

*Mathematical Model of Metabolism***Introduction**

A model was constructed in Stella Professional to capture the dynamics of human metabolism. The model considers four different nutritional inputs: glucose, fructose, fat, and protein. Fiber is also included in order to modulate absorption rates from the digestive tract. Each nutritional component is absorbed from the digestive tract and is oxidized during metabolism in order to provide energy. Also included are mechanisms to convert from one type of nutrient to another, including gluconeogenesis from proteins and fats and de novo lipogenesis from both glucose and fructose stores. Specific model parameters listed below for glucose, fructose, fat, and protein are obtained from [2].

**Glucose**

Inputs to body glucose storage include external absorption from the digestive tract, along with gluconeogenesis from both fats and proteins. Outputs include glucose oxidation to obtain energy and lipogenesis to synthesize fats. Though [2] considers glucose and glycogen as separate stores, the following model assumes that any glucose that is converted to fat does so through an intermediate glycogen stage that is not explicitly present. The rate of protein-based gluconeogenesis was assumed to be proportional to the concentration of protein normalized by its basal (initial) concentration with a proportionality constant equal to 100 kcal/day, or, using a conversion factor of 4.2 kcal/g for glucose, of  $100/(24 \cdot 4.2)$  g/hr. In the model, this is equivalent to the degradation rate of protein divided by the basal rate of 300/24 g/hr. Gluconeogenesis from fat is more complicated, as it considers input from both internal and external sources. Triglyceride hydrolysis releases glycerol, which is assumed to all be converted into glucose. The internal fat is converted to glucose by scaling the average lipolysis rate, detailed below, by the ratio of the molar masses of glycerol (92 g/mol) to triglycerides (860 g/mol). External sources are converted by scaling the fat intake by the same ratio. It is assumed that all of this released glycerol from triglyceride hydrolysis is converted into glucose. It should also be noted that the glucose derived from these sources does not subtract from the fat concentration, as the glycerol is released during hydrolysis, rather than directly converted from the fat stores in the body. The initial glucose concentration was taken to be 600 grams, which is the amount of glycogen stored in the body.

Lipogenesis from glucose stores in the liver and fat tissue is modeled by using a Hill function, in order to account for enhanced lipogenesis when glycogen stores are full. The mathematical form of this function scales the glucose intake by the normalized glucose concentration relative to its basal concentration, raised to a fitted parameter of 4. This term is divided by  $[(G/G_b)^4 + 2^4]$ , in which the two is another model parameter, chosen to correspond with *in vivo* rates of lipogenesis. Thus, at high glucose concentrations relative to baseline, when

all glycogen stores are occupied, this equation will converge to the glucose intake rate, so that all glucose is converted directly to lipid. Oxidation of all nutrients is further discussed below.

### **Fructose**

The pathway for fructose is simpler than that of glucose, as fructose does not participate in the insulin regulatory pathway. Fructose is not synthesized by gluconeogenic mechanisms, so the only input to the pathway is from external sources. Fructose, like glucose, is converted to fat when in excess through a glycogen intermediate. However, due to the lack of insulin regulation of the pathway, this is incorporated into the model as a simple proportional relationship, in which the rate of fructose-based lipogenesis is proportional to the fructose concentration normalized by the basal concentration, assumed to be 50 g, by a proportionality constant of 1.5 g/hr. Fructose has been shown to elevate overall fat concentrations preferentially in comparison to glucose, which is more highly associated with insulin concentrations.<sup>3,6</sup> Using this conversion factor of 1.5, fructose contributes more to overall fat increases than glucose does, consistent with experimental observations.

### **Protein**

Protein, like fructose, enters the stores only through external ingestion, but leaves through two pathways. Protein may be oxidized like all other nutrients to provide energy, or may be converted to glucose through protein-based gluconeogenesis. This latter mechanism has been discussed previously. Initial protein storage is taken to be 11,200 g, which is 16% of the weight of a 70 kg man. Though the quality of the protein in the ingested food has been found to affect the absorption rate<sup>7</sup>, the rate is assumed to be constant at  $0.24 \text{ min}^{-1}$ , consistent with that of glucose in [8].

### **Fat**

Fat enters into body storage through lipogenesis from both fructose and glucose storage, as well as through absorption from external sources, and is removed through oxidation and through fat-based gluconeogenesis. Due to hydrolysis of triglycerides during the digestive process into free fatty acids, the absorption rate of fat is scaled by  $3 \cdot 273/860$ , the ratio of the masses of the products and reactants. Thus, the fat concentration reflects free fatty acid values, while that in the digestive tract reflects triglycerides. Initial fat content is taken as 19000 g, which has been previously used as a value for the body fat content of healthy individuals, based on the data from [1].

### **Oxidation**

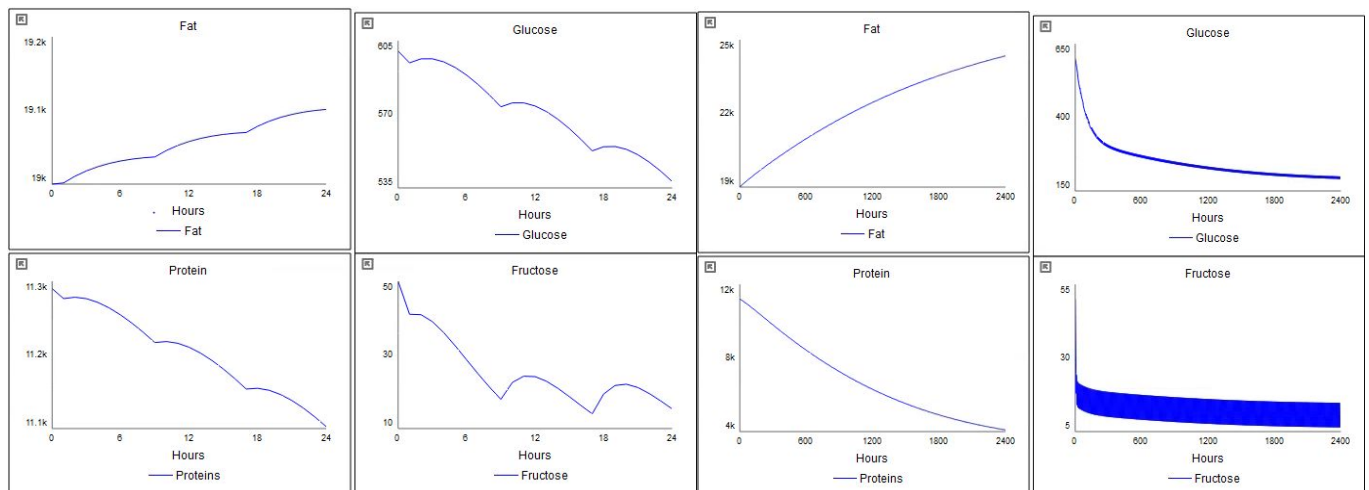
The oxidation of each component is rather complicated, and is designed to yield a daily energy expenditure equal to the basal metabolic rate, taken as 2200 kcal/day. As in [2], the minimum metabolic rate for carbohydrates is assumed to be equal to the sum of the

gluconeogenic rates, and the rest of the daily energy expenditure (“Oxidation Rate” in the model) is divided amongst the four constituents of the system by first adding the normalized degradation rates of each constituent, and multiplying the oxidation rate by the individual degradation rate normalized by this sum. It should also be noted that a conversion factor relating the energy density of each constituent to the metabolic rate is required. These are taken as 4.2 kcal/g for the two groups of carbohydrates, 4.7 kcal/g for proteins, and 9.4 kcal/g for fats. The metabolic output of each nutrient is fed into the energy stock in order to keep track of overall metabolic input and output for the system.

## Fiber

The caloric effects of fiber are not explicitly included in the model, as it is assumed that any nutrient absorbed from fiber falls into the other categories. Instead, fiber serves to modulate the overall absorption rate from the intestine. Studies have commonly looked at the effects of fiber on carbohydrate and lipid absorption, but protein absorption has been less extensively studied. The primary mechanisms underlying these effects are believed to relate to increased intestinal viscosity due to the presence of fibrous components, such as  $\beta$ -glucan or arabinoxylan, which retards overall absorption rates.<sup>4</sup> To incorporate the effects of dietary fiber into the model, the absorption rates were constructed to be variable as a function of the amount of fiber in the digestive tract. With zero fiber, each nutrient was assumed to have an absorption constant of 0.24/hr, consistent with that of glucose in [8]. Each unit of fiber is assumed to contribute a decrement of 0.05 to the carbohydrate and fat absorption rates, and 0.01 to the protein, due to the lack of evidence that fiber significantly reduces protein absorption.

## Dynamics of the Model



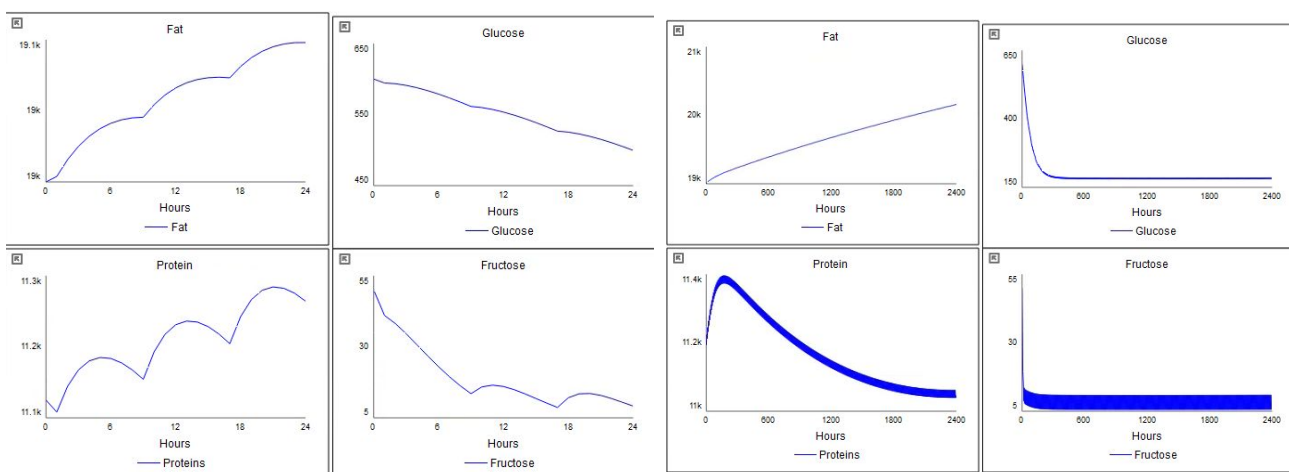
As an initial reference state, the above figures display the results of the model for three meals, administered at 8 hour intervals, consisting of 100/3 g of fat and protein, and 94/3 g of

glucose and fructose. Thus, each day, the individual will consume  $2 \times 94 \times 4.2 + 100 \times (9.4 + 4.7) = 2199.6$  kcal, just below the assumed metabolic rate of the model. Figures are presented for both a 24-hour length of time to show the acute response of the system, and a 2400-hour (100 day) length to show the chronic response of the system, which is more relevant for evaluating the overall dynamics in terms of changes in weight and body composition. Visual inspection of the metabolic energy confirms that the same amount of energy is put into the energy stock as is removed for metabolism, indicating that all excess nutrients are stored as fat, protein, or carbohydrate.

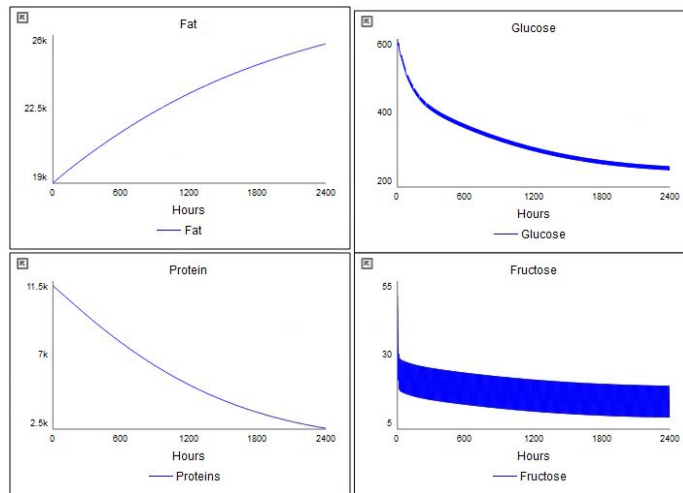
Due to some of the simplifying assumptions in the mathematical formulation of some processes, the steady-state conditions for fructose, protein, and glucose appear to be quite a bit lower than their initial values, but the dynamics of the model should ultimately reflect the behavior of the system, even with some error in absolute values. This is especially apparent in the glucose dynamics, though the combination of glucose and glycogen into one variable may be the cause of some aspects of these results.

### *Glycemic Index*

Reducing the fat and carbohydrate ingestion to 15 g and 20 g for both fructose and glucose per meal, and then increasing protein intake to 90 g per meal shows a significantly reduced amount of fat at the final time point compared to the above version of the model, as is expected from the lower glycemic index. However, as the model still preferentially converts nearly all fructose and a fair amount of glucose to fat, the fat content does still increase over the 100 day time period. Therefore, even with a low glycemic index, fat content will still increase if caloric intake and output are matched. It is dependent on the macronutrient content of the food, however, how quickly this weight gain occurs, and may potentially be offset by caloric reduction and exercise. Additionally, the amount of protein levels off in this model, with a value close to that assumed for the normal protein content of a 70 kg individual.



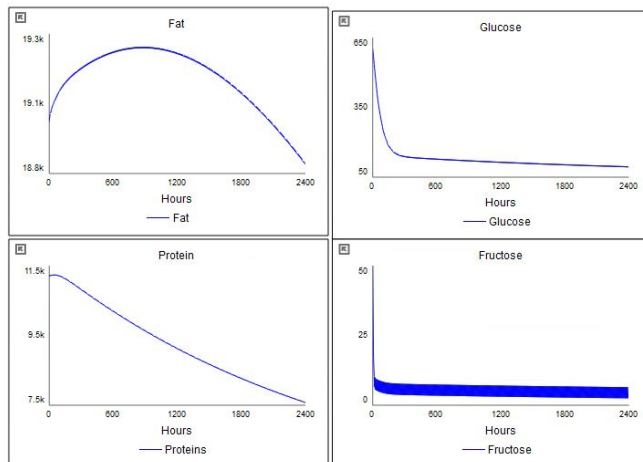
By increasing the content of glucose, fructose, and fat in the intake, and correspondingly reducing the content of protein, for example to 40 g, 40 g, 35 g, and 15 g, respectively, it is



apparent that the amount of fat stored in the body increases far more rapidly, with a final content at 100 days of nearly 26 kg, compared to the 20 kg in the previous case.

From these cases, it can be seen that the body preferentially stores energy as fat, and fat content will increase even when the energy consumed is equivalent to the basal metabolic rate. Thus, in order to lose weight, the caloric intake must be less than the output. Further reducing

carbohydrate content to 15 g of fructose and 15 g of glucose in each meal, and reducing the protein content to 80 g per meal, which amounts to a total intake of 1800 kcal/day, results in similar achievement of steady-state conditions of fructose and glucose stores, along with



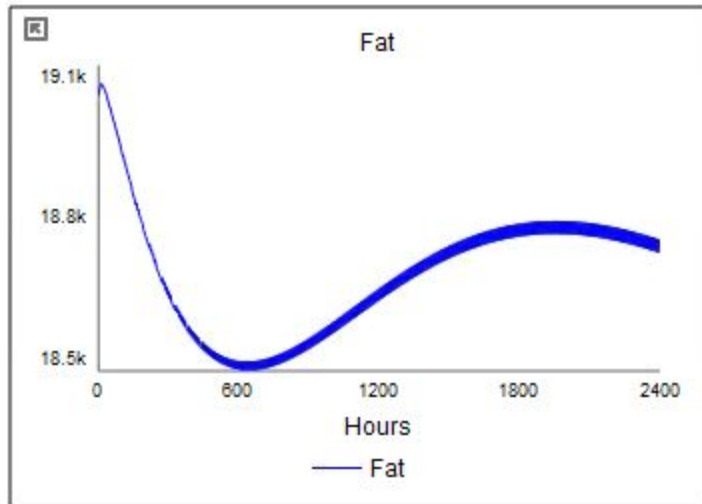
significant reductions in both fat and protein content, with fat content initially peaking and then decreasing below initial values of the system.

Up until this point, the effects of fiber have not been considered in regulating uptake of nutrients for weight loss purposes. The results from the high glycemic index and fat content meal with an added 5 units of fiber show a significant reduction in nutrient absorption content, reducing final levels of fat by 1.5 kg.

It should also be noted that fiber has been shown to increase energy content of fecal matter, a factor which is not considered in the model. This would further reduce absorption rate by reducing the concentration gradient controlling the flow of nutrients into the body from the intestine. Due to the variations in the type of fiber consumed and other factors reflecting body type, gender, and age, it is difficult to pinpoint an exact conversion rate between the “units” used in the model for fiber and a mass. For arabinoxylan, a study revealed that the greatest benefit was achieved by consuming 12 g, while results are quite varied for  $\beta$ -glucan, wherein some studies demonstrated reduced absorption with only 5 g, though others observed only delayed absorption without a change in the net amount, and still others showing no significant effects.<sup>4</sup>

## Conclusions

Based on the above dynamics, it can be seen that the most effective way to lose weight is, in fact, a combination of a high-fiber diet, which reduces absorption rate of nutrients, reduced caloric intake, and a diet consisting of appreciable amounts of protein and low-glycemic index foods, though fats and sugars will inevitably be present. For example, a fiber content of 5.4 g per meal, along with 27 g of fat and protein, and 35 g of glucose and fructose per meal, resulting in an overall caloric intake of 2024 kcal/day, reveals the following dynamics for fat:



After the 100-day time point, the fat content continues to decrease, suggesting an effective weight loss paradigm based on both modification of food content and caloric intake.

Though the effects of hunger are not explicitly investigated in the above model, they can be inferred from the content of the digestive tract and of the body. Hunger has been shown to arise from a variety of causes, including neuronal signaling from physical

intestinal distension, blood levels of glucose, amino acids, and fatty acids, hormone signaling including insulin, cholecystokinin, glucagon, and ghrelin, and psychological factors.<sup>5</sup> Though decreased levels of nutrients in the blood during a caloric deficit will inevitably trigger pathways that produce hunger, competing effects from prolonged GI tract distension can modulate these signals. In the case of a diet without any appreciable fiber content, the digestive tract is rapidly emptied after eating, resulting in hunger. With the fiber content specified above, however, the digestive tract content reaches a steady-state condition at which the influx due to food intake is balanced by the efflux due to absorption. In this situation, hunger will likely be suppressed, thus facilitating dieting. Though the actual value of the steady-state condition and its existence are not truly reflective of the human body, due to assumptions in the model regarding specific values for the influence of fiber and the absorption constants, as well as the lack of excretion, the trends do support the influence of fiber on maintaining conditions that will prevent or reduce feelings of hunger. Therefore, though fiber will not indefinitely prevent hunger, it will serve to prolong feelings of satiety, consistent with observations.

## References

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