Controlling the effects of Heroin

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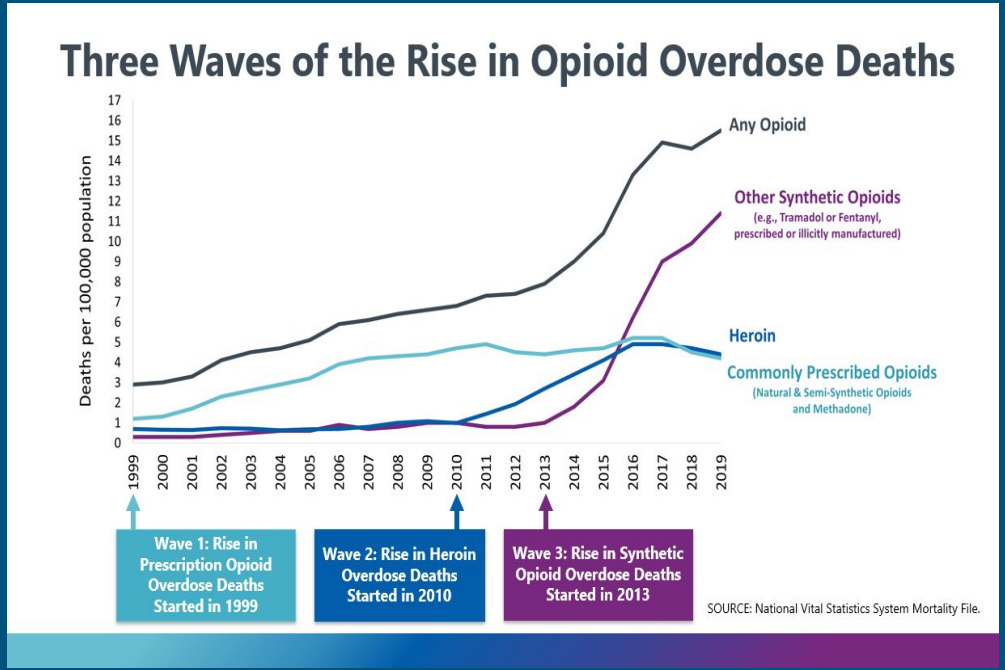
Background

- Heroin is a highly addictive drug and heroin use has increased in the last decade.
- Because of this strangely high addiction, we became interested in modeling the dopamine response to varying inputs of heroin
- Fun facts regarding the opioid epidemic :D
  - 50,000 people have used heroin for the first time in the last year
  - 745,000 people have used heroin in the last year
  - 14,480 people have died from heroin overdose
  - There's a rising incidence of newborns experiencing withdrawal syndrome due to the use and misuse of opioid during pregnancy :(

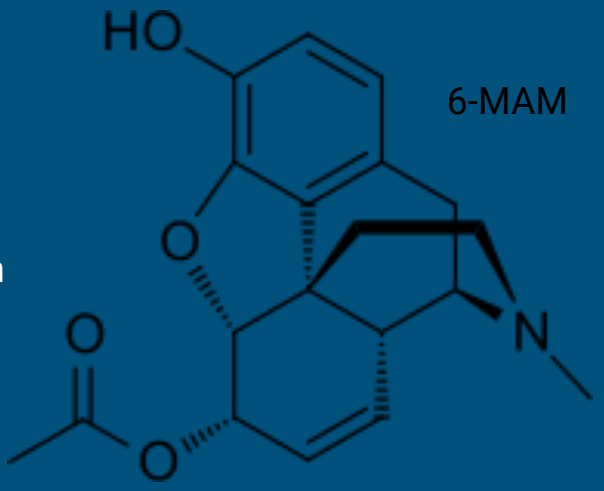
Background

- When heroin enters ours body, it's quickly metabolized into 6-monoacetylmorphine (6-MAM) - a linear process - and further hydrolyzed by erythrocyte acetylcholinesterase (AChE), carboxylase 1 (CES1) and Carboxylase 2 (CES2) into morphine.
- Half life of heroin is too short to have pharmacological effects, therefore the effects are mainly dependent on the conversion to 6-MAM and morphine.
- 6-MAM contributes to acute effects and morphine contributes to sustained effects

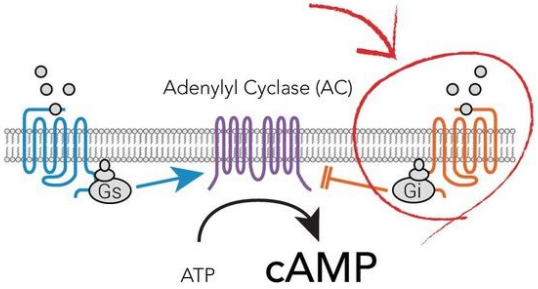


Control System

- The control system in our case is the mu-opioid receptors in the brain and the amount of dopamine released
- Input: Heroin
- Output: Increase of dopamine (1 to 1 with 6-MAM activity)
- Substance being measured is the concentration of 6-MAM
- Target value of 6-MAM concentration: 0 moles/L
- The aim is to produce this target by proportionally controlling the concentration of CES2 in the system with an inhibitor



6-MAM



System Model

We represented the system as a system of equations that describes the kinetics of heroin as it is broken down by the enzyme and the kinetics of the formation of it's substrates

$$\frac{d[heroin]}{dt} = -K_{e1}[heroin] \quad (1)$$

$$\frac{d[6-MAM]}{dt} = K_{e1}[heroin] - K_{e2}[6-MAM] \quad (2)$$

$$\frac{d[morphine]}{dt} = K_{e2}[6-MAM] - K_{e3}[morphine] \quad (3)$$

$$K_{e1} = V_{max2}\frac{[CES2]}{K_m+[CES2]} \quad (4)$$

$$K_{e2} = V_{max1}\frac{[CES1]}{K_m+[CES1]} + K_{e1} \quad (5)$$

$$V_{max1} = (439\ min^{-1})[hCE-1]_0 \quad (6)$$

$$V_{max2} = (2186\ min^{-1})[hCE-2]_0 \quad (7)$$

$$\frac{d[CES2]}{dt} = -k_{blackbox}[6-MAM] \quad (8)$$

Limited Aspect of the Control System

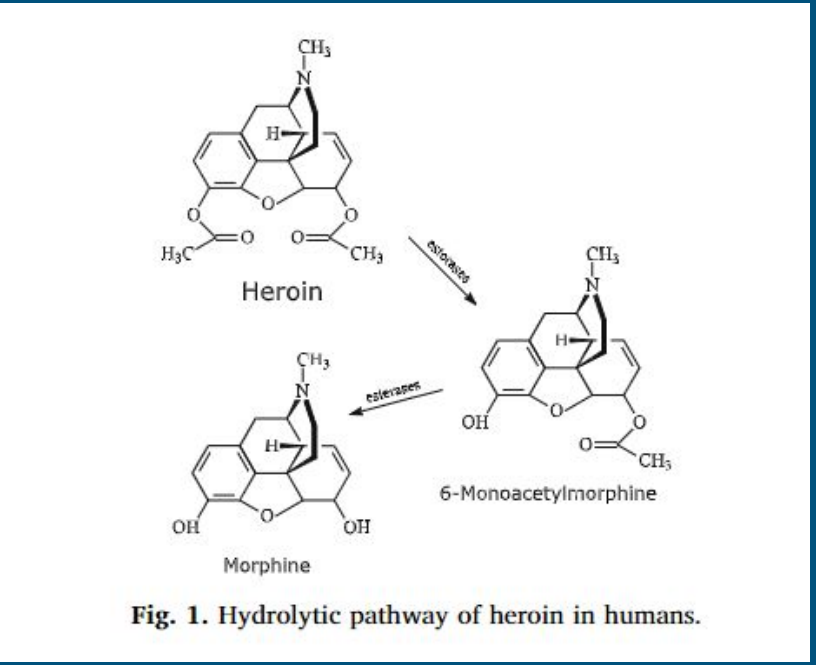
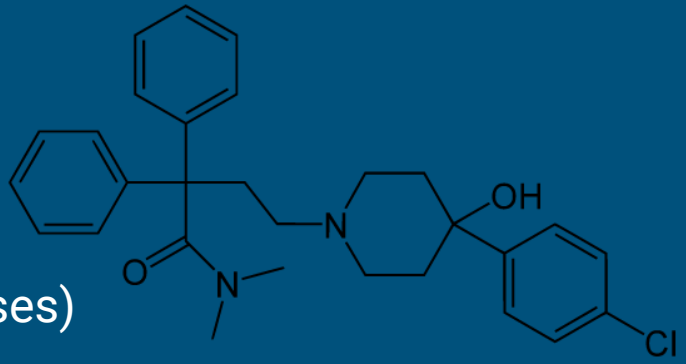


Fig. 1. Hydrolytic pathway of heroin in humans.

- We are focusing on the enzyme, carboxylesterase 2 (CES2), and its effects on 6-MAM after heroin is injected into the body
- CES2 is important in the metabolism of heroin as it breaks down heroin into metabolites that activate the mu-opioid receptors which mediate the release of dopamine. This release of dopamine is the **output** of the system.

Proportional Controller

Loperamide



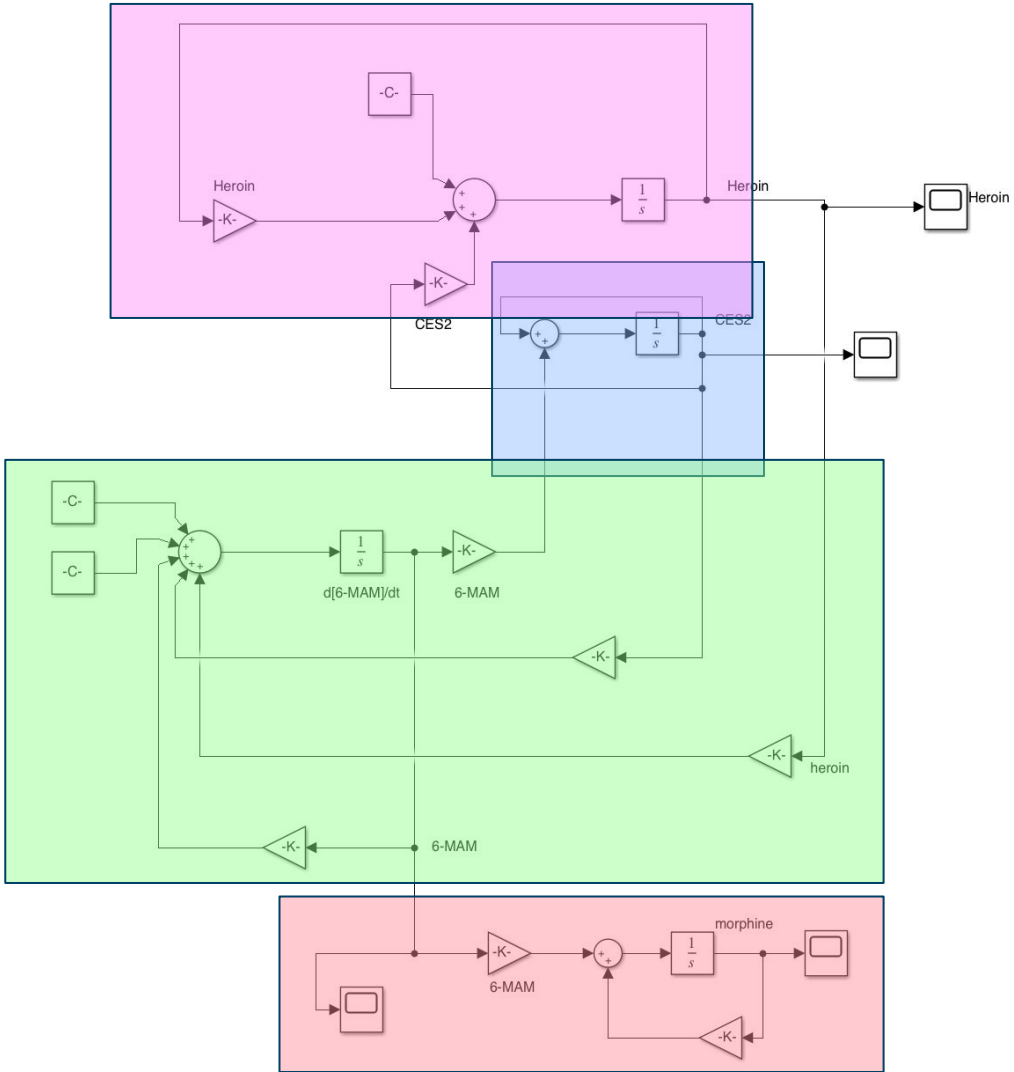
- Carboxylase 2 (CES2) doesn’t respond to the amount of heroin in the system (concentration neither increases nor decreases)
- Thus, if we want to control the effects of heroin we need to decrease the concentration of CES2
- To do this, we will need to incorporate a P controller

Assumptions

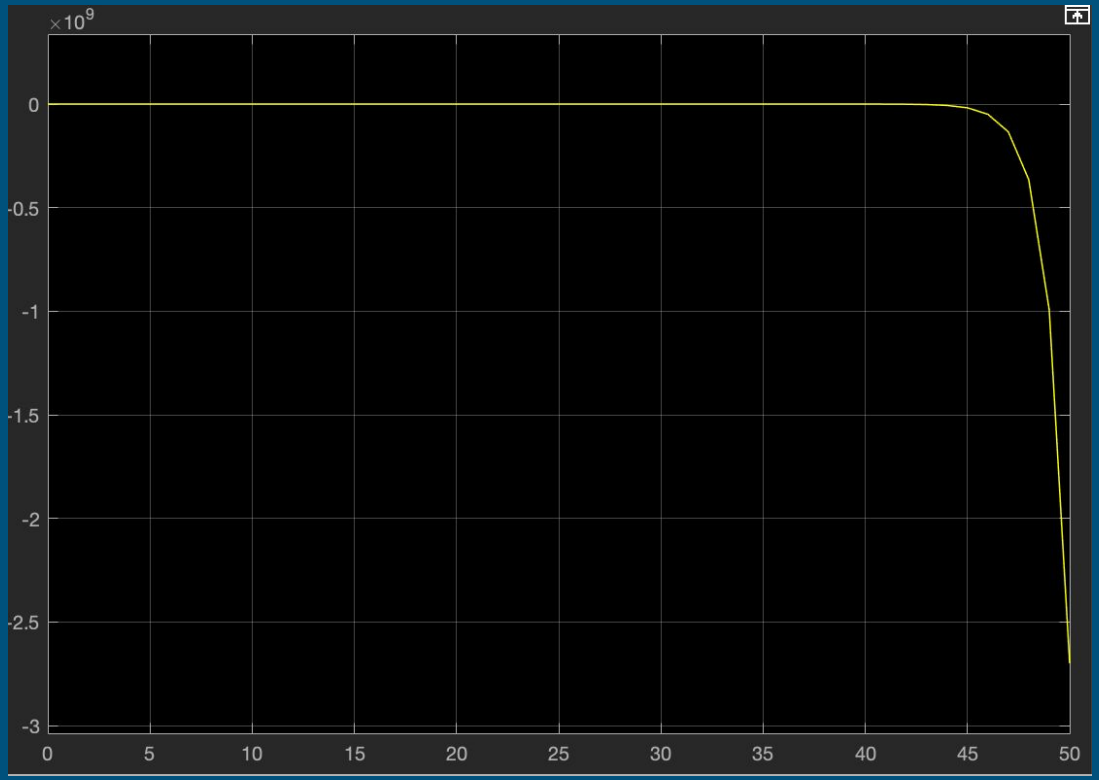
- The Heroin is metabolized to 6-MAM linearly
- 6-MAM affects the mu-receptors linearly
- Morphine has minimal effects on neurotransmitter behavior apart from an initial kick
- Concentration of 6-MAM in the blood is the main focus of measurement
- We can release an inhibitor within the system to proportionally drive down the concentration of CES2
- Inhibitor will directly affect the concentration of CES2 proportionally (1 to 1)

Block Diagram in Time Domain

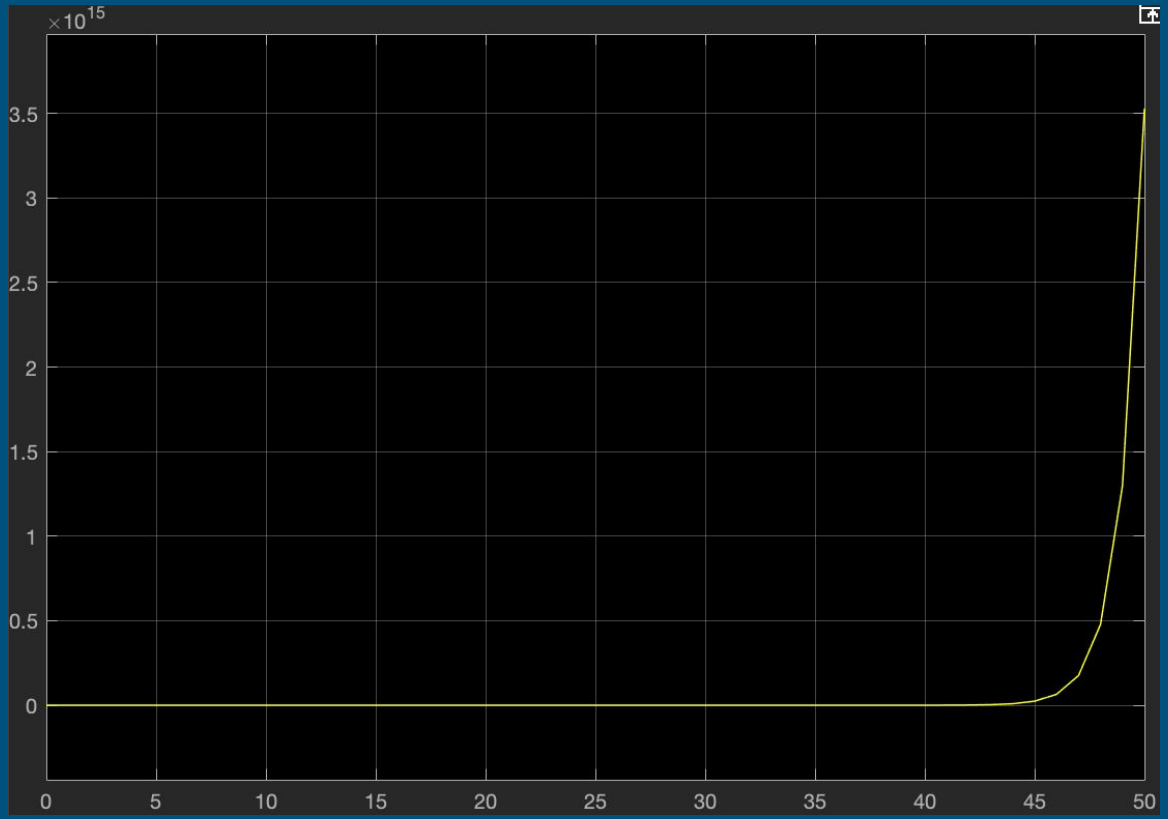
- Metabolizing of Heroine (1)
- Inhibiting of CES-2 by black box (8)
- Metabolizing of 6-MAM (2)
- Metabolizing of Morphine (3)



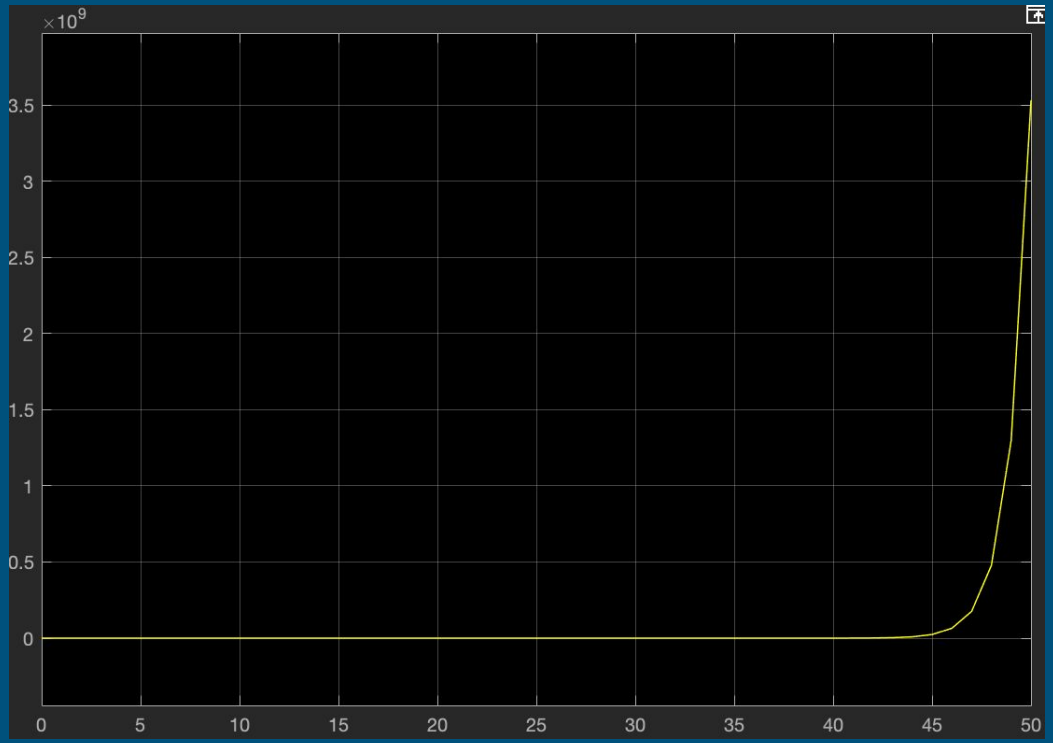
Resulting Heroin kinetics graph



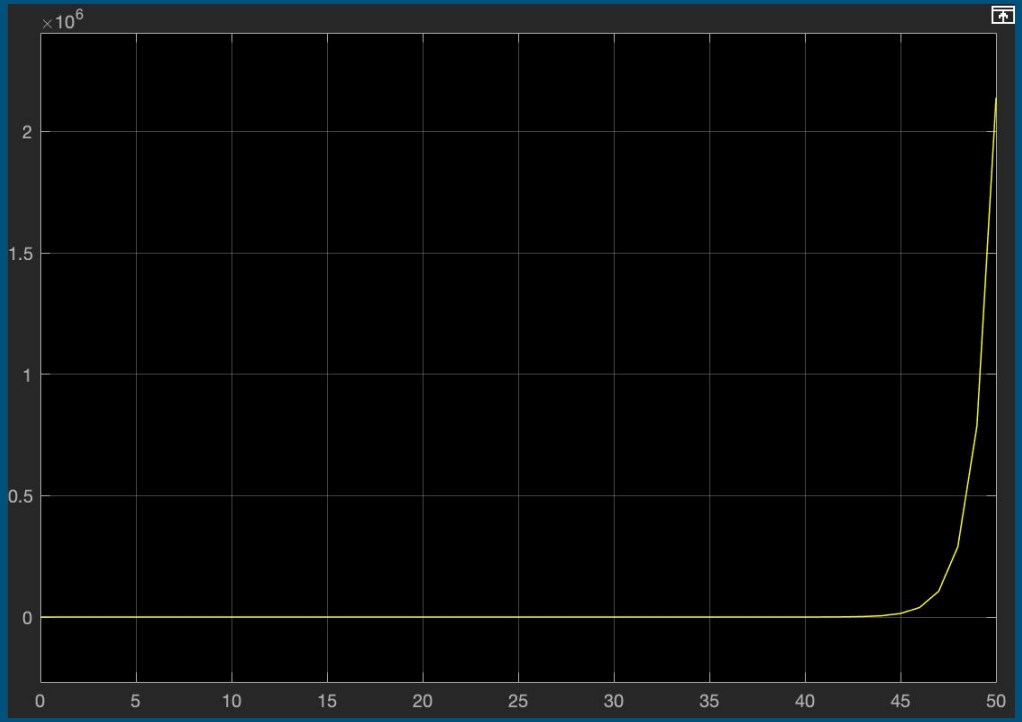
CES2



6-MAM



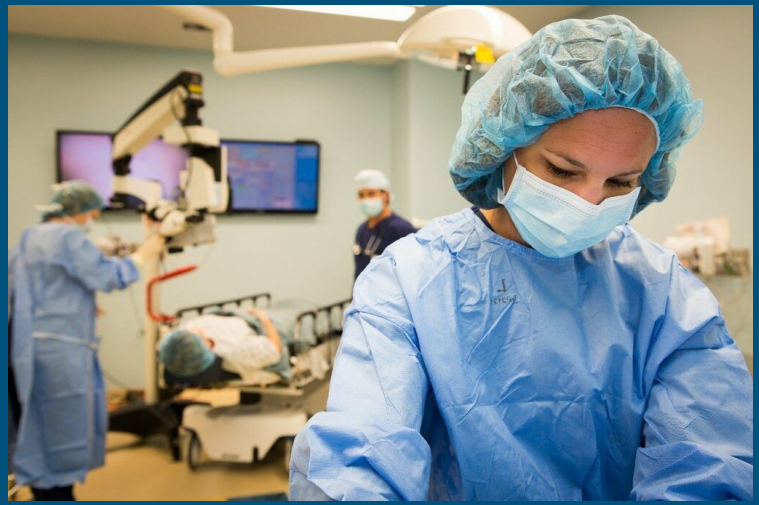
Morphine



Advantages & Disadvantages

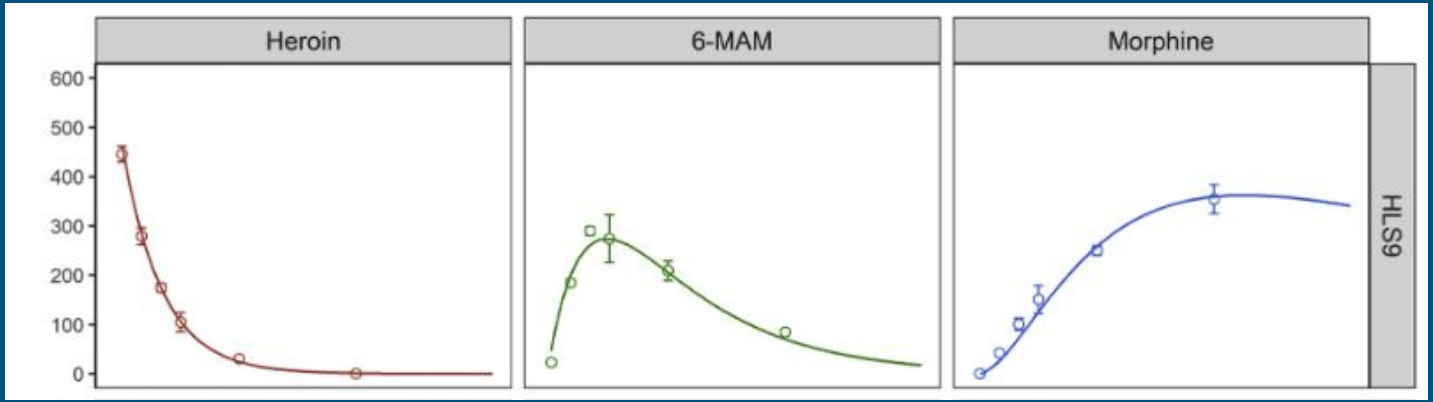
The advantages of having an accurate system that describes the effects of heroin is that it allows healthcare workers and pharmaceutical companies to properly prepare and predict negative effects on patients/users and develop strategies or drugs to combat them. With the controller included, you can even model how a potential drug would act within the system accurately.

The disadvantages we face are that the assumptions made in this model might make such strategies inaccurate on a larger scale as CES-2 and 6-MAM are found in various organs of the body including the lungs and the liver which add up to produce varying effects, making accurate prediction of enzyme kinetics and rates near impossible, and possibly leading to unforeseen side-effects.



Next steps

- Do Block Diagram in Transfer Function
- Bode Plots
- Fix concentrations to fit known behavior



Questions?

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