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Mathematical modeling of adipocyte size distributions: identifiability and parameter estimation from rat data

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1 Abstract

2 Fat cells, called adipocytes, are designed to regulate energy homeostasis by storing
3 energy in the form of lipids. Adipocyte size distribution is assumed to play a role in
4 the development of obesity-related diseases. This population of cells that do not have
5 a characteristic size, indeed a bimodal size distribution is observed in adipose tissue.
6 We propose a model based on a partial differential equation to describe adipocyte
7 size distribution. The model includes a description of the lipid fluxes and the cell
8 size fluctuations and using a formulation of a stationary solution fast computation of
9 bimodal distribution is achieved. We investigate the parameter identifiability and es-
10 timate parameter values with CMA-ES algorithm. We first validate the procedure on
11 synthetic data, then we estimate parameter values with experimental data of 32 rats.
12 We discuss the estimated parameter values and their variability within the popula-
13 tion, as well as the relation between estimated values and their biological significance.
14 Finally, a sensitivity analysis is performed to specify the influence of parameters on

15 cell size distribution and explain the differences between the model and the mea-
16 surements. The proposed framework enables the characterization of adipocyte size
17 distribution with four parameters and can be easily adapted to measurements of cell
18 size distribution in different health conditions.

19 *keywords: parameter estimation, adipocyte size distribution, parameter identifiability,*
20 *partial differential equation*

21 1 Introduction

22 Pathologies related to obesity are characterized by an important accretion of adipose
23 tissue which is mainly composed of adipose cells, called adipocytes. The adipocytes
24 are designed to regulate energy homeostasis by storing energy in form of lipids. Dur-
25 ing an excess of energy, adipocytes compensate with two mechanisms: hypertrophy
26 (increase in size) and hyperplasia (increase in number)[7]. Adipocyte size variations
27 are very large with radii ranging from $10\mu\text{m}$ to more than $100\mu\text{m}$, corresponding to
28 3 orders of magnitude in volume. In addition, cell size distribution among a tissue is
29 not unimodal but presents two peaks: one for small adipocytes (radius below $30\mu\text{m}$)
30 and one for large adipocytes (above $80\mu\text{m}$) [20]. A bimodal distribution of cell sizes
31 is striking. Indeed, most cells in the population are small adipocytes, which do not
32 contribute significantly to the storing capacity. There is no scientific consensus on the
33 functional importance of this bimodality. However, cell size has been associated with
34 metabolic properties dysfunction that may be linked to obesity-related pathologies
35 [31, 24, 20, 18] or to play a role in the development of those diseases [5].

36 Few mathematical models have been proposed for adipocyte size dynamics in var-
37 ious health conditions. In [13, 14, 15, 17], the authors consider partial differential
38 equation models that describe adipocyte size distribution dynamics. They have as-
39 sumed a size-dependent rate described by an imposed function where the associated
40 parameters are difficult to relate to physiological processes. The adipocyte modeling
41 in [19] is based on three compartments and has been developed to describe small,
42 medium and large adipocytes. The cell size evolution depends on lipid fluxes that are
43 related to protein concentration controlling lipotoxicity – a cellular dysfunction due
44 to lipid accumulation in non-adipose tissue. All these models provide studies of the
45 adipose tissue growth dynamic and its bimodality through cell hyperplasia and/or
46 hypertrophy, but the mechanisms governing lipid fluxes involved in adipocyte hy-
47 pertrophy have not been considered. Furthermore, model parameters lack biological
48 meaning.

49 A detailed model of cell hypertrophy based on lipid exchanges has been proposed
50 in [27]. Adipocyte bimodal distributions have been explained based on mathemati-

51 cal analyses. Individual-based Monte Carlo techniques were performed to solve the
 52 model. However, this approach is computationally costly so parameter estimation
 53 using biological measurements is very difficult. A similar simplified model, accounting
 54 only for lipolysis (deflation), compares well with distributions obtained from fasting
 55 rats [28].

56 The paper is organized as follows. Based on [27, 28], we formulate the mathe-
 57 matical model in section 2. It is based on partial differential equations, to describe
 58 stationary adipocyte size distribution. The contribution of our work is to have a
 59 diffusion term in the partial differential equation describing the cell size fluctuations
 60 like in [14]. Through parameter estimation, we aim at comparing the distribution
 61 obtained with the model to cell size distribution measured in rats before any manip-
 62 ulation [28, 12]. To perform parameter estimation, we first conduct an identifiability
 63 analysis in order to select model parameters that can be uniquely estimated with the
 64 available data. Using these selected parameters, we carry out a study on synthetic
 65 data (generated with model equations). The model identifiability and the parameter
 66 estimation on synthetic data are presented in section 3. Once the parameter estima-
 67 tion problem is verified, in section 4 we perform parameter estimation using adipocyte
 68 size distributions measured in 32 healthy rats [28, 12]. The estimated parameters are
 69 presented and then commented through a sensitivity analysis. We conclude this paper
 70 with some discussions in section 5.

71 **2 Mathematical model for adipocyte size distribu-** 72 **tions**

73 **2.1 Model construction**

Based on Soula *et al.* [27] work, we introduce a new model for adipocyte size distri-
 bution that we aim at fitting on experimental measurements. We first briefly recall
 the main hypotheses of the model in [27]. To represent adipocyte size density, the
 variation of the content of lipids ℓ and variation of radius r to adapt to lipid content
 are described by,

$$\begin{cases} \frac{d\ell}{dt} = \mathcal{T}(r, \ell, L(t)), & (1) \\ \frac{dr}{dt} = \mathcal{R}(r, \ell), & (2) \end{cases}$$

74 where the term $L(t)$ represents the extracellular amount of lipids at time t . These
 75 two equations refer to evolution with different characteristic times: the first equation
 76 is a rapid evolution of fatty acid content whereas the second is a slower variation of
 77 radius to adapt to cell lipid content.

78 We first assume a quasi steady state for equation (2) to describe a faster adaptation
 79 to lipid content. The relation between the lipid content ℓ and the radius r of a cell is
 80 then given by $\mathcal{R}(r, \ell) = 0$, leading to

$$\ell = \frac{V(r) - V_{em}}{V_\ell}, \quad V(r) = \frac{4}{3}\pi r^3, \quad (3)$$

81 with V_{em} the volume of the cell with no lipid, V_ℓ the conversion constant: the volume
 82 taken by 1 *nmol* of triglyceride, and the cell volume $V(r)$ is assumed to be spherical.
 83 Second, similarly to [14], we introduce a constant diffusion term D to represent cell
 84 size fluctuations.

85 With the above mentioned assumptions, we can re-write the main equation in
 86 [27], replacing ℓ by (3) and keeping only the radius variable. We then consider the
 87 cell size density f expressed as a function of time $t \in \mathbb{R}_+$ and radius $r \in [r_{min}, r_{max}]$,
 88 and we introduce the following system:

$$\begin{cases} \partial_t f(t, r) + \partial_r(v(r, L(t))f(t, r)) - D\partial_r^2 f(t, r) = 0, & (4) \\ L(t) = \lambda - \int_{r_{min}}^{r_{max}} (V(r) - V_{em}) \frac{4\pi r^2}{V_\ell^2} f(t, r) dr, & (5) \\ v(r_{min}, L(t))f(t, r_{min}) - D\partial_r f(t, r_{min}) = 0, & (6) \\ v(r_{max}, L(t))f(t, r_{max}) - D\partial_r f(t, r_{max}) = 0, & (7) \end{cases}$$

89 where v is defined by

$$v(r, L) = \frac{V_\ell}{4\pi} \left(\alpha \frac{L}{L + \kappa} \frac{\rho^3}{\rho^3 + r^3} - \frac{(\beta + \gamma r^2)}{r^2} \frac{V(r) - V_{em}}{V(r) - V_{em} + V_\ell \chi} \right). \quad (8)$$

90 The total amount of lipids λ is assumed to be constant over time and the second
 91 term of the right-hand side of (5) describes the intracellular amount of lipids at
 92 time t contained within all cells. The transport function v describes the exchange
 93 of lipids within the population of cells [27]. The lipid exchanges are based on two
 94 biochemical processes: lipogenesis – cell store lipids – and lipolysis – release of lipids in
 95 the extracellular environment. Lipogenesis depends on a surface-limited rate α , and it
 96 increases with the extracellular amount of lipids L with a saturation effect depending
 97 on the value of κ . The parameter ρ is a cell size threshold above which lipogenesis
 98 rate slows down. This parameter prevents the cell radius from becoming too large,
 99 as lipogenesis rate slows down and lipolysis rate becomes the main mechanism for
 100 lipid exchanges. Lipolysis activity includes a basal rate β and a surface-limited rate
 101 γ . The term $\frac{V(r) - V_{em}}{V(r) - V_{em} + V_\ell \chi} = \frac{\ell}{\ell + \chi}$ is small when cells contain few lipids and becomes
 102 close to one for larger lipid content through parameter χ .

103 We assume that in the measurements at the time of the biopsy the adipose tissue
 104 is at equilibrium, thus we neglect the recruitment of new cells. In addition, it has
 105 been shown that the life time of a human adipocyte is around 10 years [2], so the cell
 106 death is not taken into account. It gives the boundary conditions (6)-(7). The total
 107 number of cells is then constant and we assume the density integral is 1 between r_{min}
 108 and r_{max} , which leads to

$$\forall t \geq 0, \int_{r_{min}}^{r_{max}} f(t, r) dr = 1. \quad (9)$$

109 Table 1 reports the details on model variables and parameters. The parameter
 110 values of V_{em} , V_l , β and γ are known from literature [27, 28] and will be fixed. We
 111 choose the values of r_{min} and r_{max} as the boundary values of the measured radii in
 112 the considered adipose tissue.

113 2.2 Stationary solution

114 In model (4)-(7), the number of adipocytes is fixed and the total amount of lipids
 115 is constant, thus we expect the size distribution to reach a steady state [23]. The
 116 mathematical study of the asymptotic behavior is not the purpose of this work.

117 We denote by f^∞ and L^∞ a stationary density of cell size and the extracellular
 118 amount of lipids respectively. A stationary solution verifies $\partial_t f^\infty(r) = 0$. With the
 119 boundary conditions (6)-(7) and assuming $D \neq 0$, we obtain the following system:

$$\begin{cases} \partial_r f^\infty(r) = \frac{1}{D} v(r, L^\infty) f^\infty(r), & (10) \\ L^\infty = \lambda - \int_{r_{min}}^{r_{max}} (V(r) - V_{em}) \frac{4\pi r^2}{V_\ell^2} f^\infty(r) dr. & (11) \end{cases}$$

120 We note that assuming $f^\infty(r)$ is known for all $r \in [r_{min}, r_{max}]$, then L^∞ is de-
 121 termined by the equation (11) and only depends on the unknown parameter λ . In
 122 parameter identifiability analysis and parameter estimation we assume that the cell
 123 size distribution is observed. So to simplify the dependency on parameters we con-
 124 sider L to be a parameter instead of λ . We thus replace L^∞ by a parameter L , and
 125 it leads to the following simplified model,

$$\begin{cases} (f^\infty)'(r) = \frac{1}{D} v(r) f^\infty(r), & (12) \end{cases}$$

$$\begin{cases} \int_{r_{min}}^{r_{max}} f^\infty(r) dr = 1, & (13) \end{cases}$$

$$\begin{cases} v(r) = \frac{V_\ell}{4\pi} \left(\alpha \frac{L}{L + \kappa \rho^3 + r^3} - \frac{(\beta + \gamma r^2)}{r^2} \frac{V(r) - V_{em}}{V(r) - V_{em} + V_\ell \chi} \right), & (14) \end{cases}$$

Table 1: **Description of model variables and parameters.** Parameter units and known values are summed up in the second column and a description of each variable is given in the third column.

name	value (unit)	description
t	- (h)	time
r	$\in [7.5, 150]$ (μm)	adipocyte radius [28, 12]
$L(t)$	- ($nmol$)	extracellular amount of lipids at time t
$f(t, r)$	-	cell density at time t with respect to radius r
V_{em}	$\frac{4\pi}{3}6^3$ (μm^3)	volume of an empty adipocyte (zero lipid) [1]
V_ℓ	$1.091 \cdot 10^6$ ($\mu m^3 \cdot nmol^{-1}$)	volume taken by 1 $nmol$ of triglyceride [27]
α	- ($nmol \cdot \mu m^{-2} \cdot h^{-1}$)	surface-limited rate in lipogenesis
κ	- ($nmol$)	constant of the limiting term in lipogenesis
ρ	- (μm)	cell size threshold of the Hill function in lipogenesis
β	31.25 ($nmol \cdot h^{-1}$)	basal lipolysis rate [28]
γ	0.27 ($nmol \cdot \mu m^{-2} \cdot h^{-1}$)	surface-limited rate in lipolysis [28]
χ	- ($nmol$)	constant of the limiting term in lipolysis
D	- ($\mu m^2 \cdot h^{-1}$)	diffusion coefficient for size fluctuations
λ	- ($nmol$)	total amount of lipids

126 where the unknown parameters to be estimated are α , L , κ , ρ , χ and D .

127 Given those parameters, we can compute a stationnary solution of model (12)-(14)
 128 and we have for $r \in [r_{min}, r_{max}]$,

$$f(r) = \frac{\exp\left(\int_{r_{min}}^r \frac{1}{D}v(s)ds\right)}{\int_{r_{min}}^{r_{max}} \exp\left(\int_{r_{min}}^r \frac{1}{D}v(s)ds\right)dr}. \quad (15)$$

129 This solution can be computed numerically and when possible, the integrals are com-
 130 puted explicitly otherwise a trapezoid rule is used. Typically, in the computation, a
 131 radius step of $0.1 \mu m$ is considered and an interpolation is applied to compute f at
 132 any radius.

133 **2.3 The model can represent a bimodal distribution of cell** 134 **size**

135 We first study the impact of the diffusion parameter that is the main change with
 136 respect to model in [27]. Figure 1 shows solutions computed numerically with the

137 equation (15) for a given set of parameters. The model is able to qualitatively re-
138 produce a bimodal distribution of cell size as measured in rats. Upon investigation
139 of equations (12)-(14), it is immediate that the number of extremal points of f , and
140 their locations, will depend only on the parameters that appear in the velocity v (14).
141 We can notice in equation (12) that the introduction of parameter D does not change
142 the definition of lipogenesis and lipolysis (v is only multiplied by $\frac{1}{D}$). In addition, the
143 diffusion process does not overtake the velocity process in cell size dynamics, other-
144 wise flat curves would be obtained. However, variations in the value of the diffusion
145 parameter impact the size distribution: increasing the diffusion reduces the difference
146 between the height of the two peaks and the density value at the nadir (lowest point
147 between the two peaks) increases with diffusion.

148 In the model of Soula et al. [27], an individual-based Monte Carlo technique
149 (20,000 cells) has been performed leading to a large computational time. It was then
150 very hard to perform quantitative comparison with measurements. The proposed
151 model enables a fast computation of the cell size distribution by computing directly
152 a stationary solution with equation (15). It is now possible to perform quantitative
153 comparison with measured size distribution and estimate parameters.

154 Prior to this parameter estimation, we study which parameters are likely to be
155 estimated with the available data through model parameter identifiability analysis
156 and parameter estimation on synthetic data.

157 **3 Model identifiability and parameter estimation**

158 **3.1 Parameter identifiability analysis**

We perform an identifiability analysis of the unknown parameters of the model: α ,
 L , κ , ρ , χ and D . We define a parameterized model $\mathcal{M}(\theta)$ derived from equations
(12)-(14) and study its parameter identifiability which is an intrinsic property: from
[6], the model \mathcal{M} is said to be globally identifiable in $\theta \in \Theta$ if

$$\forall \tilde{\theta} \in \Theta, \mathcal{M}(\theta) = \mathcal{M}(\tilde{\theta}) \Rightarrow \theta = \tilde{\theta}.$$

159 The parametric structure of model (12)-(14) is complex in the sense that it includes
160 non-linear functions in which some parameters are combined in a product. This might
161 result in redundancies in the model – only a smaller set of unknown parameters can
162 be estimated – or in a non-identifiable model [4].

To study the parametric structure of the model, we first set the observed outputs,

$$x_1 = f^\infty, x_2 = r$$

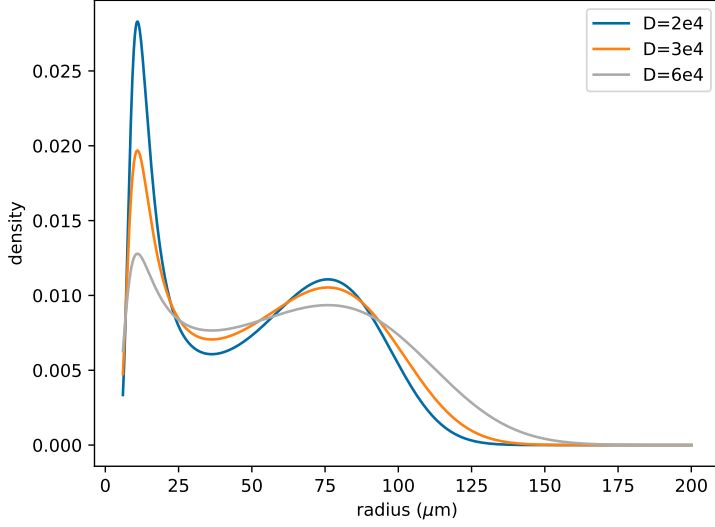


Figure 1: **Computed stationary solutions** from eq. 15 with three values for diffusion parameter. The other parameters are fixed to values reported in Table 1 and $L = 3 \text{ nmol}$, $\alpha = 0.29 \text{ nmol} \cdot \mu\text{m}^{-2} \cdot \text{h}^{-1}$, $\kappa = 0.001 \text{ nmol}$, $\rho = 200 \mu\text{m}$, $\chi = 0.0035 \text{ nmol}$.

163 and we introduce the following quantities to re-parameterize the model:

$$\theta_1 = \frac{\alpha L}{\beta(L + \kappa)}, \theta_2 = \rho^3, \theta_3 = V_\ell \chi \text{ and } \theta_4 = \frac{4\pi D}{V_\ell \beta}. \quad (16)$$

164 We obtain the system parameterized by $\theta = (\theta_1, \theta_2, \theta_3, \theta_4)$ the vector of unknown
165 quantities (assumed to be strictly positive),

$$\begin{cases} \frac{dx_1}{dr} = \frac{1}{\theta_4} \left(\theta_1 \frac{1}{1 + \frac{x_2^3}{\theta_2}} - \frac{1 + \frac{\gamma}{\beta} x_2^2}{x_2^2} \frac{\frac{4}{3}\pi x_2^3 - V_{em}}{\frac{4}{3}\pi x_2^3 - V_{em} + \theta_3} \right) x_1, \\ \frac{dx_2}{dr} = 1. \end{cases} \quad (17)$$

166 We recall that the values of V_{em} , β and γ are known (see Table 1).

167 We investigate the identifiability of unknown parameters using the **Structural**
168 **identifiability Toolbox** of Maple [32]. It is based on the Structural Identifiability
169 ANalyser (SIAN) algorithm which combines differential algebra and Taylor series
170 approaches [10, 11]. From an input ODE model, a polynomial equations system is
171 generated and the associated Gröbner basis is computed to assess the identifiability.

172 This method ranks parameters in three categories: *globally identifiable*, *locally but*
173 *not globally identifiable* and *non-identifiable*. A parameter θ_k is said to be locally
174 identifiable if there is a finite set of possible values for θ_k given the observation. When
175 a parameter is neither locally nor globally identifiable, it is called non-identifiable.

Applied to the system (17), SIAN algorithm returns that all the quantities $\theta_k, k \in \{1, \dots, 4\}$ are globally identifiable. Going back to the model parameters in equations (12)-(14), the parameters V_ℓ, β are known and the function $\rho \mapsto \rho^3$ is bijective so assuming the cell size distribution is observed, the set of identifiable quantities is

$$\left\{ \frac{\alpha L}{L + \kappa}, \rho, \chi, D \right\}.$$

176 We notice that we need at least the values of (L, κ) , (L, α) or (α, κ) to uniquely
177 estimate α, κ or L respectively. Only a combination of these values can be uniquely
178 retrieved when a size distribution $f(r)$ is given for all $r \in [r_{min}, r_{max}]$.

179 3.2 Parameter estimation procedure

180 Thanks to the parameter identifiability analysis, we know which parameters or pa-
181 rameter combinations we can expect to estimate from size distribution. We now need
182 a procedure to estimate these parameters and we want to verify this procedure on a
183 benchmark case: synthetic data.

184 **Minimization algorithm** To define a procedure to estimate model parameters,
185 we first introduce a cost function. We want to minimize this function to compare the
186 model output and the measurements. Then, we choose an algorithm to minimize this
187 function.

188 Let θ be the parameter vector to be estimated. We denote by N the number of
189 measured radii for the considered observation. Given the vector of measured radii,
190 $(r_i)_{i=1, \dots, N}$, we estimate θ by minimizing the cost function defined as follows,

$$\mathcal{L}(\theta) = - \sum_{i=1}^N \log(f(r_i, \theta)) \quad (18)$$

191 where $f(r_i, \theta)$ is the value of a density f , solution of the model, computed at (mea-
192 sured) radius r_i with the parameter vector θ .

193 To find the optimal parameter values, we use the Covariance Matrix Adaptation
194 Estimation Strategy (CMA-ES) algorithm [8]. This optimization method has been
195 widely used and has proved its effectiveness for mathematical model parameters esti-
196 mation in different fields of application like medicine [9, 26] and ecology [30]. In this

197 algorithm, from initial parameters, new possible solutions are sampled with a mul-
 198 tivariate normal distribution. The covariance matrix depends on a step-size control
 199 introduced to enhance the exploration of parameter space. A weighted combination
 200 of the best candidates is then selected according to the value of the cost function
 201 (18) and it is updated with the covariance matrix. These steps are repeated until
 202 termination criteria are reached. At each generation, this method takes into account
 203 recombination, mutation and selection of the possible candidates as an evolution al-
 204 gorithm.

205 Estimation of $(\theta_1, \rho, \theta_3, \theta_4)$ is performed with CMA-ES using cell size distribution
 206 as observation (we replace $\theta_2 = \rho^3$ by ρ). The vector of parameters is also scaled to
 207 have components of similar order of magnitude (scaling factors are $[\theta_1 10^2, \rho 10^{-3}, \theta_3 10^{-4}, \theta_4 10^2]$).
 208 Finally, to test the impact of the initial guess on the algorithm results, we perform 100
 209 runs of CMA-ES with different initial parameters, we report the mean and standard
 210 deviation of these runs.

211 In order to run the CMA-ES algorithm, we used `cma` Python package [33]. The
 212 `fmin2` function of this package is used with default parameters and an initial standard
 213 deviation of 0.05 (in each coordinate). The files to run parameter estimation are avail-
 214 able on https://plmlab.math.cnrs.fr/audebert/adipocyte_size_modeling.

215 **Parameter estimation on synthetic data** We first estimate parameters with
 216 data generated with the model (synthetic data). To generate such data, we compute
 217 the solution of the model for chosen parameters with equation (15). Then, from
 218 the obtained density, 10,000 samples are drawn leading to a first synthetic data set.
 219 To mimic the true measurements we also consider a second type of synthetic data
 220 where on the 10,000 samples only radii greater than $10\mu m$ are observed. With this
 221 procedure, we want to assess the impact of missing data on the parameter estimation.
 222 To quantify the precision of the parameter estimation we compute a relative error
 223 defined by $\mathcal{E} = |p - p_e|/p$, with p_e the parameter estimated value and p the true value
 224 of the parameter (chosen to generate synthetic data).

225 Two different parameter vectors are used to obtain synthetic data sets (*synthetic*
 226 *data set 1* and *synthetic data set 2*). The second column of Table 2 sums up the
 227 chosen parameter values (true). The parameter estimation is performed for both
 228 synthetic data sets without and with missing observations (Table 2 columns 3 to 8).

229 Columns 3 and 4 in Table 2 display the average and the standard deviation of the
 230 estimated parameter values over the 100 runs. We note that the differences between
 231 the 100 estimations can be neglected, showing that the initial guess has no impact on
 232 the estimation.

233 In both synthetic data cases, when the estimation is performed with the complete
 234 data set, the estimated parameter values are similar to the true values with relative

235 errors smaller than 5% (Table 2 column 5).

236 One can notice a difference between the two data sets when the estimation is
237 performed with missing observations in the data. The last three columns of Table
238 2 show that depending on the considered data set more or less information is lost
239 when we observe only cells with radii larger than a threshold. In *synthetic data set 1*,
240 the impact on the parameter estimation is relatively small and relative errors remain
241 below 5%. In *synthetic data set 2*, we are able to correctly estimate the values of θ_1 ,
242 ρ and θ_4 but the information about parameter θ_3 seems lost, and the relative error
243 increases to 65%.

244 The number of observed cells is reduced in these data sets and not in the same
245 way in each set. On synthetic data we know exactly the percentage of information
246 that is missing. In *synthetic data set 1* when we remove samples larger than $10\ \mu m$,
247 15% of the observation is missing, whereas in *synthetic data set 2* we remove 28%
248 of the initial distribution. This difference may explain the poor estimation of θ_3 in
249 *synthetic data set 2* with missing observations.

250 In the case of synthetic data sets, variations along θ_3 mainly affect the first mode
251 of cell size distribution: increasing θ_3 strongly reduces the density of small cells and
252 slightly increases the density of large adipocytes. Therefore, with a data set of samples
253 with radii larger than $10\ \mu m$, the missing information on the first mode has an impact
254 on the estimation of θ_3 . Moreover, this parameter is related to parameter χ that
255 drives the lipolysis mechanism in the model (size reduction). These results show that
256 lipolysis is important for driving small cell distribution.

257 **From estimated parameter values to parameter intervals** The identifiability
258 analysis ensures that the minimization problem should have only one solution and
259 the estimation procedure computes this solution. Here, we want to compute inter-
260 vals of parameter values for which the cost function remains close to its minimum.
261 Our approach follows the strategy of ABC method where parameters are sampled
262 from a prior distribution and are then selected according to a criterion based on the
263 evaluation of the model output [29].

264 To sample a parameter θ_i , a new parameter $\bar{\theta}_i$ is first generated uniformly in
265 $[0.8\hat{\theta}_i, 1.2\hat{\theta}_i]$ where $\hat{\theta}_i$ is the estimated parameter value obtained with the CMA-ES
266 algorithm. Then, the cost function is computed with parameter $\bar{\theta}_i$ while the other
267 parameters are fixed at their estimated values. The parameter is selected if the cost
268 function is below 0.1% of $\mathcal{L}(\hat{\theta})$. This threshold was set to investigate the parameter
269 space with small changes on cell size distribution. Note that the parameter sampling
270 is performed one at a time. This strategy is repeated until 1,000 replicates are selected
271 per parameter.

272 Table 3 shows for each parameter the considered range of values and the selected

Table 2: **Results of parameter estimation procedure performed on synthetic data sets without and with missing data.** The first three columns display the parameter names, orders and true values for both synthetic data sets. Columns 3 and 4 present the estimated parameters for complete data sets (10,000 samples), it shows the average over 100 estimations with different initial guesses and standard deviations. The fifth column sums up the difference between true parameter and its estimation with a relative error in percentage. The three last columns present the same values for the same data sets with missing observations: only radii over $10\mu m$ are observed (samples $> 10\mu m$). All estimations are performed with CMA-ES algorithm of `fmin2` function from `cma` Python package. We choose the default parameters and an initial standard deviation of 0.05 (in each coordinate). The parameters are scaled to have similar sensitivity ($[\theta_1 \cdot 10^2, \rho \cdot 10^{-3}, \theta_3 \cdot 10^{-4}, \theta_4 \cdot 10^2]$).

<i>synthetic data set 1</i>			10,000 samples			samples $> 10\mu m$		
parameter	order	true	esti. value	std	rel. err.	esti. value	std	rel. err.
θ_1	10^{-3}	9.60	9.61	$1 \cdot 10^{-8}$	0.2%	9.62	$2 \cdot 10^{-8}$	0.3%
ρ	10^2	1.50	1.50	$1 \cdot 10^{-8}$	0.2%	1.49	$2 \cdot 10^{-8}$	0.8%
θ_3	10^3	2.18	2.17	$5 \cdot 10^{-8}$	0.6%	2.09	$2 \cdot 10^{-7}$	4.2%
θ_4	10^{-3}	7.37	7.20	$2 \cdot 10^{-7}$	2.3%	7.35	$4 \cdot 10^{-7}$	0.3%
<i>synthetic data set 2</i>			10,000 samples			samples $> 10\mu m$		
parameter	order	true	esti. value	std	rel. err.	esti. value	std	rel. err.
θ_1	10^{-3}	9.92	9.92	$1 \cdot 10^{-8}$	0.04%	9.91	$1 \cdot 10^{-7}$	0.1%
ρ	10^2	2.00	2.00	$1 \cdot 10^{-8}$	0.2%	2.01	$5 \cdot 10^{-8}$	0.6%
θ_3	10^2	3.27	3.12	$2 \cdot 10^{-7}$	4.8%	5.39	$4 \cdot 10^{-6}$	65%
θ_4	10^{-2}	1.11	1.12	$2 \cdot 10^{-8}$	1.7%	1.12	$1 \cdot 10^{-7}$	1.2%

Table 3: **Range of selected values for the parameters.** The first three columns show the parameter names, orders and true values. For each data set, the estimated parameter value (column "esti. value") with CMA-ES method is subject to a maximum of 20% variation (column "esti. $\pm 20\%$ "). From this variation, a range of values is selected for each parameter (column "selec. values") allowing a maximum error rate of 0.1% on the value of the estimated cost function \mathcal{L} . For each parameter 1,000 samples are generated

<i>synthetic data set 1</i>			10,000 samples			samples $> 10\mu m$		
parameter	order	true	esti. value	esti. $\pm 20\%$	selec. values	esti. value	esti. $\pm 20\%$	selec. 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
<i>synthetic data set 2</i>			10,000 samples			samples $> 10\mu m$		
parameter	order	true	esti. value	esti. $\pm 20\%$	selec. values	esti. value	esti. $\pm 20\%$	selec. 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

273 intervals for each synthetic data set. For synthetic data sets without missing obser-
274 vations, the range of values selected by the procedure is reduced in comparison with
275 the initial one and contains the true parameter. This analysis gives an information
276 on the range of accepted values for each parameter. We note that, in *synthetic data*
277 *set 1*, the model output seems less sensitive to parameter θ_4 that has the largest range
278 of selected values. In *synthetic data set 2* the largest range of selected values is for
279 parameter θ_3 .

280 In data sets with missing observations, the selected ranges are not impacted for
281 *synthetic data set 1* (small difference for θ_3). In *synthetic data set 2*, the loss of
282 information about small cells leads to the selection of the total initial interval for
283 parameter θ_3 ($\pm 20\%$ of the estimated value) and an important increase of the se-
284 lected range for θ_4 (almost twice the length) compared to the case without missing
285 observations. As observed in section 2.3, parameter D (hence θ_4) controls the rela-
286 tive heights of both modes in the cell size distribution. This can explain that data
287 sets with missing observations on small sizes lead to higher uncertainty on θ_4 . These
288 results are in agreement with the computed relative errors of the previous paragraph
289 (Table 2).

4 Application to adipocyte size distribution measured in rats

4.1 Measurements of adipocyte size distribution

The measured cell size distributions used to perform parameter estimation come from previous experiments [28] and data from [12], but this part of the experiment has not been published. Here, only adipocyte size distributions of animals in normal physiological conditions are considered. We assume that these distributions represent a stable state for adipose tissue, corresponding to a steady state of the mathematical system.

We use two data sets of size distribution in retroperitoneal adipose tissue for a total of 32 male Wistar rats (20 rats METAJ, aged between 20 and 24 months, Charles River, L'Arbresle, France and, 12 rats EMPA, 12-week-old, Le Genest-Saint-Isle, France). Cell size distributions were measured with Beckman Coulter Multisizer IV (Beckman Coulter, Villepinte, France), which resulted in bimodal distributions [20, 16]. Due to limitations in measurement techniques, only cell radii larger than $7.5\mu m$ for the first experiment and $10\mu m$ in the second were measured. The measurement of large diameters is not limited by the measurement techniques. Each animal cell size distribution is composed of a minimum of 6,000 cell radii.

4.2 Parameter estimation with measured data

The estimation procedure validated on synthetic data is now applied to measured size distributions. Parameter estimation is performed with CMA-ES algorithm with radius distributions measured for 32 rats in the same experimental conditions. Figure 2 shows four examples of model-data fitting (the model fitting results of the 32 rats are available on https://plmlab.math.cnrs.fr/audebert/adipocyte_size_modeling). These results show the ability of the model to reproduce different types of cell size distribution. The height of each peak is not always correctly captured. This could be related to the loss of information due to missing observation for small cells in experimental data. In addition, the nadir is always underestimated by the model. We hypothesize that we are missing a process in the model to properly capture this point. However, the overall size distribution obtained with the model is in good agreement with the measured one.

Table 4 shows the mean, standard deviation and relative standard deviation (RSD) of the estimated parameter values obtained in the 32 rats. The RSD are relatively small for θ_1 and ρ , showing that the size distribution of adipocytes for rats in the same experimental conditions can be characterized with parameters in the same value ranges. The variability in the population is larger for parameter θ_3 and θ_4 (larger

326 RSD). However, the previous analysis on synthetic data showed that less confidence
 327 in the estimation is expected for these parameters, especially θ_3 .

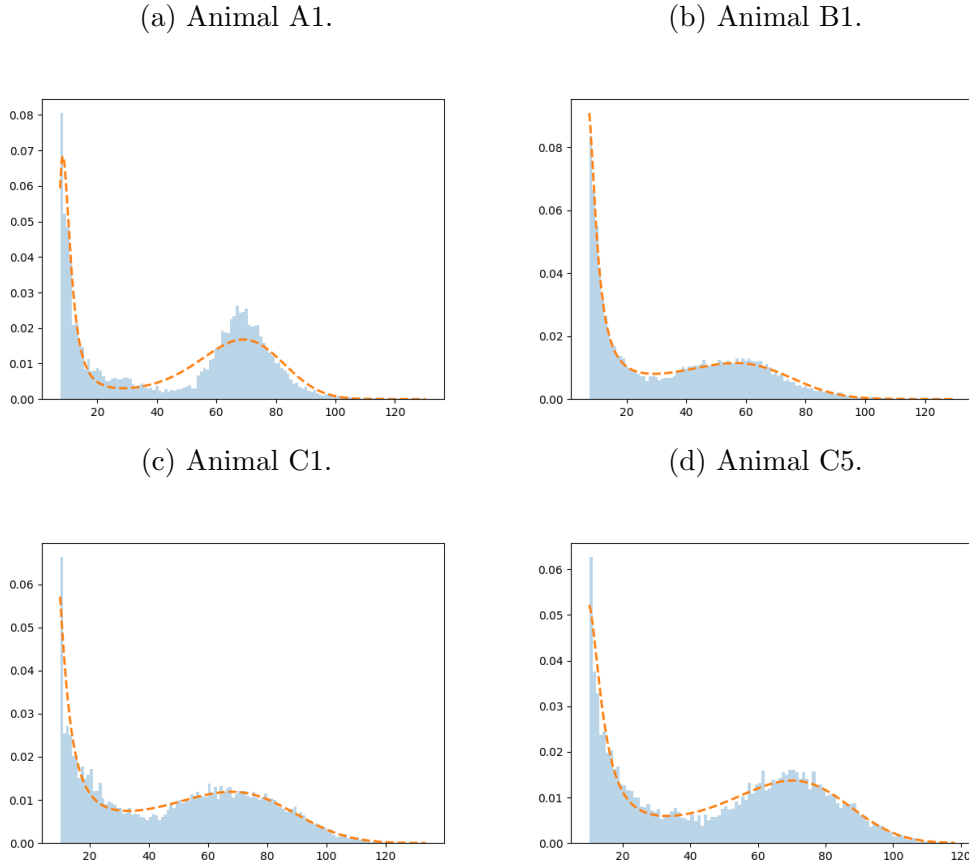


Figure 2: **Comparison model-data.** Four examples (over 32) of adipocyte radius distributions (in μm) as histograms in rat in normal physiological conditions and model output computed (dash lines) with estimated parameters (see section 4.1). The parameter estimations are performed with CMA-ES algorithm of `cma` Python package by minimizing the function \mathcal{L} eq. 18.

328 For each animal, accepted parameter ranges are also computed following the pro-
 329 cedure described in section 3.2 (Table 5). Figure 3 displays for each parameter the
 330 estimated value for each animal with the range of selected values (dots and bars).
 331 As expected, the parameter ranges are larger for parameters θ_3 and θ_4 compared to
 332 parameters θ_1 and ρ . Figure 3 also shows the mean (dash red line) and the standard
 333 deviation (gray area) over the rat population for each estimated parameter. It en-
 334 ables to compare the amplitude of the range of accepted values for each parameter

Table 4: **Parameter estimation with adipocyte size distributions measured in rats.** The first column is the parameter names. Over 32 estimations with the different animal cell size distributions, the mean is presented in the second column, the standard deviation in the third column and the fourth column is the relative standard deviation *i.e* the ratio of standard deviation over mean. The parameters are estimated with CMA-ES algorithm of `fmin2` function from `cma` Python package (with 100 initial guesses).

parameters	mean	std	RSD
θ_1	$9.6 \cdot 10^{-3}$	$2.8 \cdot 10^{-4}$	0.03
ρ	$1.57 \cdot 10^2$	$0.25 \cdot 10^2$	0.16
θ_3	$2.24 \cdot 10^3$	$1.07 \cdot 10^3$	0.47
θ_4	$8.21 \cdot 10^{-3}$	$2.58 \cdot 10^{-3}$	0.31

for each animal with the variability within the population. We can see that for each parameter the range of accepted values is always smaller than the standard deviation in the population. It shows that the largest standard deviation within the population obtained for θ_3 and θ_4 (Table 4) should not be attributed to less confidence in the estimations.

The range of selected values of parameter θ_3 in rats population is between 1070 and $4429 \mu m^3$. From this range of values, we can compute a range of radii for which the lipolysis term becomes mainly a surface based mechanism (i.e. $(V(r) - V_{em}) / (V(r) - V_{em} + \theta_3) > 0.95$). We find radii in the range $17.2 - 27.3 \mu m$.

Similarly, for lipogenesis, the parameter θ_1 is estimated within the rats population between 0.0092 and $0.010 \mu m^{-2}$. We remind that this quantity is a combination of parameters : $\theta_1 = \frac{\alpha L}{\beta(L+\kappa)}$ and parameter β is known [28]. We then obtain an estimation of $\frac{\alpha L}{(L+\kappa)}$ between 0.29 and $0.31 nmol.\mu m^{-2}.h^{-1}$. In the case of high available lipids, L is large and we can assume $\frac{L}{L+\kappa} \sim 1$. Under this assumption, the parameter α is estimated between 0.29 and $0.31 nmol.\mu m^{-2}.h^{-1}$. An alternative case is for low L , then we can assume $\frac{L}{L+\kappa} \sim L$ and the estimated values of θ_1 provide an estimation for αL .

The cell size threshold ρ of the Hill function in lipogenesis term is estimated in the range $115 - 204 \mu m$. Above this threshold, the term $\rho^3 / (\rho^3 + r^3)$ is smaller than 0.5 and limits the growth of the cell.

4.3 Sensitivity analysis

In order to investigate the differences between model output and measured cell size distribution, a sensitivity analysis is performed. Sensitivity analysis is a local analysis

358 and quantifies how sensitive the model output is to parameter changes. We choose to
359 apply the Sobol' method [25]. The sensitivity indices are based on the decomposition
360 of the output variance at each cell size point.

361 The first order index measures the singular effect of a parameter on the model
362 output. It represents the contribution part of the parameter alone in the variability of
363 model output. A high value of this index indicates a high contribution of the param-
364 eter, which means that the model output is highly sensitive to this parameter. The
365 total order index enables to include the effects depending on parameter interactions
366 (higher order indices).

367 The model output is the cell size distribution f computed with equation (15) for
368 radii from $7.5\mu m$ to $140\mu m$. To study the influence of the estimated parameters, each
369 parameter θ_i is uniformly distributed in a range of $\pm 1\%$ of estimated mean over the
370 population of rats (Table 4). The change of $\pm 1\%$ in parameters values is chosen such
371 that the adipocyte size distributions computed with these parameters are bimodal.
372 Then, Saltelli algorithm is performed to explore the parameter space leading to the
373 generation of $n(2d + 2)$ parameter samples with a Monte-Carlo approach [22, 25]. We
374 choose $n = 2048$ and $d = 4$ the number of parameters. The sensitivity analysis is
375 performed using the **SALib** Python Library [25, 22, 3, 21].

376 Figure 4(a) shows cell size distributions ranges computed with parameters from
377 the sampling design. With these small perturbations, a large variability is found
378 between the cell size distributions around the two modes. The first mode of the
379 adipocyte size density is represented by cells with radii from 7.5 to $10\mu m$. Regarding
380 large adipocytes, the higher densities present a high variability and correspond to
381 adipocyte size values from 50 to $120\mu m$. These results illustrate the heterogeneity of
382 cell sizes that can be obtained with the model with small changes in parameters.

383 Then, Sobol' indices are computed to determine which parameters are most influ-
384 ential on the cell size dynamic. The first-order indices are displayed for several radii
385 and each parameter in Figure 4(b). The results indicate that parameter θ_1 explains
386 the most the variations of cell sizes with a first-order sensitivity index between 0.6
387 and 1 for all radii. Interestingly, for the cells with radii around $40\mu m$, the index of
388 θ_1 decreases and we notice that ρ index increases (index equals 0.36). It shows that
389 parameter ρ around this point explains the variability of the model output up to
390 36% . The impacts of θ_3 and θ_4 are almost negligible on cells size distribution. From
391 $r = 90\mu m$, the results show that the influence of θ_1 decreases whereas ρ becomes
392 more influential and explains up to 18% of the output variability. The total-order
393 sensitivity indices are also computed (not shown) and are similar to first-order indices,
394 revealing that parameter interactions have a negligible influence on the adipocyte size
395 distributions.

396 The sensitivity analysis suggests that the cell size dynamics in rats is mainly driven
397 by the parameters depending on lipogenesis, and especially by θ_1 which represents

398 the combination of the unknown parameters (α, κ, L) .

399 Parameters θ_3 and θ_4 , associated with lipolysis (through χ) and diffusion (D)
400 respectively, have a negligible impact on the cell size dynamic along all cell sizes.
401 This result confirms the difficulty to identify these parameters in practice and are
402 in agreement with the largest ranges of selected parameter values. In addition, this
403 study highlights the fact that the nadir is difficult to capture since we observe an
404 opposite change in the parameter sensitivity around this radius. With this study we
405 are able to explain the results of parameter estimation on the measured data.

406 5 Discussion

407 We presented a mathematical model to describe adipocytes cell size distribution,
408 based on a partial differential equation and including lipid exchanges. With the
409 formulation of a stationary solution, we were able to solve numerically and efficiently
410 this model. Prior to the estimation of parameter with measurements, we analyzed
411 which parameter can be identifiable and how reliable are the estimations.

412 The identifiability of unknown parameters was studied with a re-parameterized
413 form of the model. We showed that only four quantities can be uniquely identified
414 and that three of our parameters of interest are related. These three parameters
415 cannot be identified separately with an observation of the cell size distribution only.
416 However, we can identify the threshold radius ρ involved in lipogenesis, the lipolysis
417 threshold χ as well as the diffusion coefficient D that describes cell size fluctuations.

418 The model calibration on synthetic data sets showed, in practice, an accurate
419 estimation of the parameters. When we considered data sets with missing observations
420 (similar to the measurements), we found that three over the four quantities can be
421 correctly estimated.

422 The model parameters were estimated on 32 adipocyte size distributions measured
423 in rats. With these estimated parameters, the overall distribution of cell size was
424 captured. However, the nadir part of the distribution as well as the height of the
425 modes were not perfectly reproduced. It is possible that the model is missing some
426 aspect of the adipocyte size dynamics that would help to better capture the nadir.
427 This is supported by the sensitivity analysis, that showed that the nadir part was not
428 sensitive specifically to one of the four considered parameters. Therefore, it makes
429 this part of the distribution difficult to fit. In addition, in the presented model, the
430 diffusion parameter D via θ_4 affects linearly both lipogenesis and lipolysis. It would
431 be interesting to change this modeling assumption with a more complex diffusion
432 process, impacting differently lipogenesis and lipolysis. For instance, considering a
433 size dependent diffusion coefficient could improve the agreement between the model
434 outputs and the observations.

435 We also think that our assumption regarding the normalization of the cell size
436 distribution (it integrates to 1 between r_{min} and r_{max}) affects the fits (especially
437 the height of the 2 modes). However, we have no background knowledge about the
438 total number of adipocytes in the distribution. In addition, we know that the data
439 collection does not include cells with a radius below a certain threshold. In [13], a
440 formulation has been proposed to approximate the total cell number in a fat pad
441 but to do this estimation, we need to have the fat pad mass which is not the case
442 in our experimental data. An other way to solve this issue would be to introduce
443 a parameter that quantifies the total number of cells. However with an additional
444 parameter, we will lose parameter identifiability. Then, we might need to fix other
445 unknown quantities, so this solution only shifts the problem.

446 Nevertheless, we have estimated parameter values for 32 rats. We found a larger
447 variability between rats in the estimated values of θ_3 and θ_4 (Figure 3). However,
448 the sensitivity analysis showed that the model is less sensitive to these parameters
449 (Figure 4). For θ_1 and ρ , the estimated values were more robust within the population
450 leading us to believe that θ_1 , ρ are less individual-specific parameters. However they
451 could change if the estimation is performed with another species. This result sug-
452 gests lipolysis (driven by χ) is more an individual-dependent process than lipogenesis
453 (driven by θ_1 and ρ) that is more constant within the population.

454 Recruitment of new cells via adipogenesis or cell death were not included in
455 our model. Since we were looking at the distribution of size at one specific time,
456 these mechanisms can be neglected. However, if one wants to represent longitudinal
457 adipocyte size distributions especially in case of diet changes, these processes should
458 be considered. This will have an impact on the cell size distribution, especially for
459 small cells, as suggested in [28]. Moreover, it is known that past diets affect the
460 adipocyte size regulation and may be irreversible [13, 27]. Indeed, past diets could
461 lead to a larger number of cells in the tissue. However, in the presented model, the
462 number of cells is not explicitly considered. This assumption should be modified to
463 take into account longitudinal size distributions and to be able to compare animals
464 with different diets. In past works [13, 14, 15, 17], the authors have considered partial
465 differential equation models that take into account a recruitment rate of new cells.
466 Our model could be extended with this extra term for adipogenesis modeling.

467 We believe that the presented framework can be adapted to estimate model pa-
468 rameters with adipocyte size distribution in other species than rats and in different
469 health conditions. Our current data set is not rich enough to enable us to study the
470 relation between model parameters and animal health conditions. With an adequate
471 data set, the presented framework may enable to establish links between the mathe-
472 matical model parameters and health conditions based on adipocyte size distribution
473 observations. The final purpose is to be able to characterize and potentially classify
474 the different obesity-related pathologies.

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- 580 [33] <https://github.com/CMA-ES/pycma>

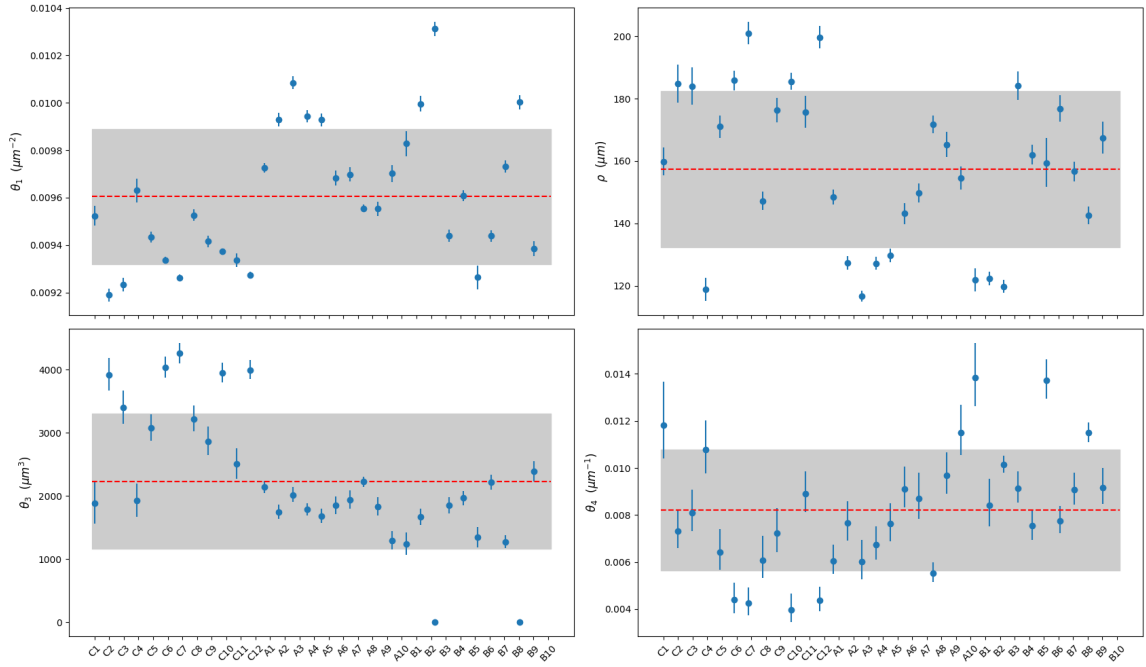


Figure 3: **Group variability and range of selected values.** Upper left and right figures display the results for parameters θ_1 and ρ . Lower left and right figures show the results for parameters θ_3 and θ_4 . For each estimated parameter the average over the population is shown with dash red line and the gray area is one standard deviation around the average computed over the population (values are reported in Table 4). For each parameter, the estimated value for each animal is displayed with dots and the bar represents the range of selected values. These ranges consist in values of the parameter (assuming the 3 others are fixed) for which the maximal cost function is 0.1% of the obtained cost function with the estimation (see section 3.2). All numerical values are reported in Table 5.

Table 5: **Parameter estimation results on measured adipocyte radius distribution in 32 rats.** First column is the animal identification. Estimation is performed with CMA-ES algorithm of `fmin2` function from `cma` Python package by minimizing the cost function \mathcal{L} , see eq. (18). The second to fourth columns show each parameter estimated value for each rat averaged over 100 runs with different initial guesses and the standard deviations are in brackets. For each estimated parameter, considering a maximum change of 20% of its estimated value, 1,000 samples are selected with a maximal error rate of 0.1% of the cost function value. The range of selected values of each parameter is given in the next four columns. These ranges consist in values of the parameter (assuming the other are fixed) for which the maximal cost function is 0.1% of the obtained cost function with the estimation. One can note that animals *B3* and *B9* have a value of θ_3 that is estimated to be zero ($10^{-12}/10^{-13}$). Indeed, these animals show particular cell size distributions with a very large number of small cells which can be due to a measurement artifact. The last column provides the cost function values associated with the parameter estimated values.

animal	estimated values				selected ranges				cost function values $\mathcal{L}(\theta) 10^4$
	$\theta_1 10^{-3}$ (std 10^{-11})	$\rho 10^2$ (std 10^{-6})	$\theta_3 10^3$ (std 10^{-4})	$\theta_4 10^{-3}$ (std 10^{-10})	$\theta_1 10^{-3}$	$\rho 10^2$	$\theta_3 10^3$	$\theta_4 10^{-3}$	
C1	9.52 (3.12)	1.60 (2.94)	1.89 (2.31)	11.8 (7.95)	9.49 - 9.56	1.56 - 1.64	1.59 - 2.21	10.5 - 13.5	5.35
C2	9.19 (1.05)	1.85 (2.16)	3.92 (1.07)	7.31 (3.43)	9.17 - 9.21	1.79 - 1.90	3.70 - 4.16	6.67 - 8.10	5.33
C3	9.23 (1.33)	1.84 (2.54)	3.40 (1.50)	8.10 (4.82)	9.21 - 9.26	1.79 - 1.89	3.17 - 3.65	7.40 - 8.99	4.29
C4	9.63 (2.27)	1.19 (1.63)	1.92 (1.52)	10.8 (5.75)	9.59 - 9.68	1.15 - 1.22	1.70 - 2.16	9.88 - 11.9	6.48
C5	9.43 (1.75)	1.71 (1.99)	3.08 (1.34)	6.43 (3.25)	9.41 - 9.45	1.68 - 1.74	2.90 - 3.27	5.75 - 7.31	4.46
C6	9.34 (1.41)	1.86 (1.92)	4.04 (1.13)	4.39 (2.33)	9.32 - 9.35	1.83 - 1.89	3.89 - 4.19	3.88 - 5.08	4.45
C7	9.26 (1.02)	2.01 (1.89)	4.26 (0.91)	4.26 (2.02)	9.25 - 9.27	1.98 - 2.04	4.12 - 4.42	3.80 - 4.86	4.44
C8	9.53 (2.15)	1.47 (1.86)	3.22 (1.36)	6.09 (3.29)	9.50 - 9.55	1.45 - 1.50	3.04 - 3.41	5.42 - 7.01	4.58
C9	9.42 (1.9)	1.76 (2.25)	2.87 (1.49)	7.24 (3.65)	9.39 - 9.44	1.73 - 1.80	2.68 - 3.08	6.52 - 8.20	4.40
C10	9.37 (1.81)	1.86 (2.19)	3.95 (1.35)	3.97 (2.25)	9.36 - 9.39	1.83 - 1.88	3.81 - 4.10	3.50 - 4.58	4.43
C11	9.34 (1.69)	1.76 (2.46)	2.51 (1.81)	8.90 (5.35)	9.31 - 9.36	1.71 - 1.80	2.30 - 2.73	8.19 - 9.76	3.17
C12	9.27 (0.95)	2.00 (1.80)	4.00 (0.83)	4.37 (1.78)	9.26 - 9.29	1.96 - 2.03	3.87 - 4.14	3.98 - 4.89	4.43
A1	9.73 (1.5)	1.48 (1.04)	2.14 (0.60)	6.06 (1.77)	9.71 - 9.74	1.46 - 1.50	2.05 - 2.23	5.55 - 6.67	5.04
A2	9.93 (2.23)	1.27 (1.12)	1.75 (0.74)	7.65 (2.87)	9.90 - 9.96	1.25 - 1.29	1.65 - 1.85	6.98 - 8.50	4.58
A3	10.1 (2.76)	1.17 (1.01)	2.02 (0.79)	6.01 (2.48)	10.1 - 10.1	1.15 - 1.18	1.92 - 2.13	5.35 - 6.86	8.69
A4	9.94 (2.01)	1.27 (1.03)	1.79 (0.60)	6.74 (2.17)	9.92 - 9.97	1.25 - 1.29	1.70 - 1.88	6.18 - 7.44	6.99
A5	9.93 (1.91)	1.30 (1.05)	1.68 (0.63)	7.62 (2.58)	9.90 - 9.95	1.28 - 1.32	1.59 - 1.79	6.98 - 8.42	4.18
A6	9.68 (1.44)	1.43 (1.15)	1.85 (0.62)	9.11 (2.70)	9.65 - 9.71	1.40 - 1.46	1.73 - 1.98	8.41 - 9.97	5.89
A7	9.70 (1.81)	1.50 (1.38)	1.93 (0.75)	8.72 (3.22)	9.67 - 9.72	1.47 - 1.53	1.81 - 2.07	7.92 - 9.68	3.90
A8	9.55 (0.98)	1.72 (1.07)	2.23 (0.49)	5.53 (1.43)	9.54 - 9.57	1.69 - 1.74	2.16 - 2.30	5.20 - 5.94	3.66
A9	9.55 (1.54)	1.65 (1.66)	1.83 (0.78)	9.70 (3.63)	9.53 - 9.58	1.62 - 1.69	1.71 - 1.97	8.98 - 10.1	3.48
A10	9.70 (1.71)	1.54 (1.35)	1.3 (0.77)	11.5 (4.09)	9.67 - 9.74	1.51 - 1.58	1.17 - 1.44	10.5 - 12.6	5.24
B1	9.83 (2.16)	1.22 (1.36)	1.24 (0.94)	13.8 (6.65)	9.78 - 9.88	1.19 - 1.25	1.09 - 1.40	12.7 - 15.2	8.73
B2	10.0 (2.31)	1.22 (1.06)	1.67 (0.70)	8.42 (2.80)	9.97 - 10.0	1.20 - 1.24	1.56 - 1.79	7.61 - 9.45	6.29
B3	10.3 (1.42)	1.20 (0.74)	9.24 10^{-16} (1.52 10^{-8})	10.1 (9.13)	10.3 - 10.3	1.18 - 1.22	0.76 - 1.09 10^{-15}	9.83 - 10.5	5.85
B4	9.44 (1.04)	1.84 (1.43)	1.85 (0.62)	9.14 (2.53)	9.41 - 9.46	1.80 - 1.88	1.74 - 1.97	8.60 - 9.81	7.71
B5	9.61 (1.16)	1.62 (1.06)	1.97 (0.61)	7.54 (2.35)	9.59 - 9.63	1.59 - 1.65	1.87 - 2.07	7.02 - 8.19	7.19
B6	9.26 (2.11)	1.59 (2.15)	1.34 (0.87)	13.7 (6.14)	9.22 - 9.31	1.52 - 1.67	1.21 - 1.49	13.0 - 14.5	2.23
B7	9.44 (0.93)	1.77 (1.2)	2.22 (0.55)	7.76 (2.44)	9.42 - 9.46	1.73 - 1.81	2.11 - 2.33	7.27 - 8.34	2.90
B8	9.73 (1.69)	1.57 (1.22)	1.28 (0.73)	9.07 (3.23)	9.71 - 9.76	1.54 - 1.59	1.19 - 1.37	8.51 - 9.72	4.54
B9	10 (1.17 10^5)	1.43 (1.25 10^3)	1.74 10^{-6} (17.4)	11.5 (8.22 10^4)	9.97 - 10.0	1.40 - 1.45	1.43 - 2.05 10^{-6}	11.1 - 11.9	4.53
B10	9.38 (1.52)	1.67 (1.98)	2.39 (0.81)	9.17 (3.68)	9.36 - 9.41	1.63 - 1.72	2.25 - 2.53	8.55 - 9.93	3.32

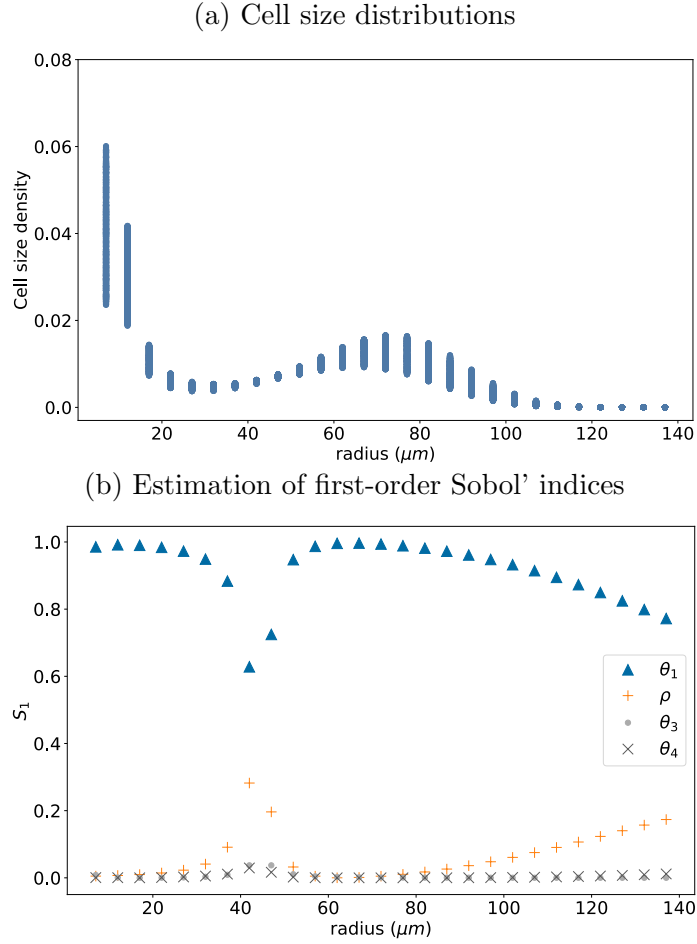


Figure 4: (a) A sample of cell size distributions. The parameter sampling design is constructed using Saltelli algorithm where each parameter is uniformly distributed in a range of values corresponding to $\pm 1\%$ of the mean of its estimated value in rats (Table 4). A number of 20,480 samples giving bimodal distributions are generated to estimate the Sobol' indices. (b) Estimation of first-order Sobol' indices for θ_1 , ρ , θ_3 and θ_4 using a Monte-Carlo based approach [25, 22, 3, 21].