Deducing cellular processes from cell-size distributions

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Laboratory of Biological Modeling

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My group focuses on

The gas tank (a.k.a. adipose tissue) and the generator (a.k.a. mitochondria)

Avoid the difficult questions of appetite control and addiction

The gas tank

- Mammals cannot excrete much excess fat directly. Apparently, there was no evolutionary pressure to include such a process.
- Mammals can sequester fat in adipose tissue and use this dense energy source as needed.
- Insulin is a signal for substrate switching, shutting off lipolysis and facilitating glucose entry into tissues that require active transport.

What happens when the gas tank overflows?

- Can adipose tissue grow indefinitely?
- Apart from mechanical stress on joints and the heart, does stored (= sequestered) fat lead to any pathology?

Working hypothesis

A dysfunction in fat storage results in an underutilization of glucose and a loss in metabolic flexibility, partly from ineffective insulin signaling. High serum glucose leads to damage in tissues that are unable to control glucose entry.

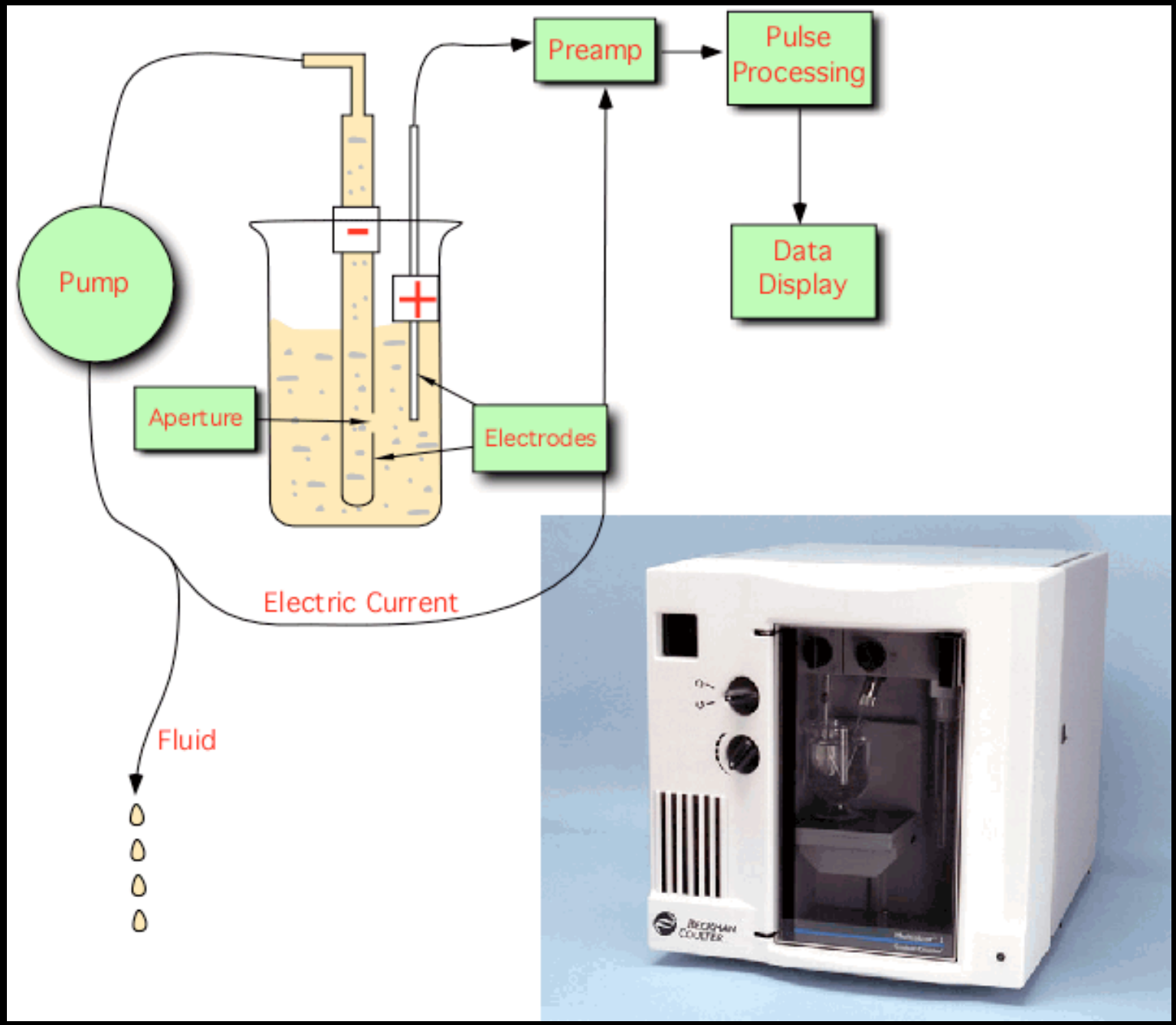
Adipose tissue growth

The dynamical aspects of adipose tissue growth have been studied but experimental limitations preclude direct observations. We use mathematical modeling of cross-sectional and longitudinal data to understand the processes by which adipose tissue grows.

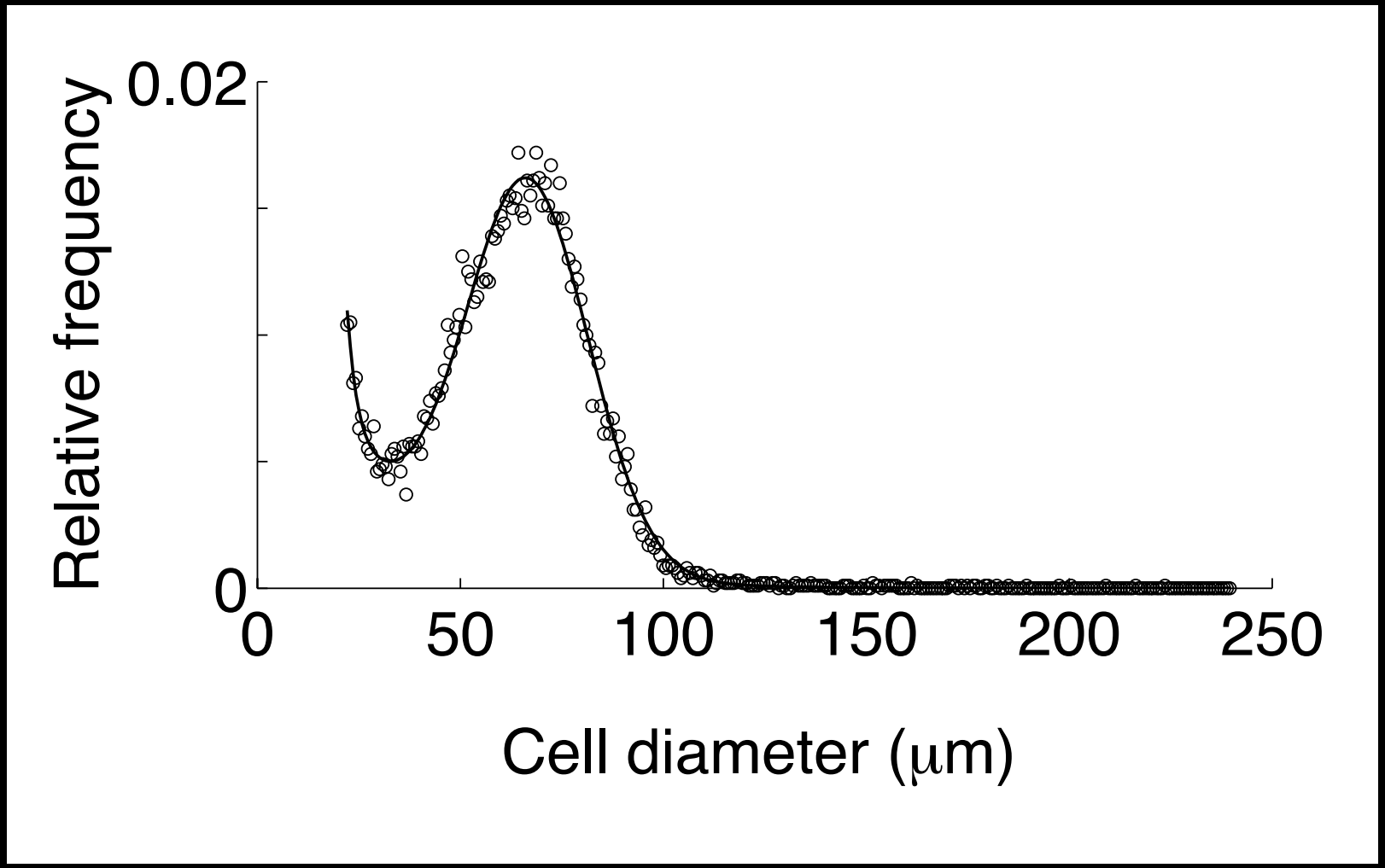
How can our body regulate energy storage capacity (fat pads) for a given diet?

- plasticity of adipose cell number (under weight gain and loss)
- differences between fat depots (visceral vs. subcutaneous fat)

Coulter counter



Cell-size distributions



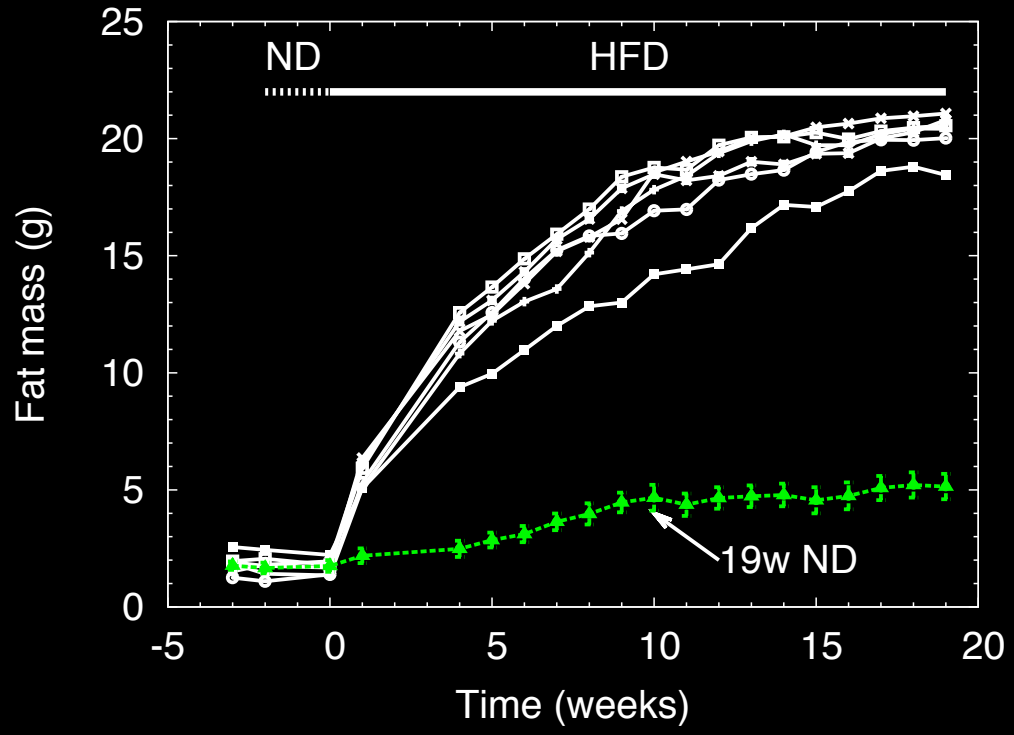
Data

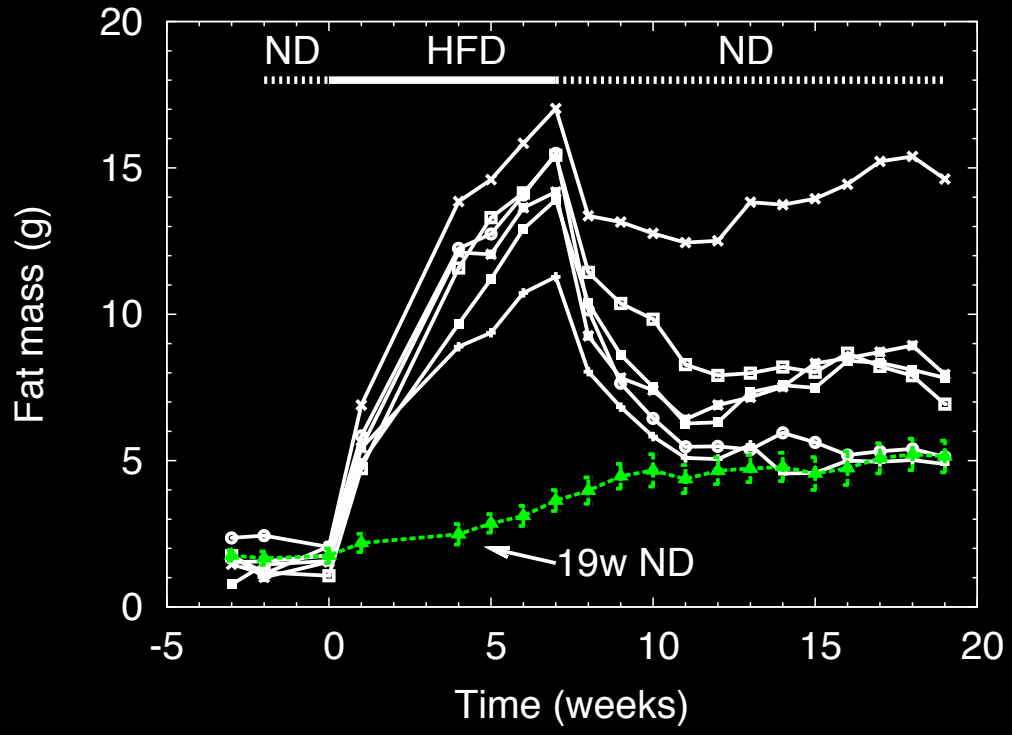
- Cell-size distributions are probability distributions of cell number as a function of cell diameter.
- The overall cell number can be deduced from the cell-size distribution and the weight of the fat pad, using the density of adipose tissue.

Moduli problem

- Smooth parametrization of cell-size distributions
- Kinetics of cell-size distributions
- Dynamics of cell-size distributions

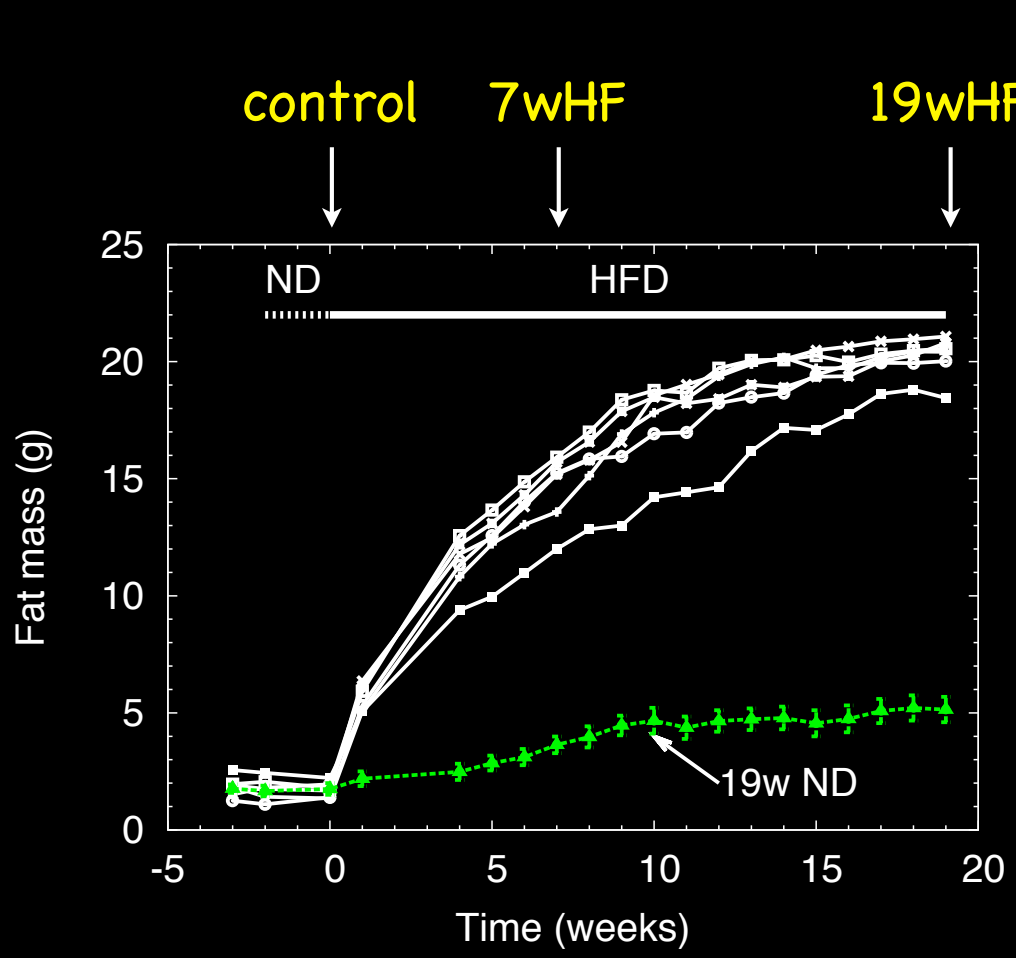
Energy storage capacity adapts dynamically to diet

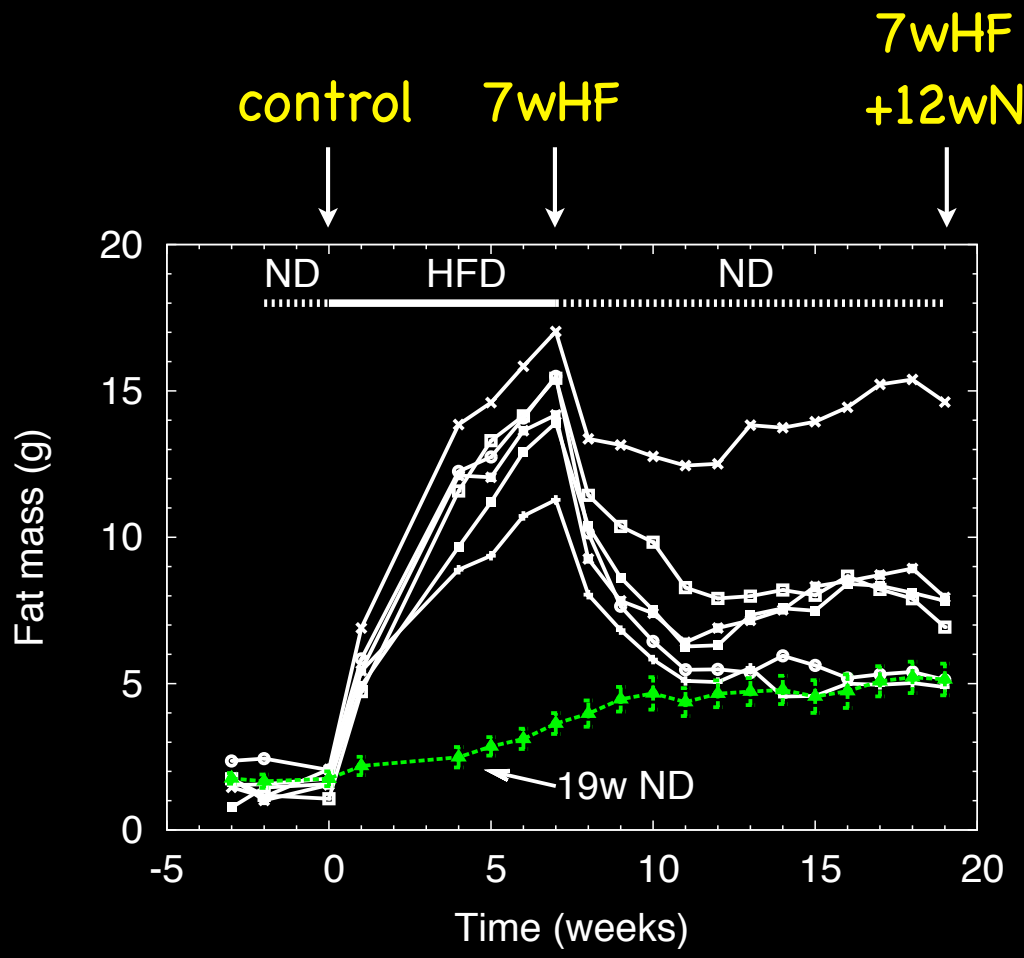




(Guo et al., 2009)

Energy storage capacity adapts dynamically to diet

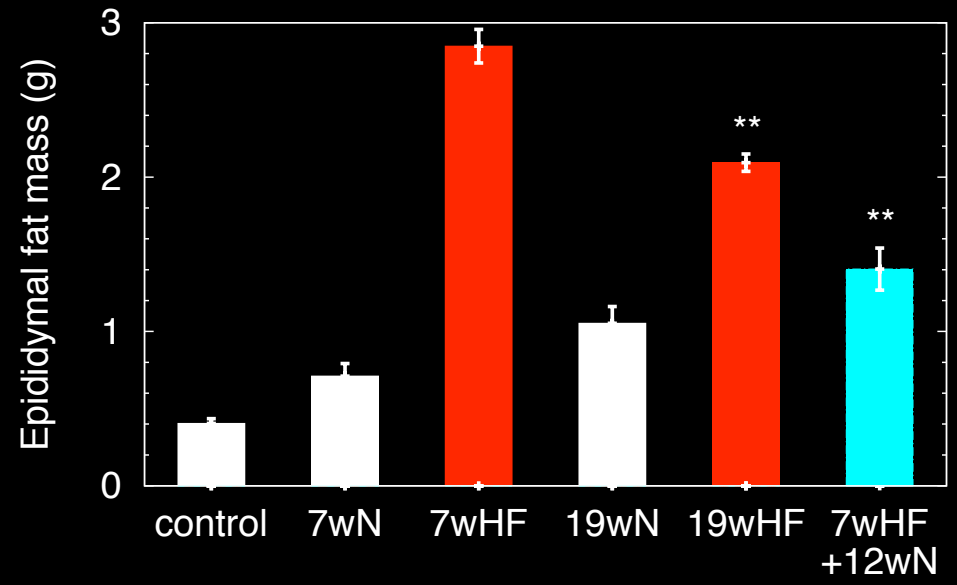


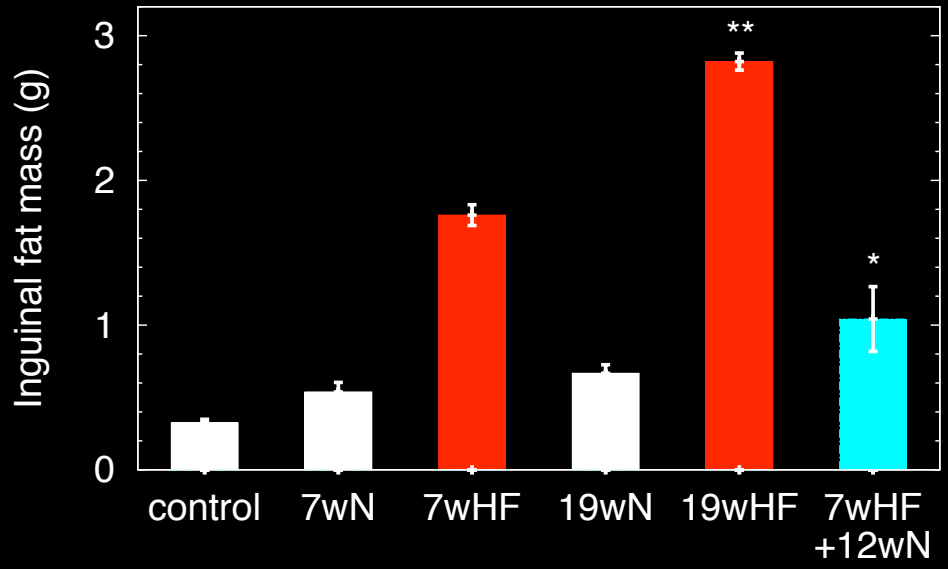


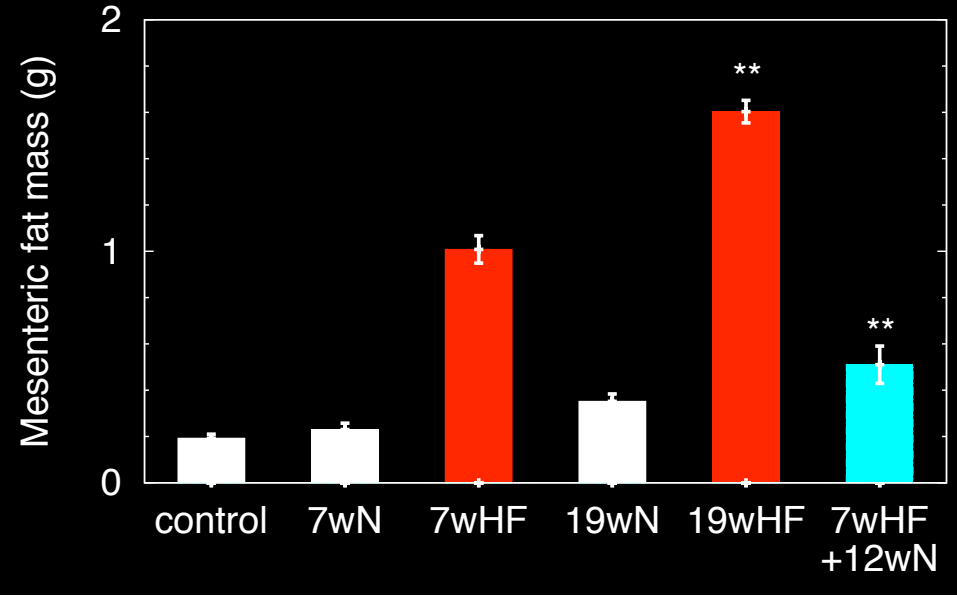
fat pad mass and cell-size distributions

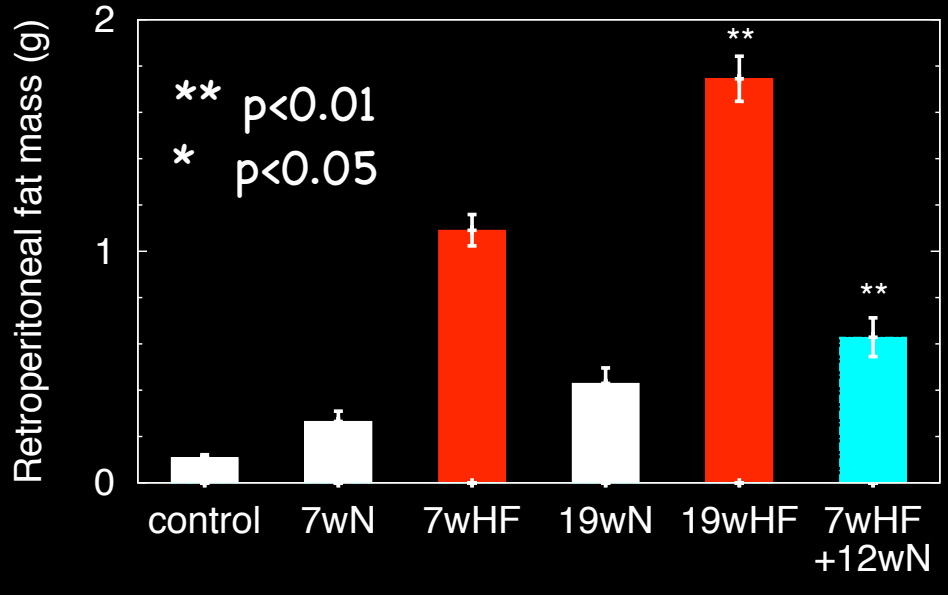
(Guo et al., 2009)

Only epididymal fat mass decreases under 19w high-fat diet



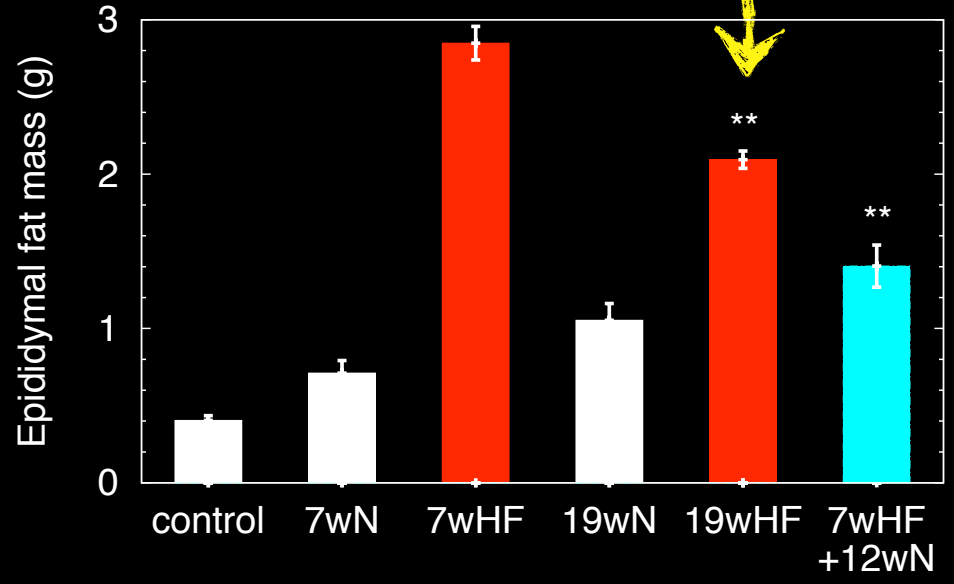


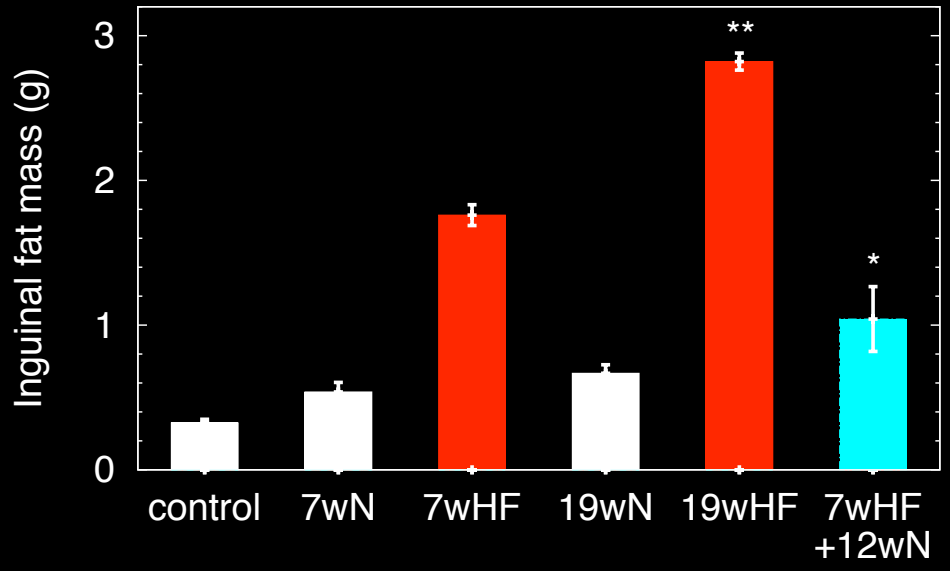


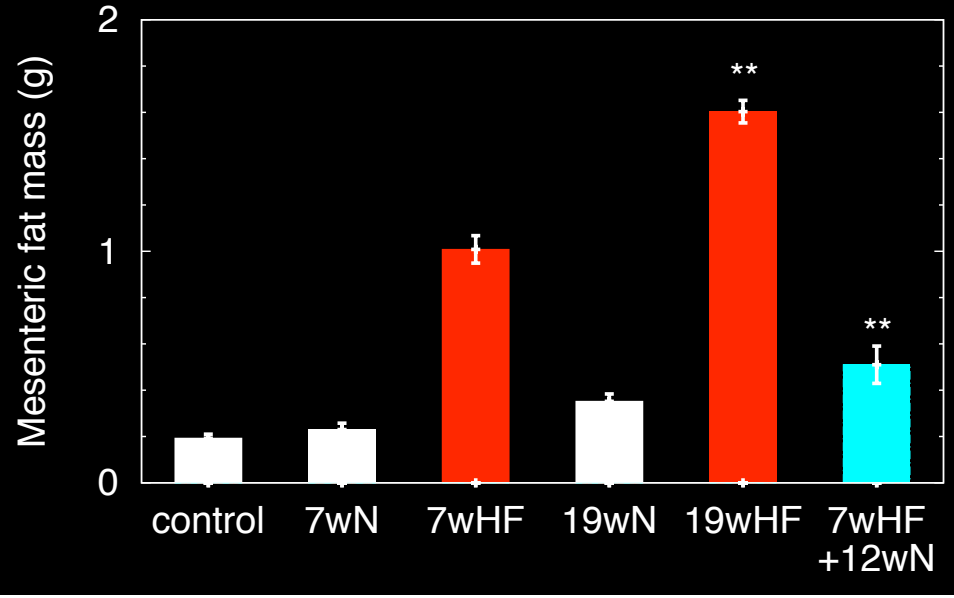


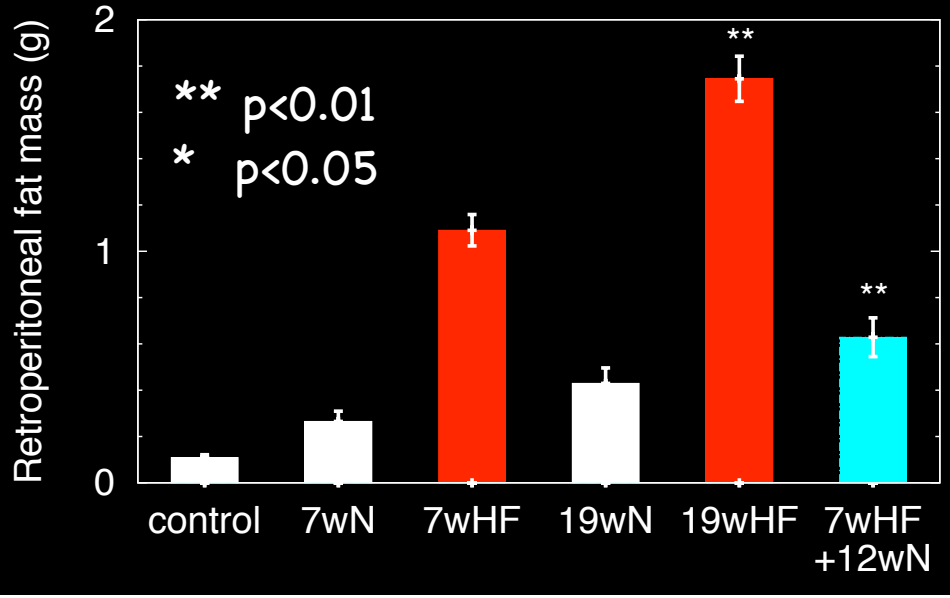
Only epididymal fat mass decreases under 19w high-fat diet

(Streissel et al., 2007)



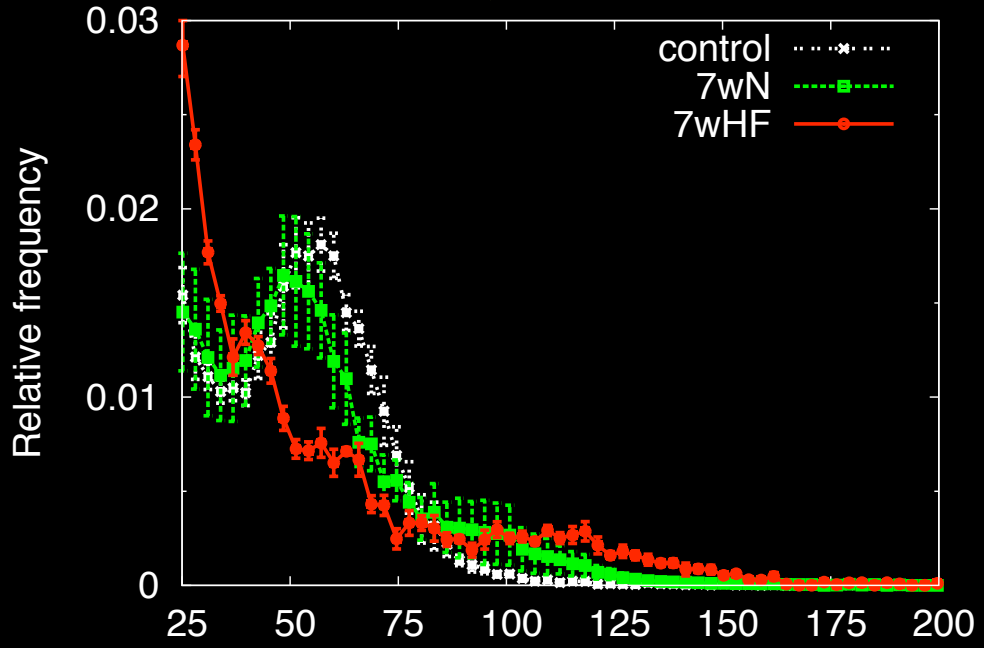


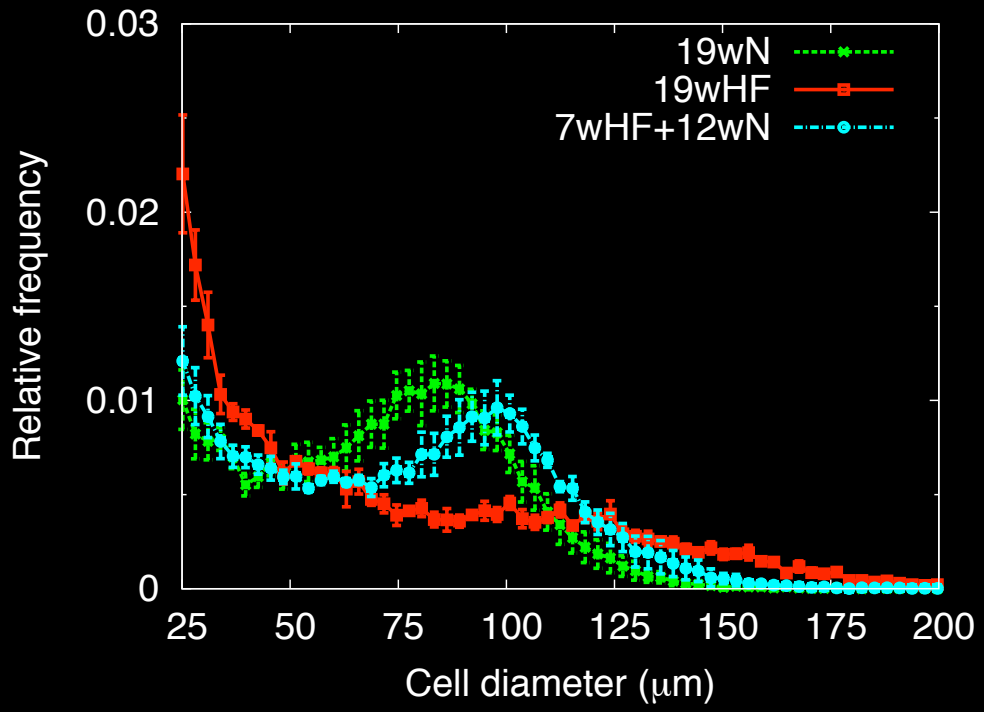




Adipose cell-size distributions

epididymal





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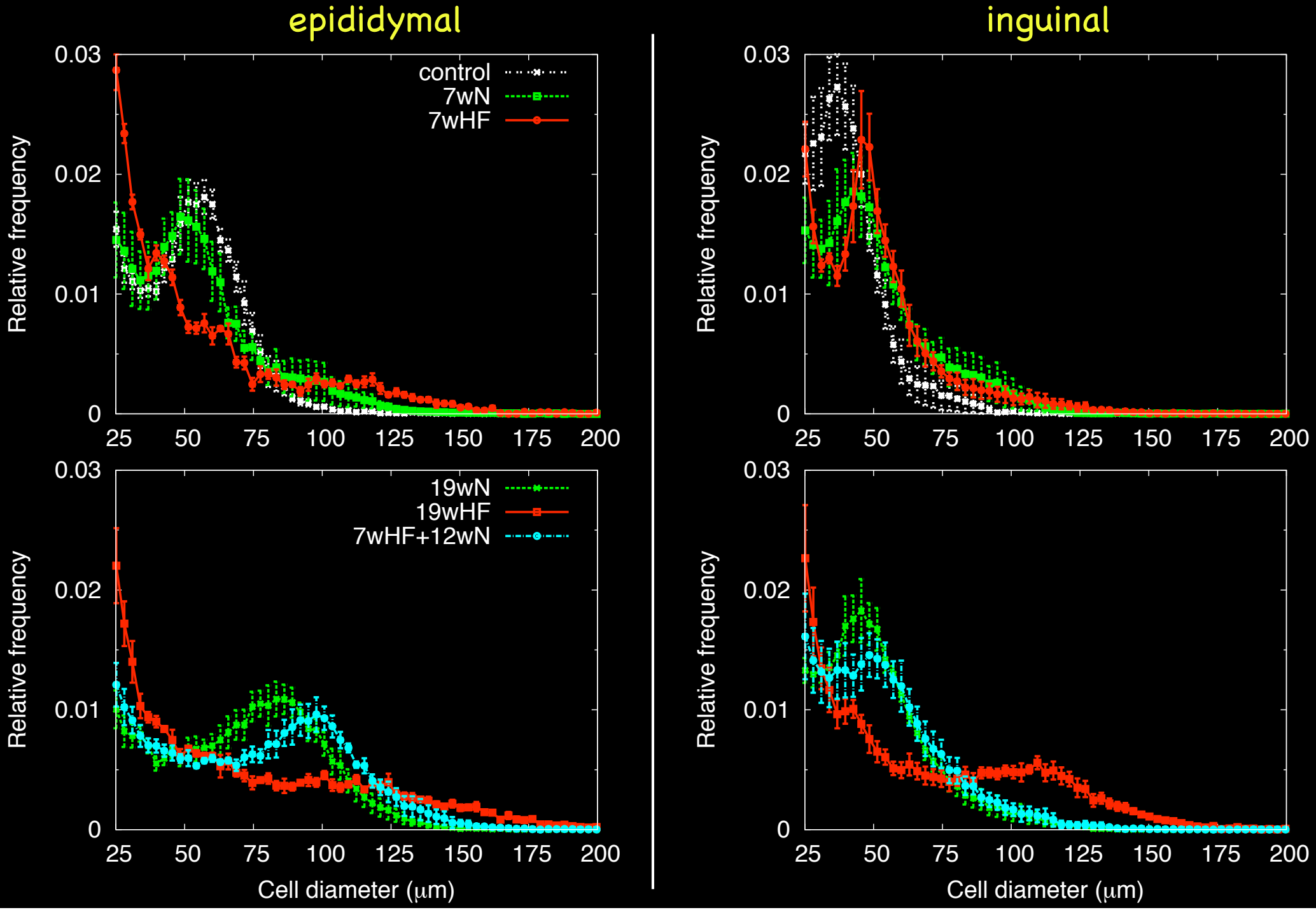
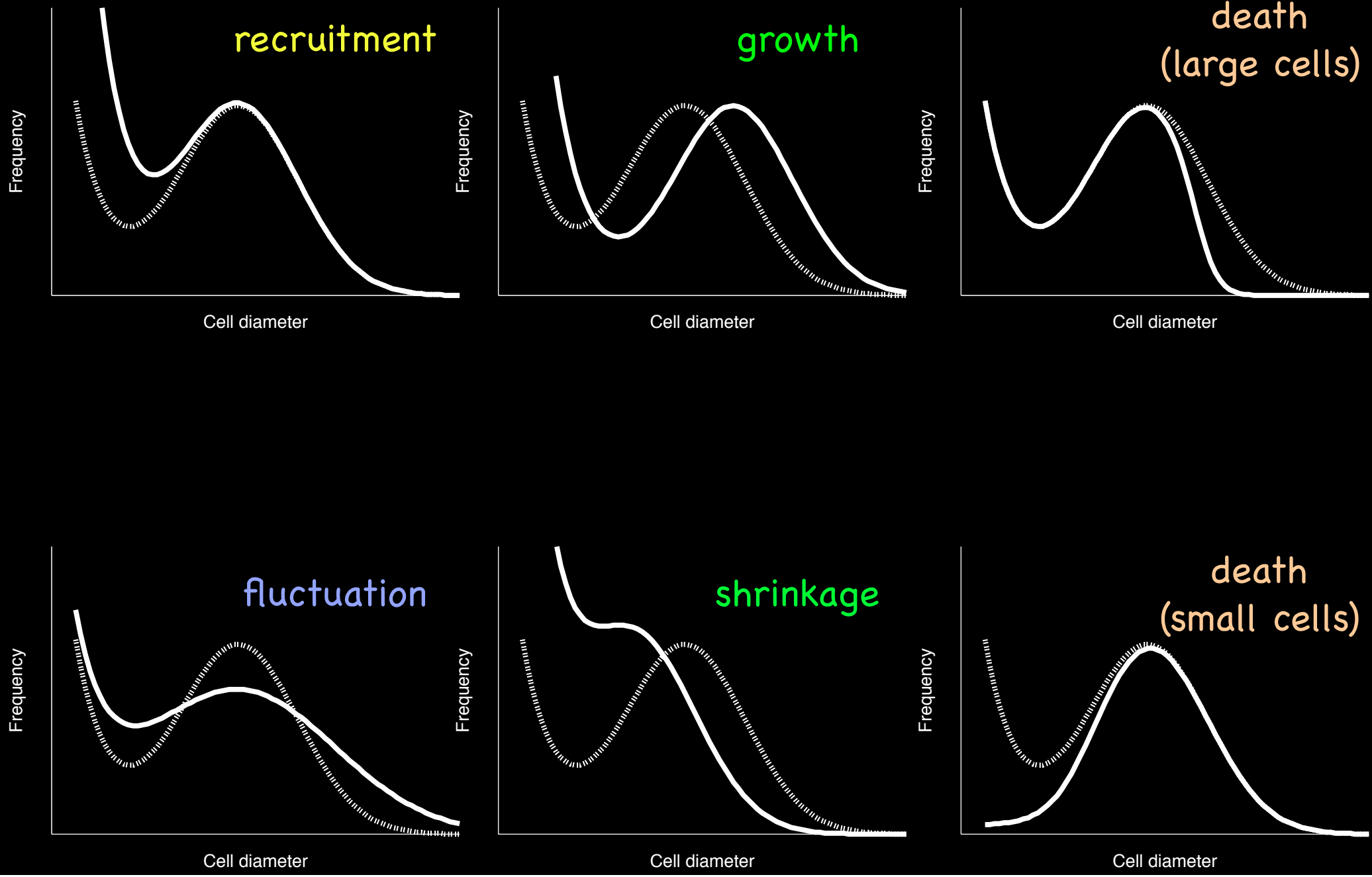


Multiple biological processes lead to cell-size distributions

(Jo et al., 2009)



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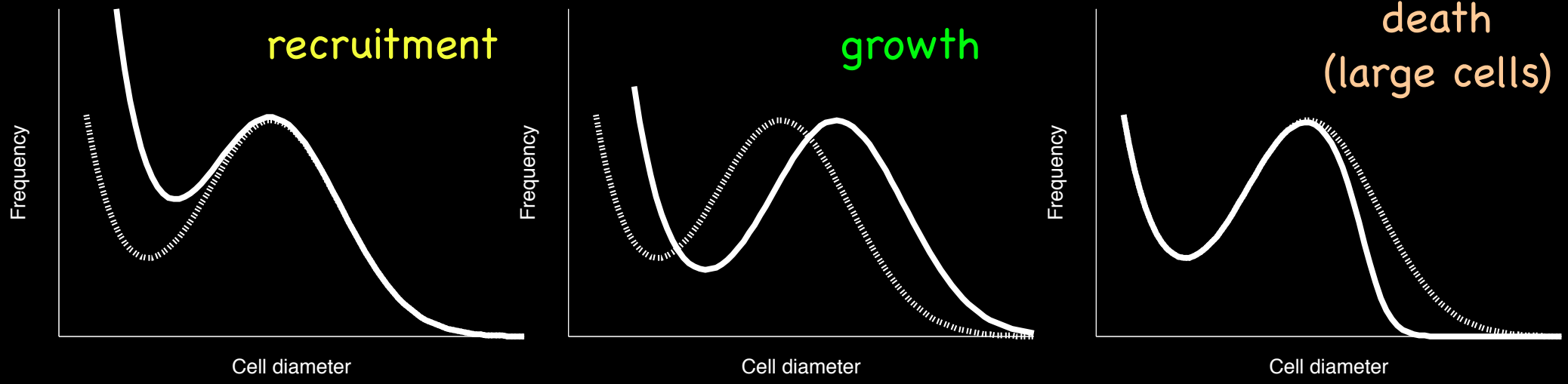
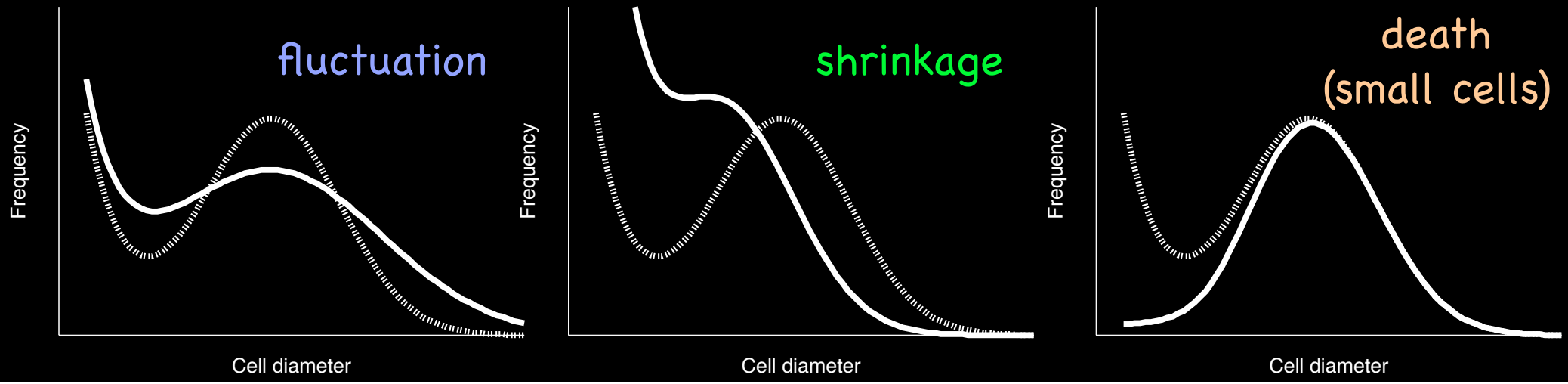
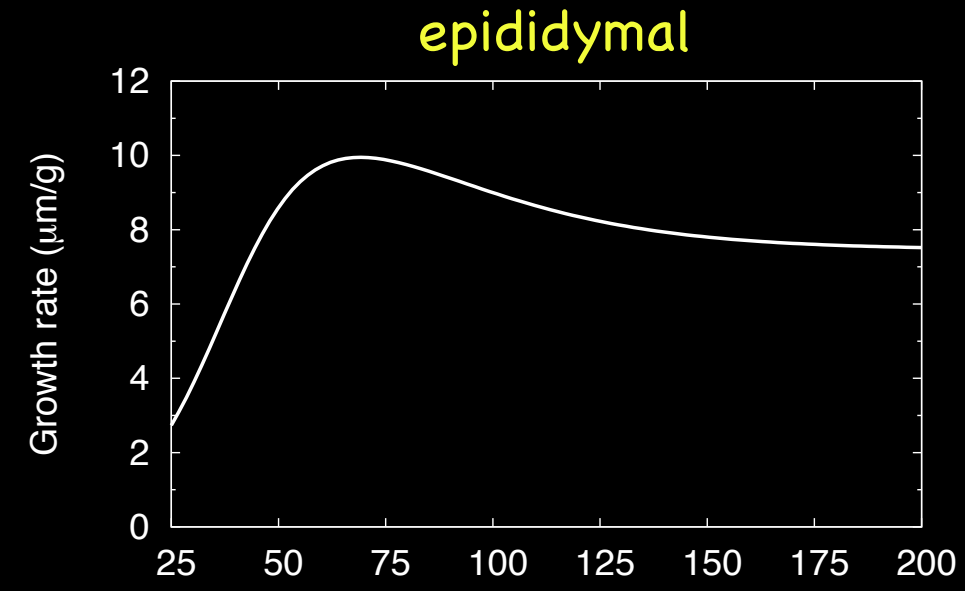
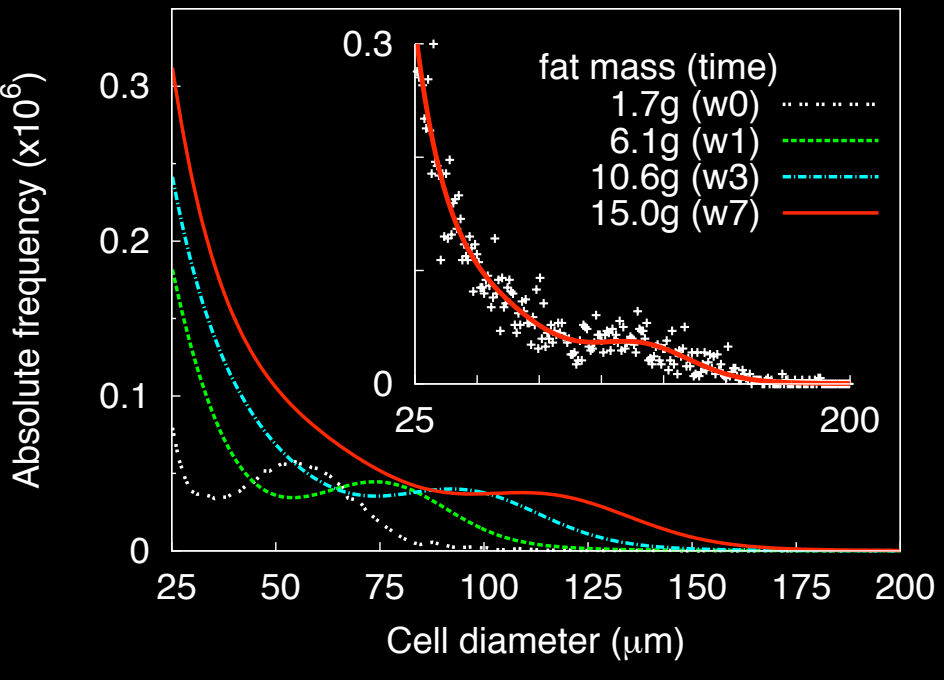


$$\frac{\partial n}{\partial m} = \beta n_p \delta(s - s_0) - v(s)\frac{\partial n}{\partial s} + D\frac{\partial^2 n}{\partial s^2} - k(s)\phi(m)n$$



The mathematical model can extrapolate changes of adipose cell-size distributions under 7w HFD





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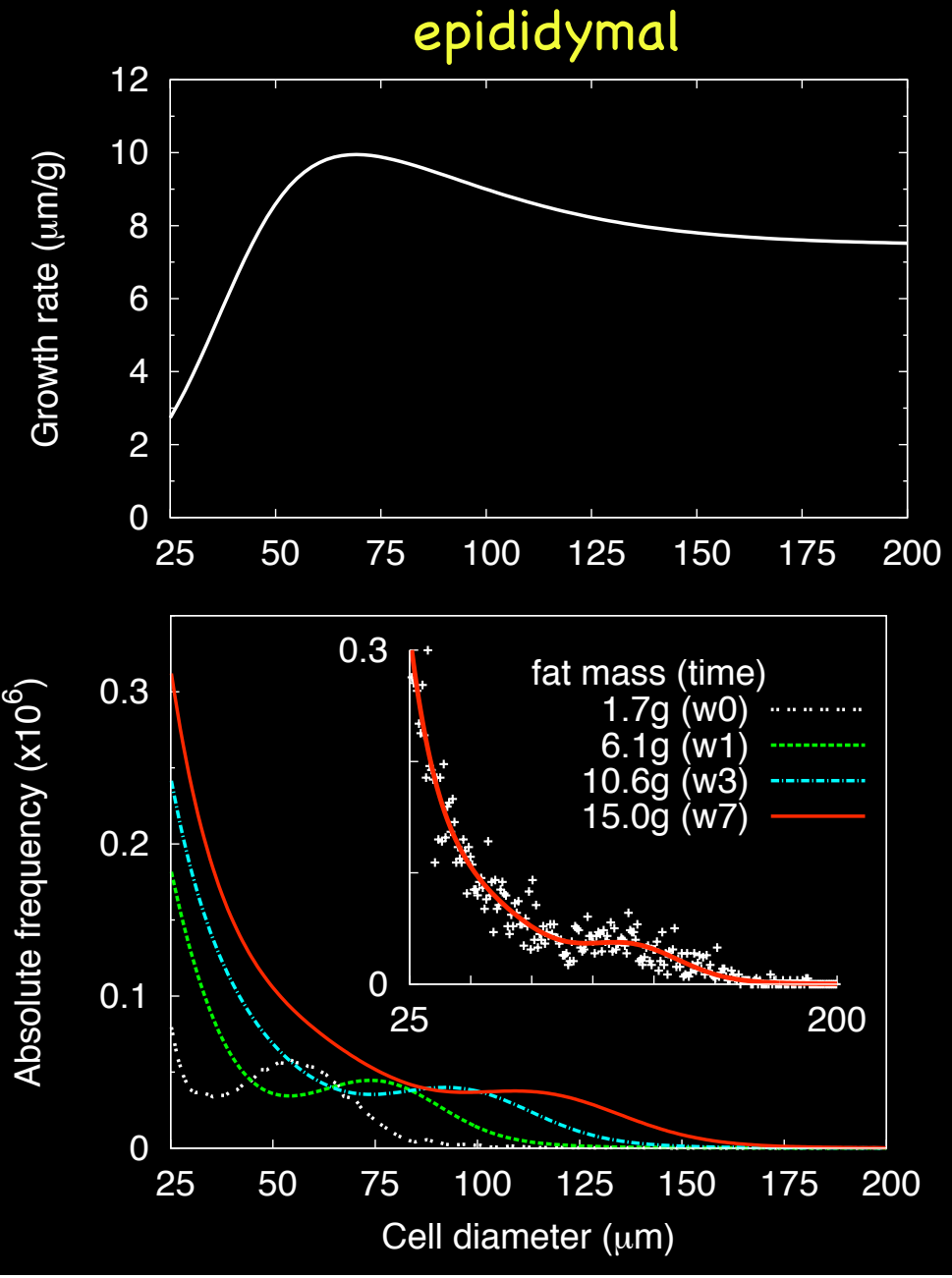
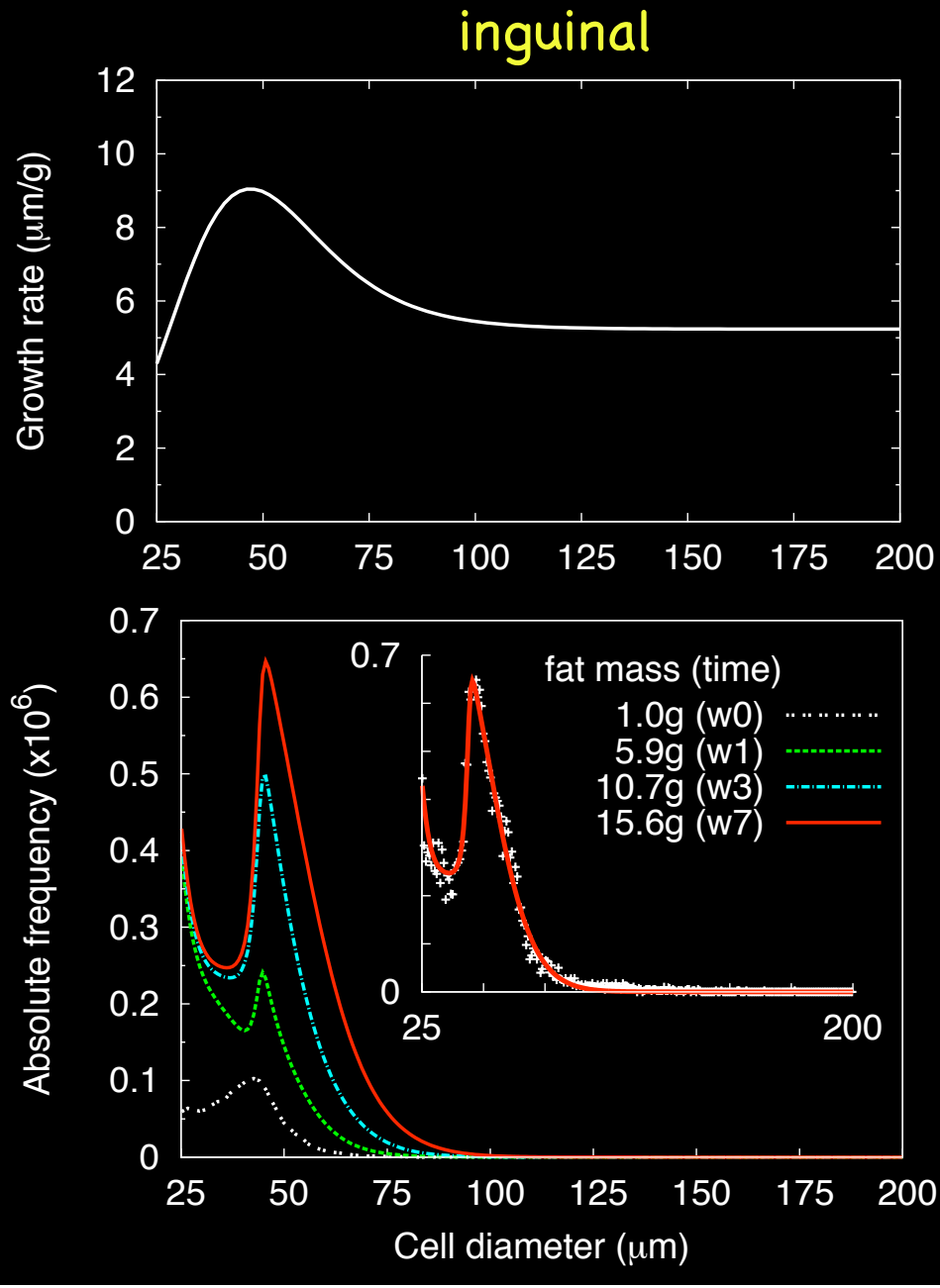
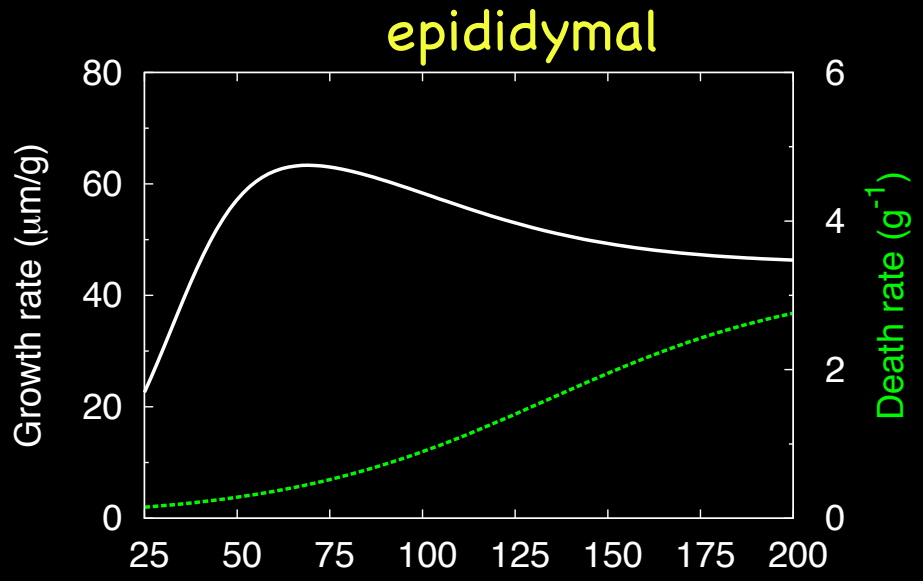
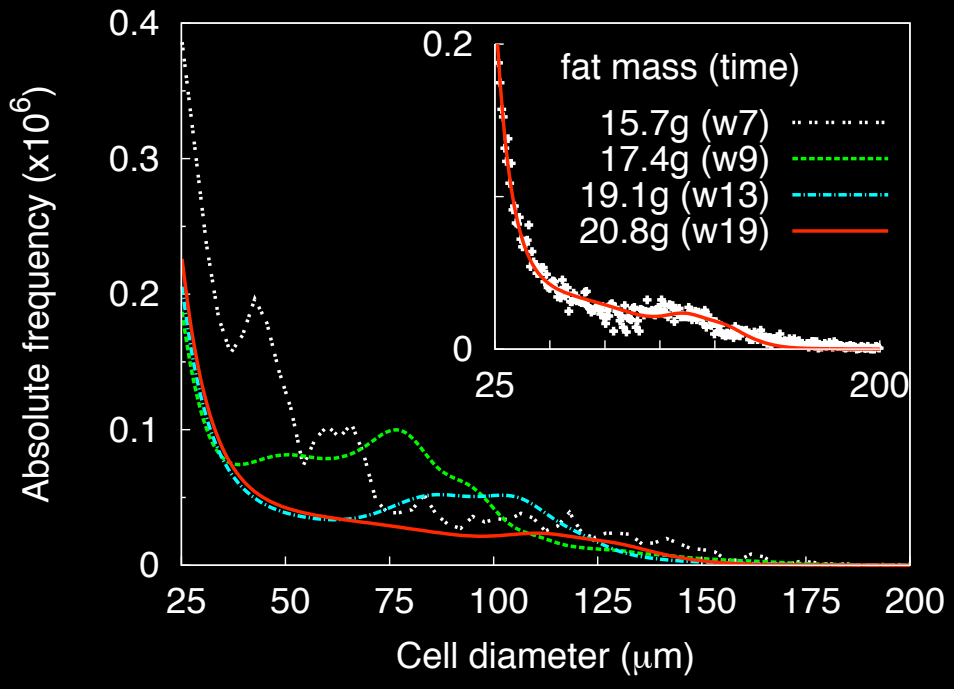




Cell loss of large cells is required to explain the changes of cell-size distributions under 19w HFD





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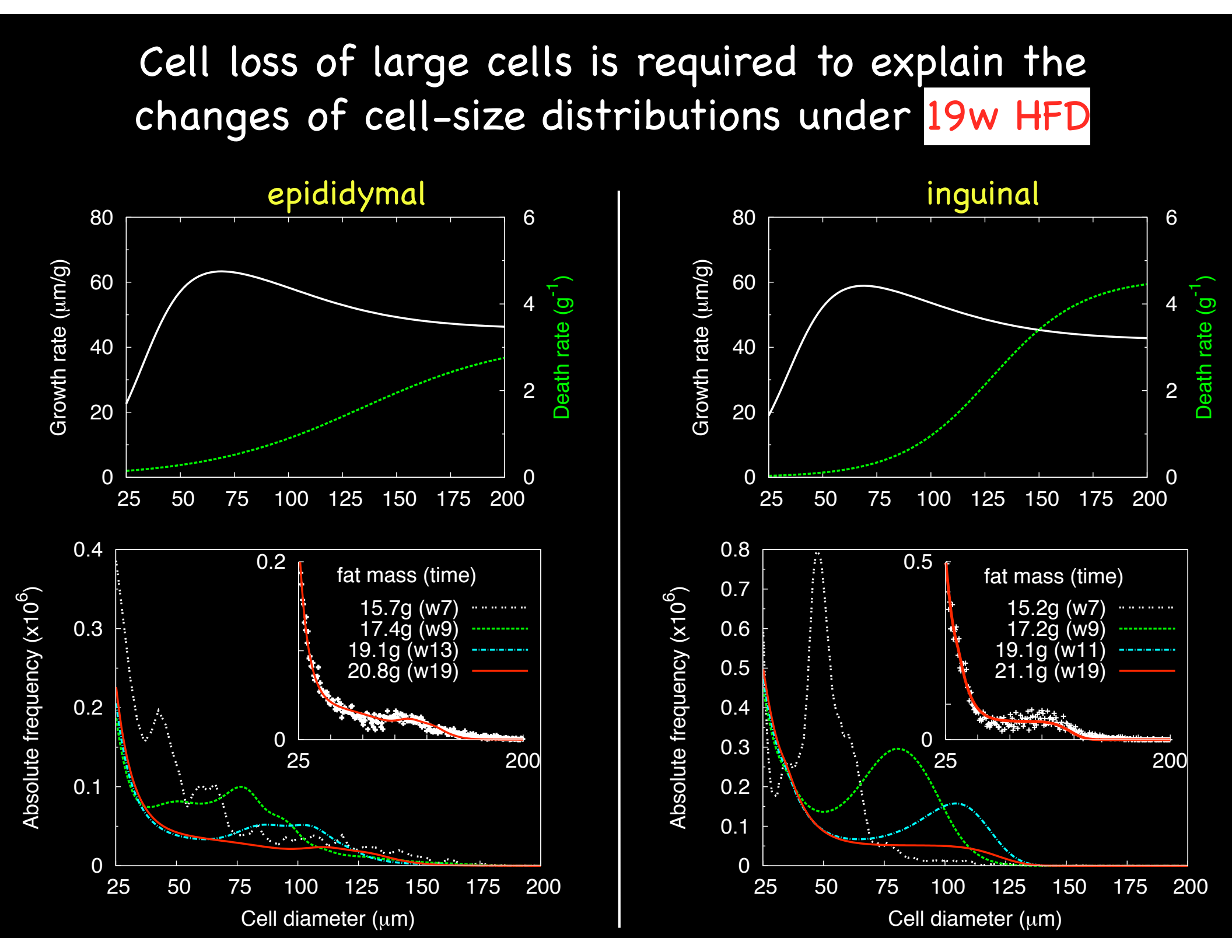
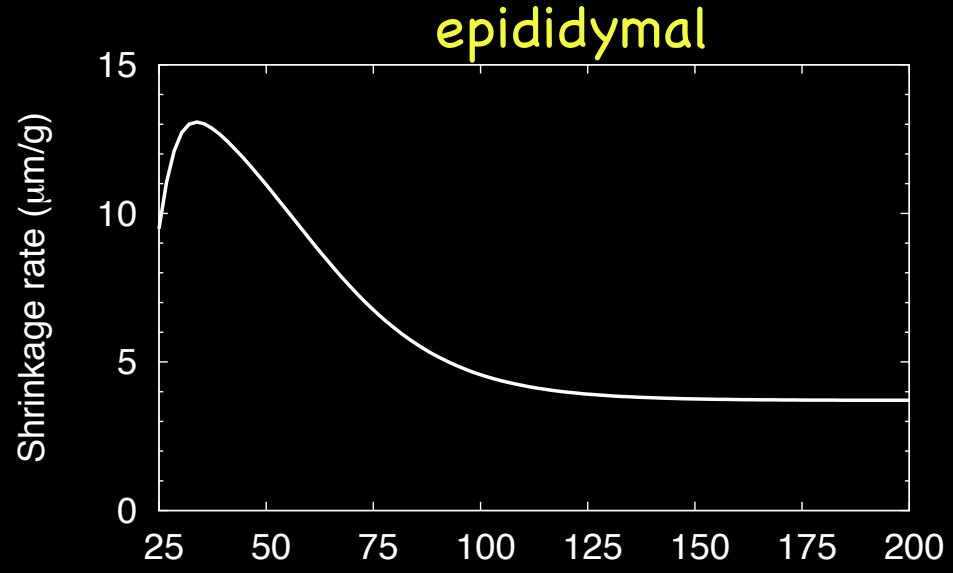
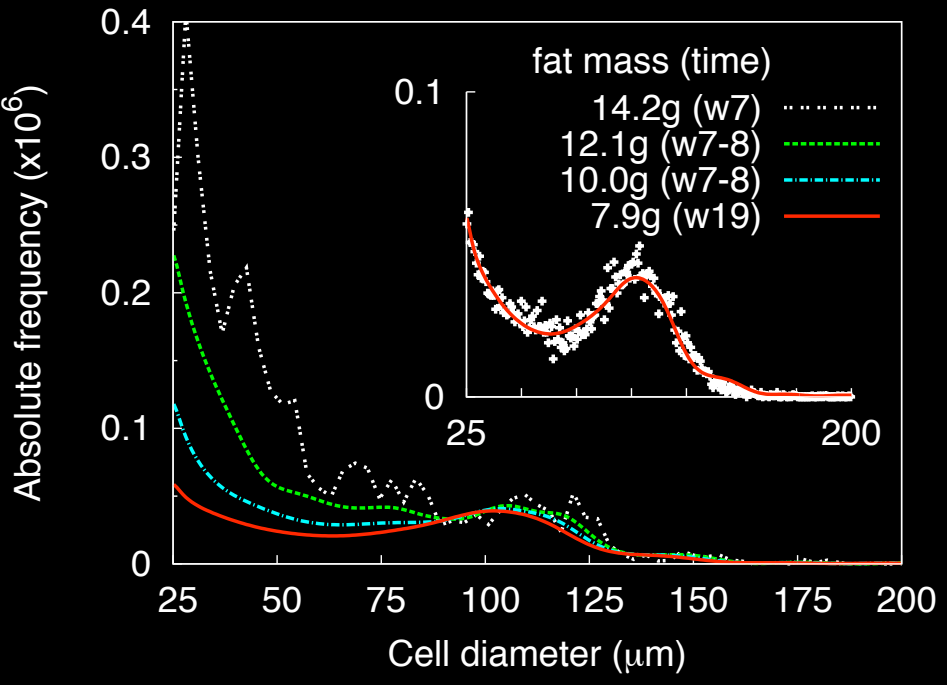


Size-dependent shrinkage of adipose cells can explain the changes of cell-size distributions under 7wHFD+12wND





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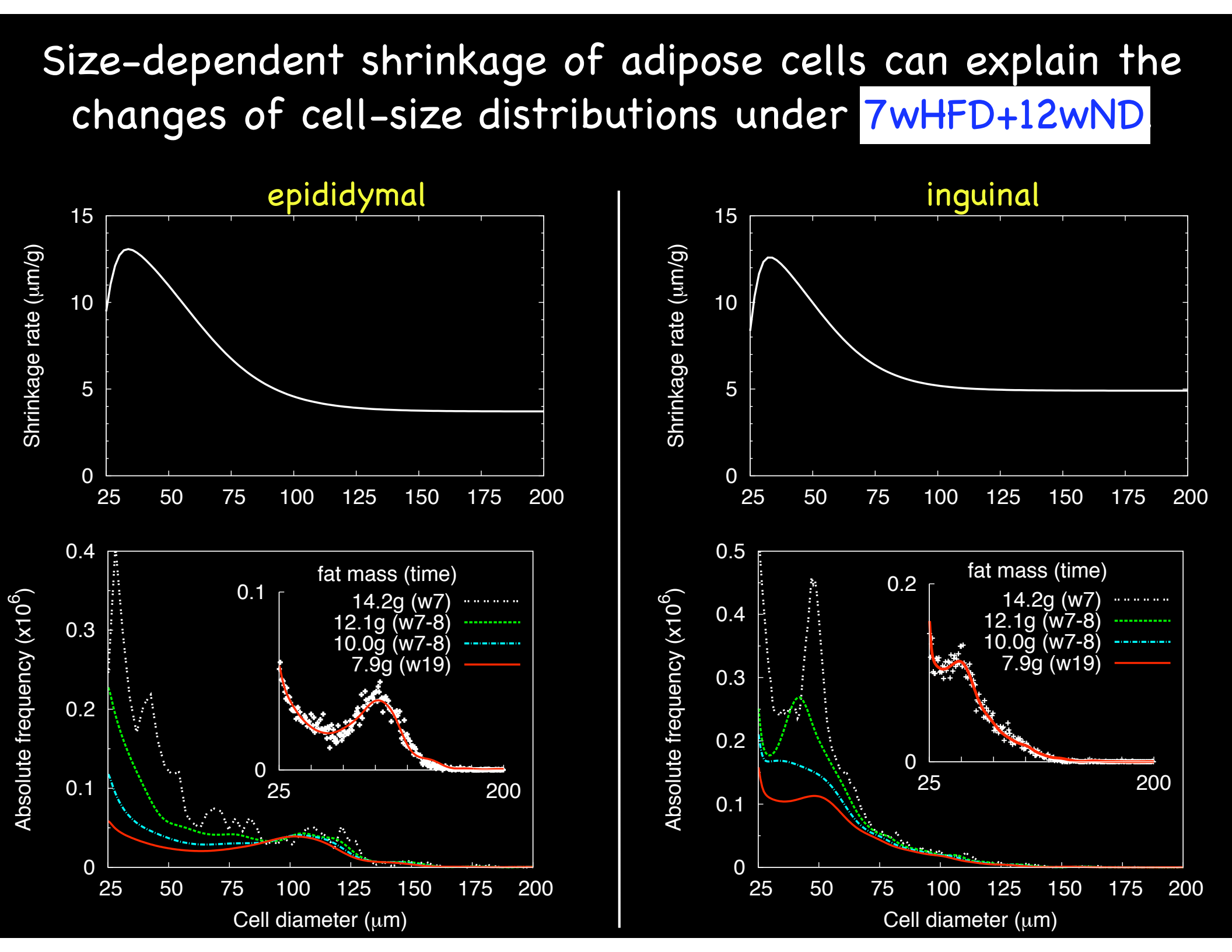
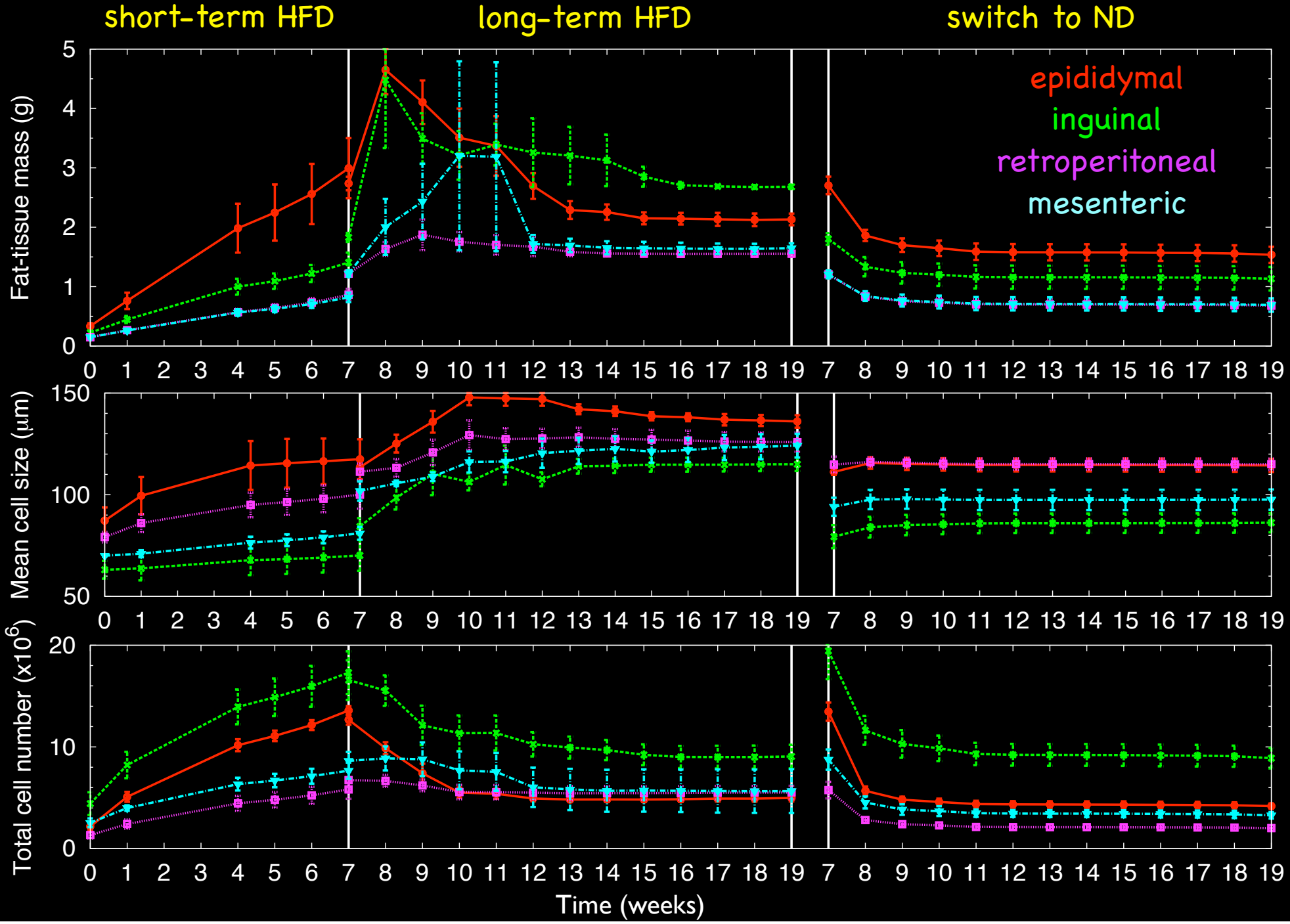
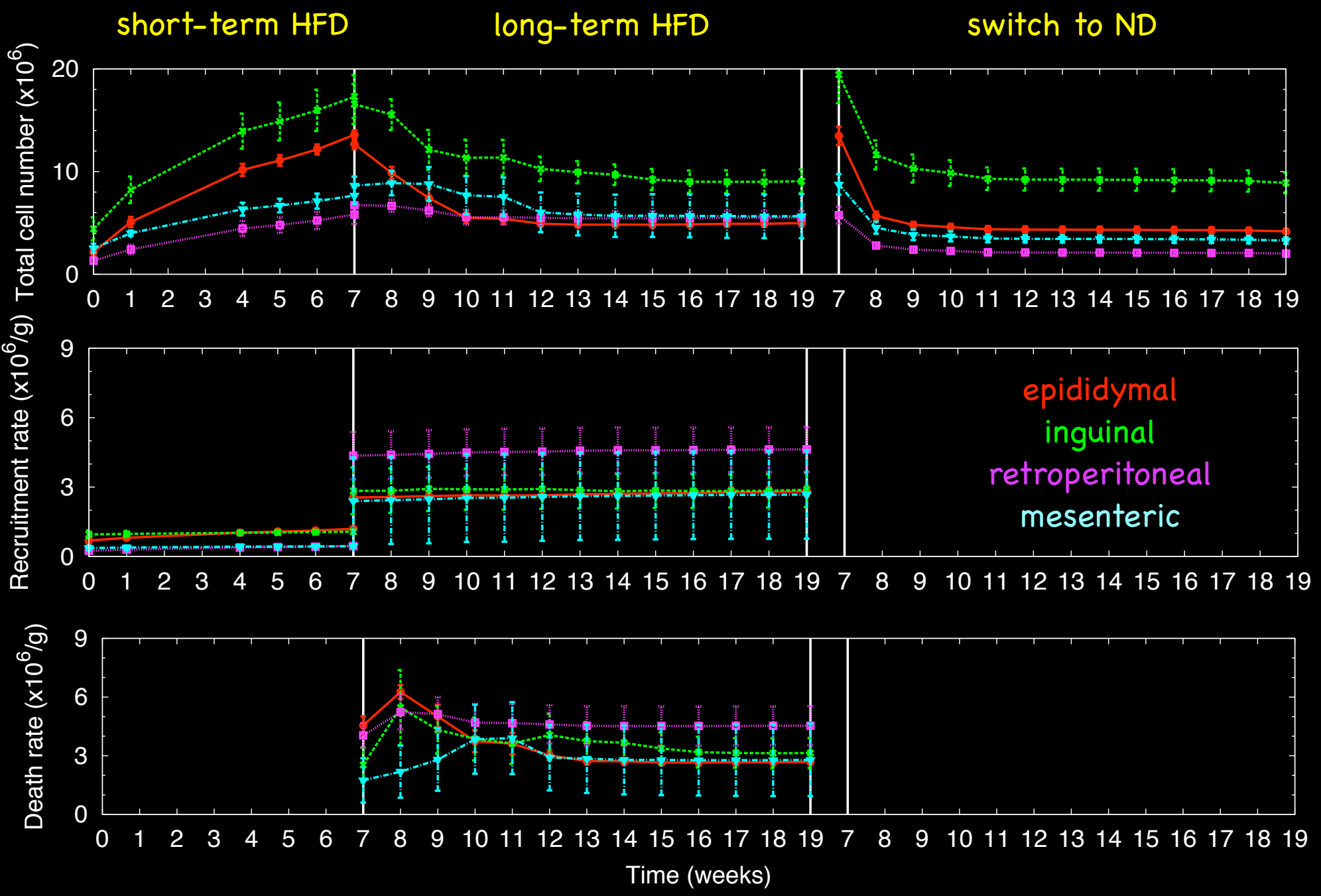


Mathematical modeling can deduce microscopic changes of adipose tissues



The model can give the detail of cell number changes in terms of recruitment (influx) and loss (outflux)



Summary

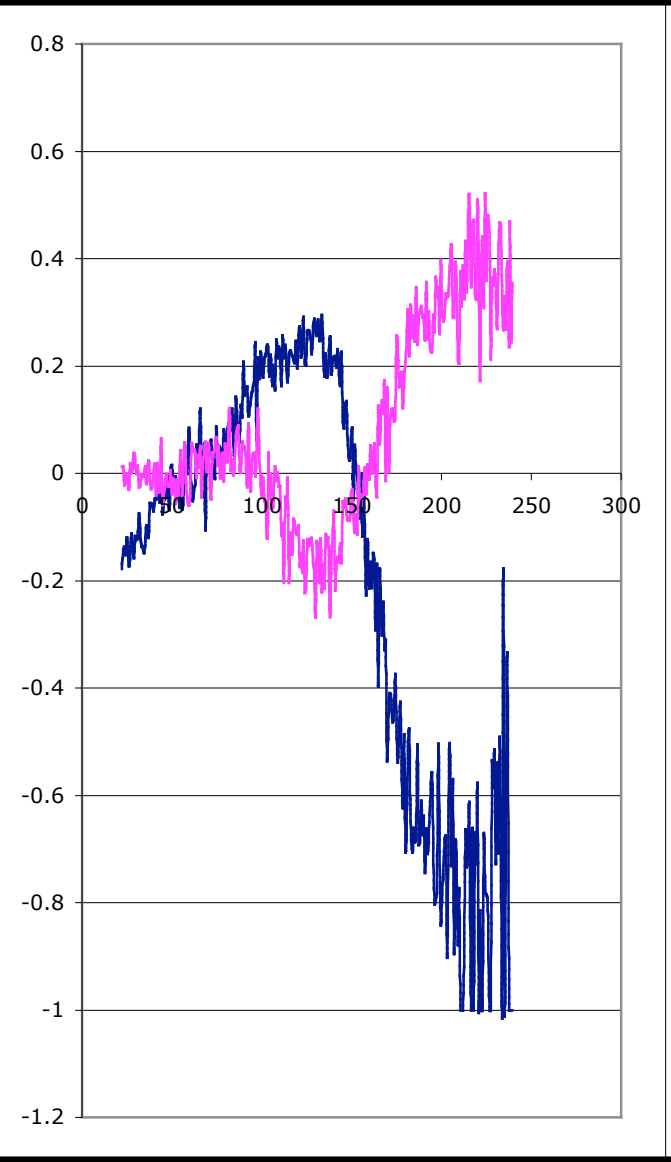
- Fat pads continuously recruited new adipose cells under a high-fat diet.
- Medium-sized adipose cells (30 to 100 μm diameter) showed the largest growth/shrinkage rate under weight gain/loss.
- Cell loss of large adipose cells (above 100 μm diameter) was observed under a prolonged high-fat diet during 19 weeks.
- Adipose tissue responds universally to diet changes to regulate energy storage capacity.

We used an appropriate modulus to find a systematic pattern in cross-sectional mouse data. We expect that there is systematic temporal behavior too. Mice are too small ...

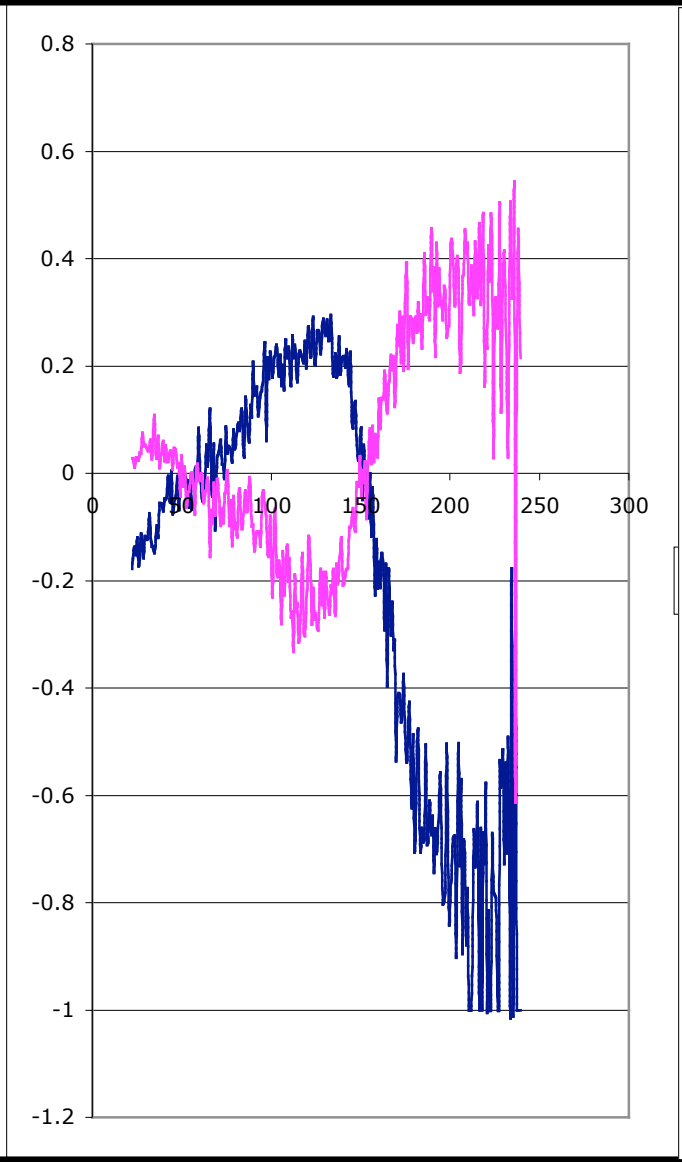
A longitudinal data set

- Zucker fatty (fa/fa) genetically obese rats
- Microbiopsies at multiple time points over 151 days (rat 1) and 163 days (rat 2)
- Cell-size distributions for each time point

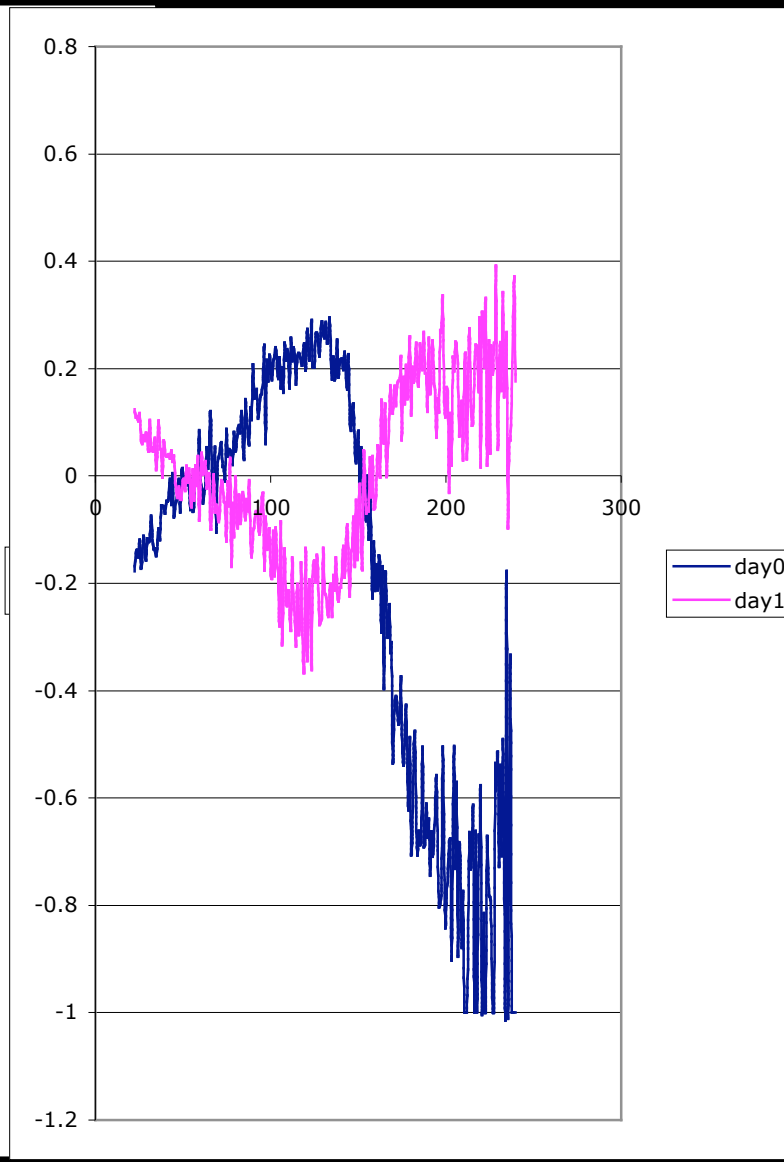
Data suggests periodicity



day 33



day 86



day 134

Problem:
Prove periodicity and determine the period

Bayesian analysis

- Sparse irregularly distributed time points
- Model period = period-bin-size X number-of-bins
- Additional variable defining a model: phase of first time-point
- Consider models with periods between 30 and 100 days
- 579 models for rat 1 and 683 models for rat 2

Cost function

- A model assigns period-bin numbers to data time-points.
- For each cell-size-bin and each period-bin, what is the probability of the cell number counts at different time points assigned to this period-bin belonging to the **same** log-normal distribution?
- For each cell-size-bin and each period-bin, two parameters for the lognormal distribution (median and width).

Data limitations

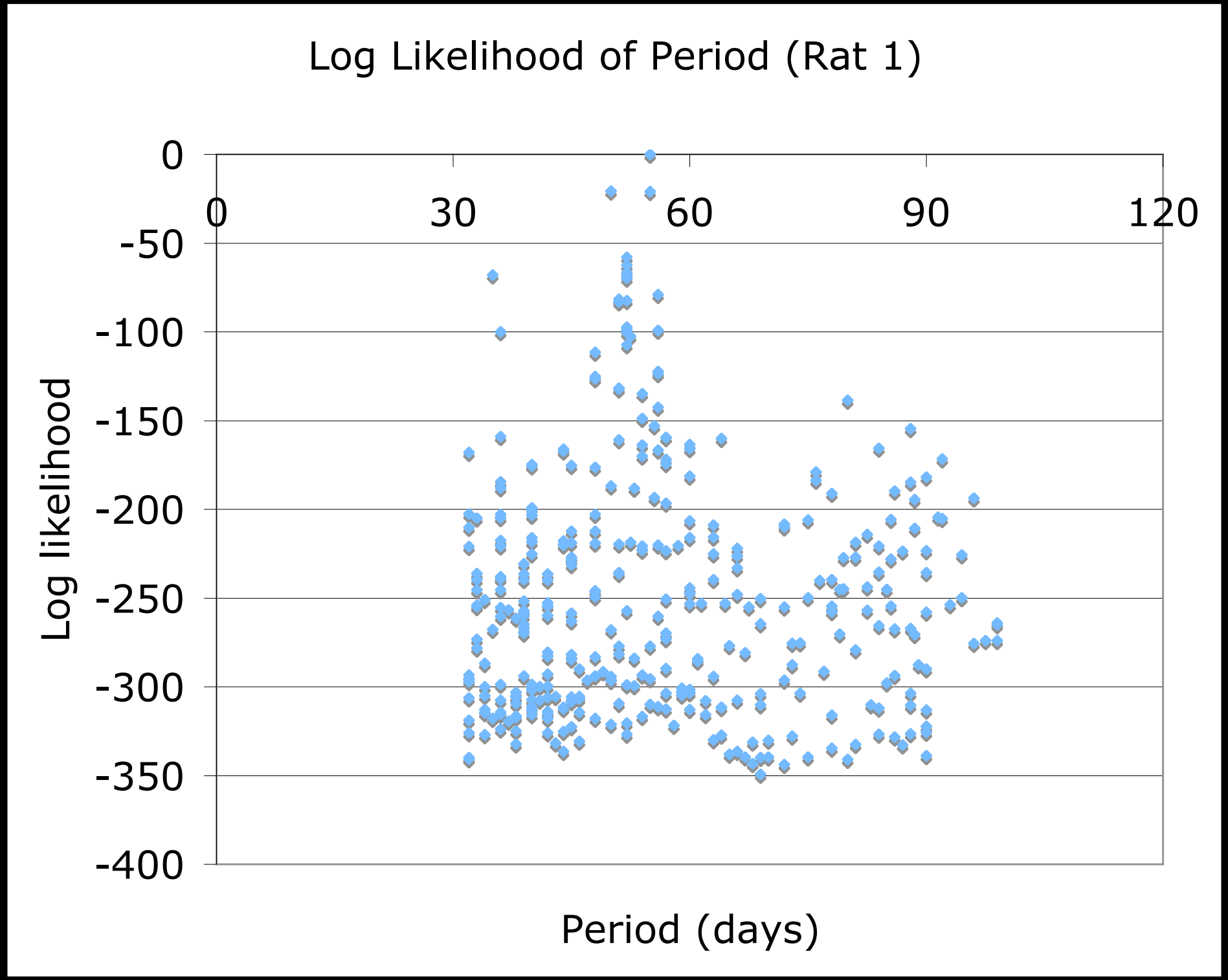
- Limited number of time points implies requirements on testable periodic models.
- (0 0 0 1 1 1) is not a model that tests periodicity because there are no non-contiguous time points that are assigned to the same period-bin. However, (0 1 0 0 1 1) and (0 1 0 1 0 1) are bin assignments that test periodicity.

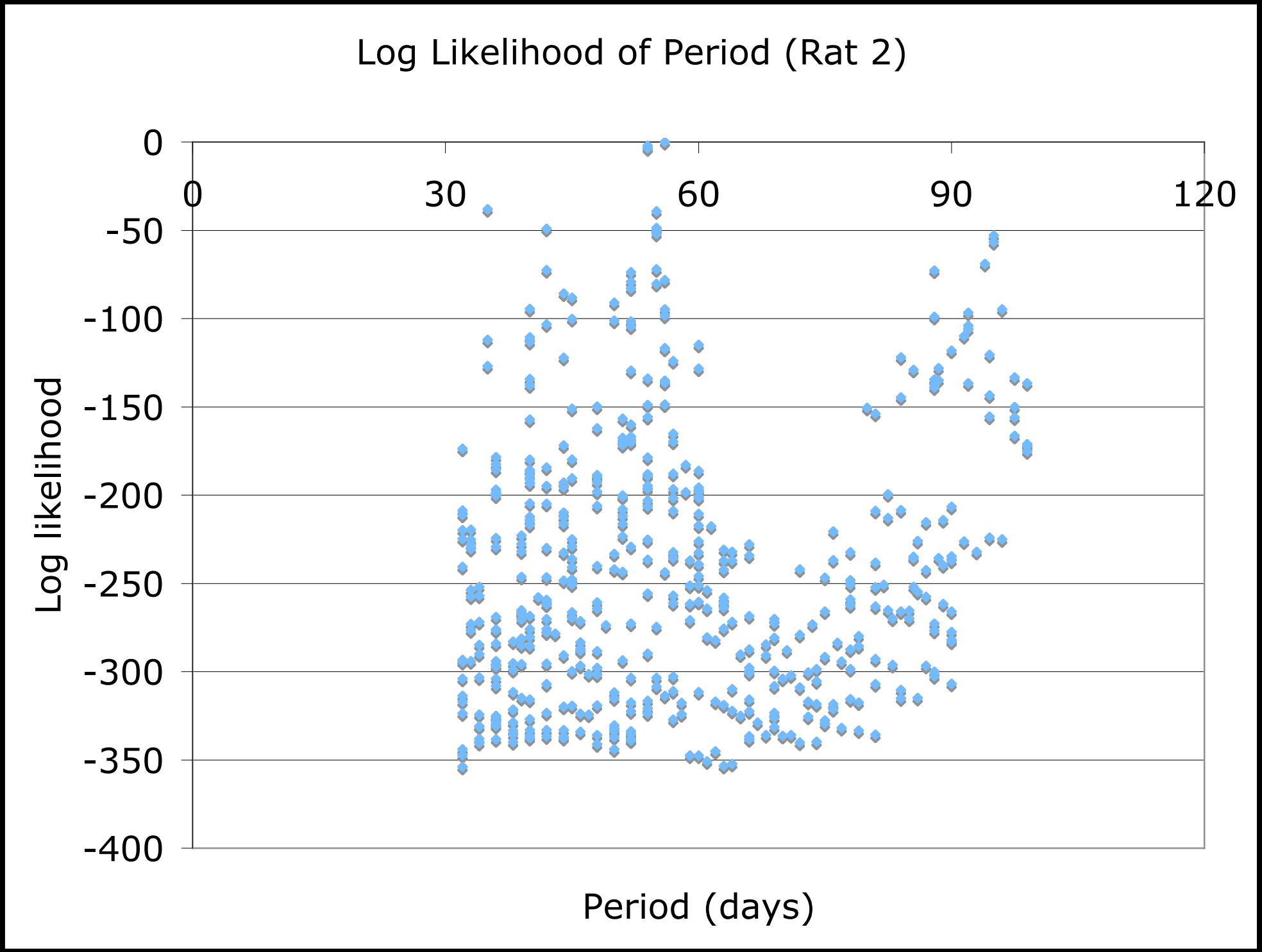
Parallel-tempering MC

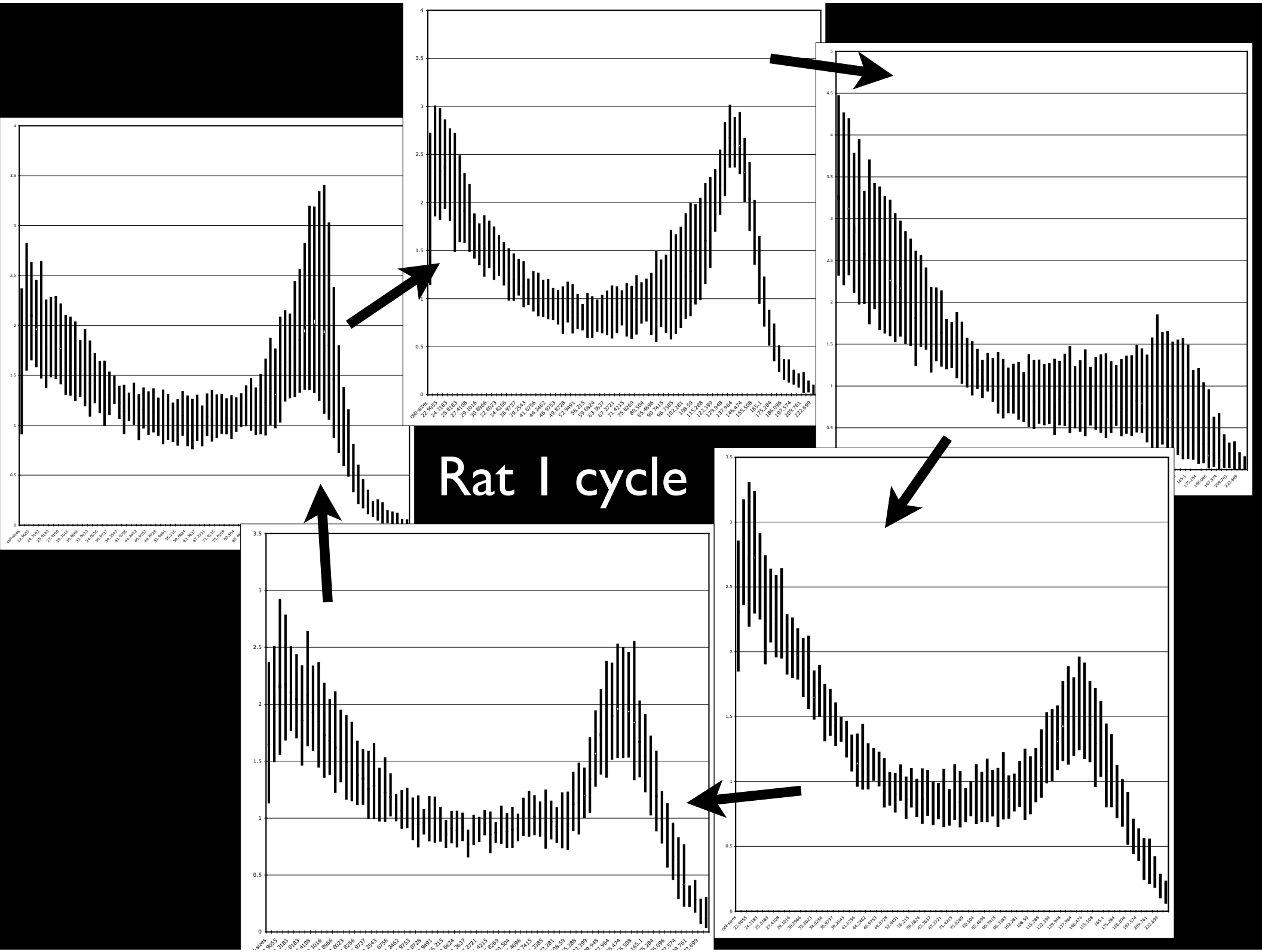
- Parallel tempering Monte Carlo to compute the model likelihood for each model
- Ten equally spaced inverse temperatures
- For each cell-size-bin and each temperature, run a Monte Carlo (10^4 steps for equilibration, 10^3 steps for integration)
- The mean likelihood for all the temperatures is the model likelihood, balancing model complexity against goodness of fit.

Results

- Periodic with period approximately 53 +/- 3 days, independently for both rats
- Different bin numbers selected for different animals for most likely model: Rat 1 -> 5 bins of 10 days each, Rat 2 -> 7 bins of 8 days each


Log Likelihood of Period (Rat 1)
0
-50
-100
-150
-200
-250
-300
-350
-400
Log likelihood
0
30
60
90
120
Period (days)


Log Likelihood of Period (Rat 2)
0
-50
-100
-150
-200
-250
-300
-350
-400
Log likelihood
0
30
60
90
120
Period (days)


Rat 1 cycle

Rat 2 cell-size distributions

Towards dynamics

- Model as a compression of data
- Model as a limited predictor
- Compressing the model - connecting hypertrophy and hyperplasia

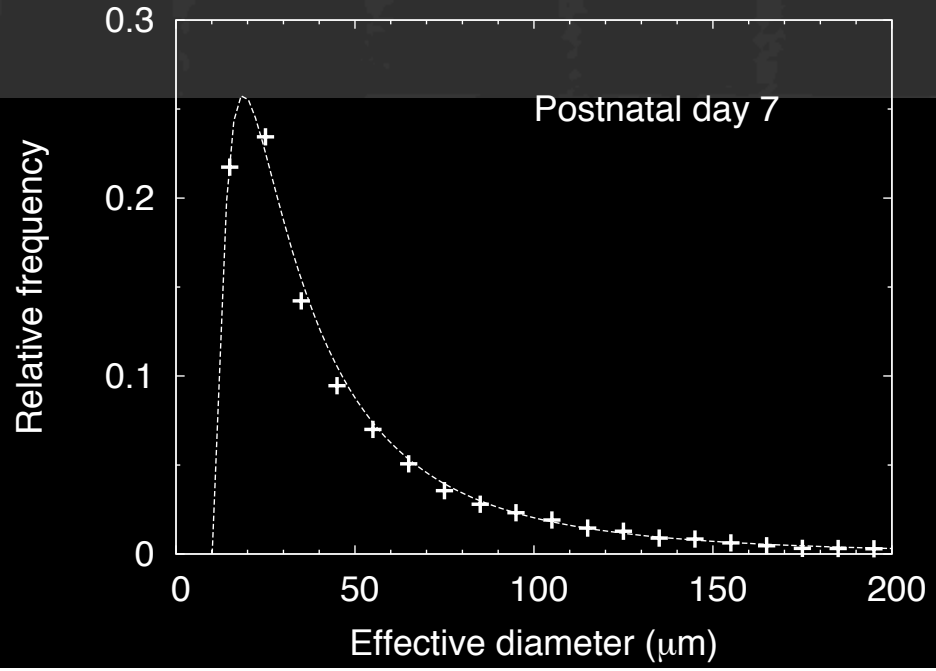
What could lead to periodicity?

- Maximal lipid uptake occurs when there are a large number of cells in the convective size range.
- If lipid is available but there is limited uptake capacity available, then new recruitment is needed.

Size distribution of pancreatic islets

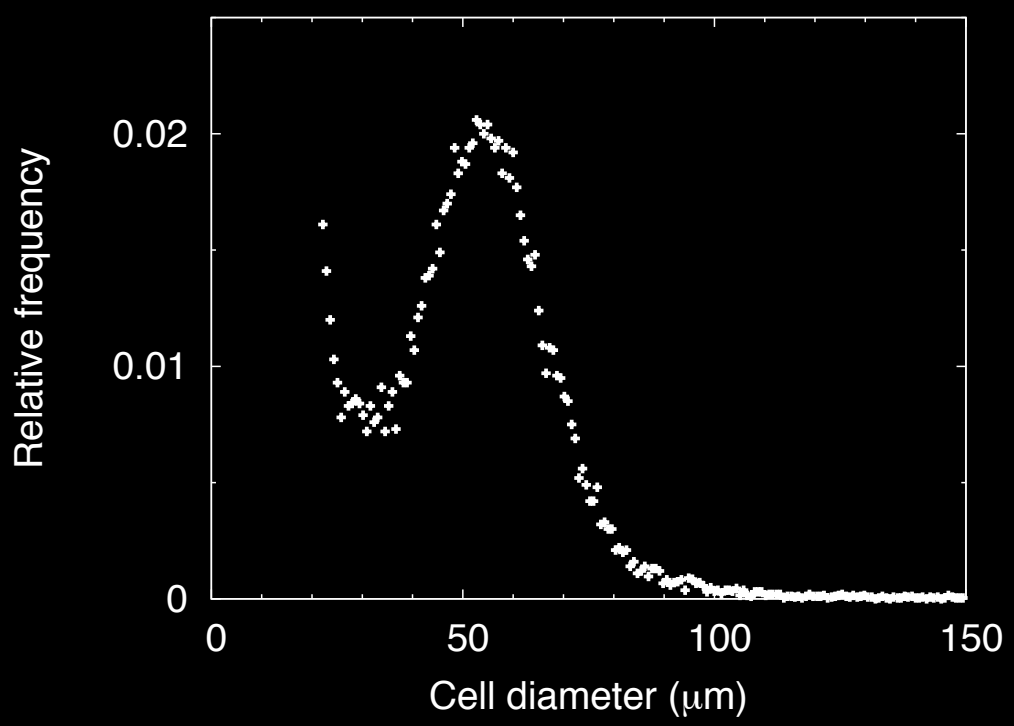
MIP-GFP mouse

5 mm

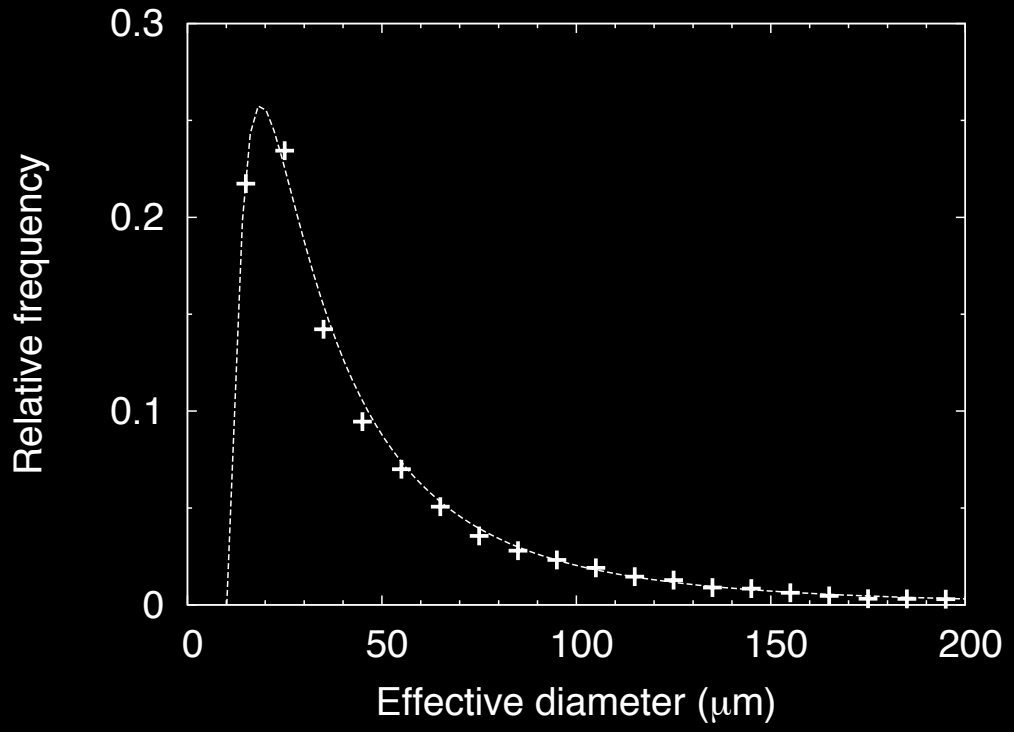


- basic development (islet neogenesis, proliferation potential, and islet fission)
- physiological and pathological conditions (aging, pregnancy, diabetes, obesity, and insulinoma)

size distribution of adipose cells



size distribution of pancreatic islets



Acknowledgment

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