Translational Systems Biology of Inflammation, Wound Healing, and Cancer

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Disclosure: Co-founder of and stakeholder in Immunetrics, Inc.
Traversing the fragmented continuum of healthcare delivery

- Pre-clinical studies
- Clinical trials
- In-hospital care
- Chronic / rehabilitative care

Inflammation

INFLAMMATION

Sepsis

Atherosclerosis

Infectious Disease

Trauma

IPF

COPD

Wound Healing

IPF

COPD

Wound Healing

Obesity

Asthma

Cancer

Reactive Airway Disease

Exercise

Rehabilitation

Other?
Inflammation is...

- The body’s way of informing itself of changes in homeostasis, either from without or within
- Evolutionarily conserved
- Complex, redundant, interconnected
- Necessary for proper healing and regeneration
- Deranged in many disease settings
- A puzzle: inflammation can be both good and bad

Is Systems Biology the solution?
**Translational Systems Biology**


### “Classical” Systems Biology

- Basic insights are primary focus, (but, how to apply clinically?)
- Used for basic insights (cellular/molecular interactions, signal transduction)
- Simulations designed for laboratory validation
- “omics” studies associate pattern with outcome

### Translational Systems Biology

- Translational insights are primary (but, how to incorporate mechanisms?)
- Used for clinical utility (in silico clinical trials, diagnostics, rational drug/device design)
- Simulations designed for eventual clinical validation
- Mechanistic simulations help explain why outcome associated with a given pattern
From a reductionist approach to inflammation...
...to a systems approach using mechanistic computational simulations

Solid arrow: induction; dashed line: suppression. An initiating stimulus (e.g., pathogen (Panel A) or trauma (Panel B)) stimulates both pro- and anti-inflammatory pathways. In the setting of infection, pro-inflammatory agents (e.g., TNF) cause tissue damage/dysfunction, which in turn stimulates further inflammation (e.g., through the release of “danger signals”). In the case of trauma, tissue damage occurs immediately and further simulates inflammation. Anti-inflammatory agents (e.g., TGF-β1) both suppress inflammation and stimulate healing.

Modeling: A rational means of traversing the fragmented continuum

Pre-clinical studies | Clinical trials | In-hospital care | Chronic / rehabilitative care

Simulate Mechanism | Simulate Clinical Trial | Simulate Individual Patient | Simulate Aging, etc.

Mining → Modeling

1. **Research Biological Mechanisms**
2. **Collect Biomarker Data**
3. **Develop Representative Models**
4. **Calibrate Models to Data**
5. **Use Model for Predictions and Clinical Trial Simulations**
THE ACUTE INFLAMMATORY RESPONSE IN DIVERSE SHOCK STATES

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Fig. A1. A simplified version of macrophage dynamics. In the model used herein, resting macrophages (M₀) are activated by a number of physiologic processes, including endotoxin (PE), damage/dysfunction, trauma and hypotension (blood pressure (BP) drop). This recruitment process can be up-regulated (green lines) in the presence of tumor necrosis factor TNF and interleukin (IL)-6, whereas IL-10 and other anti-inflammatory (CA) molecules down-regulate (red line) these activating influences. Both resting and activated macrophages (Mₐ) "die" at their respective rates (gray dotted line). Each process is supported by a literature search.

\[
M'_A = \left[ k_{MLPS} \frac{LPS(t)^2}{1 + (LPS(t)/x_{MLPS})^2} + k_{MD} \frac{D_{4}}{x_{MD} + D_{4}} \right]
\times \left( \frac{TNF^2}{x_{MTNF}^2 + TNF^2} + k_{M6} \frac{IL6^2}{x_{M6}^2 + IL6^2} \right) + k_{MTX} TR(t) + k_{MB} f(B) \frac{1}{1 + ((IL10 + CA)/x_{M10})^2} M_R - k_{MAM} M_A
\]
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[Diagram showing the acute inflammatory response in diverse shock states with nodes for LPS, Resting Macrophages, Resting Neutrophils, Activated Macrophages, Activated Neutrophils, TNF-α, IL-6, IL-10, NO, Damage, Fluids, MAP, and decrease in MAP.]
LPS Receptor Complex: Central Role for CD14

Myeloid-derived mCD14-positive cells

Non-myeloid mCD14-negative cells
Wild Type

CD14⁻⁻⁻

![Graphs showing TNF and NO₂⁻/NO₃⁻ levels over time for Wild Type and CD14⁻⁻⁻ conditions.](image)
Re-calibrate baseline model for data in CD14⁻/⁻ mice

Activation of leukocytes by LPS is ~40-fold lower in CD14⁻/⁻ mice

Altered IL-6 physiology in CD14⁻/⁻ mice
- Enhanced propensity to produce and secrete IL-6 both at rest (~20-fold) and in response to stimulation (~60-fold)
- Greater degradation rate of IL-6 (~25-fold)

Altered NO physiology
- Decreased iNOS expression (5-fold) in CD14⁻/⁻ mice
- Decreased baseline NO₂⁻/NO₃⁻ levels (5-fold) in CD14⁻/⁻ mice
The base model was never trained to any experimental data from pigs.

First step was to fit the model parameters to the time course data from any of the individual pigs.

The time course data that was used for fitting included:
- Blood pressure
- TNF, IL-6, IL-10, NO$_2^-$/NO$_3^-$
- Using a form of sensitivity analysis, a reduced list of parameters that need re-estimation was determined.

52 parameters were then estimated to fit the time course of a pig that survived endotoxemia with no subsequent complications, using a genetic algorithm.

The best scored models generated were then clustered and the centroids of the clusters are shown.
Recalibration: From Mice to Swine

R33-HL-089082
Microarray Technology (WT mice) → Biostatistics/Bioinformatics → Identification of DE genes & Expression Patterns (clusters) → Pathway Analyses IDENTIFY TARGETS! → Discovery of Regulatory Networks → Validation (RT-PCR) → Gene function: KO mice /Drugs → Predictions: Mathematical Simulations
Microarray study of mouse liver transcriptome post-trauma / HS

INGENUITY PATHWAY ANALYSIS RESULTS

MIC-1/GDF-15:
- A member of TGF-β super-family
- 2nd Network (high score)
- Focus Gene (= relevant): \( \uparrow \sim 45\)-fold
- Part of cell death/cell proliferation network
Recalibration: **GDF-15/MIC-1^-/- mice**

- Model re-calibration performed as for CD14^-/- mice
- Suggested that GDF-15/MIC-1^-/- mice have underlying alterations in parameters related to
  - Neutrophils
  - TNF
  - IL-6
In silico design of clinical trials: A method coming of age

Gilles Clermont, MD; John Bartels; Rukmini Kumar, MSc; Greg Constantine, PhD; Yoram Vodovotz, PhD; Carson Chow, PhD


A MATHEMATICAL SIMULATION OF THE INFLAMMATORY RESPONSE TO ANTHRAX INFECTION

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Agent-based model of inflammation and wound healing: insights into diabetic foot ulcer pathology and the role of transforming growth factor-β1

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A Patient-Specific in silico Model of Inflammation and Healing Tested in Acute Vocal Fold Injury

Nicole Y. K. Li1, Katherine Verdolini1,2,3,4,7,8, Gilles Clermont4,5,7, Qi Mi4,6,7, Elaine N. Rubenstein8, Patric A. Hebd1,2,7,8,9, Yoram Vodovotz1,4,7,11

Patient-specific simulations of traumatic brain injury (Okonkwo, Constantine, Solovyev, Mi)

\[ \frac{dD}{dt} = d_0 M - d_1 D \]
\[ \frac{dM}{dt} = \left( \frac{m_0 D}{1 + m_1 D} + \frac{m_2 C}{1 + m_3 C} + \frac{m_4 \text{TNF}}{1 + m_5 \text{TNF}} + \frac{m_6 \text{IL}_5}{1 + m_7 \text{IL}_5} \right) - m_8 M \]
\[ \frac{dC}{dt} = c_0 D - c_1 C \]
\[ \frac{d\text{IL}_{10}}{dt} = i_0 M - i_1 \text{IL}_{10} \]
\[ \frac{d\text{TNF}}{dt} = t_0 M - t_1 \text{IL}_{10} - t_2 \text{TNF} \]
\[ \frac{d\text{IL}_6}{dt} = b_0 M^6 \]

Terms in the model:
- Damage (D)
- Inflammatory cell (M)
- Chemokine (C)
- \( \text{IL}_{10} \)
- \( \text{IL}_6 \)

Graphs A, B, C, and D illustrate the simulation results and model terms.
Pre-clinical studies

Clinical trials

In-hospital care

Chronic / rehabilitative care

NIDRR Grant H133E070024 (Brienza). Rehabilitation Engineering Research Center on Spinal Cord Injury. Developmental Project 1: Development of a Mathematical Model of Inflammation and Healing Following Spinal Cord Injury (Vodovotz)
Agent-based Model of Pressure Ulcer Formation

- Resting Macrophage
- Activated Macrophage
- Epithelial Cell
- Blood Vessel
- TNF-α
- TGF-β1
- Oxygen
- ROS
- Force
- Damages
- Produces
- Heals
- Releases (if damaged)
- Activates

Patent application: “Modeling Wound Healing” (Serial Nos. 60/850,690 and 60/850,896; PCT/US2007/080893)

Solovyev, Ziraldo, Mi, Vodovotz, Unpublished
Effect of pressure on blood flow: Simulation and experiment (short term)

**SPARK** (Simple Platform for Agent-based Representation of Knowledge) software created at CIRM

**Simulation**
Solovyev, Ziraldo, Mi, Vodovotz, Unpublished

**Experiment**
Yi-Ting, Tzen et al.
Shear force model of pressure ulcer formation (long term)

SPARK (Simple Platform for Agent-based Representation of Knowledge) software created at CIRM

Distorted epithelial cells  Developing ulcer
Agent-based Model of Pressure Ulcer Formation via Ischemia / Reperfusion Mechanism

SCI patient: 6 weeks after first sign of ulceration

Solovyev, Ziraldo, Mi, Vodovotz, Unpublished

Same patient, 5 days later
Inflammation

↓

Wound Healing

↓

Cancer
Hepatitis C and Hepatocellular Carcinoma

• Acute HCV infection often progresses to chronic infection
• It is common for the virus to persist at low levels
  • Even when high levels of HCV RNA available, assembled virions are few and rarely overwhelm the system (in vitro or in vivo)
  • This provides a potential mechanism that encourages chronic development: replication of HCV may be too low to provide sufficient MHC I–HCV peptide complex on the surface of the hepatocyte, thereby protecting from CTL-mediated killing
Model Rules

Dutta-Moscato, Soloveyv, Mi, Vodovotz, Unpublished

Provisional patent application: “In Silico Strategies for Cancer Diagnosis and Therapy” (Serial No. 61/186,126)
Structure of the model

Baseline circulatory system providing nutrients to healthy tissue: Grid simulating hexagonal assembly of **portal triads**

Also serves as entry point for **HCV**, as a blood borne virus

*Initial*

*Cancer* progenitor cells initialized to 4, dispersed near the center of region of interest

Dutta-Moscato, Soloveyv, Mi, Vodovotz, Unpublished
Structure of the model

Underlying data layers: Allow “Monitor” multiple cytokine levels simultaneously

Dutta-Moscato, Soloveyv, Mi, Vodovotz, Unpublished
Starting with identical initial conditions, random selection from the same distribution of viral inoculation, the model stochastically results in cases where HCV resolves following acute infection, or persists as a chronic infection.
Measures of Damage: Clinical vs. Model

Clinical data
Serological course of Hepatitis C

Model simulation
Dutta-Moscato, Soloveyv, Mi, Vodovotz, Unpublished

> 1 year
Initiation and Progression of HCC: Initial Tumor Formation

Dutta-Moscato, Soloveyv, Mi, Vodovotz, Unpublished
Initiation and Progression of HCC: Formation of Hypoxic Core and Angiogenesis

Dutta-Moscato, Soloveyv, Mi, Vodovotz, Unpublished
Main problem: time required for inflammation assays and personalized modeling may be too slow for effective therapy for fast-evolving inflammatory processes

Patient-specific, inflammation-regulating bioreactor

Provisional patent application: “Self-Regulating Device for Modulating Inflammation.” (Serial No. 61/100,845)
Rational Inflammation Reprogramming

Benefits:
- Single device for FDA
- Self-regulating
- Response can be tuned
- Modular
- Infinitely modifiable
- Designed using mathematical model to be disease/stage-specific

Uses:
- Sepsis
- Trauma
- Chronic diseases
- Wound healing
- Burns?
Summary: Translational Systems
Biology of Inflammation

- **Measurement**: Novel methods of analysis for the development of cytokines as biomarkers
- **Modeling**: Computational simulations of inflammation and damage/healing in various inflammatory diseases
  - *In silico* clinical trials
  - “Smart” diagnostics
- **Modulation**: A prototype inflammation-regulating bioreactor
So... what is still needed?

- Automate literature mining → modeling
- Extraction of data for validation of conceptual models, parameter estimation
- **Example:** Gary An Shock Bioinformatics Initiative
  - Initial Premise: Scientific Societies would be a good “functional level” to implement collaborative curation to augment lexicon development
  - Develop means to capture the knowledge of the Shock Society
  - Present this knowledge in a fashion beneficial to the Shock Membership
  - Knowledge in the Abstracts Presented at the Annual Shock Society Meeting
  - Use of advances in computer technology to access, process, extract and represent knowledge published in the biomedical literature
Funding and Other Support

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http://www.scai-med.org