BEC BIOENERGETICS COMMUNICATIONS
Bioenerg Commun 2026.5
https://doi.org/10.26124/bec2026-0005
Short Communication

The bioenergetic landscape of respiratory flux control: mapping the scope of metabolic flexibility and mitochondrial fitness



Erich Gnaiger
Oroboros Instruments, Innsbruck, Austria
erich.gnaiger@oroboros.at

Contribution to MiP2026
Received 2026-09-25 – **Reviewed** 2026-10-19 – **Accepted** 202-11-11
Published 2026-11-12

Cite: Gnaiger E (2026) The bioenergetic landscape of respiratory flux control: mapping the scope of metabolic flexibility and mitochondrial fitness. Bioenerg Commun 2026.5 https://doi.org/10.26124/bec2026-0005

Respiration of living cells studied with the coupling-control protocol (CCP) provides information on cellular bioenergetics and mitochondrial function. Routine respiration R is under control of aerobic ATP demand of the living cell within limits of mitochondrial performance. ATP production is inhibited in leak respiration L and decoupled from electron transfer for measurement of electron transfer capacity (ETC) E [1,2]. Normalization of respiratory rates within the coupling-control protocol yields four complementary respiratory flux control efficiencies [3]:

coupling efficiency, $j_{E-L} = (E-L)/E$ R-ATP coupling ratio, $j_{RLE} = (R-L)/E$
$E-R$ excess ratio, $j_{E-R} = (E-R)/E$ R-ATP control efficiency, $j_{R-L} = (R-L)/R$

Although derived from only two independent flux control ratios, L/E and R/E, these indices provide complementary views of the bioenergetic landscape. Bioenergetic cluster analysis (BCA) maps mechanistically distinct trajectories through this landscape [3].

Three flux control efficiencies apply specifically to the analysis of the CCP, because they contain R which is accessible only in living cells. E is not a surrogate for OXPHOS capacity P which requires ATP production stimulated by kinetically saturating ADP concentrations in permeabilized cells [4]. Consequently, $E-R$ excess capacity must be distinguished from the actual OXPHOS reserve capacity, $P-R$.

Flux control models distinguish changes of coupling efficiency driven by leak respiration ($L\uparrow$; coupling model) or ETC ($E\downarrow$; capacity model). Compensatory changes maintain specific respiratory functions, but beyond a breakpoint further advancement requires adjustment of controlled bioenergetic variables [3]. The extent of change of the controlling rate defines advancement along trajectories up to breakpoints that limit the scope of metabolic flexibility (**Figure 1a,b**).

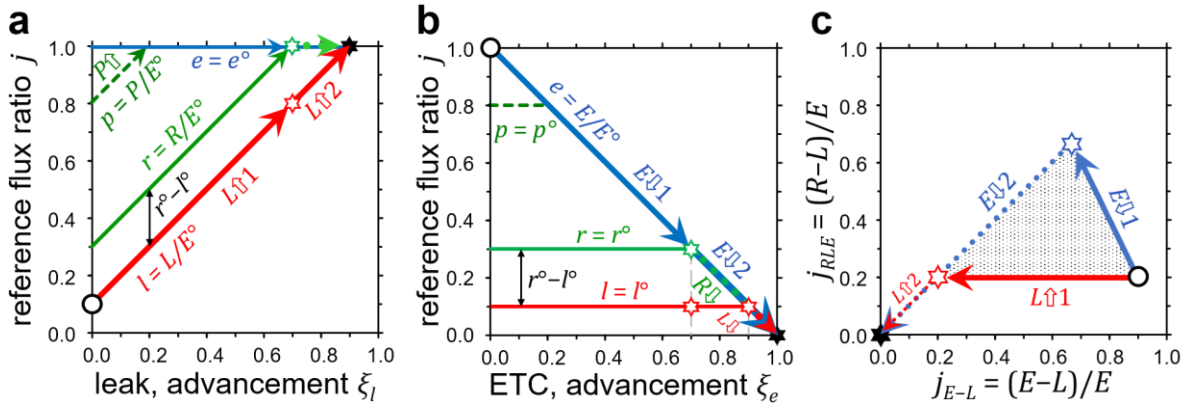


Figure 1. Mapping the scope of respiratory control indices. Reference flux ratios j are $l = L/E°$, $r = R/E°$, $p = P/E°$, and $e = E/E°$, where $E°$ is the electron transfer capacity ETC of a reference group. Trajectories (arrows) to breakpoints (asterisks) from control or initial states (circles): $l° \stackrel{\text{def}}{=} L°/E° = 0.10$; $r° \stackrel{\text{def}}{=} R°/E° = 0.30$; $p° \stackrel{\text{def}}{=} P°/E° = 0.80$. **(a)** Advancement of leak, ξ_l. **(b)** Advancement of ETC, ξ_e. **(c)** R-ATP coupling ratio, $j°_{RLE} = 0.20$; initial coupling efficiency $j°_{E-L} = 0.90$. Red arrows: coupling model ($L⇧$). Blue arrows: capacity model ($E⇩$). Shaded area indicates the data space between the coupling and capacity models (after [3]).

An increase in leak respiration can initially be compensated by increasing routine respiration, maintaining ATP turnover despite declining coupling efficiency. Once the capacity for compensation is exhausted, further dyscoupling compromises ATP-coupled respiration (coupling model; **Figure 1a**). Conversely, declining ETC may initially remain without any effect on routine respiration until $E-R$ excess capacity is exhausted (capacity model; **Figure 1b**). Hence, identical changes in coupling efficiency may reflect fundamentally different underlying mechanisms which can be distinguished by BCA (**Figure 1c**).

The direction of a bioenergetic change alone does not necessarily distinguish mitochondrial dysfunction from adaptive responses. Physiological *adaption* within an organism or cell population is distinguished from evolutionary *adaptation* across generations [5,6,7]. A decrease in mitochondrial density or coupling efficiency may represent adaption within a range of metabolic flexibility, whereas progression beyond a tipping point indicates emerging mitochondrial dysfunction.

BCA thus moves interpretation beyond descriptive increases or decreases in respiratory variables toward mechanistic evaluation of mitochondrial fitness. Respiratory control indices characterize mitochondrial quality but must be complemented by respiratory capacities when the mitochondrial content changes. The latter is the product of mitochondrial density and cell volume [1]. Implementation of BCA is an important step toward mapping the scope of metabolic flexibility for evaluation of mitochondrial fitness with quality-controlled diagnostic standards [3].

Conflicts of interest: EG holds the position of Editor-in-Chief for BEC and is blinded from reviewing or making decisions for the manuscript.

Supported by: K-Regio enterprise project MitoDrugs, funded by Standortagentur Tirol and the State of Tyrol, and co-funded by the European Union (EFRE).

Academic editor: Mateus Grings

Reviewers: Andrew Murray, Graham Holloway

Keywords: bioenergetic cluster analysis; coupling efficiency; electron transfer; excess capacity; leak respiration; oxidative capacity; oxidative phosphorylation; routine respiration; routine-ATP coupling ratio; routine-ATP control efficiency

References

1. Hütter E, Renner K, Pfister G, Stöckl P, Jansen-Dürr P, Gnaiger E (2004) Senescence-associated changes in respiration and oxidative phosphorylation in primary human fibroblasts. Biochem J 380:919-28. https://doi.org/10.1042/BJ20040095
2. Gnaiger E (2025) Mitochondrial respiratory function in living cells. Bioenerg Commun 2025.5. https://doi.org/10.26124/bec.2025-0005
3. Gnaiger E (2026) Mapping metabolic flexibility by respiratory flux control: Bioenergetic cluster analysis of mitochondrial fitness. BEC preprints 2026.5. https://doi.org/10.26124/becprep.2026-0005
4. Timón-Gómez A, Doerrier C, Sumbalová Z, Garcia-Souza LF, Baglivo E, Cardoso LHD, Gnaiger E (2026) Bioenergetic profiles and respiratory control in mitochondrial physiology: Precision analysis of oxidative phosphorylation. Exp Physiol 111:179-211. https://doi.org/10.1113/EP092792
5. Hochachka PW, Somero GN (2002) Biochemical adaptation: mechanism and process in physiological evolution. Oxford Univ Press, New York: 466 pp.
6. Debevec T, Longman DP, Bourgois JG (2024) Defining adaptation within applied physiology - is there room for improvement? Front Physiol 15:1459026. https://doi.org/10.3389/fphys.2024.1459026
7. Tanaka H, Seals DR (2024) Scientific writing in physiology: Confused/misused terms and phrases. J Appl Physiol (1985) 136:401-7. https://doi.org/10.1152/japplphysiol.00868.2023

Copyright © 2026 The author. This Open Access peer-reviewed communication is distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. © remains with the author, who has granted BEC an Open Access publication license in perpetuity.