John Bartels
Immunetrics, Inc.

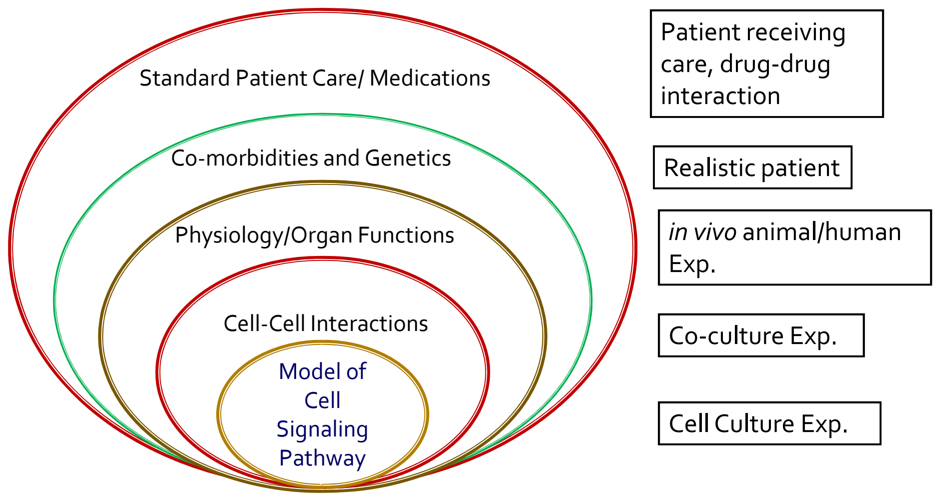
Fixed Points in Detailed Physiological Models

immunetrics

Immunetrics Background

- In-silico modeling of disease
  - Inflammation focus: sepsis, secret projects…
- Application areas
  - Drug design
  - Clinical trial design
  - Treatment optimization
- Corporate customers
  - Eli Lilly
  - Philips Medical Systems

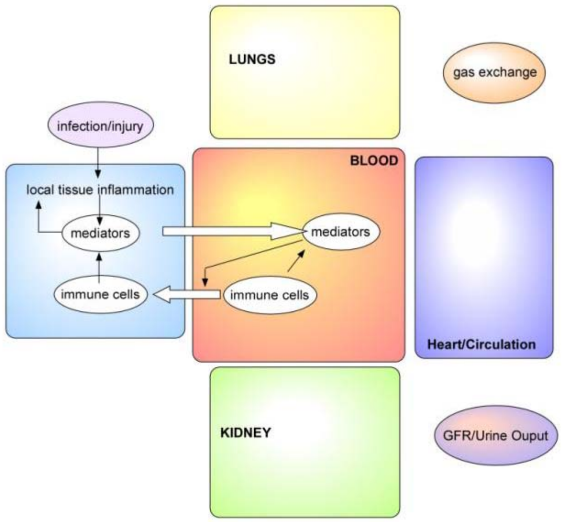
Layers of Immunetrics Model



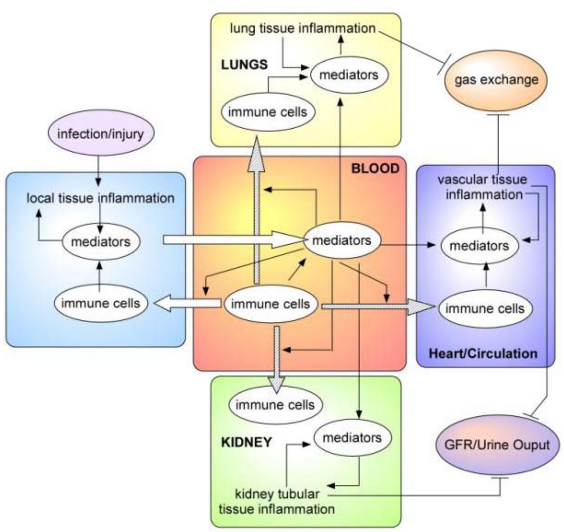
Model overview

- Large ODE system (500+ equations)
  - Inflammation / coagulation / organ systems
  - Heart / kidney / lung + cellular & molecular pathways
  - Biological pathways & parameter values from current literature
- Model patients on individual basis
  - Numerous parameters for patient personalization
- Try to maximize clinical relevance
  - Physiological definition of death
  - Support ICU interventions (fluids, pressors, ventilators, drugs)
- Today:
  - Focus on stand-alone organ system module (100 ode's)

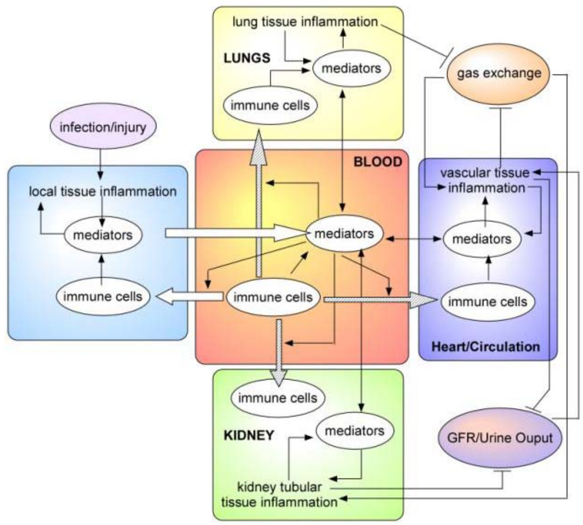
Organ Systems Model



Organ Systems Model



Organ Systems Model



Organ systems training

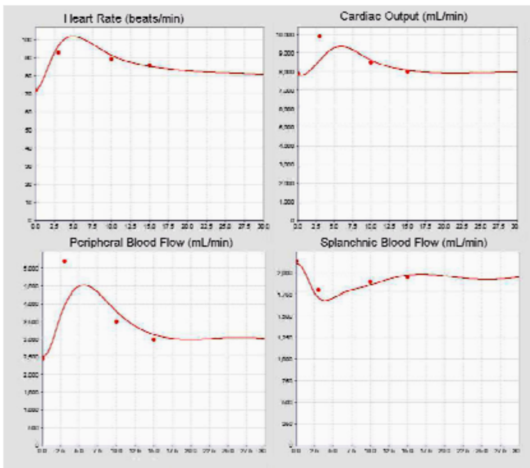
- The model was trained to a wide variety of responses to experimental stress – e.g.
  - Simulated hypoxia, hypercapnia
  - infusions (e.g. NE, saline, renin, etc.)
- Reproduce documented physiological changes:

Baroreceptor response	pH
Breathing frequency	Respiratory capacity
Vascular resistance	Air pressure changes
Per-organ O_2 extraction	

- Doesn't do:

HRV	Per-breath sim
Exercise	ECG output
….	

Sample Prediction



- The model response here is validated against data from experimental mental stress.
- The extent of stress was tuned to reproduce the correct degree of increase in heart rate
- The model prediction of cardiac output as well peripheral and splanchnic blood flow was compared to experimental data

Question: Is it any good?

- Key question: how/when can we trust the model?
- One criterion: do reasonable (untrained) behaviors emerge from the system?
- Check structure of state space
  - Realistic patients should:
    - Be robust to perturbation (up to a point)
    - Vary widely in baseline attributes
    - Exhibit certain stereotypical responses

Approach: Abuse dynamical systems ideas

- Fixed points: $\dot{x} = F(\theta, x, t) = 0$
  - Patients at **equilibrium**
  - Dimensionality reduction:
    - Cluster 100-D fixed points into a 3-D clinical space
- Stability
  - Existence of tiny ϵ / δ neighborhoods doesn't help!
  - Check stability relative to realistic perturbations
  - Ugly dependence on parameters
- Note: we ignore limit cycles for now!

Model characterization

- Study populations of (quasi) realistic in-silico patients
  - Where are the fixed points?
  - What is their "effective stability"?
  - How do they depend on patient attributes?
  - What outcomes / trajectories are possible?
- Long term goal:
  - What are the basins of attraction?
  - See which therapies will/won't work

In Silico Patient Definition

- Cohort parameters

Age	50	60	70	80	90
Weight	62	72	84		
Heart Disease	No	Yes			

- Individual parameters (continuous)

Perfusion	Brain	Gut	Heart	Kidney	Lung	Base +/- 20%

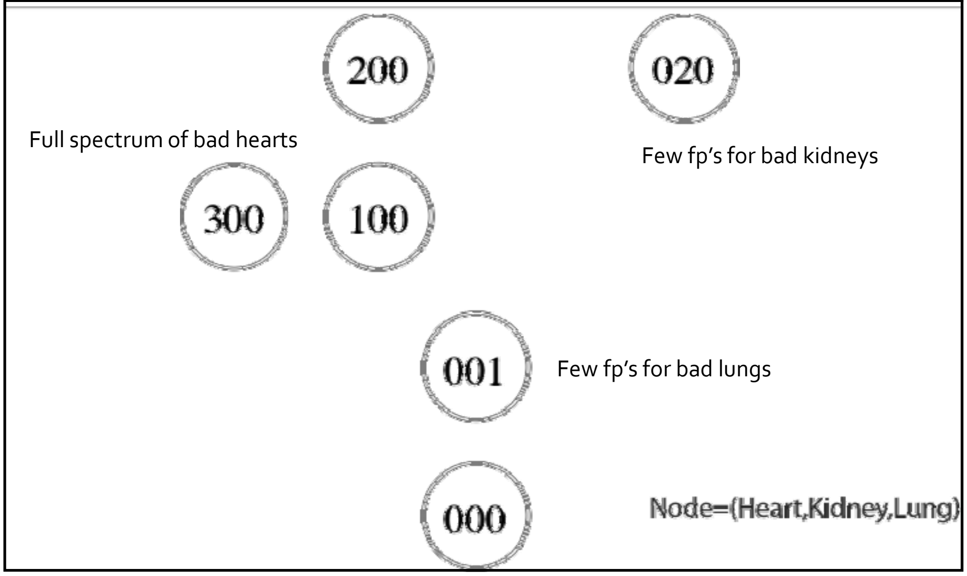
Renal Stenosis

Studying Fixed points

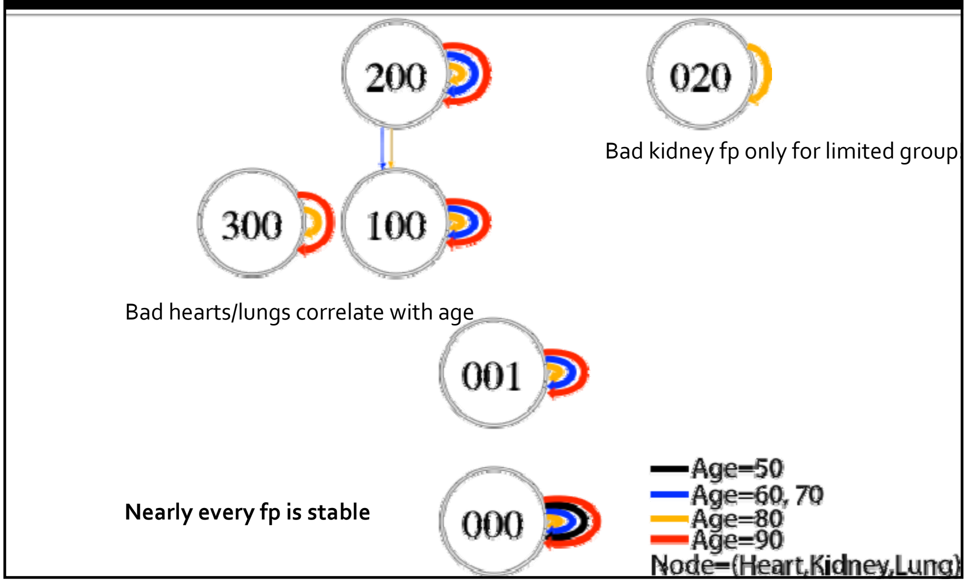
- Find patients at equilibrium (numerically)
- Perturb with lung infection: $p \in [0.01, 0.4]$
- Dimension reduction scheme:
  - Provide ready clinical interpretation
  - Rely on observable system states

	Normal	Weak	Chronic failure	Life threatening
Heart (ejection fraction)				
Kidney (creatinine)				
Lung (breath freq & o2sat)				

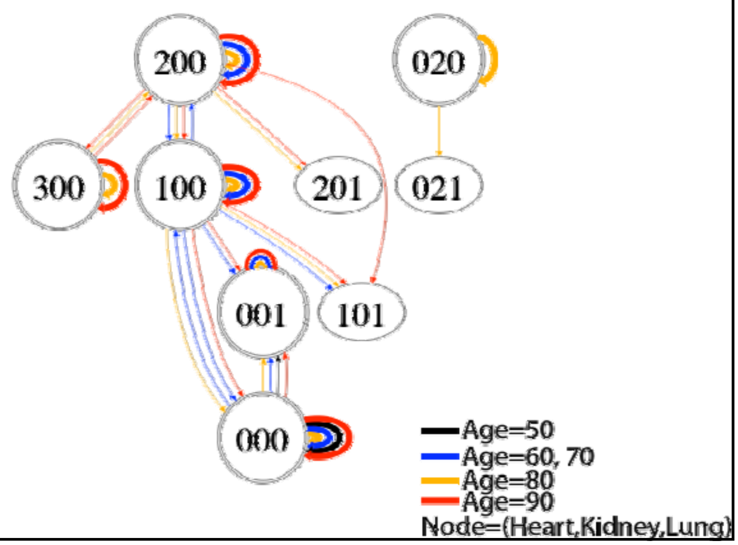
Fixed points: baseline



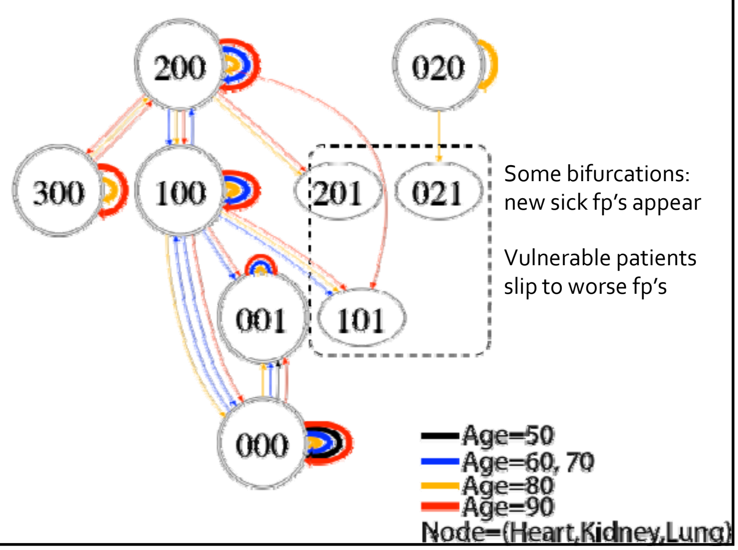
Weak perturbation (p=0.01)



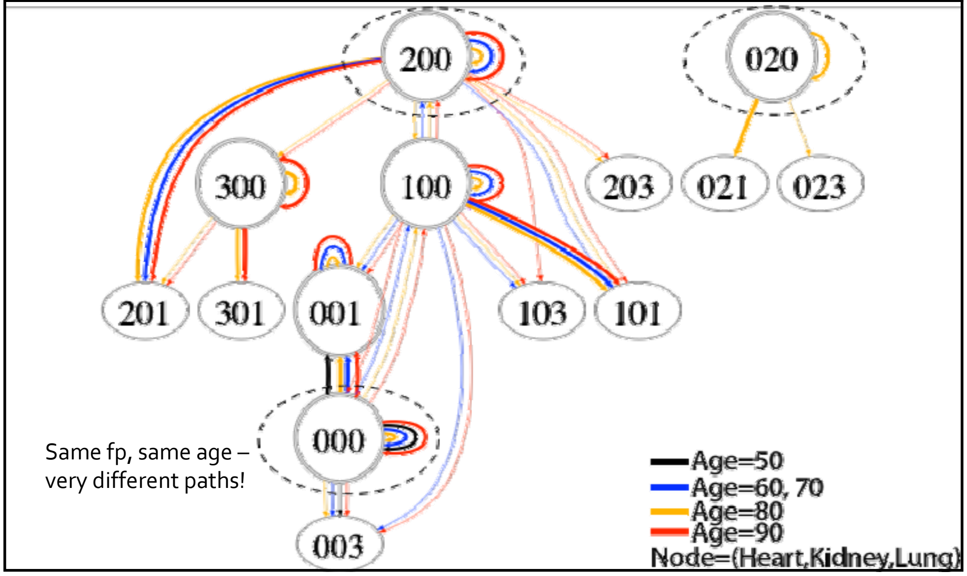
Mild perturbation (p=0.1)



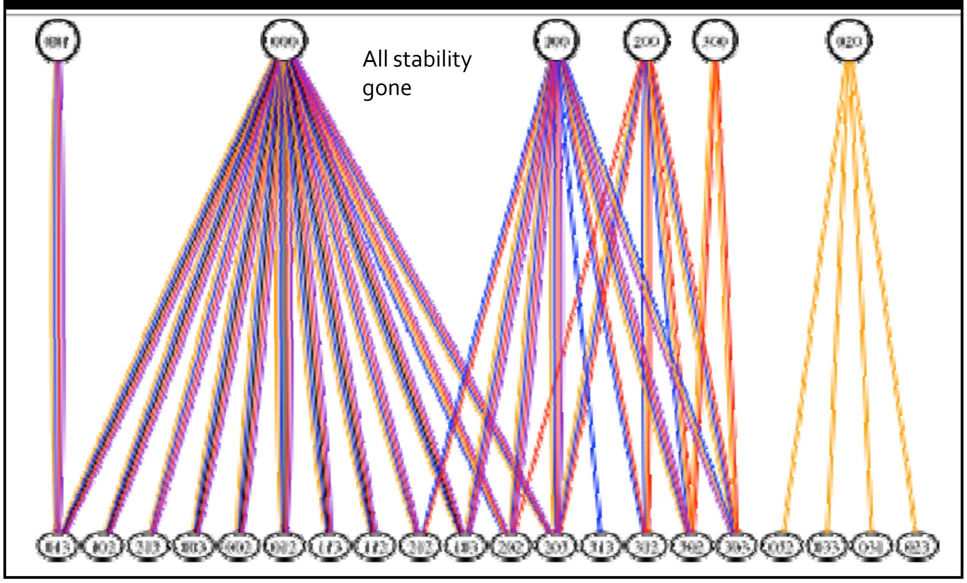
Mild perturbation (p=0.1)



Moderate perturbation (p=0.2)



Strong perturbation (p=0.4)



Treatment comparison

- What happens if we apply treatments?
  - Same cohort & tunable parameters
  - Apply pressors, ventilators, fluids
  - Use standard "Surviving Sepsis" guidelines
- Idealized case: treatment available instantly and continually
- Answer: mostly the same
  - "risky groups" still exist
  - most fp's remain with similar stability
  - populations tend to shift to healthier neighboring fp

Conclusions

- Sanity check: model reproduces many expected behaviors
  - Robustness, age correlations, progressive damage
- Method provides a basis for applying controls
  - Profusion of fixed points exist
  - Rank desirability of achievable fp's?
- Tentative prediction for kidney damage
  - Camp 1: due to hypoperfusion
  - Camp 2: due to inflammation
- Results suggest inflammation is critical
  - Kidneys **don't** worsen in standalone organ model
  - Kidneys **do** worsen for organs + inflammation model

Conclusions II

- We see "similar" patients taking very different paths in coarse clinical space
  - Prediction: uncertain where we'll end up
  - Inference: uncertain where we came from
- Models offer a way to distinguish these patients (subject to data requirements)

Acknowledgments

- Immunetrics
  - Steve Chang
  - Joydeep Sarkar
  - Kelly Hurst
  - Andrew Inglis
  - DJ Marathe
  - Michelle Jones
  - Manasi Shukla
  - Kathleen Morgan
  - Paul Barger
  - Liang Qian
- Consultants
  - Gary An
  - Yoram Vodovotz