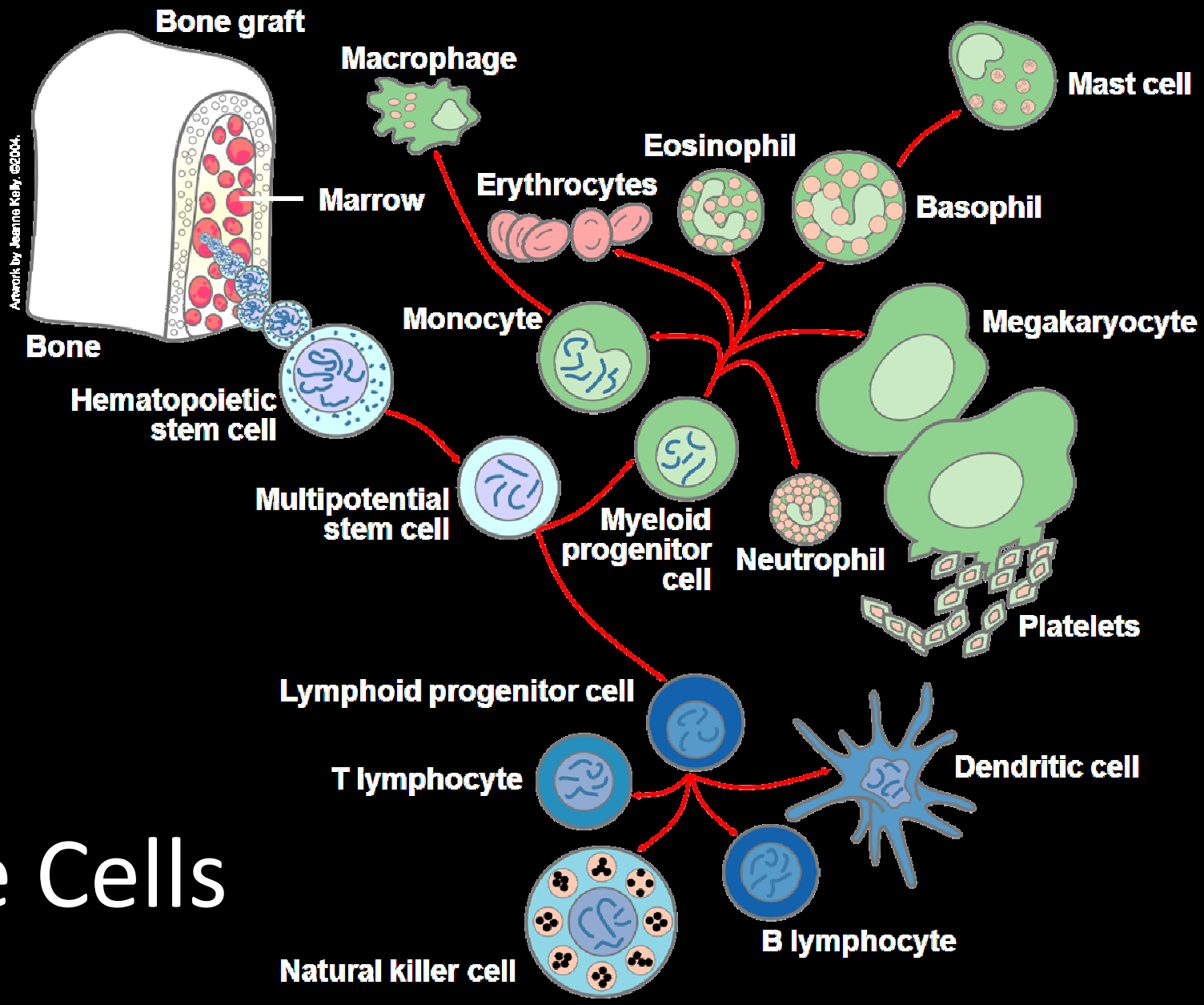
  Eradicate pathogens, tissue repair.

The Organs



www.cancer.gov/cancertopics/understandingcancer/immunesystem

The Cells



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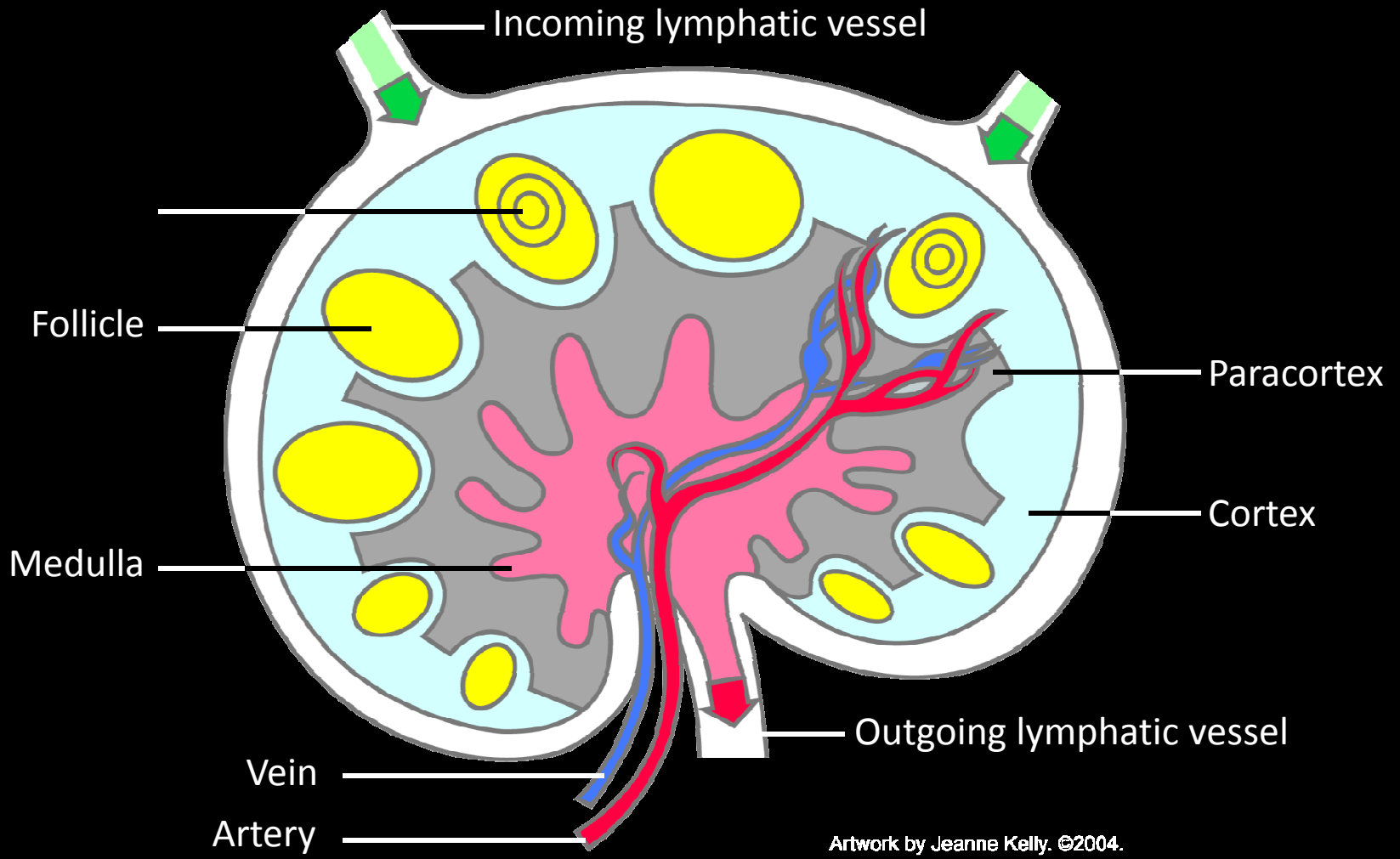
Lymph Node (where interactions take place)



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The Interactions

- **Immune System Cells Can**
  - Receive to a set of messages (R)
  - Transmit a set of messages (T)
  - May change the set R & T upon receiving $r \in R$
  - Secrete effector molecules (antibodies, toxins,..)
  - Damage tissue (secretion of toxins)
  - **Repair tissue** (secretion of growth factors)
  - **Eradicate pathogens**

An orchestra without a conductor!!

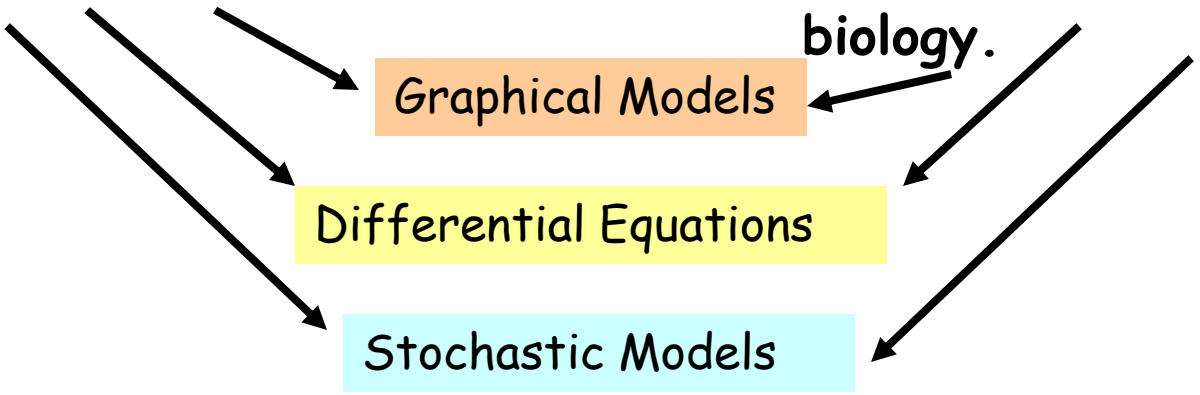
Modeling Approaches

Traditional Modeling

- Biological knowledge & hypotheses are translated into mathematics.
- The role of math is to refine our understanding (parameter ranges, …).

System Identification Black-Box Modeling

- Experimental data with little or no explanation is given.
- A mathematical formulation is done to 'discover' the biology.

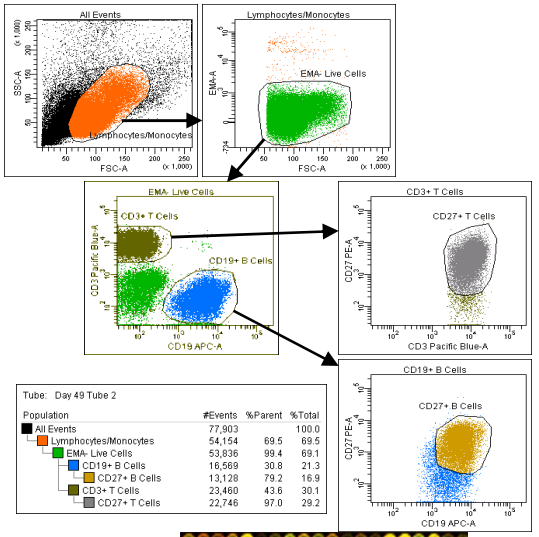


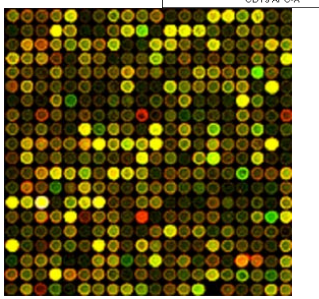
System Identification Data Driven -Black Box Modeling

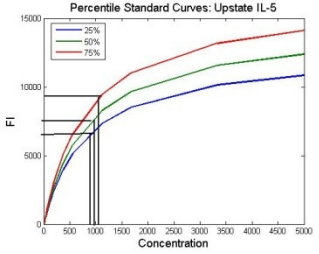
- Define a **class** of models
  - Linear, nonlinear, …
- Find the model in this class that best fit the data.
- Important Features:

  No biological knowledge is used!

  The meaning of data is insignificant!







SysID approach is now possible due to recent revolution in experimental techniques → abundant data at multiple scales

The Driving Questions:

How complex is the response?

- how many variables are needed?
- how complex is the dynamics?

How to control it?

- which interventions (variables) are most effective?
- how to apply these interventions?
- vaccination:

  what parameters does vaccination change?

Very different from traditional approach: assuming no prior biological knowledge

Understanding Response

- Dynamics on high dimensional manifold
- Building Approximations
  - Approximate space – affine variety
  - Approximate dynamics – linear, nonlinear
- Inverse problems
  - Data → Models → Intervention

System Identification Approach

Assumptions

- The immune system can be approximated as a large set of nonlinear equations

$$\frac{dX}{dt} = f(X) \qquad X = (x_1, \cdots, x_N)$$

- The immune system is in steady state in the absence of challenges

$$f(X) = 0 \qquad X = (x_1, \cdots, x_N)$$

- Important information about the system can be obtained from studying small perturbations.

Small perturbations of the immune system satisfy linear systems of equation

$$\frac{dY}{dt} = AY \quad Y = (y_1, \cdots, y_N) \qquad \text{y-equation}$$

Incomplete Information

Measurements of the system are only partial !!

$$V = (v_1, \cdots, v_K) \qquad K \ll N$$

V(t) need not satisfy a similar equation to Y(t).

In general, the model for V(t) is

$$\frac{d^n V}{dt^n} = A_1 \frac{d^{n-1} Y}{dt^{n-1}} V + A_2 \frac{d^{n-1} V}{dt^{n-1}} V + \cdots + A_n V$$

The Modeling Problem: Find the Coefficients A1, … An

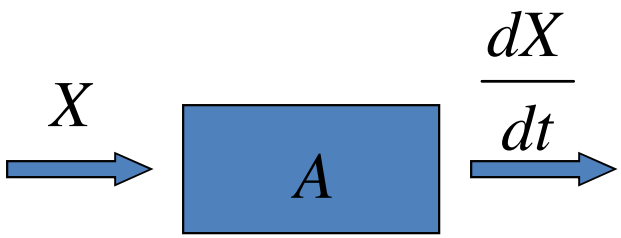
The Approach: Find the coefficients that fit the data the best.

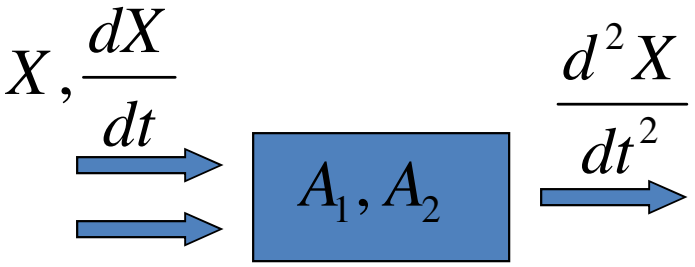
Continuous Time Models

$X(t)$ The state of the animal at time t

$u(t)$ Drug amount at time t

B The drugs mixture





$$\frac{dX}{dt} = AX(t)$$

First Order Model

$$\frac{d^2X}{dt^2} = A_1\frac{dX}{dt} + A_2X$$

Second Order Model

Higher order models are also possible.

Objective: Construct a model from measurements of X at different times.

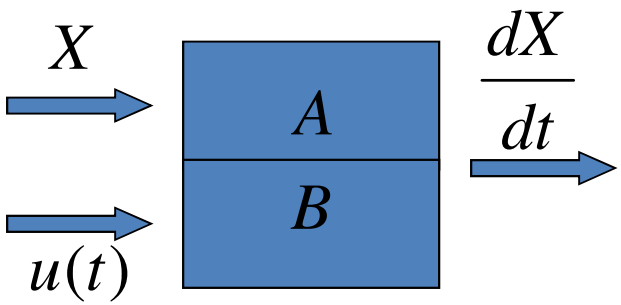
Continuous Time Models –

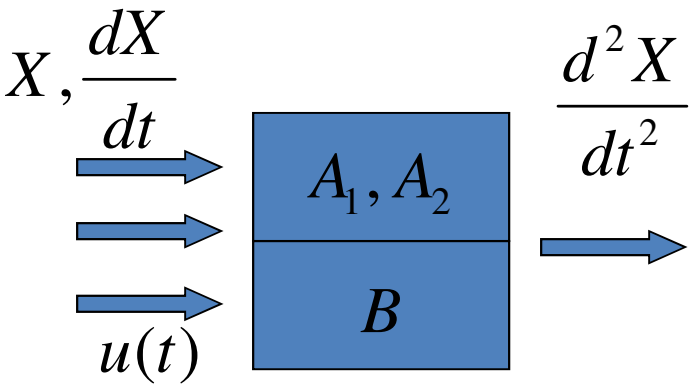
Intervention Design

$X(t)$ The state of the animal at time t

$u(t)$ Drug amount at time t

B The drugs mixture





$$\frac{dX}{dt} = AX(t) + Bu(t)$$

First Order Model

$$\frac{d^2X}{dt^2} = A_1\frac{dX}{dt} + A_2X + Bu(t)$$

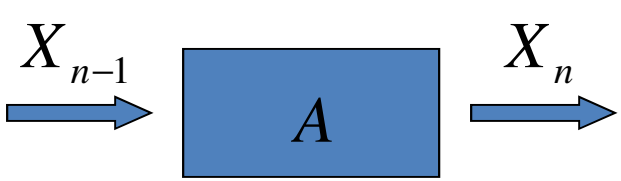
Second Order Model

Objective: Design a drug mixture B and its administration u(t), that is 'best' for …

Discrete Time Models

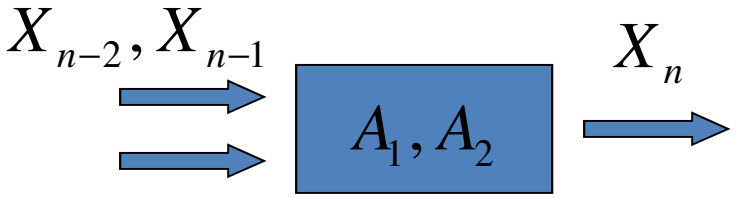
Equal Time Intervals → Can use discrete models

X_n The state of the animal at time n = 0,1,2,…



$$X_n = AX_{n-1}$$

First Order Model



$$X_n = A_1X_{n-1} + A_2X_{n-2}$$

Second Order Model

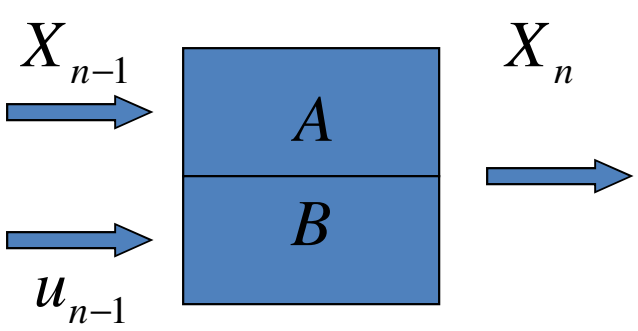
Higher order models are also possible.

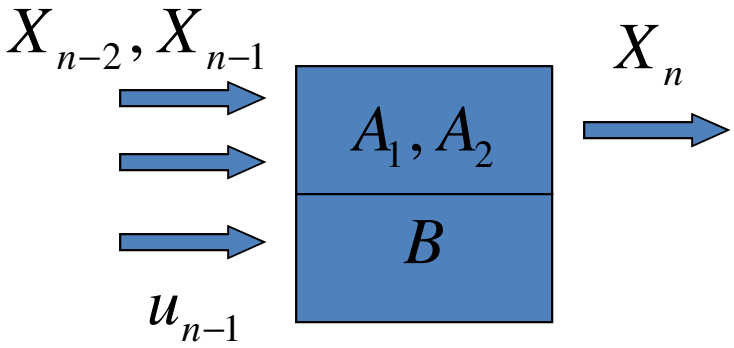
Objective: Construct a model from measurements of X at different times.

Discrete Time Models : Intervention Design

u_n Drug amount at time n = ,1,2,…

B The drugs mixture





$$X_n = AX_{n-1} + Bu_{n-1}$$

First Order Model

$$X_n = A_1X_{n-1} + A_2X_{n-2} + Bu_{n-1}$$

Second Order Model

Objective: Design a drug mixture B, and its administration u_n for a 'best' outcome …

Formulation Summary

Model Construction

Formulation: $$\min_A \sum_{k=1}^{M-1} \|Ax_k - x_{k+1}\|^2.$$

Solution $$A = \left(\sum_{k=1}^{M-1} x_{k+1}\, x_k^T\right)\left(\sum_{k=1}^{M-1} x_k x_k^T\right)^{-1}.$$

Intervention Design

Model $$x_n = Ax_{n-1} + Bu_{n-1}$$

Timing and amount Given B , (drug mixture) find 'best' u_n using control theory

Drug design: Use optimization to find best B :

$$\min_B J(x(B,u), u(B))$$

Nonlinear Data Driven Models

Quadratic nonlinearities

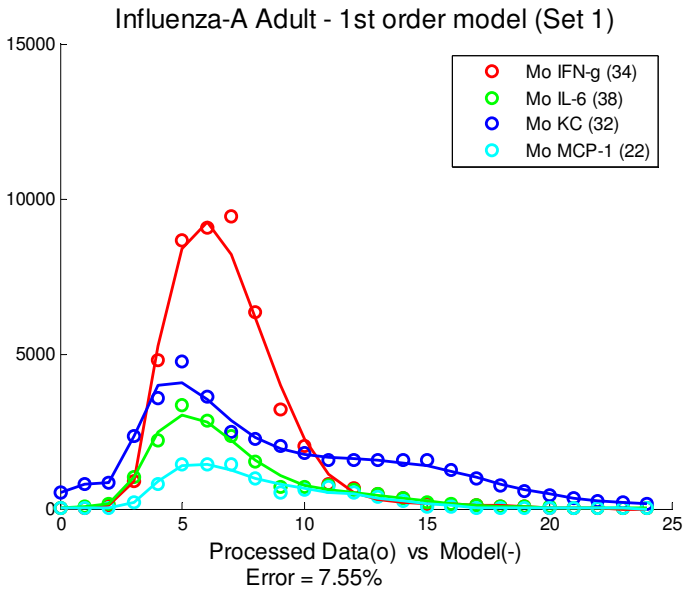
$$dX/dt = L\,X + N\,X\,X^T \qquad (1)$$

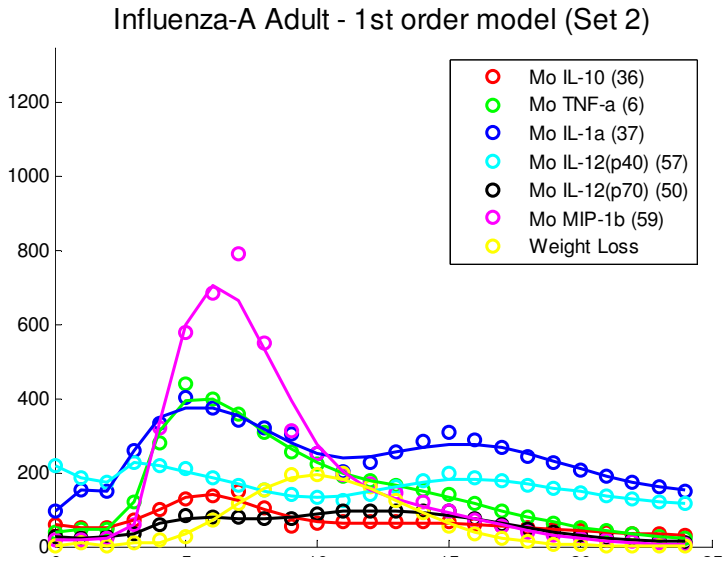
Or discrete time models

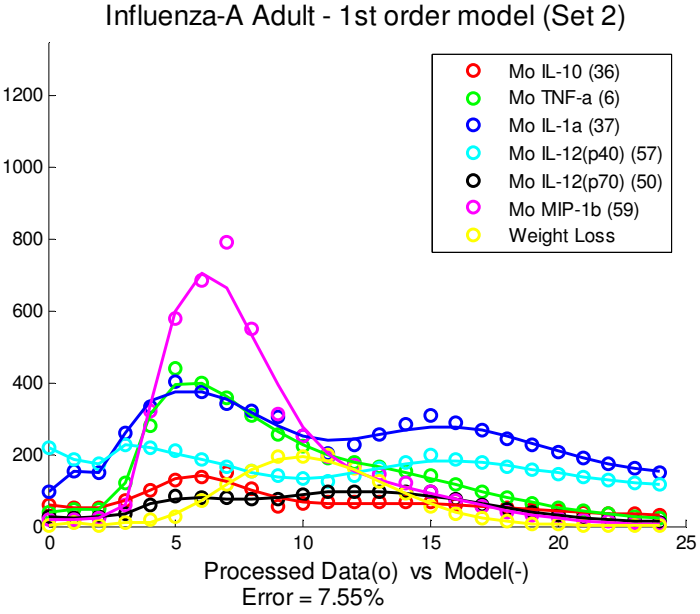
$$X_{n+1} = L\,X_n + N\,X_n\,X_n^T \qquad (2)$$

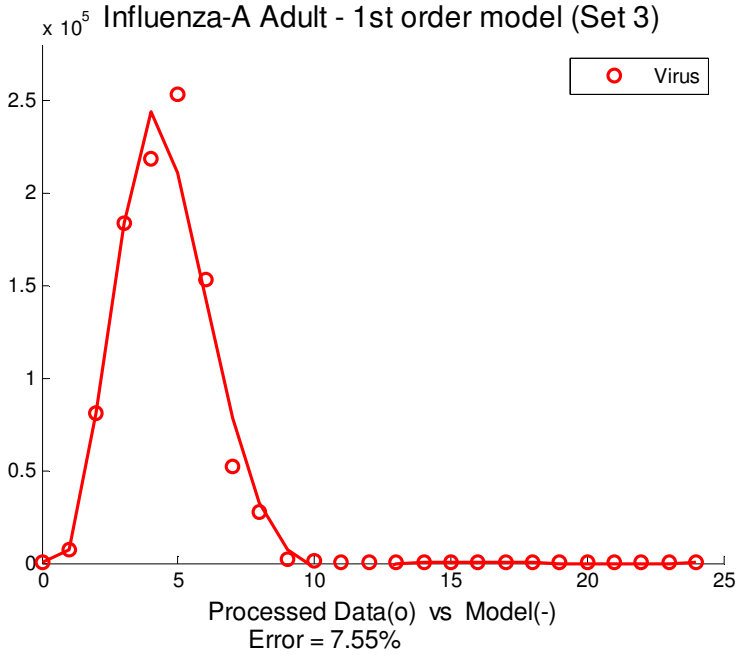
$$\text{Min}_{L,N} \quad \sum || \; X_n - X_n^* \; ||^2 \quad \text{subject to (2)}$$

Modeling Influenza A in Adult Mice





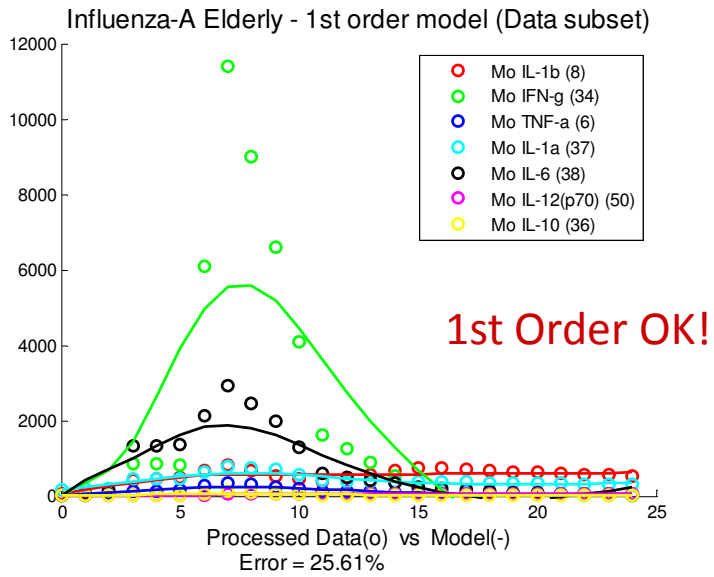


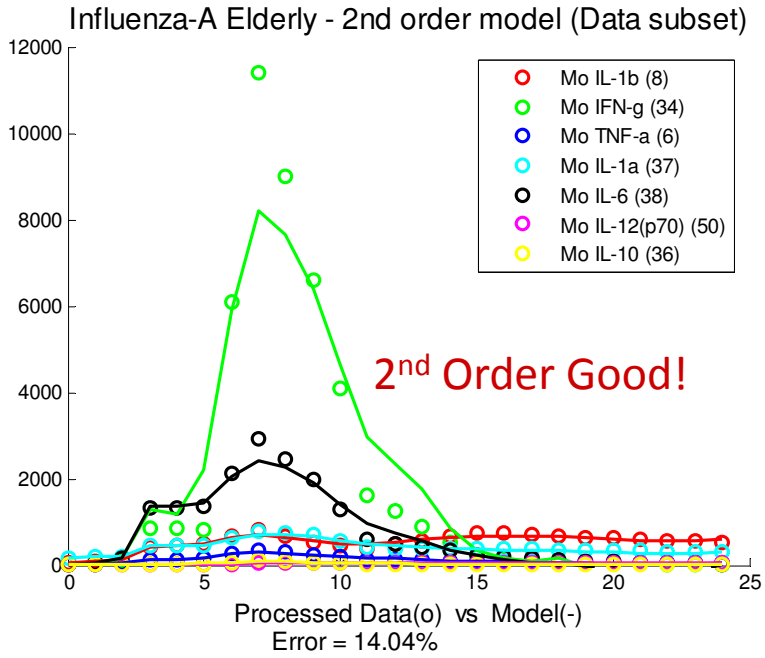


Modeling with Limited Data - case I

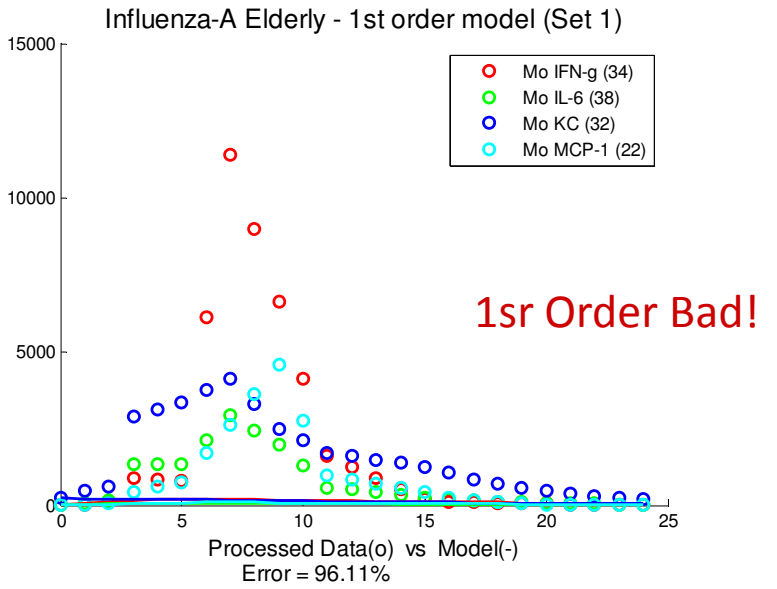
Modeling with only 7 Cytokines

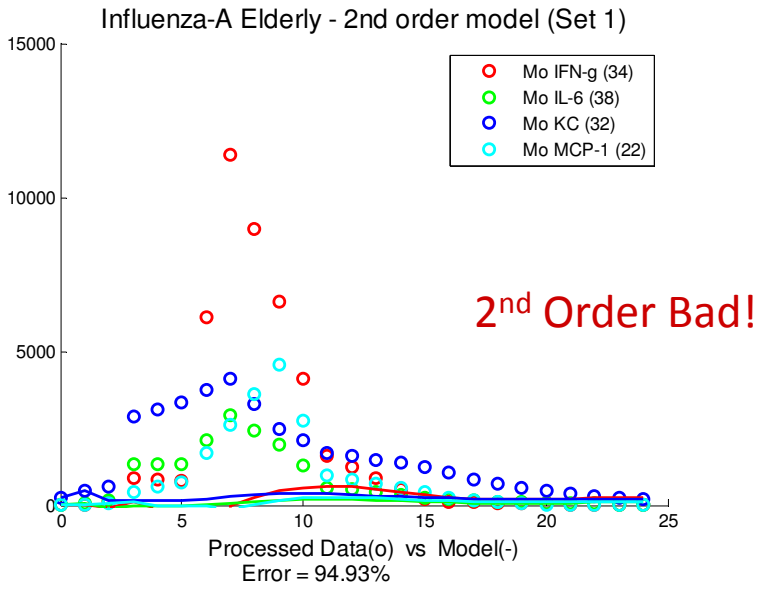
- 1st order model - insufficient
- 2nd order model ok
- 3rd order model – very good

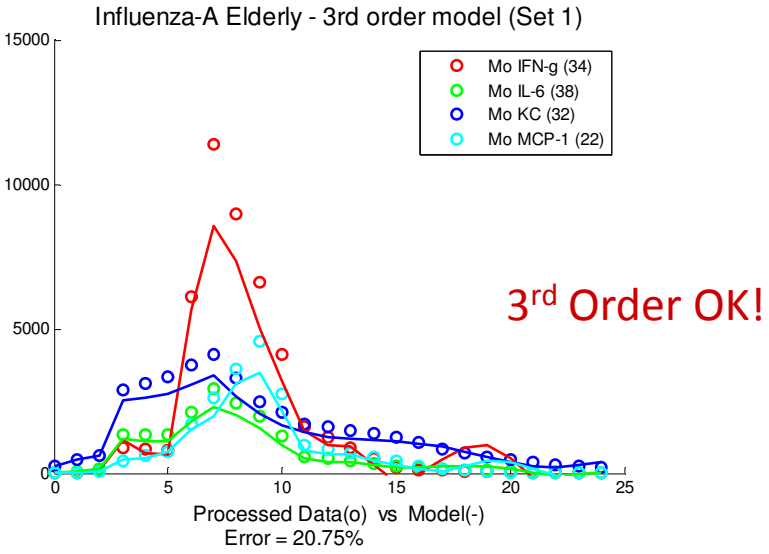




Modeling with Limited Data - case II







Intervention Design

Model $$x_n = Ax_{n-1} + Bu_{n-1}$$

Timing & Amount: Given B, (drug mixture) find 'best' u_n using control theory

Drug design: Use optimization to find best B :

$$\min_{B \in C} J(x(B,u), u(B))$$

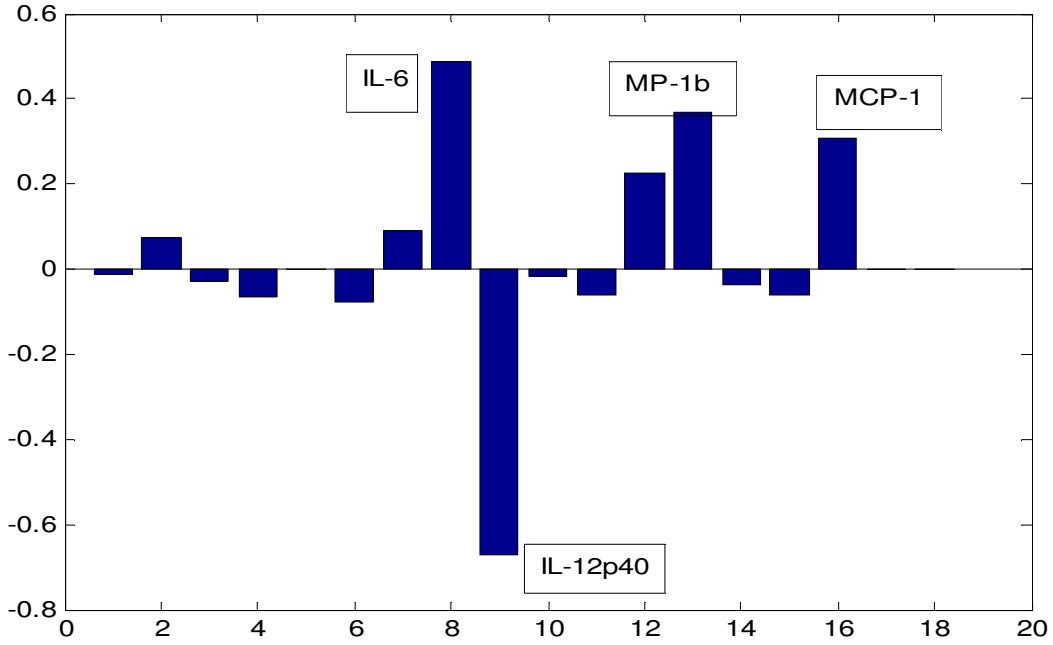
Intervention Design

Anne Yust

Drug Mixture

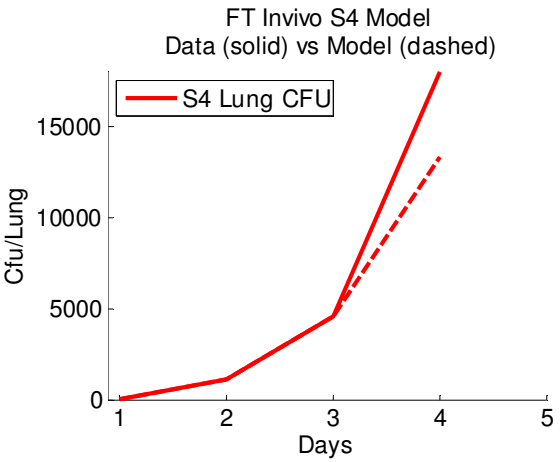
Attempt to control mouse weight loss (illness indicator) + virus load

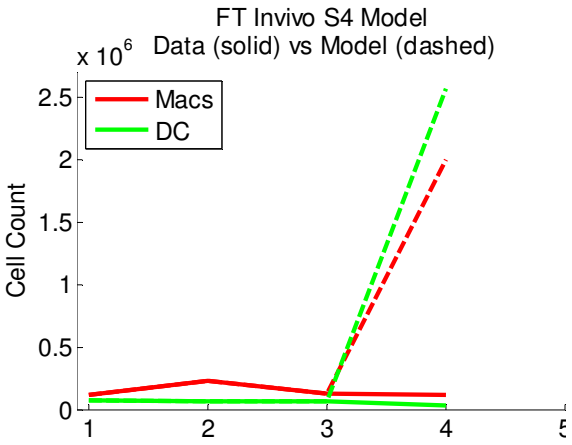
Elderly Mice

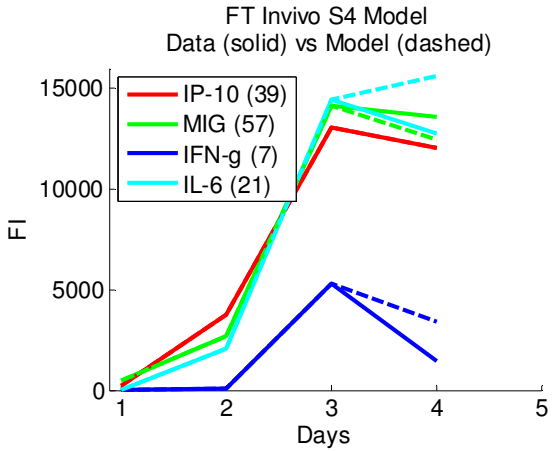


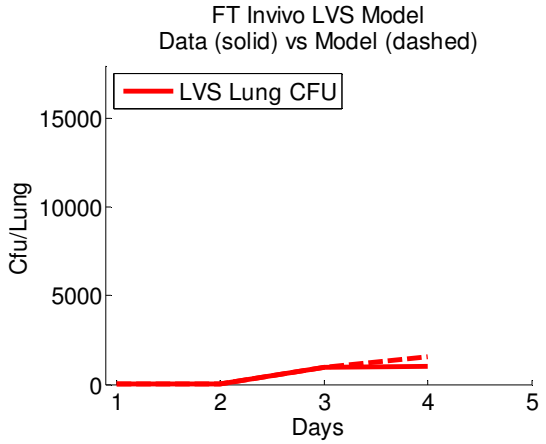
Modeling Francisella Tularensis in Mice

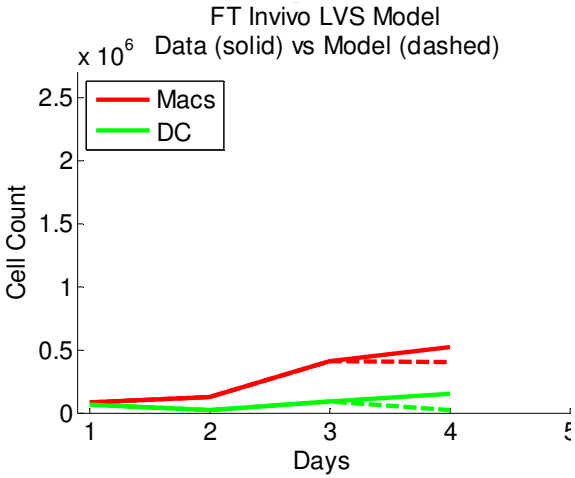
- Schu S4 strain vs. LVS

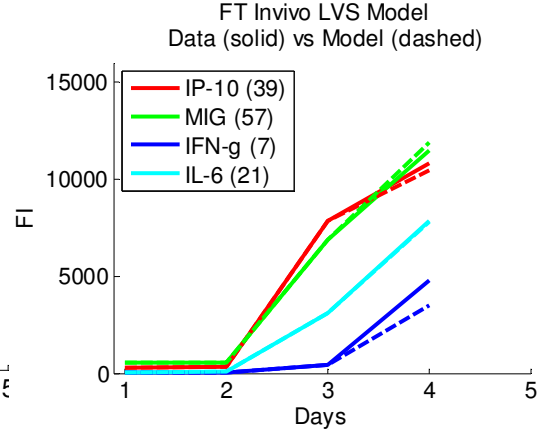






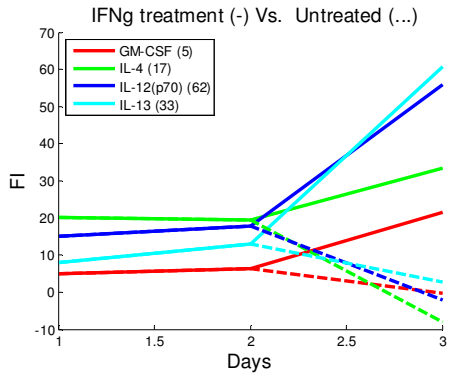


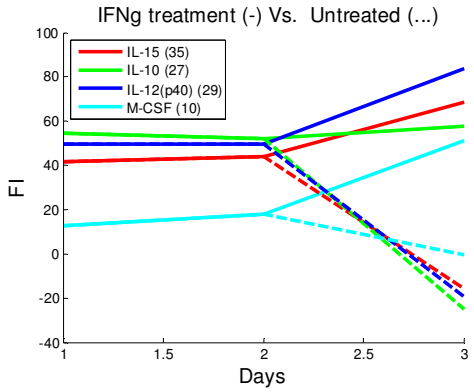


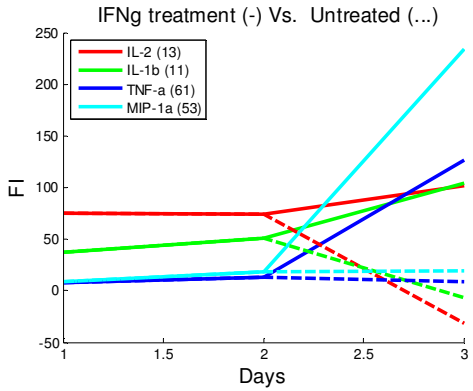


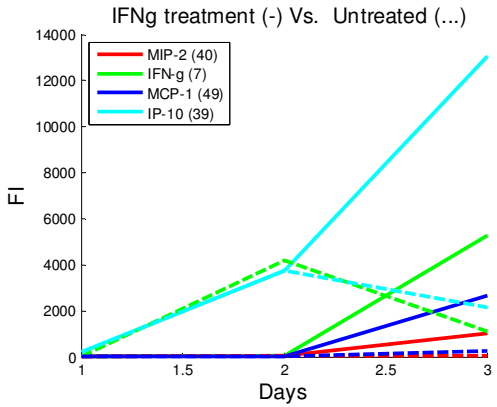
FT Intervention Design

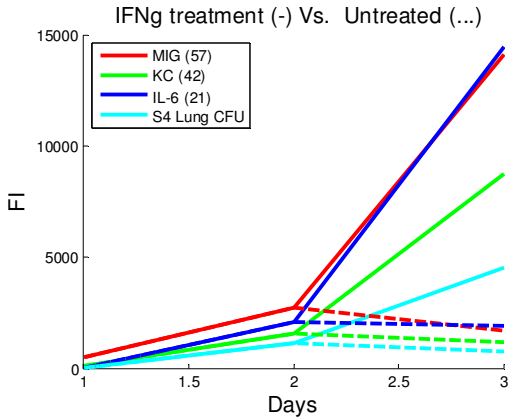
- Using Control theory. IFNγ intervention at day 1 of infection

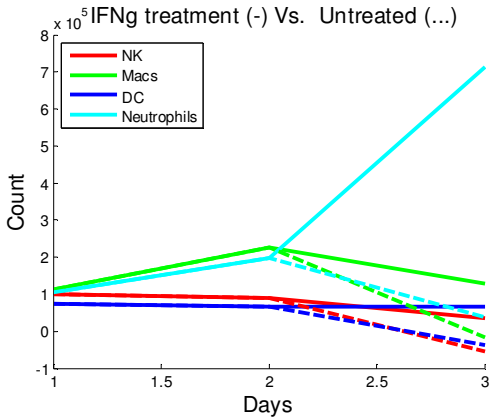












Thank You