# Multiscale Simulation Framework for Personalized Pharmacology

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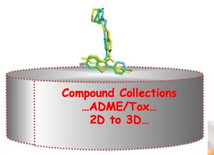
## Motivation

- Current models for PK and PD use simplistic mechanistic modeling approaches.
- Traditional PBPK approach lacks physiological input, with the exception of cardiac output, organ volumes & blood flow rates and neglects transport barriers.
- PD modeling approaches rely on even more simplistic dose-response correlations
- A **multiscale framework is needed** to integrate PBPK models, spatially resolved barrier models, and ML/AI supported mechanistic modeling approaches.

## Approach

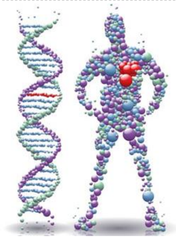
- Combine fundamental mechanistic models with AI/ML models to determine model components that are otherwise difficult to obtain through mathematical description.
- We have established this approach on different applications including
  a) Opioid and countermeasure test-case for determining PD physiology and effects,
  b) Orally inhaled drugs (OIDP), and
  c) Gastrointestinal tract (GIT) oral drugs.

## Inputs/Machine Learning Data



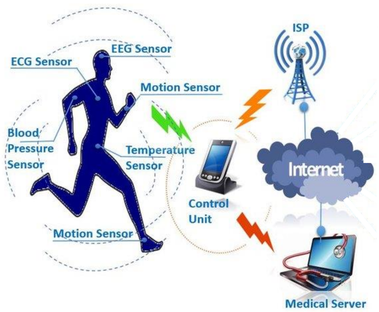

### Therapeutics

- **Drug physicochemical prop.**
  - **Mol. Wt., LogP**
  - **Solubility, Partition Coeff…**
- **Drug formulation prop.**
  - **Carrier prop., PSD**
  - **Dry powder, solution, aerosol**
- **Quantitative ttr-activity (QSAR)**
- **Biomarkers/Metabolites**



### Population & Genetics

- **Genetic predisposition**
  - **Gene mutations**
  - **Disease resistance**
- **Population variance**
  - **Anthropometric measures**

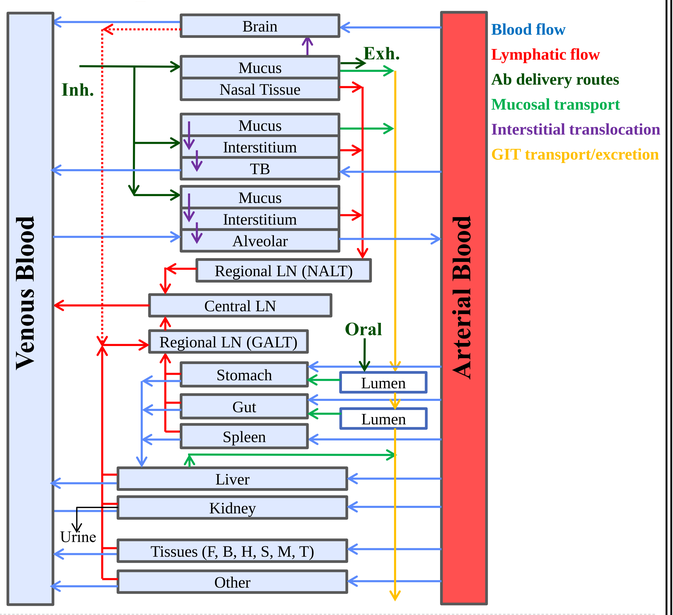



### Wearable Sensors

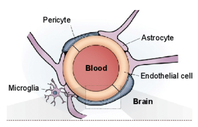
- **Physical signals (Biomechanics)**
  - **Pressure, motion,…**
- **Thermal signals**
  - **Fever, hypothermia,…**
- **Electrophysiological signals**
  - **ECG, EEG,…**
- **Biomarkers/Metabolites**

## Multiscale Framework

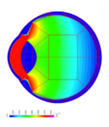
### Compartmental PBPK



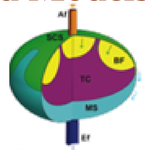

### Spatially Resolved Models



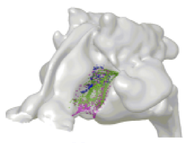

Blood Brain Barrier



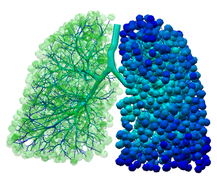
Cornea/Retina



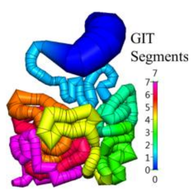
Lymph node



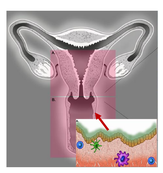
Olfactory



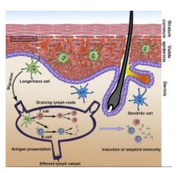
Pulmonary mucosal barrier




GIT muscosal barrier



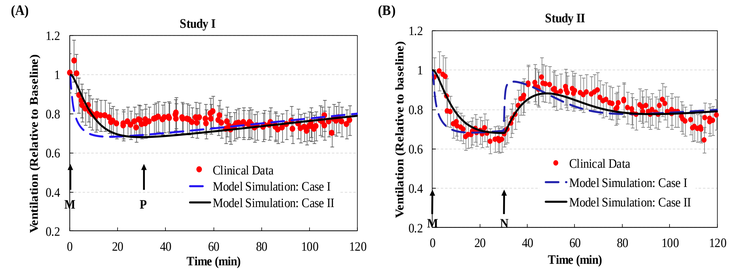
Reproductive track mucosal barrier



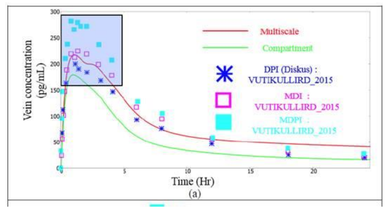
Skin topical SC, IM, µNeedle

## Output

### Opioid simulations (Morphine and Naloxone)

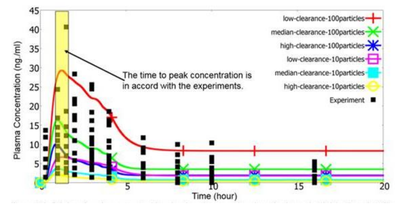



### Lung/Inhalation drug simulations (FP)




- ODIP Fluticasone (FP)
- Multiscale : 0D-3D-Q3D
- Can match the dip and bounce shown in exp's

### GIT oral drug simulations (Mebendazole)




- Mebendazole in chewable tablet form
- Multiscale 0D-Q3D model
- Inter-subject variation accounted in model

### ML/AI Tools




## Selected References

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- FDA (HHSF223201810182C): Bioequivalence of orally inhaled drugs
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- NIH (1R43GM108380-01) Mechanism-based computational tool to optimize pulmonary drug delivery