# Frequency-domain response analysis for quantitative systems pharmacology models

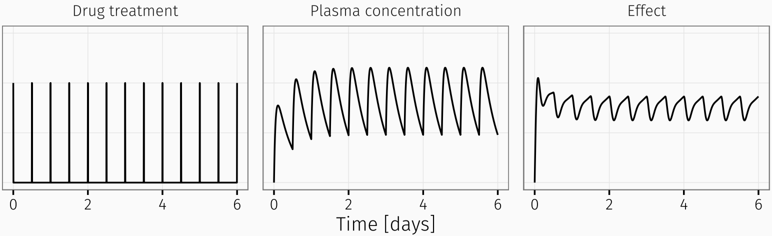
Pascal Schulthess

Systems Pharmacology
Leiden Academic Centre for Drug Research
Leiden University, The Netherlands

*Go home, get some rest, you’ll feel better in a couple of days.*

*Take this drug every 12 hours for one week.*

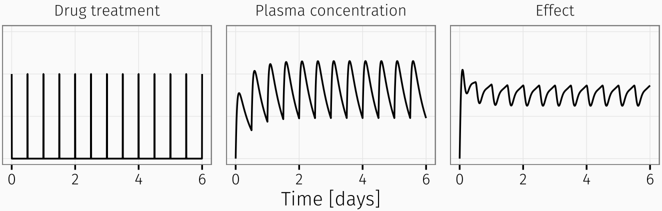
*Take this drug every 12 hours for one week.*




What is the response to dosing frequency changes?

# Introduction to frequency-domain response analysis (FdRA)

# A tolerance and rebound PD model

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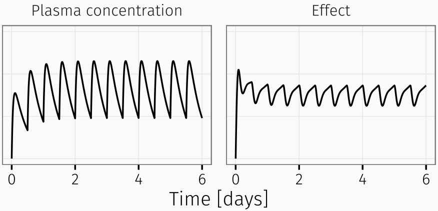


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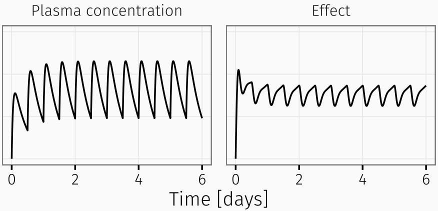
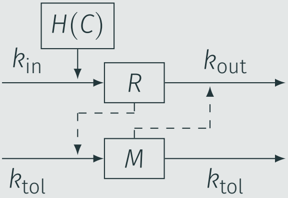


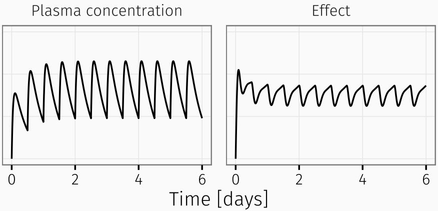

## Example: PD model structure




## Example: PD model equations

$$\frac{dR}{dt} = k_{\text{in}} H(C) - k_{\text{out}} M$$
$$\frac{dM}{dt} = k_{\text{tol}} (R - M)$$

# A tolerance and rebound PD model

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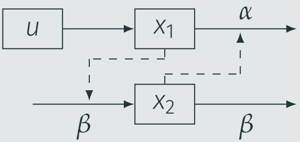


## Example: PD model equations

$$\dot{x}_1(t) = u(t) - \alpha x_2(t)$$
$$\dot{x}_2(t) = \beta(x_1(t) - x_2(t))$$

# PD model in state-space representation

## Example: PD model in matrix notation

$$
\begin{bmatrix} \dot{x}_1(t) \\ \dot{x}_2(t) \end{bmatrix} = \begin{bmatrix} 0 & -\alpha \\ \beta & -\beta \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \end{bmatrix} u(t)
$$

$$
y(t) = \begin{bmatrix} 1 & 0 \end{bmatrix} \begin{bmatrix} x_1(t) \\ x_2(t) \end{bmatrix} + 0 \cdot u(t)
$$

# PD model in state-space representation

**Example: PD model in matrix notation**

$$\dot{\boldsymbol{x}}(t) = \begin{bmatrix} 0 & -\alpha \\ \beta & -\beta \end{bmatrix} \boldsymbol{x}(t) + \begin{bmatrix} 1 \\ 0 \end{bmatrix} u(t)$$

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# PD model in state-space representation

## Example: PD model in matrix notation

$$\dot{\boldsymbol{x}}(t) = \underbrace{\begin{bmatrix} 0 & -\alpha \\ \beta & -\beta \end{bmatrix}}_{\boldsymbol{A}} \boldsymbol{x}(t) + \underbrace{\begin{bmatrix} 1 \\ 0 \end{bmatrix}}_{\boldsymbol{b}} u(t)$$

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## Definition (State-space representation)

A SISO LTI system can be written as

$$\dot{\boldsymbol{x}}(t) = \boldsymbol{A}\boldsymbol{x}(t) + \boldsymbol{b}u(t)$$
$$y(t) = \boldsymbol{c}^T\boldsymbol{x}(t) + du(t)\,.$$

What is the response to dosing frequency changes?

How are input $u$ and output $y$ connected?

# Transfer function connects input to output

$$u(t) \longrightarrow \boxed{g(t)} \longrightarrow y(t)$$

**Time domain**

$$\dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t) + \mathbf{b}u(t)$$
$$y(t) = \mathbf{c}^T\mathbf{x}(t) + du(t)$$

# Transfer function connects input to output

$$u(t) \longrightarrow \boxed{g(t)} \longrightarrow y(t) \qquad\qquad U(s) \longrightarrow \boxed{G(s)} \longrightarrow Y(s)$$

**Time domain**

$$\begin{aligned} \dot{\mathbf{x}}(t) &= \mathbf{A}\mathbf{x}(t) + \mathbf{b}u(t) \\ y(t) &= \mathbf{c}^T\mathbf{x}(t) + du(t) \end{aligned}$$

**Frequency domain**

$$\begin{aligned} s\mathbf{X}(s) &= \mathbf{A}\mathbf{X}(s) + \mathbf{b}U(s) \\ Y(s) &= \mathbf{c}^T\mathbf{X}(s) + dU(s) \end{aligned}$$

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**Definition (Transfer function)**

For a SISO LTI system and $\boldsymbol{x}(0) = \boldsymbol{x}_0$, the transfer function follows to

$$G(s) = \frac{Y(s)}{U(s)} = \boldsymbol{c}^T(s\boldsymbol{I} - \boldsymbol{A})^{-1}\boldsymbol{b} + d\,.$$

# Transfer function of PD model

**Example: PD model**

For

$$\dot{\boldsymbol{x}}(t) = \underbrace{\begin{bmatrix} 0 & -\alpha \\ \beta & -\beta \end{bmatrix}}_{\boldsymbol{A}} \boldsymbol{x}(t) + \underbrace{\begin{bmatrix} 1 \\ 0 \end{bmatrix}}_{\boldsymbol{b}} u(t)$$

$$y(t) = \underbrace{\begin{bmatrix} 1 & 0 \end{bmatrix}}_{\boldsymbol{c}^T} \boldsymbol{x}(t)$$

the transfer function follows to

$$\begin{aligned} G(s) &= \boldsymbol{c}^T (s\boldsymbol{I} - \boldsymbol{A})^{-1} \boldsymbol{b} + d = \begin{bmatrix} 1 & 0 \end{bmatrix} \begin{bmatrix} s & -\alpha \\ \beta & s+\beta \end{bmatrix}^{-1} \begin{bmatrix} 1 \\ 0 \end{bmatrix} \\ &= \frac{s+\beta}{s^2 + \beta s + \alpha\beta}\,. \end{aligned}$$

How are input $u$ and output $y$ connected?

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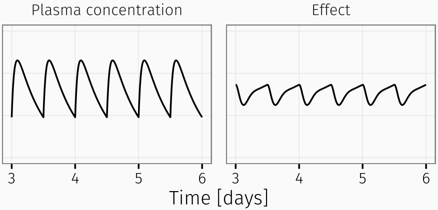
$$Y(s) = G(s)U(s)$$

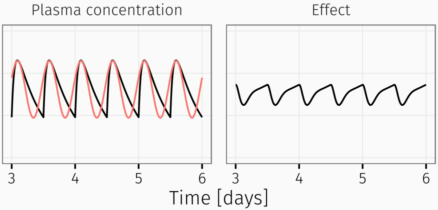
What is the response to dosing frequency changes?

# Sinusoidal inputs determine frequency response



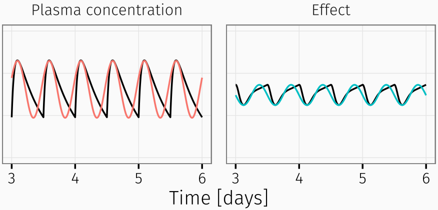

$$u(t) \longrightarrow \boxed{G(s)} \longrightarrow y(t)$$

# Sinusoidal inputs determine frequency response



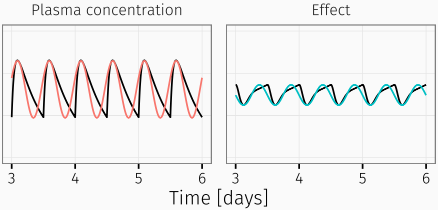

$$u(t) = \sin(\omega t) \longrightarrow \boxed{G(s)} \longrightarrow y(t)$$

# Sinusoidal inputs determine frequency response




$$u(t) = \sin(\omega t) \longrightarrow \boxed{G(s)} \longrightarrow y(t) = y_0 \sin(\omega t + \varphi)$$

# Sinusoidal inputs determine frequency response




$$u(t) = \sin(\omega t) \longrightarrow \boxed{G(i\omega)} \longrightarrow y(t) = y_0 \sin(\omega t + \varphi)$$

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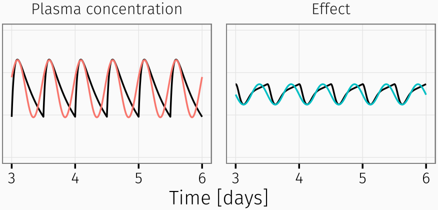


$$u(t) = \sin(\omega t) \longrightarrow \boxed{G(i\omega)} \longrightarrow y(t) = y_0 \sin(\omega t + \varphi)$$

with

- magnitude $y_0 = |G(i\omega)|$

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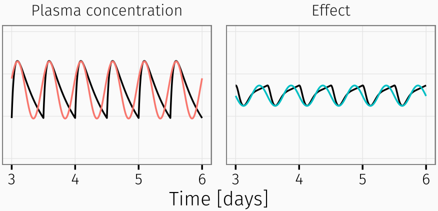
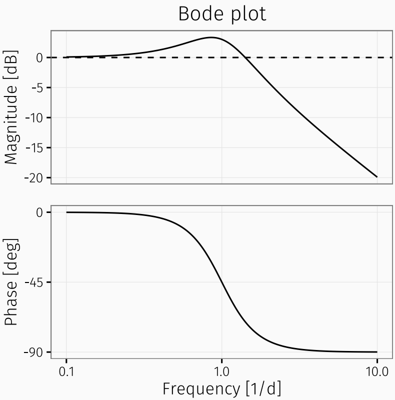



$$u(t) = \sin(\omega t) \longrightarrow \boxed{G(i\omega)} \longrightarrow y(t) = y_0 \sin(\omega t + \varphi)$$

with

- magnitude $y_0 = |G(i\omega)|$
- phase shift $\varphi_y = \arg G(i\omega)$

# Bode plot visualises frequency response



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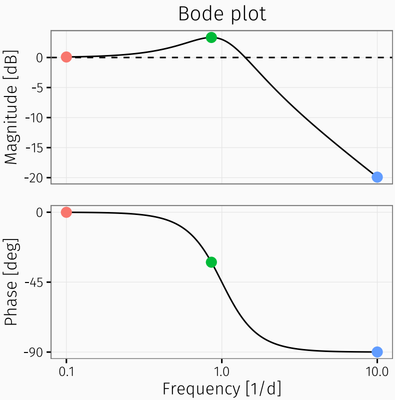

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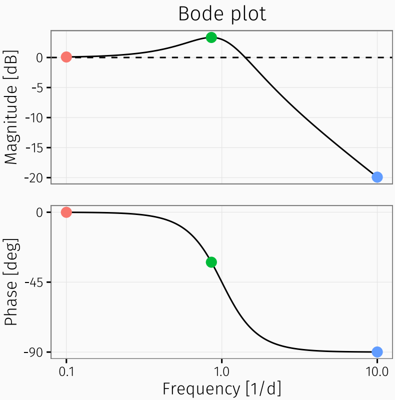


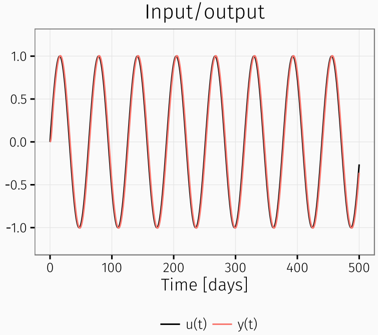

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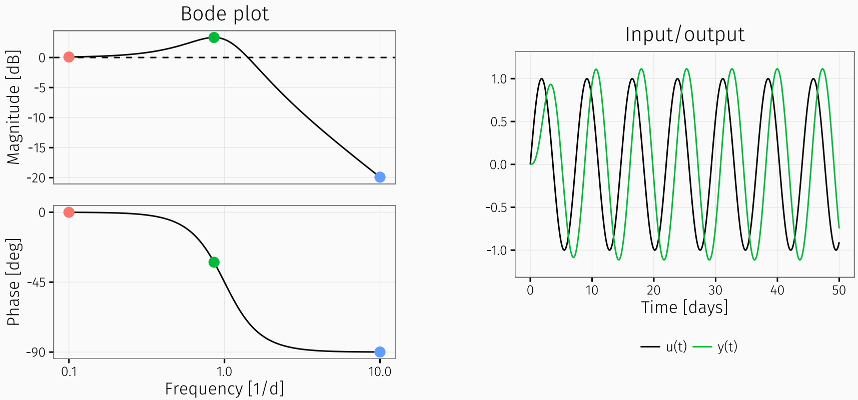

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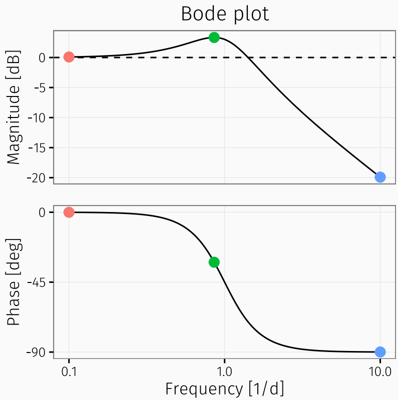
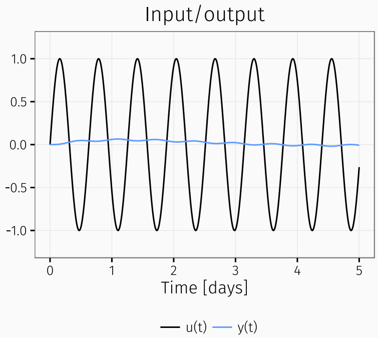
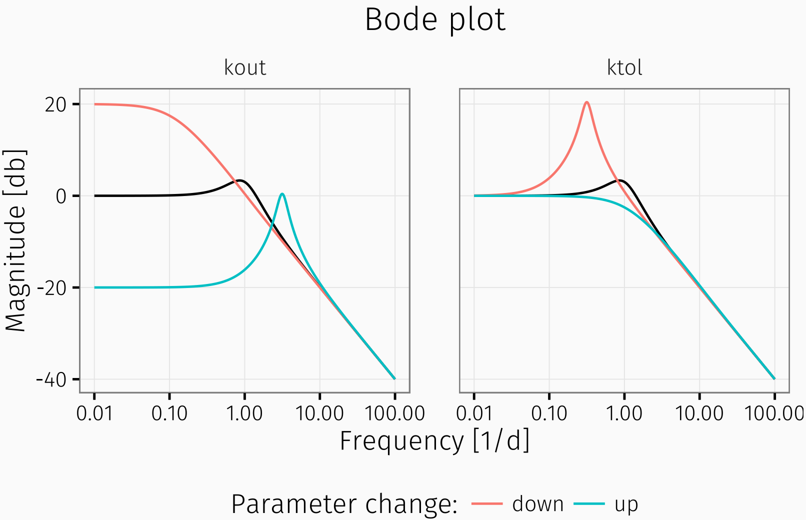
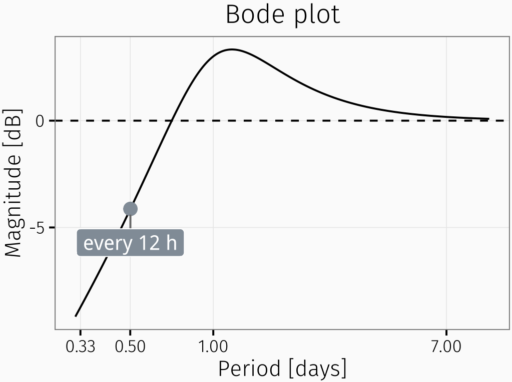


# Parameter choice affects behaviour



# Alternative treatment scheme to optimise effect amplitude



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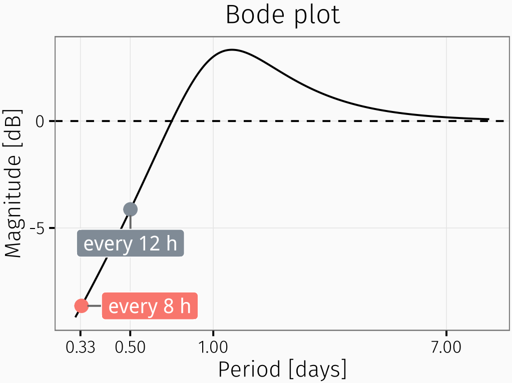
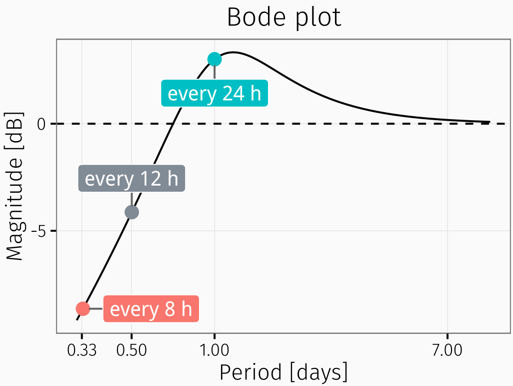



**Result**

Treatment every 8 hours minimises effect amplitude.

# Alternative treatment scheme to optimise effect amplitude



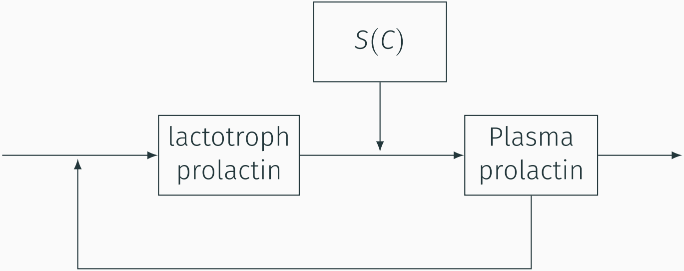

**Result**

Treatment every 24 hours maximises effect amplitude.

FdRA supports optimisation of treatment schemes.

# FdRA application 1: Prolactin model with positive feedback

# Precursor-pool model for prolactin with positive feedback




Bakshi, S. et al., 2016. CPT: Pharmacometrics & Systems Pharmacology, 5(7), pp.339–351.

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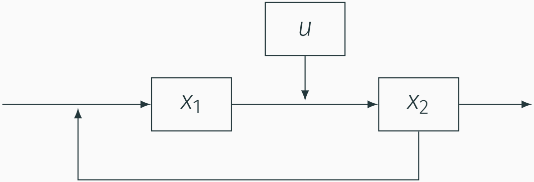


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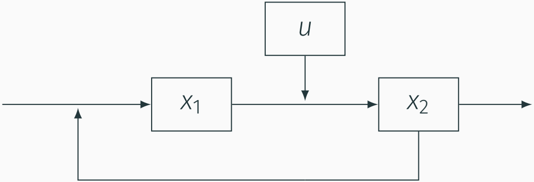


## Nonlinear ODEs of nondimensionalised model

$$
\begin{aligned}
\dot{x}_1(t) &= \alpha\left(1 + \frac{\beta(x_2(t) - 1)}{\gamma + x_2(t) - 1} - x_1(t)u(t)\right) \\
\dot{x}_2(t) &= x_1(t)u(t) - x_2(t) \\
y(t) &= x_2(t)
\end{aligned}
$$

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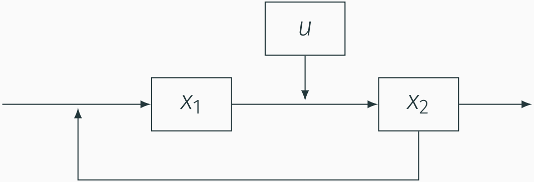


## Linearisation around stable steady state

$$\dot{\mathbf{x}}(t) = \begin{bmatrix} -\alpha & \frac{\alpha\gamma}{\beta} \\ 1 & -1 \end{bmatrix} \mathbf{x}(t) + \begin{bmatrix} -\alpha(1+\beta-\gamma) \\ 1+\beta-\gamma \end{bmatrix} u(t)$$

$$y(t) = \begin{bmatrix} 0 & 1 \end{bmatrix} \mathbf{x}(t)$$

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$$y(t) = \begin{bmatrix} 0 & 1 \end{bmatrix} \boldsymbol{x}(t)$$

## Transfer function

$$G(s) = \frac{(1+\beta-\gamma)s}{s^2 + (1+\alpha)s + \alpha(1-\frac{\gamma}{\beta})}$$

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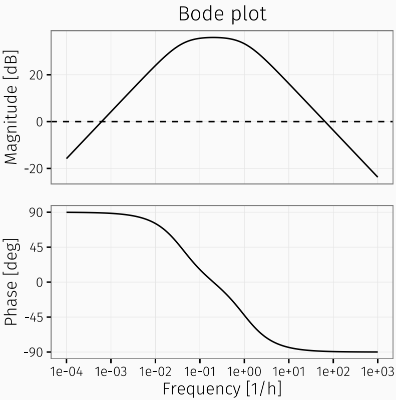
# Input/output behaviour

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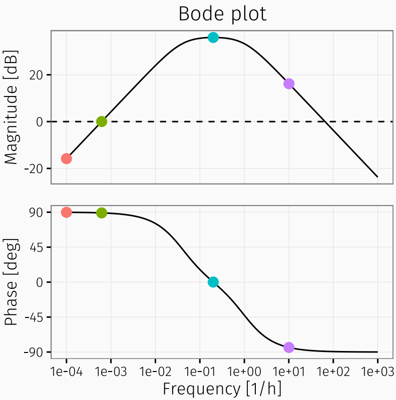


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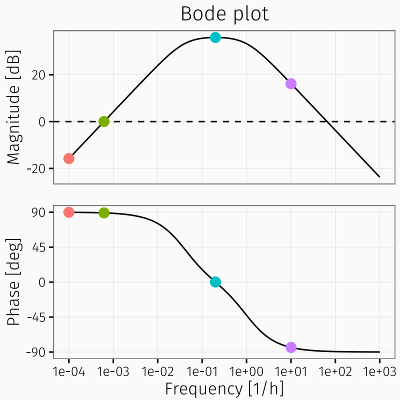


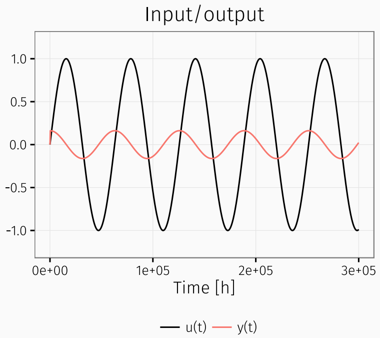


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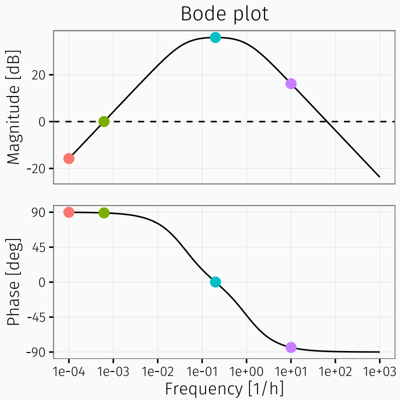


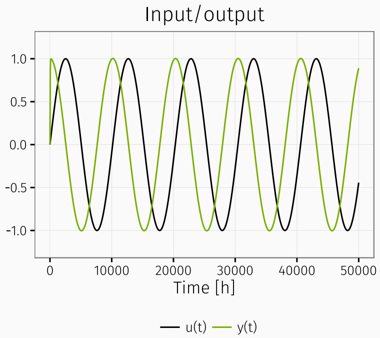

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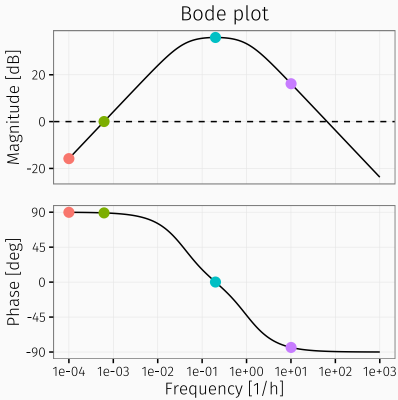


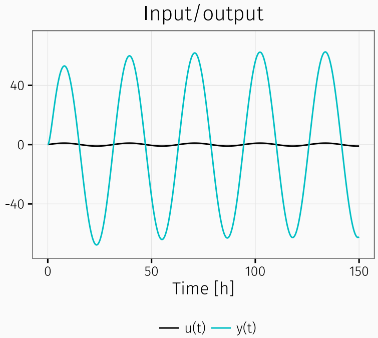


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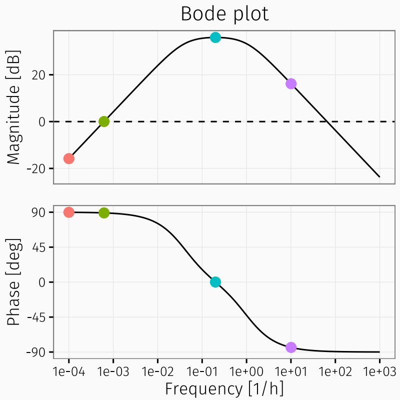


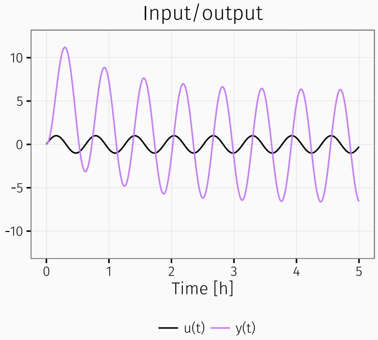


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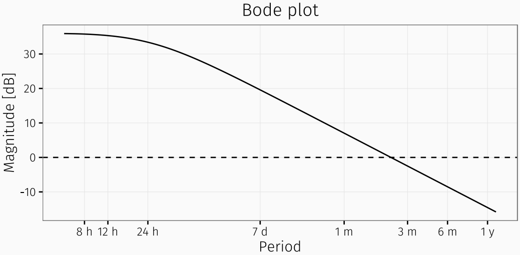
# Treatment options

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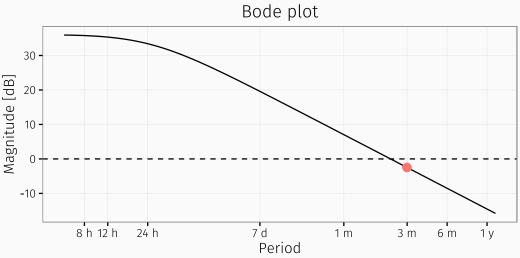


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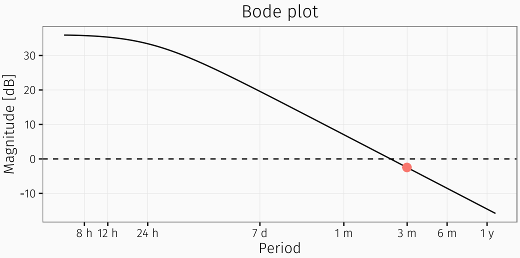


**Result**

FdRA identified an amplification of the input for all reasonable dosing intervals.

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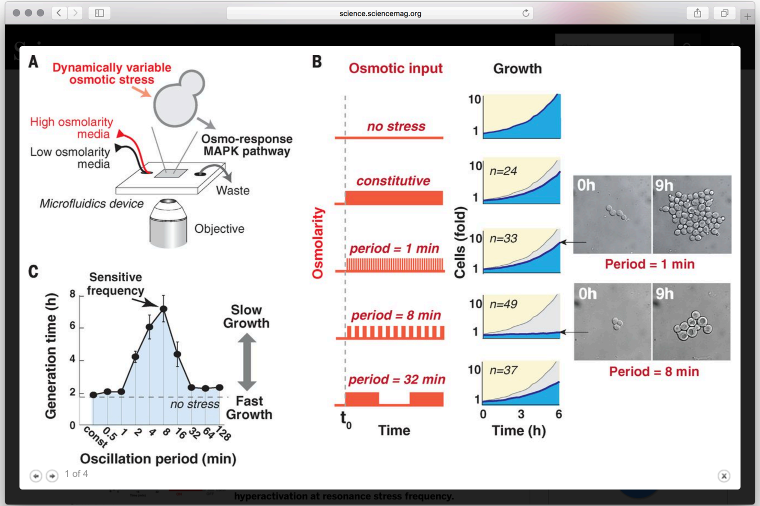
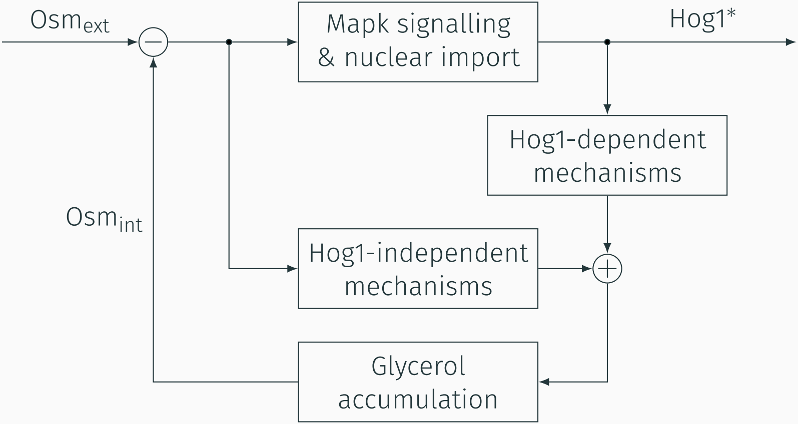
# FdRA application 2: Oscillatory stress stimulation of yeast

# Generation time has sensitive frequency at 8 min




Mitchell, A., Wei, P. & Lim, W.A., 2015. Science, 350(6266), pp.1379–1383.

# Model structure

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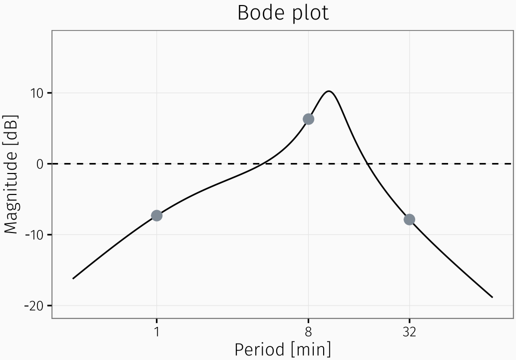
# Can FdRA confirm the results?

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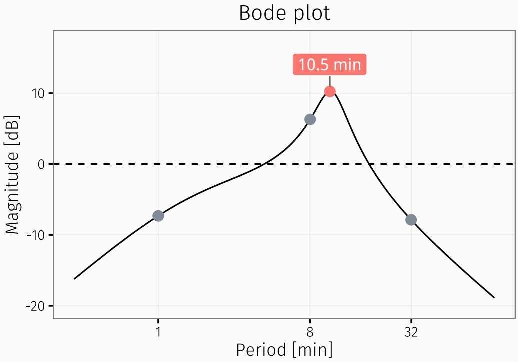
# Can FdRA confirm the results?




**Result**

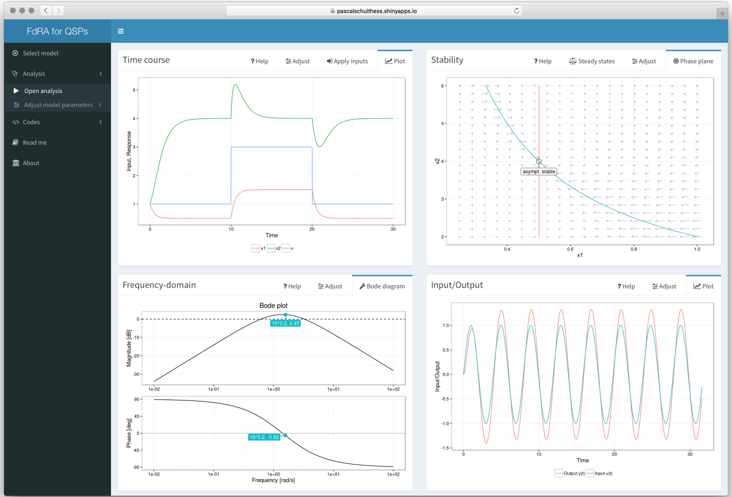
Maximal generation time is not reached at 8 min but rather at 10.5 min.

Mitchell, A., Wei, P. & Lim, W.A., 2015. Science, 350(6266), pp.1379–1383.

FdRA supports the importance of models for experiment planning.

# FdRA as an interactive semi-automated web application

# R Shiny application




pascal.schulthess.io/fdra

# Conclusion & outlook

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Frequency-domain response analysis

Prolactin model with positive feedback

Osciallatory stress stimulation of yeast

# Conclusion

## Frequency-domain response analysis

- applicable to linear time-invariant systems
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  - time scales
- allows optimisation of dosing frequency

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- input period of 10.5 min leads to maximal generation time

# Outlook

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- How to incorporate FdRA into clinical practice?

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Universiteit Leiden
Wiskunde en Natuurwetenschappen

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