Stochastic Differential Equations in NONMEM:

A diagnostic tool for pinpointing model deficiencies

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Outline of Presentation

- Aims of analysis
- Motivation
- Methods
  - Stochastic differential equations
  - Extended Kalman Filter
- Results
  - PK/PD of GnRH antagonist degarelix
  - Framework for pinpointing model deficiencies
- Conclusions

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Aims of analysis

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

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Motivation

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  - When auto-correlated residual errors are observed due to structural model misspecifications or true physiological variations.
  - 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.

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Methods

- Ordinary differential equations

$$
\begin{aligned}
d\boldsymbol{A}/dt &= \boldsymbol{g}(\boldsymbol{\theta}, \boldsymbol{A}, \boldsymbol{d}) \\
\boldsymbol{y}_k &= \boldsymbol{f}(\boldsymbol{\theta}, \boldsymbol{A}) + \boldsymbol{\epsilon}_k
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- Stochastic differential equations

$$
\begin{aligned}
d\boldsymbol{A} &= \boldsymbol{g}(\boldsymbol{\theta}, \boldsymbol{A}, \boldsymbol{d})\, dt + \boldsymbol{\sigma}_w\, d\boldsymbol{w}_t \\
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\end{aligned}
$$

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Methods

- Extended Kalman Filter

$$d\boldsymbol{A} = \boldsymbol{g}(\boldsymbol{\theta}, \boldsymbol{A}, \boldsymbol{d})\, dt + \boldsymbol{\sigma}_w\, d\boldsymbol{w}_t$$

$$\boldsymbol{y}_k = \boldsymbol{f}(\boldsymbol{\theta}, \boldsymbol{A}) + \boldsymbol{\epsilon}_k$$

$$\boldsymbol{B} = \left.\frac{\partial \boldsymbol{g}}{\partial \boldsymbol{A}}\right|_{\boldsymbol{A}=\hat{\boldsymbol{A}}} \quad \boldsymbol{C} = \left.\frac{\partial \boldsymbol{f}}{\partial \boldsymbol{A}}\right|_{\boldsymbol{A}=\hat{\boldsymbol{A}}_{k|k-1}}$$

Prediction

1. Predict the state and covariance

$$d\hat{\boldsymbol{A}}_{t|k}/dt = \boldsymbol{g}(\boldsymbol{\theta}, \hat{\boldsymbol{A}}_{t|k}, \boldsymbol{d})$$

$$d\boldsymbol{P}_{t|k}/dt = \boldsymbol{B}\boldsymbol{P}_{t|k} + \boldsymbol{P}_{t|k}\boldsymbol{B}^T + \boldsymbol{\sigma}_w^2$$

2. Predict the observations

$$\hat{\boldsymbol{y}}_{k|k-1} = \boldsymbol{f}(\boldsymbol{\theta}, \hat{\boldsymbol{A}}_{k|k-1})$$

$$\boldsymbol{R}_{k|k-1} = \boldsymbol{C}\boldsymbol{P}_{k|k-1}\boldsymbol{C}^T + \boldsymbol{\sigma}^2$$

Measurement Update

1. Calculate the Kalman gain

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

2. Update the state and covariance

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

$$\boldsymbol{P}_{k|k} = \boldsymbol{P}_{k|k-1} - \boldsymbol{K}_k\boldsymbol{R}_{k|k-1}\boldsymbol{K}_k^T$$

Initial conditions:

$$\hat{\boldsymbol{A}}_{t|t_0} = \boldsymbol{A}_0$$

$$\boldsymbol{P}_{t|t_0} = P_0$$

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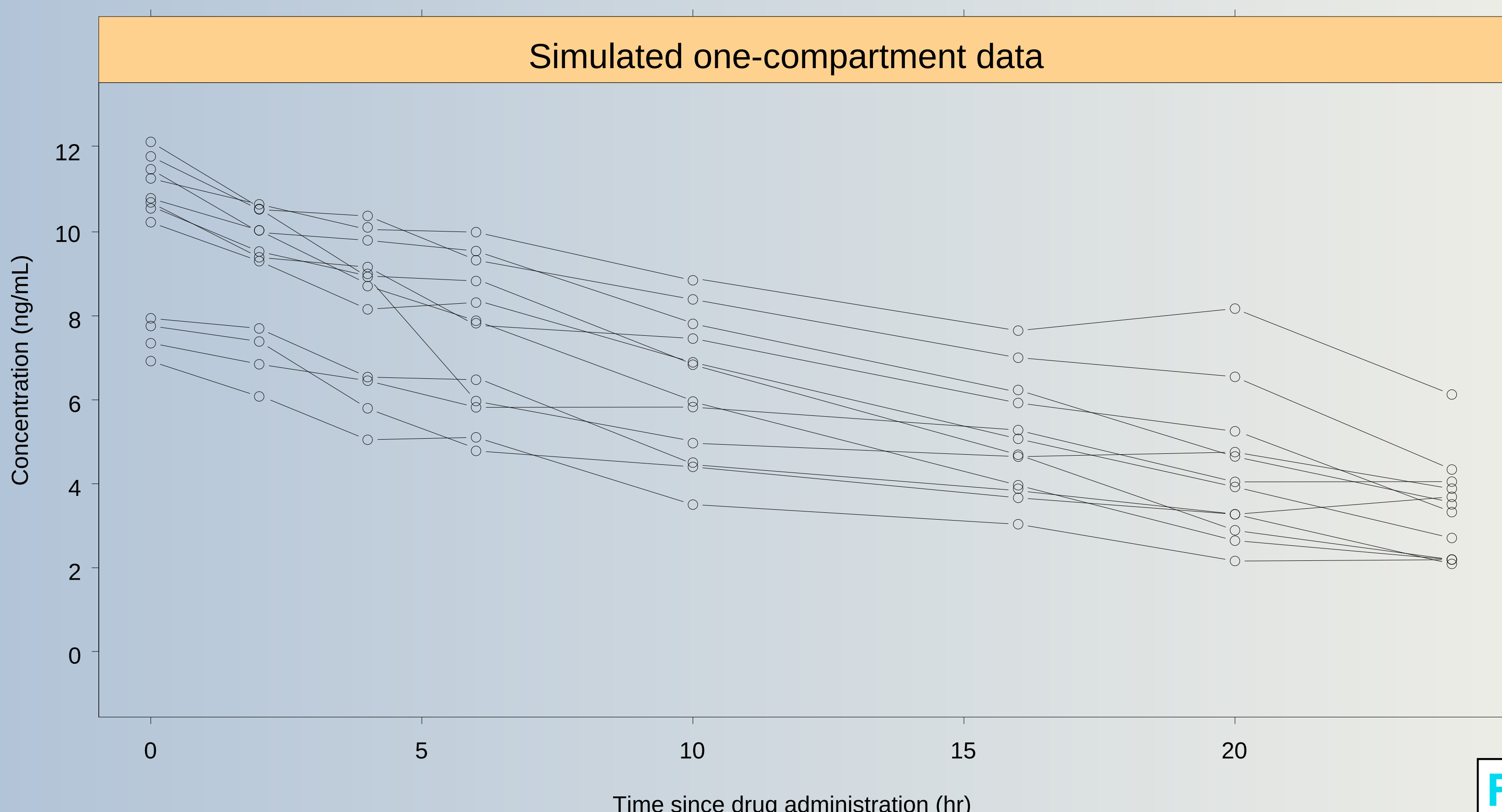

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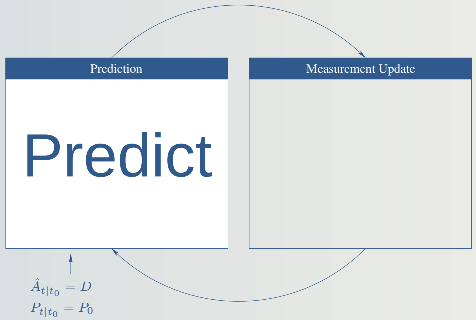

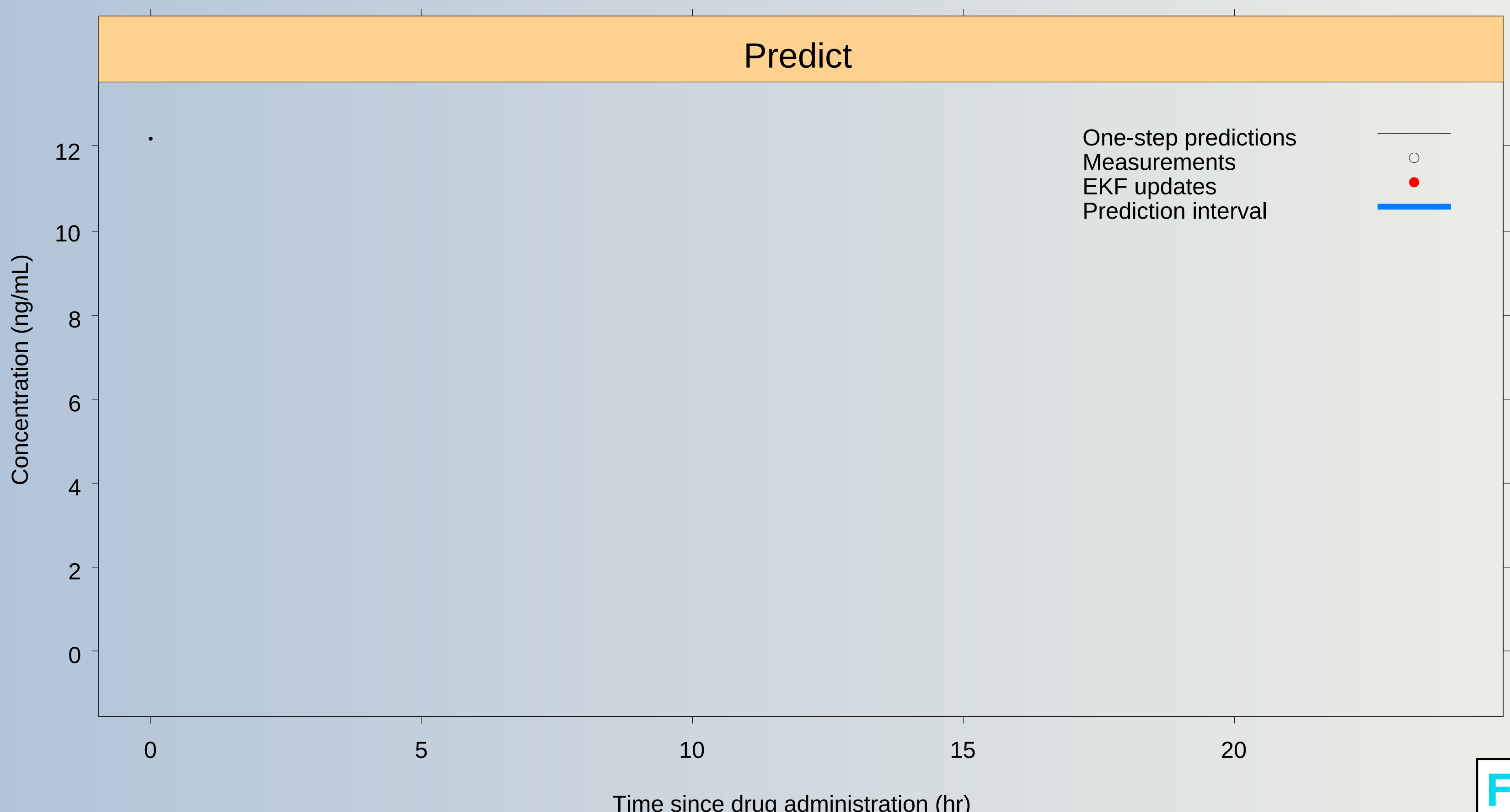

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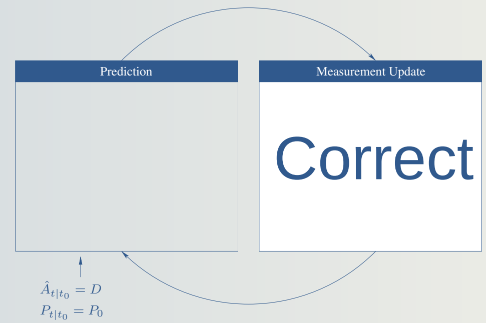

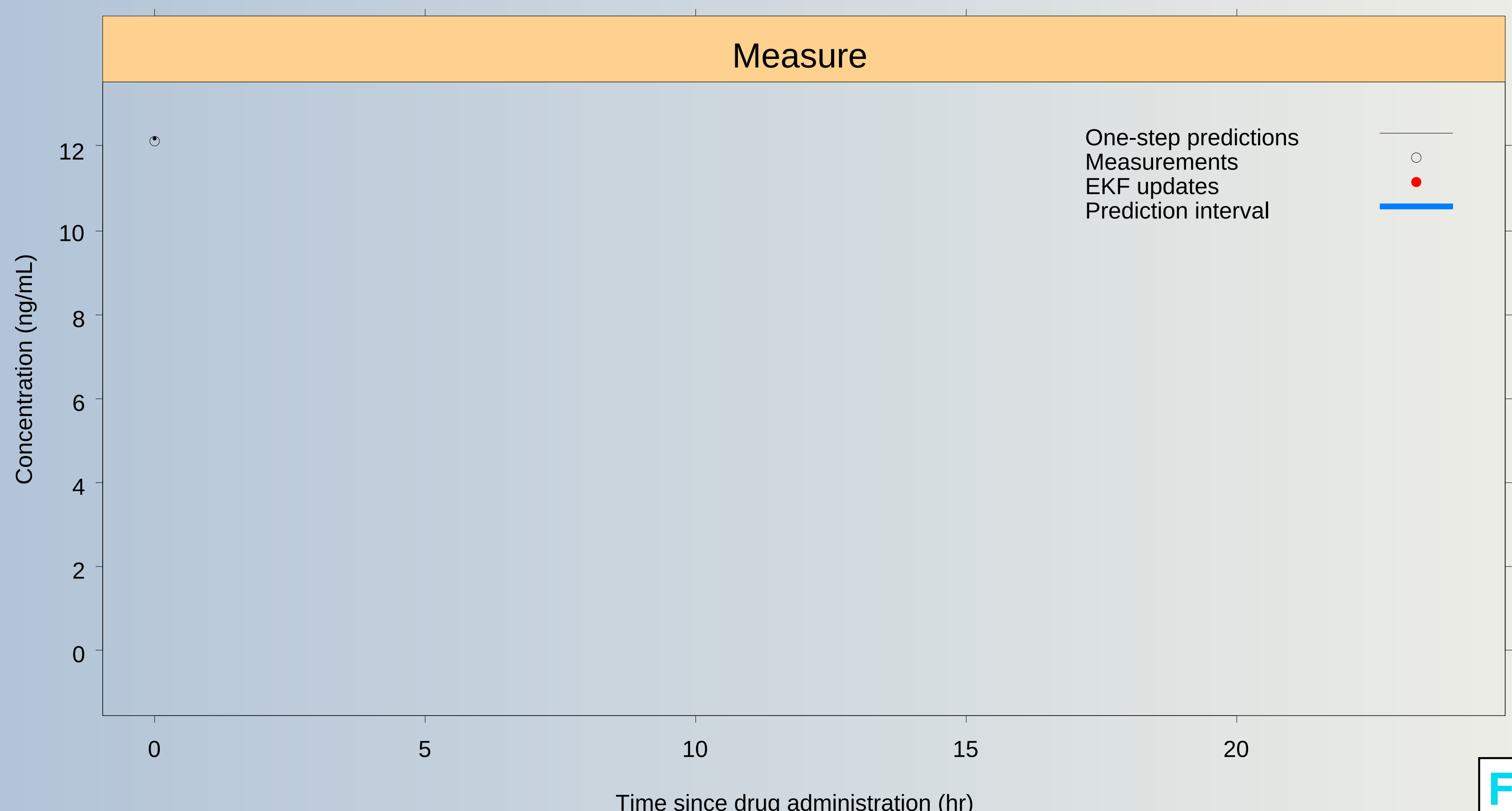

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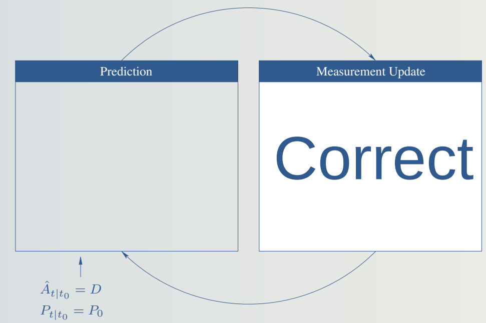

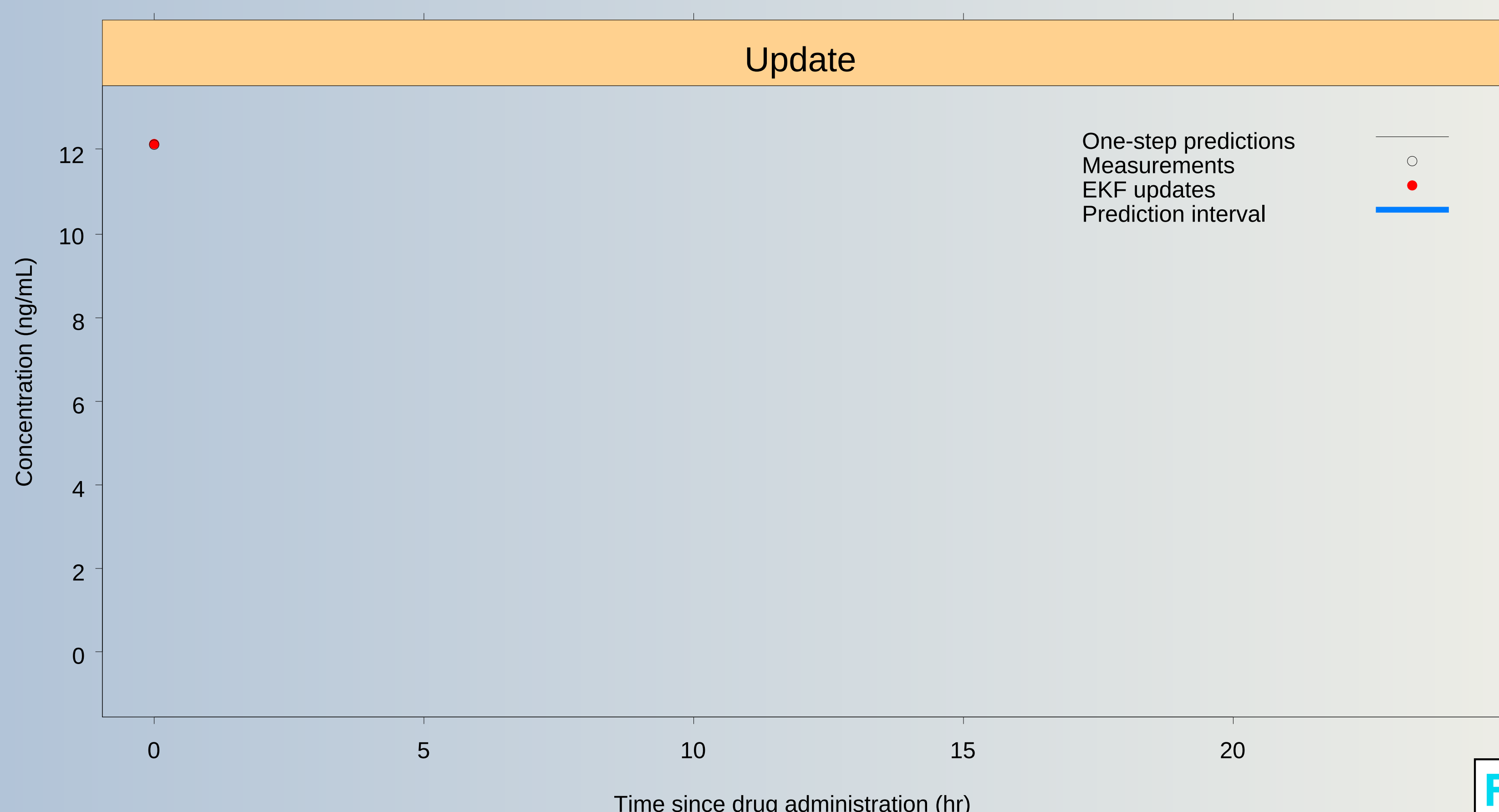

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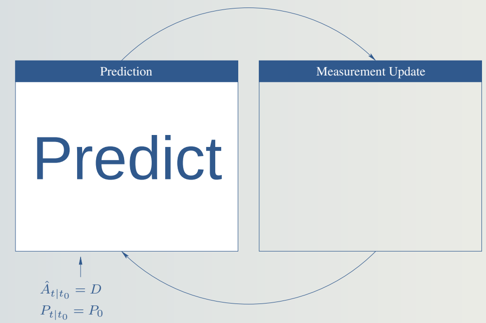

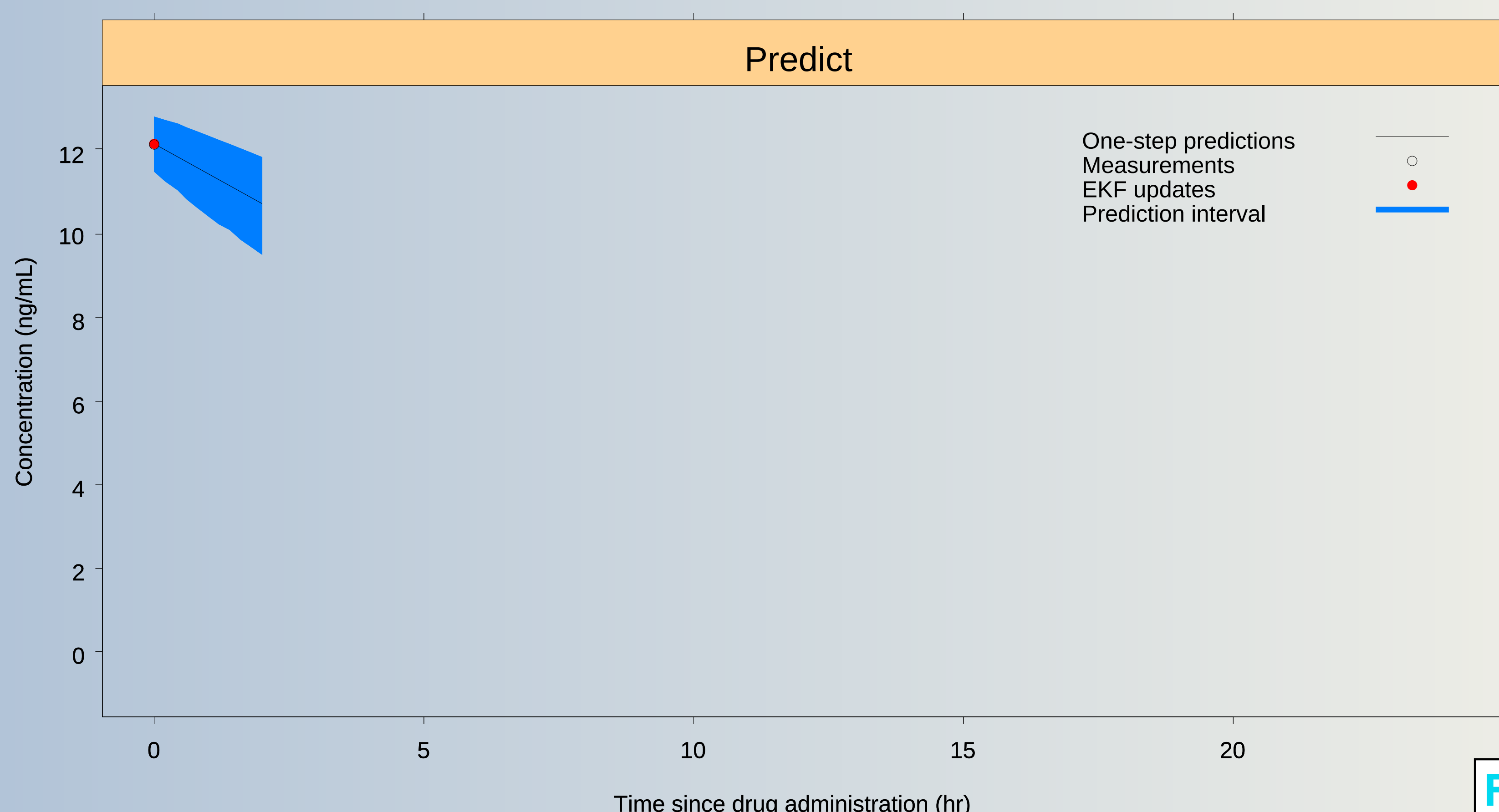

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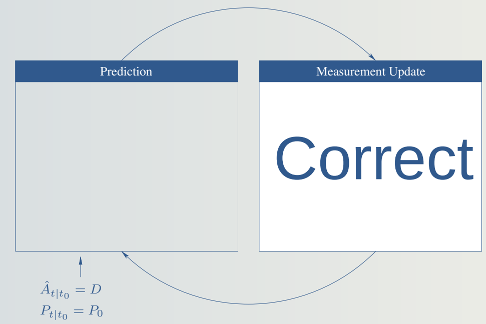

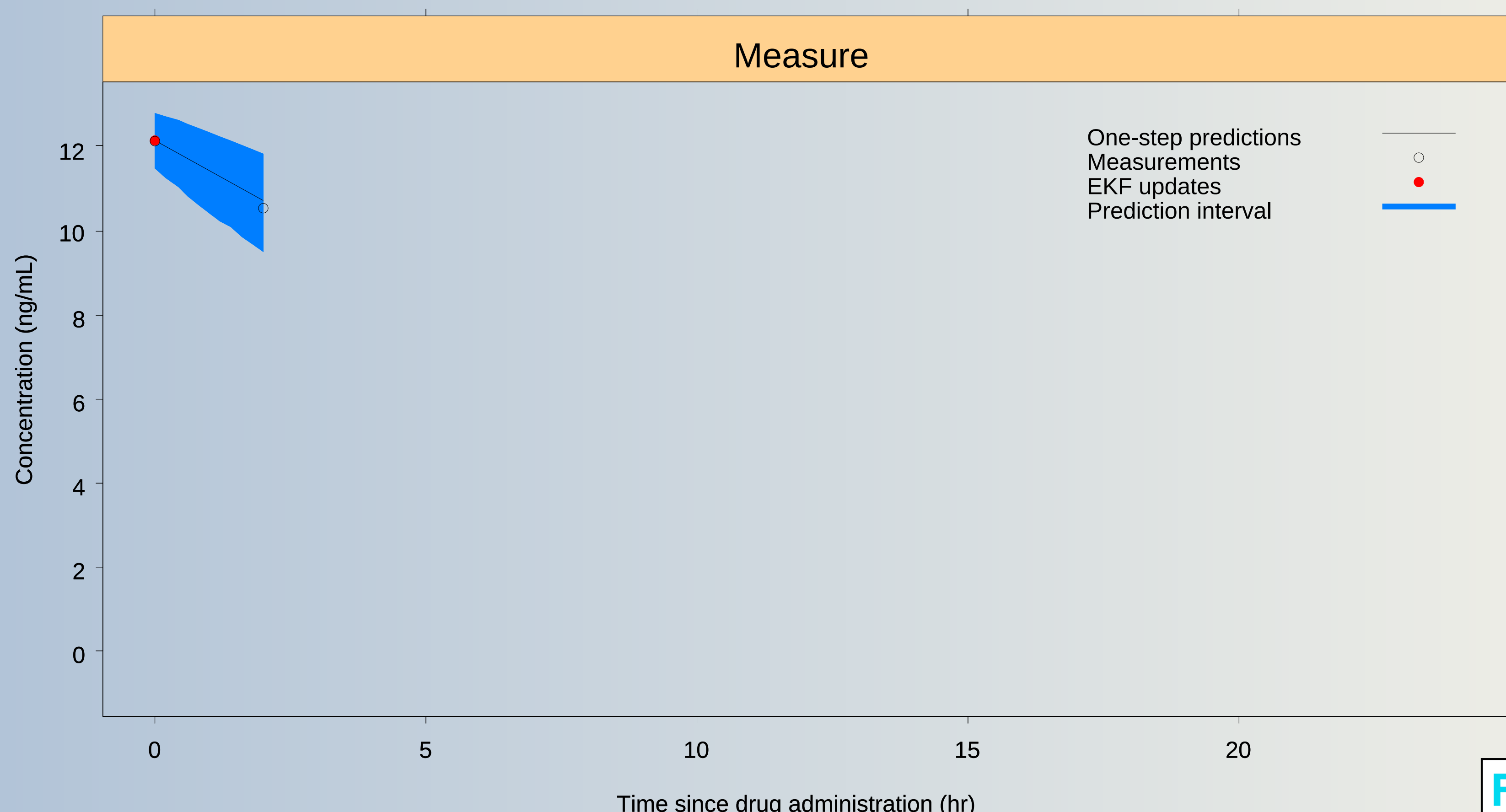

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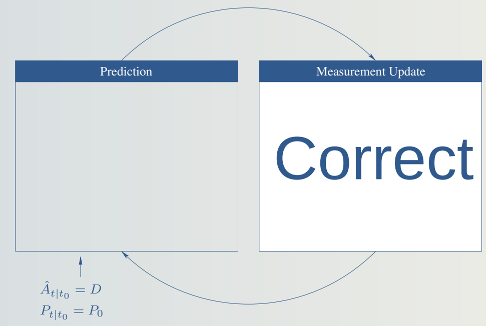

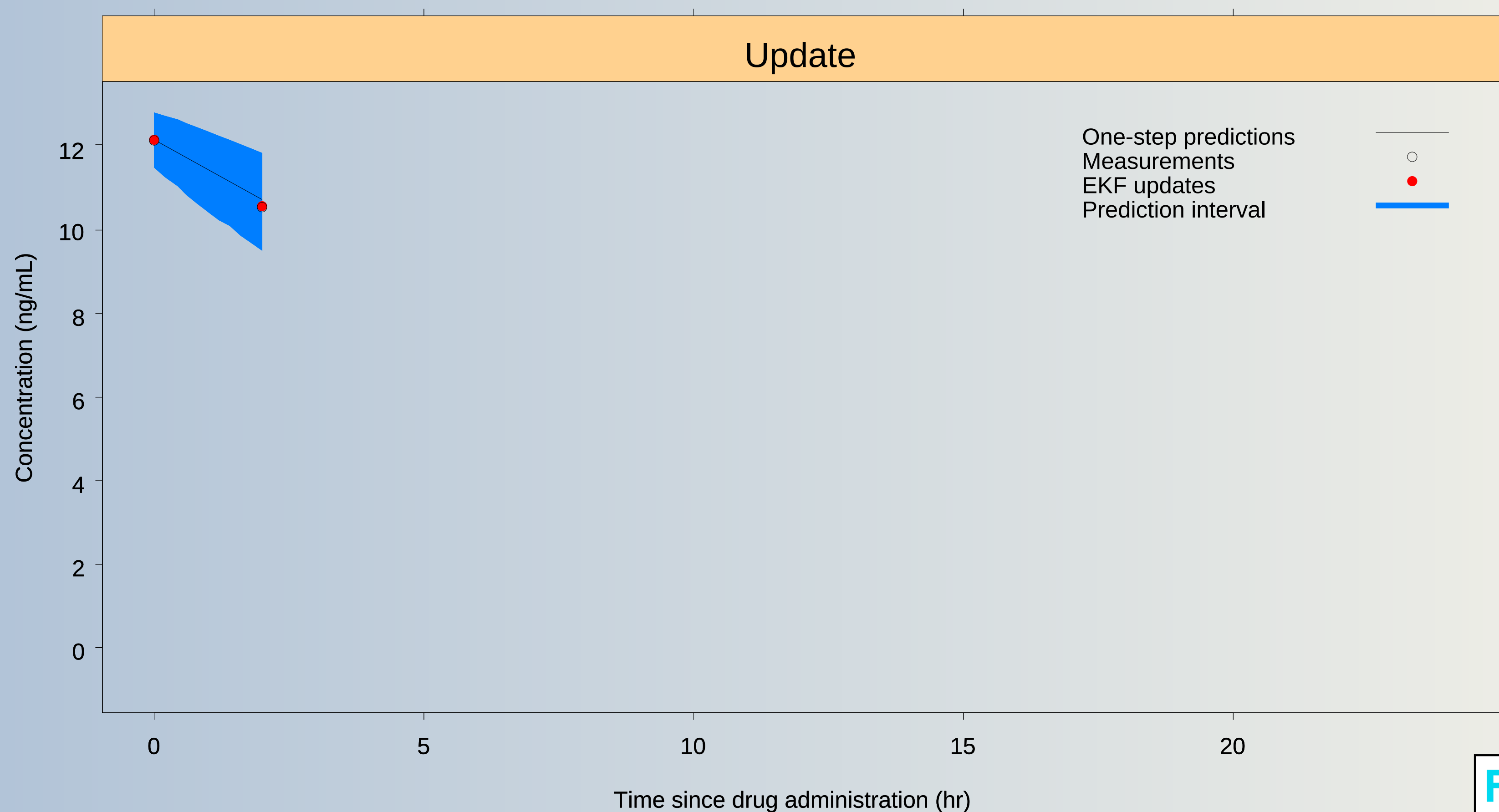

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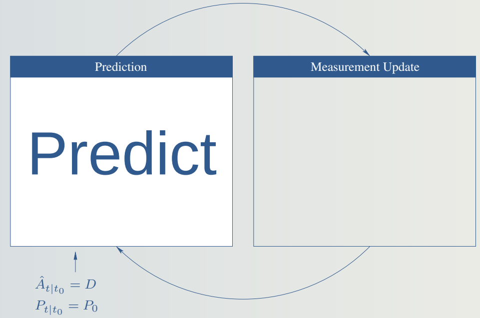

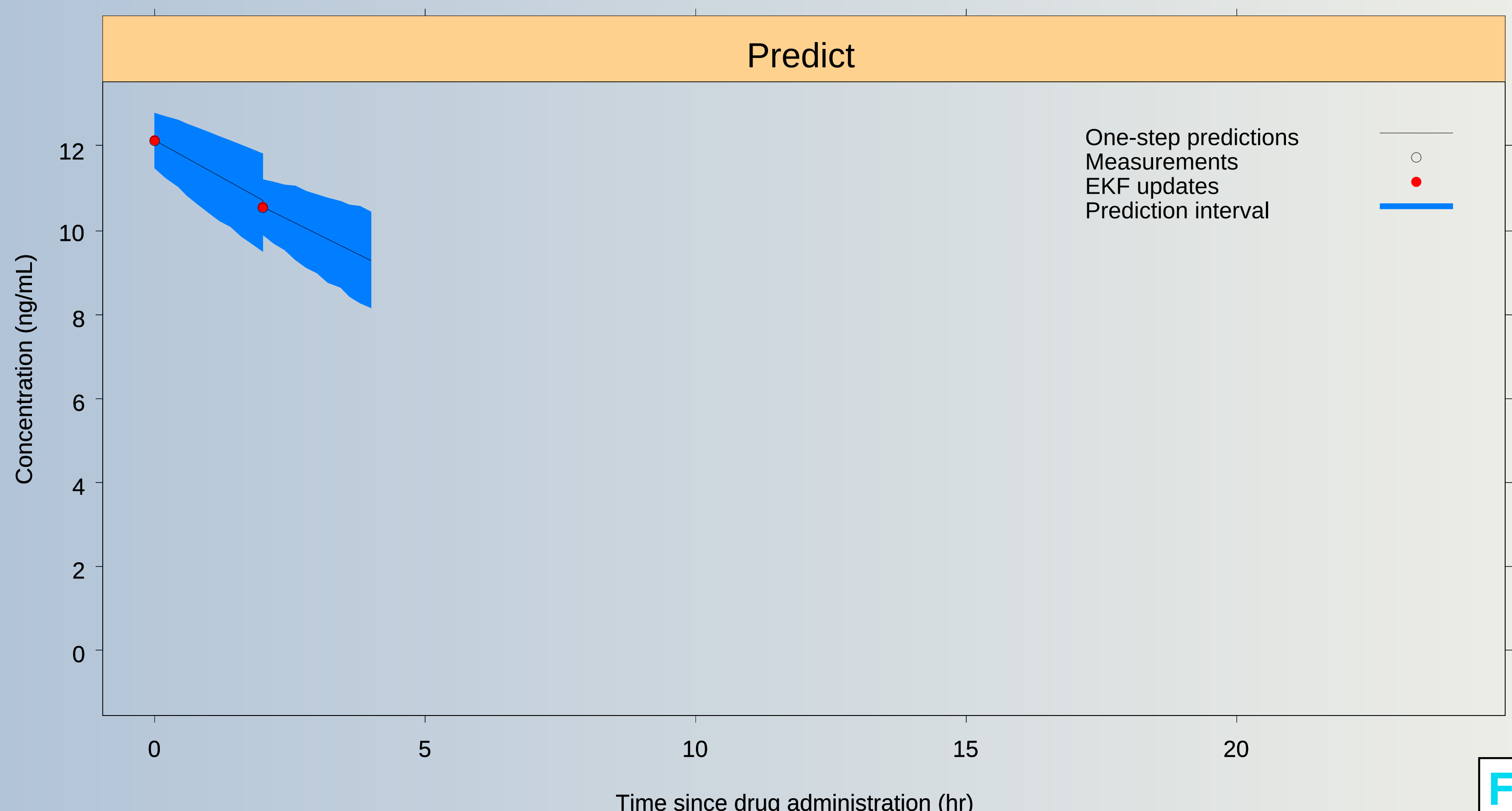

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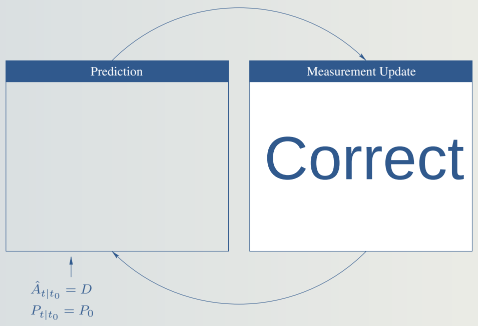

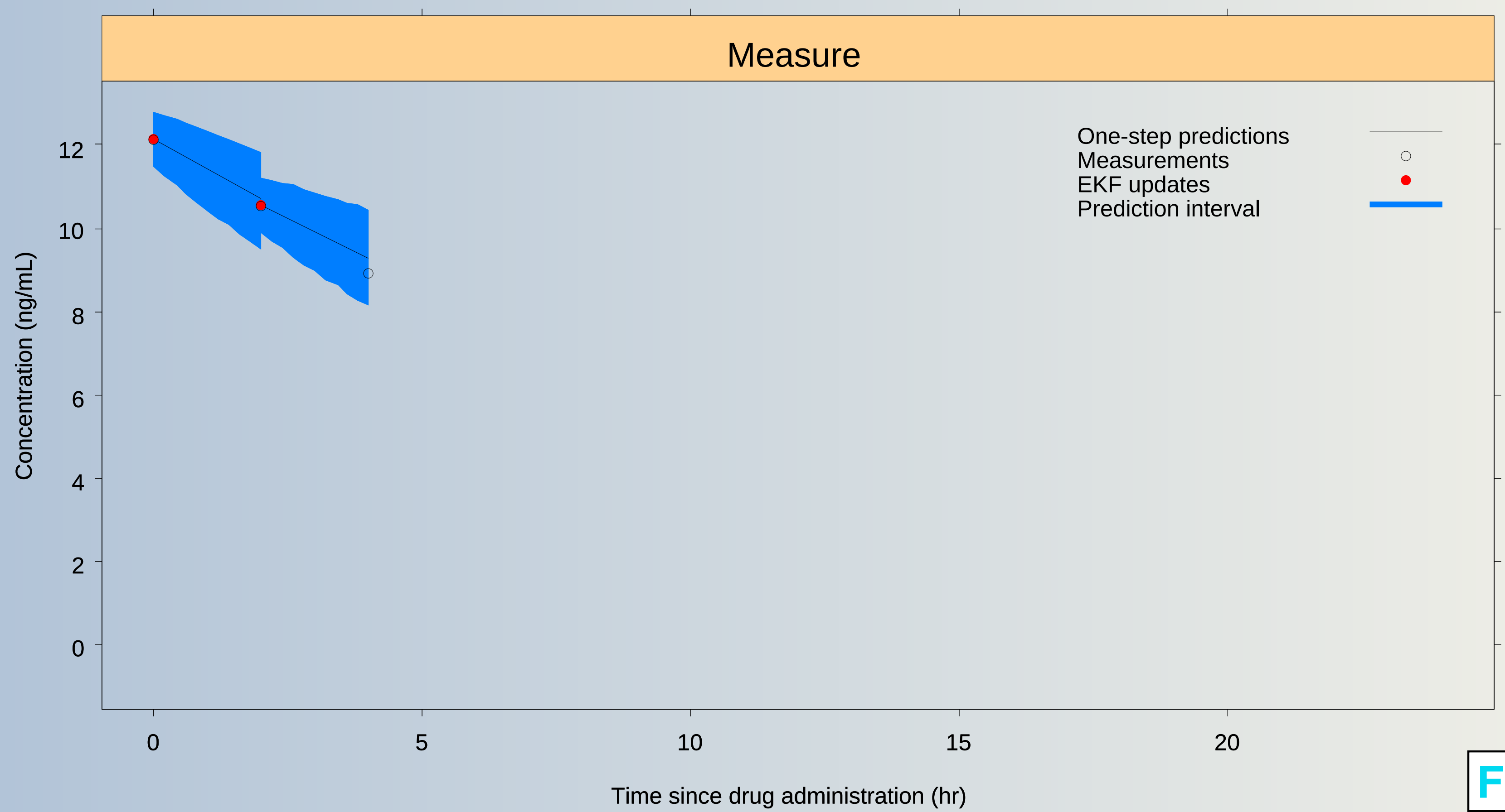

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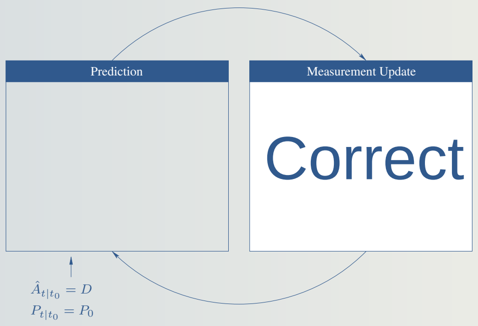

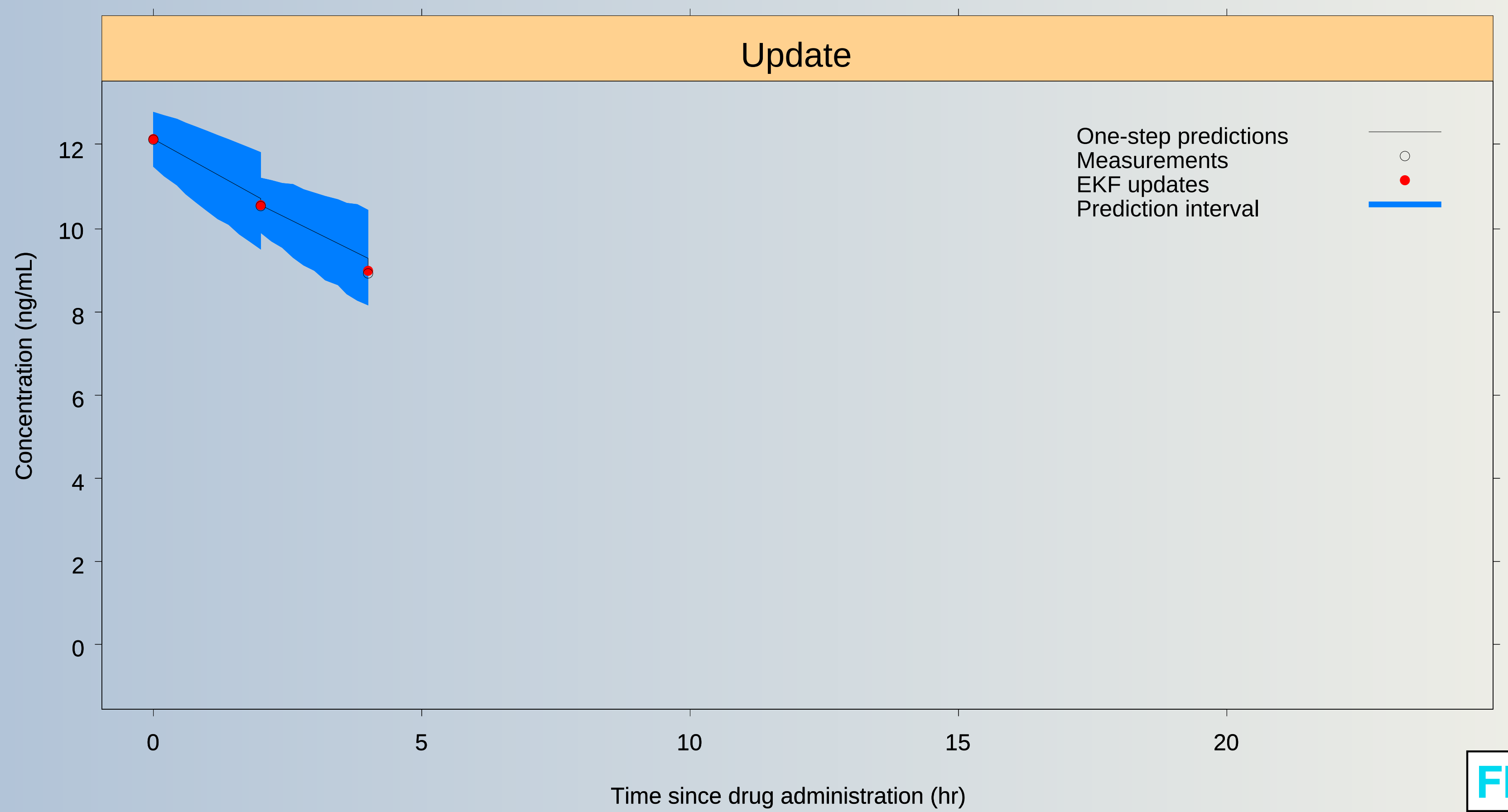

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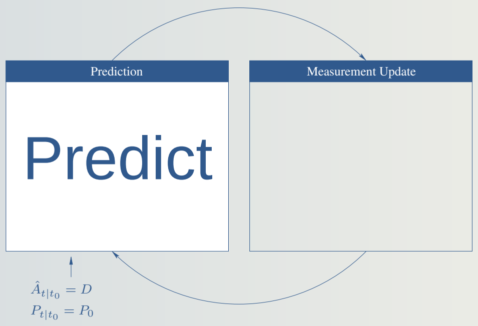

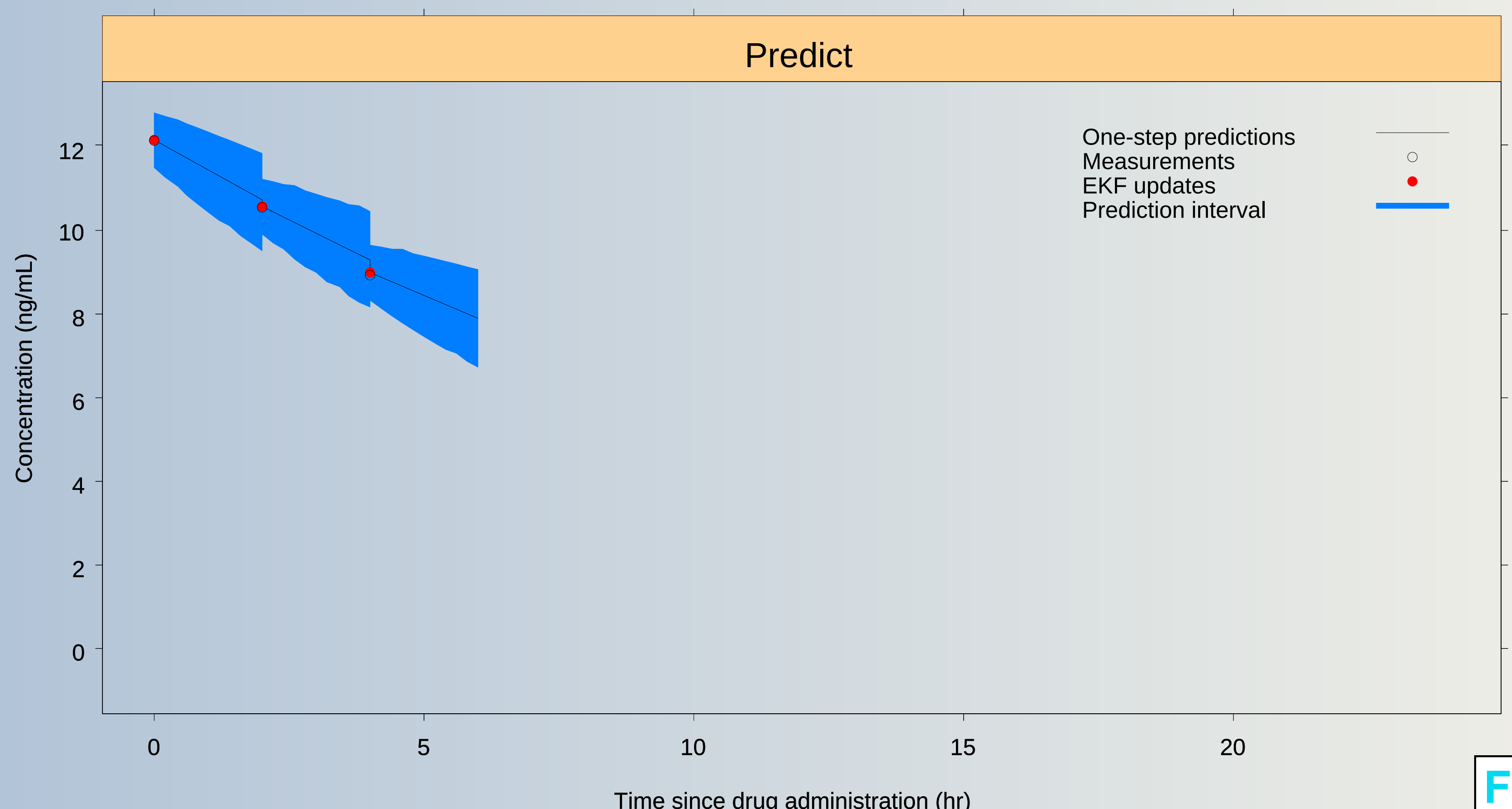

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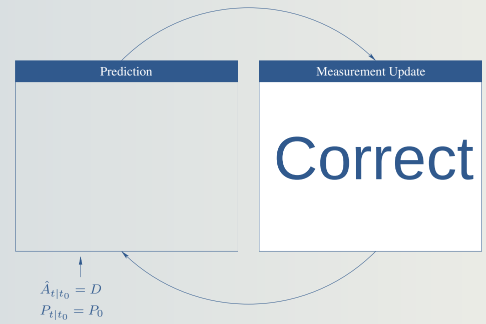

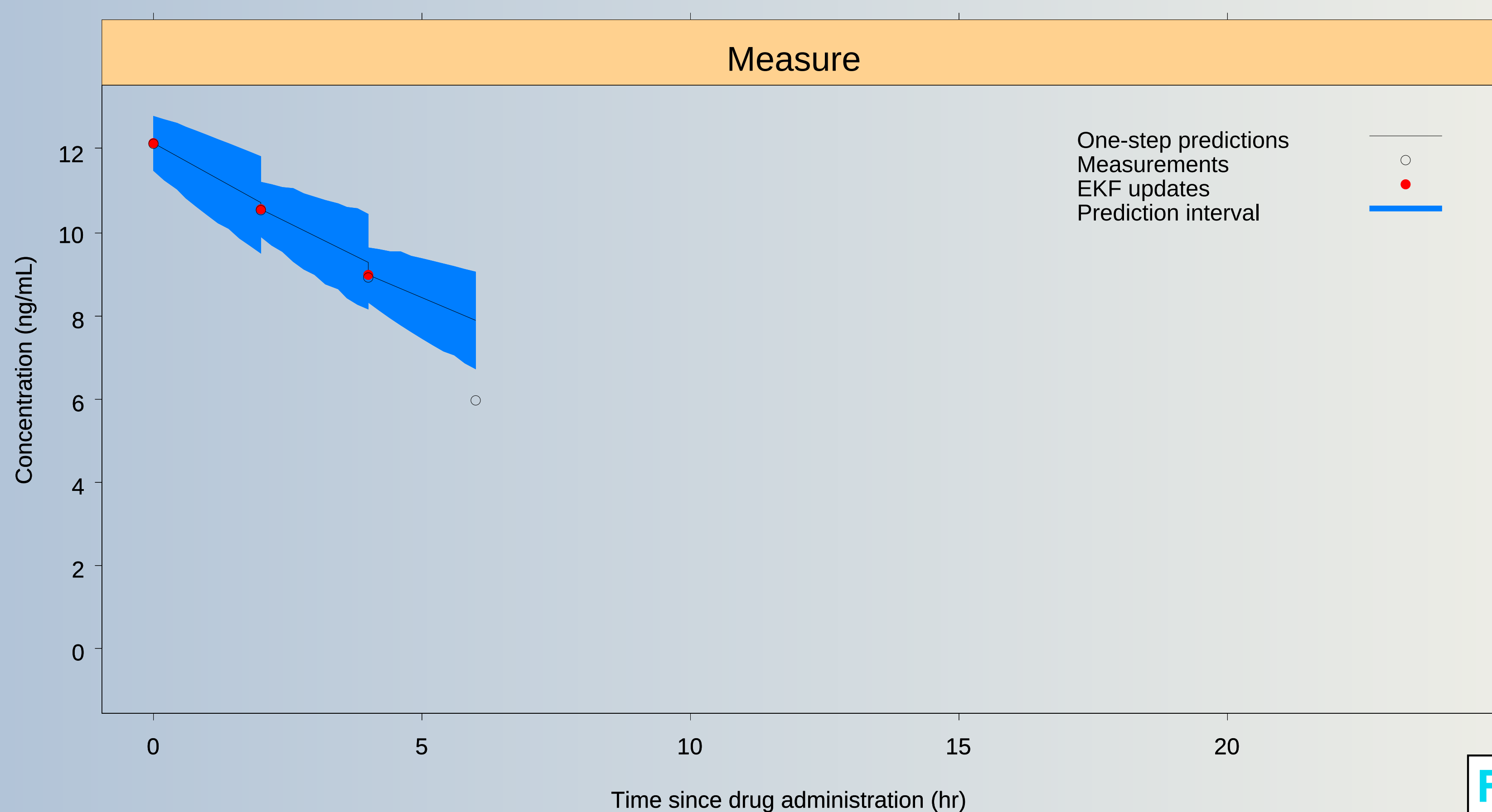

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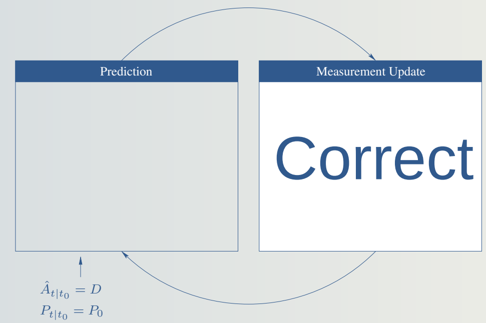

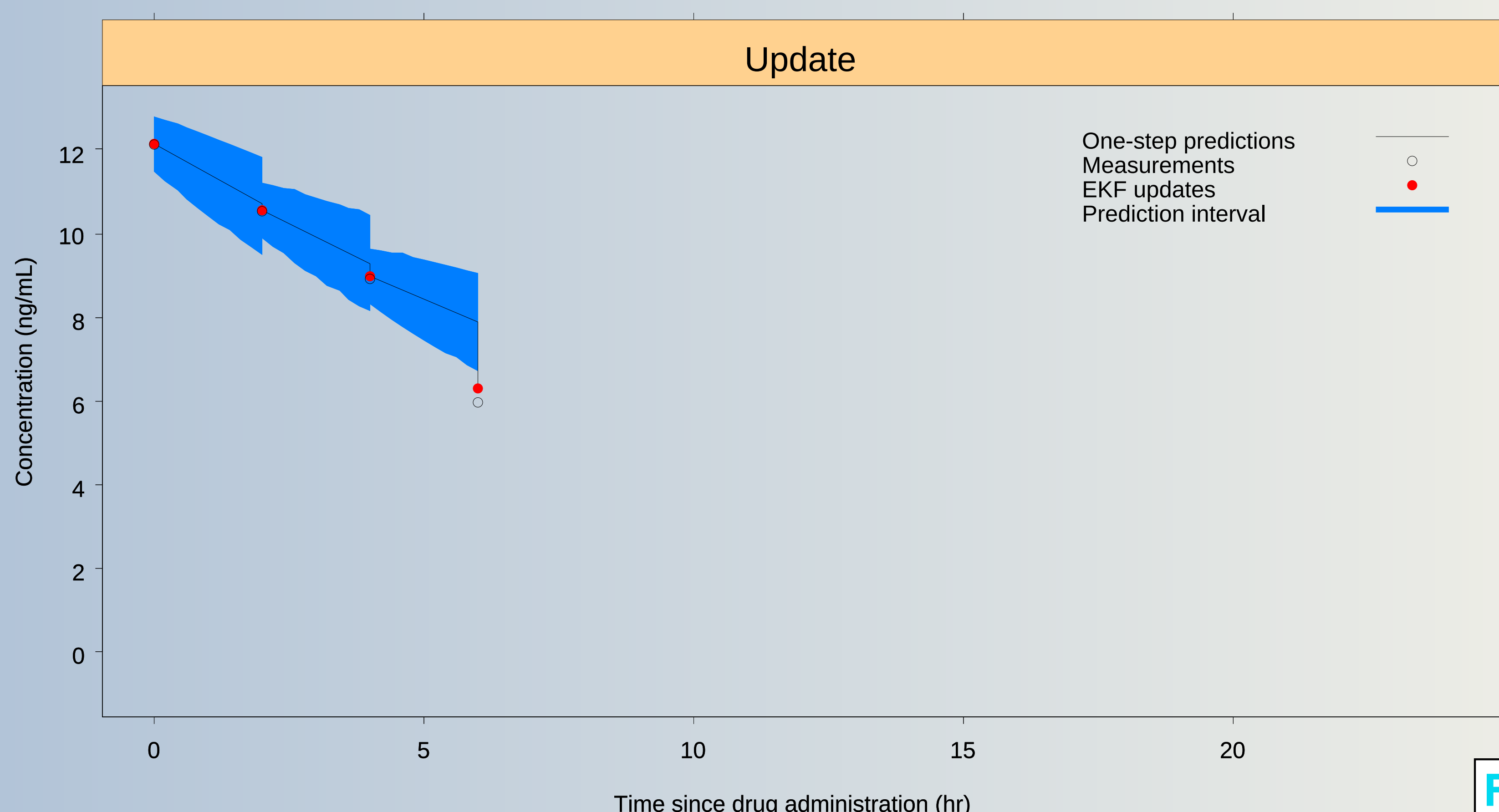

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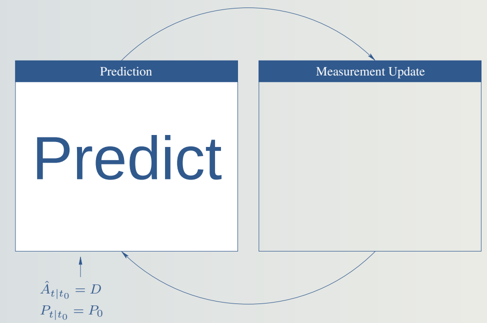

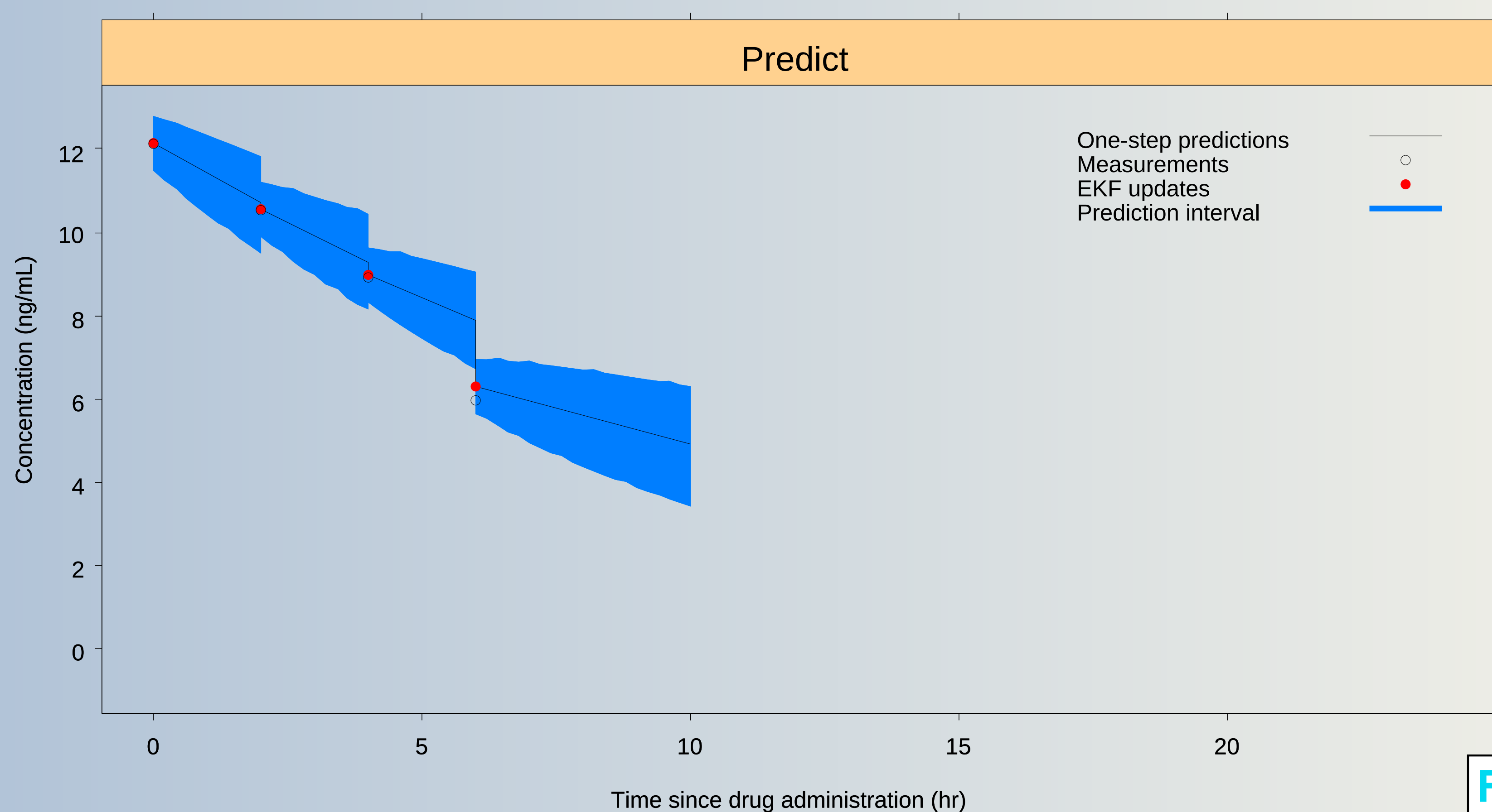

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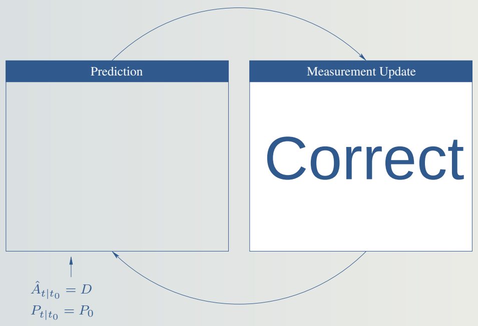

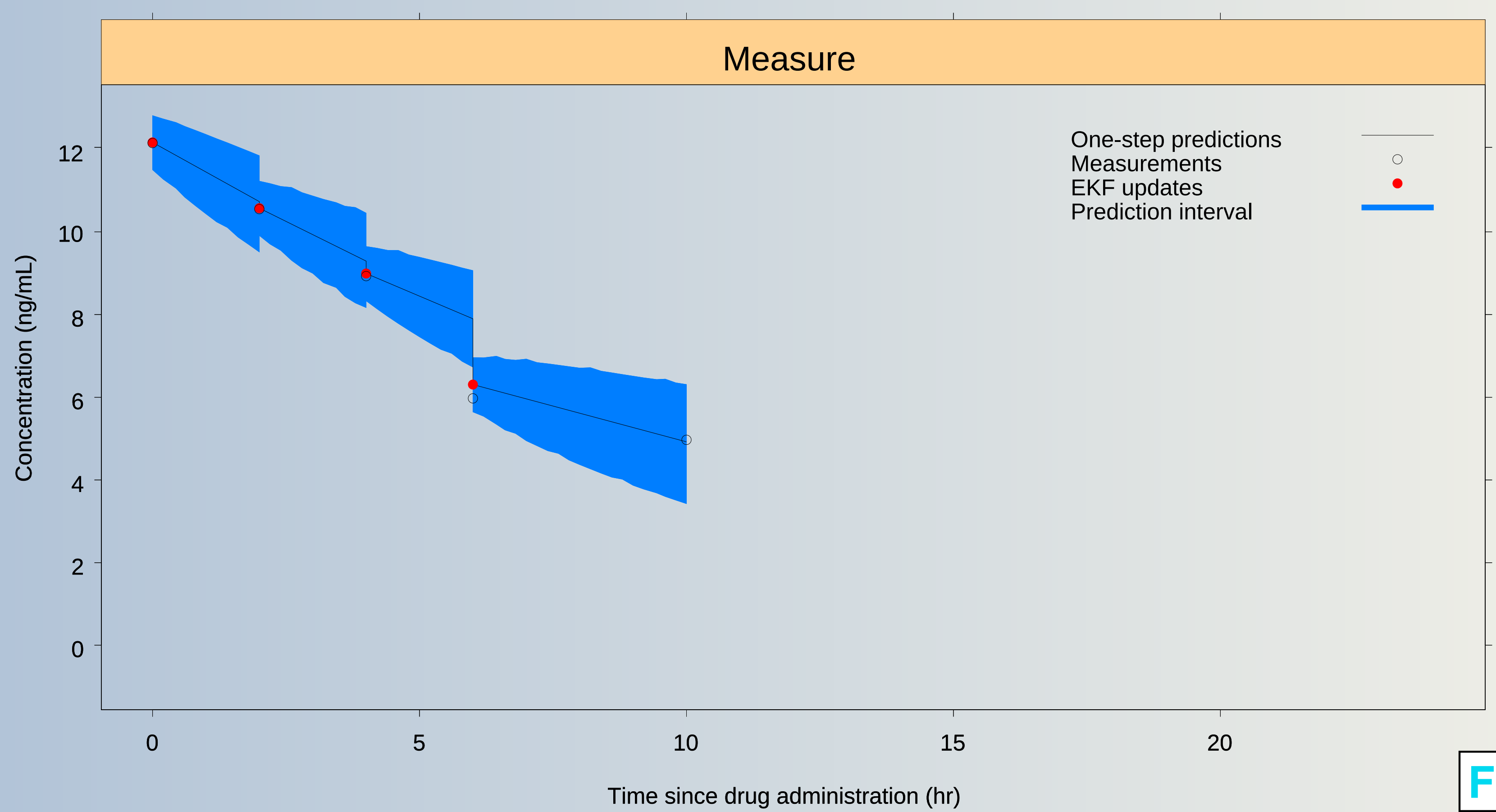

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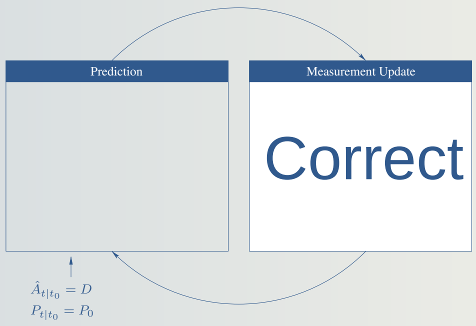

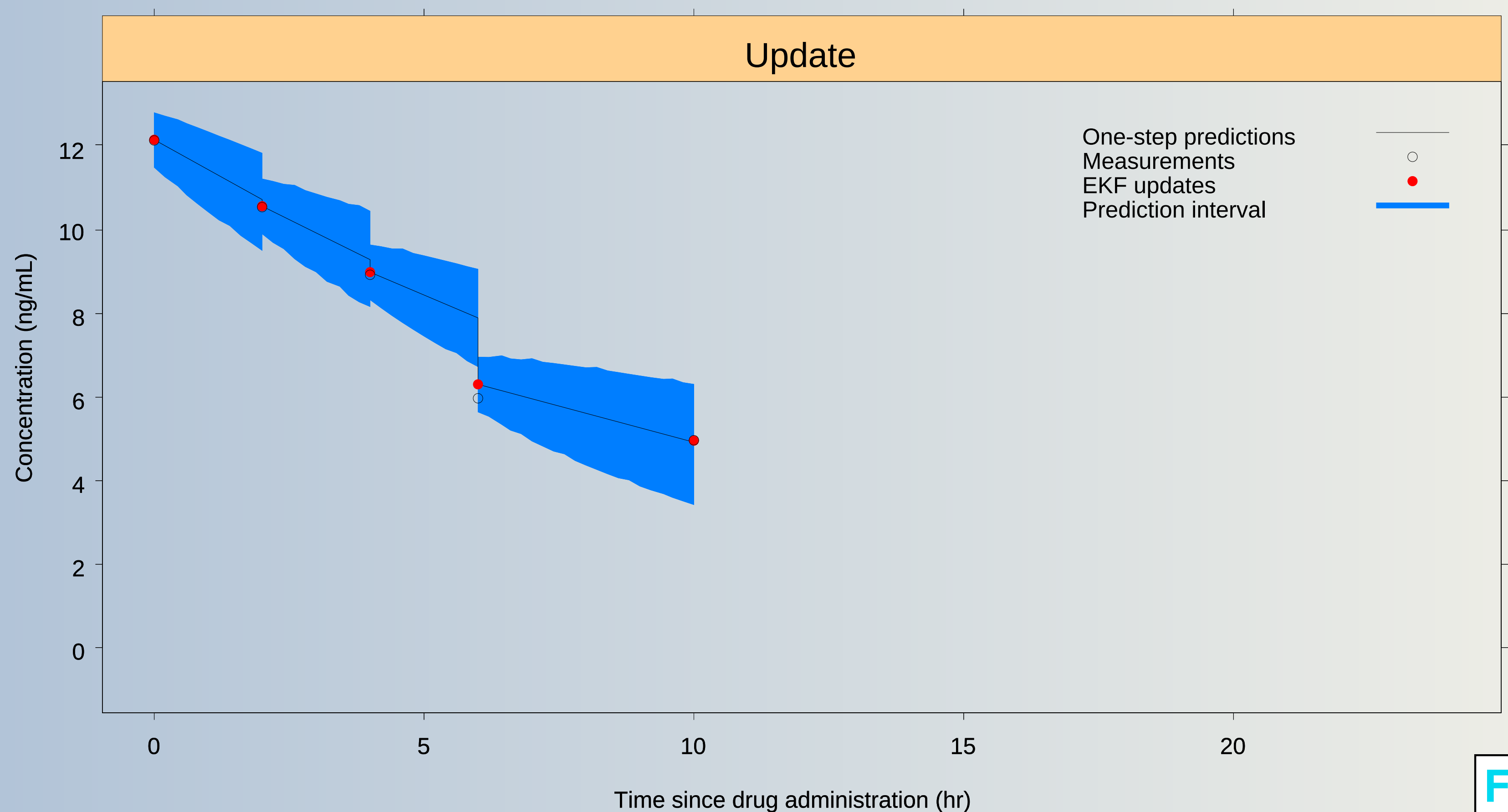

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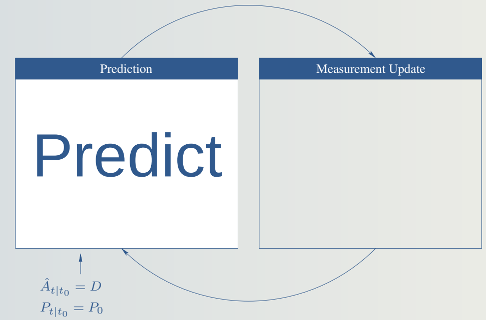

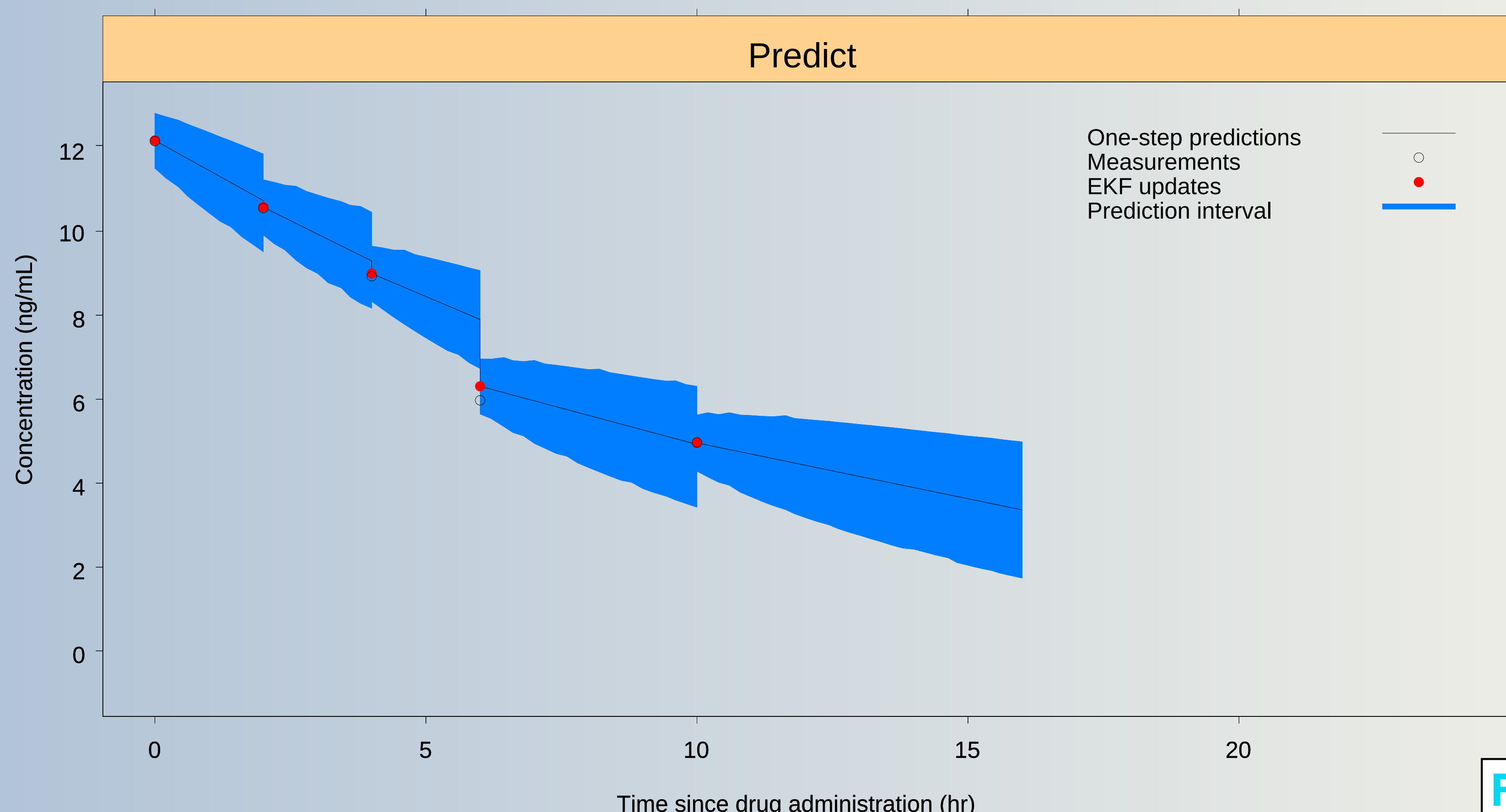

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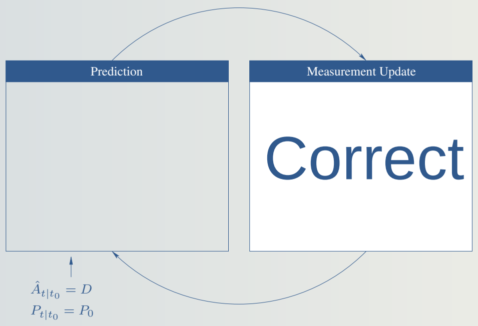

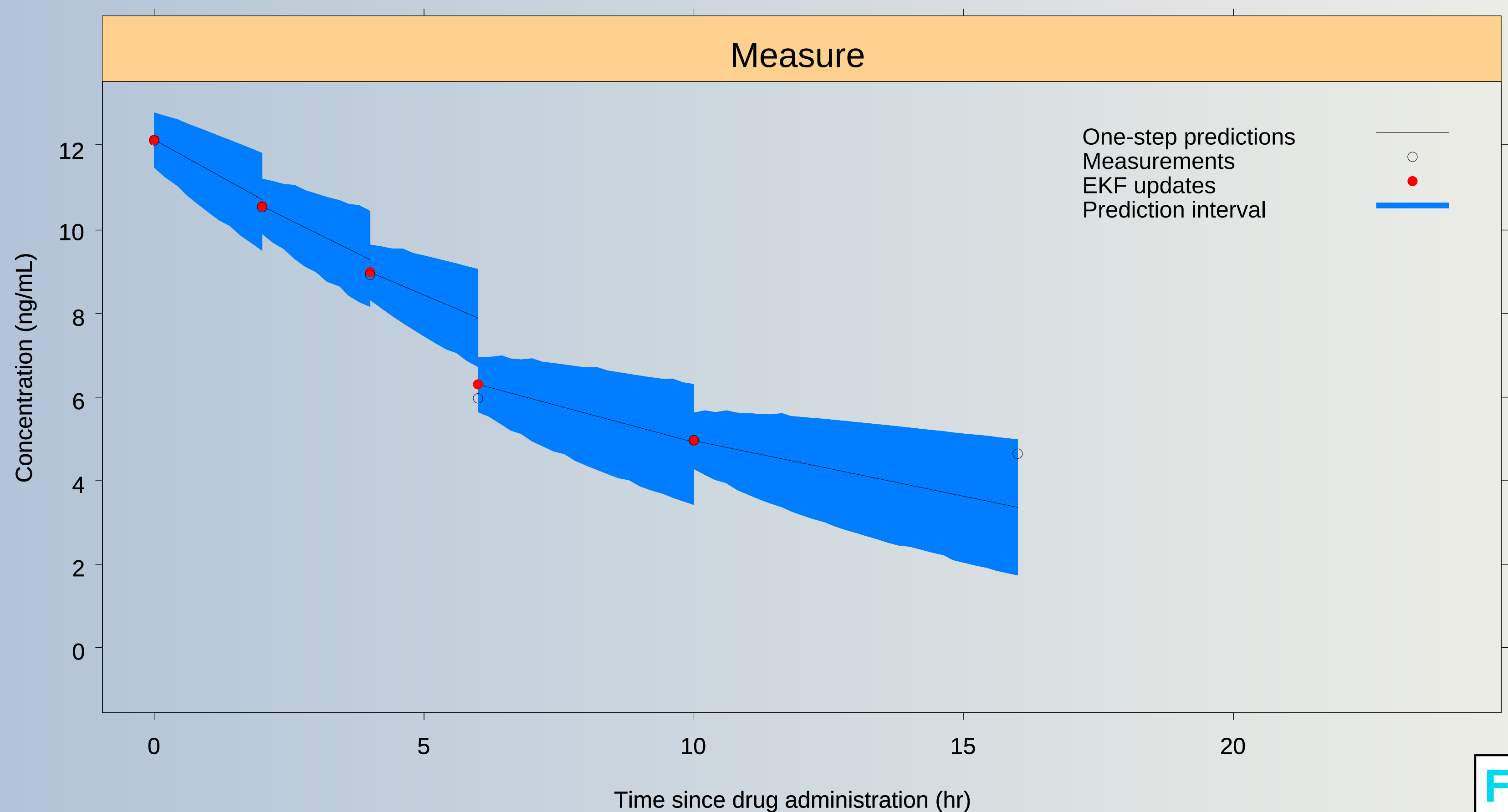

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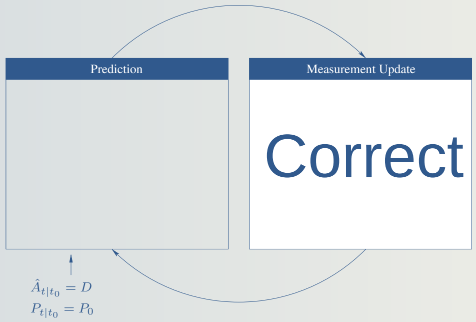

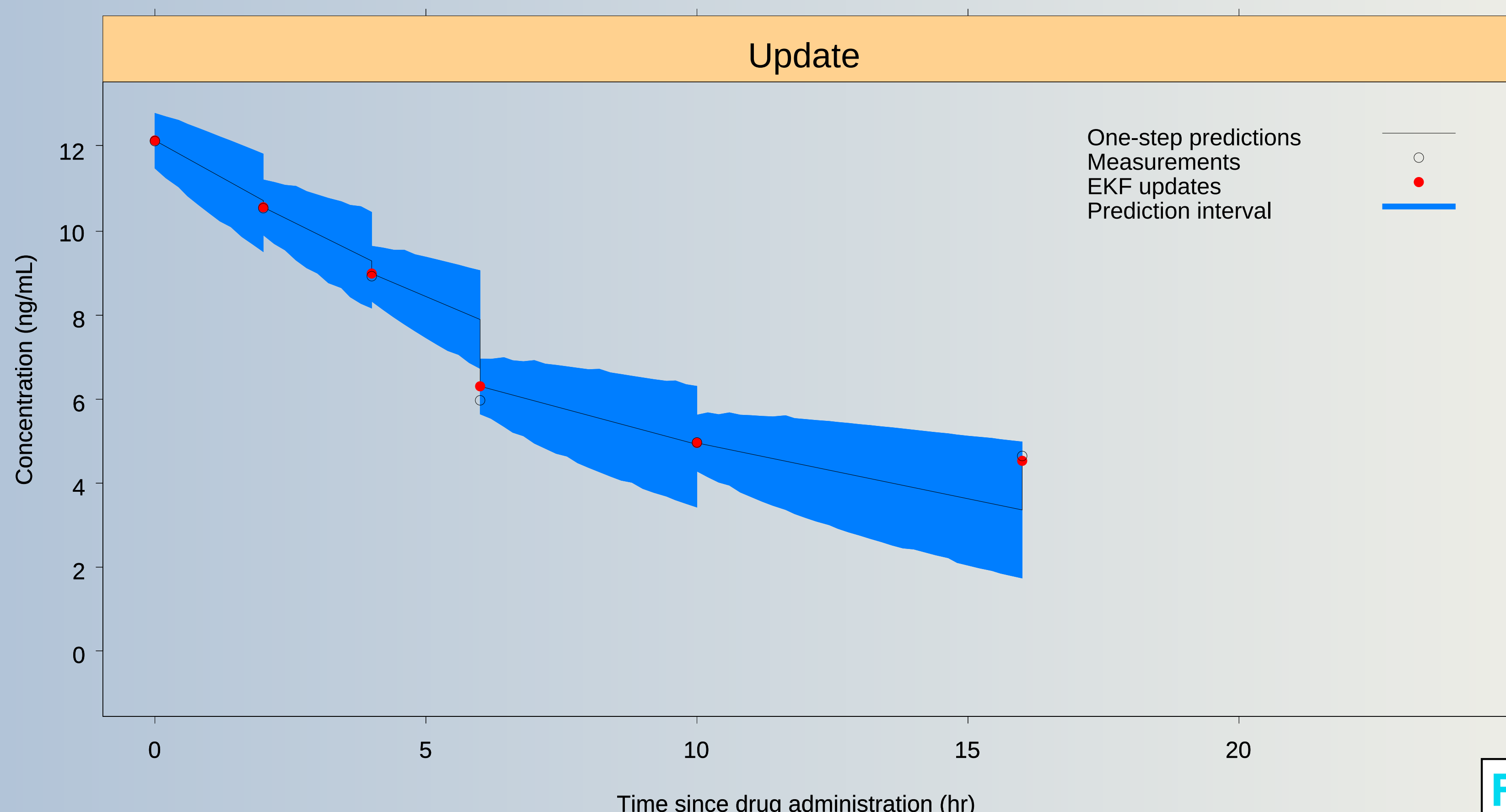

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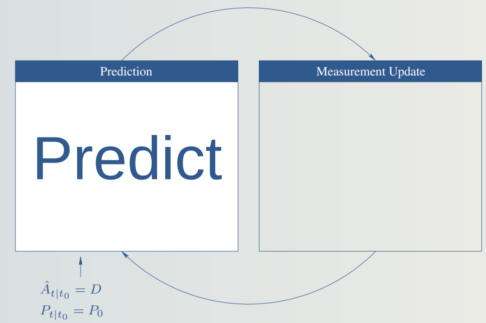

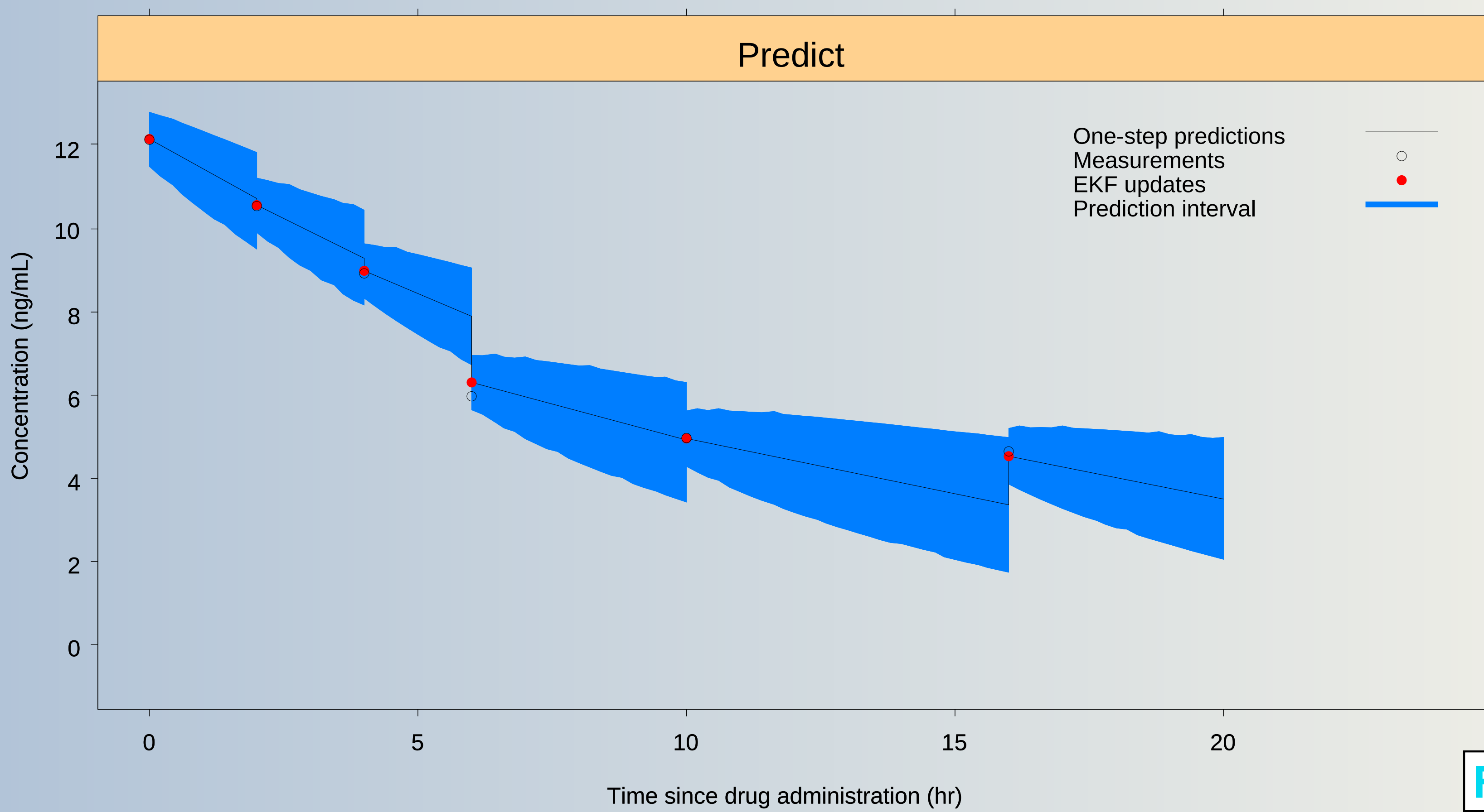

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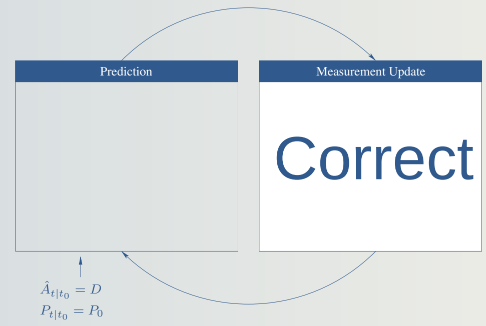

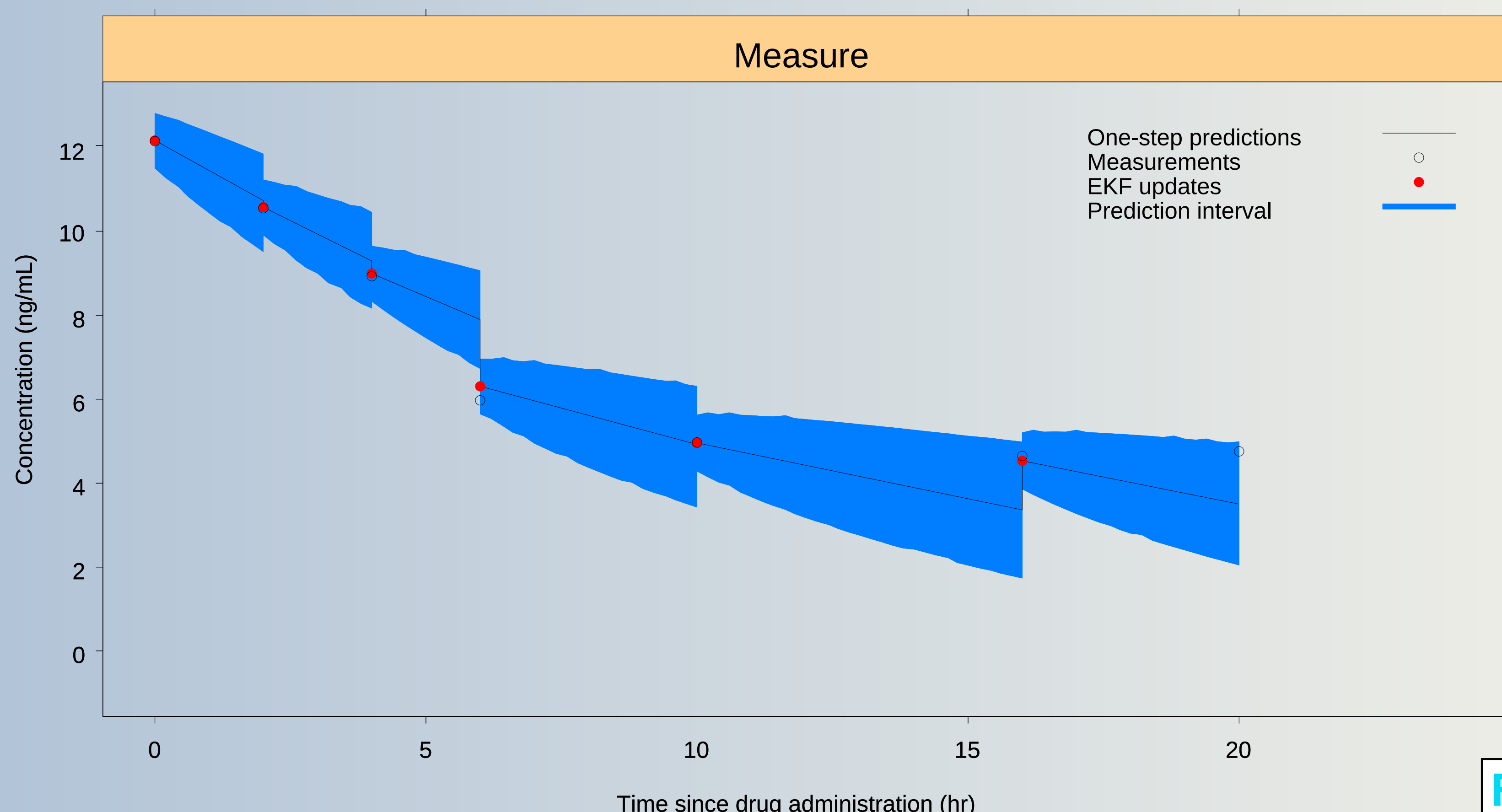

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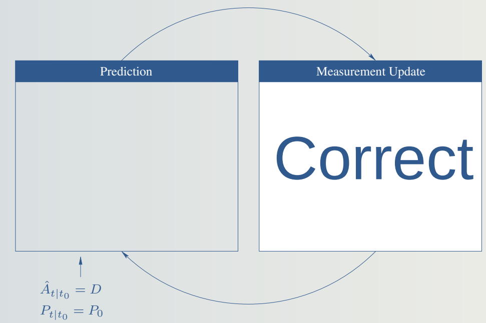

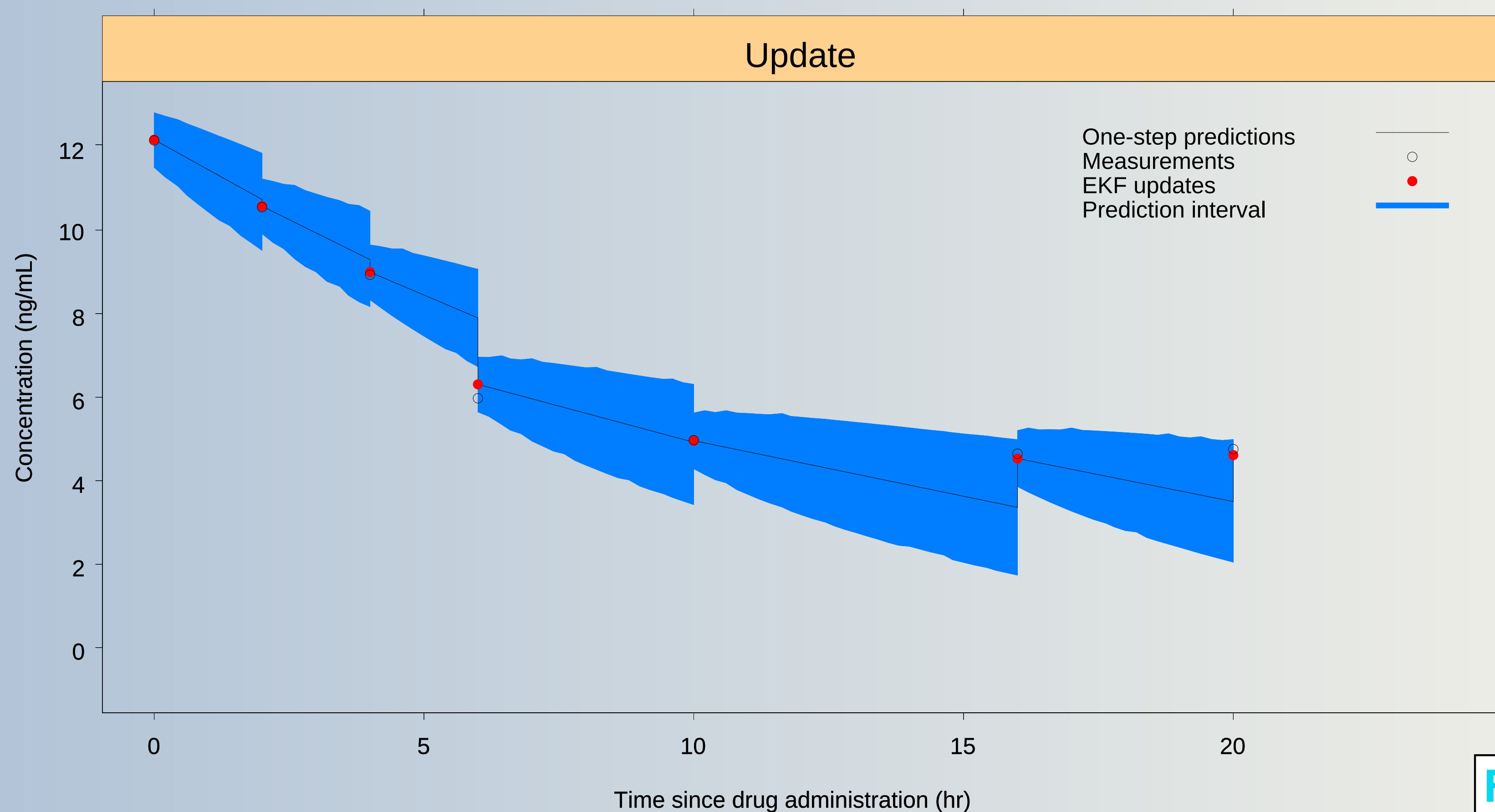

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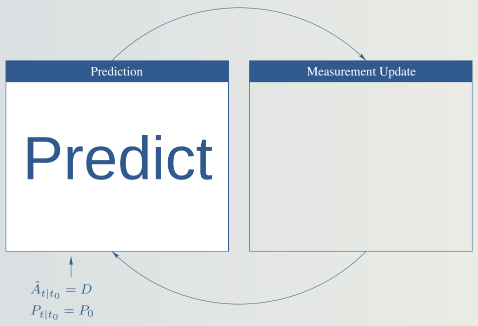

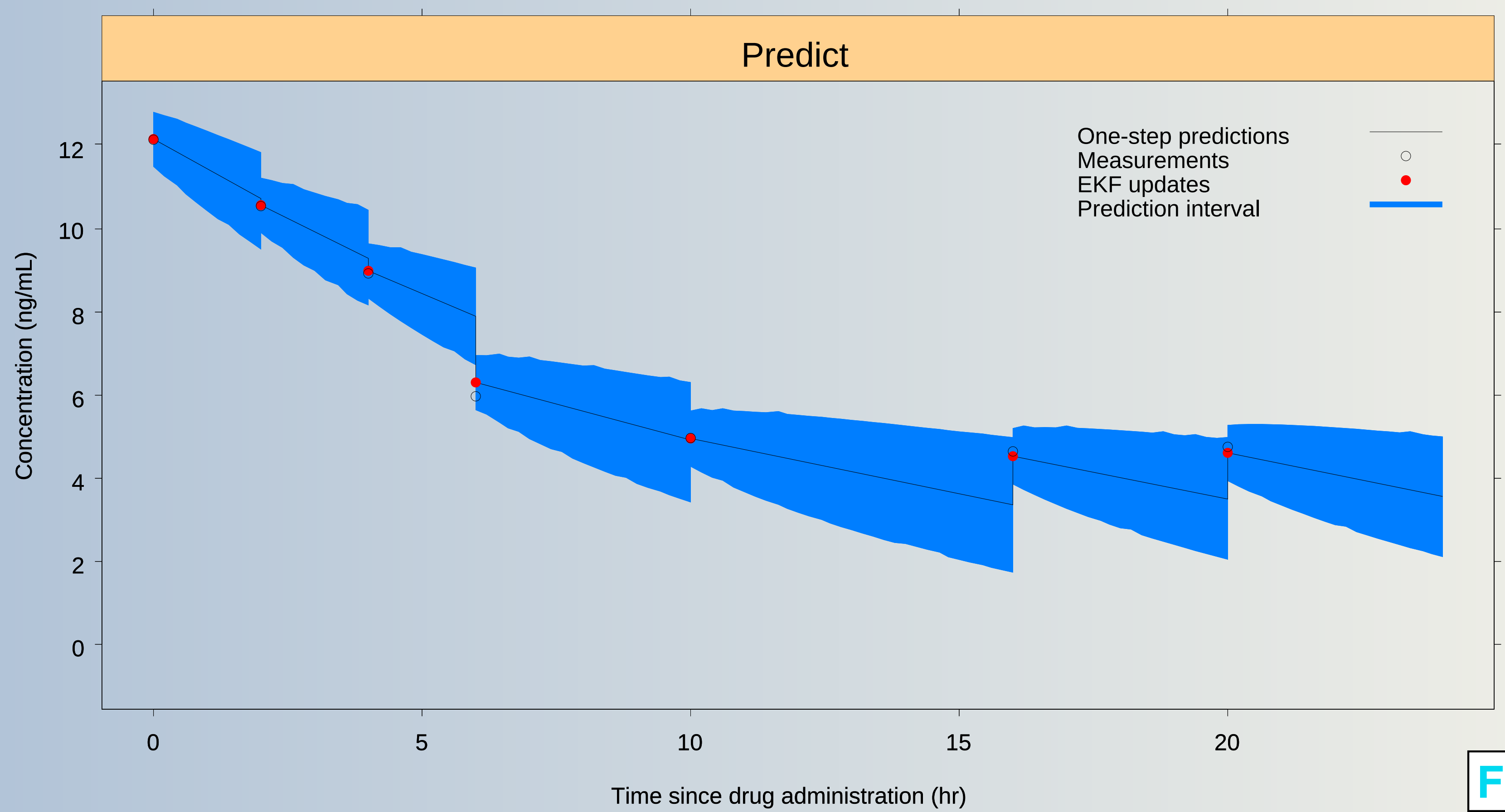

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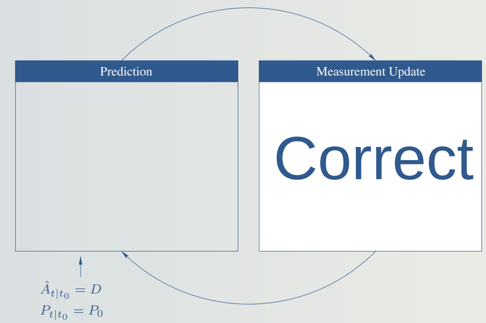

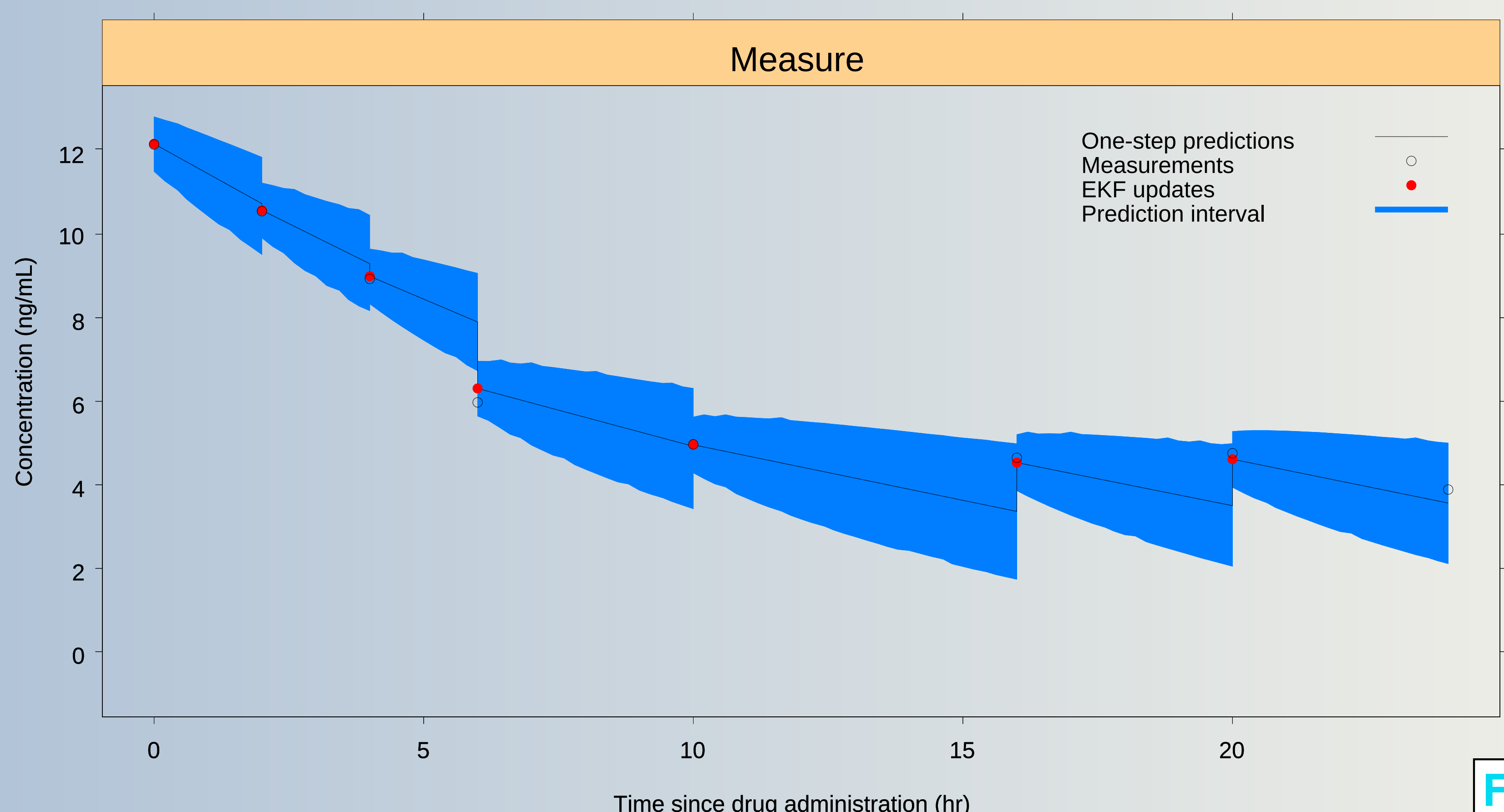

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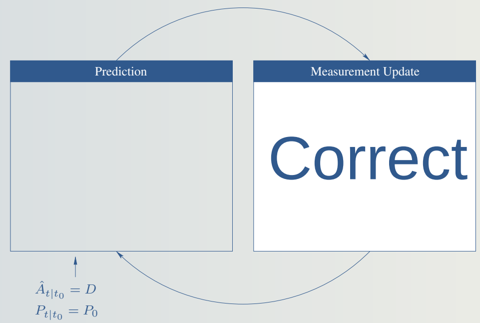

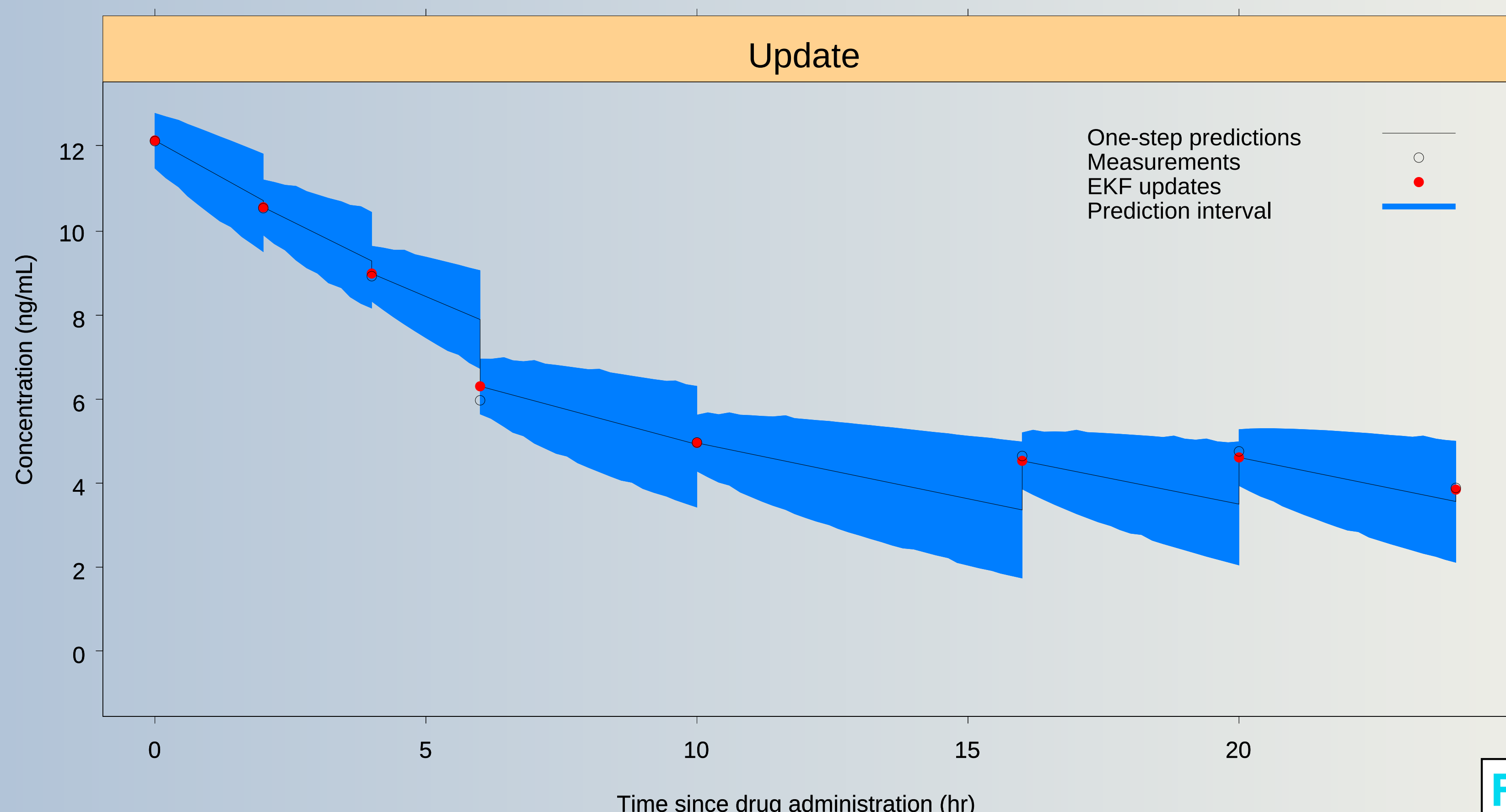

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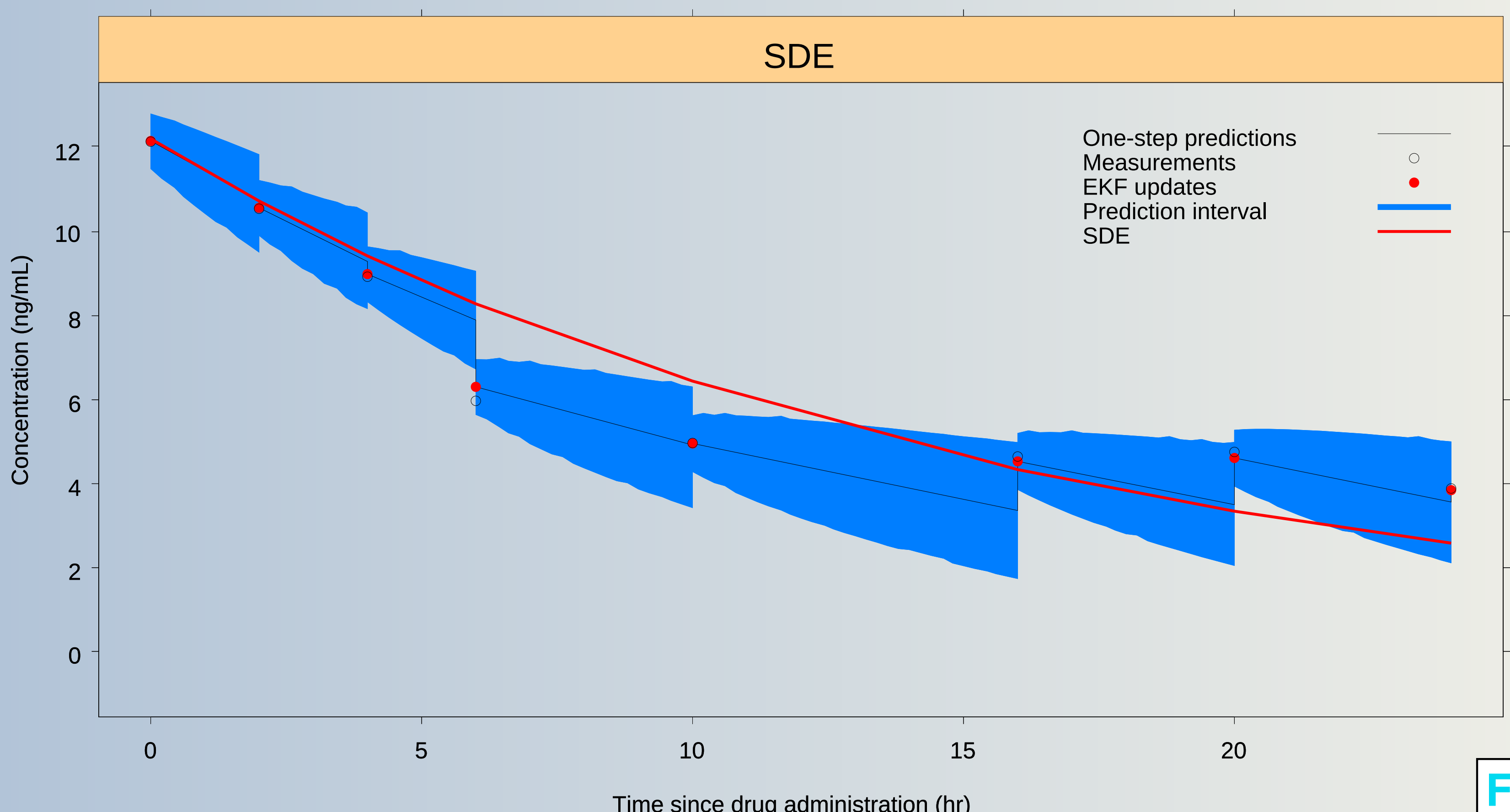

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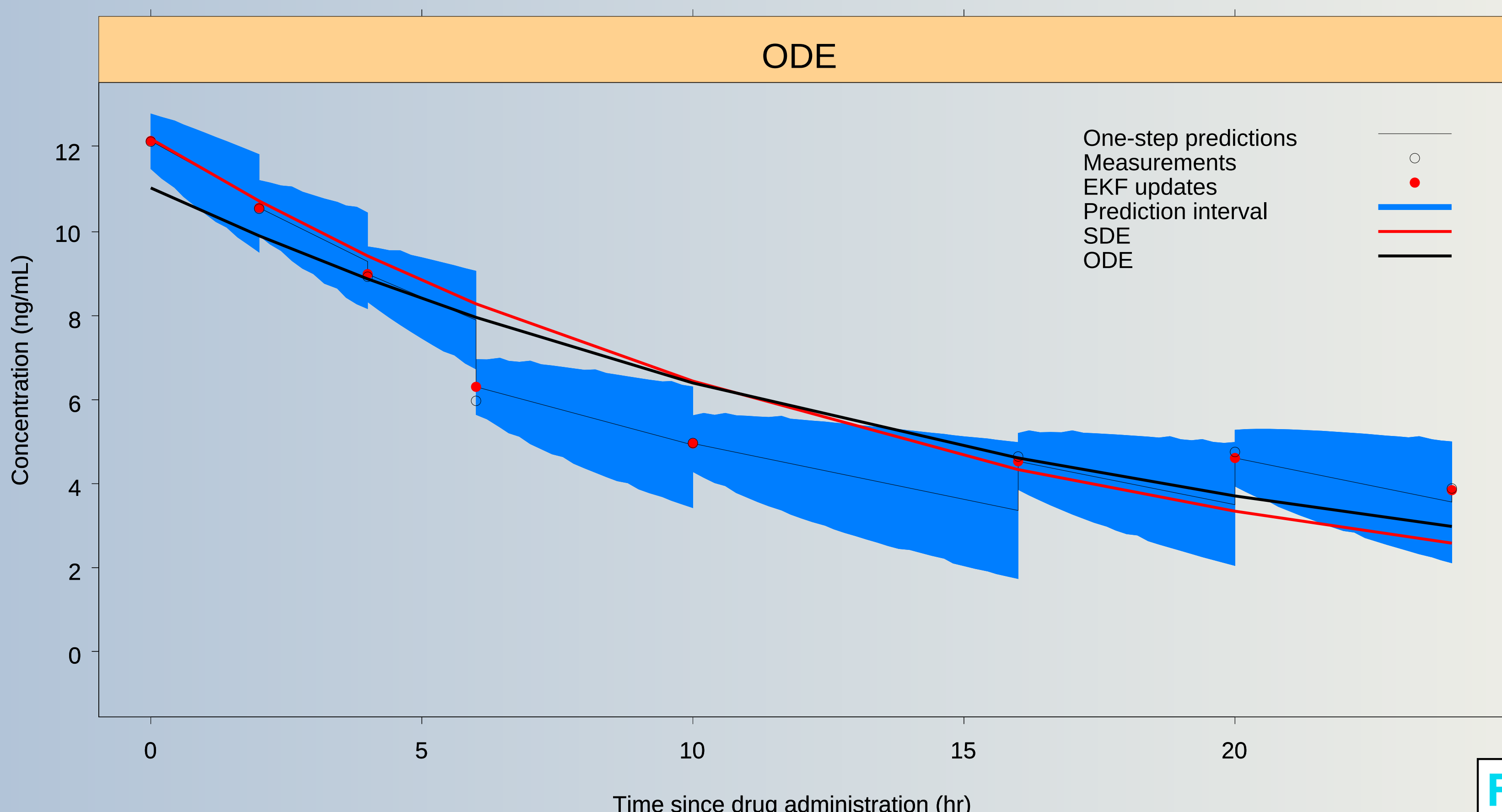

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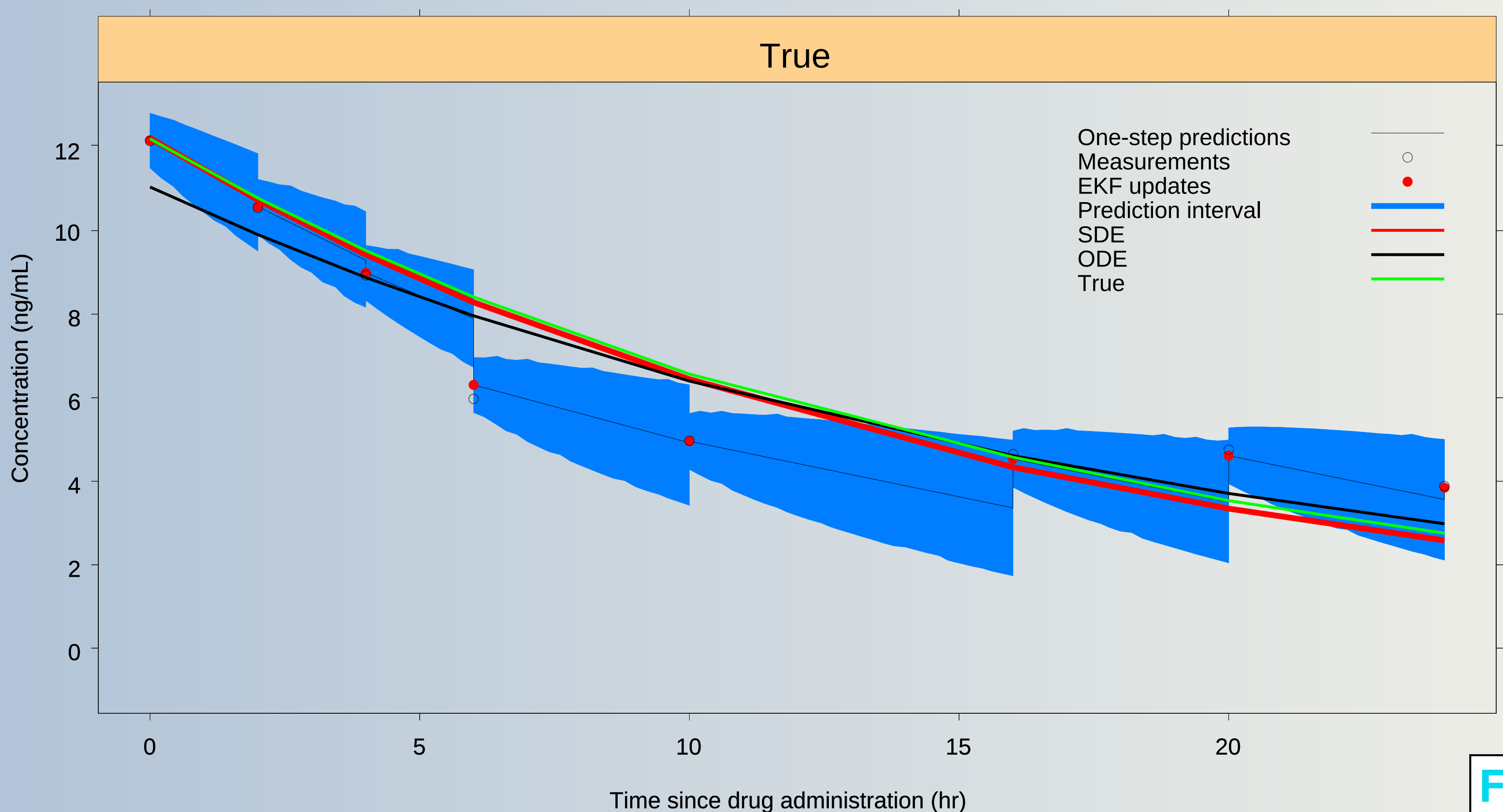

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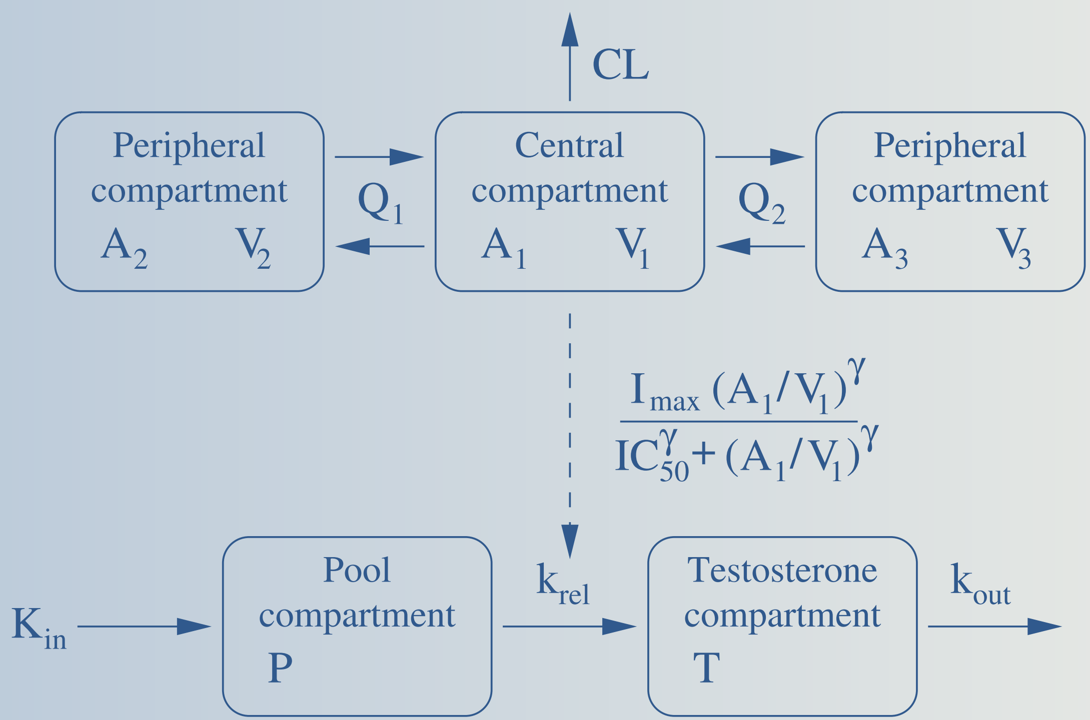
Results

- 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



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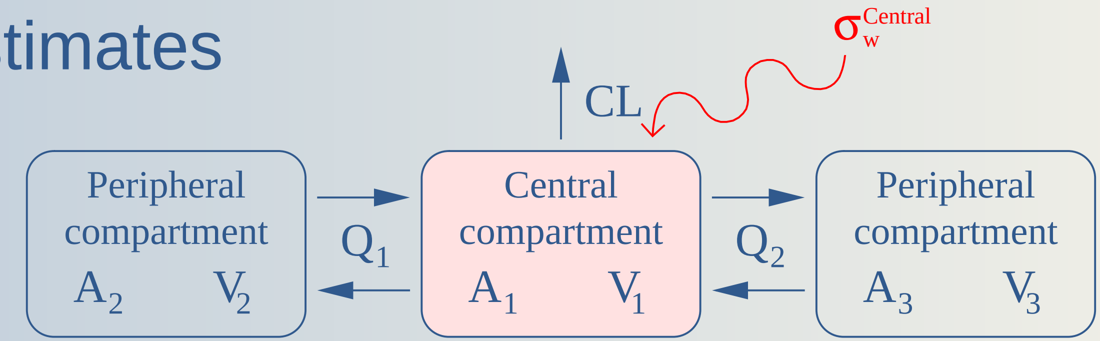
Results

- 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	19.8	18.8	5%
$\sigma_w^{Central}$		2.08	

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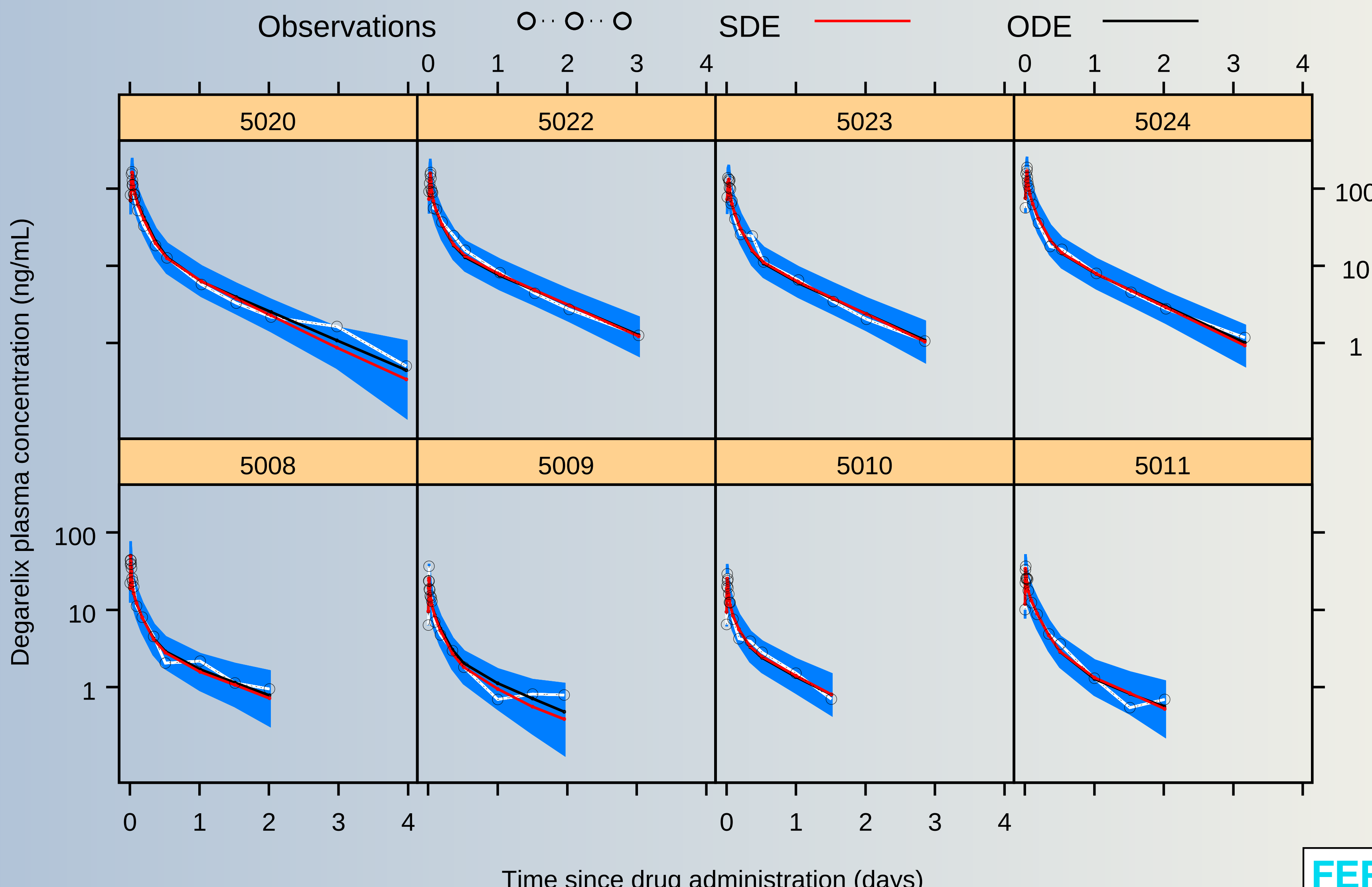
Results

- PK concentration-time profiles



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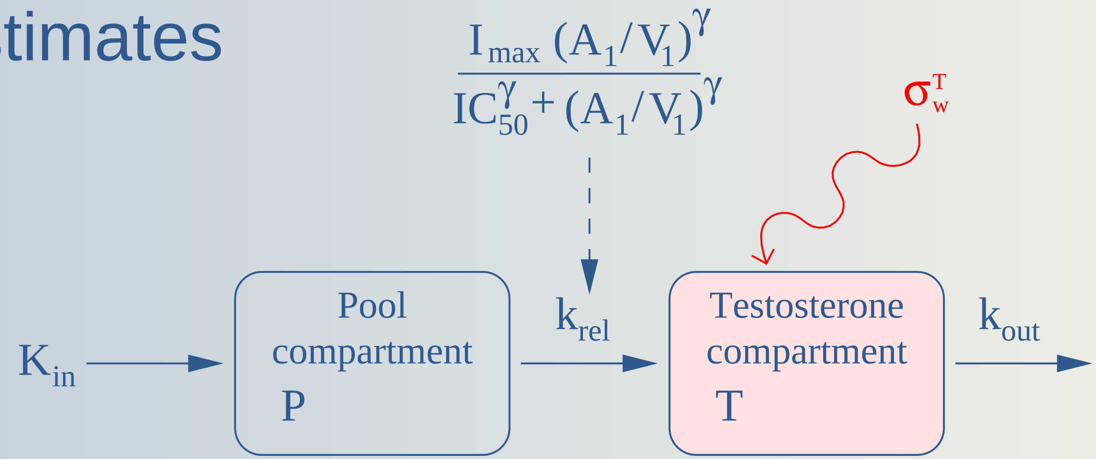
Results

- PD parameter estimates

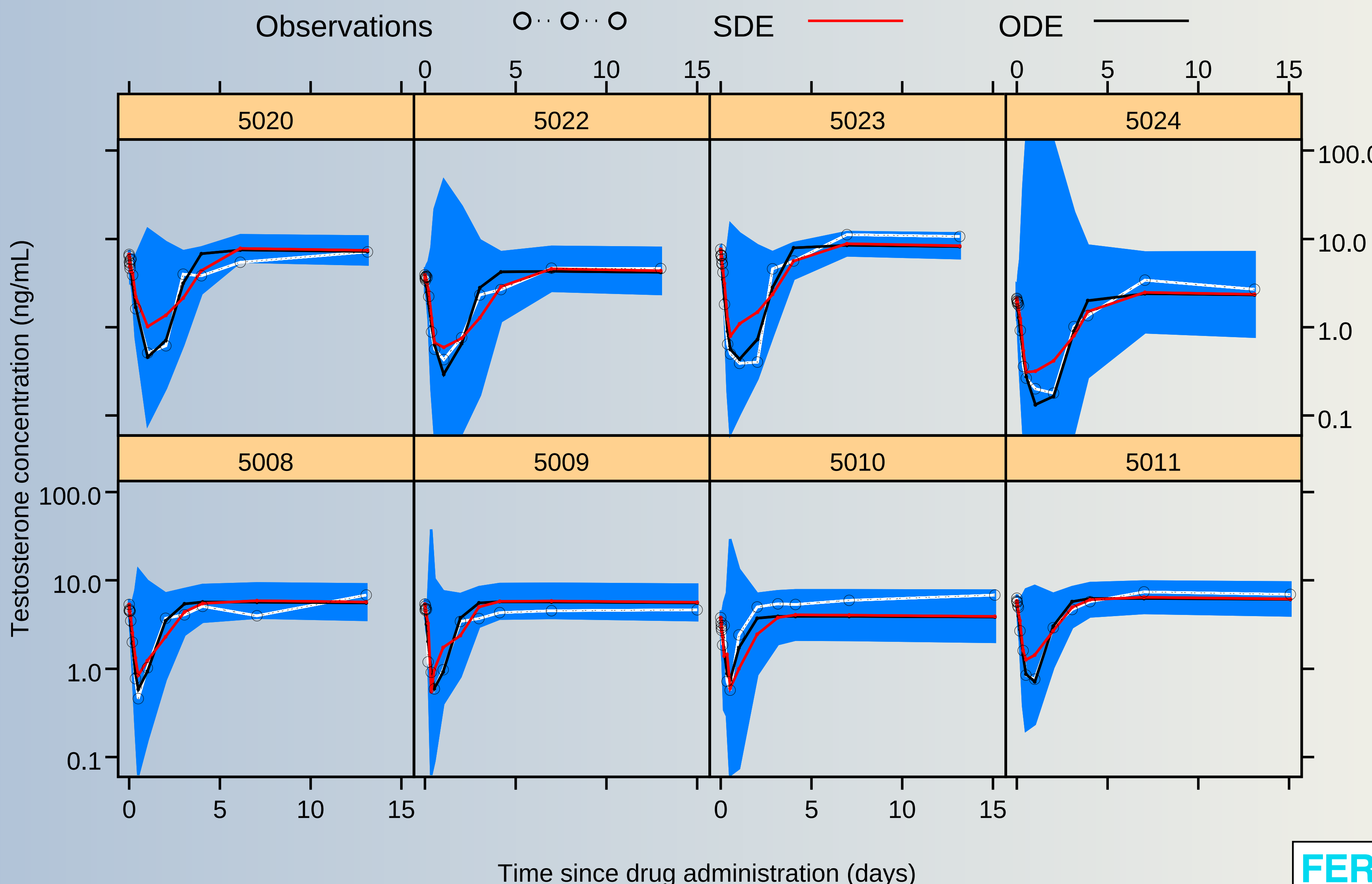


Parameter	ODE	SDE	Relative diff.
OFV	−565	−643	
k_{out}	0.22	0.21	3%
k_{rel}	0.0024	0.0035	46%
I_{max}	0.95	0.87	9%
IC_{50}	0.59	0.40	33%
γ	3.00	1.68	44%
IIV k_{out}	18.7	5.93	68%
IIV IC_{50}	54.6	32.6	40%
σ	23.9	3.69	85%
σ_w^T		0.726	

FERRING PHARMACEUTICALS

Results

- PD concentration-time profiles



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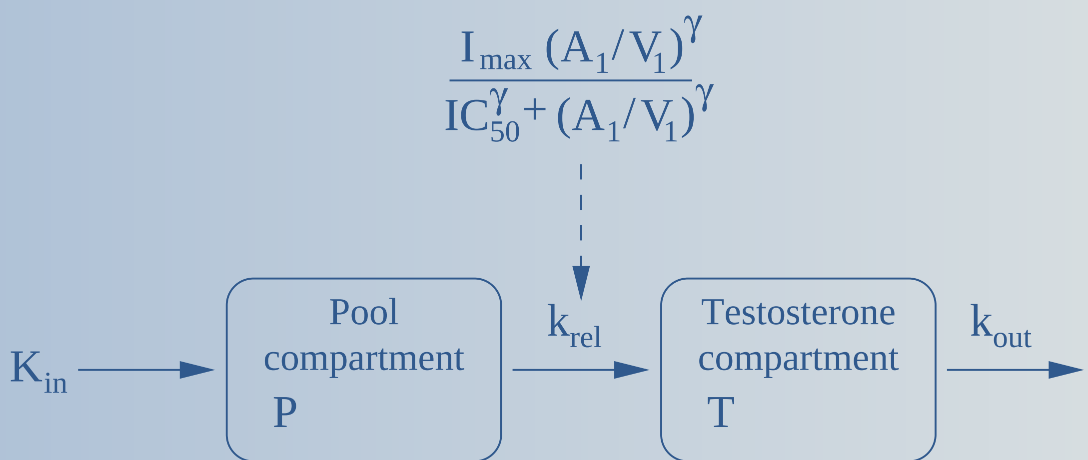
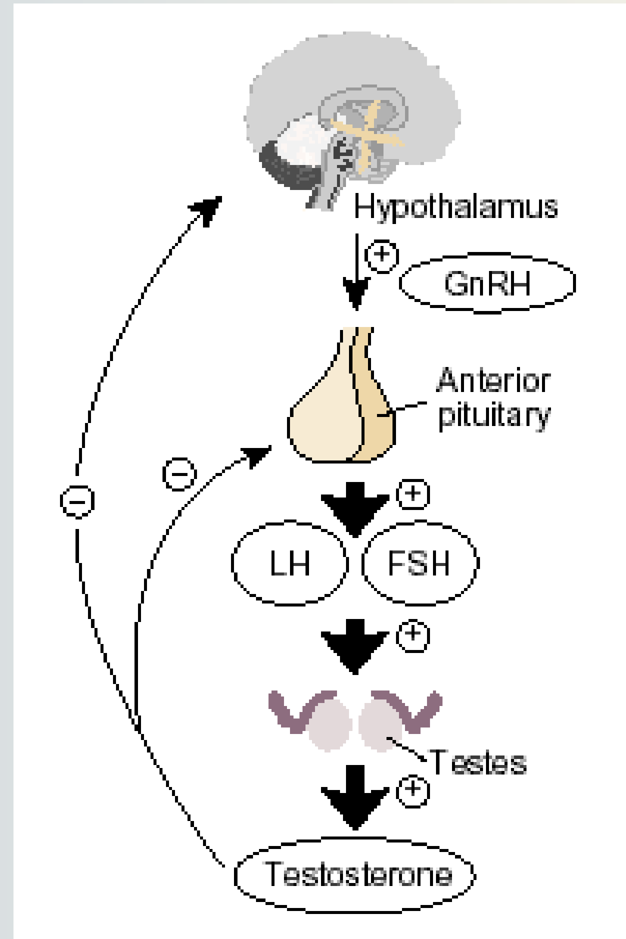
Results

- Pinpoint PD model deficiencies
  - Hypothalamic-Pituitary-Gonadal (HPG) axis

    - Variations in testosterone production

    - HPG mechanisms of action



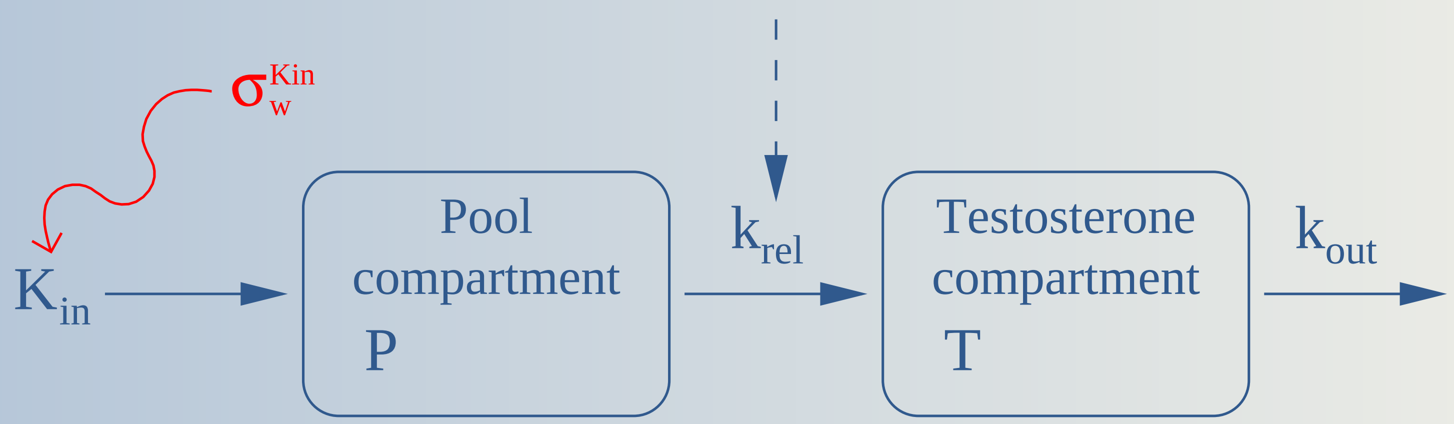


Results

- Pinpoint PD model deficiencies
  - Variations in testosterone production

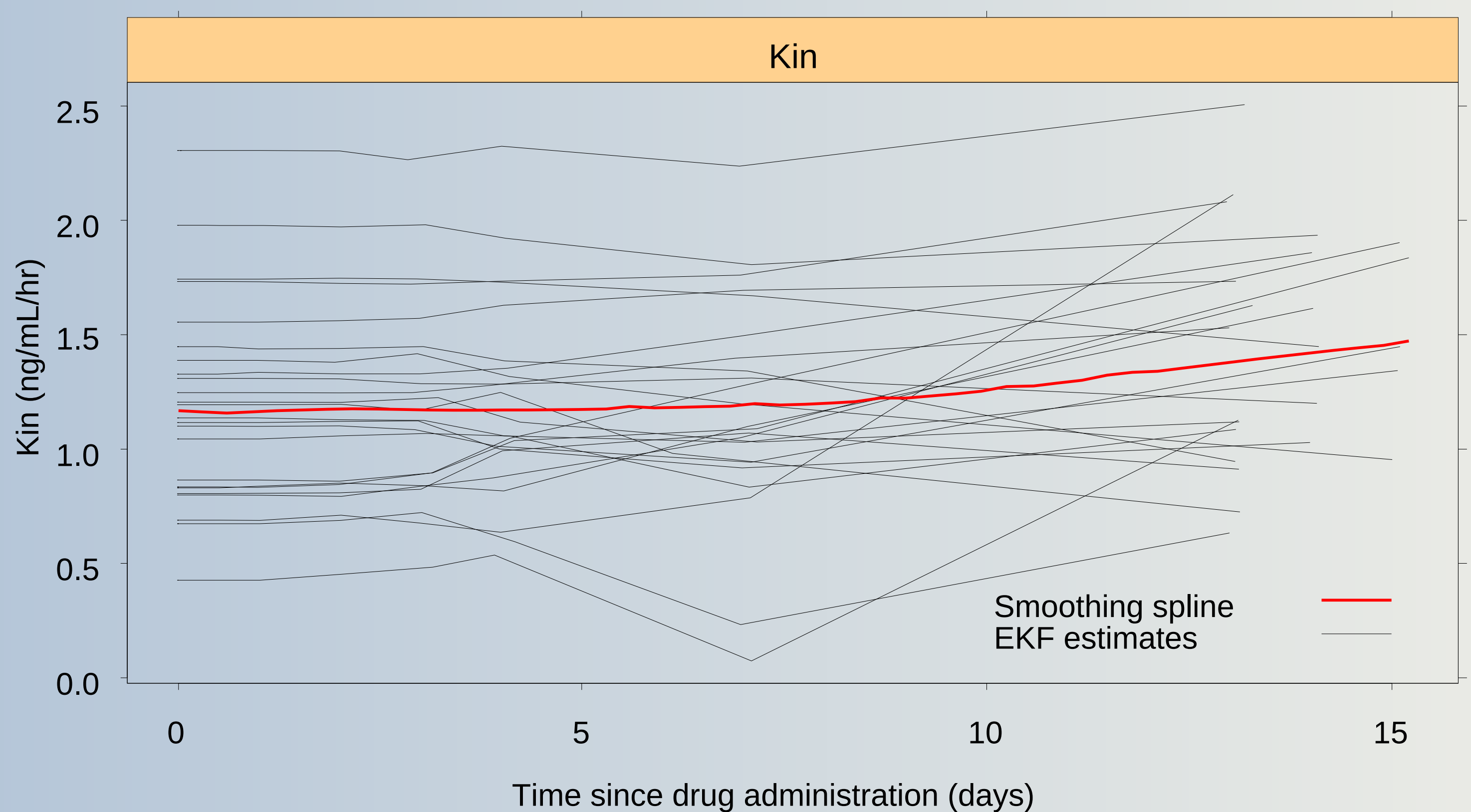
$$\begin{pmatrix} dP \\ dT \\ dK_{in} \end{pmatrix} = \begin{pmatrix} K_{in} - k_{rel}\left(1 - \frac{I_{max}\,C_p^{\gamma}}{IC_{50}^{\gamma} + C_p^{\gamma}}\right) P \\ k_{rel}\left(1 - \frac{I_{max}\,C_p^{\gamma}}{IC_{50}^{\gamma} + C_p^{\gamma}}\right) P - k_{out}\,T \\ 0 \end{pmatrix} dt + \begin{pmatrix}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

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



Results

- Pinpoint PD model deficiencies
  - Variations in testosterone production

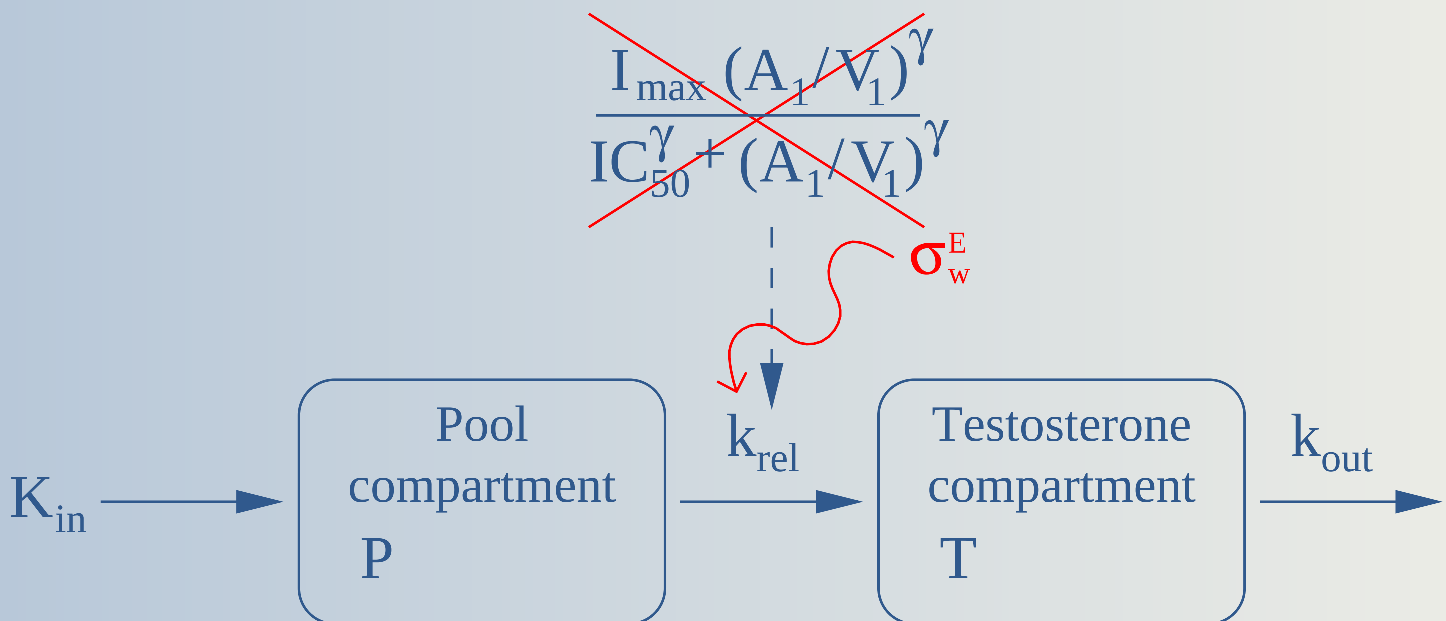


FERRING PHARMACEUTICALS

Results

- Pinpoint PD model deficiencies
  - HPG mechanisms of action

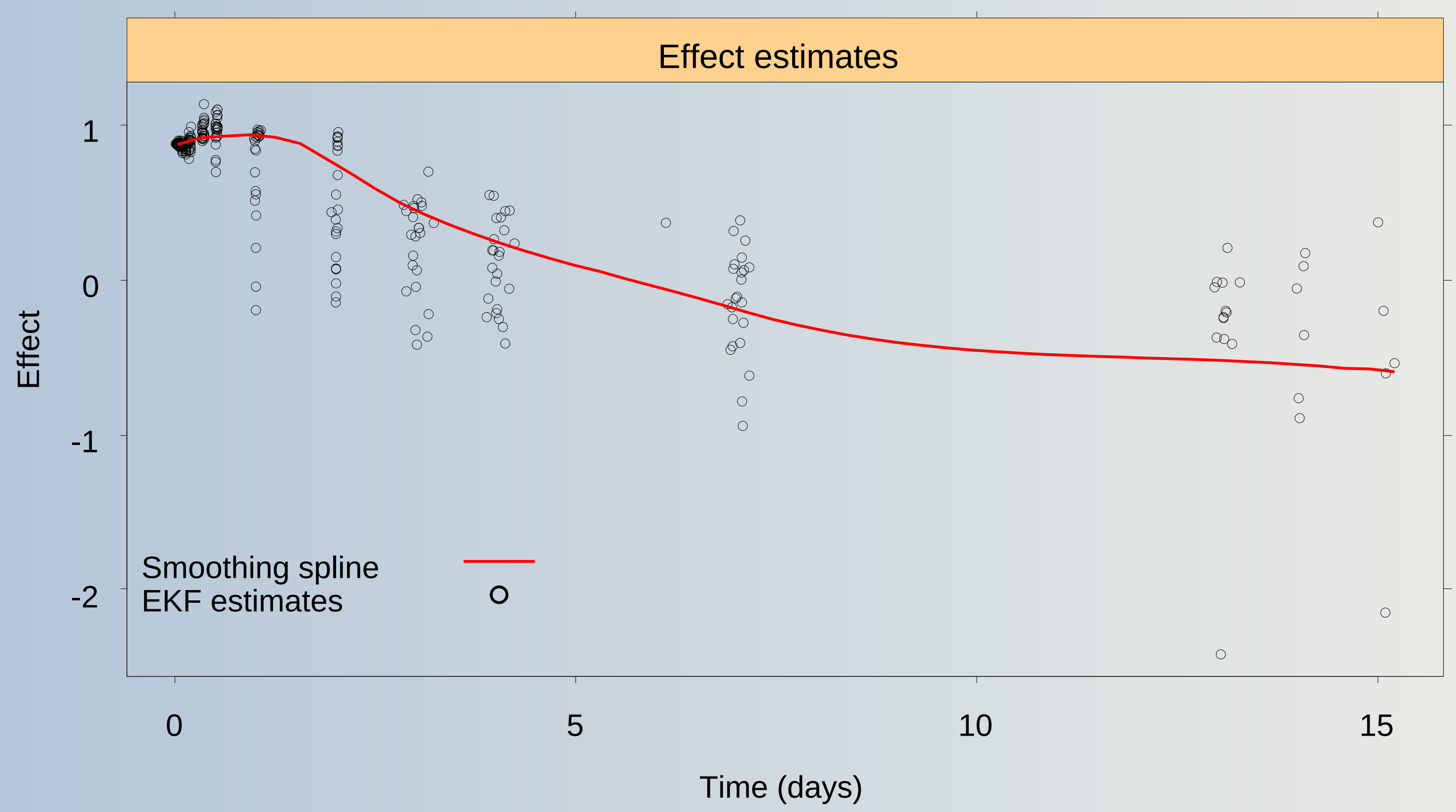
$$\begin{pmatrix} dP \\ dT \\ dE \end{pmatrix} = \begin{pmatrix} K_{in} - k_{rel}\,(1 - E)\,P \\ k_{rel}\,(1 - E)\,P - k_{out}\,T \\ 0 \end{pmatrix} dt + \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & \sigma_w^E \end{pmatrix} d\boldsymbol{w}_t$$



FERRING PHARMACEUTICALS

Results

- Pinpoint PD model deficiencies
  - HPG mechanisms of action



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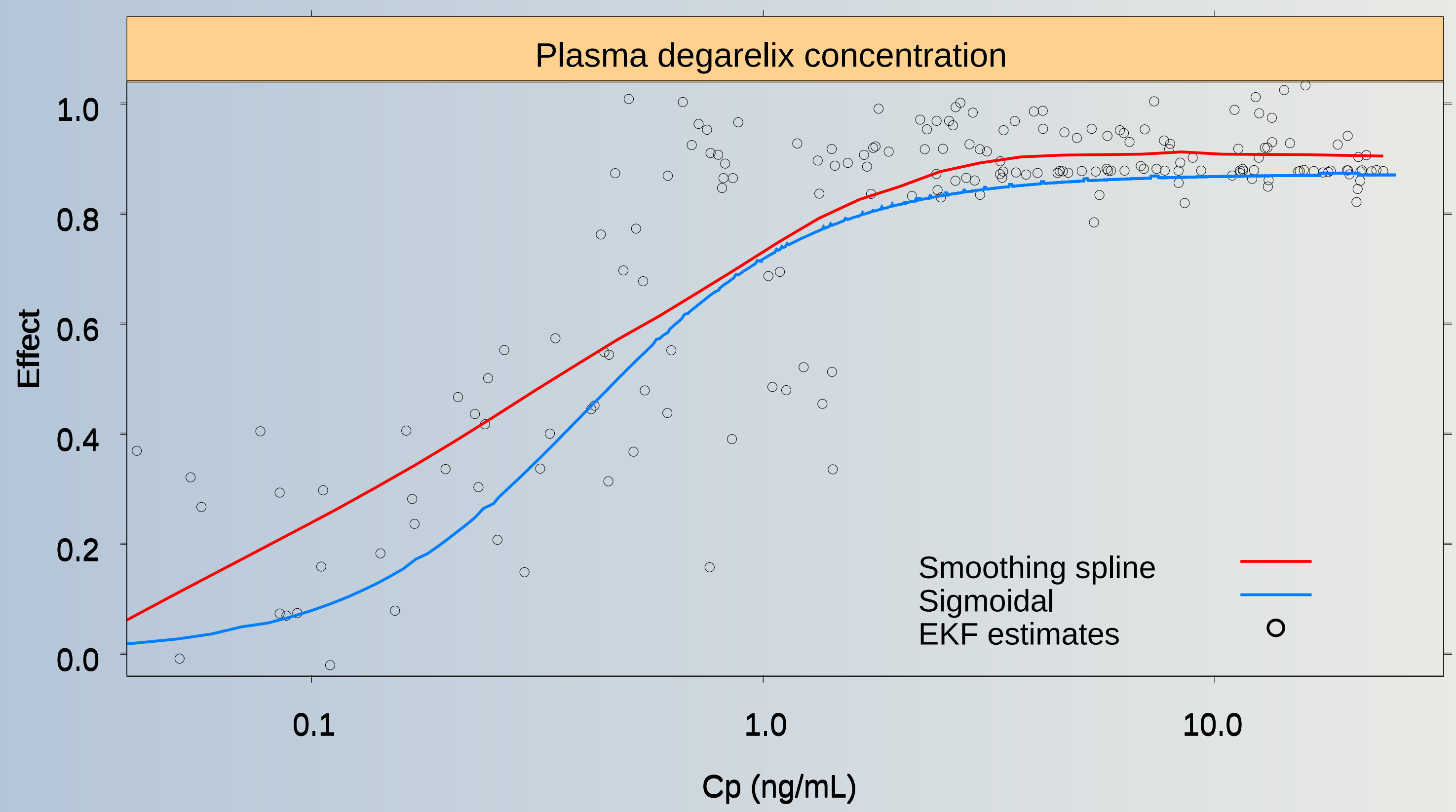
Results

- Pinpoint PD model deficiencies
  - HPG mechanisms of action



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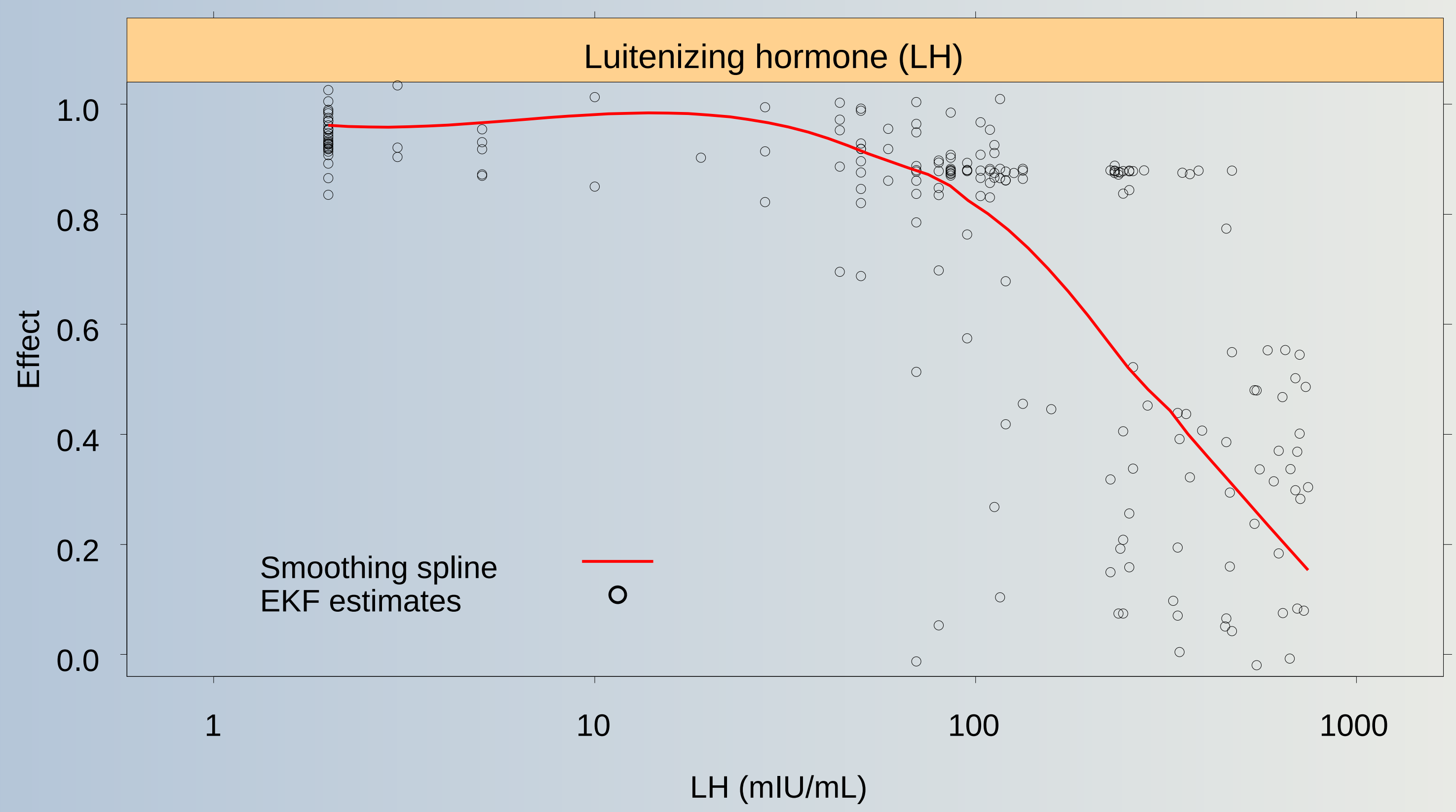
Results

- Pinpoint PD model deficiencies
  - HPG mechanisms of action



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Conclusion

- 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.

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Conclusion

- 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

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Questions ?