Optimal EPO Dosing Control in Hemodialysis

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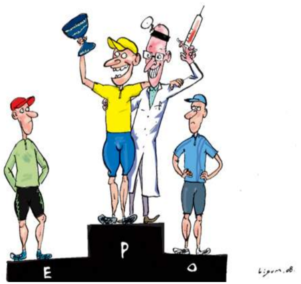

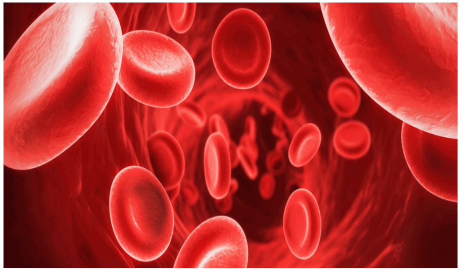

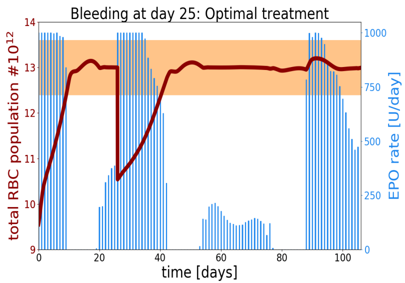

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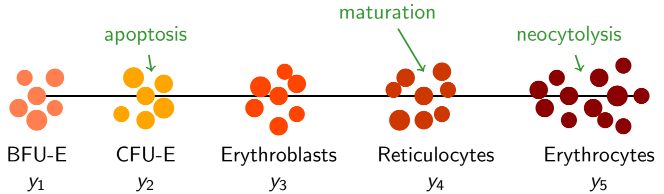
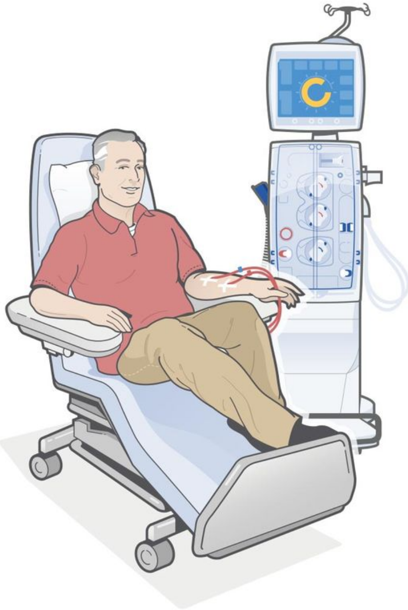
Problem Formulation

Hormone EPO (Erythropoietin):
- produced in kidneys
- drives production of new red blood cells
- low EPO levels cause neocytolysis (active reduction of erythrocytes)



Chronic kidney disease:
- insufficient production and release of EPO
- chronic anemia (chronic lack of blood)
- exogenous EPO administration during hemodialysis treatments

Question: What are the „optimal“ EPO doses?



Optimal Control Problem

PDE-Constrained Optimization Problem:

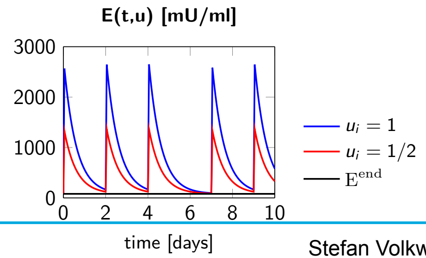
$$\min J(\boldsymbol{y},\boldsymbol{u}) \quad \text{subject to} \quad e(\boldsymbol{y},\boldsymbol{u}) = 0 \text{ and } \boldsymbol{u} \in \mathcal{U}_{\text{ad}}$$

Control input:

- administration time points (3 times per week): $t_1^*, t_2^*, t_3^*, \ldots, t_m^* \in [t_\circ, t_{\text{f}}]$
- find EPO dose in $[0, E_{\text{max}}]$ for every t_i^*, $i = 1, \ldots, m$
- vector $\boldsymbol{u} = (u_1, \ldots, u_m) \in \mathbb{R}^m$, $U_{\text{ad}} = \big\{ u \in \mathbb{R}^m \mid 0 \le u_i \le 1 \text{ for } 1 \le i \le m \big\}$
- variable EPO doses: one component refers to one time
- constant EPO doses: one component refers to several times $\underbrace{t_1^*, t_2^*, t_3^*}_{u_1}, \underbrace{t_4^*, t_5^*, t_6^*}_{u_2}, \ldots$

EPO concentration in blood:

- $E(t,\boldsymbol{u}) = E^{\text{ex}}(t,\boldsymbol{u}) + E^{\text{end}}$ with remaining endogeneous E^{end}
- $E^{\text{ex}}(t,\boldsymbol{u}) = \frac{1}{c_{\text{tbv}}} \sum_{i=1}^m u_i \chi_i(t)$ with $\chi_i(t) = E_{\text{max}} e^{-\lambda(t-t_i^*)} \chi_{(t_i^*,\infty)}(t)$
- c_{tbv} total blood volume



State vector: $\boldsymbol{y} = (y_1, \ldots, y_5)$ with population densities $y_i(t,x)$ and maturity $x \in [a_i, b_i]$

Model equations:

$$y_t(t,x) + \overbrace{v(E(t,\boldsymbol{u}))}^{\text{maturation velocity}} y_x(t,x) = \Big(\overbrace{\beta}^{\text{proliferation}} - \overbrace{\alpha(E(t,\boldsymbol{u}),x)}^{\text{apoptosis}} \Big) y(t,x)$$

$$y(t_\circ, x) = y_\circ(x)$$

Boundary conditions:

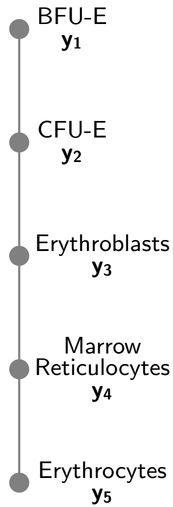
$$y_1(t,a_1) = S_0, \qquad y_2(t,a_2) = y_1(t,b_1), \qquad y_3(t,a_3) = y_2(t,b_2)$$

$$y_4(t,a_4) = \frac{y_3(t,b_3)}{v(E(t,u))}, \qquad y_5(t,a_5) = v\big(E(t,\boldsymbol{u})\big)\, y_4(t,b_4)$$

Patient-depending functions:

$$\alpha_2(E) = \frac{\mu_1}{1 + \exp\big(\mu_2 E - \mu_3\big)}, \quad \alpha_5(E,x) = \alpha_5^0 + \chi_{[x_{\text{min}}, x_{\text{max}}]}(x) \cdot \widetilde{\alpha}_5(E), \quad v(E) = \frac{\mu_4 - \mu_5}{1 + \exp\big(-\mu_6 E + \mu_7\big)} + \mu_5$$

Control input: $E(t,\boldsymbol{u}) = \frac{1}{c_{\text{tbv}}} \sum_{i=1}^{m} u_i \chi_i(t) + E^{\text{end}}$ with $\chi_i(t) = E_{\max} e^{-\lambda(t - t_i^*)} \chi_{(t_i^*, \infty)}(t)$



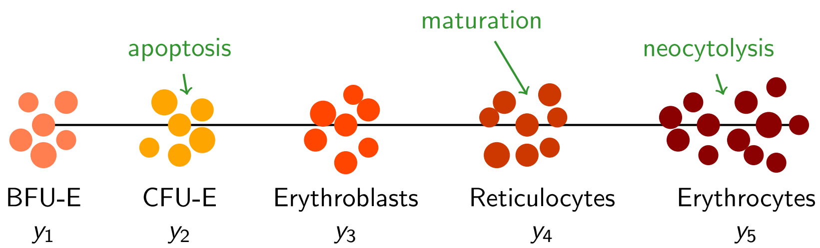
Desired total population: hemoglobin target range of 10-11 g/dl

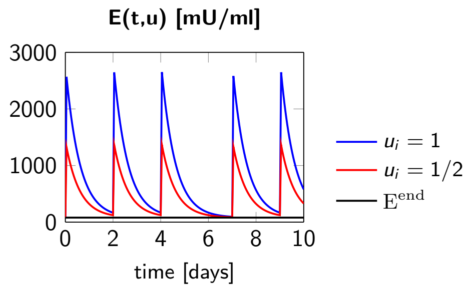
Total erythrocytes population: $\int_{a_5}^{b_5} y_5(t,x)\,\mathrm{d}x$

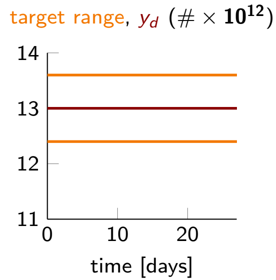
Cost functional:

$$J(\boldsymbol{y},\boldsymbol{u}) = \frac{\sigma_\Omega}{2}\int_{t_\circ}^{t_\mathsf{f}} \Big| \int_{a_5}^{b_5} y_5(t,x)\,\mathrm{d}x - y_d \Big|^2 \mathrm{d}t + \frac{\sigma_\mathsf{f}}{2} \Big| \int_{a_5}^{b_5} y_5(t_\mathsf{f},x)\,\mathrm{d}x - y_d \Big|^2 + \frac{1}{2}\sum_{i=1}^{m} \gamma_i\,|u_i|^2$$

with weights $\sigma_\Omega, \sigma_\mathsf{f}, \gamma_i > 0$



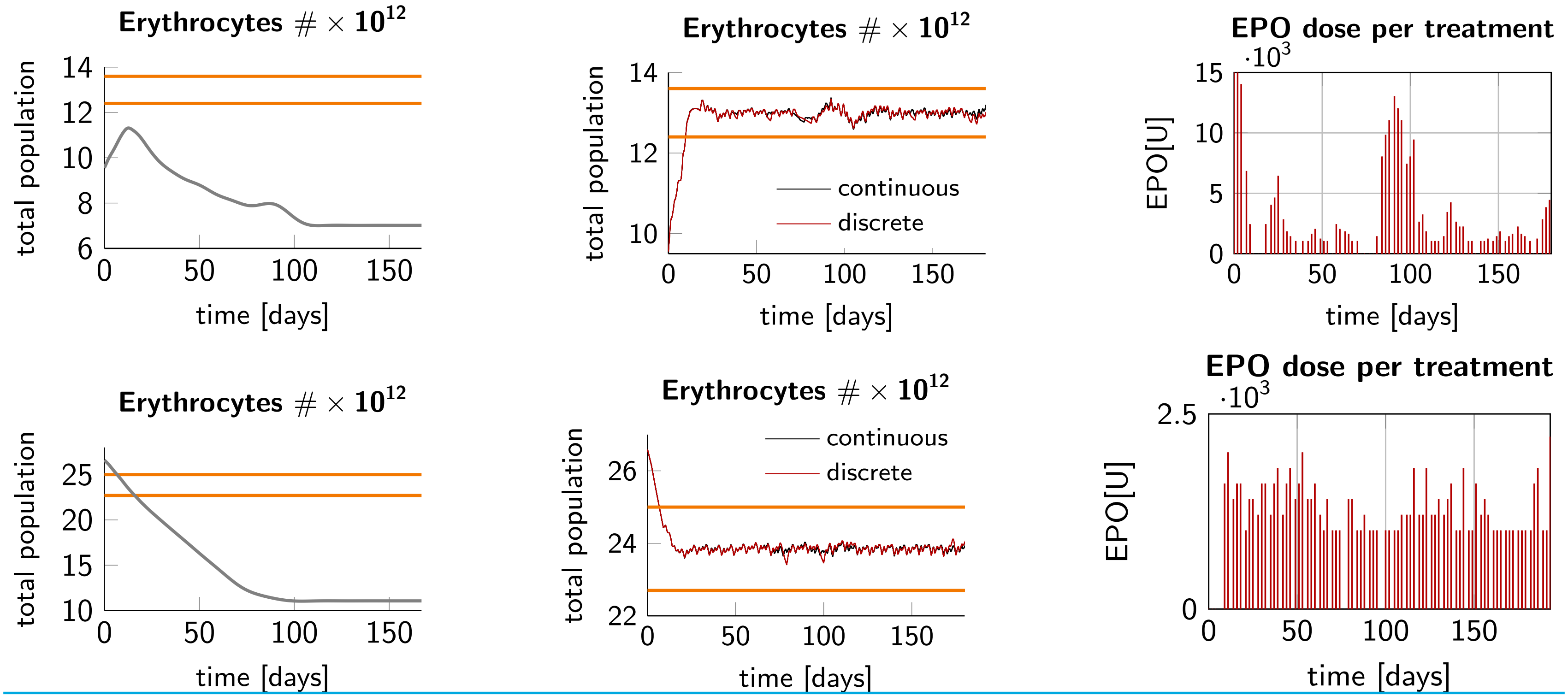


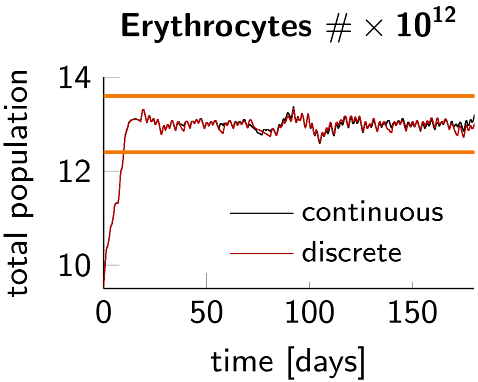


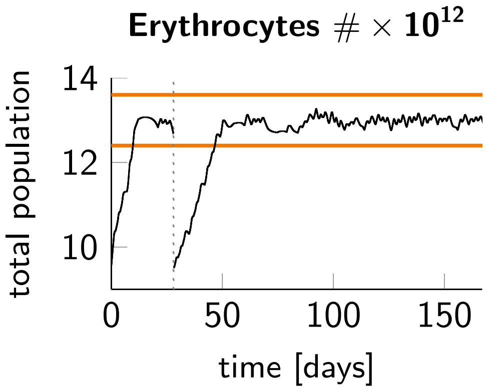
Numerical optimization: projected Quasi-Newton, BFGS, Armijo

Discretization: Legendre polynomials

Numerical Experiments




Erythrocytes # × 10^12
total population
14
12
10
0
50
100
150
time [days]
continuous
discrete


Erythrocytes # × 10^12
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14
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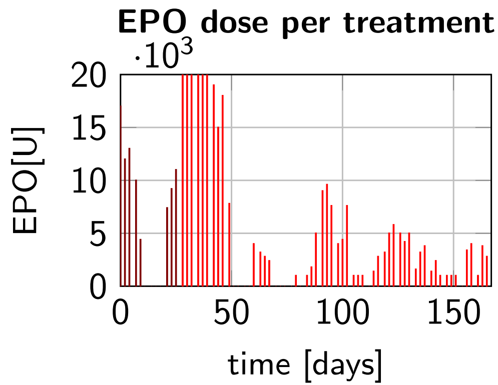
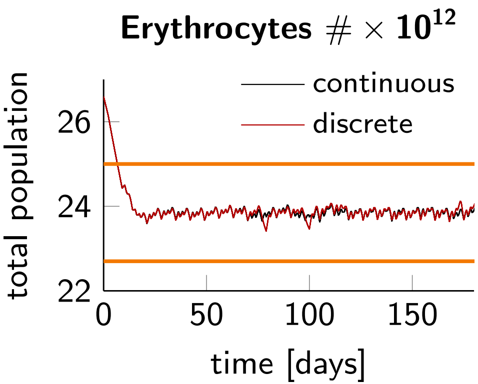
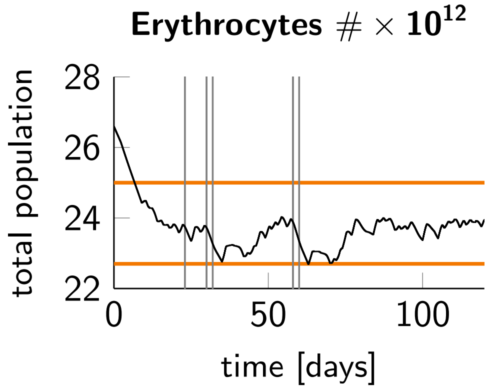
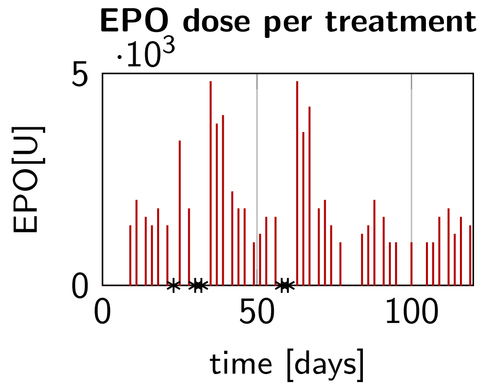

EPO dose per treatment
·10^3
EPO[U]
20
15
10
5
0
0
50
100
150
time [days]


Erythrocytes # × 10^12
total population
26
24
22
0
50
100
150
time [days]
continuous
discrete


Erythrocytes # × 10^12
total population
28
26
24
22
0
50
100
time [days]


EPO dose per treatment
·10^3
EPO[U]
5
0
0
50
100
time [days]

References

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Mutsaers/Bachar/Batzel/Kappel/V.'11: Receding horizon controller for the baroreceptor loop in a model for the cardiovascular system, Card. Eng.
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