Supplementary Materials – Tables and User Interface

Table S1: BioGears Substance Library

Substance	Class	Substance	Class
Carbon dioxide	Gas	Furosemide	Drug
Carbon monoxide	Gas	Ketamine	Drug/Anesthetic
Nitrogen	Gas	Midazolam	Drug/Sedative
Oxygen	Gas	Morphine	Drug/Opioid
Bicarbonate	Electrolyte	Naloxone	Drug
Calcium	Electrolyte	Norepinephrine	Drug
Chloride	Electrolyte	Pralidoxime	Drug
Potassium	Electrolyte	Prednisone	Drug
Sodium	Electrolyte	Propofol	Drug/Anesthetic
Epinephrine	Hormone/Drug	Rocuronium	Drug/Anesthetic
Glucagon	Hormone	Sarin	Drug/Inhaled substance
Insulin	Hormone	Succinylcholine	Drug/Anesthetic
AminoAcids	Metabolite	Vasopressin	Drug
Creatinine	Metabolite	Albumin	Protein
Glucose	Metabolite	Globulin	Protein
Ketones	Metabolite	Hemoglobin	Protein
Lactate	Metabolite	Oxyhemoglobin	Bound hemoglobin
Triacylgycerol	Metabolite	Carboxyhemoglobin	Bound hemoglobin
Urea	Metabolite	Carbaminohemoglobin	Bound hemoglobin
Albuterol	Drug/Aerosol	Oxycarbaminohemoglobin	Bound hemoglobin
Desflurane	Drug/Anesthetic	ForestFireParticulate	Inhaled substance
Fentanyl	Drug/Opioid		

Table S2: Pharmacodynamic effect modifiers currently supported by BioGears.

Effect Modifier	Description	Values
Bronchodilation	Decreases (<0) or increases (>0) the bronchi radii. A maximum value of 1.0 will completely reverse asthma attack	-1 to 1
Central Nervous Response	Suppressive effect on mu receptors directing chemoreceptor response (i.e. opioid action), with 1.0 being complete supression	0 to 1
Diastolic Pressure	Fractional change in diastolic pressure	-1 to 1
Heart Rate	Fractional change in heart rate	-1 to 1
Neuromuscular Block	Strength of neuromuscular blocking agent, with 1.0 being strongest block	0 to 1
Pupil Size	Change in pupil diameter	-1 to 1
Pupil Reactivity	Change in pupil reactivity to light	-1 to 1
Respiration Rate	Fractional change in respiration rate	-1 to 1
Sedation	Strength as sedative, with 1.0 being the strongest effect	0 to 1
Systolic Pressure	Fractional change in systolic pressure	-1 to 1
Tidal Volume	Fractional change in tidal volume	-1 to 1
Tubular Permeability	Severity of reabsorption block in renal tubules, with 1.0 being complete block. A value of -1.0 increases the permeability by a factor of two.	-1 to 1

Table S3: Additional optional substance parameters. Parameter names are written exactly as they appear in the substance schema. If the parameter is a sub-element of a complex schema type, the parent node is noted.

Parameter	Description	Parent Node
Density	Standard definition	None
MaximumDiffusionFlux	Signals BioGears Tissue system to transport substance by facilitated diffusion. This is maximum rate that a substance can be transferred by facilitated diffusion	None
MichaelisCoefficient	Faciliated diffusion occurs according to Michaelis kinetics. This parameter is required if a MaximumDiffusionFlux is defined.	None
MembraneResistance	The tendency of electrolytes (i.e. sodium, potassium) to diffuse across the cell membrane	None
MolarMass	Standard definition	None
RelativeDiffusionCoefficient	Defines tendency of gases to be transported in alveoli (value relative to oxygen)	None
Aerosolizaton	Indicates that substance is an aerosol	None
BronchioleModifier	PD modifier for aerosol effect on bronchioles	Aersolization
InflammationCoefficient	PD modifier for aerosol tendency to inflame lungs	Aerosolization
ParticulateSizeDistribution	Histogram defining aerosol particle sizes to determine where in lungs substance is deposited	Aerosolization
ChargeInBlood	Ion charge	RenalDynamics
FractionUnboundInPlasma	Standard definition (required here for data encapsulation)	RenalDynamics
ReabsorptionRatio	Amount ubstance reabsorbed in kidneys per unit volume water reabsorbed	RenalDynamics
TransportMaximum	The maximu rate of substance transport in the kidneys	RenalDynamics

Table S4: Water and lipid volume fractions and tissue to plasma protein ratios for BioGears compartments. Values are used in the equations of Rodgers and Rowland to predict Tissue:Plasma partition coefficients for substances in each compartment.

Tissue	f_{EW}	f_{IW}	f_{NL}	f_{NP}	**Protein K_{TP}**		
--	--	--	--	--	**Albumin**	**Lipoprotein**	**AAG**
Adipose (Fat)	0.135	0.017	0.853	0.0016	0.049	0.068	0.049
Bone	0.1	0.346	0.017	0.0017	0.100	0.050	0.100
Brain	0.162	0.620	0.039	0.0015	0.048	0.041	0.048
Gut	0.282	0.475	0.038	0.0125	0.158	0.0141	0.158
Kidney	0.273	0.483	0.012	0.2420	0.130	0.137	0.13
Liver	0.161	0.573	0.014	0.2400	0.086	0.161	0.086
Lung	0.336	0.446	0.022	0.0128	0.212	0.168	0.212
Muscle	0.118	0.630	0.010	0.0072	0.064	0.059	0.064
Myocardium	0.320	0.456	0.014	0.0111	0.157	0.160	0.157
Skin	0.382	0.291	0.060	0.0044	0.277	0.096	0.277
Spleen	0.207	0.579	0.0077	0.0113	0.277	0.207	0.277

- f_{EW} = Extracellular water fraction
- f_{IW} = Intracellular water fraction
- f_{NL} = Neutral lipid fraction
- f_{NP} = Neutral phospholipid fraction
- K_{TP} = Tissue:Plasma partition coefficient

Table S5: Tissue:Plasma partition coefficients for Vasopressin predicted by BioGears PK/PD model

Tissue	K_{TP}	Tissue	K_{TP}
Adipose (Fat)	0.1523	Lung (Left and Right)	0.7823
Brain	0.8138	Muscle	0.7461
Bone	0.4432	Myocardium	0.7812
Gut	0.7622	Skin	0.6765
Kidney (Left and Right)	0.7608	Spleen	0.7944
Liver	0.7449		

Model-Code S1: Vasopressin extensible markup language (XML) schema definition.

```
<?xml version="1.0" encoding="UTF-8" standalone="yes"?>
<Substance xmlns="uri:/mil/tatrc/physiology/datamodel"
xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" contentVersion="BioGears_6.3.0-
beta" xsi:schemaLocation="">
    <Name>Vasopressin</Name>
    <MolarMass value="1084.24" unit="g/mol"/>
    <State>Liquid</State>
    <Clearance>
        <Systemic>
            <FractionExcretedInFeces value="0.0"/>
            <FractionUnboundInPlasma value="0.99"/>
            <IntrinsicClearance value="0.0" unit="mL/min kg"/>
            <RenalClearance value="1.13" unit="mL/min kg"/>
            <SystemicClearance value="15.17" unit="mL/min kg"/>
        </Systemic>
        <RenalDynamics>
            <Clearance value="1.13" unit="mL/min kg"/>
        </RenalDynamics>
    </Clearance>
    <Pharmacokinetics>
        <Physicochemicals>
            <AcidDissociationConstant value="9.8"/>
            <BindingProtein>Albumin</BindingProtein>
            <BloodPlasmaRatio value="1.0"/>
            <FractionUnboundInPlasma value="0.99"/>
            <IonicState>Neutral</IonicState>
            <LogP value="-4.8"/>
        </Physicochemicals>
    </Pharmacokinetics>
    <Pharmacodynamics>
        <Bronchodilation value="0.0"/>
        <DiastolicPressureModifier value="0.9"/>
        <EC50 value="0.001" unit="ug/mL"/>
        <EMaxShapeParameter value="1"/>
        <HeartRateModifier value="0.0"/>
        <NeuromuscularBlock value="0.0"/>
        <PupillaryResponse>
            <ReactivityModifier value="0.0"/>
            <SizeModifier value="0.0"/>
        </PupillaryResponse>
        <RespirationRateModifier value="0.0"/>
        <Sedation value="0.0"/>
        <SystolicPressureModifier value="0.9"/>
        <TidalVolumeModifier value="0.0"/>
        <TubularPermeabilityModifier value="-1.0"/>
        <CentralNervousModifier value="0.0"/>
        <EffectSiteRateConstant value="0.0" unit="1/min"/>
    </Pharmacodynamics>
</Substance>
```

Model-Code S2: VasopressinInSaline Substance Compound XML definition. In BioGears, a Substance Compound is defined by a list of components. The concentration of each component in the compound must be explicitly defined. All components must be already defined in the *Substances* folder. We create this particular Substance Compound by copying the definition of the Saline Substance Compound and appending a Vasopressin component.

```
<?xml version="1.0" encoding="UTF-8" standalone="yes"?>
<SubstanceCompound xmlns="uri:/mil/tatrc/physiology/datamodel"
xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" contentVersion="BioGears_6.3.0-beta"
xsi:schemaLocation="">
    <Name>VasopressinInSaline</Name>
    <Component Name="Sodium">
        <Concentration value="0.354" unit="g/dL"/>
    </Component>
    <Component Name="Chloride">
        <Concentration value="0.546" unit="g/dL"/>
    </Component>
    <Component Name="Oxygen">
      <Concentration value="0.0329" unit="g/L"/>
    </Component>
    <Component Name="CarbonDioxide">
      <Concentration value="0.786" unit="g/L"/>
    </Component>
    <Component Name="Vasopressin">
      <Concentration value="1.0" unit="mg/L"/>
      <!--Assuming 200 Units / 500 mL and 2 U = 5 ug-->
    </Component>
</SubstanceCompound>
```

Figure S1: BioGears GUI scenario window defining the cardiovascular pharmacodynamic scenario.

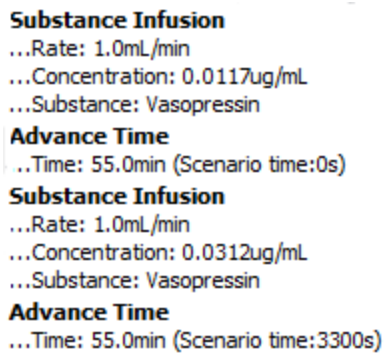

Figure S2: BioGears GUI scenario window defining the renal pharmacodynamic scenario.

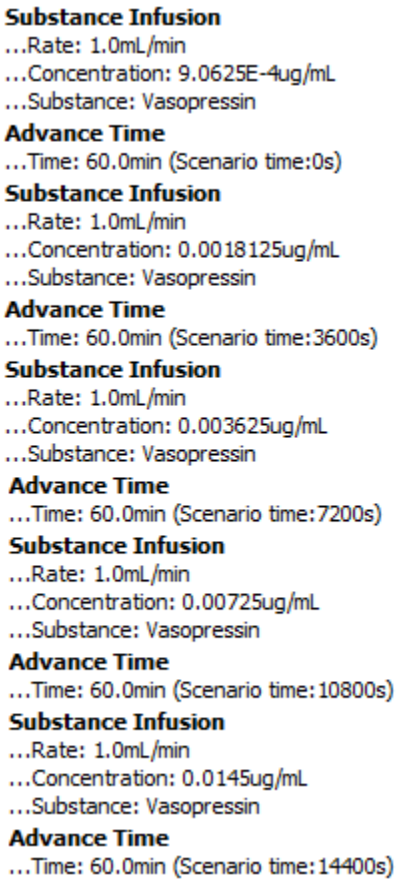

Figure S3: BioGears GUI scenario windows comparing two treatment regimens for resuscitation from massive hemorrhage: saline only (left) and saline with vasopressin (right). The treatments are identical except for the fifth action.

Hemorrhage
...Compartment: VenaCava
...Initial Bleeding Rate: 350.0
...Injury Code: 52660
Advance Time
...Time: 15.0min (Scenario time:0s)
Stop Hemorrhage
...Compartment: VenaCava
Compound Infusion
...Rate: 200.0mL/min
...Bag Volume: 1000.0mL
...Substance Compound: Saline
Compound Infusion
...Rate: 0.5mL/min
...Bag Volume: 500.0mL
...Substance Compound: Saline
Advance Time
...Time: 15.0min (Scenario time:900s)
Compound Infusion
...Rate: 200.0mL/min
...Bag Volume: 1000.0mL
...Substance Compound: Saline
Advance Time
...Time: 15.0min (Scenario time:1800s)
Compound Infusion
...Rate: 30.0mL/min
...Bag Volume: 300.0mL
...Substance Compound: Blood
Advance Time
...Time: 10.0min (Scenario time:2700s)
Compound Infusion
...Rate: 30.0mL/min
...Bag Volume: 300.0mL
...Substance Compound: Blood
Advance Time
...Time: 10.0min (Scenario time:3300s)

Hemorrhage
...Compartment: VenaCava
...Initial Bleeding Rate: 350.0
...Injury Code: 52660
Advance Time
...Time: 15.0min (Scenario time:0s)
Stop Hemorrhage
...Compartment: VenaCava
Compound Infusion
...Rate: 200.0mL/min
...Bag Volume: 1000.0mL
...Substance Compound: Saline
Compound Infusion
...Rate: 0.5mL/min
...Bag Volume: 500.0mL
...Substance Compound: VasopressinInSaline
Advance Time
...Time: 15.0min (Scenario time:900s)
Compound Infusion
...Rate: 200.0mL/min
...Bag Volume: 1000.0mL
...Substance Compound: Saline
Advance Time
...Time: 15.0min (Scenario time:1800s)
Compound Infusion
...Rate: 30.0mL/min
...Bag Volume: 300.0mL
...Substance Compound: Blood
Advance Time
...Time: 10.0min (Scenario time:2700s)
Compound Infusion
...Rate: 30.0mL/min
...Bag Volume: 300.0mL
...Substance Compound: Blood
Advance Time
...Time: 10.0min (Scenario time:3300s)

Additional help build source code form github:

Youtube Link