BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
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NAME	POSITION TITLE
Kevin D. Hall, Ph.D.	Tenure-Track Investigator

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
McMaster University, Hamilton, Ontario, Canada	B. Sc.	1989-1993	Physics
McGill University, Montreal, Quebec, Canada	Ph. D.	1994-1999	Biophysics

A. Positions and Honors

Positions and Employment

1999-2003 Principal Investigator of Metabolic Diseases, *In Silico* R&D, Entelos Inc. Foster City, California.
2003- Intramural NIH Investigator, Tenure-Track, Laboratory of Biological Modeling, National Institute of Diabetes & Digestive & Kidney Diseases, Bethesda, Maryland.
2006- Adjunct Professor, Department of Agriculture, Food and Nutritional Science, University of Alberta, Edmonton, AB, Canada

Other experience and positions

1997 - Regular referee for the following journals: American Journal of Physiology, Physical Review Letters, and Physical Review E.

2002 Member of the organizing committee for the first Society for Industrial and Applied Mathematics (SIAM) Conference on the Life Sciences held in Boston in March 2002.

2003 - Research Management Committee of MITACS – the Mathematics of Information Technology and Complex Systems, a Canadian Network of Excellence. I am an expert representative for the MITACS Biomedical Sector and my role on the Research Management Committee is to help establish the scientific vision and goals for MITACS, determine appropriate research themes, review new and existing research proposals and associated peer review reports and determine which projects to fund at what dollar level.

2008 Lead organizer of an international workshop on Mathematical Modeling of Human Metabolism and Body Weight Regulation that was held on September 27-28, 2008 in Bethesda, MD. http://www.mitacs.ca/conferences/HMBW/

B. Peer-reviewed publications

1. F. Amellal, **K. Hall**, L. Glass, J. Billette. 'Alternation of atrioventricular nodal conduction time during atrioventricular reentrant tachycardia: Are dual pathways necessary?' Journal of Cardiovascular Electrophysiology. 7, 943-951, (1996).
2. **K. Hall**, D.J. Christini, M. Tremblay, J.J. Collins, L. Glass, J. Billette. 'Dynamic control of cardiac alternans.' Physical Review Letters 78, 4518-4521, (1997).
3. **K. Hall** and L. Glass. 'Locating ectopic foci.' Journal of Cardiovascular Electrophysiology 10, 387-398 (1999).
4. **K. Hall** and L. Glass. 'How to tell a target from a spiral: the two probe problem.' Physical Review Letters 82, 5164-5167 (1999).
5. L.P. Endresen, **K. Hall**, J.S. Hoye, J. Myrheim. 'A theory for the membrane potential of living cells.' European Biophysics Journal 29, 90-103, (2000).
6. **K. Hall** and D.J. Christini. 'Restricted control of one-dimensional maps.' Physical Review E 63, Article 046204 (2001).
7. L. Glass, Y. Nagai, **K. Hall**, C. Villemaire, S. Nattel, M. Talajic. 'Predicting the Entrainment of Reentrant Cardiac Waves Using Phase Resetting Curves' Physical Review E 65, Article 021908 (2002).

8. **K.D. Hall**. 'Computational model of in vivo human energy metabolism during semistarvation and re-feeding.' American Journal of Physiology 291, E23-37 (2006).
9. **K.D. Hall**. 'Body Fat and Fat-Free Mass Interrelationships: Forbes's Theory Revisited.' British Journal of Nutrition 97, 1059-1063 (2007)
10. **K.D. Hall**, H.L. Bain, C.C. Chow. 'How Adaptations of Substrate Utilization Regulate Body Composition.' International Journal of Obesity 31, 1378–1383 (2007).
11. **K.D. Hall**. 'What is the required energy deficit per unit weight loss?' International Journal of Obesity. 32, 573-576 (2008).
12. P.N. Jordan **and K.D. Hall**. 'Dynamic coordination of macronutrient balance during infant growth: Insights from a mathematical model.' American Journal of Clinical Nutrition. 87, 692-703 (2008).
13. C.E. Hallgreen and **K.D. Hall**. 'Allometric relationship between changes of visceral fat and total fat mass.' International Journal of Obesity. 32, 845-852 (2008).
14. **K.D. Hall** and C.E. Hallgreen. 'Increasing Weight Loss Attenuates the Preferential Loss of Visceral versus Subcutaneous Fat: a Predicted Result of an Allometric Model.' International Journal of Obesity. 32, 722 (2008).
15. **K.D. Hall** and V.E. Baracos. 'Computational Modeling of Cancer Cachexia.' Current Opinion in Clinical Nutrition and Metabolic Care. 11, 214-221 (2008).
16. C.C. Chow and **K.D. Hall**. 'The Dynamics of Human Body Weight Change.' PLoS Computational Biology. 4(3), e1000045. doi:10.1371/journal.pcbi.1000045 (2008).
17. **K.D. Hall** and P.N. Jordan. 'Modeling Weight-Loss Maintenance to Help Prevent Body Weight Regain.' American Journal of Clinical Nutrition. (In press).

C. Research Support

Ongoing

Research is supported by the Intramural Research Program of the NIH, NIDDK (1 Z01 DK013036-02 LBM, 1 Z01 DK013037-02 LBM, 1 Z01 DK013038-02 LBM).

Past Funding

None

Description of Current and Future Research Program
Kevin D. Hall, Ph.D.

Understanding the dynamics of human body weight change has important consequences for conditions such as obesity, diabetes, cardiovascular disease, starvation, and wasting syndromes such as anorexia nervosa and cancer cachexia. By using mathematical modeling to quantitatively integrate metabolism data with body weight and composition data, my research aims to substantially improve our understanding of body weight regulation and develop practical tools for research and clinical use. My research group at the Intramural Program of the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) uses mathematical and computational modeling to investigate three interrelated subjects: body composition, weight loss, and metabolic fuel selection.

Body Composition

A) Changes of Body Fat versus Lean Tissue

Weight gain and loss are attributable to changes of lean tissue mass as well as body fat. Ideally, weight loss interventions would primarily result in body fat loss, but unfortunately lean tissue is also reduced. We sought to mathematically model the factors that determine the proportion of weight loss coming from body fat versus lean tissue. The basis for our model was a classic theory of Gilbert Forbes who hypothesized that longitudinal body composition changes are described by movement along a logarithmic curve relating lean body mass to fat mass [1]. Our new equation accounted for the effects of the initial body fat mass as well as the direction and magnitude of weight change as depicted in Figure 1 showing the proportion of weight loss from body fat mass as a function of initial fat mass for different degrees of weight loss [2].

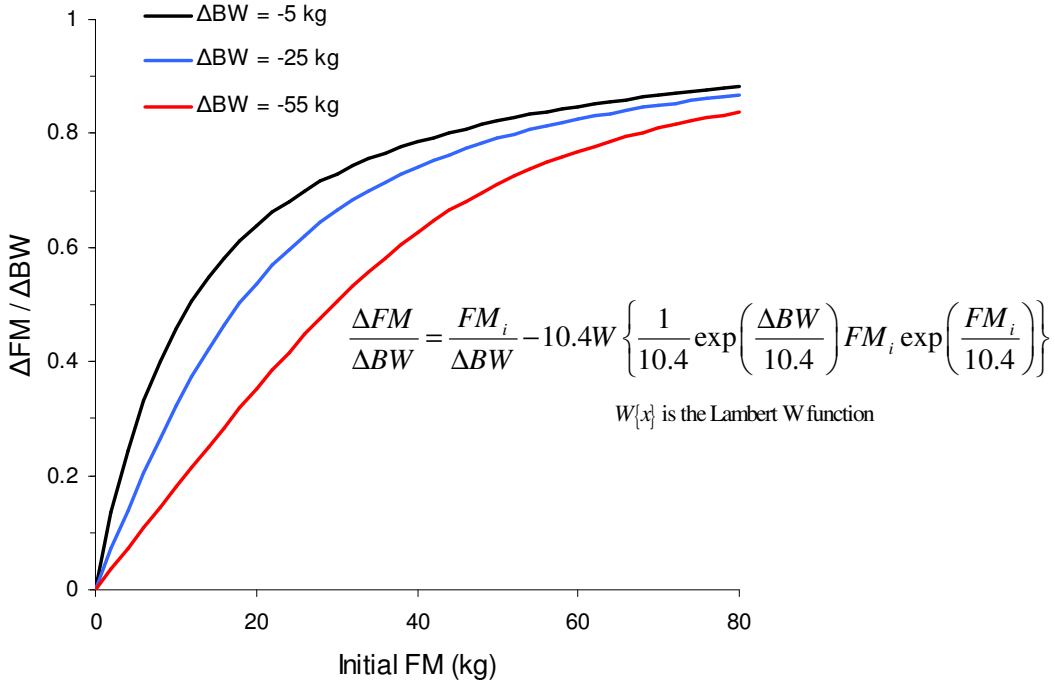

Figure 1

The predictions of the new equation compared favorably with data from human under-feeding and over-feeding experiments and accounted for previously unexplained trends in the data. For large weight changes, such as the massive weight losses found in obese patients following bariatric surgery, Forbes's original equation consistently underestimated the lean tissue loss – a potentially dangerous result. Because our new equation accounted for the magnitude of the weight loss, it provided better predictions of the body composition changes observed in bariatric surgery patients.

B) Allometric Model of Visceral Adipose Tissue Changes

The anatomical location of body fat storage is another important issue of body composition. A common question is whether there are ways to target the reduction of fat in specific areas of the body. In particular, it would be desirable to target visceral adipose tissue, commonly called belly fat, since fat storage in this area is believed to confer greater risk of cardio-metabolic disease. But what determines the relative change of fat storage in some locations compared with others? Is it possible to "spot reduce" belly fat with certain diet or exercise programs?

A large number of clinical studies have investigated whether diet interventions, exercise, or bariatric surgery can preferentially target the reduction of belly fat. However, our mathematical modeling analysis of these data found that changes of visceral adipose tissue do not depend on the type of weight loss intervention. Rather, we showed that a simple allometric equation with a single parameter explained more than 70% of the variability of the data relating the changes of visceral adipose tissue to changes of overall body fat [3]. The model showed that changes of visceral adipose tissue are primarily determined by overall body fat changes as well as the initial ratio of visceral to total body fat – a variable that also accounted for the influence of gender. Other predictions of the simple model relating visceral to subcutaneous fat have subsequently been confirmed [4].

Our simple allometric equation has clinical utility because it can be used as the appropriate null hypothesis to test whether an intervention specifically targets the reduction of visceral adipose tissue. We are presently developing more mechanistic models to better understand the relative mass changes of visceral versus subcutaneous fat depots. Specifically, we are interested in how the allometric relationship between fat depots is determined by differential lipolysis or triglyceride synthesis rates in visceral versus subcutaneous fat.

Weight Loss

A) Modeling the Caloric Equivalent of Lost Weight

Weight loss is caused by eating fewer calories than are expended to perform physical work and maintain life. But how many calories translate to one pound of body weight change and what are the biological determinants of this calorie to weight loss conversion? The ubiquitous dieting rule that "3500 kcal equals 1 pound" has been used for more than half a century to estimate expected weight loss. But despite its popularity, the biological basis of this rule has been mysterious. A recent mathematical model by our group showed that the caloric equivalent of lost weight depends nonlinearly on initial body fat mass, with fatter people requiring a greater energy deficit than lean people for the same amount of weight loss [5]. The magnitude of weight loss also plays a role in determining the caloric equivalent of lost weight and the popular dieting rule was found to be approximately valid only for obese people with initial body fat above 30 kg.

B) Modeling Weight-Loss Maintenance

Diet and exercise can successfully cause significant weight loss in obese individuals, at least temporarily. Unfortunately most people who lose weight are unsuccessful at maintaining weight loss. But what permanent changes of diet or physical activity required to prevent weight regain? In other words, if an obese person wishes to achieve a specified goal weight then how would their diet or physical activity have to change to maintain their weight loss? A quantitative answer to this question would be helpful for goal-setting at the outset of an obesity intervention since both patient and physician could assess whether long-term adherence to the calculated lifestyle change is a realistic proposition. Before our work on this important topic, such a calculation was not possible.

To address this issue and account for the decreased energy requirements at a reduced body weight, we developed a mathematical model of how whole-body energy expenditure changes with weight loss [6]. Our model incorporates the nonlinear relationship between body fat and lean mass changes and was used to calculate the expected change of steady-state body weight arising from a given dietary energy intake change. Conversely, the model equations were also solved for the energy intake change required to maintain a particular body weight loss. The model was developed using data from 8 longitudinal weight loss studies representing 157 subjects with initial body weights ranging from 68-160 kg and stable weight changes between -7 and -54 kg. Our model provided the first realistic calculations of body weight and composition change as well as the dietary modifications required for weight loss maintenance. Importantly, the model was implemented using standard spreadsheet software and can therefore be widely used by physicians and weight management professionals.

Metabolic Fuel Selection

A) Computational Modeling of Human Macronutrient Metabolism

The food we eat has three macronutrients that the body can use to provide energy: carbohydrate, fat, and protein. But how does the body decide what fuel mixture to use? The composition of our diet clearly plays a strong role, but does our body composition also provide feedback that influences fuel selection? How does fuel selection change during under-feeding or over-feeding? To better understand the complex interactions among metabolic fluxes contributing to whole-body fuel selection, we developed a detailed computational model to make predictions about how dietary manipulations affect various whole-body metabolic fluxes and energy expenditure rate to result in body weight and composition changes [7]. The mathematical model, represented by nonlinear ordinary differential equations, uses dietary carbohydrate, fat, and protein as inputs and computes the various components of whole-body energy expenditure, rates of macronutrient oxidation, respiratory exchange, lipogenesis, gluconeogenesis, and turnover of fat, glycogen, and protein. Based on the computed macronutrient imbalances, the model predicts changes of body weight and composition. The model was developed using published human data from over 50 previous experimental studies and has been subsequently validated using a wide variety of clinical data where the food intake was controlled, including studies of over-feeding, under-feeding, and isocaloric exchange of dietary macronutrients.

Our computational model was designed with the specific goal of helping to design, predict, and analyze the results of prospective clinical studies to be conducted in the new NIH Metabolic Clinical Research Unit which houses specialized, state-of-the-art facilities for research on human metabolism and body composition regulation. We have recently used our computational model to design and predict the results of a novel clinical research protocol

that has cleared NIDDK Scientific Review and is presently under IRB review with Kevin Hall as the lead investigator. Our computational model will also provide an integrative framework for the analysis of clinical data from our studies as well as from our collaborators.

B) Computational Modeling of Cancer Cachexia

Often, patients with advanced cancer experience debilitating involuntary weight loss. This wasting condition, called cancer cachexia, is associated with a variety of metabolic changes that affect macronutrient and energy balance. Our computational model of macronutrient balance was recently used to integrate the available data on the metabolic changes in patients with cancer cachexia. The resulting computer simulations showed how the known metabolic derangements synergize with reduced energy intake to result in a progressive loss of body weight, fat mass, and lean tissue [8]. The model was also used to simulate the effects of nutritional support and investigate inhibition of lipolysis versus proteolysis as potential therapeutic approaches for cancer cachexia. This is an example of how computational modeling provides a new tool that can integrate clinical data on metabolic alterations and predict the effects of potential therapies. Importantly, our model helps understand the mechanisms of body weight change in this complex and serious disorder where it would be prohibitively difficult and invasive to attempt a comprehensive clinical study.

C) Quantifying the Relationship between Fuel Selection and Body Composition Change

Our detailed computational model provided important insights into the dynamics of fuel selection, macronutrient balance, and body composition change. But we were also interested in determining a more simple mathematical relationship between fuel selection and the relative change of body fat versus lean mass. We constructed a simplified two-dimensional ordinary differential equation model of macronutrient balance and constrained the dynamics of the model to obey the Forbes logarithmic body composition curve. This procedure allowed us to determine a single equation that explained how interactions of diet, energy expenditure, and fat oxidation are quantitatively connected to changes of body composition [9]. Remarkably, the equation (containing no free parameters) accurately predicted the observed changes of body composition and macronutrient oxidation rates during both experimental under- and over-feeding when the measured food intake and total energy expenditure were provided as inputs to the model. This study was the first to explicitly describe how body composition changes are quantitatively related to diet and fuel selection.

D) Modeling the Dynamic Coordination of Fuel Selection and Tissue Deposition in Human Infant Growth

We subsequently used a similar approach to quantitatively integrate longitudinal data on body composition changes and CO_2 production rates from the doubly-labeled water method to calculate both the energy intake requirements and the net oxidation rates of fat, carbohydrate and protein during normal infant growth [10]. Our model was able to extract important physiologic information from the data that would otherwise be unavailable and thereby presented the first dynamic picture of how metabolism adapts in concert with changes of diet and energy expenditure to give rise to normal tissue deposition and growth in human infancy. In particular, our analysis showed that fat oxidation must somehow be inhibited over the first 6 months of life to account for the measured body fat deposition rates. The physiological mechanisms underlying this inhibition of fat oxidation are not presently understood.

Future Research

Mathematical modeling is best applied in combination with experiments to predict, analyze, and integrate data and subsequently drive new experiments. We have begun this iterative process by developing various mathematical models of metabolic fuel selection and the relationship to body composition regulation using published data. Further development of these models will use data generated from our own clinical studies at the NIH Metabolic Clinical Research Unit as well as mouse studies at the NIDDK Mouse Metabolic Phenotyping Laboratory.

Significant progress has already been made in the development of integrative mathematical models of mouse metabolism for quantitative phenotyping. Our models integrate data on body composition, food intake, energy expenditure, and metabolic fuel selection and provide a quantitative dynamic picture of how mouse metabolism adapts to changes of diet and body weight. For example, Figure 2 depicts a mathematical model simulation (solid curves) of body weight changes (top panel) and energy balance dynamics (bottom panel) in our research group's first wet-lab experiment using C57BL/6 mice. These mice developed obesity after 7 weeks of eating a high-fat diet, but then lost most of their excess body weight following a switch to standard chow. The open triangles in the top panel are the body weight data and the blue curve in the bottom panel was fit to the energy intake measurements (crosses) and was used as an input to the mathematical model. The red curve shows the predicted energy expenditure dynamics responsible for the observed body weight changes.

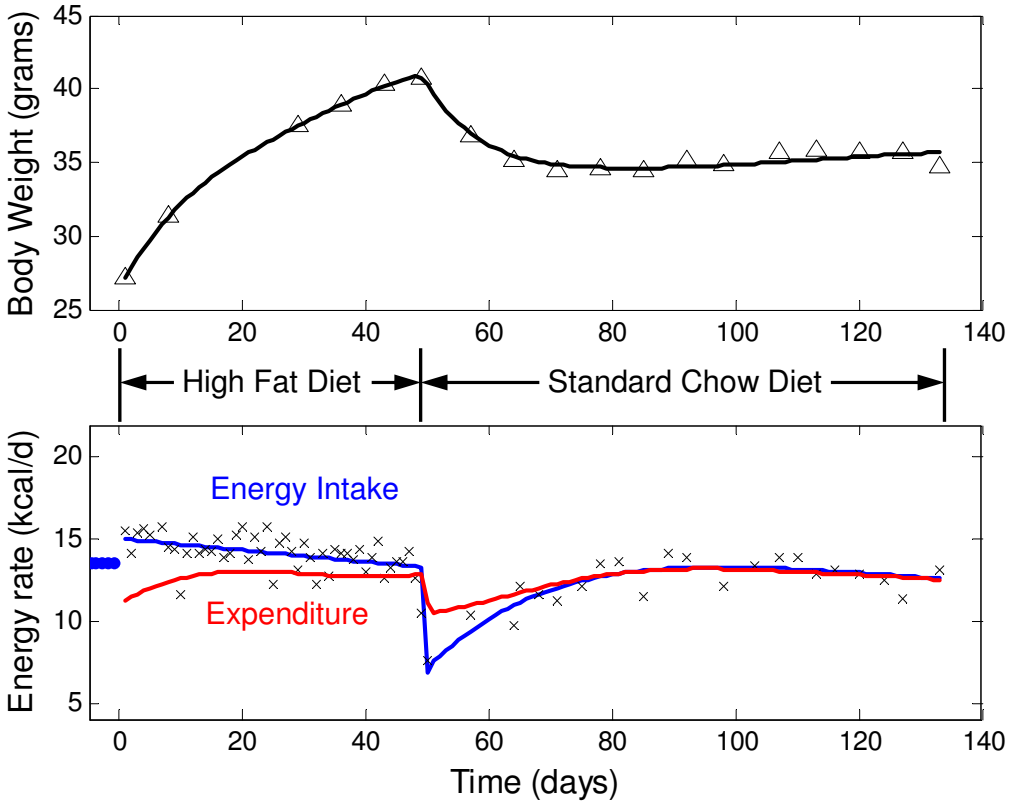

Figure 2

Figure 3 shows the model simulations of how metabolic fuel selection adapted to the changes of diet, body weight and composition. The resulting mathematical model represents a quantitative description of the metabolic phenotype of these mice and can be used as the basis for understanding how various genetic perturbations alter this phenotype. We are presently collaborating with other intramural investigators at NIDDK, including Alex McPherron and Oksana Gavrilova, to use this mathematical phenotyping methodology to characterize mice with a knockout of the myostatin gene.

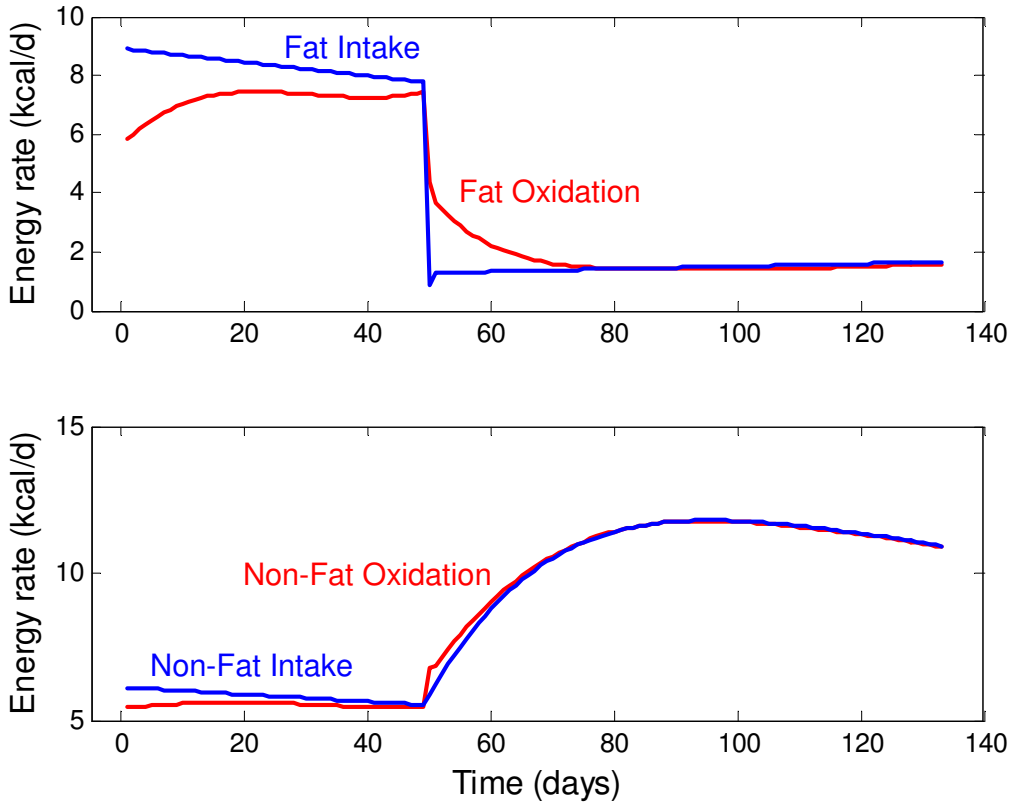

Figure 3

Clearly, there is great opportunity to apply and expand our mathematical models, both in their physiological content as well as their application. For our human metabolism and body composition models, we plan to use individual subject data to model and analyze the inter-individual variability of body composition changes and metabolic adaptations. Our current models were built using group average data and if every individual was adequately represented by these models, then providing the average model with the individually measured model inputs should result in accurate predictions of the individual changes of body composition and metabolism. The extent to which these model predictions match the individual subject data indicates how well an individual is represented by the average model parameters. By adjusting key model parameters to improve the model fit to individual subject data, we hope to obtain some insights regarding physiological differences between individual subjects and possibly design biomarkers to identify various metabolic phenotypes. In addition to collecting our own individual subject data at the NIH Metabolic Clinical Research Unit, we are collaborating with Eric Ravussin and Steve Smith at the Pennington Biomedical Research Center, Dympna Gallagher at St. Luke's-Roosevelt Hospital, and Reed Hoyt at

USARIEM to provide us with a wide range of metabolism and body composition data for mathematical analysis, model development, and the design of future experiments.

We will also use our computational models of human metabolism to provide dynamic feedback to obese subjects engaged in an out-patient clinical weight loss program. Based on individual measurements of metabolic phenotype during an in-patient stay at the NIH Metabolic Clinical Research Unit, we will calibrate a personalized computational model of each subject and use the model to target individual weight loss goals over a 12 week diet intervention period. Body weight will be tracked on a daily basis and feedback regarding the predicted state of energy imbalance and the projected weight loss trajectory will be conveyed weekly to each subject along with calculated adjustments of diet and physical activity to target their weight loss goal. To assess the accuracy of our model predictions, a number of measurements will take place periodically during the 12 week period, including assessment of food intake, body composition, energy expenditure, and physical activity. A clinical research protocol describing this study (with Kevin Hall as the lead investigator) has cleared NIDDK Scientific Review and has recently been submitted for IRB review.

References

1. Forbes, G.B., *Lean body mass-body fat interrelationships in humans.* Nutr Rev, 1987. **45**(8): p. 225-31.
2. Hall, K.D., *Body fat and fat-free mass inter-relationships: Forbes's theory revisited.* Br J Nutr, 2007. **97**(6): p. 1059-63.
3. Hallgreen, C.E. and K.D. Hall, *Allometric relationship between changes of visceral fat and total fat mass.* Int J Obes (Lond), 2008. **32**(5): p. 845-52.
4. Hall, K.D. and C.E. Hallgreen, *Increasing weight loss attenuates the preferential loss of visceral compared with subcutaneous fat: a predicted result of an allometric model.* Int J Obes (Lond), 2008. **32**(4): p. 722.
5. Hall, K.D., *What is the required energy deficit per unit weight loss?* Int J Obes (Lond), 2008. **32**(3): p. 573-6.
6. Hall, K.D. and P.N. Jordan, *Modeling weight-loss maintenance to help prevent body weight regain.* Am J Clin Nutr, 2008. **In press**.
7. Hall, K.D., *Computational model of in vivo human energy metabolism during semistarvation and refeeding.* Am J Physiol Endocrinol Metab, 2006. **291**(1): p. E23-37.
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Calculating the permanent lifestyle changes required for weight-loss maintenance

Kevin D. Hall and Peter N. Jordan, Laboratory of Biological Modeling, NIDDK, NIH, Bethesda, Maryland 20892

Lifestyle changes can successfully induce weight loss in obese individuals, at least temporarily. But there is presently no way to quantitatively estimate the permanent changes of diet or physical activity required to prevent weight regain. Such a tool would be helpful for goal-setting since obese patients and their physicians could assess whether adherence to the calculated lifestyle change is realistic. To address this issue, we developed a mathematical model to calculate the body weight change arising from a given energy intake change, and conversely, the modification of energy intake required to maintain a particular body weight change. We used data from 8 longitudinal weight loss studies representing 157 subjects with initial body weights ranging from 68-160 kg and stable weight changes between -7 and -54 kg. Model calculations closely matched the weight change data (R^2 = 0.83, χ^2 = 2.1, $p < 0.01$ for weight changes, R^2 = 0.91, χ^2 = 0.87, $p < 0.0004$ for energy intake changes) and also accurately predicted the proportion of weight change resulting from the loss of body fat (R^2 = 0.90). Therefore, our model provides the first realistic calculations of lifestyle modifications required for weight loss maintenance. Standard spreadsheet files of the model can be freely downloaded at http://www2.niddk.nih.gov/NIDDKLabs/LBM/lbmHall.htm and can therefore be widely used by physicians and weight management professionals.

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