biogears™

BioGears: New Models and Capabilities

The Advantages of Continuous Model Development

17 MARCH 2020

ARA

Outline

- New model motivation
- Inflammation
  - Infection / Sepsis
  - Burn
  - Antibiotic Pharmacodynamics
- Cerebral Model expansion
- Whole Blood
- Models in development

Motivation

- BioGears model development is driven by:
  - Demonstrated past performance to JPC-1
  - BioGears Follow-On contract
  - Collaboration with medical simulation community
    - Virtual Heroes Division (VHD) at ARA
    - United States Army Institute of Surgical Research (USAISR)
    - University of Washington—WWAMI Institute for Simulation in Healthcare (WISH)
    - Advanced Modular Manikin (AMM)
  - User Buy-In
    - Outreach on Github

BioGears Inflammatory Response Model

A dynamic system that mediates response to thermal injury and infection

Applications

SUSTAIN

ADVANCED MODULAR MANIKIN ™

Inflammatory Response

- WBC = White blood cell count
- T = Temperature
- RR = Respiration rate
- NO = Nitric oxide
- D = Tissue Damage

Pain Sub-model

- Epi = Epinephrine
- RR = Respiration rate

Hypovolemia Response

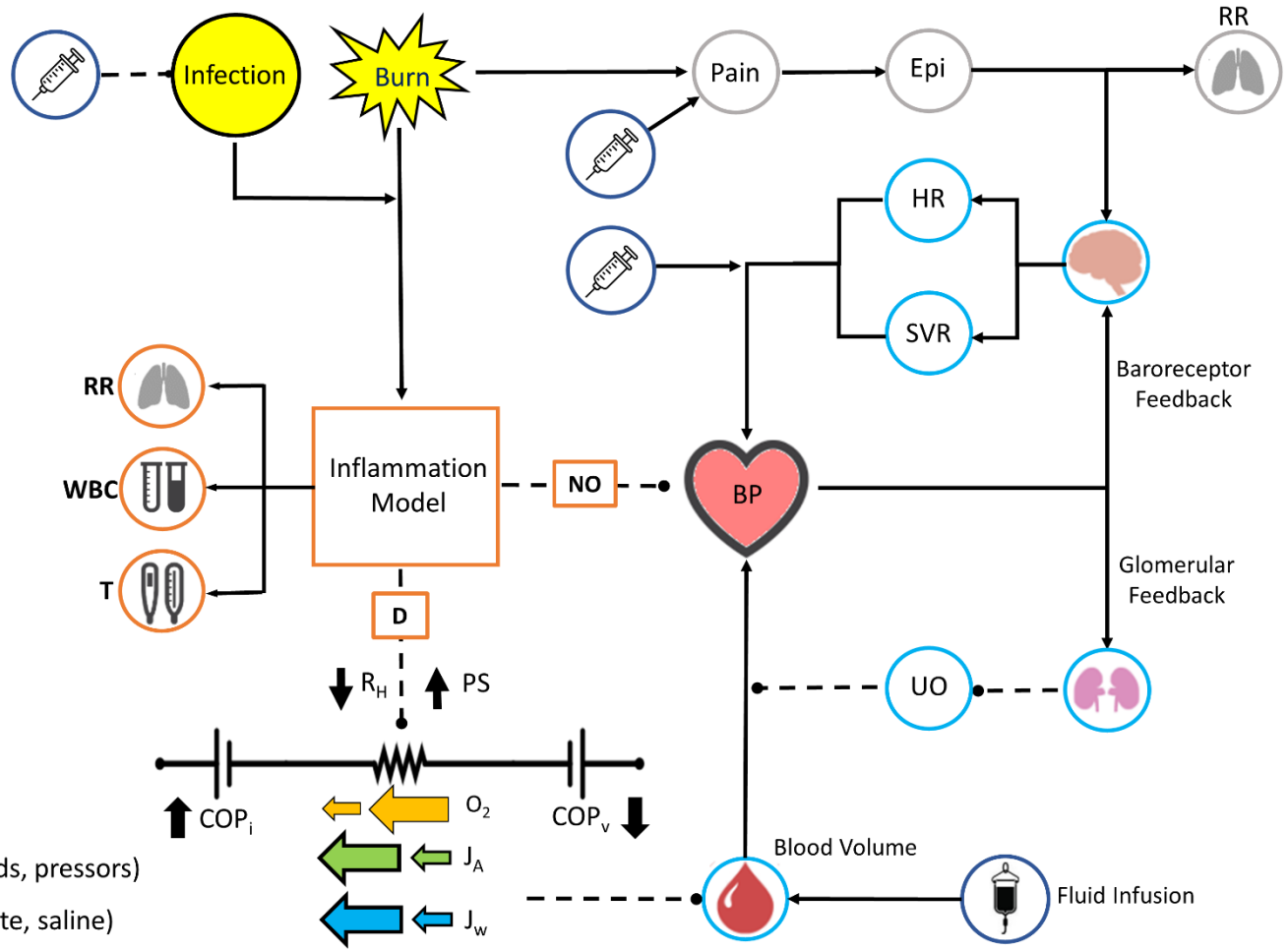
- HR = Heart rate
- SVR = Systemic vascular resistance
- UO = Urine output
- BP = Blood pressure

Microcirculation Sub-model

- $COP_{i/v}$ = Colloid osmotic pressure
- J_W = Fluid flux
- J_A = Albumin flux
- R_H = Hydraulic resistance
- PS = Solute permeability

Treatment Options

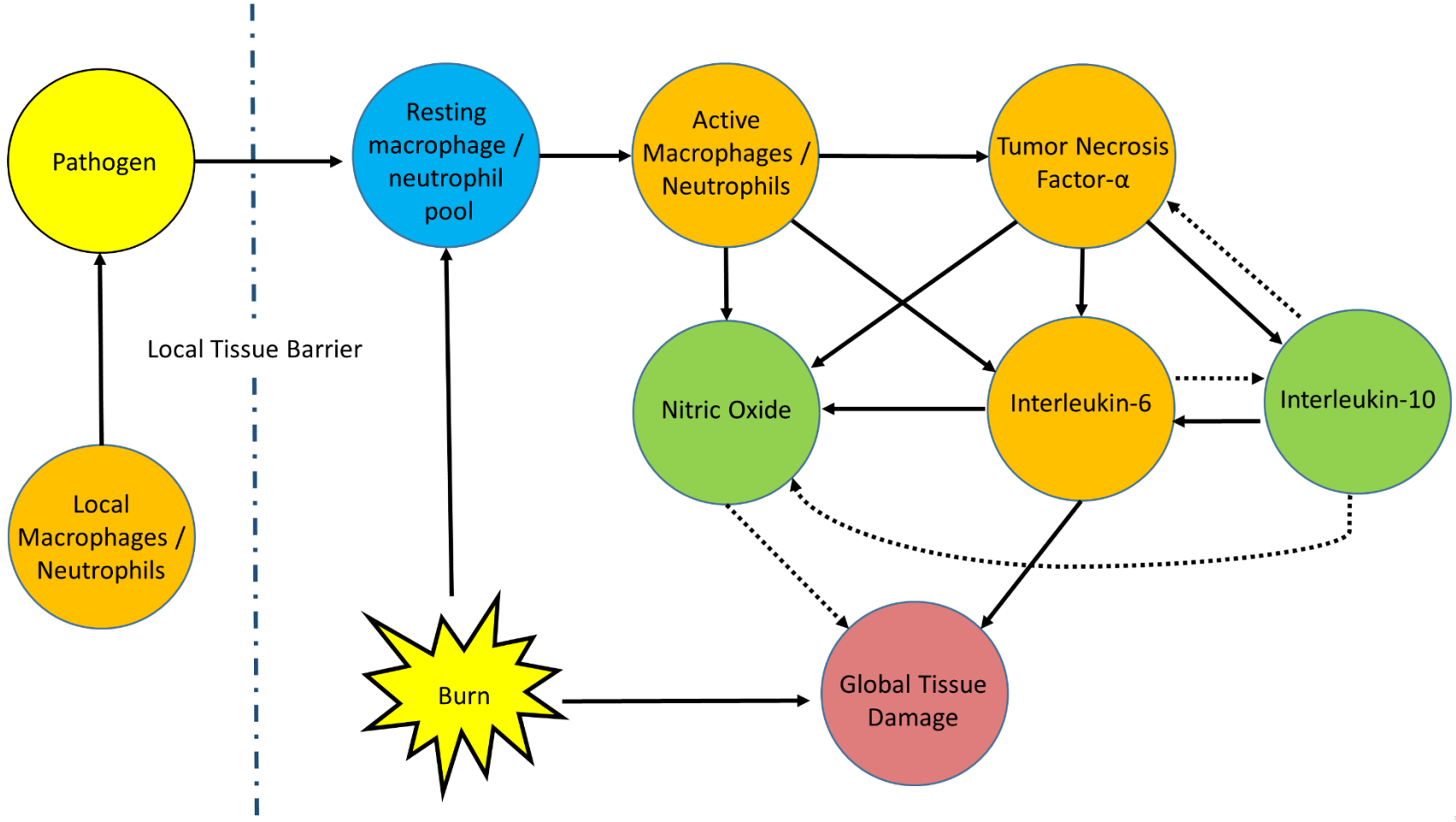
- Medication (antibiotics, pain meds, pressors)
- Fluid resuscitation (Ringer's lactate, saline)



Inflammation Model

Pathogen invasion and thermal trauma initiate the inflammatory response model

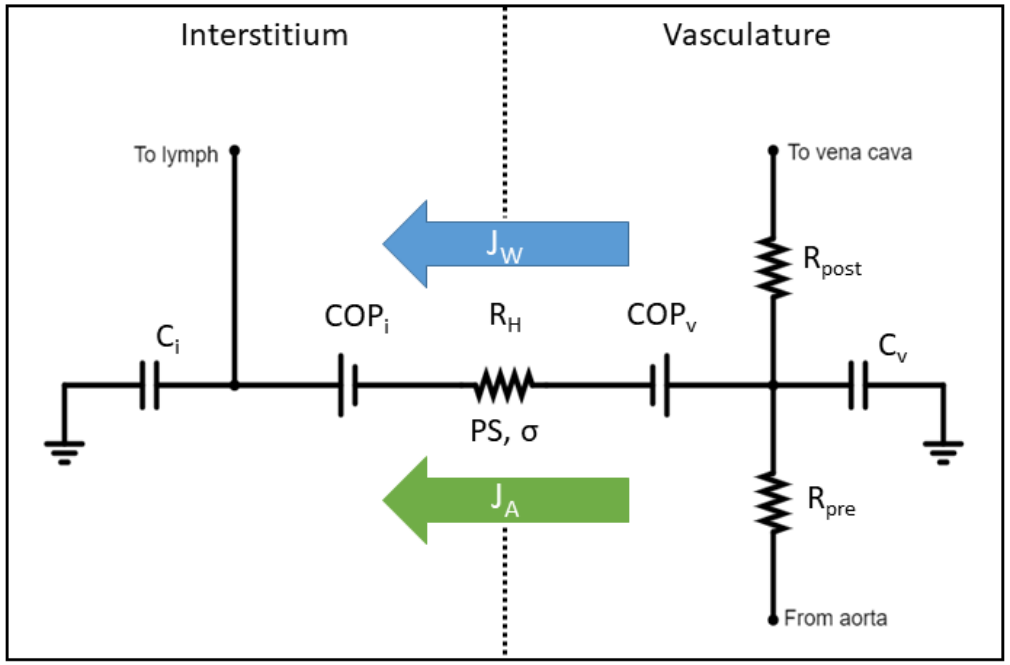
- Infection[1-4]
  - Pathogen originates in tissue where it is combated by local immune mediators
  - Inflammation weakens tissue barrier integrity
  - Pathogen can enter circulation, leading to systemic inflammatory response (SIRS)
- Burn[2,4]
  - Thermal trauma activates systemic inflammatory response
  - Inflicts initial hit on global tissue health



Microcirculation Model

Inflammatory-mediated tissue damage causes fluid shift and relative hypovolemia

- BioGears models the cardiovascular system as a fluid circuit with compartments representing distinct regions (e.g. muscle, skin, liver)
- Each vascular compartment communicates with an interstitial compartment, transferring fluid and substances
- Filtered fluids and substances are returned to the vasculature via a lymph pathway (amount returned = amount filtered at steady state)



1. Query volumetric flux (J_W) from BioGears circuit solver
2. For vascular (v) and interstial (i) compartments:
   1. Calculate total plasma protein concentration (C_{pp}) from albumin concentration (C_A) assuming:[8]

$$C_{PP} = 1.6C_A$$

   2. Calculate colloid osmotic pressure (COP) [8]

$$COP = 2.1 \cdot C_{PP} + 0.18 \cdot C_{PP}^2 + 0.009 \cdot C_{PP}^3$$

3. Calculate albumin flux (J_A)[9]

$$J_A = J_W \cdot (1-\sigma) \left(\frac{C_{A,v} - C_{A,i} \cdot \exp\left(-J_W \cdot \frac{(1-\sigma)}{PS} \right)}{1 - \exp\left(-J_W \cdot \frac{(1-\sigma)}{PS} \right)} \right)$$

4. Update J_W (function of COP, hydrostatic pressure, and R_H)

σ = Membrane reflection coefficient $C_{i/v}$ = Interstitial / vascular compliance $R_{pre/post}$ = Pre / post-capillary resistance

* For more on lumped-parameter cardiopulmonary modeling, see refs [6, 7]

Antibiotic Pharmacodynamics Model

- Assume that antibiotics act by decreasing the net bacterial growth rate[10-11]

$$k_{net} = k_{max} - \frac{(k_{max} - k_{min}) \cdot (C_u/MIC)^{\delta}}{(C_u/MIC)^{\delta} - k_{min}/k_{max}}$$

  - k_{net} = Net bacteria growth rate
  - k_{max} = Bacteria growth rate in absence of antibiotic (set by model)
  - k_{min} = Minimum growth rate imposed by antibiotic (< 0 → bacteria death)
  - C_u = Free antibiotic concentration
  - MIC = Minimum inhibitory concentration (set in Infection Action)
  - δ = Shape parameter

- Noteworthy Features
  - C_u = MIC → k_{net} = 0
    - Slow bacteria growth when C_u < MIC
    - Bacteria death when C_u > MIC
  - Users set k_{min} rather than an EC_{50}
    - This seems to be a more intuitive input

Demo: Action Initiation

- Infection Demonstration
  - Progression of three levels of infection (“Mild”, “Moderate”, “Severe”)
  - Antibiotic administration in a severely infected case
  - Fluid and pressor administration in a septic case
  - Setup:
    - Initiation requires a severity, bacteria MIC, and location (for future implementations when localized interactions are better modeled)

```
<Action xsi:type="InfectionData" Severity="Severe">
    <MinimumInhibitoryConcentration value="8.0" unit="mg/L"/>
    <Location>Skin</Location>
</Action>
```

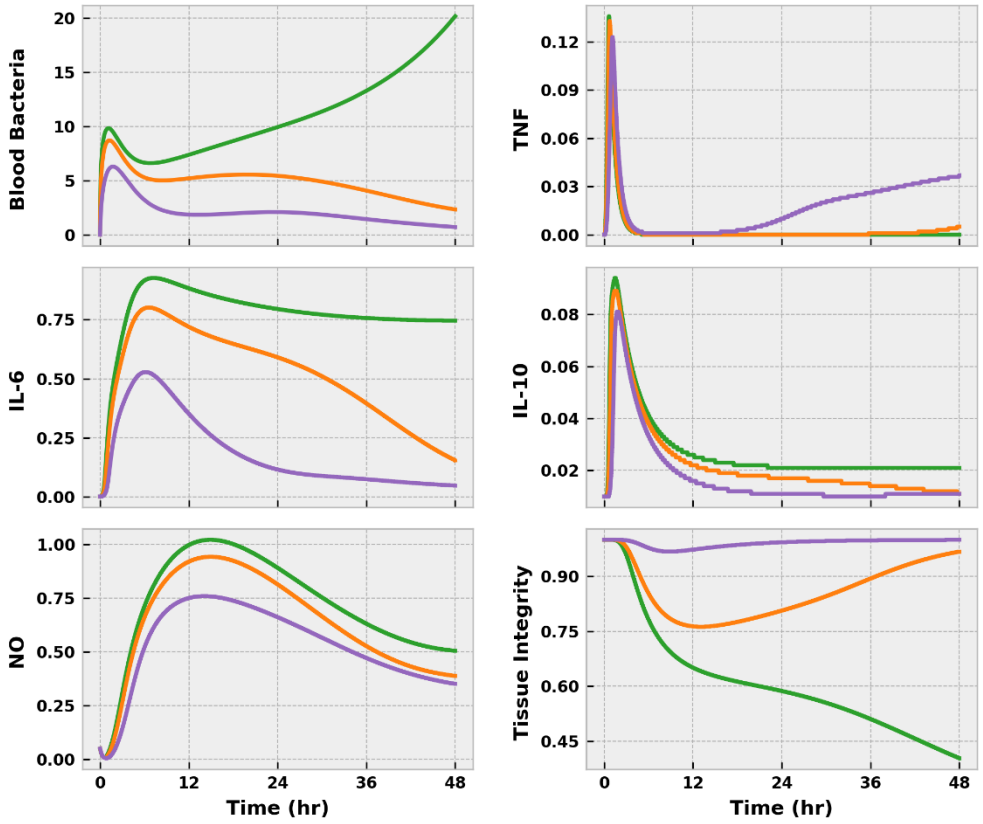
    - Note: Infection scenarios are *very* long.
      - BioGears library includes infection simulations saved at various points throughout simulation
      - These saved states can be loaded into new scenarios
      - Useful for cases in which latter stages of infection are main interest of simulation (such as two treatment simulations to be shown)

- Burn Wound Demonstration
  - Progression of three burn wounds: 10%, 25%, and 40% TBSA
  - Fluid resuscitation and pain management in the 25% TBSA case
  - Setup:

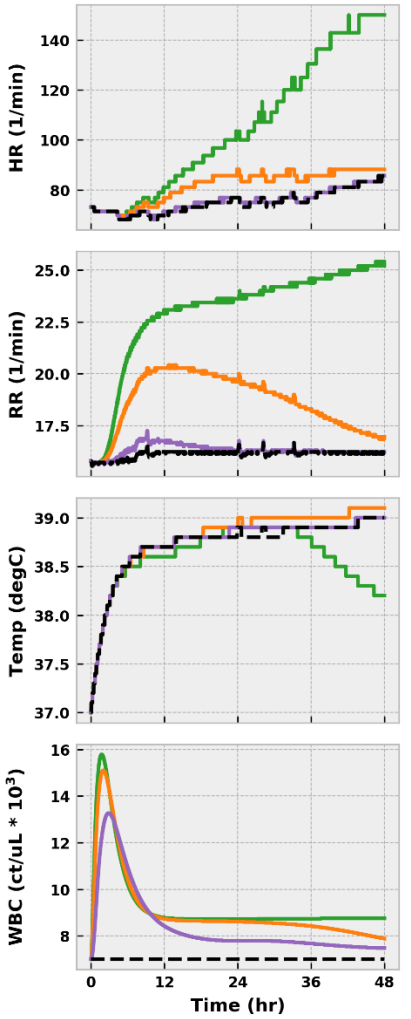
```
<Action xsi:type="BurnWoundData">
    <TotalBodySurfaceArea value="0.25"/>
</Action>
```

Output: Infections of varying severities

Prolonged and excessive inflammation leads to symptoms of systemic inflammatory response syndrome (SIRS)*



- Purple = Mild Case
- Orange = Moderate Case
- Green = Severe Case
- Black = Baseline

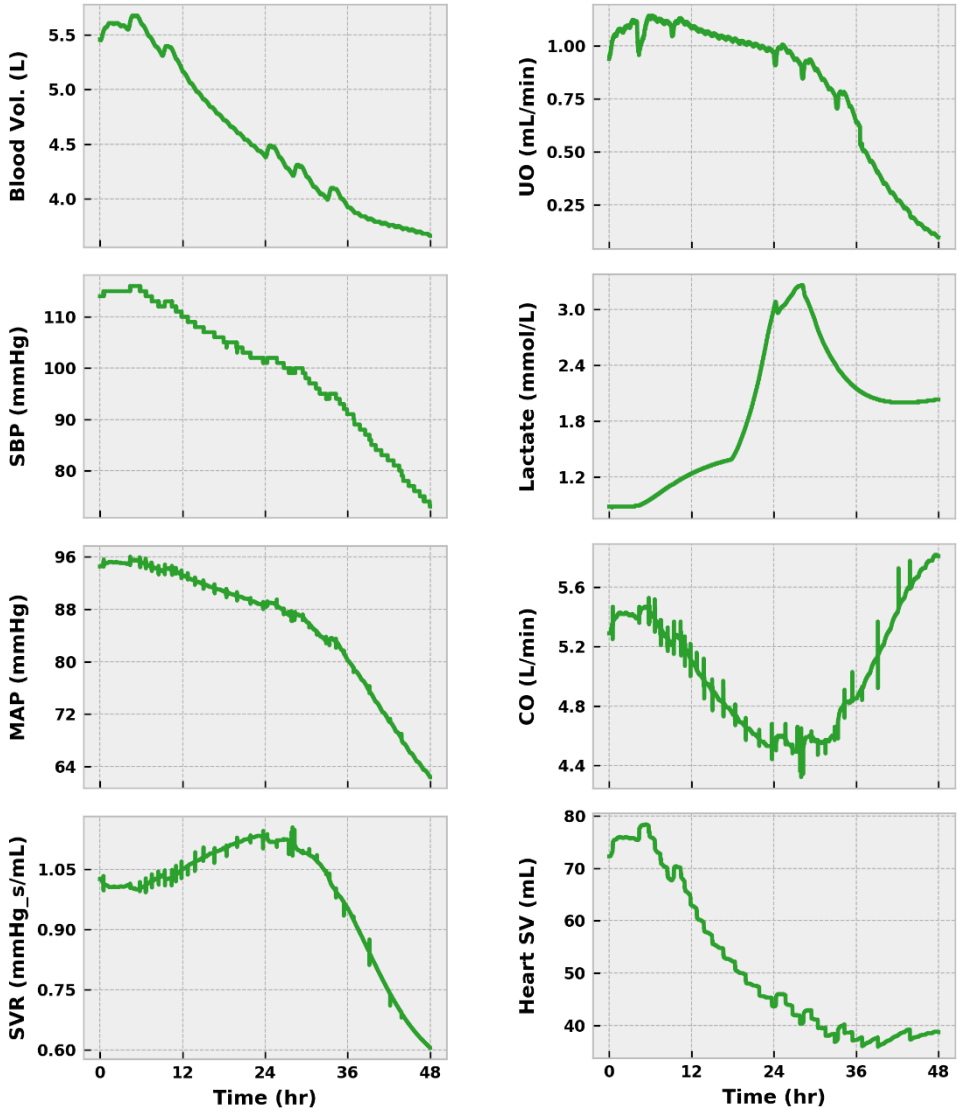


* See McDaniel et al. 2019a [12] for more detail

Output: Septic Infection

Clinically-relevant markers for sepsis and septic shock diagnosis according to Sepsis-3[11] definitions*

- Sepsis
  - Systolic blood pressure < 100 mmHg
  - Respiration rate > 22 (previous slide)
  - Renal organ failure assessment score
    - UO < 500 mL/day (0.34 mL/min) = 3
    - UO < 200 mL/day (0.14 mL/min) = 4
- Septic Shock
  - MAP < 65 mmHg
  - Serum lactate > 2.0 mmol/L

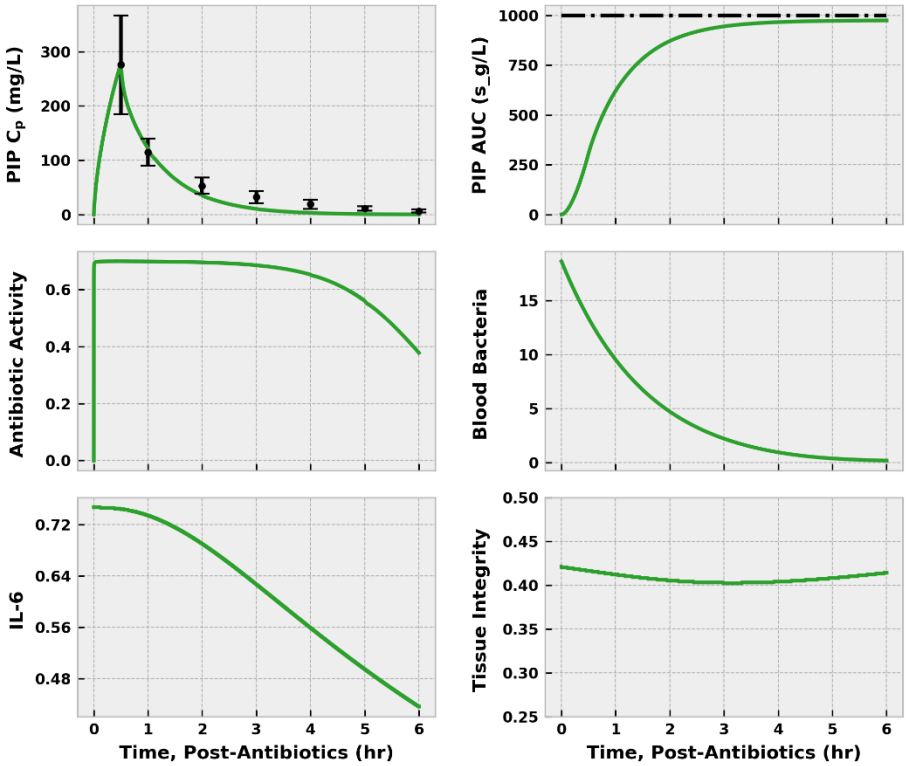


- SBP = Systolic blood pressure
- MAP = Mean arterial pressure
- SVR = Systemic vascular resistance
- UO = Urine output
- CO = Cardiac output
- SV = Stroke volume

* See McDaniel et al. 2019a [12] for more detail

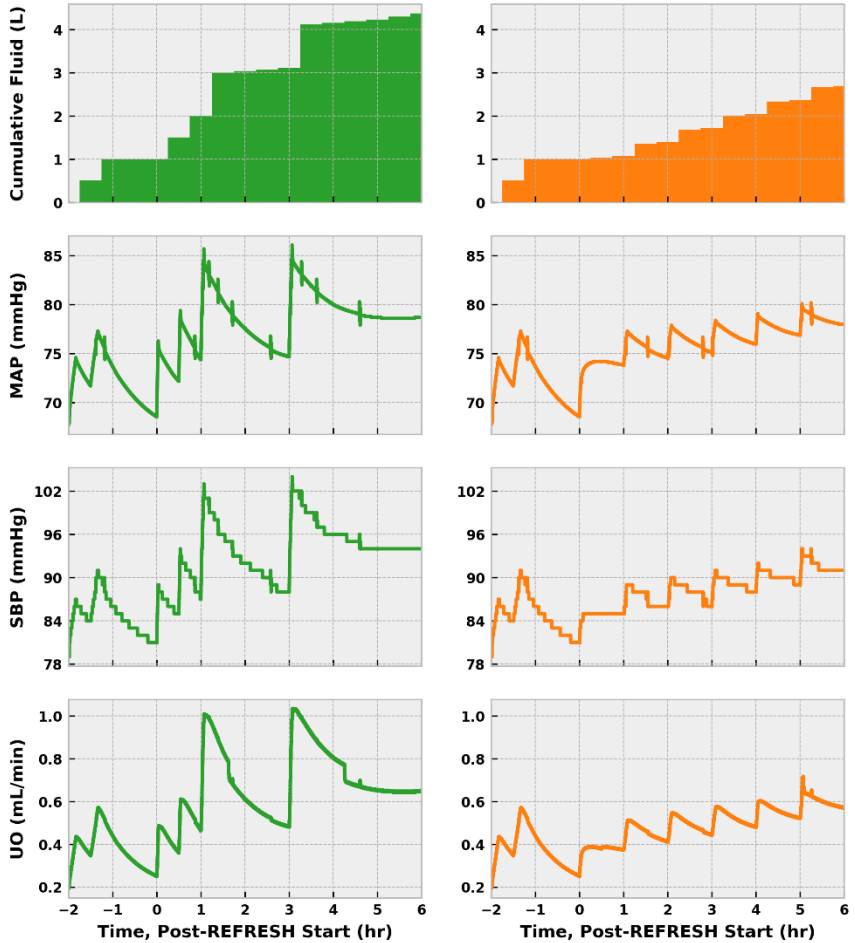
Output: Sepsis Treatment

Model demonstrates distinct outcomes depending on treatment strategy*



Administration of piperacillin/tazobactam. Plasma concentration (C_P) and area under curve (AUC) compared to values in literature[14]. The antibiotic reduces the bacteria population, leading to reduction in inflammatory IL-6 population and improvement in tissue integrity.

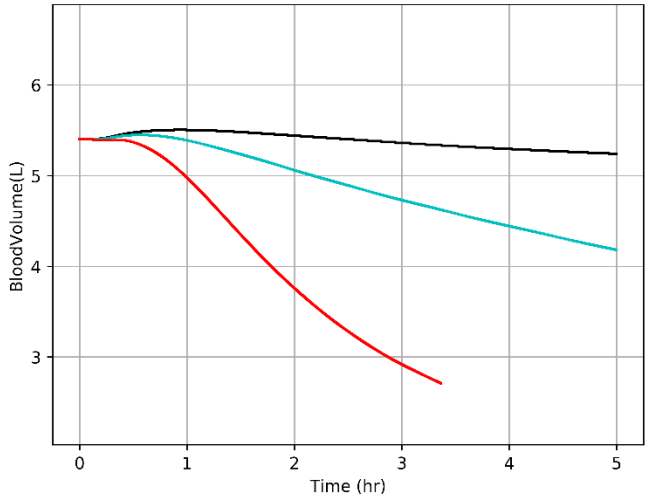
* See McDaniel et al. 2019a [12] for more detail

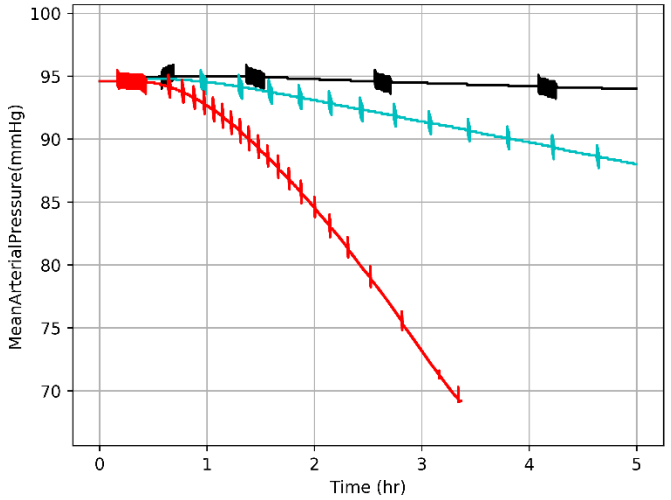


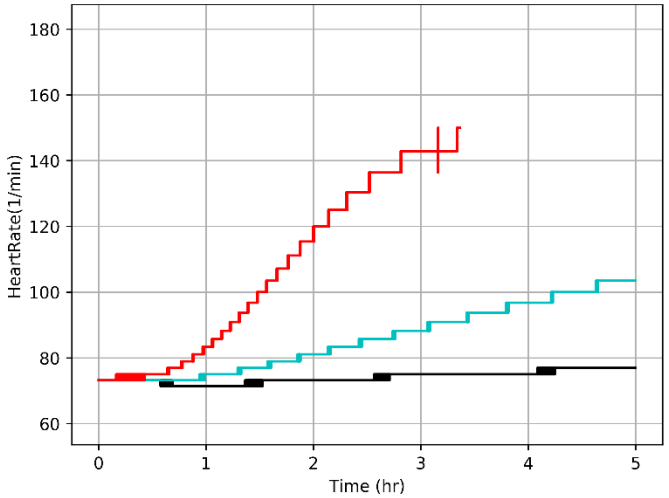
Comparing two treatment strategies described in MacDonald[15-16]. Left: Early goal directed therapy. Right: Early pressors, reduced fluids

Output: Burns of Varying Severity

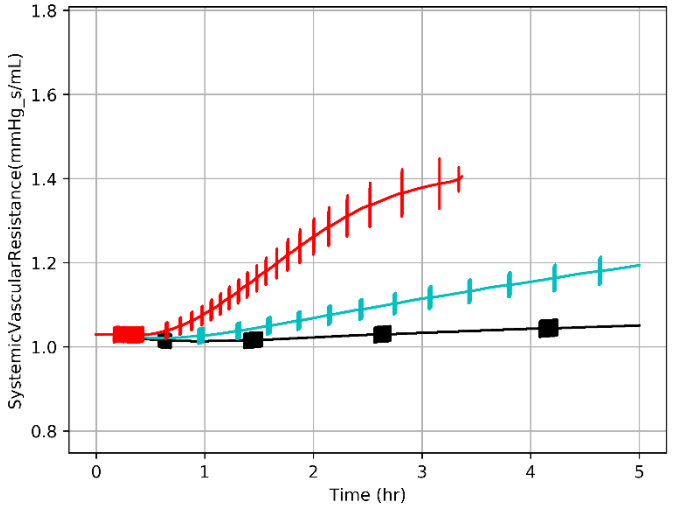
Large burns cause massive fluid shift that can lead to death*

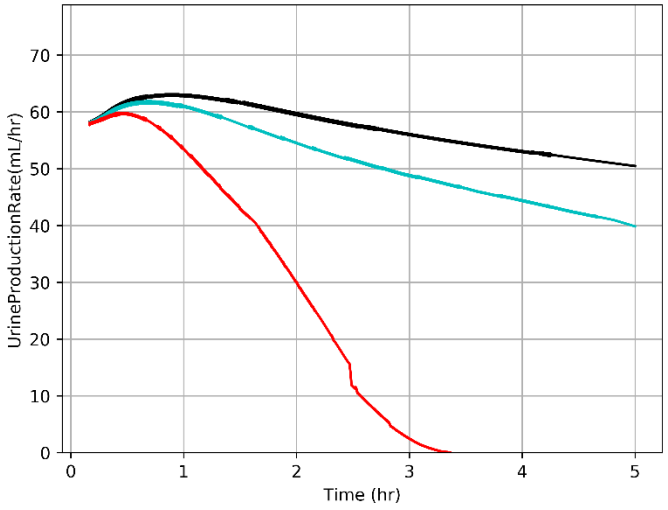






- Black = 10% TBSA (fraction of total body surface area)
- Blue = 25% TBSA
- Red = 40% TBSA

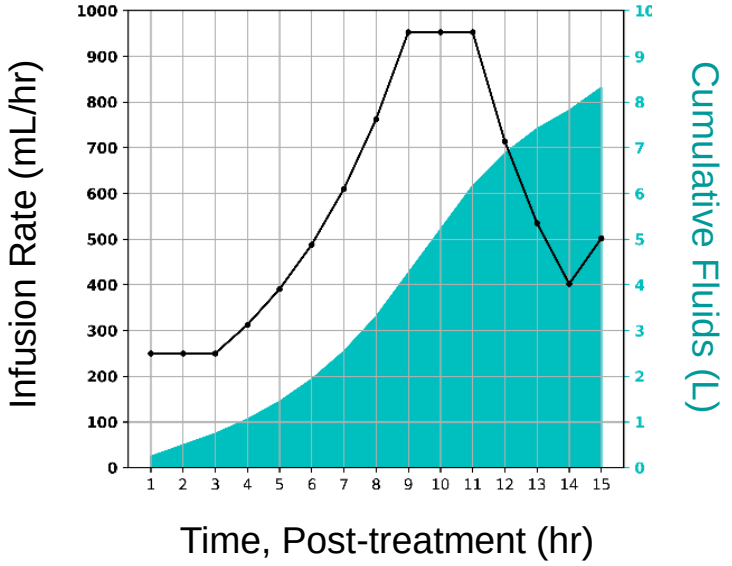


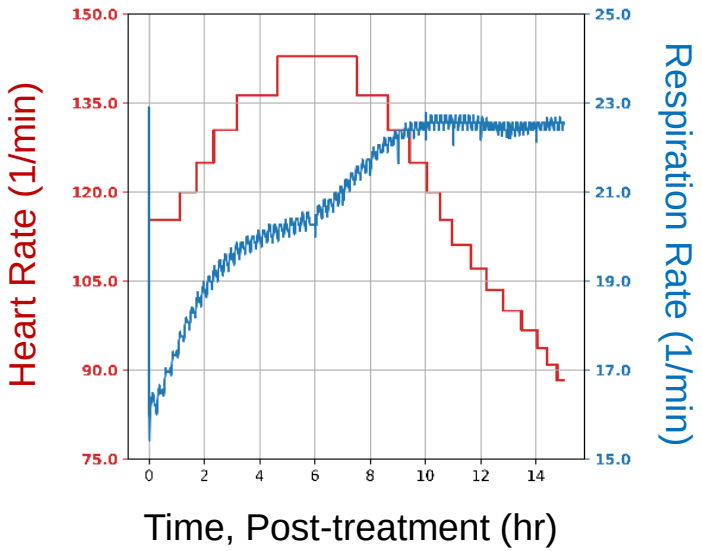


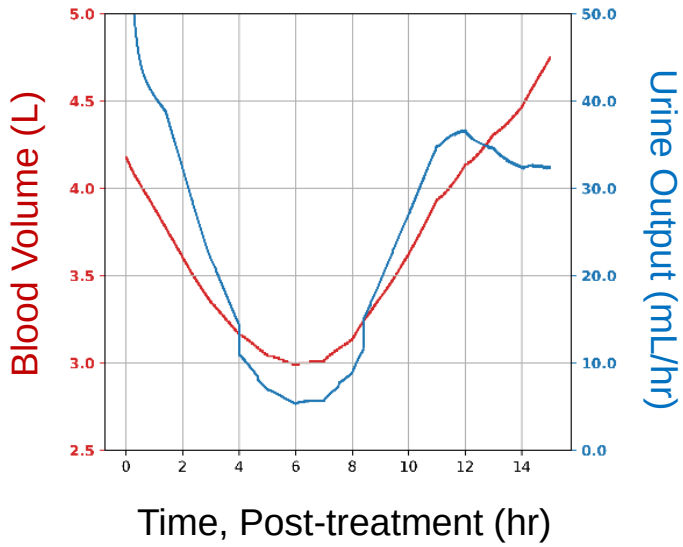
* See McDaniel et al. 2019b[17] for more detail

Output: Burn Treatment

Burn size and volume resuscitation status (as indicated by UO) drive treatment*







A 25% TBSA burn treated with ketamine infusion (for pain) and administration of ringer's lactate solution (250 mL/hr initial infusion rate). Rate of fluids adjusted each hour according to resuscitation status. Treatment strategy derived from [18-20].

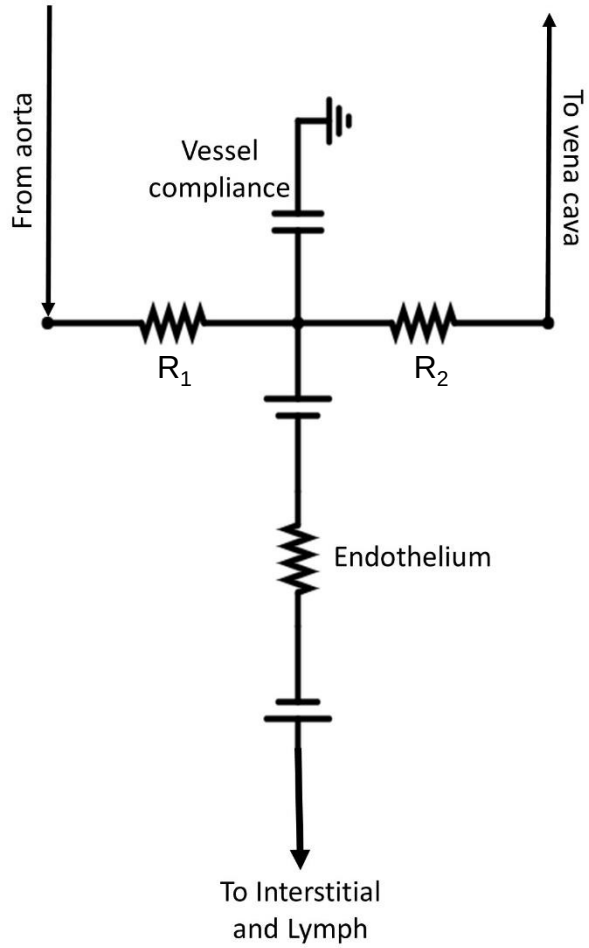
* See McDaniel et al. 2019b[17] for more detail

Inflammation: Future Work

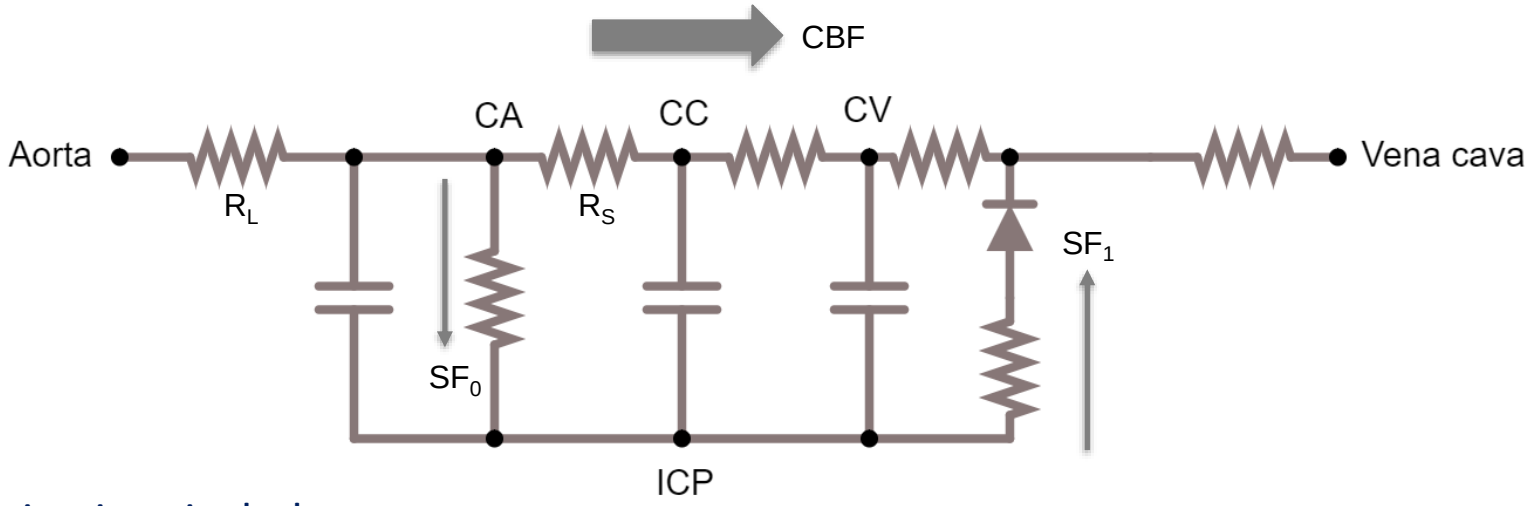
- Model variability
  - Patient inflammatory response parameters (e.g. up-regulation of IL-6 by TNF)
  - Bacteria characteristics (e.g. growth rate)
  - Initial infection levels (expand from “Mild”, “Moderate”, “Severe”)
- Model of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)
- Tune fluid loss during burn
- Coagulopathy
- Define inflammatory mediators as BioGears Substance types
  - Improved spatial resolution
  - Drug-pathogen interactions at compartment-level
- Link hemorrhage model to inflammation cascade

Cerebral Model Expansion

- Background
  - Cerebral circuit previously implemented a three-element *windkessel* model
    - Additional pathway for interstitial space
  - Traumatic Brain Injury action increased resistance on pre-capillary (R_1) and post-capillary (R_2) paths
  - No autoregulation
- Goals
  - Increase fidelity of circuit for more accurate blood and oxygen tracking
  - Introduce cerebral regulation to prioritize oxygen delivery to brain



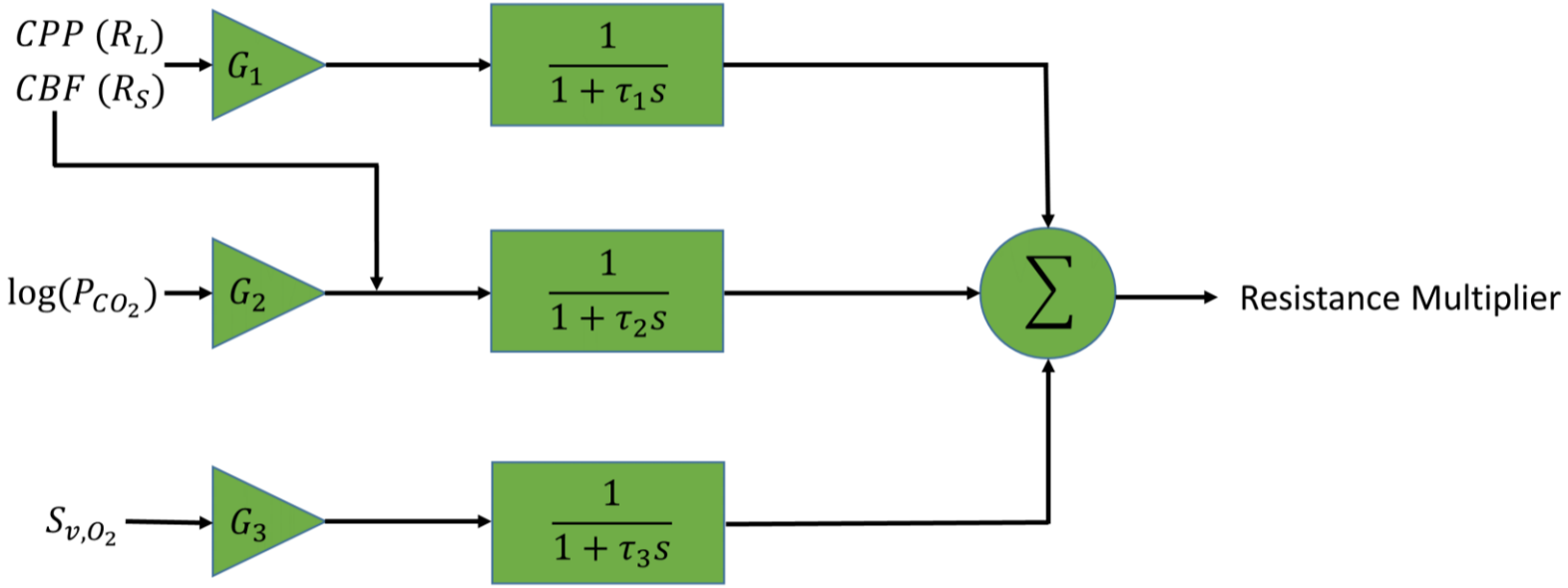
Updated Cerebral Circuit



- Discretize brain sub-circuit to include:
  - Cerebral arteries (CA)
  - Cerebral capillaries (CP)
  - Cerebral veins (CV)
- The volume of each region responds to pressure changes (compliance paths)
- Intracranial pressure (ICP) determined by fluid stored in brain
- Cerebral blood flow (CBF) calculated according to total pressure drop and resistance across sub-circuit
- Large (R_L) and small artery (R_S) resistances are subject to auto-regulatory control (next slide)
- Some fluid flows into interstitial space as spinal fluid (SF_0) and returns to vasculature (SF_1)
- Circuit design and baseline parameters adapted from [21]

Cerebral Autoregulation

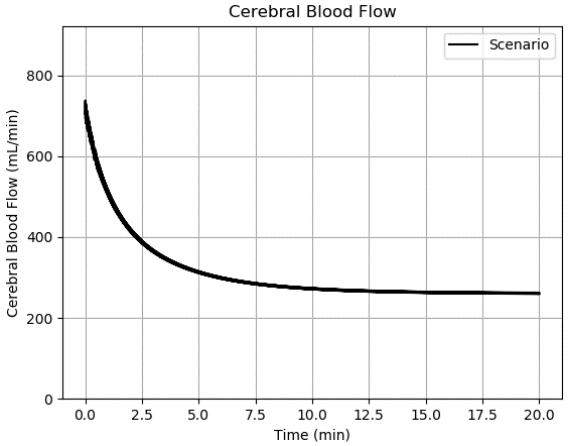
- Model assumptions[22-23]
  - R_L subject to first-order control via CPP
  - R_S subject to first-order control via CBF
  - R_L and R_S subject to first-order control via $\log(P_{CO2})$ → Reflects pH dependence
  - The effects of CO_2 are attenuated by low CBF
  - R_L and R_S subject to first-order control via venous cerebral O_2 saturation
- Model outputs
  - R_L resistance multiplier: Bounds = [0.8, 1.2]
  - R_S resistance multiplier: Bounds = [0.75, 1.25]

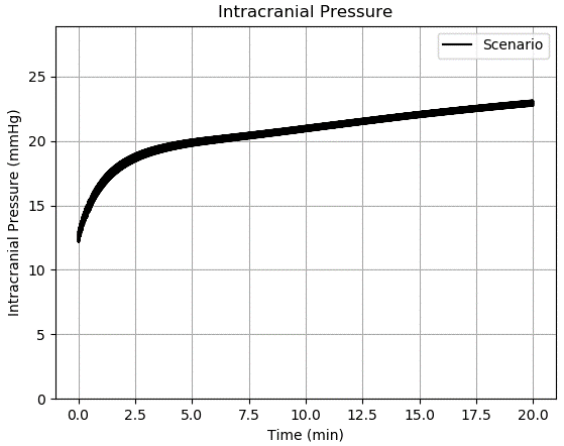


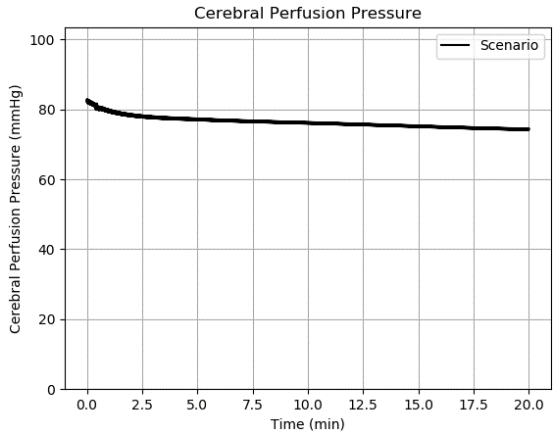
*Gains (G) and time constants (τ) obtained from [23]

Cerebral Model: Example Results

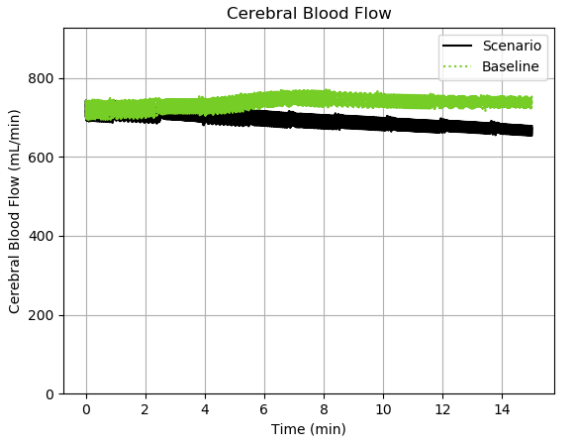
- Traumatic Brain Injury
  - Severity Input = 0.75
  - Results follow trends reported in [24]







- Effect of autoregulation
  - Hemorrhage (initial bleeding rate = 100 mL/min) for 15 minutes
  - Green = Cerebral autoregulation ON
  - Black = Cerebral autoregulation OFF

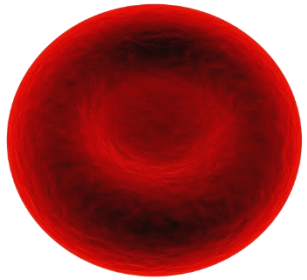


Cerebral Model: Future Work

- No short-term work planned
- Long-term
  - Improve blood-gas tracking in brain to increase fidelity of feedback model
  - Possible integration with ARA TBI project

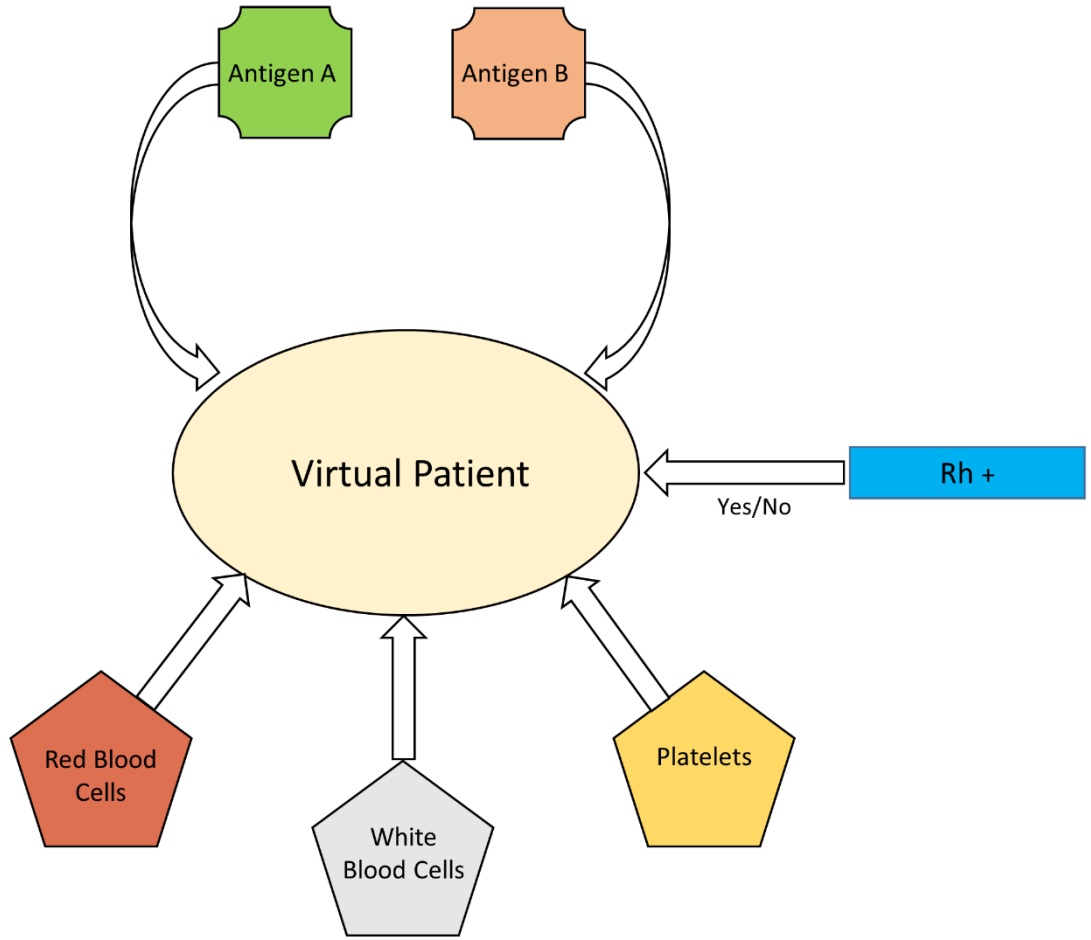
Whole Blood

- Background
  - Previous model
    - One substance compound: Blood
    - Constituent components
      - Hemoglobin
      - Oxyhemoglobin
      - Sodium
      - Albumin
      - Urea
      - Glucose
      - Triacylglyercols
      - Calcium
      - Creatinine
  - New model goals
    - Support ABO blood type definition for virtual patients
    - Support Rh factor definition for virtual patients
    - Distinguish between whole blood and plasma
    - Support transfusion action that checks for blood acceptor – donor compatibility



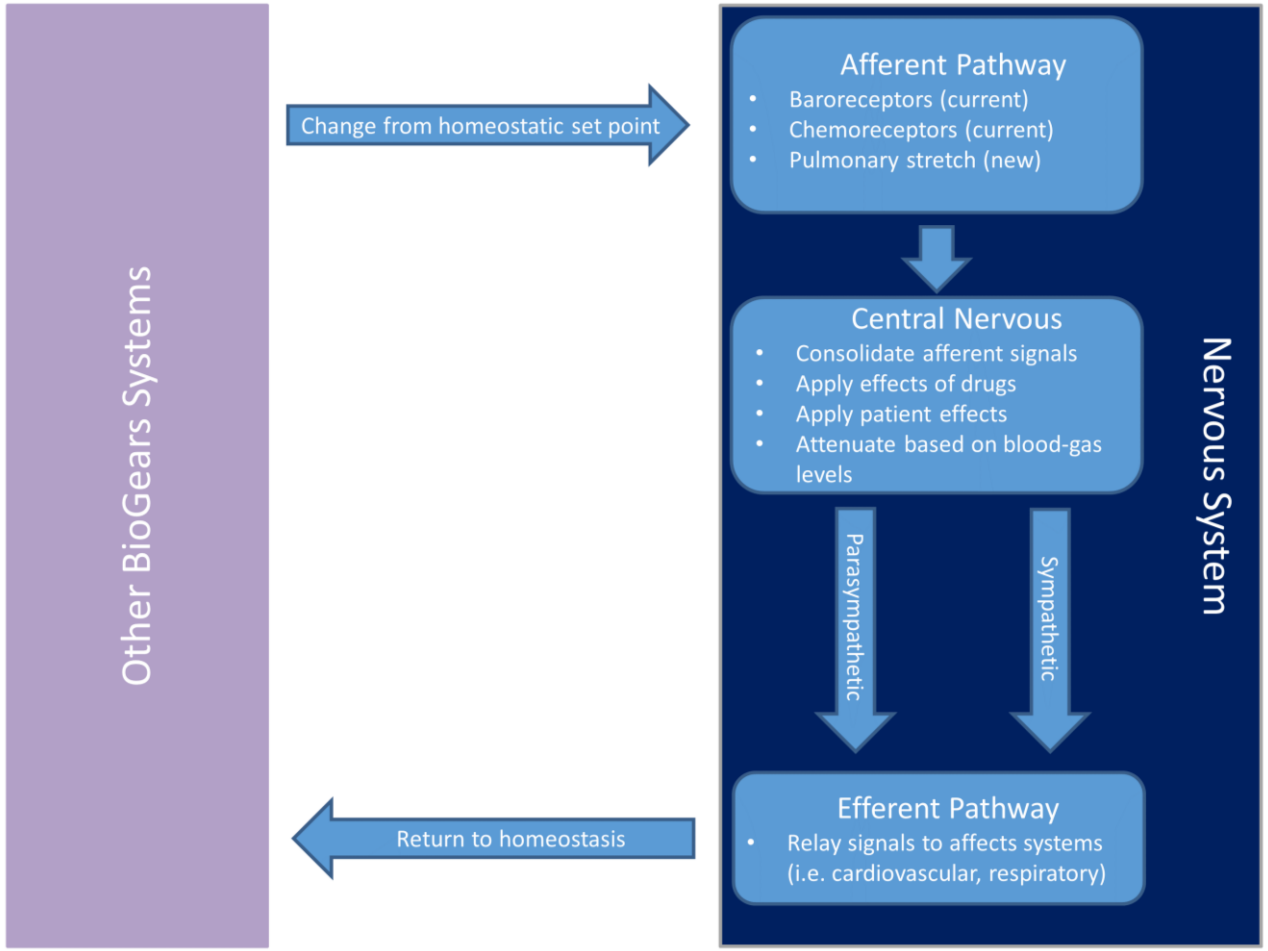
Whole Blood

- New Substance Definitions
  - Antigen A, B
  - Red Blood Cells, White Blood Cells, Platelets
  - Concentrations set according to standard literature values[Boron]
- Rh Classification (Boolean)
  - Set to True (+) or False (-)
- No antibodies
  - Inferred by presence/absence of antigens
- Transfusion Action
  - Covered in detail in Multi-Trauma Presentation



Models in Development

- Advanced Stages: Integrated Nervous Model
  - Current
    - Feedback systems treated as separate entities
    - Response of one system does not inform the others
  - Proposed
    - Increase fidelity of existing baroreceptor and chemoreceptor models
    - Introduce new feedback mechanisms
    - Process all signals simultaneously



Models in Development

- Preliminary Stages—Long term goals
  - Updated Nutrient Kinetics model
  - Updated Insulin / Glucose regulation model

Acknowledgements

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  - Dr. Jon Keller (Pulmonary and Critical Care Medicine, WISH)

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References

1. Dominguez-Huttinger, E., Boon, N.J., Clarke, T.B., and Tanaka, R.J. (2017). Mathematical modeling of *Streptococcus pneumoniae* colonization, invasive infection, and treatment. Front. Physiol. 8(115). doi: 10.3389/fphys.2017.00115
2. Chow, C.C., Clermont, G., Kumar, R., Lagoa, C., Tawadrous, Z., Gallo, D. et al. (2005). The acute inflammatory response in diverse shock states. Shock 24(1), 74-84. doi: 10.1097/01.shk.0000168526.97716.f3.
3. Reynolds, A., Rubin, J., Clermont, G., Day, J., Vodovotz, Y., and Ermentrout, G.B. (2006). A reduced mathematical model of the acute inflammatory response: I. Derivation of model and analysis of anti-inflammation. J Theor Biol 242, 220-236.
4. Brown, B., Namas, R.A., Almahmoud, K., Zaaqoq, A., Sarkar, J., Barclay, D.A., et al. (2015). Trauma in silico: Individual-specific mathematical models and virtual clinical populations. Sci Transl Med, 7. doi: 10.1126/scitranslmed.aaa3636
5. Nieman, G., Brown, D., Sarkar, J., Kubiak, B., Ziraldo, C., Dutta-Moscato, J., et al. (2012). A two-compartment mathematical model of endotoxin-induced inflammatory and physiologic alterations in swine. Crit Care Med. 40(4), 1052-1063. doi:10.1097/CCM.0b013e31823e986a
6. Lu, K., Clark Jr., J.W., Ghorbel, F., Ware, D.L. and Bidani. A. (2001) . A human cardiopulmonary system model applied to the analysis of the Valsalva maneuver. Am J Physiol Heart Circ Physiol. 281(6), H2661-79
7. Lu, K., Clark, J.W., Ghorbel, F., Robertson, C., Ware, D., Zwischenberger, J., and Bidani, A. (2004). Cerebral autoregulation and gas exchange studied using a human cardiopulmonary model. Am J Physiol Heart Circ Physiol. 286(2), H584-601.
8. Mazzoni, M.C., Borgstrom, P., Arfors, K., and Intaglietta, M. (1988). Dynamic fluid distribution in hyperosmotic resuscitation of hypovolemic hemorrhage. Am. J. Physiol. 255, H629-H637.
9. Rippe, B. and Haraldsson, B. (1994). Transport of macromolecules across microvascular walls: the two-pore theory. Physiological Reviews 74 (1)
10. Ankomah, P. and Levin, B. R. (2014). Exploring the collaboration between antibiotics and the immune response in the treatment of acute, self-limiting infections. Proceedings of the National Academy of Sciences, 111(23), 8331-8338.
11. Regoes, R. R., Wiuff, C., Zappala, R. M., Garner, K. N., Baquero, F., & Levin, B. R. (2004). Pharmacodynamic functions: a multiparameter approach to the design of antibiotic treatment regimens. Antimicrobial agents and chemotherapy, 48(10), 3670-3676.
12. McDaniel, M., Keller, J.M., White, S., and Baird, A. (2019). A whole-body mathematical model of sepsis progression and treatment designed in the BioGears physiology engine. Front. Physiol. 10. doi: 10.3389/fphys.2019.01321
13. Singer, M., Deutschman, C.S., Seymour, C.W., Shankar-Hari, M., Annane, D., Bauer, M., et al. (2016). The third international consensus definitions for sepsis and septic shock (Sepsis-3). Jama, 315(8), 801-810.
14. Sorgel, F. and Kinzig, M. (1993). The chemistry, pharmacokinetics, and tissue distribution of piperacillin/tazobactam. Journal of Antimicrobial Chemotherapy, 31, Suppl. A, 39-60.
15. Macdonald, S.P., Taylor, D.M., Keijzers, G., Arendts, G., Fatovich, D.M., Kinnear, F.B., et al. (2017). REstricted Fluid REsuscitation in Sepsis-associated Hypotension (REFRESH): study protocol for a pilot randomised controlled trial. Trials, 18(1), 399. doi:10.1186/s13063-017-2137-7
16. Macdonald, S.P., Keijzers, G., Taylor, D.M., Kinnear, F., Arendts, G., Fatovich, D.M. et al. (2018). Restricted fluid resuscitation in suspected sepsis associated hypotension (REFRESH): a pilot randomised controlled trial. Intensive care medicine, 44(12), 2070-2078. doi: 10.1007/s0013
17. McDaniel, M. and Baird, A. (2019). A Full-Body Model of Burn Pathophysiology and Treatment Using the BioGears Engine. In *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 261-264. IEEE.
18. Candio, L.C., Powell, D., Adams, B., Bull, K., Keller, A., Gurney, J. et al. (2016). Management of burn wounds under prolonged field care. J. Special Operations in Medicine. 16, 87-98.
19. Driscol, I.R., Mann-Salinas, E., Boyer, N., Pamplin, J., Serio-Melvin, M, Salinas, J., et al. (2018). Burn casualty care in the deployed setting. Military Med. 83, 61-67.
20. Alvardo A., Chung, K., Cancio, L., and Wolf, S. (2009). Burn Resuscitation. Burns 35(1), 4-14.
21. Lu, K., Clark Jr, J. W., Ghorbel, F. H., Robertson, C. S., Ware, D. L., Zwischenberger, J. B., and Bidani, A. (2004). Cerebral autoregulation and gas exchange studied using a human cardiopulmonary model. American Journal of Physiology-Heart and Circulatory Physiology, 286(2), H584-H601.
22. Ursino, M. and Lodi, C. A. (1998). Interaction among autoregulation, CO2 reactivity, and intracranial pressure: a mathematical model. American Journal of Physiology-Heart and Circulatory Physiology, 274(5), H1715-H1728.
23. Ursino, M. and Magosso, E. (2001). Role of tissue hypoxia in cerebrovascular regulation: a mathematical modeling study. Annals of biomedical engineering, 29(7), 563-574.
24. Steiner, L. A. and Andrews, P. J. D. (2006). Monitoring the injured brain: ICP and CBF. BJA: British Journal of Anaesthesia, 97(1), 26-38.