Scaling Rules for Designing Intra-vaginal Rings and PK Studies in Animals vs. Humans

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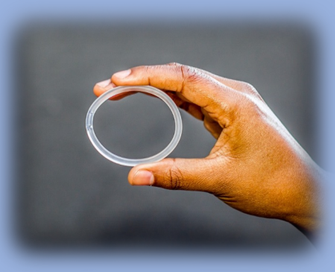
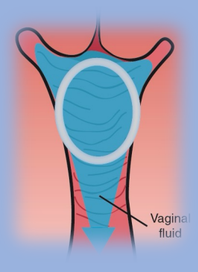
Intravaginal rings (IVRs) provide controlled release of drug/s for up to 1 year - for systemic (e.g. contraception) and topical (e.g. prophylaxis against ST-HIV) targets.

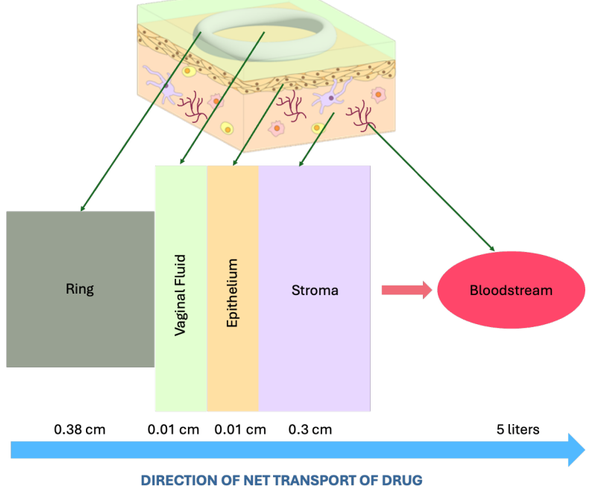




Experimental design (e.g. drug loads) of PK studies across different species (sheep, macaque, human) for IVR-drug combos must be rationally scaled for meaningful interpretation and application of resulting PK data.

Our PK scaling analysis is based on a **1D, multicompartment, diffusional mass transport model** which predicts topical delivery via IVR for the anti-HIV drug Islatravir

Representative Human Model:



Computational ODE/PDEs Model:

IVR
$$\frac{\partial C}{\partial t} = D_r \cdot \frac{\partial^2 C}{\partial x^2} + \frac{D_r}{x} \cdot \frac{\partial C}{\partial x}$$

Vaginal Fluid
$$\frac{\partial C}{\partial t} = D_f \cdot \frac{\partial^2 C}{\partial x^2} - k_f \cdot C$$

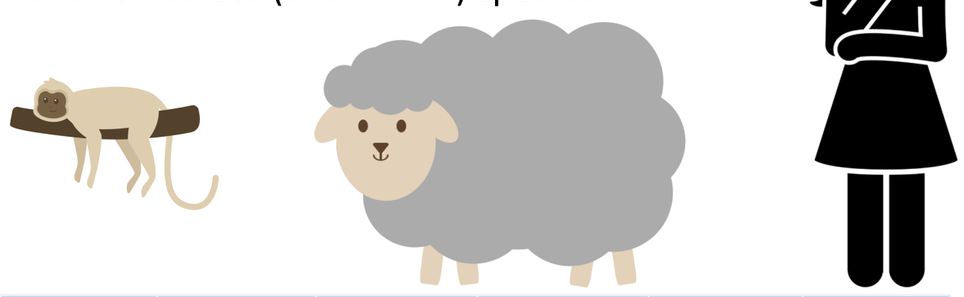
Epithelium
$$\frac{\partial C}{\partial t} = D_e \cdot \frac{\partial^2 C}{\partial x^2}$$

Stroma
$$\frac{\partial C}{\partial t} = D_s \cdot \frac{\partial^2 C}{\partial x^2} - k_s \cdot C$$

Bloodstream
$$\frac{dB}{dt} = \frac{k_s \cdot V_s}{V_b} \cdot T - k_b \cdot B, \quad T = \frac{1}{x_4 - x_3} \int_{x_3}^{x_4} C dx$$

Scaling Across Species:

Scaling is necessary to account for biophysiological variation across (and within) species.



	V. Fluid Surface Area	Epithelial Thickness	Stromal Thickness	Blood Volume	Stromal Volume
Human	70 – 130 cm^2	100-200 µm	1.26 – 1.54 mm	3.5 - 6.5 L	8.8 – 20 cm^3
Macaque	32 – 59 cm^2	200-300 µm	0.9-1.1 mm	0.7 – 1.3 L	2.9 – 6.5 cm^3
Sheep	53 – 97 cm^2	70-100 µm	1.17-1.43 mm	2.73 – 5.07 L	2.9 – 6.5 cm^3

Scaling even just ring thickness across species has a significant effect on model output

AFTER 28 DAYS, HUMAN: 20% Drug Released
MACAQUE: 39% Drug Released

Rules for Scaling:

- To ensure comparable PK across species, we implement two new scaling rules and compare performance with traditional allometric scaling.
- The two rules deduce drug loads for sheep and macaque IVRs vs human IVRs by computing ratios of (animal to human) IVR drug loads.

Rule 1: Time and volume-averaged drug concentration in stroma over 28 days (C^*_{28}) is conserved across two species.

Rule 2: RMS (root-mean-square difference) of instantaneous volume-averaged drug concentrations in stroma (C^*) between two species is minimized over 28 days.

Conventional Allometric Rule: Ratio of initial drug mass in IVR to stromal tissue volume is conserved across two species.

Scaling Results:

Rules 1 and 2 have similar results for optimal ratio of macaque to human IVR drug loads for varied parameter combos:

0 avg, + large, - small size
Ratio = C_{oM} / C_{oH}

Parameter Combination	Rule 1	Rule 2	Allometric
0 0	0.66	0.64	1.04
0 +	1.18	1.17	1.87
0 -	0.41	0.39	0.63
+ 0	0.38	0.37	0.65
+ +	0.68	0.67	1.17
+ -	0.24	0.23	0.39
- 0	1.26	1.25	1.96
- +	2.25	2.26	3.52
- -	0.78	0.76	1.17

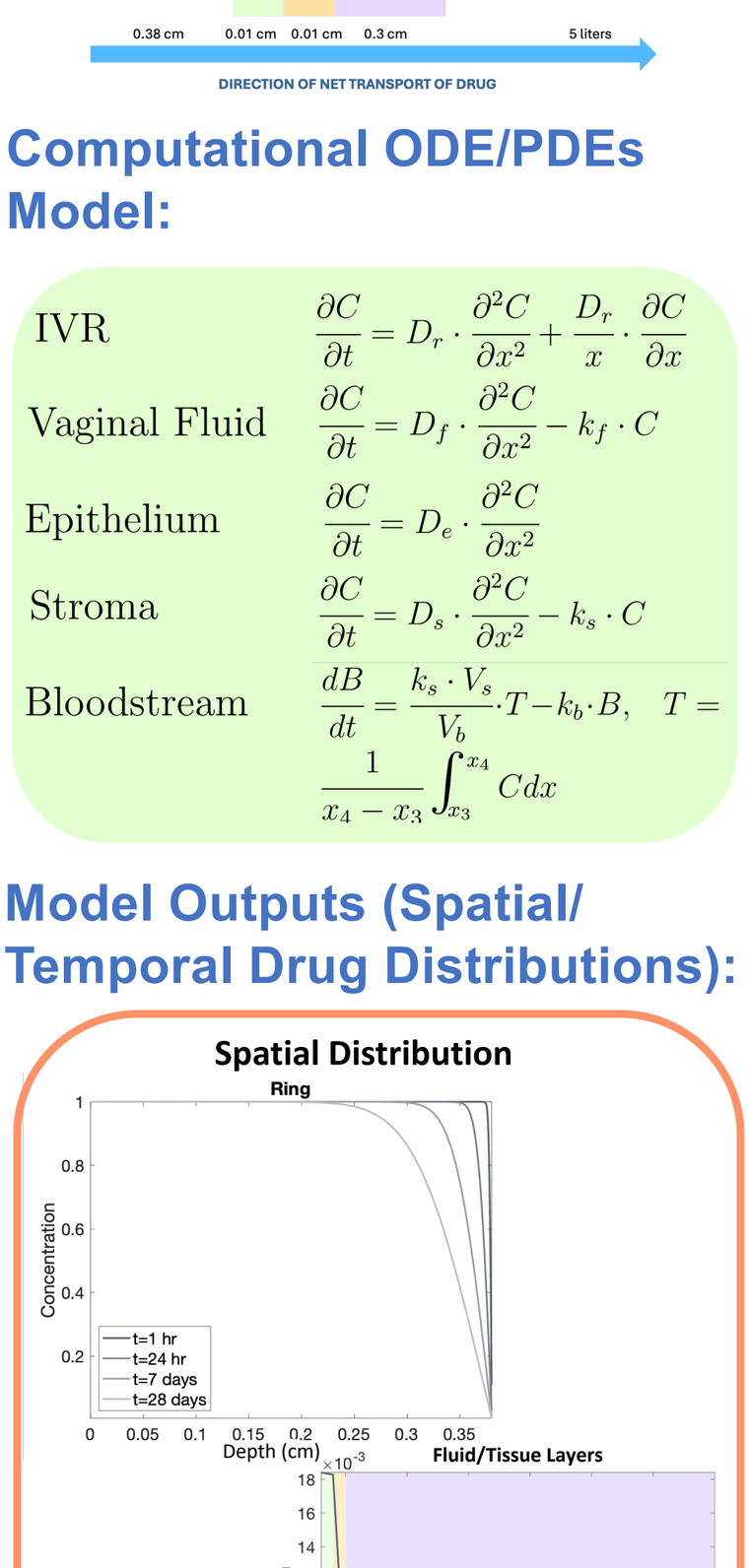
Rule 1 vs Allometric Scaling:

Species	Relative C_o		t_{max} (hrs) (1=a)
	Rule 1	Allometric	
Human	1	1	7.26
Sheep	1.52	1.43	6.91
Macaque	0.50	0.78	9.60
	C_{max}/C_o x 10^{-3}		
Human	5.95	5.95	
Sheep	5.95	6.24	
Macaque	9.60	6.08	

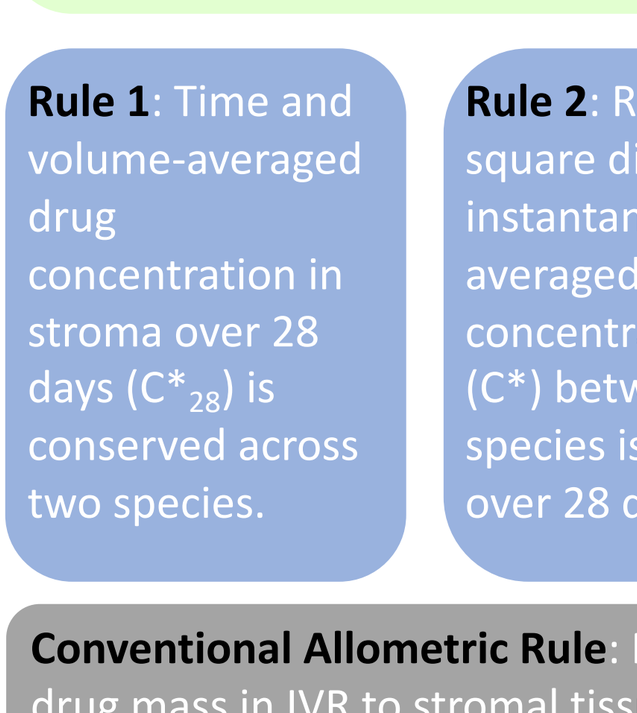
Key Takeaways:

- Our two new Scaling Rules gave similar results.
- Model-determined drug loading was higher in sheep and lower in macaques vs. humans.
- Rules vs. Allometric differences were greater for macaques than sheep.
- PK cannot be entirely equated across species, and model predictions guide experimental protocols/interpretations of PK results.
- Results show the importance of mass transport theory for harmonizing PK measures of IVR performance via scaling across species.

Model Outputs (Spatial/ Temporal Drug Distributions):

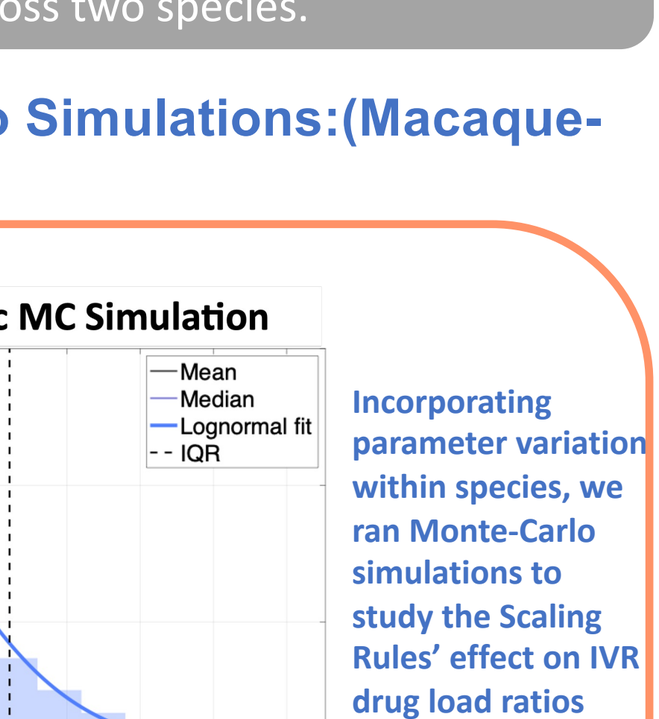


Monte Carlo Simulations:(Macaque-Human)



Incorporating parameter variation within species, we ran Monte-Carlo simulations to study the Scaling Rules' effect on IVR drug load ratios

Compared to the Allometric Rule, Rule 1 shifts the histogram of ratios to the left.



Next Steps:

- Expanded sensitivity analysis/uncertainty quantification
- Expanded comparison of model and experimental results
- Incorporate drug solubility variation across compartments

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