Computing Optimal Drug Dosing with Constraints on Model States in NONMEM

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What?

Setting **PMX model + dosing schedule**

Goal **compute** **optimal drug doses**

doses necessary to achieve a certain desired response

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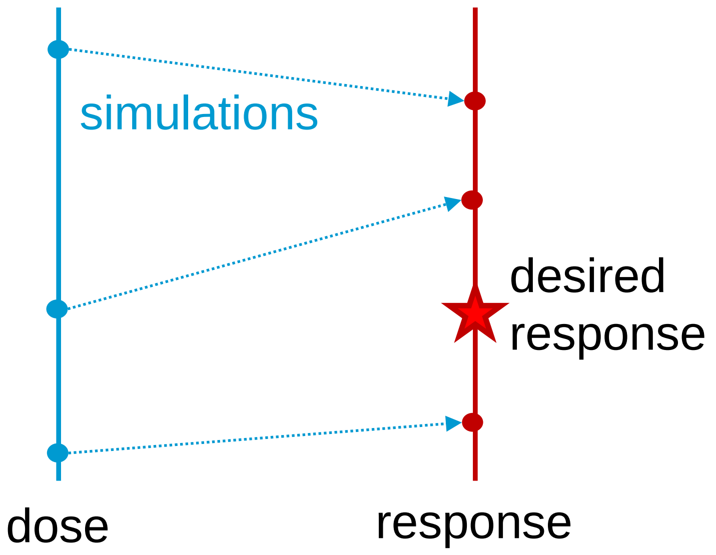

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"modeling and optimization"

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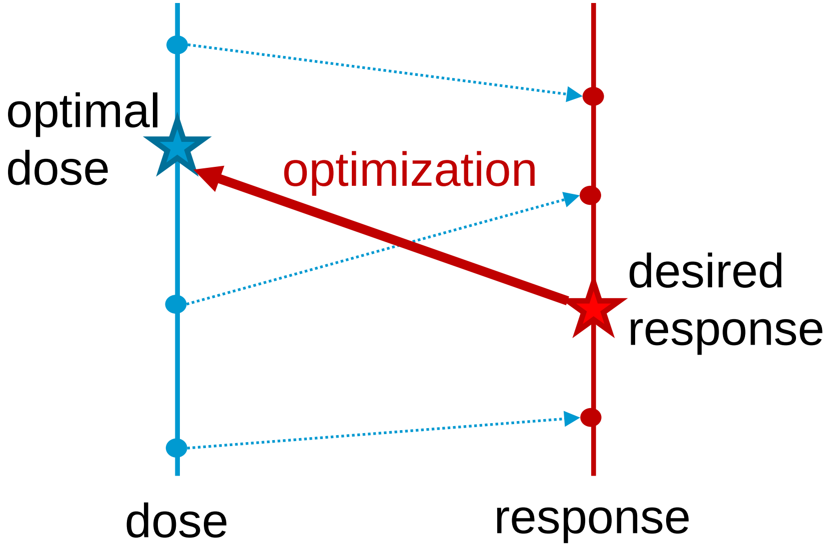

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Example **tumor weight reduction** **myelosuppression**

Why?

Goal **compute** **optimal drug doses** **with** **state constraints**

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Example tumor weight reduction myelosuppression

→ **compute optimal drug doses regarding** efficacy + safety **targets**

Examples

efficacy + safety

Compute optimal drug doses which:

Efficacy		Safety
• minimize tumor weight	while	avoiding myelosuppression $neutrophils \geq 1\ [10^9]$
• eradicate bacteria $bacterial\ count \leq 100$	with	minimal AUC of the drug
• maximize AUC of the drug	with	safe trough concentration $C_{min} \leq 5$
• reach peak concentration $C_{max} \geq 25$	with	minimal AUC of the drug

Transform into easier problem

Original problem:

- compute optimal drug doses which **minimize objective function subject to state constraint**, e.g.,

  minimize tumor weight W subject to safe neutrophil count N

$$\int_{t_0}^{t_f} W(t)dt$$

$$1 - N(t) \leq 0, \qquad t \in [t_0, t_f]$$

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Classical optimization problem:

- compute optimal drug doses which **minimize (objective function + penalty function)**

  $$\int_{t_0}^{t_f} W(t)dt + \frac{1}{2\gamma}\int_{t_0}^{t_f} (\max(0, \mu + \gamma(1 - N(t))))^2 - \mu^2 \, dt$$

How to implement in NONMEM

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objective function value (OFV)

penalty function value (PFV)

$\mu = 1$
shift function

e.g., $\gamma = 10^4$
penalty parameter

How to implement in NONMEM

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objective function value (OFV) — **penalty function value (PFV)**

$\mu = 1$
shift function

e.g., $\gamma = 10^4$
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- compute OFV and PFV utilizing additional differential equations, e.g.:
  $\frac{d}{dt} obj = W, \;\; obj(t_0) = 0$, then $OFV = obj(t_f)$, PFV analogously

Solving an optimal dosing task in NONMEM

- utilizing standard commands, cf. Bachmann et al. [1]

DATA FILE

- **indicate dosing time points with AMT = 1**
- **indicate final time with “dummy” observation DV = 0**

Solving an optimal dosing task in NONMEM

CONTROL FILE

- fix model parameters in $PK
- associate doses with estimation parameters THETA
- assign scale factor F = THETA, because F*AMT = F serves as dose in NONMEM
- code PMX model and additional equations to compute OFV and PFV in $DES
- assign output Y = OFV + PFV in $ERROR
- minimize via $EST -2LL

Example 1

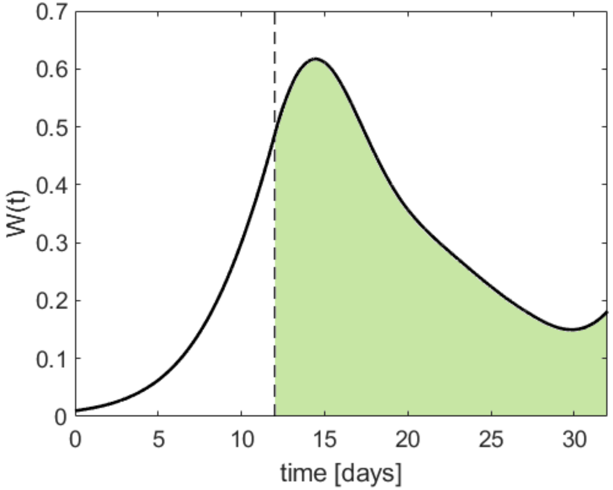
minimize tumor weight with safe neutrophil count $\gamma = 10^4, \mu = 1$

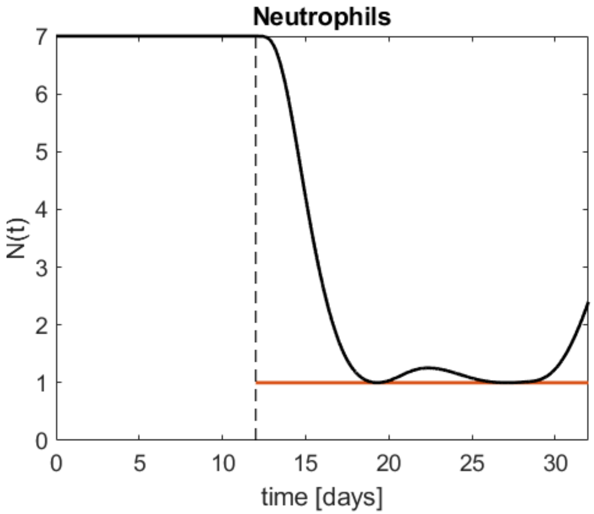
$$OFV = \int_{12}^{32} W(t)dt = 6.8$$

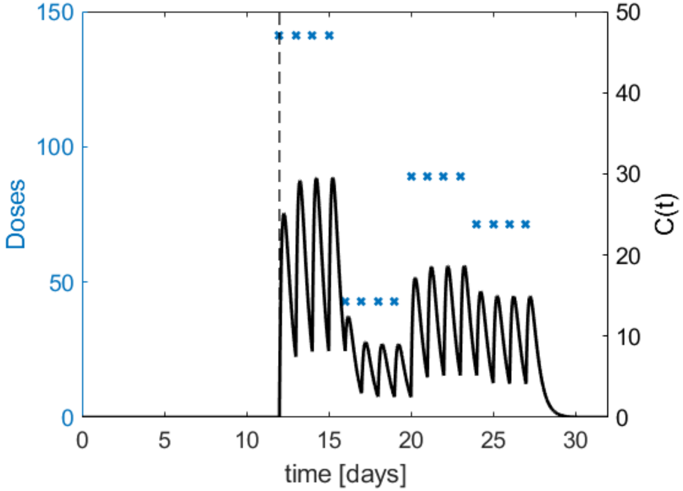
$$N(t) \geq 1, \qquad 12 \leq t \leq 32$$

$$PFV = -9.7 \cdot 10^{-4}$$

optimal doses:
$(141, 43, 89, 71)$







Example 2

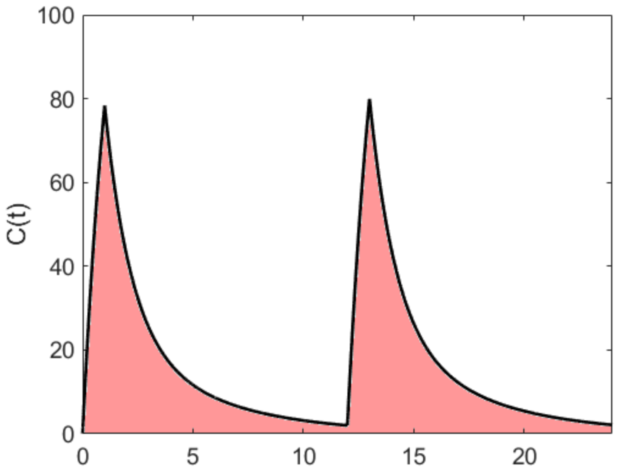
minimize AUC of antibiotic drug with efficacious bacterial eradication $\gamma = 10^4, \mu = 1$

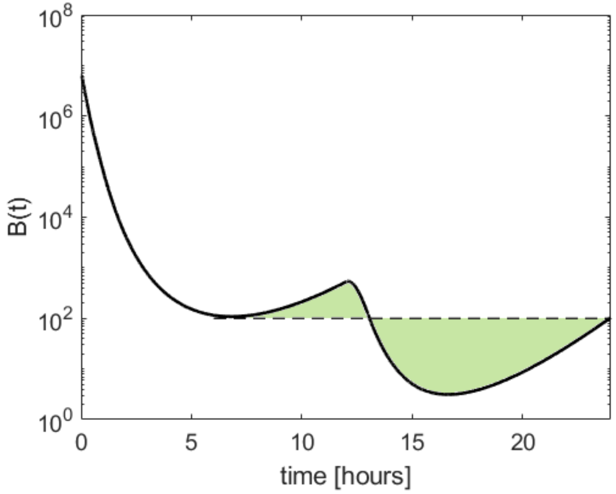
$$OFV = AUC = \int_0^{24} C(t)dt = 419$$

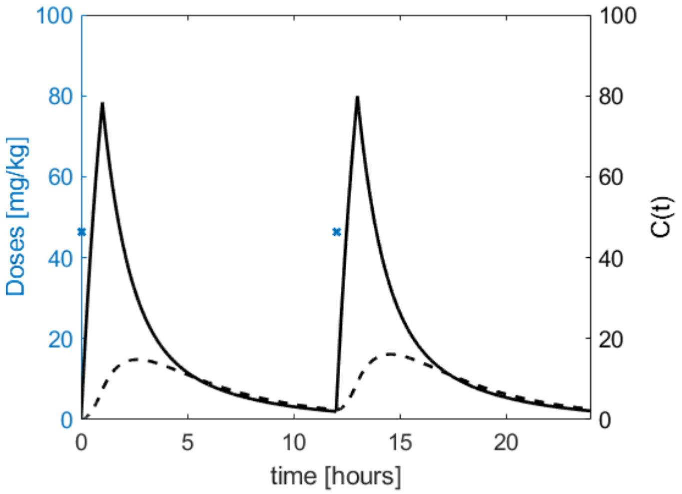
$$\frac{1}{18}\int_6^{24} B(t)dt \leq 100$$

$$PFV = -2.9 \cdot 10^{-5}$$

optimal dose: $46 \frac{mg}{kg}$







Conclusion

Input

NONMEM

- **PMX model with model parameters**
- **dosing schedule**
- **efficacy + safety targets**
  - **“top priority” target → state constraint → penalty function**
  - **“as good as possible” target → objective function**

Output **optimal drug doses** **regarding** efficacy + safety

Analysis **check + plot results**

Thank you!

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Team

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References

[1] Bachmann, F., Koch, G., Bauer, R.J. *et al.* Computing optimal drug dosing with OptiDose: implementation in NONMEM. *J Pharmacokinet Pharmacodyn* **50**, 173– 188 (2023). https://doi.org/10.1007/s10928-022-09840-w

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