MATHEMATICAL AND COMPUTER MODELING OF NONLINEAR BIOSYSTEMS I

COMPUTER LABORATORY XV: Projects presentations

Ph. D. Programme 2013/2014

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UNIA EUROPEJSKA
EUROPEJSKI
FUNDUSZ SPOŁECZNY

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CARDIOVASCULAR BAROREFLEX MECHANISM

Leszek PSTRAŚ

Mathematical and computer modelling of nonlinear biosystems

10.06.2014

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BAROREFLEX MECHANISMS

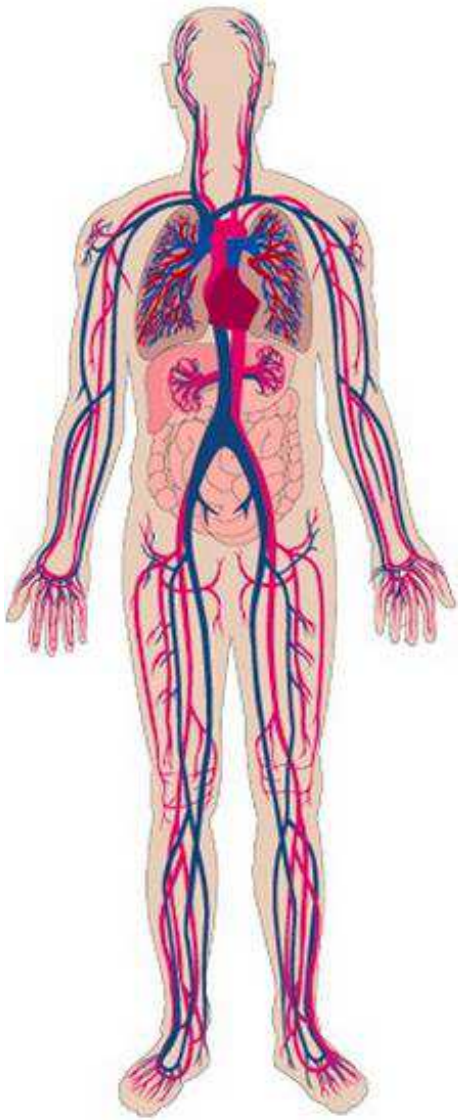


Fig 1. Human cardiovascular system
[source: www.resmedica.pl]

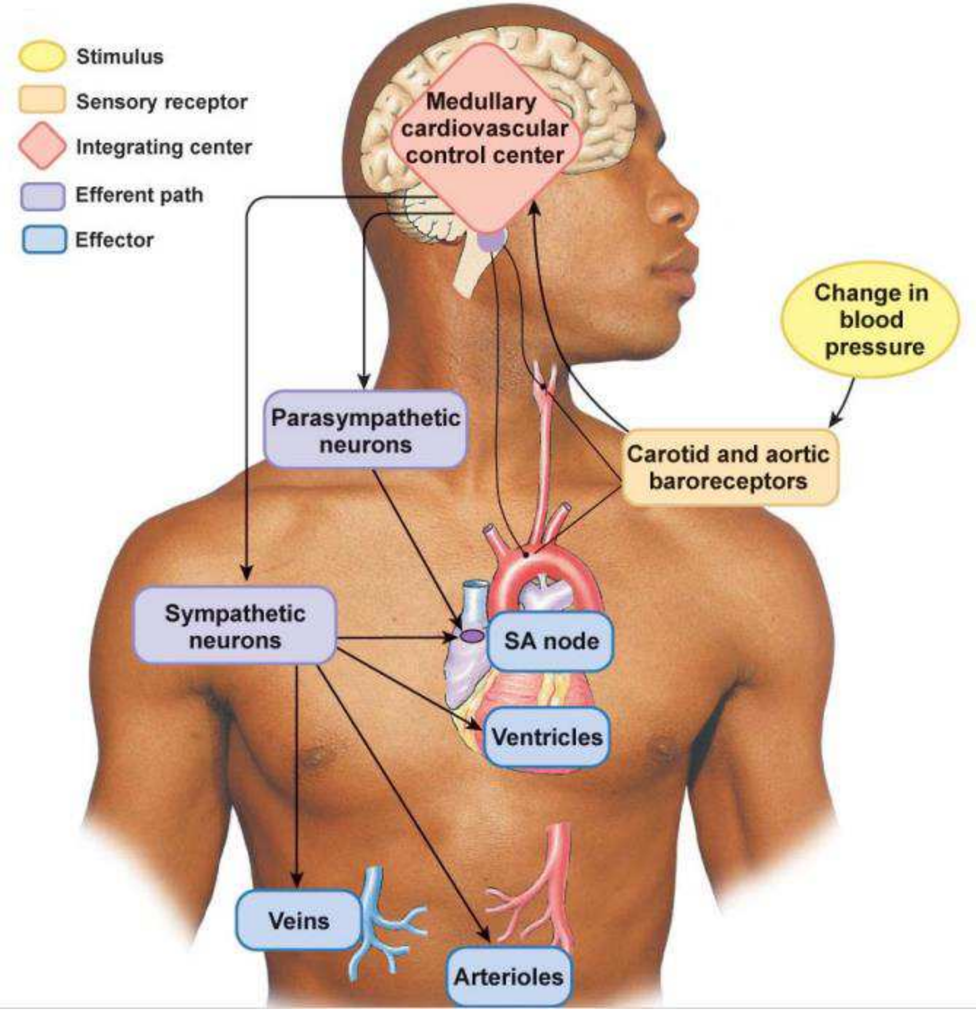


Fig 2. Sympathetic and parasympathetic baroreflex
(source: The McGraw-Hill Companies, Inc)

OVERVIEW

MODELLING STEPS

1. Build the cardiovascular system model
2. Use parameters from the literature (resistances, compliances, pressures etc.)
3. Fit missing parameters (to assure steady-state)
4. Add baroreflex mechanisms
5. Add a possibility of simulating an open-loop or closed-loop system
6. Add a possibility of simulating a hemorrhage

SIMULATIONS

1. Perturb some parameters and find new steady-state
2. Show Frank-Starling relationship for different arterial pressures (different afterload)
3. Check sensitivity of arterial pressure and cardiac output to all vascular resistances
4. Show the operation of baroreflex in open-loop system
5. Show the importance of baroreflex in closed-loop system (simulate a hemorrhage)
6. Compare partial baroreflex with full baroreflex
7. Show venous capacity control

CARDIOVASCULAR SYSTEM

- 2 cardiac compartments
- 4 vascular compartments (systemic arterial, systemic venous, pulmonary arterial, pulmonary venous)
- Windkessel model - each compartment represented by:
    - hydraulic resistance (energy dissipation, pressure losses)
    - capacity (blood volume stored in the compartment at a given pressure)

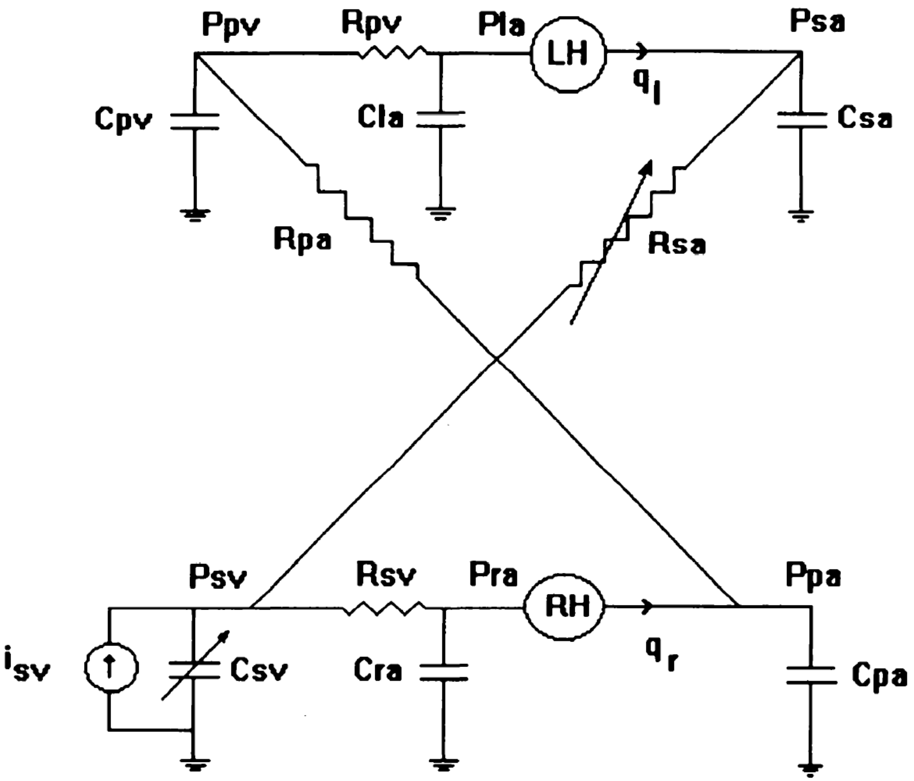


Fig 3. An electric analogue of the cardiovascular system [Ursino et al.]

P – pressure
C – capacity/compliance
R – resistance
sa – systemic arteries
sc – systemic veins
ra/la – right/left atrium
pa/pv – pulmonary arteries/veins
q_l/q_r – left/right cardiac output
i_{sv} – amount of blood volume injected into or subtracted from the sv compartment

Compartment volume:
(unstressed volume + stressed volume)

$$V_j = V_{u,j} + C_j p_j$$

CVS EQUATIONS

$$C_{sa}\frac{dp_{sa}}{dt} = q_l - \frac{p_{sa} - p_{sv}}{R_{sa}}$$

$$C_{pa}\frac{dp_{pa}}{dt} = q_r - \frac{p_{pa} - p_{pv}}{R_{pa}}$$

$$C_{pv}\frac{dp_{pv}}{dt} = \frac{p_{pa} - p_{pv}}{R_{pa}} - \frac{p_{pv} - p_{la}}{R_{pv}}$$

$$C_{ra}\frac{dp_{ra}}{dt} = \frac{p_{sv} - p_{ra}}{R_{sv}} - q_r$$

$$C_{la}\frac{dp_{la}}{dt} = \frac{p_{pv} - p_{la}}{R_{pv}} - q_l$$

$$q_l = S_l \cdot f$$

$$q_r = S_r \cdot f$$

$$S_l = \frac{k_l(p_{la} - p_{la0})}{a_l}$$

$$S_r = \frac{k_r(p_{ra} - p_{ra0})}{a_r}$$

$$a_l = \begin{cases} 1 & if\ p_{sa} \le p_{san} \\ \sqrt{\frac{p_{sa}}{p_{san}}} & if\ p_{sa} > p_{san} \end{cases}$$

$$a_r = \begin{cases} 1 & if\ p_{pa} \le p_{pan} \\ \sqrt{\frac{p_{pa}}{p_{pan}}} & if\ p_{pa} > p_{pan} \end{cases}$$

$$p_{sv} = \frac{1}{C_{sv}}\left(V_t - V_u - C_{sa}p_{sa} - C_{pa}p_{pa} - C_{pv}p_{pv} - C_{ra}p_{ra} - C_{la}p_{la}\right)$$

CAROTID BAROREFLEX MECHANISM

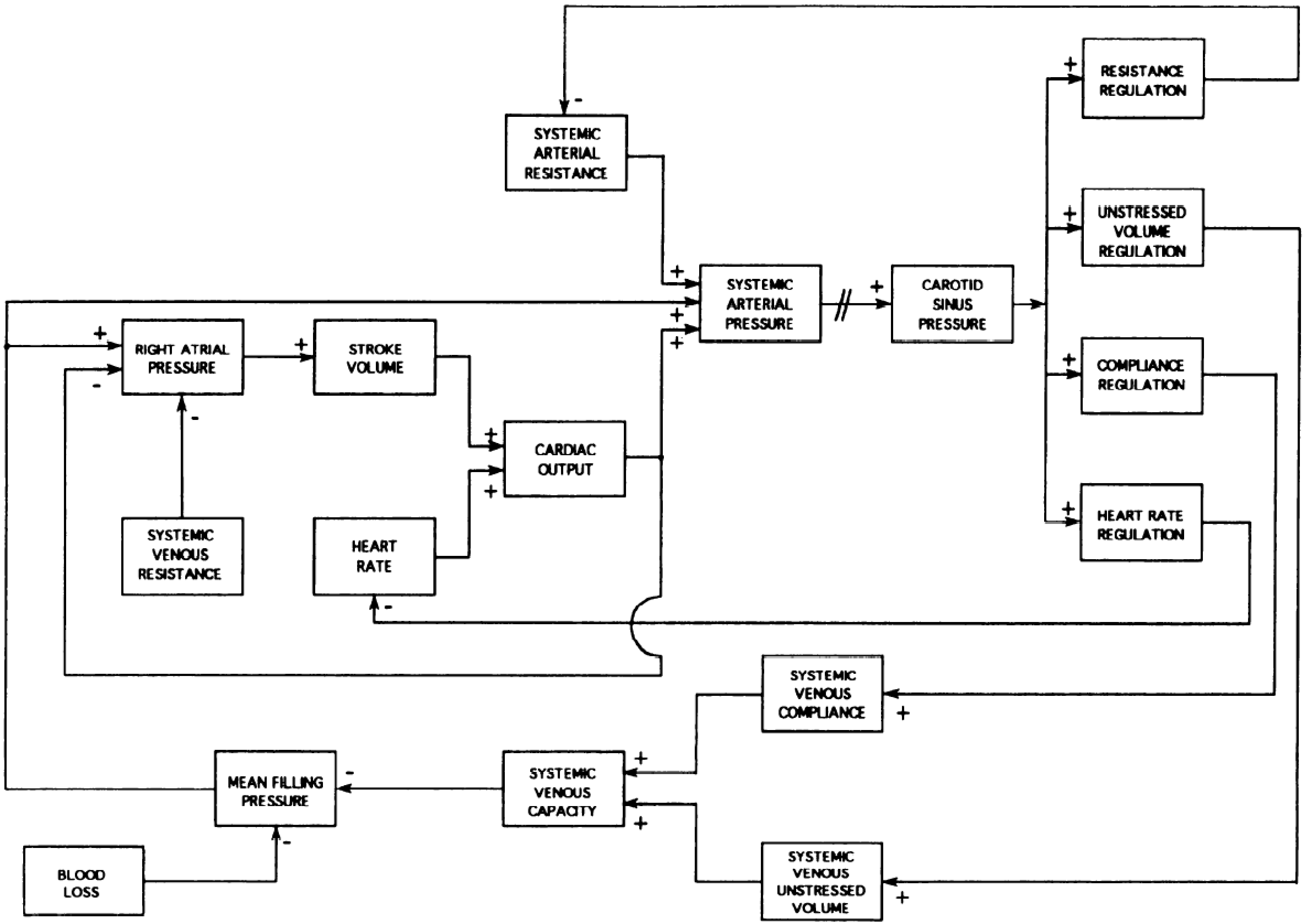


Fig 4. Feedback regulatory mechanism acting on the cardiovascular system [Ursino et al.]

BAROREFLEX MECHANISM

$$\frac{dR_{sa}}{dt} = \frac{1}{\tau_R}(\sigma_R - R_{sa})$$

$$\sigma_R = \frac{R_{max} + R_{min} \cdot exp\left(\frac{p_{cs} - p_{csn}}{r_1}\right)}{1 + exp\left(\frac{p_{cs} - p_{csn}}{r_1}\right)}$$

$$\frac{dT}{dt} = \frac{1}{\tau_T}(\sigma_T - T)$$

$$\sigma_T = \frac{T_{max} + T_{min} \cdot exp\left(\frac{p_{csn} - p_{cs}}{r_2}\right)}{1 + exp\left(\frac{p_{csn} - p_{cs}}{r_2}\right)}$$

$$\frac{dV_{usv}}{dt} = \frac{1}{\tau_V}(\sigma_V - V_{usv})$$

$$\sigma_V = \frac{V_{max} + V_{min} \cdot exp\left(\frac{p_{csn} - p_{cs}}{r_3}\right)}{1 + exp\left(\frac{p_{csn} - p_{cs}}{r_3}\right)}$$

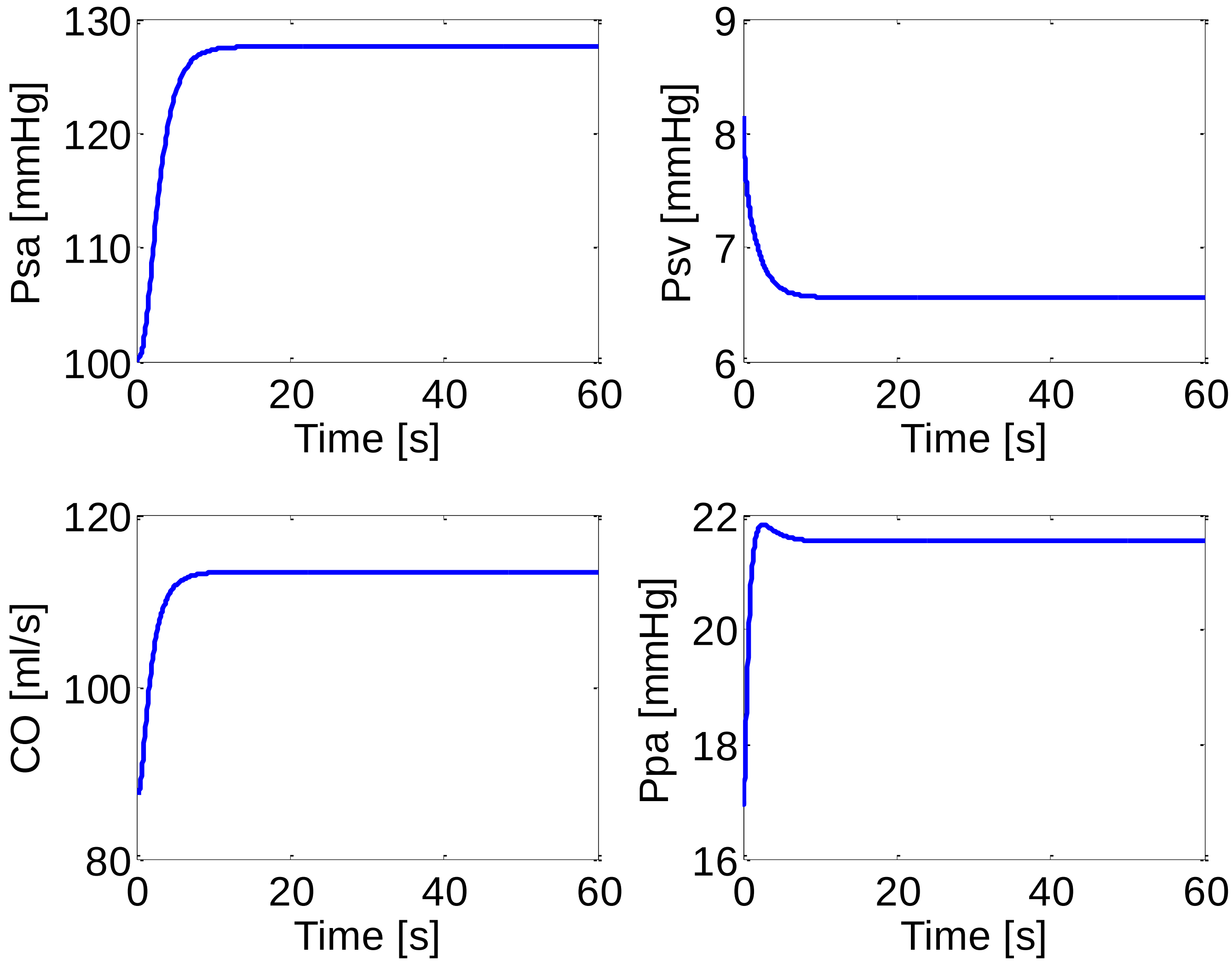
$$\frac{dC_{sv}}{dt} = \frac{[-(C_{sv} - C_{svn}) + G_4 \cdot (p_{cs} - p_{csn})]}{\tau_C}$$

SIMULATIONS

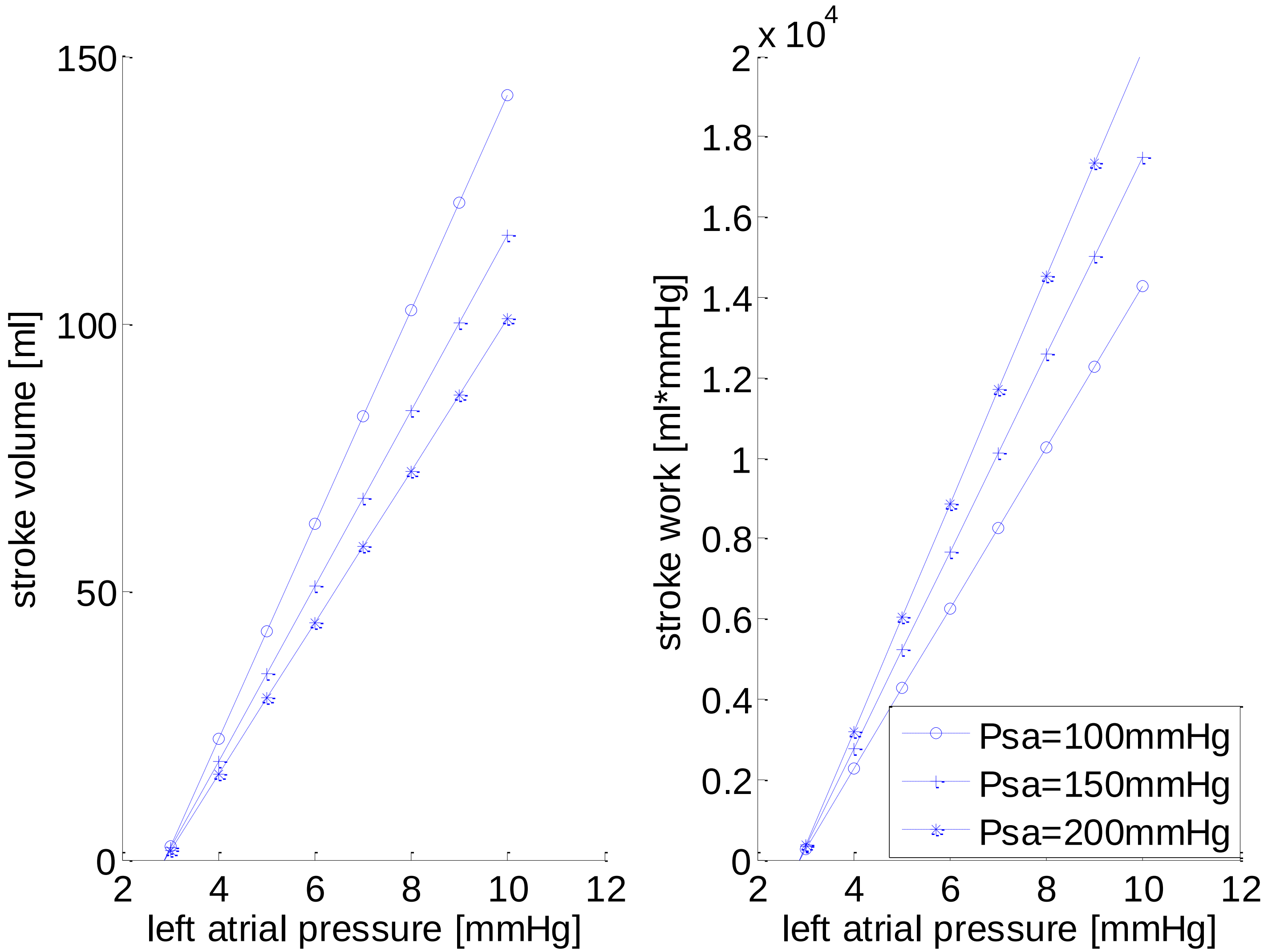
FINDING NEW STEADY-STATE OF THE SYSTEM

Example:

a decrease in systemic arterial compliance (from 4 ml/mmHg to 1 ml/mmHg) – stiffness of systemic arteries

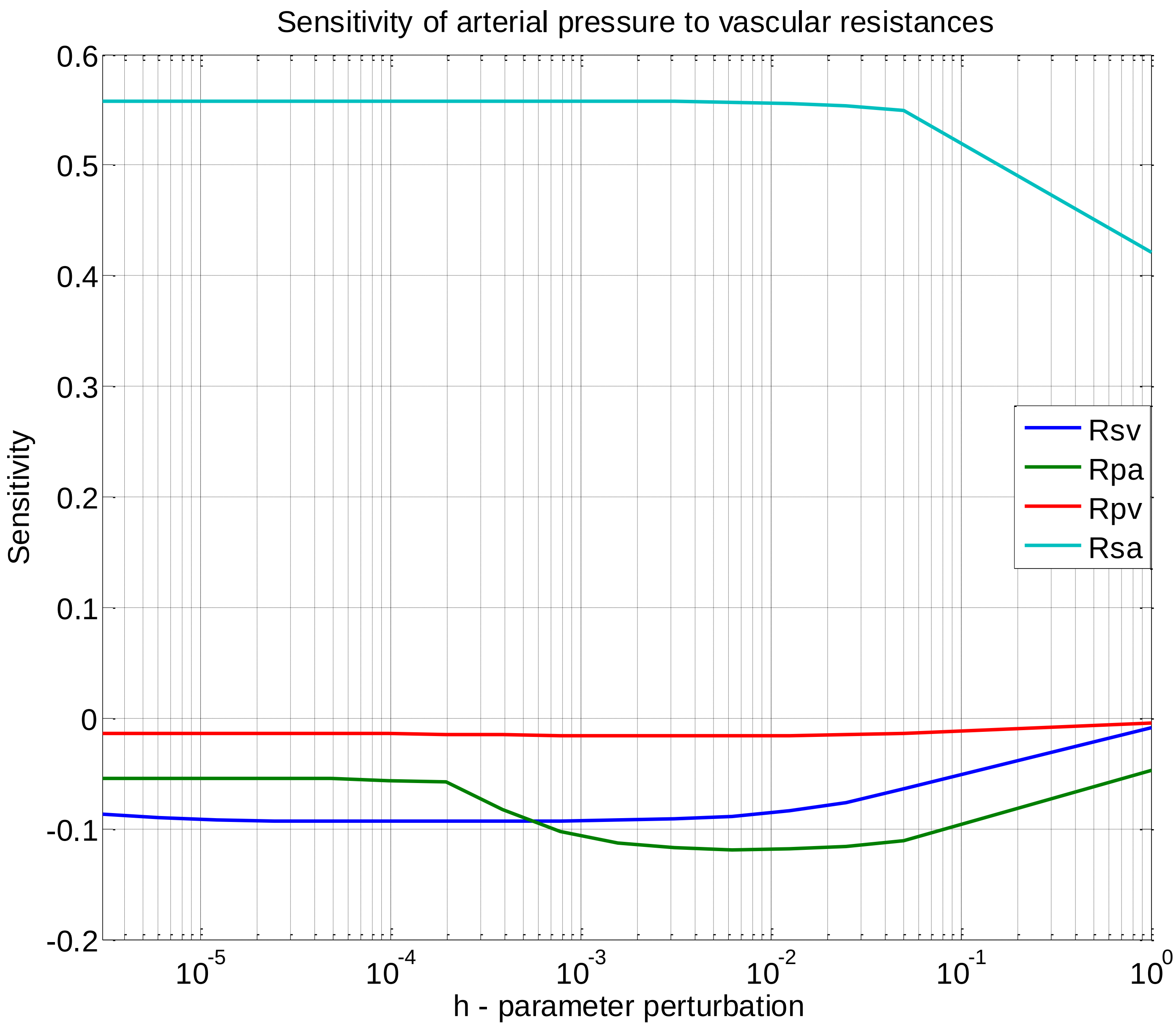


FRANK-STARLING RELATIONSHIP



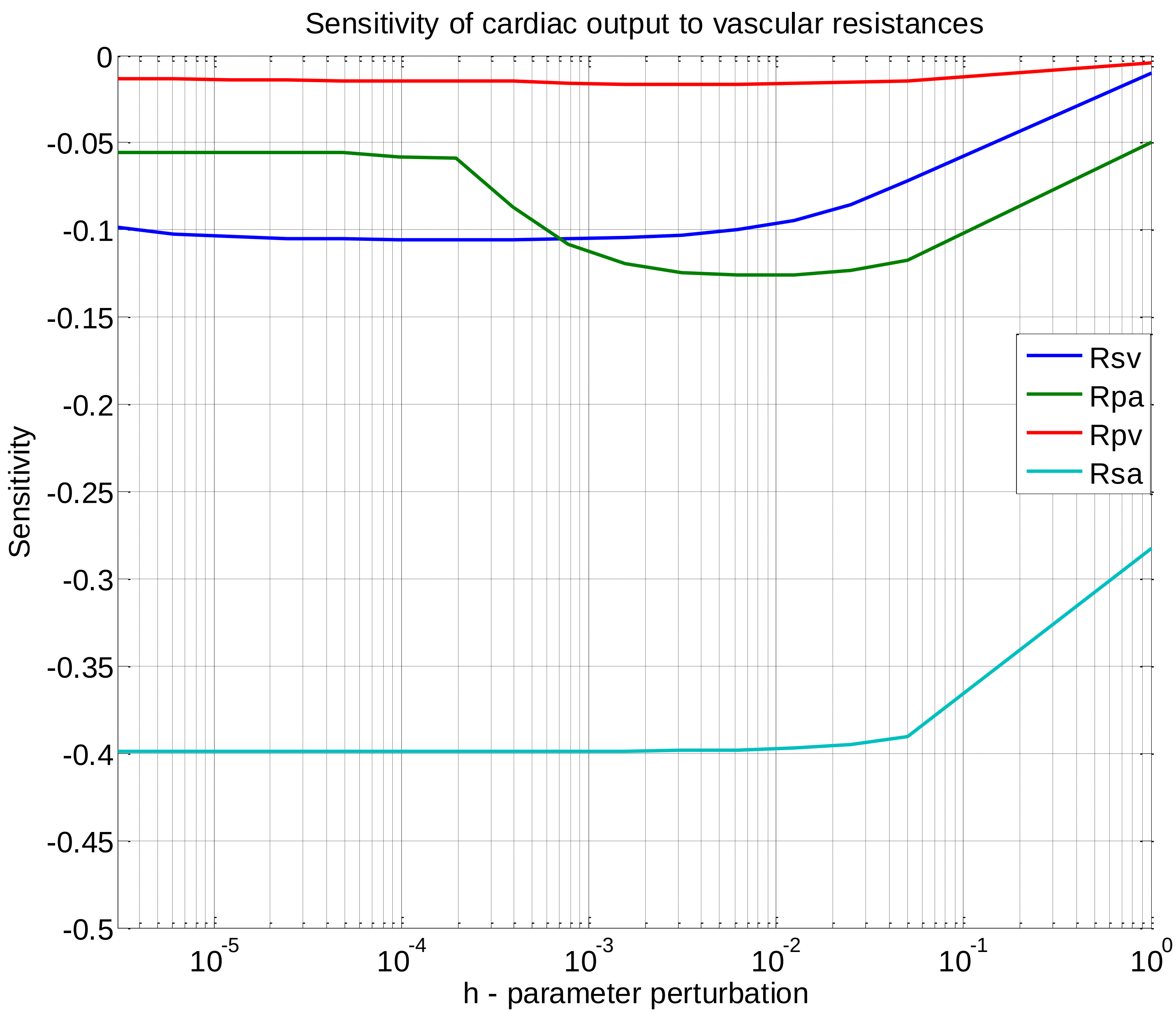
Stroke volume slightly decreases while stroke work slightly increases with increasing afterload (arterial pressure)

SENSITIVITY



Systemic arterial resistance has the highest impact on arterial pressure.

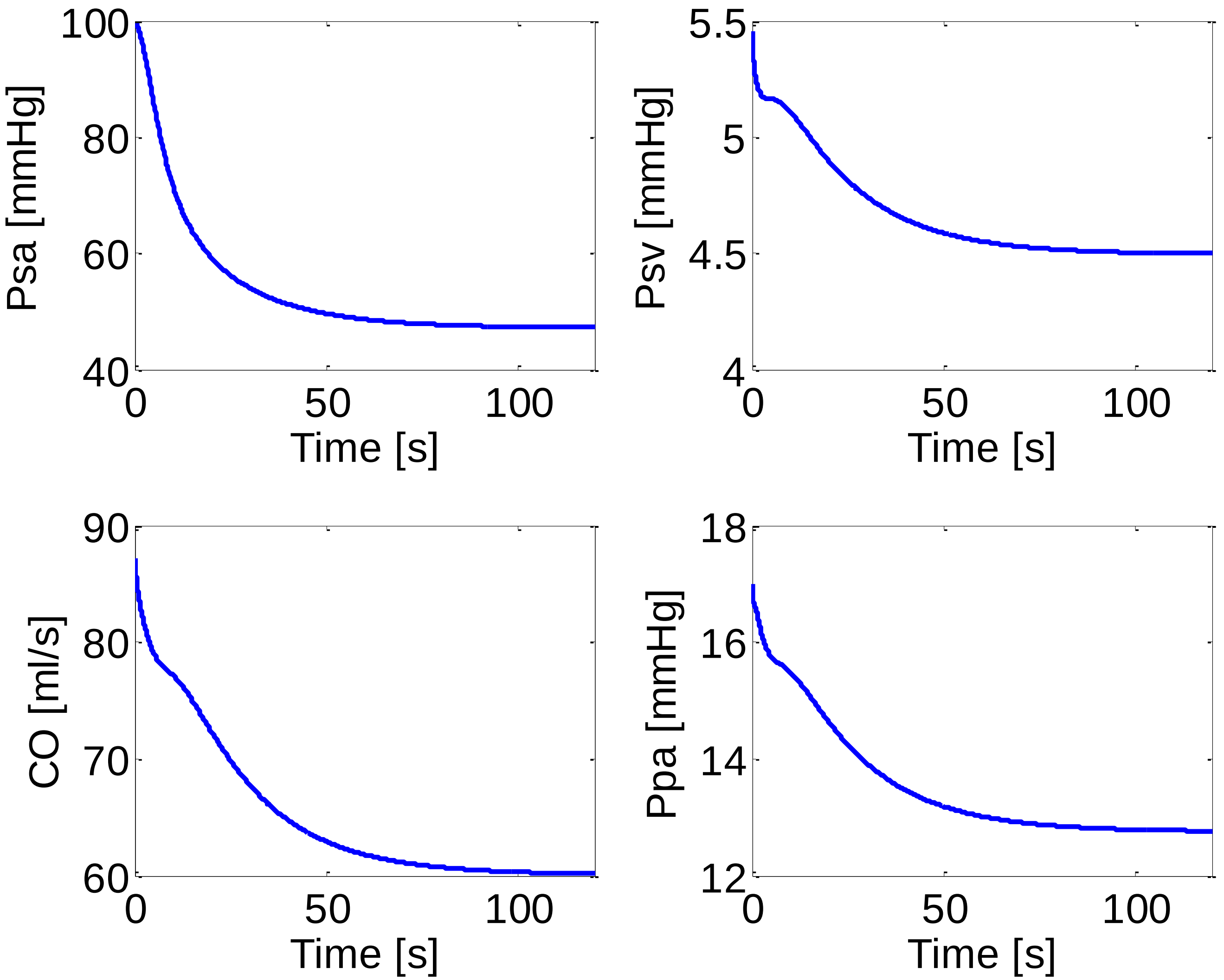
SENSITIVITY



Systemic arterial resistance has the highest impact on cardiac output.

BAROREFLEX IN OPEN-LOOP SYSTEM

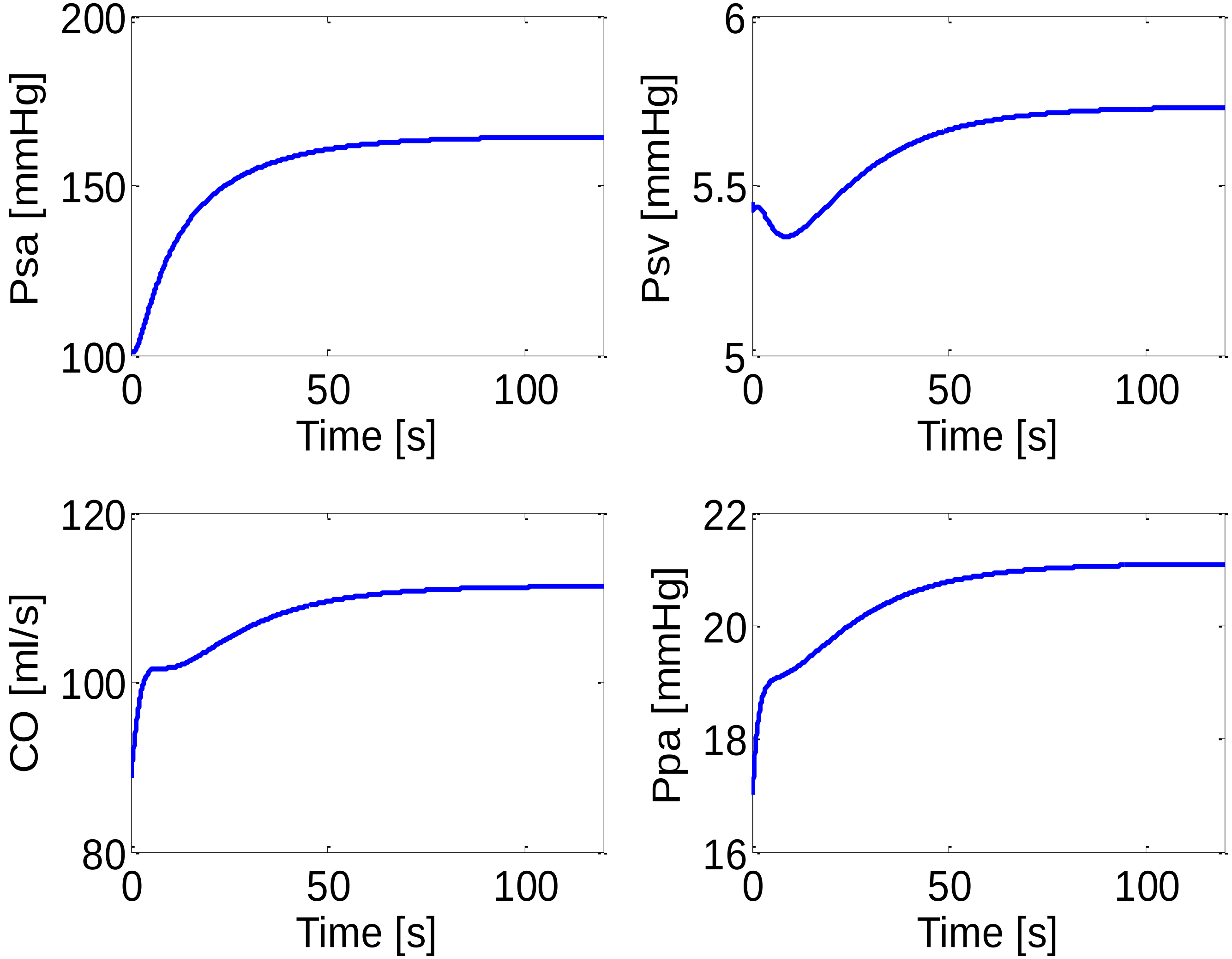
params.Pcs = 150;   % mmHg



High pressure sensed by baroreceptors initiates baroreflex mechanisms leading to a decrease in systemic arterial pressure.

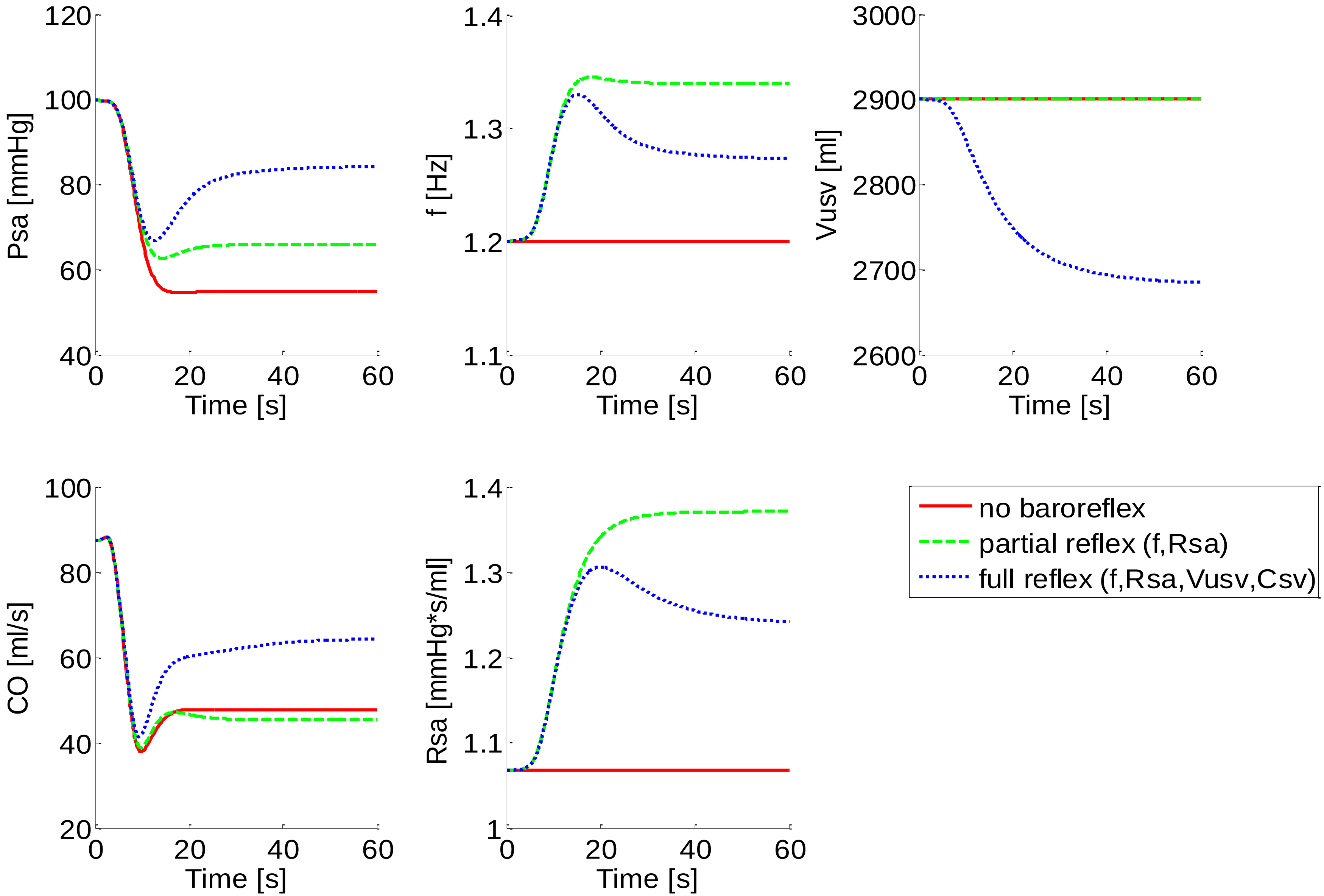
BAROREFLEX IN OPEN-LOOP SYSTEM

params.Pcs = 50;   % mmHg



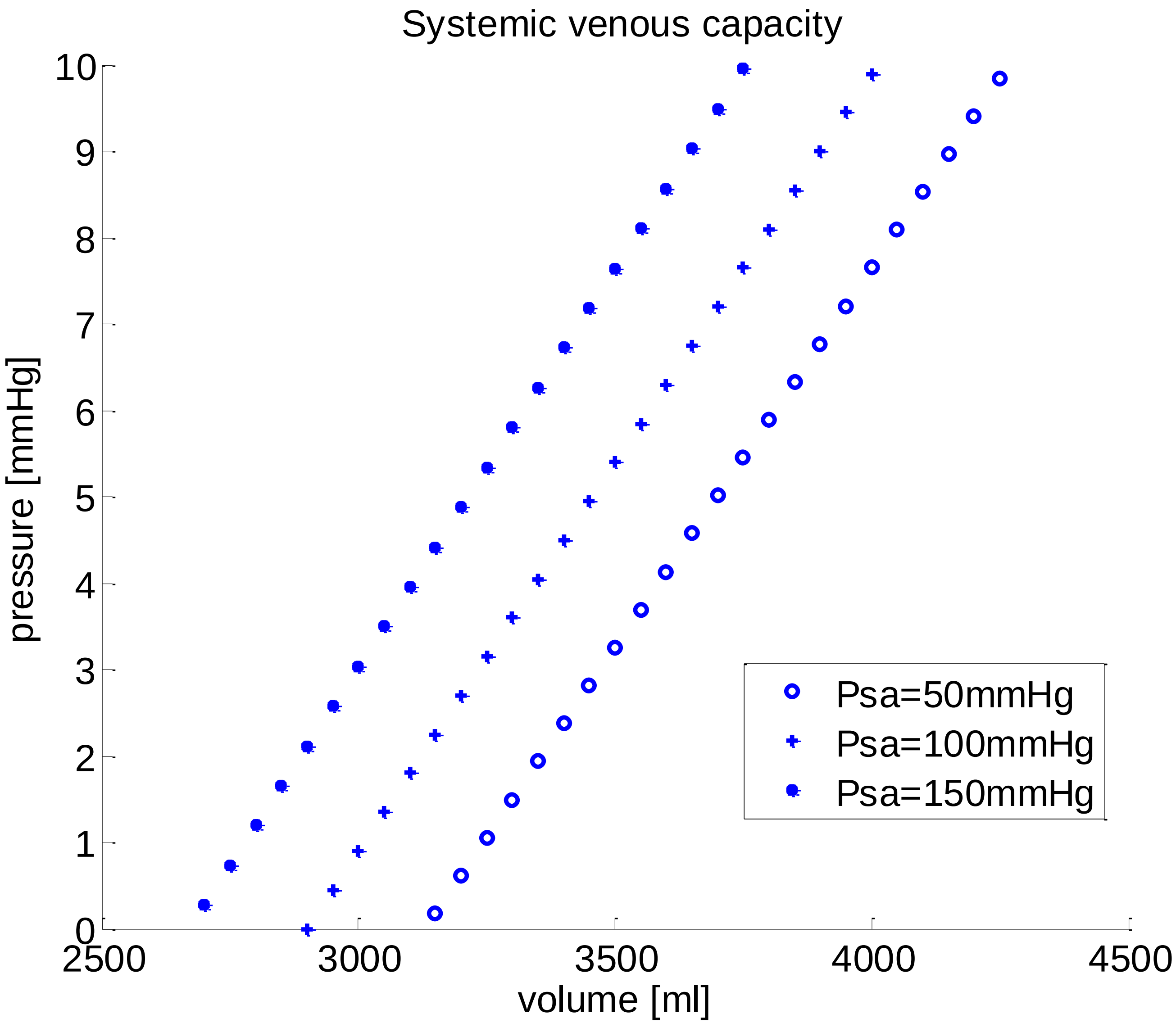
Similarly, a low pressure sensed by baroreceptors initiates baroreflex mechanisms leading to an increase in systemic arterial pressure.

HEMORRHAGE (CLOSED-LOOP SYSTEM)



Partial baroreflex (working only on heart rate and systemic resistance) is not as effective in restoring arterial pressure as full baroreflex when the mechanism controls also venous capacity.

VENOUS CAPACITY CONTROL



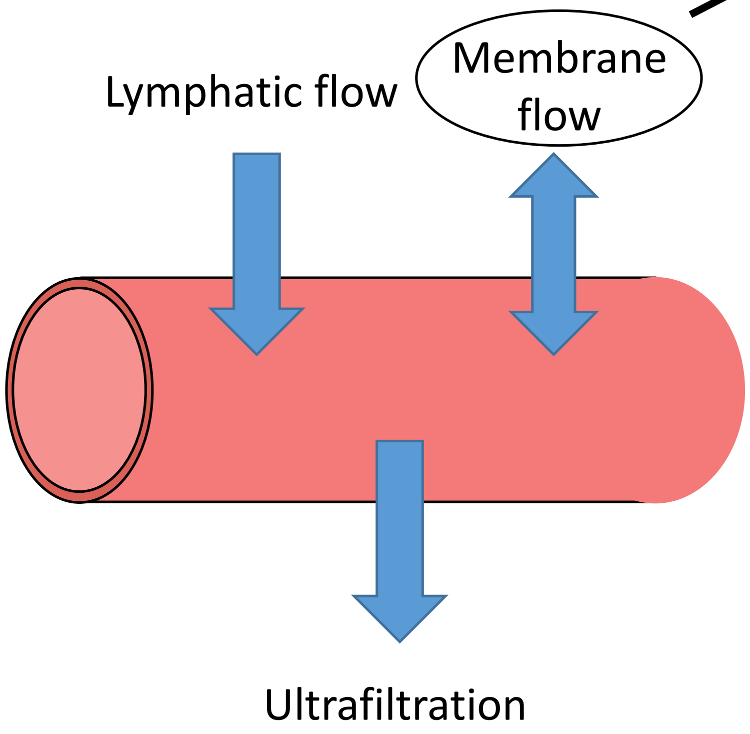
Changes in arterial pressure correspond to active changes in systemic venous capacity (a big change in venous unstressed volume and a very slight change in venous compliance).

THANK YOU

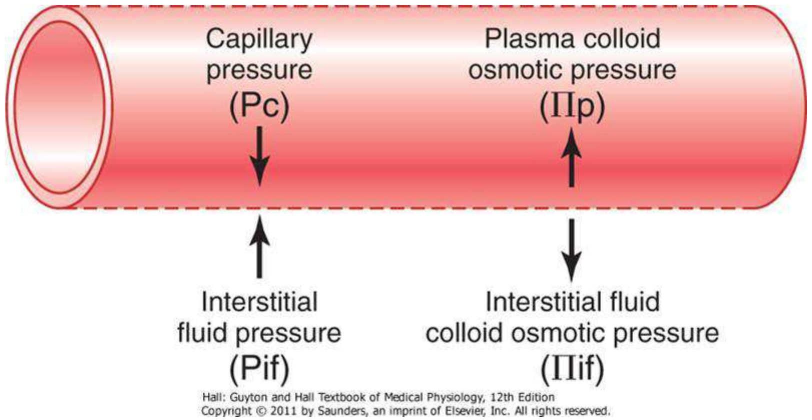
A two-pore model of protein transport through capillary membrane

Mauro Pietribiasi

Background



Starling Forces:



Starling Equation:

Filtration coefficient

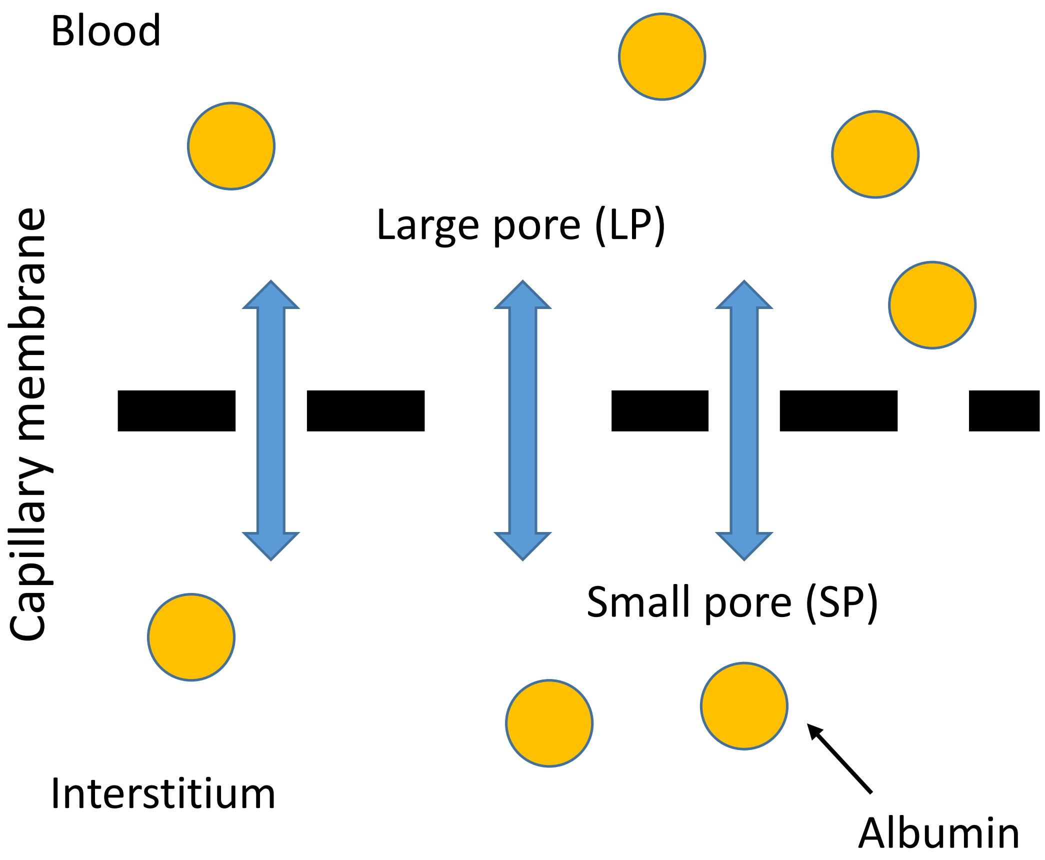
Oncotic pressure gradient

Hydraulic pressure gradient

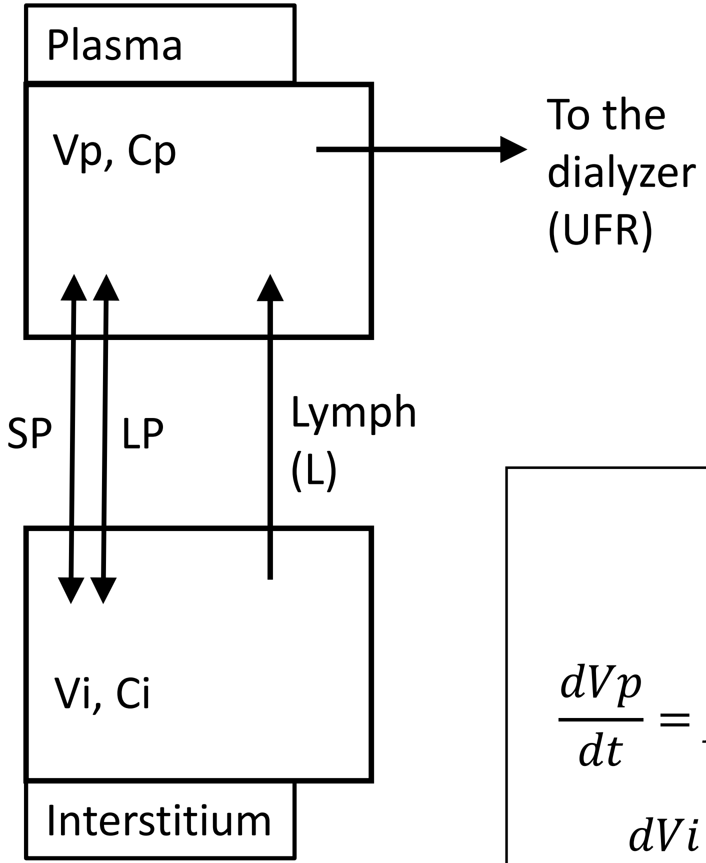
$$\frac{dV_p}{dt} = Lp * [\Delta\Pi(t) - \Delta p(t)]$$

Plasma volume variation

The model



Large pores fraction ≈ 5%
Small pores fraction ≈ 95%



V – fluid volume

C – protein concentration

Jv – solvent flow
Js – solute flow

Model equations:

$$\frac{dVp}{dt} = JvLP + JvSP + JvL \; - UFR$$

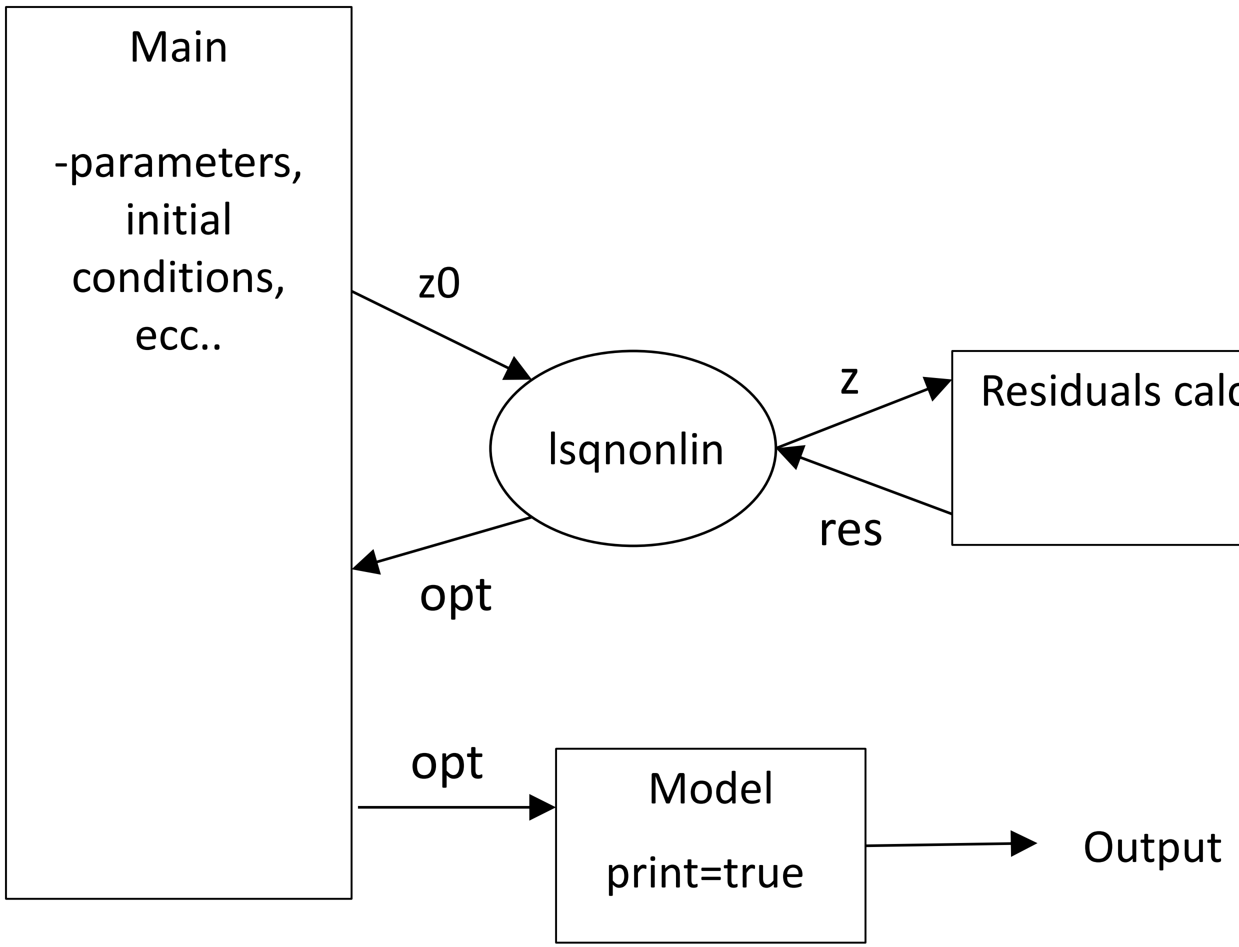
$$\frac{dVi}{dt} = -JvLP - JvSP - JvL$$

$$\frac{dCp}{dt} = JsSP + JsLP + JsD + JsL$$

$$\frac{dCi}{dt} = -\frac{dCp}{dt}$$

The code

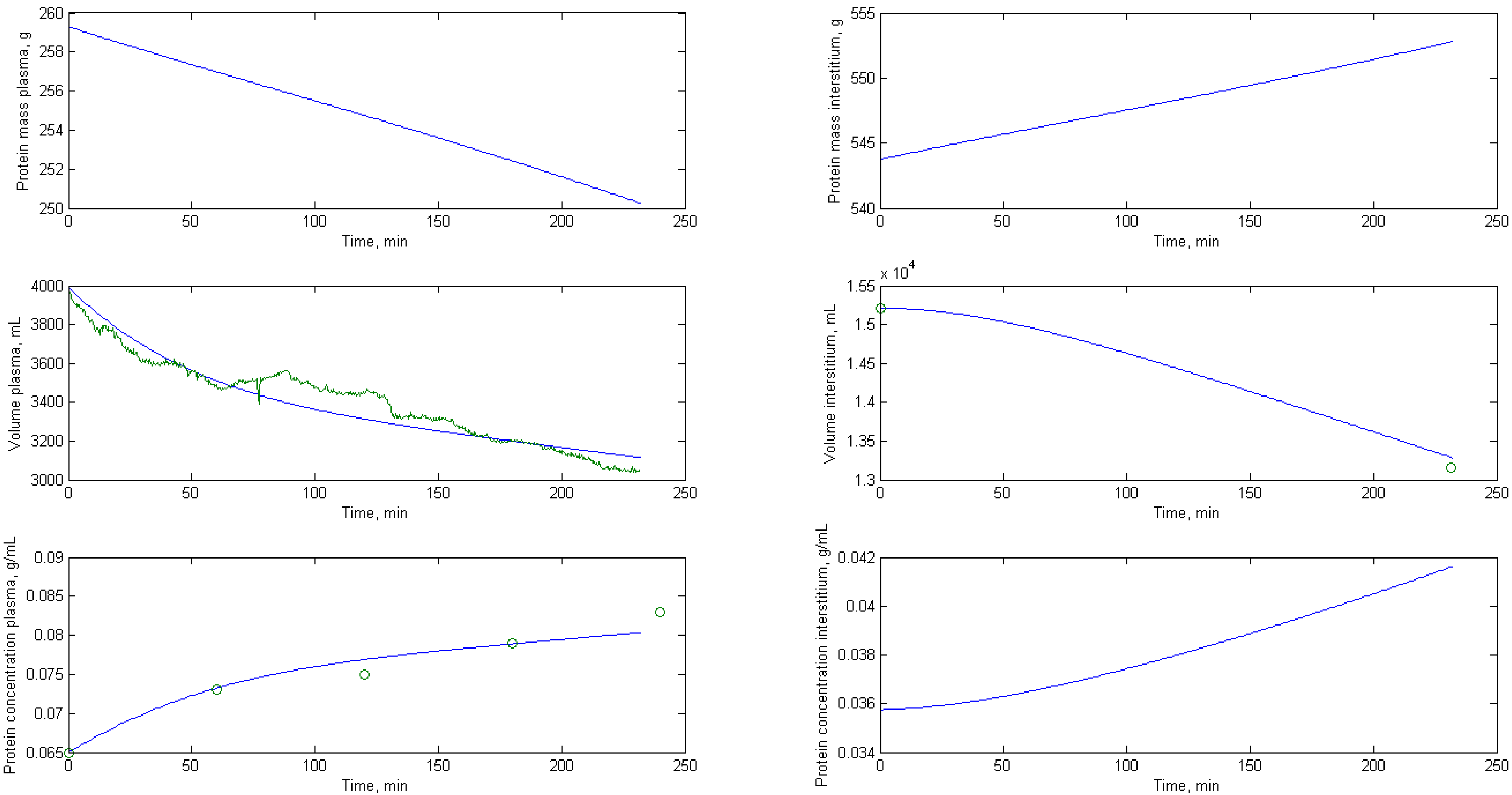
Aim: fitting the model's output to patients data of plasma volume and protein concentration. The parameters to estimate are the filtration coefficient (Lp) and the fraction of large pores (αLP).



z – optimization variables
opt – optimal parameters
sol – solution
res - residuals

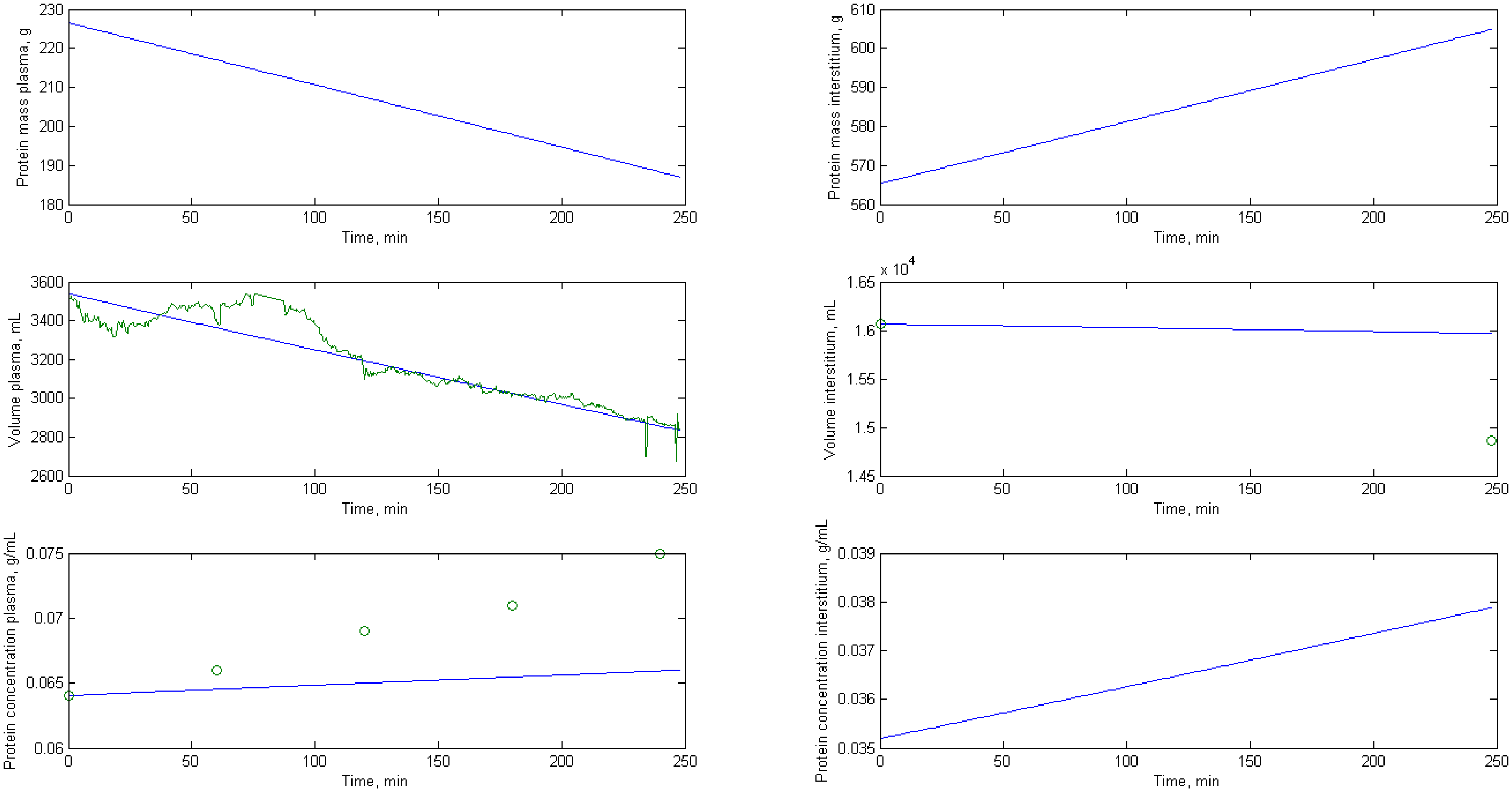
Results (good ones…)

Optimal parameters: Lp – 1.85 mL/min/mmHg, αLP – 0.05



Results (…bad ones)

Optimal parameters: Lp – 7.57 mL/min/mmHg, αLP – 0.05



Multi-parameter sensitivity analysis based on the information theoretical measure

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10 Jun 2014

Outline

Mutual Information

Entropy

The **entropy** of a random variable $X \sim g(x)$ is defined as

$$H(X) := \mathbb{E}[-\log g(x)] = \int_X -\log(g(x))g(x)dx.$$

Mutual information

Mutual information between continous variables $X \sim g(x)$ and $Y \sim f(x)$ is defined by

$$I(X;Y) := \mathbb{E}\left[\log \frac{h(x,y)}{g(x)f(y)}\right] = H(Y) + H(X) - H(X,Y)$$

where $(X,Y) \sim h(x,y)$

Sensitivity indices

Definition (sensitivity indices of first order)

Let's suppose X_i are parameters of the model and Y is model output, then **first order sensitivity measure** can be defined as

$$s_i = \frac{I(X_i;Y)}{H(Y)} = 1 - \frac{H(X_i) - H(X_i,Y)}{|H(Y)|}.$$

Definition (sensitivity indices of second order)

Analogously the **second order sensitivity measure** for pairs of parameters can be defined as

$$s_{i,j} = \frac{I(X_i,X_j;Y)}{H(Y)} = 1 - \frac{H(X_i,X_j) - H(Y,X_i,X_j)}{|H(Y)|}.$$

The procedure can be extended for any subset of parameters.

Problems

- Estimation of multidimensional entropy X and Y can have many dimensions;
- Efective estimation with no need to discretize variables;
- Entropy continous vs. discrete, continous entropy can be negative;
- Speed of convergence;
- Stability of the estimators - dependence on sample;

Nearest neighbour entropy estimator

NN Entropy Estimator

$$\widehat{H}(X) := \frac{1}{n}\sum_{i=1}^{n}[-\log \hat{p}(x_i)] + EMc$$

$$\hat{p}(x_i) = [(n-1)\cdot r_d(x_i)\cdot V_d]^{-1}$$

- $r_d(x_i)$ is the distance of point x_i to nearest neighbour in the sample in d-dimendional space
- V_d is d-dimensional volume of unit ball
- $EMc \simeq 0.5772$ is the Euler-Mascheroni constant

Convergence of estimator

$$\widehat{H}(X) \xrightarrow{a.s.} H(X)$$

Drawbacks of the nn entropy estimator

1. Does not prevent inequality $H(X, Y) \leqslant H(X) + H(Y)$
2. Slow convergence for higher dimension for some distributions eg exponential
3. Does not behave well for marginal distributions

Advantages of the nn entropy estimator

1. It is computtationaly efficient
2. Does not require large samples
3. It is easy to implement!

ODE model of p53

ODE's

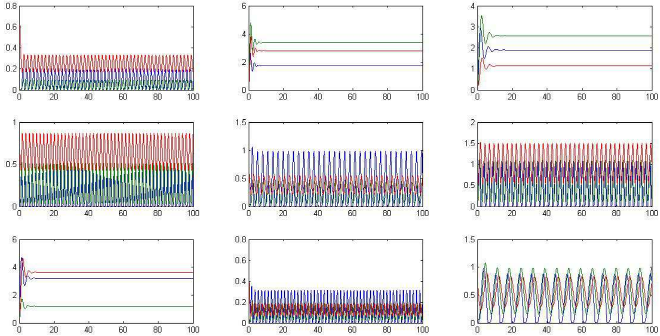
$$\dot{x} = \beta_x - \alpha_x x - \alpha_{xy} y \frac{x}{x+k}$$
$$\dot{y}_0 = \beta_y x - \alpha_0 y_0$$
$$\dot{y} = \alpha_0 y_0 - \alpha_y y$$

1. $x = 0$ - nuclear p53
2. $y = 0.8$ - nuclear Mdm2
3. $y_0 = 0.1$ - Mdm2 precursor

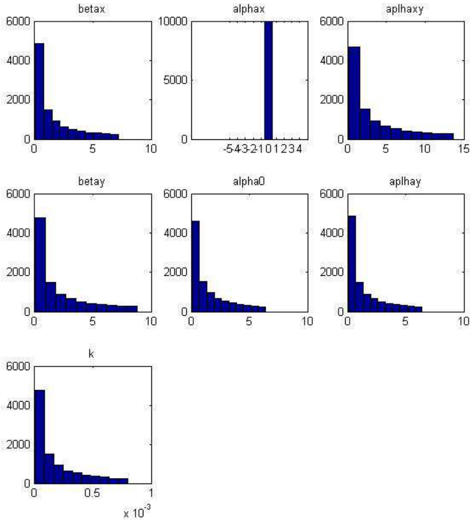
1. $\beta_x = 0.9$ - p53 production rate
2. $\alpha_x = 0$ - Mdm2-independent p53 degradation rate
3. $\alpha_{xy} = 1.7$ - Mdm2-dependent p53 degradation rate
4. $\beta_y = 1.1$ - p53-dependent Mdm2 production rate
5. $\alpha_y = 0.8$ - Mdm2 degradation rate
6. $\alpha_0 = 0.8$ - Mdm2 maturation rate
7. $k = 0.0001$ - p53 threshold for deg. by Mdm2

Posible trajectories

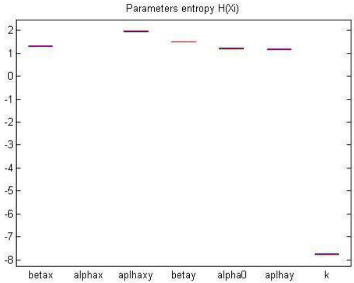
Preturbated parameters trajectories

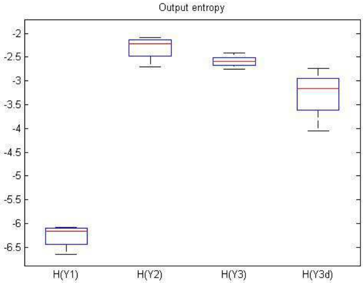


Perturbated parameters histograms

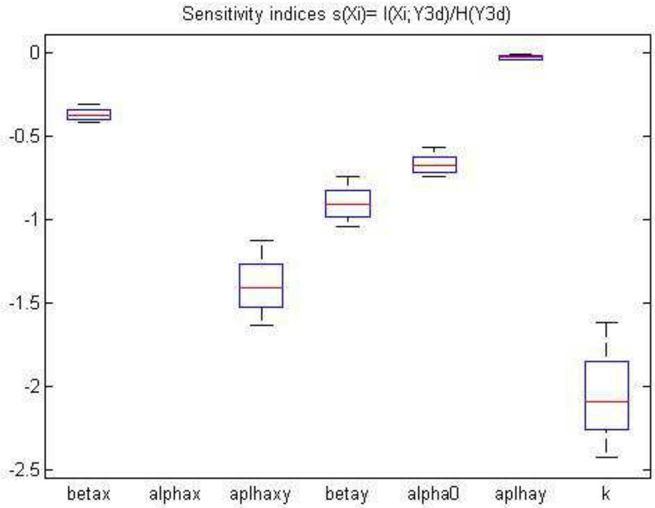


Entropy of parameters and output

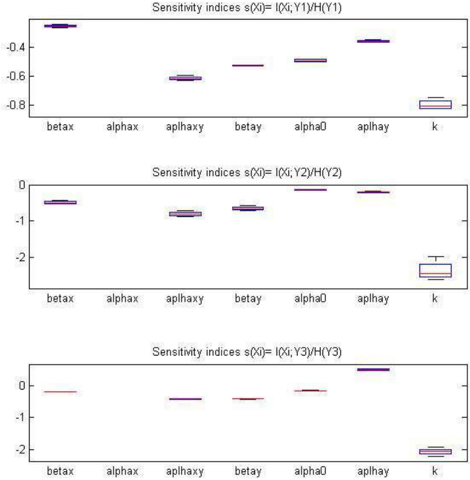




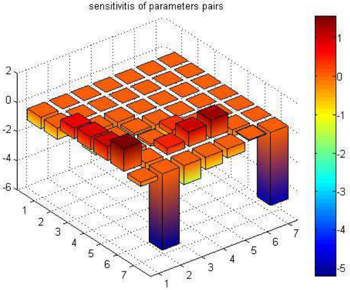
Sensitivity indices of parameters on the global output

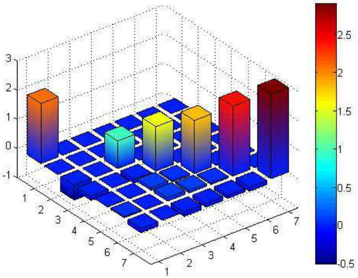


Sensitivity indices of parameters on several outputs



Sensitivity indices and interactions of pairs of parameters





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SDE for electricity prices – simulations of trajectories in Matlab and R

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10\06\2014

Form of the equation

The dynamics of the spot electricity price is driven by the SDE:

$$dS_t = \alpha(\rho(t) - \ln S_t)S_t dt + \sigma S_t dW_t + S_t(e^{J_t} - 1)dN_t,$$

where

- S_t is the electricity price,
- $\rho(t) = \frac{1}{\alpha}\left(\frac{dg(t)}{dt} + \frac{1}{2}\sigma^2\right) + g(t)$,
- $g(t)$ is a deterministic seasonality function,
- σ is a volatility,
- W_t is a Wiener process,
- $J_t = \sum_{i=1}^{N_t} Z_i$, with N_t a Poisson process of a constant intensity and Z's are i.i.d. jump magnitudes of translated mixed-exponential distribution, i.e. with density

$$f(z) = q_d \sum_{i=1}^{m} q_i \theta_i e^{\theta_i (z - m_d)} \mathbb{1}_{\{z < m_d\}} + p_u \sum_{j=1}^{n} p_j \eta_j e^{-\eta_j (z - m_u)} \mathbb{1}_{\{z > m_u\}},$$

where $q_d, p_u \geqslant 0, \;\; q_d + p_u = 1, \; q_i, p_j \in (-\infty, \infty)$,
$\sum\limits_{i=1}^{m} q_i = \sum\limits_{j=1}^{n} p_j = 1, \; \theta_i > 0, \eta_j > 1.$
q_d and p_u are the probabilities of negative and positive jumps, respectively. $m_d < 0$ is a minimal (with respect to the absolute value) value of negative jumps, $m_u > 0$ is a minimal value of positive jumps.
After decomposing the process into seasonality and noise, one obtains

$$S_t = \exp(g(t) + X_t),$$

where

$$dX_t = -\alpha X_t dt + \sigma dW_t + dJ_t.$$

X_t mean reverts to 0 with the speed α.

Discretization of the process

Integration of the SDE for X_t yields the relation

$$X_t = X_{t-1} \exp\left(\frac{-\alpha}{365}\right) + \sigma \sqrt{\frac{1 - \exp\left(\frac{-2\alpha}{365}\right)}{2\alpha}} N(0,1) + B\left(\frac{\lambda}{365}\right) Z(\mathbb{p}),$$

where

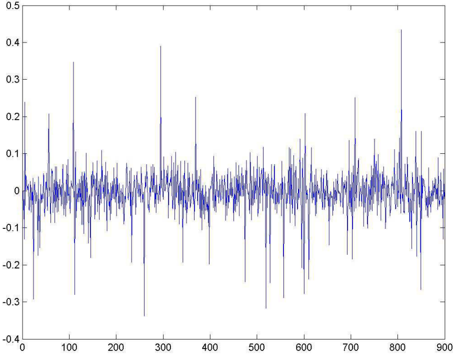
- $N(0,1)$ is a standard normally distributed variable,
- $B\left(\frac{\lambda}{365}\right)$ is a Bernoulli variable taking value 1 with the probability $\frac{\lambda}{365}$, or 0 with the probablility $1 - \frac{\lambda}{365}$; λ is an intensity of the Poisson process,
- $Z(\mathbb{p})$ is a mixed-exponentially distributed random variable with a vector of estimated parameters $\mathbb{p}$.

Results

Time needed for a generation of the trajectories depends on the chosen software. The calculations for 50 000 trajectories, each with 900 time steps, took:

- in Matlab 15 seconds,
- in R package more than 12 hours

Sample trajectory:



BLOCH SYMULATOR

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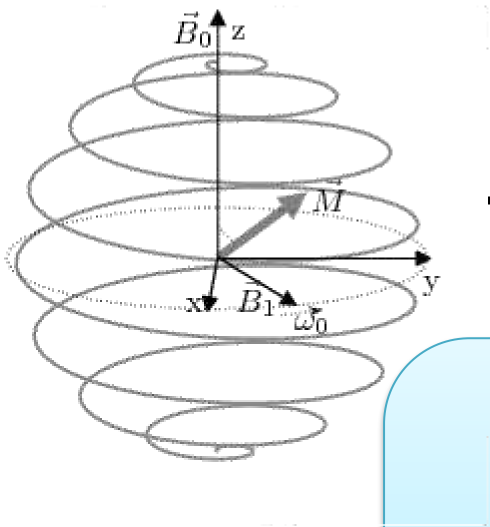
EUROPEJSKI
FUNDUSZ SPOŁECZNY

THEORY

- In physics and chemistry, specifically in nuclear magnetic resonance (NMR), magnetic resonance imaging (MRI), and electron spin resonance (ESR), the Bloch equations are a set of macroscopic equations that are used to calculate the nuclear magnetization M = (Mx, My, Mz) as a function of time when relaxation times T1 and T2 are present
- These are phenomenological equations that were introduced by Felix Bloch in 1946



BLOCH EQUATIONS

$$\frac{dM_x(t)}{dt} = \gamma(M(t) \times B(t))_x - \frac{M_x(t)}{T_2}$$

$$\frac{dM_y(t)}{dt} = \gamma(M(t) \times B(t))_y - \frac{M_y(t)}{T_2}$$

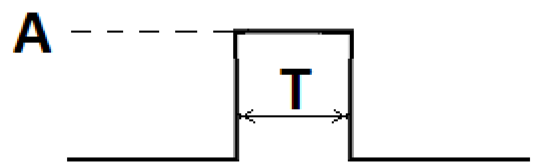
$$\frac{dM_z(t)}{dt} = \gamma(M(t) \times B(t))_z - \frac{M_z(t) - M_0}{T_1}$$

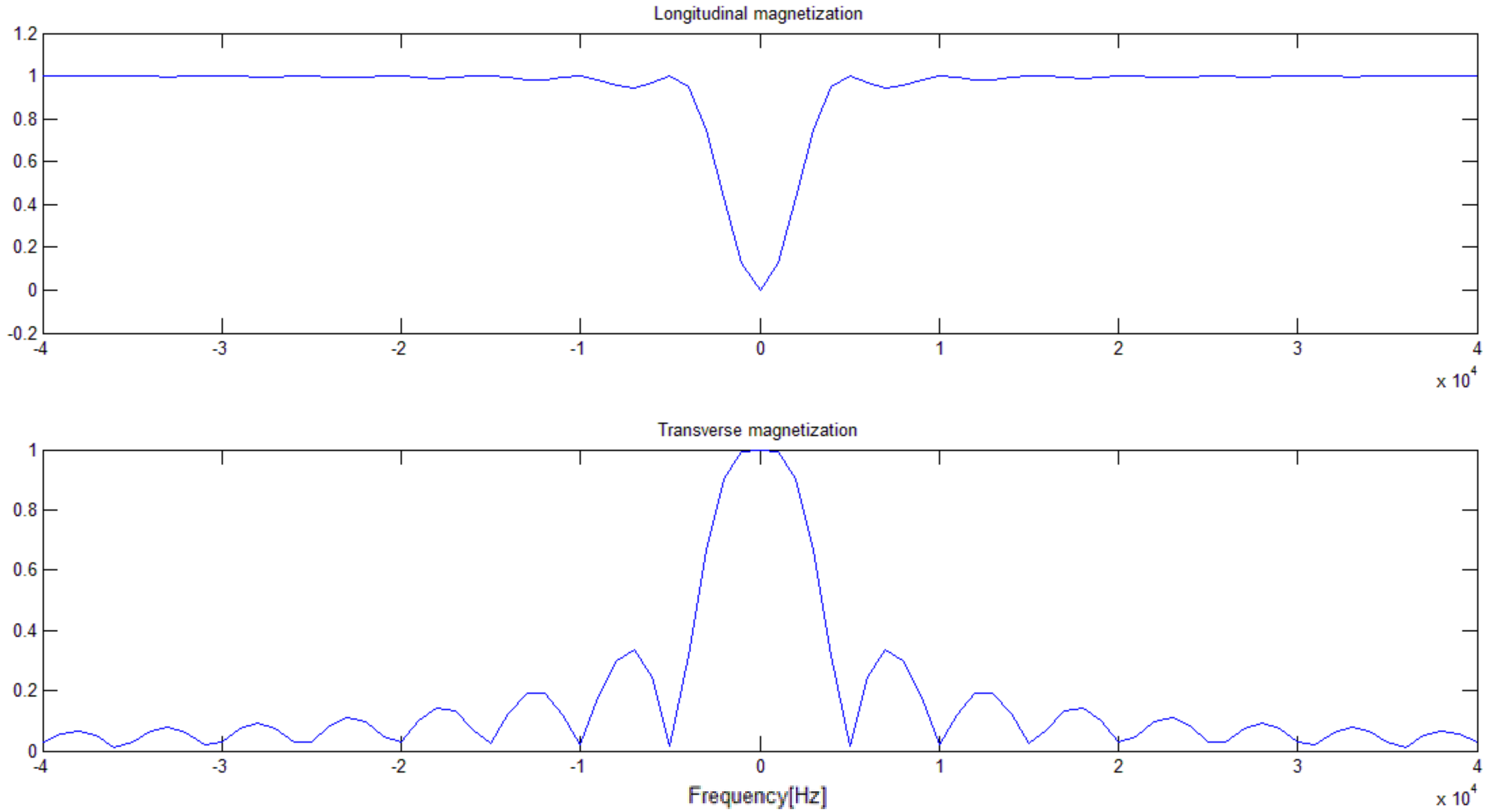
M(t) = ($M_x(t)$, $M_y(t)$, $M_z(t)$) – nuclear magnetization
γ - gyromagnetic ratio
B(t) = (Bx(t), By(t), B0 + ΔBz(t)) - magnetic field experienced by the nuclei
T_1,T_2 – relaxation times

INPUT SIGNALS

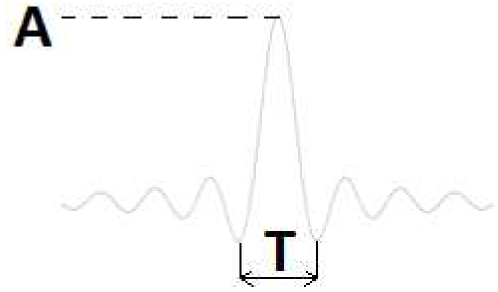
- Rectangular
- SINC
- Adiabatic pulse
- SSFP – Steady State Free Procession

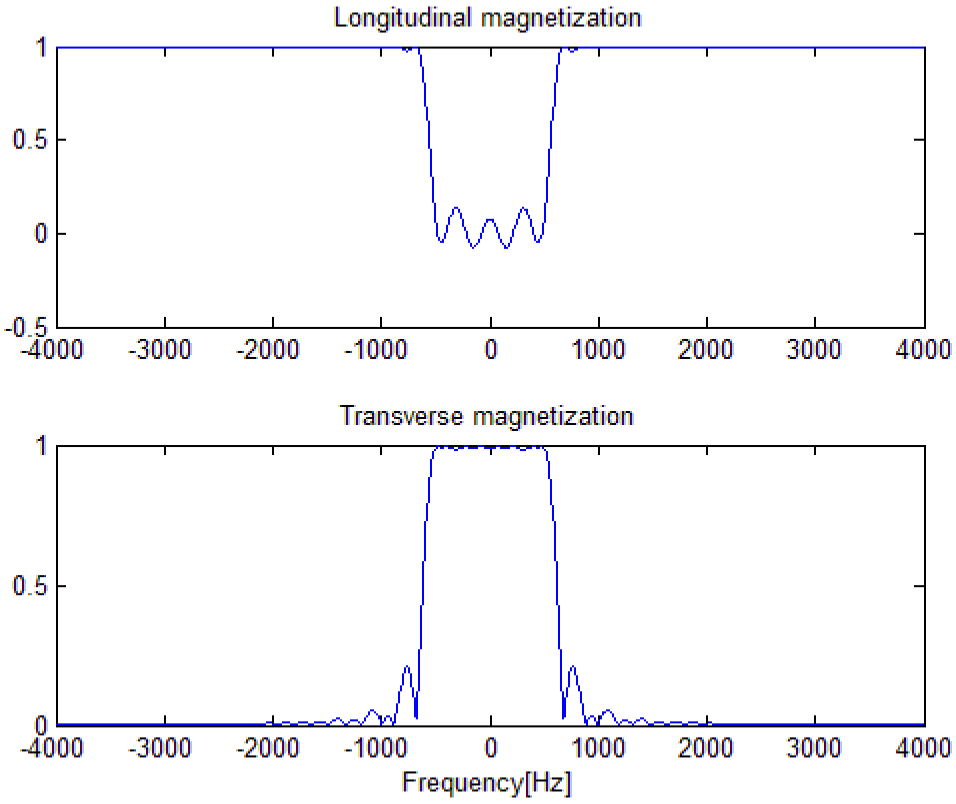
RESULTS: RECTANGLE SIGNAL



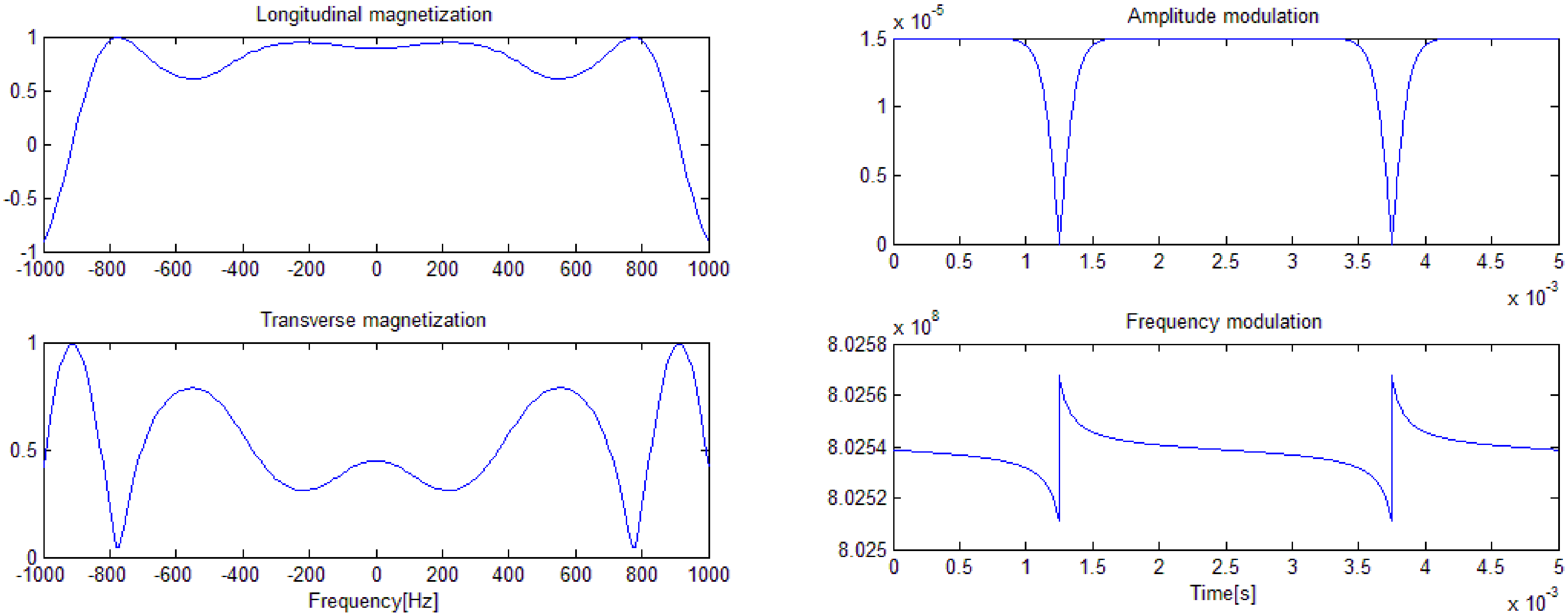


RESULTS: SINC SIGNAL

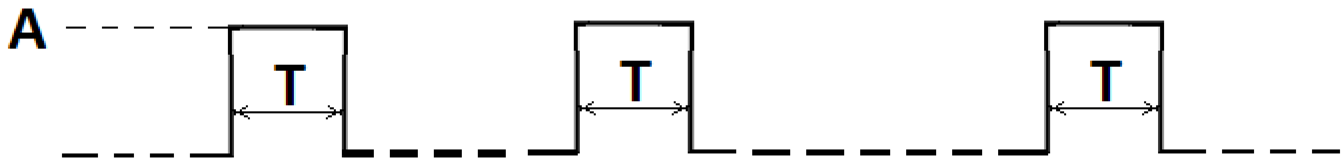


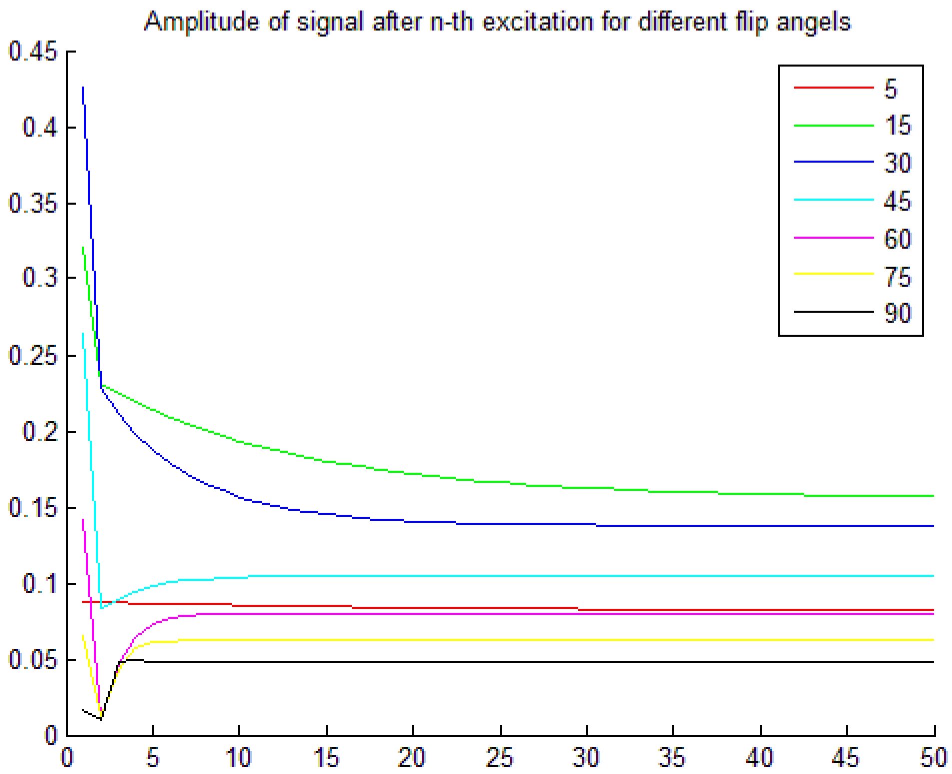


RESULTS: ADIABATIC PULSE



RESULTS: SSFP





CONCLUSSIONS

- Preliminary results for different input signals were presented
- Future works should be focused on addition noise to our model

Thank you for your attention

SCRIPT

```
function [Mt Ml] = bloch (grad, omega, amp, T, params)
   Mt = zeros(length(params.omegaf),length(params.zrange));
   Ml = zeros(length(params.omegaf),length(params.zrange));
   k=1; l=1;
   opt = odeset('RelTol',1e-5,'AbsTol',1e-6);
   for omega0 = params.omegaf
      k=1;
      for z = params.zrange
         sol = ode45(@model, [0 T],params.x0,opt);
         Mt(l,k) = sqrt(sol.y(1,end).^2+sol.y(2,end).^2);
         Ml(l,k) = sol.y(3,end);
         k = k+1;
      end
      l = l+1;
   end
```

```
function dM=model(t,M)
        dM=zeros(3,1);
        B1 = feval(amp,t);
        omegarf = feval(omega,t);
        B0eff = params.B0 + z*feval(grad,t);
        dM(1) = M(2)*(B0eff*params.gyro+omega0-omegarf) - M(1)/params.T2;
        dM(2) =-M(1)*(B0eff*params.gyro+omega0-omegarf) + params.gyro*M(3)*B1-M(2)/params.T2;
        dM(3) =-params.gyro*M(2)*B1 - (M(3)-1)/params.T1;
    end
end
```