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MOLECULAR METABOLISM

Why lipostatic set point systems are unlikely to evolve

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ABSTRACT

Objectives: Body fatness is widely assumed to be regulated by a lipostatic set-point system, which has evolved in response to trade-offs in the risks of mortality. Increasing fatness makes the risk of starvation lower but increases the risk of predation. Yet other models are available. The aim of this work is to evaluate using mathematical modeling whether set-point systems are more likely to evolve than the alternatives.

Methods: I modeled the trade-off in mortality risks using a simple mathematical model, which generates an optimum level of fatness that is presumed to be the driver for the evolution of a set-point. I then mimicked the likely errors in this optimum level, that derive from the variation in the component parameters of the mortality curves using Markov Chain Monte Carlo (MCMC) simulation by Bayesian inference Using Gibbs Sampling (BUGS).

Results: The error propagation generated by the simulations showed that even very small errors in the model parameters were magnified enormously in the location of the optimum fatness level. If the model parameters had coefficients of variation of just 1% then the coefficient of variation in the optimum level of fatness was between 20 and 90%. In that situation, a set-point centered at the mathematical optimum from the component curves would be at the correct level of fatness that minimizes mortality, and hence maximizes fitness, on less than 8% of occasions.

Conclusions: Set-point regulation of body fatness is hence highly unlikely to evolve where there is any realistic level of variation in the parameters that define mortality risks. Using further MCMC modeling, I show that a dual-intervention point system is more likely to evolve. This mathematical simulation work has important implications for how we interpret molecular work concerning regulation of adiposity.

1. INTRODUCTION

It is widely assumed that body fatness is regulated by a lipostatic regulatory system, as originally proposed by Kennedy [1]. By this model a signal from the body reflecting the level of stored fat is compared to a set-point in the brain, and deviations of the body fat from the set-point result in compensatory responses in both energy intake and expenditure [2–8]. The discovery of leptin [9] provided a potential molecular reality for the signal reflecting the level of stored fat. The molecular basis of the lipostatic set-point to which it is hypothetically compared, however, has never been discovered. Set-point models are not the only possible theoretical way in which body fatness can be regulated, and various other models are available: including settling point and dual intervention point models [10]. Moreover, mathematical models of body fatness changes have called into question whether animal responses to metabolic perturbations actually behave as expected from a lipostatic set-point regulation system [11]. How the supposed set point system for body fatness evolved has been a no less active but largely independent area of enquiry from studies aiming to elucidate the molecular basis of the system. It has been suggested that the lipostatic set-point evolves because of two contrasting evolutionary pressures relating to mortality consequences of fat storage [12–14]. One of these pressures favors storage of more fat. This is generally presumed to be the risk of starvation (but see [15] for an argument that it is more likely to be disease risk). The starvation argument is that under conditions of complete failure in the food supply those individuals storing more fat will survive longer. Hence, storing more fat reduces the risk of starvation-induced mortality. However, there is a counteracting pressure which favors storage of less fat. This has widely been assumed to be the risk of predation. Individuals storing more fat may be less maneuverable and slower to evade predators and hence storing more fat increases predation mortality [13,14].

The tension between these opposing forces then generates an optimal level of fat storage that minimizes mortality. This situation can be modeled by a juxtaposition of negative and positive exponential relationships between mortality and fat storage [15]. If the mortality due to starvation (M_s) follows a negative exponential relationship $M_s = ae^{-bx}$, where x is fat storage, and mortality due to predation rises as a positive exponential $M_p = ce^{gx}$. Then overall mortality at any given level of fat storage $M_{tot} = M_s + M_p$ and the optimal fat storage level that minimizes mortality turn out to be analytically defined as

$$F_A = \log(ab/cg) / (b + g). \quad (1)$$

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This fitness landscape is presumed to provide the selective environment in which a lipostatic set-point system can evolve, centered around the point F_A. That is, individuals regulating body fatness at levels that do not coincide with the optimal level F_A would suffer greater mortality; hence, the genes defining these deviant levels of fatness regulation would be purged from the population. What would then evolve is a lipostatic set-point regulating fatness at F_A. It is my contention here that such an evolutionary scenario is untenable and that such set-point regulatory systems for body fatness are unlikely to evolve (at least by this proposed mechanism).

The problem with such mathematical models is that they assume that the curves defining the risks of mortality are stable in space and time. That is, the constants defining the mortality curves (*a, b, c* and *g*) are truly constant. This is extremely unlikely. The curve relating level of fatness to mortality risk from predation, for example, will likely depend on the local population of predators and the populations and sizes of other potential prey. Such variation may make the position of the optimal fatness unstable and hence make it difficult for a lipostatic set-point system to evolve. The key question is how much this likely variation in these parameters would affect the value of F_A. If, for example, changing the parameters up or down by 5% has only minimal impacts on F_A then the optimal solution will be robust to the parameter estimates and a lipostatic set-point system could still evolve. However, if F_A turns out to be highly variable dependent on the component parameter variation then this would make evolution of a lipostatic set-point system unlikely.

2. METHODS

To investigate this question, I used Markov Chain Monte Carlo (MCMC) simulation by Bayesian inference using Gibbs Sampling (BUGS) (using the winBUGS software; [16]). I used the mortality trade-off model from [15], briefly outlined above, as the basis of the simulation. I selected the values of the model parameters *a, b, c, g* so as to generate an optimal body fatness (F_A) of 5 units. I will refer to this from now on as 5 g as if we were modeling fat storage in a typical small mammal, but the units are arbitrary and the model can be applied to any size of animal. If you are more familiar with human fat storage then you may prefer to think about the units as kg rather than grams. I then selected six combinations of the four parameters that reflected different potential mortality landscapes. These combinations are detailed in Table 1, and the mortality patterns they generate are illustrated in Figure 1. The scenarios are identified as A to F and involve an escalating dependence of the mortality curves on body fatness. This is reflected in the fold change in mortality risk from both sources as fatness increases from 1 to 10 g (Table 1). Hence, in scenario A, the least sensitive situation, this 10-fold increase in fatness increases mortality due to predation by a factor of 2.7 but decreases the mortality from starvation by a factor of 1.9. In contrast, for scenario F, the most sensitive situation, the 10-fold increase in fatness from 1 to 10 g resulted in a 36-fold increase in mortality due to predation and a 90-fold reduction in mortality due to starvation.

Table 1 — Six different scenarios that were used to model evolution of set-points. The scenarios are labeled A to F and are ordered by the increasing sensitivity of mortality to changes in body fatness. Sensitivity is expressed as the fold change in mortality due to starvation (M_s) and predation (M_p) that accompanies a 10 fold change in the level of stored fat. The model involves contrasting positive and negative exponentials and generates an optimal fatness (F_A). Parameters of the model (*a, b, c, g*) for each scenario are shown.

Scenario	A	B	C	D	E	F
Sensitivity to						
M_s	1.9	6.04	9.48	14.9	23.3	90.0
M_p	2.7	7.99	5.03	6.0	11.1	36.6
Mean	2.3	7.02	7.26	10.4	17.2	63.3
Parameters						
a	0.53	1.0	1.0	1.0	1.5	2.5
b	0.07	0.2	0.25	0.3	0.35	0.5
c	0.123	0.1	0.16	0.123	0.087	0.035
g	0.117	0.231	0.18	0.2	0.27	0.4

I then assumed that variation in the four parameters followed a normal distribution, with the means defined as in Table 1 and that the standard deviation of each distribution was defined by a given coefficient of variation. The winBUGS model specification text is available on request. The six levels of the coefficients of variation studied included 0.0001%, 0.001%, 0.01%, 0.1%, 1%, and 2%. I applied these equally to all 4 parameters. That is, I didn't model the situation where the coefficients of variation themselves varied between parameters. The program was allowed to generate initial values based on the distributions. In each condition, I ran 10,000 iterations of the program, drawing random samples from the respective parameter distributions. These were then combined in Eq. (1) to generate a sample of the output variable F_A. This resulted in 36 separate output distributions (6 scenarios multiplied by 6 different levels of parameter variation). The output distributions of F_A were then characterized by their means and standard deviations.

In a second set of simulations, I used the same scenarios to generate the profile of mortality (M_{tot}) at different levels of fatness. For this model, the mortality was simulated by drawing random samples from the same distributions of the four parameters that define the mortality curves, but this time instead of calculating F_A the program calculated total mortality (M_{tot}) as a result of both predation and starvation. I set the CV of the defining parameters at 1%, and allowed the program to generate initial values from the starting distributions. The model was then iterated for 10,000 samples at each of 31 values of body fatness between 2 and 8 g (at 0.2 g intervals) for all 6 mortality scenarios. The mean and Monte Carlo standard error for mortality at each fat level was recorded.

3. RESULTS

As expected, given the assumed normal distributions for the component parameter values, the resultant distribution of F_A was also roughly normal. I therefore characterized the distributions based on their coefficients of variation and plotted these against the modeled coefficient of variation in the component parameters (Figure 2). This showed that when the component parameters had only very low levels of variation (CV = 0.0001 and 0.001%), the coefficient of variation in the output F_A was between 0.16 and 2.0% depending on the mortality consequences of the fat storage. Hence, there was a dramatic impact of even minute levels of variation in the components on the position of the optimum fatness. When the variation in the components was higher (1%), the coefficient of variation in the optimum F_A varied between 20 and 90%. The gradients of exponential fits to these relationships all had exponents around 1.2. The intercepts (equal to the coefficients at component variances of 1%) were strongly linked to the average of the mortality impacts of the initial relationships (Figure 3). In other words, when the scenario was strongly sensitive to mortality effects the optimum was less variable. Nevertheless, even when the average mortality effect was 60-fold (Scenario F), 1% coefficients of variation in the 4 component parameters led to a 20% coefficient of variation in F_A.

