Modeling adipocytes dynamic

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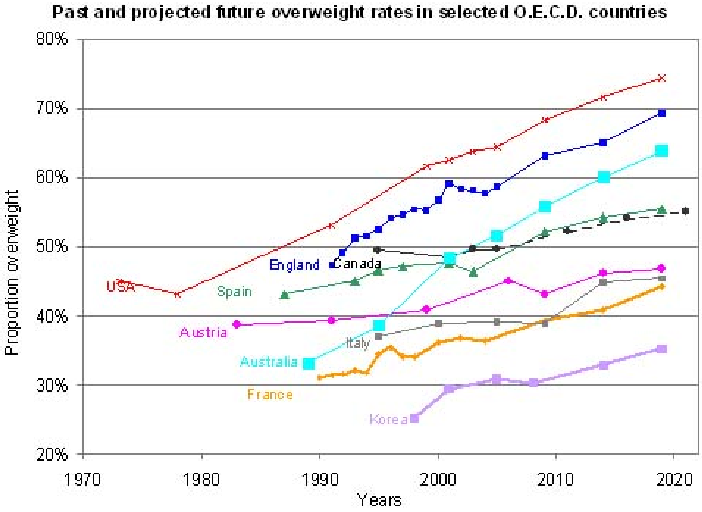

Figure: Evolution of the prevalence of overweight in different countries.
Source: `http://www.downeyobesityreport.com`

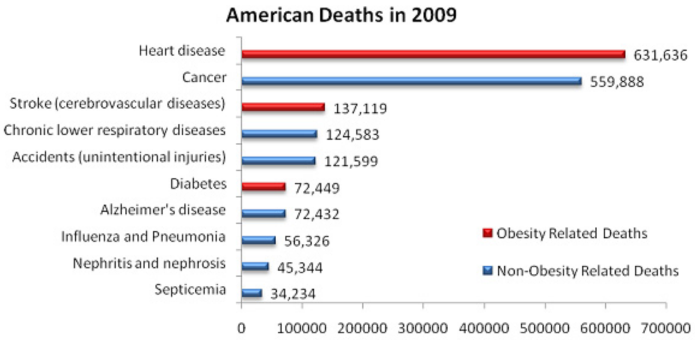

Figure: Causes of death in the United States in 2009.. Source: M. Bertucci, A. Miller, S. Jaggi, S. Wilding, Cutting the Fat on Healthcare: An Investigation of Preventive Healthcare and the Fight on Obesity, *Undergraduate Research Journal for the Human Sciences*.

https://www.youtube.com/watch?v=W4ax_3qFsuc

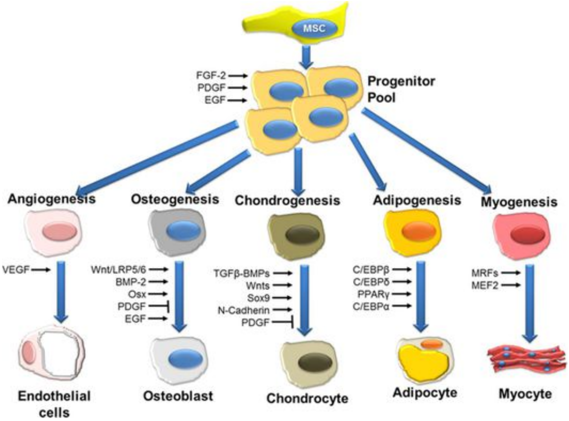

Figure: Development of the mesenchymal cells. Source: https://www.ahajournals.org/journal/res

The interactions between the three populations

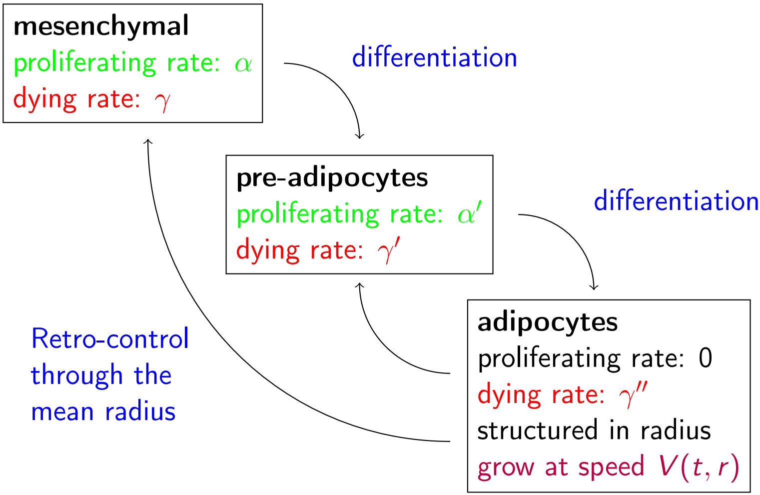

Figure: Schematic representation of the three populations.

A coupled system of ODEs and a PDE

$$\begin{cases} \frac{\mathrm{d}m}{\mathrm{d}t} = -\gamma m(t) + \alpha m(t) - \beta(\bar{r}(t))m(t), & t \geqslant 0, \\ \frac{\mathrm{d}p}{\mathrm{d}t} = -\gamma' p(t) + \alpha' p(t) - \beta'(\bar{r}(t))p(t) + \beta(\bar{r}(t))m(t), & t \geqslant 0, \\ \frac{\partial a}{\partial t}(t,r) + \partial_r(Va)(t,r) = -\gamma'' a(t,r), & t > 0, r > r_*, \\ Va(t,r_*) = \beta'(\bar{r}(t))p(t), & t > 0, \\ m(0) = m_{init} \geqslant 0, \quad p(0) = p_{init} \geqslant 0, \quad a(0,r) = a_{init}(r) \geqslant 0. \end{cases}$$

- r_* : minimal radius of the adipocytes (experimentally)
- $\bar{r}(t) = \dfrac{\int_{r_*}^{\infty} ra(t,r)\,\mathrm{d}r}{\int_{r_*}^{\infty} a(t,r)\,\mathrm{d}r}$ mean radius

Modeling of the velocity/growth rate and the retro-control

- $k(t)$: (excess of) available lipid droplets at time t
- $S(t) = \int_{r_*}^{\infty} 4\pi r^2 a(t,r)\,\mathrm{d}r$ total surface
- No adipocytes smaller than r_* nor larger than r_c (experimentally)

Velocity: $\boxed{V(t,r) = \frac{k(t)}{S(t)} \mathbb{1}_{[r_*,r_c)}(r) \geqslant 0}$

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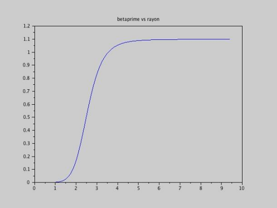


Figure: Typical shape for the retro-control functions β and β'.

Sigmoid:

$$\beta(\bar{r}) = \beta_m + \frac{\beta_M - \beta_m}{1 + e^{-\frac{\bar{r} - r_\beta}{R_\beta}}},$$

- $0 < \beta_m < \beta_M$
- $0 < r_\beta, R_\beta$

Mathematical framework

$$\left.\begin{array}{l}\text{a is a measure}\\ \text{V is discontinuous}\end{array}\right\}\ Va \text{ is not defined as a distribution.}$$

V is one-sided Lipschitz:

$$\left(V(t, r_1) - V(t, r_2)\right)\left(r_1 - r_2\right) \leqslant C\left|r_1 - r_2\right|^2$$

Characteristics can be defined forward in time thanks to Filippov theory. In one dimension:

$$\frac{\mathrm{d}X_t(r,s)}{\mathrm{d}t} \in \bigcap_{\substack{h>0\\ N\subset\mathbb{R}:|N|=0}} Conv\left(V\left(t, (X_t(r,s)-h, X_t(r,s)+h)\setminus N\right)\right) \text{ a.e.}$$

$$X_s(r,s) = r \tag{1}$$

$\hookrightarrow$ Unique Lipschitz solution defined on $[s, +\infty)$

Example

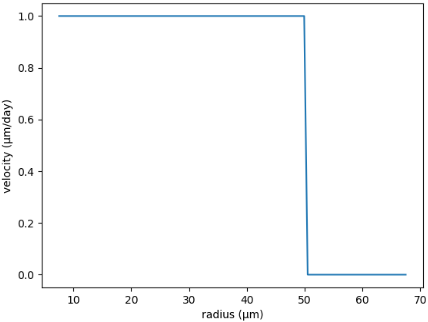


Figure: Velocity

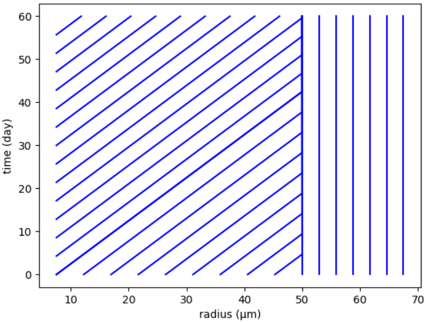


Figure: corresponding characteristics

In our case $X_t(r,s) = \min(r + \int_s^t \frac{k(u)}{S(u)}\,\mathrm{d}u, r_c)$

Notion of solution

Solution in Poupaud and Rascle sense. In our case :
$a \in C^0([0, +\infty), \mathcal{M} - w*)$ is a solution of

$$\partial_t a + \partial_r (Va) = -\gamma'' a \tag{2}$$

$$Va(t, r_*) = f(t) \tag{3}$$

if the Duhamel formula holds. $\forall \phi \in C_b^0([r_*, +\infty))$,

$$\int_{r_*}^{+\infty} \phi(r)\, \mathrm{d}a_t(r) = \int_{r_*}^{+\infty} \phi(X_t(0, r)) e^{-\gamma'' t}\, \mathrm{d}a_0(r) + \int_0^t \phi(X_t(s, r_*)) e^{-\gamma''(t-s)} f(s)\, \mathrm{d}s$$

Theoretical results

- Existence and uniqueness result based on a fixed-point method
- Necessary and sufficient condition for the existence of stationary solution(s) and (in case of existence) explicit expression
- Asymptotic behavior in some simple cases

Stationary solutions

Case $\gamma'' = 0$, $\alpha' - \gamma' - \beta'(r_*) < 0$, $\alpha - \gamma - \beta(r_*) < 0$:

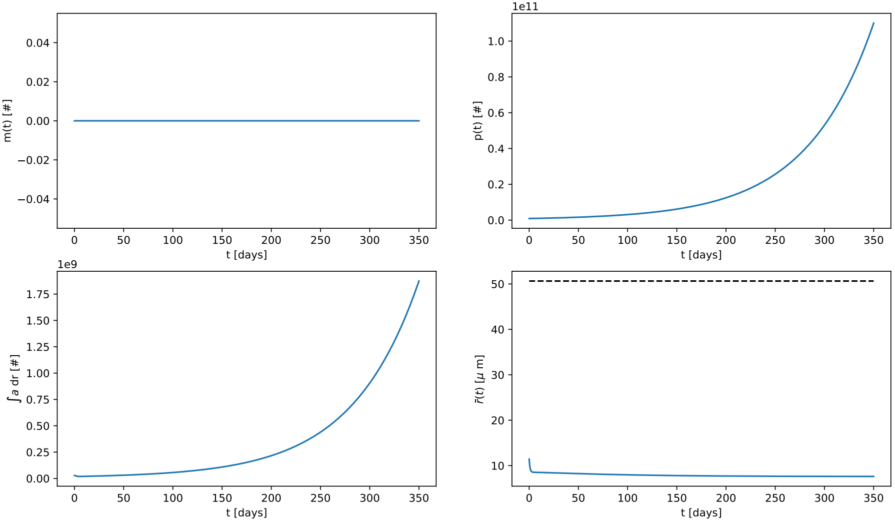
$$a_t \overset{*}{\rightharpoonup} \left(\int_{r_*}^{+\infty} \mathrm{d}a_0(r) + \int_0^{+\infty} \beta'(\bar{r}(s))p(s)\,\mathrm{d}s \right) \delta_{r_c}$$

Case $\gamma'' > 0$ and $\alpha' - \gamma' \in \beta'([r_*, r_c])$ or $\alpha - \gamma \in \beta([r_*, r_c])$, form of the stationary distributions:

$$\bar{a} = \lambda \left(e^{-\frac{\gamma''}{v}(r - r_*)}\,\mathrm{d}r + \frac{v e^{-\frac{\gamma''}{v}(r_c - r_*)}}{\gamma''} \delta_{r_c} \right)$$

where λ and v depend on the parameters in an explicit way.

Stability of stationary solutions



Discretisation of the ODEs, explicit scheme

Explicit Euler:

$$
\begin{aligned}
\frac{\mathrm{d}m}{\mathrm{d}t} &= (\alpha - \gamma)m(t) - \beta(\bar{r}(t))m(t) \\
\frac{m_{k+1} - m_k}{\Delta t} &= (\alpha - \gamma)m_k - \beta(r_k)m_k \\
\Rightarrow m_{k+1} &= \left(1 + \Delta t \left(\alpha - \gamma - \beta(r_k)\right)\right) m_k
\end{aligned}
$$

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\Rightarrow m_{k+1} &= (1+\Delta t\,(\alpha-\gamma-\beta(r_k)))\,m_k
\end{aligned}$$

In the same spirit:

$$p_{k+1} = \left(1+\Delta t\left(\alpha'-\gamma'-\beta'(r_k)\right)\right)p_k + \Delta t\beta(r_k)m_k$$

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\end{aligned}
$$

In the same spirit:

$$
p_{k+1} = \left(1 + \Delta t\,(\alpha' - \gamma' - \beta'(r_k))\right) p_k + \Delta t \beta(r_k) m_k
$$

$\boxed{\text{Conditionally stable!}}$

Discretisation of the ODEs, semi-implicit scheme

Semi-implicit Euler:

$$\begin{aligned}\frac{\mathrm{d}m}{\mathrm{d}t} &= (\alpha - \gamma)m(t) - \beta(\bar{r}(t))m(t) \\ \frac{m_{k+1} - m_k}{\Delta t} &= (\alpha - \gamma)m_k - \beta(r_k)m_{k+1}\end{aligned}$$

Discretisation of the ODEs, semi-implicit scheme

Semi-implicit Euler:

$$\frac{\mathrm{d}m}{\mathrm{d}t} = (\alpha - \gamma)m(t) - \beta(\bar{r}(t))m(t)$$

$$\frac{m_{k+1} - m_k}{\Delta t} = (\alpha - \gamma)m_k - \beta(r_k)m_{k+1}$$

$$\Rightarrow m_{k+1} = \frac{1 + \Delta t(\alpha - \gamma)}{1 + \Delta t\beta(r_k)} m_k$$

Discretisation of the ODEs, semi-implicit scheme

Semi-implicit Euler:

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$$\Rightarrow m_{k+1} = \frac{1+\Delta t(\alpha-\gamma)}{1+\Delta t\beta(r_k)}m_k$$

In the same spirit:

$$p_{k+1} = \frac{1+\Delta t(\alpha'-\gamma')}{1+\Delta t\beta'(r_k)}p_k + \frac{\Delta t\beta(r_k)}{1+\Delta t\beta'(r_k)}m_{k+1}$$

$$\boxed{\text{Unconditionally stable!}}$$

Discretisation of the PDE, upwind scheme

Classical upwind, but for measures:

- discretisation of $[r_*, r_c]$: $(r_j)_{0\leqslant j\leqslant J}$, $r_j = r_* + j\Delta r$
- time discretisation $t^k = k\Delta t$
- $V_j^k = V(t^k, r_j)$
- at each point r_j, the measure a_{t^k} has approximately weight a_j^k

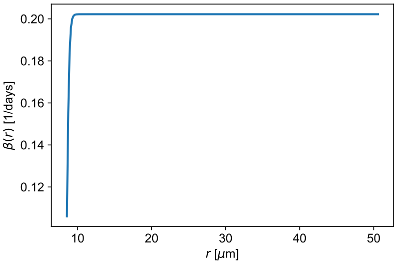
$$a_{t^k} \approx \sum_{j=0}^{J} a_j^k \delta_{r_j}$$

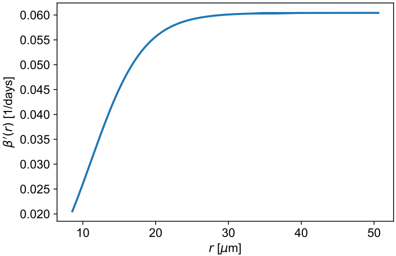
$$\begin{cases} a_j^{k+1} = a_j^k - \frac{\Delta t}{\Delta r}\left(V_j^k a_j^k - V_{j-1}^k a_{j-1}^k\right) - \Delta t \gamma'' a_j^k, & 1 < j < J, \\ V_0^k a_0^k = \beta'(r_k) p^k \end{cases}$$

Parameters setting

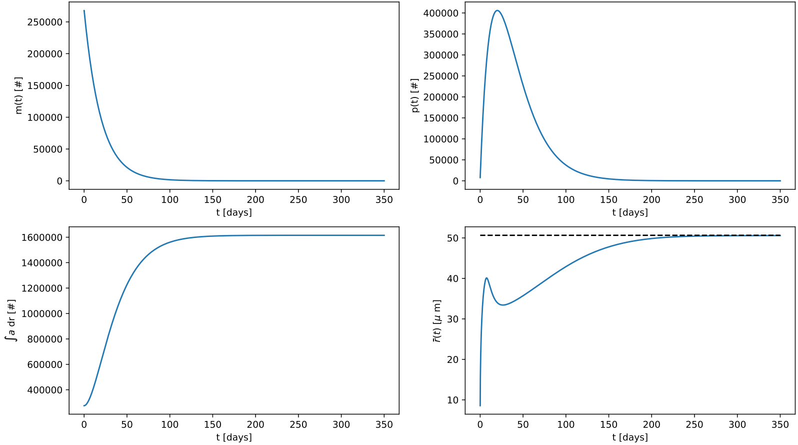
$$\alpha - \gamma - \beta(r) < 0 \qquad \forall r \in [r_*, r_c]$$
$$\alpha' - \gamma' - \beta'(r) < 0 \qquad \forall r \in [r_*, r_c]$$

$$t \in (0, 350) \ [\text{days}]$$

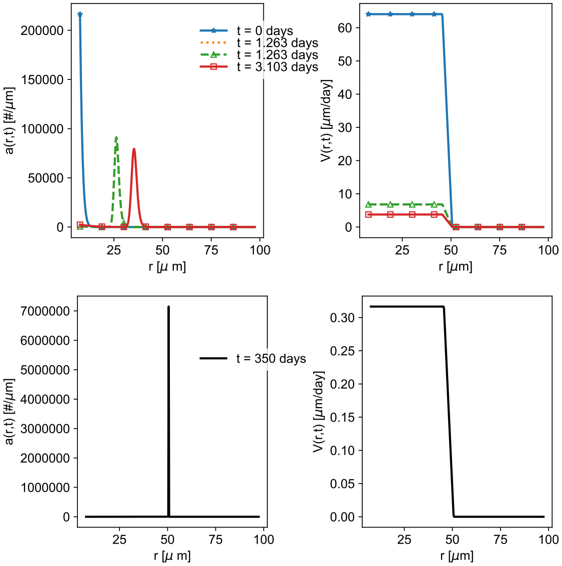




Population dynamic



Adipocytes distribution and growth rate



Spatial model

- $s(t,x)$: volume fraction of the surrounding material at time t and at point x.
- $u(t,x)$: spatial velocity of the species at time t and at point x

$$\frac{\partial m}{\partial t} + \nabla_x \cdot (um) = (\alpha - \gamma - \beta(\bar{r}))\, m \tag{4}$$

$$\frac{\partial p}{\partial t} + \nabla_x \cdot (up) = \left(\alpha' - \gamma' - \beta'(\bar{r})\right) p + \beta(\bar{r}) m \tag{5}$$

$$\frac{\partial s}{\partial t} + \nabla_x \cdot (us) = 0 \tag{6}$$

$$\partial_t a + \nabla_x \cdot (ua) + \partial_r (Va) = -\gamma'' a \tag{7}$$

Closure condition

Constraint on the volume fractions:

$$s(t,x) + \frac{4\pi}{3}\left(r_*^3 m(t,x) + r_*^3 p(t,x) + \int_{r_*}^{r_c} r^3 a(t,x,r)\,\mathrm{d}r\right) = 1$$

Constraint on u:

$$\nabla_x \cdot u = \frac{4\pi}{3}\left(r_*^3(\alpha-\gamma)m + r_*^3(\alpha'-\gamma')p + 3\int_{r_*}^{r_c} r^2 Va\,\mathrm{d}r\right)$$

Choice of spatial velocity u

$q(t,x)$: pressure at time t in x

Assumption: u derives from q through a Darcy's law:

$$u(t,x) = -\nabla q(t,x)$$

Thus:

$$\Delta q = -\nabla \cdot u$$

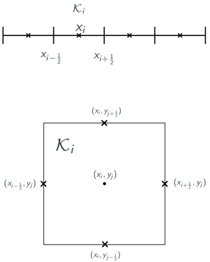
Boundary conditions

- $q = 0$ on $\partial\Omega$
- Non incoming flux for m,p and a.

Numerical scheme: finite volume method

- **Darcy's law**: Laplace problem

$$\Omega = \bigcup_{i=1,\dots N} \mathcal{K}_i$$

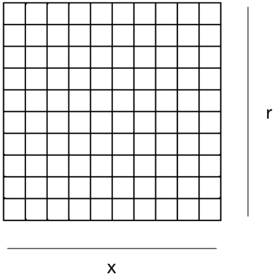


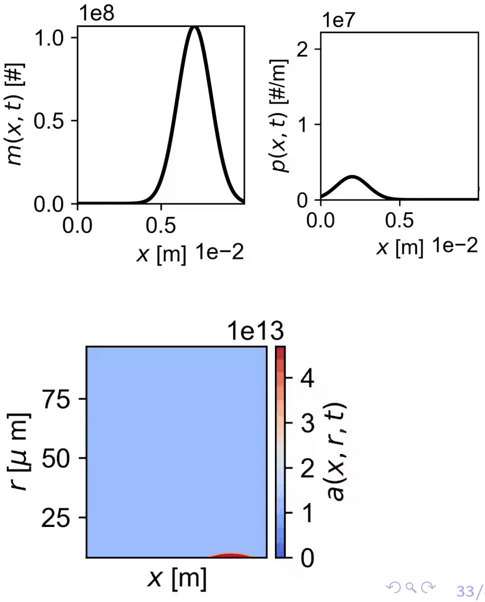
$$\begin{aligned} -\Delta q &= \mathrm{div}\mathbf{u} \qquad \text{in } \Omega \\ q &= 0 \qquad \text{on } \partial\Omega \\ \mathbf{u} &= \nabla q \end{aligned}$$

$$-\int_{\mathcal{K}_i} \Delta q \mathrm{dx} = \int_{\mathcal{K}_i} \mathrm{div}(\mathbf{u})\mathrm{dx} \quad \Rightarrow \quad -[\nabla q \cdot \mathbf{n}]_{\partial \mathcal{K}_i} = \int_{\mathcal{K}_i} \mathrm{div}(\mathbf{u})\mathrm{dx}$$

- **Transport system**: explicit upwind scheme

1D simulations



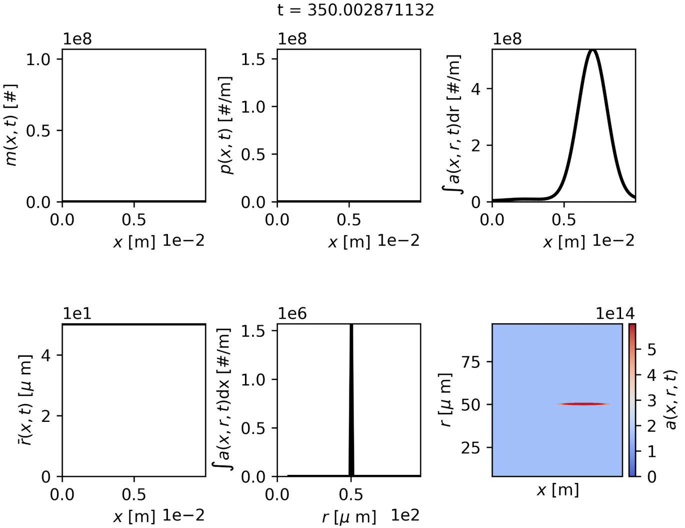


$x \in (0, 0.01)$ $J = 100$

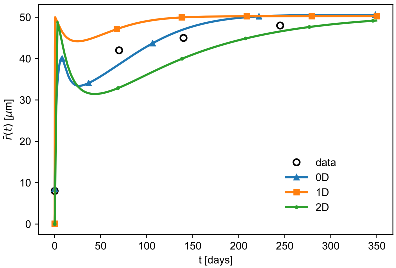
$r \in (0, 9\text{e-}5)$ $K = 300$

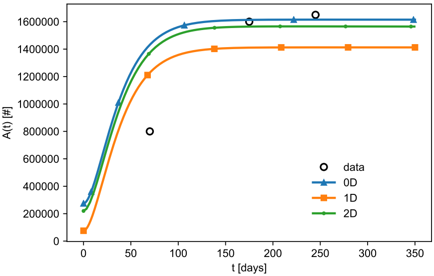
1D simulations

1D simulations



Comparison with experimental data





Conclusions

Observations from the theoretical and numerical study:

- With the current configuration of parameters, the surface has the strongest influence on the dynamic of adipocytes.
- With the current parameters of the spatial model, we have two different timescales: one for the spatial displacement and one for the growth of adipocytes.

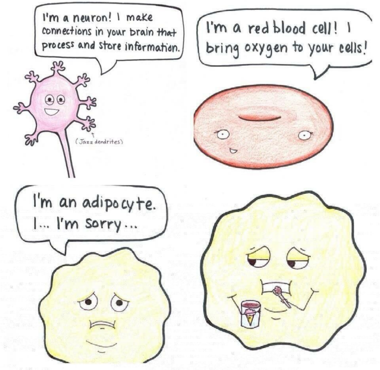
Encountered difficulties:

- The 0D and spatial models are highly sensitive to a change of initial conditions.
- Few experimental data with respect to the parameters.

Perspectives

- Data calibration of the model.
- Set boundary conditions in the spatial model with a biological meaning.
- Stability of stationary solutions of the 0D model (both theoretically and numerically for a wider range of parameters).
- Adaptation of the numerical scheme to deal with discontinuous velocity.
- Adaptation of the numerical scheme for the spatial model to deal with two times scales.

Thank you!!


I'm a neuron! I make connections in your brain that process and store information.
I'm a red blood cell! I bring oxygen to your cells!
(Jazz dendrites)
I'm an adipocyte. I... I'm sorry...