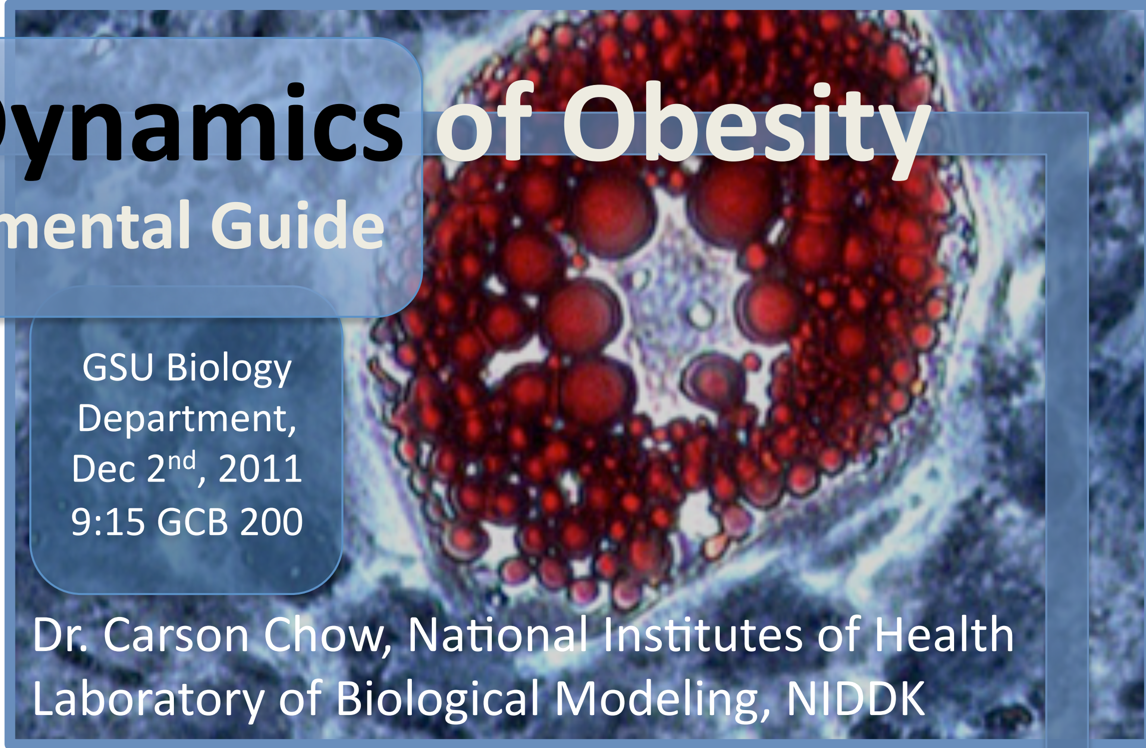

The Dynamics of Obesity

A Supplemental Guide

GSU Biology Department, Dec 2nd, 2011 9:15 GCB 200

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What does Carson Chow do?

Modeling human weight dynamics has been a prevalent topic among Dr. Chow's recent publications (especially in collaboration with Dr. Kevin Hall at NIH), but his work also includes the application of mathematics to questions ranging from biomolecular processes to physiology. At the biomolecular level, he has used information theory and graph theory to elucidate the functional conformations of the trans-membrane region of G-protein coupled receptors. Chow's interests in physiology include modeling immune and inflammatory responses. Additionally, he works with small neural networks to understand working memory and autism. To find out more, visit his blog, *Scientific Clearing House*, at sciencehouse.wordpress.com.

How do we study the energetics of food consumption?

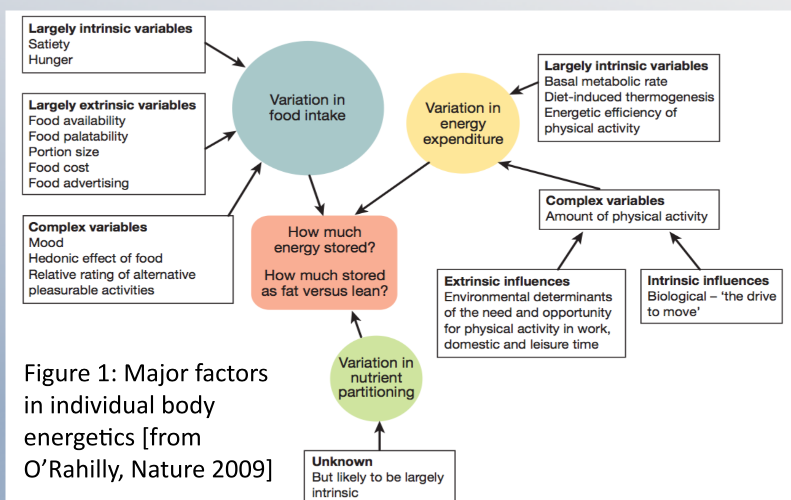


Figure 1: Major factors in individual body energetics [from O'Rahilly, Nature 2009]

Obesity is a disorder occurring at several levels. At the level of an individual's eating habits, it is simply a case of measuring (*calories in*) – (*calories out*).

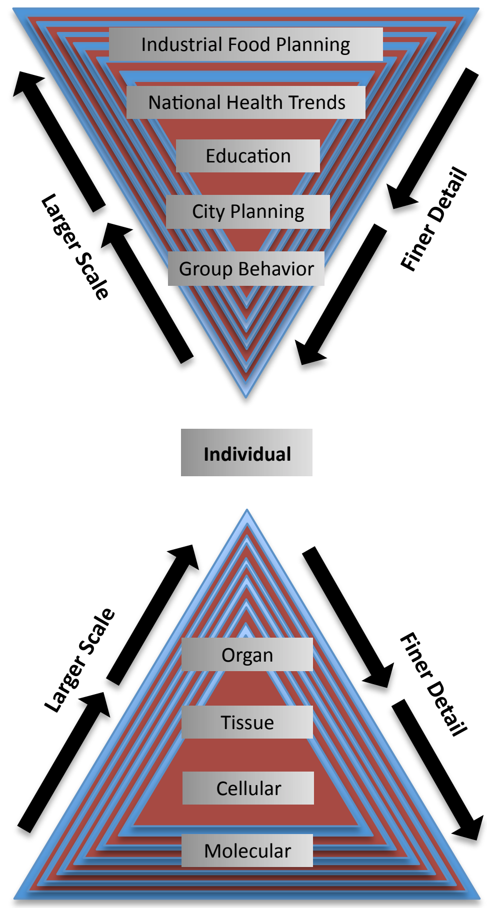
However, a comprehensive approach should include factors on different spatial and temporal scales (Figure 1).

Credits. All text and diagrams were created collaboratively by the students of the class NEUR 8790, *Introduction to Modeling for the Life Sciences*, led by Dr. Robert Clewley in the Neuroscience Institute. In alphabetical order, the authors are: William Barnett, May Chen, Bryce Chung, Patrick Dougall, Shannon Nolen, David Sinkiewicz, Tessa Solomon-Lane, Jeremy Wojcik . See http://www2.gsu.edu/~matrhc/NEUR8790.html for further details.

At the **macroscopic level**, obesity can be analyzed as a result of changes in industrial food production, such as the predominance of high fructose corn syrup as a sweetener instead of table sugar. National trends also indicate an increase in sedentary lifestyles and in the consumption of processed food. For example, it is well known that in "food deserts," where fresh fruits and vegetables are harder to come by, food is often sourced from convenience stores where processed and pre-packed food is more commonly stocked. This situation is particularly common in poorer urban areas, where grocery stores are uncommon or difficult to access.

Closer to the scale of an individual, unhealthy eating habits may be spread through interactions with family and other social networks.

Figure 2: At a societal level, macroscopic factors (upper triangle) influencing obesity include public policy, education, and demographic trends. Scientists who study these kinds of issues may focus on the history and environment surrounding obesity in a population rather than in individual people. Many issues at this scale tend to disproportionately affect lower-income demographics.



Chow and Hall's whole body energy model conveniently sits at the intersection of macroscopic and microscopic scales (Figure 2).

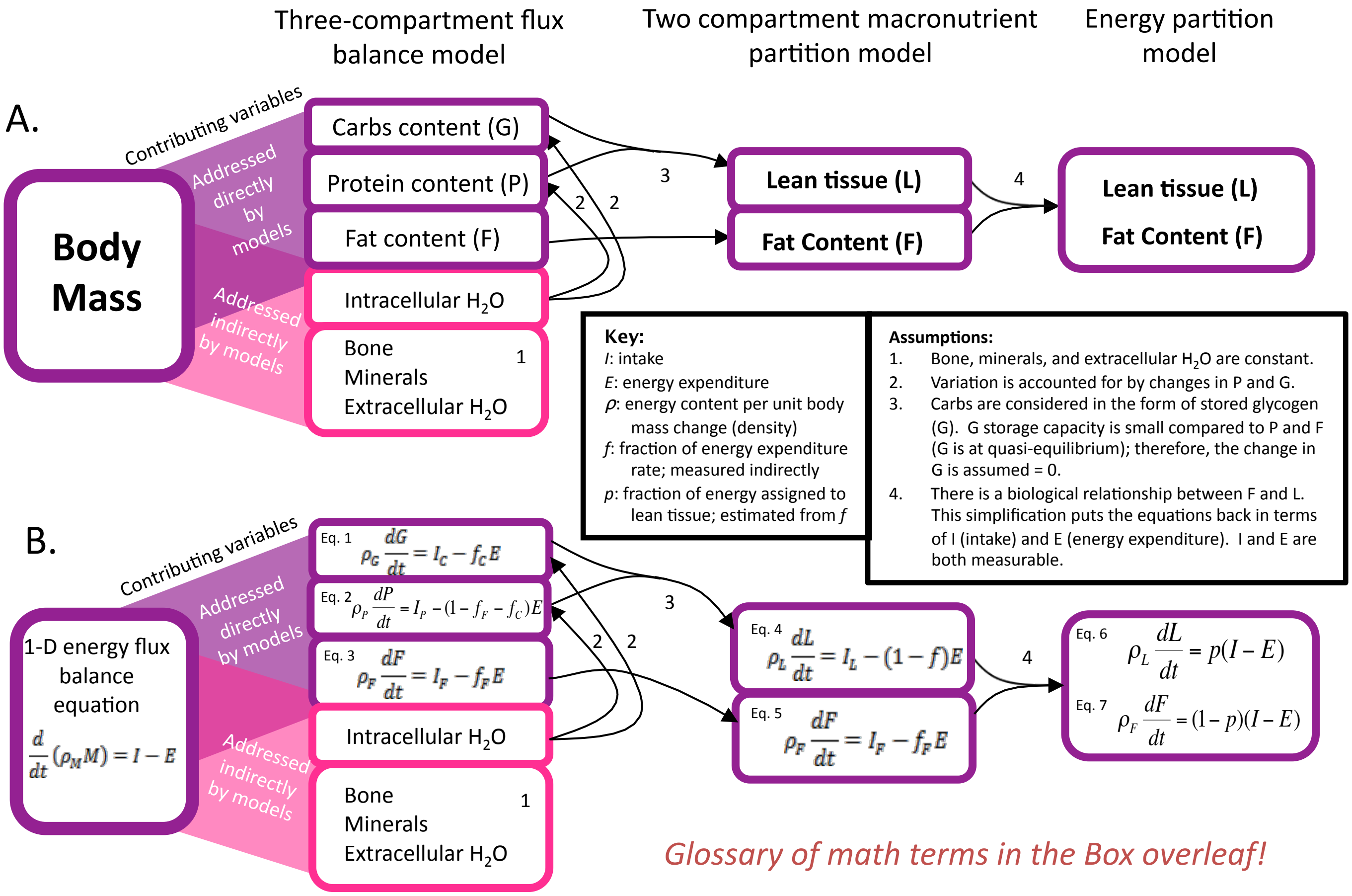
At the **microscopic level**, within an individual's metabolism, obesity can be divided into analysis at different temporal and spatial scales. Obesity can be analyzed by looking at molecular interactions that take place over a timescale of milliseconds up to cellular mechanisms up to the order of seconds.

Beyond that, the effect of diet and exercise can change tissue and organ functioning over longer term timescales (from hours to days), which in turn, affect the accumulation and loss of adipose or lean tissue over even longer time periods, in terms of years or decades.

Figure 2 (cont'd): At levels within an individual (lower triangle), there are models of obesity that take into account details on a range of scales from total body mass down to molecular kinetics.

The **epidemiology** of obesity not only affects the individual, but also society as a whole in the form of increased healthcare costs and reduced productivity. While each type of model explains a piece of the puzzle and models it within a specific spatial or temporal scale, different kinds of models can be integrated together in order to make more comprehensive **hybrid models** that address obesity at *all* levels. It's not hard to see how the nationwide approach to the treatment of obesity will require an *interdisciplinary approach* involving contributions from different branches of academia, the food industry, policy planners, and government.
Obesity research at GSU spans all the levels: see http://www.gsu.edu/44042.html for details.

How does the biology map onto the math?



Glossary of math terms in the Box overleaf!

Figure 3: Models discussed in Chow and Hall, 2008. Biological (A) and mathematical (B) representations of the models. All quantities in (A) and (B) refer to rates of change over time.

How is Chow's model derived mathematically?

Understanding the Chow-Hall model begins with the law of energy conservation. The law states that the amount of change in stored energy is equal to the difference between the change in energy input and the change in energy output, or $\Delta U = \Delta Q - \Delta W$ (equation "EC").

To express a change of stored energy in terms of body mass (M), we determine the energy content per unit of body mass, or energy density, (ρ_M). Change in stored energy can then be interpreted as a change in the product of energy density per unit body mass and total body mass, or $\Delta\rho_M M$.

To understand how body mass changes *over time*, we divide equation (EC) by some interval of time and turn it into a *rate equation* with the help of calculus. Doing so yields a *1-D energy flux balance equation*, shown in Figure 3.B in the first column. This differential equation represents the rate of change of stored energy in the body as a function.

The energy density of body mass may not be constant and could change as a function of body composition and time. So, we need a way to understand and track how this quantity might change. One way of doing this is to track changes in the different components that our bodies store as energy, mainly fats (F), carbohydrates stored as glycogen (G), and proteins (P). This gives us the *3-D macronutrient flux balance equations*, with one for each of the macronutrients (second column in Figure 3). Taken together, these three equations represent the total change in the amount of stored energy in the body (i.e. summing equations 1-3 in Figure 3 will yield the first equation in B).

BOX: What mathematical concepts are important for understanding the Chow-Hall model?

Differential equations: Often written as

$$dy/dt = g(x,y,t) \quad \text{or} \quad y' = g(x,y,t)$$

differential (or "rate") equations describe how state variables (such as *y* in this example) in a system change over time, as a function *g* of other variables and time.

Dynamical systems theory: A framework for analyzing systems of differential equations and describing how the model behaves as time or parameters vary.

Phase plane: A two-dimensional plot used to visualize the behavior of a system of differential equations.

Trajectories: The possible behaviors exhibited by a system of differential equations, often visualized as directional curves in a phase plane.

Fixed point: Special equilibrium or "steady state" values of the state variables that do not change through time, i.e. where all rates of change are zero. Around attracting ("stable") fixed points, trajectories come together to converge at the fixed point. Trajectories move away from each other near repelling ("unstable") fixed points.

Stability analysis: A mathematical calculation used to determine if fixed points are attracting or repelling.

Nullcline: The set of variable values where there is no change in just *one* of the differential equations ($dy / dt = 0$). In a system, each equation defines a nullcline.

Invariant manifold: A curve defined by a set of points such that trajectories starting in the set will will remain in it over time.

Derivation continued …

Various biological facts are used to constrain the model, reducing the macronutrient flux balance equations from a 3-D model to a 2-D model. Reducing the model has two key benefits: (1) it allows the model to be understood using the mathematical tools of dynamical systems analysis [see Box]; and (2) it results in variables that correspond to real-world quantities that can be measured and plugged into the resulting equations.

The resulting 2-D model is given in terms of fat mass and lean mass, where $L = M - F$. The lean mass component (L) includes the protein and glycogen forms of stored energy from the 3-D model, plus the components of body mass that don't change significantly over time (such as bone, water, etc). The fat mass component (F) is represented by the same equation as in the three-compartment flux balance model. The resulting model (equations 4 and 5) is termed the *two compartment macronutrient partition model* (see Figure 3, third column).

The equations in the macronutrient partition model contain a state-dependent fraction f between 0 and 1, which is a function that determines energy expenditure rate attrib-uted to fat utilization (the remaining energy expenditure rate for the lean compartment is thus $1-f$). Further algebraic steps result in the *energy partition model* (Figure 3, equations 6 and 7).

In the fourth column of the figure, the energy partition model is put back in terms of generic intake (I) and expenditure (E), only now the fraction of $I-E$ that is assigned to lean body tissue is given by a function $p(F,L)$ estimated from f and experimental data on body composition and the mechanisms of weight change. The advantage of this model is that I and E are both measurable quant-ities, and the resultant dynamics of the lean and fat compartments are still amenable to dynamical systems analysis.