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PKPD: Transmucosal and Gastrointestinal Absorption

17 March 2020

ARA

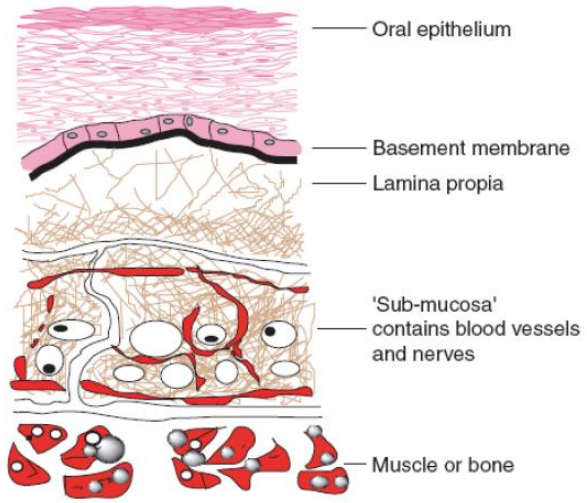
Outline

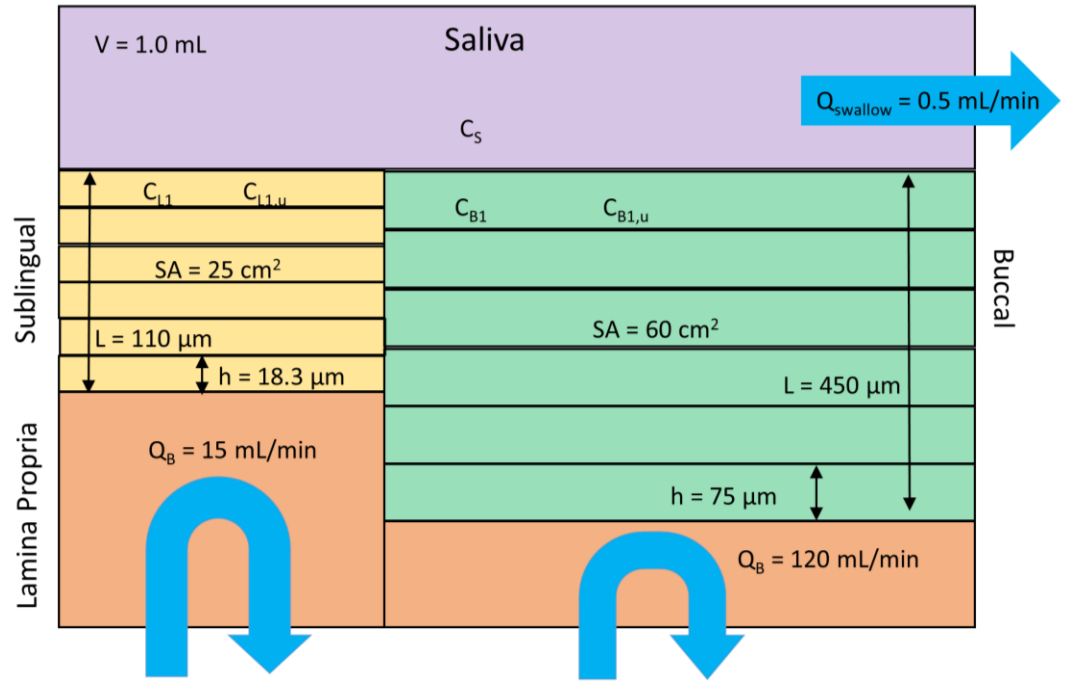
- Background and Motivation
- Oral Transmucosal Model
  - Overview
  - Physicochemical Inputs
  - Demo and Results
- Gastrointestinal Model
  - Overview
  - Model Equations
  - Physicochemical Inputs
  - Demo and Results
- Future Work

Background

- Transmucosal Drug Administration
  - Transmucosal route offers advantages over GI absorption for some drugs
    - Mouth more favorable environment than GI
      - Less acidic than stomach[1]
      - Lower chance of enzymatic degradation[2]
    - More efficient entry to systemic circulation compared to GI
      - Avoid first-pass metabolism[1]
      - Sub-lingual area is rich in capillaries, leading to rapid systemic uptake[2]
  - Oral Transmucosal Fentanyl Citrate (OTFC) as model substance
    - Approved for treatment of break-through cancer pain for opioid-tolerant patients in 1998[3]
    - Added as battlefield analgesia option to Tactical Combat Casualty Care (TCCC) guidelines in 2004[4]
    - 2014 TCCC guidelines recommend OTFC as preferable to morphine in treating moderate to severe pain[4]
      - OTFC has similar analgesic effect as morphine with shorter onset time to relief
      - Does not require IV access to patient
    - For these reasons, Prolonged Field Care project has great interest in an OTFC model
- Gastrointestinal Drug Administration
  - Required for OTFC: Swallowed fentanyl (about 75% of dose[5]) is absorbed in GI[3]
  - Prolonged Field Care Project: Support for orally administered antibiotics
  - Preferred route for many drugs
  - Fills a gap in BioGears PKPD model

OTFC: Model Overview





- Model considers absorption through buccal and sublingual regions
  - Buccal (cheek), sublingual, and top of tongue comprise ~60% of oral mucosal surface area[3]
  - Buccal and sublingual regions are most permeable areas (best target for drug delivery)[3]
  - Two regions preferable because speed of absorption differs due to their disparate thicknesses
- Estimates for buccal and sublingual properties obtained from ranges reported in [2, 6-7]

- Calculate diffusion across layers using central finite difference approximations (six layers considered[6])
- Assumptions
  - Solid drug dissolves according to Nernst-Brunner equation[8-9]
  - Concentration in saliva and unbound concentrations in top layers are in instantaneous equilibrium[6]
  - Partitioning between unbound drug and protein-bound drug occurs in each region[6]
  - Unbound drug is available for diffusion
  - Rate of swallowing is constant
  - Perfusion-limited diffusion between bottom sublingual/lamina and buccal/lamina interfaces

OTFC: Physicochemical Considerations

- Goal: Use physicochemical relationships so that model can be extended to numerous substances
- Reality: Tune parameters where necessary to achieve satisfactory fentanyl pharmacokinetics

- Drug dissolution in saliva
  - General Nernst-Brunner equation[9,8]: $\frac{dm_{dis}}{dt} = \frac{SA(t) \cdot D_{sal}}{\delta} \cdot \left(Sol - \frac{m_{dis}(t)}{V_{saliva}}\right)$
  - Simplification for spherical particles[19,11,Parrot]: $\frac{dm_{dis}}{dt} = \frac{3 \cdot m_s(t) \cdot D_{sal}}{r \cdot \rho \cdot \delta} \cdot \left(Sol - \frac{m_{dis}(t)}{V_{saliva}}\right)$
    - Assumes that particle radius is constant during dissolution process
  - Estimate for diffusion coefficient[19] : $D_{sal} = (9.9 \cdot 10^{-5}) \cdot MW^{-0.453}$

- Drug diffusion through mucosa[6]
  - $D_{muc} = \begin{cases} 10^{-0.08023 \cdot (logD)^2 + 0.5006 \cdot logD - 6.7316} & logD \leq 3 \\ 10^{-5.9514} & logD > 3 \end{cases}$

- Saliva : Epithelium partition coefficient[6]
  - $K = 2.12 \cdot e^{0.523 \cdot logD}$

Symbol	Unit	Value	Description
State Variables			
m_{dis}	ug	--	Dissolved drug mass
SA	cm^2	--	Surface area
m_s	ug	--	Remaining solid drug mass
Physicochemical Parameters (Fentanyl)			
Sol	ug/mL	200	Solubility coefficient[10]
logD	--	4.05	Log of distribution coefficient at pH = 7.4[12]
MW	g/mol	336.5	Molecular weight
ρ	ug/mL	1.1×10^6	Drug density[10]
Parameters Derived from Physicochemical Data			
D_{muc}	cm^2/s	1.1×10^{-6}	Diffusion coefficient in mucosa
K_P	--	19	Saliva : Epithelium Partition
Tuned Parameters			
D_{sal}	cm^2/s	8.0×10^{-6}	Diffusion coefficient in saliva
r	cm	5.0×10^{-4}	Particle radius[11]
δ	cm	3.0×10^{-3}	Diffusion layer thickness[11]
V_{sal}	mL	1.0	Volume of saliva[6]

Demo: OTFC Action Initiation

- Transmucosal drug administration utilizes the BioGears *SubstanceOralDose* action
- Demonstration: 800 µg dose of OTFC
  - Recommended dose in TCCC guidelines[4]

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      <Dose value="800" unit="ug"/>
</Action>
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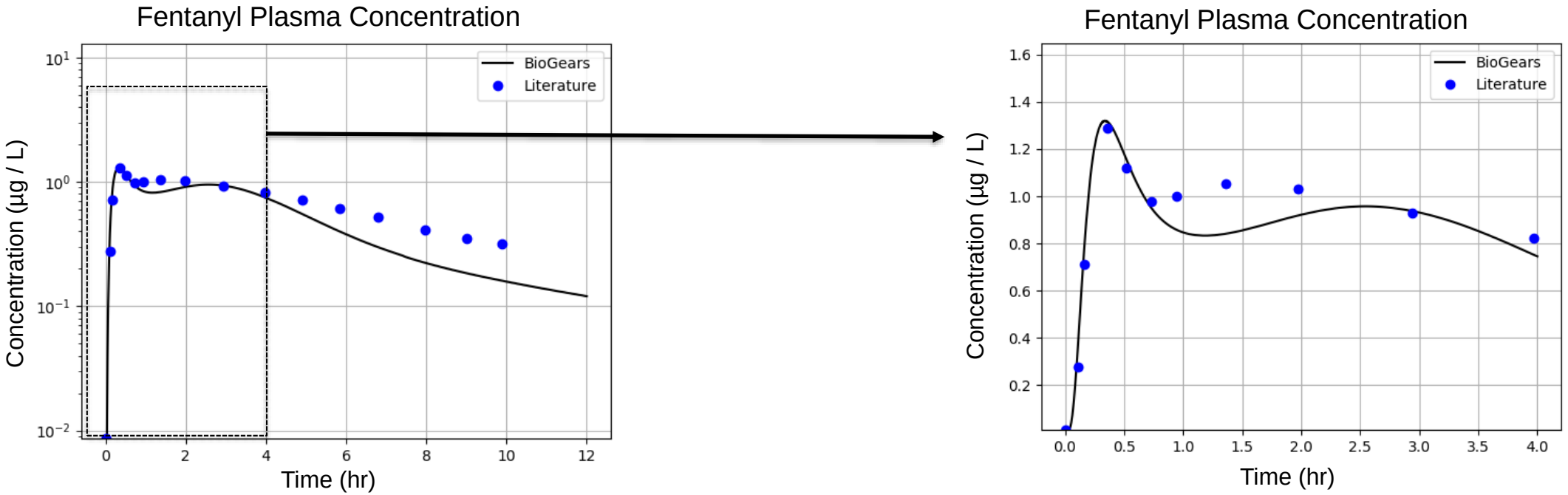
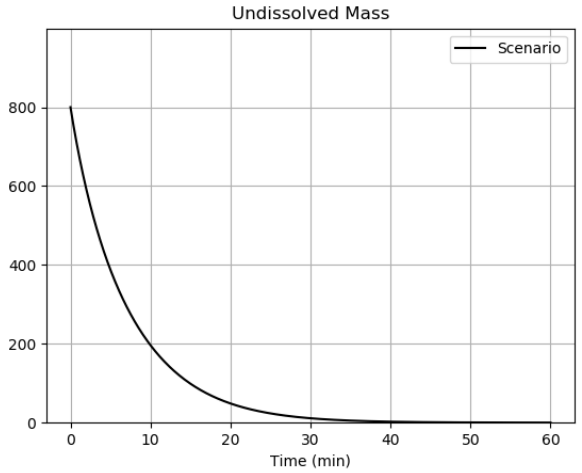
Demo: OTFC Results

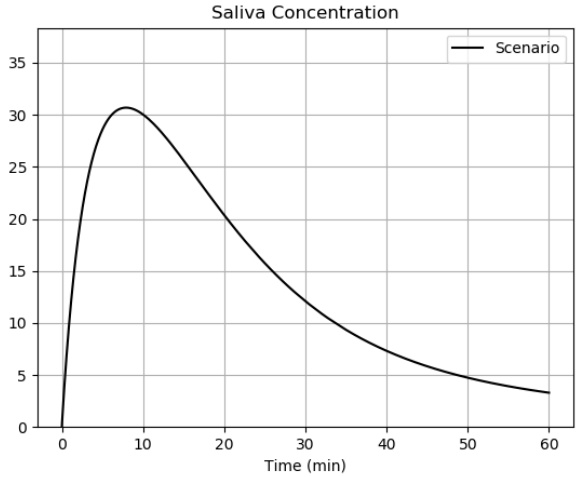


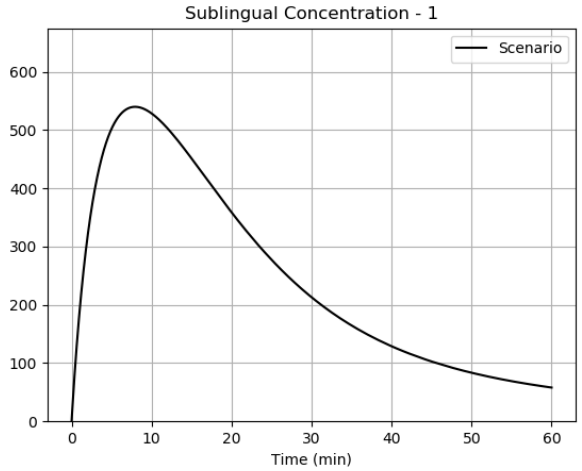
- Literature data obtained from [20]
- Observations
  - Characterizes C_{max} and T_{max} well
  - Captures existence of a second local maximum stemming from gastrointestinal absorption of swallowed fentanyl
  - Timing of second peak is delayed—absorption of fentanyl in GI is slower than expected

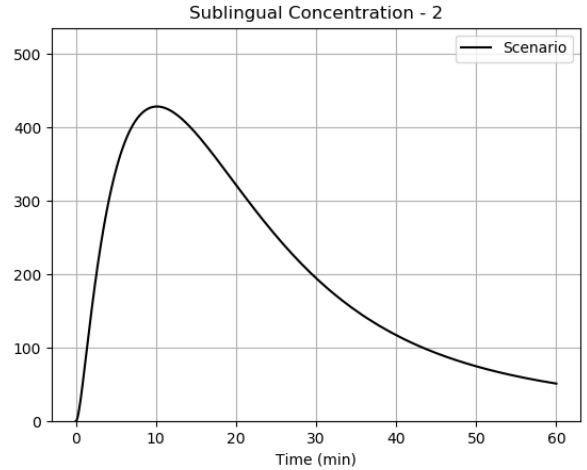
OTFC: Demo Results

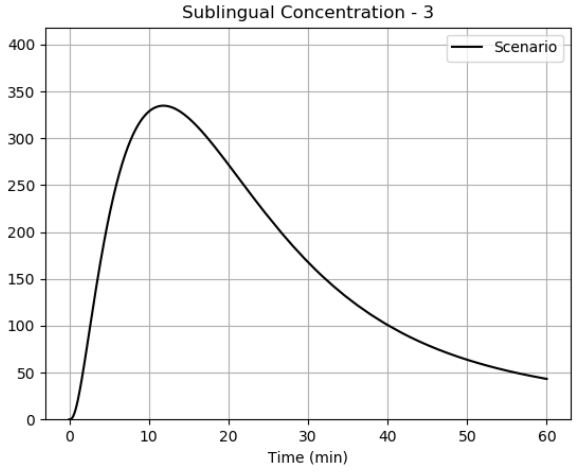
- Solid fentanyl dissolves in about 30 min (about 2x that reported in some studies)[21]
- Saliva concentration peaks in <10 min
- Diffusion wave through sublingual and buccal (next slide) mucosa clearly visible

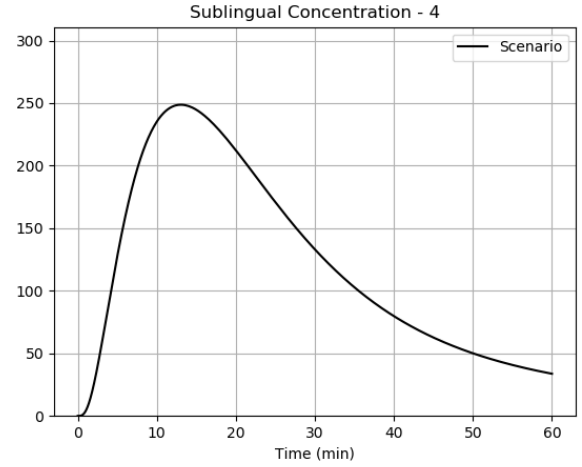


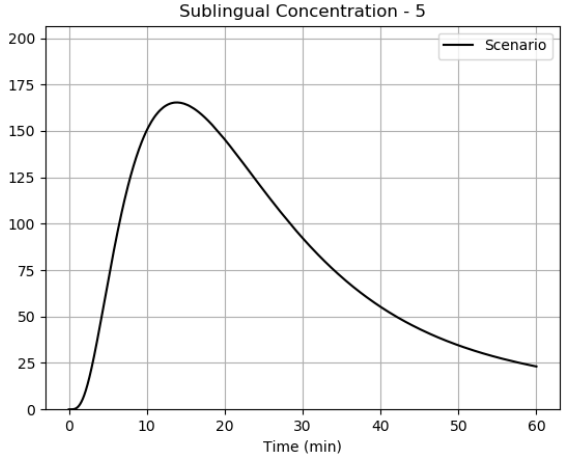


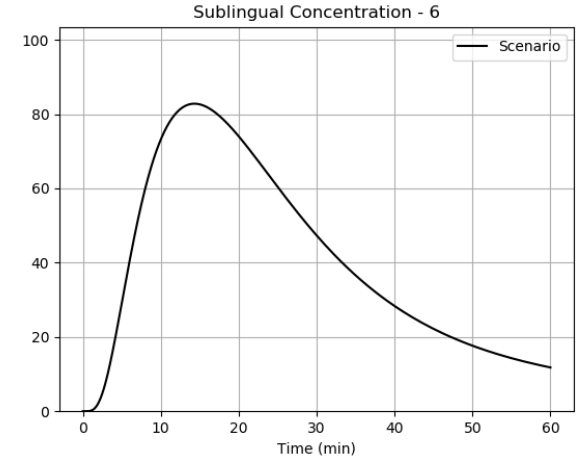




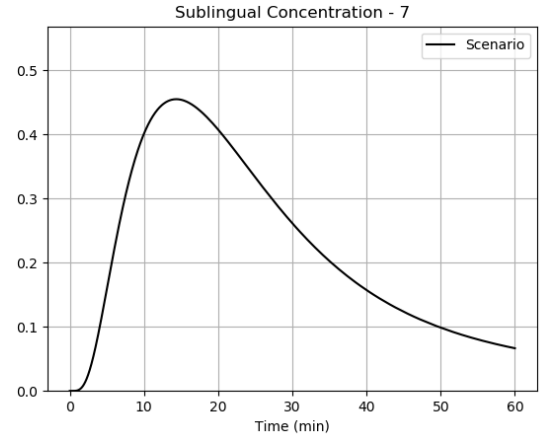


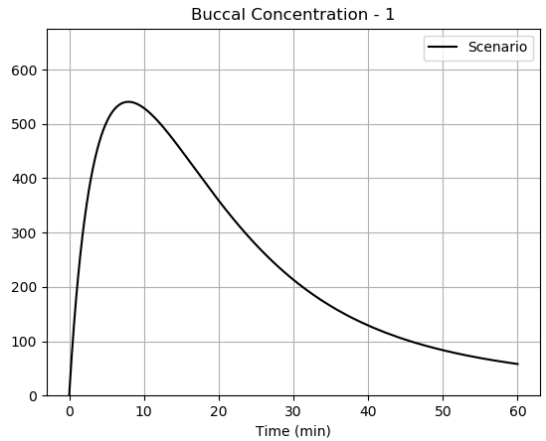


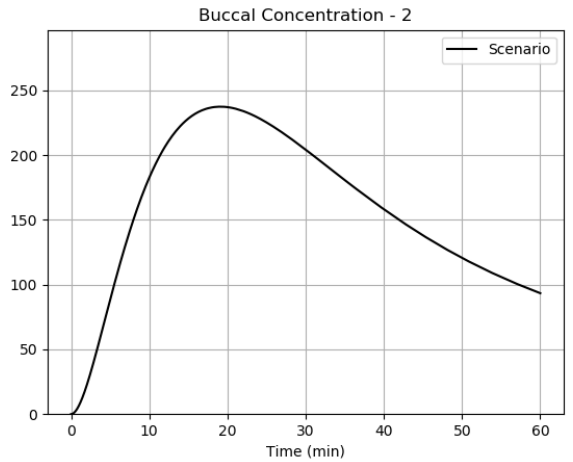


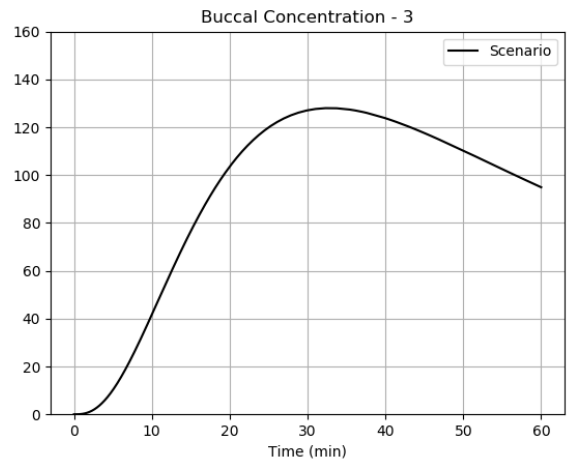


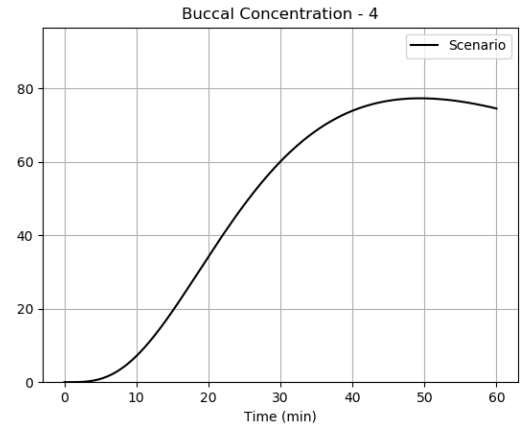
OTFC: Demo Results

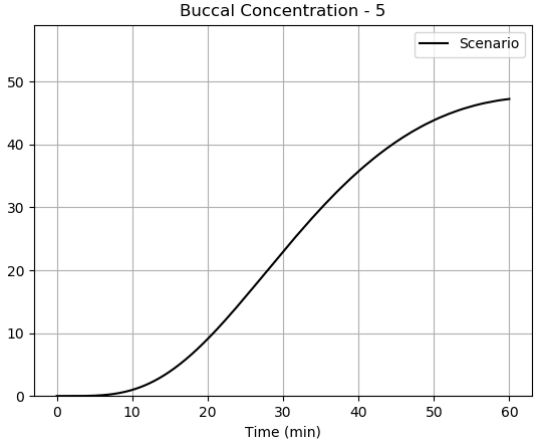


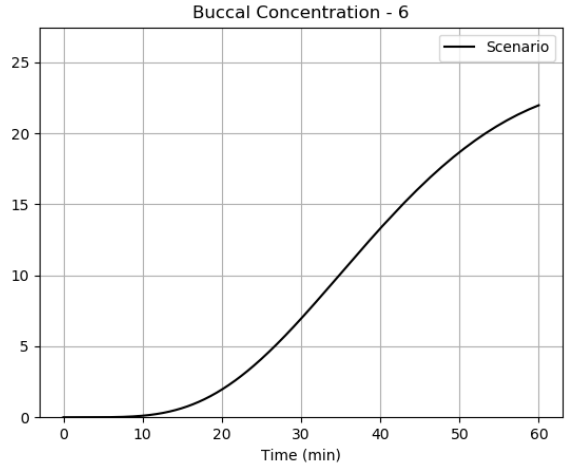


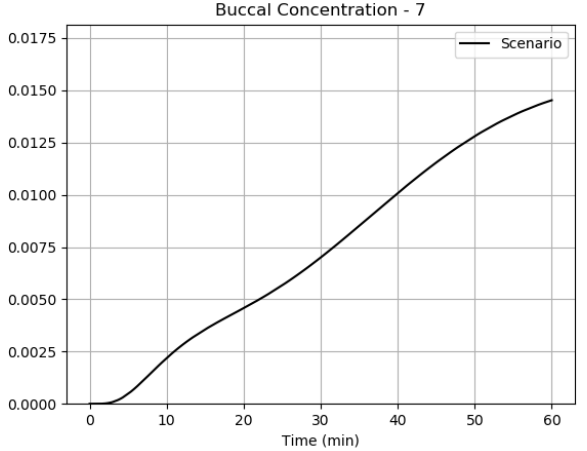






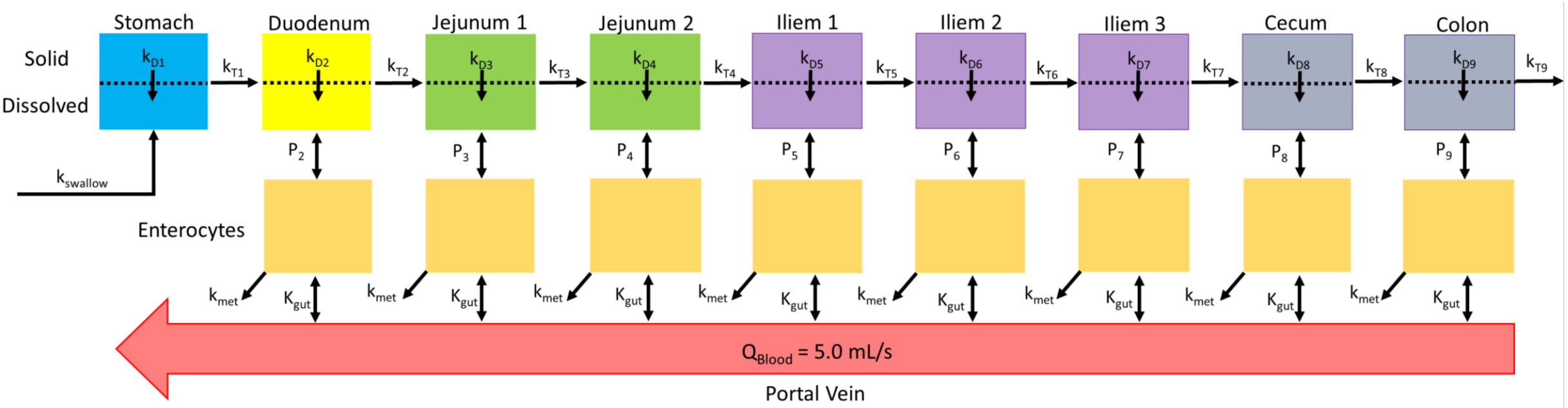






GI Absorption: Model Overview

- Advanced Compartment and Transit (ACAT) model based on [11,13-14]
- Assumptions
  - Solid formulations enter in solid portion of stomach compartment
  - Swallowed transmucosal drug enters in dissolved portion of stomach compartment
  - Transit constants (k_{TN}) are identical for solid and dissolved portions
  - Some drug is metabolized in the enterocyte layer of the intestines
  - Perfusion-limited diffusion between enterocyte layer and portal vein according to gut partition coefficient calculated by BioGears



GI Absorption: Equations

- Mass balance for the n^{th} compartment

Solid Drug		
Influx	$k_{T,n-1}m_{s,n-1}$	Note: Stomach has no influx term. Initial solid mass in stomach set to value of dose for oral drug admin
Dissolution	$-\frac{3 \cdot m_{n,s} \cdot D_{sal}}{r \cdot \rho \cdot \delta} \cdot \left(Sol - \frac{m_{d,n}}{V_n}\right)$	Note: m_s = solid drug mass, m_d = dissolved drug mass
Efflux to next compartment	$-k_{T,n}m_{s,n}$	

Dissolved Drug		
Influx	$k_{T,n-1}m_{d,n-1}$	Note: Stomach influx term is $k_{swallow}m_{swallow}$ when transmucosal drug given, else 0
Dissolution	$\frac{3 \cdot m_{n,s} \cdot D_{sal}}{r \cdot \rho \cdot \delta} \cdot \left(Sol - \frac{m_{d,n}}{V_n}\right)$	
Efflux to next compartment	$-k_{T,n}m_{d,n}$	
Efflux to enterocyte	$-P_n \cdot SA \cdot f_u \cdot \left(\frac{m_{d,n}}{V_n} - \frac{m_{e,n}}{V_{e,n}}\right)$	Note: f_u = fraction of drug that is un-ionized, $m_{e,n}$ = mass in enterocyte layer

Enterocyte Layer		
Influx from compartment	$P_n \cdot SA \cdot f_u \cdot \left(\frac{m_{d,n}}{V_n} - \frac{m_{e,n}}{V_{e,n}}\right)$	
Metabolism	$-k_{met}m_{e,n}$	
Efflux to portal vein	$-f_B \cdot Q_B \cdot \left(\frac{1}{K_{gut}} \cdot \frac{m_{e,n}}{V_{e,n}} - C_{portal}\right)$	Note: f_B = fraction of total villous blood flow that goes to n^{th} compartment. Assumed to be 1/8 (that is, equally distributed flow to all 8 enterocyte compartments)

Parameter Values: Transit constants ($k_{T,n}$), surface areas (SA), compartment volumes (V_n) and enterocyte volumes (V_e) as in [11]

GI Absorptions: Physicochemical Considerations

- Fraction Un-ionized[15]
  - Base: $f_{u,base} = \frac{1}{1+10^{pKa-pH}}$
  - Acid: $f_{u,acid} = \frac{1}{1+10^{pH-pKa}}$
  - Zwitterion: Requires information regarding substance microconstants (See [16-17] for procedure regarding Moxifloxacin)
  - pH estimate for each intestinal segment obtained from [11]

- Effective Permeability (P_n)[15]

$$P_n = (3.67 \cdot 10^{-5})logP + (3.45 \cdot 10^{-5})f_u - (1.04 \cdot 10^{-7})MW - (5.48 \cdot 10^{-6})H - (3.67 \cdot 10^{-5})PSA + 1.46 \cdot 10^{-4}$$

  - H = Hydrogen bond count
  - PSA = Polar surface area

- Solubility
  - Set to substance value in water
  - Plan to incorporate pH and bile salt effects in future release (See [11,18-19])

- Metabolism
  - Tuned for fentanyl to improve plasma profile
  - Set to 0 for other substances until values can be determined (if necessary)

Demo: Action Initiation

- Like Transmucosal action, Gastrointestinal drug administration utilizes the BioGears *SubstanceOralDose*
- Demonstration: Moxifloxacin 400 mg
  - Chosen because MFX was a model substance during infection and antibiotic model development

```
<Action xsi:type="SubstanceOralDoseData" AdminRoute=“Gastrointestinal“>
      <Substance>Moxifloxacin</Substance>
      <Dose value=“400" unit=“mg"/>
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```
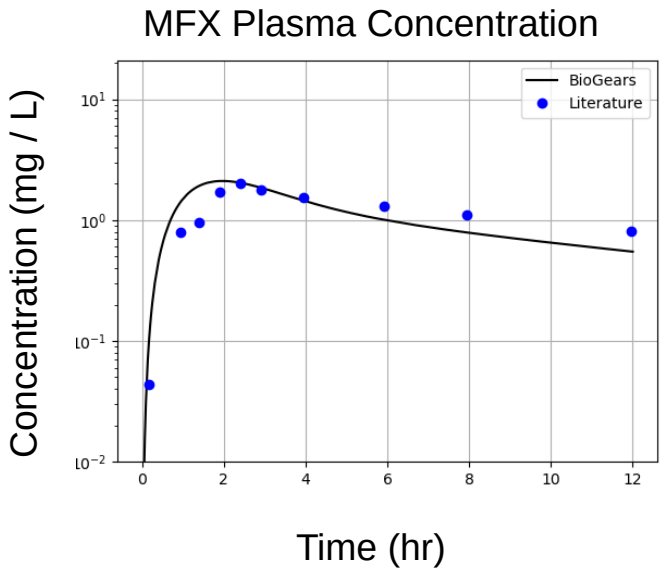
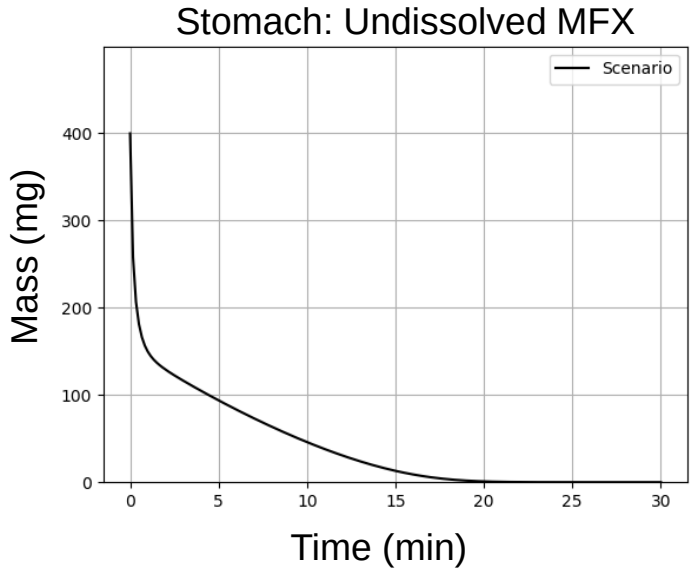
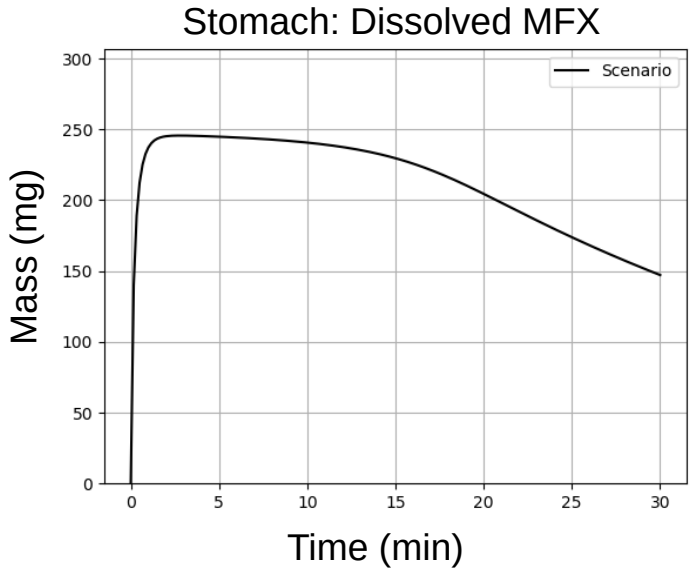

Moxifloxacin: Demo Results





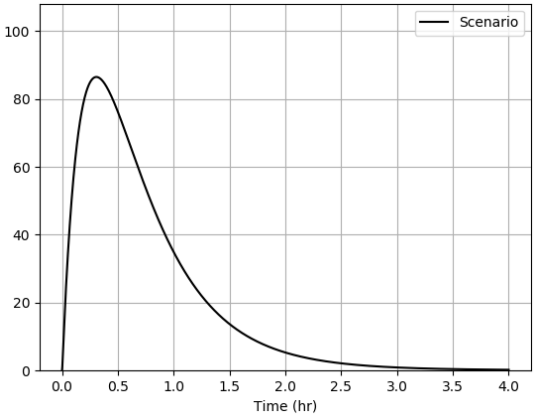


- Left: 12-hr plasma profile (Literature data obtained from [22])
- Center and Right: Dissolution in stomach over first 30 minutes
- Observations
  - Characterizes C_{max} well
  - T_{max} occurs early—though other studies have reported peak concentrations occuring between 1.5-1.75 hrs[23-24]

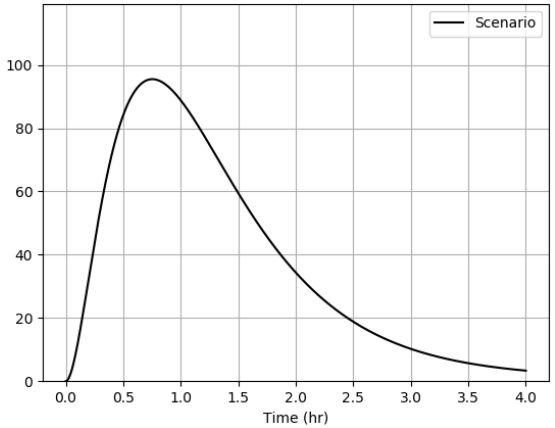
Moxifloxacin: Demo Results

Dissolved mass in intestinal lumen compartments (all units = mg)

Duodenum



Jejunum 1



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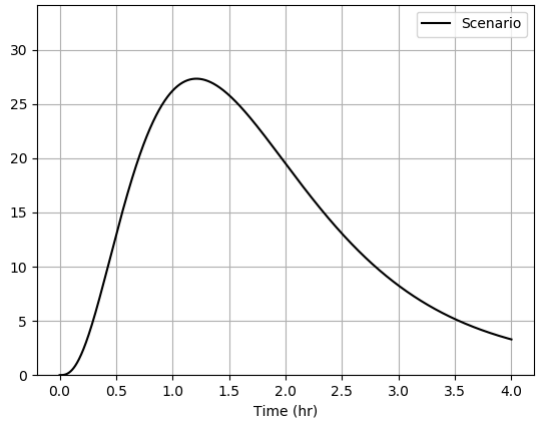

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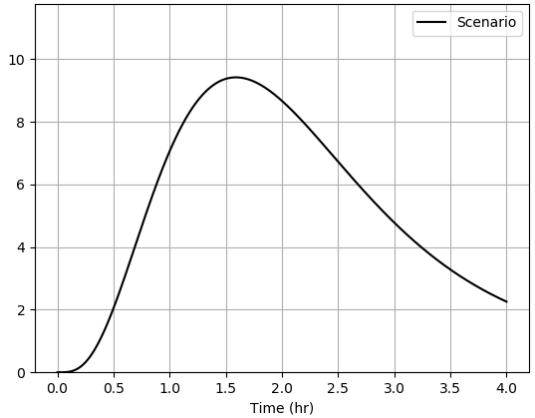

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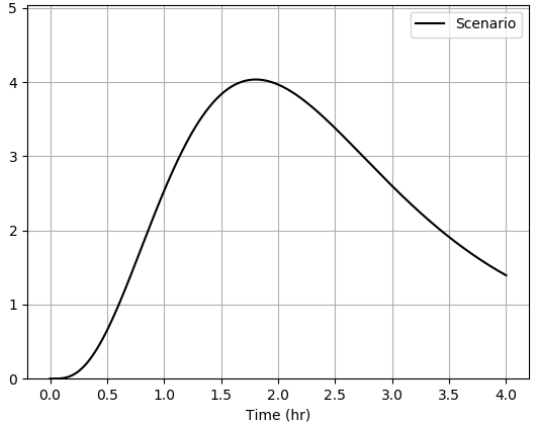

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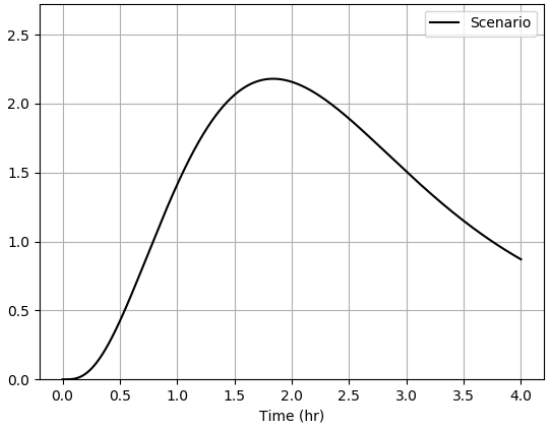

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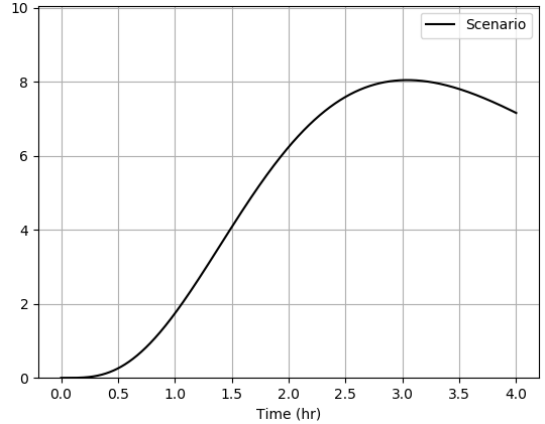

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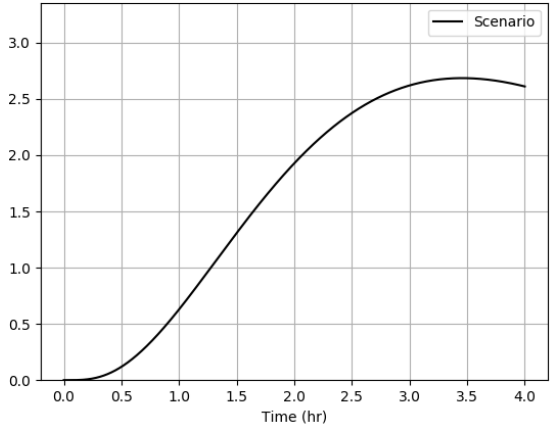

Future Work

- Expand library of validated oral substances
  - Technically, any BioGears substance can be administered orally
  - Only Moxifloxacin has had oral pharmacokinetics validated to this point
  - Investigate new substances that can feasibly be added to BioGears now that oral admin option exists
- Re-visit substance solubility in GI
  - Introduce pH effects
  - Introduce bile salt effects
- Generalize transmucosal model
  - Possible extension to other drugs administered via this route

Acknowledgments

- BioGears Team
  - Steven White
  - Austin Baird
  - Jenn Carter
  - Nathan Tatum
  - Lucas Marin

References

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