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A SIMPLE MOLECULAR MATHEMATICAL MODEL OF MAMMALIAN HIBERNATION

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Abstract

A simple model of the dynamics of the body temperature of a hibernating mammal is presented. Our model provides a good match to experimental data, showing the interruption of low-temperature torpor bouts with periodic interbout arousals (IBAs). In this paper we present a mathematical model of the molecules that participate in the initiation, regulation and maintenance of the hibernating state. This model can be used to describe the role of regulatory molecules, signal transducers, downstream target enzymes, structural proteins or metabolites. Because many of the biochemical mechanisms are unknown, this is a preliminary and largely phenomenological model that we hope will inspire further investigation.

Key words and phrases

Hibernation; interbout arousal

1. Introduction

The ability of many members of the class Mammalia to hibernate is an amazing feat. Impressive in itself, this ability is also correlated with resistance to cellular and systemic damage of many types, which makes hibernation of keen interest for medical applications (Bradbury, 2001; Roth and Nystul, 2005; Trivedi, 2006).

Mammalian hibernation is characterized by profound reductions in metabolism, oxygen consumption and heart rate in order to survive environmental extremes of sub-freezing temperatures and reduced food availability during the late fall and winter. A thorough review of the physiological characteristics of hibernating mammals can be found in Lyman et al. (1982). For a small mammal like a ground squirrel, these characteristics typically include body temperatures ranging from 2 to 10 °C, oxygen consumption that holds at 2 – 3% of the aroused condition and heart rate as low as 3 – 10 beats/minute, compared to 200 – 300 beats/minute when the animal is awake and active. Even more extreme versions of this

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phenotype have been seen in the Arctic ground squirrel (*Spermophilus parryi*) where core body temperatures have been measured at -2.9°C (Barnes, 1989).

The biochemical and genetic regulatory mechanisms of hibernation in mammals is not well understood. This is in striking contrast to research on circadian rhythms, which has a large and rapidly growing literature of models that span the metazoans (Forger and Peskin, 2003; Leise and Siegelmann, 2006; Nakajima et al., 2005; Tyson et al., 1999). The difference is largely due to the ubiquity of circadian rhythms, in particular their presence in several invertebrate and vertebrate model organisms including mammals (Dunlap and Loros, 2004; Hardin, 2005; K. et al., 2005; Salome and McClung, 2004; Reppert and Weaver, 2002; Tamai et al., 2005; Wager-Smith and Kay, 2000).

Despite the fact that hibernators are widespread among the Mammalia (Carey et al., 2003), the study of mammalian hibernation in the past has not benefited from the availability of defined mutants, stock centers, or sequenced genomes. Low coverage genome sequencing has only recently begun on three distantly related hibernating mammals: the little brown bat (*Myotis lucifugus*), European hedgehog (*Erinaceus europaeus*), and thirteen-lined ground squirrel (*Spermophilus tridecemlineatus*). The hedgehog, bat, and ground squirrel genomes have been shotgun sequenced at $2\times$ coverage as part of the National Human Genome Research Institute (NHGRI) funded Mammalian Genome Project at the Broad Institute (Cambridge, MA). The availability of genomic data for hibernators will provide many new opportunities for improving our understanding and modeling of the underlying molecular mechanisms.

Mechanisms of regulating hibernation could vary greatly among mammals - certainly the patterns of body temperatures do (Grigg et al., 2004; Hut et al., 2002a). Our model is derived primarily from species of the order Rodentia, particularly ground squirrels and chipmunks.

Depending on the species and time of year, a hibernating mammal tends to arouse to a normal (or near-normal) body temperature every 1 to 14 days, remain at that temperature for 8 to 48 hours, and then return to torpor. The reason and cause of these interbout arousals (IBAs) is one of the most intriguing mysteries of hibernation. A striking feature of IBAs is that they often decrease in frequency until a steady, near-periodic pattern of torpor and arousal is attained (for example, see Boyer and Barnes (1999)); often the frequency of IBAs increases near the end of hibernation as well (Boyer and Barnes, 1999; Epperson and Martin, 2002; Hut et al., 2002a). IBAs are very energetically expensive, accounting for about 70% of the energy used during a hibernation season (Wang, 1979).

2. The model

An important variable in hibernation is the core body temperature, T_b , which can be experimentally observed. In our model, T_b tracks a setpoint, or metabolic temperature, T_{set} , which is the steady-state temperature for a given metabolic rate at the ambient temperature T_a . In other words, T_{set} expresses the metabolic rate as a temperature.

The focus of our model is a type of molecular mechanism for controlling the IBAs. This mechanism uses two proteins (or complexes of proteins) denoted as A and B . A is presumed to affect the post-translation modification of B to a form B_p . A high level of B_p induces an IBA. The interaction of A , B , and B_p with all other factors is modeled phenomenologically and at a highly aggregated hierarchical level. These interactions are modeled as switches (S_i) and kinetic factors (h_i) as shown in Figure 2.

The four switches, S_i , in our model have values between 0 and 1. S_1 and S_2 are functions of the circannual signal C , assumed to be sinusoidal. When S_1 is close to zero, it allows other model components to affect the body temperature; correspondingly when S_1 is close to 1, hibernation is impossible regardless of the state of the other components. The switch S_2 affects the production of component A : when $S_2 = 1$, the production of A is completely suppressed. S_3 is B_p dependent, and induces an IBA when B_p levels are high during hibernation. S_4 is T_b dependent, and controls the amplitude of body temperature oscillations from circadian rhythms. These switches are largely phenomenological, and may represent intercellular signals such as hormones as well as intracellular events such as the action of transcription factors. We chose them to be sigmoidal Goldbeter-Koshland switches (Goldbeter and Koshland, 1981), of the form

$$GK(a_1, a_2, a_3, a_4) = \frac{2a_1a_4}{a_4a_1 - a_1 + a_2 + a_2a_3 + \sqrt{(a_4a_1 - a_1 + a_2 + a_2a_3)^2 - 4a_1(a_2 - a_1)a_4}}$$

This is the steady-state of a system of the form

$$x' = \frac{a_1(1-x)}{a_3+1-x} - \frac{a_2x}{a_4+x}.$$

The steady-state is assumed to be attained on a fast timescale compared with the other reactions. The particular switches in our model are:

$$\begin{aligned} S_1 &= GK(C(t - k_s), k_{w_1}, \varepsilon_1, \varepsilon_2) \\ S_2 &= GK(C(t), k_{w_2}, \varepsilon_1, \varepsilon_1) \\ S_3 &= GK(B_p, k_B, \varepsilon_2, \varepsilon_2) \\ S_4 &= GK(T_b, T_c, \varepsilon_2, \varepsilon_2) \end{aligned}$$

The behavior of these switches is shown in Figure 2, where the outputs are plotted as functions of an argument normalized to be between 0 and 1. Because of our normalizations, the parameters a_i do not have a simple correspondence with experimental kinetic constants. More explanation of switches of this form and their relation to Michaelis-Menten kinetics can be found in Tyson et al. (2003).

For simplicity we use a sinusoidal function for the circannual signal:

$$C(t) = (\cos 2\pi t / 365 + 1) / 2,$$

normalized to be between 0 and 1, with a period of one year (for convenience we have chosen $t = 0$ to correspond to mid-summer). Note that this signal is always modulated in our models by switches S_1 and S_2 , so that the model is very robust under changes to the form of $C(t)$.

The metabolic temperature T_{set} is the steady state temperature for a given ambient temperature T_a and internal (physiological) state; in our model we use the following phenomenological function:

$$T_{set} = k_{ca} \sin(2\pi t) S_4 + T_{max} S_1 + (1 - S_1) \text{Min} \left\{ \begin{array}{l} T_{max} \\ \text{Max} \left\{ \begin{array}{l} T_a + T_{ao} \\ T_{min} + (T_{max} - T_{min}) S_3 \end{array} \right. \end{array} \right.$$

Here k_{ca} is the amplitude of circadian system's effect on T_b . When $S_1 \approx 1$ the body temperature simply has small circadian oscillations around T_{max} . If $S_1 \approx 0$, then the body temperature is allowed to fall to either slightly above ambient ($T_a + T_{ao}$) or a failsafe minimum temperature (T_{min}) unless $S_3 \approx 1$. The switch S_4 starts to shut down the circadian oscillation at a body temperature T_c . While the exact role of the circadian system in hibernation remains unknown, there is evidence that circadian oscillations in T_b are largely damped or shut down during torpor (Heller and Ruby, 2004; Hut et al., 2002b; Körtner and Geiser, 2000). On the other hand, the superchiasmatic nucleus (SCN) in the brain, which is thought to play a major role in coordinating circadian rhythms, stays active during torpor and there is evidence that it influences the timing of IBAs (DeCoursey, 2004; Ruby et al., 2002). We defer the attempt to model these interactions until more is known about the relevant molecular mechanisms. The parameter T_{ao} controls the offset from the ambient temperature T_a unless that falls below the threshold level (controlled by the term $T_{min} + (T_{max} - T_{min}) S_3$).

The body temperature T_b follows T_{set} but rewarming is faster than passive cooling (i.e. $k_{T1} > k_{T2}$):

$$T'_b = \begin{cases} T_{set} - T_b > 0: & k_{T1} (T_{set} - T_b) \\ T_{set} - T_b < 0: & k_{T2} (T_{set} - T_b) \end{cases}$$

Kinetic effects from temperature, as well as additional down-regulation of processes (Geiser, 1988), are modeled by multiplying the rate of processes by exponential functions of the form

$$h_i(T_b) = e^{k_{hi}(T_b - T_{max})}.$$

There are three such functions, with i between 1 and 3. T_{max} is the normal maximum temperature (chosen to be 37°C for our simulations). We choose the k_{hi} so that h_1 is more temperature sensitive (larger Q10 value) and models the near cessation of protein translation in torpor (van Breukelen et al., 2004). The functions h_2 and h_3 are less temperature dependent and model purely kinetic effects for most biochemical reactions. For simplicity, in our simulations we always choose $h_2 = h_3$; when applying the model to a more specific system it may be appropriate to use k_{h3} k_{h4}

The heart of the model is the interaction between the substances A and $B_p = 1 - B$ and the temperature (through the switch S_3):

$$\begin{aligned} A' &= h_1 k_{a1} (1 - S_2) - h_3 k_{a2} A \\ B' &= h_2 \left(k_{b1} \frac{1-B}{k_{b2} + 1-B} - k_{b3} \frac{AB}{k_{b4} + B} \right) \end{aligned}$$

The rate of formation of A is posited to be limited by protein translation, and so the more temperature sensitive function h_1 is used. On the other hand, B_p can be thought of as the fraction of a molecular species that is post-translationally modified, which can still occur at low temperatures. The post-translation modification of B is catalyzed by A . Note that B and B_p are dimensionless, and always between 0 and 1.

In Figure 3 we show a typical graph of T_b for our model under the laboratory-like ambient temperature

$$T_a = \begin{cases} 23^\circ\text{C} & \text{if } t < 65 \text{ or } t > 300 \\ 5^\circ\text{C} & \text{if } 65 \leq t \leq 300 \end{cases}$$

(with t in days) and for the parameters in Table 1. Figure 4 shows the amounts of the model components A and B_p and Figure 5 is a detail of an IBA for the same simulation as in Figure 3. This particular simulation gives results that are in reasonable agreement with data from ground squirrels (for example that from Boyer and Barnes (1999), Hut et al. (2002a) and Kondo et al. (2006)). Changing the form of the ambient temperature function to be more like outdoor ambient ground temperatures does not appreciably alter the dynamics of the IBAs.

By changing some of the parameters in our model, we can obtain simulated T_b values that qualitatively match the patterns observed in several species. For example, since marmots are more massive than ground squirrels, it would be appropriate to decrease the values of k_{T1} and k_{T2} . A more complicated case is the variance in frequency change at the beginning and end of the hibernation season, which can be observed between individuals and species. Some of this variance can be handled in our model with a relative offset between the effect of the circannual signal in the switches S_1 and S_2 . An example of this with $k_s = 10$, $e_1 = 0.3$, and all other parameters as before, is shown in Figure 7.

Table 1 shows the values of all parameters used for the simulations shown in Figures 3, 4, and 5. As previously noted, the simulation shown in Figure 7 had identical parameter values apart from $k_s = 10$ and $e_1 = 0$.

3. Discussion

Our model should be regarded as providing a plausible basic molecular mechanism for the observed patterns of IBAs. The more phenomenological components, such as the circannual signal $C(t)$ and the switches S_1 , S_2 , and S_3 , should be viewed as aggregated systems and probably do not consist of a single molecular species. Based on what is currently known we can speculate on pieces of these systems. Components A and B are assumed to be particular proteins, and so it makes more sense to assign them specific identities; however the broad mechanism of our model could occur in parallel, with different proteins serving similar roles in different tissues.

Many genes are differentially regulated between summer and winter in hibernators, and many proteins undergo post-translational modifications (Carey et al., 2003; Lee et al., 2006). These differentially expressed genes include α_2 -macroglobulin (Srere et al., 1995), the H3 histamine receptor (Sallmen et al., 2003), TBG (thyroxine binding globulin) (Epperson and Martin, 2002), and the ‘early-intermediate’ genes such as c-fos and c-jun (O’Hara et al., 1999). The role of these proteins in our model is unclear. The uncoupling protein UCP1 and its paralogs are involved in thermogenesis in hibernators, corresponding to switches S_1 or S_3 in our model.

For the circannual signal $C(t)$, one of the only current known possibilities is the HP-complex (Kondo et al., 2006). It is natural to assume that there are also some links between the circadian and circannual systems, and some evidence exists for those relationships (Heller et al., 1978; Körtner and Geiser, 2000). Although the circannual system can output such a signal with no external cues, in the wild environmental factors such as lack of nutrition and changes in day length could significantly modulate the endogeneous system.

Because the switch to and from lipid metabolism is so crucial to hibernation, this is another natural place to look for elements of a control mechanism (Andrews, 2004; Dark, 2005). A candidate for substance A is the enzyme pyruvate dehydrogenase kinase 4 (PDK4) (Andrews, 2004) and therefore candidate B is the pyruvate dehydrogenase (PDH) complex. We have shown that levels of PDK4 mRNA and protein increase at the onset of hibernation in heart, skeletal muscle and white adipose tissue of thirteen-lined ground squirrels (Buck et al., 2002). Regulated long-term inhibition of PDH activity is the result of phosphorylation of the PDH complex (conversion of substance B to B_p) by the activity of various isoenzymes of the PDK family (substance A). In hibernating golden mantled ground squirrels, Brooks and Storey observed a 96% reduction in cardiac PDH activity during hibernation (Brooks and Storey, 1992). In the hearts of Djungarian hamsters, Heldmaier et al. (1999) showed that inactivation of PDH closely correlates with metabolic rate reduction seen during daily torpor. Inactivation of PDH by this post-translational modification impedes carbohydrate oxidation by blocking the conversion of pyruvate to acetyl CoA thus leading to metabolic rate reduction and a reliance on stored lipids as the primary source of fuel. Another differentially expressed protein involved in lipid metabolism is PTL (pancreatic triacylglycerol lipase). Its expression outside the pancreas could be mediated by our circannual signal $C(t)$, and therefore it could play a role in the switch S_1 .

Post-translational modifications are likely to be of great importance in the regulation of hibernation, since translation to protein is almost entirely shut down during torpor (Frerichs et al., 1998; van Breukelen and Martin, 2001; van Breukelen et al., 2004). The torpor-specific phosphorylation of pp98 (Ohtsuki et al., 1998) is a good example, although the function of that protein remains unknown. The phosphorylation-dependent differential activity of the initiation factor eIF4E and its binding protein 4E-BP1 between torpor and IBA make these proteins leading candidates for the oscillator components of our model (van Breukelen et al., 2004). Other modifications such as SUMOylation, which occur in mammalian circadian rhythm systems (Cardone et al., 2005) and hibernation (Lee et al., 2006), are also possibilities.

In our model we did not attempt to include the known differences in hibernation behavior between sexes. Male sciurids usually emerge from hibernation earlier than females, and there is some evidence that they are more sensitive to the ambient temperature as an emergence cue (Barnes and York, 1990). However, there do not appear to be other significant differences in the timing and pattern of the IBAs between the sexes. Another interesting phenomenon not covered by our model is the synchronization of interbout arousals in social hibernators such as marmots (Arnold, 1988).

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Figure 1.

Model components. Phenomenological models for circannual signals and metabolic rate are coupled via switches S_1 , S_2 , and S_3 to a molecular model of hibernation control. A and B are protein-like components which are not produced at low body temperatures. The circannual system can activate production of A . B can be converted to and from a modified form, B_p . Component A shifts the equilibrium of these states to the B_p form. Arrows labeled h_1 , h_2 , and h_3 represent kinetic effects from temperature and the inhibition of protein translation.

Figure 2. Goldbeter-Koshland switches $GK(t, .5, \epsilon_1, \epsilon_2)$ (solid, corresponding to S_1), $GK(t, .5, \epsilon_1, \epsilon_1)$ (small dashes, corresponding to S_2), and $GK(t, .5, \epsilon_2, \epsilon_2)$ (long dashes, corresponding to S_4 and S_3), with $\epsilon_1 = 0.1$, $\epsilon_2 = 0.001$.

Figure 3.
Model ambient temperature T_a (dashed) and body temperature T_b (solid).

Figure 4. Model components A (dashed) and B_p (solid). Solid gray line at 0.5 is the switch point for B_p to induce arousal

Figure 5.
Detail of model body temperature T_b for a pair of interbout arousals. Ambient temperature T_a is dashed.

Figure 6. Model components A (dashed) and B (solid). Solid gray line at 0.5 is the switch point for B_p to induce arousal.

Figure 7. Model body temperature T_b (solid) with a shifted circannual signal and relaxed hibernation switch. Ambient temperature T_a is dashed.

Table 1

Parameter values for figures 3, 4, 5, and 6

Parameter	Value	Parameter	Value	Parameter	Value
e_0	0.1	e_1	0.1	e_2	0.001
k_{h1}	0.25	k_{h2}	0.075	k_{h3}	0.075
k_{a1}	0.4	k_{a2}	0.6	kb_1	0.8
kb_2	0.01	k_{b3}	4	k_{b4}	0.01
T_{min}	2	T_{max}	37	k_{T1}	30
k_{T2}	5	k_s	0	k_B	0.5
k_{w1}	0.5	k_{w2}	0.5	T_c	35
k_{ca}	0.5	T_{ao}	1		