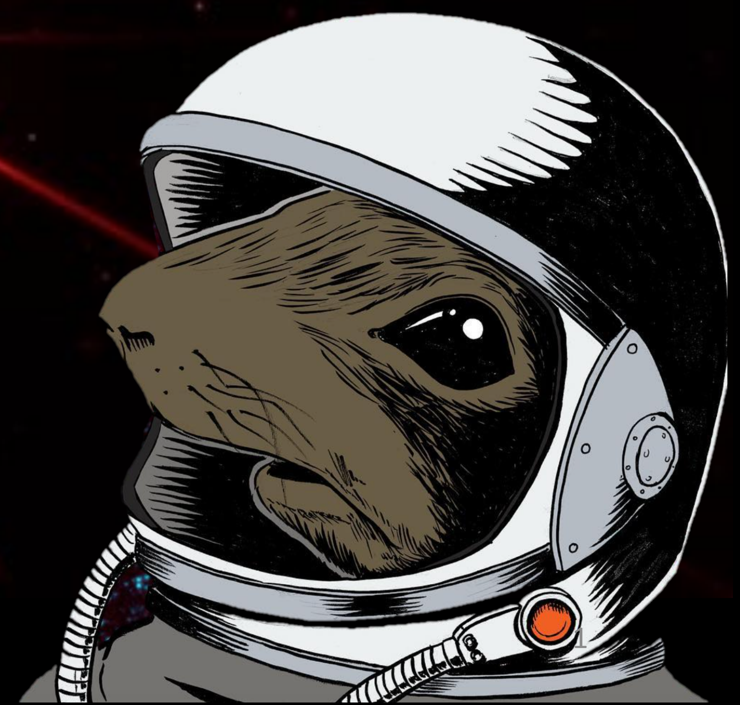
Translating hibernation metabolism to human spaceflight

Matt Regan, PhD
University of Montréal



Spacefaring squirrel illustration by Dr. Rush Dhillon

Outline

6 questions for today:

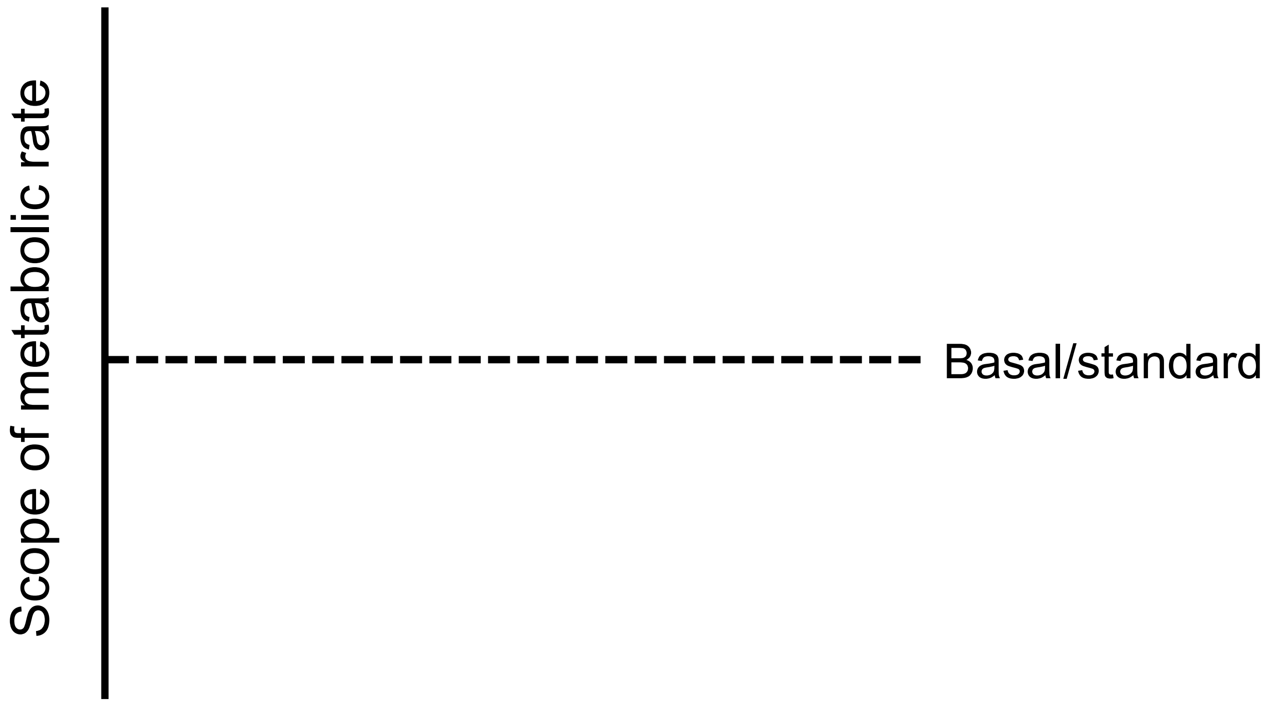
1. **What is metabolic depression?**
2. **How might metabolic depression benefit human spaceflight?**
3. **How to hibernators naturally induce metabolic depression (torpor)?**
4. **How close are we to inducing “synthetic” torpor in humans?**
5. **How might synthetic torpor be applied to human spaceflight?**
6. **What are some next steps for spaceflight applications?**

Metabolism | The totality of life-sustaining chemical reactions that occur within an organism

Scope of metabolic rate

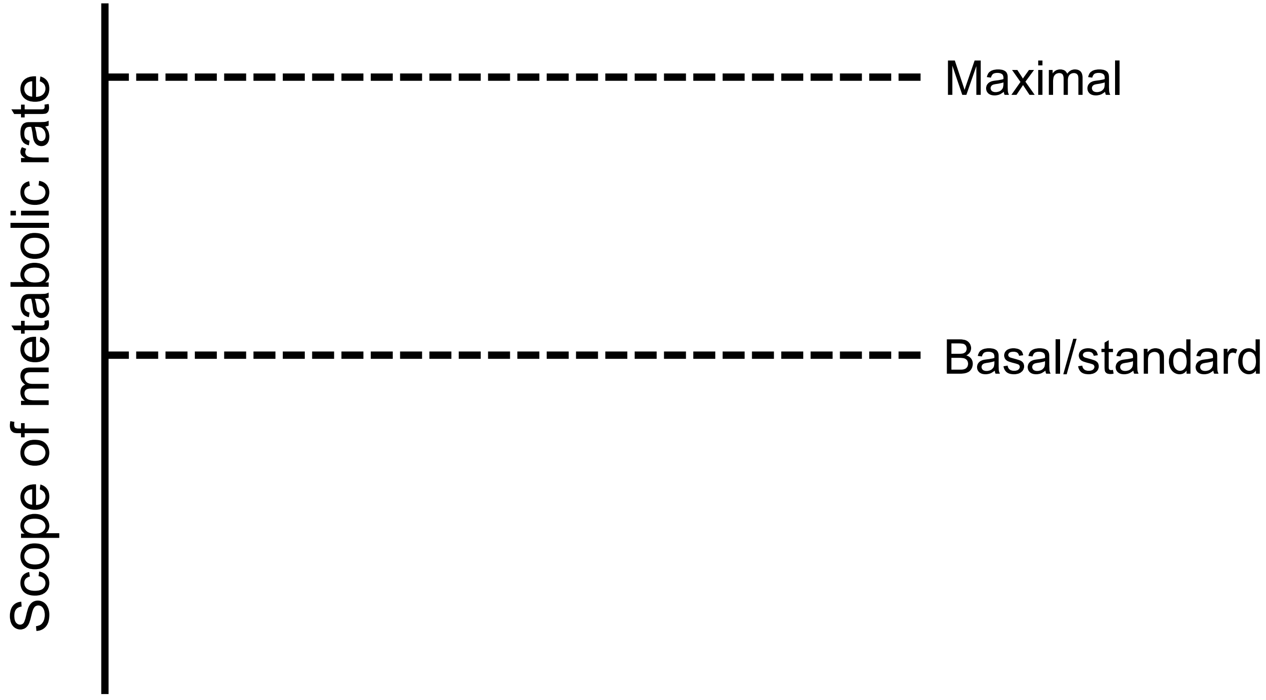
What is metabolic depression?

Metabolism | The totality of life-sustaining chemical reactions that occur within an organism



What is metabolic depression?

Metabolism | The totality of life-sustaining chemical reactions that occur within an organism



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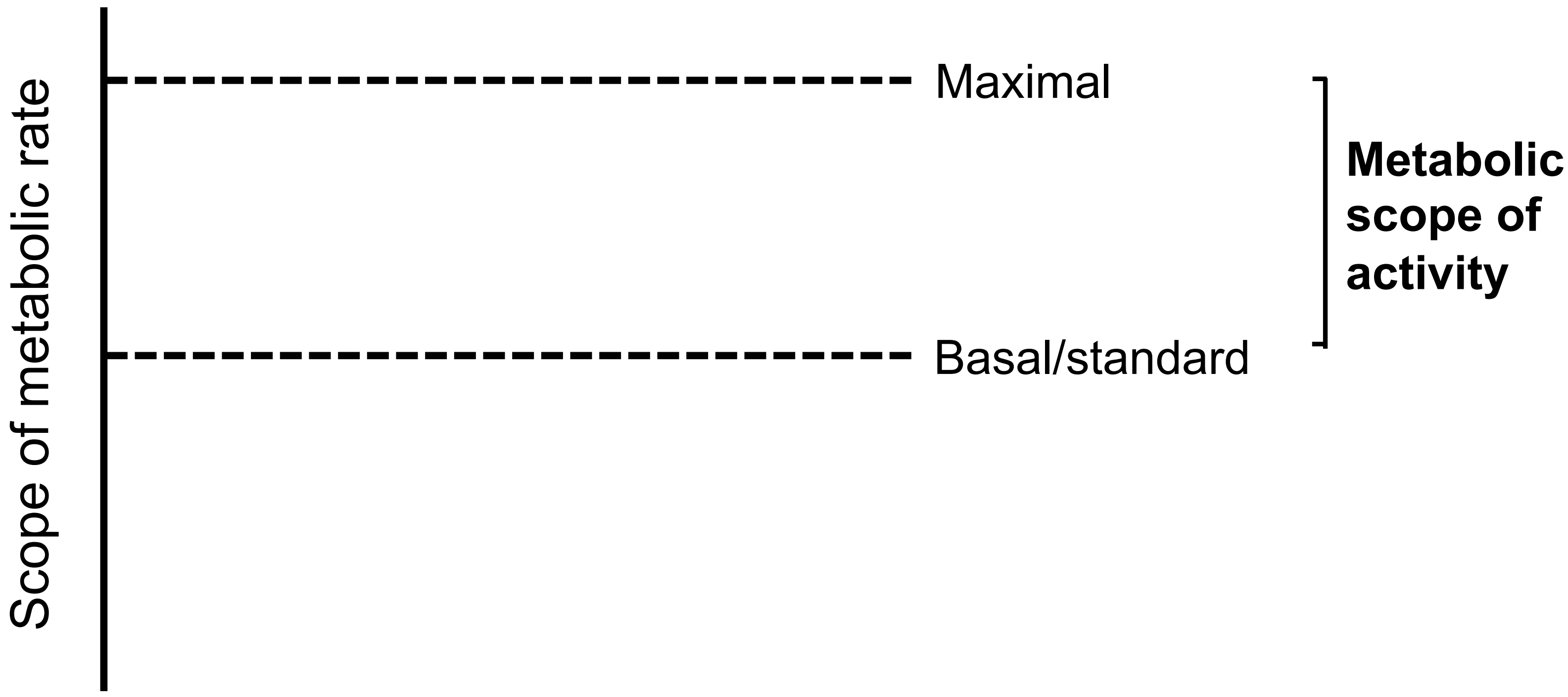

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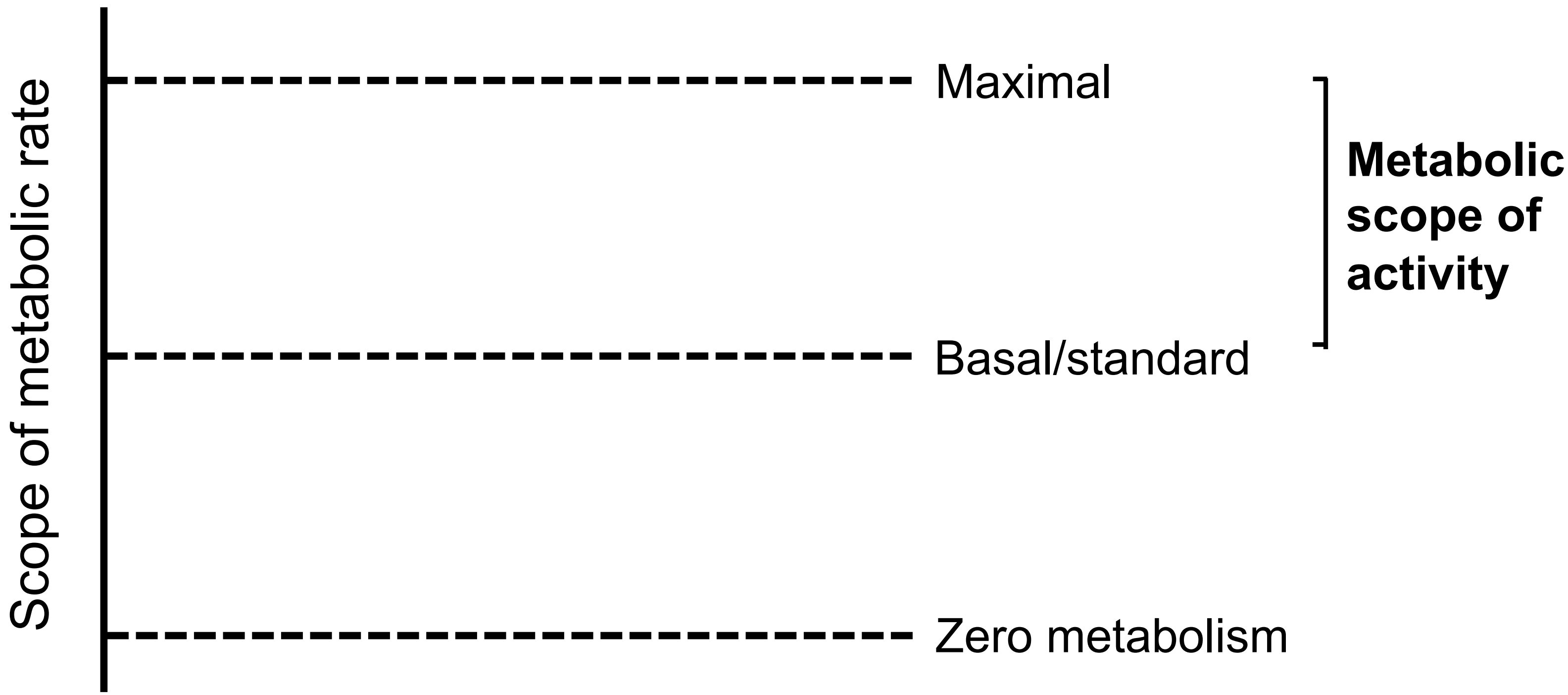

What is metabolic depression?

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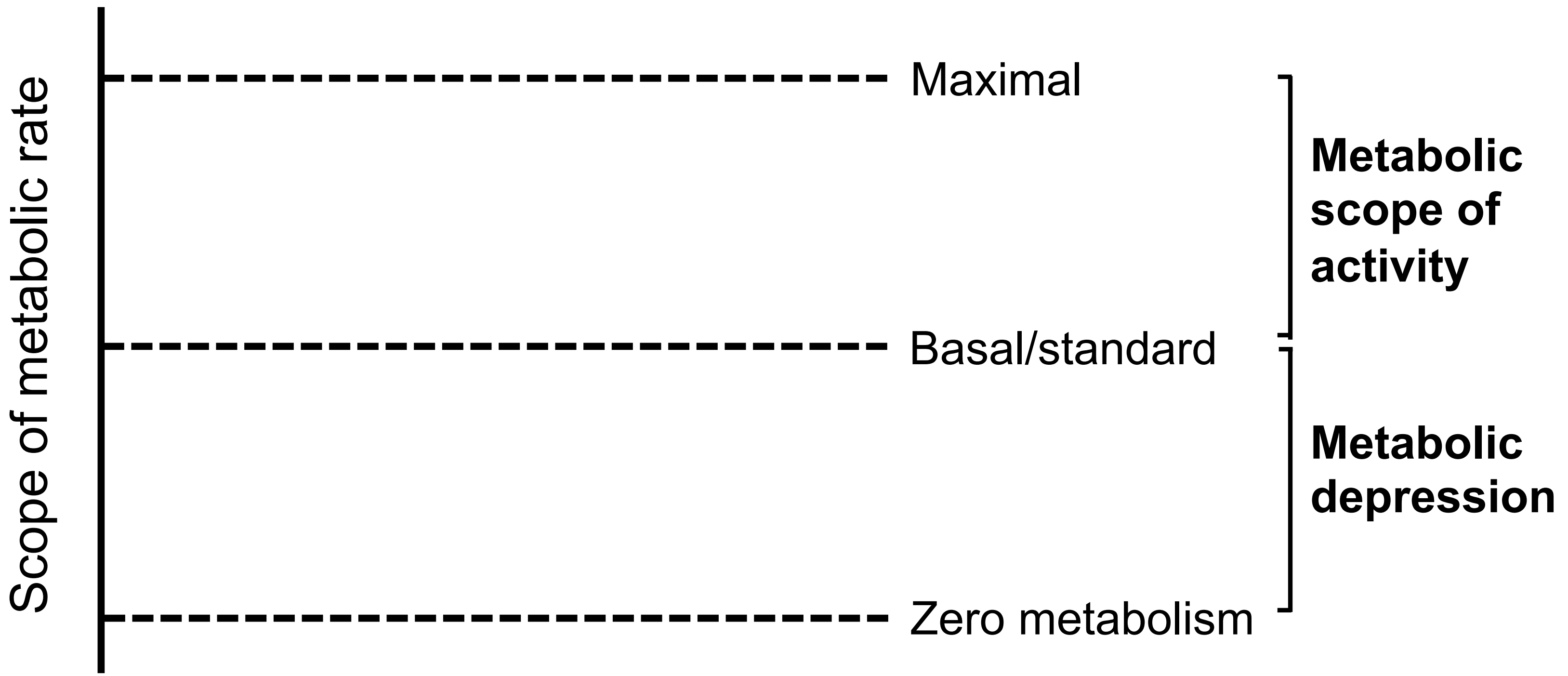


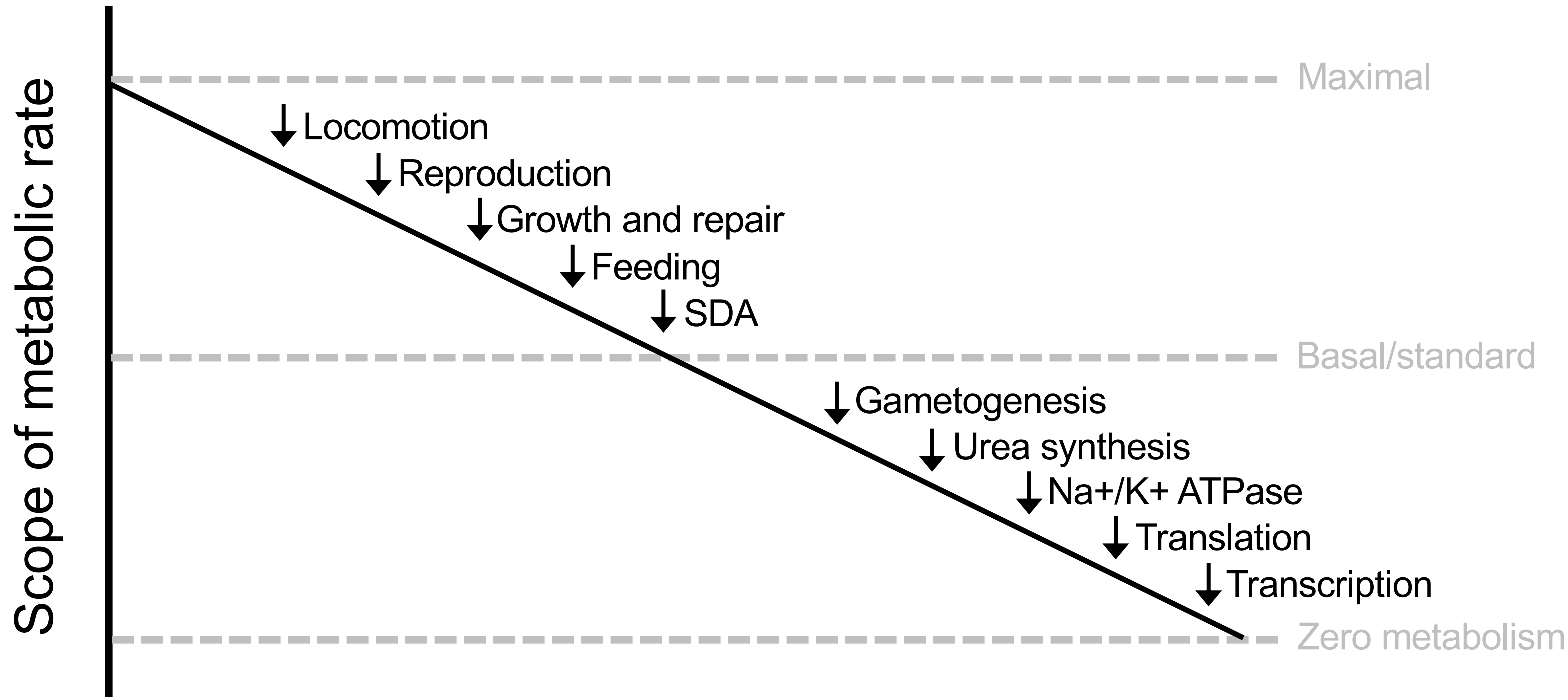
What is metabolic depression?

metabolic depression |
A regulated and reversible depression of metabolic rate below basal (endotherms) or standard (ectotherms) metabolic rate.

What is metabolic depression?

Metabolic depression

Mechanisms span levels of biological organization



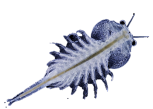
What is metabolic depression?

Metabolic depression

Present in taxonomically diverse animals










Metabolic depression

Prolongs survival in environments
that lack some essential abiotic factor

What is metabolic depression?

Metabolic depression

Prolongs survival in environments that lack some <u>essential abiotic factor</u> →

- low O_2
- low water
- low heat
- low food

(deep sea O_2 minimum zone)

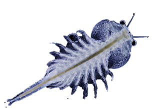
What is metabolic depression?

Metabolic depression

Present in taxonomically diverse animals







Metabolic depression

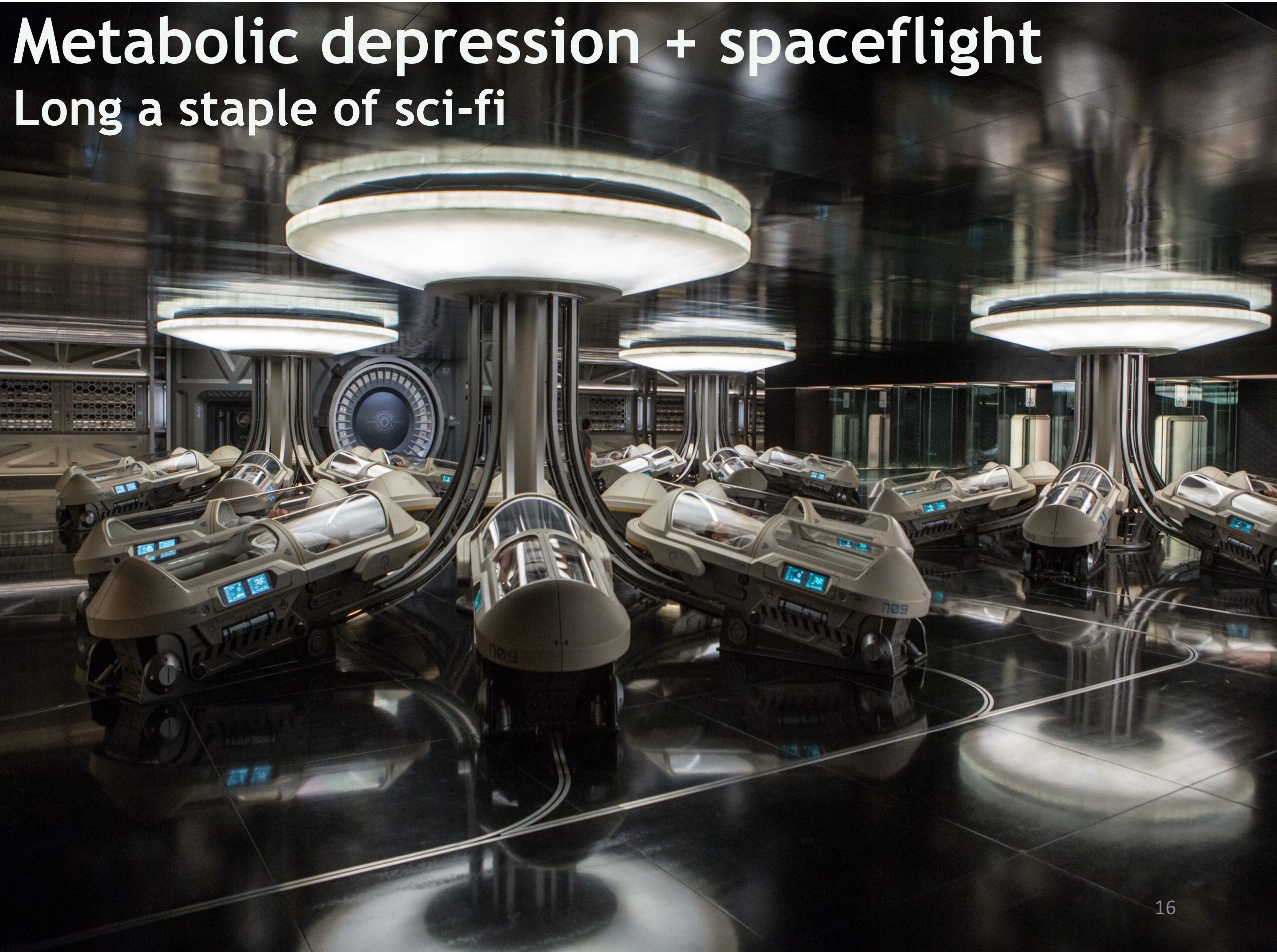
Present in taxonomically diverse animals

What mechanisms are common to each of these independent uses?

What is metabolic depression?

Metabolic depression + spaceflight

Long a staple of sci-fi



Metabolic depression could mitigate numerous spaceflight challenges

Challenge type	Challenge	MD-mediated mitigation
Logistical		
Biological		

How might metabolic depression benefit human spaceflight?

Metabolic depression could mitigate numerous spaceflight challenges

Challenge type	Challenge	MD-mediated mitigation
Logistical	Spacecraft mass & volume constraints	Reduced consumables use (food, water, O_2)
Biological		

How might metabolic depression benefit human spaceflight?

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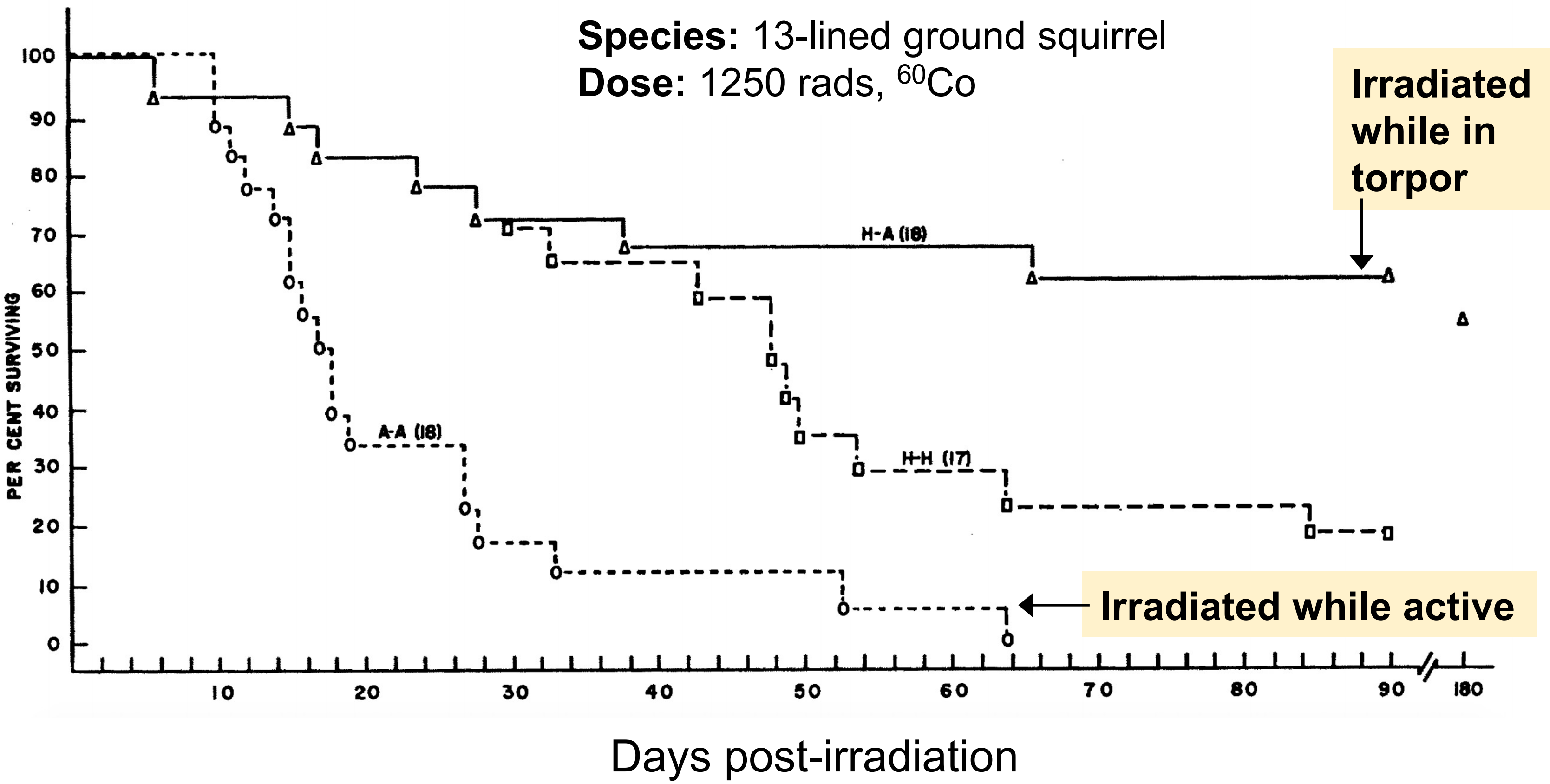
How might metabolic depression benefit human spaceflight?

Metabolic depression confers radiation resistance



From Barr & Musacchia (1969) *Rad. Res.*

How might metabolic depression benefit human spaceflight?

Metabolic depression confers radiation resistance

Possible mechanisms:

- Halting the cell cycle and DNA replication may reduce magnitude of acute damage.
- Depressed cellular respiration and peripheral blood flow reduce O_2 levels in cells and, subsequently, ROS damage.
- DNA repair mechanisms may be enhanced by cold temperature.

→ Inducing torpor *after* irradiation bestows similar radioprotection.

How might metabolic depression benefit human spaceflight?

Metabolic depression could mitigate numerous spaceflight challenges

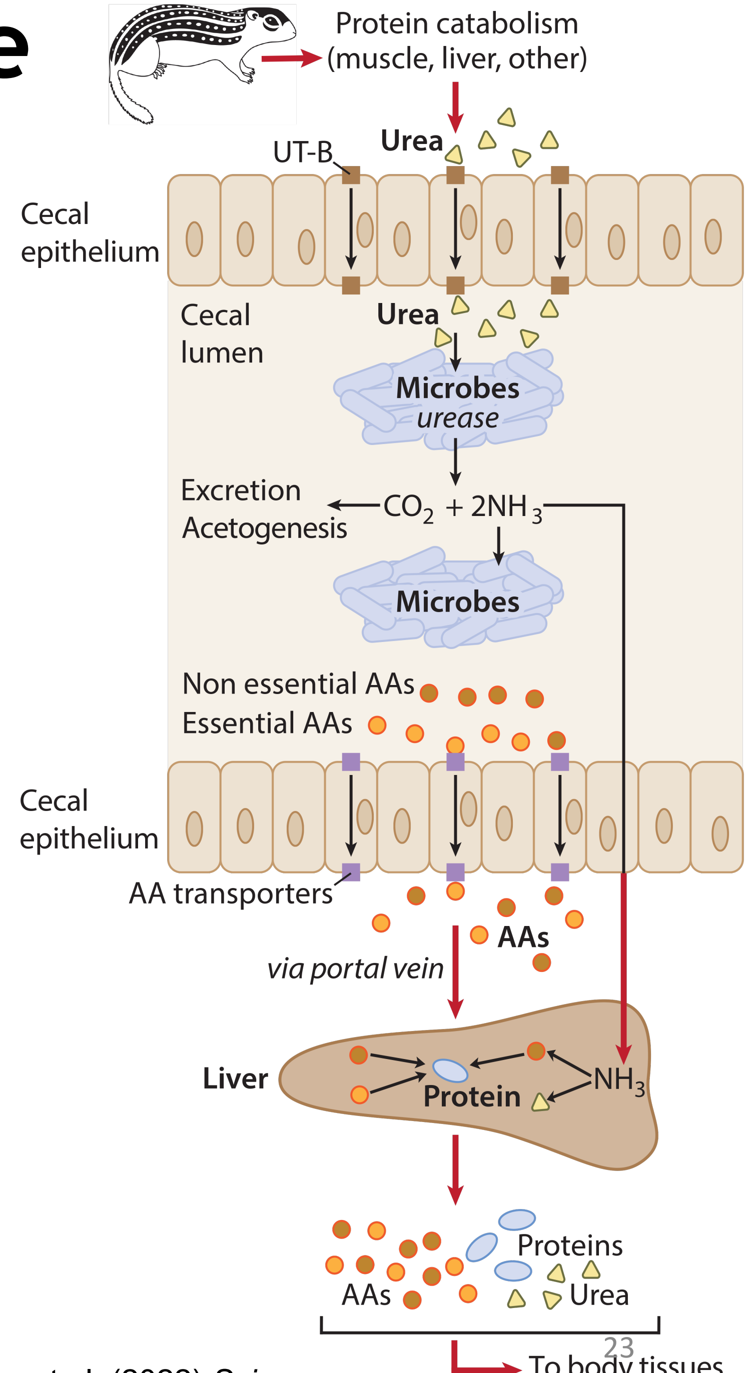
Challenge type	Challenge	MD-mediated mitigation
Logistical	Spacecraft mass & volume constraints	Reduced consumables use (food, water, O_2)
Biological	Radiation-related biological damage	MD confers radiation resistance
	Gravity-related muscle/bone atrophy	Hibernators are highly resistant to muscle/bone atrophy over hibernation season

How might metabolic depression benefit human spaceflight?

Hibernators resist muscle and bone atrophy

Possible mechanism:

- Urea nitrogen recycling via gut microbes



From Regan et al. (2022) *Science*

How might metabolic depression benefit human spaceflight?

Metabolic depression could mitigate numerous spaceflight challenges

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Logistical	Spacecraft mass & volume constraints	Reduced consumables use (food, water, O_2)
Biological	Radiation-related biological damage	MD confers radiation resistance
	Gravity-related muscle/bone atrophy	Hibernators are highly resistant to muscle/bone atrophy over hibernation season
	Challenging socio-psychological environment	MD could provide a hiatus

How might metabolic depression benefit human spaceflight?

Metabolic depression would also mitigate challenges on earth

Hibernating mammals could serve as useful models for various biomedical scenarios:

- **Depressed metabolism would benefit**
  - Donor organ viability
  - Ischemic injury treatment (stroke, heart attack, blood loss, etc.)
- **Hibernators could be useful models for Alzheimer's disease, longevity.**
- **Potential hibernation-related therapies for sarcopenia, mal/undernourishment.**

How might metabolic depression benefit human spaceflight?

Metabolic depression offers promise as a multipronged spaceflight countermeasure…

…but its benefits are at this point pretty well all theoretical.

Hibernation |

How do hibernators induce metabolic depression (torpor)?

Hibernation | an adaptation to seasonal (usually winter) food scarcity.

Comprised of multiple traits, but its central feature is a state of deep metabolic depression called **torpor**.

How do hibernators induce metabolic depression (torpor)?

Hibernation → not all hibernators hibernate the same way.

Obligation to hibernate → **Facultative hibernators**

Obligation to hibernate → **Obligate hibernators**

How do hibernators induce metabolic depression (torpor)?

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Torpor depth → **Shallow torpor (~80% depressed)**
Torpor depth → **Deep torpor (up to 99% depressed)**

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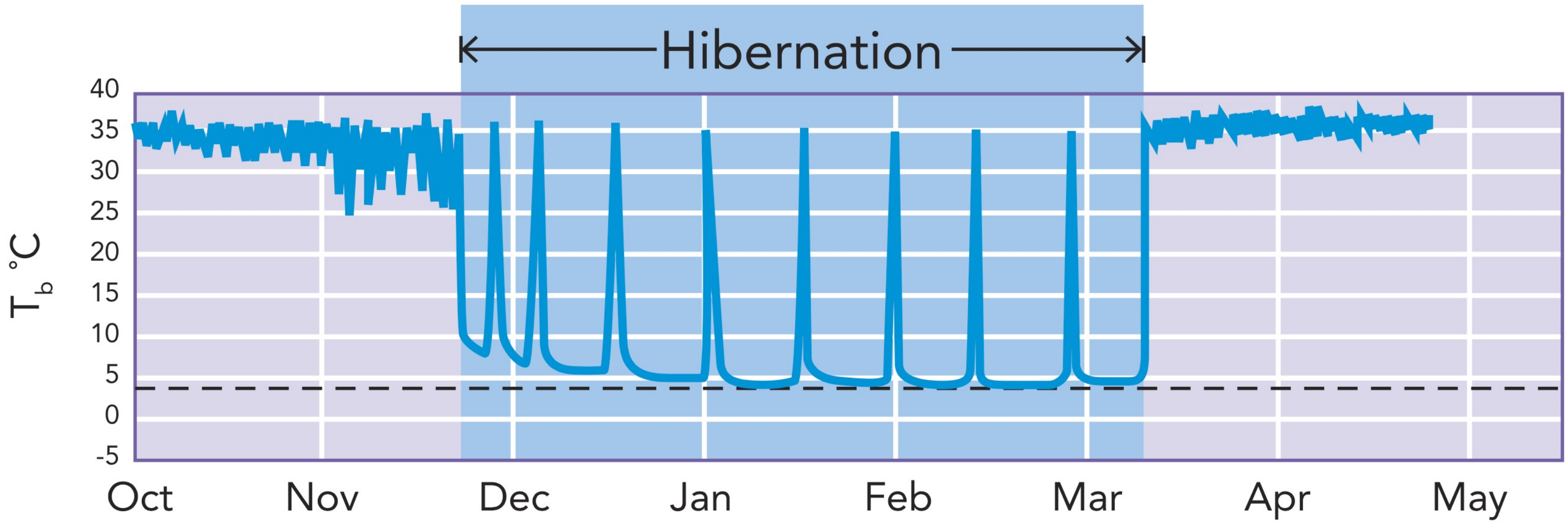
Obligation to hibernate
- **Facultative hibernators**
- **Obligate hibernators**

Torpor depth
- **Shallow torpor (~80% depressed)**
- **Deep torpor (up to 99% depressed)**

Food use
- **Food-caching**
- **Fasting**

How do hibernators induce metabolic depression (torpor)?

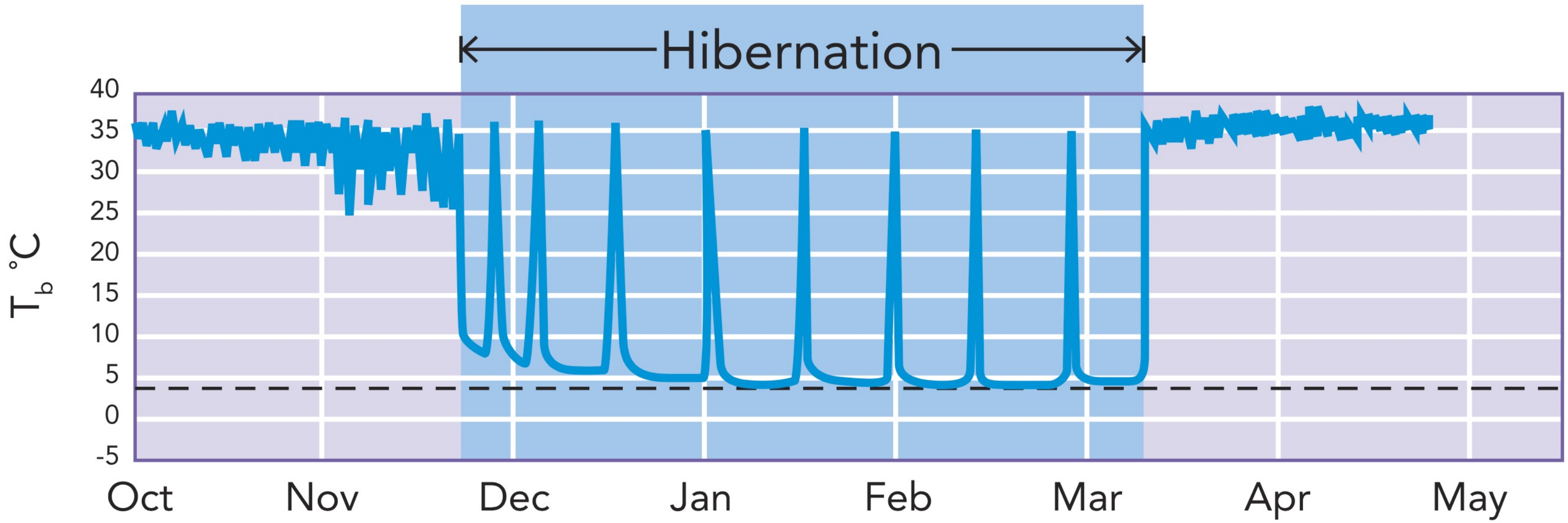
Seasonal and intra-hibernation metabolic plasticity



From Nordeen & Martin (2019) *Physiology*

How do hibernators induce metabolic depression (torpor)?

Seasonal and intra-hibernation metabolic plasticity



From Nordeen & Martin (2019) *Physiology*

Throughout hibernation season, torpor is interrupted every ~12 days by period interbout arousals (IBAs).

IBAs account for >80% of energy used during hibernation season, but why they are necessary is not yet know.

How do hibernators induce metabolic depression (torpor)?

Steps involved in torpor induction in hibernators

1. **Active depression of cellular metabolism.**

2. **Resetting of body temperature setpoint.**

3. **Q10 (thermodynamic) effect.**

How do hibernators induce metabolic depression (torpor)?

Steps involved in torpor induction in hibernators

1. **Active depression of cellular metabolism.** → **Reversible post-translational mods (PTMs) to various proteins & enzymes that reduce ATP supply & use.**
2. **Resetting of body temperature setpoint.**
3. **Q10 (thermodynamic) effect.**

↓ ATP supply

PTMs to mito complexes.

H_2S involvement.

Work by Jim Staples' group.

↓ ATP use

PTMs to proteins involved in ion pumping & protein synthesis.

Work by Ken Storey's group.

How do hibernators induce metabolic depression (torpor)?

Steps involved in torpor induction in hibernators

1. Active depression of cellular metabolism.
2. **Resetting of body temperature setpoint.** →
3. Q10 (thermodynamic) effect.

From 37°C to as low as -2.9°C in arctic ground squirrels.

Adenosine is involved via A_1 adenosine receptors in the hypothalamus:

- A_1AR agonists will cause ground squirrels to induce torpor.
- A_1AR antagonists will cause ground squirrels to arouse from torpor.

Work by Kelly Drew's group and Matteo Cerri's group.

How do hibernators induce metabolic depression (torpor)?

Steps involved in torpor induction in hibernators

1. Active depression of cellular metabolism.

2. Resetting of body temperature setpoint.

3. **Q10 (thermodynamic) effect.** → **Low body temperature reduces rates of metabolic reactions.**

How do hibernators induce metabolic depression (torpor)?

Steps involved in torpor induction in hibernators

1. **Active depression of cellular metabolism.**
2. **Resetting of body temperature setpoint.**
3. **Q10 (thermodynamic) effect.**

However, there are many other physiological, biochemical and molecular responses associated with torpor and hibernation. **But it is still unclear which is a cause, and which is a consequence.**

How do hibernators induce metabolic depression (torpor)?

We still don’t know what the trigger for torpor induction is.

How close are we to inducing states of “synthetic” torpor in humans?

We’re still a ways away. But there has been significant progress towards this goal over the past ~15 years.

Different research groups have been placing non-torpor-inducing species (rats) into torpor-like states using different approaches which relate somehow to the 3 main processes involved in natural torpor induction.

Some approaches are more promising than others.

Methods of synthetic torpor induction

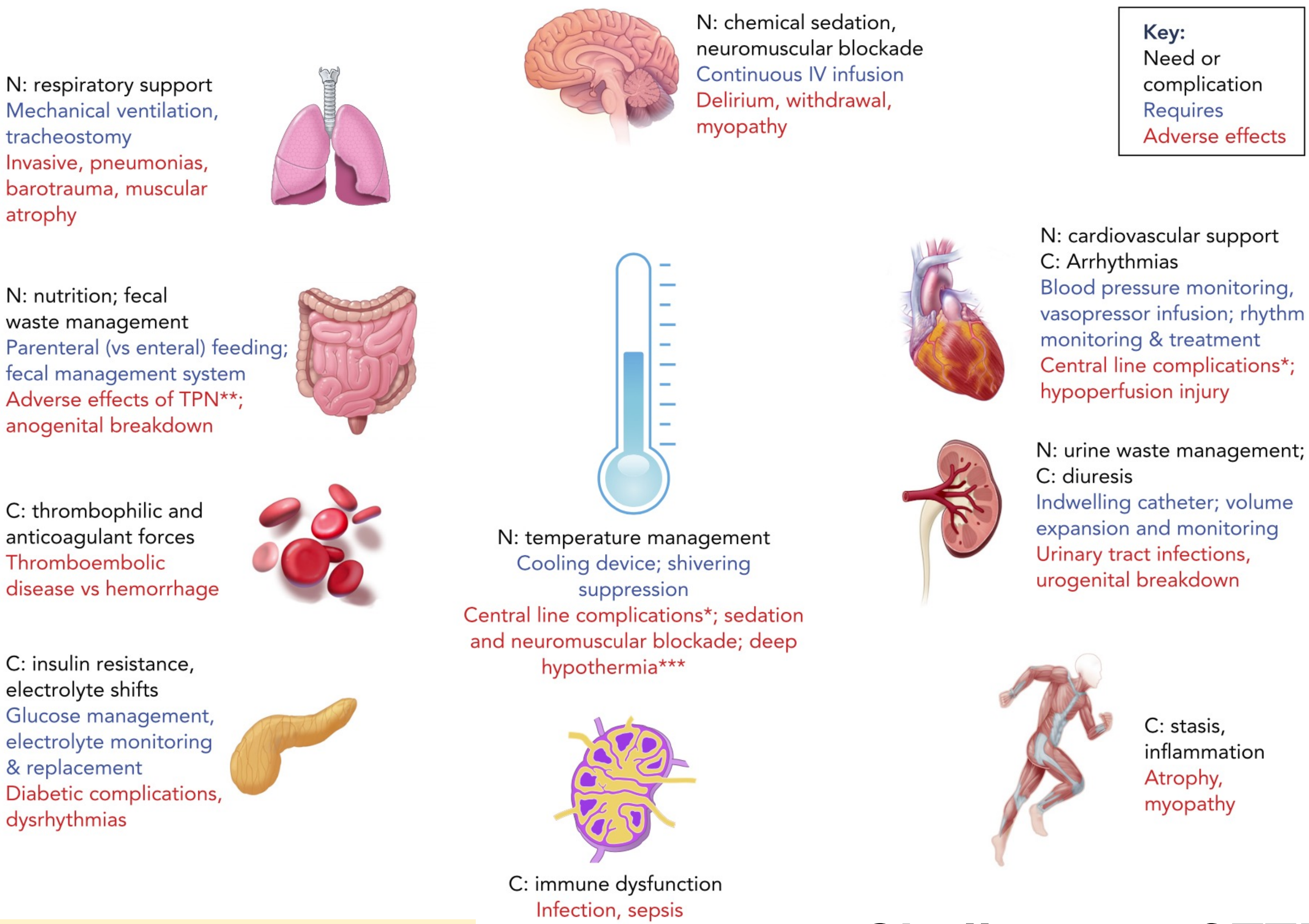
1. Active depression of cellular metabolism.

2. Resetting of body temperature setpoint.

3. **Q10 (thermodynamic) effect.** → **Therapeutic hypothermia / targeted temperature management**

How close are we to inducing synthetic torpor in humans?

Methods of synthetic torpor induction



How close are we to inducing synthetic torpor in humans?

Challenges of TTM

From Nordeen & Martin (2019) *Physiology*

Methods of synthetic torpor induction

1. Active depression of cellular metabolism.
2. Resetting of body temperature setpoint.
3. **Q10 (thermodynamic) effect.** → **Therapeutic hypothermia / targeted temperature management**

↑

Very different than natural torpor induction and perhaps unlikely to produce sustainable state of torpor in humans.

How close are we to inducing synthetic torpor in humans?

Methods of synthetic torpor induction

1. **Active depression of cellular metabolism.** → **Mitochondrial arrest via H_2S**

2. Resetting of body temperature setpoint.

3. Q10 (thermodynamic) effect.

How close are we to inducing synthetic torpor in humans?

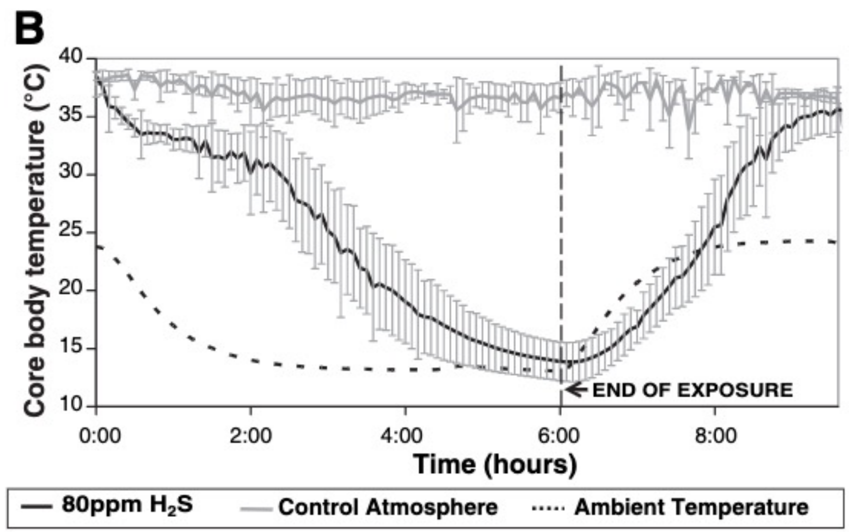
Methods of synthetic torpor induction

1. **Active depression of cellular metabolism.** → **Mitochondrial arrest via H_2S**

BREVIA

H_2S Induces a Suspended Animation–Like State in Mice

Eric Blackstone,[1,2] Mike Morrison,[2] Mark B. Roth[2]*



2. Resetting of body temperature setpoint.

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How close are we to inducing synthetic torpor in humans?

Blackstone et al. (2005) *Science*

Methods of synthetic torpor induction

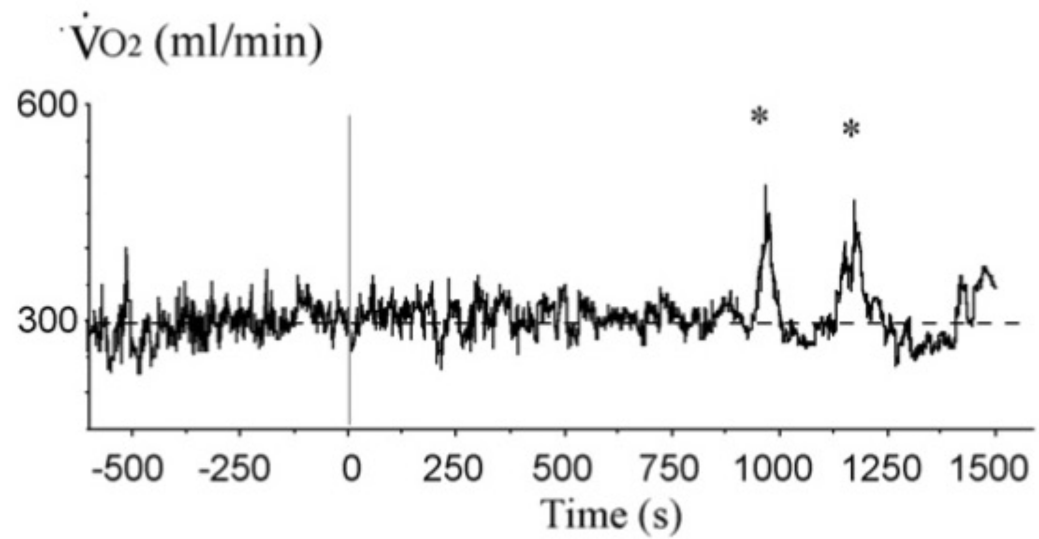
1. **Active depression of cellular metabolism.** → **Mitochondrial arrest via H_2S**

2. Resetting of body temperature setpoint.

3. Q10 (thermodynamic) effect.

H_2S induced hypometabolism in mice is missing in sedated sheep

Philippe Haouzi [a,*], Véronique Notet [b], Bruno Chenuel [c], Bernard Chalon [c], Isabelle Sponne [b], Virginie Ogier [b], Bernard Bihain [b]



How close are we to inducing synthetic torpor in humans?

Haouzi et al. (2008) *Resp Physiol Neurobiol*

Methods of synthetic torpor induction

1. Active depression of cellular metabolism.

2. **Resetting of body temperature setpoint.** → **Altering T_b set point, like a hibernator**

3. Q10 (thermodynamic) effect.

How close are we to inducing synthetic torpor in humans?

Methods of synthetic torpor induction

1. Active depression of cellular metabolism.

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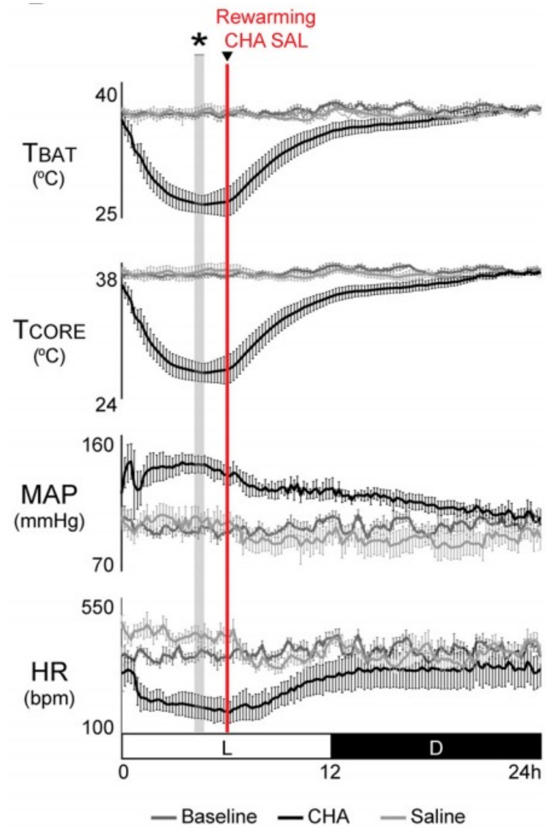
Altering T_b set point, like a hibernator

Central Activation of the A1 Adenosine Receptor (A1AR) Induces a Hypothermic, Torpor-Like State in the Rat

Domenico Tupone, Christopher J. Madden, and Shaun F. Morrison
Department of Neurological Surgery, Oregon Health & Science University, Portland, Oregon 97239-3098



Tupone et al. (2013) *J Neurosci*

How close are we to inducing synthetic torpor in humans?

Methods of synthetic torpor induction

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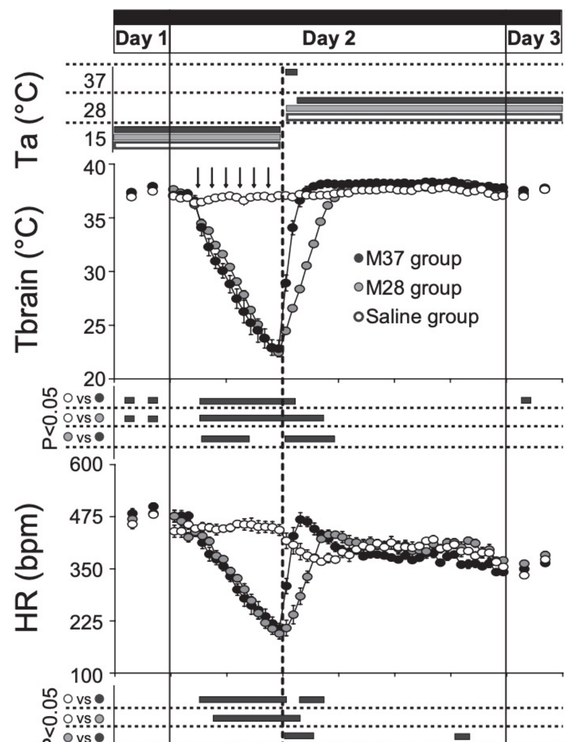
Altering T_b set point, like a hibernator

The Inhibition of Neurons in the Central Nervous Pathways for Thermoregulatory Cold Defense Induces a Suspended Animation State in the Rat

Matteo Cerri, Marco Mastrotto,* Domenico Tupone,* Davide Martelli, Marco Luppi, Emanuele Perez, Giovanni Zamboni, and Roberto Amici
Department of Biomedical and NeuroMotor Sciences, Alma Mater Studiorum–University of Bologna, 40126 Bologna Italy



Cerri et al. (2013) *J Neurosci*

How close are we to inducing synthetic torpor in humans?

Methods of synthetic torpor induction

1. Active depression of cellular metabolism.

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3. Q10 (thermodynamic) effect.

How close are we to inducing synthetic torpor in humans?

Altering T_b set point, like a hibernator

By abandoning a T_b set point of 37C, biochemical reactions slow and the body does not initiate thermogenic processes.

Adenosine is involved in natural torpor induction, so there's precedence.

Used successfully in rats and pigs, and becoming less invasive to administer agent (CHA).

Methods of synthetic torpor induction

1. Active depression of cellular metabolism.

2. **Resetting of body temperature setpoint.**

3. Q10 (thermodynamic) effect.

Altering T_b set point, like a hibernator

Most promising technique so far because it recapitulates some - *but not all* - aspects of natural torpor.

Central activation of the A_1 adenosine receptor in fed mice recapitulates only some of the attributes of daily torpor

Maria A. Vicent[1] · Ethan D. Borre[1] · Steven J. Swoap[1]

Vicent et al. (2017) *J Comp Physiol*

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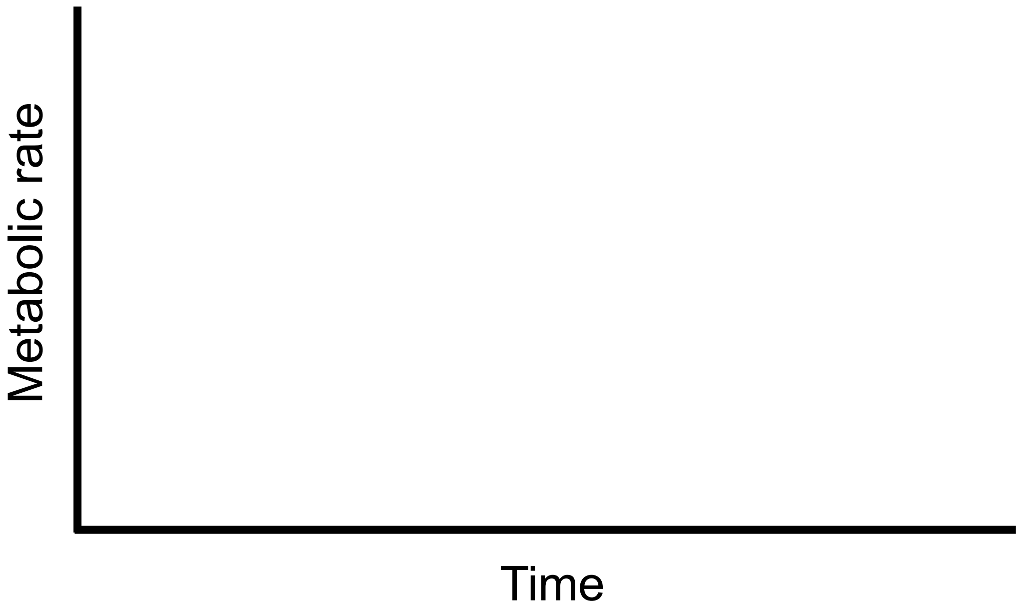
Vicent et al. (2017) *J Comp Physiol*

Thus, still unclear how sustainable these metabolic states are.

How close are we to inducing synthetic torpor in humans?

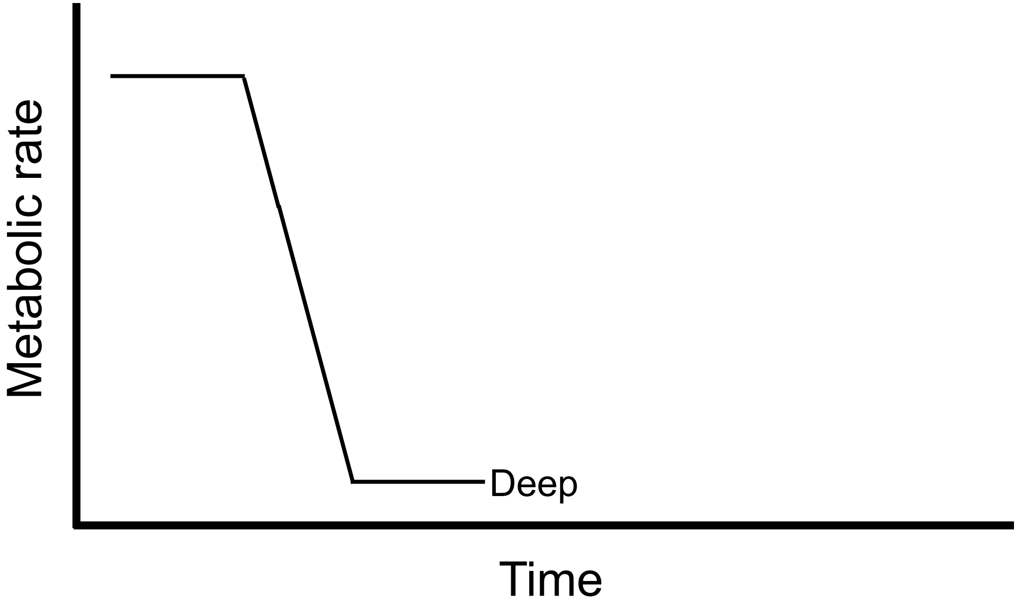
Advancements towards placing some species in synthetic torpor, but still a ways away from doing so in humans.

Synthetic torpor could be applied to spaceflight in different ways



How might synthetic torpor be applied to human spaceflight?

Synthetic torpor could be applied to spaceflight in different ways



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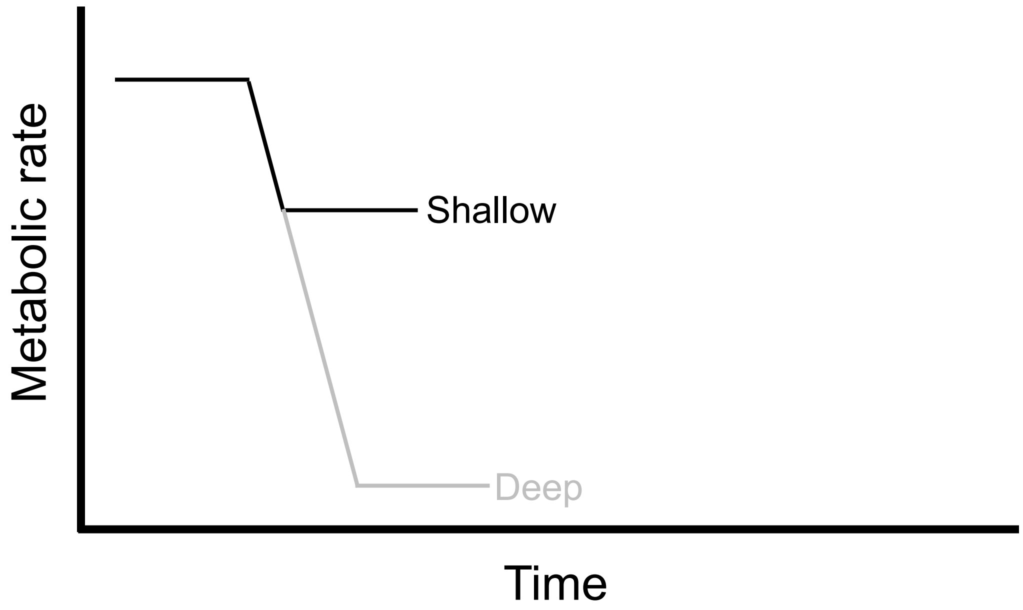

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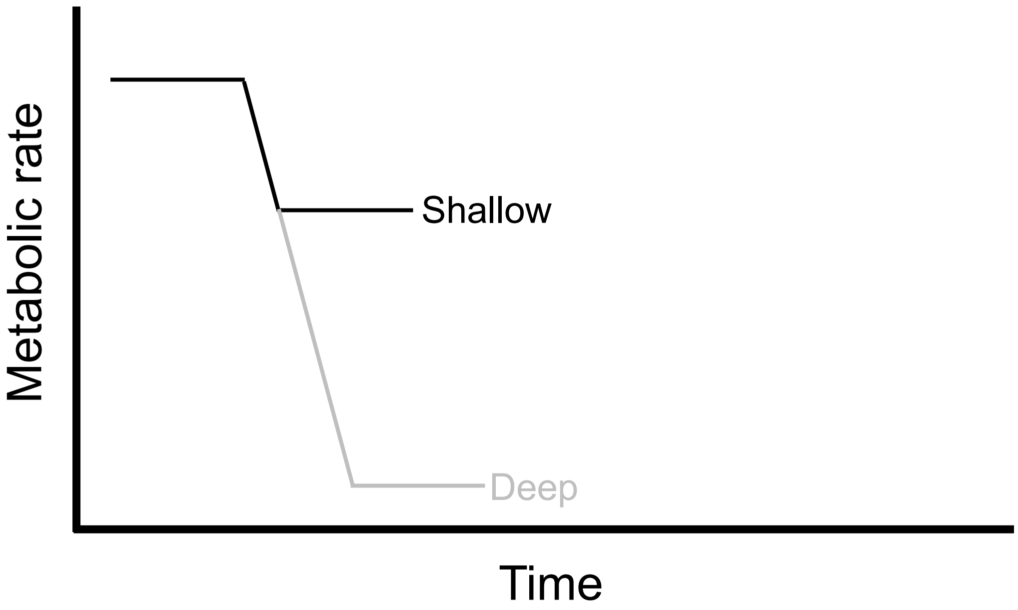
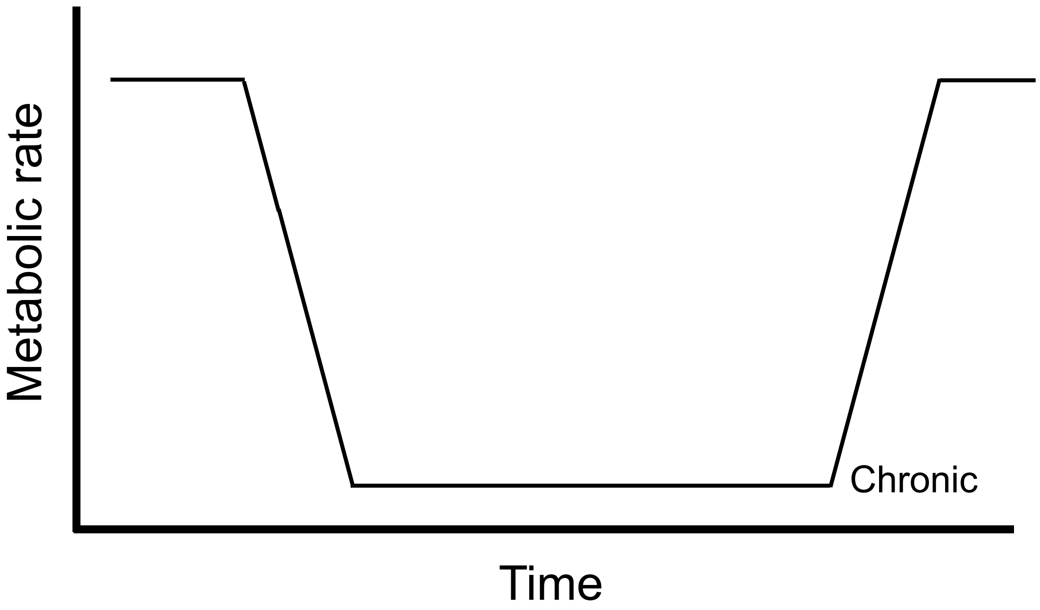


Limits of human physiology may determine the ideal depth of torpor.

How might synthetic torpor be applied to human spaceflight?

Synthetic torpor could be applied to spaceflight in different ways



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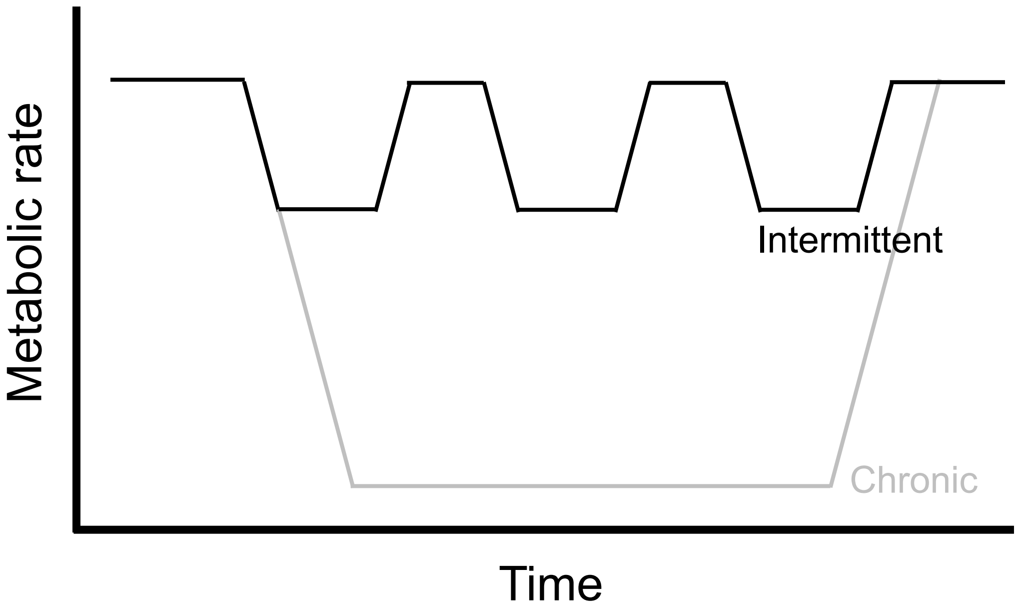

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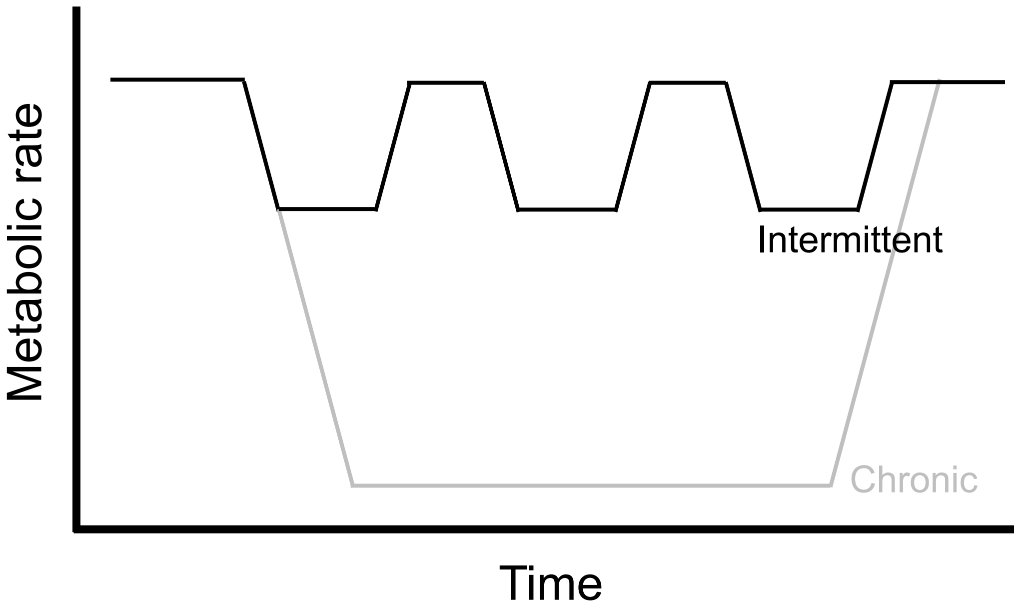


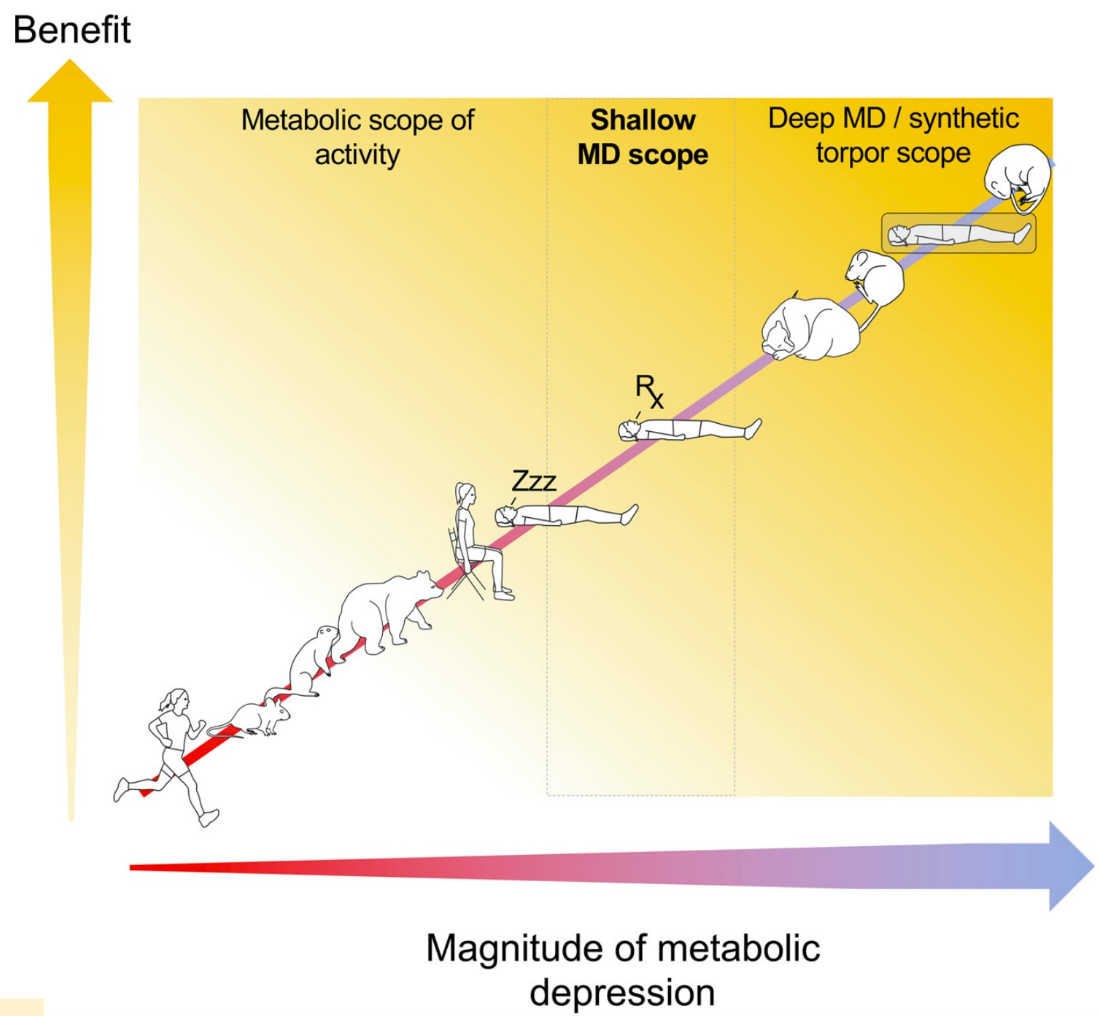
Torpor could also be used in a targeted fashion in response to a particular situation.

How might synthetic torpor be applied to human spaceflight?

Deep torpor presents high benefits and low feasibility

Ground squirrel-like torpor would present greatest biological and logistical spaceflight benefits.

But this is currently limited by methodology, human biology, and spacecraft design.



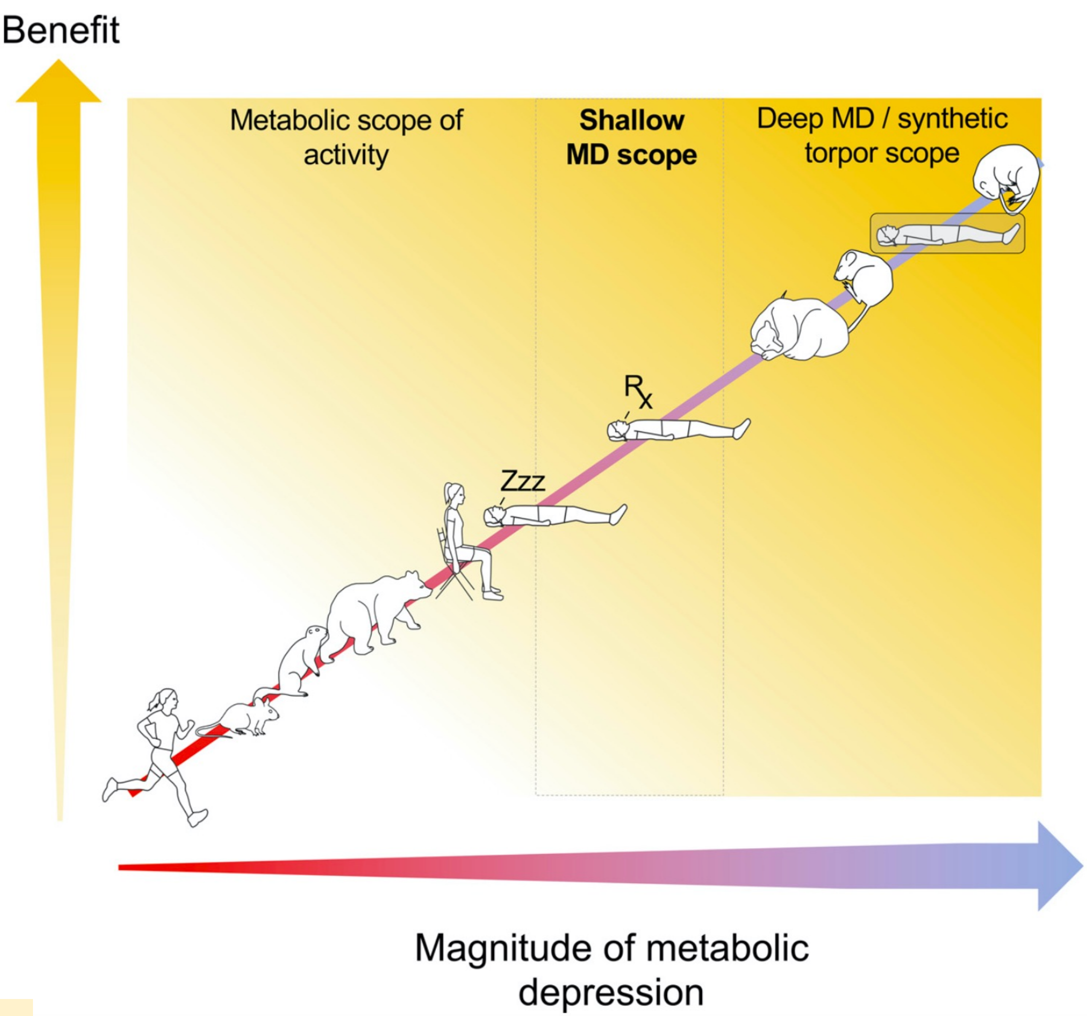
How might synthetic torpor be applied to human spaceflight?

Regan et al. (2020) *J Appl Physiol*

Shallow torpor presents tangible benefits with high(ish) feasibility

Bear-like torpor (T_b ~31C) would present more modest <u>but still useful</u> benefits.

"Shallow" torpor states would be more feasible than deep states biologically, cognitively, infrastructure-wise, etc.



Regan et al. (2020) *J Appl Physiol*

How might synthetic torpor be applied to human spaceflight?

Next steps - Important questions & possible experiments

Possible next steps for spaceflight applications?

Next steps - Important questions & possible experiments

Question: Does *natural* metabolic depression really confer protection against space radiation and zero-*g*?

Experiment: Natural metabolic depressors in space.

- Natural metabolic depression will avoid complications of synthetic torpor for initial tests.
- Model species choice will need careful consideration.
- Aboard ISS or, ideally, outside Van Allen Belts

What it could reveal:

- If metabolic depression can be induced in space.
- How metabolic depression affects consumables use.
- If metabolic depression offers radiation and/or zero-*g* protection.

Possible next steps for spaceflight applications?

Next steps - Important questions & possible experiments

Question: Does *synthetic* torpor confer radioprotection?

Experiment: Ground-based irradiation of rats in synthetic torpor states.

- Induce synthetic torpor in rats using CHA method.
- Irradiate the torpid rats with space-type radiation (e.g., at NASA's Space Radiation Lab at Brookhaven).

What it could reveal:

- If the answer is "yes", then the development of this technique could be pursued with increased confidence.
- If the answer is "no", then it minimizes chance of wasted resources.

Possible next steps for spaceflight applications?

Next steps - Important questions & possible experiments

Question: How viable is synthetic torpor to spaceflight?

Experiment: Characterize cognition, motor function, latency periods, etc. in rats *following* synthetic torpor bouts.

- Natural hibernators recover from torpor fully and quickly, but we don't know about animals in synthetic torpor.

What it could reveal:

- Potential performance deficits following synthetic torpor, including latency periods.
- Best to learn about these sooner than later.

Possible next steps for spaceflight applications?

Next steps - Important questions & possible experiments

Question: Can hibernation-related atrophy resistance mechanisms be translated to humans?

Experiment: Develop a pre- or probiotic to promote a hibernator-like gut microbiota capable of urea nitrogen salvage (UNS).

- UNS has recently been shown to contribute to tissue protein synthesis during hibernation.

What it could reveal:

- If humans' existing capacity for UNS could be optimized so as to facilitate muscle protein synthesis during microgravity exposure.

Possible next steps for spaceflight applications?

Next steps - Important questions & possible experiments

Question: How does natural hibernation work?

Experiment: Basic biology research into the natural phenotype of hibernation.

What it could reveal: The better we understand natural mechanisms of hibernation/torpor, the better we can translate this phenotype to humans.

Possible next steps for spaceflight applications?

The upshot

Synthetic torpor could benefit multiple spaceflight and earthbound challenges.

We are still some ways from placing humans in synthetic torpor, and the resources to do this – especially aboard spacecraft – will likely be significant.

But the field is advancing quickly.

Now is the right time to invest in this research and determine whether or not synthetic torpor's theoretical benefits to spaceflight are realizable and worth pursuing.