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Including Pathogenesis and Transport Physics for Inhalation Dose Response of *Bacillus anthracis*

Mark H. Weir and Charles N. Haas
Center for Advancing Microbial Risk Assessment (CAMRA)

Drexel University, Philadelphia, PA

Currently in Dose Response Modeling

- Dose dependent
  - What is it
    - Carcinogenic
    - Non-carcinogenic
  - How much
  - How long
  - How often
- Average Daily Dose
- Extrapolate from incident

- A specific dose
  - Probability of causing response
    - Choose response
      - Get data
        - Model it
- Current Modifications
  - Focusing on parameters

$$P(response) = f(dose;\theta)$$

Dose Response Parameters

- Depending on the functional form used
  - Potential determinants of dose response parameters

$$P(response) = 1 - \left[1 + {dose}/{N_{50}} \cdot \left(2^{1/\alpha} - 1\right)\right]^{-\alpha}$$

$$P(response) = 1 - e^{-k \cdot dose}$$

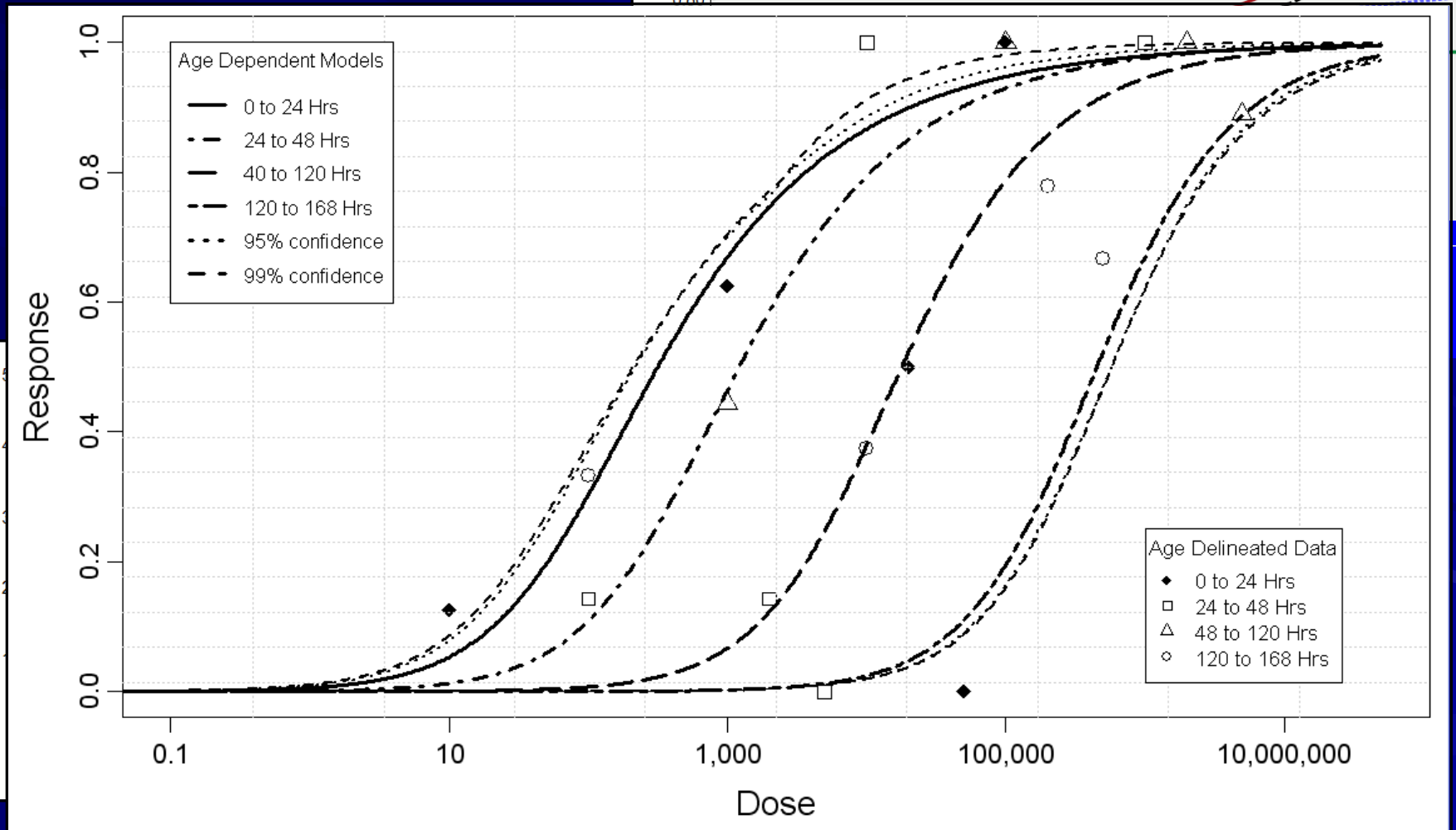
  - N_{50}: median infectious dose
  - k: probability of one organism causing infection or disease
  - α: No descriptive quality, affects slope

Current Dose Response Models

- Proven adaptable and modifiable
- Age dependent dose response parameters

First Steps: Age Dependency

$$\alpha^* = \alpha_0 + \alpha_1(age)$$



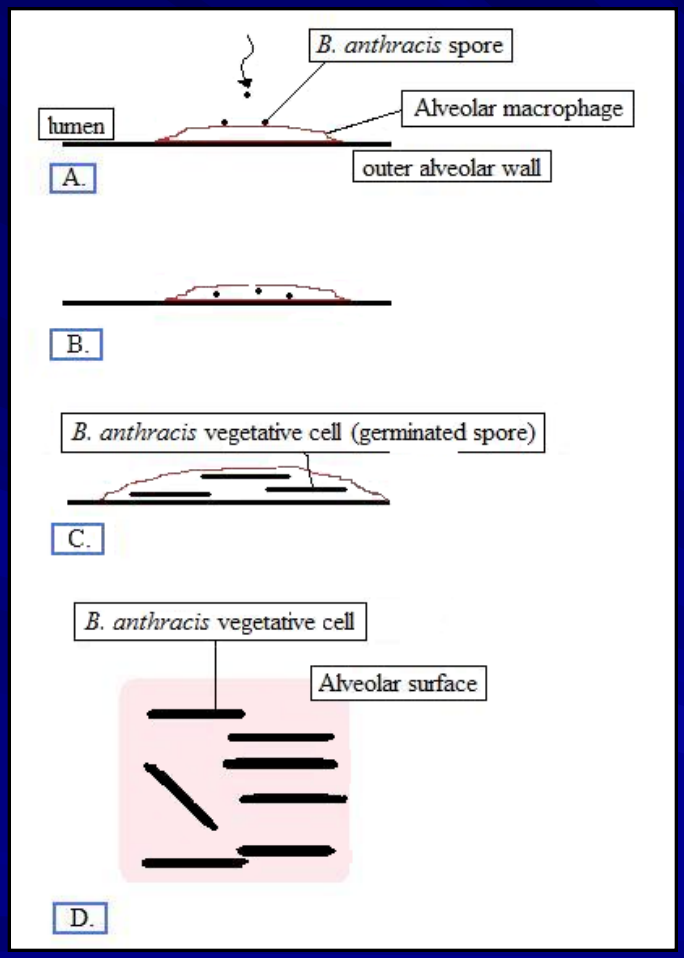
Scope of Work

- Dose Response Parameters
  - Are fitted using animal model data
    - No adaptation proposed
- Structure of Dose Response Models
  - Functional forms currently used
    - Will not be altered
- Exposed Dose versus Effective Dose
  - Pathogens
    - Present internal stresses
    - A certain burden to overcome
  - Host responses
    - React to invasion
      - Specific and known processes
- Two-stage modeling approach
  - Stochastic through respiratory tract
    - Will manage variability with small amounts of pathogens.
  - Deterministic at alveoli and alveolar macrophages
    - Higher structure less variability to these processes.

Current Work

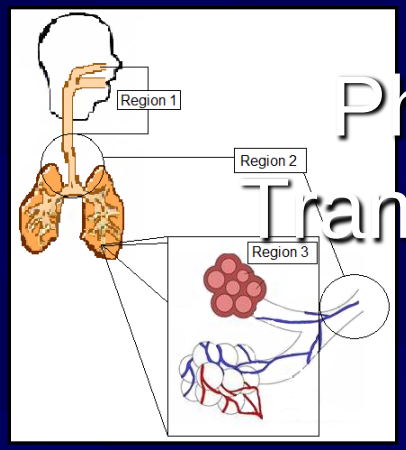
- The respiratory tract
  - Various pathogen sinks
  - Main aims
    - Transfer oxygen into blood
    - Protect the body from infection / harm
- Pathogens
  - Defense responses have coevolved with host responses
  - ∴ exposed dose ≠ body burden
- Physiologically Based Pharmacokinetic (PBPK) models
  - Follow metabolism and harmful effects of chemicals
- Physiologically Based Pathogen Transport and Kinetics (PBPTK) model
  - Follow for pathogens
    - Transport
    - Pathogenesis
    - Kinetics

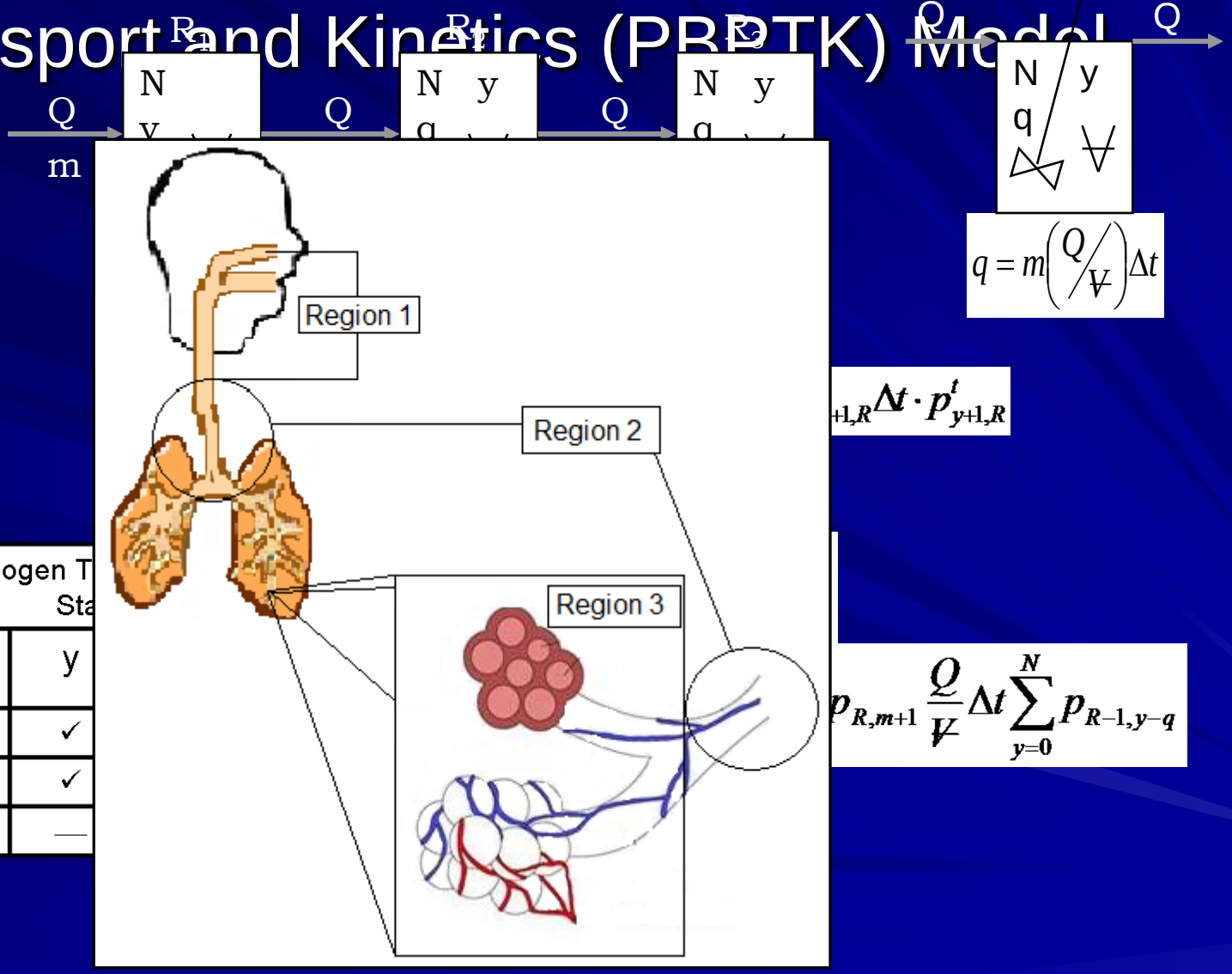
PBPTK



First need to understand pathogenesis of *Bacillus anthracis*

Physiologically Based Pathogen Transport and Kinetics (PBPTK) Model





	Pathogen T Sta	
	y – 1	y
R - 1	✓	✓
R	✓	✓
R + 1	✓	—

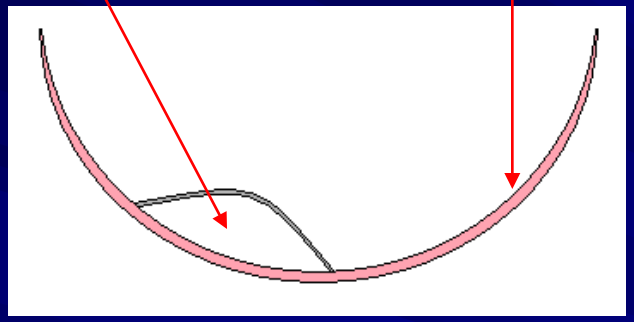
$$q = m\left(Q/V\right)\Delta t$$

$$_{+1,R}\Delta t \cdot p^{t}_{y+1,R}$$

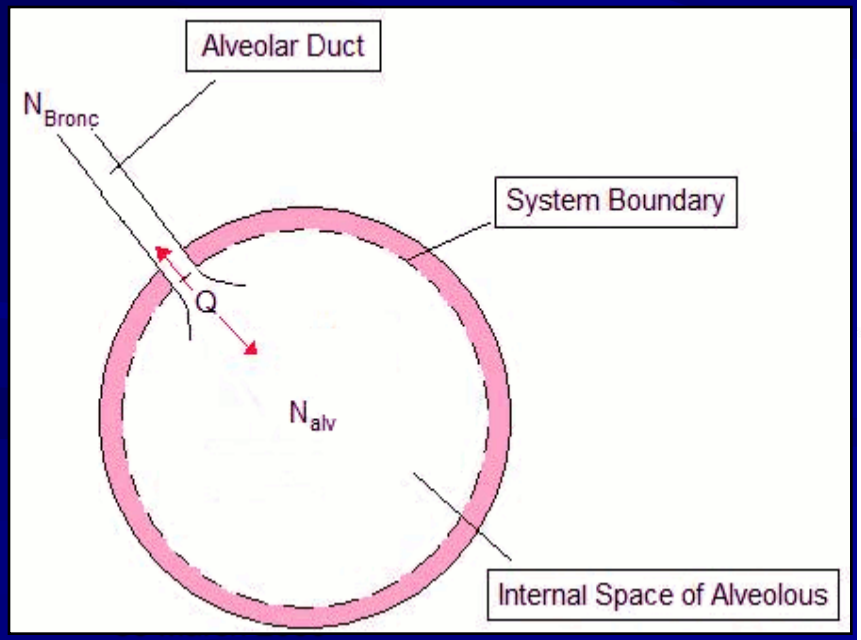
$$p_{R,m+1}\frac{Q}{V}\Delta t\sum_{y=0}^{N} p_{R-1,y-q}$$

Bacillus anthracis-Alveolar Macrophage Interaction

Alveolar Macrophage Internal Alveolar Surface



Human alveoli and alveolar macrophage are homogeneous compartments



$$\frac{dN_{Bronc}}{dt}V_{Bronc} = QC_{in} - QN_{Bronc} + QN_{alv}$$

$$\frac{dN_{alv}}{dt}V_{ao} = QN_{Bronc} - QN_{alv} - N_{alv}k_{dep}$$

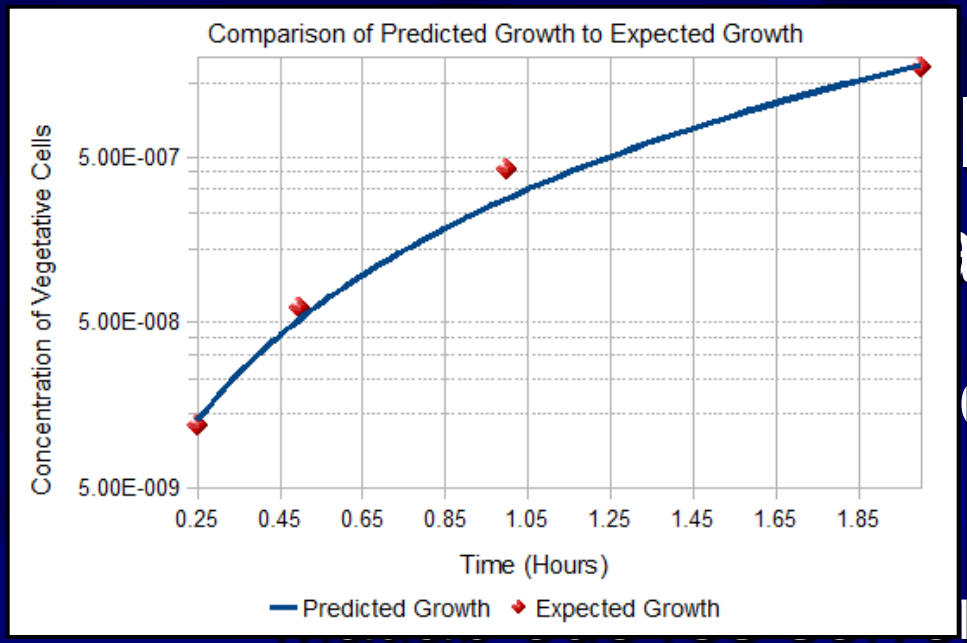
$$\frac{dx}{dt} = N_{alv}k_{dep} - xk_{dep}$$

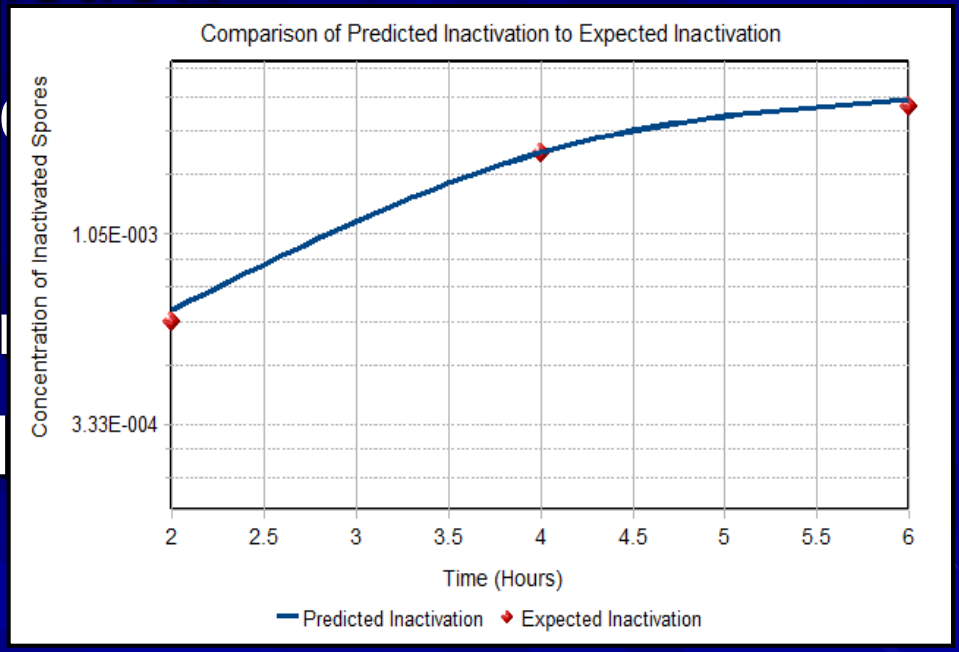
$$\frac{dm}{dt}V_{am} = \left(N_{alv}k_{dep} - xk_{dep}\right)A_{am} - k_{ger}mV_{am} - k_{ina}mV_{am}$$

$$\frac{dm_i}{dt}V_{am} = k_{ina}mV_{am}$$

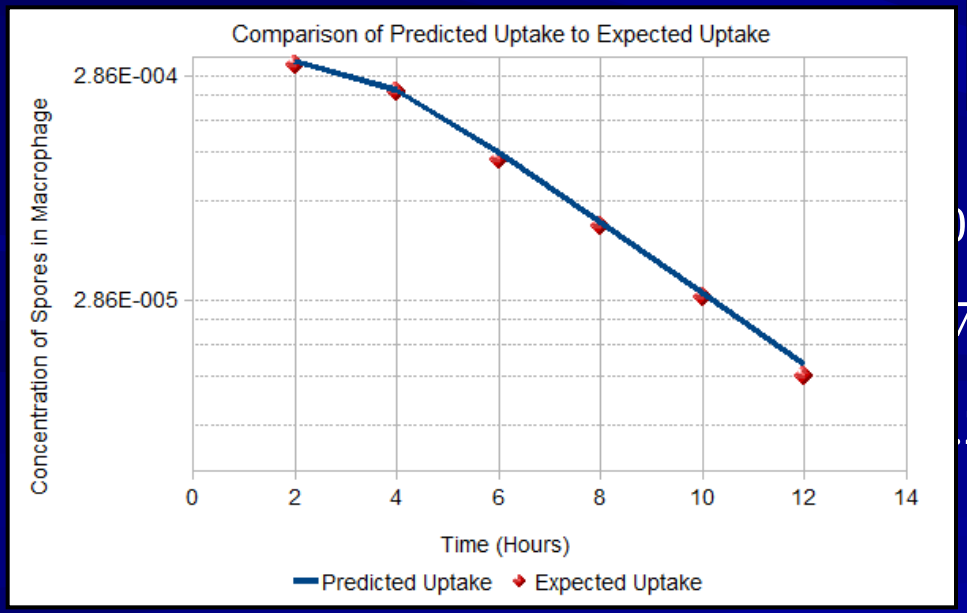
$$\frac{dv}{dt}V_{am} = k_{ger}mV_{am} + k_{grow}vV_{am} - k_{dec}vV_{am}$$

lveolar Macrophage
ction





- Minimization using N



$087\ \mu m/hr$

$740/hr$

$211/hr$

Summary

- Proved that we can
  - Include additional factors to dose response
    - Adapting the parameters, thereby modifying the models
- We will be
  - Altering the dose
    - Moving from an exposed dose to an effective dose
    - Improving the risk estimates with thorough pathogenesis and kinetic modeling
- Similar work
  - Building invivo fate
    - Also using *Bacillus anthracis*
    - Also including transport and pathogenesis
  - Deterministic models
- Two-stage modeling approach
  - Stochastic through respiratory tract
  - Deterministic at alveoli and alveolar macrophages

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