



Energy flows through all living organisms constantly.

Should we reconsider how we think about energy?

Making energy dynamics key to biomedical studies could improve our understanding of health and disease. **By Martin Picard & Christopher P. Kempes**

Every biological process requires energy, from a neuron firing to a cell making proteins, and from digesting dinner to taking a stroll. Energy flows constantly through every part of a cell, in chemical, thermal, mechanical or electromagnetic form.

Discovering the molecular processes associated with this energy flow has led to fields of research dedicated to metabolism. Still, much of the biomedical research literature omits explicit considerations

of energy dynamics in health and disease, focusing instead on genes, proteins and molecular mechanisms.

In our view, more biomedical scientists should pay attention to energy. Why? Because a focus on molecules is not enough to help us to understand what underpins biological processes and diseases. Both a cadaver and a thinking, feeling, living person are made up of molecules, cells, tissues and organs – the fundamental distinguishing factor is energy flow.

Molecular pathways that control diverse aspects of biology vary between individuals and between species because they are underpinned by genetics. It is no surprise, then, that molecular mechanisms of disease found in mice, fruit flies, zebrafish and other model systems often fail to hold up when studied in humans.

By contrast, the behaviour of energy in living systems follows several first principles from physics that apply across species more generally.

Take the metabolic theory of ecology, which explains why cells in large mammals burn energy more slowly than do cells in smaller ones. Simply put, nutrient and oxygen supplies are limited by fundamental physical constraints¹. Oxygen-carrying blood cells, for instance, must be pumped through vascular tubes that face hydraulic resistance – it takes longer for blood cells to travel optimally through a larger body than through a smaller one.

This general principle has been used to explain many physiological, ecological and evolutionary phenomena for which answers are not just written in genes². For example, it can explain why most large animals live longer and reproduce more slowly than do smaller ones.

To encourage debate, here we speculate on how making energy dynamics a central focus of biomedical studies might help researchers to unearth a fundamental layer of biological regulation that underlies health and goes awry in disease. Biologists should get into the habit of asking simple questions, such as ‘how much energy does this cost?’.

Energy constraints

In our view, developing a theoretical framework of ‘energy constraints’ is a promising way to learn more about the underpinnings of health and disease in a way that translates across species.

This framework^{1–3} describes how organisms allocate their finite energy budgets to various cellular, physiological and behavioural processes. It rests on two facts, both of which have been accepted for decades.

First, every organism’s energy budget is limited³ – it’s impossible for eating ever more food to produce infinitely more energy. Scaling arguments based on physical constraints, such as hydraulics, tell us that rates of energy supply to an organism are already optimized. And data show that the ability of organisms to dissipate thermal energy could, under some conditions, be part of why living beings can’t increasingly speed up their metabolism⁴.

Second, organisms require specific amounts of energy for each function and system that cannot be reduced easily. The brain might need 20% of the body’s total energy supply to keep functioning, digesting food might cost 10–15% and so on. The total energy cost of all body functions, each running at maximum capacity, would be greater than the overall energy budget.

Taking both points together, it follows that not all of the body’s systems can be ‘on’ at once. Organisms must continually divide finite energy resources between cellular functions, organs and behaviours. If an individual process needs more energy than usual, that energy has to be ‘stolen’ from other processes. Those decisions are called energy trade-offs.

Proponents of energy-constraint theories

have begun to gather evidence that such a framework could explain a range of physiological phenomena³. For instance, healthy young female athletes sometimes stop menstruating when their training regime becomes too intense. Studies suggest that the body’s finite energy budget might be allocated to performance in a trade-off with reproduction⁵.

Similarly, energy constraints might explain why a group of Shuar Amazonian children who were exposed to viral and parasitic pathogens throughout childhood experienced stunted growth⁶. Having one’s immune system activated constantly over years might require that less energy is expended on processes associated with optimal growth.

Moreover, when a person’s immune system is activated by a virus, they might feel ill, want to stay at home rather than socialize and experience low moods temporarily. The immune system is consuming extra energy to fight off the virus, potentially stealing energy from other body functions⁷ – a phenomenon well described in animal models.

Moving the needle

In our view, any process – from ageing to the growth of cancers – that takes a non-negligible amount of energy might be driven not just by molecular changes, but also by such energetic considerations. If researchers approach their system of study by asking key questions about its energetics (see ‘An energetic lens on biomedicine’), they might be able to uncover fresh targets for disease prevention and treatment.

Many scientists would push back on the idea of reframing all diseases around bioenergetics, given that molecular mechanisms have transformed our understanding of biology. We agree. Without molecular studies,

humanity wouldn’t have drugs to treat infections, weaken some types of cancer and dissolve blood clots after a stroke. Such work will continue to be crucial for both basic biology and medicine.

But there are areas in which a wealth of expensive molecular investigations has yet to lead to effective treatments (including for Alzheimer’s disease, mental-health conditions and some cancer types), pointing to a need to consider other avenues, too. In time, we think that a person’s energy status could be considered a dimension of their health, in much the same way that a doctor might currently consider the impact of any nutrient deficiencies or genetic mutations before beginning treatment.

One challenge for energy-based studies will be developing the right set of tools. Measuring energy is hard, because it is always in flux throughout cells, organs and bodies. Some techniques, however, are already available to make a start.

For example, researchers can quantify, using calorimetry or isotope-labelling techniques, the energy someone uses while performing a task. These methods measure the amounts of oxygen consumed and carbon dioxide produced over minutes to days – all from a person’s breath or urine⁸. Refining such approaches to study energy use at the organ or cellular level, or over shorter time frames, could help researchers to understand the trade-offs taking place in the body and brain in detail. That would enable us to understand under which circumstances energy is diverted from one organ or process to another, for instance.

Markers of ‘energy resistance’ can also give an indication of how well energy is flowing through a system. Low resistance might indicate that there is abundant capacity for energy flow under the studied conditions; high resistance could mean that the system is operating at or near an unsustainable rate⁹. Currently, researchers can measure energy resistance⁹ in single cells by analysing the ratio between two molecules, NADH and NAD⁺, or in the body as a whole using markers in the blood, such as the metabolite lactate or the protein GDF15. In future, the identification of organ-specific markers of energy resistance might allow us to examine energy flow in particular processes more clearly.

Low-hanging fruit

What might we learn, if we examine energy flow in pressing areas of health and disease? Here we propose three areas ripe for study.

Cancer. Not all tumours can be understood on the basis of genetic mutations alone, because cells without such alterations can still become cancerous¹⁰. However, one thing that cancer cells do have in common is that they are

An energetic lens on biomedicine

Some simple questions can help scientists to consider their system of study in terms of the energy trade-offs that might be involved. Here are five examples.

- What are the energy costs of this function or disease?
- Which other processes are simultaneously competing for the finite energy budget?
- Could this trait be driven by energy constraints or trade-offs?
- How much energy do the side effects of this treatment cost?
- What patient behaviours might compete with the energetic costs of healing?



Finite energy resources mean that the body cannot keep going without resting.

energy-hungry, because they grow and divide rapidly. As a result, many tumours stimulate the production of new blood vessels surrounding the cancer to provide the cells with access to the oxygen and glucose they need.

Could understanding how much energy tumour cells consume inspire metabolic and nutritional strategies^{11,12} that starve them while nourishing healthy tissues? Could changes in energy balance help to explain why cancer is associated with fatigue and muscle-wasting? And might these phenomena be symptoms of an organism-wide energy budget on the brink of bankruptcy?

Fasting. Many animals fast when ill. Digesting food uses energy – about 10–15% of daily energy expenditure can be saved by not processing new food. Perhaps these energy savings explain why intermittent fasting can have health benefits, improving control of blood sugar levels and decreasing fatigue¹³. Might these savings help to explain why, in intensive-care units, waiting one week before intravenously feeding people who show no sign of hunger improves clinical outcomes and decreases mortality, compared with feeding them earlier¹⁴ – a trend that clinicians struggle to rationalize? And could this effect account for the widespread health benefits of drugs that mimic a natural hormone called glucagon-like peptide-1 (GLP-1)? These medications help people to eat less, thus addressing metabolic problems close to their root cause (excess calorie intake), whereas previous strategies

tried to manage the conditions' downstream consequences, such as high blood pressure and insulin resistance.

Alzheimer's disease. Research has linked Alzheimer's disease to insulin resistance, which involves impaired energy flux (increased resistance) from the blood into cells, and to a slowing of the brain's metabolic rate, called hypometabolism¹⁵. Some proteins, such as amyloid- β and tau, can accumulate in the brain. Could investigating the energy costs of producing protein aggregates tell researchers about the energetic

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burdens that diseased brain cells bear, on top of their usual functions? If so, could such findings help scientists to identify a crucial point of convergence for this disease, mental-health conditions and other disorders that have a metabolic syndrome as a common risk factor?

Each of these questions requires thinking from first principles. In 2024, we demonstrated the usefulness of this approach when examining mitochondrial diseases, which are characterized by mutations in genes needed for energy transformation. These were long assumed to be caused by a deficiency in energy-carrying ATP molecules, but first-principles thinking helped us to uncover

a counter-intuitive disease feature: excess energy expenditure¹⁶. Mitochondrial defects don't slow metabolism down; they speed it up, using up the body's finite energy resources. Other disease states and disorders, including various types of cancer, probably act as 'energy sinks', too, challenging the whole organism's energy-transformation capacity.

To move forwards, we encourage scientists in inter-disciplinary teams to converge around the idea of looking at their central question energetically, from first principles. We would also like to see researchers seeking out other biomarkers of energy resistance, such as GDF15, which has proved to be a strong predictor of disease and poor health across conditions¹⁷.

If we head down this path, in 20 years' time, we might do a lot less molecular-mechanism research for which the main purpose is to develop symptom-targeting drugs. Instead, we might do a lot more thinking in terms of energetics, which could inform energy-based preventative and therapeutic approaches. However, if we continue to ignore the energetic dimension of life and healing, we risk pursuing blind molecular alleyways, with findings in mice and other animals that fail to stack up in humans. To build an accurate and actionable picture of what keeps us healthy and flourishing, we must understand our energetic nature.

Martin Picard is a mitochondrial psychobiologist in the departments of Psychiatry and Neurology and in the Robert N. Butler Columbia Aging Center, Columbia University Irving Medical Center, New York City, New York. **Christopher P. Kempes** is a theoretical biophysicist at the Santa Fe Institute, Santa Fe, New Mexico, and at the Complexity Science Hub in Vienna. e-mail: martin.picard@columbia.edu

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