

Tufts



# Designing a Computer Simulation Tool for PET Neuroimaging

Tom Morin

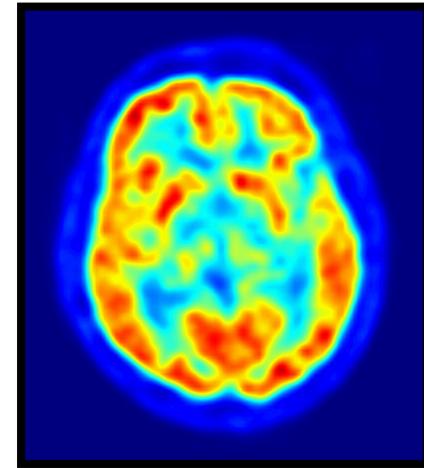
Hooker Research Group

Athinoula A. Martinos Center for Biomedical Imaging

Massachusetts General Hospital

Harvard Medical School

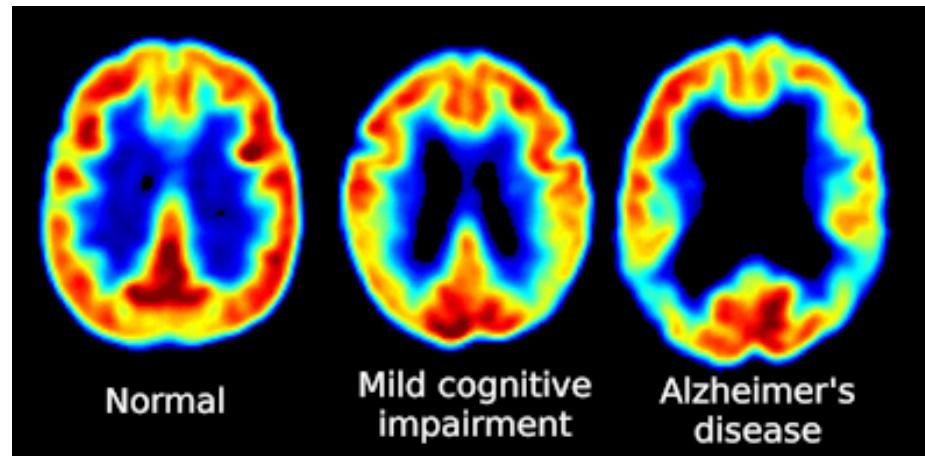
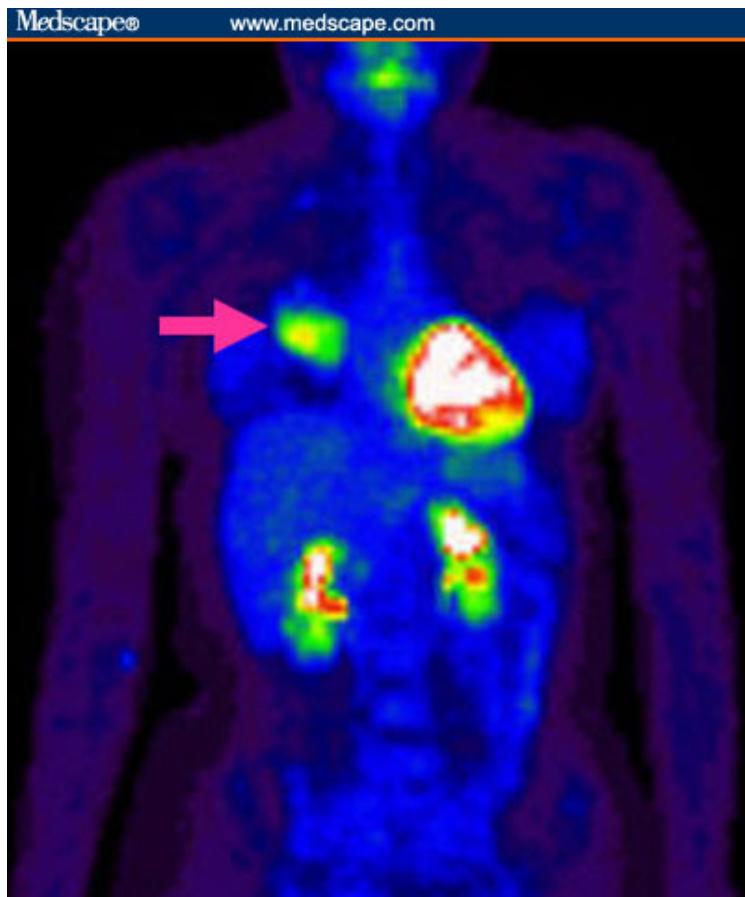
# Positron Emission Tomography (PET)



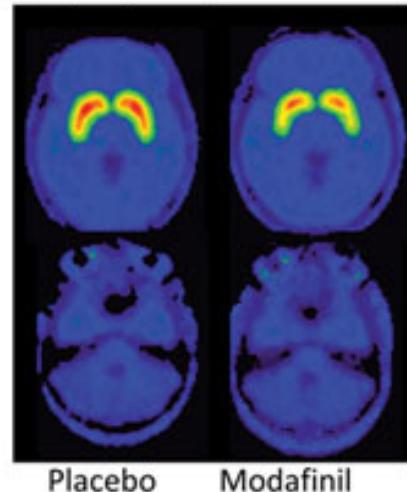
## Procedure:

1. Inject a Radiotracer
2. Take the Scan
3. Get Blood Data (optional)
4. Analyze Data

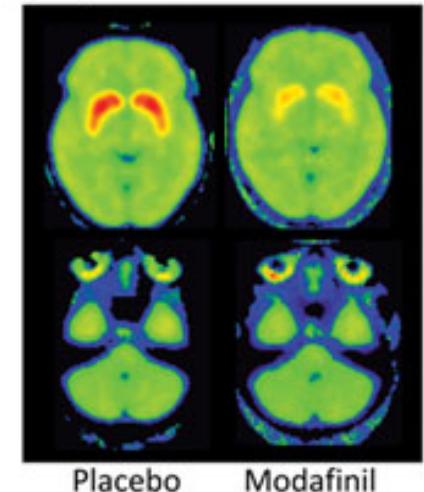
# Applications of PET



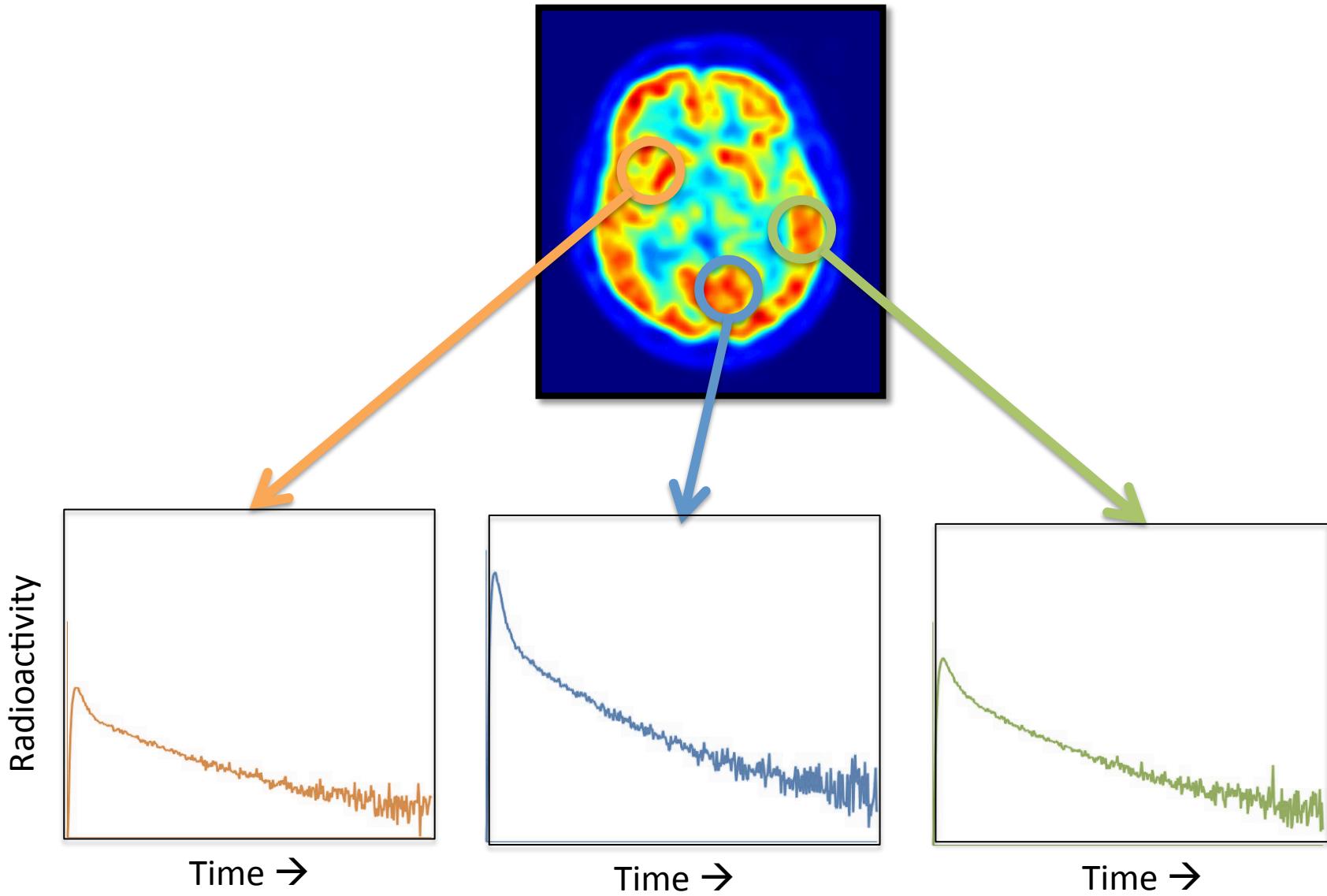
A  $[^{11}\text{C}]\text{raclopride}$



B  $[^{11}\text{C}]\text{cocaine}$



# Time Activity Curves (TACs)



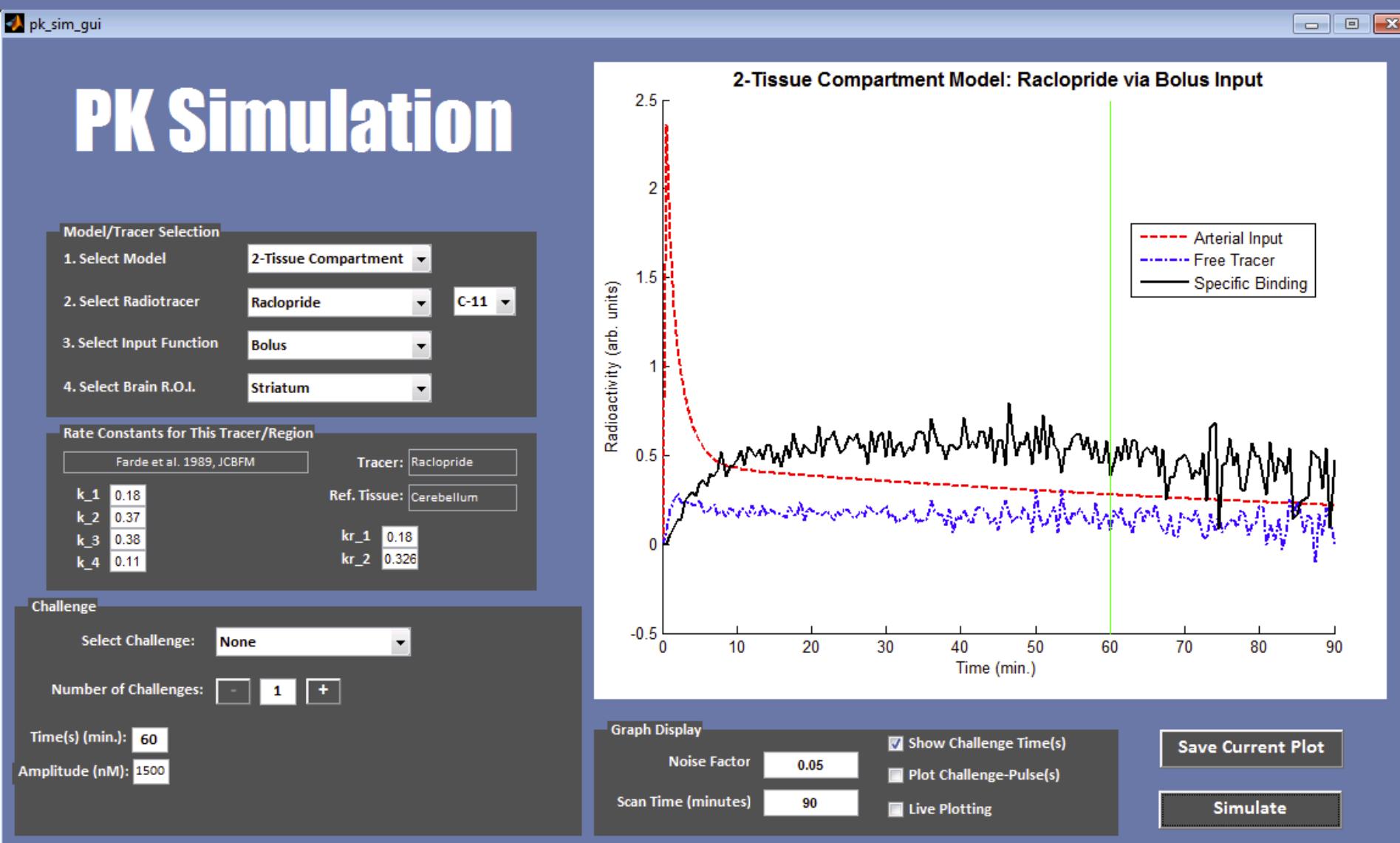
# Problems With PET

- High cost machinery & staff
- Scan requires intense coordination and advanced planning
- Small procedural changes can have a big impact on results

# Why Use Simulation?

- Evaluate study feasibility (conserve resources)
- Strategically choose and optimize experimental design
- Facilitate new methods development

# Simulation Tool Screenshot



# Kinetic Models

pk\_sim\_gui

## PK Simulation

Model/Tracer Selection

1. Select Model
2. Select Radiotracer
3. Select Input Function
4. Select Brain R.O.I.

Farde et al. 1989, JCBFM      Tracer: Raclopride      Ref. Tissue: Cerebellum

k <sub>1</sub> _1	0.18
k <sub>2</sub>	0.37
k <sub>3</sub>	0.38
k <sub>4</sub>	0.11

kr <sub>1</sub>	0.18
kr <sub>2</sub>	0.326

Challenge

Select Challenge: Endogenous Dopamine      kend<sub>1</sub>: 13.5      kend<sub>2</sub>: 25

Number of Challenges: - + \*      Time(s) (min): 100      Amplitude (nM): 1000

Graph Display

Noise Factor: 0      Scan Time (minutes): 200

2-Tissue Compartment Model: Raclopride via Bolus Input

Radioactivity (arb. units)

Time (min)

Model/Tracer Selection

1. Select Model
2. Select Radiotracer
3. Select Input Function
4. Select Brain R.O.I.

Rate Constants for This Tracer/Region

2-Tissue Compartment

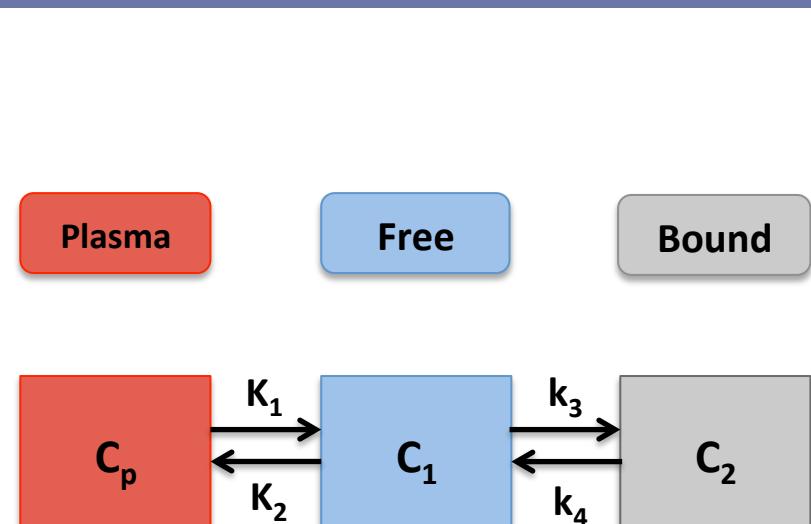
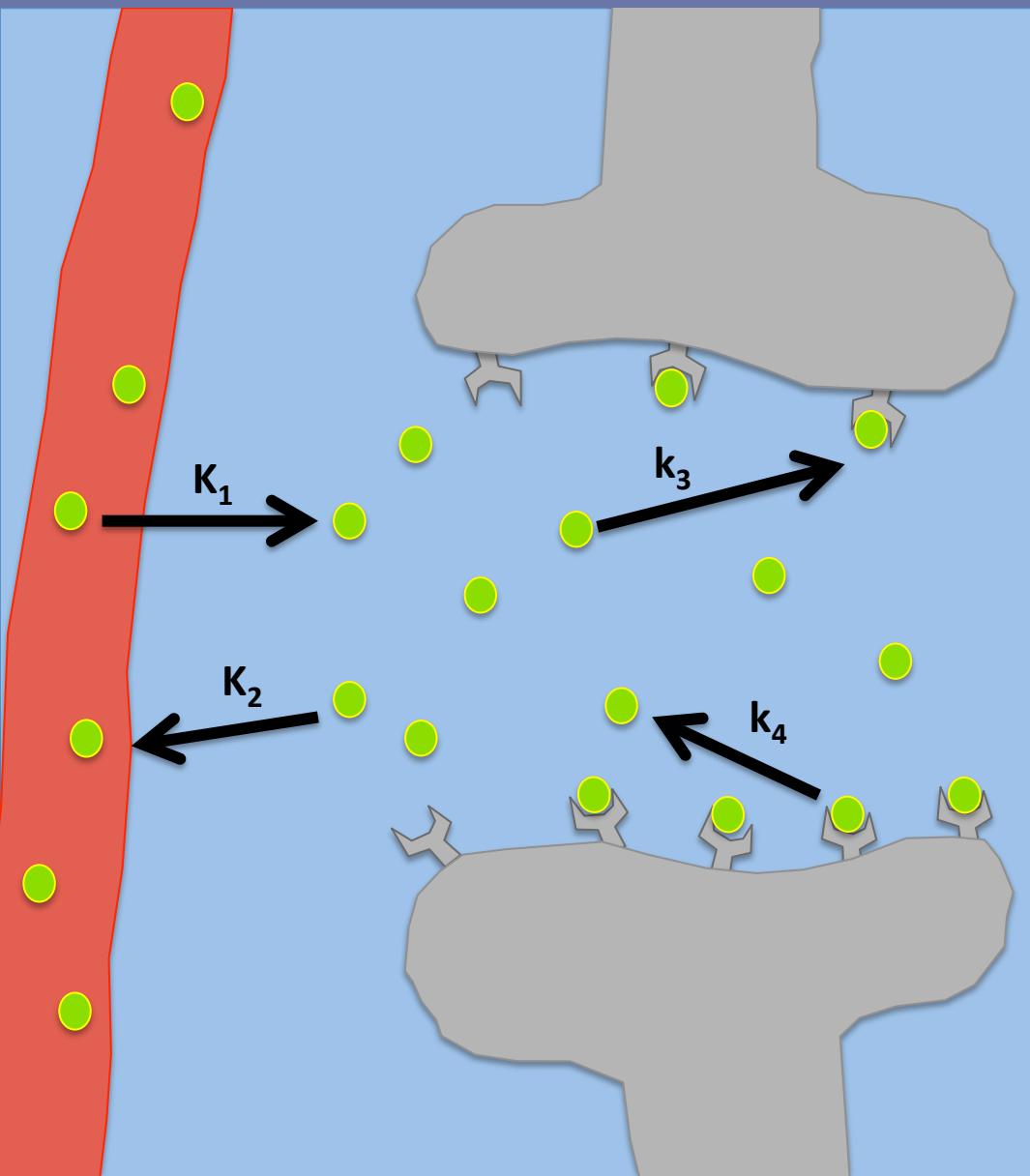
2-Tissue Irreversible

1-Tissue Compartment

SRTM

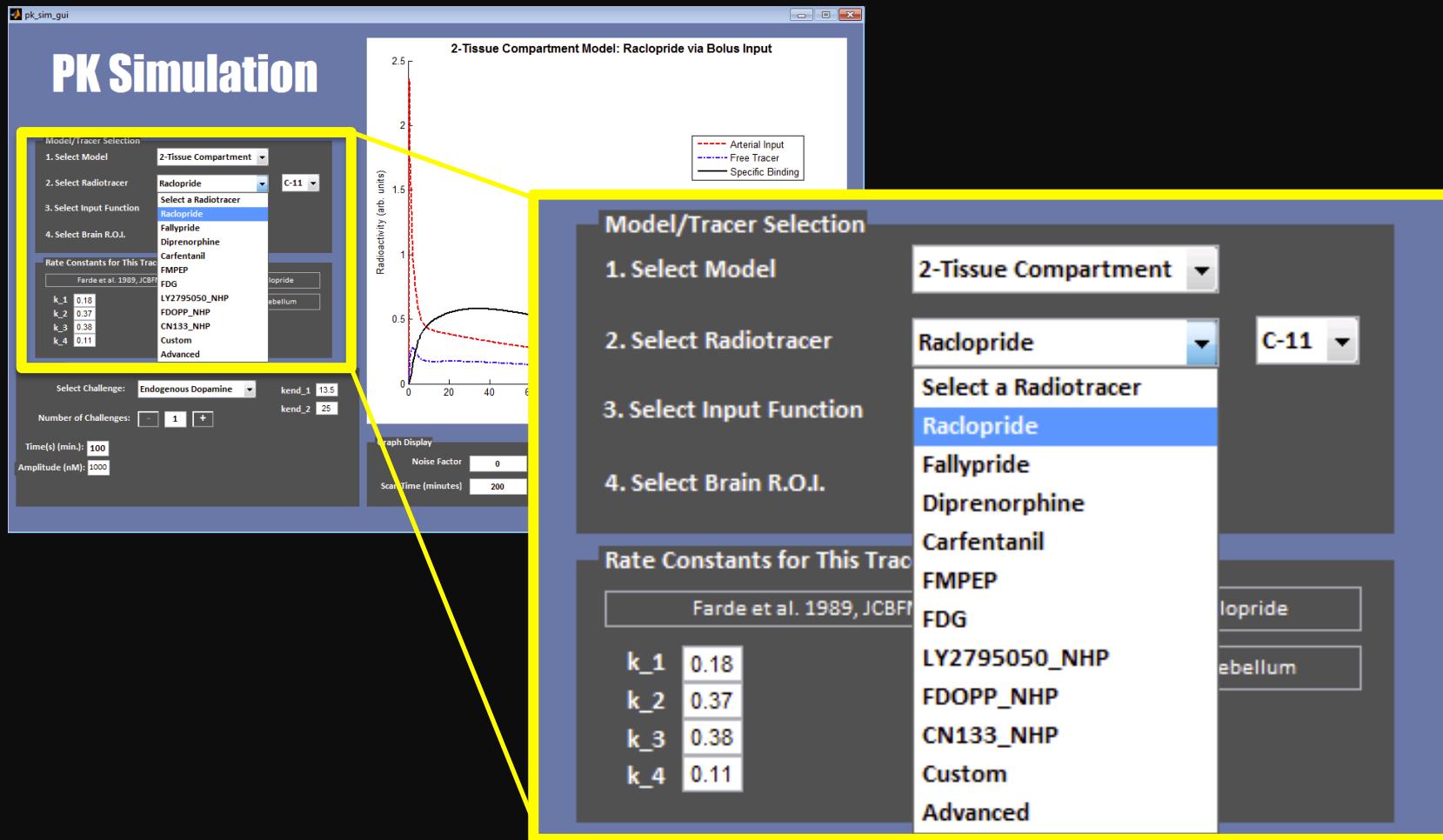
Bolus/Infusion Optimization

# 2-Tissue Compartment Model



$$\begin{aligned}\frac{dC_1(t)}{dt} &= K_1 C_p(t) - (k_2 + k_3) C_1(t) + k_4 C_2(t) \\ \frac{dC_2(t)}{dt} &= k_3 C_1(t) - k_4 C_2(t)\end{aligned}$$

# Radiotracers



# Plasma Input Functions

**PK Simulation**

**Model/Tracer Selection**

1. Select Model: 2-Tissue Compartment
2. Select Radiotracer: Raclopride C-11
3. Select Input Function: Bolus
4. Select Brain R.O.I.: Select an Input Function

Rate Constants for This Tracer: Farde et al. 1989, JCBFM

Challenges: Endogenous Dopamine, k<sub>end</sub>\_1: 13.5, k<sub>end</sub>\_2: 25

Number of Challenges: 1

Time(s) (min): 100, Amplitude (nM): 1000

Graph Display: Noise Factor: 0, Scan Time (minutes): 200

**2-Tissue Compartment Model: Raclopride via Bolus Input**

Arterial Input  
Free Tracer  
Specific Binding

**Model/Tracer Selection**

1. Select Model: 2-Tissue Compartment
2. Select Radiotracer: Raclopride C-11
3. Select Input Function: Bolus
4. Select Brain R.O.I.: Select an Input Function

Rate Constants for This Tracer: Farde et al. 1989, JCBFM

Tracer: Raclopride

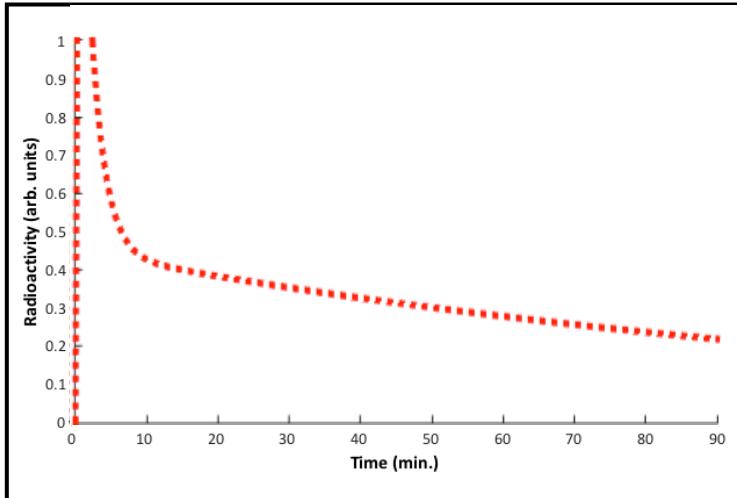
**Select an Input Function**

- Bolus (selected)
- Infusion
- Custom

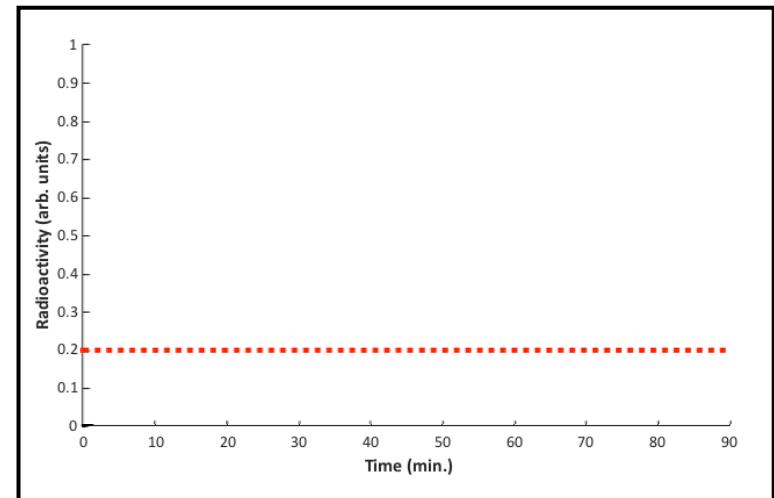
# Plasma Input Functions

Example. [ $^{11}\text{C}$ ]Raclopride (dopamine D<sub>2</sub>/3 selective)

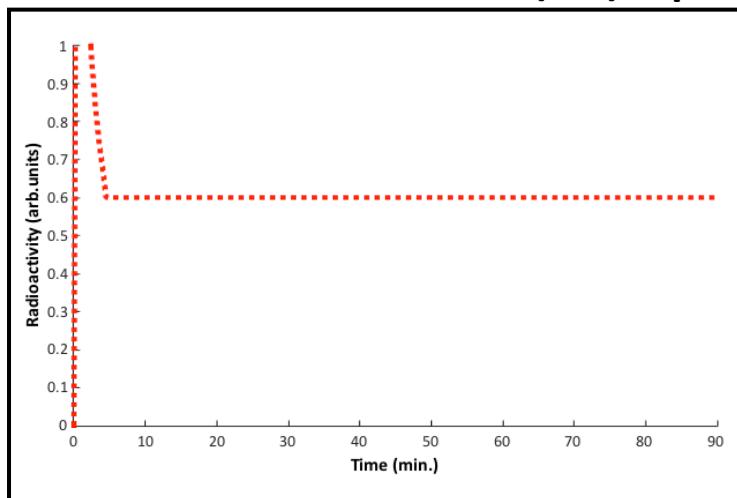
Bolus Input



Constant Infusion Input

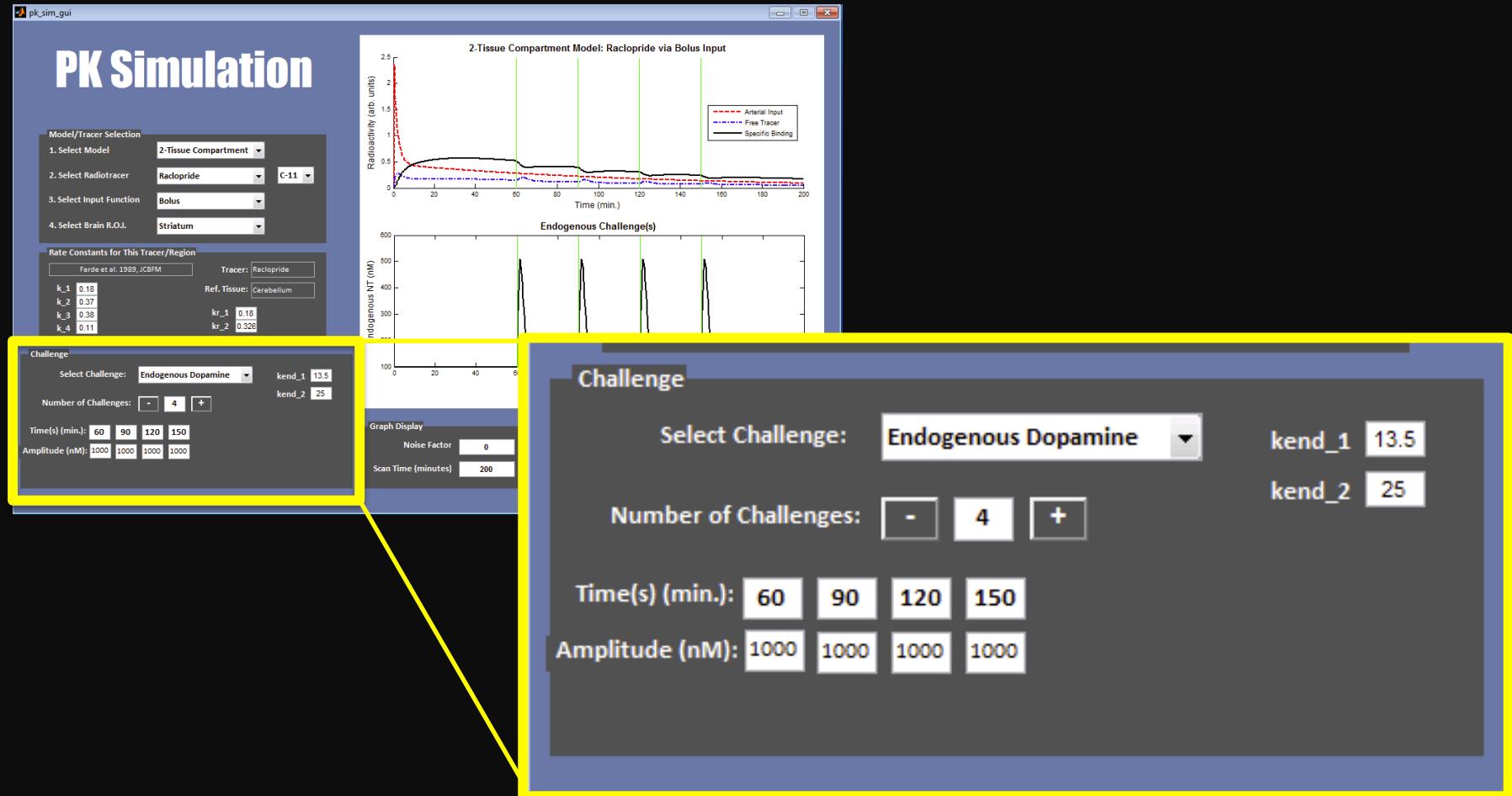


Bolus + Constant Infusion (B/I) Input



Plasma Input

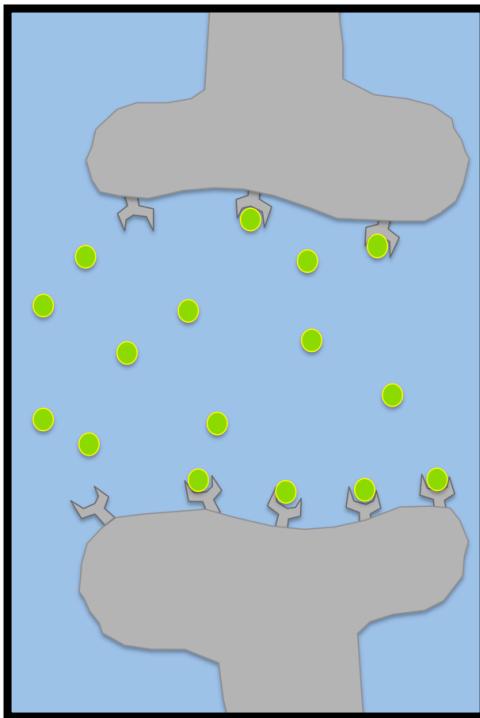
# Competition



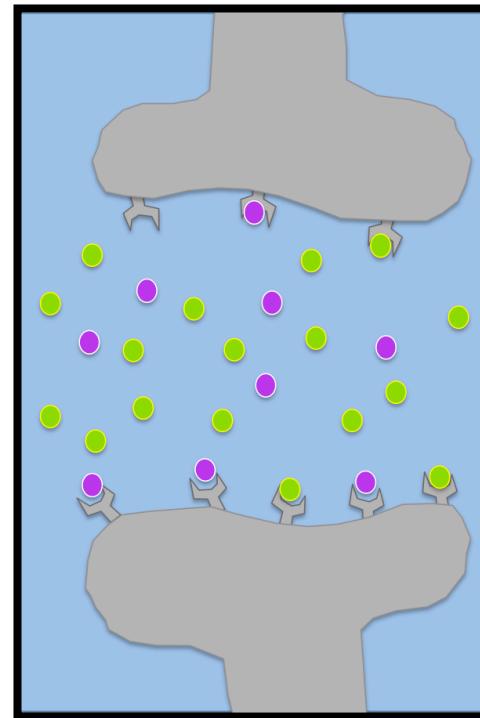
# Competition

- **Endogenous**
  - ex.  $[^{11}\text{C}]\text{raclopride}$  & dopamine-releasing reward task
- **Exogenous (pharmacological challenge)**
  - ex.  $[^{11}\text{C}]\text{carfentanil}$  with morphine

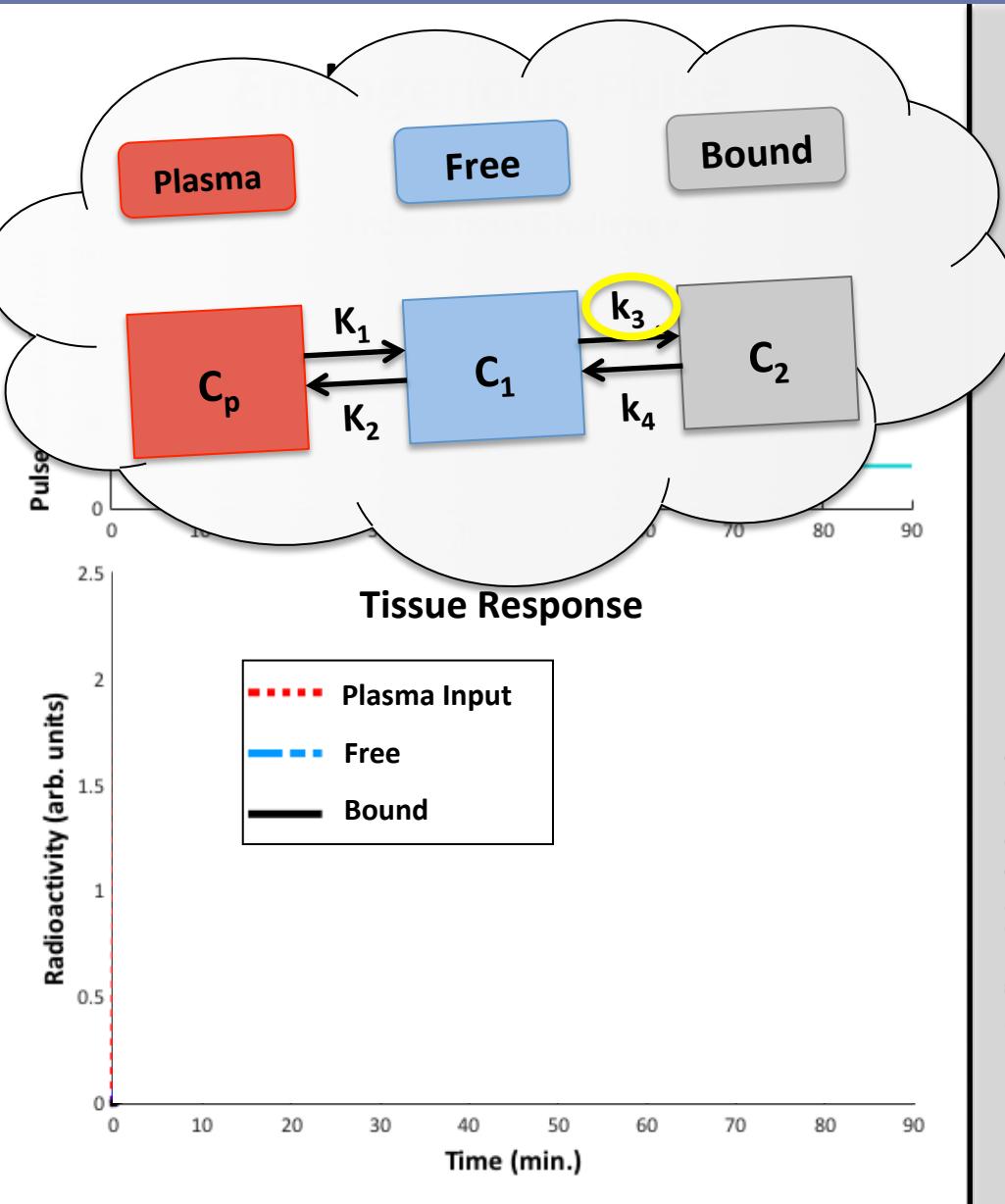
**Before  
Challenge**



**After  
Challenge**



# Simulating Competition



## Alter Rate Constants (One Method to Simulate Exogenous Challenge)

Challenge

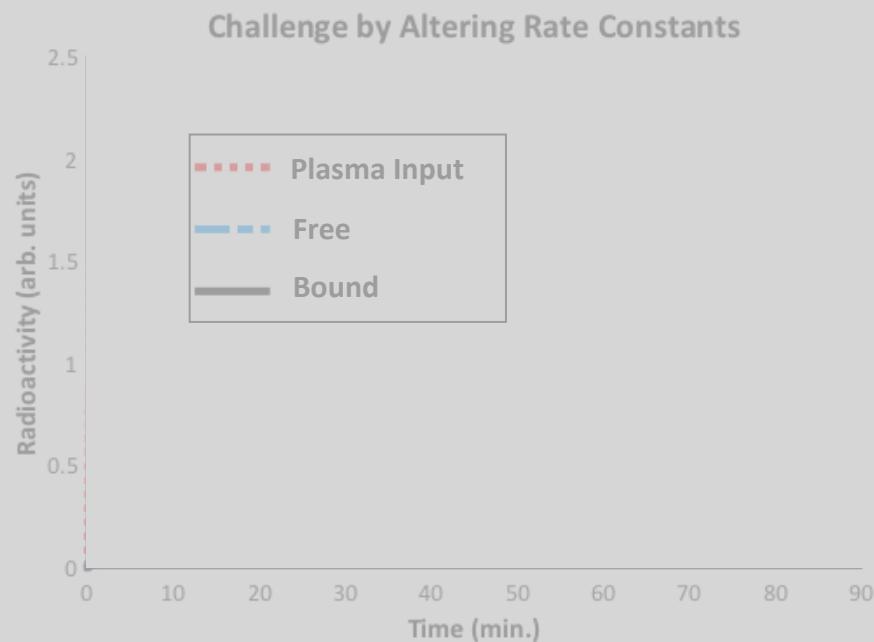
Select Challenge: Alter Rate Constants

Number of Alterations: 2

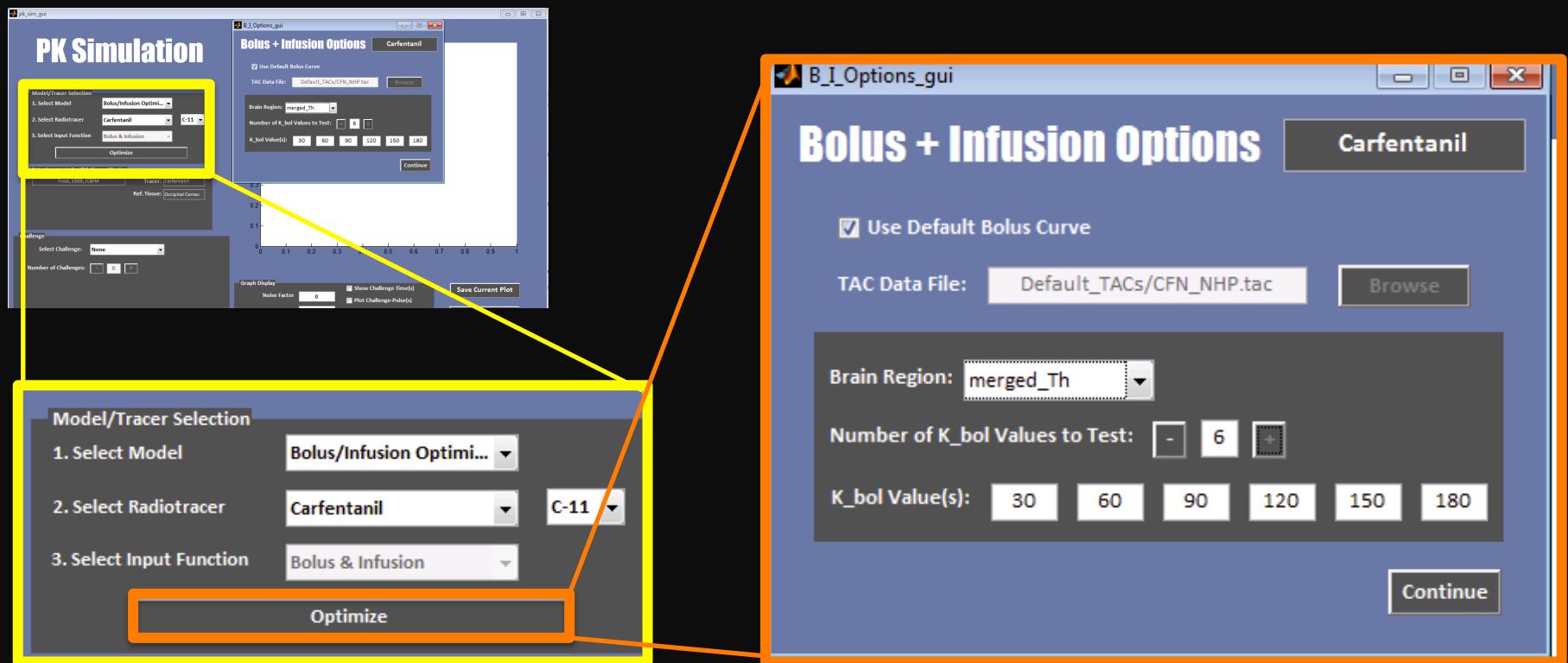
Time(s) (min.): 60 70

$k_3$  Value(s): 0.2 0.38

$k_4$  Value(s): 0.11 0.11



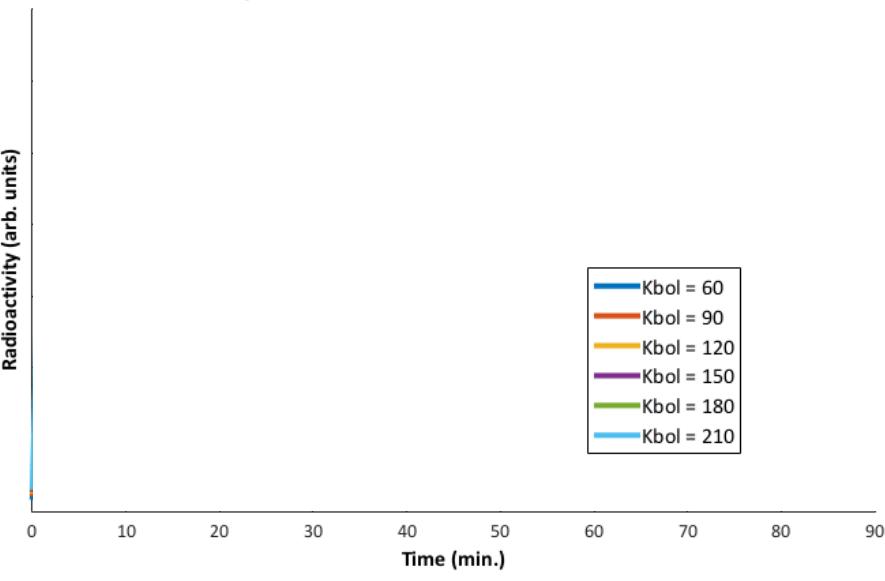
# Bolus + Constant Infusion



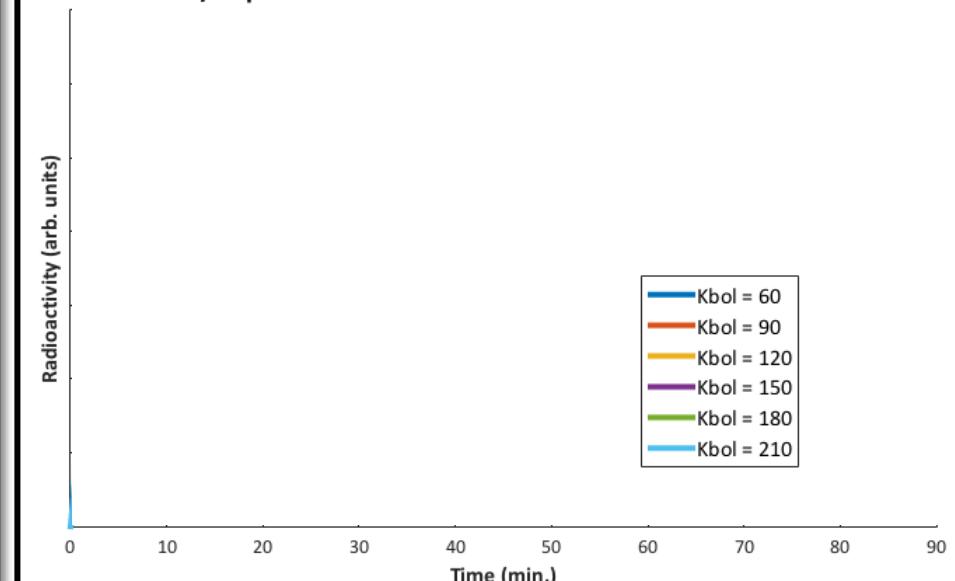
# Bolus + Constant Infusion Optimization

- Regular bolus injection followed by continuous infusion
- $K_{bol}$ 
  - Bolus dose measured in minutes of infusion dose
  - Units = minutes
- Adjusting  $K_{bol}$  (adjusting how much radiotracer is initially injected), allows tracer to reach equilibrium more quickly
- Optimal  $K_{bol}$  will vary slightly between subjects and must be determined for each radiotracer

B/I Optimization for Carfentanil with REAL Data



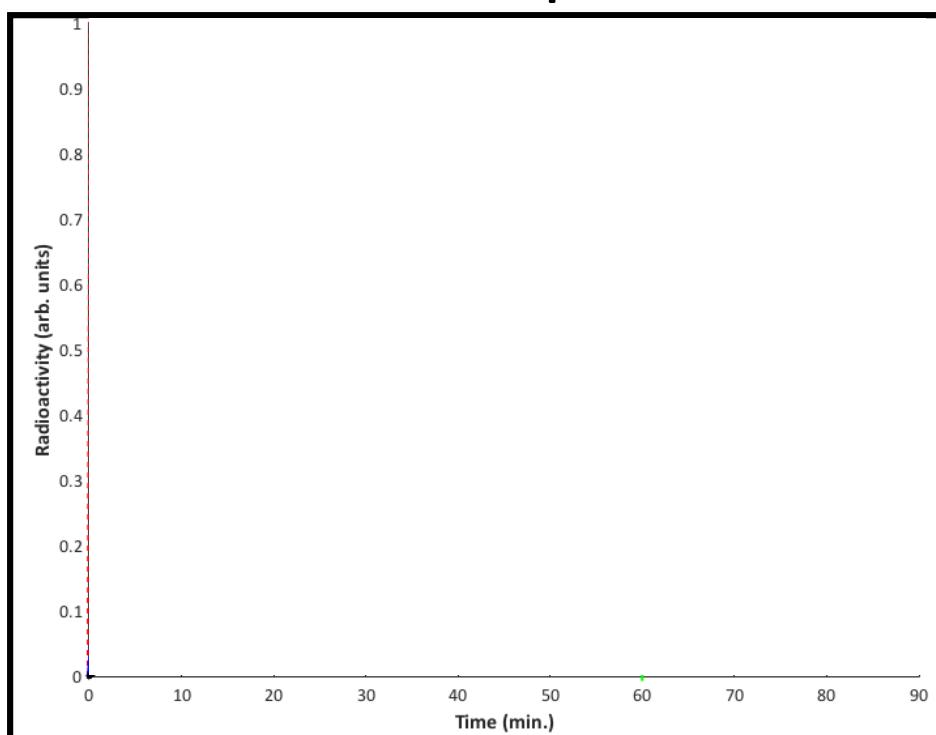
B/I Optimization for Carfentanil with SIMULATED Data



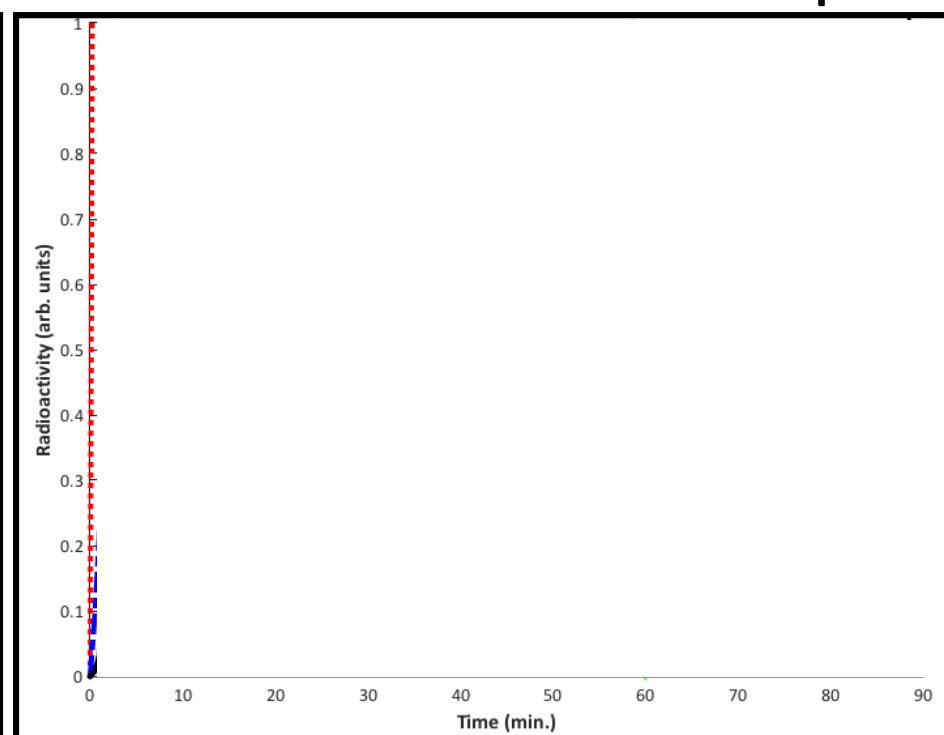
# Competition with Bolus + Constant Infusion

Example: [<sup>11</sup>C]Raclopride with Endogenous Dopamine Challenge at 60 min.

BOLUS Input



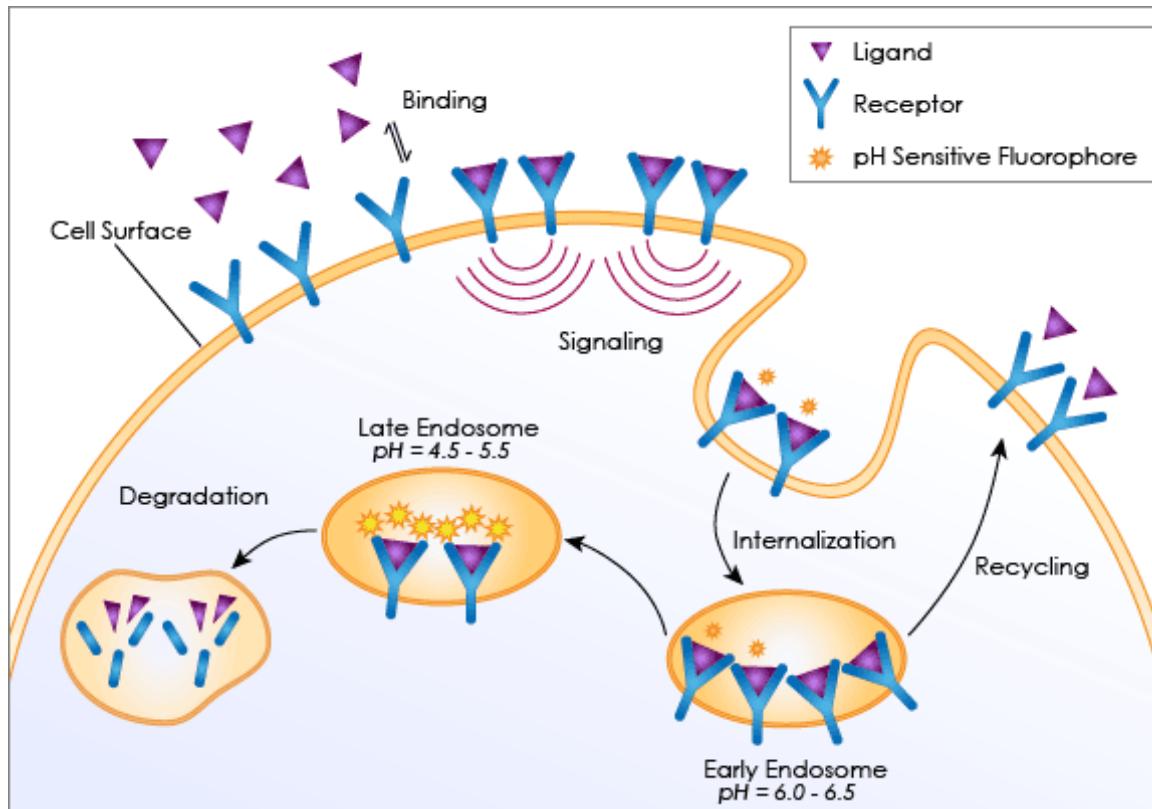
BOLUS + CONSTANT INFUSION Input



..... Plasma Input    - - - Free    — Bound

# Future Direction

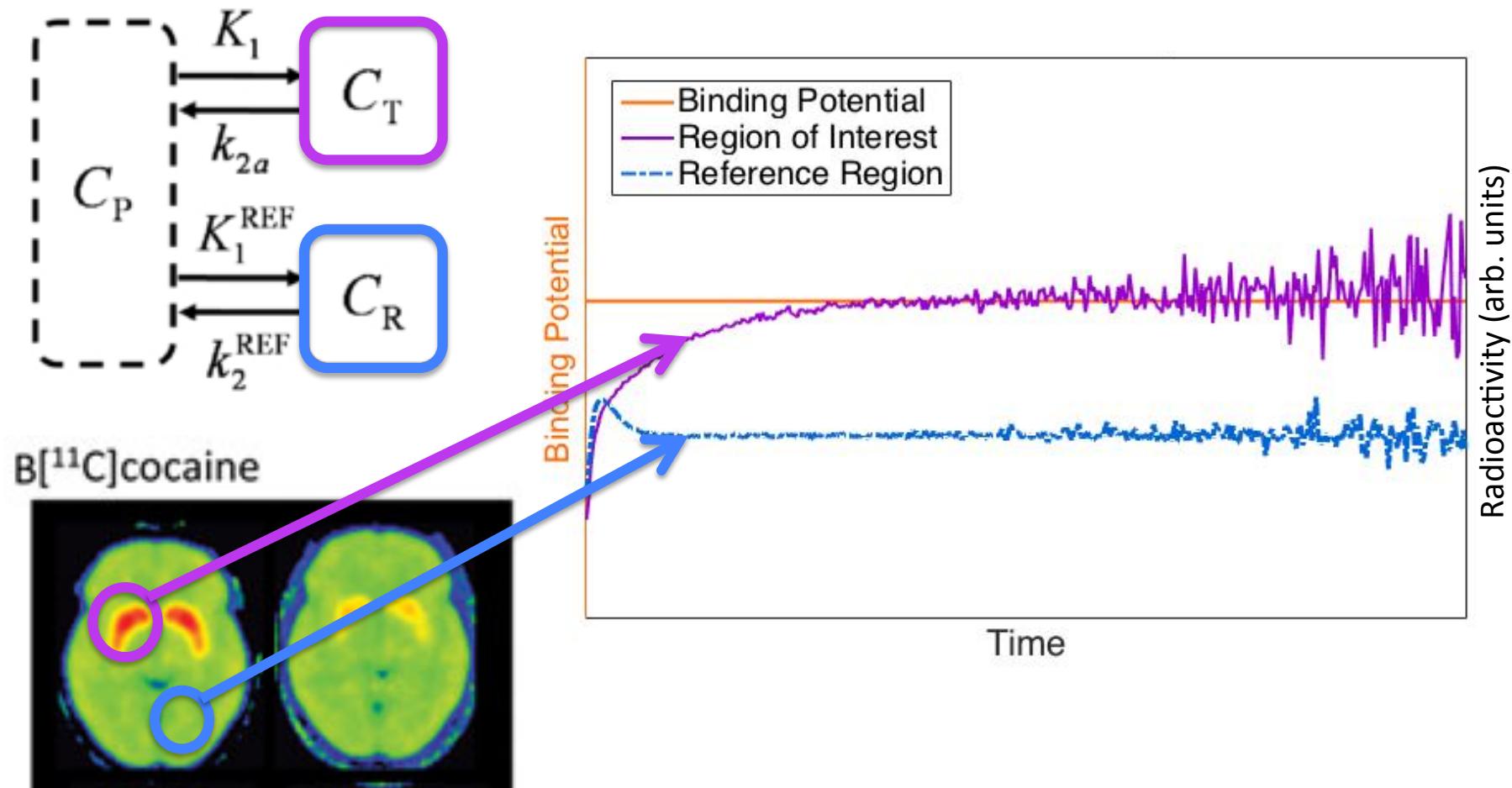
## Receptor Internalization Models:



<http://www.nexcelom.com/Celigo/receptor-internalization-assay.php>

# Future Direction

## Reference Tissue Models:



# Acknowledgements



## **Project Mentor:**

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## **Principle Investigator:**

Dr. Jacob Hooker

## **Hooker Research Group Members:**

Dr. Changing Wang  
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