The Rhesus Macaque as an Animal Model for Human Nutrition: An Ecological-evolutionary Perspective

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Malnutrition (over-nutrition, under-nutrition, and imbalanced nutrition) remains a leading public health concern, with poor diets responsible for 1 in 5 preventable deaths worldwide.

Among the most important, complex, and contested areas in biomedical and public health research is nutrition.

? **Scope and appropriateness of methods applied in nutritional research**

Afshin et al., 2019

Colon bacillus
(Escherichia coli)

Arabidopsis
(Arabidopsis
thaliana)

Fruit fly
(Drosophila
melanogaster)

Zebrafish
(Danio rerio)

Mouse (Mus musculus)

Ethical

Theoretical

What is a model organism?

Practical

Whether model animals are an optimal, or even necessary tool to address a research question?

Which model is best suited for the purpose?

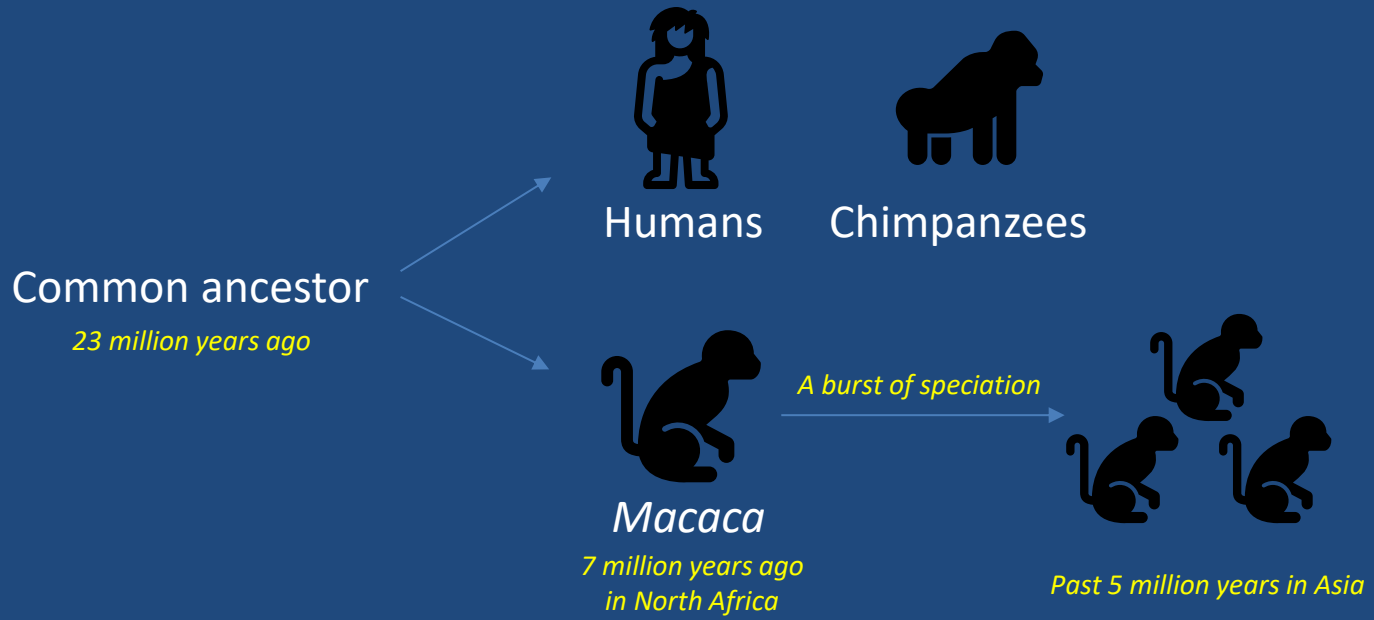
猕猴（*Macaca mulatta*）

These considerations are paramount in the use of non-human primate models.

Rhesus macaques (*Macaca mulatta*) (henceforth RM) are among the most widely used in biomedical research

Xue et al., 2016; Cooper er al., 2022

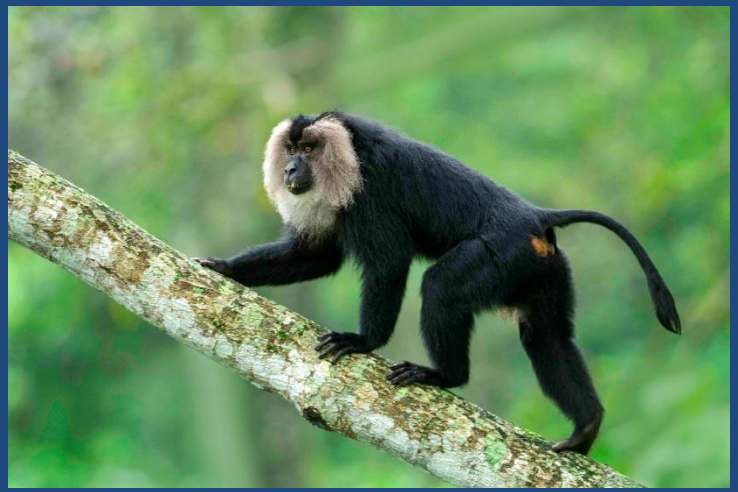
THE ECOLOGICAL DIVERSITY OF MACAQUES



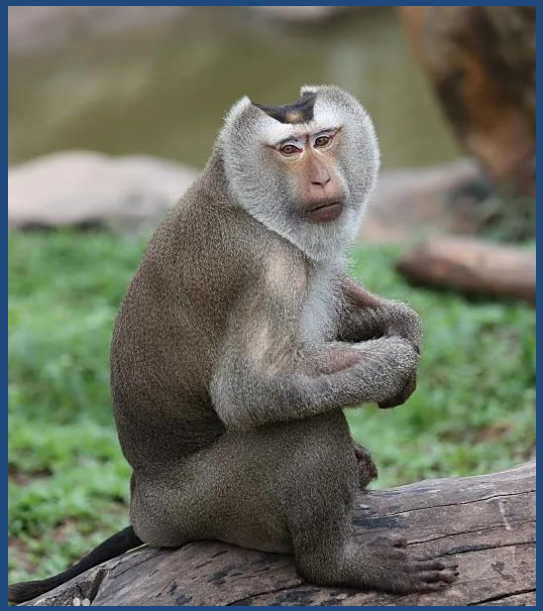
Zhang et al., 2023 Roos et al., 2015

The 24 extant macaque species are classified into four species groups:

1. Silenus



Macaca silenus



Macaca nemestrina

2. Fascicularis

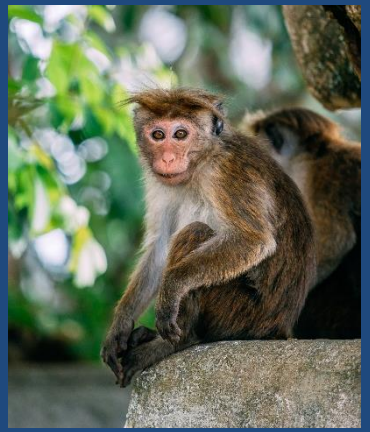
Macaca fascicularis

Macaca mulatta

Macaca fuscata

Macaca cyclopis

3. Sinica



Macaca sinica

Macaca radiata

Macaca assamensis

Macaca thibetana

4. Sylvanus

Macaca sylvanus

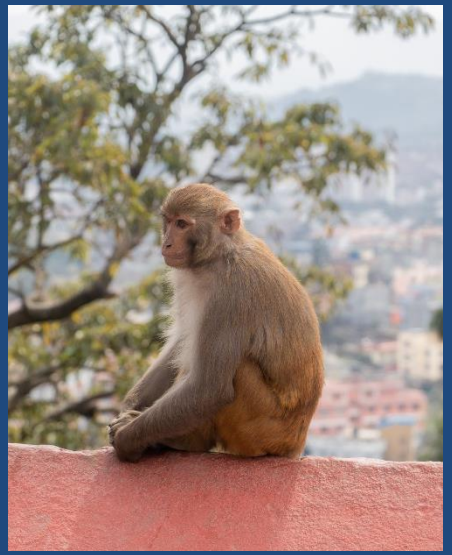
The macaques are the most geographically and ecologically widespread of all non-human primates. Of all macaques, the RM are the most geographically widespread and ecologically diverse. RM readily adapt to disturbed and modified environments, such as secondary forests, agricultural landscapes, and (peri) urban environments.

Like humans, RM are considered broad dietary generalist omnivores with a notably flexible and varied diet. For example, the Taihangshan macaque (*Macaca mulatta tchelinesis*) has significant seasonal and interannual variations in food availability.

The wide adaptability of RM

Secondary forest

Cropland



Edge of city

SOCIAL ECOLOGY OF MACAQUES

A degree of genetic divergence among populations has played a role in the adaptation of RM to diverse environments, as is the case for humans.

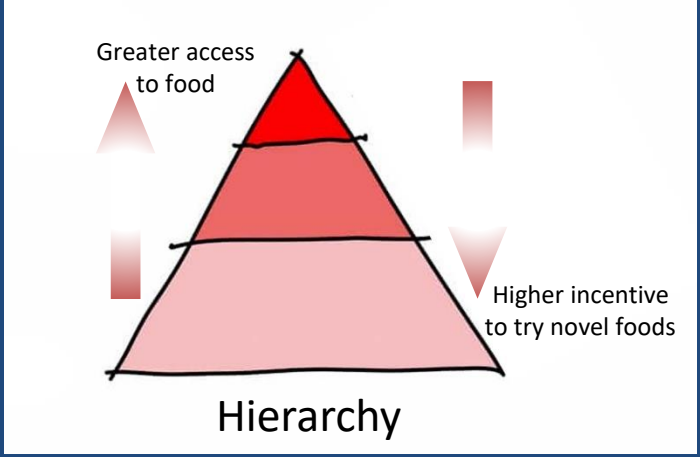
Their social structure and behavioural flexibility contribute to the generalized ecology of RM. RM are considered to have notably complex and flexible behavioural repertoires.

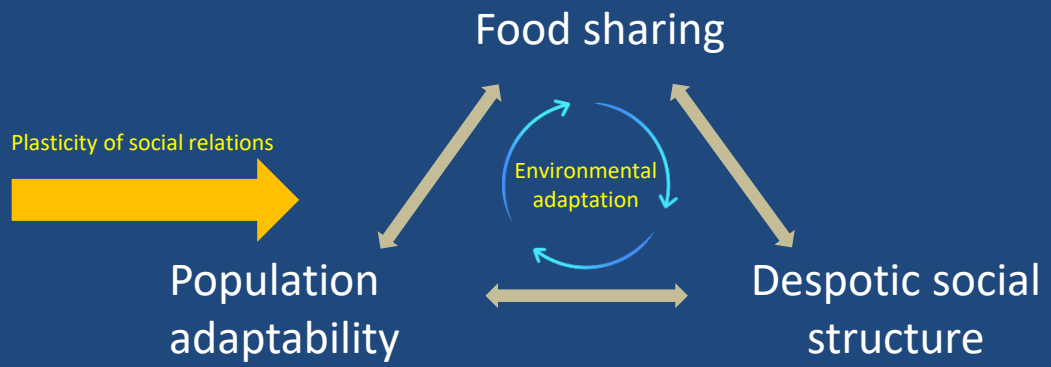
RM societies are strongly nepotistic with steep dominance hierarchies, categorised as Grade 1 (least socially tolerant) among four macaque species groups that vary along the spectrum from despotic to egalitarian. Nepotism has, likewise, been implicated in the adaptability of human societies.

Thierry et al., 2007; Adams et al., 2015

A social factor that has been implicated as important in the ecological adaptability of humans is non-kin food sharing, and has been documented in RM and long-tailed macaques.

Social tolerance over food was higher in more despotic species, and higher ranking and more socially integrated individuals achieved greater access to food.





Roberts et al., 2018; Dubuc et al., 2012; Amici et al., 2020

The majority of alpha male replacements occurred through direct male-male challenges, competition between males for the top dominant position is high and escalated fights are common between competitors. Defeated alpha male usually leave the group after being injured.

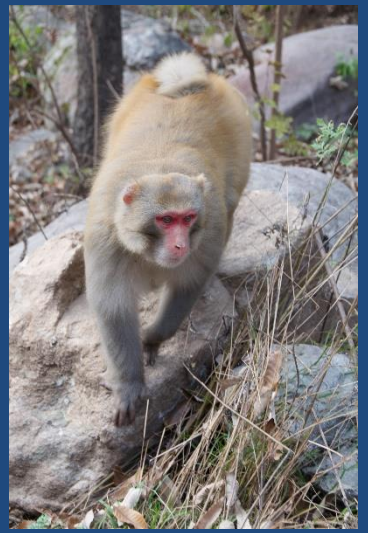
But in our previous study of Taihangshan RM, we observed an interesting anomaly:

Did not leave the group
Helped new α-female raise pups

Alpha male replacement

No fighting was observed
Cooperation and alliance

Social cohesion



Testard et al. documented increases in social connectivity among free-ranging RM in the Cayo Santiago research colony following the devastating impact of hurricane Maria in 2017.

Social cohesion is an important mechanism through which primates can adapt to, even extreme, environmental change.

This is the basis for RM‘s ecological and dietary flexibility.

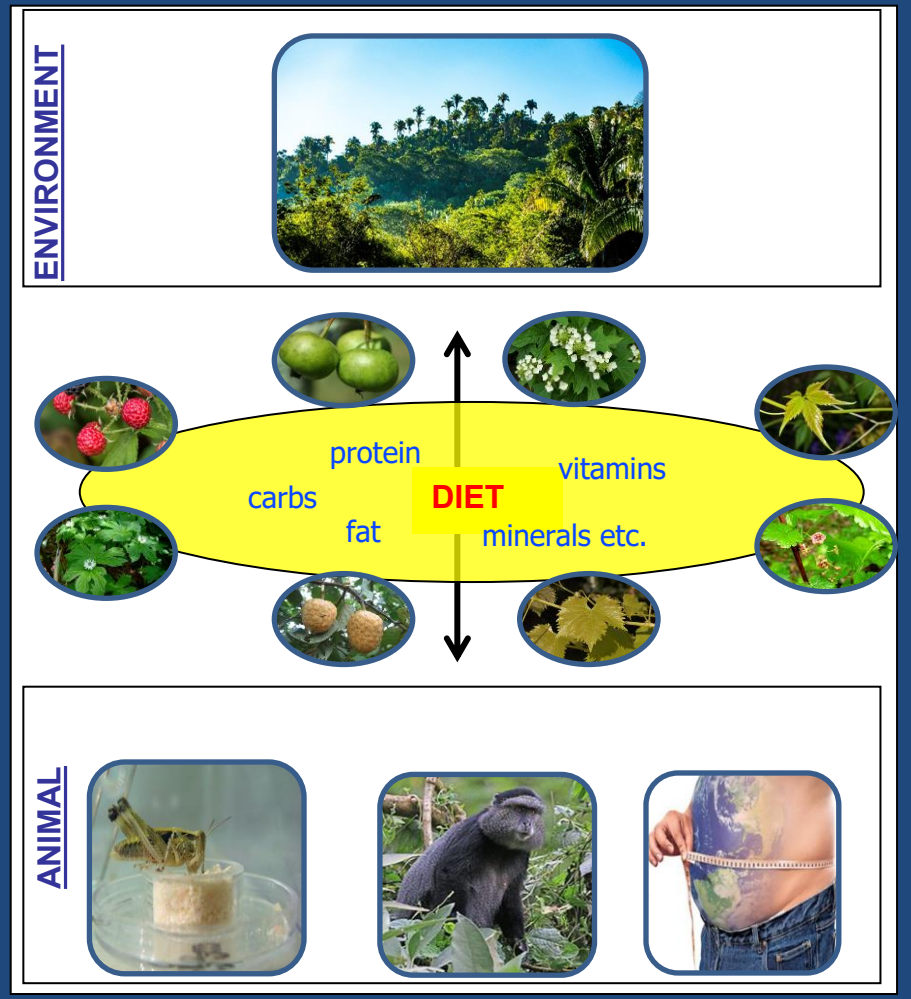
INSIGHTS FROM NUTRITIONAL ECOLOGY

- **Nutritional Ecology**

  Nutritional ecology is an integrative field that conceptualises nutritional outcomes such as health and disease as emerging from the interactions of organisms and food environments

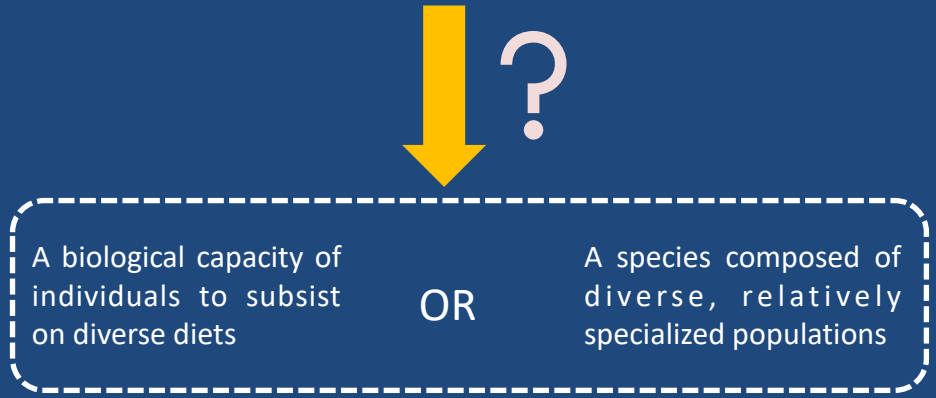
- **Nutritional Geometry**

  Nutritional geometry has enabled dimensions of dietary flexibility to be quantified.

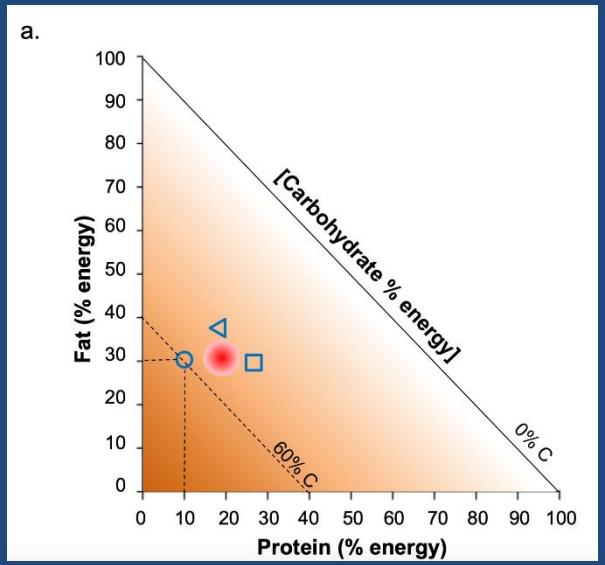


Dietary diversity

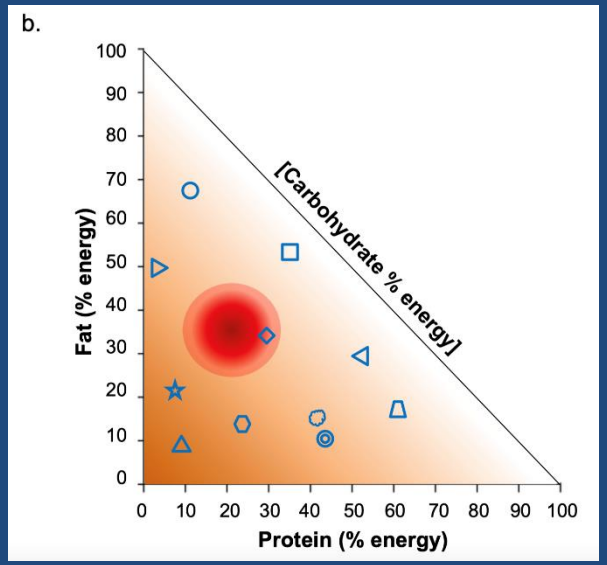
The diets of RM as a species are clearly diverse, but there is also substantial variation across populations in the nature and diversity of foods eaten.



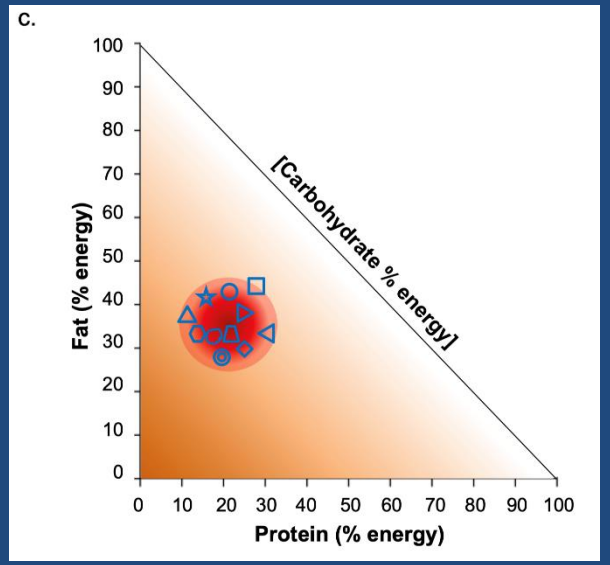
If RM and humans occupy the "generalist specialist" niche, how much of that based on genetic differentiation between populations, genetic variation within populations, and individual and social learning?



A hypothetical animal that eats few foods (a food specialist), which are similar in macronutrient composition (food composition specialist) and has narrow macronutrient requirements (small red area = macronutritional specialist).



An animal that is generalist at the levels of food (many foods), food composition (foods vary widely in composition), and macronutritional needs (adapted to a wide range of dietary compositions)

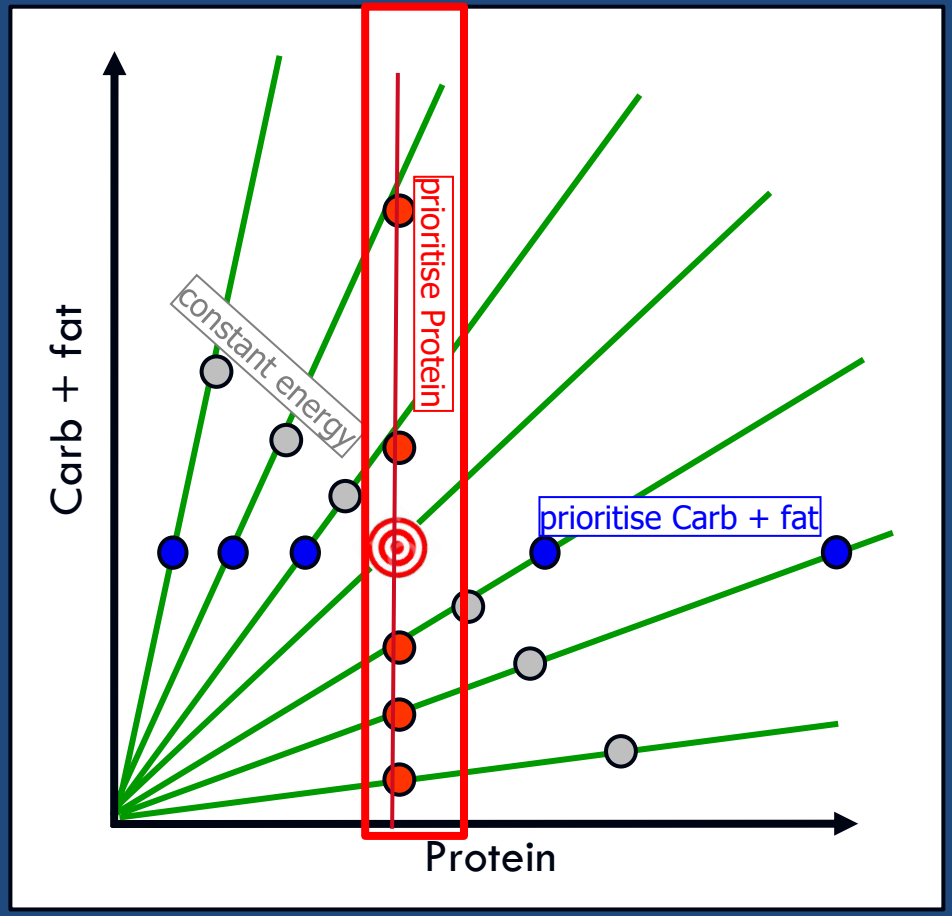


An animal that eats many foods (food generalist), which have similar macronutrient compositions (food composition specialist), and can tolerate wide variation in diet macronutrient composition (macronutritional generalist).

The degree of flexibility an animal has at the various dietary levels is critical to understanding how diet constrains its ecological flexibility, and an area that requires more research attention.

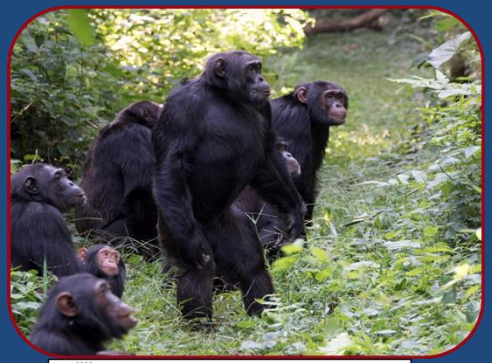
Nutritional geometry has enabled dimensions of dietary flexibility to be quantified that are important when comparing humans and RM in biomedical and ecological research.

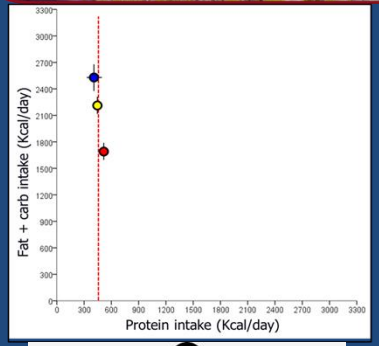
Obesity



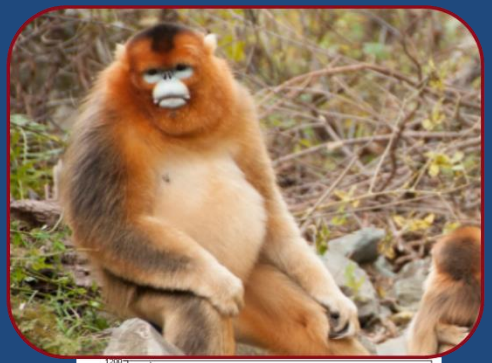
In nutritional ecology, a key node for understanding obesity is the interface where organismal biology interacts with food environments to generate excess intakes of energetic substrates that trigger fat storage.

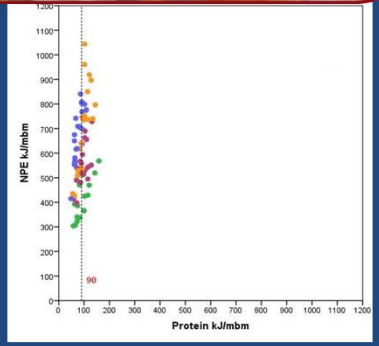
Chimpanzees



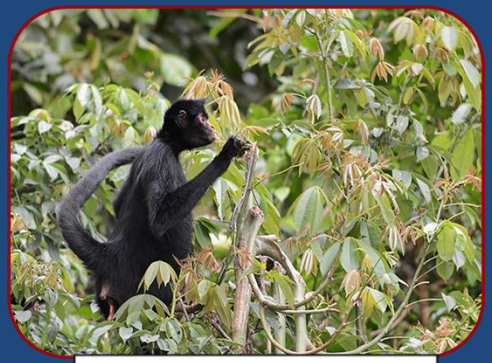


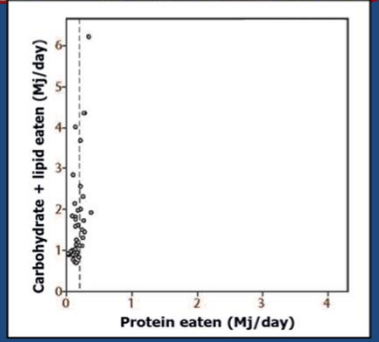
Golden snub-nosed monkeys

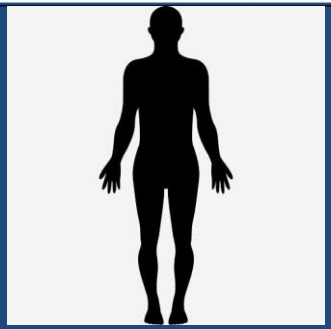




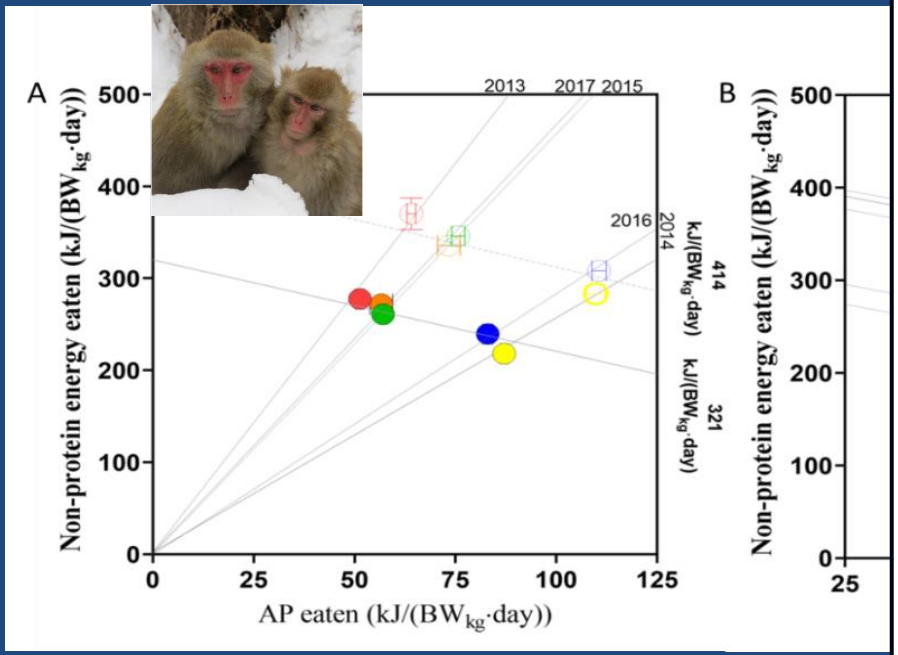
Spider monkeys

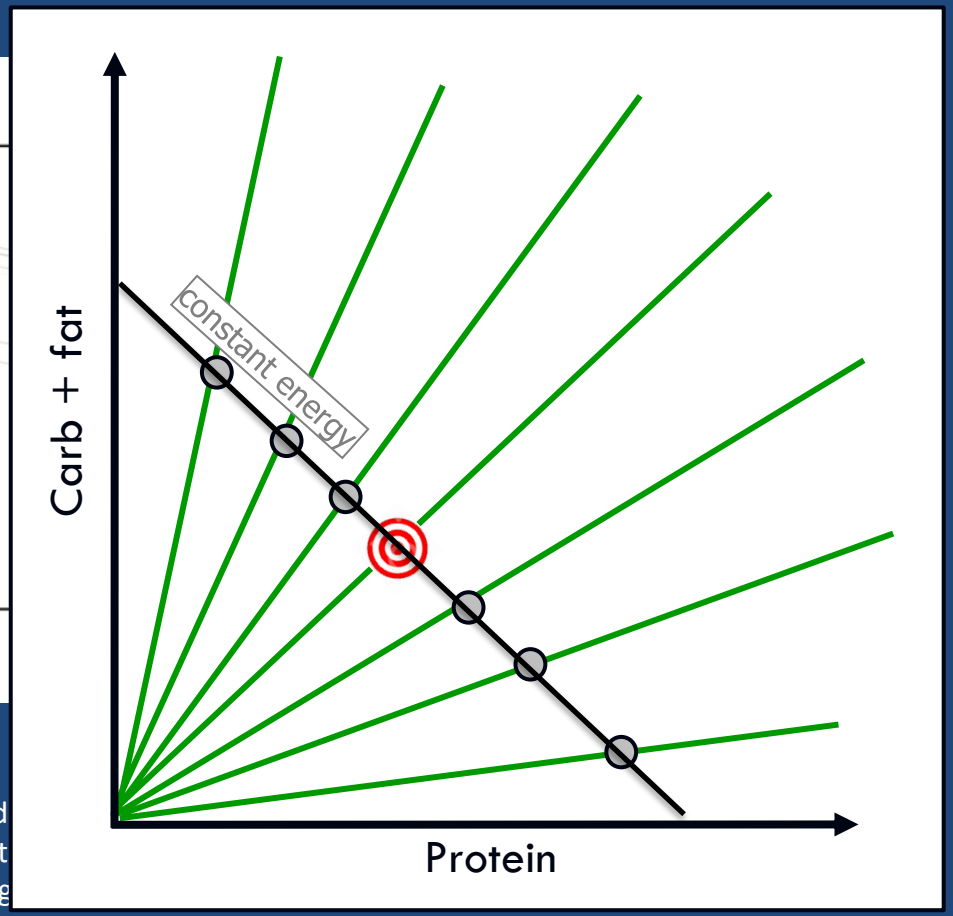






There is evidence that increased consumption of protein-diluted ultra-processed foods in recent decades has driven an epidemic of obesity and related diseases (protein leverage hypothesis).





However, our previous studies on RM in Taihangshan showed d
Although there were differences in the proportion of macronut
difference in energy intake between years in both non-lactating

It is not known whether CE is a species characteristic of macaques or a local adaptation to meet energy requirements in the temperate environment of Taihangshan macaques.

We are answering this question by comparing nutritional strategies, energy balance and nitrogen balance, in field studies of Taihangshan RM and subtropical RM using behavioral observation, nutritional geometry modelling, and urine biomarker measurement.

Further studies on the relationships between ecological variation in food supply, dietary macronutrient mixtures, and body fat cycles across RM populations are needed to evaluate where they stand in relation to different models of human obesity.

Energy Balance Model, EBM

Obesity results when environmental circumstances (e.g., increased availability of hyperpalatable foods) interact with brain mechanisms and cause energy intake to increase to levels that exceed energy expenditure (positive energy balance), regardless of the nutritional source of that energy.

Glucose: Carbohydrate Insulin Model, CIM

Obesity is driven specifically when the ingestion of high glycaemic load carbohydrates, such as glucose and sucrose, triggers fat storage which in turn causes increased hunger and energy intake.

Fructose Survival Hypothesis, FSH

Fructose reduces intracellular ATP levels causing increased hunger and impaired satiety.

Protein Leverage Hypothesis, PLH

The tight regulation of protein intake by humans results in incidental overconsumption of fats and carbohydrates on diets with low protein:energy ratio.

Fat: Hedonic Overdrive Model, HOM

Obesity results when high fat diets stimulate the hedonic system in the brain which overrides normal homeostatic systems resulting in excessive intake and storage of energy.

Several experiments performed on RM are thus potentially relevant to models of human obesity, but no consistent picture has emerged as to which of the models is appropriate for this species.

Further studies on the relationships between ecological variation in food supply, dietary macronutrient mixtures, and body fat cycles across RM populations are needed to evaluate where they stand in relation to different models of human obesity.

THE RHESUS MACAQUE AS A MODEL SYSTEM FOR HUMAN NUTRITION

In biomedical research, model organisms primarily serve as a tractable system in which to study a more complex or inaccessible phenomenon in humans.

→ Surrogate models

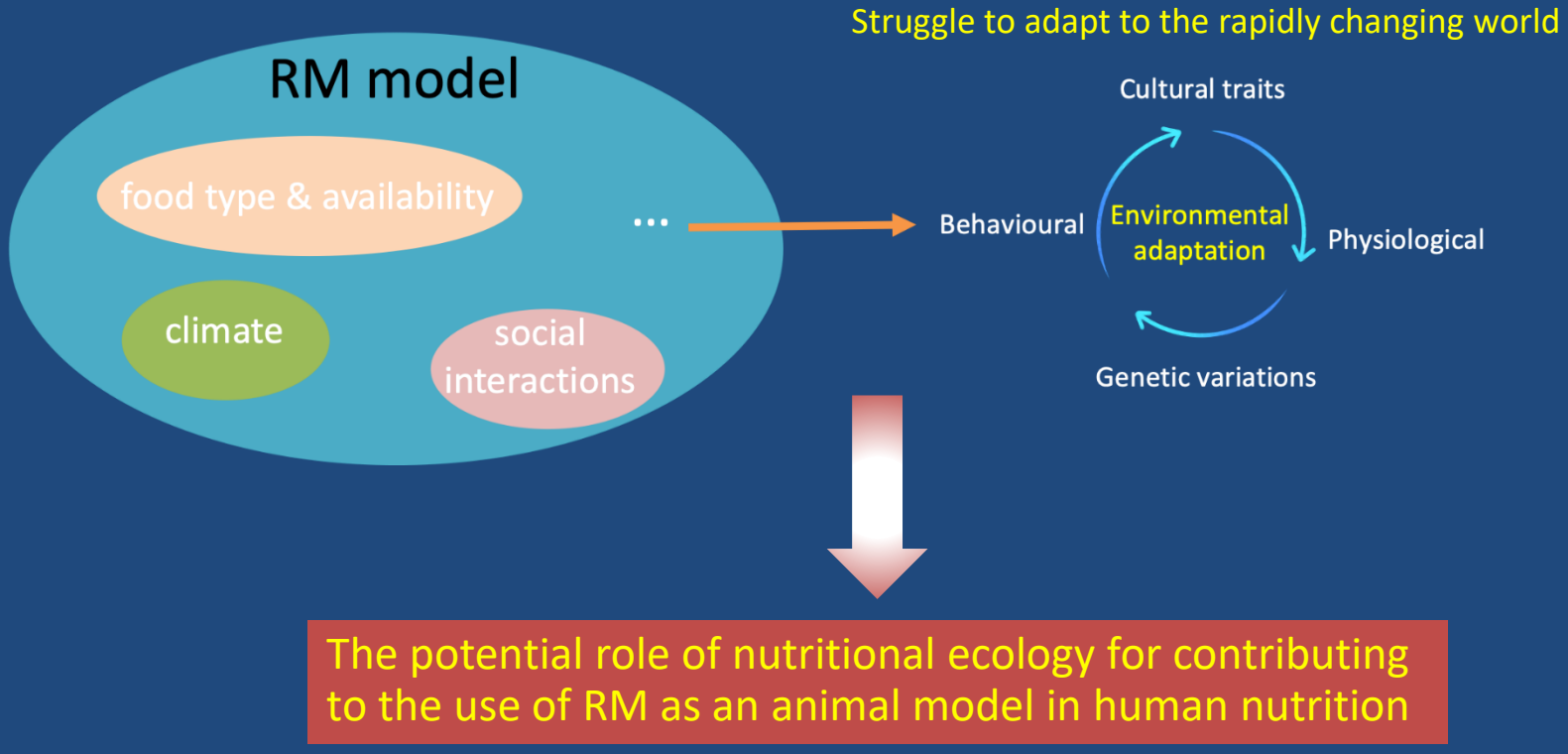
Models differ from humans (e.g. Taihangshan RM).

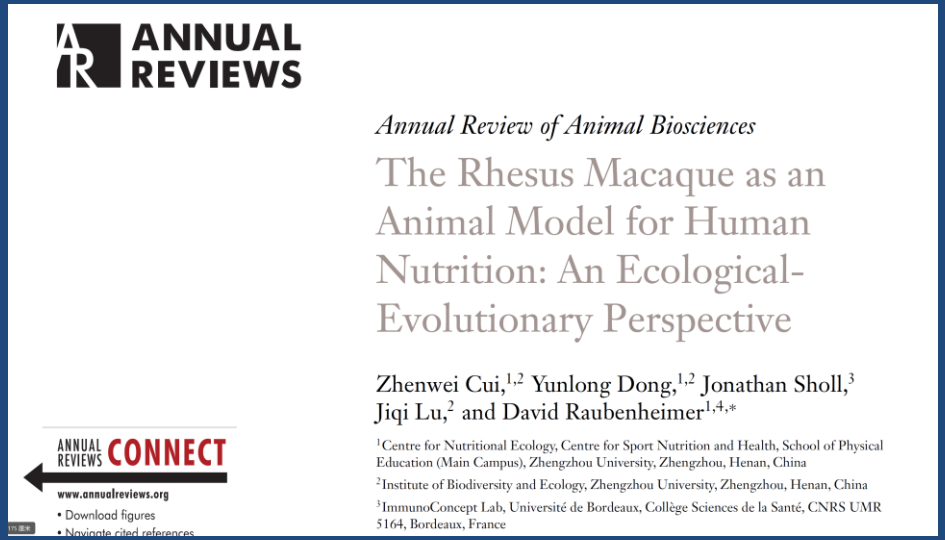
↓ Negative models

Environmental adaptation

- Foster understanding of the biological diversity of a trait
- Help understand and manage the conservation crisis in relation to most primates and other taxa
- Help expose blind spots from standardized models

Green et al., 2018


RM model
food type & availability
...
climate
social interactions
Struggle to adapt to the rapidly changing world
Cultural traits
Behavioural
Environmental adaptation
Physiological
Genetic variations
The potential role of nutritional ecology for contributing to the use of RM as an animal model in human nutrition



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