Stochastic Differential Equations in NONMEM

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Aims of analysis

- Introduce stochastic differential equations (SDEs) to population PK/PD modelling.
- Illustrate the Extended Kalman Filter for parameter estimation in SDEs
- Show implementation of SDEs in NONMEM VI
- Application to PK/PD data of GnRH antagonist degarelix for tracking of parameters and deconvolution of effect model.

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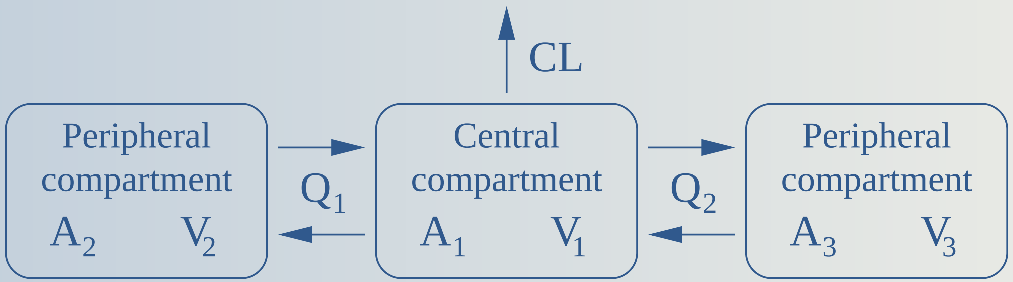
  - Decomposes the residual error into system and measurement noise.
  - Can be used as a diagnostic tool for model appropriateness.
  - Provides a framework for pinpointing model deficiencies.

ODEs vs SDEs

- Ordinary differential equations (ODEs)
  - General
$$\begin{aligned} d\boldsymbol{A}_i/dt &= \boldsymbol{g}(\boldsymbol{\phi}_i, \boldsymbol{A}_i, \boldsymbol{d}) \\ \boldsymbol{y}_{ij} &= \boldsymbol{f}(\boldsymbol{\phi}_i, \boldsymbol{A}_{ij}) + \boldsymbol{\epsilon}_{ij} \end{aligned}$$
  - Example



$$\begin{aligned} \frac{dA_1}{dt} &= \frac{Q_1}{V_2}A_2 + \frac{Q_2}{V_3}A_3 - \frac{CL + Q_1 + Q_2}{V_1}A_1 \\ \frac{dA_2}{dt} &= \frac{Q_1}{V_1}A_1 - \frac{Q_1}{V_2}A_2 \\ \frac{dA_3}{dt} &= \frac{Q_2}{V_1}A_1 - \frac{Q_2}{V_3}A_3 \end{aligned}$$

$$C_p = \frac{A_1}{V_1} + \epsilon$$

ODEs vs SDEs

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$$\begin{aligned} d\boldsymbol{A}_i &= \boldsymbol{g}(\boldsymbol{\phi}_i, \boldsymbol{A}_i, \boldsymbol{d})\,dt + \boldsymbol{\sigma}_w\,d\boldsymbol{w}_t \\ \boldsymbol{y}_{ij} &= \boldsymbol{f}(\boldsymbol{\phi}_i, \boldsymbol{A}_{ij}) + \boldsymbol{e}_{ij} \end{aligned}$$

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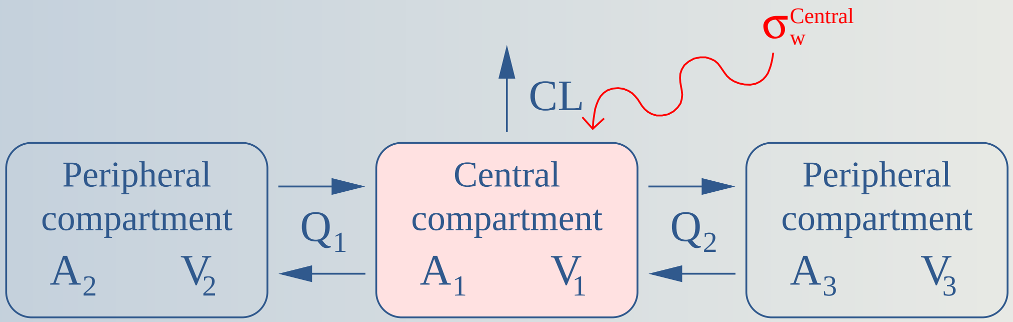

$$\begin{aligned} dA_1 &= \left(\frac{Q_1}{V_2}A_2 + \frac{Q_2}{V_3}A_3 - \frac{CL + Q_1 + Q_2}{V_1}A_1\right)dt + \sigma_w^{\text{Central}}dw_t \\ dA_2 &= \left(\frac{Q_1}{V_1}A_1 - \frac{Q_1}{V_2}A_2\right)dt \\ dA_3 &= \left(\frac{Q_2}{V_1}A_1 - \frac{Q_2}{V_3}A_3\right)dt \\ C_p &= \frac{A_1}{V_1} + e \end{aligned}$$

Extended Kalman Filter

- EKF algorithm for parameter estimation in SDEs

$$d\boldsymbol{A}_i = \boldsymbol{g}(\boldsymbol{\phi}_i, \boldsymbol{A}_i, \boldsymbol{d})\, dt + \boldsymbol{\sigma}_w\, d\boldsymbol{w}_t \qquad \boldsymbol{B} = \left.\frac{\partial \boldsymbol{g}}{\partial \boldsymbol{A}}\right|_{\boldsymbol{A}=\hat{\boldsymbol{A}}_{it}} \quad \boldsymbol{C} = \left.\frac{\partial \boldsymbol{f}}{\partial \boldsymbol{A}}\right|_{\boldsymbol{A}=\hat{\boldsymbol{A}}_{i(j|j-1)}}$$

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Prediction

1. Predict the state and covariance

$$\frac{d\hat{\boldsymbol{A}}_{t|j-1}}{dt} = \boldsymbol{g}(\phi, \hat{\boldsymbol{A}}_{t|j-1}, \boldsymbol{d})$$
$$\frac{d\boldsymbol{P}_{t|j-1}}{dt} = \boldsymbol{B}\boldsymbol{P}_{t|j-1} + \boldsymbol{P}_{t|j-1}\boldsymbol{B}^T + \boldsymbol{\sigma}_w^2$$

2. Predict the observations

$$\hat{\boldsymbol{y}}_{j|j-1} = \boldsymbol{f}(\phi, \hat{\boldsymbol{A}}_{j|j-1})$$
$$\boldsymbol{R}_{j|j-1} = \boldsymbol{C}\boldsymbol{P}_{j|j-1}\boldsymbol{C}^T + \boldsymbol{\sigma}^2$$

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Measurement Update

1. Calculate the Kalman gain

$$\boldsymbol{K}_j = \boldsymbol{P}_{j|j-1}\boldsymbol{C}^T\boldsymbol{R}_{j|j-1}^{-1}$$

2. Update the state and covariance

$$\hat{\boldsymbol{A}}_{j|j} = \hat{\boldsymbol{A}}_{j|j-1} + \boldsymbol{K}_j(\boldsymbol{y}_j - \hat{\boldsymbol{y}}_{j|j-1})$$

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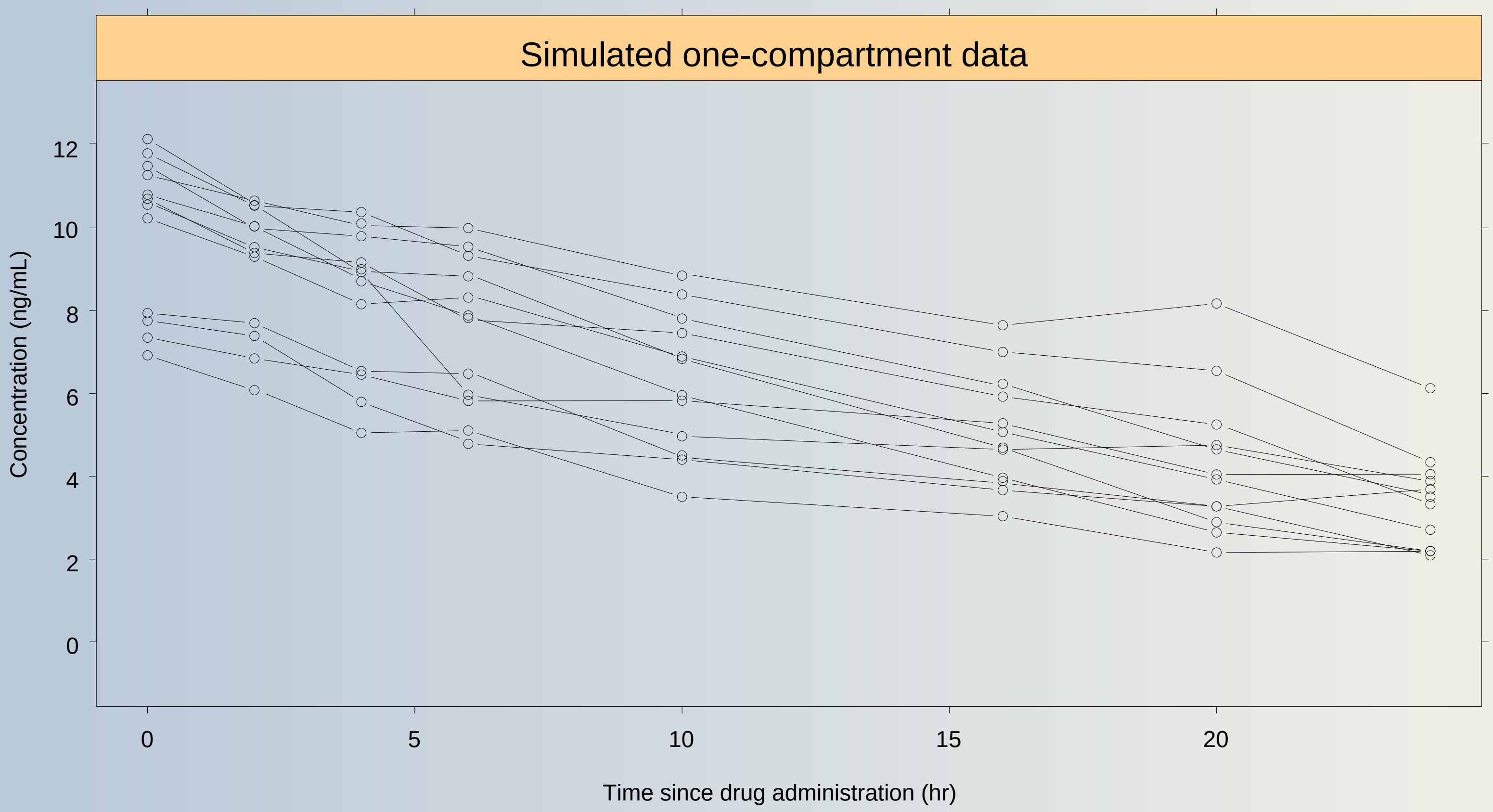
Visualization of Extended Kalman Filter



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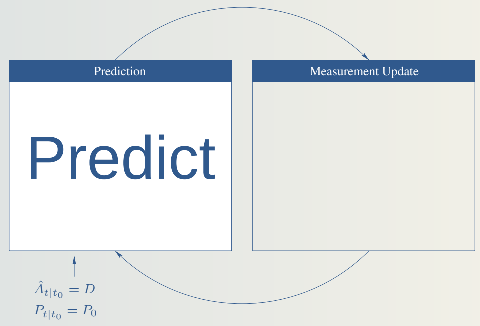

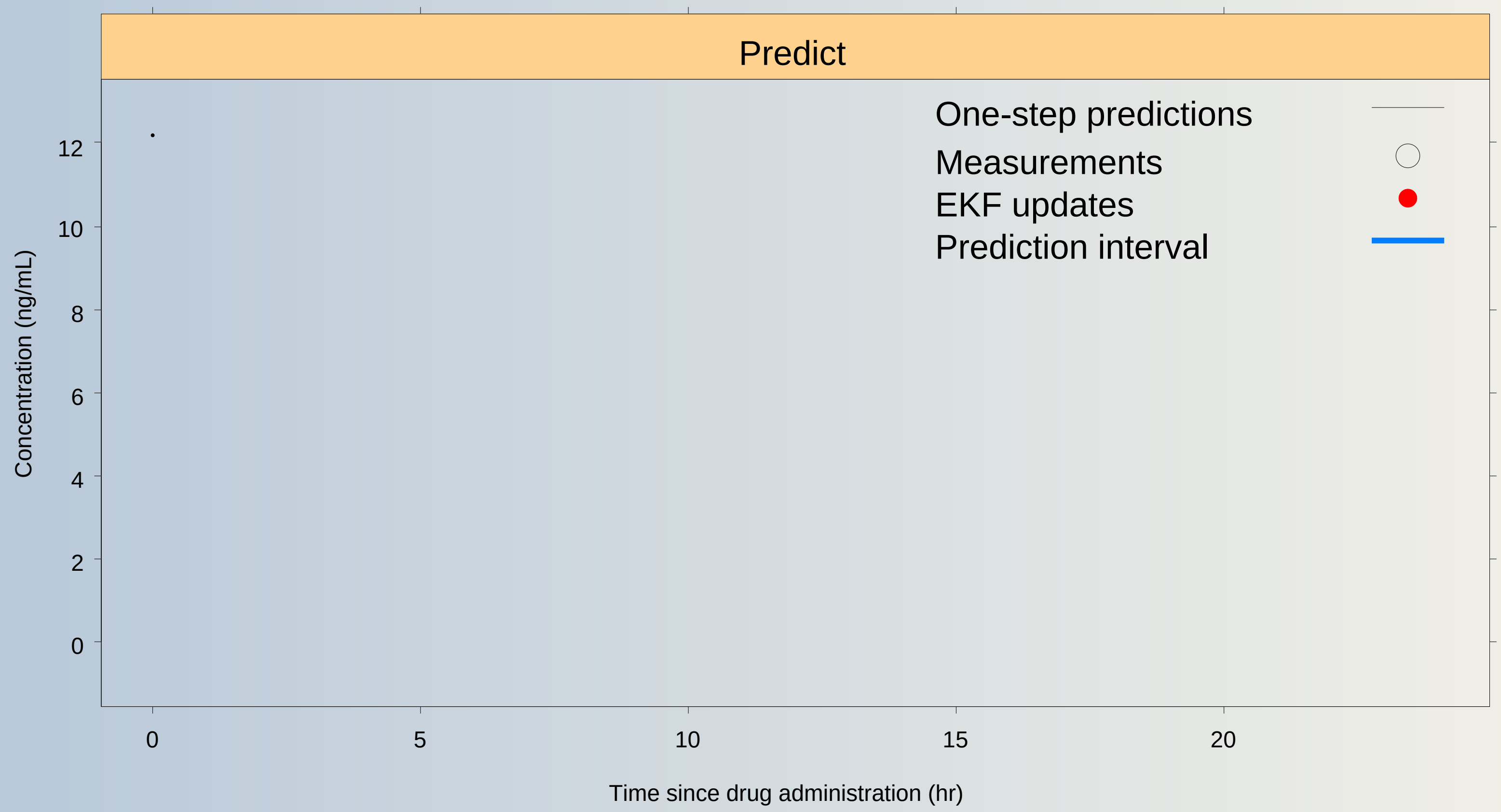

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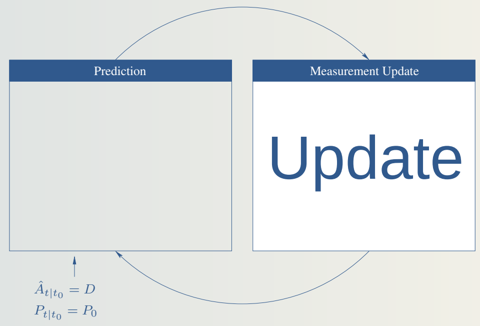

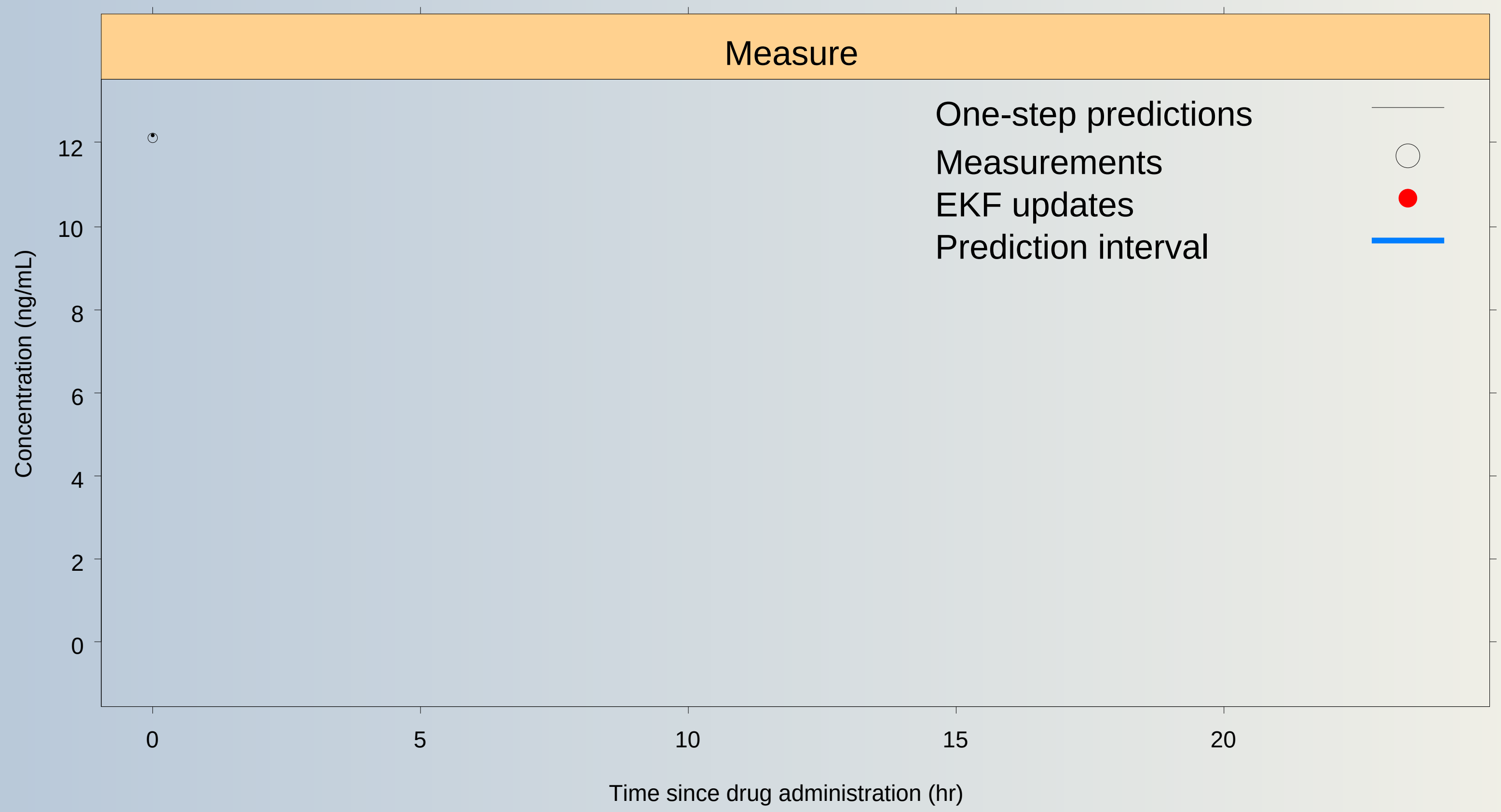

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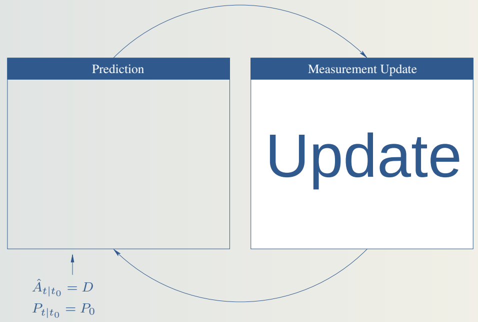

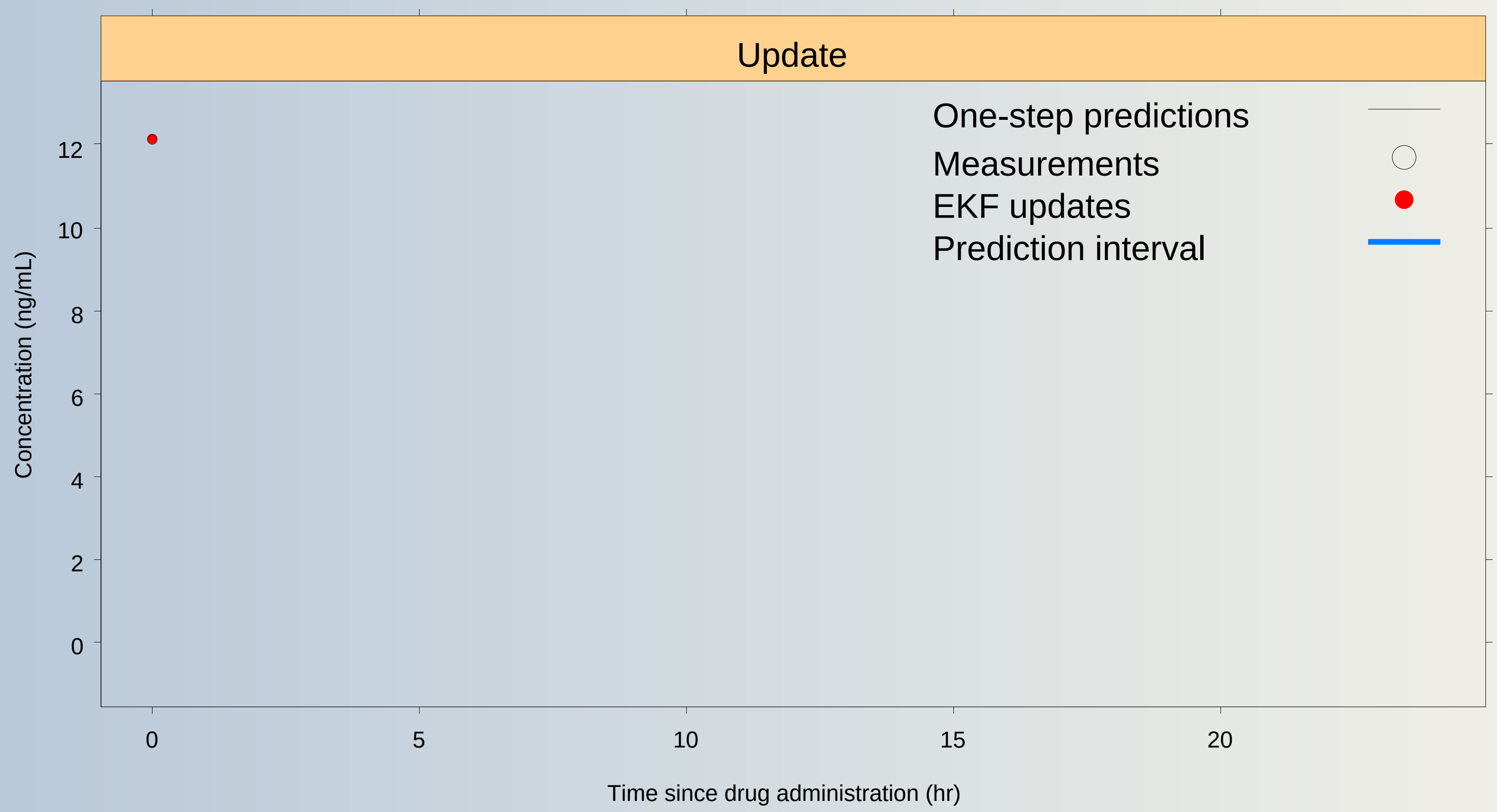

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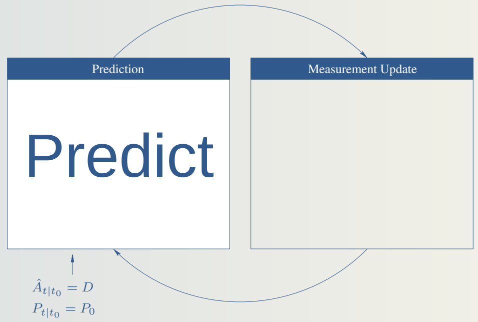

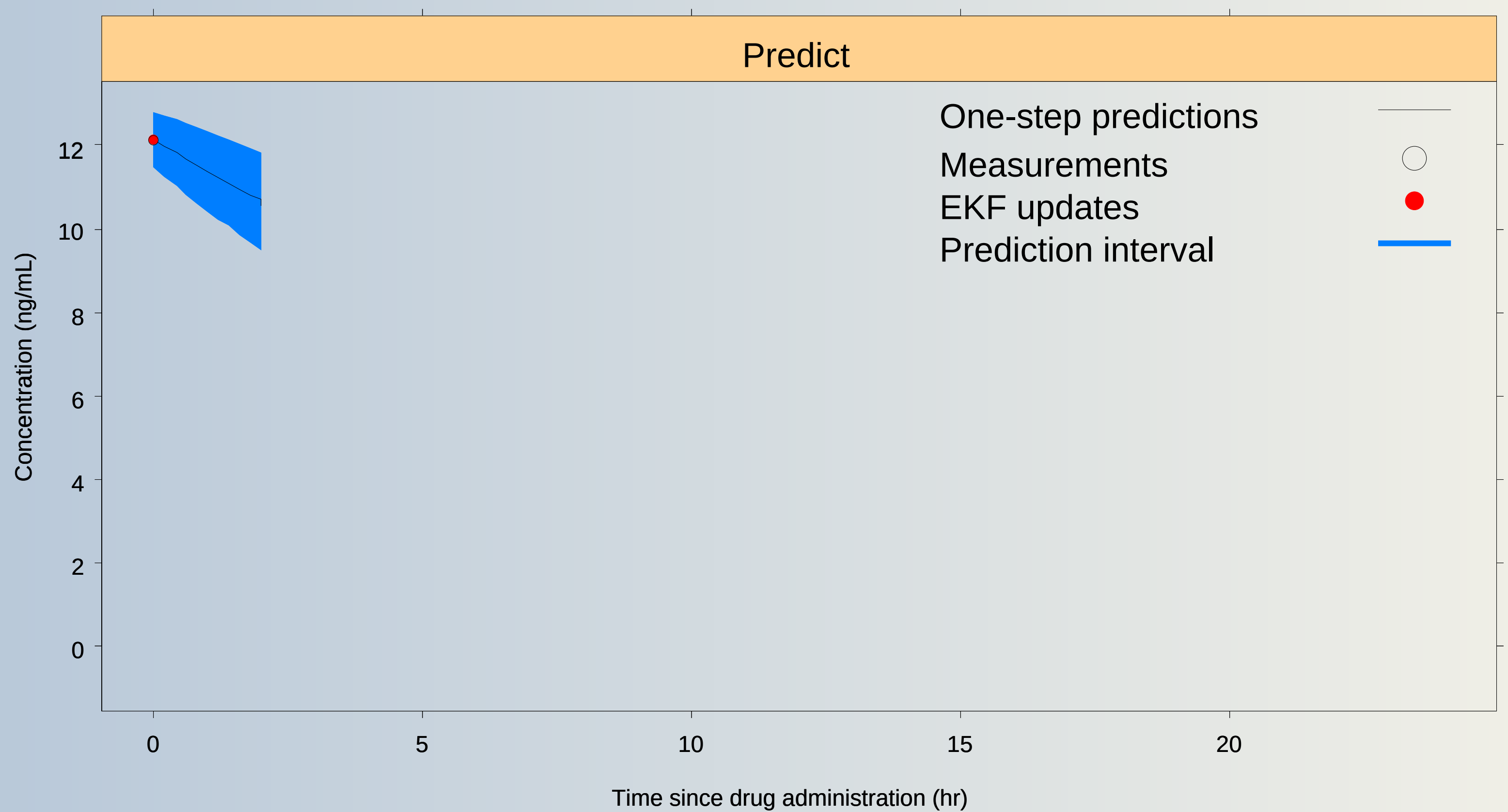

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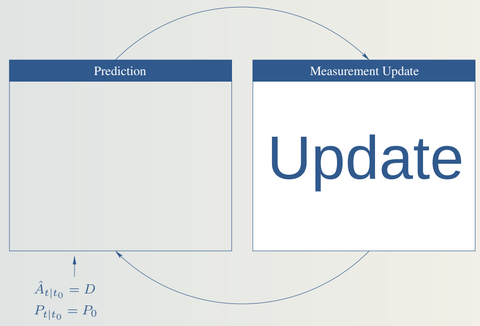

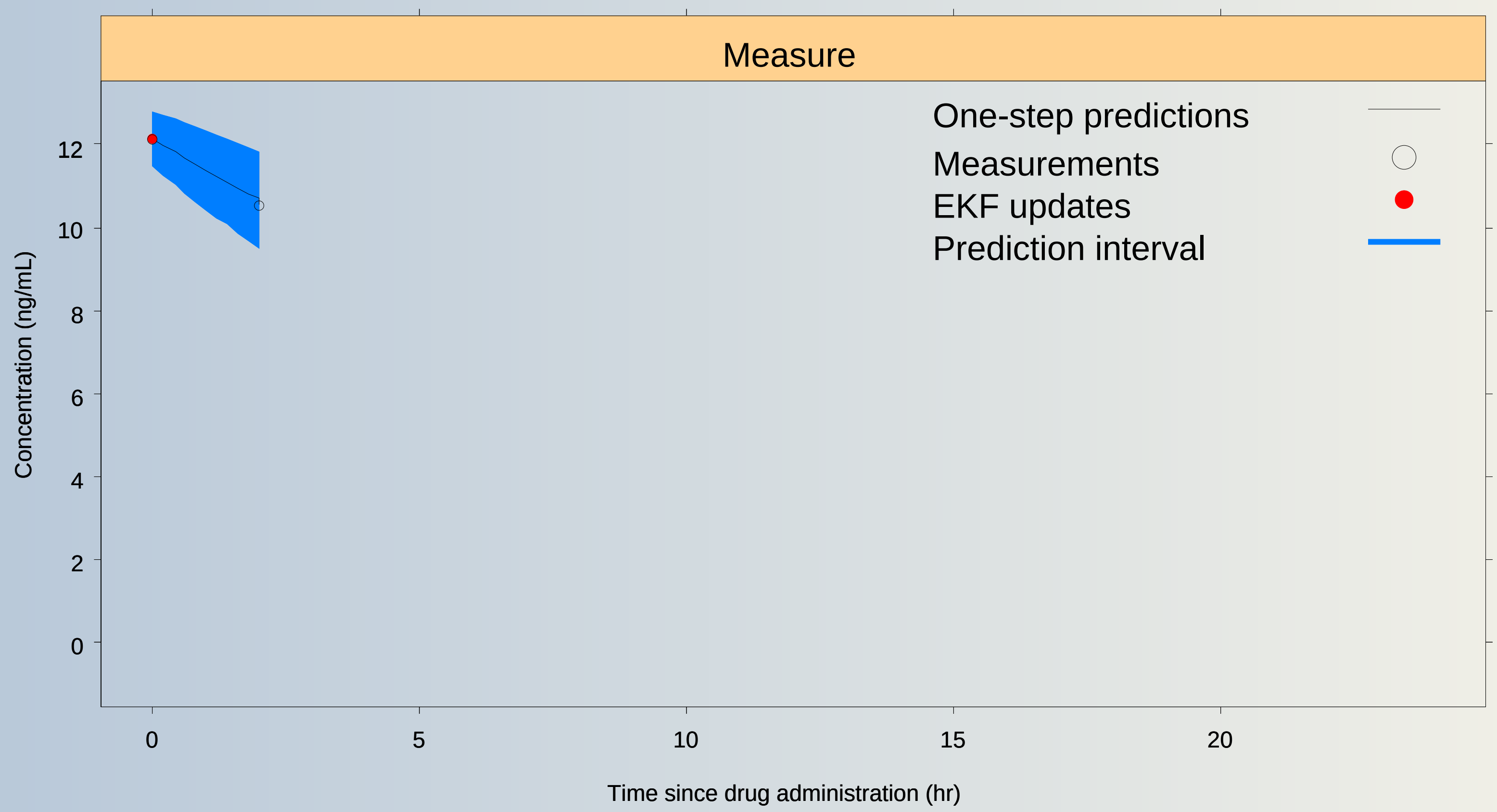

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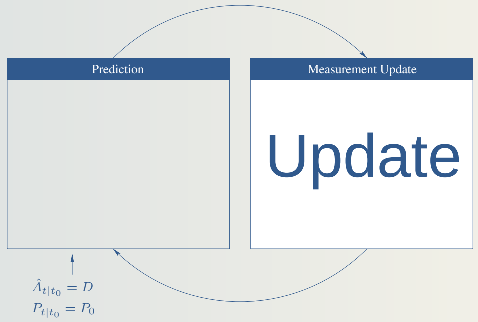

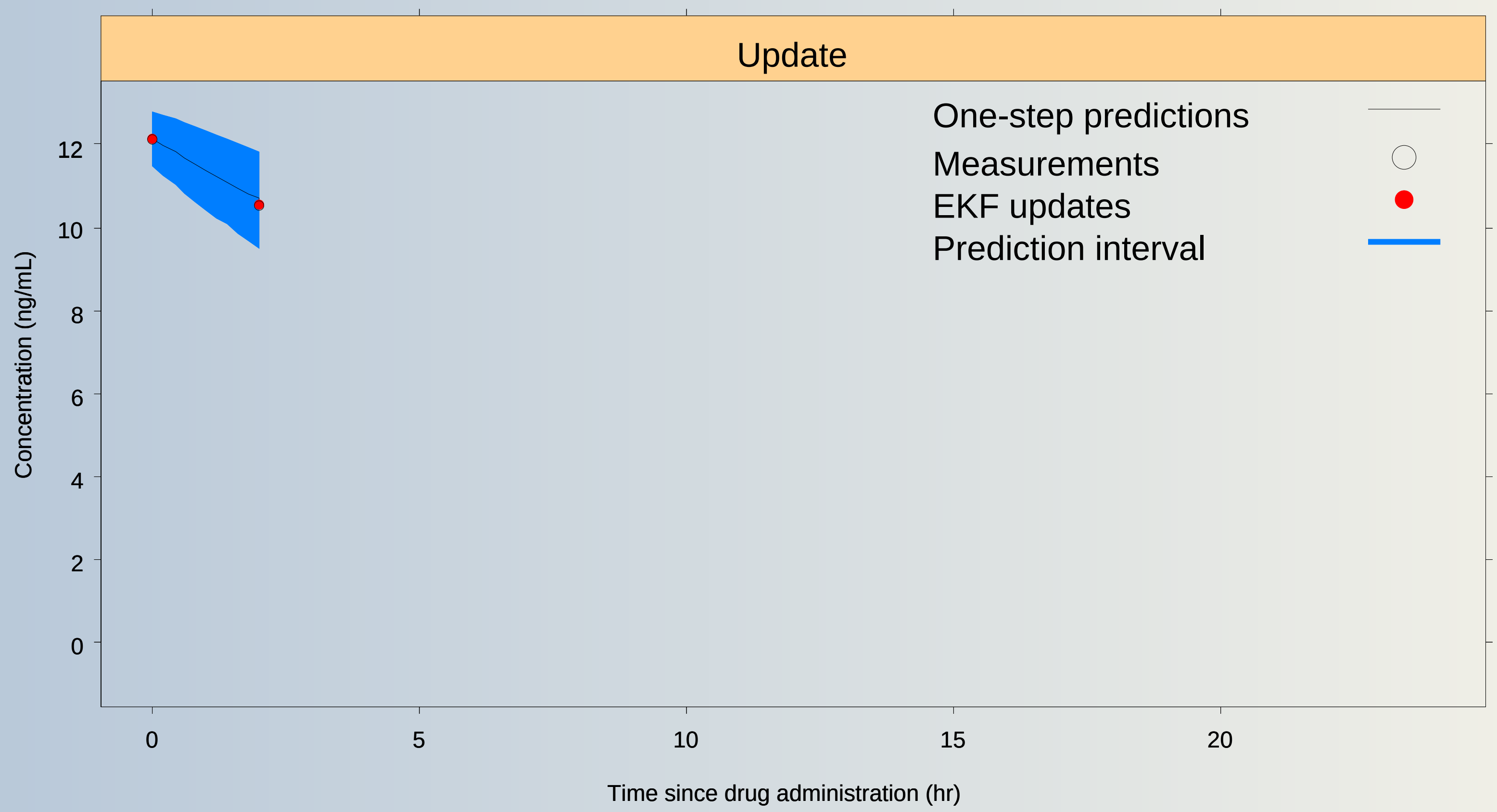

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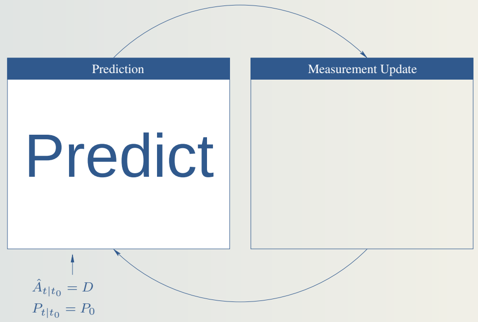

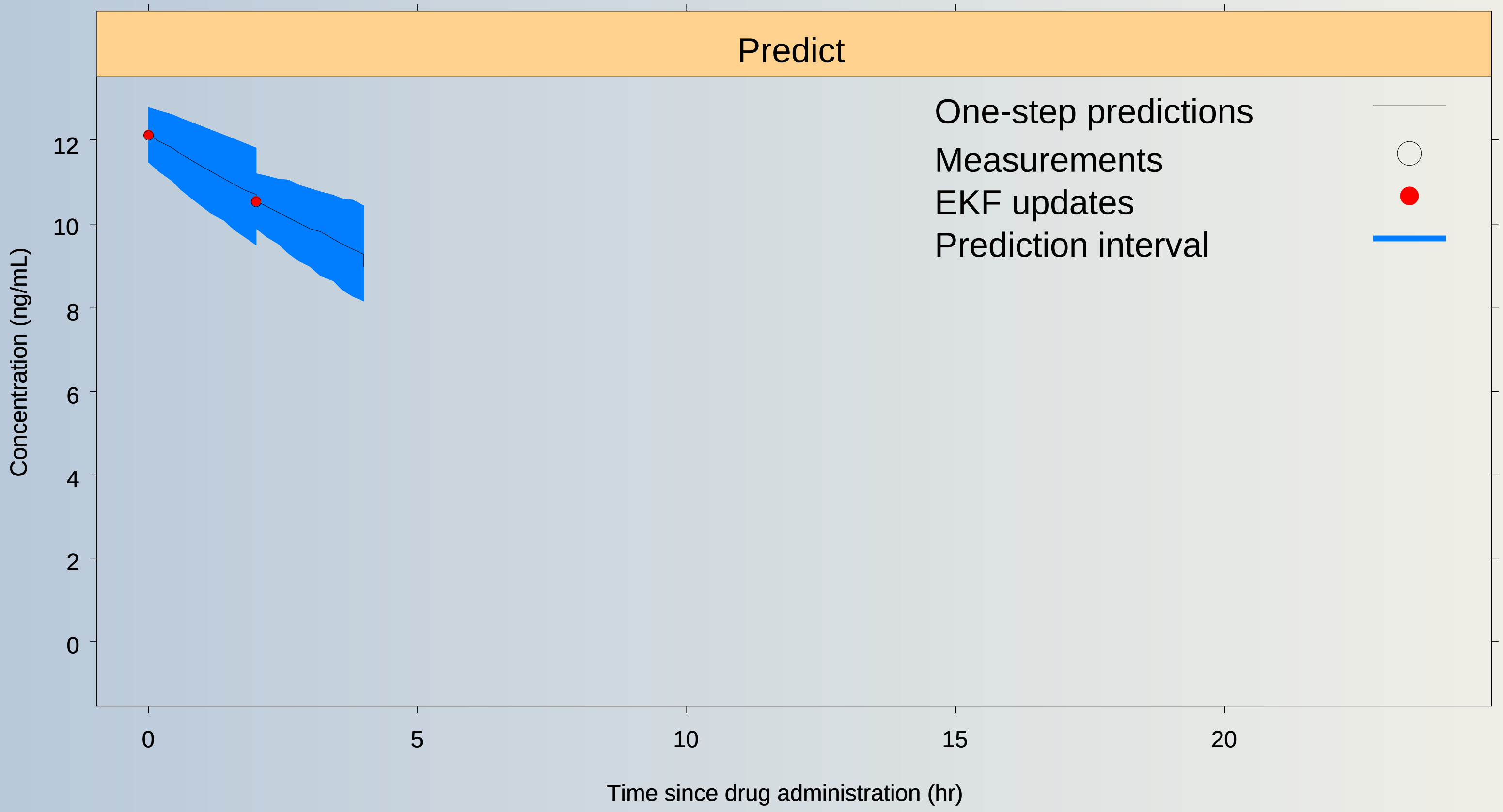

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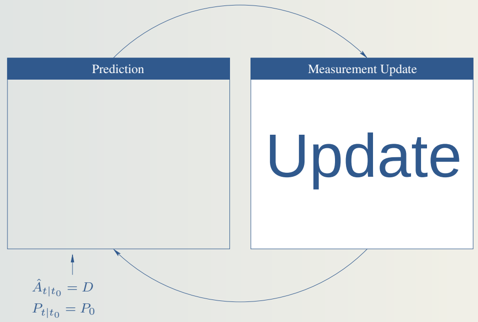

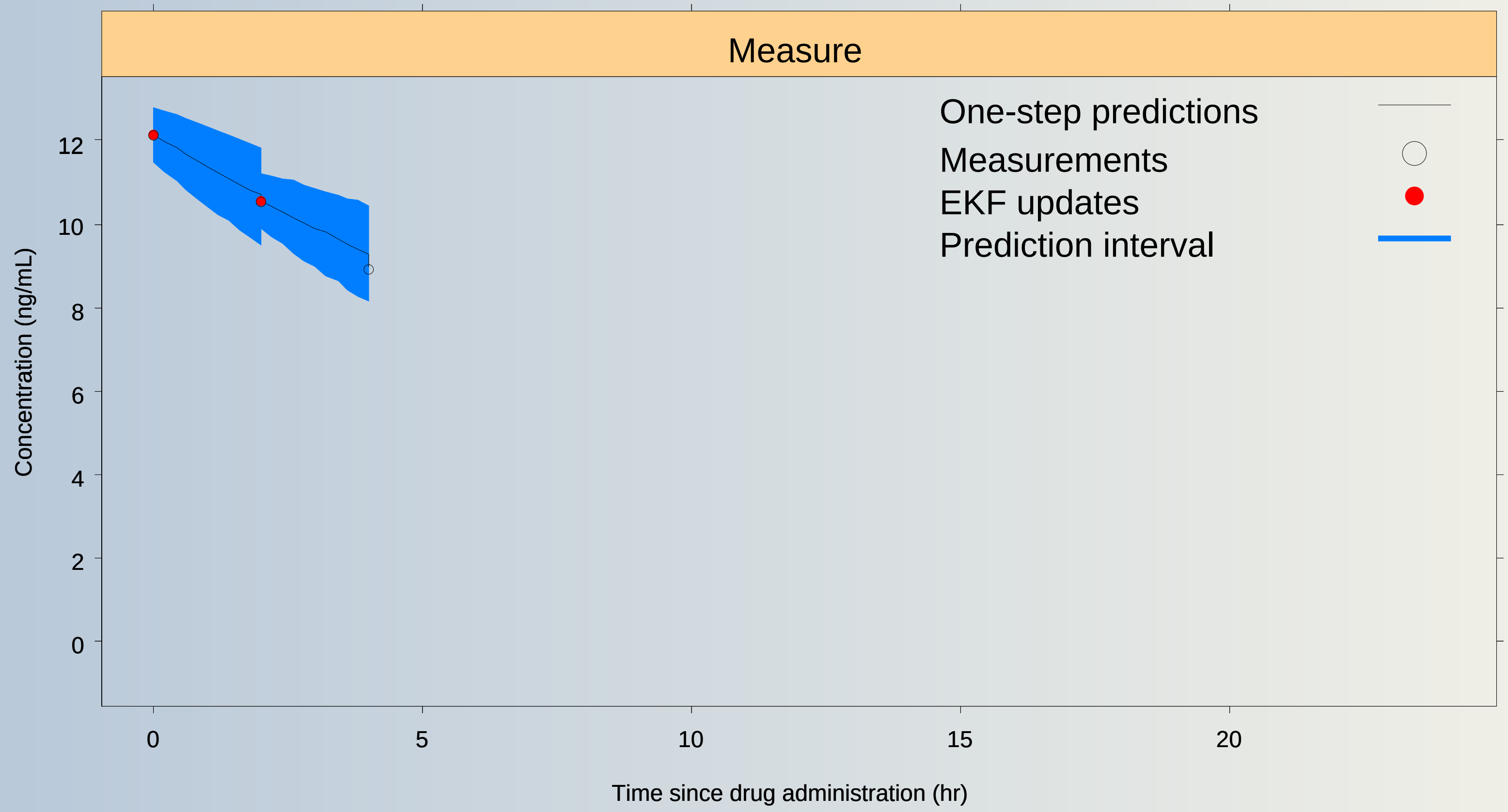

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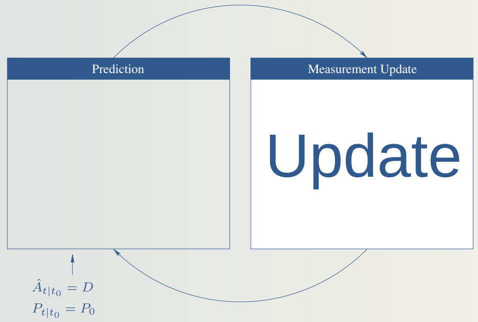

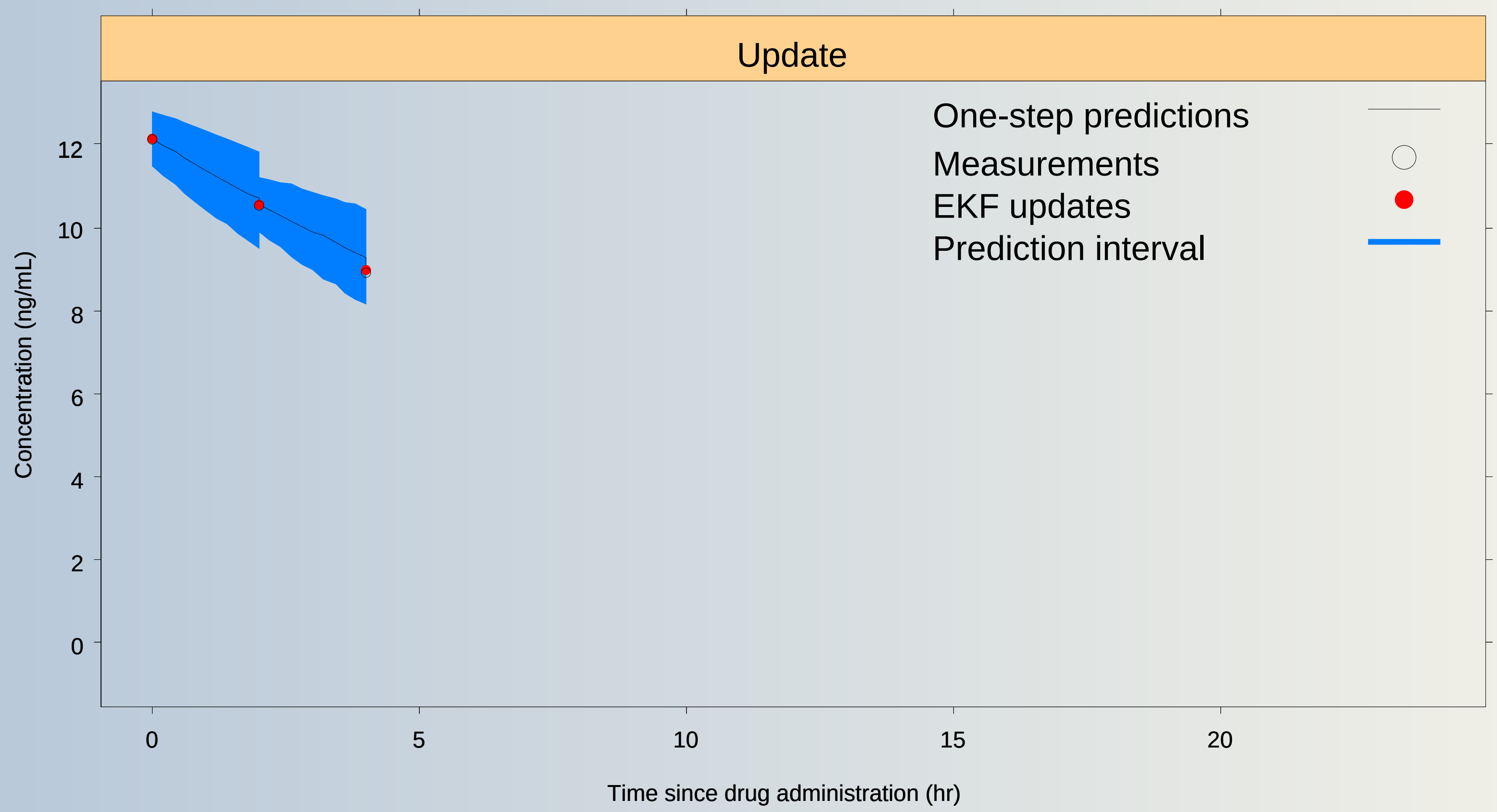

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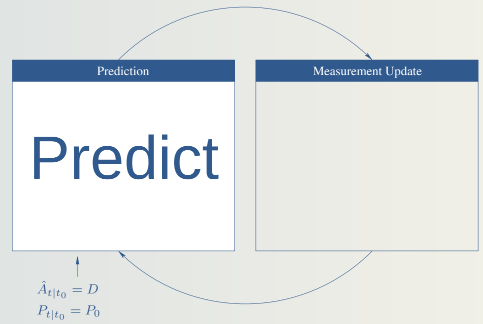

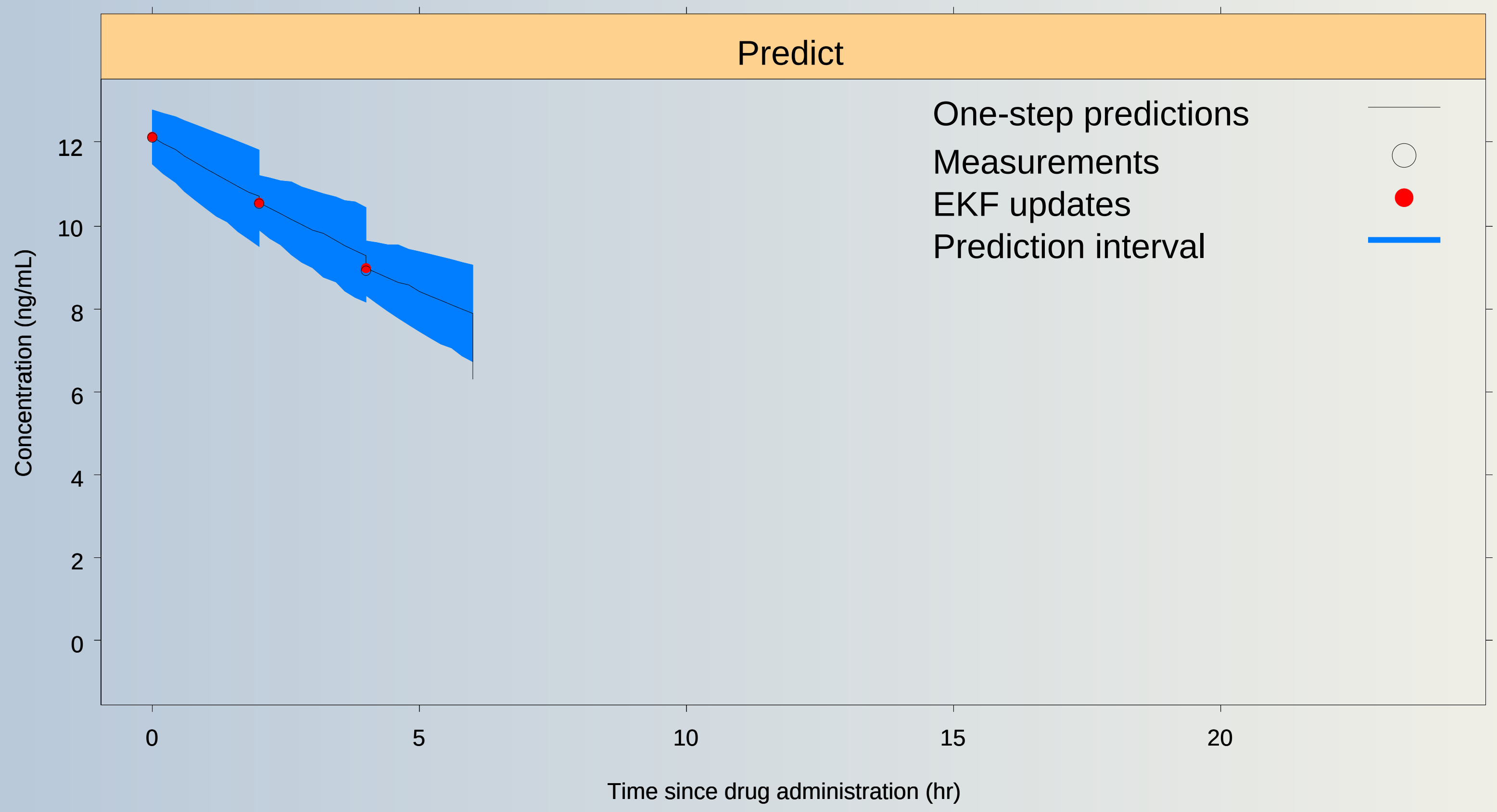

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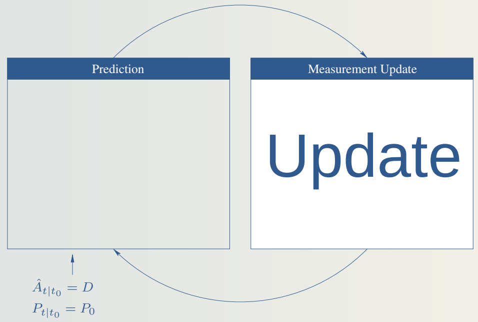

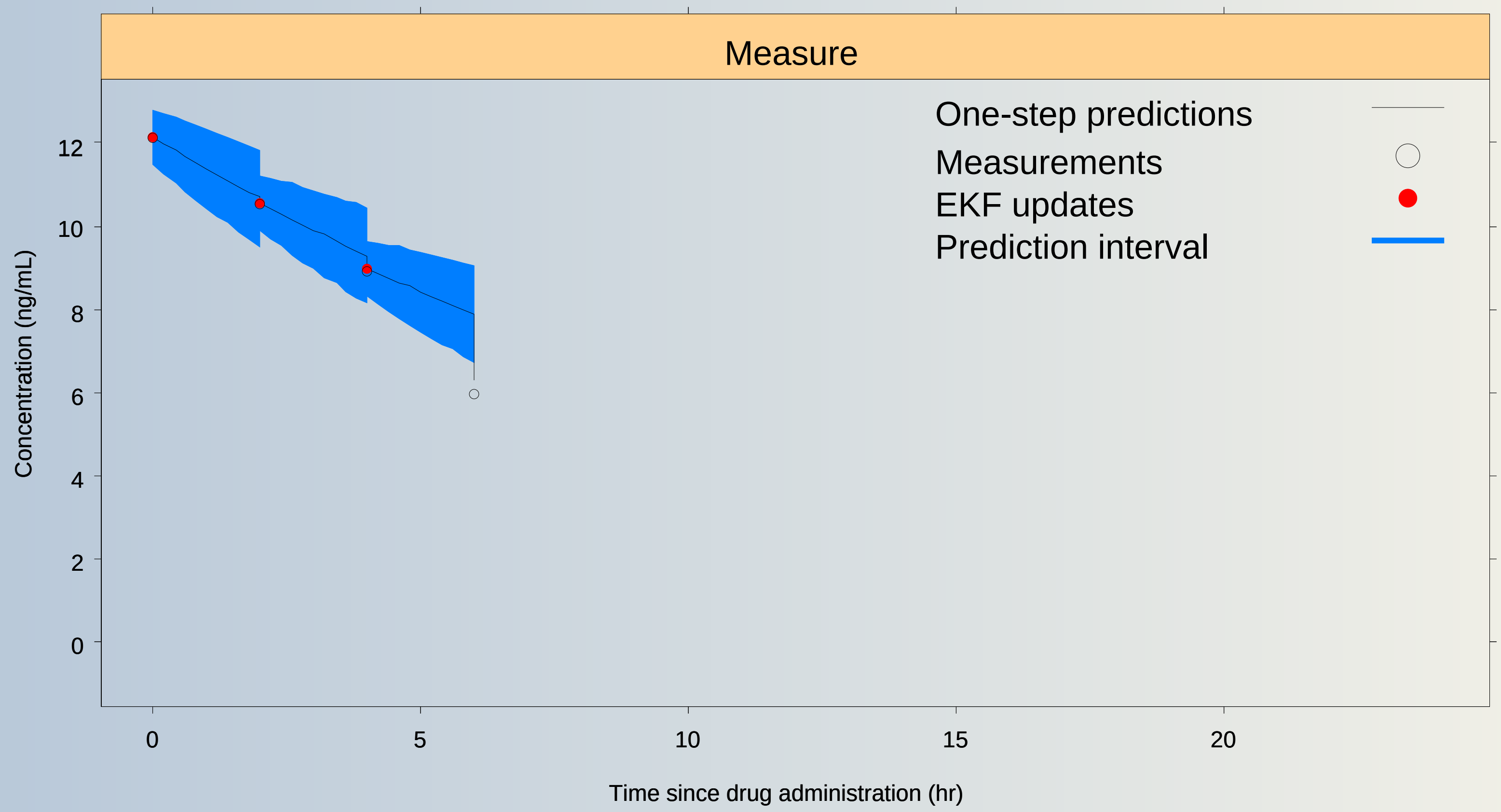

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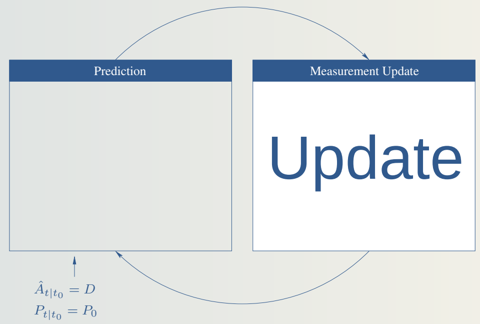

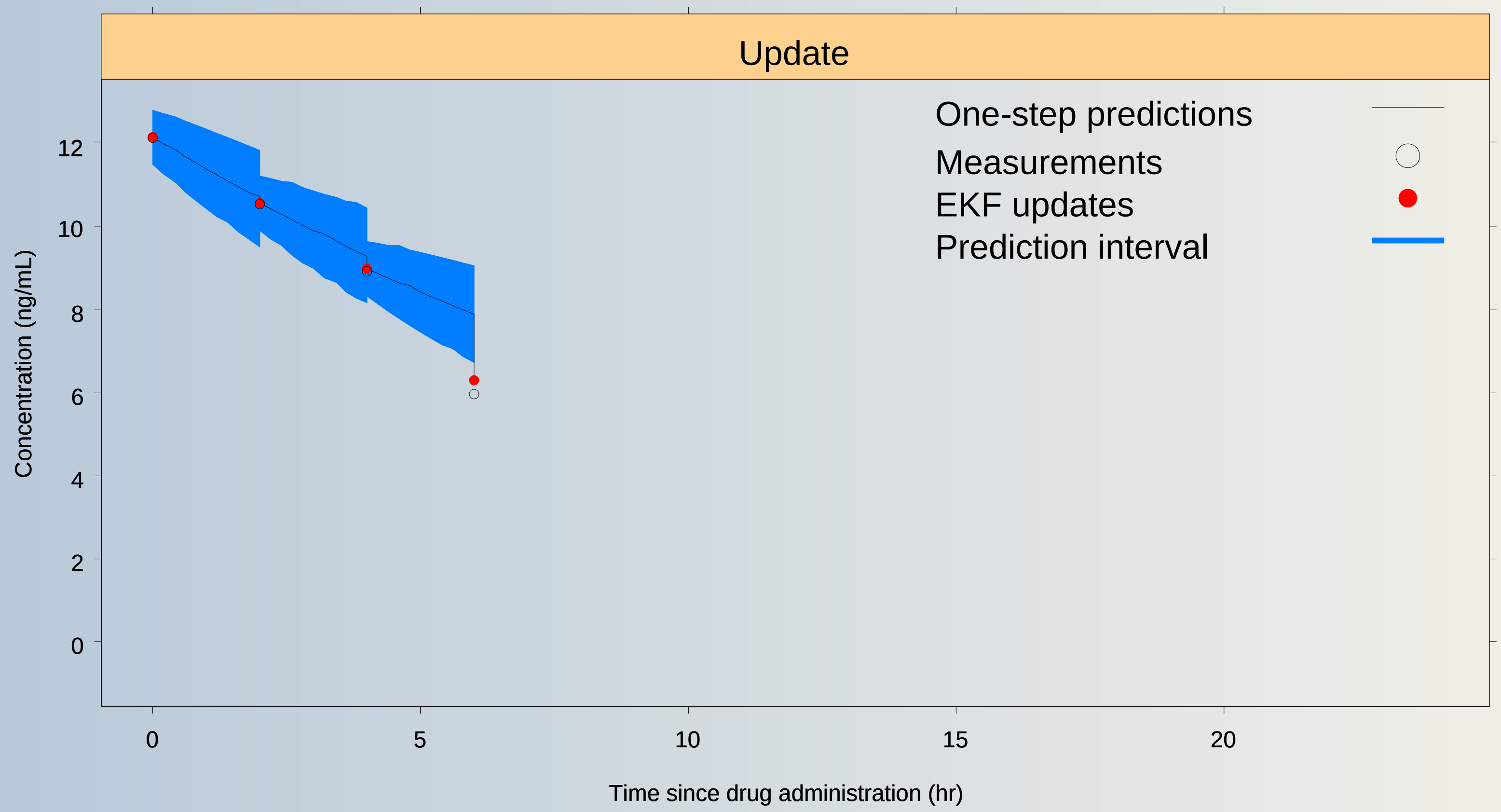

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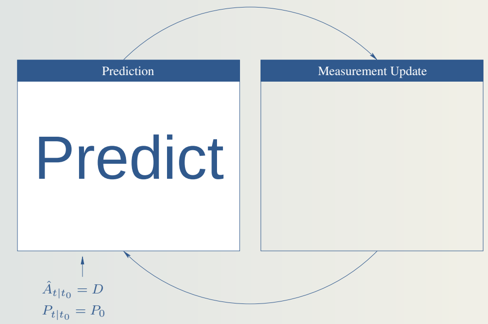

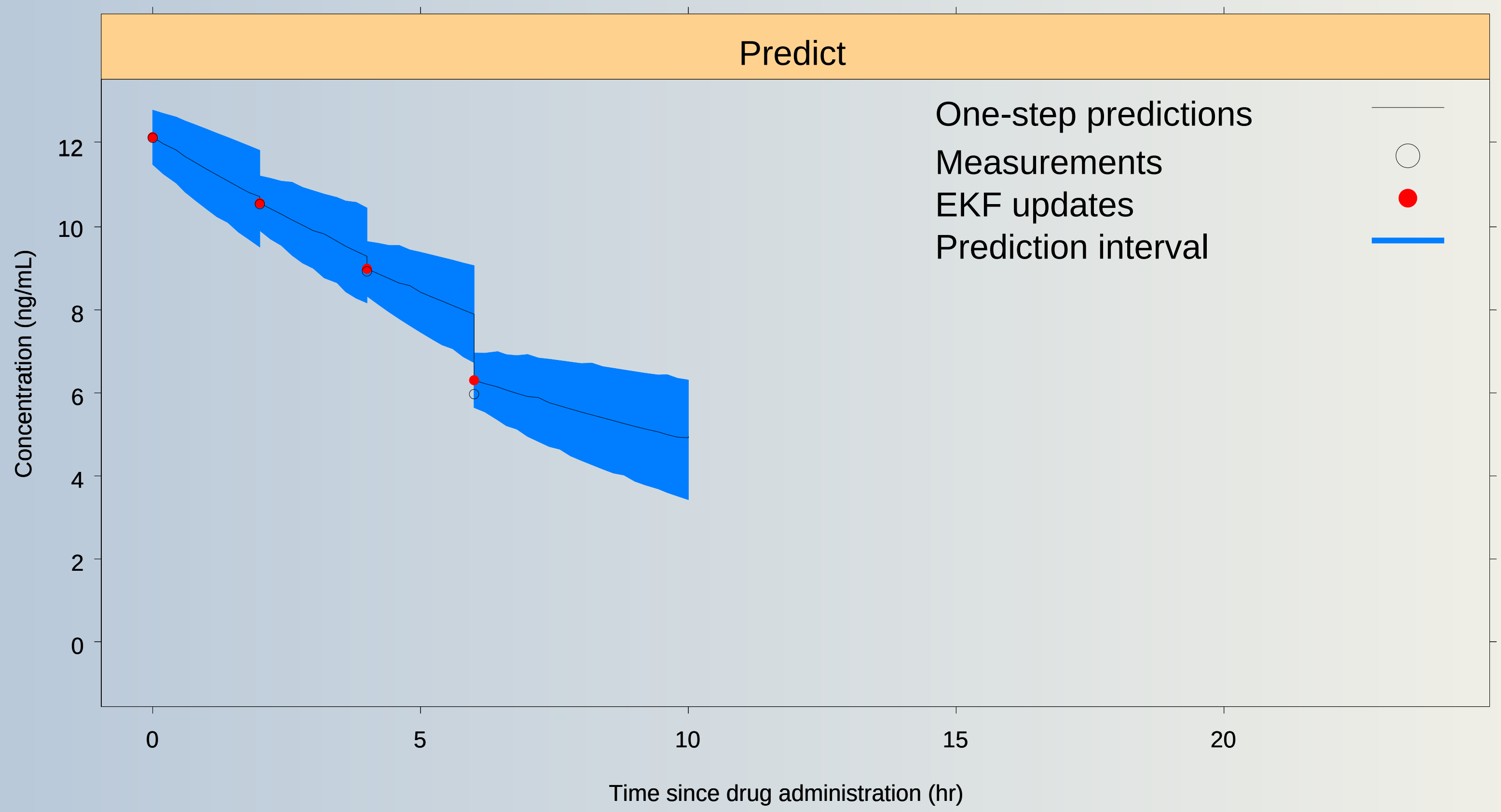

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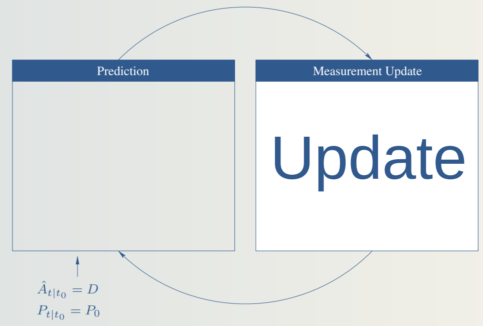

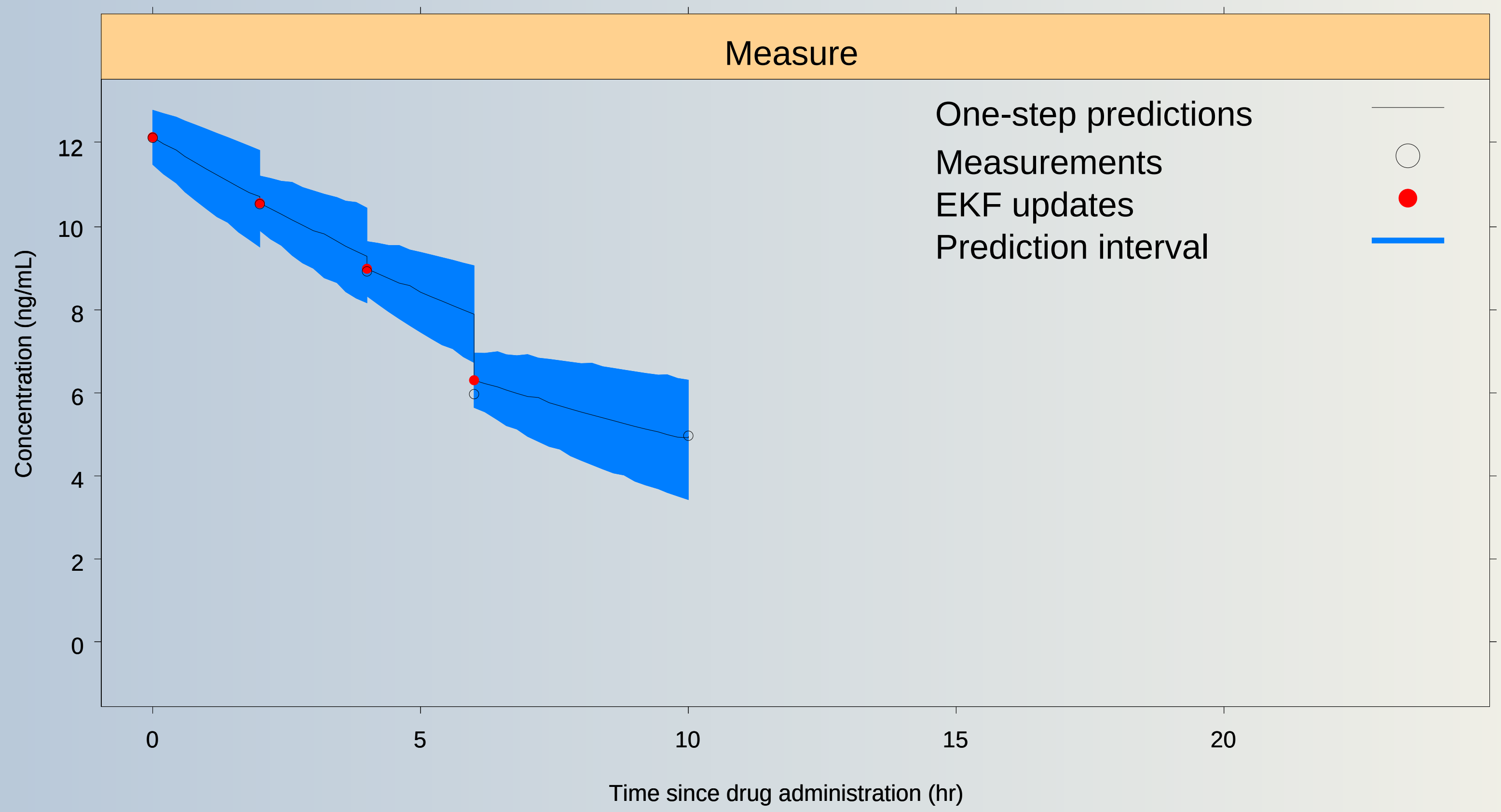

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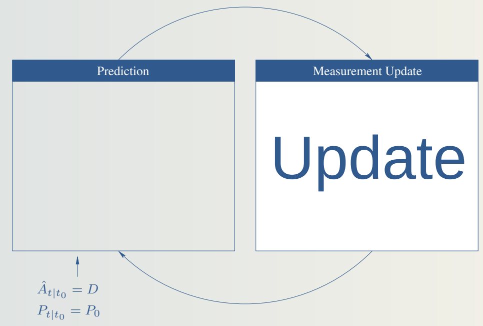

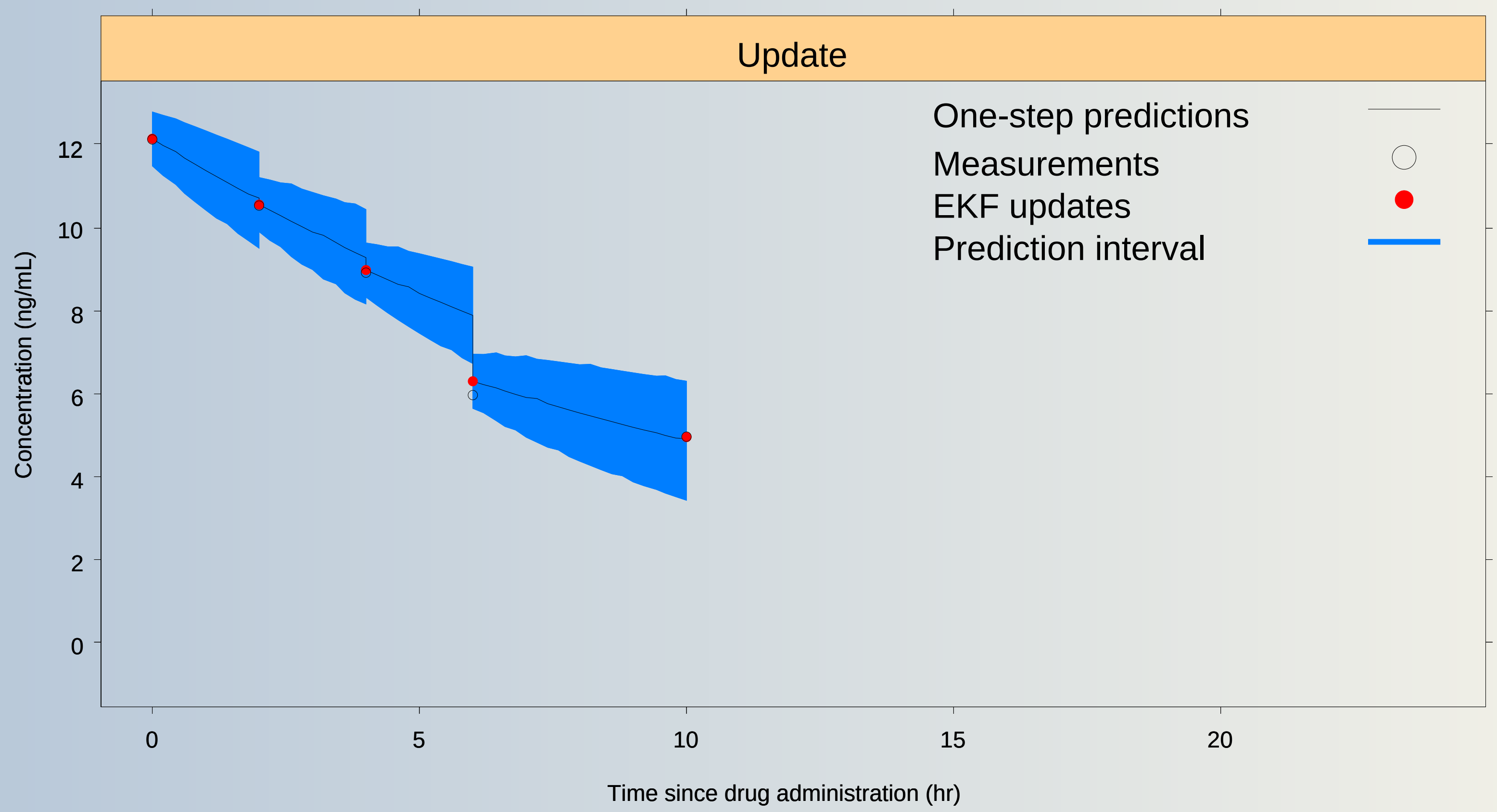

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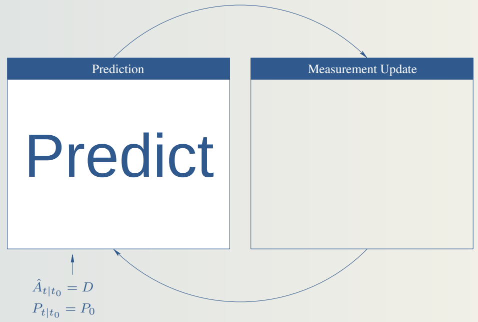

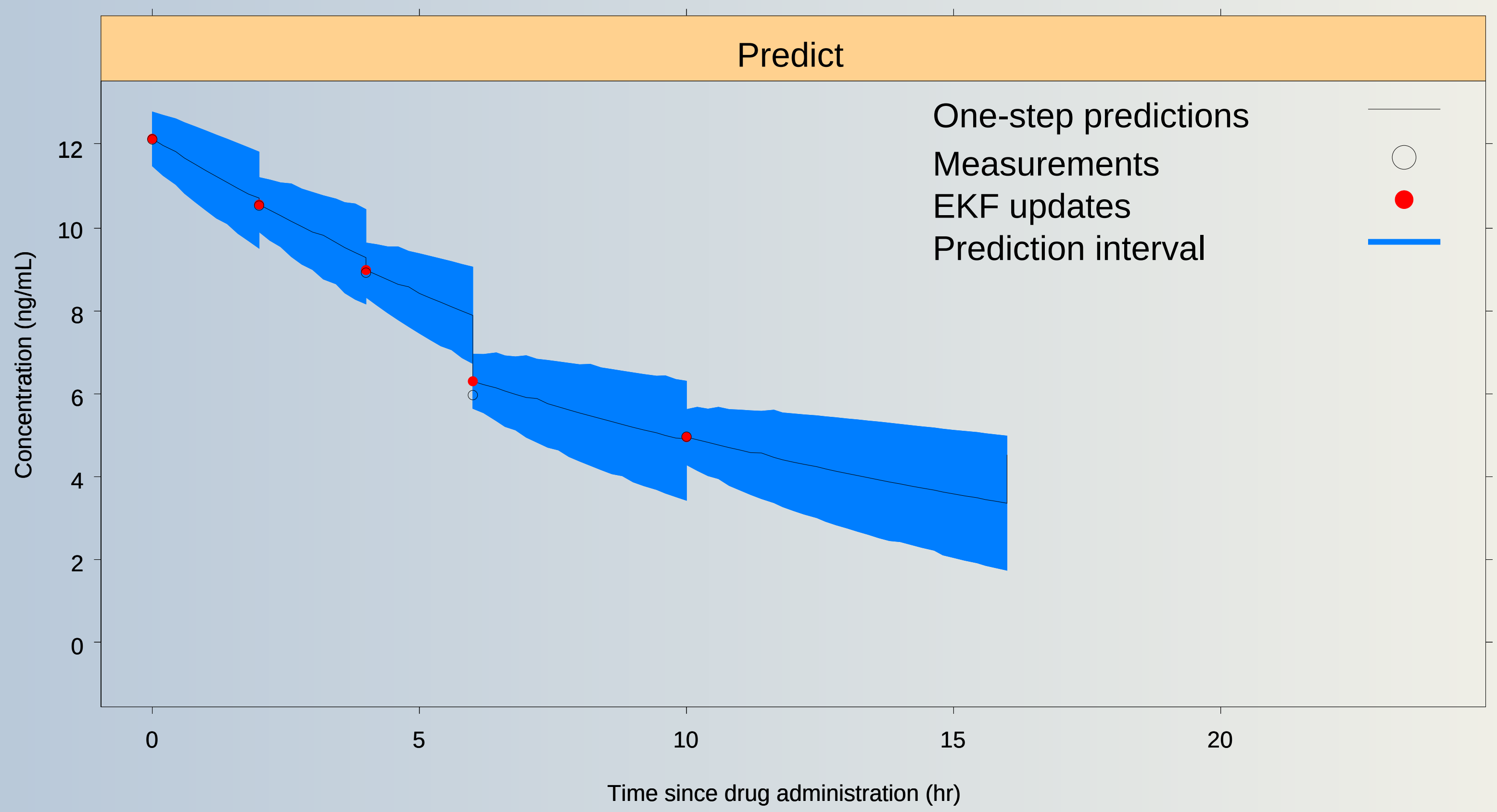

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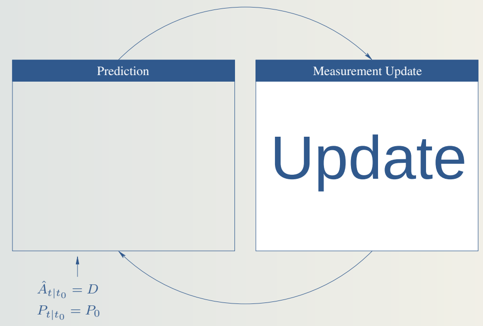
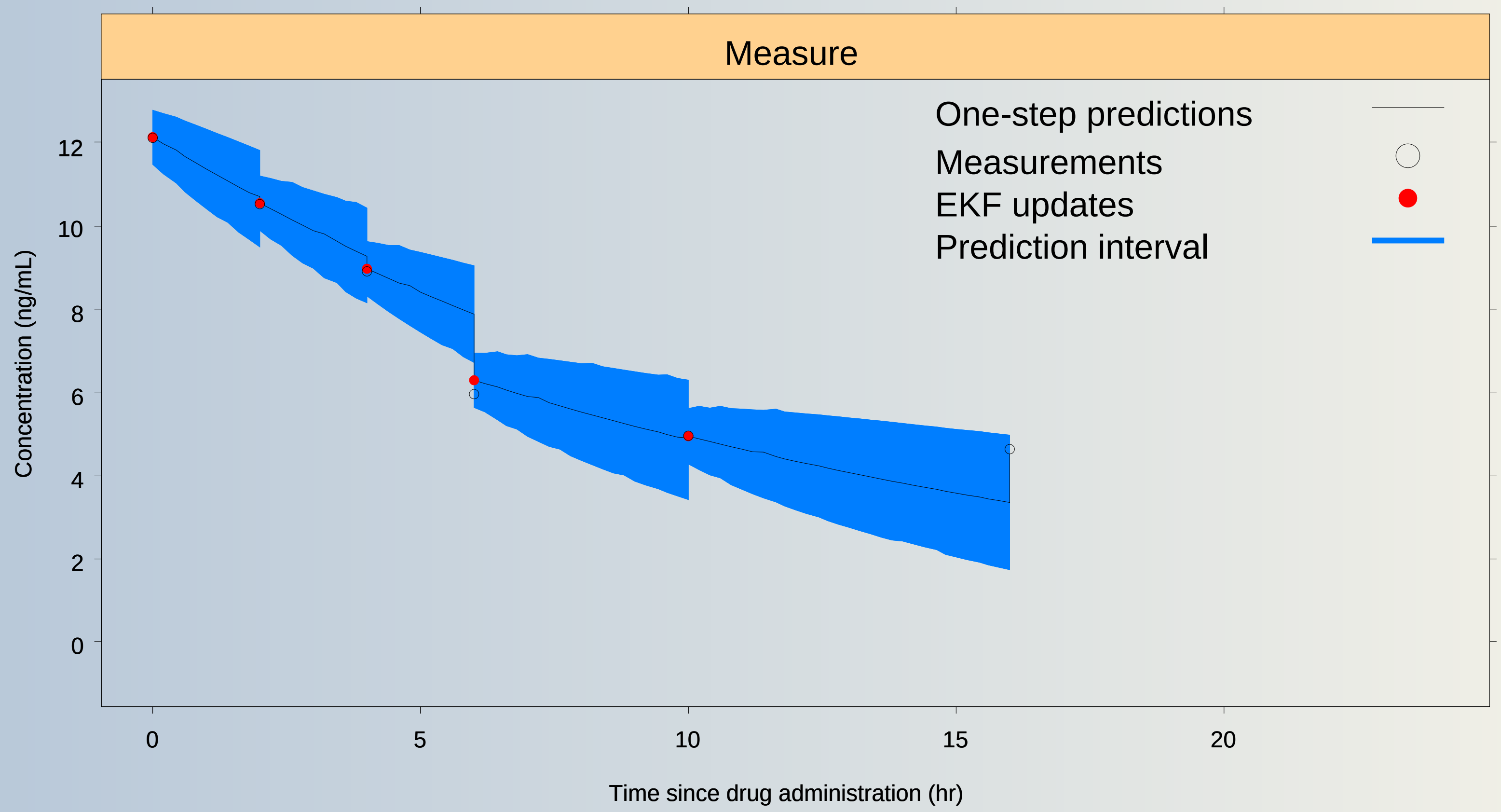
Introduction

Methods
- ODEs vs SDEs
- Extended Kalman Filter
- Visualization of EKF
- Implementation

Results

Conclusions





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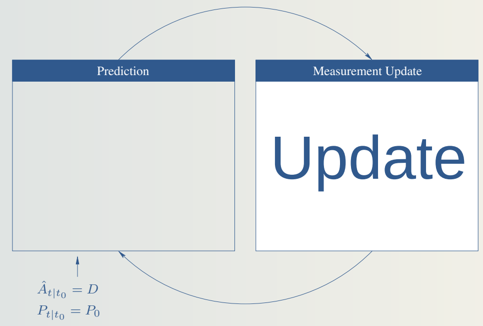

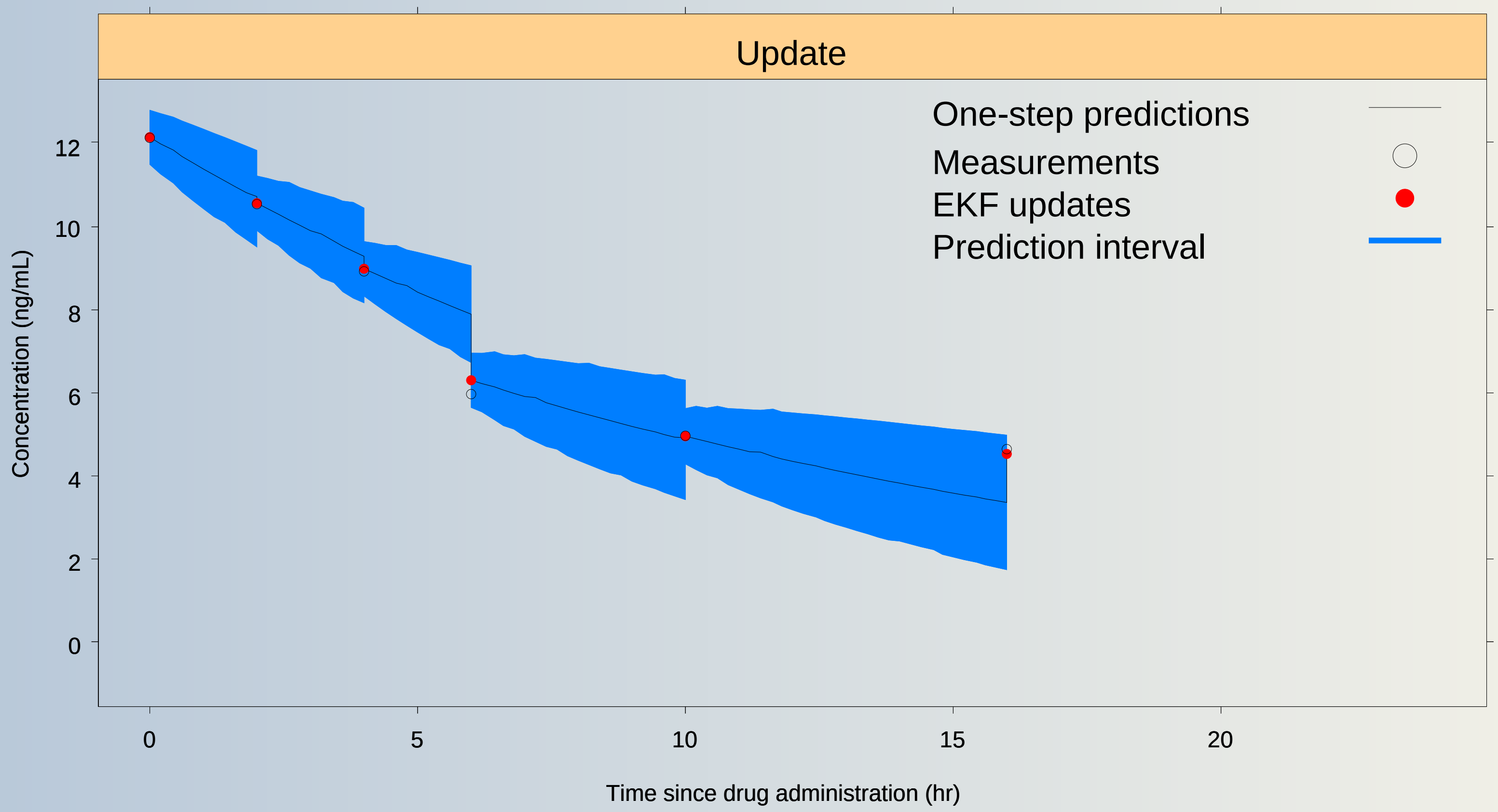

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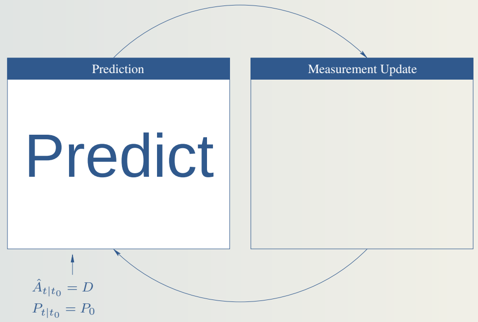

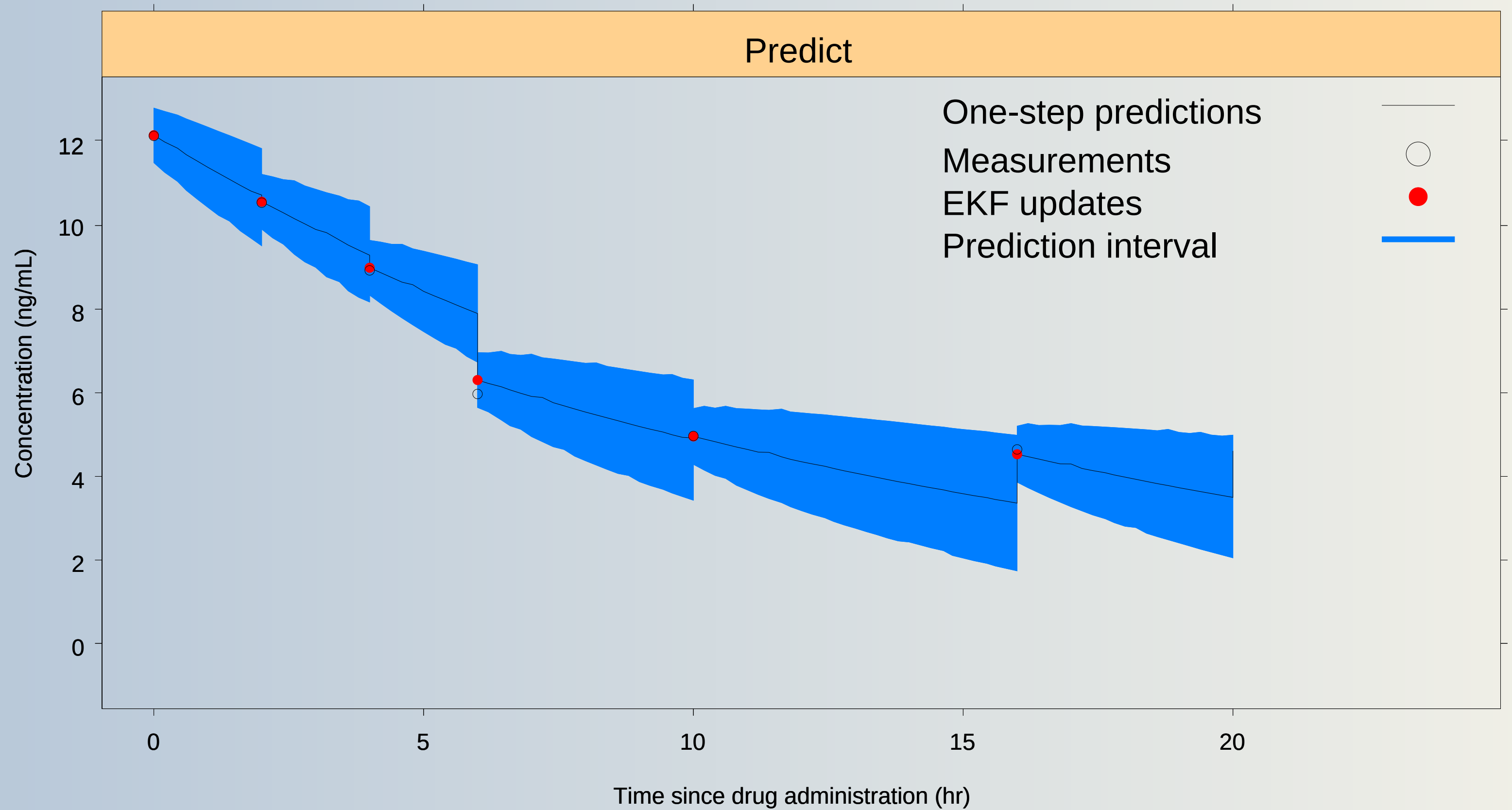

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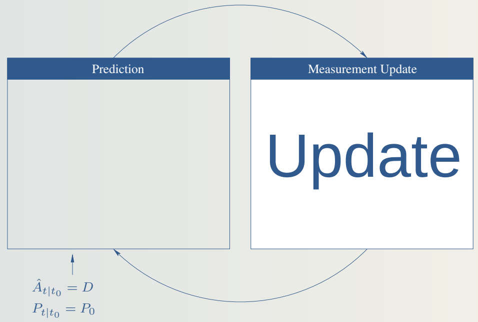

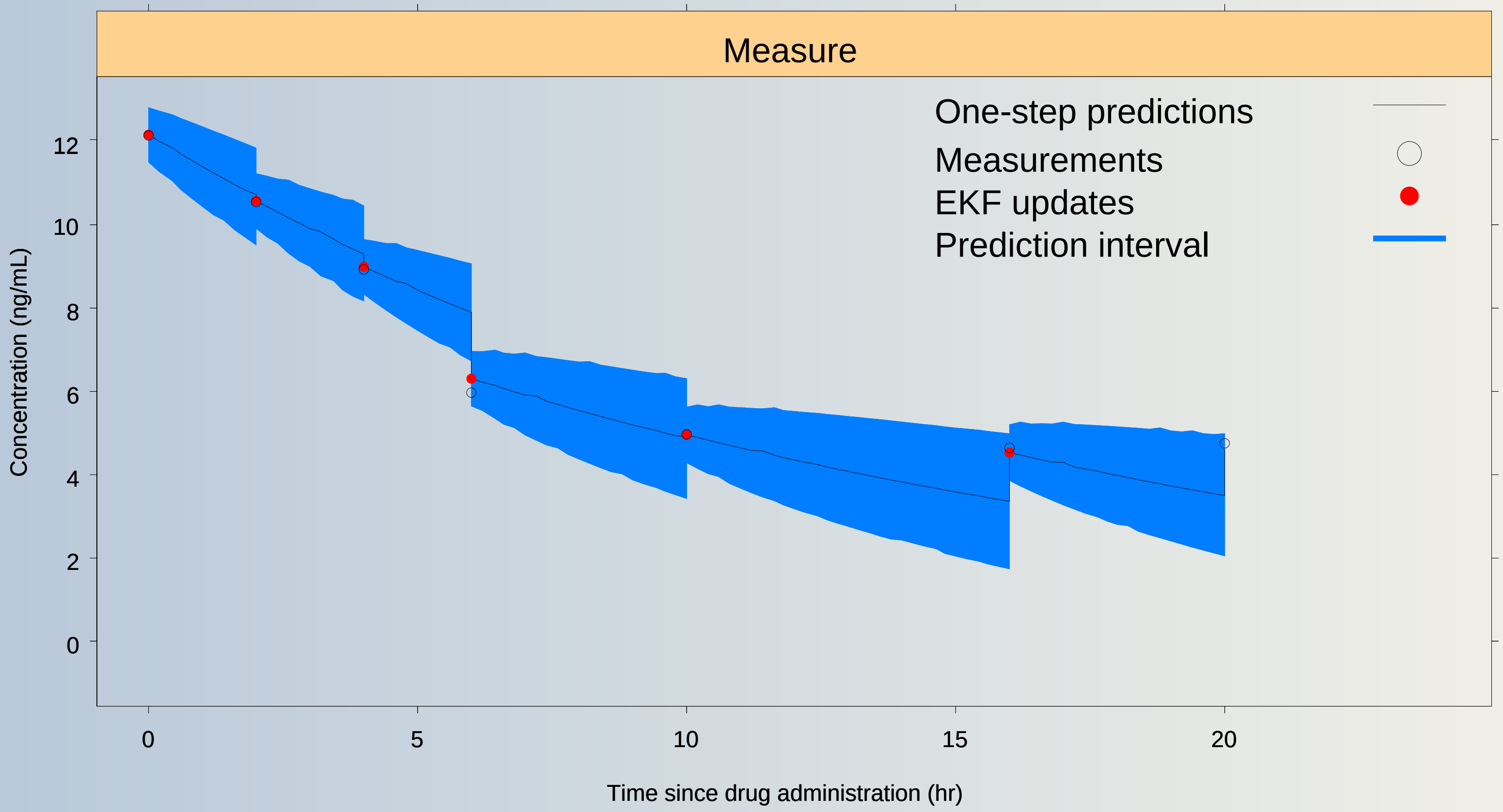

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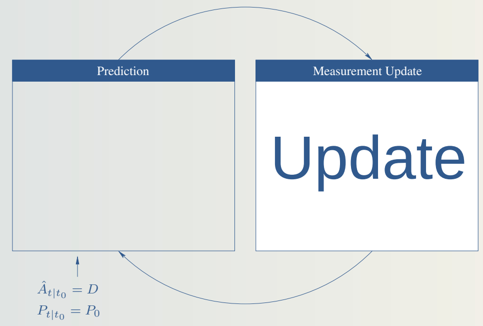

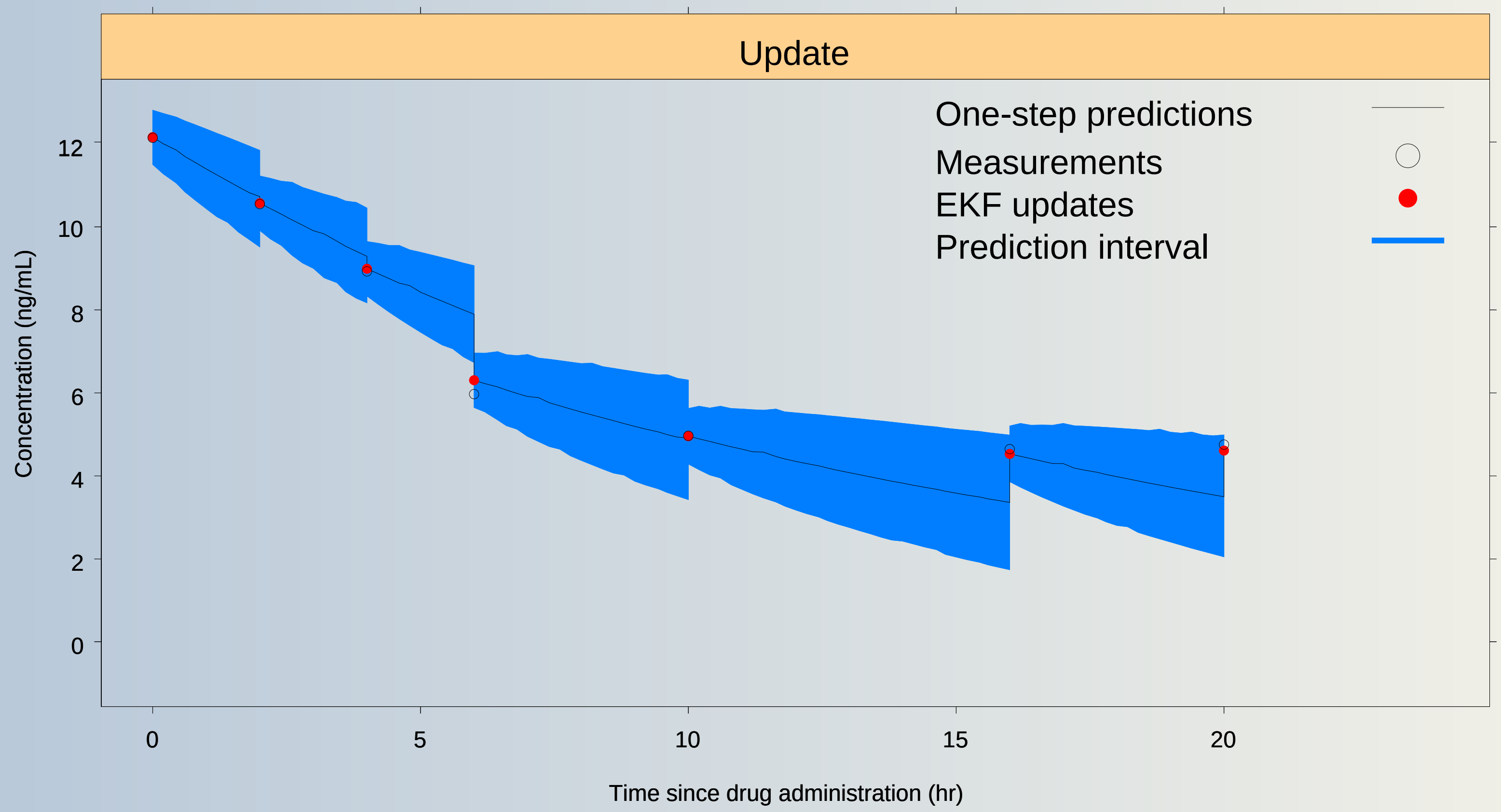

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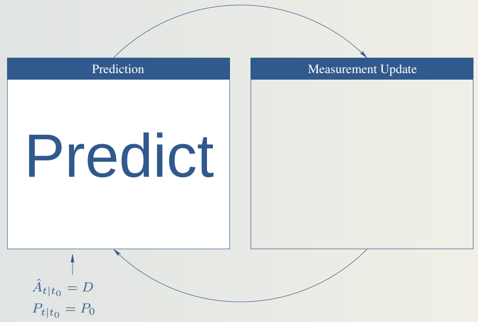
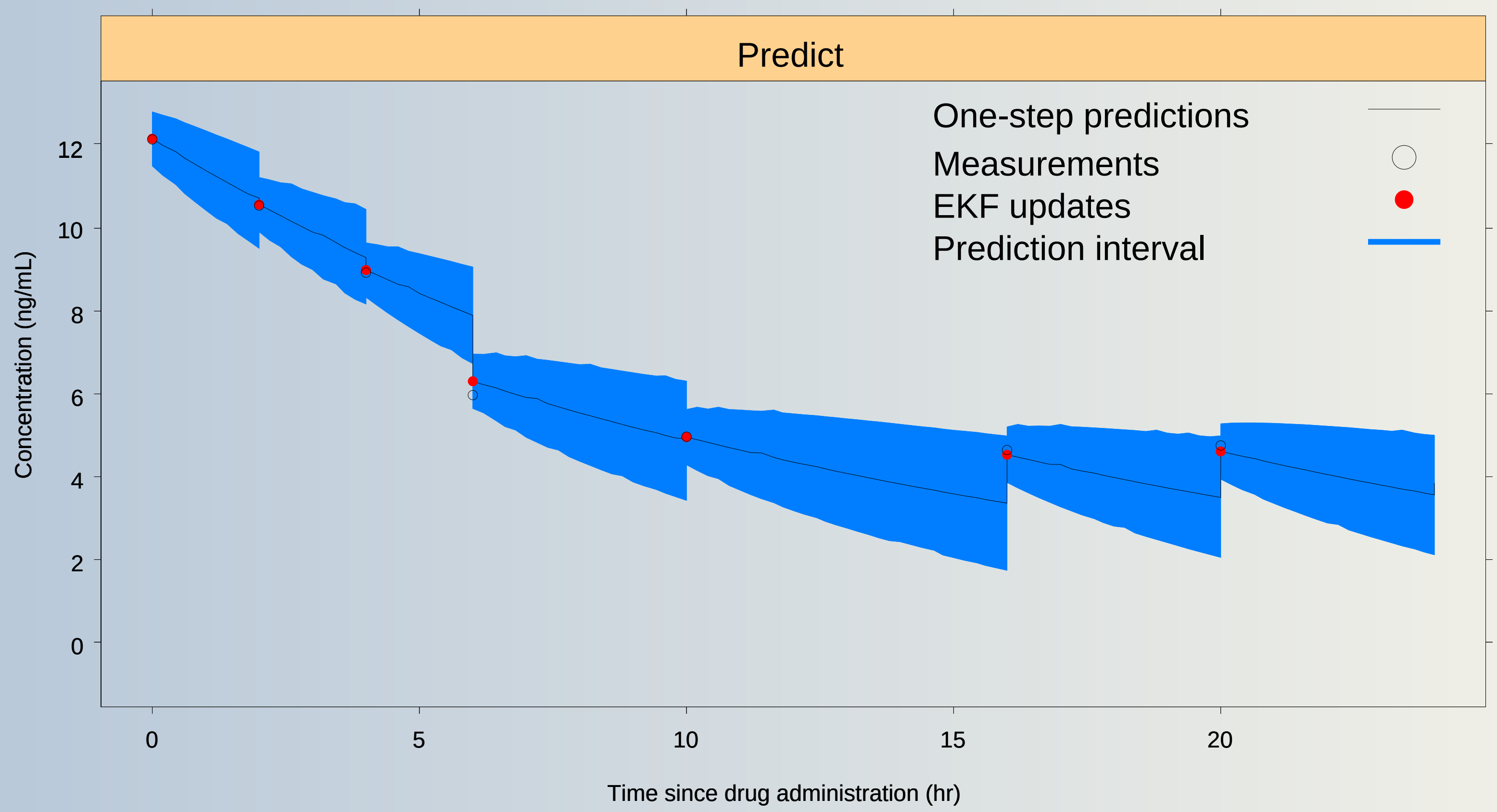
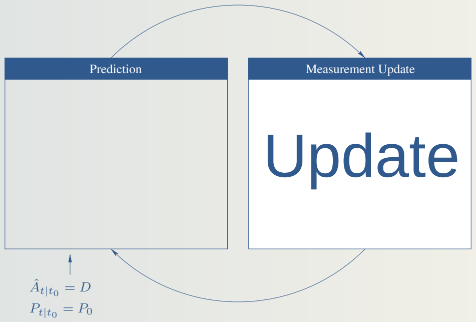
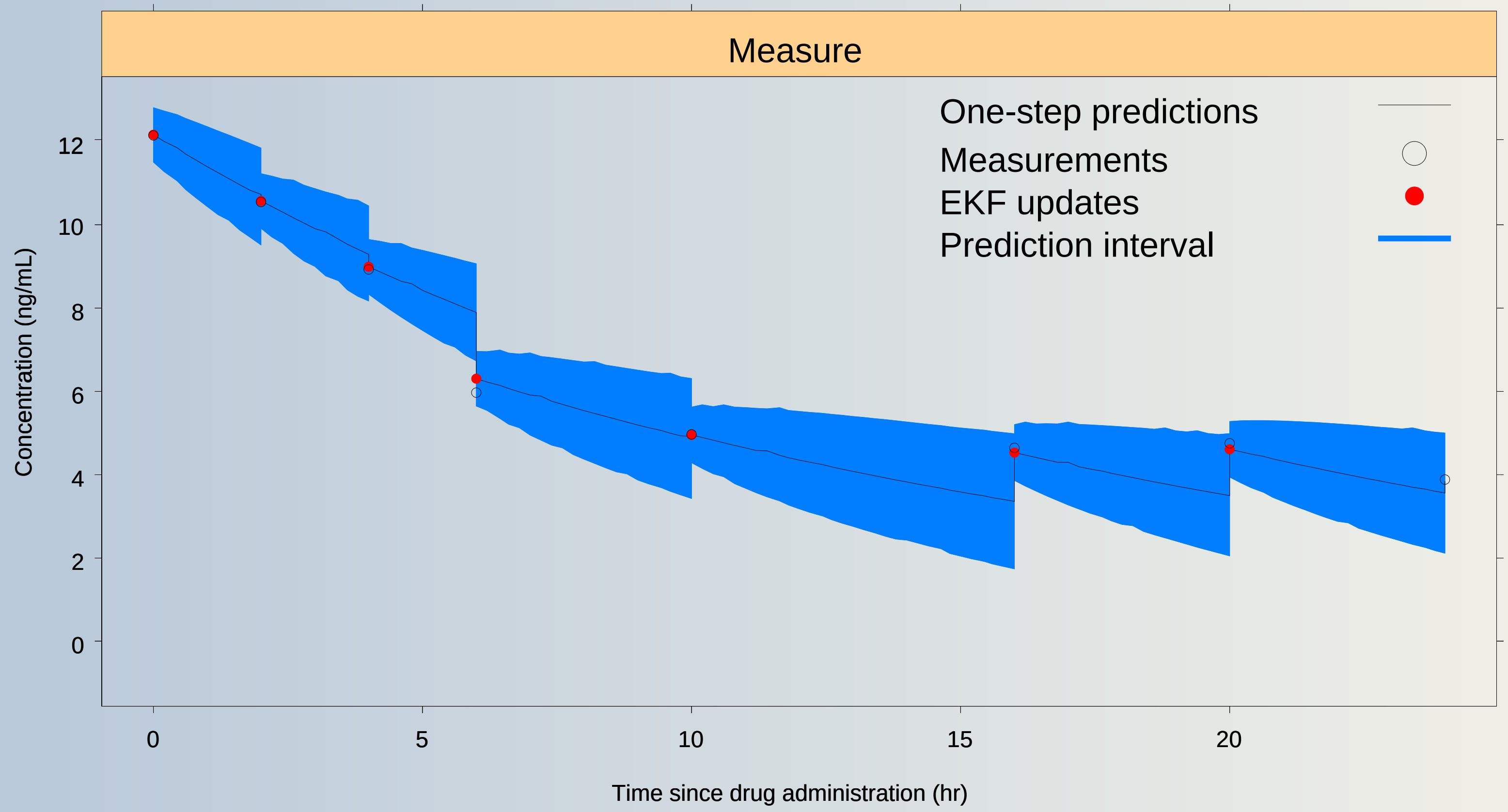


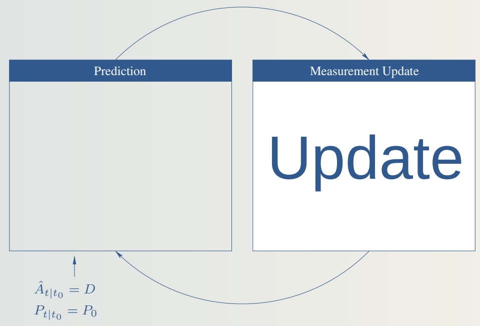


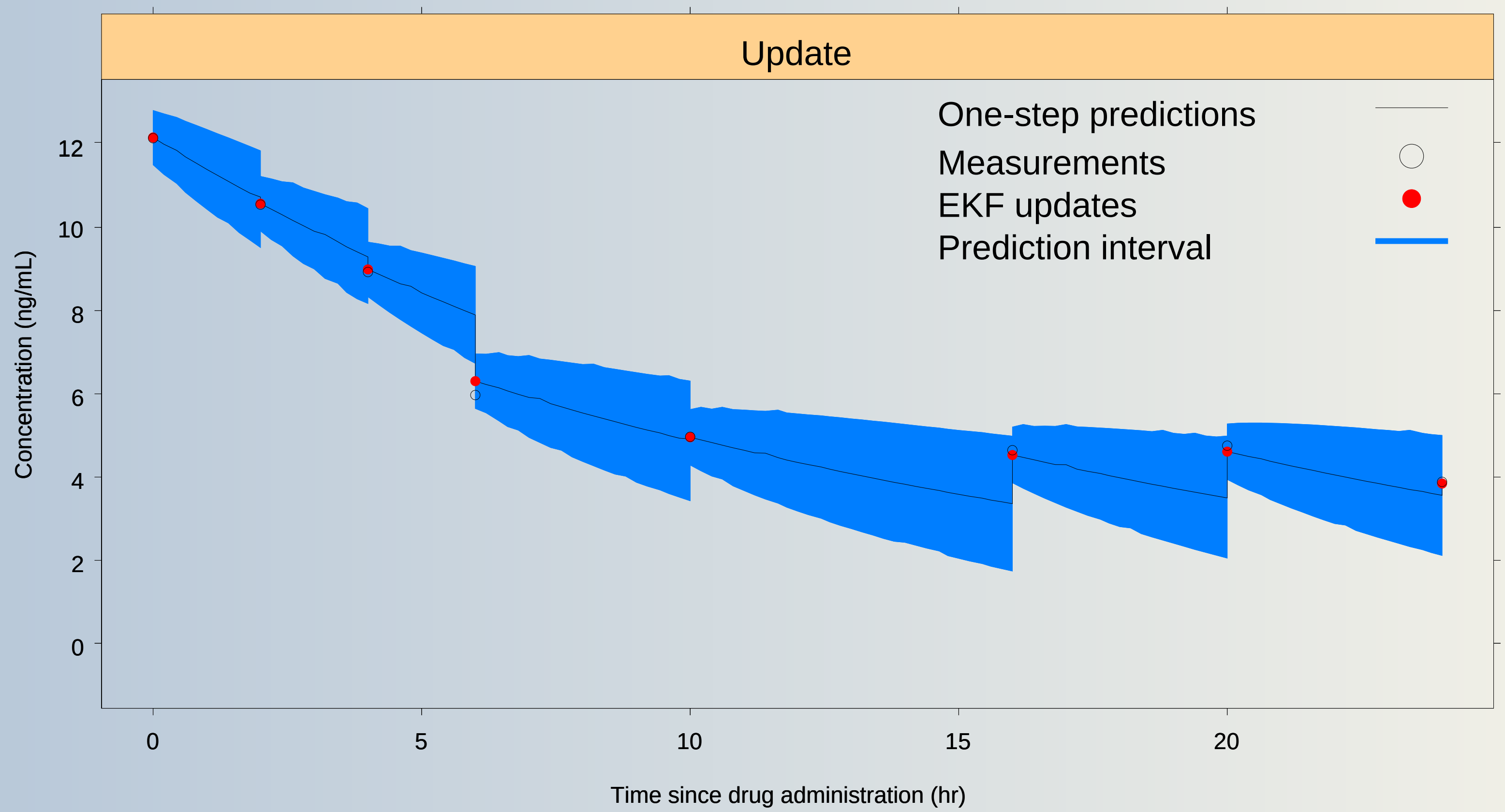
Visualization of Extended Kalman Filter



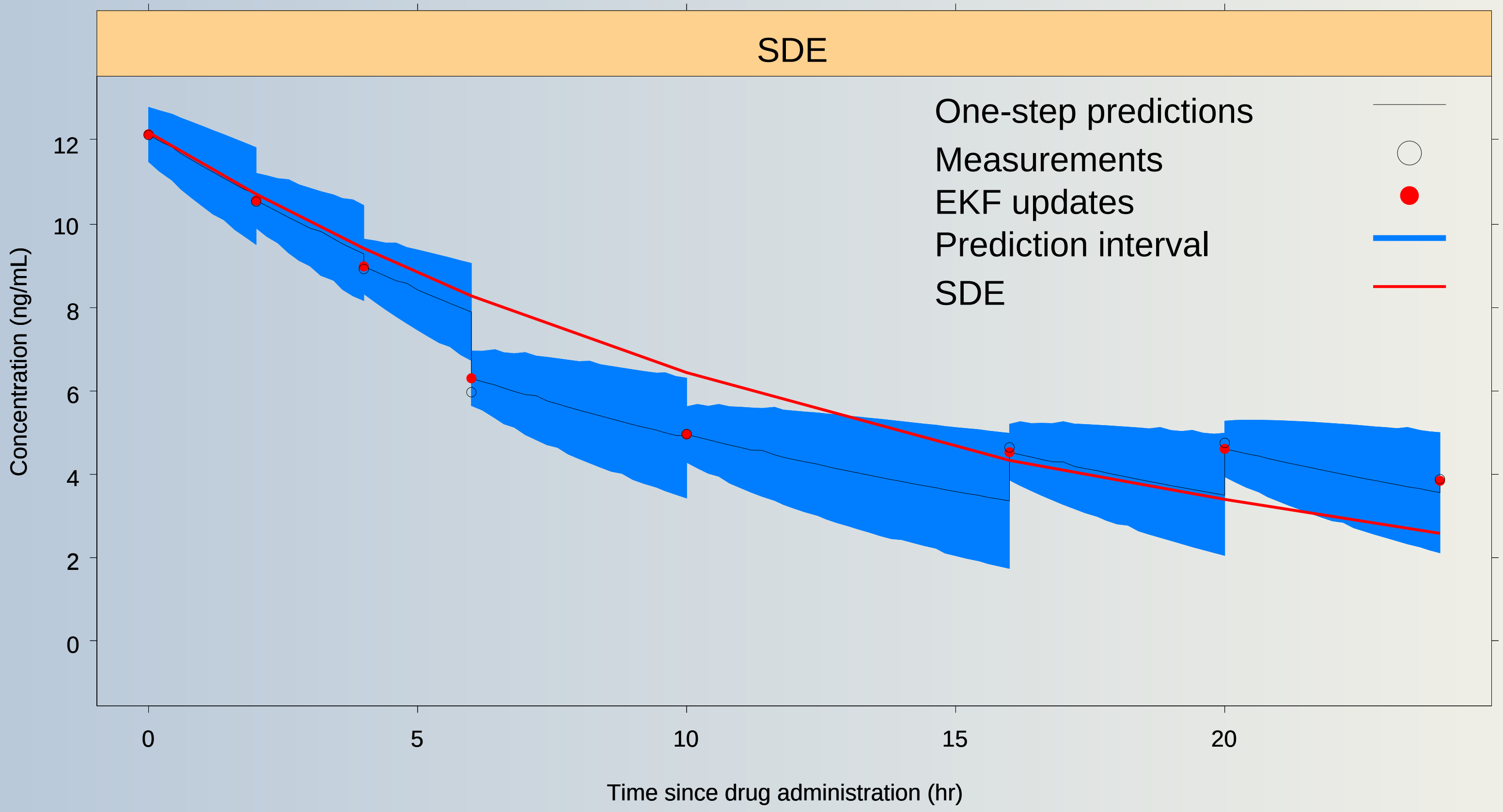


Visualization of Extended Kalman Filter

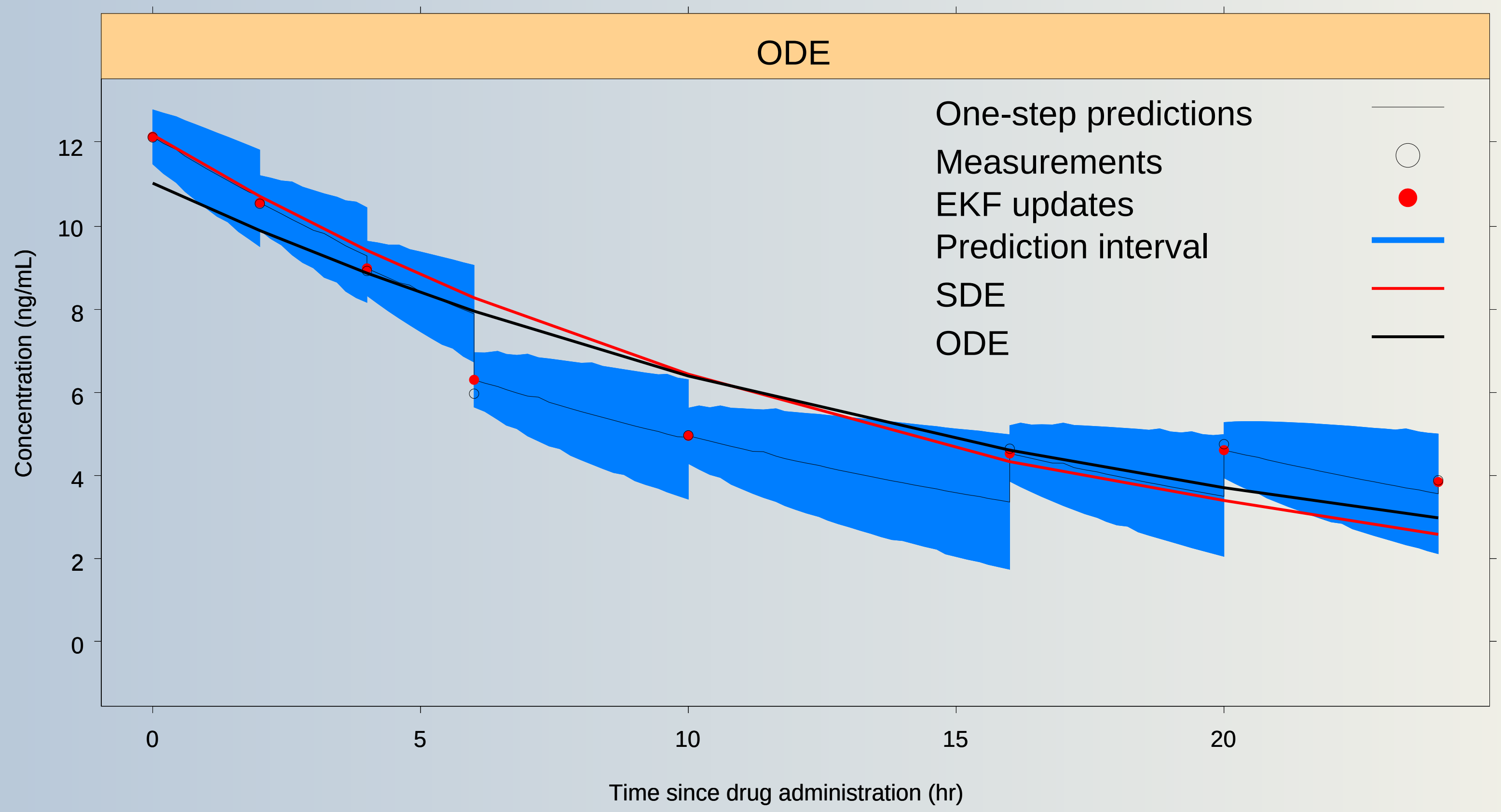




Visualization of Extended Kalman Filter



Visualization of Extended Kalman Filter



Visualization of Extended Kalman Filter

Implementation in NONMEM VI

- Control stream modifications

```
$PK ; Update equations
  CL   = THETA(1)*EXP(ETA(1))
  V    = THETA(2)*EXP(ETA(2))
  K    = A(2)/(V*R)
  A(1) = A(1) + K*(DV - A(1)/V)
  A(2) = A(2) - K*R*K
```

; $K_j = P_{j|j-1} C^T R^{-1}_{j|j-1}$
; $A_{j|j} = A_{j|j-1} + K_j (y_j - y_{j|j-1})$
; $P_{j|j} = P_{j|j-1} - K_j R_{j|j-1} K_j^T$

```
$DES ; State prediction equations
  DADT(1) = -CL/V*A(1)
  DADT(2) = -2*CL/V*A(2)+SGW*SGW
```

; $dA_{t|j-1}/dt = g(\phi, A_{t|j-1}, d)$
; $dP_{t|j-1}/dt = BP_{t|j-1} + P_{t|j-1}B^T + \sigma_w^2$

```
$ERROR ; Output prediction equations
  IPRED = A(1)/V
  R     = A(2)/(V*V)+SIG*SIG
  W     = SQRT(R)
  Y     = IPRED + W*EPS(1)
```

; $\hat{y}_{j|j-1} = f(\phi, \hat{A}_{j|j-1})$
; $R_{j|j-1} = CP_{j|j-1}C^T + \sigma^2$

Implementation in NONMEM VI

- Data file modifications

ID	HOUR	TIME	DV	EVID	MDV	AMT	CMT
1	-2	0	.	0	1	.	1
1	0	2	.	1	1	100	1
1	0	2	12.2	0	0	.	1
1	0	2	.	2	1	.	1
1	0	2	.	3	1	.	1
1	2	4	10.6	0	0	.	1
1	2	4	.	2	1	.	1
1	2	4	.	3	1	.	1
1	4	6	8.93	0	0	.	1
1	4	6	.	2	1	.	1
1	4	6	.	3	1	.	1
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

Explanation:

$P_0 = \int_{t_1}^{t_2} e^{-2\frac{CL}{V}t} \sigma_w^2 \, dt$

IV bolus dose

One-step prediction

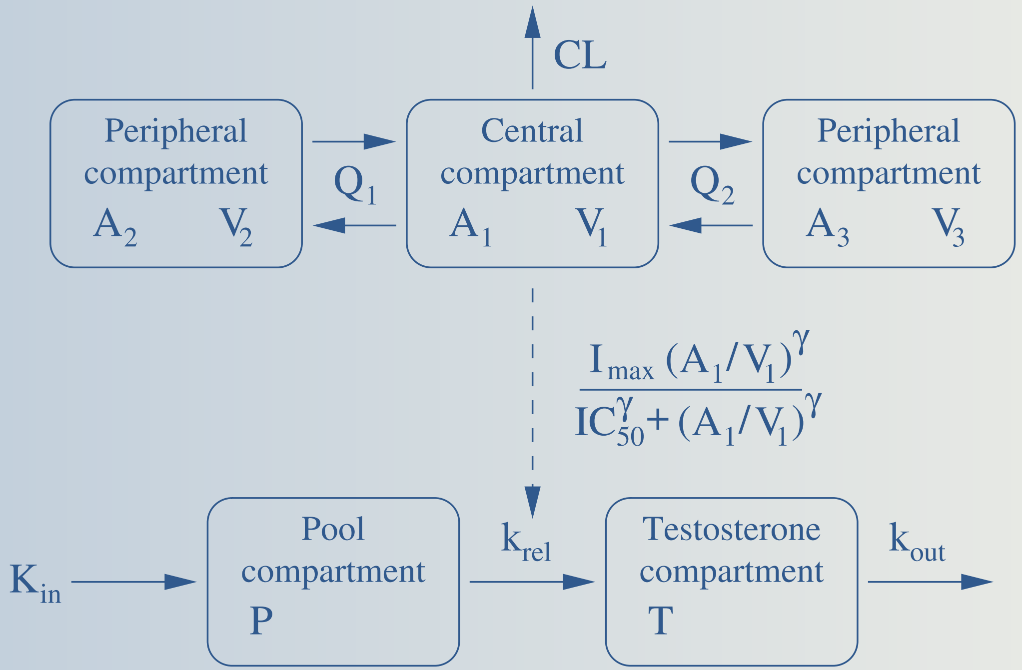
Store $A(\cdot)$ from $PK

Reset and update $A(\cdot)$

FERRING PHARMACEUTICALS

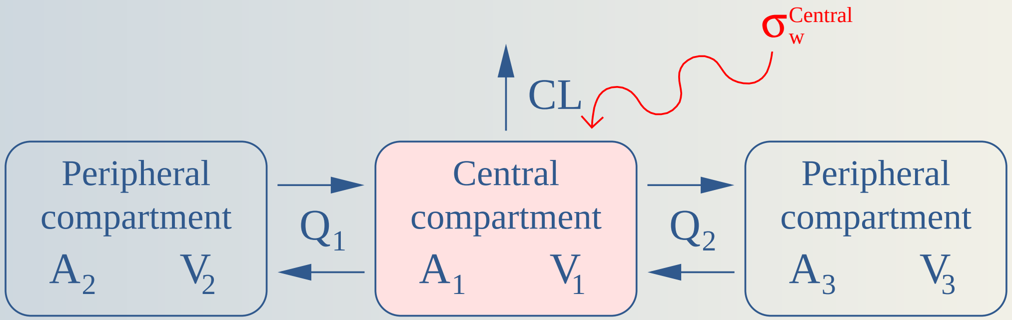
Material and methods

- PK/PD modelling of GnRH antagonist degarelix
  - Degarelix IV infusion phase I study with 24 subjects
  - Sequential PK/PD data analysis
  - FOCE method with INTERACTION



Pharmacokinetic model

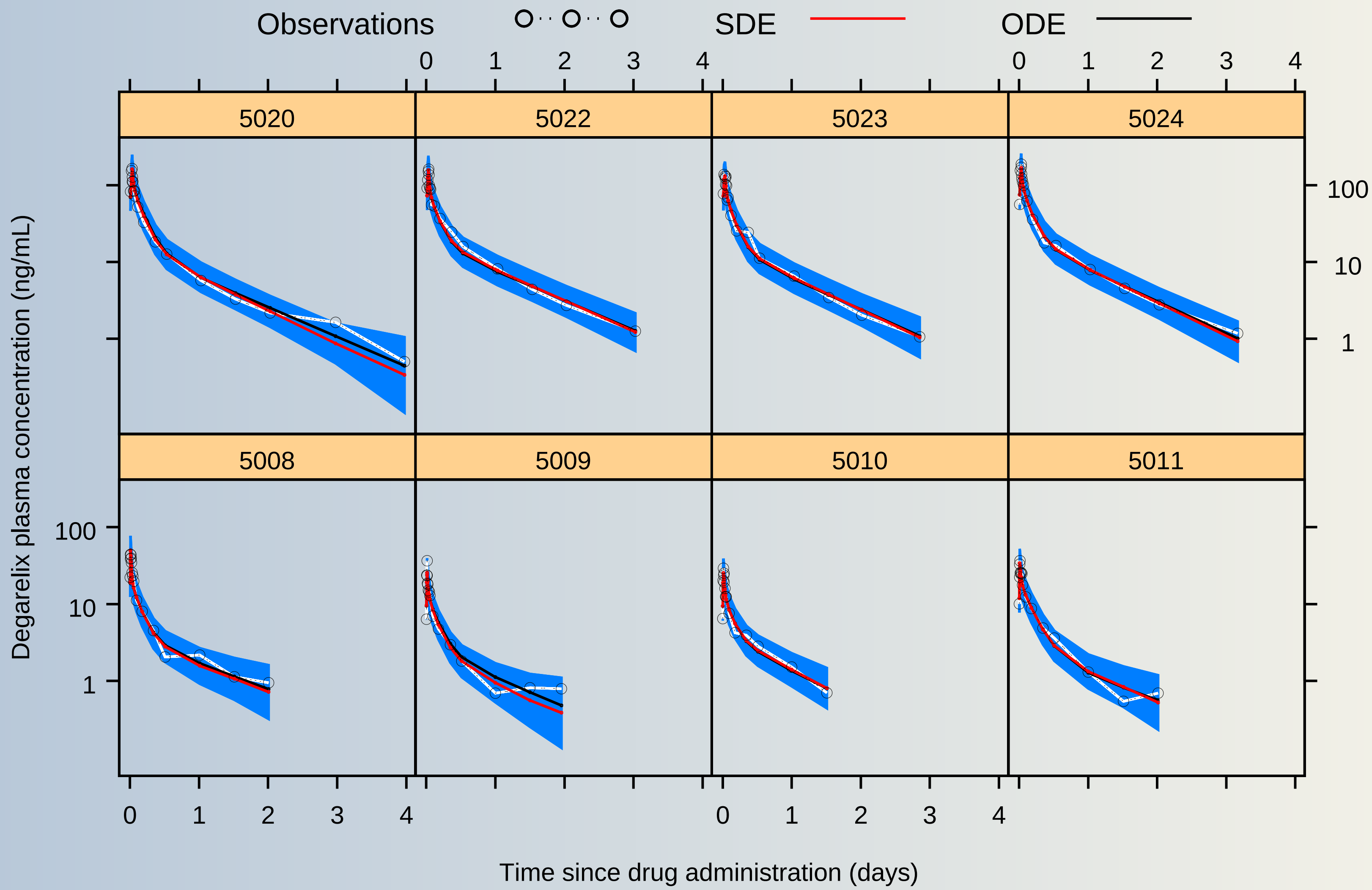
- PK parameter estimates



Parameter	ODE	SDE	Relative diff.
OFV	−714	−721	
CL	3.29	3.32	0%
Q_1	2.57	2.63	2%
Q_2	10.7	11.0	3%
V_1	9.78	9.69	1%
V_2	31.7	30.4	4%
V_3	8.87	8.70	2%
IIV CL	17.6	17.6	0%
IIV Q_1	30.8	32.7	6%
IIV V_1	27.7	27.8	0%
σ_{prop}	19.8	18.8	5%
$\sigma_w^{Central}$		2.08	

Pharmacokinetic model

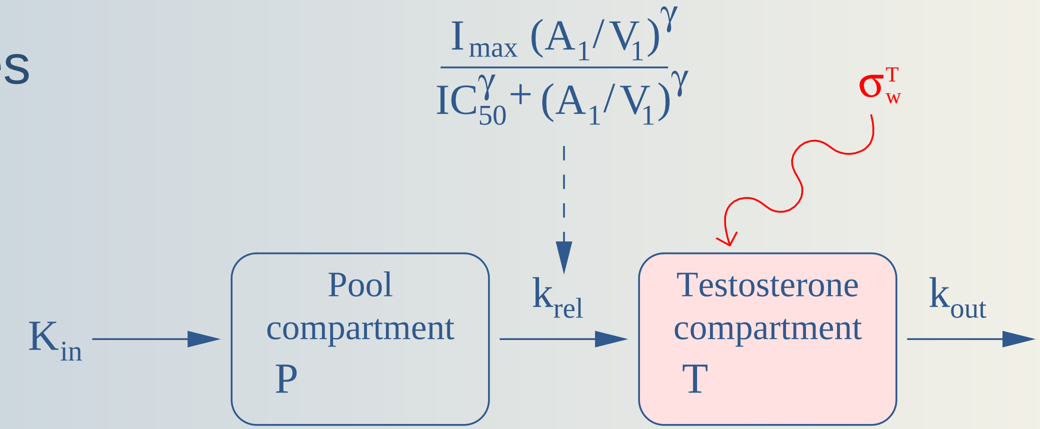
- PK concentration-time profiles



FERRING PHARMACEUTICALS

Pharmacodynamic model

- PD parameter estimates

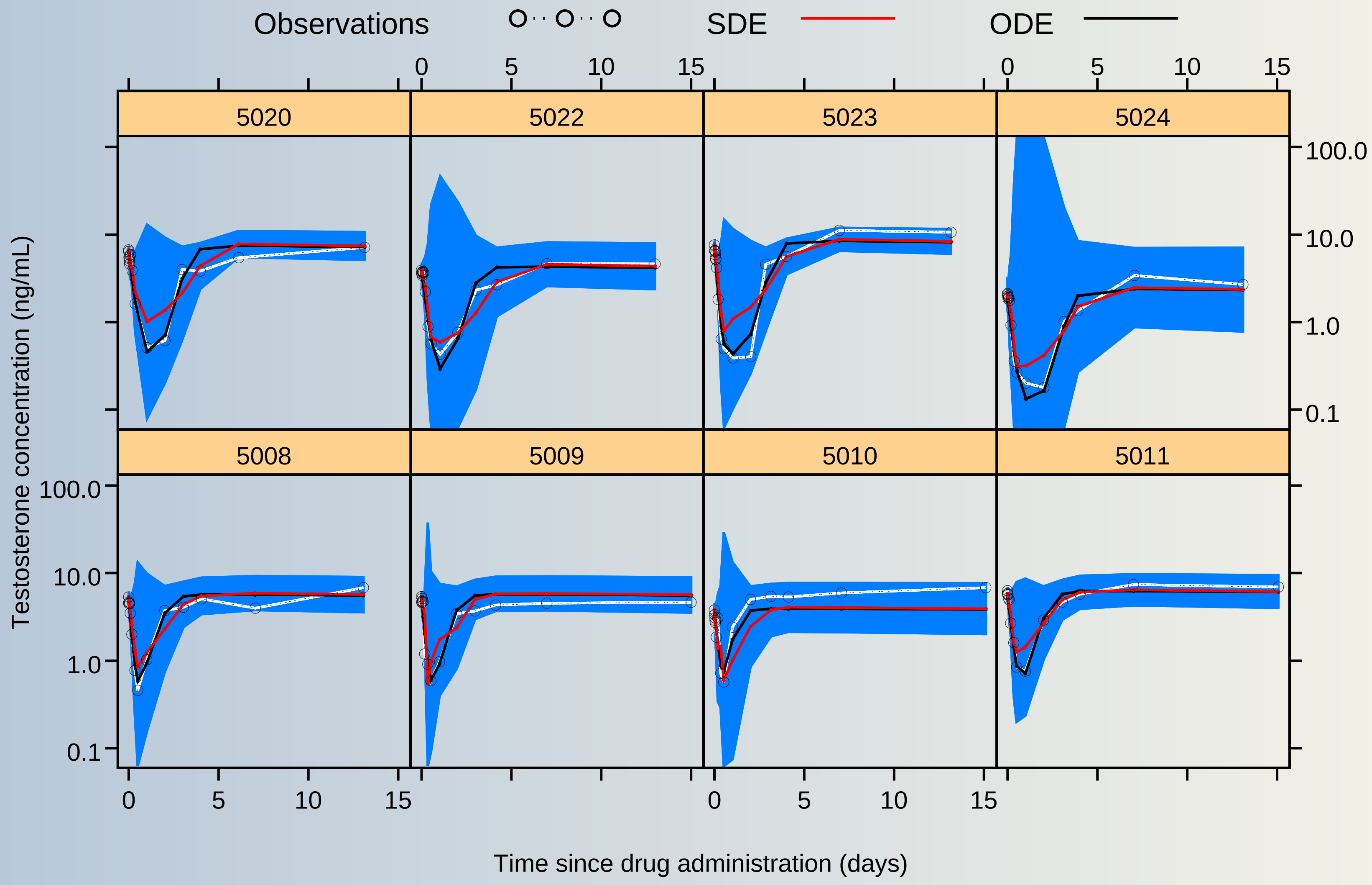


Parameter	ODE	SDE	Relative diff.
OFV	−565	−643	
k_{out}	0.22	0.21	3%
k_{rel}	0.0024	0.0035	46%
I_{max}	0.95	0.87	9%
IC_{50}	0.59	0.40	33%
γ	3.00	1.68	44%
IIV k_{out}	18.7	5.93	68%
IIV IC_{50}	54.6	32.6	40%
σ_{prop}	23.9	3.69	85%
σ_w^T		0.726	

FERRING PHARMACEUTICALS

Pharmacodynamic model

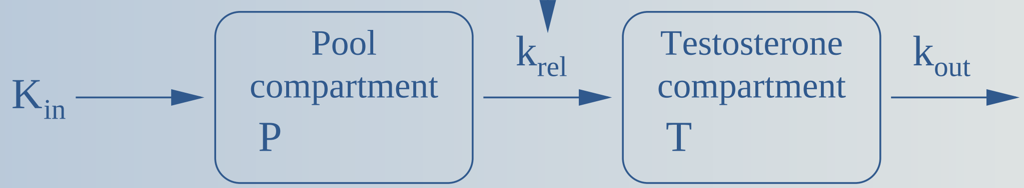
- PD concentration-time profiles

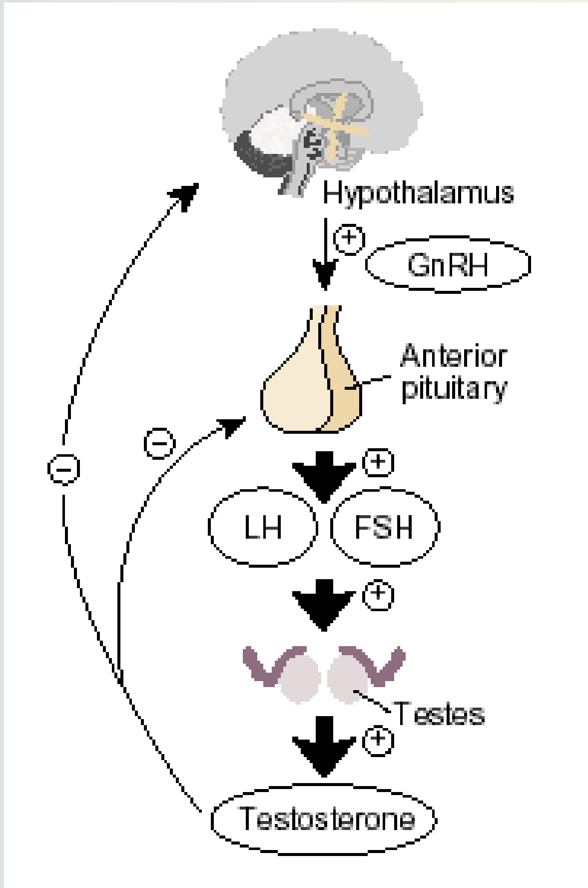


Pinpointing model deficiencies

- Hypothalamic-Pituitary-Gonadal (HPG) axis
  - Variations in testosterone production
  - HPG mechanisms of action

$$\frac{I_{max}\,(A_1/V_1)^{\gamma}}{IC_{50}^{\gamma} + (A_1/V_1)^{\gamma}}$$



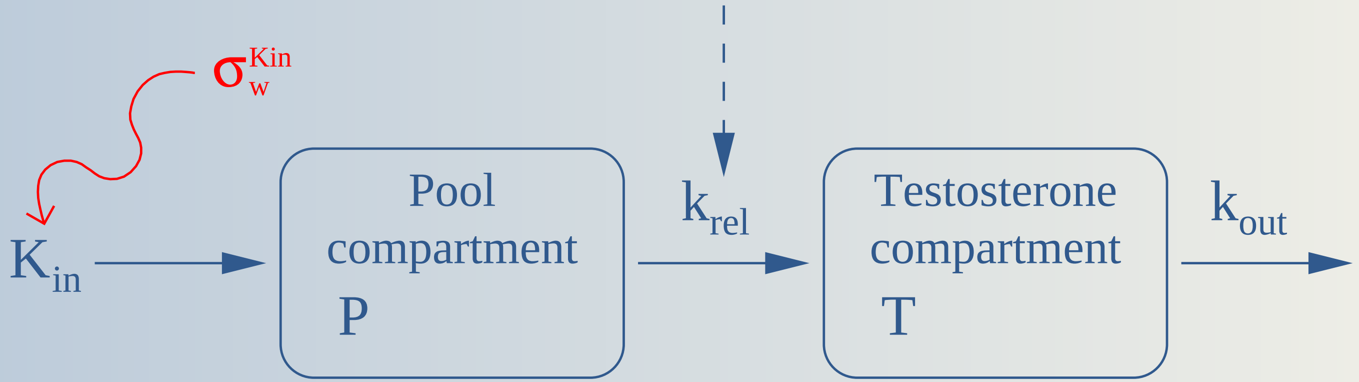


Pinpoint PD model deficiencies

- Variations in testosterone production

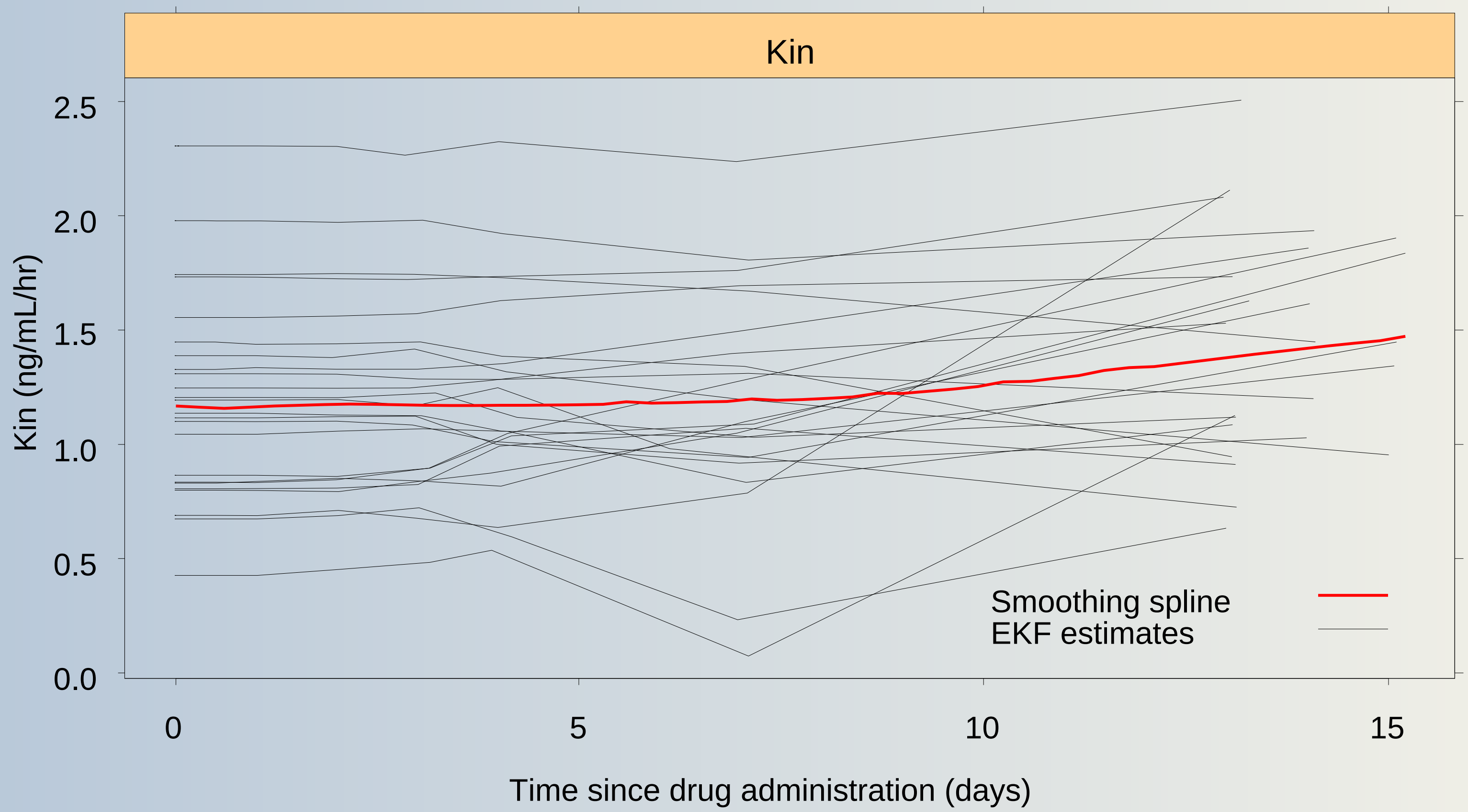
$$\begin{pmatrix} dP \\ dT \\ dK_{in} \end{pmatrix} = \begin{pmatrix} K_{in} - k_{rel}\left(1 - \frac{I_{max}\, C_p^{\gamma}}{IC_{50}^{\gamma} + C_p^{\gamma}}\right) P \\ k_{rel}\left(1 - \frac{I_{max}\, C_p^{\gamma}}{IC_{50}^{\gamma} + C_p^{\gamma}}\right) P - k_{out}\, T \\ 0 \end{pmatrix} dt + \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & \sigma_w^{\mathrm{K_{in}}} \end{pmatrix} d\boldsymbol{w}_t$$

$$\frac{\mathrm{I_{max}}\,(\mathrm{A_1/V_1})^{\gamma}}{\mathrm{IC}_{50}^{\gamma} + (\mathrm{A_1/V_1})^{\gamma}}$$



Pinpoint PD model deficiencies

- Variations in testosterone production

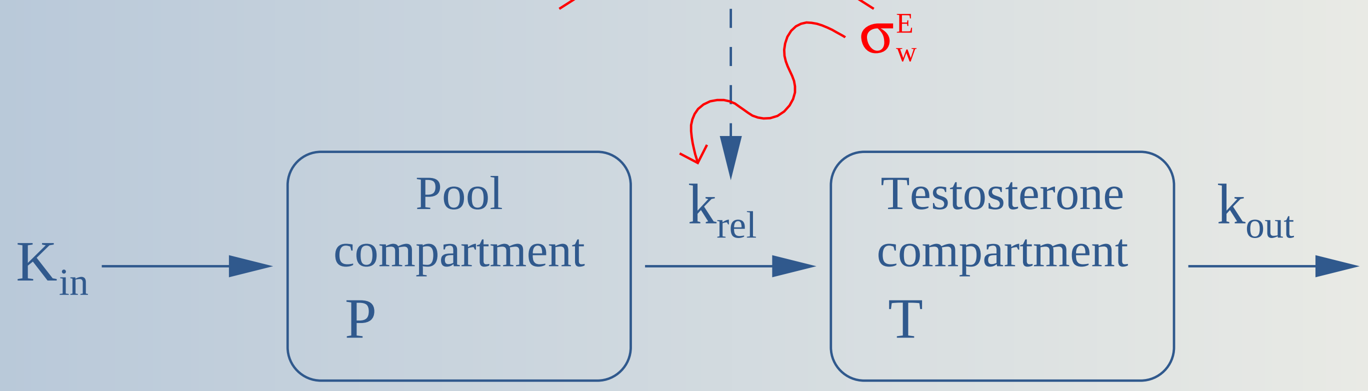


Pinpoint PD model deficiencies

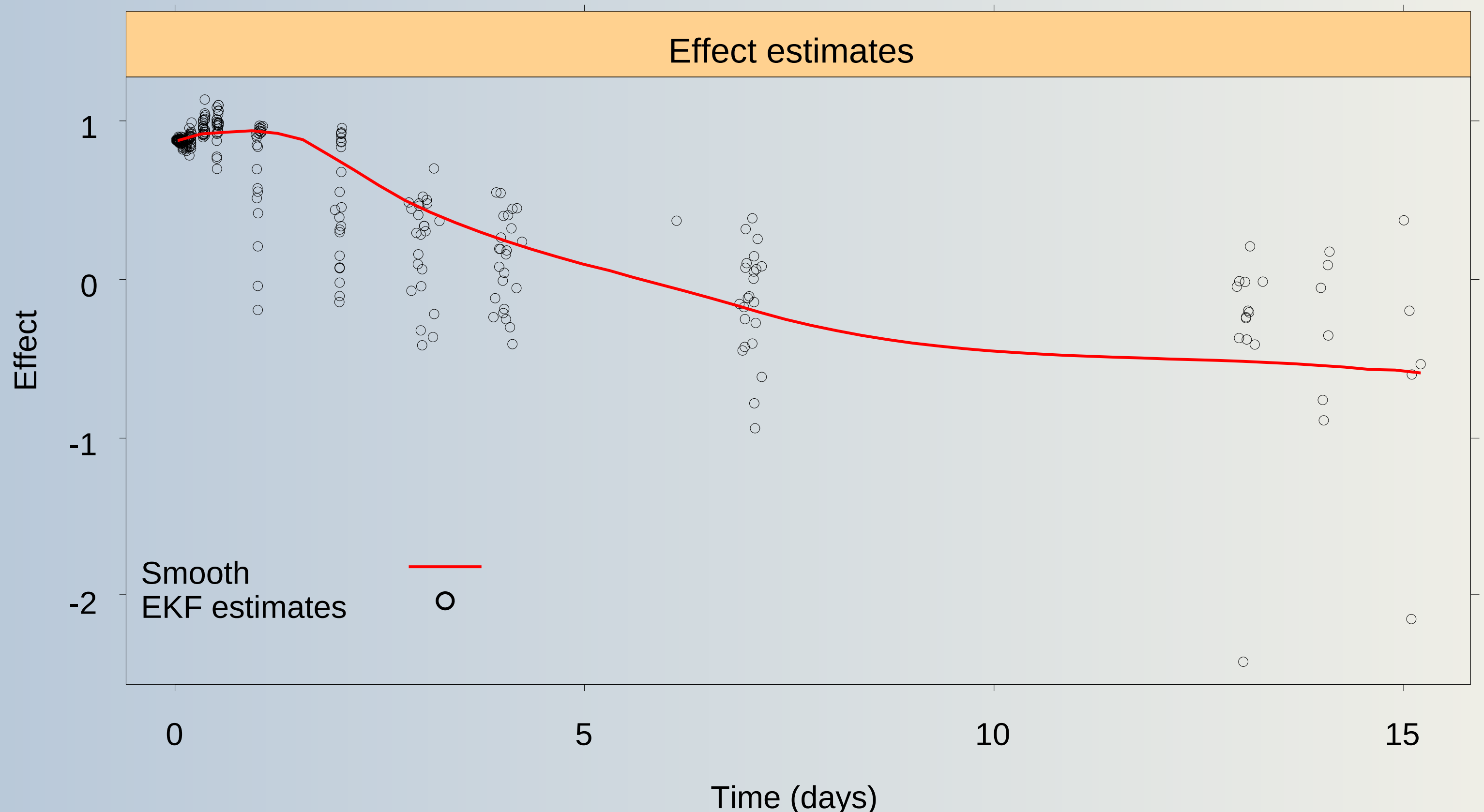
- HPG mechanisms of action

$$\begin{pmatrix} dP \\ dT \\ dE \end{pmatrix} = \begin{pmatrix} K_{in} - k_{rel}\ (1 - E)\ P \\ k_{rel}\ (1 - E)\ P - k_{out}\, T \\ 0 \end{pmatrix} dt + \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & \sigma_w^E \end{pmatrix} d\boldsymbol{w}_t$$

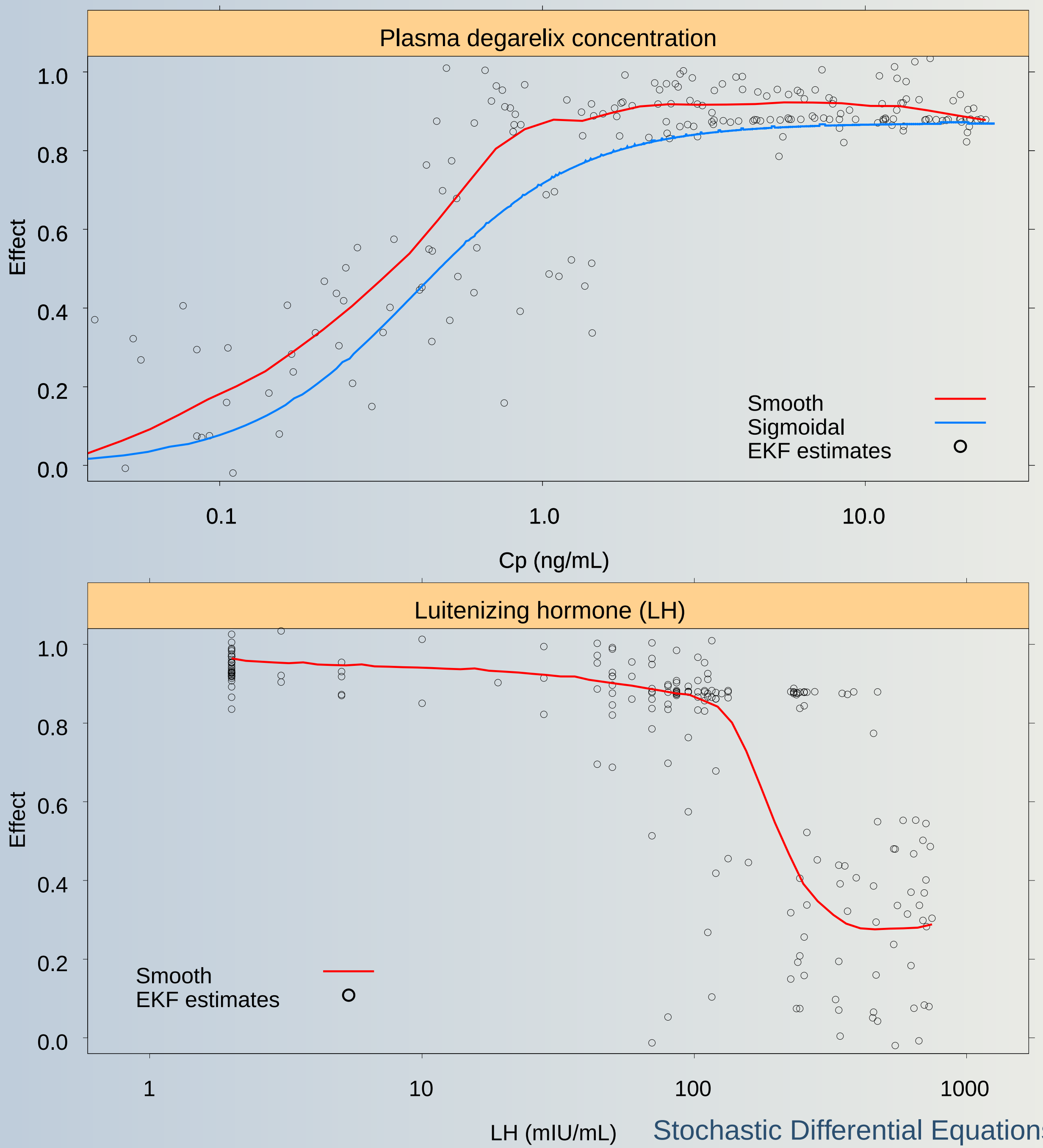
$$\xcancel{\frac{\mathrm{I}_{\mathrm{max}}\,(\mathrm{A}_1/\mathrm{V}_1)^{\gamma}}{\mathrm{IC}_{50}^{\gamma} + (\mathrm{A}_1/\mathrm{V}_1)^{\gamma}}}$$



Pinpoint PD model deficiencies

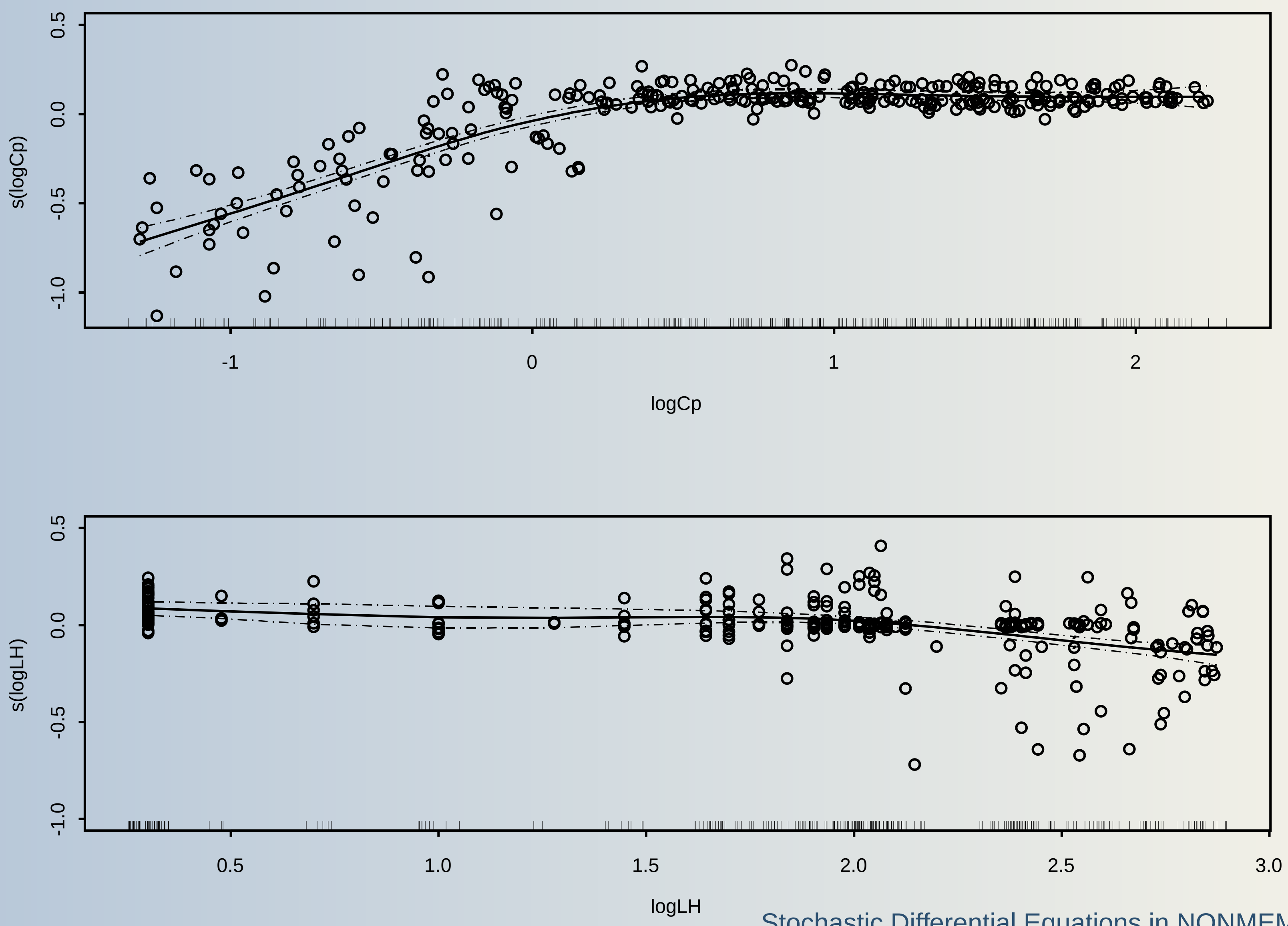


Pinpoint PD model deficiencies



Pinpoint PD model deficiencies

- GAM (Effect $\sim$ s(log Cp) + s(log LH))



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Conclusions

- Stochastic differential equations
  - Residual error is decomposed into system and measurement noise.
  - SDE model reduces to ODE model if the system noise is insignificant.
  - Provide a diagnostic tool for pinpointing model deficiencies.

FERRING PHARMACEUTICALS

Conclusions

- Stochastic differential equations
  - Residual error is decomposed into system and measurement noise.
  - SDE model reduces to ODE model if the system noise is insignificant.
  - Provide a diagnostic tool for pinpointing model deficiencies.

- PK/PD of GnRH antagonist degarelix
  - Significant system noise parameters in PK/PD model
    - PK: Random physiological fluctuations
    - PD: Model misspecification
  - Pinpoint PD model deficiencies
    - Tracking of K_{in} parameter
    - Deconvolution of effect model

Questions ?