Mathematical modeling of adipocyte size distribution

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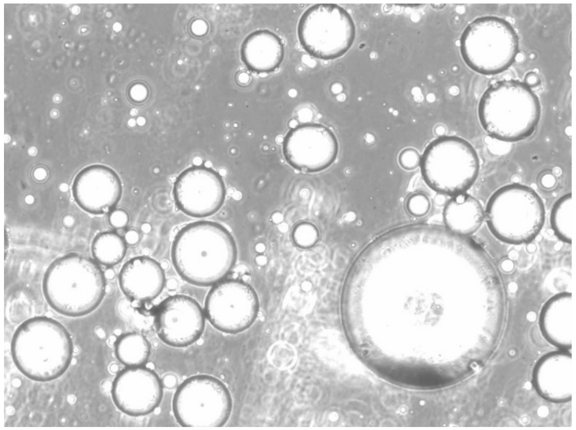
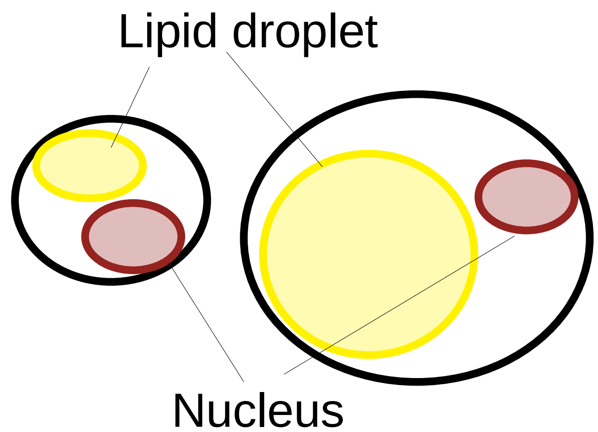
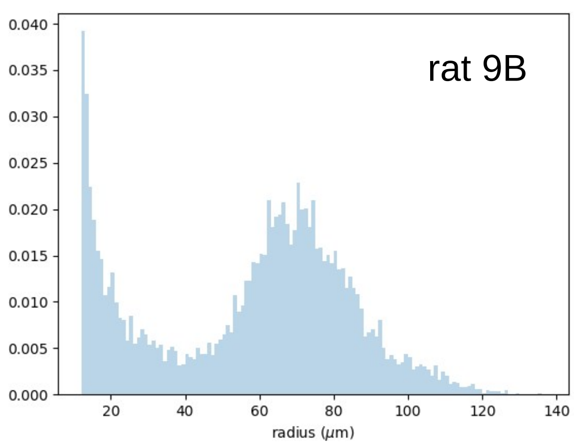
PROJET FINANCÉ PAR L'ANR - PROJECT FUNDED BY THE ANR

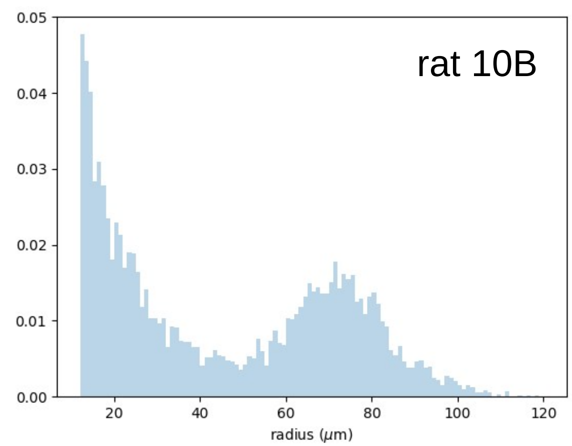
Cells that store energy as fat





No characteristic size :





Thanks to Hedi Soula for the data. Soula et al. JTB 2015

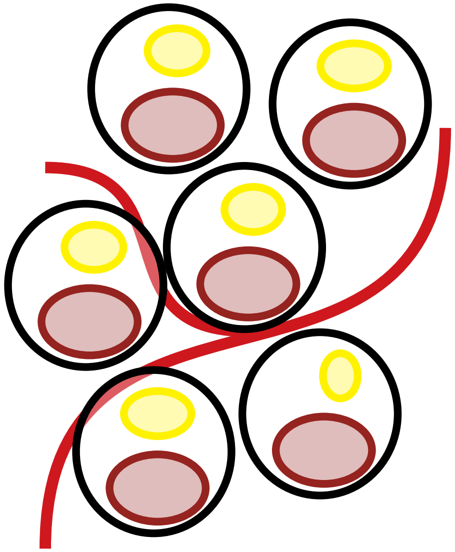
Lipid fluxes

Cells that store energy as fat

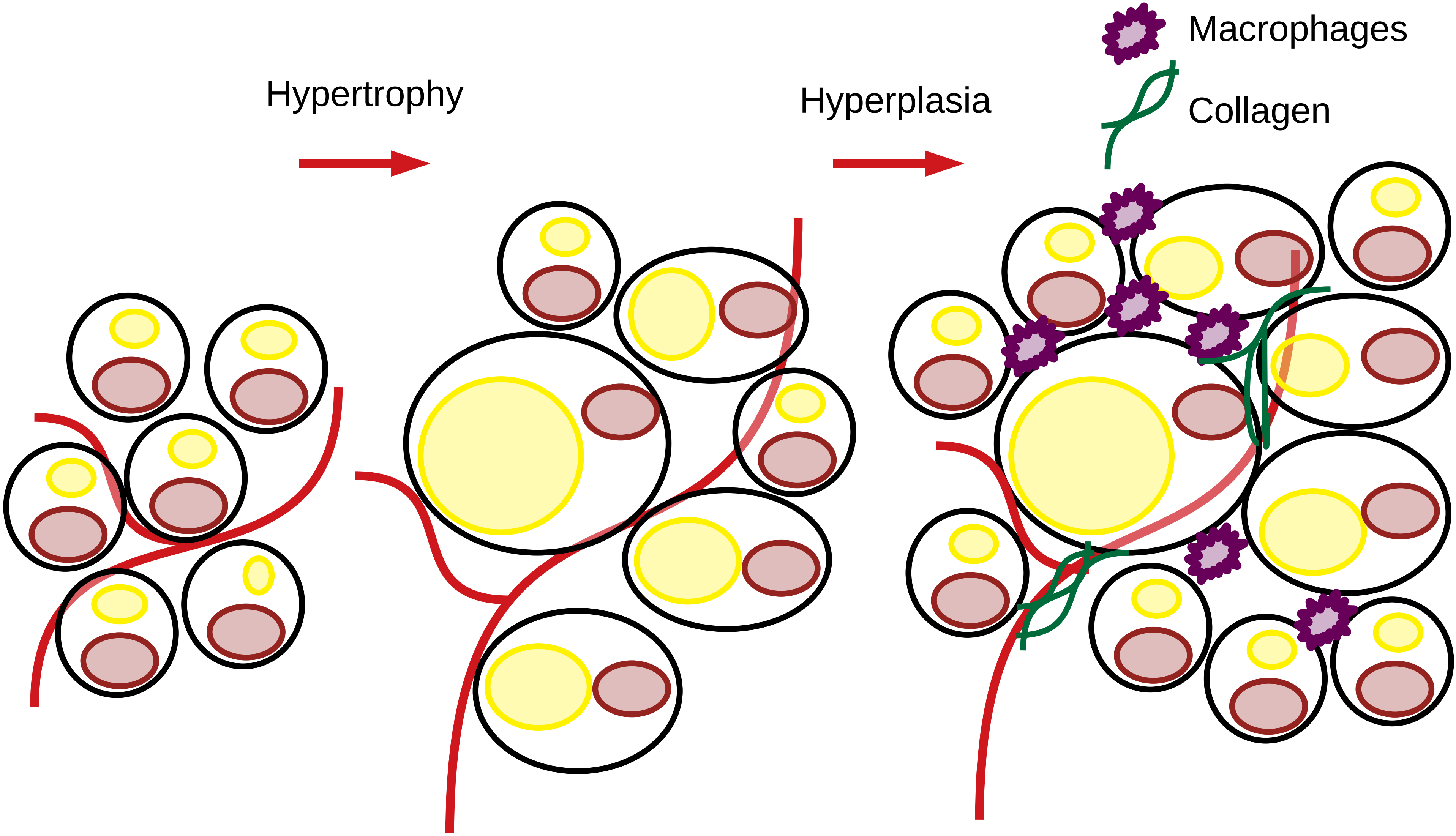
Size dynamics

Lipogenesis: influx, triglycerides are intracellularly stored

Lipolysis: exflux, excretion in form of glycerol and non-esterified fatty acids



Tissue dynamics



Dysfunction

Cells that store energy as fat

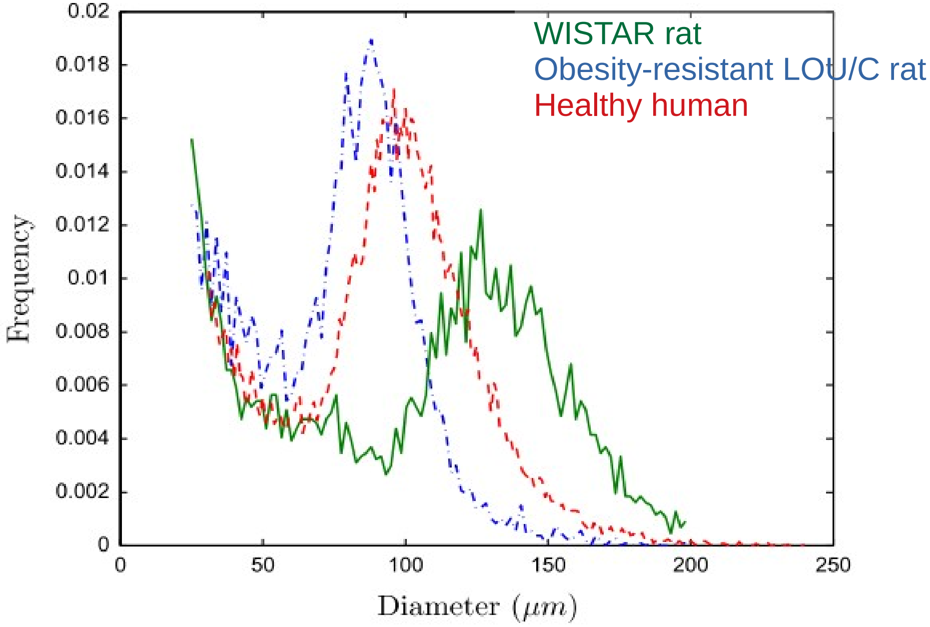
Size dynamics

Lipogenesis: influx, triglycerides are intracellularly stored

Lipolysis: exflux, excretion in form of glycerol and non-esterified fatty acids

~ 10% adipocytes are renewed annually

Soula et al. JTB 2013



* Extracellular matrix remodeling
* Inability to store fatty acids
  fat depots in muscle and liver
  promotes insulin resistance
* Tissue inflammation
* Metabolic alteration

Mathematical modeling of cell size distribution

$$\begin{cases} \partial_t f(t,r) + \partial_r (v(r, L(t)) f(t,r)) - D\partial_r^2 f(t,r) = 0 \\ L(t) = \lambda - \int_{r_{min}}^{r_{max}} (V(r) - V_{em}) f(t,r) \frac{4\pi r^2}{V_\ell^2} dr \\ v(r_{min}, L(t)) f(t, r_{min}) - D\partial_r f(t, r_{min}) = 0 \\ v(r_{max}, L(t)) f(t, r_{max}) - D\partial_r f(t, r_{max}) = 0 \end{cases}$$

$f(t, r)$: cell density at time t of radius r

$L(t)$: extracelullar amount of lipid

Based on the model of Soula et al. JTB 2013
Giacobbi et al. JTB 2024

Mathematical modeling of cell size distribution

$$\begin{cases} \partial_t f(t,r) + \partial_r (v(r, L(t)) f(t,r)) - D\partial_r^2 f(t,r) = 0 \\ L(t) = \lambda - \displaystyle\int_{r_{min}}^{r_{max}} (V(r) - V_{em}) f(t,r) \frac{4\pi r^2}{V_\ell^2} dr \\ v(r_{min}, L(t)) f(t, r_{min}) - D\partial_r f(t, r_{min}) = 0 \\ v(r_{max}, L(t)) f(t, r_{max}) - D\partial_r f(t, r_{max}) = 0 \end{cases}$$

$f(t, r)$: cell density at time t of radius r
$L(t)$: extracelullar amount of lipid

Total amount of lipid λ is assumed constant

Number of cells is assumed constant

$$v(r, L(t)) = \underbrace{\frac{\alpha V_\ell}{4\pi} \frac{L(t)}{L(t)+\kappa} \frac{\rho^3}{\rho^3 + r^3}}_{\text{lipogenesis}} - \underbrace{\frac{V_\ell}{4\pi r^2}(\beta + \gamma r^2) \frac{V(r) - V_{em}}{V(r) - V_{em} + V_\ell \chi}}_{\text{lipolysis}}.$$

lipogenesis

lipolysis

Based on the model of Soula et al. JTB 2013
Giacobbi et al. JTB 2024

Mathematical modeling of cell size distribution

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$f^\infty(r)$: stationary cell density at time t of radius r

$L^\infty(t)$: stationary extracelullar amount of lipid

$$\forall r \in \Omega, \quad f^\infty(r) = \frac{1}{\int_{r_{min}}^{r_{max}} \exp\left(\int_{r_{min}}^{r} \frac{1}{D} v(s, L^\infty) ds\right) dr} \exp\left(\int_{r_{min}}^{r} \frac{1}{D} v(s, L^\infty) ds\right)$$

$$L^\infty = \lambda - \int_{r_{min}}^{r_{max}} (V(r) - V_{em}) f^\infty(r) \frac{4\pi r^2}{V_\ell^2} dr$$

fixed point problem: resolution based on Powell hybrid method (*Python*)

Powell, M. J. D. (1970) Nonlinear Algebraic Equations. Gordon and Breach.

$$\partial_r f(r) = \left(\frac{\boxed{\alpha} V_\ell}{4\pi \boxed{D}} \frac{L}{L+\boxed{\kappa}} \frac{\boxed{\rho}^3}{\rho^3+r^3} - \frac{V_\ell}{4\pi \boxed{D} r^2}(\beta+\gamma r^2)\frac{V(r)-V_{em}}{V(r)-V_{em}+V_\ell \boxed{\chi}}\right) f(r)$$

$$L = \boxed{\lambda} - \int_{r_{min}}^{r_{max}} (V(r)-V_{em}) f(r) \frac{4\pi r^2}{V_\ell^2} dr$$

6 parameters to identify

The model is simplified: L is now a parameter

$$\begin{cases} f'(r) = \frac{1}{\boxed{D}} v(r) f(r) \\ \int_{r_{min}}^{r_{max}} f(r) dr = 1 \\ v(r) = \frac{\boxed{\alpha} V_\ell}{4\pi} \frac{\boxed{L}}{L+\boxed{\kappa}} \frac{\boxed{\rho^3}}{\rho^3+r^3} - \frac{V_\ell}{4\pi r^2}(\beta+\gamma r^2)\frac{V(r)-V_{em}}{V(r)-V_{em}+V_\ell \boxed{\chi}} \end{cases}$$

$$f^\infty(r) = \frac{\exp\left(\int_{r_{min}}^{r} \frac{1}{D} v(s) ds\right)}{\int_{r_{min}}^{r_{max}} \exp\left(\int_{r_{min}}^{r} \frac{1}{D} v(s) ds\right) dr}$$

Giacobbi et al. JTB 2024

Parameter identifiability

$$\begin{cases} f'(r) = \frac{1}{D} v(r) f(r) \\ \int_{r_{min}}^{r_{max}} f(r) dr = 1 \\ v(r) = \frac{\alpha V_\ell}{4\pi} \frac{L}{L+\kappa} \frac{\rho^3}{\rho^3 + r^3} - \frac{V_\ell}{4\pi r^2} (\beta + \gamma r^2) \frac{V(r) - V_{em}}{V(r) - V_{em} + V_\ell \chi} \end{cases}$$

Re-parameterized : $x_1 = f,\ x_2 = r,$

$$\theta_1 = \frac{\alpha L}{\beta(L+\kappa)},\ \theta_2 = \rho^3,\ \theta_3 = V_\ell \chi \text{ and } \theta_4 = \frac{4\pi D}{V_\ell \beta}$$

$$\begin{cases} \frac{dx_1}{dr} = \frac{1}{\theta_4} \left(\theta_1 \frac{1}{1 + \frac{x_2^3}{\theta_2}} - \frac{1 + \frac{\gamma}{\beta} x_2^2}{x_2^2} \frac{\frac{4}{3}\pi x_2^3 - V_{em}}{\frac{4}{3}\pi x_2^3 - V_{em} + \theta_3} \right) x_1 \\ \frac{dx_2}{dr} = 1 \end{cases}$$

Giacobbi et al. JTB 2024

Parameter identifiability

Re-parameterized : $x_1 = f,\ x_2 = r,$

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SIAN algorithm: combines differential algebra, Taylor series approaches

Structural identifiability Toolbox of Maple
Hong H., et al. (2019) Bioinformatics
Hong H., et al. (2020) Communications on pure and applied mathematics

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All quantities θ are identifiable $\quad \dfrac{\alpha L}{\beta(L+\kappa)}, D, \rho^3, \chi$

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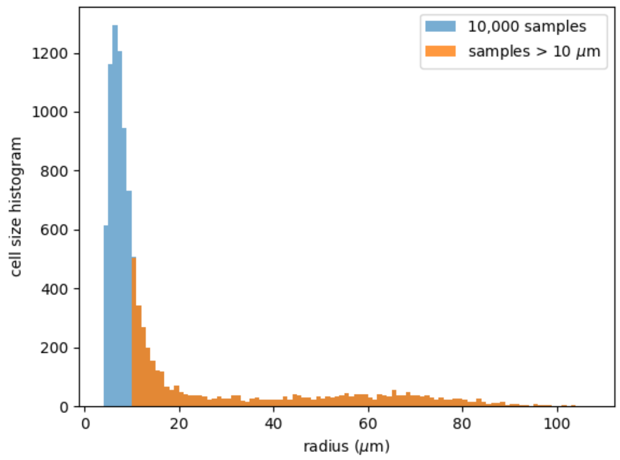
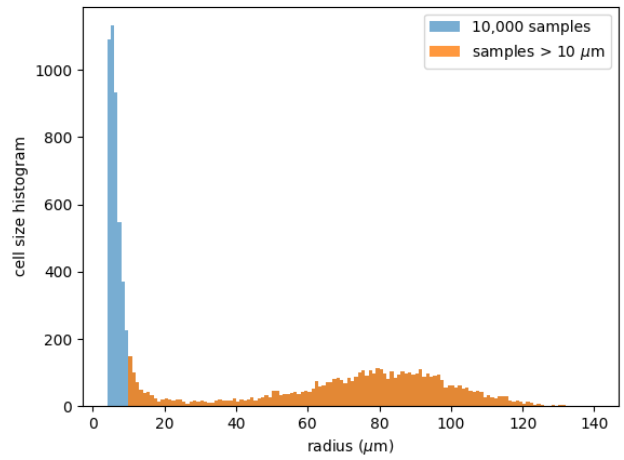
Covariance Matrix Adaptation Estimation Strategy (CMA-ES)

$$\mathcal{L}(\theta) = -\sum_{i=1}^{N} \log(f(r_i, \theta))$$

Synthetic data: generated with the model





Hansen N, The CMA Evolution Strategy : A Tutorial, arXiv, 2016.

Parameter estimation ?

Covariance Matrix Adaptation Estimation Strategy (CMA-ES)

$$\mathcal{L}(\theta) = -\sum_{i=1}^{N} \log(f(r_i, \theta))$$

param.	order	true	esti. value	std	rel. err.	esti. value	std	rel. err.
Synthetic data set 1			10,000 samples – $\mathcal{L}_N(\theta) = 4.20$			Samples > 10 µm – $\mathcal{L}_N(\theta) = 4.26$		
θ_1	10^{-3}	9.60	9.61	$1\,10^{-8}$	0.1%	9.62	$2\,10^{-8}$	0.2%
ρ	10^{2}	1.50	1.50	$1\,10^{-8}$	0.0%	1.49	$2\,10^{-8}$	0.7%
θ_3	10^{3}	2.18	2.17	$5\,10^{-8}$	0.5%	2.09	$2\,10^{-7}$	4.1%
θ_4	10^{-3}	7.37	7.20	$2\,10^{-7}$	2.3%	7.35	$4\,10^{-7}$	0.3%
Synthetic data set 2			10,000 samples – $\mathcal{L}_N(\theta) = 4.18$			Samples > 10 µm – $\mathcal{L}_N(\theta) = 4.54$		
θ_1	10^{-3}	9.92	9.92	$1\,10^{-8}$	0.0%	9.91	$1\,10^{-7}$	0.1%
ρ	10^{2}	2.00	2.00	$1\,10^{-8}$	0.0%	2.01	$5\,10^{-8}$	0.5%
θ_3	10^{2}	3.27	3.12	$2\,10^{-7}$	4.6%	5.39	$4\,10^{-6}$	65%
θ_4	10^{-2}	1.11	1.12	$2\,10^{-8}$	0.9%	1.12	$1\,10^{-7}$	0.9%

Hansen N, The CMA Evolution Strategy : A Tutorial, arXiv, 2016.
Giacobbi et al. JTB 2024.

Parameter estimation – how confident ?

Parameters are taken in the interval +/- 20% estimated value

Kept when $\mathcal{L}(\theta)$ < 0.1% of the selected one (similar to ABC method)

Giacobbi et al. JTB 2024

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synthetic data set 1			10,000 samples			samples $> 10\mu m$		
parameter	order	true	esti. value	esti. $\pm 20\%$	select. values	esti. value	esti. $\pm 20\%$	select. values
θ_1	10^{-3}	9.60	9.61	7.69 - 11.53	9.58 - 9.63	9.62	7.70 - 11.54	9.59 - 9.65
ρ	10^2	1.50	1.50	1.20 - 1.80	1.47 - 1.53	1.49	1.19 - 1.79	1.46 - 1.52
θ_3	10^3	2.18	2.17	1.74 - 2.60	2.05 - 2.29	2.09	1.67 - 2.51	1.91 - 2.29
θ_4	10^{-3}	7.37	7.20	5.76 - 8.64	6.54 - 8.02	7.35	5.88 - 8.82	6.58 - 8.32
synthetic data set 2			10,000 samples			samples $> 10\mu m$		
parameter	order	true	esti. value	esti. $\pm 20\%$	select. values	esti. value	esti. $\pm 20\%$	select. values
θ_1	10^{-3}	9.92	9.92	7.94 - 11.90	9.90 - 9.95	9.91	7.92 - 11.89	9.86 - 9.95
ρ	10^2	2.00	2.00	1.60 - 2.40	1.97 - 2.03	2.01	1.61 - 2.41	1.99 - 2.05
θ_3	10^3	3.27	3.12	2.49 - 3.74	2.69 - 3.58	5.39	4.31 - 6.47	4.32 - 6.47
θ_4	10^{-2}	1.11	1.12	0.90 - 1.34	1.05 - 1.21	1.12	0.90 - 1.34	0.98 - 1.28

Giacobbi et al. JTB 2024

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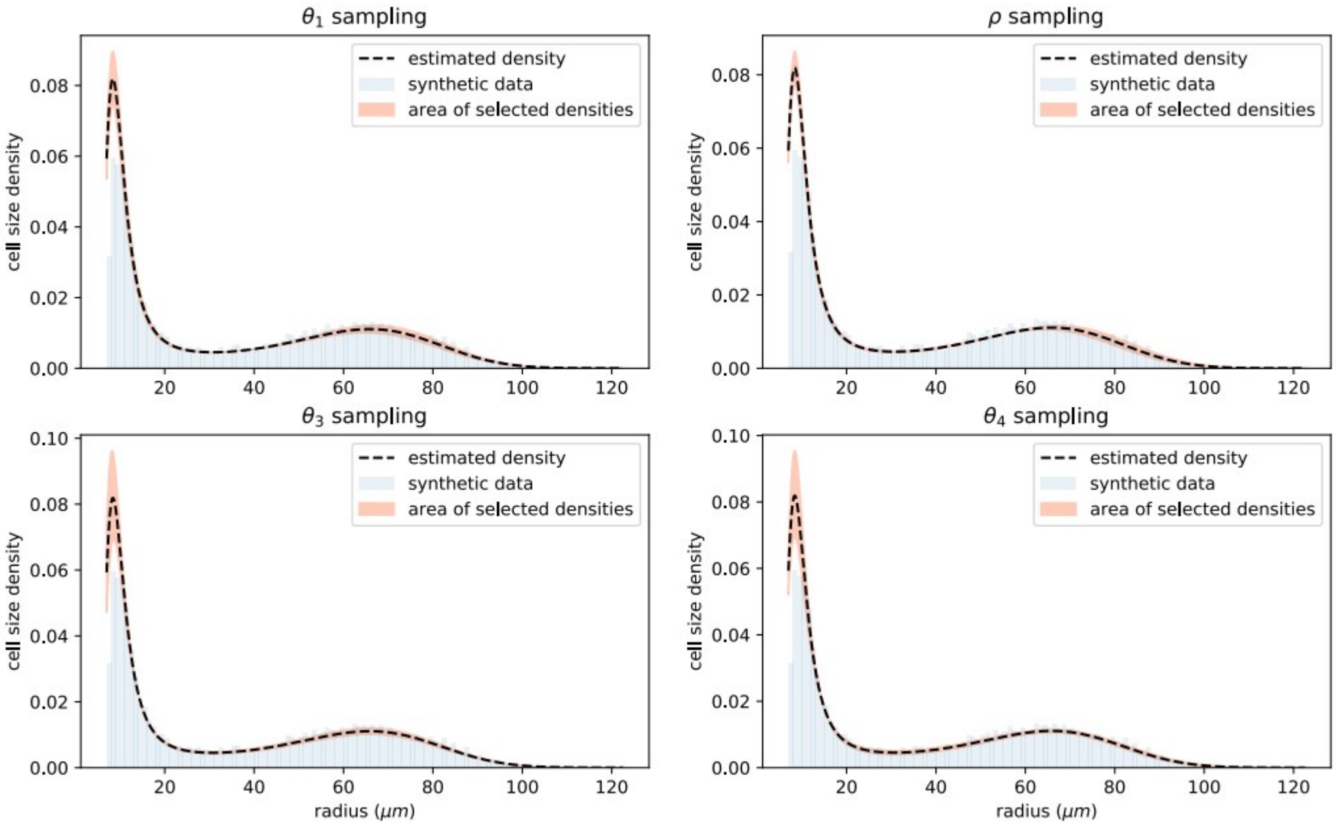

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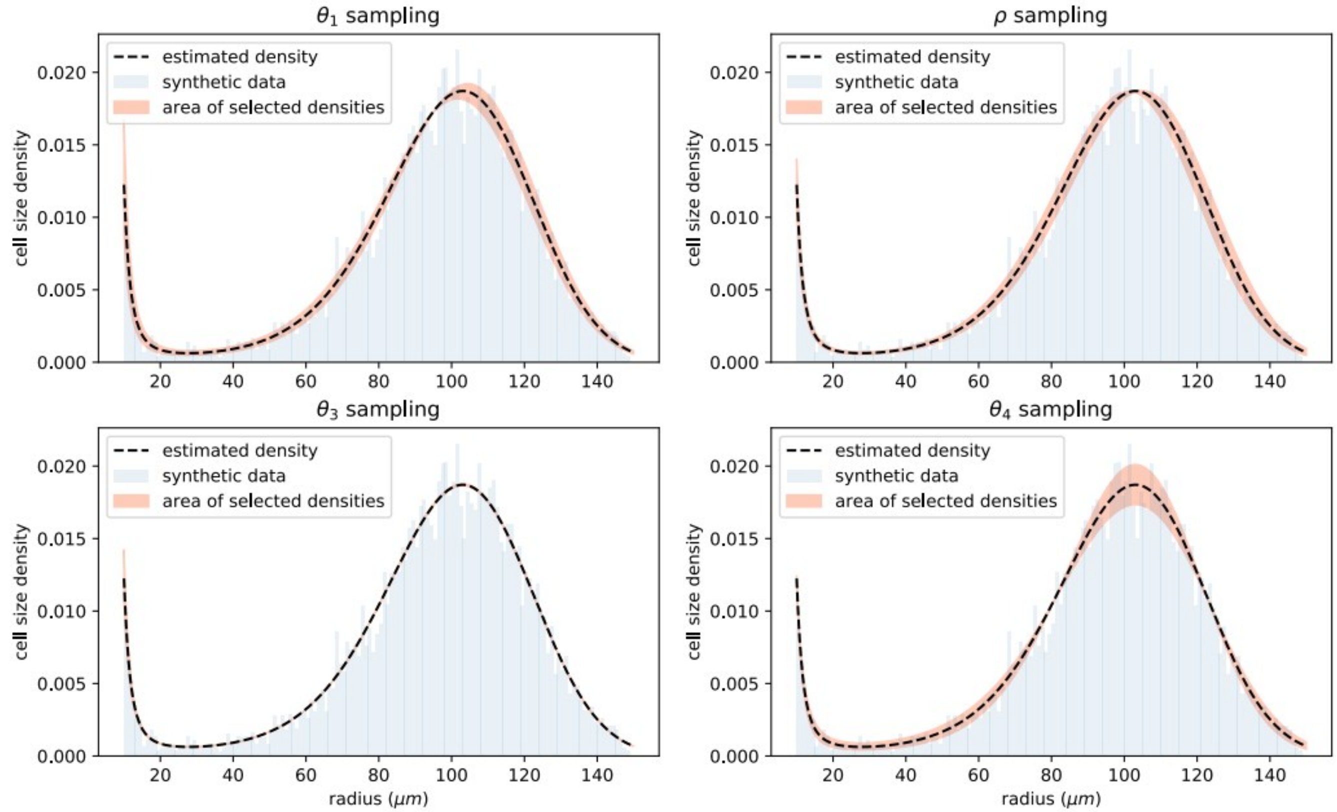
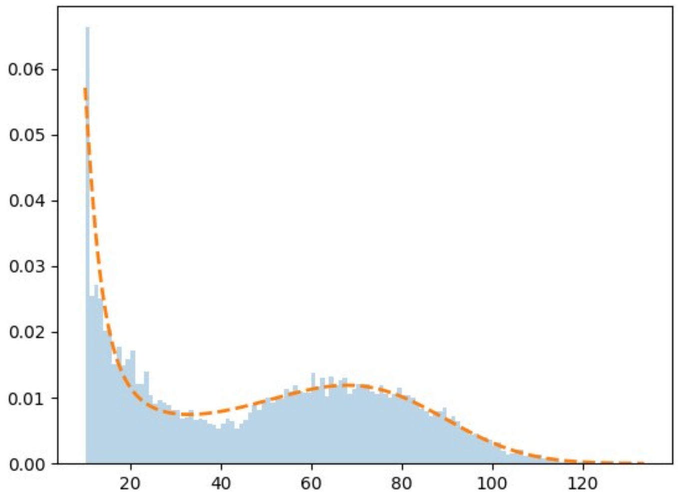
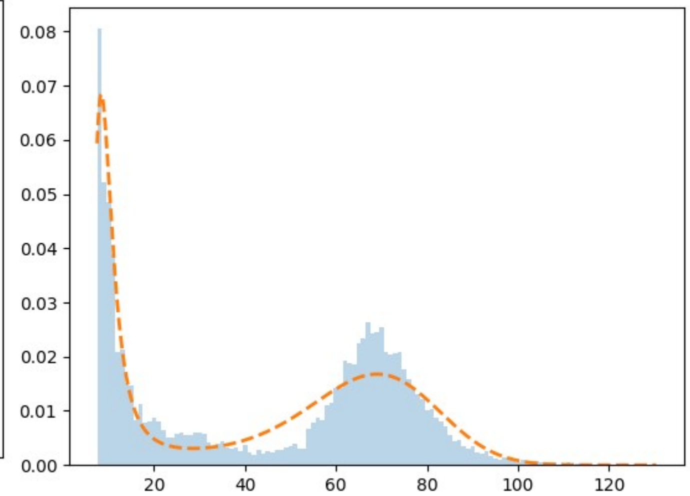


32 Wistar rats – D0 of experiment





parameter	mean	std	CV (std/mean)
θ_1	$9.6\ 10^{-3}$	$2.8\ \ 10^{-4}$	0.03
θ_2	$1.57\ 10^{2}$	$0.25\ \ 10^{2}$	0.16
θ_3	$2.24\ 10^{3}$	$1.07\ 10^{3}$	0.47
θ_4	$8.21\ 10^{-3}$	$2.58\ 10^{-3}$	0.31

Difficult to conclude on the biological processes … But

$$\theta_1 = \frac{\alpha L}{\beta(L+\kappa)},\ \theta_2 = \rho^3,\ \theta_3 = V_\ell \chi \text{ and } \theta_4 = \frac{4\pi D}{V_\ell \beta}$$

$$v(r, L(t)) = \frac{\alpha V_\ell}{4\pi} \frac{L(t)}{L(t)+\kappa} \frac{\rho^3}{\rho^3 + r^3} - \frac{V_\ell}{4\pi r^2}(\beta + \gamma r^2) \frac{V(r) - V_{em}}{V(r) - V_{em} + V_\ell \chi}.$$

Large L: estimation of alpha (0.29-0.31) same order to gamma (0.27)

Difficult to conclude on the biological processes … But

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Large L: estimation of alpha (0.29-0.31) same order to gamma (0.27)

For radius > 27 µm lipolysis mainly a surface based mechanism

Intra-cell variability – Indiv. Based Model

Aloïs Dauger
(PhD : 2023 - , Nutriomics-LJLL, Sorbonne University)

Hedi Soula
(Nutriomics, Sorbonne University)

Intra-cell variability – Indiv. Based Model

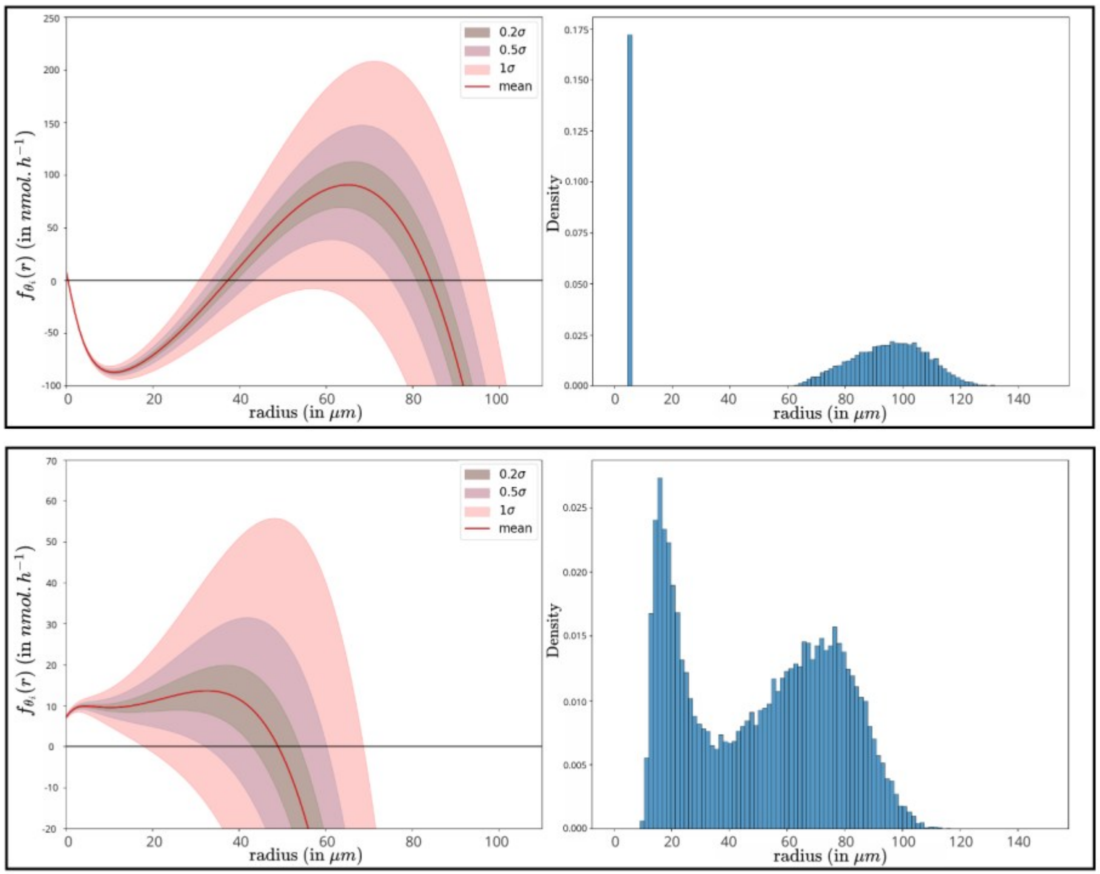
Individual based model – one ODE = one cell

$$
\begin{cases}
\dfrac{d\ell_i}{dt} & = \alpha_i r_i^2 \dfrac{L}{L+\kappa_i} \dfrac{\rho_i^n}{\rho_i^n + r_i^n} - (\beta_i + \gamma_i r_i^2) \dfrac{\ell_i}{\ell_i + \chi_i} = f_{\theta_i}(r_i, L) \text{ for } i \in \{1 \dots N\} \\
L & = \mathcal{L}_{tot} - \displaystyle\sum_{i=1}^{N} \ell_i = \mathcal{L}_{tot} - \sum_{i=1}^{N} V(r_i)
\end{cases}
$$

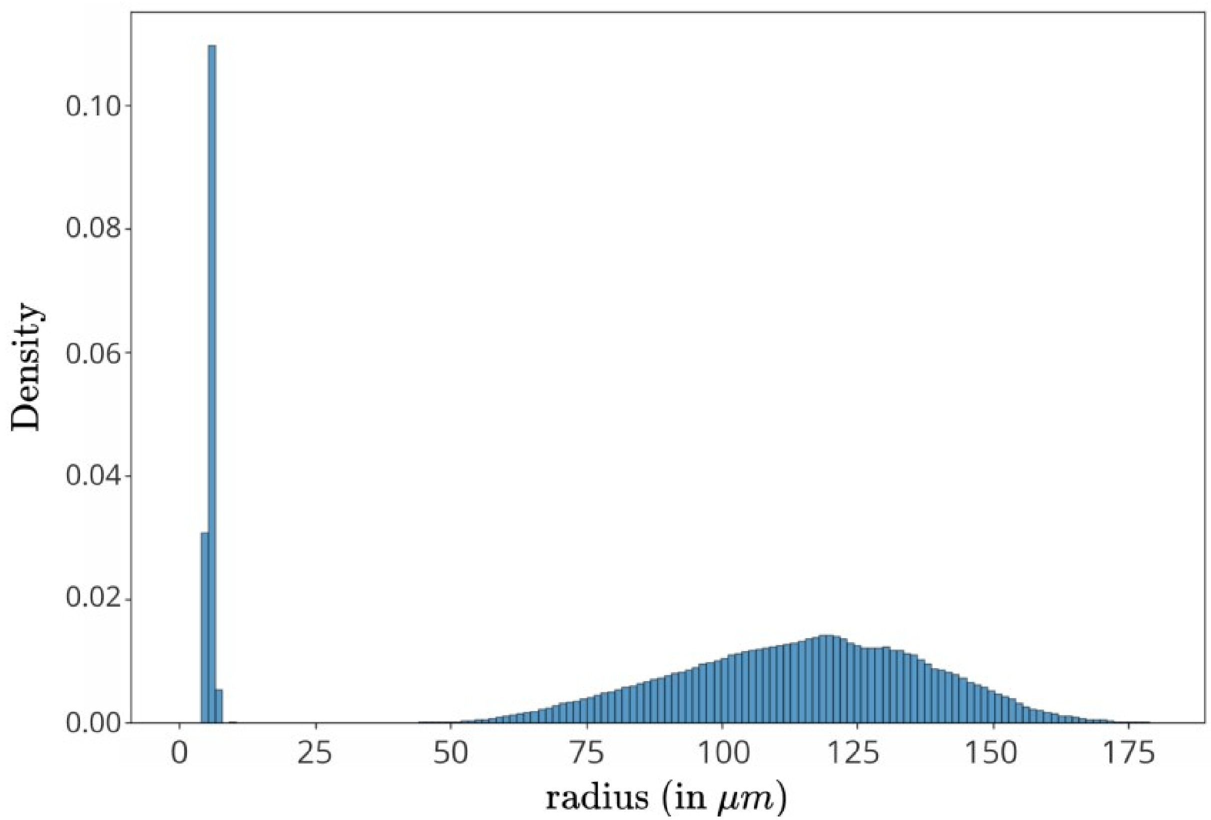
Compute the steady state of the system of ODEs (10 000 cells)

Individual based model – one ODE = one cell

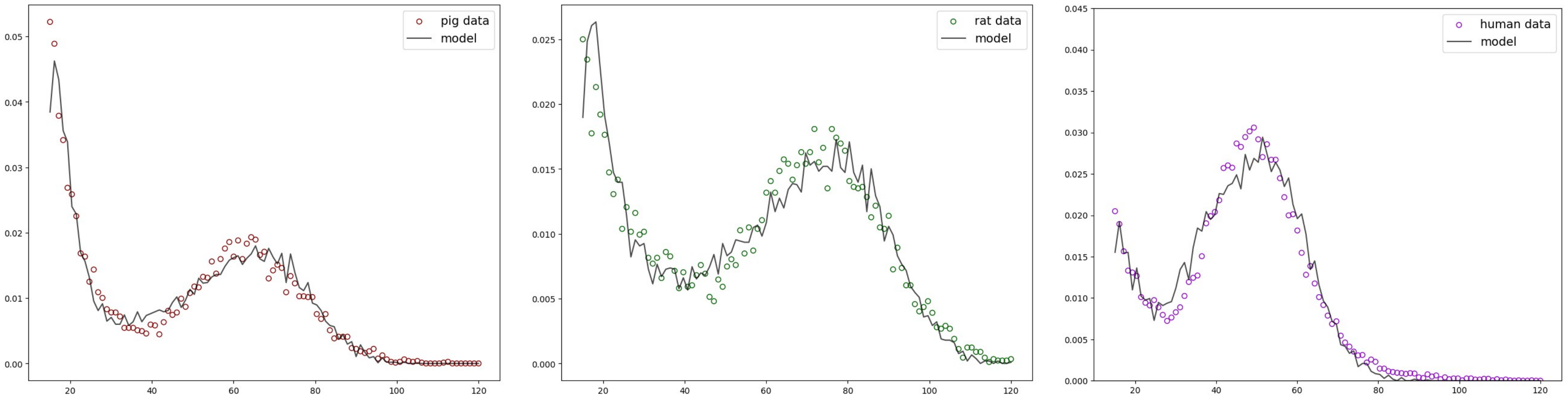
$$\begin{cases} \dfrac{d\ell_i}{dt} & = \alpha_i r_i^2 \dfrac{L}{L+\kappa_i} \dfrac{\rho_i^n}{\rho_i^n + r_i^n} - (\beta_i + \gamma_i r_i^2) \dfrac{\ell_i}{\ell_i + \chi_i} = f_{\theta_i}(r_i, L) \text{ for } i \in \{1 \dots N\} \\ L & = \mathcal{L}_{tot} - \displaystyle\sum_{i=1}^{N} \ell_i = \mathcal{L}_{tot} - \sum_{i=1}^{N} V(r_i) \end{cases}$$



The cumulative histogram of cells with different combination of parameters
The histogram summaries 7910 × 5000 = 3.955 × 107 cells size



Comparison model – data for 3 species : mini pig, rat and human



radius µm

Dauger A., Soula H. Audebert C. Adipocyte size distribution: mathematical model of a tissue property. Submitted.

Positive growth – PDE model

Magali Ribot
(Institute Denis Poisson, Orléans University)

Hedi Soula
(Nutriomics, Sorbonne University)

Romain Yvinec
(INRAE Nouzilly, Inria team MUSCA)

Positive growth – PDE model

PDE model – includes recruitment of adipocytes and death

$$\partial_t u + \frac{\partial}{\partial r}(V(r)u) = -\sigma u$$

$$V(r_{min})u(t, r_{min}) = \rho$$

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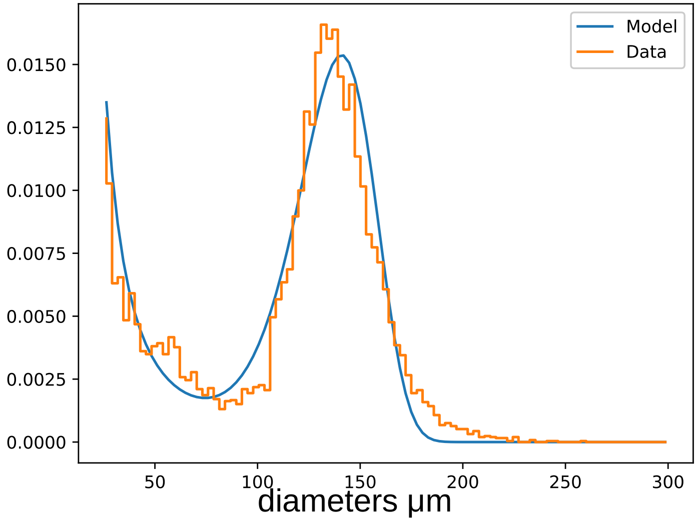

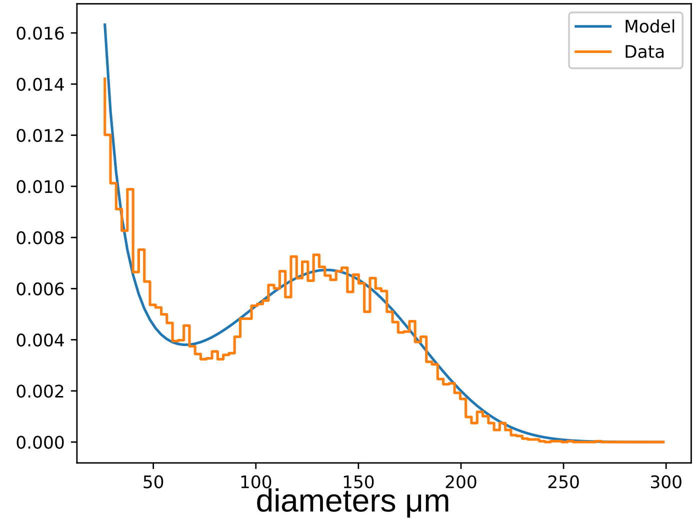

Include fibrosis – PDE model

Aleksandra Tomaszek
(PhD : 2023 - , LJLL-LCQB, Sorbonne University)

Laurent Boudin
(LJLL, Sorbonne University)

PDE model – includes recruitment of adipocytes and fibrosis
– change velocity

$$f(t) = \frac{f_{\max}}{1 + \exp(t - \tau)}.$$

$$\frac{\mathrm{d}m}{\mathrm{d}t}(t) = (\alpha_m - \delta_m)m(t) - \beta_p m(t),$$

$$\frac{\mathrm{d}p}{\mathrm{d}t} = (\alpha_p - \delta_p)p(t) + \beta_p m(t) - \gamma_a p(t),$$

$$\partial_t a(t,r) + \partial_r \left[v\left(r, L(t), \frac{f(t)}{N(t)}\right) a(t,r) \right] = -d\left(r, \frac{f(t)}{N(t)}\right) a(t,r),$$

$$L(t) = \lambda - \int_{r_{\min}}^{+\infty} \frac{(4\pi r)^2}{3{V_\ell}^2}(r^3 - r_{\min}^3) a(t,r) dr.$$

$$v\left(r_{\min}, L(t), \frac{f(t)}{N(t)}\right) a(t, r_{\min}) = \gamma_a p(t)$$

Include fibrosis – PDE model

PDE model – includes recruitment of adipocytes and fibrosis
– change velocity

$$f(t) = \frac{f_{\max}}{1 + \exp(t - \tau)}.$$

$$\frac{\mathrm{d}m}{\mathrm{d}t}(t) = (\alpha_m - \delta_m)m(t) - \beta_p m(t),$$

$$\frac{\mathrm{d}p}{\mathrm{d}t} = (\alpha_p - \delta_p)p(t) + \beta_p m(t) - \gamma_a p(t),$$

$$\partial_t a(t,r) + \partial_r \left[v\left(r, L(t), \frac{f(t)}{N(t)}\right) a(t,r) \right] = -d\left(r, \frac{f(t)}{N(t)}\right) a(t,r),$$

$$L(t) = \lambda - \int_{r_{\min}}^{+\infty} \frac{(4\pi r)^2}{3{V_\ell}^2}(r^3 - r_{\min}^3)a(t,r)dr.$$

$$v\left(r_{\min}, L(t), \frac{f(t)}{N(t)}\right) a(t, r_{\min}) = \gamma_a p(t)$$

Include fibrosis – PDE model

PDE model – includes recruitment of adipocytes and fibrosis
– change velocity

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$$\partial_t a(t,r) + \partial_r \left[v\left(r, L(t), \frac{f(t)}{N(t)}\right) a(t,r)\right] = -d\left(r, \frac{f(t)}{N(t)}\right) a(t,r),$$

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$$v\left(r_{\min}, L(t), \frac{f(t)}{N(t)}\right) a(t, r_{\min}) = \gamma_a p(t)$$

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