

## Motivation

- Obesity pharmacotherapy leads to clinically meaningful long-term body weight loss [1].
- In early Proof-of-Concept studies, drug effects on body weight are often measured for a period of few weeks only.
- How do body weight changes develop over a long period of treatment, i.e., several years?
- Quantification of drug-induced energy intake changes are limited by self-reports or extrapolation from short-term meal tests [2].

## Modeling Approach

Quantify drug-induced energy intake (EI) changes based on conservation of energy [4,5]:

$$\Delta EI = \Delta ES + \Delta EE$$

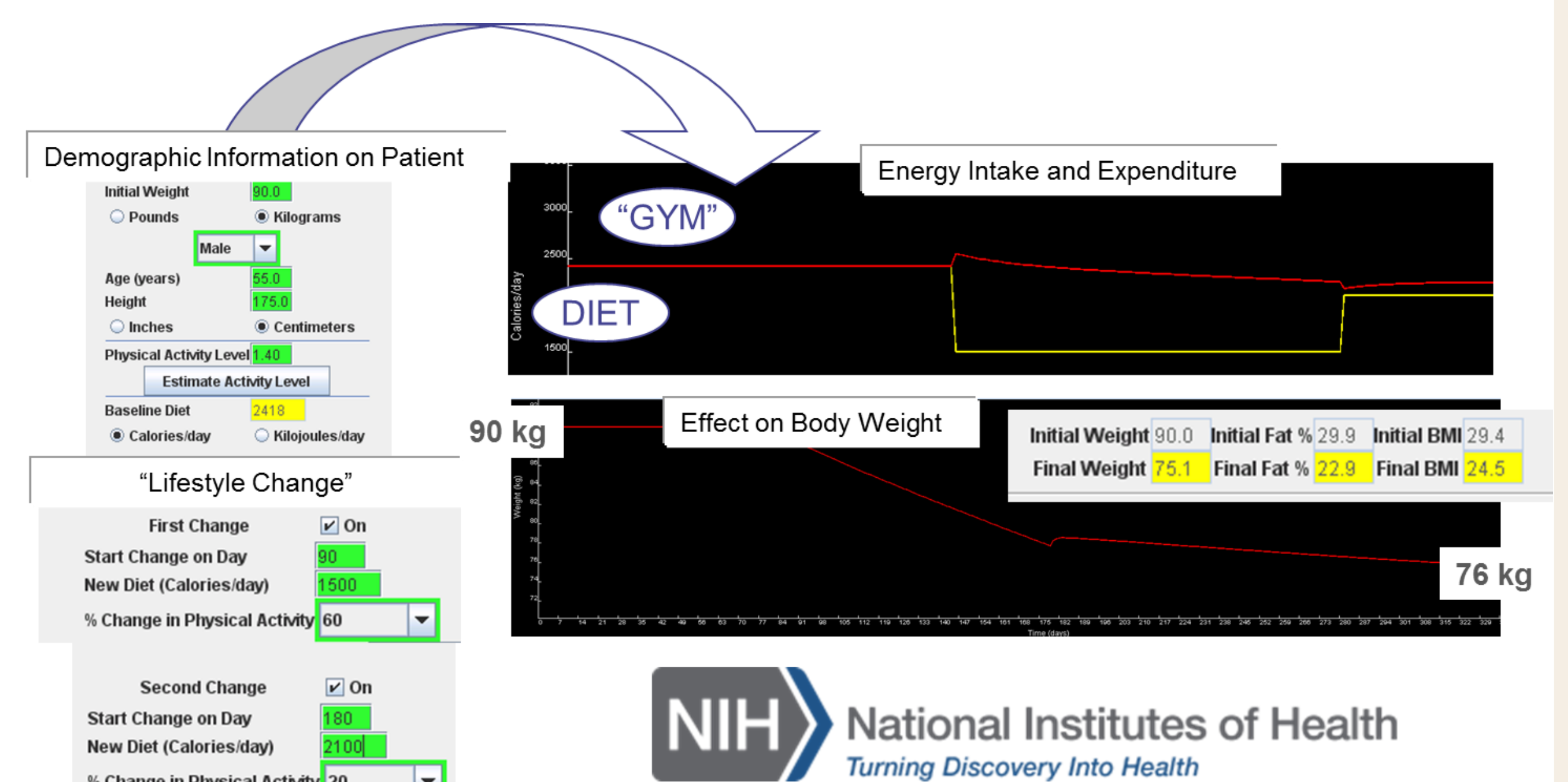
$$\Delta EI = \rho \frac{dBW}{dt} + \varepsilon(BW_i - BW_0)$$

$$\rho = \frac{\eta_F + \rho_F + \alpha \eta_L + \alpha \rho_L}{(1-\beta)(1+\alpha)}$$

$$\varepsilon = \frac{1}{(1-\beta)} \left[ \frac{\gamma_F + \alpha \gamma_L}{(1+\alpha)} + \delta_0 \right]$$

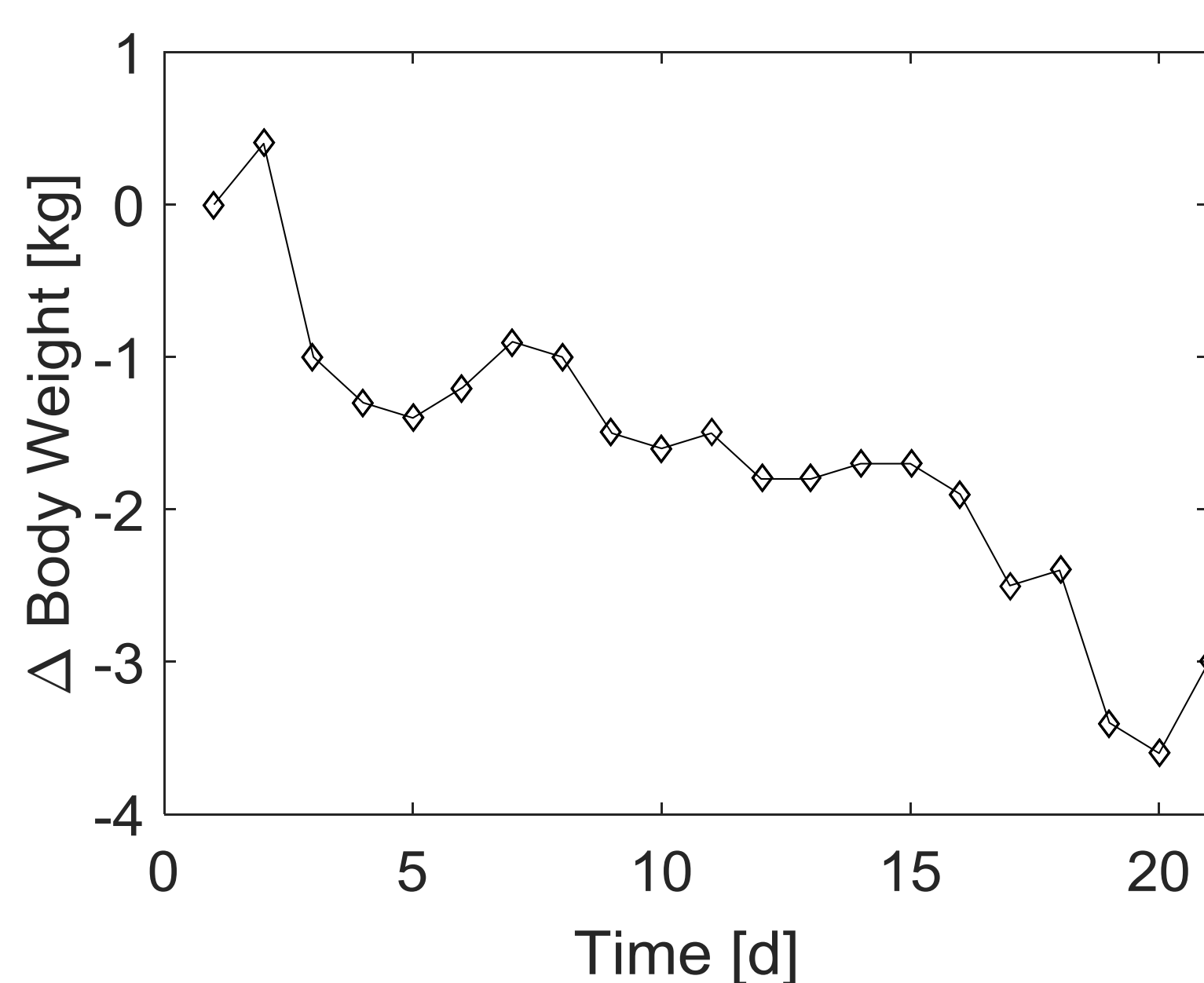
Energy density associated with BW change (kcal/kg)      Relates energy expenditure to BW (kcal/kg/d)

Estimate long-term weight loss by applying the NIH body weight simulator [3]:

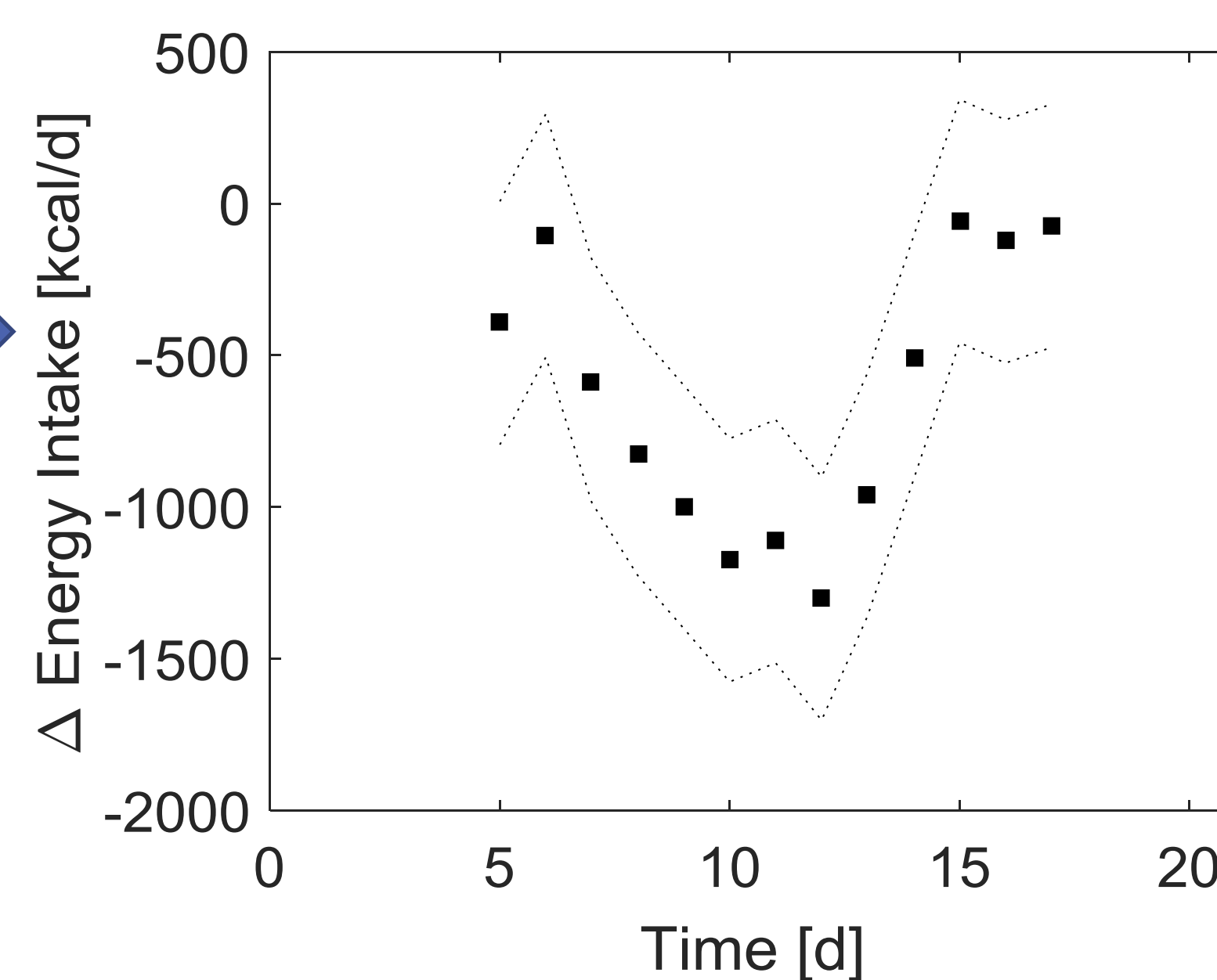


## Results

Body weight data for patient under study drug for 3 weeks



Quantified EI changes mediated by study drug within first 3 weeks of treatment



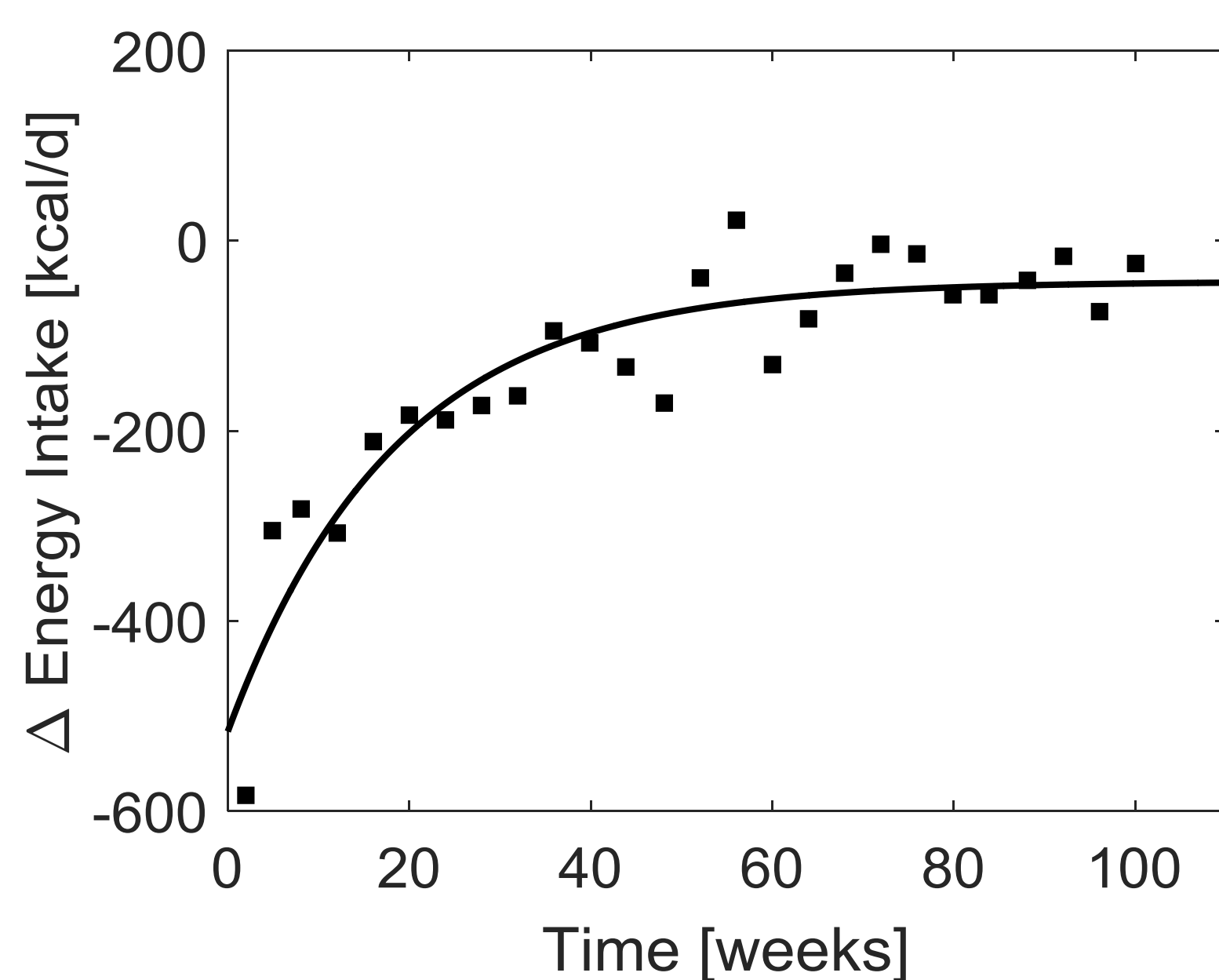
Drug-induced EI changes are well described by exponential pattern, with early large EI changes followed by slow transition to smaller persistent drug effect [6]

$$\Delta EI = -(p_1 - p_3) e^{-\left(t - \frac{(N-1)T}{2}\right) / p_2} - p_3$$

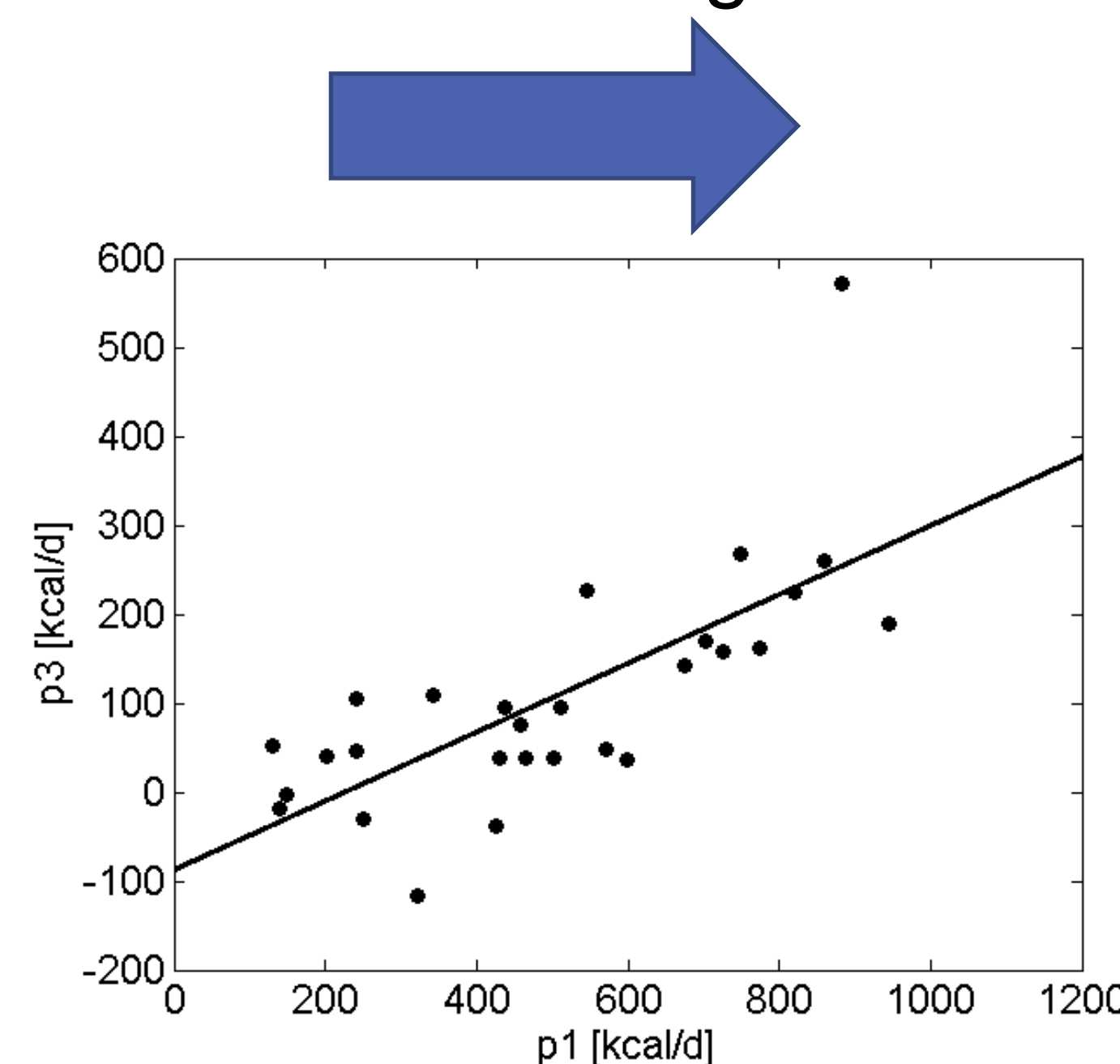
Initial reduction in energy intake from baseline (kcal/d)      Long term reduction in energy intake from baseline (kcal/d)

Time scale of transition from short term to long term (d)

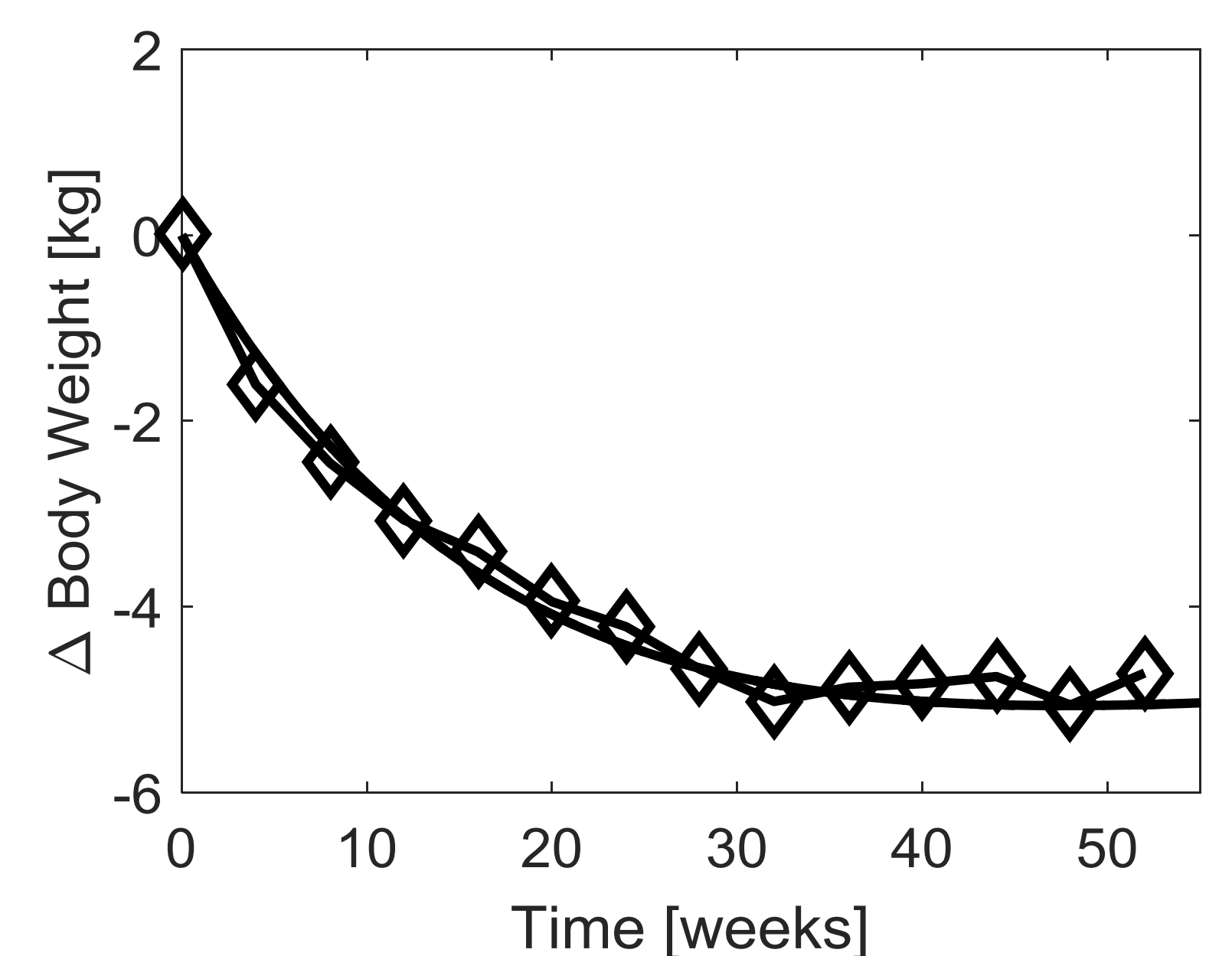
Drug-induced EI changes for long-term treatment



High correlation between early and late drug effects on EI suggests that short-term data can be used to estimate long-term outcomes



Simulated long-term weight loss in agreement with experimental data for 1 year of treatment



## Conclusions & Critical Impact

- Repeated body weight measurements along with a mathematical model of human metabolism are used to quantify drug-induced EI changes following an universal exponential pattern.
- The described systems pharmacology approach allows translating short-term drug effects into long-term estimations of body weight loss.
- For novel weight reducing drug candidates with a body weight time profile only covering the first weeks of treatment, long-term weight loss can be estimated early in clinical development.

## References

- [1] Yanovski et al. JAMA 2014;311:74-86
- [2] Schoeller et al. Am J Clin Nutr 2013;97:1413-5
- [3] Hall et al. Lancet 2011;378:826-37
- [4] Hall et al. Am J Clin Nutr 2011;94:66-74
- [5] Sanghvi et al. Am J Clin Nutr. 2015;102:353-8
- [6] Goebel et al. Obesity 2014;22:2105-8