BioGears: Drug Modeling Overview

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Outline

BioGears Background

- Lumped-parameter approach
- System overview

Methods: PK / PD Methodology

- Substance definitions
- Pharmacokinetic model
- Pharmacodynamic model

Results: Complex Treatment Scenarios

- Development
- Results

Technical overview of the BioGears engine

BACKGROUND

Background

Features and Goals	Strategies
• Accurate whole-body physiology modeling	• Physics-based, lumped-parameter models • Mechanistic compartment modeling
• Increased access to medical training technology	• Open-source • Graphical user interface • Multi-platform build testing
• Interface with medical hardware	• Common data model • Open standards development and documentation
• Encourage and support community development	• Community forum • Software-development kit

Background

The Cardiovascular Circuit

- Time-varying compliance in heart mimics pumping
- Adapted from Stergiopulos et al
- Pathways to tissue compartments

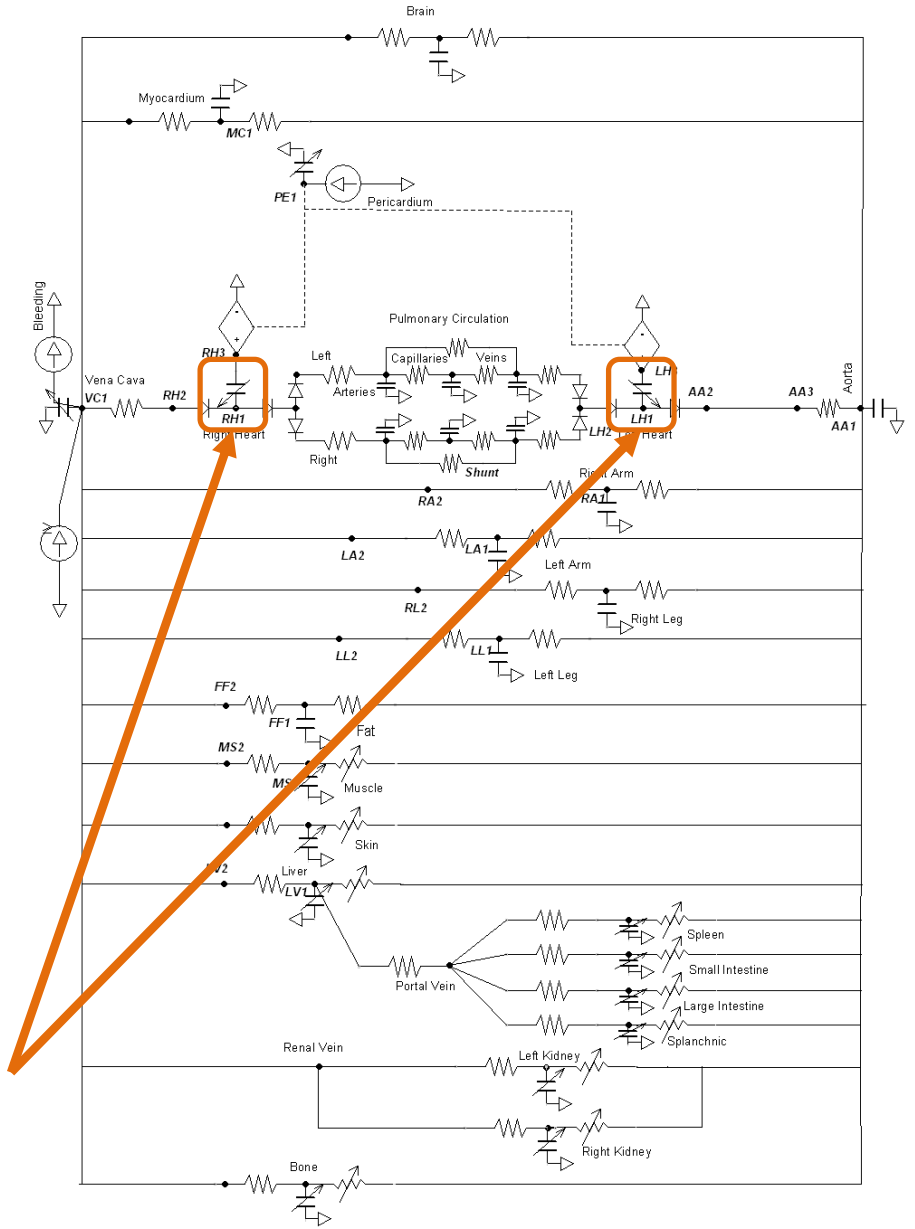
Define the change in elastance to be:

$$E_v(E_{\max,v} - E_{\min,v})\left(\frac{f(t)}{f_{\max}}\right) + E_{\min,v}$$

Double hill time-varying relationship:

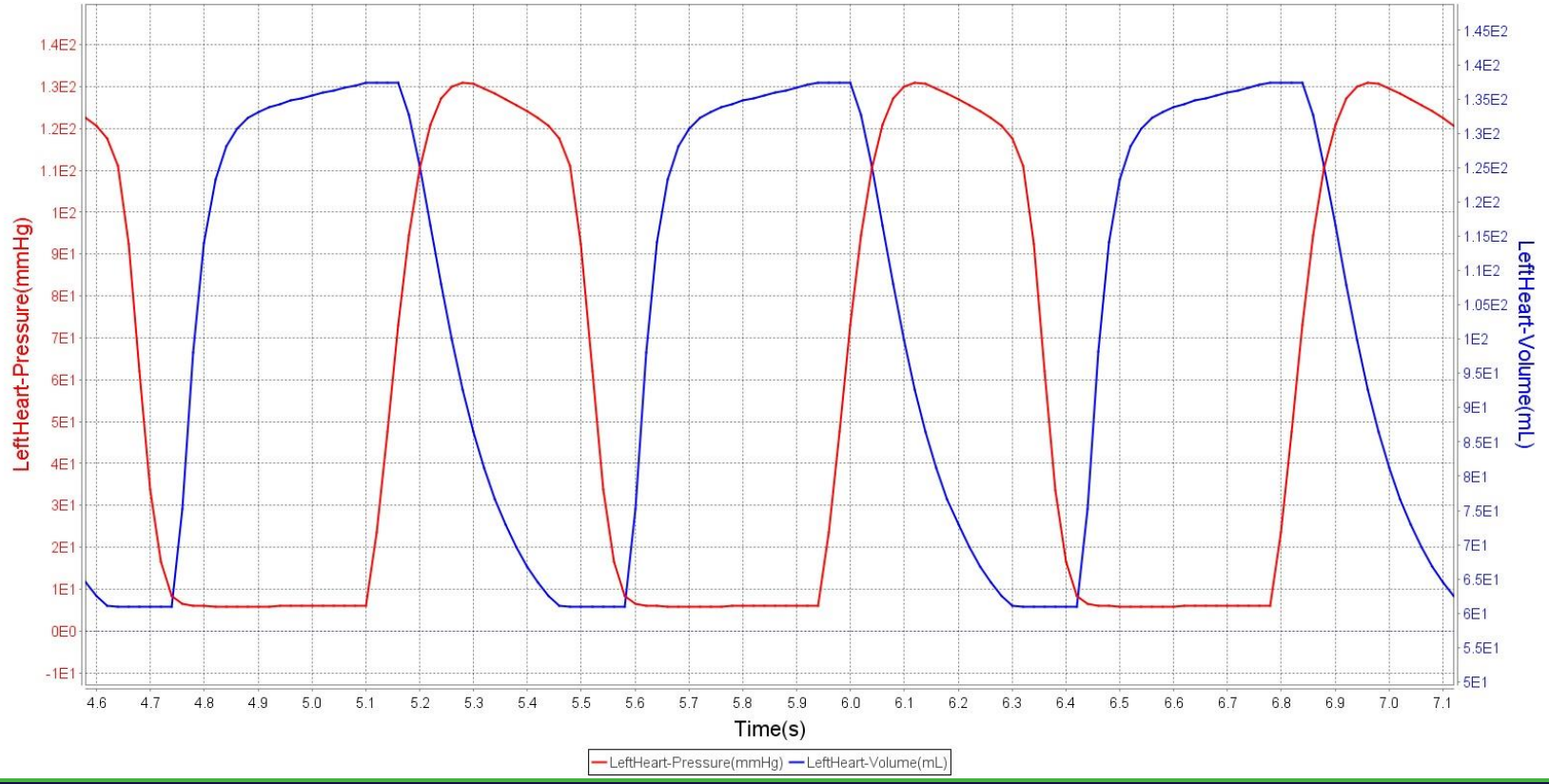
$$f(t) = \left[\frac{\left(\frac{t}{\alpha_1 T}\right)^{n_1}}{1+\left(\frac{t}{\alpha_1 T}\right)^{n_1}}\right]\left[\frac{1}{1+\left(\frac{t}{\alpha_2 T}\right)^{n_2}}\right]$$

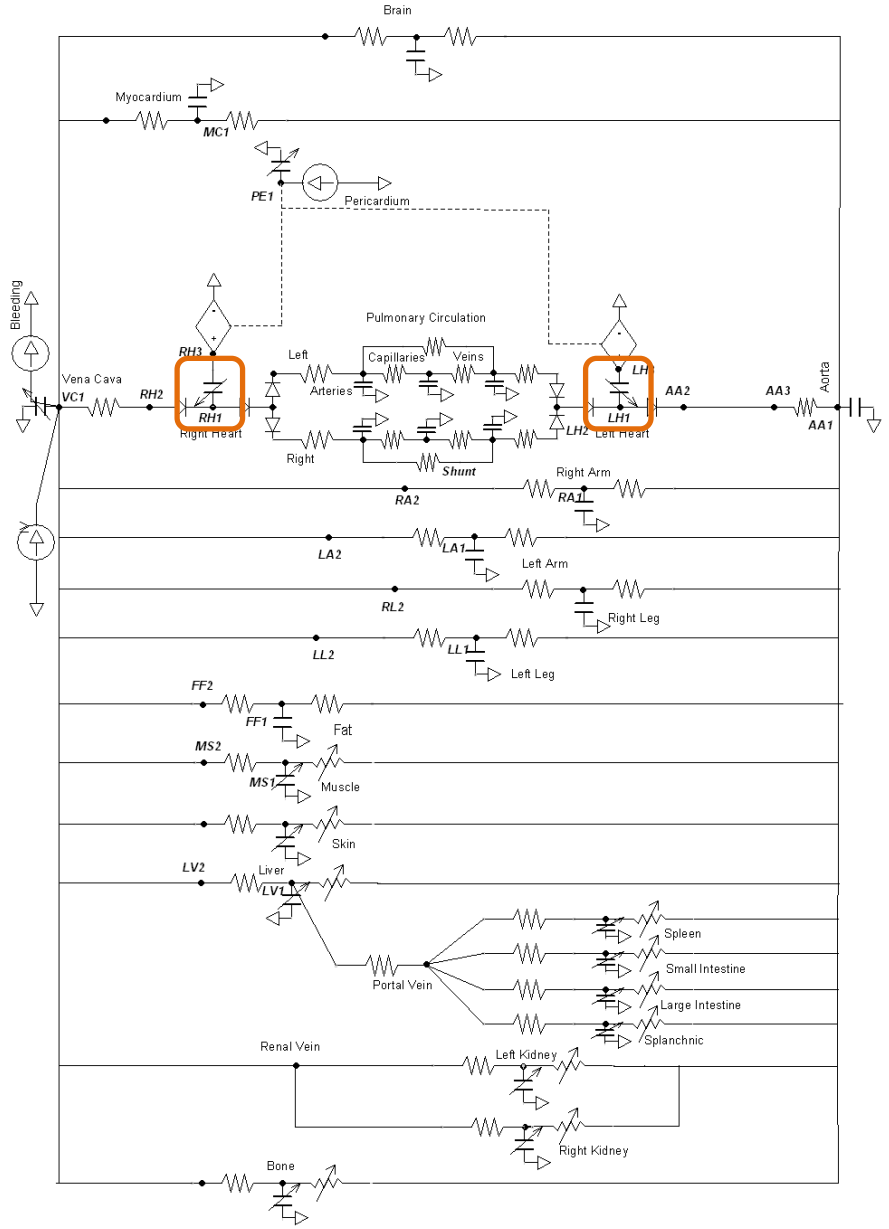
Set the left and right heart compliance to be the inverse of elastance



Background

Pressure volume curve over time

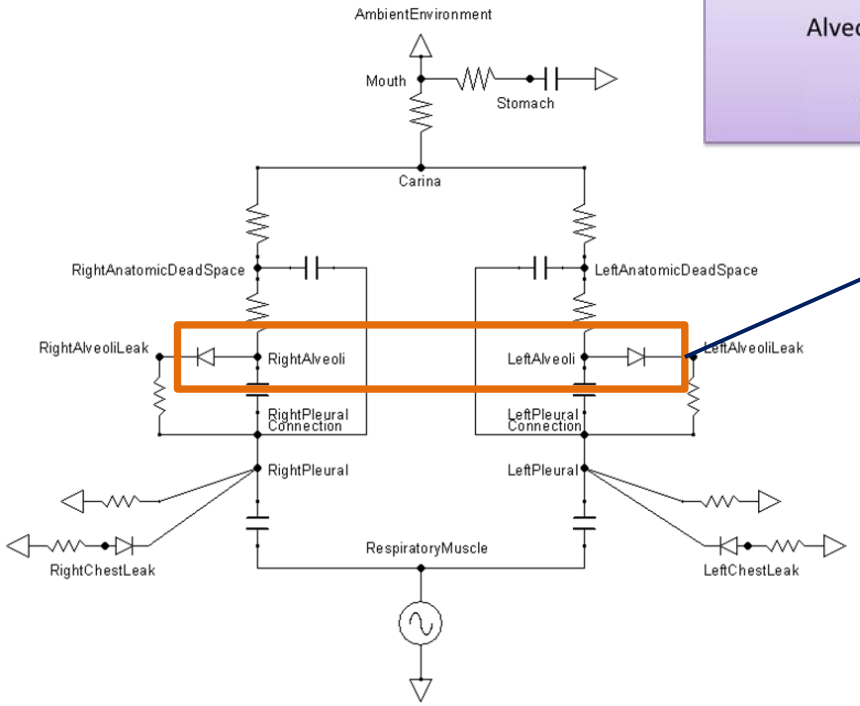


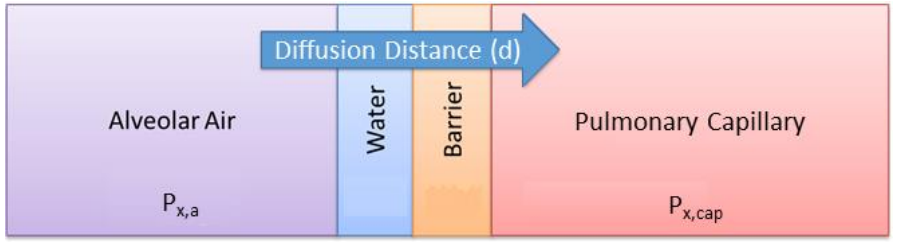


Background

The Respiratory Circuit

- Variable pressure source drives air in and out of lungs
- Alveolar transfer of blood gases
- Adopted from model by Albanese et al.
- Driver pressure is coupled to chemoreceptors





$$\dot{D}_x = \frac{D_{cap,O_2} \cdot C_{D,x} \cdot \left(P_{x,a} - P_{x,cap}\right) \cdot SA_a}{d}$$

D_{cap,O_2} = Oxygen diffusive capcity

$C_{D,x}$ = Diffusity of gas x relative to O_2

SA_a = Alveolar surface area

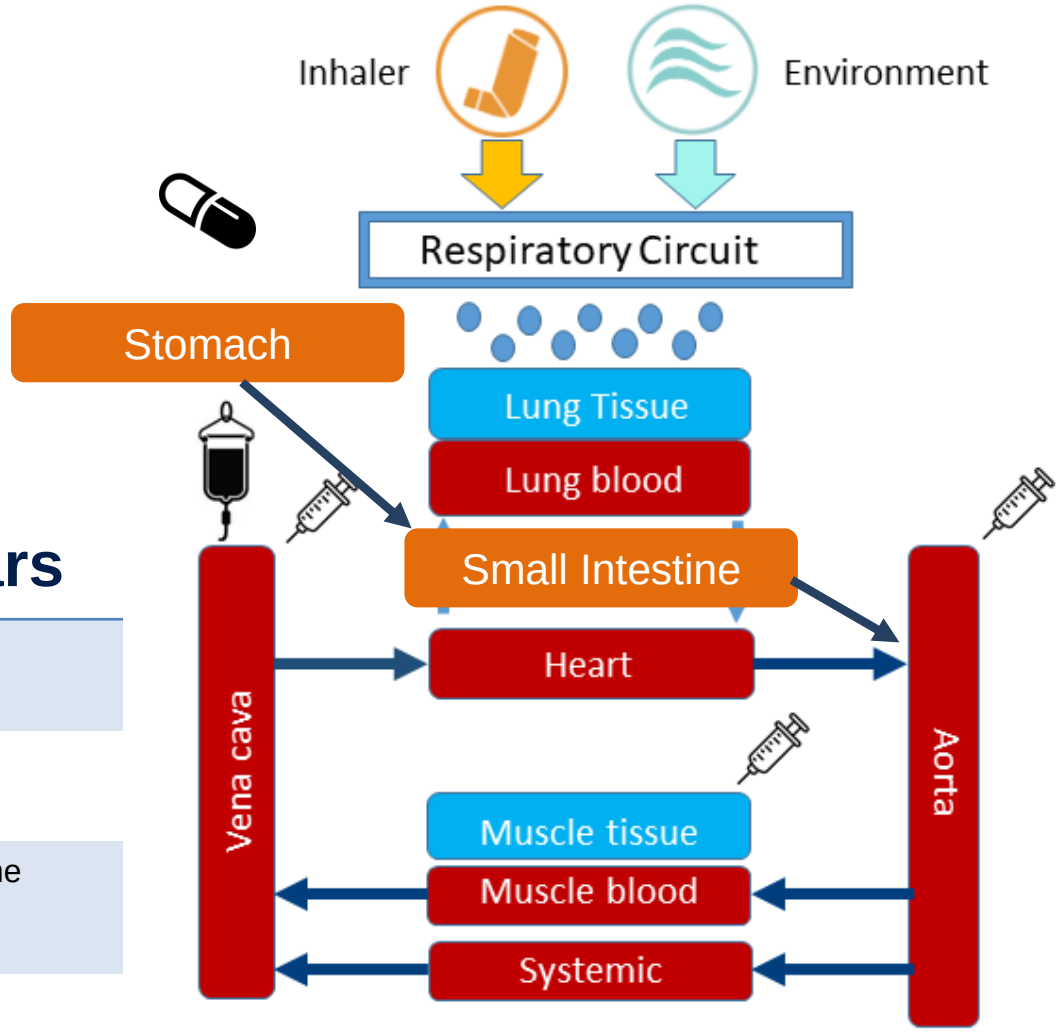
BioGears drug model description

METHODS

Methods

Administration routes in BioGears include

- Intravenous/intraarterial (infusion or bolus)
- Intramuscular
- Oral
- Inhaled



Current supported/validated drugs in BioGears

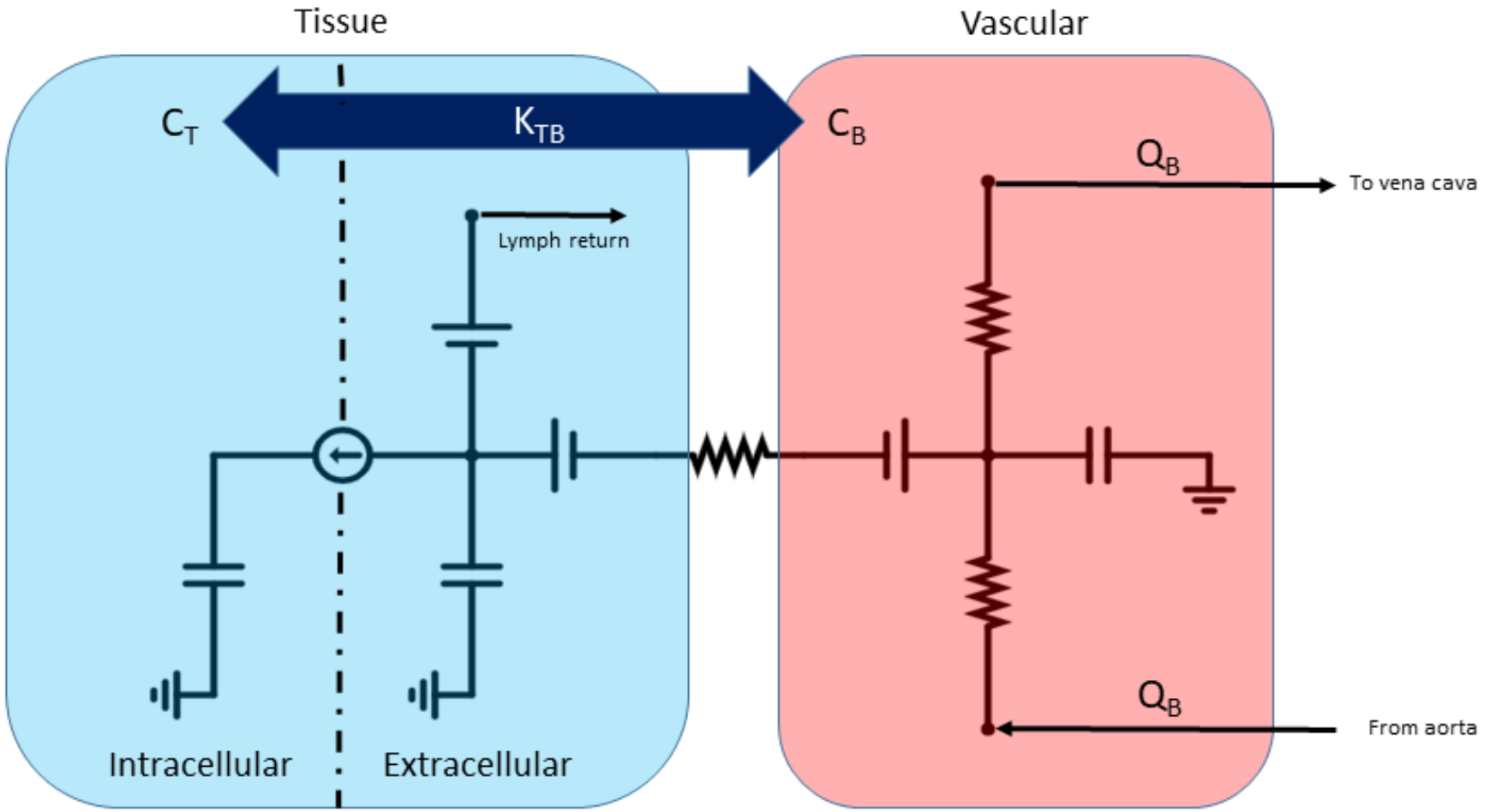
Prednisone	Desflurane	Morphine	Midazolam	Fentanyl
Naloxone	Insulin	Succinylcholine	Rocuronium	Albuterol
Epinephrine	Sarin	Propofol	Ketamine	Pralidoxime
Acetaminophen	Tranexamic acid	Vasopressin	Furosemide	

Methods: Partition Coefficient

Perfusion-limited diffusion assumed for each organ:

$$\frac{dm}{dt} = Q_B\left(C_B - \frac{C_T}{K_{TB}}\right)$$

- Q is flow rate,
- C denotes the concentration in blood and tissue,
- K is the given tissues computed partition coefficient



Methods: Partition Coefficient

Moderate to strong bases (Rogers, Leahy, and Rowland, 2004)

$$K_{TB} = \frac{f_u}{\lambda_{BP}}\left[f_{EW} + \frac{1+10^{pK_a - pH_{IW}}}{1+10^{pK_a - pH_p}} f_{IW} + \frac{K_a\left[AP^-\right]_T \cdot 10^{pK_a - pH_{IW}}}{1+10^{pK_a - pH_p}} + \frac{P \cdot f_{NL} + (0.3P + 0.7) f_{NP})}{1+10^{pK_a - pH_p}} \right]$$

Acids, neutral compounds, weak bases (Rogers and Rowland, 2005)

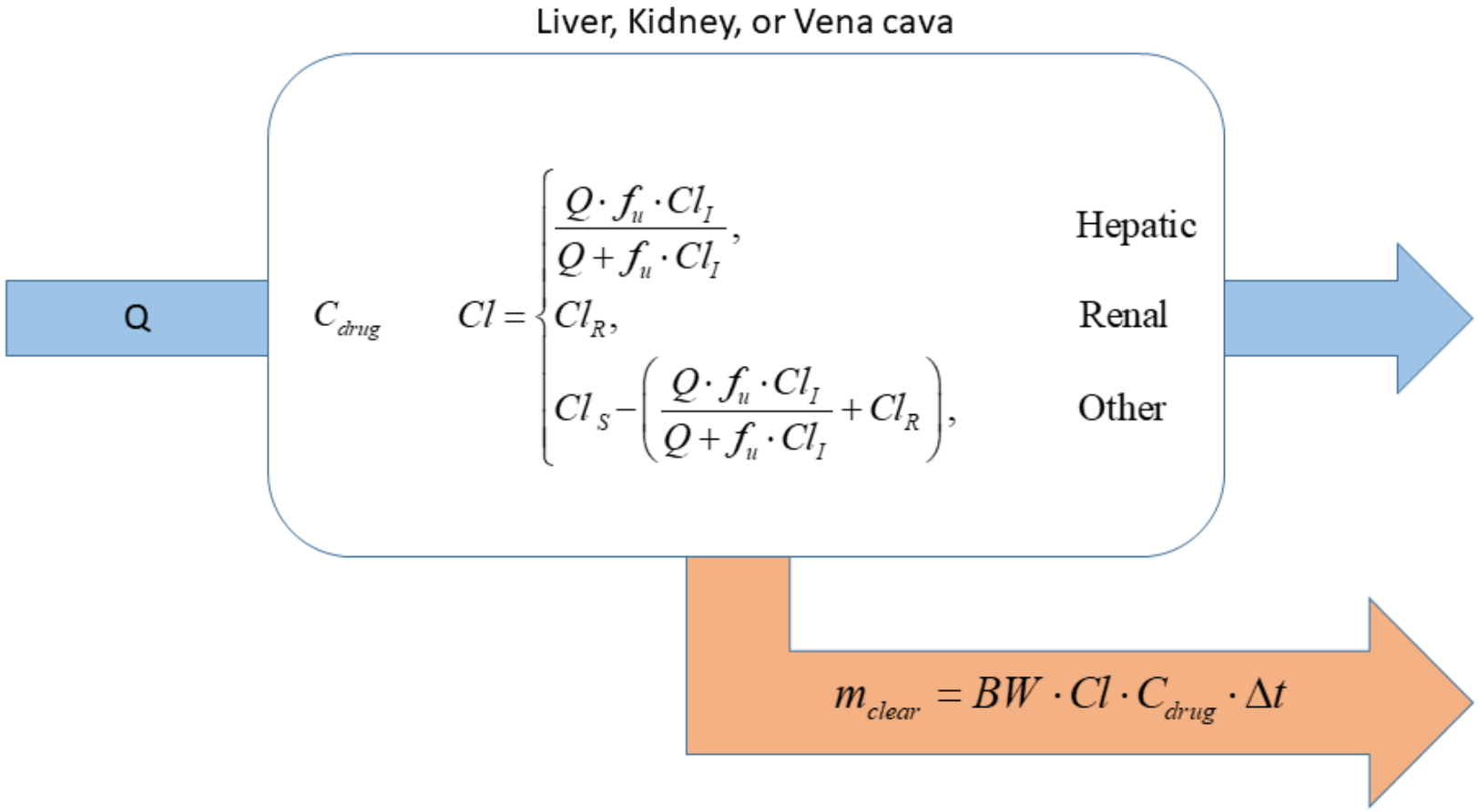
$$K_{TB} = \frac{f_u}{\lambda_{BP}}\left[f_{EW} + \frac{X \cdot f_{IW}}{Y} + \frac{P \cdot f_{NL} + (0.3P + 0.7) f_{NP}}{Y} + K_{Bind}\left(\frac{1}{f_u} - 1 - \left(\frac{P \cdot f_{NL} + (0.3P + 0.7) f_{NP}}{Y} \right) \right) \right]$$

$$X = \begin{cases} 1+10^{pH_{IW} - pK_a} & \text{Acid} \\ 1+10^{pK_a - pH_{IW}} & \text{Weak base} \\ 1 & \text{Neutral} \end{cases} \qquad Y = \begin{cases} 1+10^{pH_P - pK_a} & \text{Acid} \\ 1+10^{pK_a - pH_P} & \text{Weak base} \\ 1 & \text{Neutral} \end{cases}$$

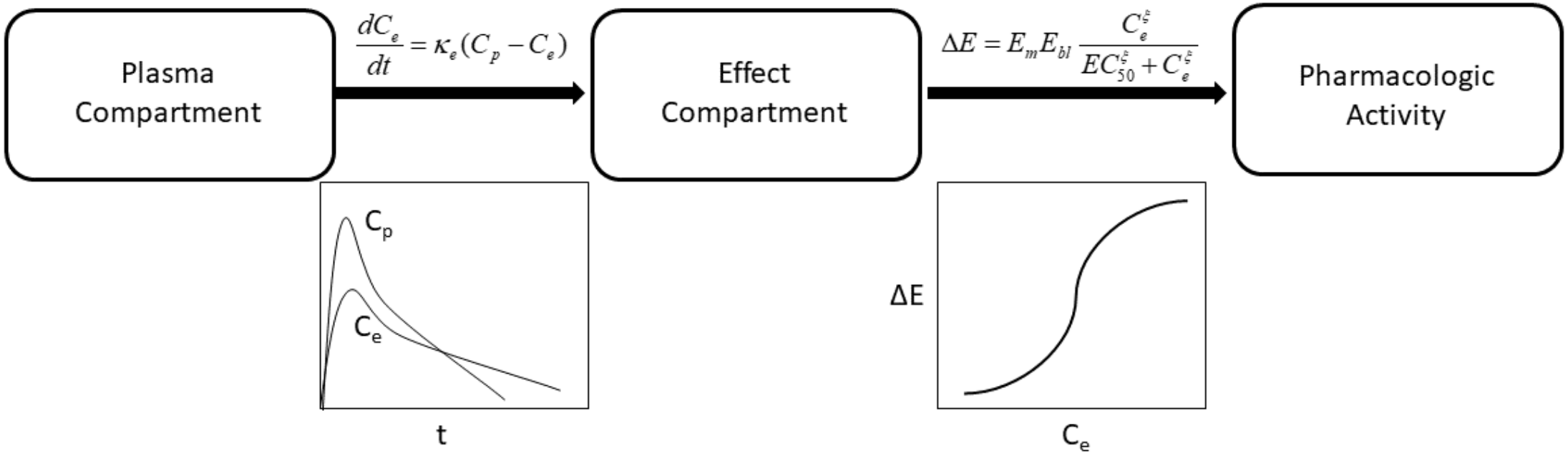
Methods: Clearance

Cl_I, Cl_R, Cl_S, and f_u defined in substance schema and are:

- Hepatic
- Renal
- Systemic
- Fraction unbound in plasma



Methods: Pharmacodynamics

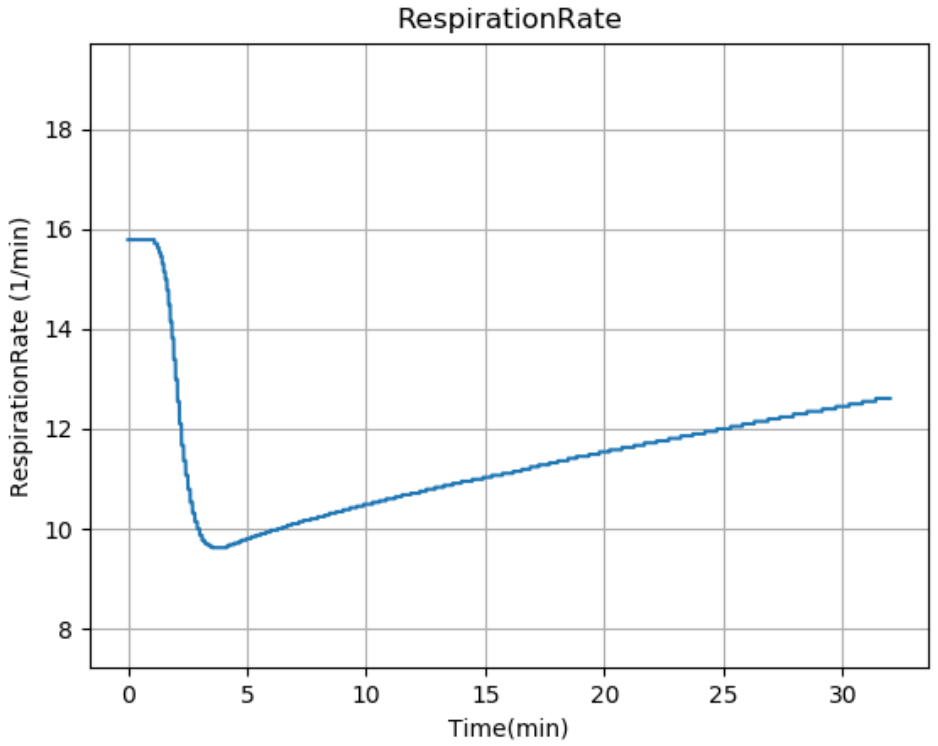


Methods

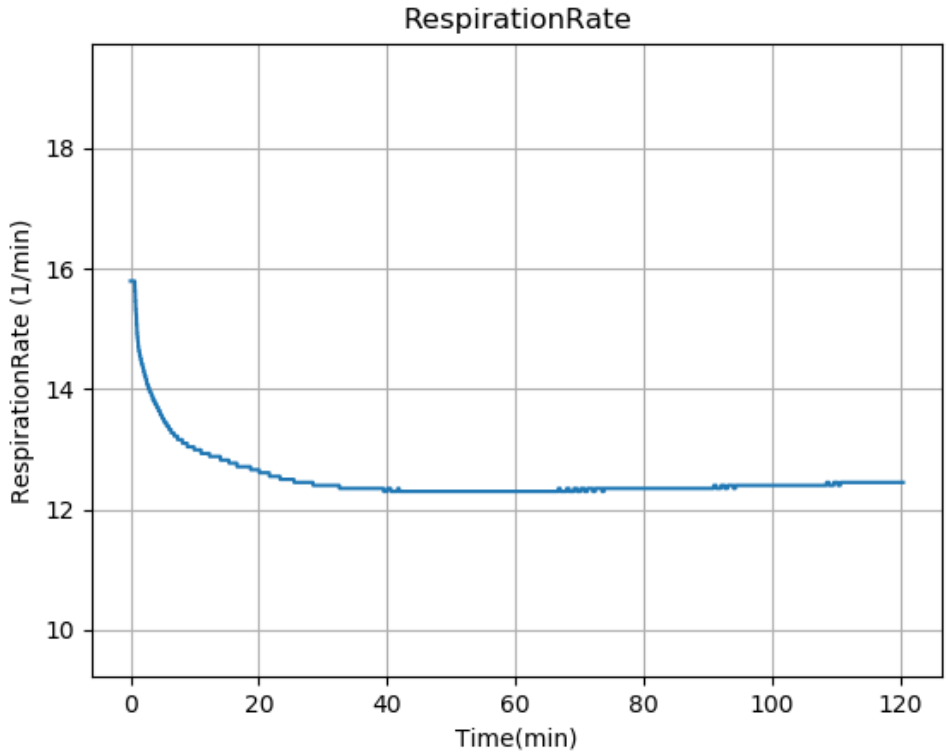
Consequences of effect compartment

- Example: More rapid onset/offset of Fentanyl compared to Morphine

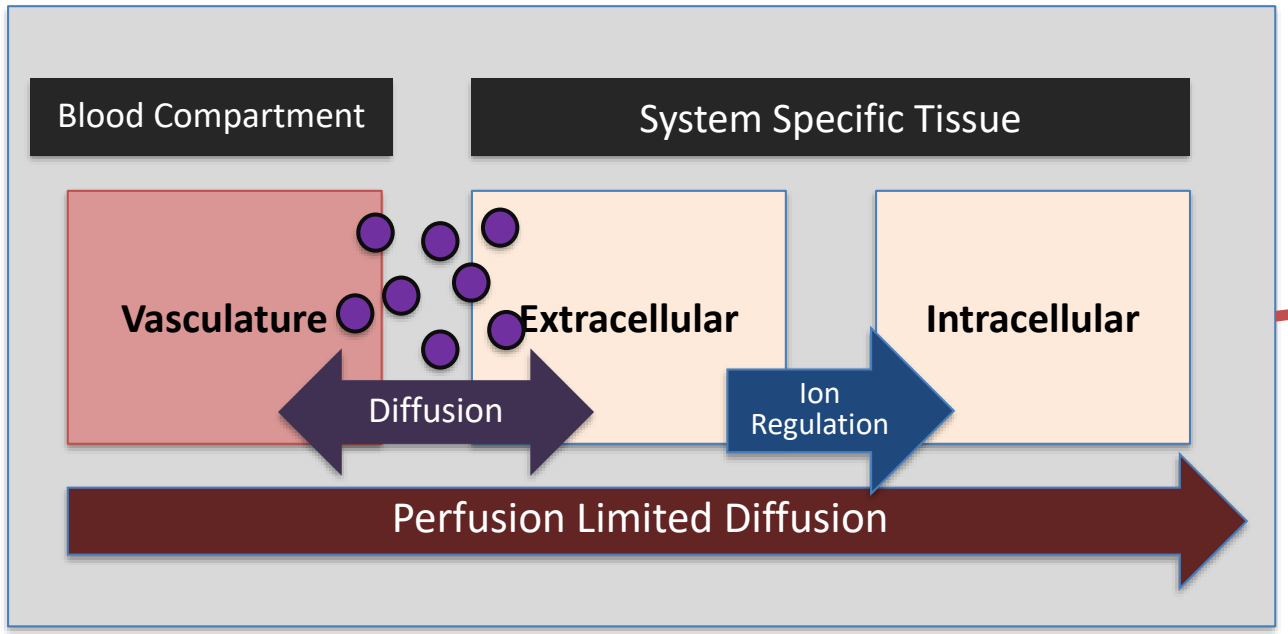
Fentanyl



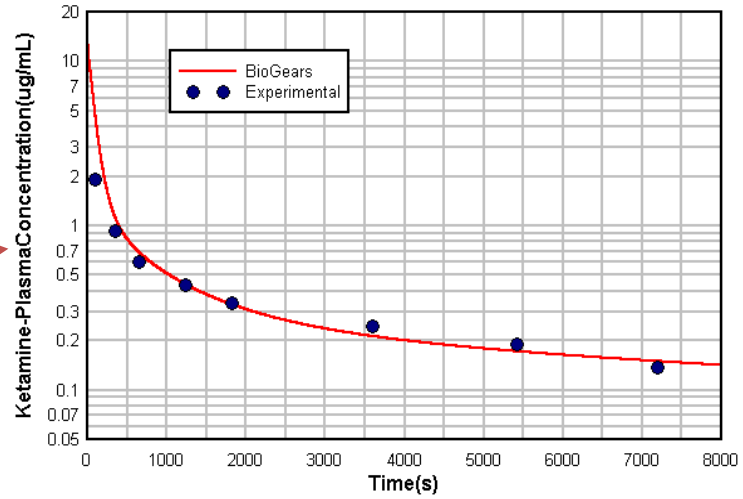
Morphine

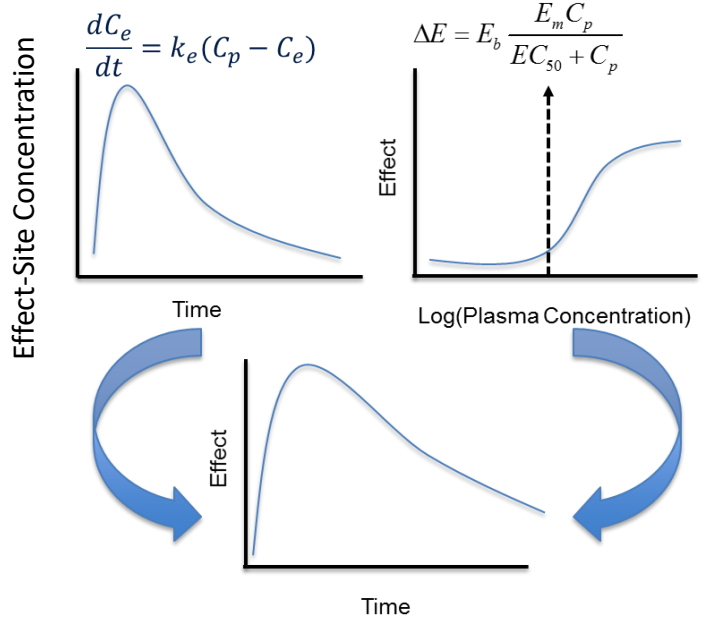


Methods



4 hour Plasma Concentration Curve





PK

- Perfusion-limited diffusion

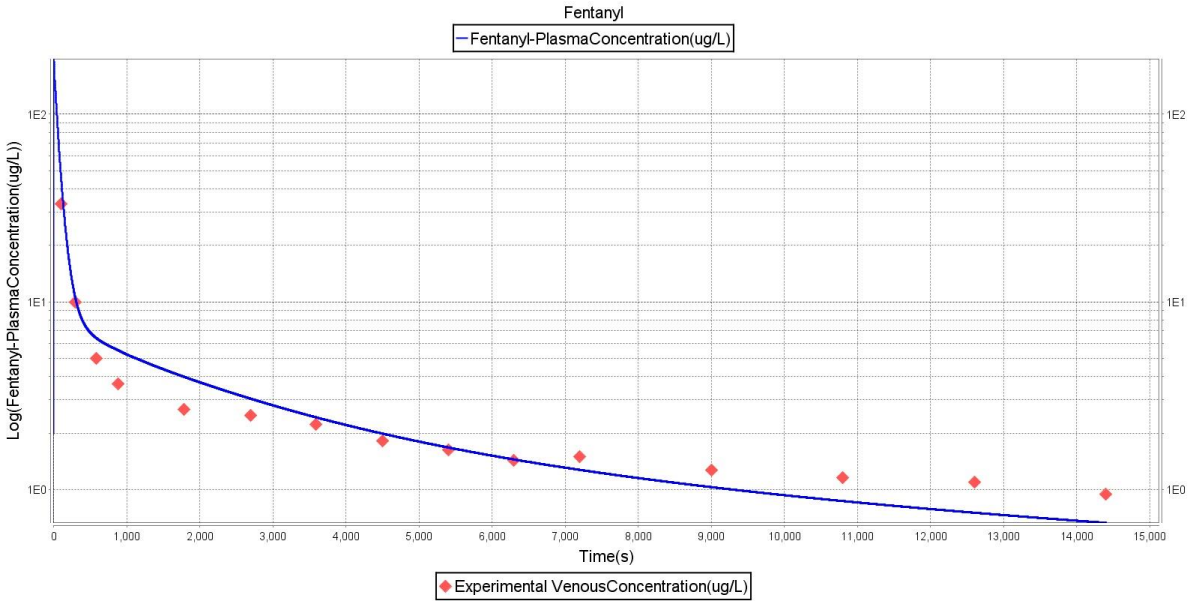
- Physiochemical properties used to calculate partition coefficients, K_p
- ***Or*** partition coefficient can be an input
- Renal, Hepatic, and Systemic Clearance

PD

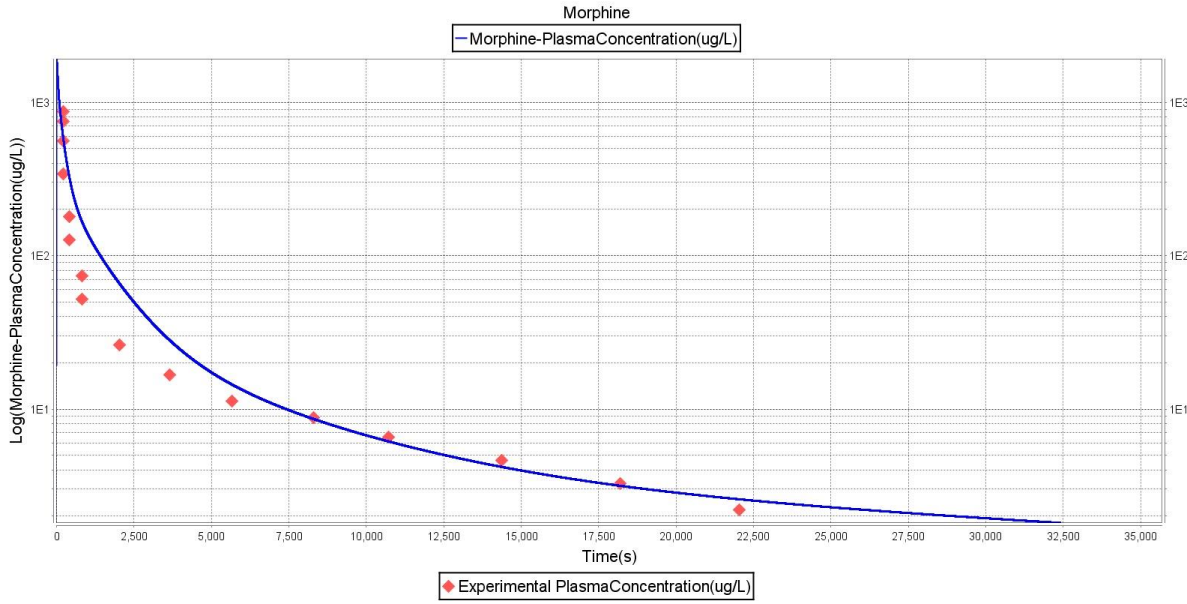
- Patient Physiological response is governed by the saturation of the drug at the "effect-site compartment" within the body
  - The rate constant is specific to the drug

Worked with subcontractor UNC Eshelman School of Pharmacy
Pharmacodynamics also validated through scenario validation
All drugs validated in this manor

Fentanyl-Bolus



Morphine-Bolus



Investigate vasopressin during a severe hemorrhage scenario

RESULTS

Substance Test Case

Vasopressin

- Endogenously produced hormone
- Pharmacological implications for multiple systems
  - Cardiovascular
  - Renal
- Exogenous administration in multiple shock states
  - Distributive shock (e.g. sepsis)
  - Hypovolemic shock

```
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    <Systemic>
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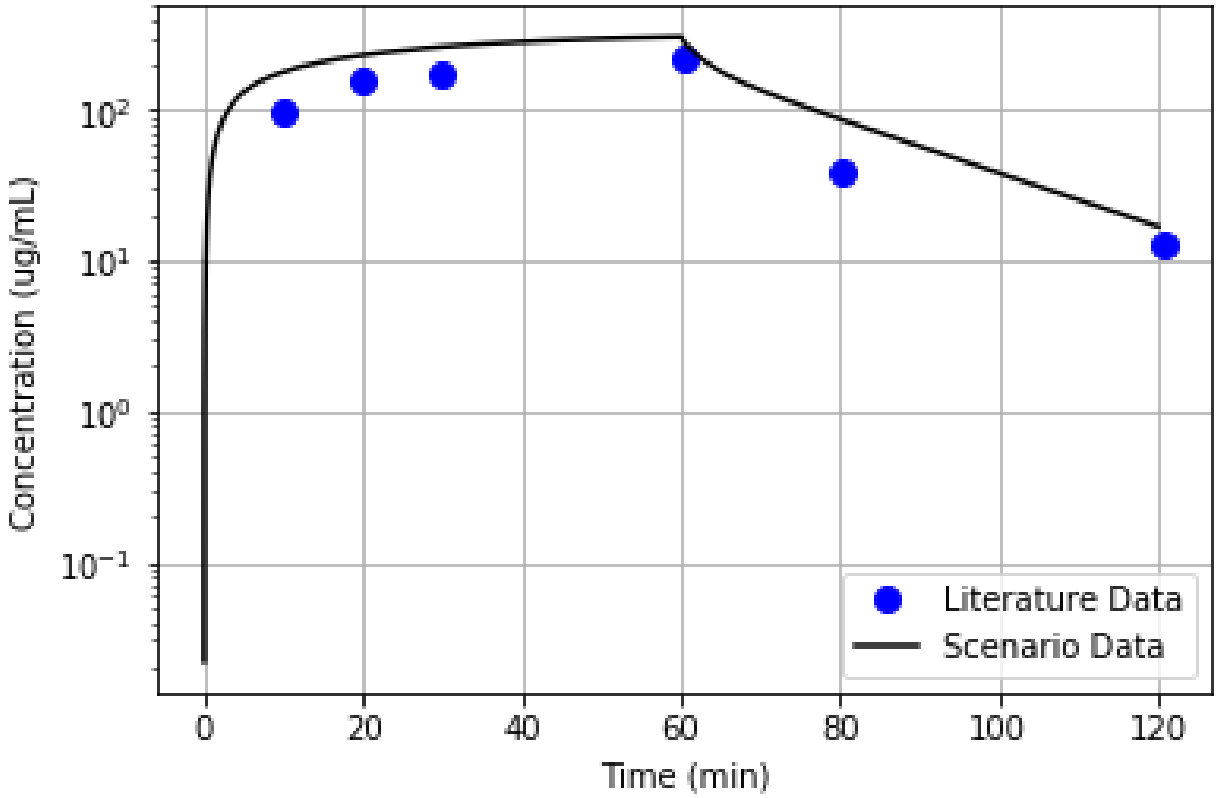
Pharmacokinetic Validation, Part 1

Scenario Definition

- Modeled after Glanzer, 1982
- Study design
  - Male volunteers
  - Intravenous vasopressin infusion
    - Rate: 160 pmol/min (0.174 µg/min)
    - Length: 60 min
  - Post-infusion observation
    - Length: 60 min



Scenario Background

Vasopressin as hemorrhagic shock therapeutic

- Rationale
  - Blood pressure support in the case of catecholamine-resistant shock (Beloncle, 2013)
  - Splanchnic vasoconstriction could improve vital organ perfusion (Beloncle, 2013)
    - Decreased fluid requirements during resuscitation
    - Lower risk of tissue edema
  - Some success in animal studies (Voelckel, 2003; Ready et al, 1991)

Controlled clinical studies provide sparse data

- Vasopressin in Traumatic Shock (VITRIS) Study (Cohn et al, 2010)
  - Exploratory, not enough participants enrolled
- University Hospital in San Antonio (Cohn et al, 2011)
  - Treatment: 0.2 Unit/min vasopressin
  - Placebo: Saline
  - Conclusion: Patients in vasopressin group required fewer fluids but no difference in 30-day mortality found
  - No patient metrics recorded

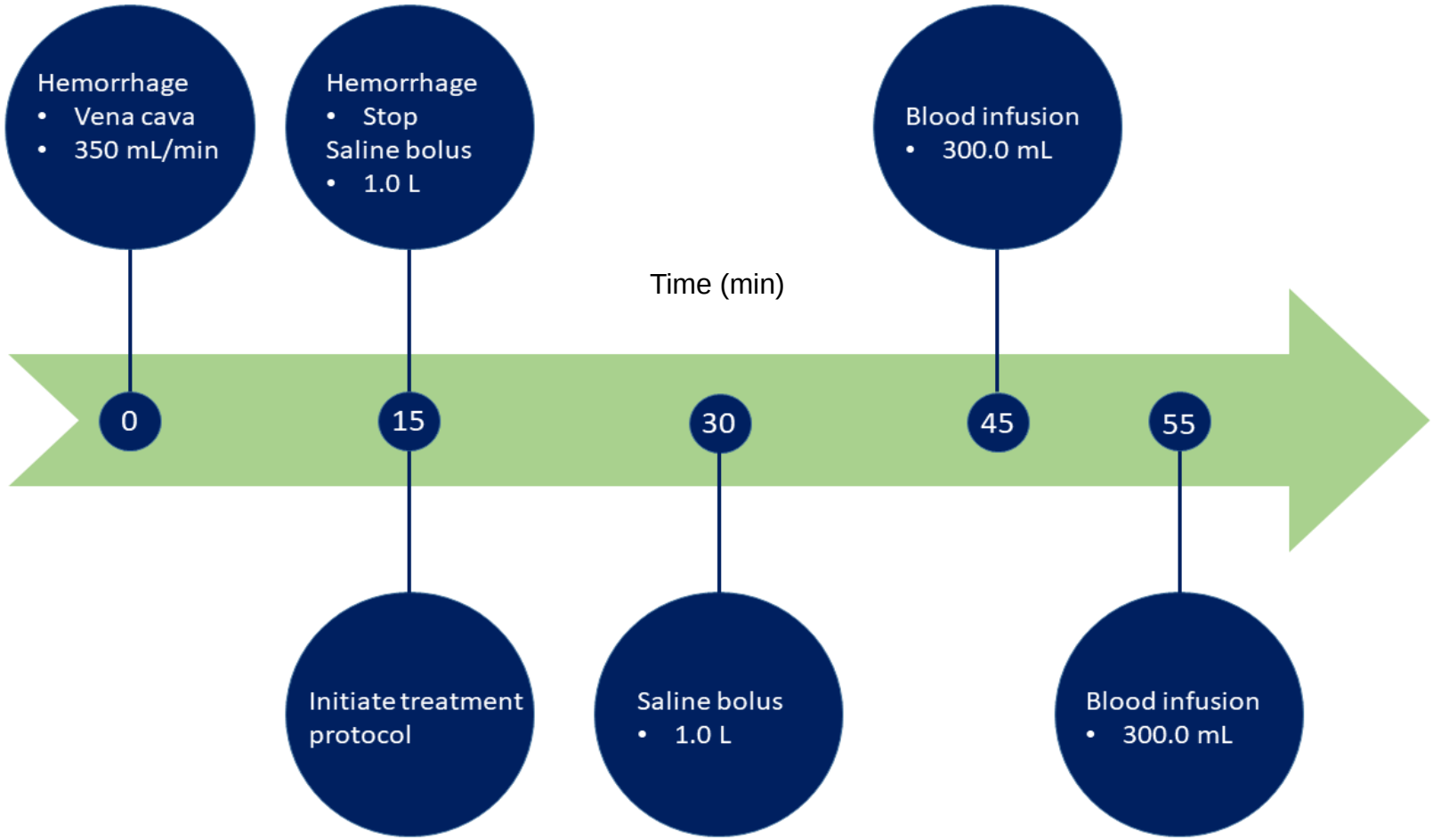
Case for BioGears

- Results from *in silico* experiments can provide direction for future studies
- Tool for medical training

BioGears Vasopressin Treatment Scenario

Treatment protocols similar to Cohn et al, 2011

- 0.5 mL / min saline (control)
- 1 Unit / min vasopressin (1 U = 2.5 µg)
  - Administered at same volumetric rate as control



Complex Scenario: Results

Treatment protocols similar to Cohn et al, 2011

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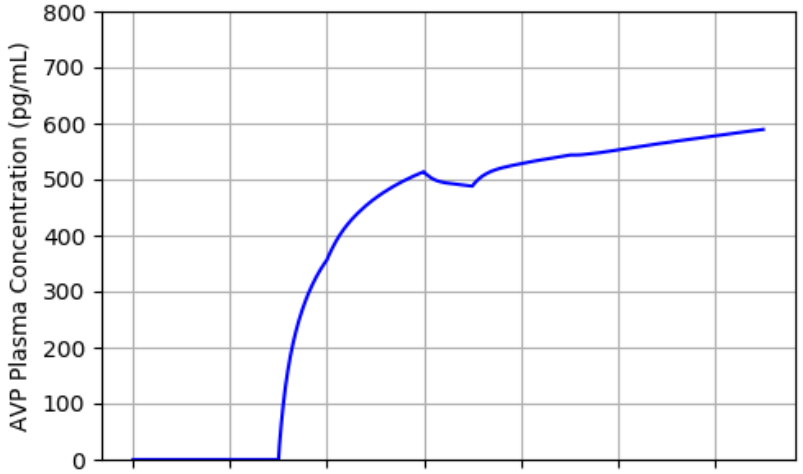

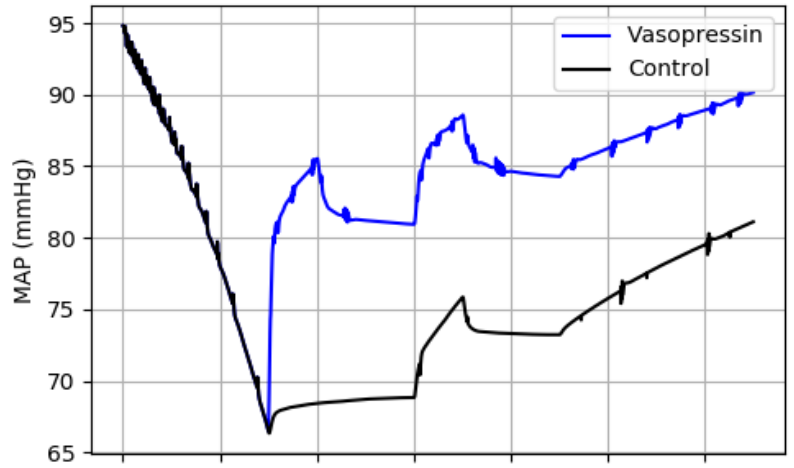

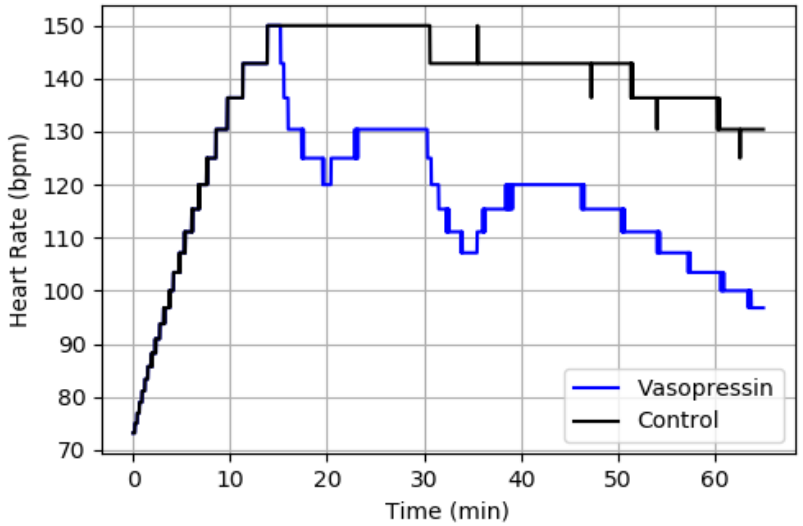

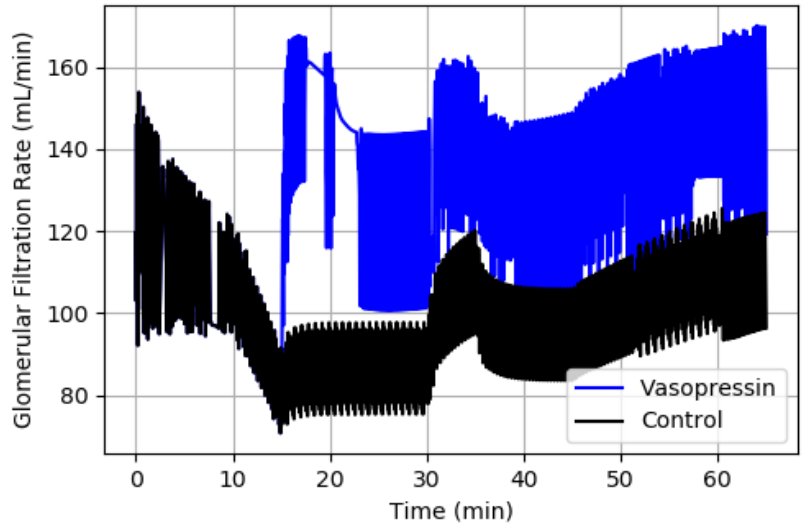

Complex Scenario: Comments

Pre-treatment

- BioGears captures feedback responses to massive blood loss
  - Baroreceptor-mediated increase in heart rate
  - Decrease in glomerular filtration (and urine output)

Treatment

- Less fluid required to achieve MAP increase
- Tachycardia reversal
- Increased urine output indicative of end-organ perfusion

Possible improvements

- Baroreceptor decompensation (Foex, 1999)
- Site-of-action pharmacodynamics
  - Vasopressin-mediated vasoconstriction occurs mainly in liver, smooth muscle, and peripheral tissue (Ready, 1991)

Conclusions: BioGears PK/PD System

Current Capabilities

- Whole-body, physiologically-based pharmacokinetic model
- Wide range of pharmacologic effects with potential for delayed-onset
- Multiple routes of administration
- Extendable to new drugs
- Integration with BioGears Physiology Engine promotes simulation of complex medical training scenarios
- Graphical User Interface (GUI) removes coding burden from users
- Ability to create simulated clinical studies and treatment protocols

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