IMAG / MSM Meeting
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Mathematical Modeling of Inflammation in Acute Respiratory Distress Syndrome

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Disclosure: Co-founder of and stakeholder in Immunetrics, Inc.

Points for Discussion

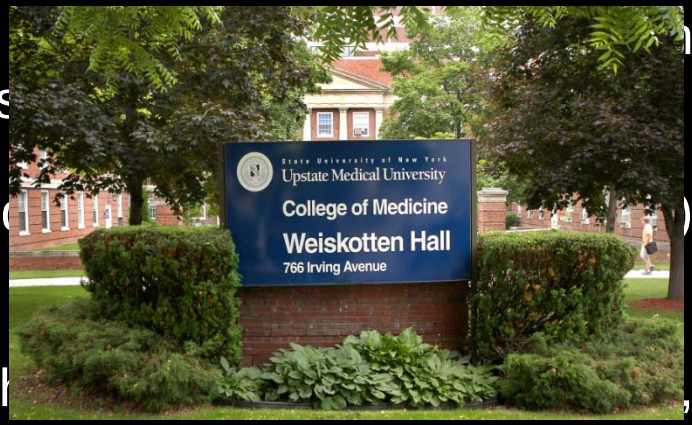
- Which fields would best benefit and provide opportunities for translation?
- Uncertainty quantification
- Bridging to higher scales
- Role of inverse methods

Sepsis

- Sepsis is common
- At least 750,000 cases annually in the US (Angus et al. Crit. Care Med. 2001)
- Mostly in the elderly
- Incidence will increase significantly in next decade
- Associated with acute organ dysfunction, including Acute Respiratory Distress Syndrome (ARDS)
- High moribidity, mortality
- High costs ($16.7 billion)
- Endotoxemia, while not true sepsis, is a commonly-used experimental surrogate

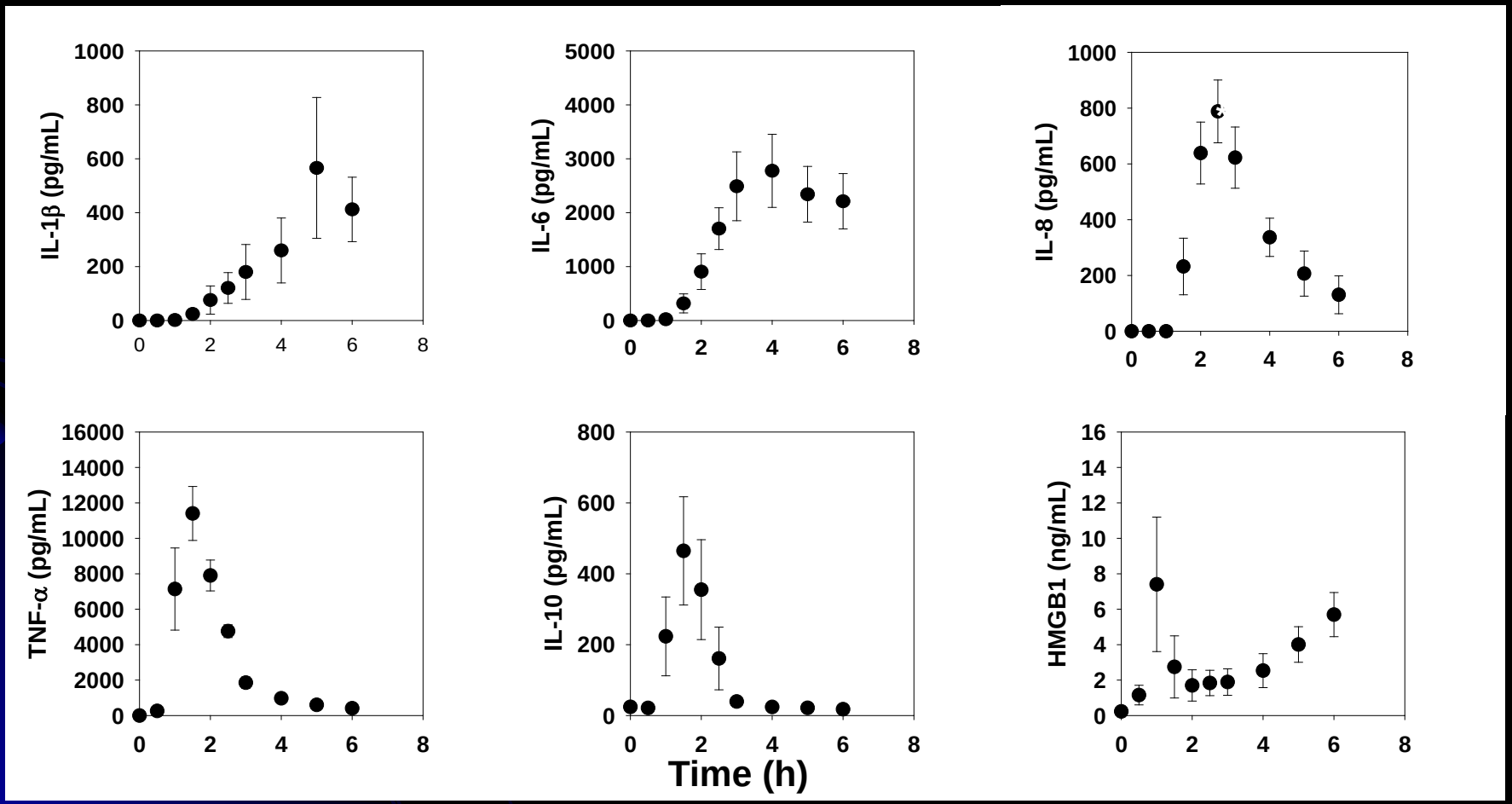
Mathematical Modeling of Inflammation in ARDS (R33-HL-089082)
Experimental Methods: Endotoxemia

- Yorkshire [illegible] anesthetized and [illegible] surgica[illegible]r vascular access[illegible]
- Follow[illegible]asurements end[illegible] mixed [illegible]as infused over [illegible]
- Animals w[illegible]wed for 6 hrs with h[illegible], blood chemistry
- Plasma samples were collected hourly for measurement of inflammatory media[illegible]
- Lung, liver, intestin[illegible]sted for histopathology and edema assess[illegible]



Immunetrics

Dynamics of inflammation in porcine endotoxemia



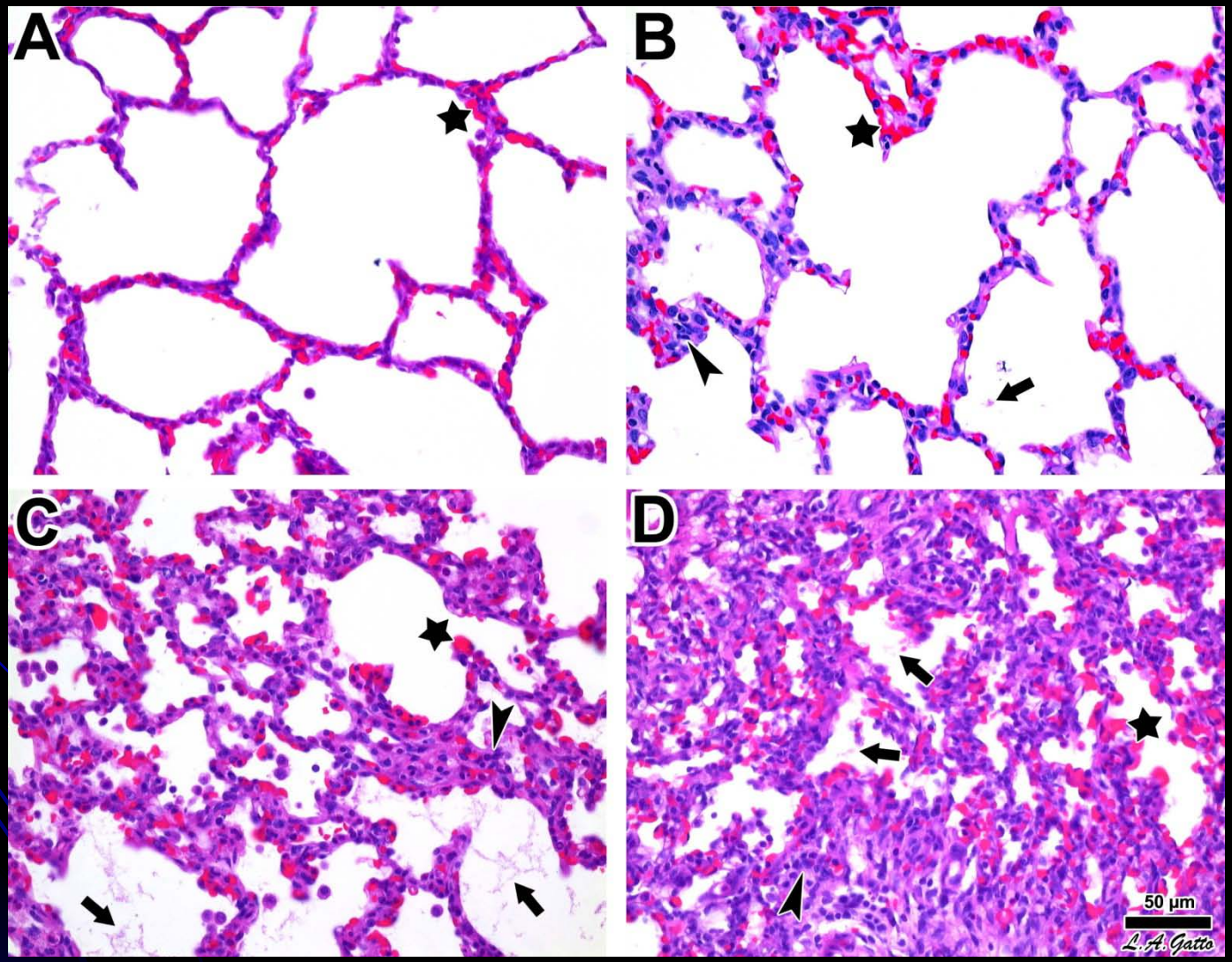
Histology shows varying degrees of lung injury

A: Pig 2588

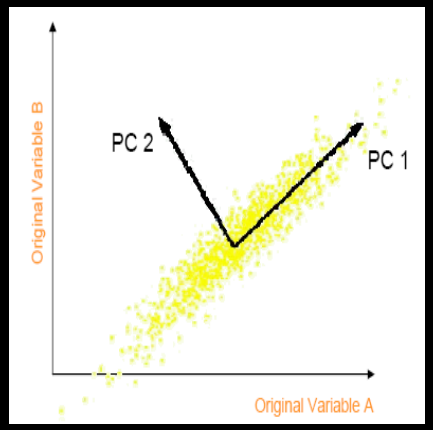
B: Pig 2595

C: Pig 2583

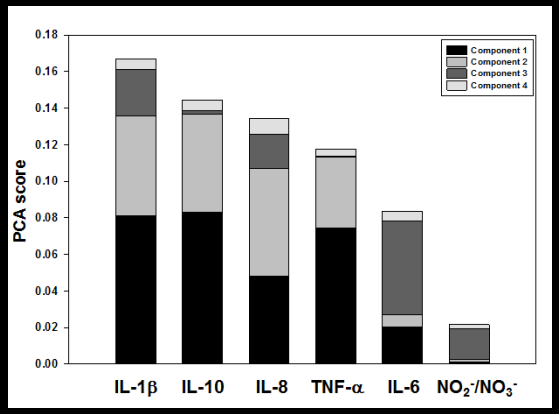
D: Pig 2589



Principal Component Analysis (PCA)

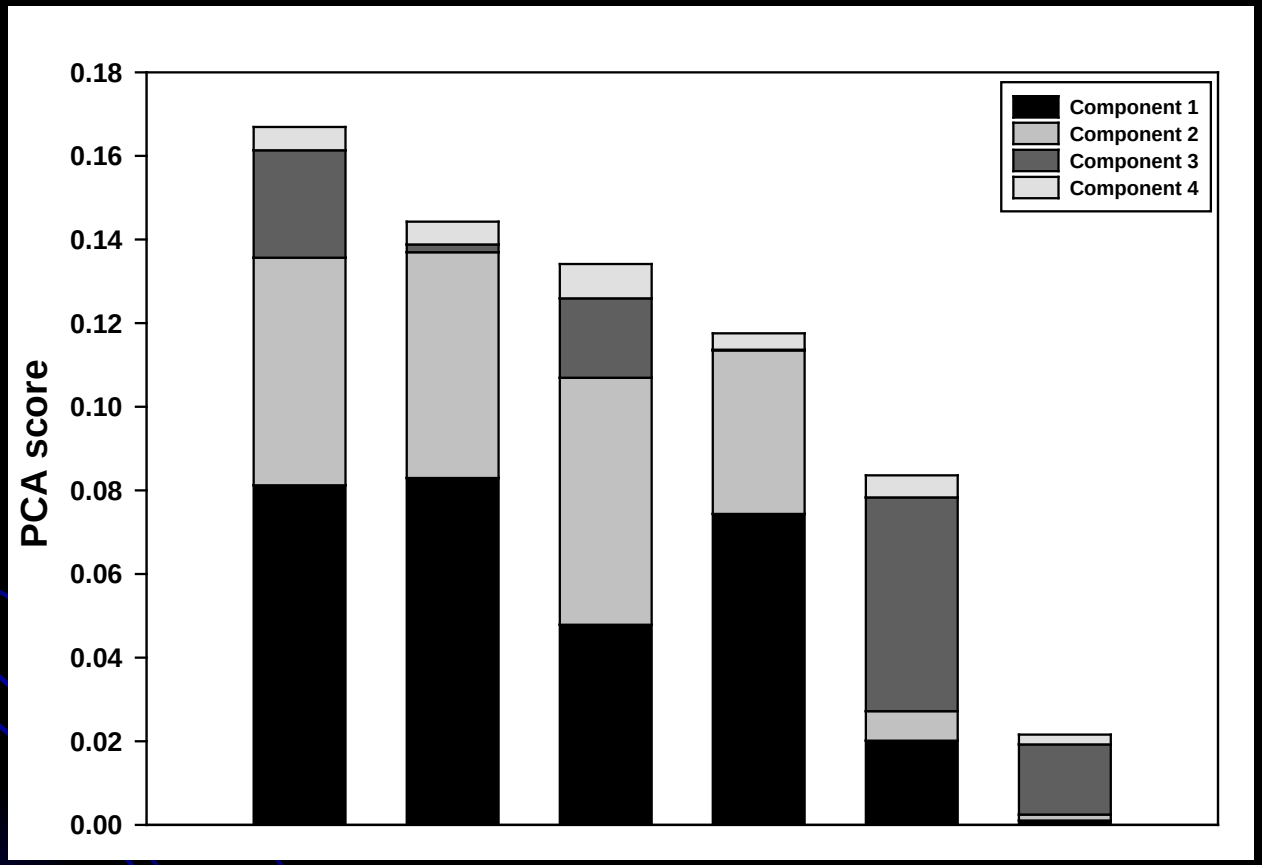


- Well-established tool for defining the primary characteristics of a highly-dimensional dataset (e.g. 25 Luminex™ cytokines in plasma)
- PCA achieves accurate dimension reduction by extracting a few PCs (not all PCs) that describe most of the variation in the original multivariate data with the least loss of information
- Based on linear transformation and decomposition of a number of correlated variables of a multidimensional data set to a number of uncorrelated components → Principal components (PCs)
- These Principal components are estimated as the projections of the data set on the eigenvectors of the covariance or correlation matrix of this data set

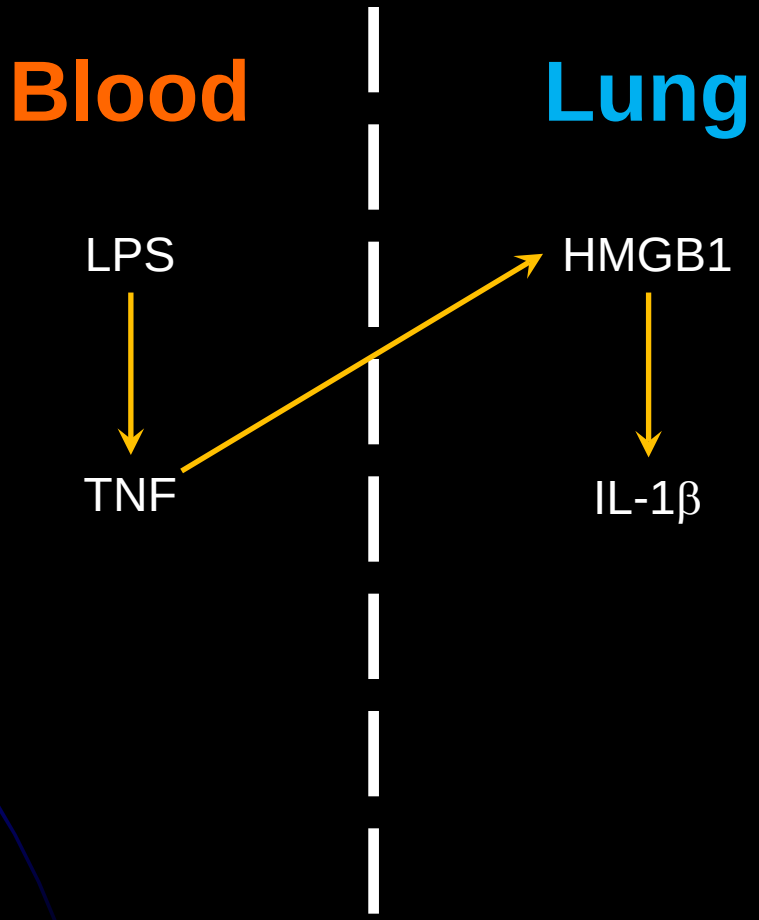


Janes, K.A.; Yaffe, M.B.. Nat.Rev.Mol.Cell.Biol. 2006. 7:820; Mi *et al*, PLoS ONE. 2011. 6:19424

Porcine endotoxemia: PCA results

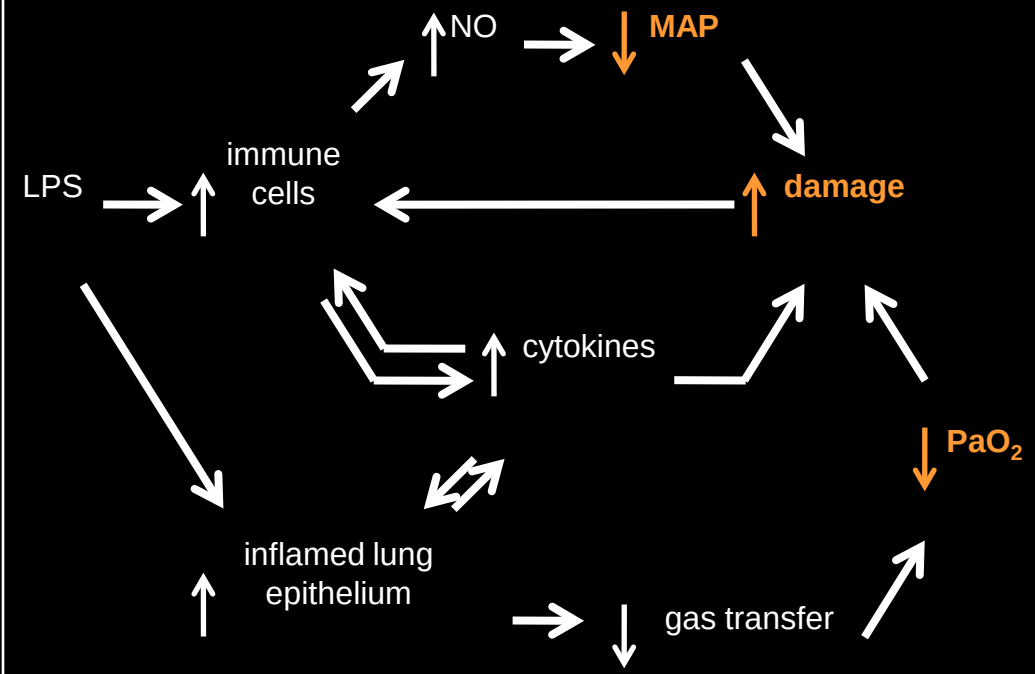


2-compartment model of sepsis/ARDS: Key Module Inferred from PCA



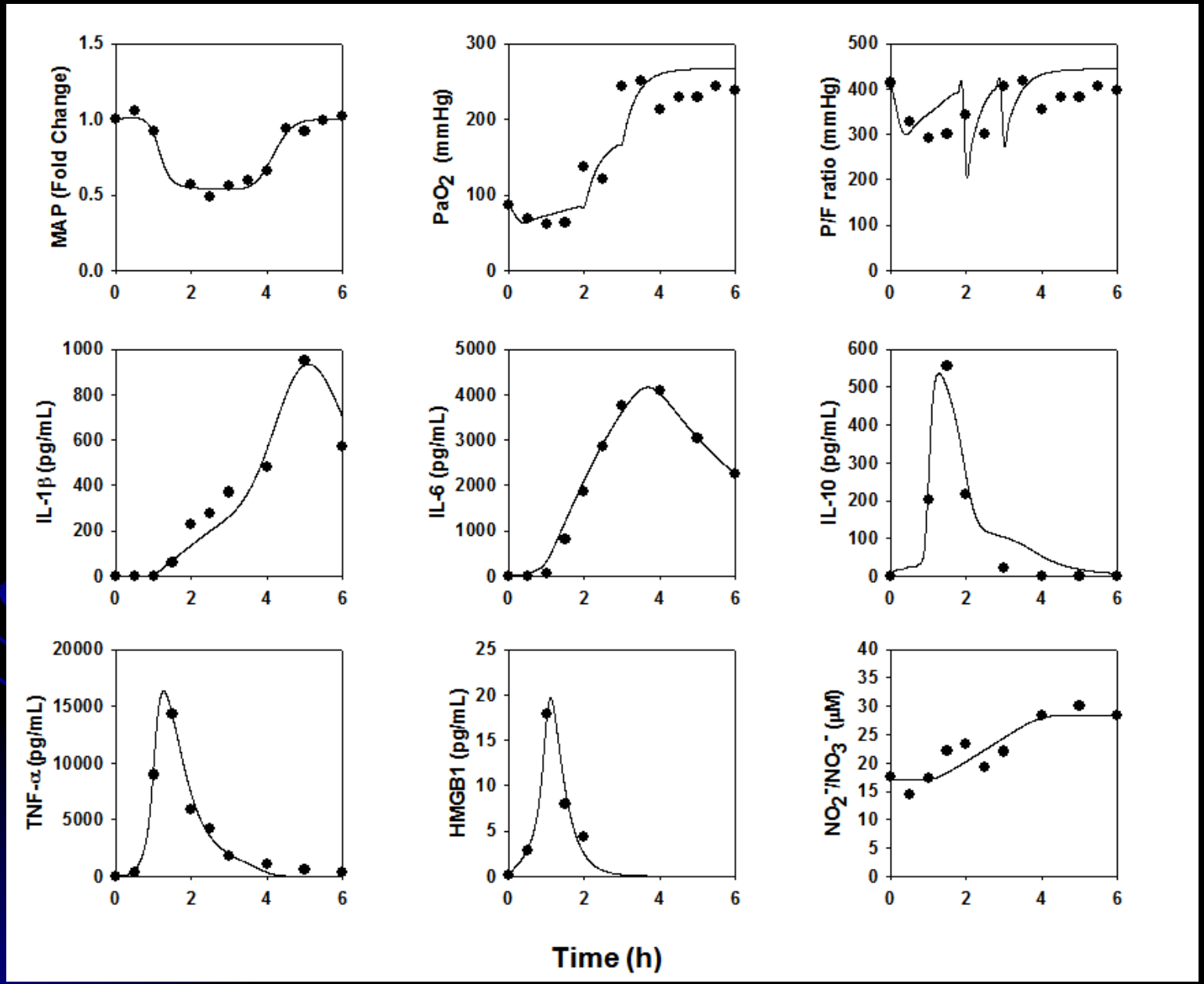
Modeling LPS Injection → Physiological Responses

- LPS activates immune cells and lung epithelium, leading to release of cytokines and NO
- Elevations in NO lead to decreases in MAP
- Inflammation of the lung epithelium inhibits the transfer of oxygen from inspired air to the blood, causing a drop in PaO_2
- The combination of decreased PaO_2, increased cytokines, and decreased MAP causes overall damage to the system
- Overall damage can then feed back to cause more inflammation
- The positive feedback loop can either be offset by anti-inflammatory mediators or run unchecked to cause shock, ARDS, and death

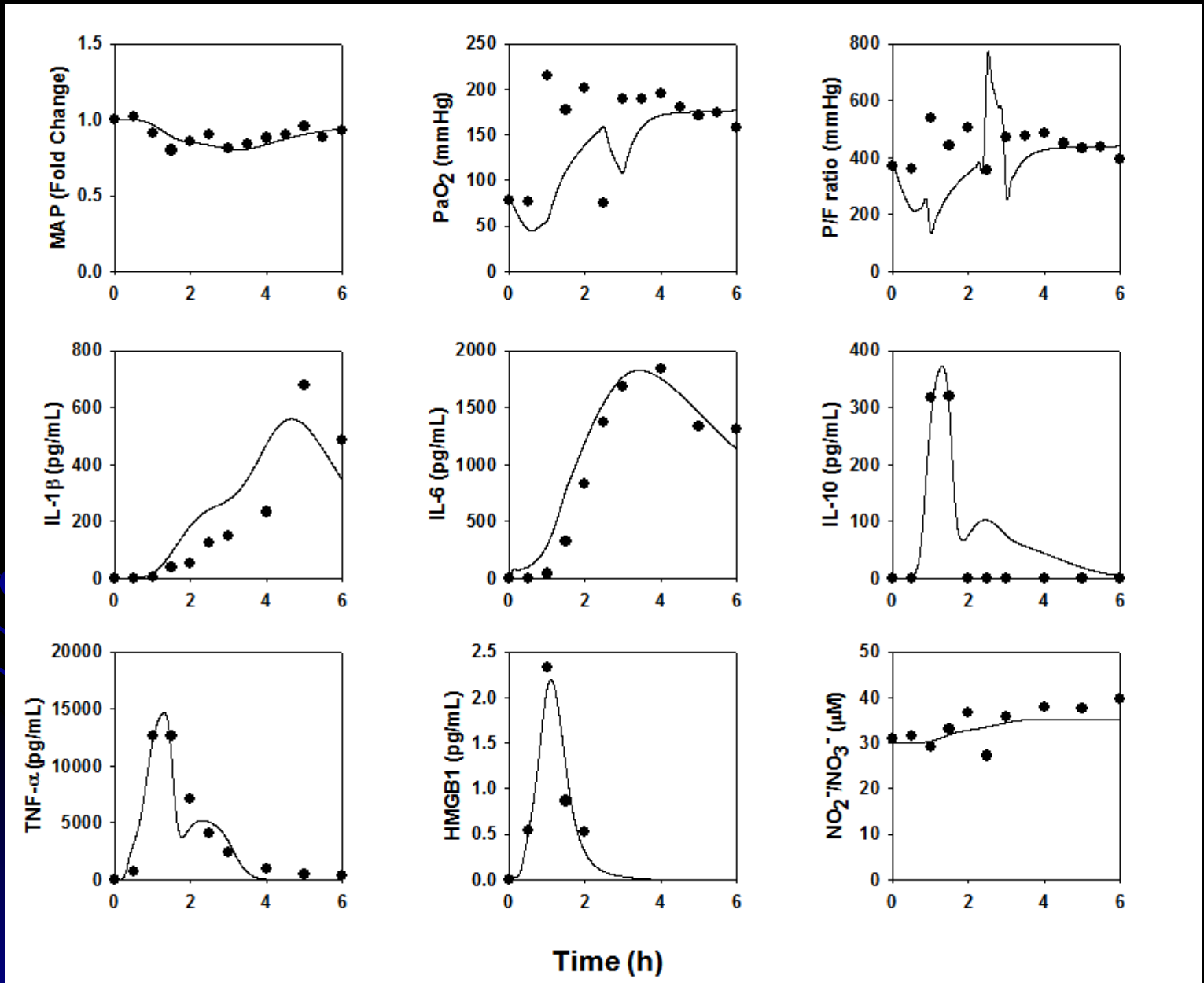


Individual-Specific, Multiscale Modeling

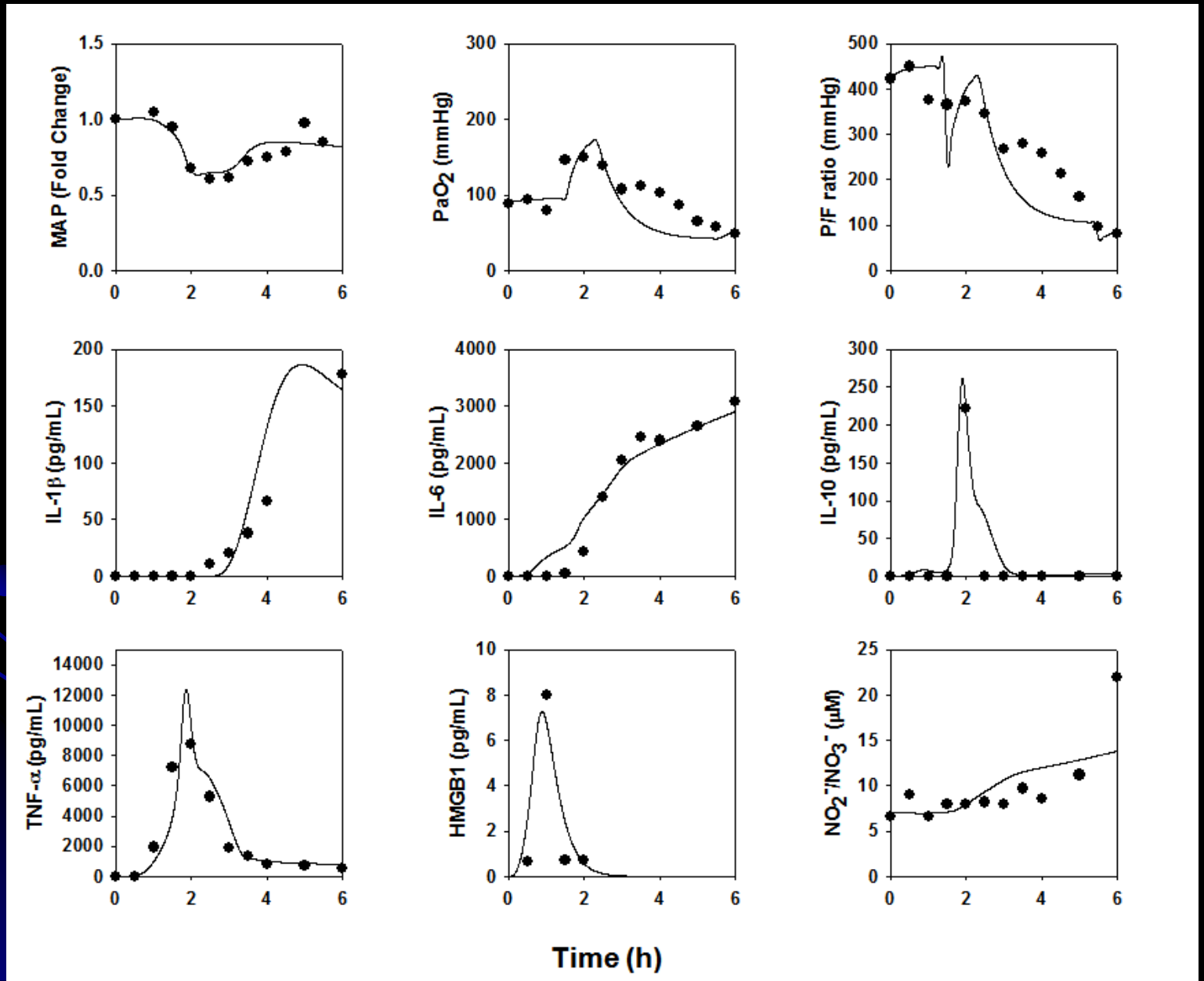
Pig 2588: A resolving inflammatory response



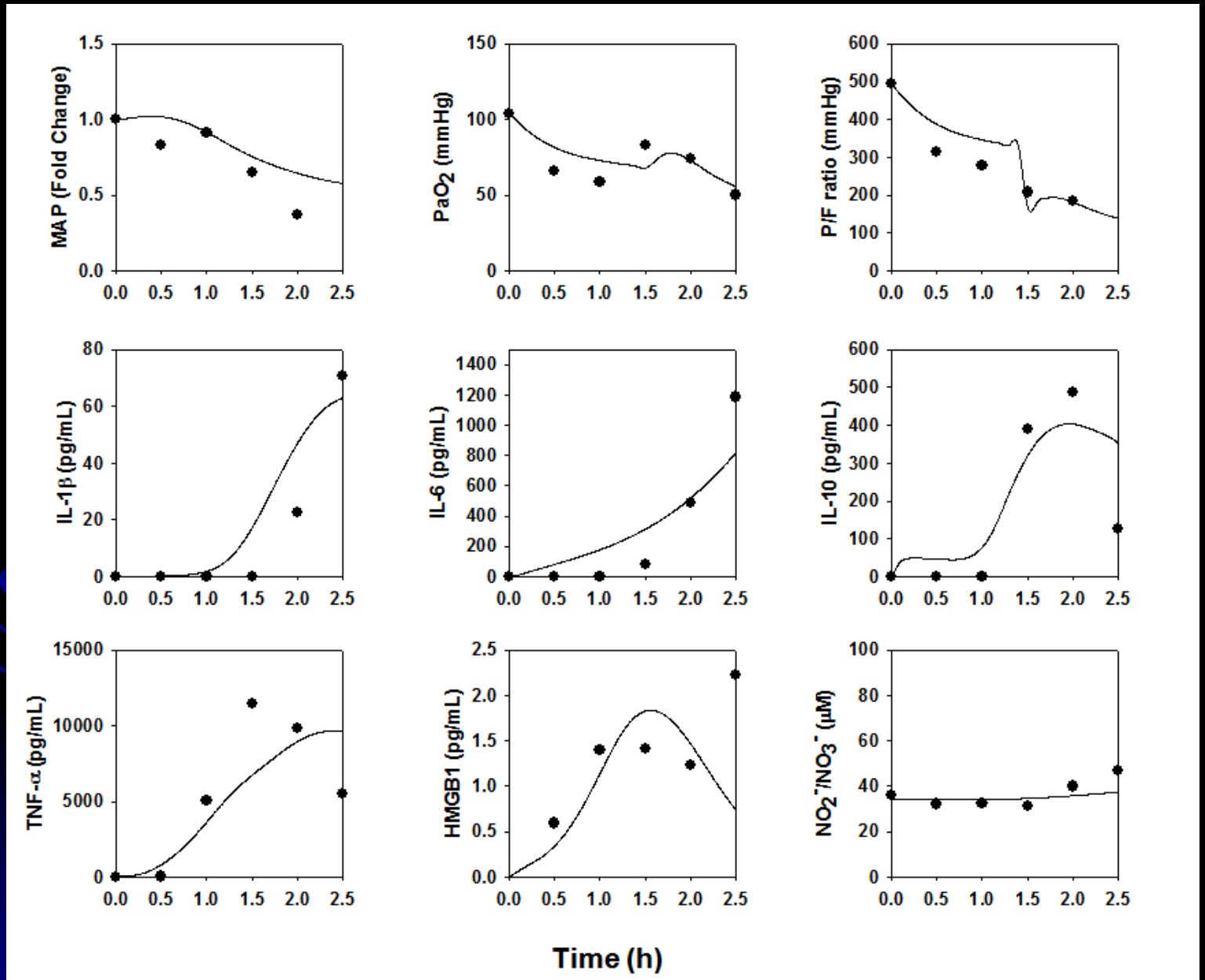
Pig 2595: Somewhat sick



Pig 2583: Fairly sick

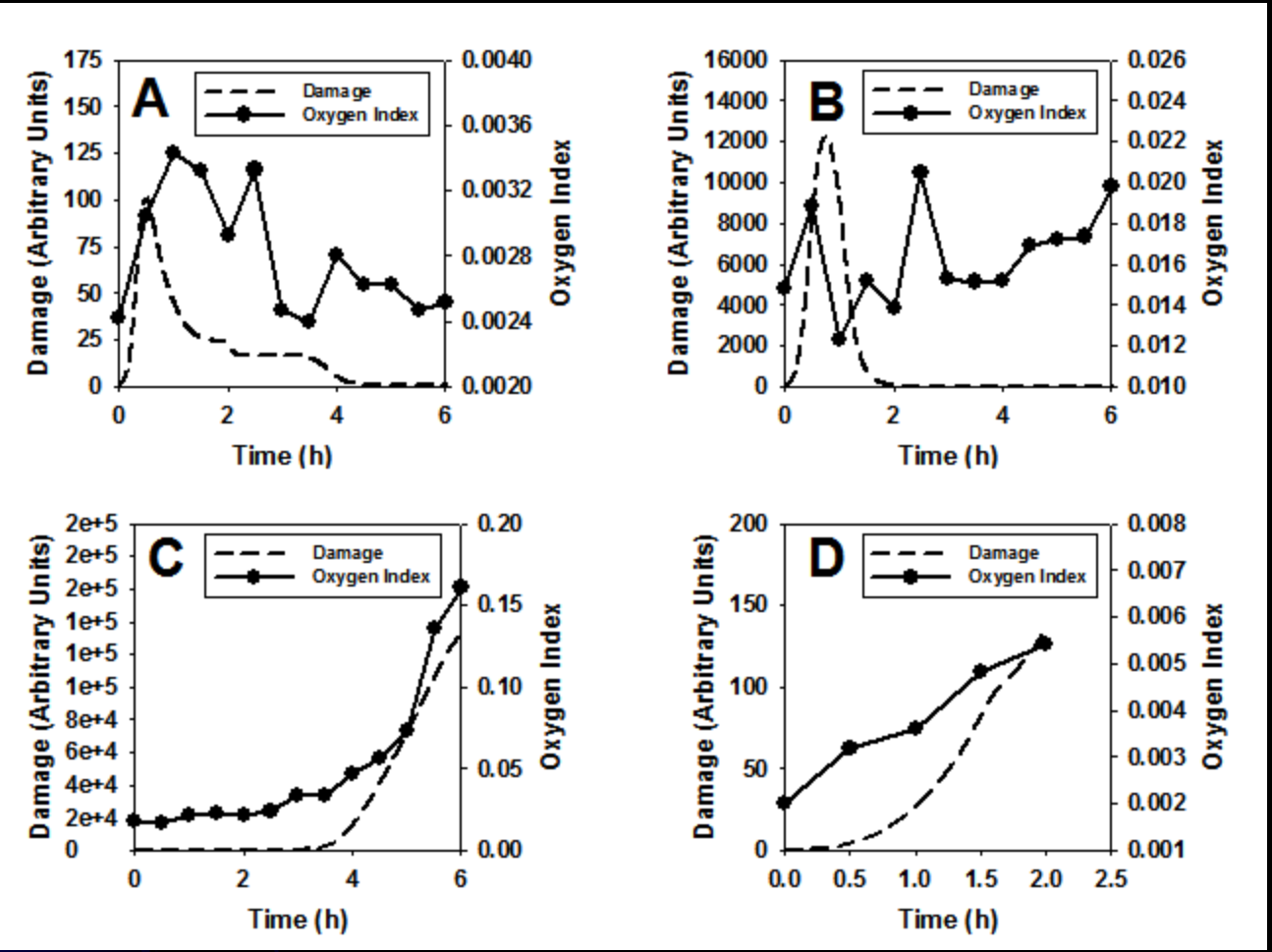


Pig 2589: Died before the end of the experiment



Predicted damage tracks fairly well with Oxygen Index

OI = FiO_2 * Airway Pressure / PaO_2



Summary and Conclusions

- A generalized inflammation framework based on inflammation → damage → inflammation was used to develop multiple models that could reproduce the responses of individuals in endotoxemia
- Linking data-driven (PCA) and mechanistic (ODE) modeling methods
- May have applications for diagnosis or clinical trials simulations

Translational Systems Biology:
Merging data and mechanism in multiscale models of disease

Pre-clinical studies

Clinical trials

In-hospital care

Chronic / rehabilitative care

Simulate Mechanism

Simulate Clinical Trial

Simulate Individual Patient

Simulate Aging, etc.

Y. Vodovotz et al. Math. Biosci. 2009. 217:1

Funding and Other Support

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- Pittsburgh Lifesciences Greenhouse
- IBM