Population Pharmacokinetic Modelling of a Subcutaneous Depot for Degarelix

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Outline of Presentation

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- Aims of the analysis
- Mechanism of action
- Methods
  - Flexible zero-order input model
  - Diffusion out of a SC depot
  - B-spline estimation of effective SC depot-volume
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- Results
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  - Analytical and discretized solution
  - Controlling factors for SC depot release
- Conclusion

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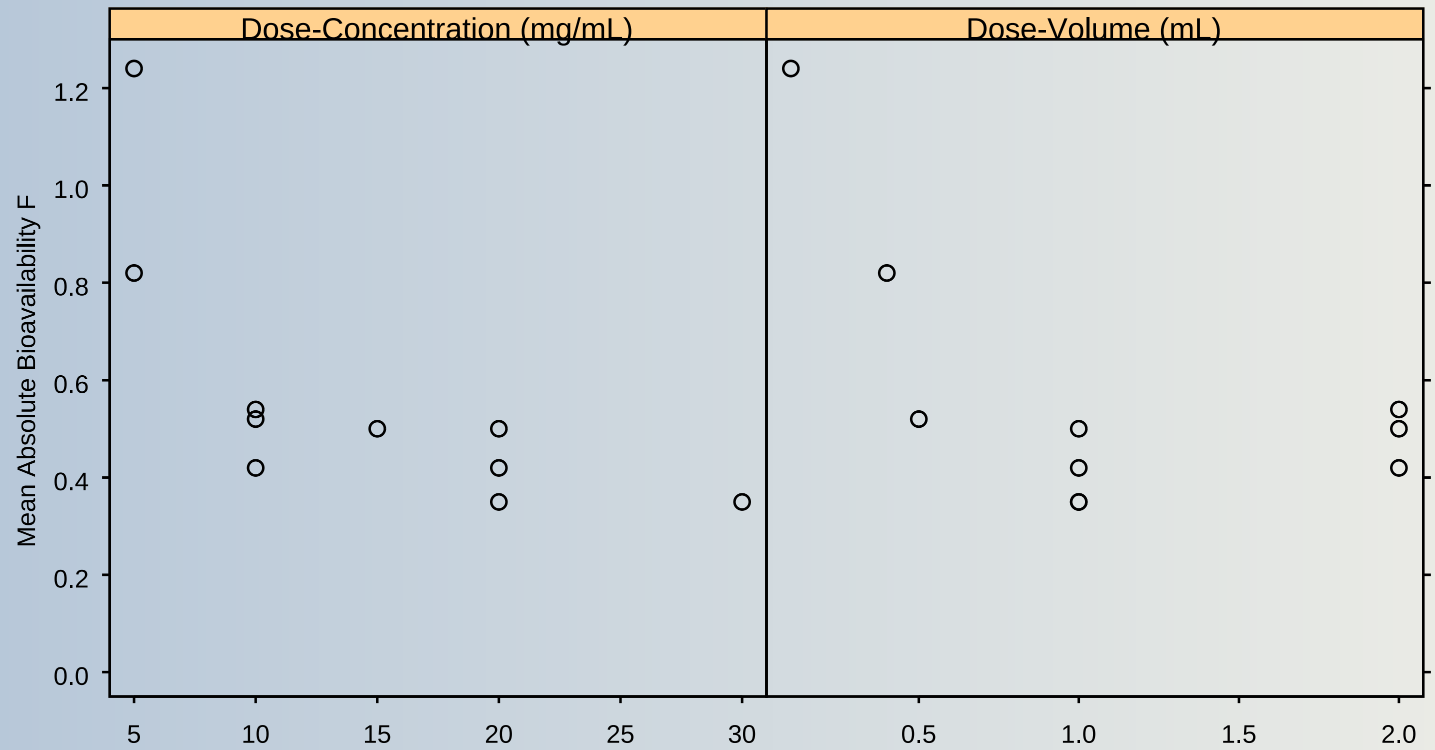
Background

- GnRH antagonist degarelix, which currently is being developed for prostate cancer treatment, forms a spontaneous SC depot after SC injections.
- From non-compartmental analysis (NCA), the release from the depot appears to be both dose-concentration and dose-volume dependent.



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Aims of the analysis

- Describe PK profile of SC injected degarelix
- Determine controlling factors for SC release
  - Dose-concentration effect on bioavailability
  - Dose-volume effect on rate of absorption
- Build a population PK model of a SC depot

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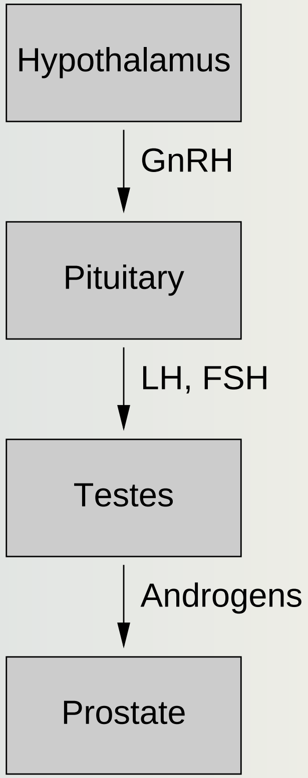
Mechanism of action

- Hypothalamic-Pituitary-Gonadal (HPG) Axis
  - GnRH is released in a pulsatile fashion from the hypothalamus
  - Binding at pituitary stimulates LH and FSH secretion
  - Gonadotrophs stimulates production of androgens in the testes
  - Prostate growth depends on androgen levels



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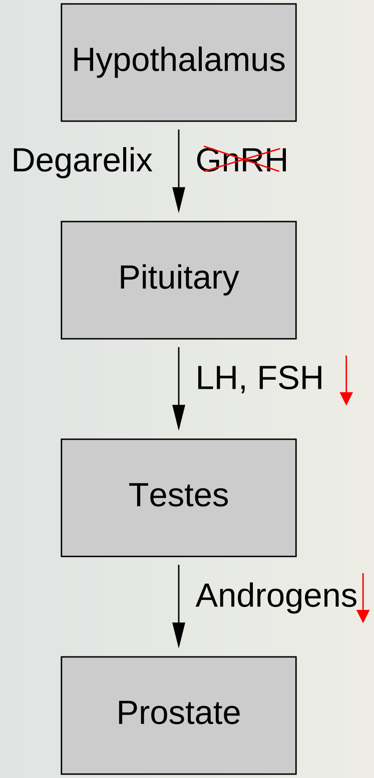
  - GnRH is released in a pulsatile fashion from the hypothalamus
  - Binding at pituitary stimulates LH and FSH secretion
  - Gonadotrophs stimulates production of androgens in the testes
  - Prostate growth depends on androgen levels
  - Degarelix is a competitive GnRH antagonist which inhibits gonadotroph secretion and thereby testosterone production



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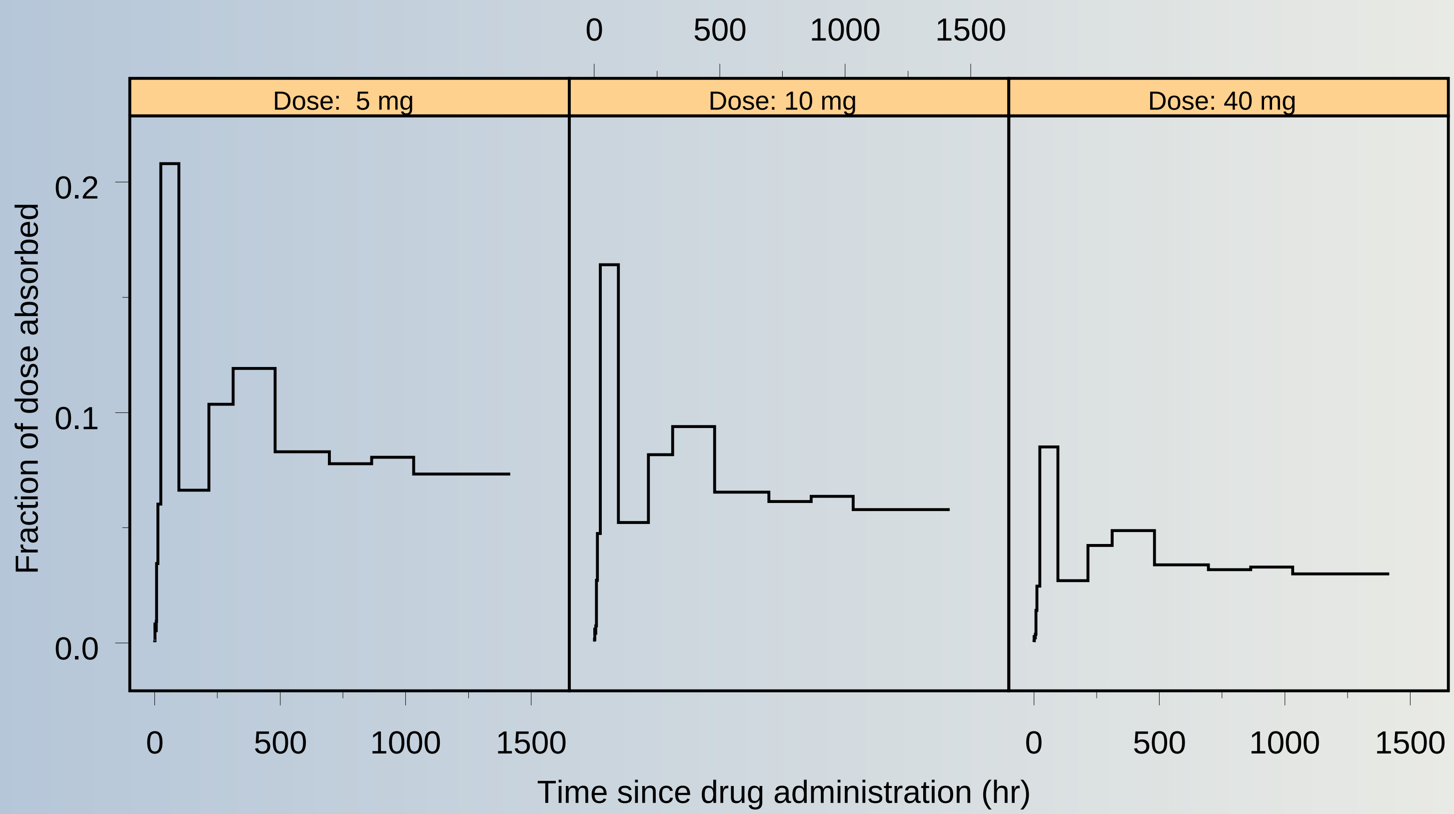
Methods

- Deconvolution of subcutaneous release
  - Flexible zero-order input model



Lindberg-Freijs *et al.*, *Biopharm. Drug Dispos.*, **15**(1):75–86 (1994)

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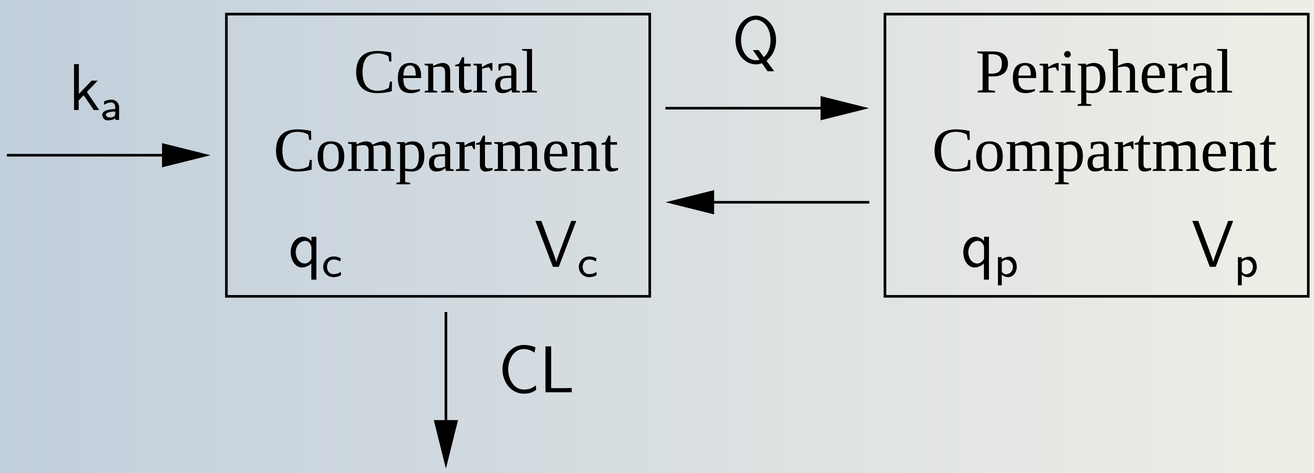
Methods

- Absorption model
  - First-order absorption kinetics
  - The rate-limiting step is the diffusion from the injection site to the blood vessels



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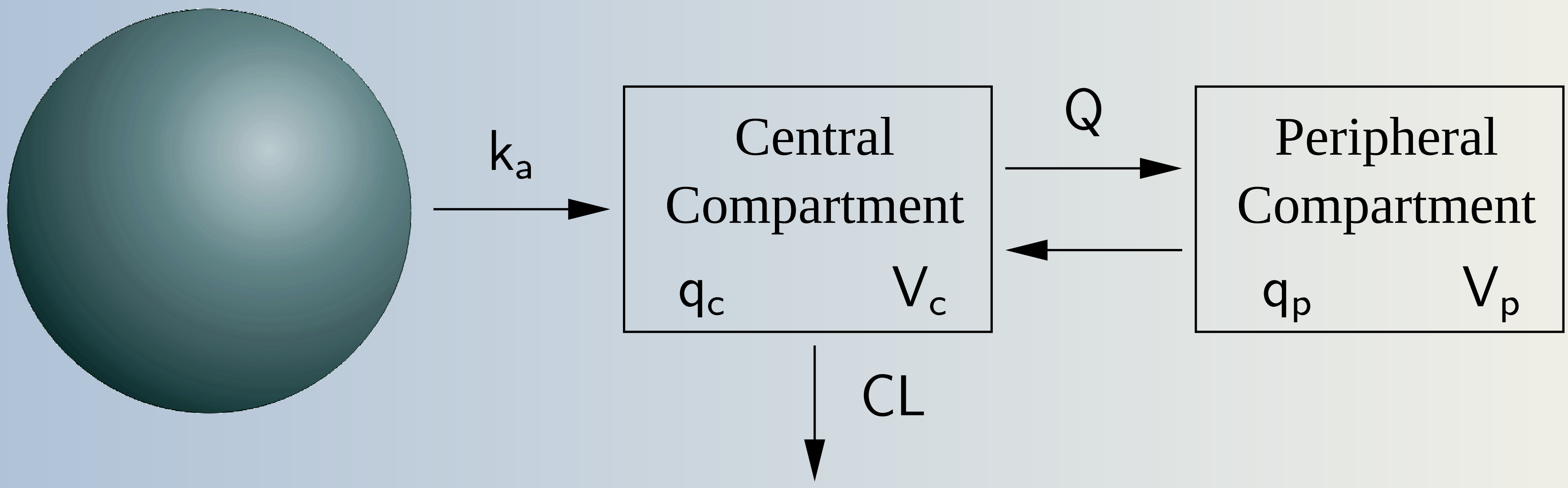
Methods

- Absorption model
  - Diffusion out of SC depot
  - The rate-limiting step is the diffusion out of the depot



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Methods

- Diffusion out of a spherical SC depot
  - Fick's second law of diffusion over a spherical control volume yields

$$\frac{\partial C}{\partial t} = D\nabla^2 C = D\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial C}{\partial r}\right), \quad 0 < r \leq R_d, \quad t \geq 0$$

  - Partial differential equation with both time and radial distance as independent variables.
  - Not suitable for estimation of parameters in NONMEM.
  - A numerical approximation is therefore needed.

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Methods

- Spatial discretization of SC depot
  - Assuming spatially constant flow from a shell with radius $\bar{R}_i$ to a shell with radius $\bar{R}_{i+1}$, Fick's second law for shell $i+1$ can be approximated by

$$\frac{\partial C_{i+1}}{\partial t} \approx \frac{C_{i+1,n+1} - C_{i+1,n}}{\Delta t} = -\frac{1}{V_{i+1}}\left(f_{i+1,n} - f_{i,n}\right)$$

where

$$f_i = 4\pi D \frac{\bar{R}_{i+1}\bar{R}_i}{\bar{R}_i - \bar{R}_{i+1}}\left(C_{i+1} - C_i\right)$$

is the flow out of shell i.

Wach *et al.*, *Med.Biol.Eng Comput.*, **33**(1):18–23 (1995)

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Methods

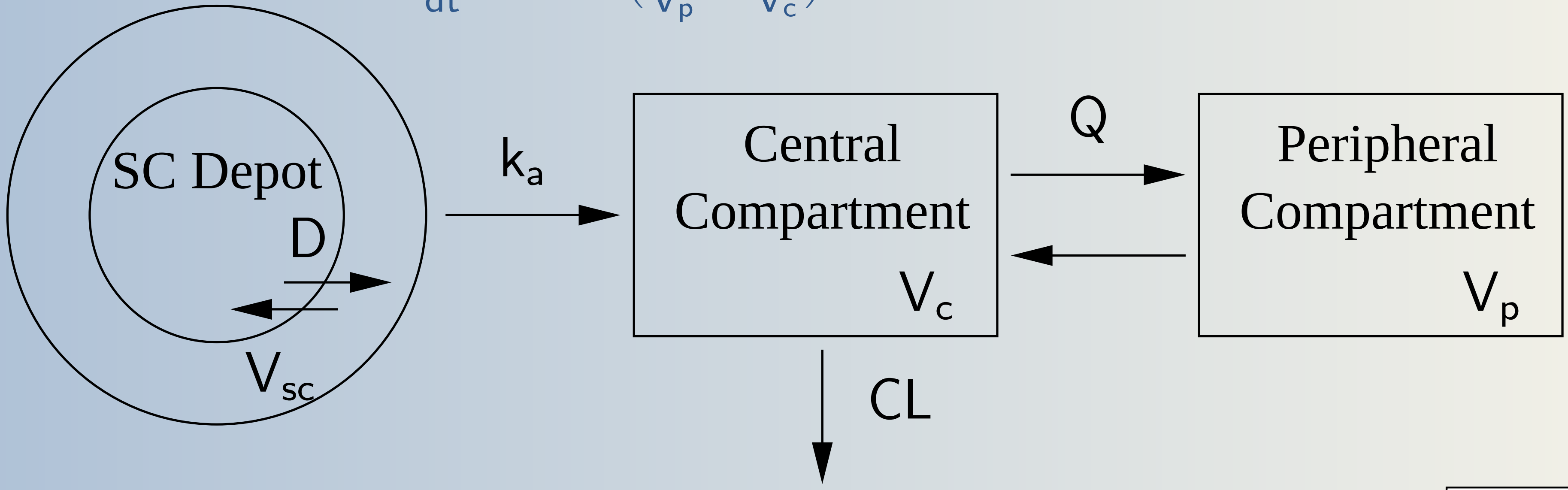
- Population PK model of a spherical SC depot

$$\frac{dq_{sc,0}}{dt} = -4\pi D \frac{\bar{R}_1 \bar{R}_0}{\bar{R}_0 - \bar{R}_1}\left(\frac{q_{sc,0}}{V_{sc,0}} - \frac{q_{sc,1}}{V_{sc,1}}\right)$$

$$\frac{dq_{sc,1}}{dt} = 4\pi D \frac{\bar{R}_1 \bar{R}_0}{\bar{R}_0 - \bar{R}_1}\left(\frac{q_{sc,0}}{V_{sc,0}} - \frac{q_{sc,1}}{V_{sc,1}}\right) - k_a F q_{sc,1}$$

$$\frac{dq_c}{dt} = k_a F q_{sc,1} + Q \cdot \left(\frac{q_p}{V_p} - \frac{q_c}{V_c}\right) - CL \cdot \frac{q_c}{V_c}$$

$$\frac{dq_p}{dt} = -Q \cdot \left(\frac{q_p}{V_p} - \frac{q_c}{V_c}\right)$$



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Methods

- Population PK model of a spherical SC depot

$$\frac{dq_{sc,0}}{dt} = -4\pi D \frac{\bar{R}_1 \bar{R}_0}{\bar{R}_0 - \bar{R}_1} \left(\frac{q_{sc,0}}{V_{sc,0}} - \frac{q_{sc,1}}{V_{sc,1}} \right)$$

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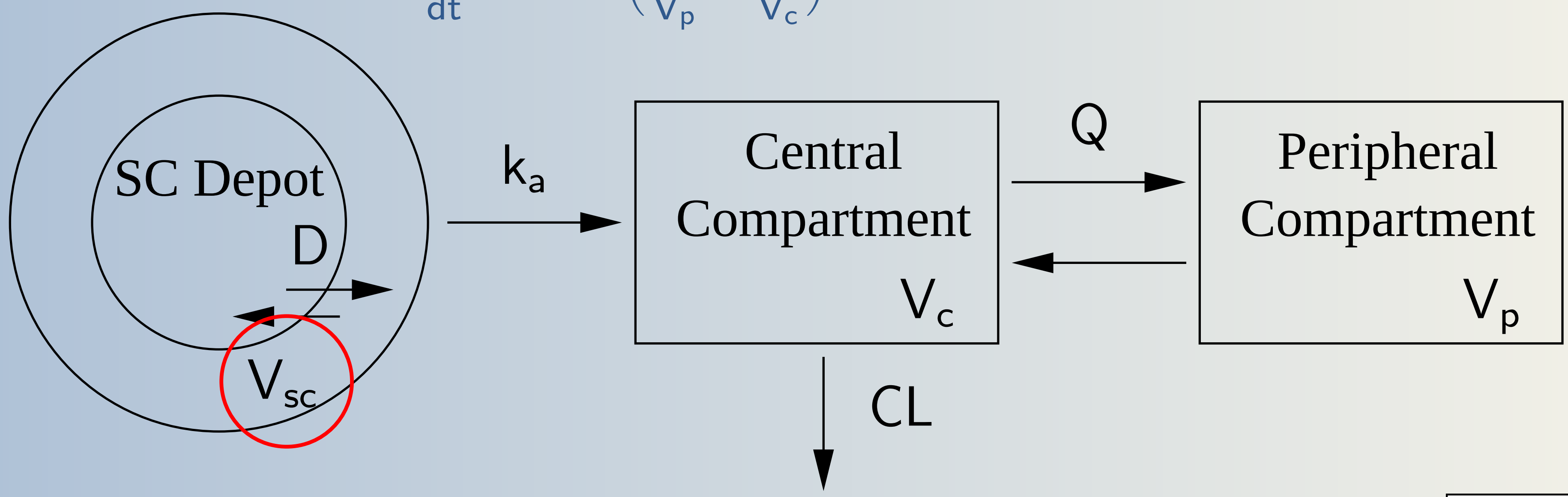

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Methods

- Estimation of effective depot-volume
  - Relate dose-volume to effective depot-volume
  - B-spline basis function

$$f(x) = \sum_{i=1}^{p} \phi_i B_i(x)$$

where x is the dose-volume, ϕ_i are the parameters to be estimated, and the $B_i(x)$ values are the B-spline basis functions.

  - Knots placed at the different dose-volumes.
  - Piecewise linear function assumed between knots.
  - Monotone non-decreasing spline function ($\phi_i \leq \phi_{i+1}$)

Fattinger *et al.*, *Biometrics*, **51**(4):1236–1251 (1995)

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Data

- Dosing schemes for SC and IV phase I studies

Group	Dose-Level	Dose-Volume	Dose-Concentration	Route
1	0.5 mg	0.1 mL	5 mg/mL	SC
2	2.0 mg	0.4 mL	5 mg/mL	SC
3	5.0 mg	0.5 mL	10 mg/mL	SC
4	10 mg	1.0 mL	10 mg/mL	SC
5	20 mg	1.0 mL	20 mg/mL	SC
6	30 mg	2.0 mL	15 mg/mL	SC
7	30 mg	1.0 mL	30 mg/mL	SC
8	40 mg	1.0 mL x 2 [a]	20 mg/mL	SC
9	40 mg	2.0 mL x 2 [a]	10 mg/mL	SC
10	40 mg	2.0 mL	20 mg/mL	SC
A	1.5 μg/kg	0.3 mL/kg	5 μg/mL	IV (15 min.)
B	6.0 μg/kg	1.2 mL/kg	5 μg/mL	IV (15 min.)
C	15 μg/kg	3.0 mL/kg	5 μg/mL	IV (45 min.)
D	30 μg/kg	6.0 mL/kg	5 μg/mL	IV (45 min.)

[a] These groups received the dose as two SC injections.

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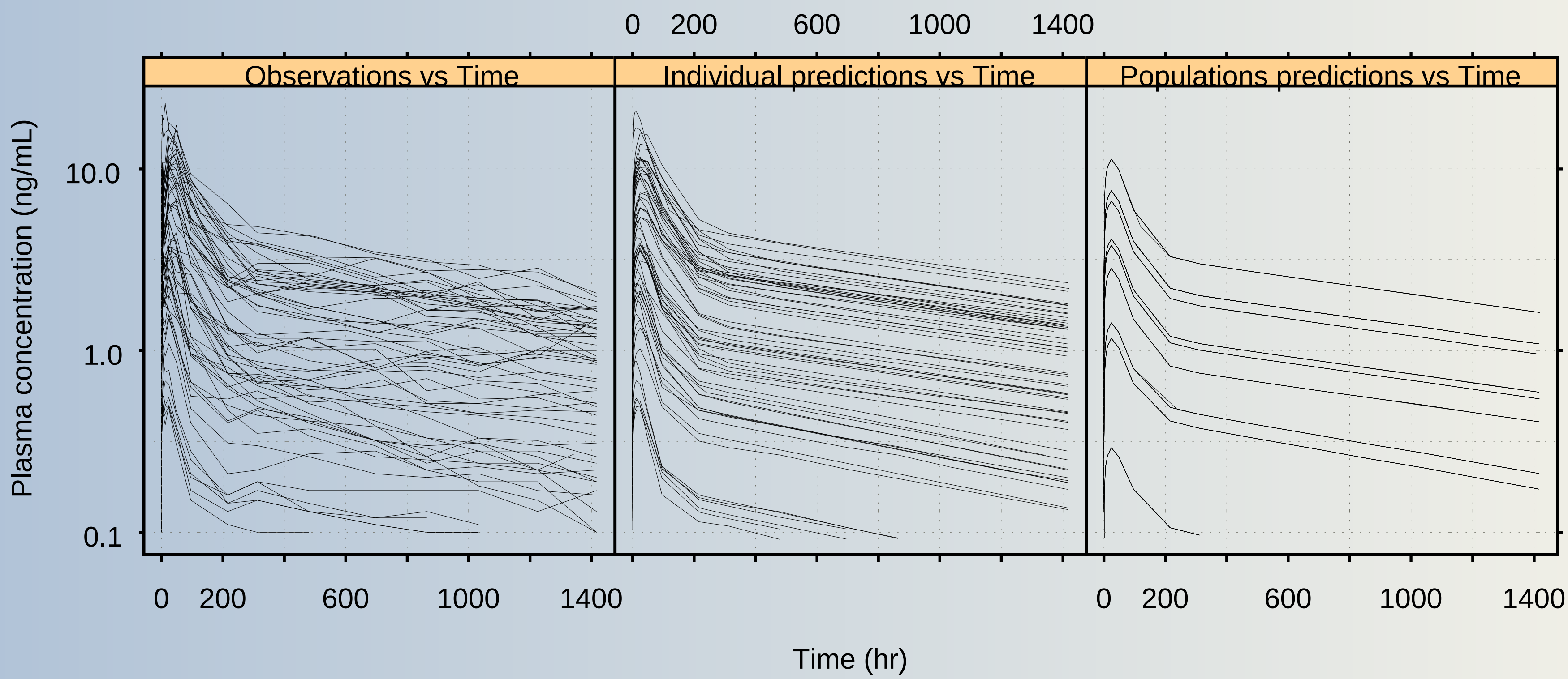
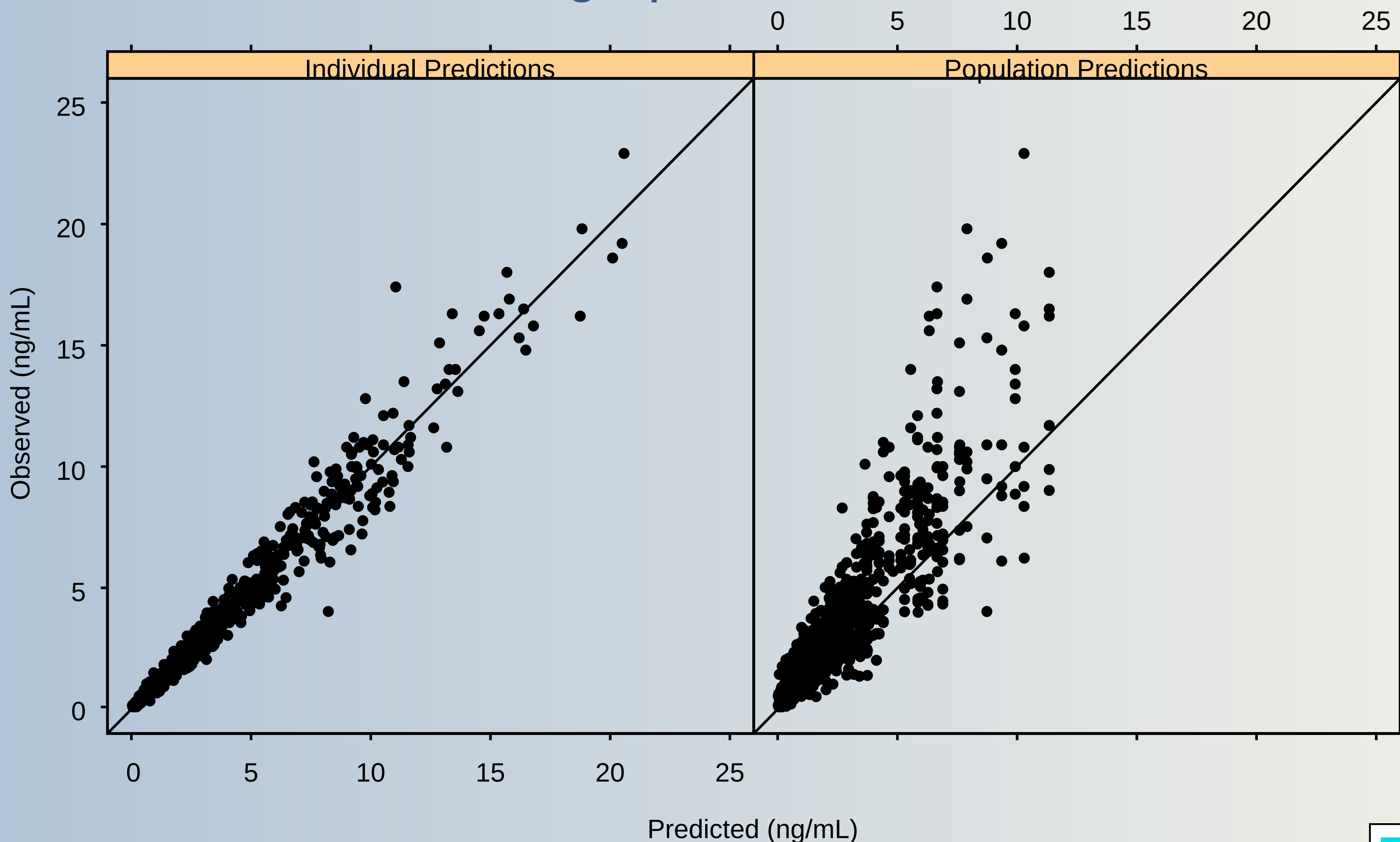
Results

- Population PK Model of a SC depot
  - Observed and predicted plasma concentrations



Results

- Population PK Model of a SC depot
  - Goodness-of-fit graphs



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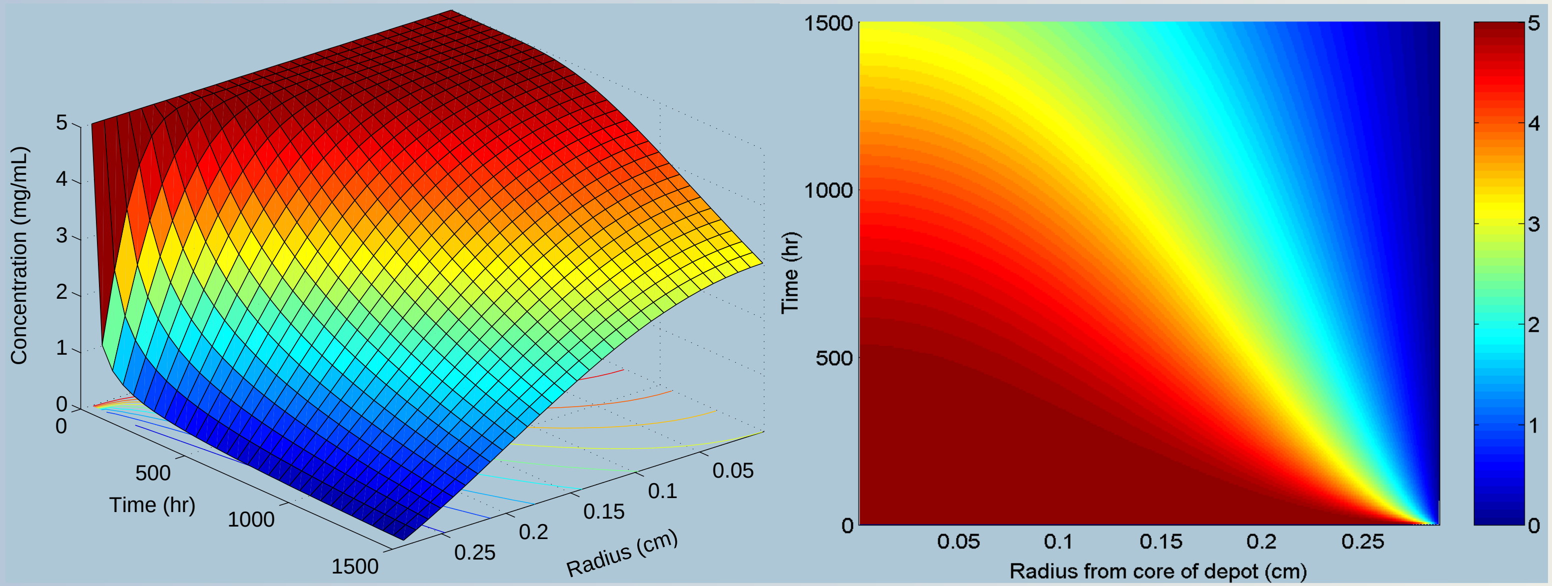
Results

- Population PK Model of a SC depot
  - Solution to Fick's second law of diffusion

$$C(r,t) = C_0 \sum_{n=1}^{\infty} E_n \exp\left(-k_n^2 \frac{D}{R_d^2} t\right) \frac{R_d}{r} \sin\left(k_n \frac{r}{R_d}\right)$$

  - Analytical SC depot concentration



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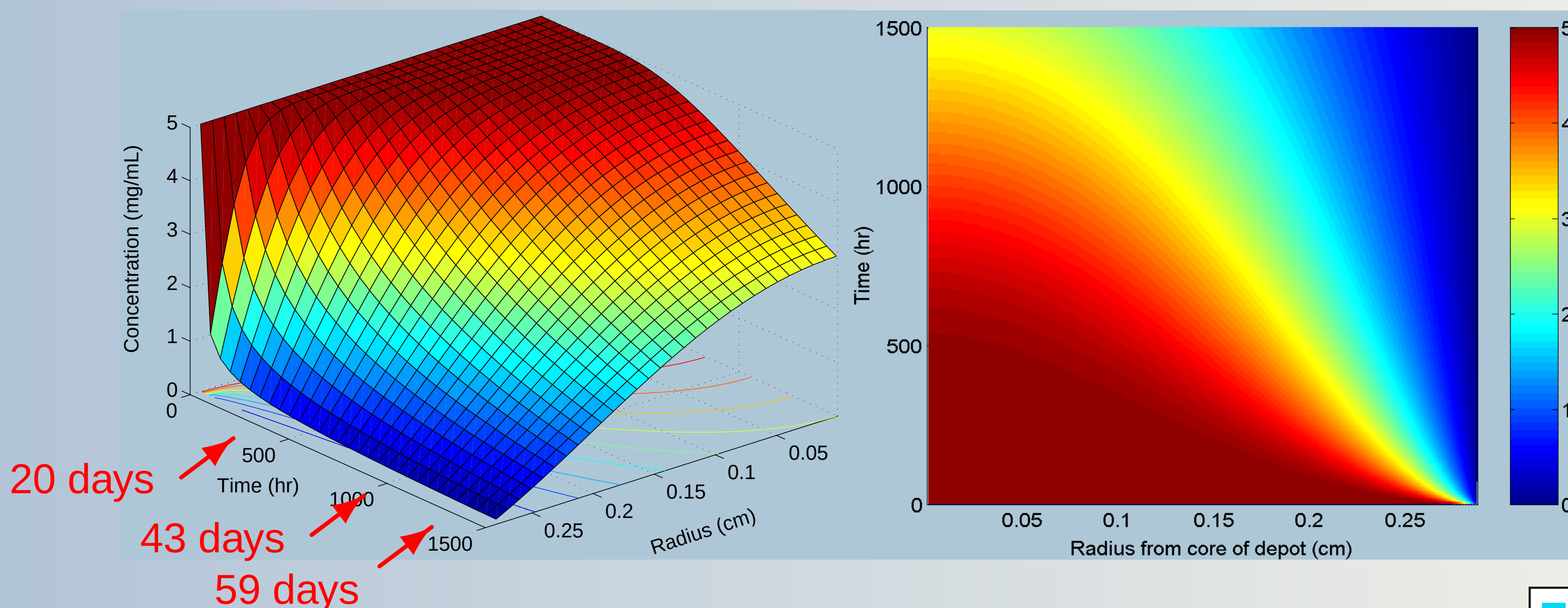

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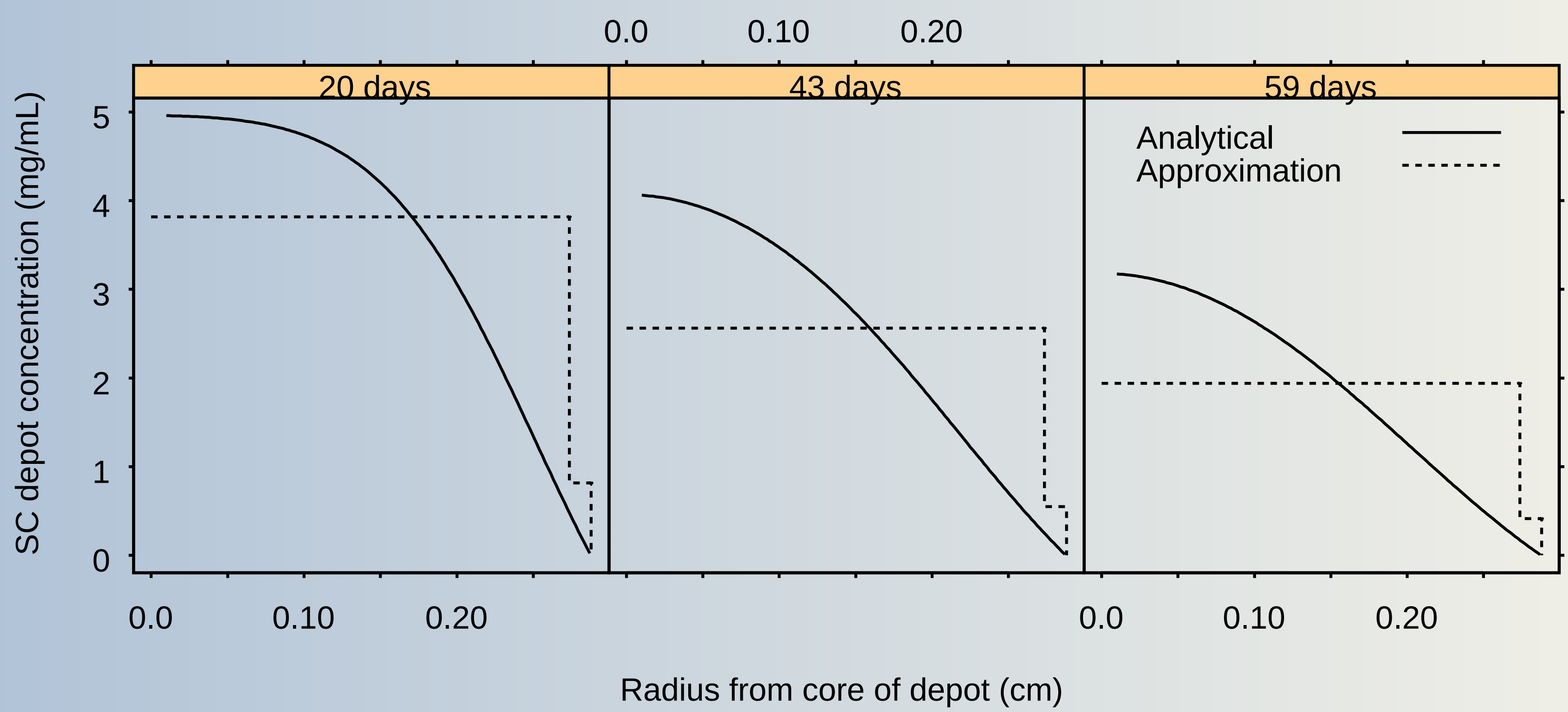
Results

- Population PK Model of a SC depot
  - Analytical and discretized SC depot concentration



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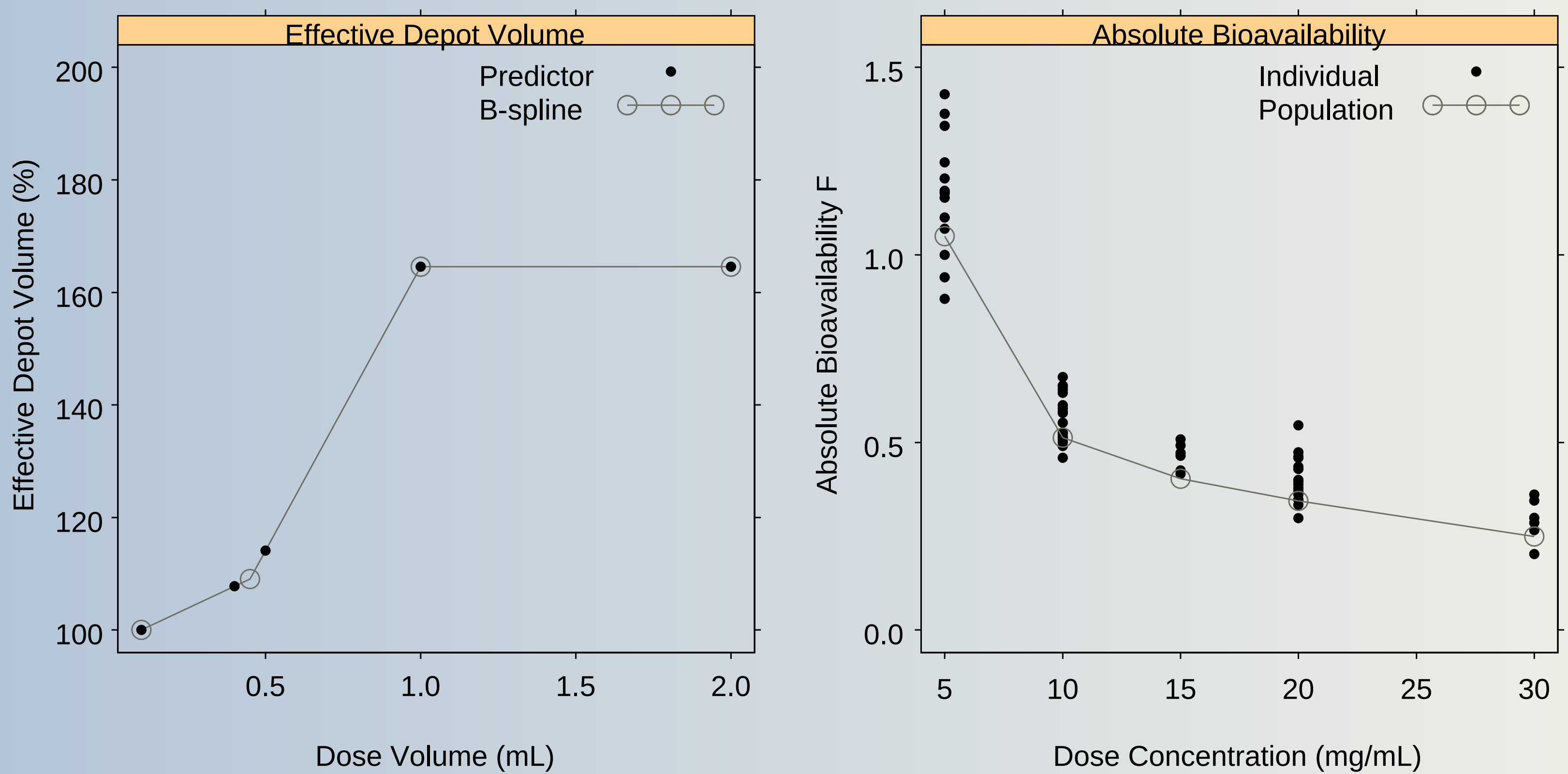
Results

- Controlling factors for SC release
  - Dose-volume effect only at low injection volumes
  - Bioavailability ↓ when dose-concentrations ↑



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Conclusion

- Subcutaneous depot
  - Initial fast release before rigid depot formation
  - Sustained slow release out of depot
  - Modelled as diffusion out of a spherical SC depot
- Controlling factors for SC release
  - Low dose-volumes results in faster SC release due to shorter distance out of the depot
  - Diminishing dose-volume effect at injection volumes of 1 mL and above due to slower formation of a rigid gel in large SC depots.
  - Bioavailability decreases with increasing dose-concentrations
- Manuscript submitted to Pharmaceutical Research in May 2003

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