Comparison between modes of contraceptive delivery with a focus on estradiol pharmacokinetics

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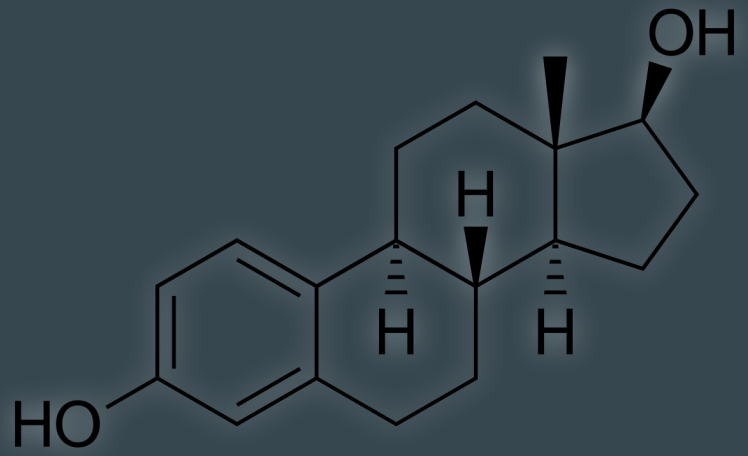


Introduction:

Three estrogens in human body:

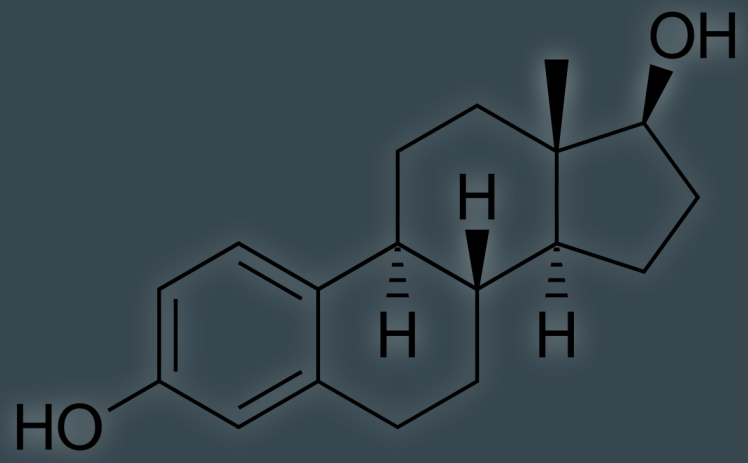
- Estradiol being the strongest

Main functions of estrogen:

1. Reproductive system
2. Menstruation cycle

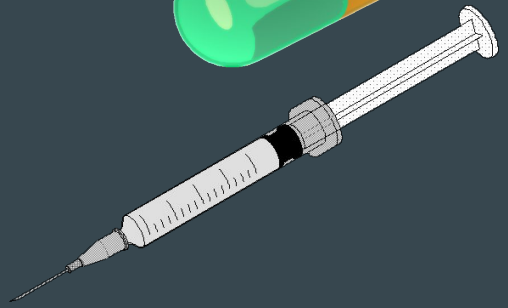
Therefore:

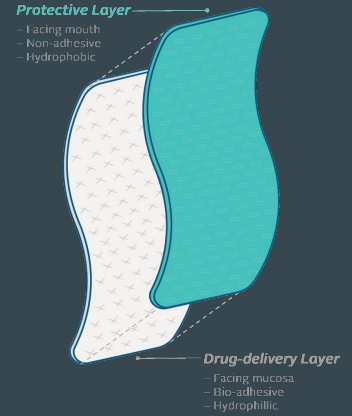
3. A mean to control bodily behaviors



Introduction:

	Injection	Patches	Pill	IUD
Frequency	Every 3-4 months	Every 3 weeks	Everyday	3-10 years
Cost	$140-300 per year	$0-1800 per year covered	$0-$600 per year covered	$0-$1300 per operation
Reliability	94%	91%	91%	99%





What is PBPK ?

PBPK = Physiologically Based Pharmacokinetics

A mathematical modeling technique for predicting the absorption, distribution, metabolism and excretion (ADME) of substances in humans.

Multi-compartment models, with compartments corresponding to predefined organs or tissues, with interconnections corresponding to blood or lymph flows

A system of differential equations for concentration or quantity of substance on each compartment can be written, and its parameters represent blood flows, pulmonary ventilation rate, organ volumes etc

Model description and implementation:

Venous and arterial blood + 16 tissue compartments

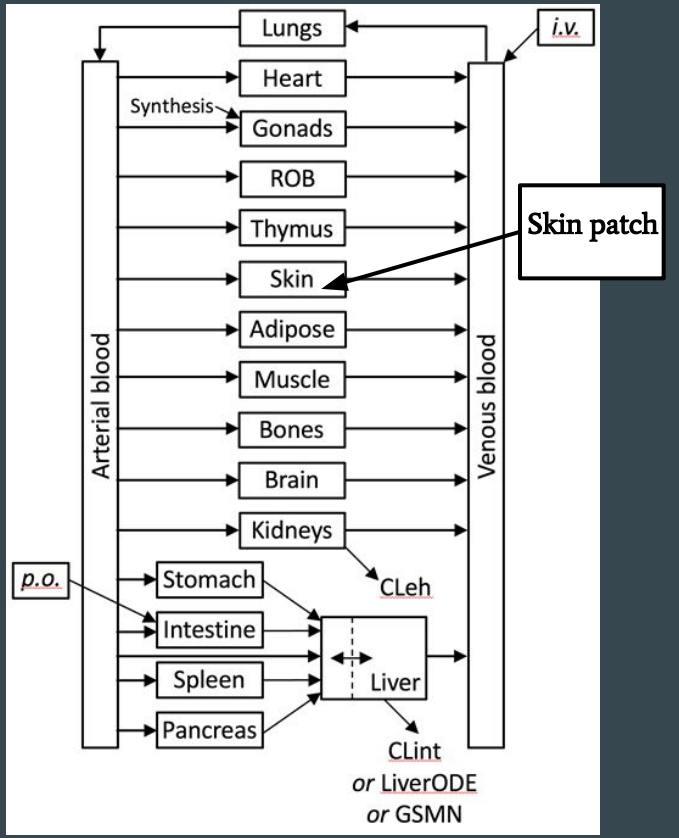
Except liver, all compartments are described as well-mixed, rapid equilibrium compartments, governed by convective flow of blood.

The liver is treated as a permeability-limited compartment with a separate tissue blood compartment.

Compartments to represent intravenous and oral delivery were added to the model, and a i.v. infusion constant was included to account for infusion delivery.

Skin patch: transdermal diffusion into blood

Volume, blood flow estimated based on body weight,height and age.



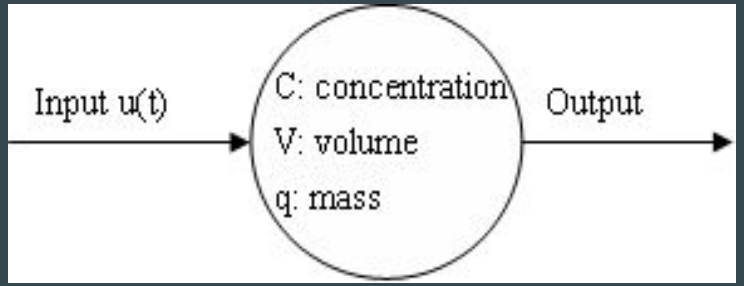
Model description and implementation: General Compartment

For a general compartment i :

$$\frac{dC_i}{dt} = Q_i * (C_a - C_i) + R$$

The flux Q is governed by convection of blood flow.
Ca: arterial level Ci: compartment level

R: reactions, such as binding to ER or SHBG
Solved by scipy.odeint

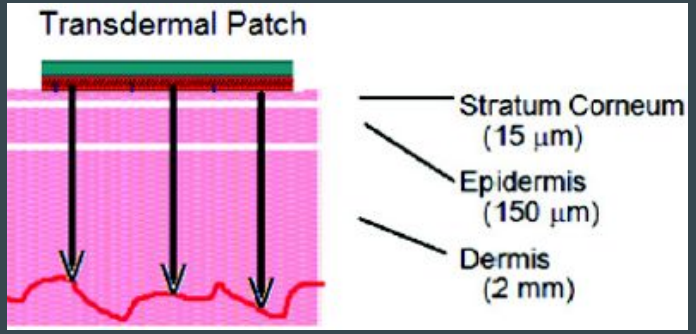


Model description and implementation: Epidermal Diffusion

For dermal absorption, FTCS model:

$$C_{i,j+1} = \frac{\Delta t D}{\Delta x^2}\left(C_{i-1,j} - 2C_{i,j} + C_{i+1,j}\right) + C_{i,j}$$

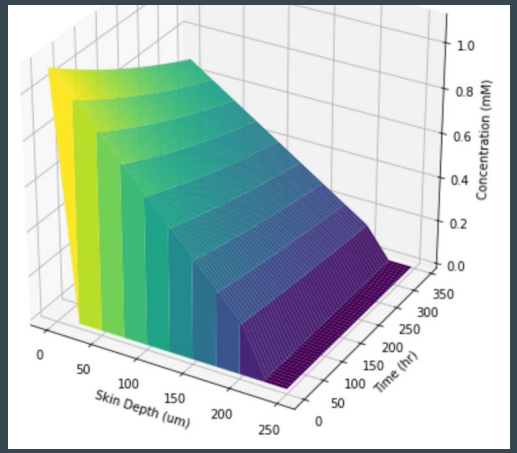
D is diffusivity, i is distance step, j is time step.
Recursive formulation solved by dynamic programming



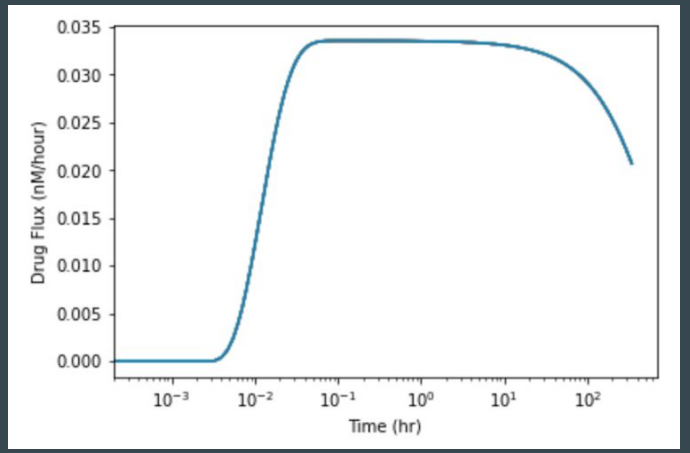
Assumptions:
1. Blood concentration is negligible compared to skin concentrations
2. Transdermal patch has first order drug release kinetics
3. Blood is evenly situated 250 μm from surface
4. Skin layers are of even depth

Finite Element Analysis

Drug Concentration vs Skin Depth and Time



Drug Flux vs Time

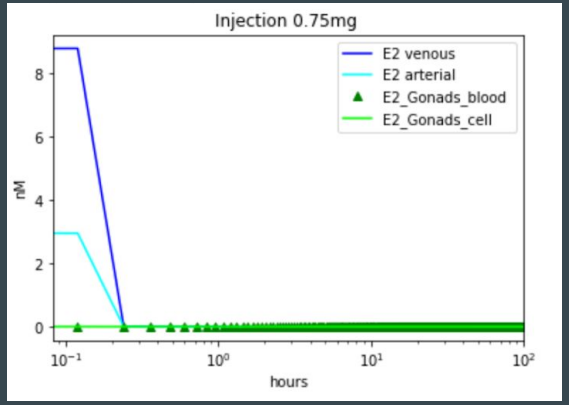


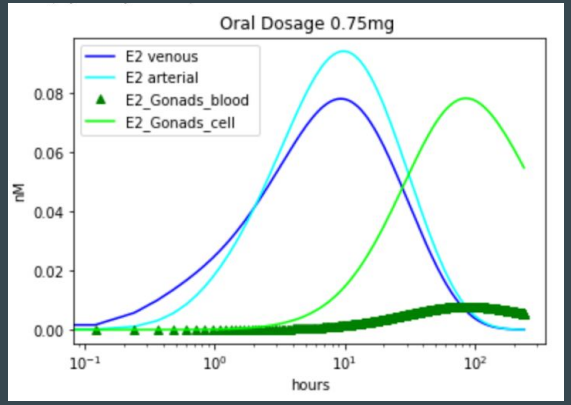
Finite element method to approximate drug diffusion from skin patch to layers of human skin, stratum corneum, viable epidermis and dermis.

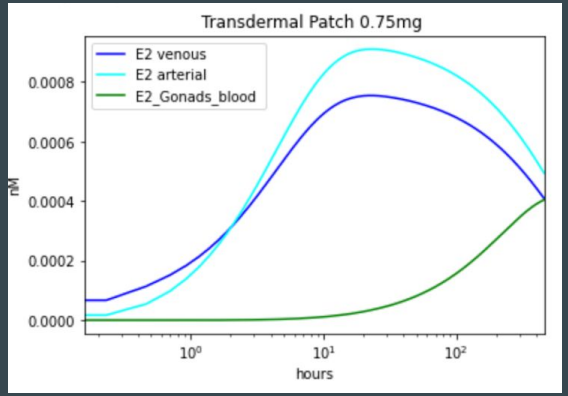
Generate a vector of drug fluxes into last layer of skin compartment across time.

Drug dosage: 0.75 mg estradiol (2753.5 nanomoles)

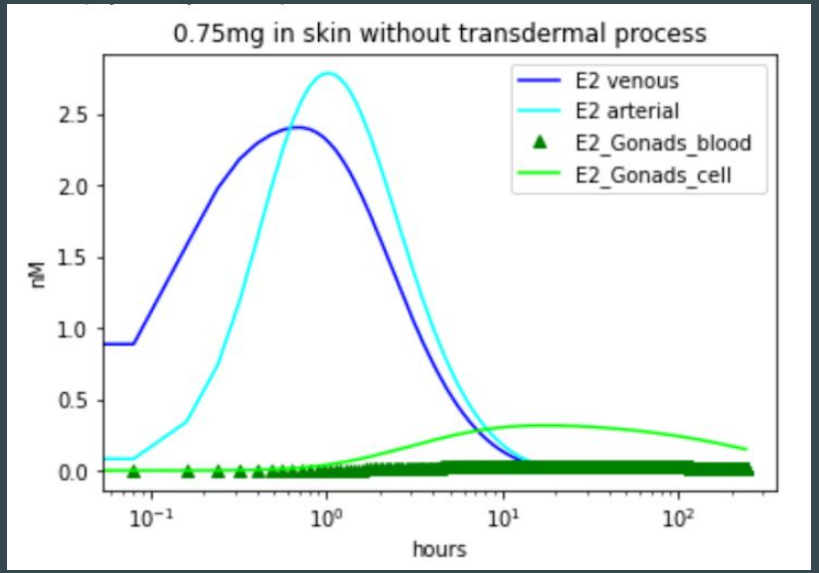
System of differential equations to simulate PBPK I.V. Injection/Skin Patch/Oral Uptake

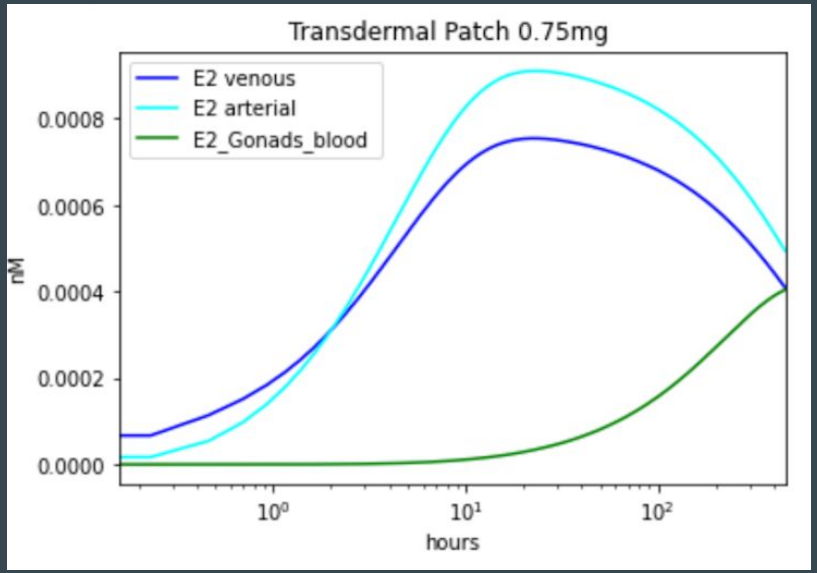






Before and After the addition of transdermal process



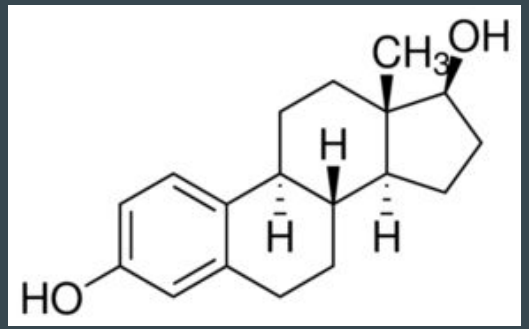


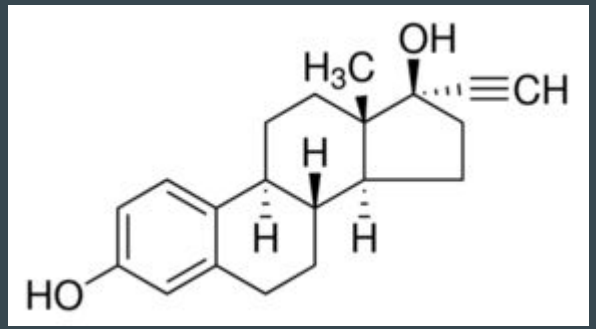
Discussion: Injection, Transdermal, Oral

- Distribution of estradiol in gonads mirrors blood concentration with time delay
- Presence of barriers decreases blood concentration but increases sustained presence-stronger barriers have a larger effect
- Oral and transdermal delivery allow for higher sustained blood concentrations relative to injection but lower maximal concentration
- Transdermal delivery has lower maximal concentration and higher sustained concentration relative to oral delivery

Discussion-Relevance to Real World Systems

- Addition of FTCS transdermal diffusion increases relevance to experimental results of transdermal patches
- Concentrations of oral and transdermal modes of delivery yield lower than physiological values
    - We model using estradiol, most contraceptives use synthetic analogues such as ethinyl estradiol





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Thanks for watching