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BioGears: Past Present and Future

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1. Applied Research Associates Inc.

ARA

We appreciate the attendance

WELCOME USERS AND INTERESTED PARTIES!

BioGears: Past

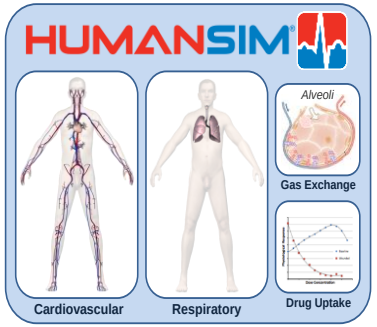
Develop the idea: address the problem (2012)

- Solicitation to develop an open source physiology engine
- ***Lower barriers to creating medical training content***
- Developer tools for medical education public physiology research platform (DTME-PRP solicitation)

TATRC

Imagine the solution (2013)

- Original PhACTS project proposal
- ***Leverage ARA's software development skills***
- Leverage the HumanSim platform as a jumping point for development



Implement the plan (2013 – 2020)

- Provide a high fidelity, validated engine to the community
- ***Implement open source best practices***
- Grow the user community
- Expand physiology simulations across the military medical community

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BioGears: Past

From the beginning ARA has developed BioGears with the original core principals in mind:

- ✓ Open-source
- ✓ Whole-body,
- ✓ Validated physiology platform
- ✓ Consistent, accurate
- ✓ Real-time
- ✓ State-of-the-art in medical modeling and simulation (MM&S)
- ✓ Documentation and standards

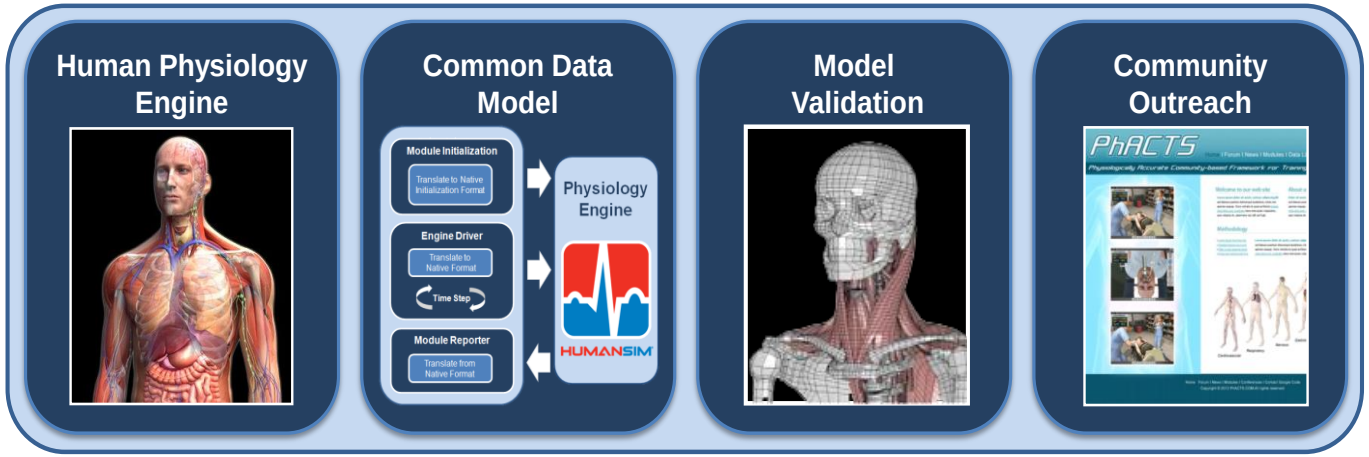
> *"[BioGears is an] open source validated reliable physiology engine and is essential and critical to the foundation of all future simulation technology... [BioGears] has great potential for a foundational product."* – ***Government Reviewer, JPC-1; BioGears Interim Progress Review, 2015***

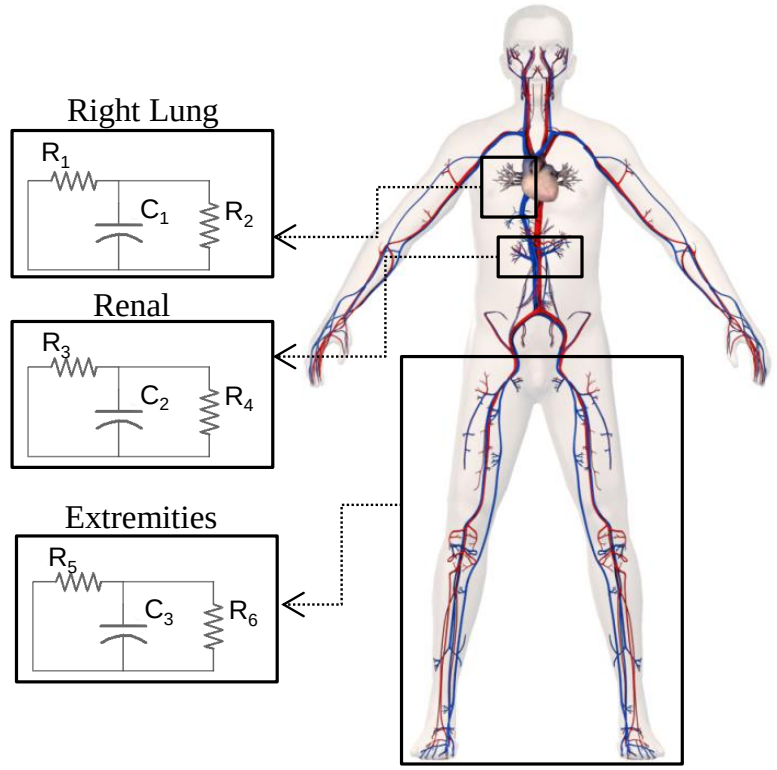
> *"Using and contributing back to open source software can fuel innovation, lower costs, and benefit the public."* – ***Second Open Government National Action Plan for the United States of America, 2014***

> *"When properly implemented and documented, releasing code as open source can benefit Federal agencies by allowing professional communities of practice to develop around software libraries and Application Programming Interfaces (APIs)."* – ***White House OMB, Draft Federal Source Code Policy , 2015***

BioGears: Past

- HumanSim began ARA's development of the BioGears engine
  - Was a key piece of the proposal submitted to TATRC
- Four pillars of the initial development:
  - ✓ Human Physiology engine
  - ✓ Common data model
  - ✓ Extensive validation and verification
  - ✓ Community outreach





BioGears: Past

Determine license
Do you want license to persist for new projects? Permissive? How to handle new users?

Documenting your process
Where to provide information to the community? How do we best communicate with their needs, contribute their changes?

Automating as much as possible
What tools can we leverage to successfully support the project? How much time/effort will creating that infrastructure take?

Progression 2013-2020

Source Forge
(2015) v2.0

Website
(2015-2017) v2.0-7.3

Github
(2017-2020) v6.2-7.3

Good
Alpha release hosted on the site. Only supported windows platform.

Better
Hosting multiple platforms for download on the BioGears website. Github API allows for estimate of users

Best
All source code provided on github. User issues and code changes addressed and integrated through the site.

BioGears: Past

Multi-platform support

Who are our targeted users? Supported applications and platforms?

Windows support

The only platform tested on for Alpha release (2014-2015, v1.0-2.0). Supported in every release since (v2.0-7.3). Military and private industry user groups.

MacOS support

Began building and testing in 2015 for the Beta release (v3.0-7.3. Academic and small business support (mostly).

Continuous Integration and Testing

Began testing on local machines, not automated. Transitioned to Jenkins build server. Later transitioned to Buildbot

Linux support

Began testing on Ubuntu virtual machines (2015, v3.0-7.3), now automated with Buildbot. Supported in every release since. Primarily academic.

ARM Architecture support

Began support in v4.0. Tested manually on a local machine. Cross compiling support now automated with Buildbot. Academic and small business support.

BioGears: Past

2013

→ **Milestone: Project Kick Off (Sept 15, 2013)**

2014

- ✓ Creation of Common Data Model
- ✓ Re-architecture of Physiology Engine
- ✓ Base System Development
- ✓ Base System Validation

→ **Milestone: Alpha Build Release and Website Launch (Oct 2014)**

2015

- ✓ Base System Additions & Improvements
- ✓ Feature Development & Validation
- ✓ Community Outreach & Conference Planning

→ **Milestone: Beta Build Release and Users Conf. (Oct 2015)**

2016

- ✓ Feature Development & Validation
- ✓ System Development / Engine Maintenance
- ✓ User Community Support
- ✓ Publications & Conference Presentations

2017

2018

→ ***Follow-on contract started***

BioGears: Present

FY 2017

Major Release: Version 6.1.0 (10 March 2017)

Completed Work

- Nutrient kinetics (protein, glucose, fat)
- Drug intoxication (morphine)
- Gastrointestinal system (feeding, dehydration, starvation updates)

Major Release: Version 6.2.0 (Sept 2017)

FY 2018

Completed Work

- Ketoacidosis
- Energy – weakness / fasciculation / sweat rate
- Substances updates
- Tissue - extravascular exchange updates

Major Release: Version 6.3.0 (March 2018)

Completed Work

- Nerve agent (Sarin)
- Ion transport and regulation
- Diabetes type 1 and 2
- New drug: Vasopressin

BurnCare contract started

BioGears: Present

FY 2018

Major Release: Version 7.0.0 (August 2018)

Completed Work

- Full github integration with CMAKE build support
- Pain and sepsis model (Advanced Modular Manikin (AMM) collaboration)
- Gastrointestinal System (Feeding, dehydration, starvation updates)
- Full ARM cross compiling support and testing

Major Release: Version 7.1.0 (Sep 2018)

Completed Work

- Override functionality released
- Chemoreceptor and blood pressure updates
- Build time reduced by 73%

FY 2019

Major Release: Version 7.2.0 (Jan 2019)

Completed Work

- Lymphatic system
- ***Burn model***
- Unit testing (Google Test) implemented
- Publications

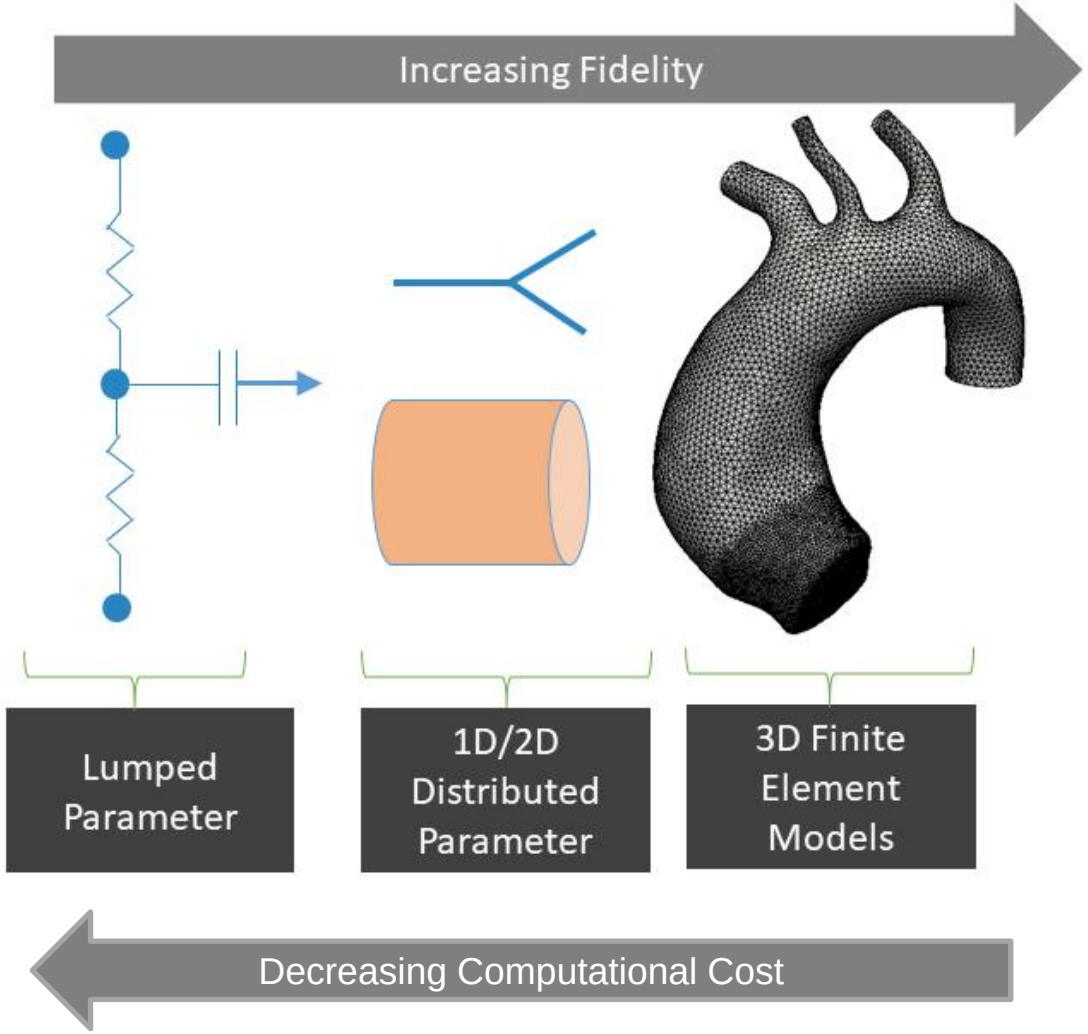
Prolonged Field Care contract started

BioGears: Present

Major Release: Version 7.3.0 (Jan 2020)

- ✓ Updates to CMD_BIO executable for batch validation and scenario execution
- ***Transmucosal Fentanyl*** implementation
- ✓ Tourniquet action for use with hemorrhage scenarios
- **New drug:** Tranexamic Acid
- ✓ Expansion of the cerebral circuit to a larger more complex system
  - ✓ Added cerebral autoregulation, hemorrhage, and updated TBI model
- **New drugs:** Moxifloxacin (oral) and Ertapenem (intravenous and intramuscular)
- ✓ Validation updates to Fentanyl drug
- ✓ New whole blood model/substance
  - ✓ Antigens, agglutination model and typed blood substance files for administration during runtime
- **New drug administration route:** oral tablet
- ✓ New complex how-to files covering burn and sepsis for developers use
- ✓ Unreal Engine integration

BioGears: Present

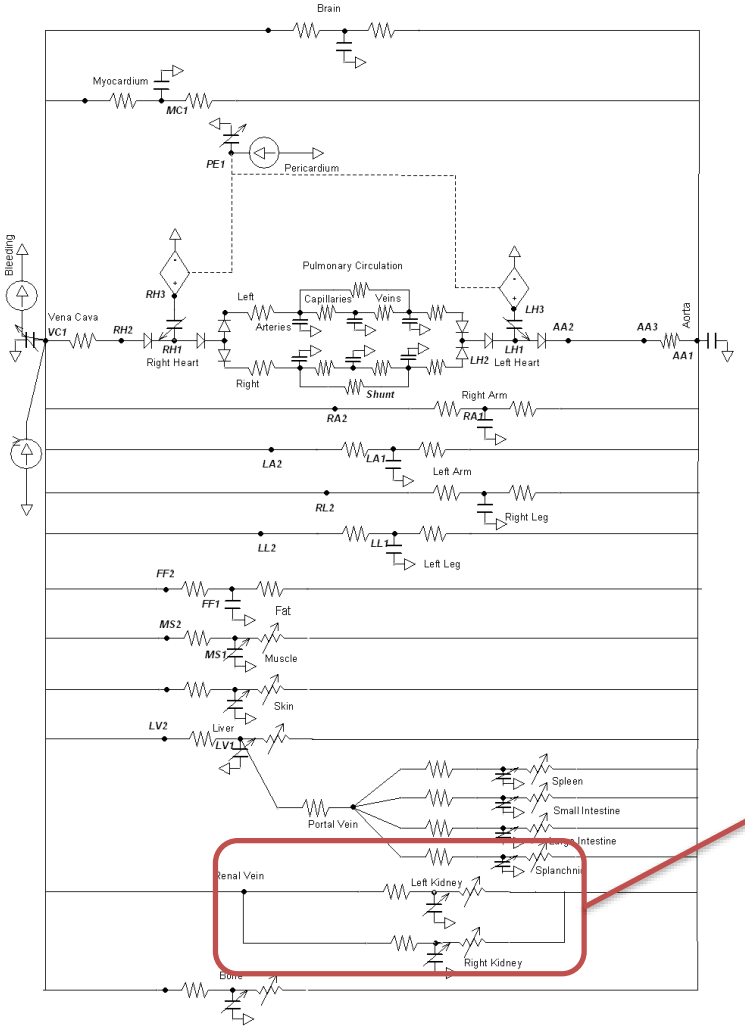


Physics based circulation model: Lumped Parameter (0-D)

- ✓ Fluid circuit analogue
- ✓ No spatial element
- ✓ Properties calculated at each node
  - ✓ Pressure
  - ✓ Flow rate
  - ✓ Volume
- ✓ Enhancing circuit resolution improves approximation
- ✓ Lower computational cost than higher fidelity models
- ✓ Appropriate for global distributions

BioGears: Present

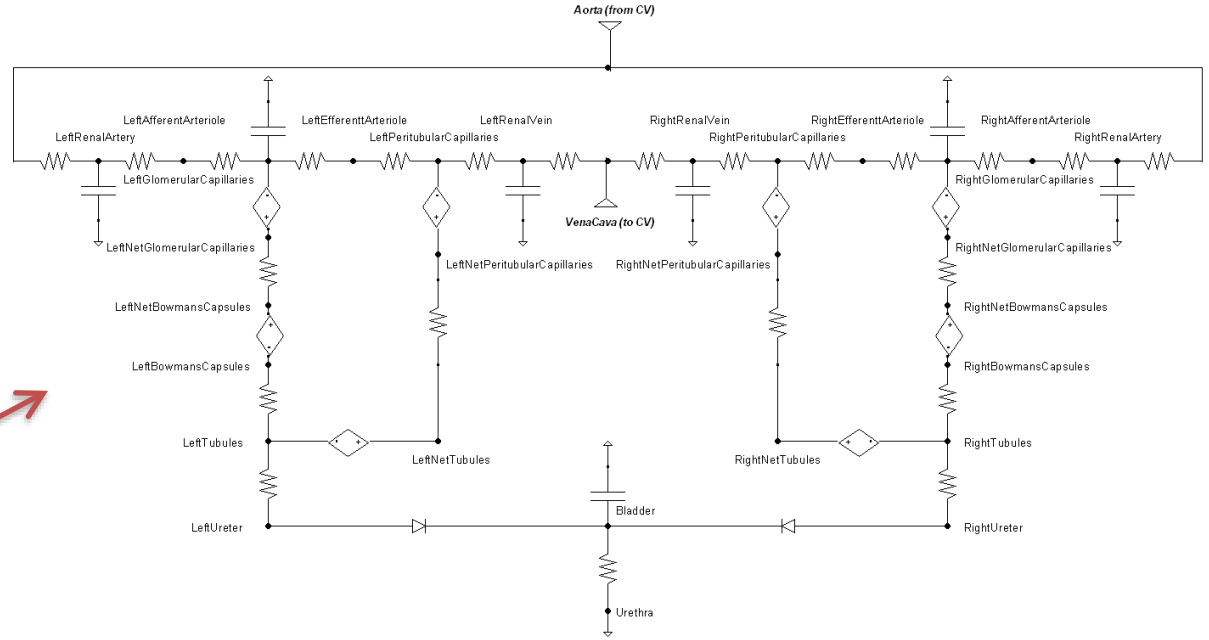
Cardiovascular Circuit



Increased Spatial Resolution of Renal System at a Single Temporal Scale

Build out and connect new complex circuits for your specific application

Renal System



BioGears: Present

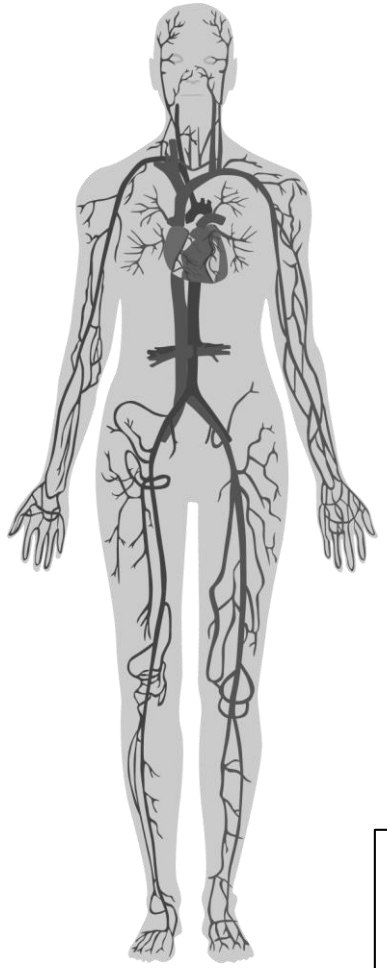
Support/validate requirements

As number of applications grow so does the core engine functionality

Anesthesia Machine:
Ventilator mask or intubation
- ✓ Equipment leak
- ✓ Gas sources
- ✓ Relief valve

Nervous:
Sympathetic/Parasympathetic responses
- ✓ Pain
- ✓ Chemo/Baroreceptors

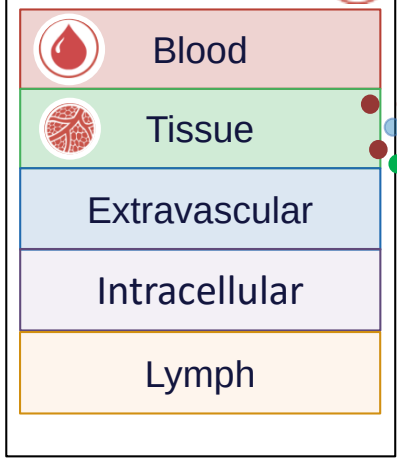
Endocrine:
Hormone regulation models
- ✓ Epinephrine
- ✓ Insulin
- ✓ Glucagon



Inhaler

Respiratory

Cardiovascular



Hepatic:
Nutrient storage and conversion
- ✓ Gluconeogensis
- ✓ Lipogensis

Renal:
Filtration and urine production
- ✓ GFR/RBF
- ✓ Autoregulation

Gastrointestinal:
Nutrient absorption/digestion
- ✓ Eat meals, drink water

Energy:
Thermal feedback and metabolic demands
- ✓ Exercise
- ✓ Environment

Drugs:
Administration, kinetics, and dynamics
- ✓ Opioid
- ✓ Sedative
- ✓ Antibiotic
- ✓ Anesthetic

BioGears: Present

Total Compartments

In total 154 ***total*** compartments with mapped hierarchy

Vascular Compartments

In total 60 ***liquid*** compartments with mapped hierarchy

Pulmonary Compartments

In total 17 ***gas*** compartments with mapped hierarchy

Tissue Compartments

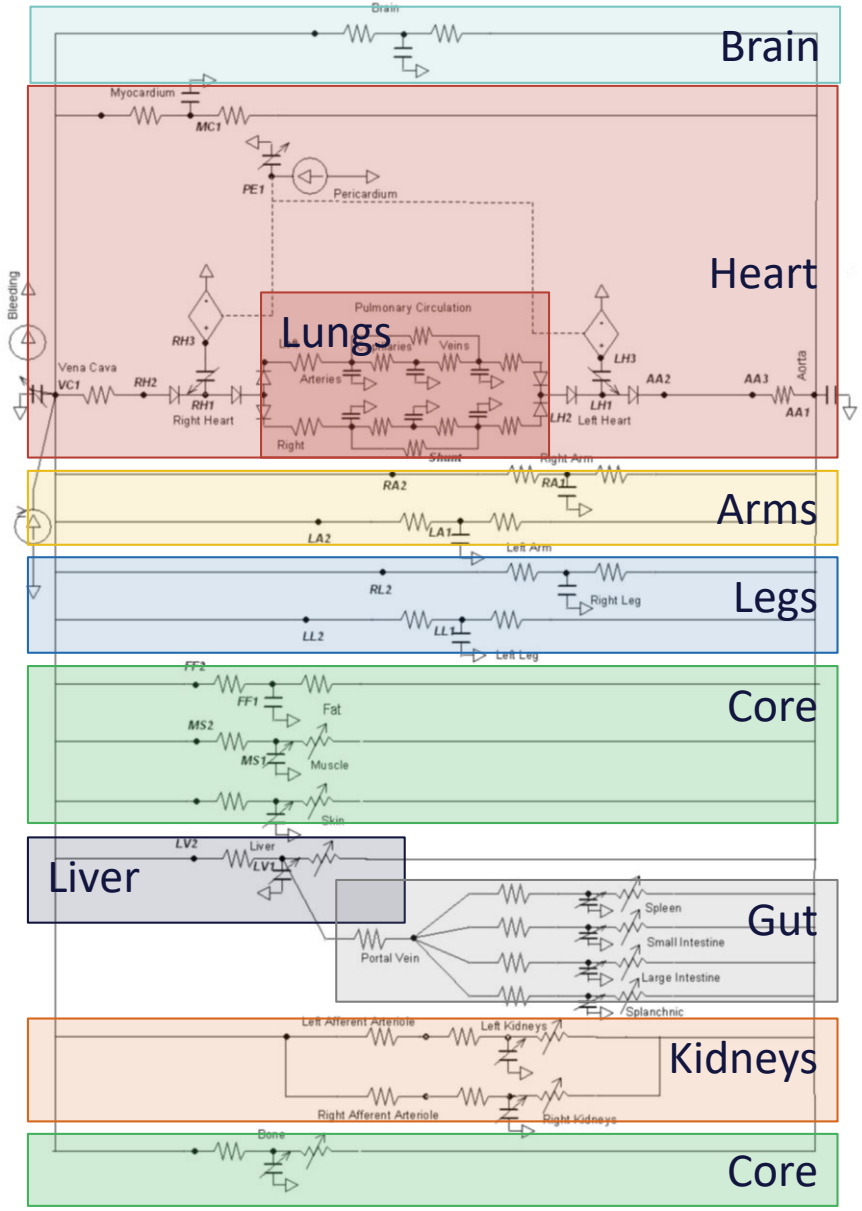
In total 40 ***liquid*** compartments with mapped hierarchy

Environment Compartments

In total 20 ***thermal*** compartments with mapped hierarchy

Miscellaneous Compartments

In total 4 ***liquid*** urine compartments, 1 ***liquid*** lymph compartment, and 12 ***gas*** anesthesia machine and inhaler compartments



BioGears: Present

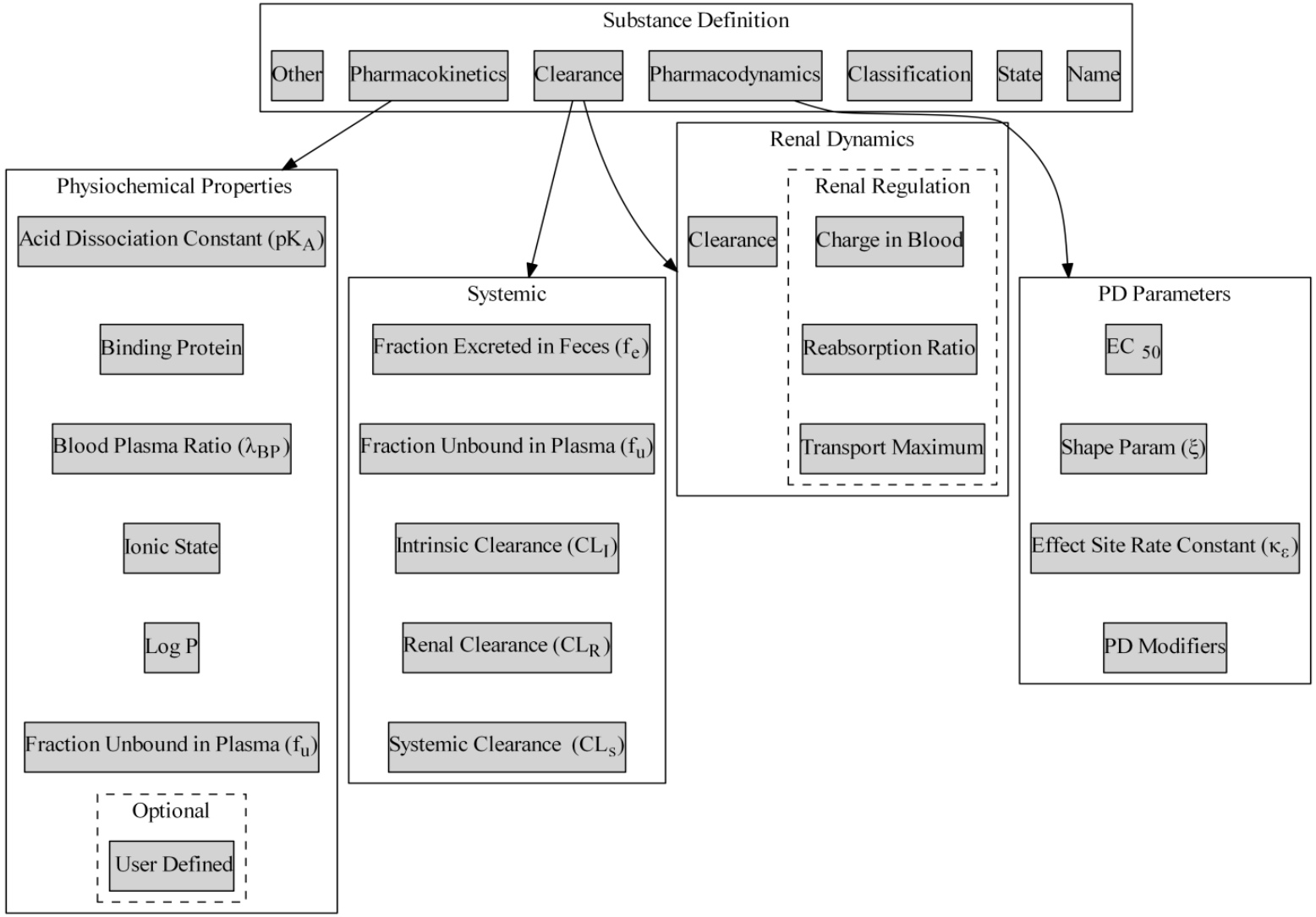
Substance definition standards

In total 68 ***Substances*** with appropriate defined data. Data determines:

- ✓ Diffusion
- ✓ Clearance
- ✓ Free mass

Covered types:

- ✓ Environmental gasses
- ✓ Nutrients
- ✓ Blood composition
- ✓ Drugs
- ✓ Solid particulate
- ✓ Hormones
- ✓ Proteins
- ✓ Acids
- ✓ Ions



BioGears: Present

Substance definition standards

Code agnostic implementation for portability and extensibility

Flexible unit input

Generic unit conversion engine can be leveraged in xml formatting

Examples in source and downloads

All substance files provided to the community

```
<Name>Acetoacetate</Name>
  <MolarMass value="102.09" unit="g/mol"/>
  <State>Liquid</State>
  <Clearance>
    <Systemic>
      <FractionExcretedInFeces value="0.0"/>
      <FractionUnboundInPlasma value="1.0"/>
      <IntrinsicClearance value="0.0" unit="mL/min kg"/>
      <RenalClearance value="0.0" unit="mL/min kg"/>
      <SystemicClearance value="17.8" unit="mL/min kg"/>
    </Systemic>
    <RenalDynamics>
      <Regulation>
        <ChargeInBlood>Neutral</ChargeInBlood>
        <FractionUnboundInPlasma value="1.0"/>
        <ReabsorptionRatio value="INF"/>
        <TransportMaximum value="INF" unit="mg/min"/>
      </Regulation>
    </RenalDynamics>
  </Clearance>
</Substance>
```

BioGears: Present

Circuit Solver

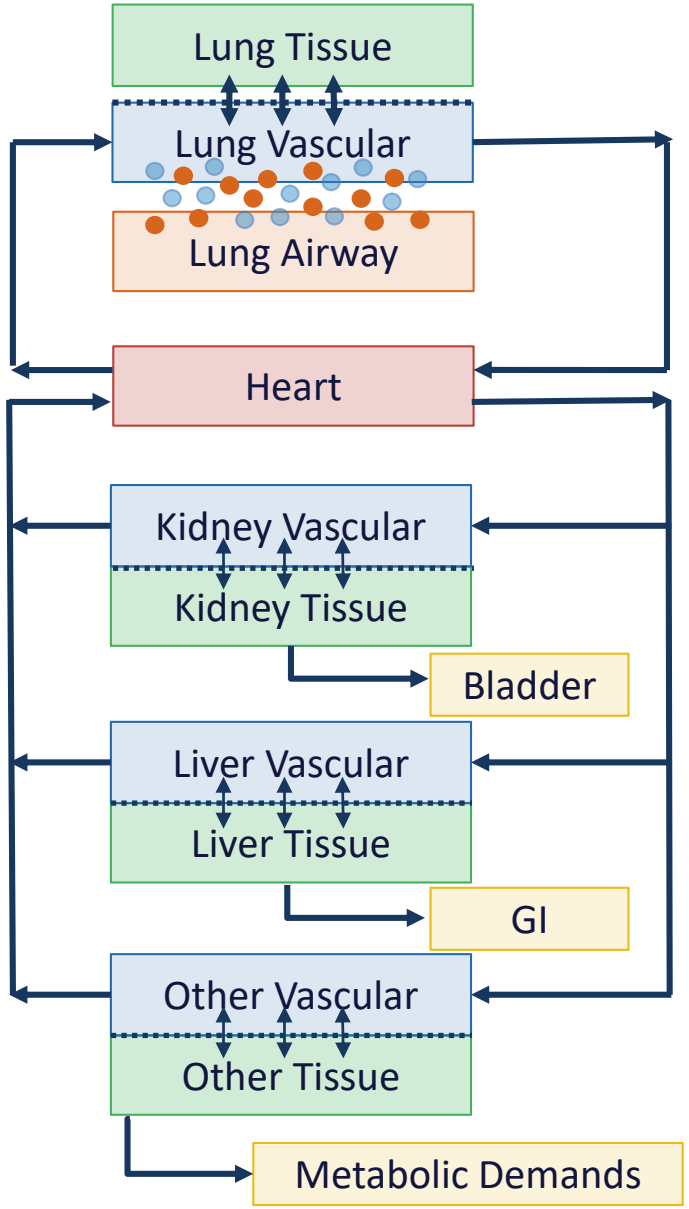
Generic mathematical formulation to cover any closed loop system:

- ✓ Modified Nodal Analysis solver
- ✓ Solves circuit types with any units: Electrical, Fluid, Thermal

Substance Transporter:

Generic conservation of mass transporter for substances in the body and environment

- ✓ Mass moves with the fluid to each node in the circuit
- ✓ Gas diffusion between the pulmonary vasculature and the alveoli
- ✓ Oxygen is consumed and carbon dioxide is produced in the tissues
- ✓ Substances are cleared from the body via renal filtration clearance, hepatic clearance, and metabolism



BioGears: Present

Applications continue to grow and diversify

- ✓ Docker containerized deployment
- ✓ AWS cloud computing
- ✓ Biological sensor integration
- ✓ Phone application data viewer

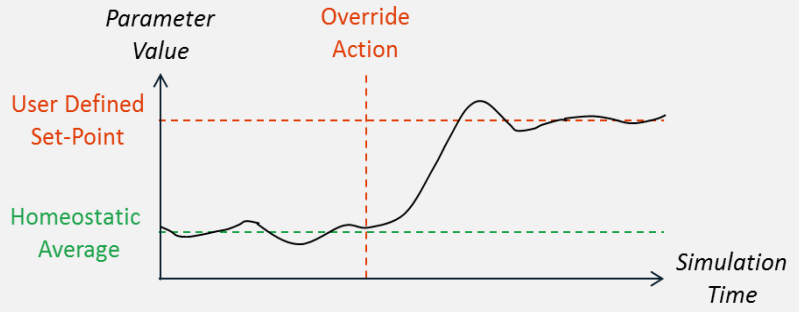
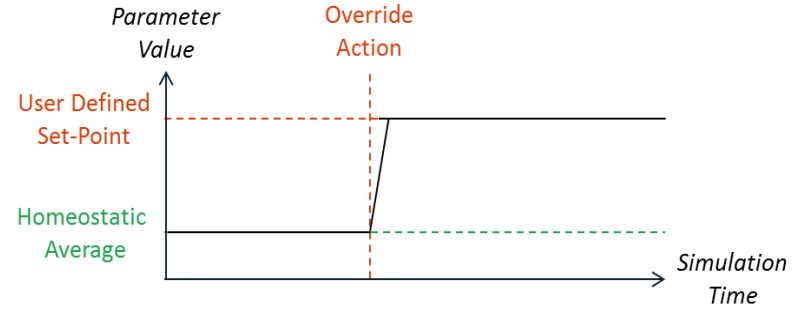
BioGears: Present

Parameter override functionality

Can be set as a static set point or a physiologically driven dynamic state. This distinction is denoted conformant and non-conformant physiology engine.

Originally released in 7.0

Dynamic functionality implemented in 7.2 release.

Type	System Properties	Expected Behavior
	Parameter Override	
Dependent Feedback parameter (Dynamic)	• Heart Rate • Respiration Rate • Blood Pressue	
Independent Feedback parameter (Static)	• Skin Temperature • Cardiac Output • Tidal Volume • Glomerular Filtration Rate • Renal Blood Flow	

BioGears: Present

Record years for community outreach

- ✓ 3 publications [1,2,3]
- ✓ 4 conference presentations and posters
- ✓ Over 8000 downloads from the website
- ✓ Average of 10 unique clones over ten days
- ✓ Fully documented wiki site pages on github
- ✓ 5 new complex How-to.cpp files for community reference

A Full-Body Model of Burn Pathophysiology and Treatment Using the BioGears Engine*

Matthew McDaniel and Austin Baird, Ph.D.

Abstract—**We have created a model of systemic burn pathophysiology by incorporating a mathematical model of acute inflammation within the BioGears Engine. This model produces outputs consistent with burns of varying severities and leverages existing BioGears functionality to simulate the effect of treatment on virtual patient outcome. The model performs well for standard resuscitation scenarios and we thus expect it to be useful for educational and training purposes.**

on learner actions. The purpose of this paper is to describe the burn model developed in BioGears for this trainer.

II. METHODS

A. BioGears Overview

BioGears is an open-source, object-oriented application programming interface (API) written in C++ that implements a whole-body physiology engine. This API

frontiers in Physiology

TECHNOLOGY AND CODE
published: 18 October 2019
doi: 10.3389/fphys.2019.01321

A Whole-Body Mathematical Model of Sepsis Progression and Treatment Designed in the BioGears Physiology Engine

Matthew McDaniel[1], Jonathan M. Keller[2], Steven White[3] and Austin Baird[3]*

[1] Applied Research Associates, Littleton, CO, United States, [2] Pulmonary and Critical Care Medicine, WISH Simulation Center, University of Washington, Seattle, WA, United States, [3] Applied Research Associates, Raleigh, NC, United States

Sepsis is a debilitating condition associated with a high mortality rate that greatly strains hospital resources. Though advances have been made in improving sepsis diagnosis and treatment, our understanding of the disease is far from complete. Mathematical modeling of sepsis has the potential to explore underlying biological mechanisms and patient phenotypes that contribute to variability in septic patient outcomes. We developed a comprehensive, whole-body mathematical model of sepsis pathophysiology using the BioGears Engine, a robust open-source virtual human modeling project. We describe the development of a sepsis model and the physiologic response within the BioGears framework. We then define and simulate scenarios that compare sepsis treatment regimens. As such, we demonstrate the utility of this model as a tool to augment sepsis research and as a training platform to educate medical staff.

Citation: CPT Pharmacometrics Syst. Pharmacol. (2019) 8, 12–25; doi:10.1002/psp4.12371

TUTORIAL

Open Source Pharmacokinetic/Pharmacodynamic Framework: Tutorial on the BioGears Engine

Matthew McDaniel[1], Jennifer Carter[1], Jonathan M Keller[2], Steven A. White[1] and Austin Baird[1,*]

BioGears is an open-source, lumped parameter, full-body human physiology engine. Its purpose is to provide realistic and comprehensive simulations for medical training, research, and education. BioGears incorporates a physiologically based pharmacokinetic/pharmacodynamic (PK/PD) model that is designed to be applicable to a diversity of drug classes and patients and is extensible to future drugs. In addition, BioGears also supports drug interactions with various patient insults and interventions allowing for a realistic research framework and accurate dose-patient responses. This tutorial will demonstrate how the generic BioGears PK/PD model can be extended to a new substance for prediction of drug administration outcomes.

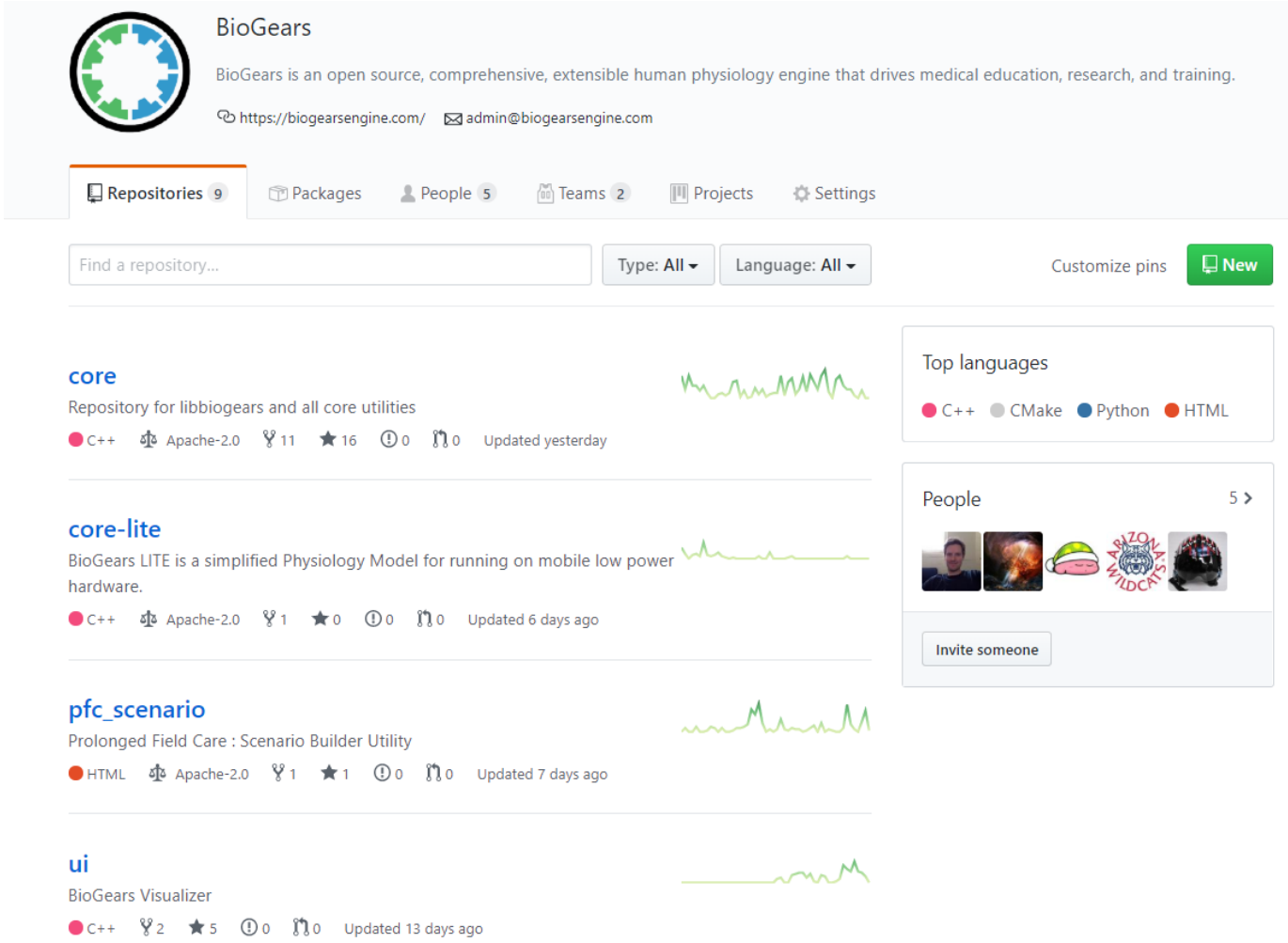
BioGears: Present

Our github project page has expanded!

- ✓ Core engine source code with live updates
- ✓ Lite project
- ✓ Prolonged field care (PFC) scenario builder
- ✓ BioGears user interface
- ✓ Published paper data for peer reviewers
- ✓ PFC framework library
- ✓ PFC python learning record store
- ✓ PFC assessment web portal

Projects highlight extensions and possibilities

Users get access to all documentation and code for each project we've created



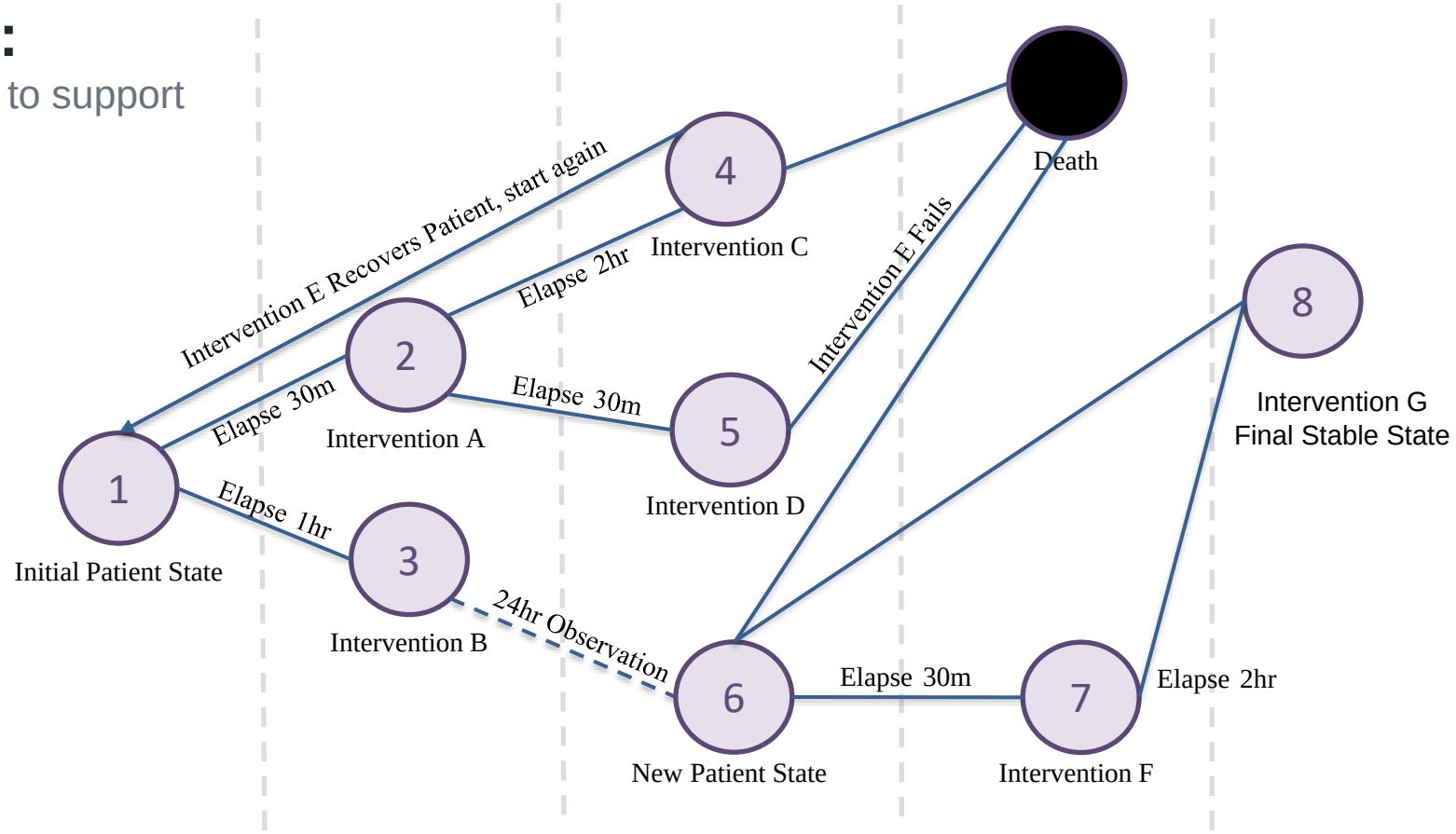
BioGears: Future

State machine framework:

Generic extensions to scenario language to support parallel simulations and branching

1) Female patient with anemia; open tension pneumothorax
3) Perform needle decompression
6) Jump ahead 1 day
12) Success

1) Female patient with anemia; open tension pneumothorax
2) Assess; perform needle decompression
4) Jump ahead 2 hr
11) Patient death



BioGears: Future

User interface v1.0 release:

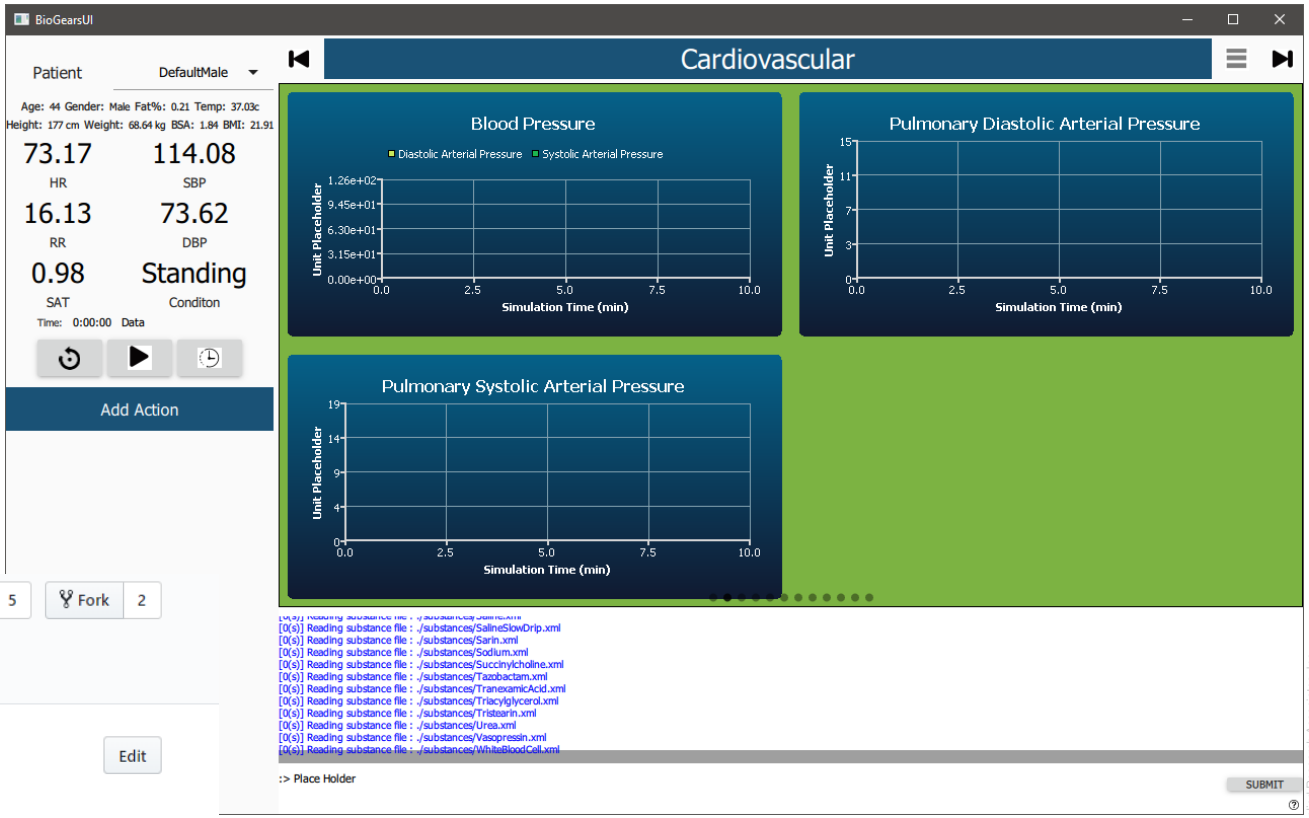
Developed and designed in collaboration with Dr. Thomas Talbot

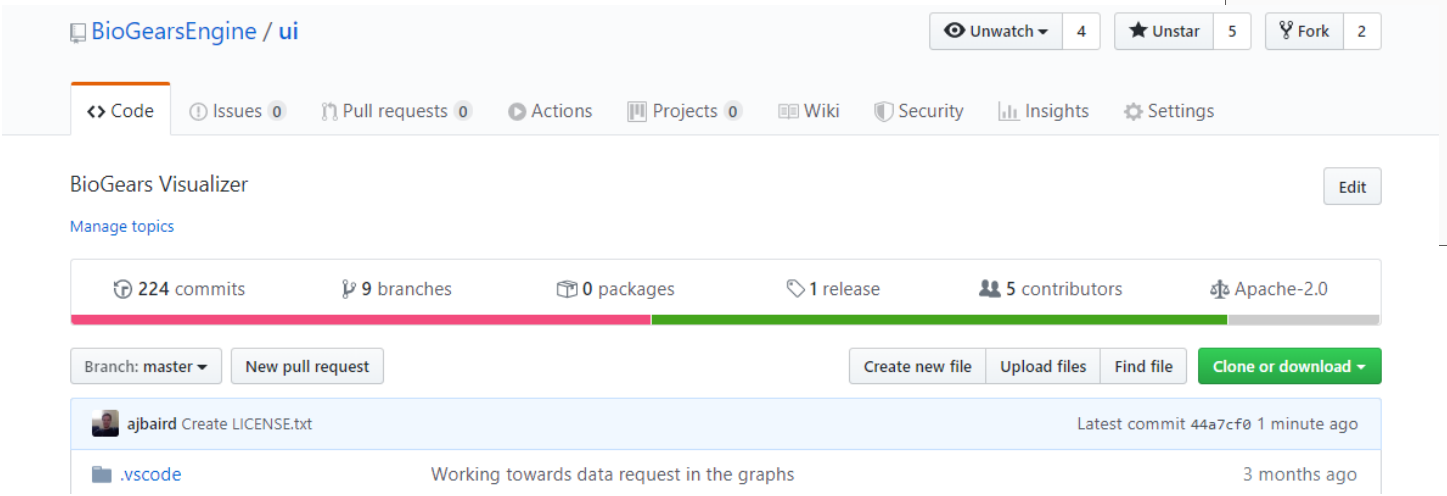
Goal:

Ease of use, broad adoptability, contained releases

Date:

Development ongoing on github, 1.0 release expected in the summer





BioGears: Future

BioGears Lite v1.0 release:

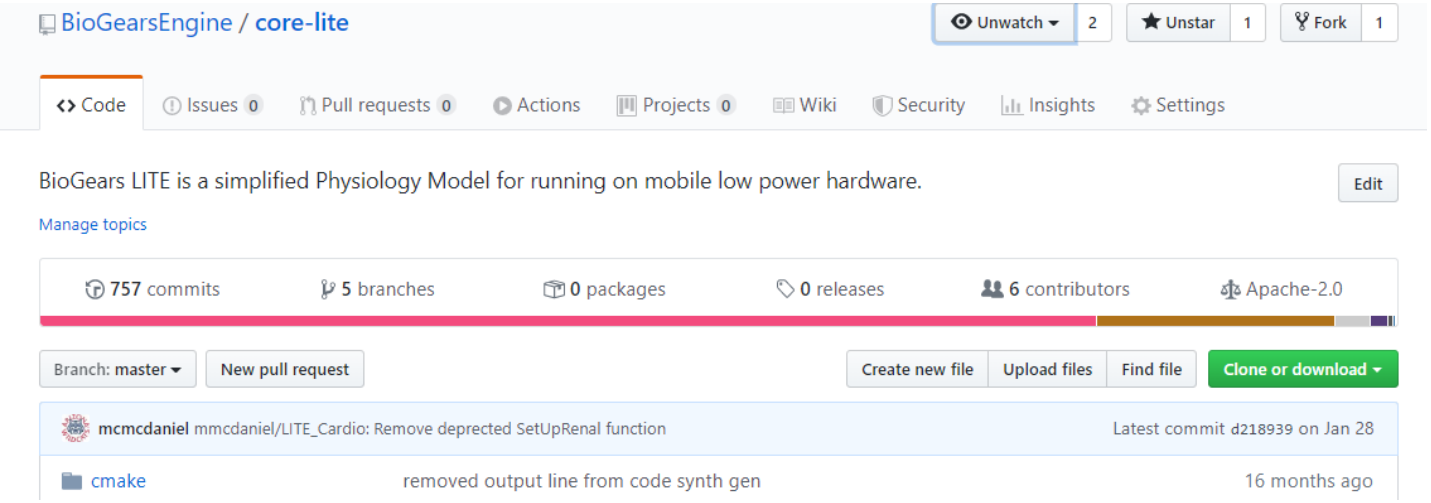
Developed and designed for lightweight use/applications

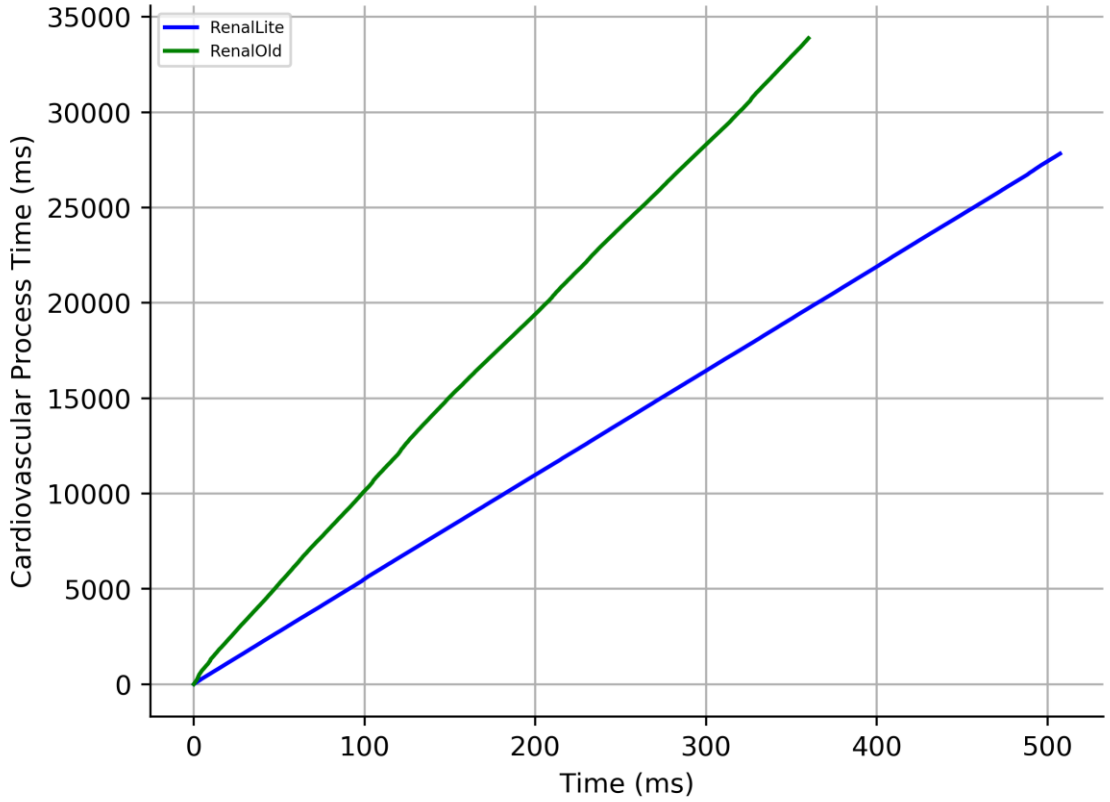
Goal:

Maximum capabilities while still running at/faster than real time on current microcontrollers and mobile devices

Date:

Development ongoing on github, 1.0 release expected in the summer





Speed increases already on master branch

~40% speed increase with limited decrease in functionality

BioGears: Future

BurnCARE training application

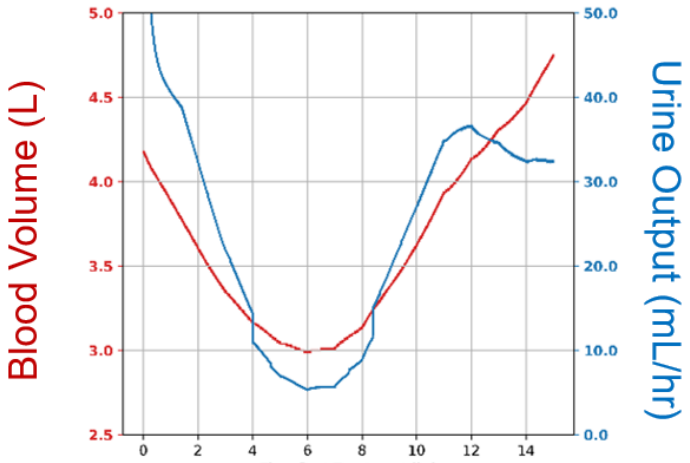
Train for complex burn treatments on a portable tablet application with validated BioGears burn model

Goal:

Allow users with no prior knowledge of burn patient physiology and treatment requirements to train in any environment

Date:

First ***free*** release on google play store early summer. Final release late 2021



BioGears: Future

Cloud deployment and planning applications

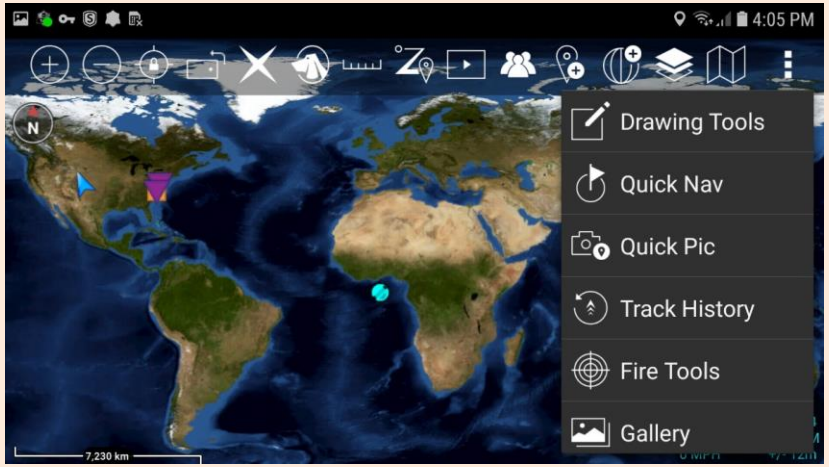
Mass casualty, CBRN exposure scenarios, medical logistics planning

Mobile platform tactical planning application?

Local or global applications

Physiology simulations can run in parallel, enabling large scale injury simulations.

Global pandemic planning simulations?



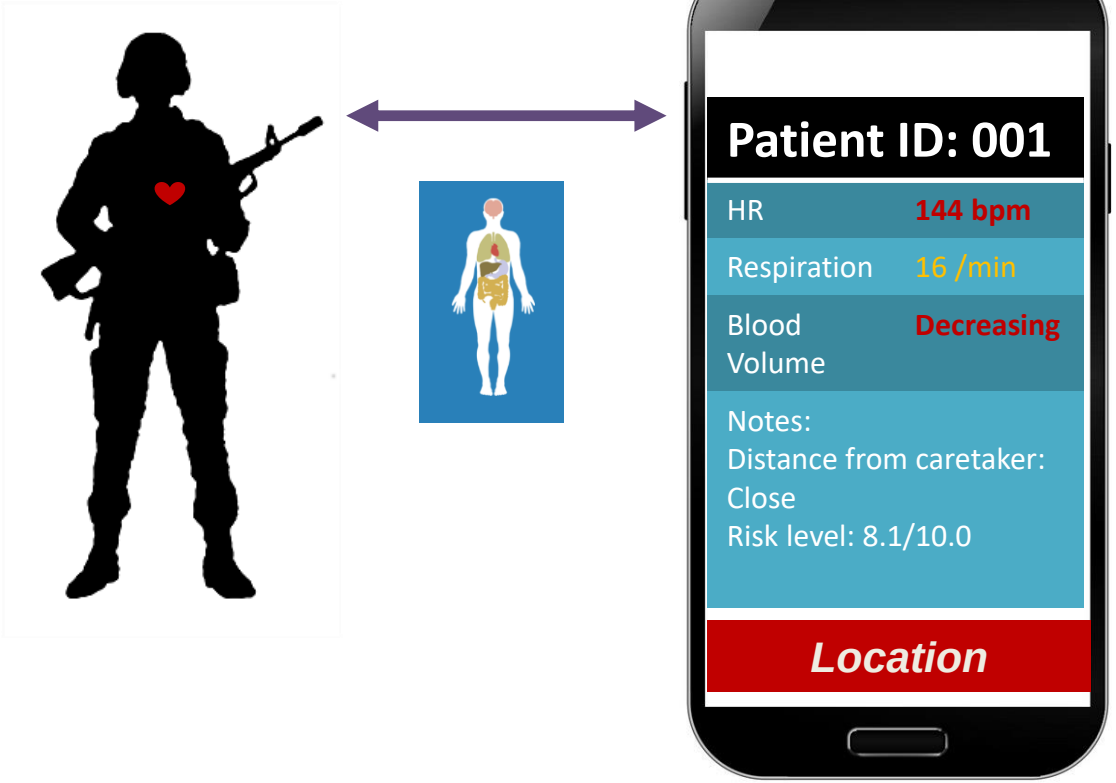
BioGears: Future

Digital Twin Monitoring

Heart Rate sensor integration, BioGears may approximate other physiology metrics

Interactive application

Monitor individual digital twins as well as triage groups



BioGears: Future

8.0 release models

Release will conclude our current contract, expected in the fall

Drug: Acetaminophen

Pain and temperature management

Drug: Atropine

Collaboration with Google summer of code

Sleep model

Scales metabolism, alertness data request

Updated nervous model

Combined sympathetic and parasympathetic response

Updated metabolism

Further validation of exercise and its effect on metabolism, blood glucose

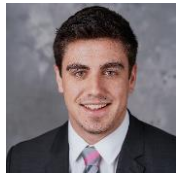
BioGears: Future

Thank you!

Team







Contracts

W81XWH-17-C-0172

Select Government Collaborators/Users

Select University Collaborators/Users

Select Commercial Collaborators/Users

Background: Talk about WHY we are doing this model, the impact, research that's been done, ect…

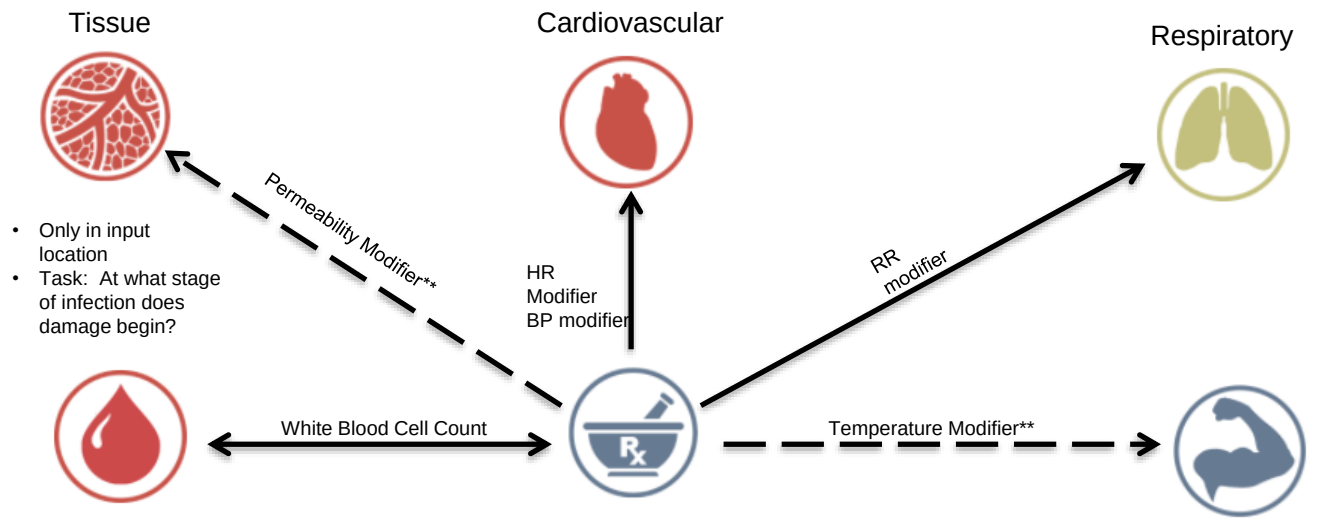
- Stages and Diagnosis
  - Sepsis
    - Presence of infection
    - At least two symptoms of Systemic Inflammatory Response Syndrome (SIRS), table reproduced from Remick[1]

1) Body temperature >38°C or <36°C
2) Heart rate >90 beats per minute
3) Respiratory rate >20 breaths per minute or arterial CO_2 tension less than 32 mm Hg or a need for mechanical ventilation
4) White blood count greater than 12,000/mm^3 or <4000/mm^3 or >10% immature forms

Sepsis represents SIRS, which has been induced by an infection.

Methods: high level introduction

- Early stages of infection



- Only in input location
- Task: At what stage of infection does damage begin?

Blood Chemistry
- Store White Blood Cell Count
- Output Blood Panel
- Lactate and bilirubin concentrations

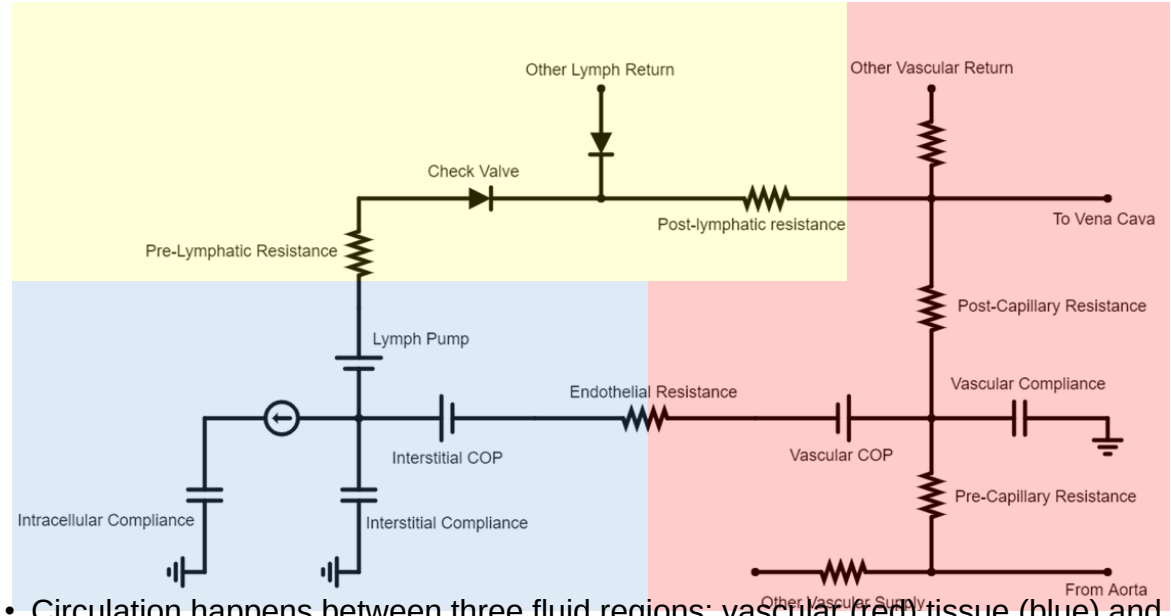
PK/PD
- Site of Kumar Model
- Use ratio of $m(t):m_0$ to calculate change in White Blood Cell Count from baseline
- Use White Blood Cell Count in PD Effects Model
- Tune heart rate, blood pressure, respiration rate modifiers

Energy
- Task: Adjust temperature circuit resistors

→ = Existing BioGears interaction

→ = New interaction developed

Methods: Talk about the details of the model/software, be specific



- Circulation happens between three fluid regions: vascular (red) tissue (blue) and lymph (yellow)
- Amount is determined by the endothelial resistance and relative contributions of the vascular and interstitial colloid osmotic pressure (COP)
- Allows for protein rich infusions (albumin)

Mathods: Is there a new action? Describe it

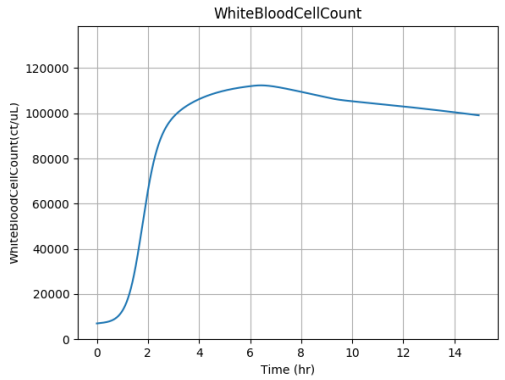
- User specifies:
  - Compartment
    - Options: Gut, Kidney, Liver, Skin, Spleen, Muscle
    - No support for multiple inputs
  - Severity
    - Scale: 0-1
    - Controls the time evolution of virtual patient response
      - 1.0 → septic shock in 15-20 minutes
      - 0.2 → septic shock in ~15 hrs

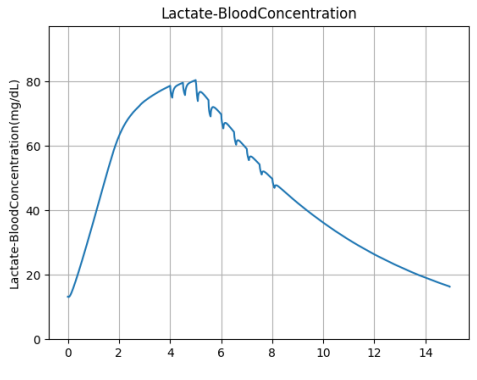
```
<Action xsi:type="SepsisData" Compartment="Gut">
    <Severity value="1.0"/>
</Action>
```

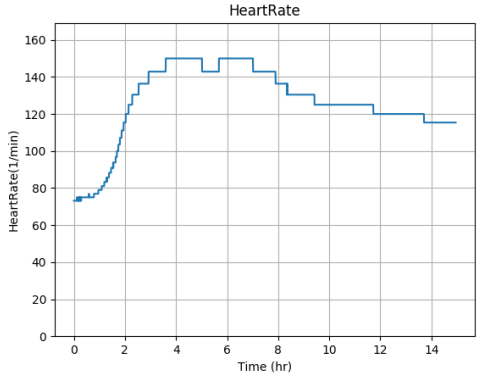
Methods: Show how to create a scenario (if relevant) AND possibly how how a list like this translates to xml, cpp, or a demo

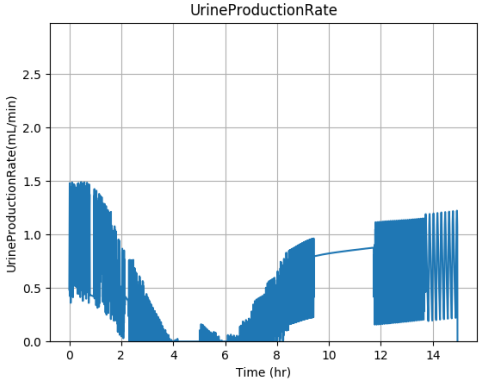
1. Fast Progression
   a. Compartment = Gut
   b. Severity = 1.0
2. Fast Progression w/ Treatment
   1. Treatment designed to mimic early-goal directed therapy (Rivers et all[12]) and that proposed by Keller/Barnes/Kiberenge/Konia
   2. Scenario Actions (time, min)
   3. Sepsis (t = 0 min)
      1. Severity = 1.0
      2. Compartment = Gut
   4. Administer antibiotic (t = 30 min) [Barnes/Kiberenge/Konia]
      1. 4.5 g over 4 hrs
      2. Monitor for 4 hrs
   5. Administer saline (t = 30 + 30n, n = 0-5)[12]
      1. 500 mL bolus every 30 min
      2. Each bolus infused over 5 min
   6. Start norepineprhine infusion (t = 120 min)
      1. 14 ug/min (0.19 ug/kg/min) = Highest dose explored by Ensinger[17]
      2. Cited study in healthy volunteers with consideration of septic shock implications
      3. From previous runs, t = 120 is about the time MAP < 65 mmHg
   7. End norepinephrine infusion (t = 150 min)
   8. Administer antibiotic (t = 510 min)
      1. 4.5 g over 4 hrs

Show figures, talk through them









Conclusions

- Overview

Acknowledgements

- Thanks team and outside people

References

1. Blah blah blah, Use APA formatting