CMACS Kickoff Meeting
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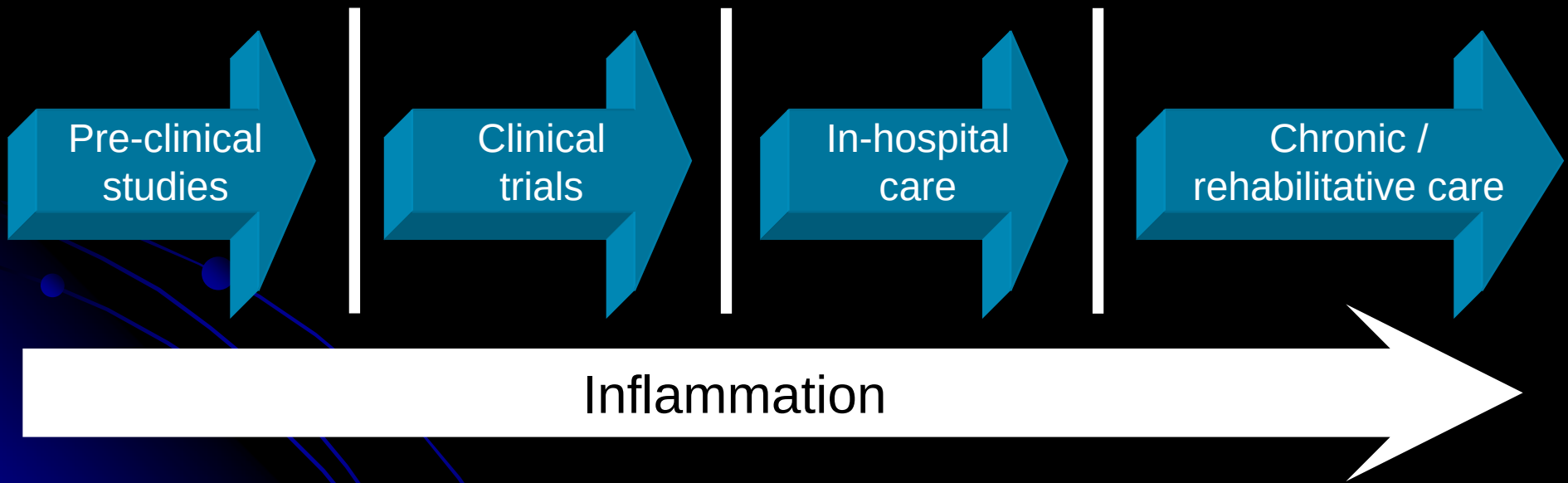
Translational Systems Biology of Inflammation, Wound Healing, and Cancer

Yoram Vodovotz

Director, Center for Inflammation and Regenerative Modeling
Professor of Surgery, Immunology, and Communication Science and Disorders
Visiting Professor of Computational Biology
University of Pittsburgh
www.mirm.pitt.edu/cirm

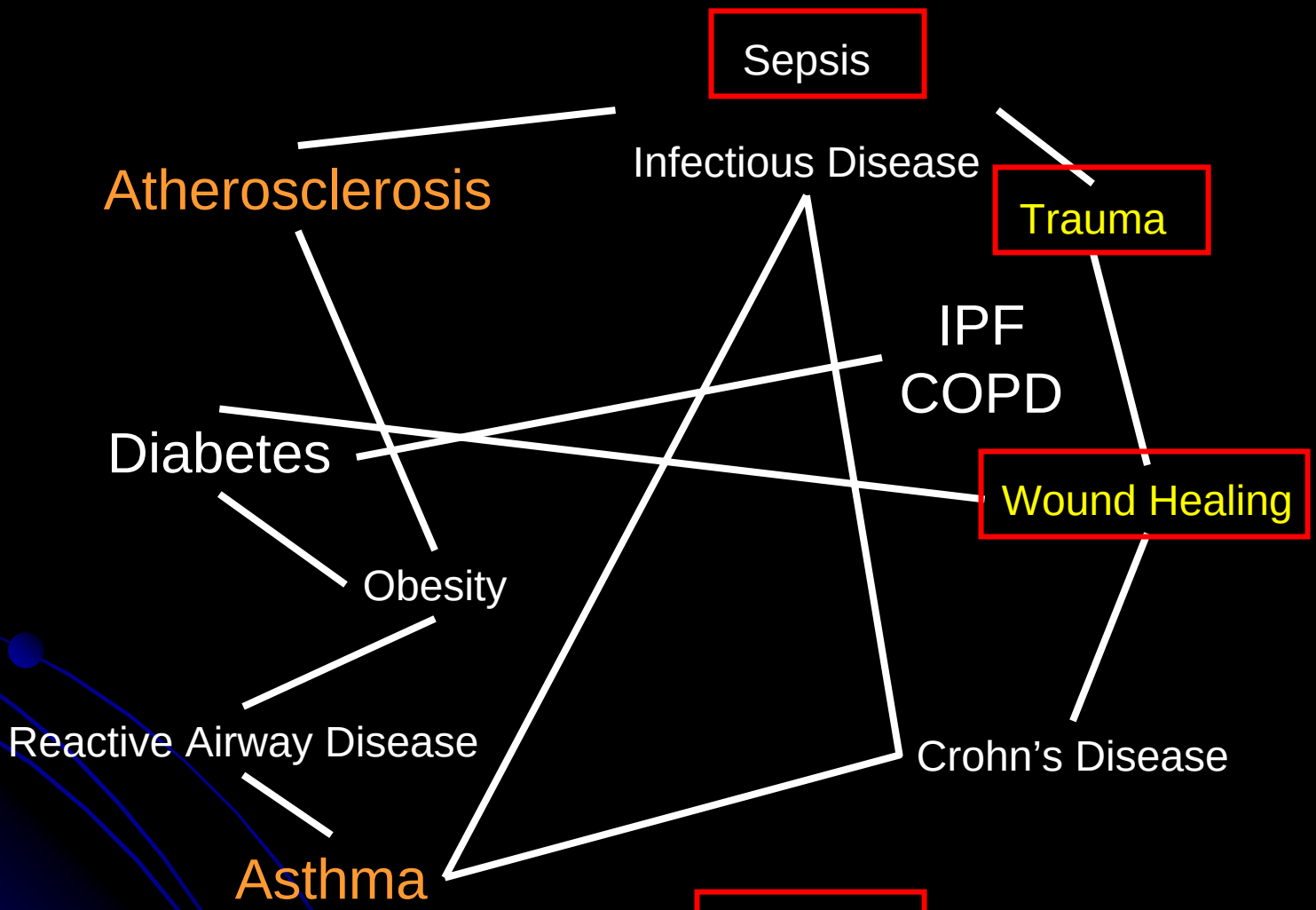
Disclosure: Co-founder of and stakeholder in Immunetrics, Inc.

Traversing the fragmented continuum of healthcare delivery



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

INFLAMMATION



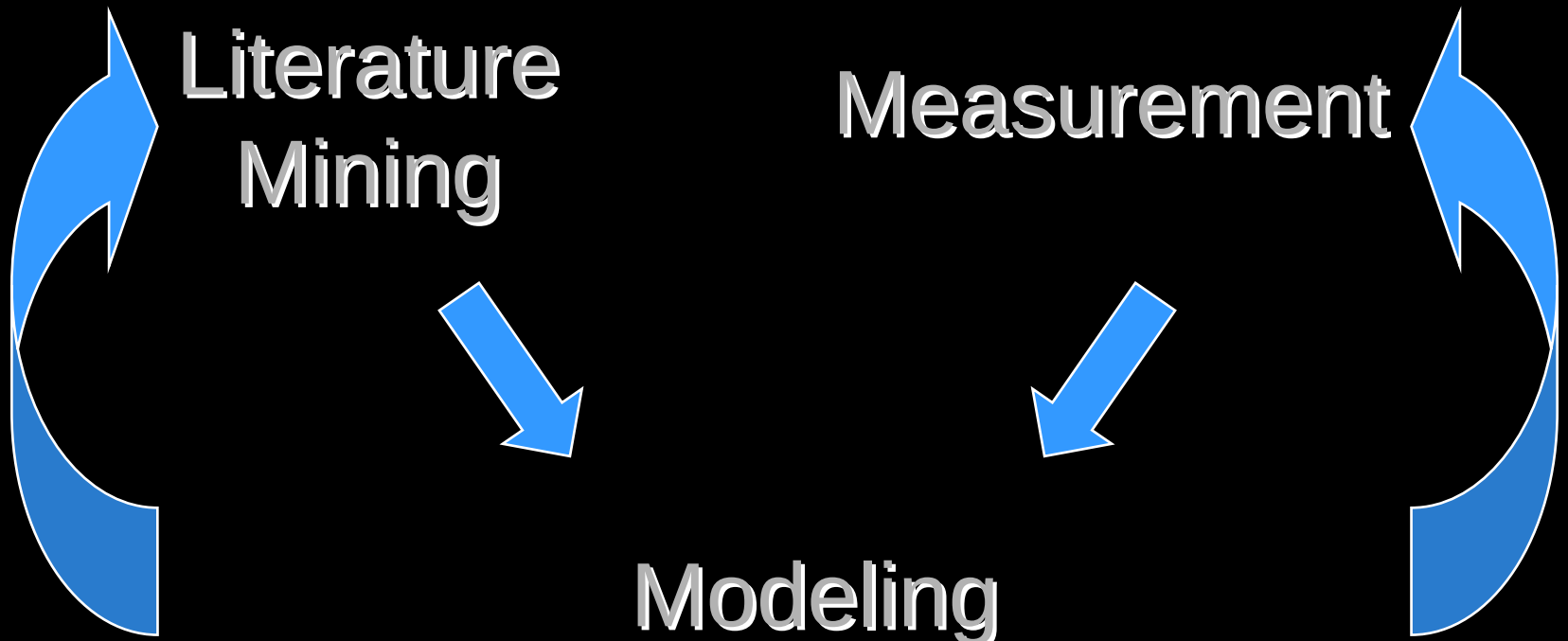
Inflammation is…

- 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

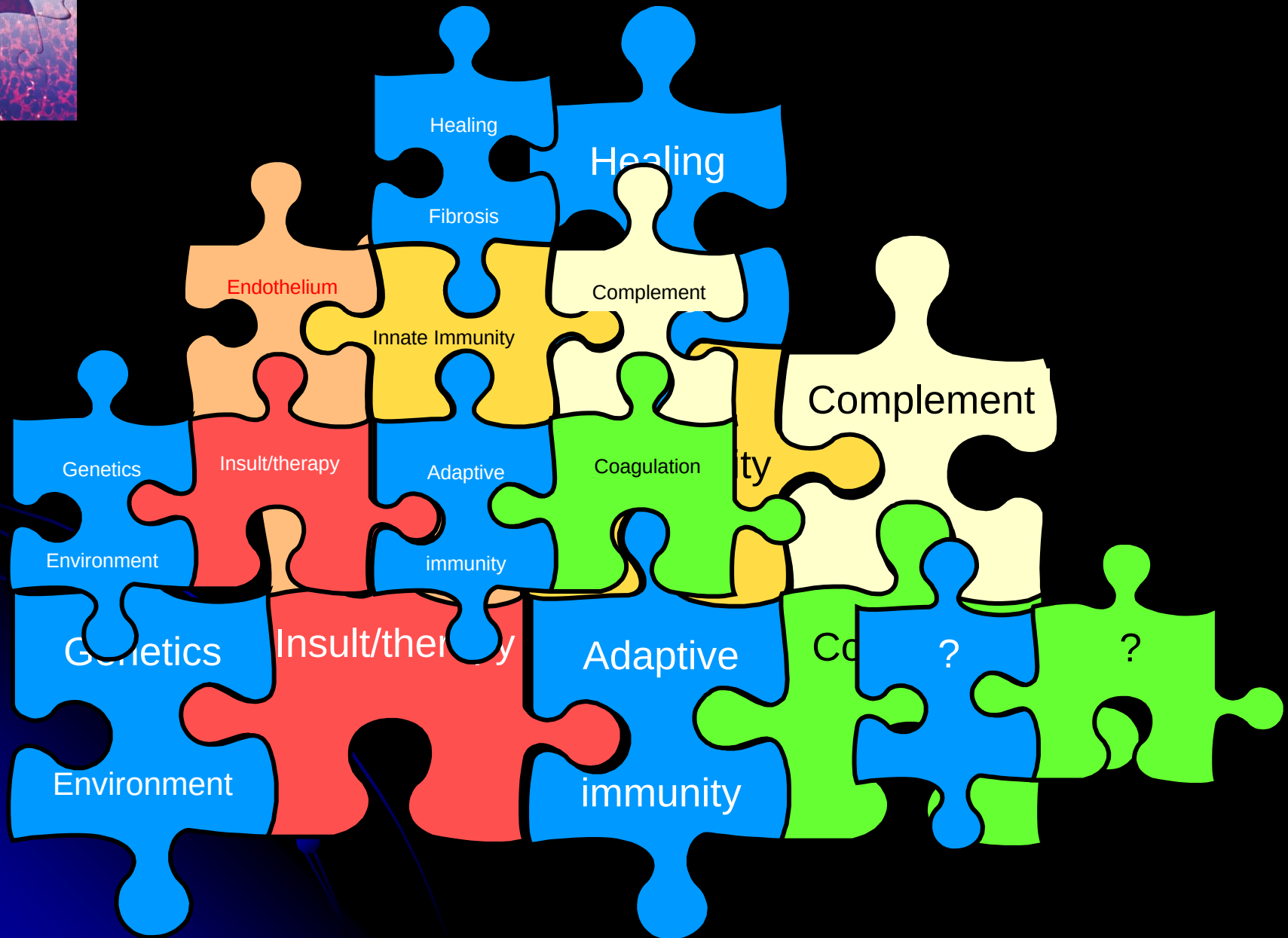
An et al. J. Crit. Care. 2007 22:169; An & Vodovotz, J. Burn Care Res. 2008 29:277; Vodovotz et al, PLoS Comput. Biol. 2008 4:1

"Classical" Systems Biology		Translational Systems Biology
Basic insights are primary focus, (but, how to apply clinically?)	⟺	Translational insights are primary (but, how to incorporate mechanisms?)
Used for basic insights (cellular/molecular interactions, signal transduction)	⟺	Used for clinical utility (*in silico* clinical trials, diagnostics, rational drug/device design)
Simulations designed for laboratory validation	⟺	Simulations designed for eventual clinical validation
"omics" studies associate pattern with outcome	⟺	Mechanistic simulations help explain why outcome associated with a given pattern

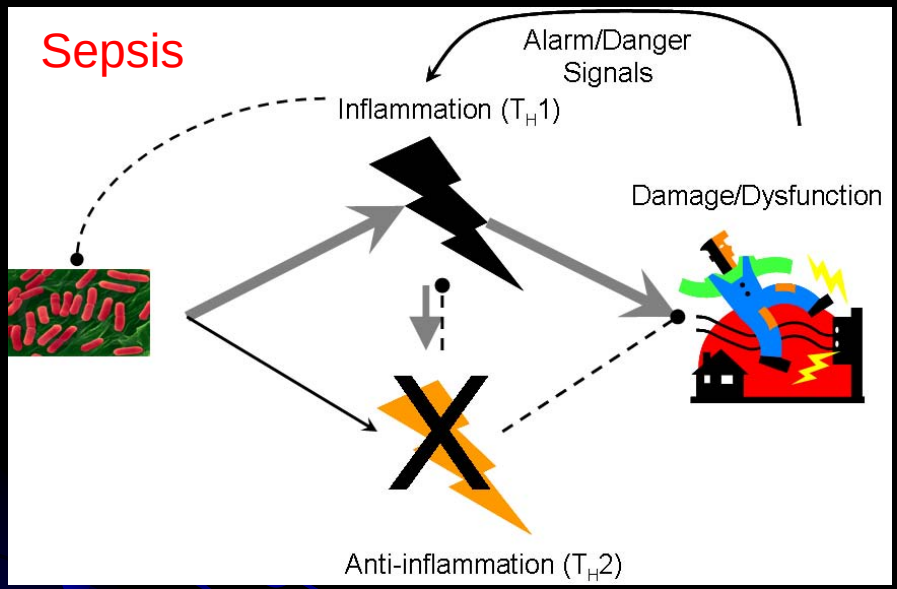


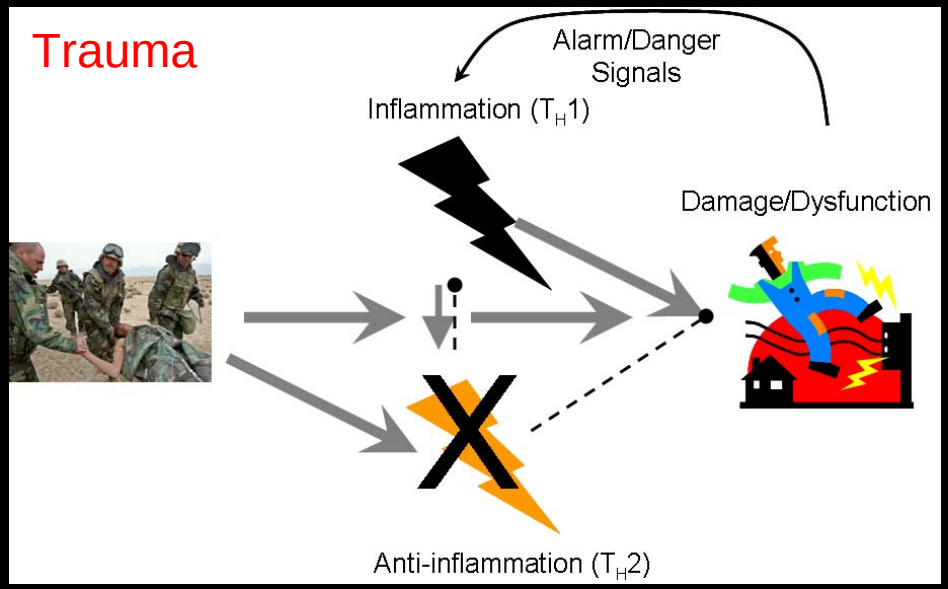
Modulation

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

(Vodovotz et al, Math Biosci, 2009. 217:1-10).

Modeling: A rational means of traversing the fragmented continuum

Simulate Mechanism

Simulate Clinical Trial

Simulate Individual Patient

Simulate Aging, etc.

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

Pre-clinical studies

Available online at www.sciencedirect.com
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www.elsevier.com/locate/yjtbi

The dynamics of acute inflammation

Rukmini Kumar[a], Gilles Clermont[b], Yoram Vodovotz[c], Carson C. Chow[d,*]

[a]Departments of Physics and Astronomy, University of Pittsburgh, Pittsburgh, PA 15260, USA
[b]Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA 15260, USA
[c]Department of Surgery, University of Pittsburgh, Pittsburgh, PA 15260, USA
[d]Department of Mathematics, University of Pittsburgh, Pittsburgh, PA 15260, USA

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A reduced mathematical model of the acute inflammatory response II. Capturing scenarios of repeated endotoxin administration

Judy Day[a], Jonathan Rubin[a,*], Yoram Vodovotz[b,c,d], Carson C. Chow[e], Angela Reynolds[a], Gilles Clermont[f,c,d]

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SHOCK, Vol. 24, No. 1, pp. 74–84, 2005

THE ACUTE INFLAMMATORY RESPONSE IN DIVERSE SHOCK STATES

Carson C. Chow,* Gilles Clermont,† Rukmini Kumar,‡ Claudio Lagoa,§ Zacharia Tawadrous,† David Gallo,§ Binnie Betten,§ John Bartels,¶ Gregory Constantine,* Mitchell P. Fink,† Timothy R. Billiar,§ and Yoram Vodovotz§

*Department of Mathematics, †Department of Critical Care Medicine, ‡Department of Physics and Astronomy, and §Department of Surgery, University of Pittsburgh, Pittsburgh, Pensylvania; and ¶Immunetrics, Inc., Pittsburgh, Pennsylvania

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SHOCK, Vol. 26, No. 3, pp. 235–244, 2006

Review Article

IN SILICO MODELS OF ACUTE INFLAMMATION IN ANIMALS

Yoram Vodovotz,[1,*] Carson C. Chow,[1,†,‡] John Bartels,[§] Claudio Lagoa,[*] Jose M. Prince,[*] Ryan M. Levy,[*] Rukmini Kumar,[†] Judy Day,[†] Jonathan Rubin,[†] Greg Constantine,[†] Timothy R. Billiar,[1,*] Mitchell P. Fink,[1,*,‖] and Gilles Clermont[1,‖]

Departments of *Surgery and †Mathematics, University of Pittsburgh, Pittsburgh, PA; ‡Laboratory of Biological Modeling, NIDDK NIH, Bethesda, MD; §Immunetrics, Inc., Pittsburgh, PA; and ‖Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA

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SHOCK, Vol. 26, No. 6, pp. 592–600, 2006

THE ROLE OF INITIAL TRAUMA IN THE HOST'S RESPONSE TO INJURY AND HEMORRHAGE: INSIGHTS FROM A CORRELATION OF MATHEMATICAL SIMULATIONS AND HEPATIC TRANSCRIPTOMIC ANALYSIS

Claudio E. Lagoa,* John Bartels,† Arie Baratt,† George Tseng,‡ Gilles Clermont,§‖ Mitchell P. Fink,§ Timothy R. Billiar,* and Yoram Vodovotz*‖

*Department of Surgery, University of Pittsburgh; †Immunetrics, Inc.; ‡Departments of Biostatistics and Human Genetics, University of Pittsburgh; §Department of Critical Care Medicine, University of Pittsburgh; and ‖Center for Inflammation and Regenerative Modeling McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pennsylvania

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A MATHEMATICAL SIMULATION OF THE INFLAMMATORY RESPONSE TO ANTHRAX INFECTION

Rukmini Kumar,* Carson C. Chow,† John D. Bartels,‡ Gilles Clermont,§ and Yoram Vodovotz‖

Departments of *Physics, and †Mathematics, University of Pittsburgh; ‡Immunetrics, Inc; Departments of §Critical Care Medicine, and ‖Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania

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In Silico and In Vivo Approach to Elucidate the Inflammatory Complexity of CD14-deficient Mice

Jose M Prince,[1] Ryan M Levy,[1] John Bartels,[2] Arie Baratt,[2] John M Kane, III,[1] Claudio Lagoa,[1] Jonathan Rubin,[3,5] Judy Day,[3] Joyce Wei,[2] Mitchell P Fink,[1,4,5] Sanna M Goyert,[6] Gilles Clermont,[4,5] Timothy R Billiar,[1,5] and Yoram Vodovotz[1,5,7]

[1]Department of Surgery, University of Pittsburgh, Pittsburgh, PA, USA; [2]Immunetrics, Inc., Pittsburgh, PA, USA; [3]Department of Mathematics, University of Pittsburgh, Pittsburgh, PA, USA; [4]Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA; [5]McGowan Institute for Regenerative Medicine, Center for Inflammation and Regenerative Modeling, University of Pittsburgh, Pittsburgh, PA, USA; [6]North Shore-Long Island Jewish Research Institute/New York University School of Medicine, Manhasset, NY, USA; [7]Department of Immunology, University of Pittsburgh, Pittsburgh, PA, USA

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An ensemble of models of the acute inflammatory response to bacterial lipopolysaccharide in rats: Results from parameter space reduction

Silvia Daun[a,b,c], Jonathan Rubin[b,c], Yoram Vodovotz[b,d], Anirban Roy[e], Robert Parker[e], Gilles Clermont[a,b,*]

[a]Department of Critical Care Medicine, School of Medicine, University of Pittsburgh, Scaife 606B, 3550 Terrace St, Pittsburgh, PA 15261, USA
[b]Center for Inflammation and Regenerative Modeling, 100 Technology Drive, University of Pittsburgh, Pittsburgh, PA 15219, USA
[c]Department of Mathematics, 301 Thackeray Hall, University of Pittsburgh, Pittsburgh, PA 15260, USA
[d]Department of Surgery, 200 Lothrop St, University of Pittsburgh, Pittsburgh, PA 15213, USA
[e]Department of Chemical and Petroleum Engineering, 1249 Benedum Hall, University of Pittsburgh, Pittsburgh, PA 15261, USA

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Journal of Theoretical Biology
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A reduced mathematical model of the acute inflammatory response: I. Derivation of model and analysis of anti-inflammation

Angela Reynolds[a], Jonathan Rubin[a,*], Gilles Clermont[b,c,d], Judy Day[a], Yoram Vodovotz[b,c,d], G. Bard Ermentrout[a]

[a]Department of Mathematics, 301 Thackeray, University of Pittsburgh, Pittsburgh, PA 15260, USA
[b]CRIM (Center for Inflammation and Regenerative Modeling), 100 Technology Drive Suite 200, Pittsburgh, PA 15219-3110, USA
[c]CRISMA Laboratory, University of Pittsburgh, Pittsburgh, PA 15261, USA
[d]Department of Critical Care Medicine, 3550 Terrace St., University of Pittsburgh Medical Center, Pittsburgh, PA 15261, USA
[e]Department of Surgery, University of Pittsburgh Medical Center, W1542 Biomedical Sciences Tower, 200 Lothrop St., Pittsburgh, PA 15213, USA

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Journal of Pediatric Surgery

Review article

Mathematical modeling in necrotizing enterocolitis—a new look at an ongoing problem

Jeffrey S. Upperman[a,g,*], Victoria Camerini[a,f,g], Brian Lugo[a], Ivan Yotov[c], Joshua Sullivan[c], Joshua Rubin[c], Giles Clermont[d,e], Ruben Zamora[a], G. Bard Ermentrout[c], Henri R. Ford[a,g], Yoram Vodovotz[b,e]

SHOCK, Vol. 32, No. 2, pp. 172–178, 2009

MATHEMATICAL MODELING OF POSTHEMORRHAGE INFLAMMATION IN MICE: STUDIES USING A NOVEL, COMPUTER-CONTROLLED, CLOSED-LOOP HEMORRHAGE APPARATUS

Andres Torres,* Timothy Bentley,† John Bartels,‡ Joydeep Sarkar,‡ Derek Barclay,* Rajaie Namas,* Gregory Constantine,§ Ruben Zamora,* Juan Carlos Puyana,*¶§ and Yoram Vodovotz‖

*Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; †Walter Reed Army Institute of Research, Washington, District of Columbia; and ‡Immunetrics, Inc, and §Department of Mathematics, ‖Center for Inflammation and Regenerative Modeling, McGowan Institute for Regenerative Medicine, and ¶Department of Critical Care Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

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Mining → Modeling

Research Biological Mechanisms

Develop Representative Models

Collect Biomarker Data

Calibrate Models to Data

Use Model for Predictions And Clinical Trial Simulations

P50-GM-53789

MINING

SHOCK, Vol. 24, No. 1, pp. 74–84, 2005

THE ACUTE INFLAMMATORY RESPONSE IN DIVERSE SHOCK STATES

Carson C. Chow,* Gilles Clermont,† Rukmini Kumar,‡ Claudio Lagoa,§ Zacharia Tawadrous,† David Gallo,§ Binnie Betten,§ John Bartels,‖ Gregory Constantine,* Mitchell P. Fink,† Timothy R. Billiar,§ and Yoram Vodovotz§

*Department of Mathematics, †Department of Critical Care Medicine, ‡Department of Physics and Astronomy, and §Department of Surgery, University of Pittsburgh, Pittsburgh, Pensylvania; and ‖Immunetrics, Inc., Pittsburgh, Pennsylvania

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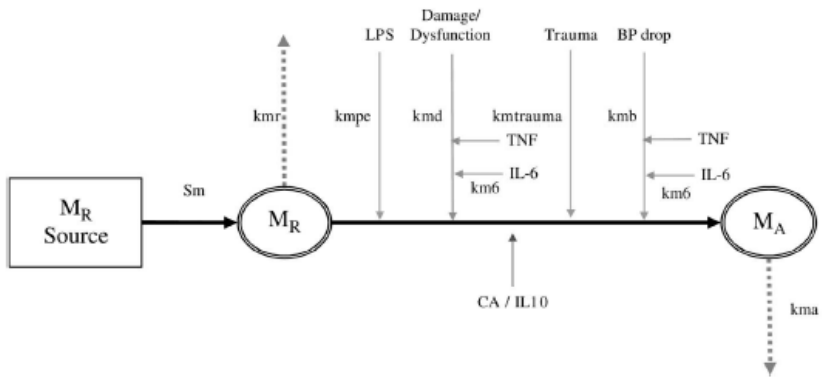

FIG. A1. **A simplified version of macrophage dynamics.** In the model used herein, resting macrophages (M_R) are activated by a number of physiologic processes, including endotoxin (PE), damage/dysfunction, trauma and hypotension (blood pressure [BP] drop). This recruitment process can be upregulated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

MODELING

$$M_A' = \left[\left(k_{MLPS}\frac{LPS(t)^2}{1+(LPS(t)/x_{MLPS})^2} + k_{MD}\frac{D^4}{x_{MD}^4+D^4}\right) \times \left(\frac{TNF^2}{x_{MTNF}^2+TNF^2} + k_{M6}\frac{IL6^2}{x_{M6}^2+IL6^2}\right) + k_{MTR}TR(t) + k_{MB}f_B(B)\right]\frac{1}{1+((IL10+CA)/x_{M10})^2}M_R - k_{MA}M_A$$

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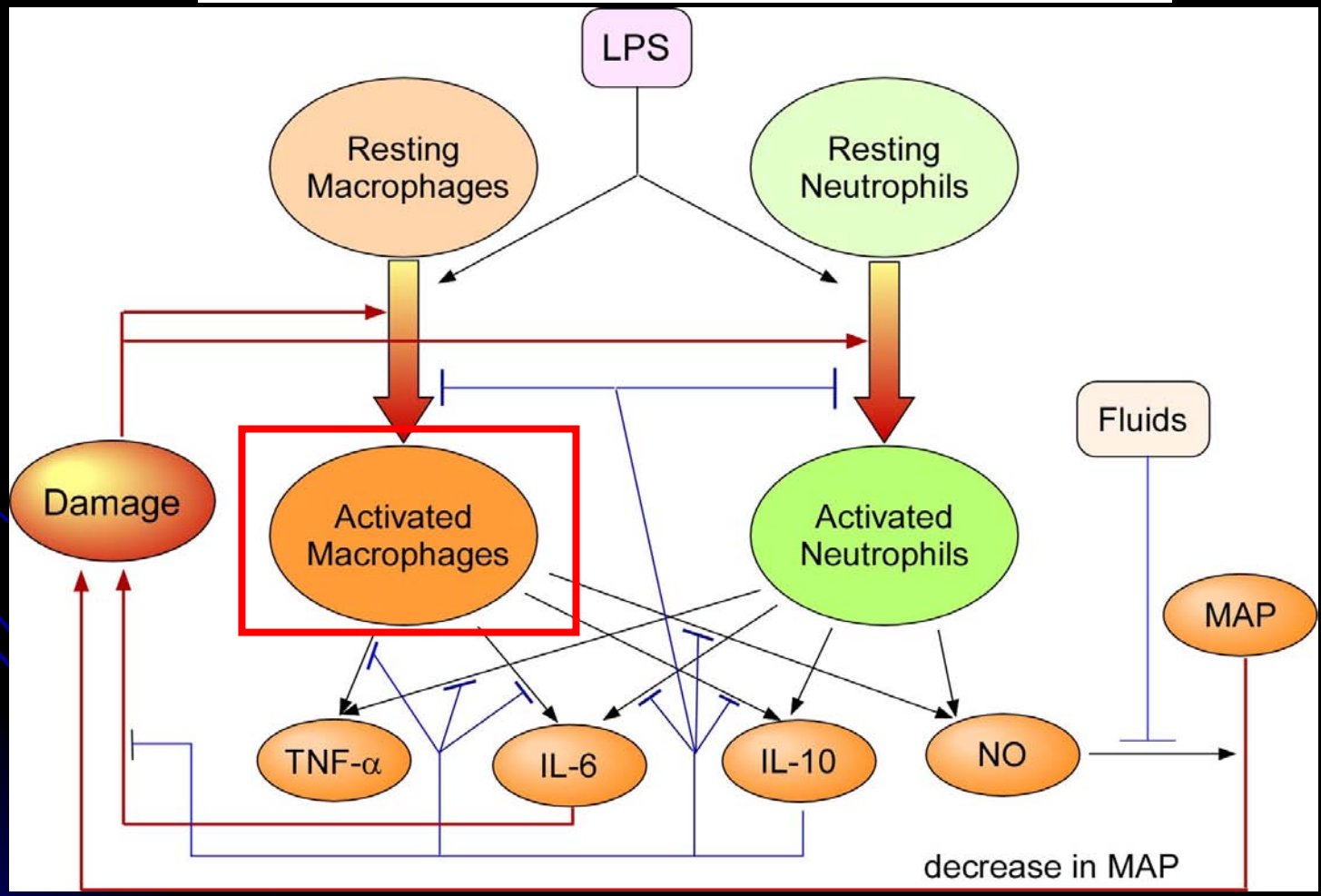
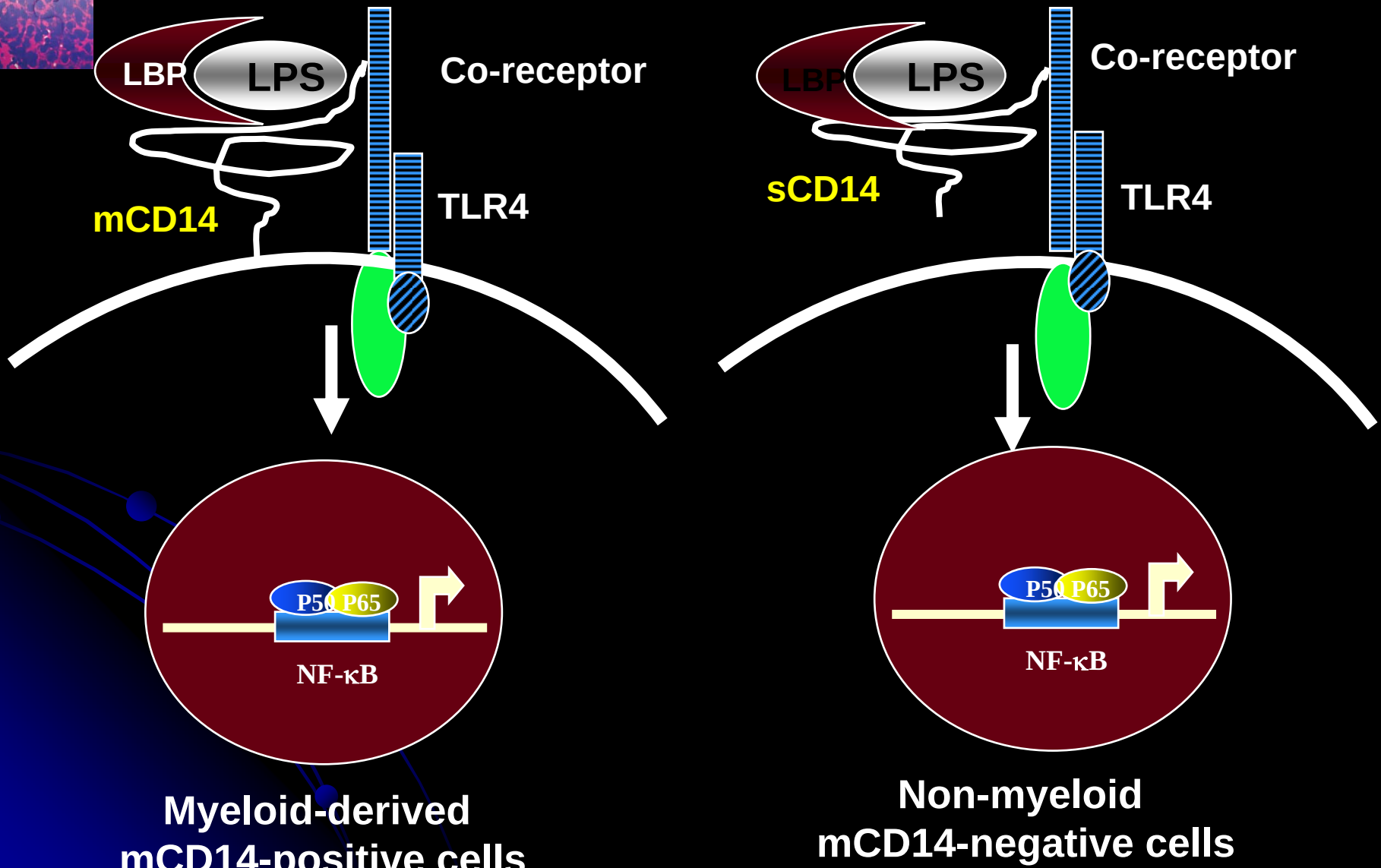
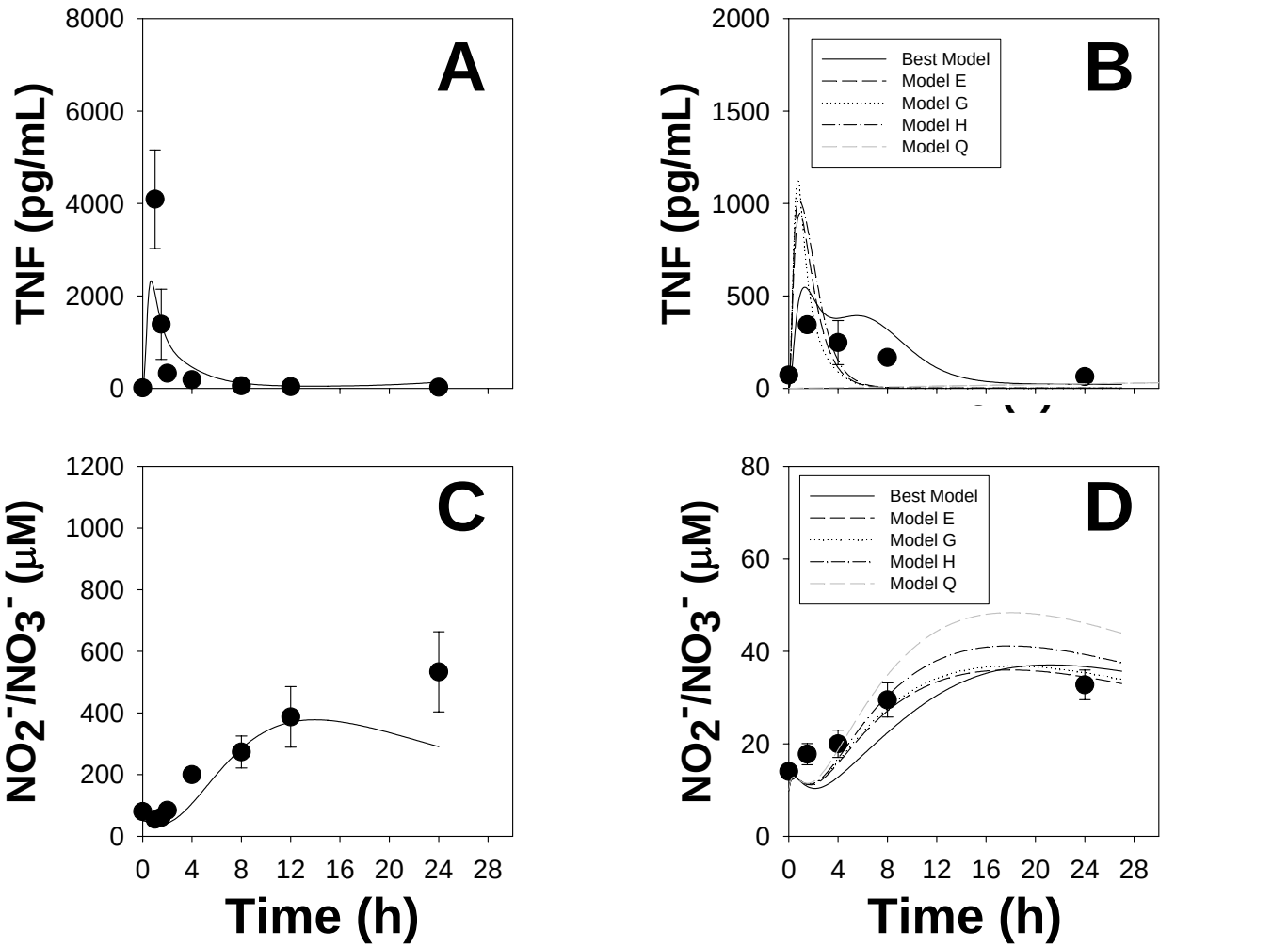


LPS Receptor Complex: Central Role for CD14



Wild Type CD14$^{-/-}$



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In Silico and In Vivo Approach to Elucidate the Inflammatory Complexity of CD14-deficient Mice

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[1]Department of Surgery, University of Pittsburgh, Pittsburgh, PA, USA; [2]Immunetrics, Inc., Pittsburgh, PA, USA; [3]Department of Mathematics, University of Pittsburgh, Pittsburgh, PA, USA; [4]Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA; [5]McGowan Institute for Regenerative Medicine, Center for Inflammation and Regenerative Modeling, University of Pittsburgh, Pittsburgh, PA, USA; [6]North Shore-Long Island Jewish Research Institute/New York University School of Medicine, Manhasset, NY, USA; [7]Department of Immunology, University of Pittsburgh, Pittsburgh, PA, USA

- 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 NO_2^-/NO_3^- levels (5-fold) in $CD14^{-/-}$ mice

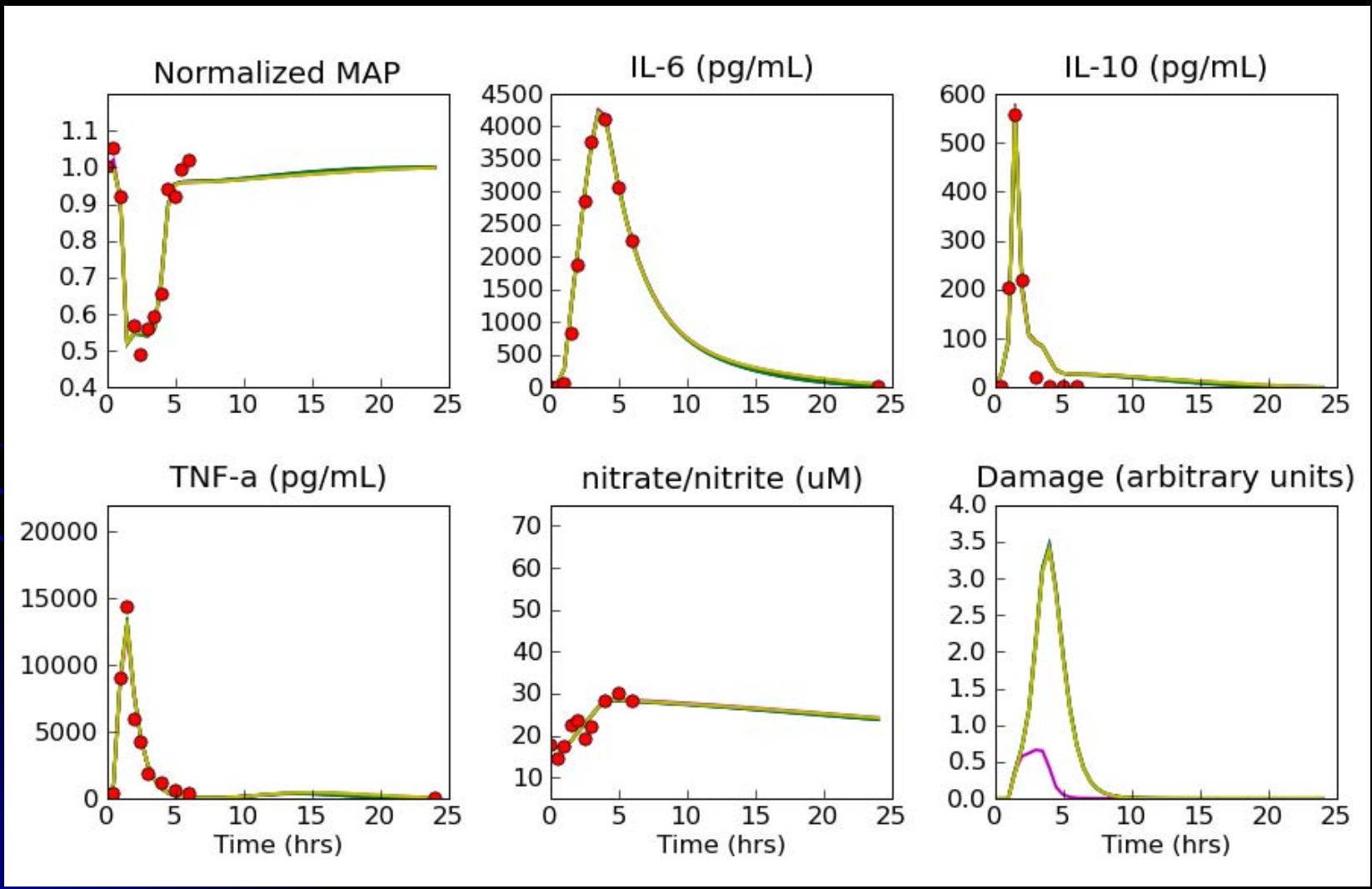
Recalibration: From Mice to Swine…

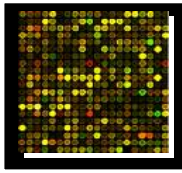
R33-HL-089082

- 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

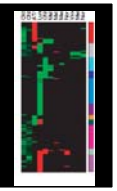
Identification of DE genes & Expression Patterns (clusters)

Pathway Analyses

INGENUITY SYSTEMS

IDENTIFY TARGETS!

Discovery of Regulatory Networks



Validation (RT-PCR)

Gene function: KO mice /Drugs

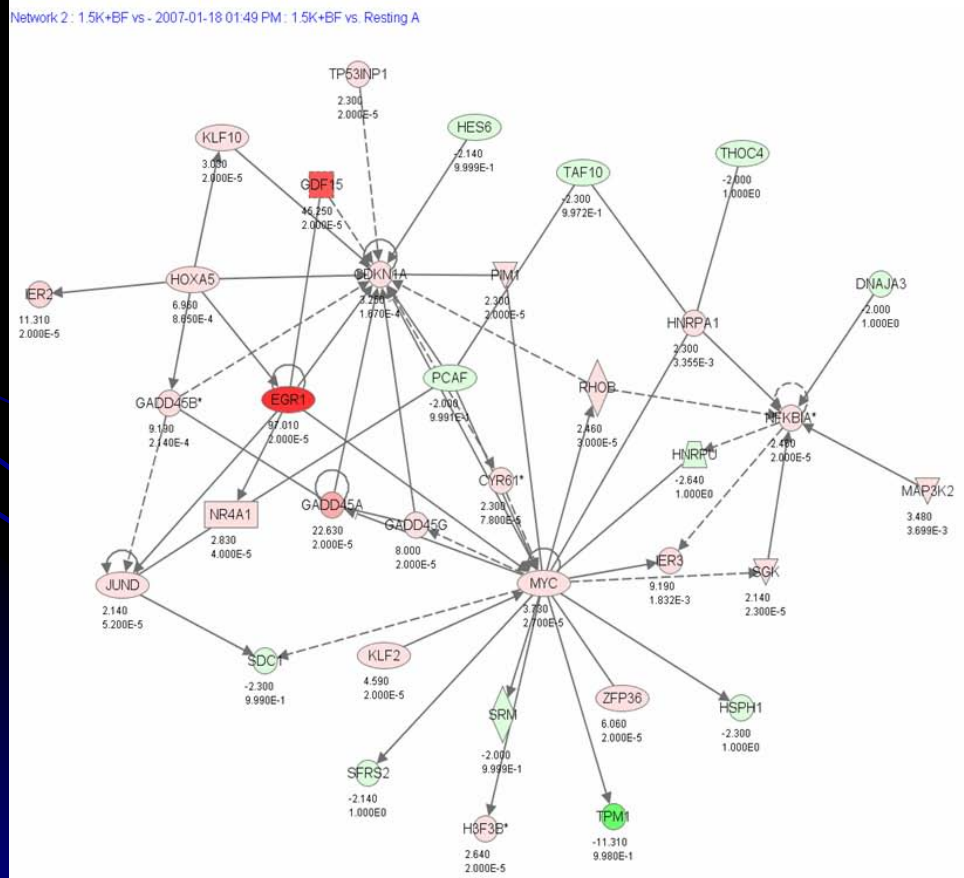
Predictions: Mathematical Simulations

Microarray study of mouse liver transcriptome post-trauma / HS

INGENUITY PATHWAY ANALYSIS RESULTS

2

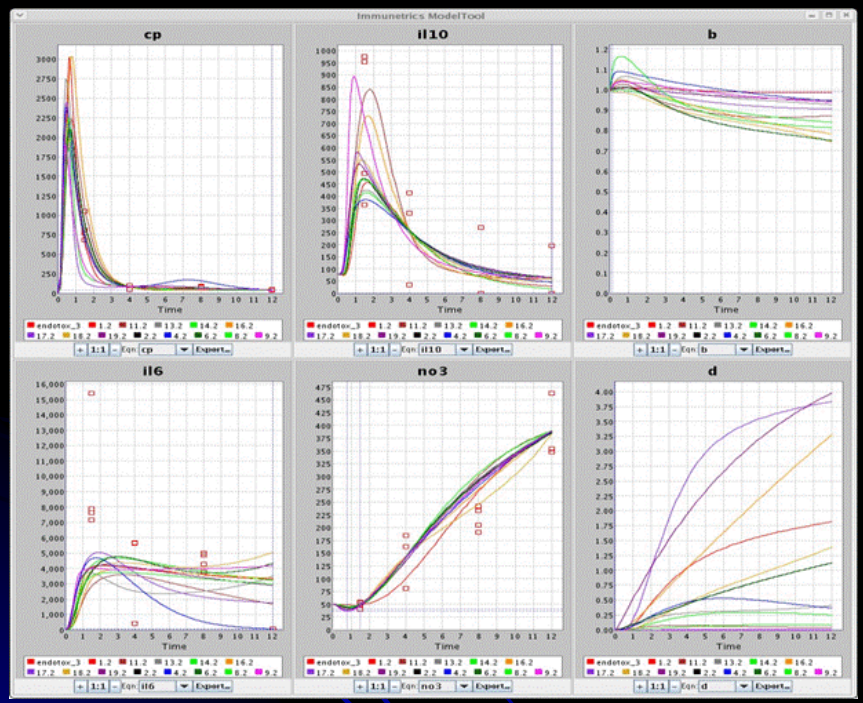
↑AACS, ↑CCRL2, ↑CEBPD, ↑CHKA, ↑DUSP4, ↑ECGF1, ↑EGR1, ↑EGR2, ↑FASN, ↑FLT1, ↓G0S2, ↑GCK, ↓GCLC, ↑GDF15, ↓GHR, ↑HMGCR, ↑IER3, ↑IL1B, ↑INSIG2*, ↑IRG1, ↑ITPKB, ↑KLF2, ↑MEFV, ↑MMP8, ↑PIM3*, ↑PLK3, ↓PNN, ↑S100A6, ↑S100A9, ↑SCD, ↑SLC16A1, ↑SLC20A1, ↑SLFN5 (includes EG:342615), ↑SREBF1, ↑VEGF



MIC-1/GDF-15:

- A member of TGF-β super-family
- 2nd Network (high score)
- Focus Gene (= relevant): ↑ ~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

Pre-clinical studies

nic / tive care

SHOCK, Vol. 29, No. 1, pp. 104–111, 2008

A MATHEMATICAL SIMULATION OF THE INFLAMMATORY RESPONSE TO ANTHRAX INFECTION

Rukmini Kumar,* Carson C. Chow,† John D. Bartels,‡ Gilles Clermont,§ and Yoram Vodovotz‖

*Departments of *Physics, and †Mathematics, University of Pittsburgh; ‡Immunetrics, Inc; Departments of §Critical Care Medicine, and ‖Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania*

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Wound Repair and Regeneration

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

Qi Mi[1]; Beatrice Rivière[1,2]; Gilles Clermont[2,3]; David L. Steed[4]; Yoram Vodovotz[2,4]

1. Department of Mathematics,
2. Department of Center for Inflammation and Regenerative Modeling, McGowan Institute for Regenerative Medicine,
3. Department of Critical Care Medicine, and
4. Department of Surgery, University of Pittsburgh, Pittsburgh, PA

Immunetrics

Pre-clinical studies

trials

care

rehabilitative care

Wound Repair and Regeneration

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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2. Department of Center for Inflammation and Regenerative Modeling, McGowan Institute for Regenerative Medicine,
3. Department of Critical Care Medicine, and
4. Department of Surgery, University of Pittsburgh, Pittsburgh, PA

OPEN ACCESS Freely available online

PLoS one

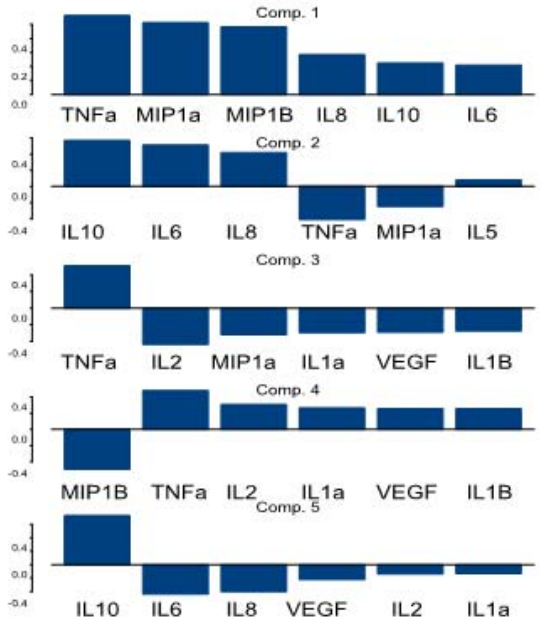
A Patient-Specific *in silico* Model of Inflammation and Healing Tested in Acute Vocal Fold Injury

Nicole Y. K. Li[1], Katherine Verdolini[1,2,3,4,7]*, Gilles Clermont[4,5,7], Qi Mi[4,6,7], Elaine N. Rubinstein[8], Patricia A. Hebda[1,2,7,9,10], Yoram Vodovotz[1,4,7,11]

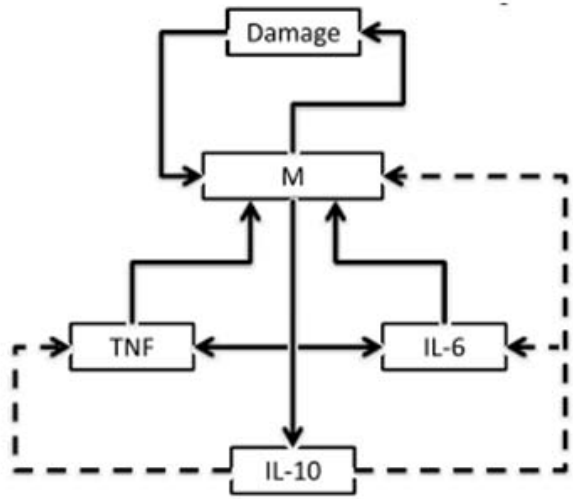
1 Department of Communication Science and Disorders, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **2** Department of Otolaryngology, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **3** University of Pittsburgh Voice Center, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **4** Center for Inflammation and Regenerative Modeling, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **5** Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **6** Department of Sports Medicine and Nutrition, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **7** McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **8** Office of Measurement and Evaluation of Teaching, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **9** Otolaryngology Wound Healing Laboratory, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **10** Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **11** Department of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America

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

A



B



C

$$\frac{dD}{dt} = d_0 M - d_1 D$$

$$\frac{dM}{dt} = \left(\frac{m_0 D}{1 + m_1 D} + \frac{m_2 C}{1 + m_3 C} + \frac{m_4 TNF}{1 + m_5 TNF} + \frac{m_6 IL_6}{1 + m_7 IL_6} \right) \frac{1}{1 + m_8 IL_{10}} - m_9 M$$

$$\frac{dC}{dt} = \frac{c_0 D}{1 + c_1 D} - c_2 C$$

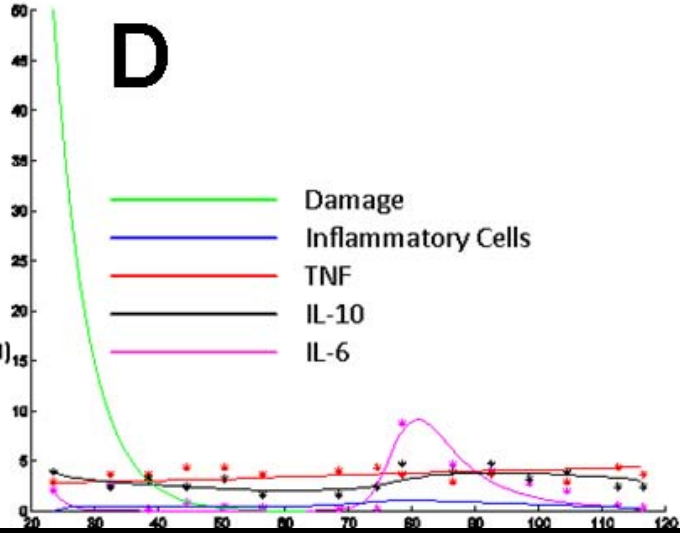
$$\frac{dIL_{10}}{dt} = i_0 M - i_1 IL_{10}$$

$$\frac{dTNF}{dt} = \frac{t_0 M}{1 + t_1 IL_{10}} - t_2 TNF$$

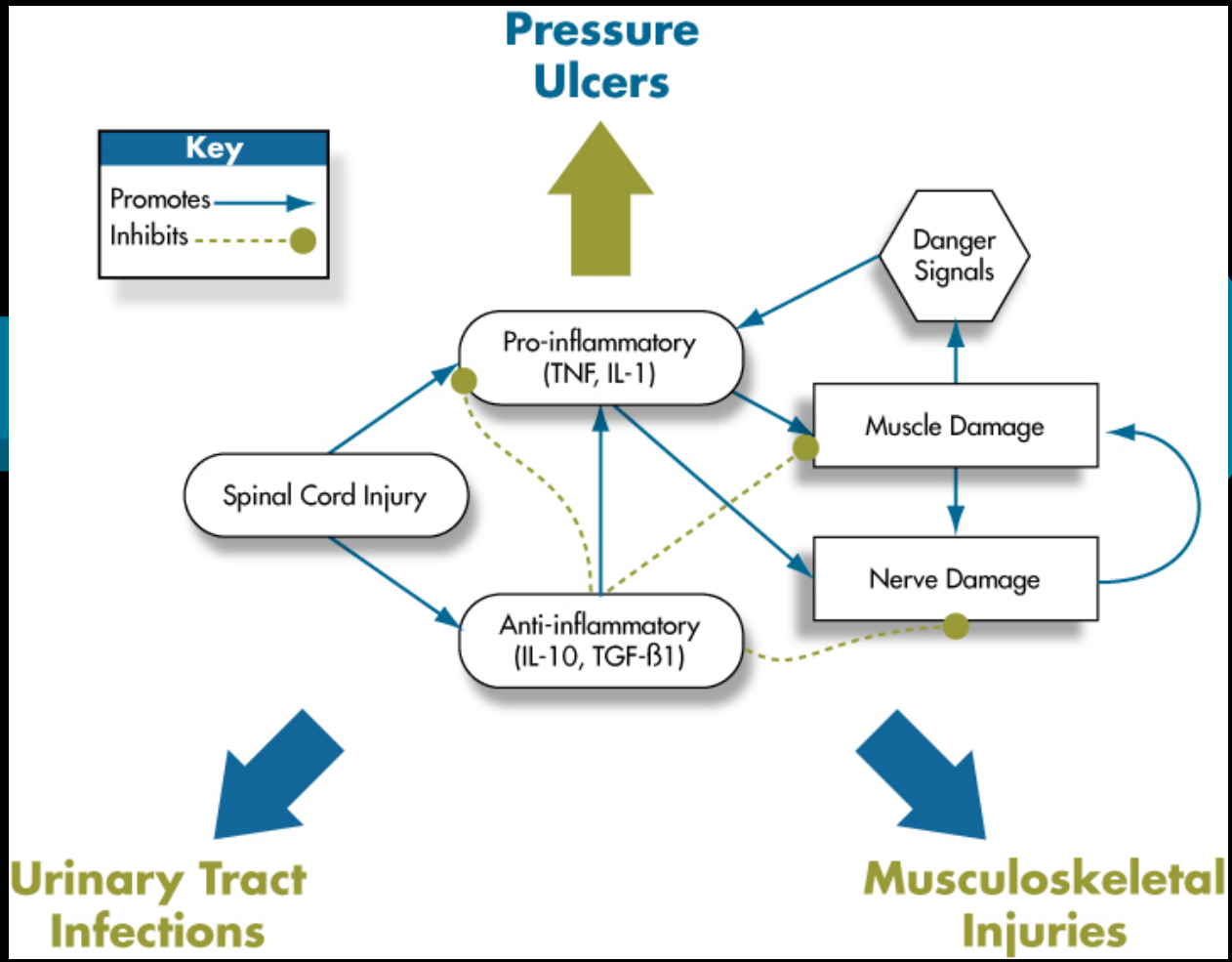
$$\frac{dIL_6}{dt} = \frac{b_0 M^6}{1 + b_1 IL_{10}} - b_2 IL_6$$

Terms in the model:
Damage (D)
Inflammatory cell (M)
Chemokine (C)
IL-10 (IL_{10})
TNF (TNF)
IL-6 (IL_6)

D

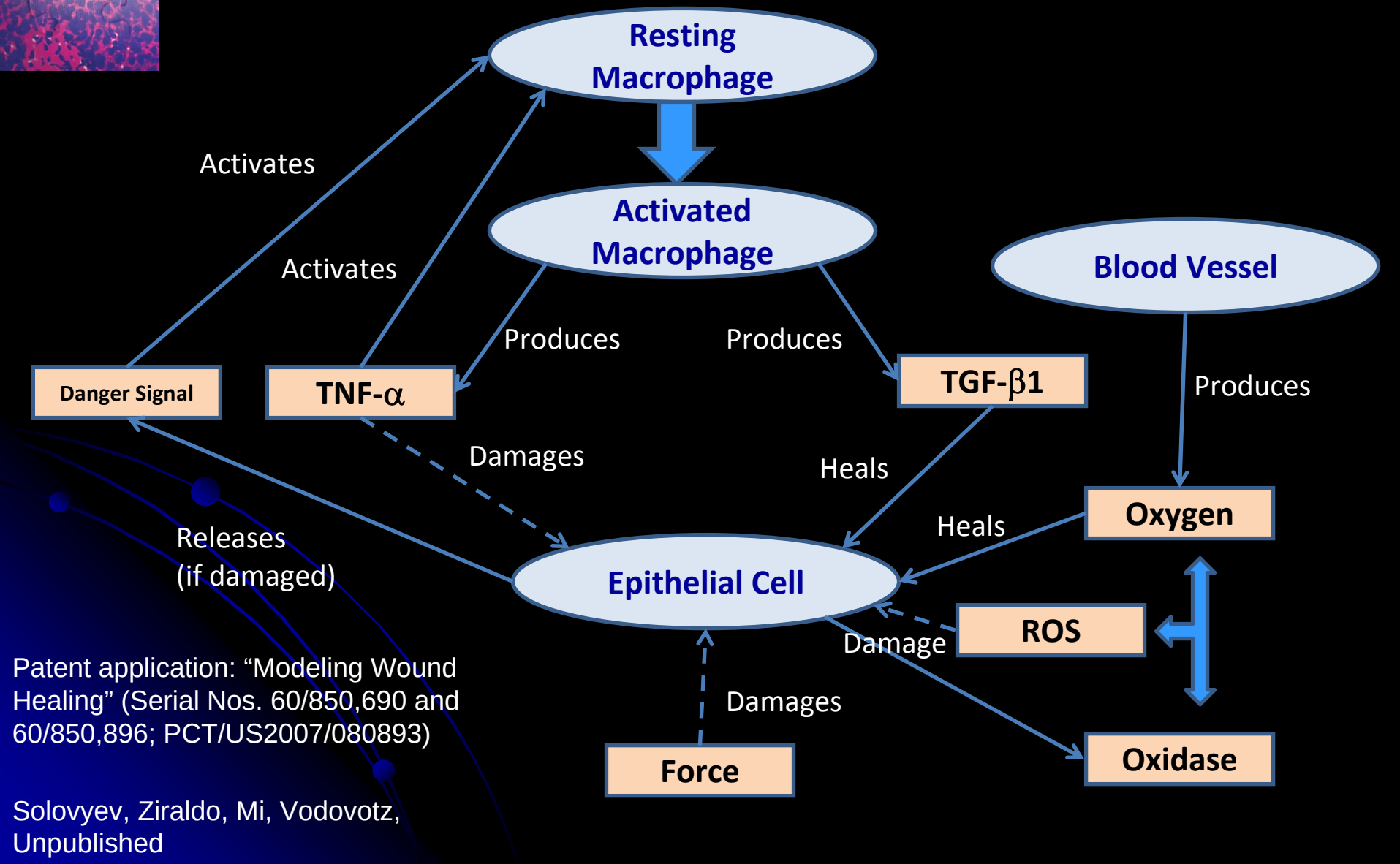


Pre-clinical studies



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



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

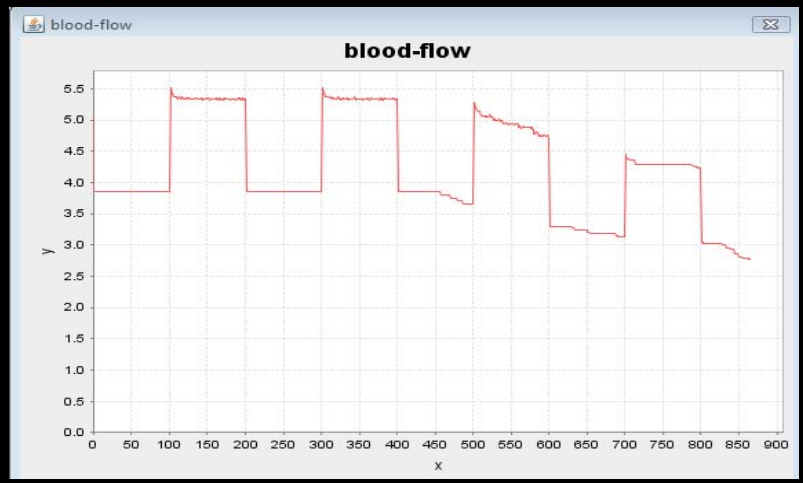
Solovyev, Ziraldo, Mi, Vodovotz, Unpublished

Effect of pressure on blood flow: Simulation and experiment (short term)

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

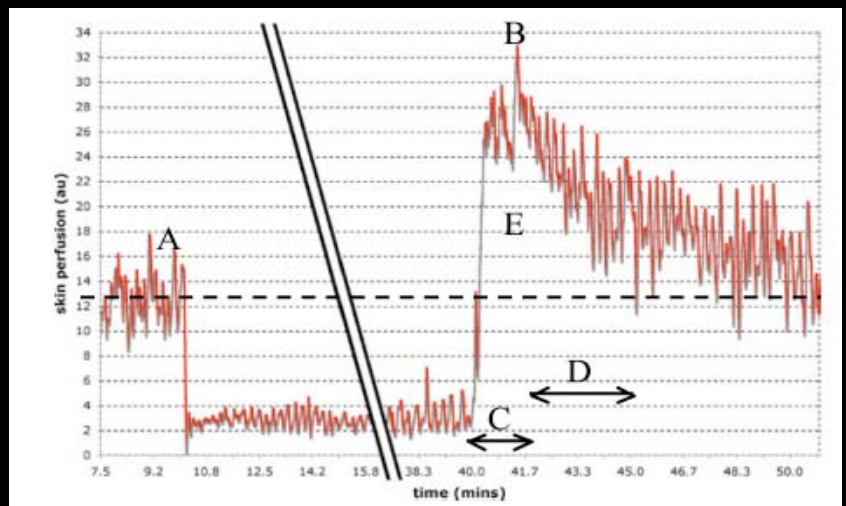
Simulation

Solovyev, Ziraldo, Mi, Vodovotz, Unpublished



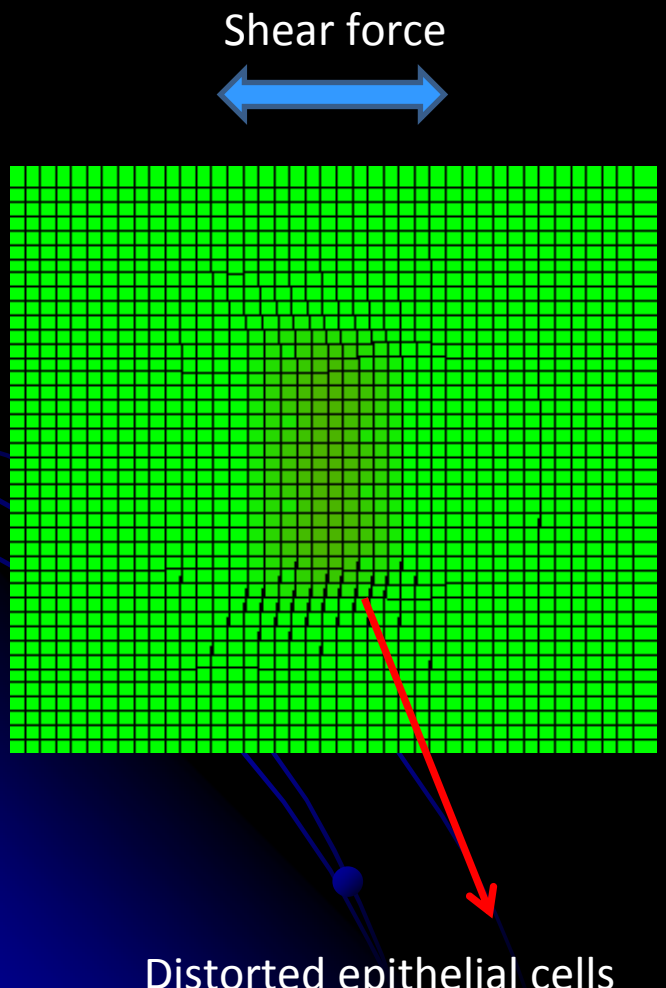
Experiment

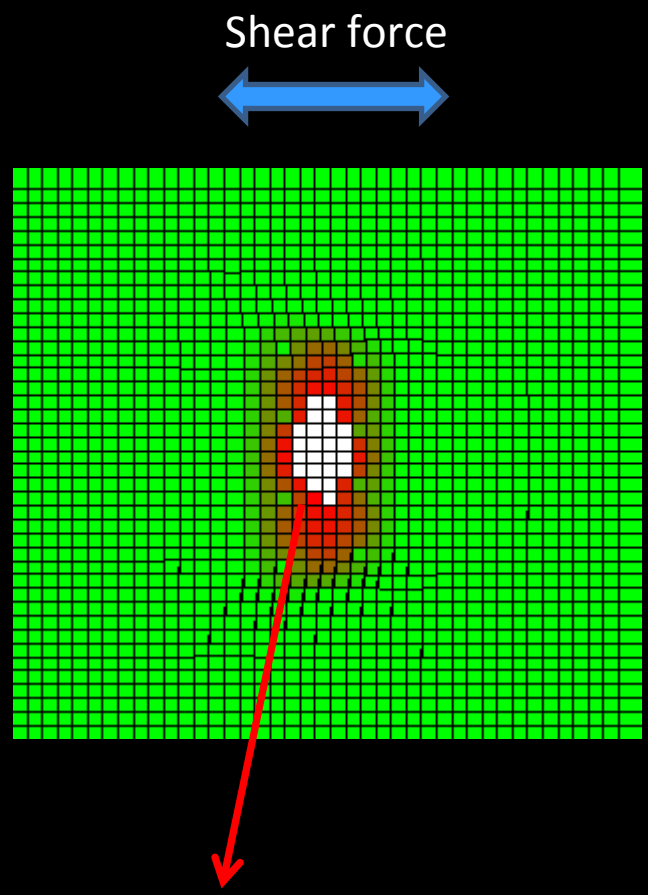
Yi-Ting, Tzen et al.



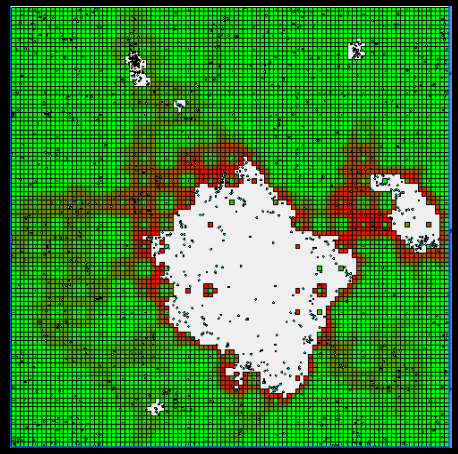
Shear force model of pressure ulcer formation (long term)

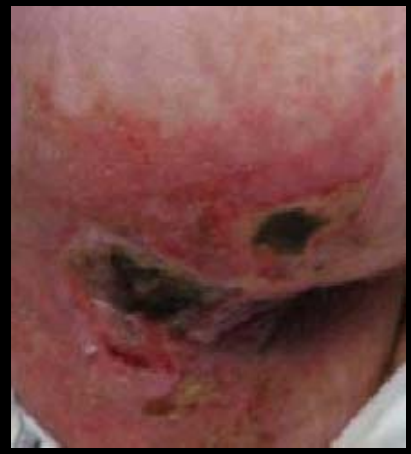
SPARK (Simple Platform for Agent-based Representation of Knowledge) software created at CIRM



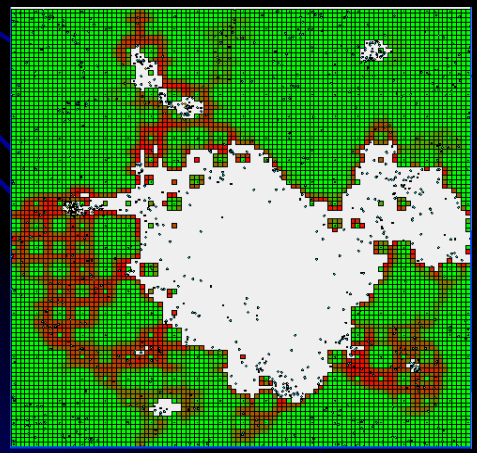


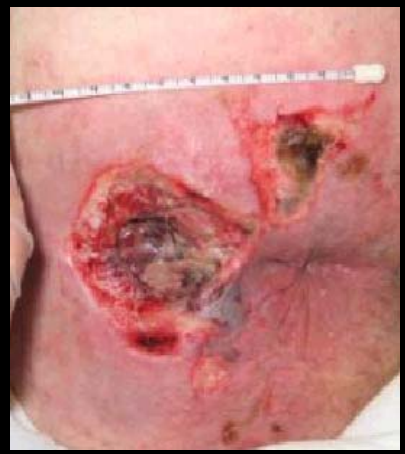
Agent-based Model of Pressure Ulcer Formation via Ischemia / Reperfusion Mechanism





SCI patient:
6 weeks after first sign of ulceration





Same patient, 5 days later

Solovyev, Ziraldo, Mi, Vodovotz, Unpublished

Inflammation

Wound Healing

Cancer

Hepatitis C and Hepatocellular Carcinoma

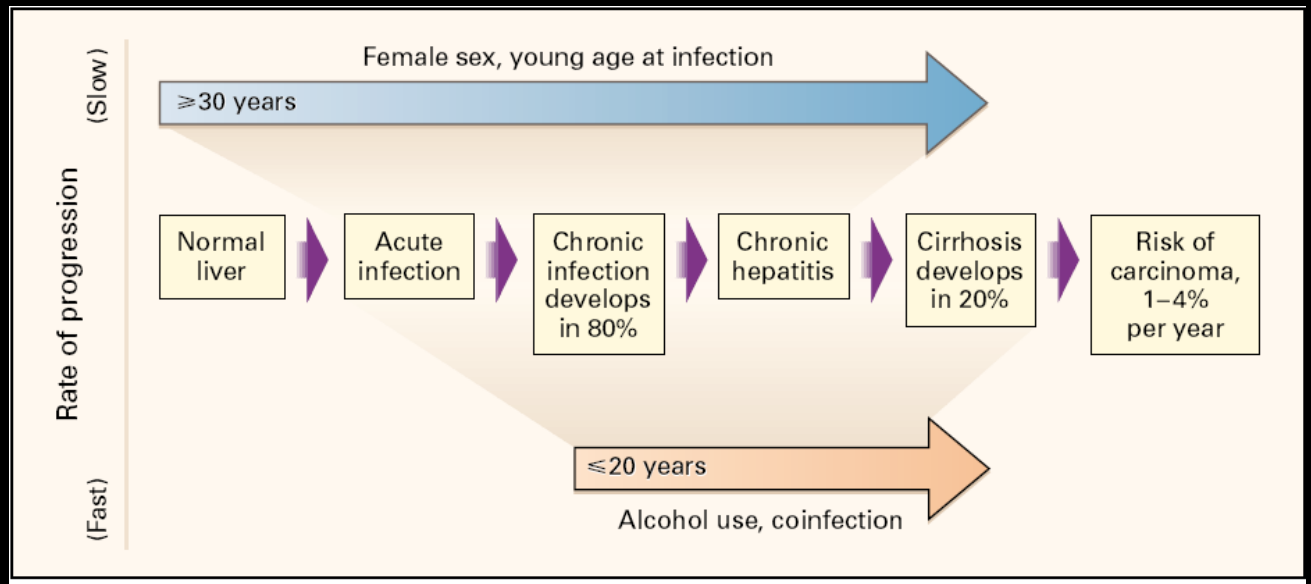
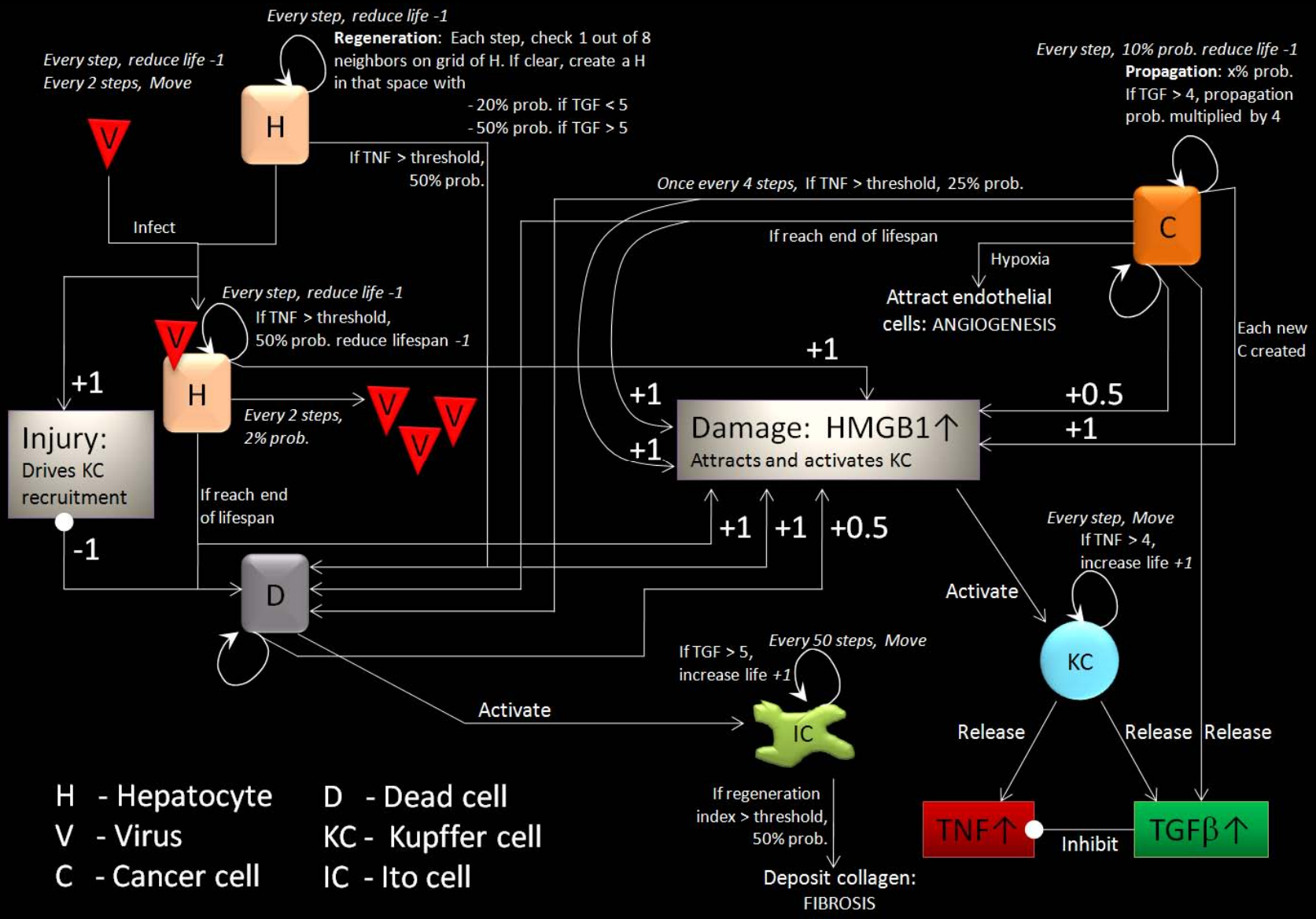


Figure 2. The Natural History of HCV Infection and Its Variability from Person to Person.

- 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

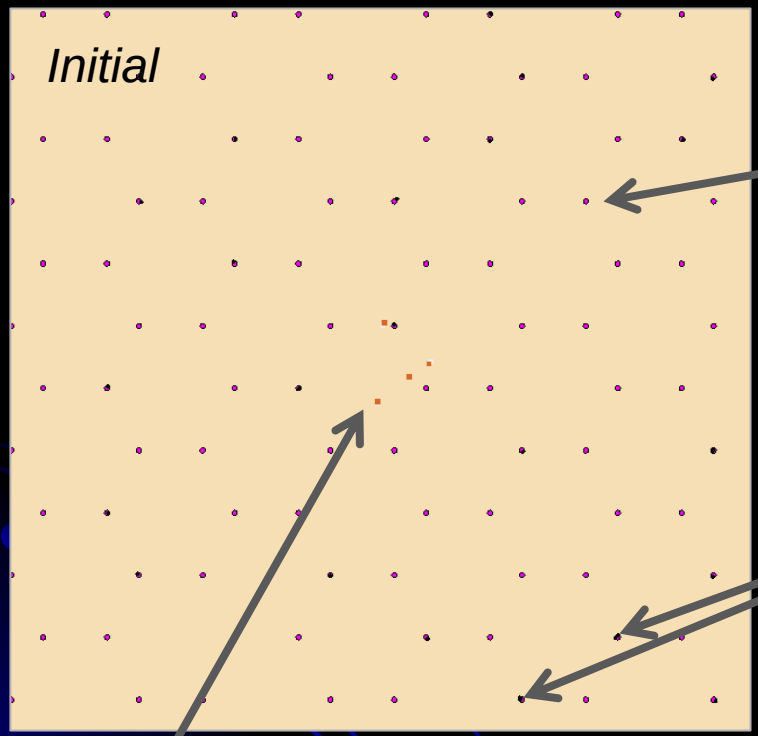


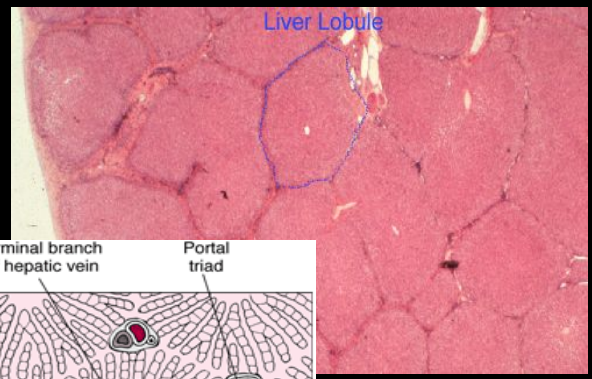
Dutta-Moscato, Soloveyv, Mi, Vodovotz, Unpublished

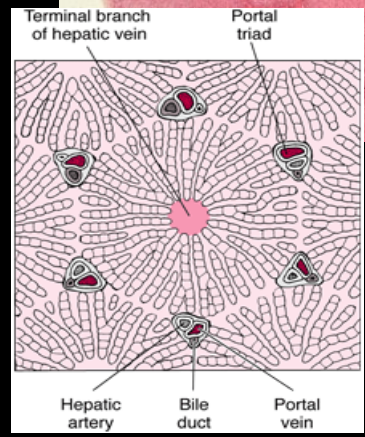
Provisional patent application: “In Silico Strategies for Cancer Diagnosis and Therapy” (Serial No. 61/186,126)

Structure of the model

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







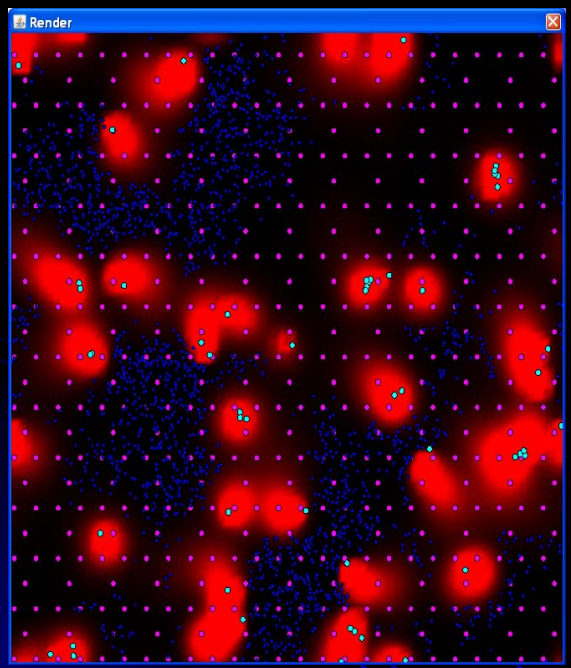
Also serves as entry point for HCV, as a blood borne virus

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

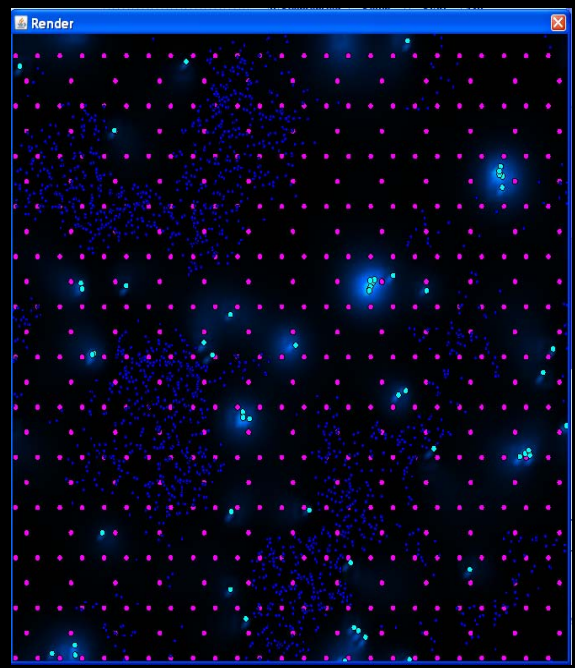
Dutta-Moscato, Soloveyv, Mi, Vodovotz, Unpublished

Structure of the model

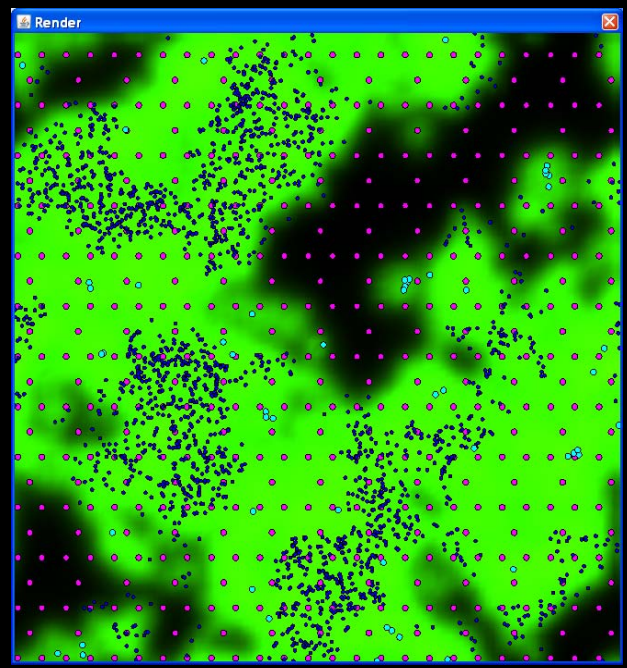
Underlying data layers: Allow “Monitor” multiple cytokine levels simultaneously



TNF



TGF-β1

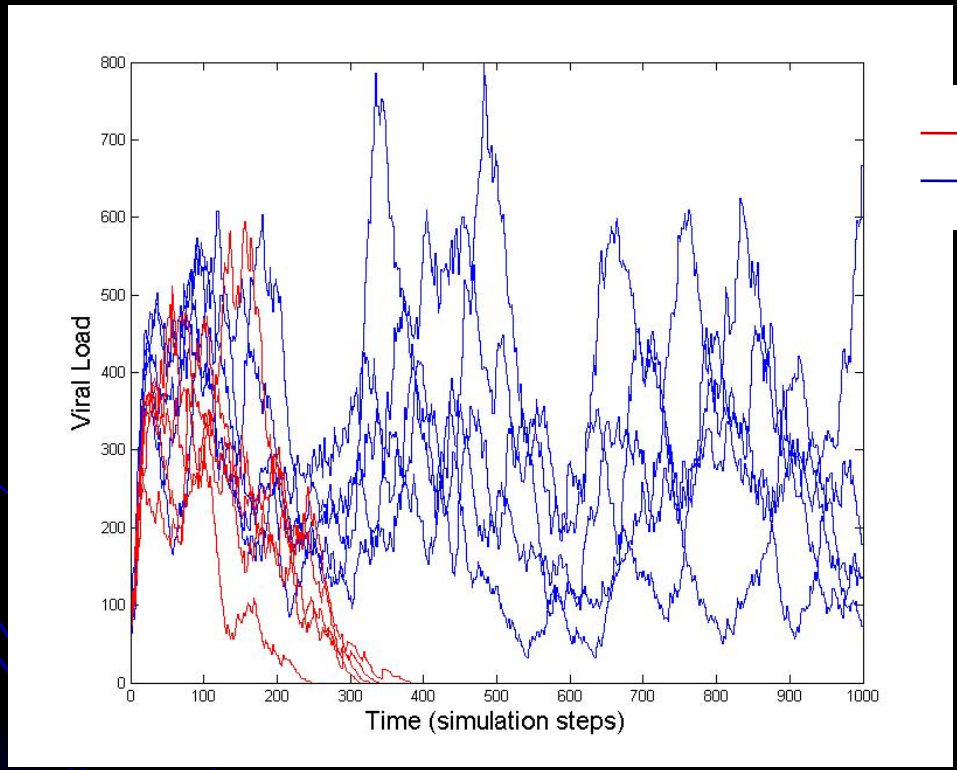


HMGB1

Dutta-Moscato, Soloveyv, Mi, Vodovotz, Unpublished

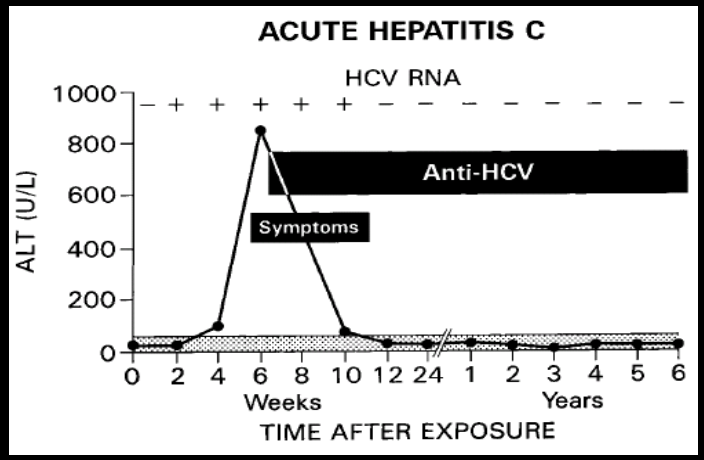
Model: Acute vs Chronic

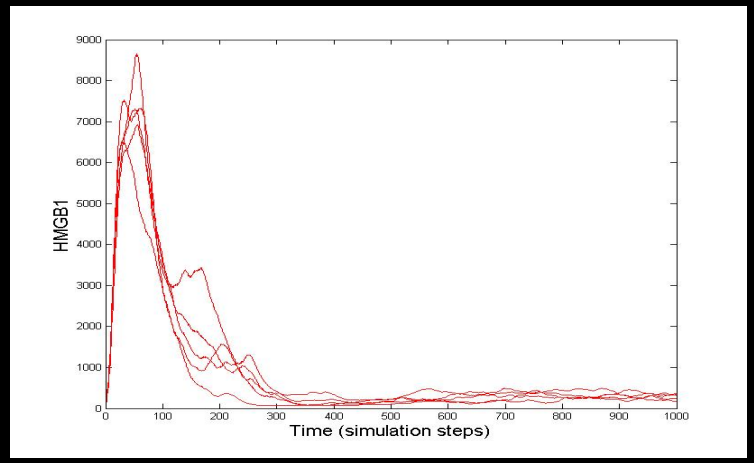
Starting with identical initial conditions, random selection from the same distribution of viral inoculation, the model stochastically results in cases where HCV resolves following acute infection, or persists as a chronic infection

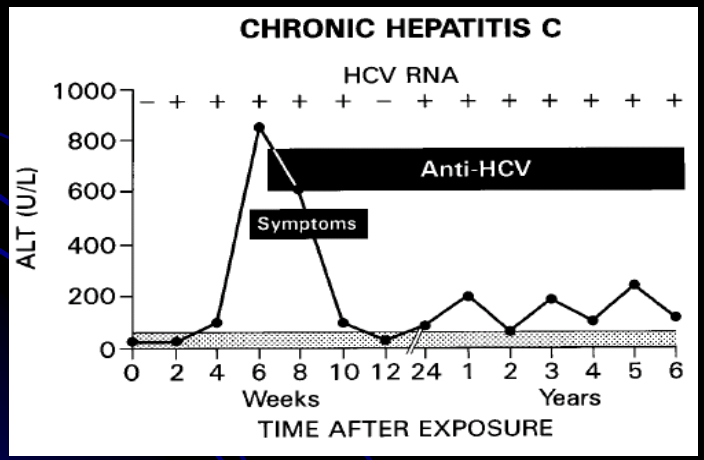


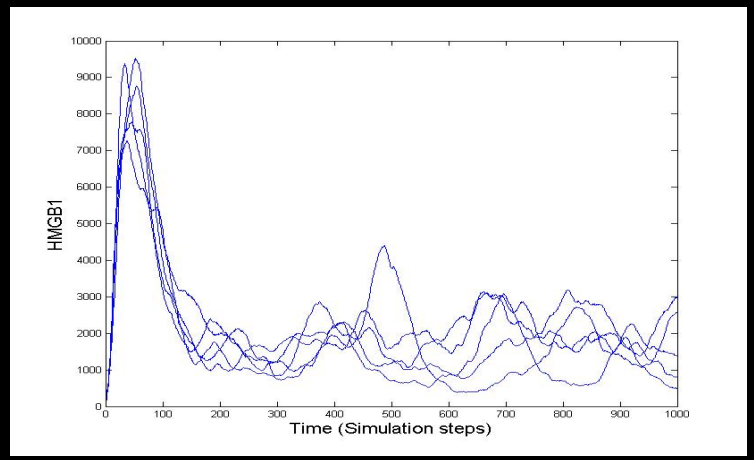
Dutta-Moscato, Soloveyv, Mi, Vodovotz, Unpublished

Measures of Damage: Clinical vs. Model









Clinical data

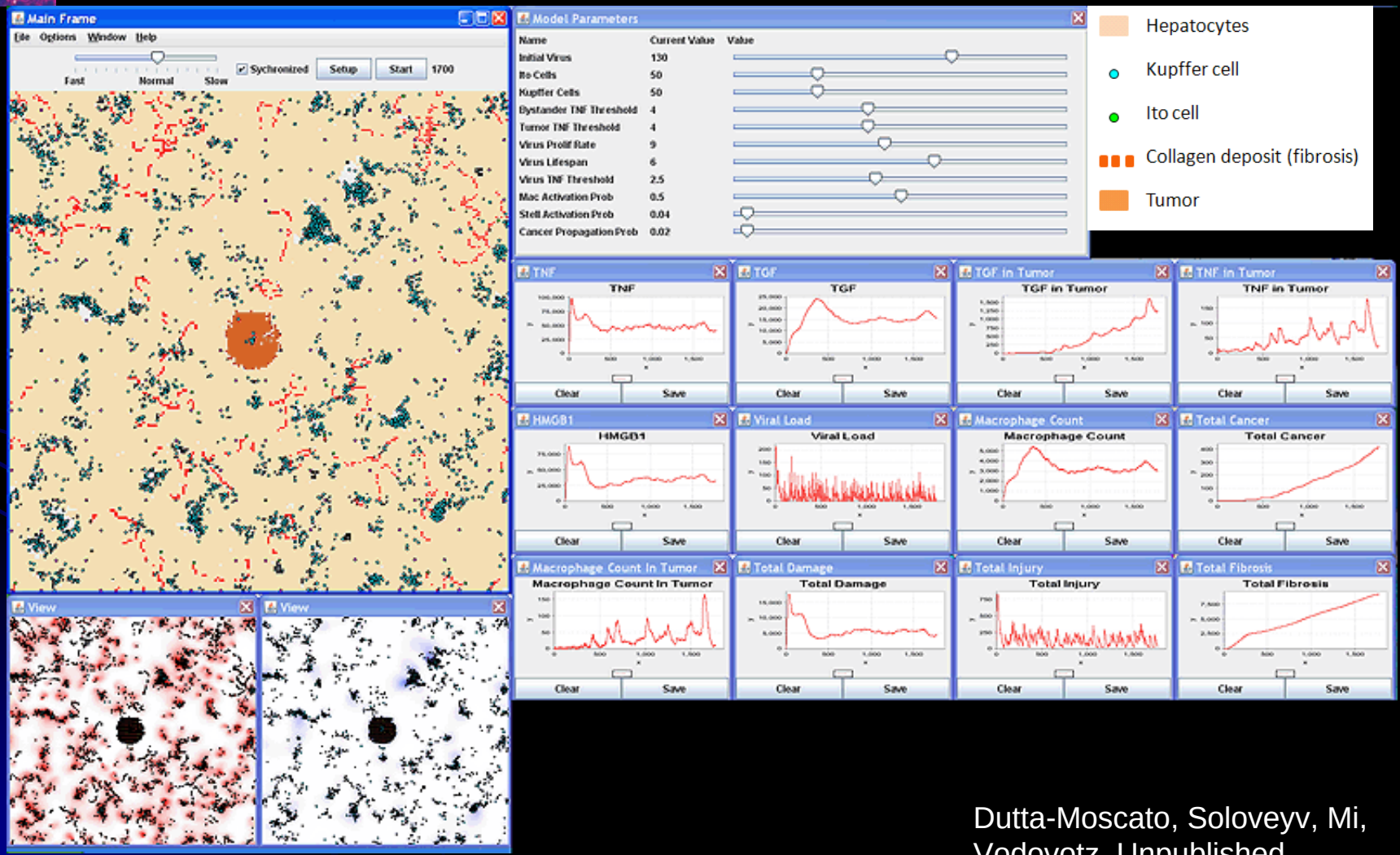
Serological course of Hepatitis C

Hoofnagle JH (1997) Hepatology 26(Suppl 1):15S-20S

Model simulation > 1 year

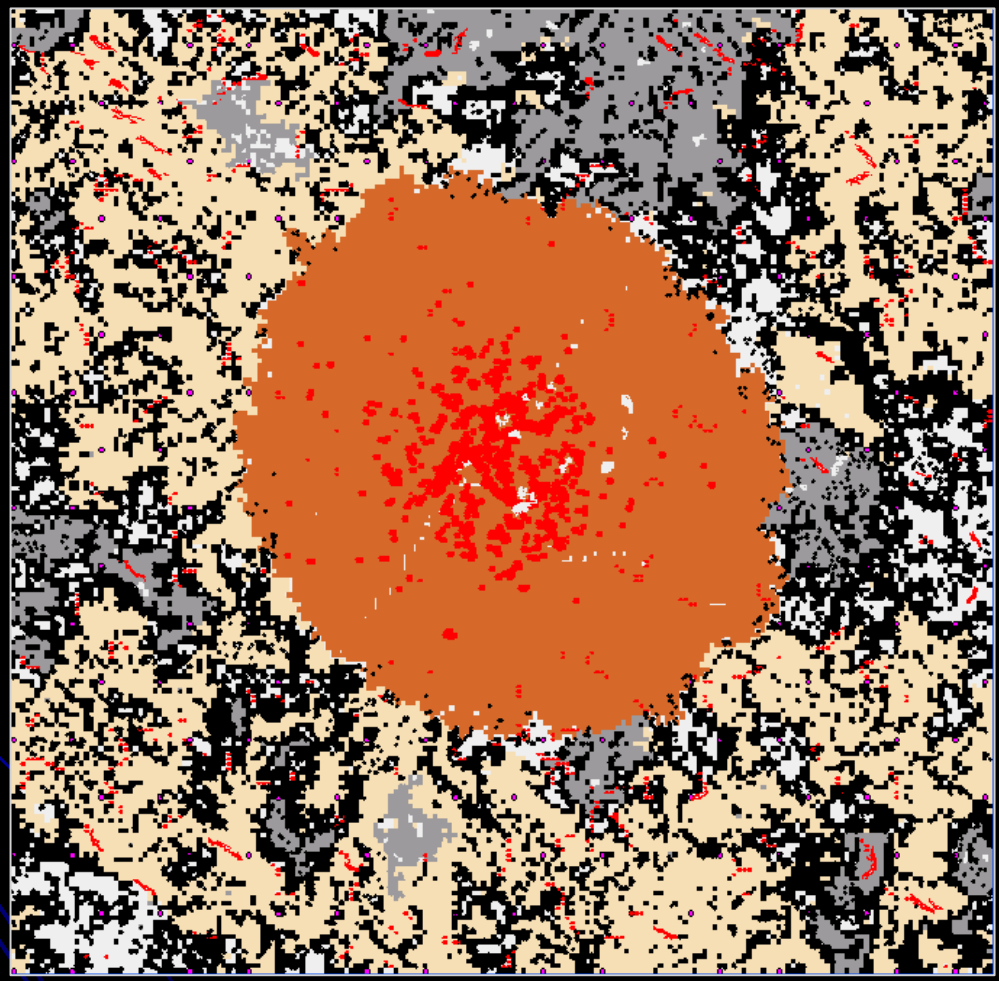
Dutta-Moscato, Soloveyv, Mi, Vodovotz, Unpublished

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

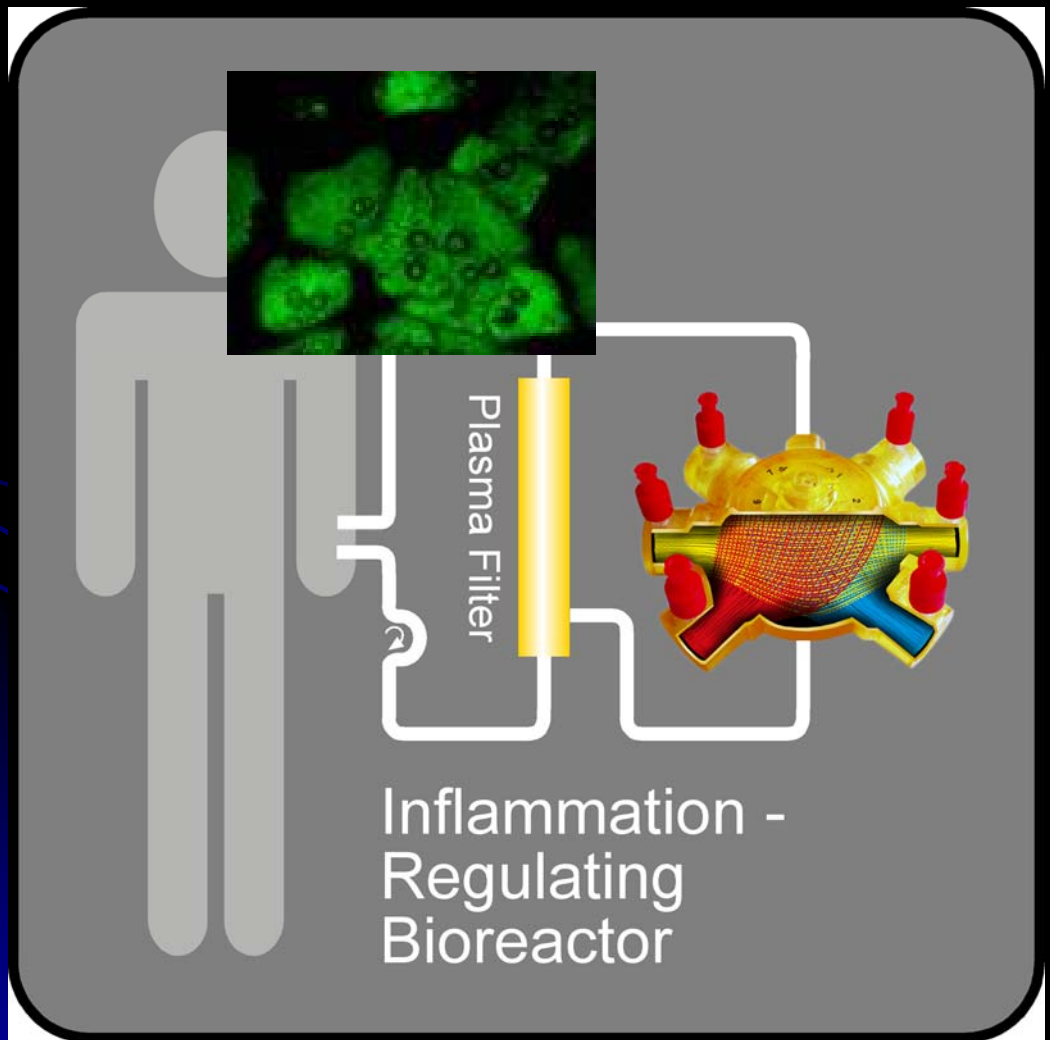
Patient-specific, inflammation-regulating bioreactor

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

DoD X81XWH-07-1-0415

Rational Inflammation Reprogramming

CYTOKINE PROMOTER | **ENDOGENOUS INHIBITOR**



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

- National Institutes of Health
- National Institute on Disability Rehabilitation Research
- Commonwealth of Pennsylvania
- Department of Defense / Pittsburgh Tissue Engineering Initiative
- Pittsburgh Lifesciences Greenhouse
- IBM

Our work is an interdisciplinary team project

- Critical Care Medicine (Pitt)
  - **Gilles Clermont**
  - **Mitchell Fink**
  - **John Kellum**
  - **Russ Delude**
  - **Juan Carlos Puyana**
- Mathematics (Pitt)
  - **Carson Chow**
  - **Bard Ermentrout**
  - **Jonathan Rubin**
  - **Beatrice Riviere**
  - **Ivan Yotov**
  - **David Swigon**
  - Judy Day
- Mathematics (CMU)
  - **Shlomo Ta'asan**
  - Rima Gandlin
- Statistics (Pitt)
  - **Greg Constantine**
- Immunetrics, Inc.
  - **John Bartels**
  - **Steve Chang**
  - **Arie Baratt**
  - Joydeep Sarkar
- IBM
  - **Fred Busche**
- Northwestern University
  - **Gary An**
- University of Cologne
  - **Eddy Neugebauer**
  - **Rolf Lefering**
- Ludwig Boltzmann Institute
  - **Heinz Redl**
- SUNY-Upstate
  - **Gary Nieman**
  - **David Carney**
- Urology (Pitt)
  - **Michael Chancellor**
  - **Pradeep Tyagi**
- Surgery (Pitt)
  - **Tim Billiar**
  - **Ruben Zamora**
  - **Rosie Hoffman**
  - **David Steed**
  - **Juan Ochoa**
  - Claudio Lagoa
  - Andres Torres
  - Rajaie Namas
  - Derek Barclay
  - Mia Jefferson
- McGowan Institute (Pitt)
  - **Alan Russell**
  - **John Murphy**
  - **William Federspiel**
  - **William Wagner**
- SHRS (Pitt)
  - **Cliff Brubaker**
  - **Kittie Verdolini**
  - **Qi Mi**
  - **Scott Lephart**
  - **David Brienza**
  - **Kelly Fitzgerald**
  - Nicole Li
- Medicine (Pitt)
  - **David Whitcomb**
  - **Marc Roberts**
- Children's Hospital of Pittsburgh
  - **David Hackam**
  - **Pat Hebda**
  - **Raphael Hirsch**
- Children's Hospital of Los Angeles
  - **Jeffrey Upperman**

All the students of the Systems Approach to Inflammation Course

International Conference on Complexity in Acute Illness

Atlanta, GA, September 10-11, 2010

http://www.scai-med.org