PRINCIPLES OF MATHEMATICAL MODELLING

# 3. MODEL OF BIOREACTOR

# 3.1.Growth model with nutrition restriction

In the case of no restriction on nutritions, growth is described by

$$P' = b\,P$$

When nutrition is restricted (there is no renewal of nutrition)

$\rightarrow$ increase of population, decrease of nutrition amount (decrease of availability)

$\rightarrow$ decrease of growth rate

Anotate

- $S(t)$ - nutrition concentration
- $P(t)$ - population concentration

Remark.

- volume $\cdot\, S(t)$ - total amount of nutrition
- $N(t) =$ volume $\cdot\, P(t)$ - total population size

Growth rate ($b$) depends on $S \quad \rightarrow \quad b(S)$

# Assumptions on $b(S)$

- $S = 0$ - no nutrition $\rightarrow$ no growth
  $\rightarrow$ $b(0) = 0$
- Nutrition amount is unrestricted - $S = \infty$ $\rightarrow$ exponential growth
  $\rightarrow$ $b(\infty) = V$

Simplest function $b$ satisfying

$$b(0) = 0 \quad \text{i} \quad b(\infty) = V$$

is

$$b(S) = V\frac{S}{K+S}$$

# Jacques Monod

- 1910, Paris, France – 1976.,Cannes, France
- 1965. Nobel Prize in Physiology or Medicine
- One of founders of molecular biology
- J. Monod (1949). The growth of bacterial cultures, Ann. Rev. Microbiol., 3, 371—393

- Studied growth rate for bacterial cultures of Escherichia Coli K12.
- Dependence of growth rate on nutrition concentration (glucose)
- Growth rate is constant when concentration of glucose ($S$) is constant: $P' = b(S)\,P$.
- Experimentally determined specific growth rate for fixed glucose concentrations

Experimentally determined relation between specific growth rate and nutrition concentration:

$$b(S) = V\frac{S}{K+S}$$

- Monod function
- $V$ - maximal specific growth rate
- $K$ - half-saturation constant = nutrition concentration when specific growth rate equals to half of maximal specific growth rate

Now, population growth rate is given by

$$P'(t) = V\frac{S(t)}{K+S(t)}P(t)$$

Mass conservation: total mass of a szstem is constant

$\rightarrow$ Whole nutrition transforms into biomass.

- Population mass = volume $\cdot\, P(t) \cdot m_P$
  ($m_P$ mass of one cell)
- Nutrition mass = volume $\cdot\, S(t) \cdot m_S$
  ($m_S$ unit mass for nutrition)

$$\text{volume} \cdot P(t) \cdot m_P + \text{volume} \cdot S(t) \cdot m_S = \text{const}$$

Define $Y = \dfrac{m_S}{m_P}$

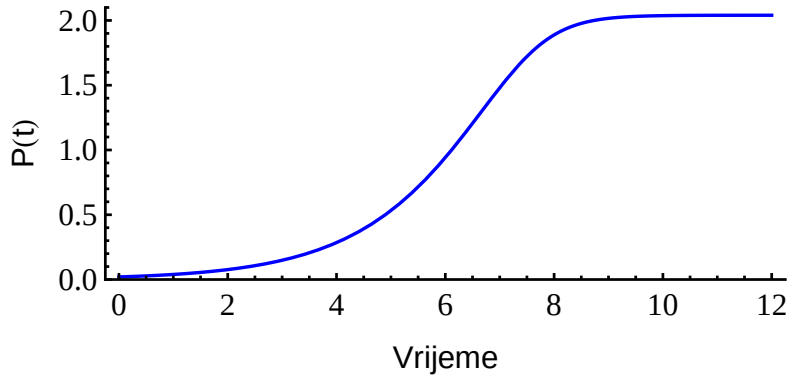
$$Y\,S(t) + P(t) = \text{const} \quad \Leftrightarrow \quad \frac{d}{dt}[Y\,S(t) + P(t)] = 0$$

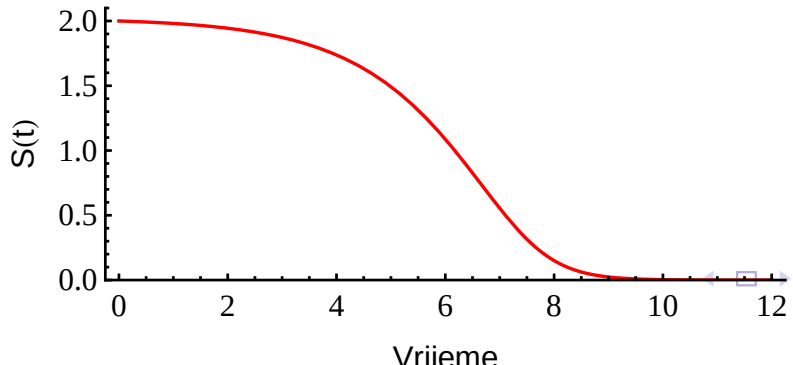
$$\Rightarrow S'(t) = -\frac{P'(t)}{Y} = -V\frac{S(t)}{K + S(t)}\frac{P(t)}{Y}$$

# Monod model

$$P'(t) = V\frac{S(t)}{K+S(t)}P(t)$$

$$S'(t) = -V\frac{S(t)}{K+S(t)}\frac{P(t)}{Y}$$



From

$$Y\,S + P = C$$

it follows

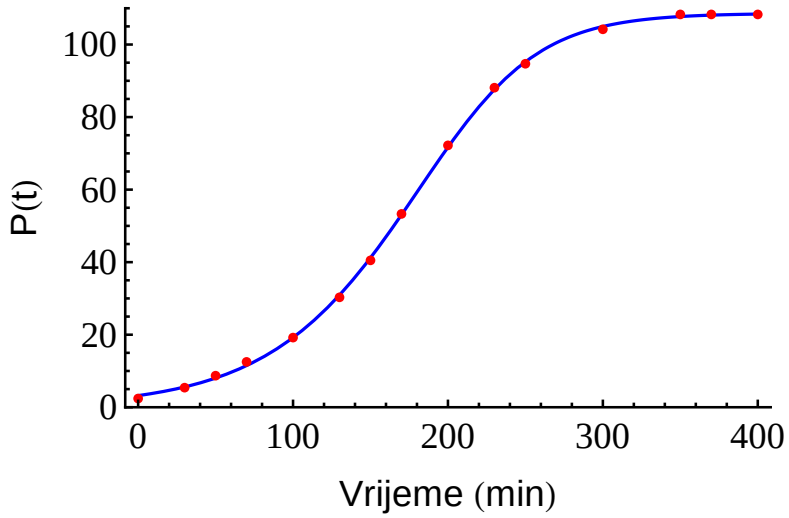
$$S = \frac{1}{Y}(C - P)$$

$$\begin{aligned} P' &= V\frac{S}{K+S}P \\ &= \frac{V}{Y}\frac{C-P}{K+\frac{1}{Y}(C-P)}P \\ &= \frac{V(C-P)}{K\,Y+C-P}P \end{aligned}$$

$$P' = \frac{V(C-P)}{K\,Y+C-P}P$$

Model describes experimental data well.

Data for E. coli growth



# Phase portrait of the system.

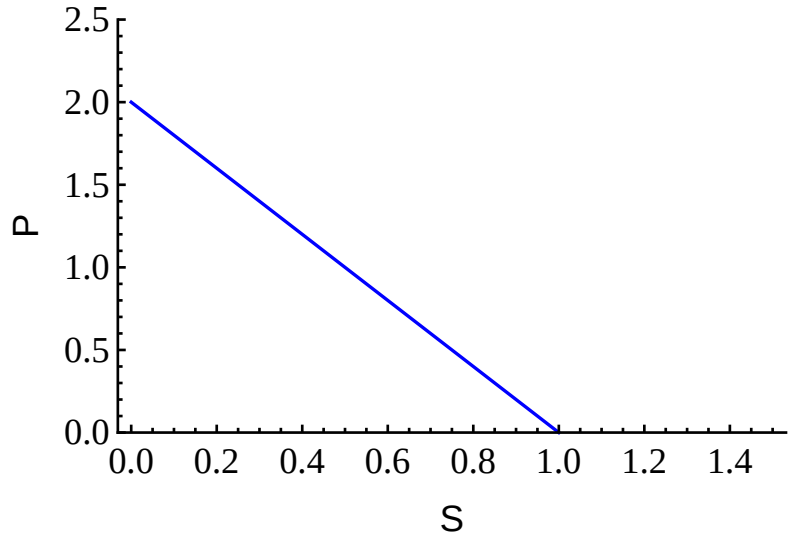
- Parametric graph $\{(S(t), P(t)) | t \geq 0\}$

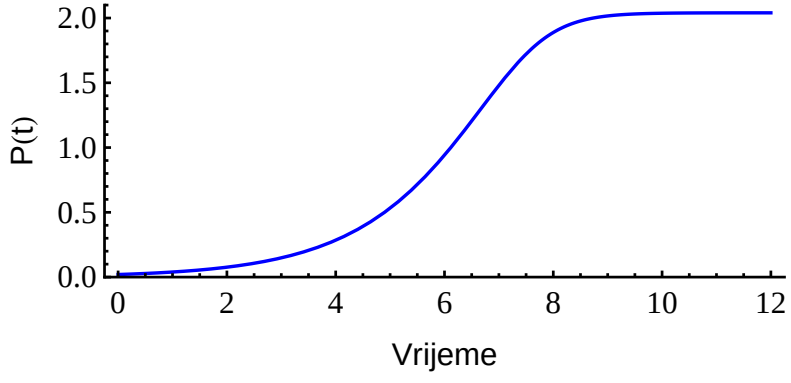
Monod model:

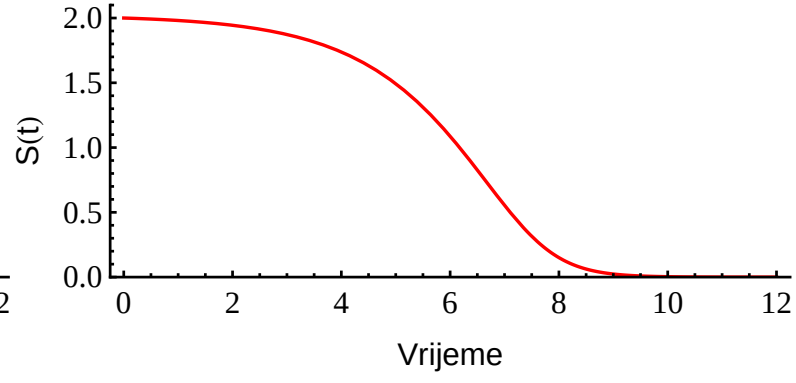
$$P + Y\,S = C$$

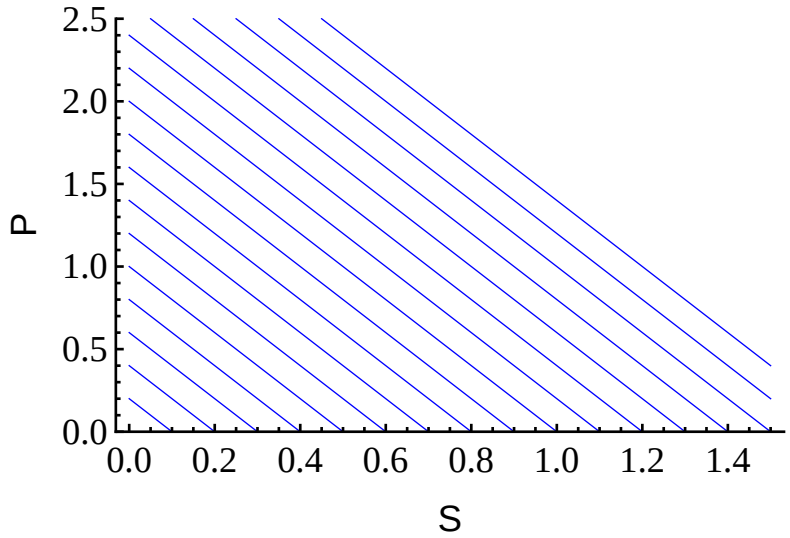
Linear relation.

$C$ is defined by initial conditions: $C = P(0) + Y\,S(0) = P_0 + Y\,S_0$

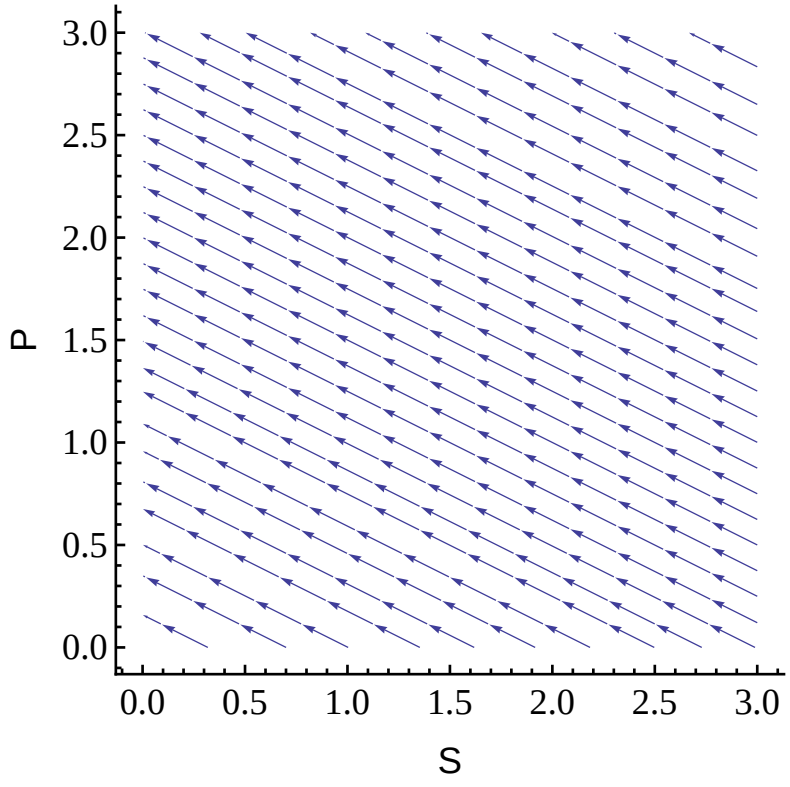

2.5
2.0
1.5
1.0
0.5
0.0
P
0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4
S


2.0
1.5
1.0
0.5
0.0
P(t)
0 2 4 6 8 10 12
Vrijeme


2.0
1.5
1.0
0.5
0.0
S(t)
0 2 4 6 8 10 12
Vrijeme


2.5
2.0
1.5
1.0
0.5
0.0
P
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
S

# Phase portrait for Monod model



# 3.2.Growth and quiescence

When nutrition is consumed, cells may go to the quiescence stage.

Here they can be for a long time.

Introduce another cell population (quiescent cells), $Q$:

- $S$ - concentration (limited) of nutrition
- $P$ - proliferating cells population (concentration)
- $Q$ - quiescent cells population (concentration)

We start from the previous model:

$$\begin{aligned} S' &= -V\frac{S}{K+S}\frac{P}{Y} \\ P' &= V\frac{S}{K+S}P - Q' \\ Q' &= ? \end{aligned}$$

**Remark.**
Quiescent cells do not consume nutrition. $\rightarrow$ $S'$ does not depend on $Q$

Assumptions:

- Transfer rate from $P \to Q$ is proportional to $P$
- Transfer rate from $Q \to P$ is proportional to $Q$
- Both depend on $S$ (nutrition concentration):

$$Q' = \alpha(S)P - \beta(S)Q$$

Choice of functions $\alpha(S)$ and $\beta(S)$:

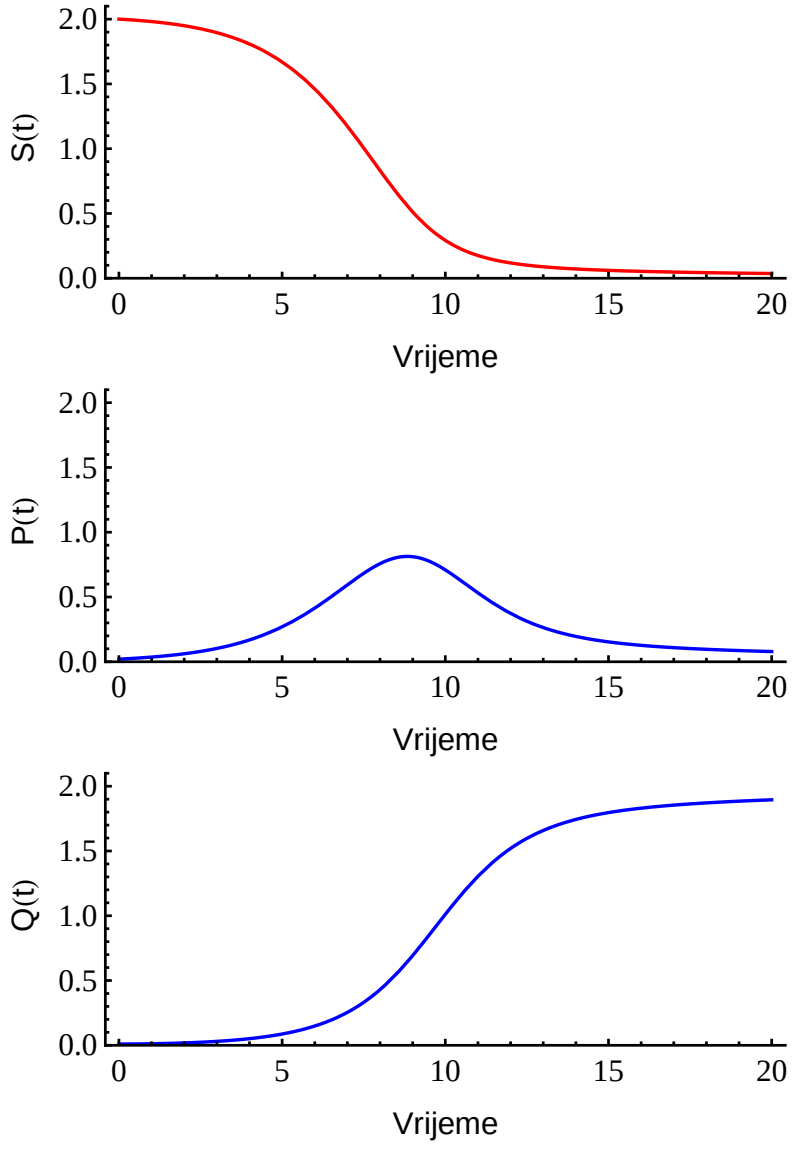
- Sufficient concentration of nutrition ($S$ large)
  $\to \quad \alpha(S) \approx 0$ i $\beta(S) > 0$
- No nutrition ($S \approx 0$)
  $\to \quad \alpha(S) > 0$ i $\beta(S) \approx 0$
- $\alpha(0) > 0, \quad \alpha(\infty) = 0$ i
  $\beta(0) = 0, \quad \beta(\infty) > 0 \quad \to$

$$\alpha(S) = \frac{1}{1+S} \quad \text{i} \quad \beta(S) = \frac{S}{1+S}$$

Model:

$$\begin{aligned} S' &= -V\frac{S}{K+S}\frac{P}{Y} \\ P' &= V\frac{S}{K+S}P - \alpha(S)P + \beta(S)Q \\ Q' &= \alpha(S)P - \beta(S)Q \end{aligned}$$

**Remark.** If we model death instead of quiescence.
There is no transfer $Q \to P$, $\beta \equiv 0$

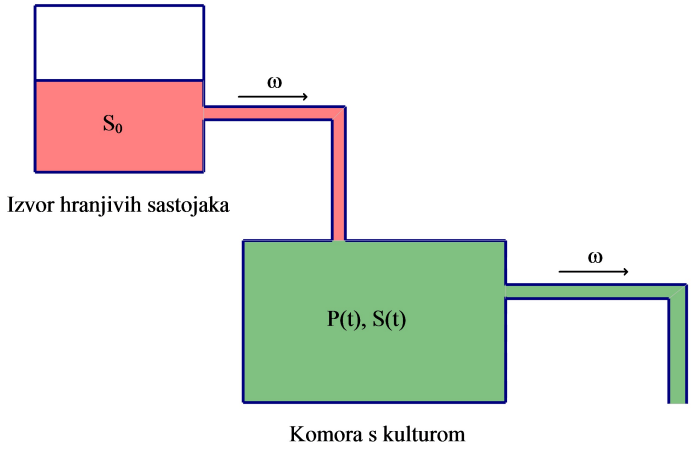

S(t)
2.0
1.5
1.0
0.5
0.0
0
5
10
15
20
Vrijeme
P(t)
2.0
1.5
1.0
0.5
0.0
0
5
10
15
20
Vrijeme
Q(t)
2.0
1.5
1.0
0.5
0.0
0
5
10
15
20
Vrijeme

# 3.3. Chemostat model

Monod model - growth in closed system.

No nutrition inflow or removal of the part of population.

It is possible to grow cell culture in fixed volume where nutrition is constantly regenerated by the flow of media.




- In the chamber (in media) are cells and nutrition (substrat)
- They are idealy mixed (cell concentration and nutrition concentration in chamber are uniform)
- Substrat by constant flow inflows into the chamber
- Content of the chamber outflows by the same speed (keeping a volume constant).
- $\omega$ - washout rate = flow speed (volume/time) / chamber volume

- Such bioreactor is named **chemostat** ( **Chem***ical environment is* **stat***ic*)
- or **CSTR** ( *continuosly stirred tank reactor*)
- Inflow of nutrition/substrat may be regulated
- Temperature, oxygen concetration may be also regulated, . . .
- Several populations may be grown in the same time (in different interactions)
- biological model for complex ecosystems

# Derivation of the model

## Change of substrat concentration:

$Q'$ = inflow from the tank - consumption by population - wash out

## Change of population concentration:

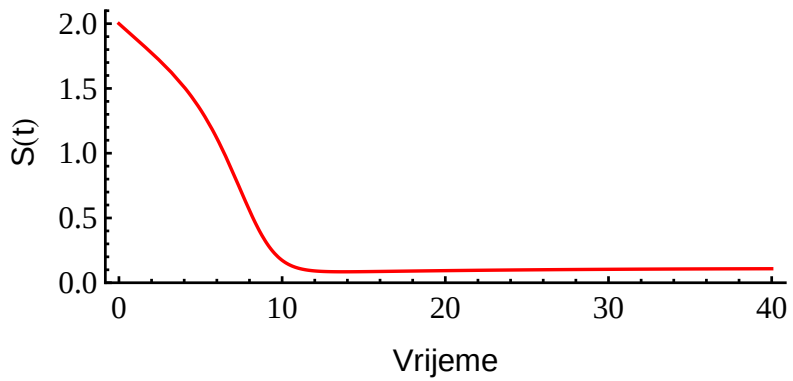
$P'$ = division - wash out

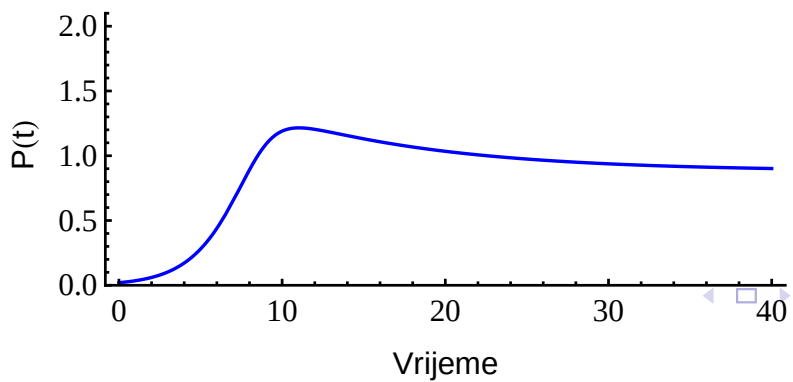
- speed of division: $V\frac{S}{K+S}P$ (Monoda function)
- speed of substrat consumption: $V\frac{S}{K+S}\frac{P}{Y}$
- speed of substrat inflow: $\omega S_0$
  - Total inflow (speed): $\omega\nu$ ($\nu$ - volumen komore)
  - Total substrat inflow: $\omega\nu S_0$
  - Increase of substrat concentration: $\omega\nu S_0/\nu = \omega S_0$
- Total outflow (speed):: $\omega\nu$ (= ukupan dotok)
  - Outflow - population: $\omega P(t)$
  - Outflow - substrat: $\omega S(t)$

# Chemostat model.

$$S' = -V\frac{S}{K+S}\frac{P}{Y} + \omega S_0 - \omega S$$

$$P' = V\frac{S}{K+S}P - \omega P$$



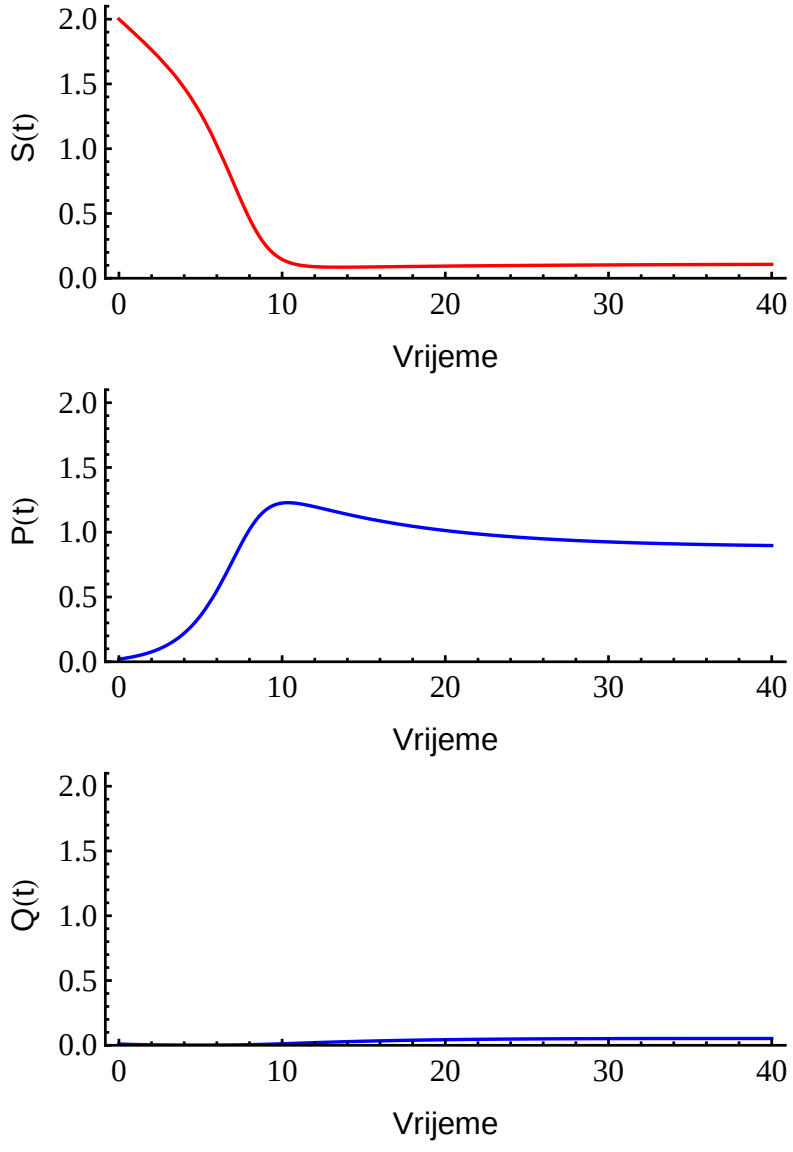



# Biofilm.

- Tijekom rasta u komori stanice se mogu početi lijepiti za stijenku komore.
- $\rightarrow$ Biofilm.
- Sada se u komori nalaze
  - stanice koje slobodno plutaju u mediju ($P$)
  - stanice priljepljene za zid komore ($Q$)
- Stanice priljepljene za zid komore
  - imaju drugačiju potrošnju hranjivih sastojaka (manja dostupnost) $\rightarrow$ manja specifična brzina rasta
  - ne istječu s medijem iz komore
- Stanice se priljepljuju za stijenku komore brzinom $\alpha = \alpha(S)$ (prijelaz iz populacije $P$ u populaciju $Q$)
- Uslijed protoka medija, stanice se odljepljuju od stijenke komore brzinom $\beta = \beta(S)$ (prijelaz iz populacije $Q$ u populaciju $P$)

Model:

$$
\begin{aligned}
S' &= -\frac{V\,S}{K+S}\frac{P}{Y} - \frac{V_Q\,S}{K_Q+S}\frac{P}{Y} - \omega\,(S-S_0)\,S \\
P' &= V\frac{S}{K+S}\,P - \omega\,P - \alpha(S)\,P + \beta(S)\,Q \\
Q' &= \frac{V_Q\,S}{K_Q+S}\,P + \alpha(S)\,P - \beta(S)\,Q
\end{aligned}
$$


S(t)
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
Vrijeme
P(t)
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
Vrijeme
Q(t)
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
Vrijeme

# Hranidbeni lanac.
# Rast s ograničenim hranjivim sastojcima

- U posudi su tri vrste mikroba ($P_1, P_2, P_3$).
- Populacija $P_1$ konzumira supstrat $S_1$ koji koji se nalazi u posudi.
- $P_1$ proizvodi supstrat $S_2$ za populaciju $P_2$
- $P_2$ proizvodi supstrat $S_3$ za populaciju $P_3$
- $S_1 \rightarrow P_1 \rightarrow S_2 \rightarrow P_2 \rightarrow S_3 \rightarrow P_3$
- Populacija $P_1$ supstrat $S_2$ proizvodi brzinom $m_2$
- Populacija $P_2$ supstrat $S_3$ proizvodi brzinom $m_3$

Krenut ćemo od Monodovog nodela.

Pretpostavljamo da sve stanice proizvode suptrat.

Izvedimo jednadžbu za populaciju $P_1$. Rast populacije je opisan s:

$$P_1' = \frac{V_1\, S_1}{K_1 + S_1}\, P_1$$

Proizvodnja supstrata: $m_2\, P_1$.

Promjena supstrata $S_1$:

$$S_1' = -\frac{V_1\, S_1}{K_1 + S_1}\frac{P_1}{Y_1} - \frac{m_2}{Y_1} P_1$$

Jednadžbe:

$$\begin{aligned} P_1' &= \frac{V_1\, S_1}{K_1 + S_1}\, P_1 \\ S_1' &= -\frac{V_1\, S_1}{K_1 + S_1}\frac{P_1}{Y_1} - \frac{m_2}{Y_1} P_1 \end{aligned}$$

Druga populacija analogno.
Povećanje koncentracije supstrata: $m_2\, P_1$.

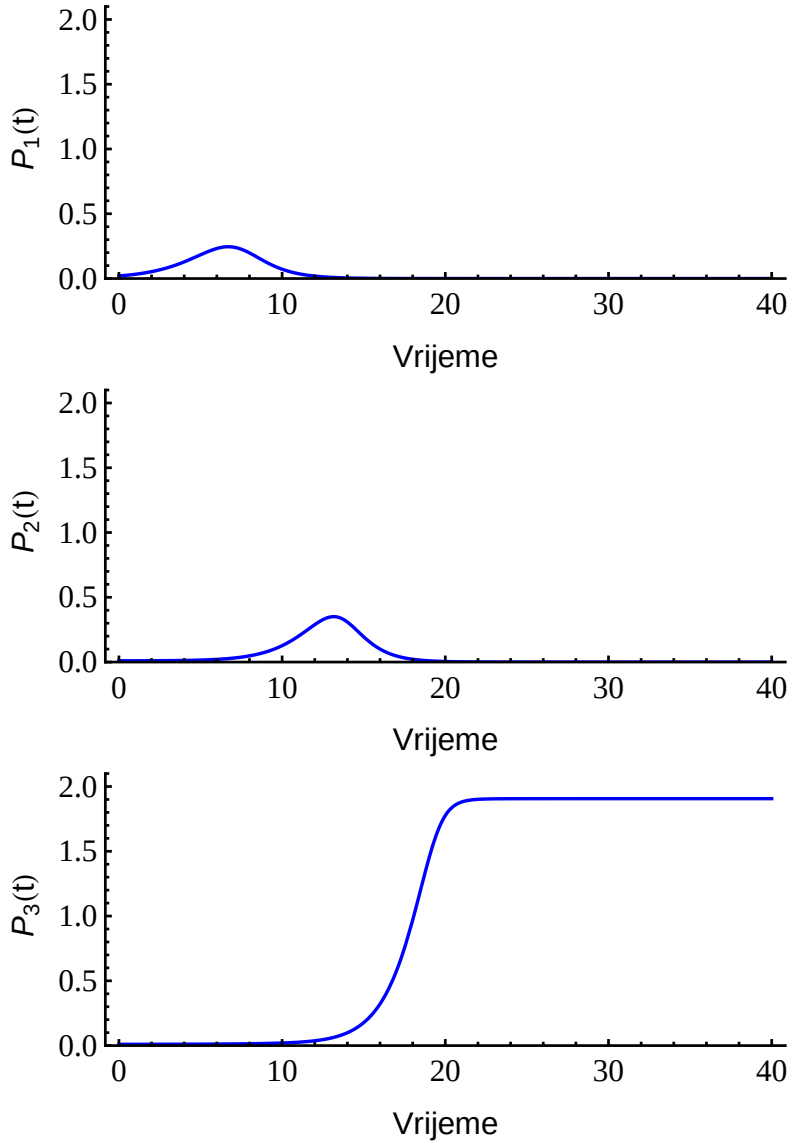
$$\begin{aligned} P_2' &= \frac{V_2\, S_2}{K_2 + S_2}\, P_2 \\ S_2' &= m_2\, P_1 - \frac{V_2\, S_2}{K_2 + S_2}\, \frac{P_2}{Y_2} - \frac{m_3}{Y_2}\, P_2 \end{aligned}$$

Isto i za populaciju $P_3$, jedino što nema proizvodnje supstrata:

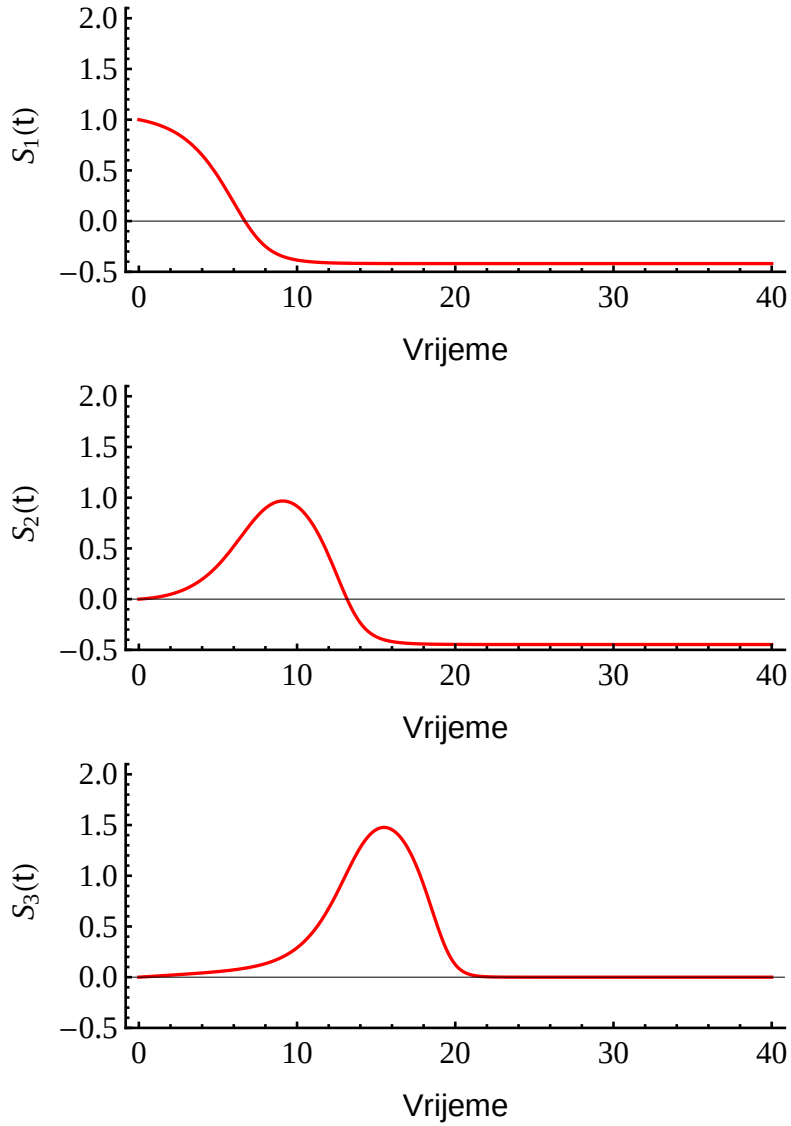
$$\begin{aligned} P_3' &= \frac{V_3\, S_3}{K_3 + S_3}\, P_3 \\ S_3' &= m_3\, P_2 - \frac{V_3\, S_3}{K_3 + S_3}\, \frac{P_3}{Y_3} \end{aligned}$$

Model:

$$
\begin{aligned}
S_1' &= -\frac{V_1\, S_1}{K_1 + S_1}\frac{P_1}{Y_1} - \frac{m_2}{Y_1}P_1 \\
P_1' &= \frac{V_1\, S_1}{K_1 + S_1}\, P_1 \\
S_2' &= m_2\, P_1 - \frac{V_2\, S_2}{K_2 + S_2}\frac{P_2}{Y_2} - \frac{m_3}{Y_2}P_2 \\
P_2' &= \frac{V_2\, S_2}{K_2 + S_2}\, P_2 \\
S_3' &= m_3\, P_2 - \frac{V_3\, S_3}{K_3 + S_3}\frac{P_3}{Y_3} \\
P_3' &= \frac{V_3\, S_3}{K_3 + S_3}\, P_3
\end{aligned}
$$




**Populacija se smanjuje!**




**Negativne koncentracije supstrata!**

Stanice proizvode supstrat i kada više nemaju svojih hranjivih sastojaka!

Treba koristiti model s uključenim stanicama u mirovanju.

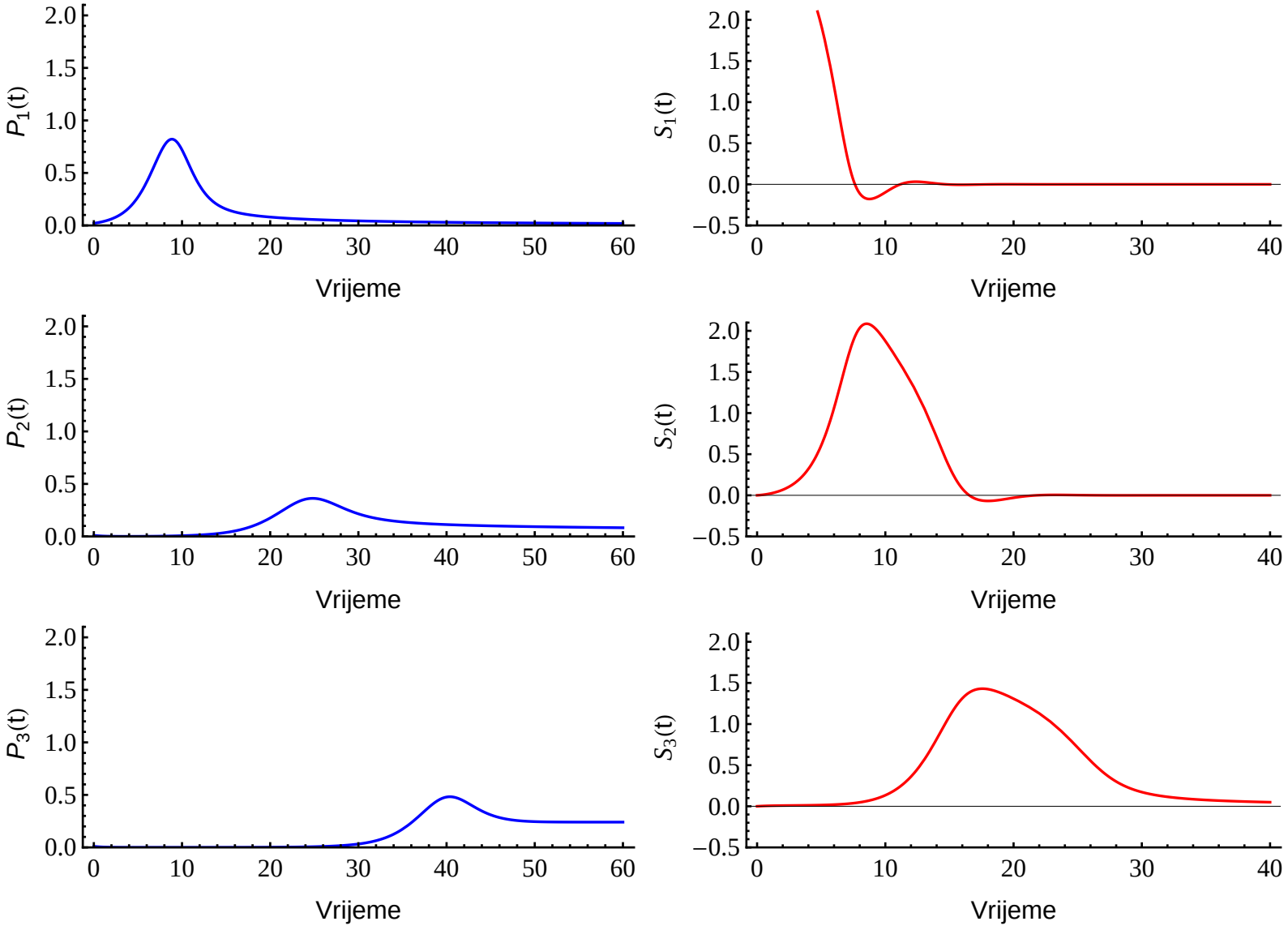
Supstrat proizvode samo aktivne stanice. Kada nema hranjivih sastojaka, stanice su u stanju mirovanja i nema proizvodnje supstrata.

**Problem**

Modificirajte prethodni model tako da uključite i populaciju stanica u mirovanju.

**Rješenje.**

$$
\begin{aligned}
S_1' &= -\frac{V_1\, S_1}{K_1 + S_1}\frac{P_1}{Y_1} - \frac{m_2}{Y_1}P_1 \\
P_1' &= \frac{V_1\, S_1}{K_1 + S_1}P_1 - \alpha_1(S_1)\, P_1 + \beta_1(S_1)\, Q_1 \\
Q_1' &= \alpha_1(S_1)\, P_1 - \beta_1(S_1)\, Q_1 \\
S_2' &= m_2\, P_1 - \frac{V_2\, S_2}{K_2 + S_2}\frac{P_2}{Y_2} - \frac{m_3}{Y_2}P_2 \\
P_2' &= \frac{V_2\, S_2}{K_2 + S_2}P_2 - \alpha_2(S_2)\, P_2 + \beta_2(S_2)\, Q_2 \\
Q_2' &= \alpha_2(S_2)\, P_2 - \beta_2(S_2) Q_2 \\
S_3' &= m_3\, P_2 - \frac{V_3\, S_3}{K_3 + S_3}\frac{P_3}{Y_3} \\
P_3' &= \frac{V_3\, S_3}{K_3 + S_3}P_3 - \alpha_3(S_3)\, P_3 + \beta_3(S_3)\, Q_3 \\
Q_3' &= \alpha_3(S_3)\, P_3 - \beta(S_3) Q_3
\end{aligned}
$$




**Negativne koncentracije supstrata!**

I dalje se troši supstrat kada ga nema.

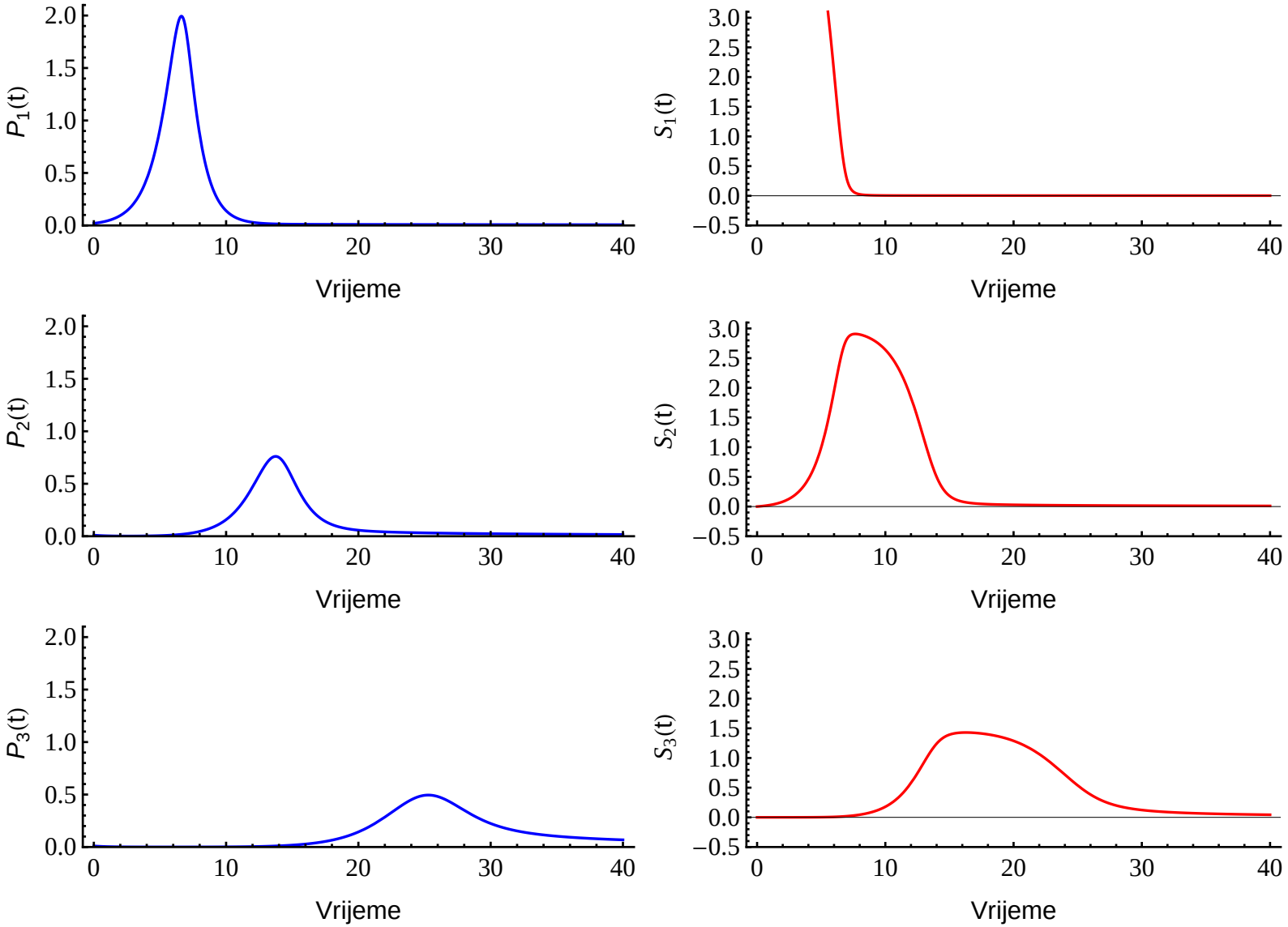
Modificirajmo proizvodnju supstrata.

Ako nema supstrata $S_1$ onda nema niti proizvodnje supstrata $S_2$.

Proizvodnja:

$$\frac{S_1}{1+S_1}\, m_2\, P_1$$

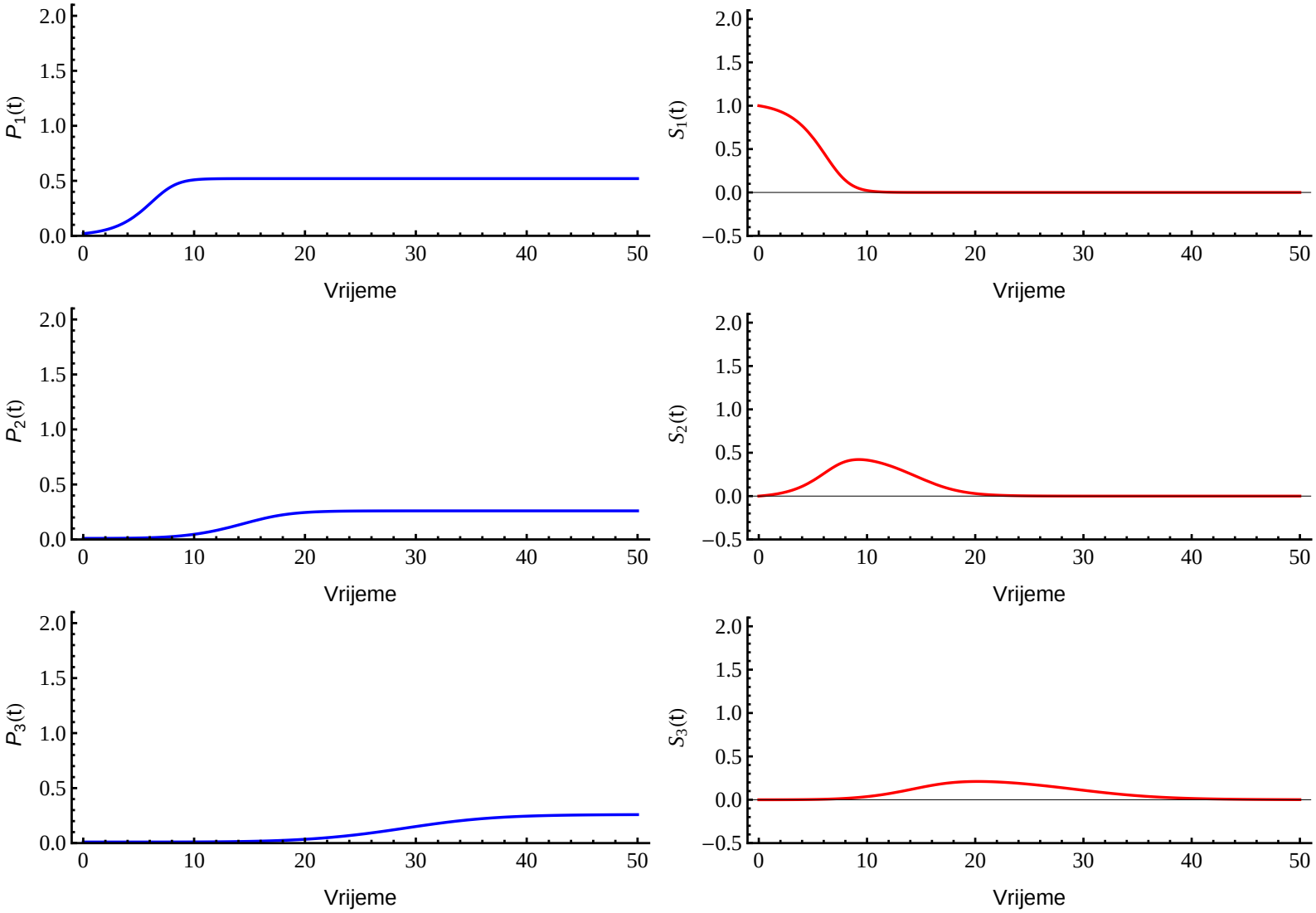
$$\frac{S_2}{1+S_2}\, m_3\, P_2$$


$P_1(t)$
$S_1(t)$
$P_2(t)$
$S_2(t)$
$P_3(t)$
$S_3(t)$
Vrijeme

Ako na isti način modificiramo model rasta s ograničenjem (bez populacije stanica u mirovanju) dobijamo

Model:

$$
\begin{aligned}
S_1' &= -\frac{V_1\, S_1}{K_1 + S_1}\frac{P_1}{Y_1} - \frac{S_1}{1 + S_1}\frac{m_2}{Y_1}P_1 \\
P_1' &= \frac{V_1\, S_1}{K_1 + S_1}P_1 \\
S_2' &= \frac{S_1}{1 + S_1}m_2\, P_1 - \frac{V_2\, S_2}{K_2 + S_2}\frac{P_2}{Y_2} - \frac{S_2}{1 + S_2}\frac{m_3}{Y_2}P_2 \\
P_2' &= \frac{V_2\, S_2}{K_2 + S_2}P_2 \\
S_3' &= \frac{S_2}{1 + S_2}m_3\, P_2 - \frac{V_3\, S_3}{K_3 + S_3}\frac{P_3}{Y_3} \\
P_3' &= \frac{V_3\, S_3}{K_3 + S_3}P_3
\end{aligned}
$$

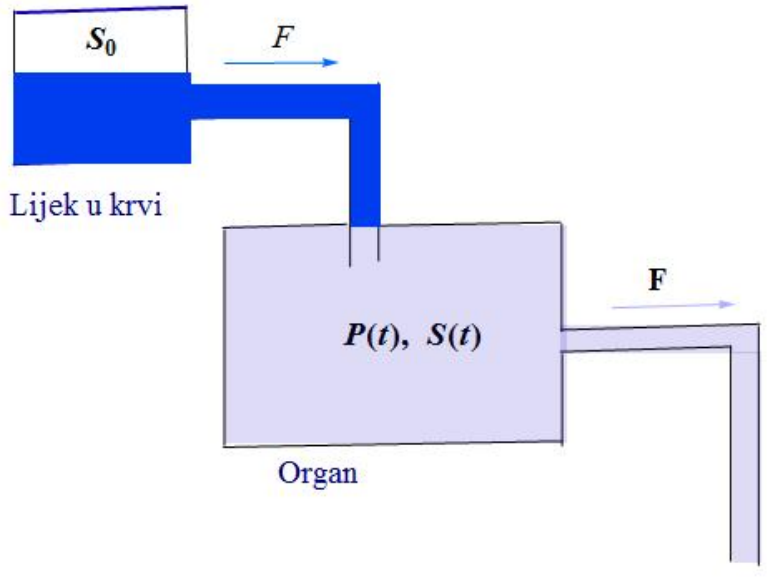

$P_1(t)$
$S_1(t)$
$P_2(t)$
$S_2(t)$
$P_3(t)$
$S_3(t)$
Vrijeme
2.0
1.5
1.0
0.5
0.0
−0.5
0
10
20
30
40
50

# 7. Domaća zadaća

Izvedite model hranidbenog lanca s tri populacije za rast u chemostatu.

# 4.4. Model infuzije lijeka

Modifikacija 'chemostat' modela se može iskoristiti kao jednostavan model utjecaja lijeka u krvi (npr. kemoterapija).




Ovdje je $S_0$ - koncentracija lijeka u krvi koja ulazi u organ (u 'chemostat' modelu je to bila oznaka za koncentraciju hranjivih sastojaka).

- $P(t)$ - broj stanica izloženih lijeku (pretpostavka: sve su stanice jednake mase)
- $V$ volumen krvi u organu, tj. volumen krvi u području u kojem se stanice tretiraju.
- $F = F_{in} = F_{out}$ - brzina protoka krvi (l/s)
- $S_0, S(t)$ - koncentracija lijeka

Pretpostavka: stanice i lijek u organu su 'dobro izmiješani'. Realističniji modeli npr. uključuju da lijek djeluje samo na vanjske stanice tumora.

$F$ je brzina toka krvi koja arterijom dolazi u organ i izlazi iz njega..

Glavna razlika u odnosu na 'chemostat' model:

- stanice se razmnožavaju brzinom koja je, u principu, nezavisna o lijeku.
- ali lijek ima negativni utjecaj na rast populacije stanica ubijajući ih.

  Brzinu ubijanja opisujemo nekom funkcijom $K(S)$.
- krv na izlazu sadrži samo (neiskorišteni) lijek a ne i stanice.

Pretpostavke su:

- stanice se razmnožavaju eksponencijalno
- brzina ubijanja je proporcionalna s $K(S) \cdot P$.

Uočimo da je brzina ubijanja stanica modelirana s $K(S) \cdot P$.

- Broj ubijenih stanica u jedinici vremena ovisi o ukupnom broju stanica.
- Povećanjem broja stanica očekujemo i povećanje broja ubijenih stanica
- $K(S) \cdot P$ je najjednostavnija funkcija koja to opisuje (parsimonija!)

Chemostat model:

$$\begin{aligned} P' &= K(S)P - \omega P \\ S' &= -K(S)\frac{P}{Y} + \omega(S - S_0) \end{aligned}$$

Rast populacije ne ovisi o koncentraciji lijeka ($S$):

$\Longrightarrow \quad K(S)P \to kP$

Nema otjecanja stanica:

$\Longrightarrow \quad \omega P \to 0$

Model infuzije lijeka:

$$\begin{aligned} P' &= kP - K(S)P \\ S' &= -\alpha K(S)P + \omega(S - S_0) \end{aligned}$$

Kako definirati funkciju $K(S)$ ?

$K(0) = 0$ i $K(\infty) = \beta < \infty$

$$\Longrightarrow \quad K(S) = \frac{\beta S}{a + S}.$$

**Zadatak.** Modificirajte model. Pretpostavku o eksponencijalnom rastu zamijenite logističkim ili Gompertzovim modelom.