

Thermodynamic Cost-Controllability Tradeoff in Metabolic Currency Coupling

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Cellular metabolism is globally regulated by various currency metabolites such as ATP, GTP, and NAD(P)H. These metabolites cycle between charged (high-energy) and uncharged (low-energy) states to mediate energy transfer. While distinct currency metabolites are associated with different metabolic functions, their charged and uncharged forms are generally interconverted through biochemical reactions such as $\text{ATP} + \text{GDP} \rightleftharpoons \text{ADP} + \text{GTP}$ and $\text{NADP}^+ + \text{NADH} \rightleftharpoons \text{NADPH} + \text{NAD}^+$. Thus, their energetic states are generally coupled and influence each other, which would hinder the independent regulation of different currency metabolites. Despite extensive knowledge of the molecular biology of individual currency metabolites, it remains poorly understood how the coordination of various coupled currency metabolites shapes metabolic regulation, efficiency, and ultimately the evolution of organisms. Here, we present a minimal theoretical model of metabolic currency coupling and reveal a fundamental tradeoff relationship between metabolic controllability and thermodynamic cost: increasing the capacity to independently regulate multiple currency metabolites generally requires comparable abundances of those metabolites, which in turn incurs a higher entropy production rate. The tradeoff suggests that in complex environments, organisms evolutionarily favor comparably sized currency-metabolite pools to enhance metabolic controllability at the expense of a higher thermodynamic cost; conversely, in simple environments, organisms are expected to evolve more imbalanced currency pools to reduce heat dissipation. These considerations also offer a hypothesis regarding evolutionary trends in nucleotide-pool balance and genomic GC content.

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I. INTRODUCTION

Living organisms must continually consume energy to maintain their order and avoid reaching thermodynamic equilibrium. In the 1940s, Schrödinger famously argued that life persists by avoiding equilibrium through metabolism [1,2]. Since then, cellular metabolism has remained a central topic in the study of nonequilibrium thermodynamics, attracting the interest of physicists and biologists alike [3,4]. Remarkably, recent advancements in stochastic thermodynamics have provided a rigorous nonequilibrium thermodynamic description for open chemical reaction networks, applicable to general metabolic reaction networks [5–10]. However, most theoretical efforts to date have taken one of two extremes: they either derive very general thermodynamic constraints applicable to arbitrary chemical reaction networks [6,8,9], or they analyze

specific, simple biochemical processes such as single-enzyme kinetics [11,12] and molecular machines [13]. A substantial conceptual gap remains between broad theoretical frameworks and detailed, context-specific biochemical studies. To reveal the key biophysical principles of metabolism, we must bridge this gap by developing a coarse-grained theory that preserves the unique characteristics of metabolic systems.

One approach to coarse-graining metabolic complexity appropriately is to focus on a special class of compounds that globally mediate energy transfer across many metabolic reactions: *coenzymes*. A coenzyme is a small, nonprotein organic compound that associates loosely with enzymes and participates in enzymatic reactions as a transferable carrier of chemical groups or electrons [14,15]. Well-known examples of coenzymes include adenosine triphosphate (ATP), which carries high-energy phosphate groups, and nicotinamide adenine dinucleotide (NADH/NAD⁺), which carries high-energy electrons. Coenzymes typically cycle between high-energy (charged) and low-energy (uncharged) forms. ATP, for instance, is converted by hydrolysis into its lower-energy forms ADP or AMP (adenosine diphosphate or monophosphate), releasing energy, whereas ADP can be recharged back into ATP through processes such as cellular respiration or photosynthesis.

Because of their central role in energy transfer, coenzymes are often referred to as *currency metabolites* or *metabolic*

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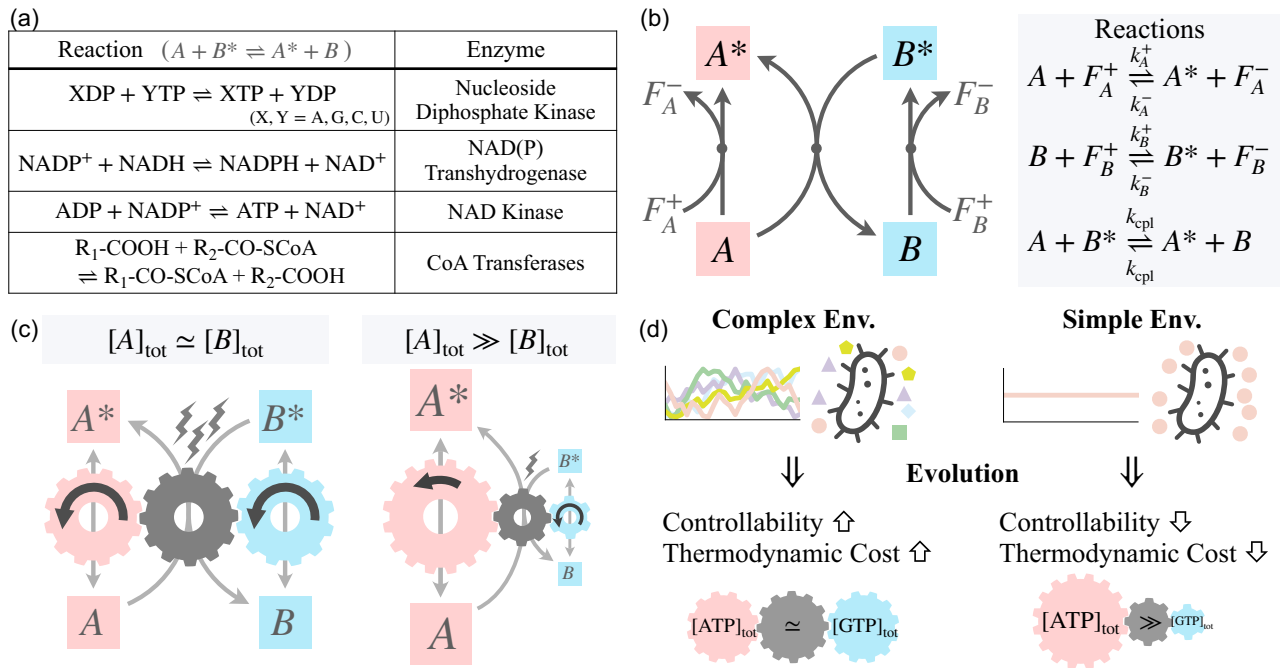


FIG. 1. Metabolic currency coupling. (a) Examples of transferases and their associated currency coupling reactions. (b) Model of the coupling of currency metabolites. All reactions are reversible. Table I collects all the notation in one place. (c) Schematics of how the balance in currency metabolite pools affects metabolic controllability and thermodynamic cost. Coupling reactions cause the ratios $[A^*]/[A]$ and $[B^*]/[B]$ to shift in the same direction. The former strongly influences the latter when $[A]_{\text{tot}} \gg [B]_{\text{tot}}$. Conversely, a large $[A]_{\text{tot}}/[B]_{\text{tot}}$ ratio reduces the entropy production rate required to maintain the metabolic currency coupling, which is analogous to the “friction” between different currency metabolites. (d) A theoretical connection between organism or habitat complexity and pool sizes of multiple currency metabolites.

currencies [16,17]. Much like money in an economy, currency metabolites fulfill Jevons’s functions of money [18,19]: they serve as a medium of exchange (transferring energy or chemical groups), a unit of account (providing a characteristic energy metric across reactions), and a store of value (storing energy). The charged/uncharged ratios of currency metabolites, such as the ATP/ADP ratio, regulate metabolic activity globally and can serve as macroscopic indicators of the cellular metabolic state [15,20–22]: a higher ratio biases metabolism toward overall ATP-driven reactions over ADP-driven ones, while a lower ratio favors ADP-driven reactions.

Cellular metabolic systems employ multiple currency metabolites [e.g., ATP, GTP, NAD(P)H, and acetyl-CoA], each generally associated with specific biochemical functions [22–24]: for example, ATP is known as the primary energy currency for most biochemical reactions, while GTP functions in signaling and protein synthesis, for example by powering G-proteins and mRNA translation [25,26]; among the electron carriers, NADPH predominantly drives anabolic (biosynthetic) reactions, while NADH feeds into catabolic reactions, such as cellular respiration [27,28]. Cells are considered to coordinate various metabolic demands separately by allocating different currency metabolites to different tasks.

Despite their distinct roles, the energetic states of different currency metabolites are thermodynamically and chemically coupled rather than isolated. In general, the charged and uncharged forms of distinct currency metabolites can be interconverted through specific enzymatic reactions [29]. For example, nucleoside diphosphate kinase catalyzes a reversible phosphate exchange between nucleoside diphosphates and

triphosphates (NDPs and NTPs), effectively linking the ATP/ADP and GTP/GDP ratios through the reaction $\text{ATP} + \text{GDP} \rightleftharpoons \text{ADP} + \text{GTP}$ [30]; other transferases (EC 2) perform analogous exchanges [Fig. 1(a)]. Such coupling reactions will hinder the independent regulation of different currency metabolites: if the intracellular ATP/ADP ratio is increased, for instance, coupling reactions will inevitably push the GTP/GDP ratio upward as well.

While extensive knowledge of the molecular biology of individual currency metabolites has been accumulated, how the coordination of various coupled currency metabolites influences metabolic regulation, efficiency, and ultimately the physiology and evolution of organisms remains poorly understood. To address this gap, we theoretically elucidate inherent, systemwide constraints on how cellular metabolism is regulated via metabolic currency coupling.

In this study, we develop a minimal theoretical model of metabolic currency coupling. We thereby derive a fundamental tradeoff between metabolic controllability and thermodynamic cost: balanced currency metabolite pools enhance metabolic control at the expense of increased entropy production rate (EPR) as a thermodynamic cost [see also Fig. 1(c)]. From a biological standpoint, this tradeoff suggests that organisms in complex environments would evolutionarily favor uniformity in currency metabolite pools to increase their metabolic controllability; in contrast, those in simpler environments would evolutionarily favor a skewed distribution of currency pools to reduce the thermodynamic cost [Fig. 1(d)]. We then explore biological and evolutionary implications of this tradeoff, including a hypothetical link between

TABLE I. Symbols and units. Concentrations are expressed in molar units, $M = \text{mol L}^{-1}$. A dash indicates that the symbol denotes a chemical species rather than a physical quantity.

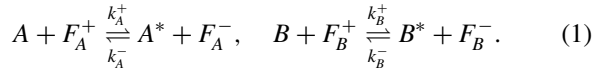
Symbol	Description	Unit
X, X^*	Currency metabolite in the uncharged/charged state ($X=A, B$)	–
$[X]_{\text{tot}}$	Pool size of currency metabolite X	M
k_{cpl}	Rate constant for the coupling reaction [Eq. (2)]	$M^{-1} \text{ s}^{-1}$
$k_X^\pm$	Rate constant for the driving reactions [Eq. (1)]	$M^{-1} \text{ s}^{-1}$
$F_X^\pm$	Fuel (F_X^+) and product (F_X^-) for the driving reactions	–
$\kappa_X^\pm, \kappa_X$	Effective rate constant for the driving reactions ($\kappa_X^\pm := k_X^\pm [F_X^\pm]$; $\kappa_X := \kappa_X^+ + \kappa_X^-$)	s^{-1}
Γ_X	Charged/uncharged ratio of X ($\Gamma_X := [X^*]/[X]$)	1
Γ_0	Γ_X in the strong coupling limit [Eq. (6)]	1
$e_{XY}^\pm$	Elasticity of Γ_X by $\kappa_Y^\pm$ [Eq. (7)]	1
e_X	Geometric mean of $e_{XX}^\pm$ [Eq. (11)]	1
e	Mean elasticity [Eq. (12)]	1
$\tilde{e}_X^\pm$	$e_{XY}^\pm$ in the strong coupling limit	1
σ_{cpl}	Entropy production rate of the coupling reaction	$\text{J K}^{-1} \text{ L}^{-1} \text{ s}^{-1}$

ATP-GTP coupling, organismal complexity, and genomic GC content.

II. MODEL

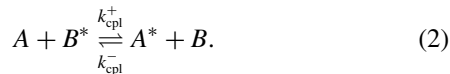
As the simplest case, we consider the coupling of two currency metabolites, A and B [see also Fig. 1(b) and Table I].

Each currency metabolite is driven from its uncharged state X into its charged state X^* via a single effective reaction ($X=A, B$):



Here, F_X^+ coarse-grains a pool of energy-rich “fuel” substrates (e.g., nutrients or reducing equivalents), and F_X^- represents a lumped set of lower-energy products or waste. Thus, this reversible reaction represents both catabolic (rightward) and anabolic (leftward) processes.

Different currency metabolites interconvert between their charged and uncharged states as



For the sake of simplicity, it is assumed that the difference in standard chemical potentials between X^* and X , $\Delta\mu_X^\circ := \mu_{X^*}^\circ - \mu_X^\circ > 0$, is identical for both currency metabolites $X = A, B$. From the local detailed balance condition, $k_{\text{cpl}}^+ = k_{\text{cpl}}^-$ then holds, which will be denoted by k_{cpl} hereafter.

Assuming mass-action kinetics, the rate equation for this system is given by

$$\frac{d}{dt} \begin{pmatrix} [A] \\ [A^*] \\ [B] \\ [B^*] \end{pmatrix} = \begin{pmatrix} -1 & 0 & -1 \\ 1 & 0 & 1 \\ 0 & -1 & 1 \\ 0 & 1 & -1 \end{pmatrix} \begin{pmatrix} J_A \\ J_B \\ J_{\text{cpl}} \end{pmatrix},$$

$$\begin{aligned} J_A &= \kappa_A^+ [A] - \kappa_A^- [A^*], \\ J_B &= \kappa_B^+ [B] - \kappa_B^- [B^*], \\ J_{\text{cpl}} &= k_{\text{cpl}} [A][B^*] - k_{\text{cpl}} [A^*][B]. \end{aligned} \quad (3)$$

Here, the effective rate constants for the driving reactions, defined as $\kappa_X^\pm := k_X^\pm [F_X^\pm]$, quantify how strongly currency metabolite X is driven toward its charged and uncharged state by catabolic and anabolic processes. In reality, $\kappa_X^\pm$ can vary over time via transcriptional or translational regulation, while these regulatory processes typically occur on slower timescales than the relaxation of the coupling reactions [31]. In the following analysis, we therefore treat $F_X^\pm$ as effectively *chemostated* and $\kappa_X^\pm$ as constants.

Each reaction conserves the total pool of each currency metabolite: $[A]_{\text{tot}} := [A^*] + [A]$ and $[B]_{\text{tot}} := [B^*] + [B]$ are conserved moieties. By exploiting the symmetry between currency metabolites, we order their total pool sizes as $[A]_{\text{tot}} \geq [B]_{\text{tot}}$, unless otherwise stated.

III. RESULTS

The present study focuses on the charged/uncharged ratios of currency metabolites X , $\Gamma_X := [X^*]/[X]$. These ratios determine the macroscopic state of intracellular metabolism: when Γ_X increases (decreases), the net fluxes of X^* -driven reactions are preferentially promoted (suppressed) overall.

First, Γ_X at the steady state, denoted by Γ_X^{st} , is calculated as (Appendix A)

$$\begin{aligned} \Gamma_A^{\text{st}} &= \frac{[A^*]^{\text{st}}}{[A]^{\text{st}}} = \frac{k_{\text{cpl}} [A]_{\text{tot}} \kappa_A^+ + k_{\text{cpl}} [B]_{\text{tot}} \kappa_B^+ + \kappa_A^+ \kappa_B}{k_{\text{cpl}} [A]_{\text{tot}} \kappa_A^- + k_{\text{cpl}} [B]_{\text{tot}} \kappa_B^- + \kappa_A^- \kappa_B}, \\ \Gamma_B^{\text{st}} &= \frac{[B^*]^{\text{st}}}{[B]^{\text{st}}} = \frac{k_{\text{cpl}} [A]_{\text{tot}} \kappa_A^+ + k_{\text{cpl}} [B]_{\text{tot}} \kappa_B^+ + \kappa_A \kappa_B^+}{k_{\text{cpl}} [A]_{\text{tot}} \kappa_A^- + k_{\text{cpl}} [B]_{\text{tot}} \kappa_B^- + \kappa_A \kappa_B}, \end{aligned} \quad (4)$$

where $\kappa_X := \kappa_X^+ + \kappa_X^-$ [see also Fig. 2(a)]. Γ_X^{st} ($1/\Gamma_X^{\text{st}}$) increases linearly with the driving strength $\kappa_X^+ / (\kappa_X^-)$.

Without currency coupling (i.e., $k_{\text{cpl}}=0$), the steady-state ratio satisfies $\Gamma_X^{\text{st}} = \kappa_X^+ / \kappa_X^-$. Currency coupling therefore shifts Γ_X^{st} from the ratio of the effective rate constants for the driving reactions, κ_X^+ / κ_X^- , depending on the pool size of the other currency metabolite as well as the coupling constant k_{cpl} . In the limit of weak currency coupling, $k_{\text{cpl}} \ll \kappa_X^\pm / [X]_{\text{tot}}$, we

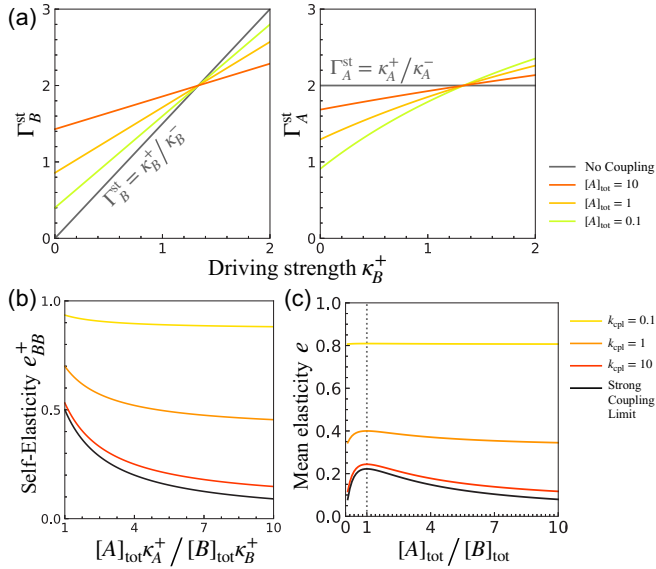


FIG. 2. Elasticity of the charged/uncharged ratios with metabolic currency coupling. (a) Dependence of charged/uncharged ratio Γ_X^{st} ($X=A, B$) on κ_B^+ . Colored lines show the cases with $k_{\text{cpl}}=1$, $[B]_{\text{tot}}=1$ and different $[A]_{\text{tot}}$, while the gray line shows the no coupling case. (b) Dependence of self-elasticity e_{BB}^+ on $[A]_{\text{tot}}\kappa_A^+ / [B]_{\text{tot}}\kappa_B^+$. Colored lines show different coupling strength k_{cpl} and the black line shows the large coupling limit, $\tilde{e}_B^+$ [Eq. (9)]. (c) Relationship between $[A]_{\text{tot}}/[B]_{\text{tot}}$ and mean elasticity e . The black line shows the strong coupling limit. In panels (b) and (c), $\kappa_B^+ = 1/3$ and $[A]_{\text{tot}} + [B]_{\text{tot}} = 2$ are fixed. The other parameters are set as $\kappa_A^+ = 2/3$, $\kappa_A^- = 1/3$, and $\kappa_B^- = 2/3$.

obtain

$$\begin{aligned}\Gamma_A^{\text{st}} &= \frac{\kappa_A^+}{\kappa_A^-} + k_{\text{cpl}}[B]_{\text{tot}} \frac{\kappa_B^-}{\kappa_B \kappa_A^-} \left(\frac{\kappa_B^+}{\kappa_B^-} - \frac{\kappa_A^+}{\kappa_A^-} \right) + O(k_{\text{cpl}}^2), \\ \Gamma_B^{\text{st}} &= \frac{\kappa_B^+}{\kappa_B^-} + k_{\text{cpl}}[A]_{\text{tot}} \frac{\kappa_A^-}{\kappa_A \kappa_B^-} \left(\frac{\kappa_A^+}{\kappa_A^-} - \frac{\kappa_B^+}{\kappa_B^-} \right) + O(k_{\text{cpl}}^2).\end{aligned}\quad (5)$$

Γ_X^{st} deviates more from κ_X^+/κ_X^- toward κ_Y^+/κ_Y^- ($Y \neq X$), as $[Y]_{\text{tot}}$ increases.

By contrast, in the strong coupling limit, $k_{\text{cpl}} \gg \kappa_X^\pm/[X]_{\text{tot}}$, both steady-state ratios Γ_A^{st} and Γ_B^{st} converge to the identical value

$$\begin{aligned}\Gamma_0 &:= \frac{[A]_{\text{tot}}\kappa_A^+ + [B]_{\text{tot}}\kappa_B^+}{[A]_{\text{tot}}\kappa_A^- + [B]_{\text{tot}}\kappa_B^-} \\ &= \frac{([A]_{\text{tot}}/[B]_{\text{tot}})\kappa_A^+ + \kappa_B^+}{([A]_{\text{tot}}/[B]_{\text{tot}})\kappa_A^- + \kappa_B^-},\end{aligned}\quad (6)$$

which is a weighted average of the individual driving-force ratios, κ_A^+/κ_A^- and κ_B^+/κ_B^- . From Eq. (6), the charged/uncharged ratio with strong currency coupling depends on the currency pool sizes, $[A]_{\text{tot}}$ and $[B]_{\text{tot}}$, only through their ratio, $[A]_{\text{tot}}/[B]_{\text{tot}}$.

A. Controllability of charged/uncharged ratios

The adaptive regulation of cellular metabolism requires the appropriate modulation of the charged/uncharged ratios Γ_X in response to changing environmental conditions such as

nutrient availability. To quantify this controllability, we adopt the concept of *elasticity* from economics [32], measuring the susceptibility of the steady-state charged/uncharged ratios Γ_X^{st} to variations in the effective rate constant for a driving reaction, $\kappa_Y^\pm$:

$$e_{XY}^\pm := \pm \frac{\partial \log \Gamma_X^{\text{st}}}{\partial \log \kappa_Y^\pm} = \pm \frac{\kappa_Y^\pm}{\Gamma_X^{\text{st}}} \frac{\partial \Gamma_X^{\text{st}}}{\partial \kappa_Y^\pm} \quad (X, Y = A, B). \quad (7)$$

Each elasticity $e_{XY}^\pm$ is dimensionless and takes a value between 0 and 1: by substituting Eq. (4) into the definition in Eq. (7) we obtain

$$\begin{aligned}e_{AA}^\pm &= \frac{k_{\text{cpl}}[A]_{\text{tot}}\kappa_A^\pm + \kappa_A^\pm \kappa_B}{k_{\text{cpl}}[A]_{\text{tot}}\kappa_A^\pm + k_{\text{cpl}}[B]_{\text{tot}}\kappa_B^\pm + \kappa_A^\pm \kappa_B}, \\ e_{AB}^\pm &= \frac{k_{\text{cpl}}[B]_{\text{tot}}\kappa_B^\pm}{k_{\text{cpl}}[A]_{\text{tot}}\kappa_A^\pm + k_{\text{cpl}}[B]_{\text{tot}}\kappa_B^\pm + \kappa_A^\pm \kappa_B}, \\ e_{BA}^\pm &= \frac{k_{\text{cpl}}[A]_{\text{tot}}\kappa_A^\pm}{k_{\text{cpl}}[A]_{\text{tot}}\kappa_A^\pm + k_{\text{cpl}}[B]_{\text{tot}}\kappa_B^\pm + \kappa_A^\pm \kappa_B}, \\ e_{BB}^\pm &= \frac{k_{\text{cpl}}[B]_{\text{tot}}\kappa_B^\pm + \kappa_A \kappa_B^\pm}{k_{\text{cpl}}[A]_{\text{tot}}\kappa_A^\pm + k_{\text{cpl}}[B]_{\text{tot}}\kappa_B^\pm + \kappa_A \kappa_B^\pm}.\end{aligned}\quad (8)$$

Note that the elasticity of Γ_X^{st} against different driving reactions satisfies $e_{XA}^\pm + e_{XB}^\pm = 1$ ($X=A, B$).

Equation (8) shows that elasticity is governed not only by the rate constants for the driving and coupling reactions, $\kappa_X^\pm$ and k_{cpl} , but also by the currency metabolite pool sizes, $[X]_{\text{tot}}$ [Fig. 2(b)]. In particular, each elasticity $e_{YX}^\pm$ depends on the relative magnitude of $[X]_{\text{tot}}\kappa_X^\pm$. This is particularly evident in the strong coupling limit, $k_{\text{cpl}} \gg \kappa_X^\pm/[X]_{\text{tot}}$:

$$e_{YX}^\pm \rightarrow \tilde{e}_X^\pm := \frac{[X]_{\text{tot}}\kappa_X^\pm}{[A]_{\text{tot}}\kappa_A^\pm + [B]_{\text{tot}}\kappa_B^\pm}. \quad (9)$$

This $\tilde{e}_X^\pm$ satisfies

$$e_{XX}^\pm \geq \tilde{e}_X^\pm \geq e_{YX}^\pm \quad (Y \neq X), \quad (10)$$

and it thus provides the lower (upper) bound of the dimensionless elasticity $e_{XX}^\pm$ ($e_{YX}^\pm$) [see also Fig. 2(b)].

Remarkably, when the currency metabolite pools become imbalanced ($[A]_{\text{tot}} \gg [B]_{\text{tot}}$), the less abundant currency B loses susceptibility to its own drives $\kappa_B^\pm$ and becomes predominantly slaved to Γ_A^{st} and $\kappa_A^\pm$ [Figs. 2(a) and 2(b)]. In other words, the model effectively behaves as a single-degree-of-freedom system. Intuitively, this occurs because the more abundant currency metabolite A acts as a chemical bath for the less abundant currency metabolite B [Fig. 1(c)].

Taking the geometric mean of “self-elasticity” $e_{XX}^\pm$ yields a single measure of the controllability of each Γ_X^{st} :

$$e_X := \sqrt{e_{XX}^+ e_{XX}^-} \quad (X = A, B). \quad (11)$$

Furthermore, the geometric mean of e_X yields a single measure of the system-wide controllability:

$$e := \sqrt{e_A e_B} = (e_{AA}^+ e_{AA}^- e_{BB}^+ e_{BB}^-)^{1/4}. \quad (12)$$

Consistent with the above discussion, imbalanced currency metabolite pools ($[A]_{\text{tot}} \gg [B]_{\text{tot}}$) increase the bias between $e_{AA}^\pm$ and $e_{BB}^\pm$, as well as between e_A and e_B , thereby reducing mean elasticity e [Fig. 2(c)].

In addition to the controllability based on elasticity, the achievable ranges of the charged/uncharged ratios Γ_X^{st} are constrained by the $[A]_{\text{tot}}/[B]_{\text{tot}}$ ratio (Appendix A 4). To achieve the wide range of charged/uncharged ratios observed *in vivo* [33], cells must regulate not only the driving reactions but also the pool sizes of currency metabolites.

B. Entropy production rate as a thermodynamic cost

The EPR represents a thermodynamic or energetic cost of maintaining nonequilibrium states homeostatically [34,35], including the dissipation generated by metabolic currency coupling. Microscopically, the EPR σ quantifies the ensemble-averaged irreversibility of stochastic forward and reverse reaction events per unit time.

The EPR associated with the coupling reaction, σ_{cpl} , is defined as [9]

$$\begin{aligned} \sigma_{\text{cpl}} &:= R(k_{\text{cpl}}[A][B^*] - k_{\text{cpl}}[A^*][B]) \log \frac{[A][B^*]}{[A^*][B]} \\ &= R k_{\text{cpl}} [A]_{\text{tot}} [B]_{\text{tot}} \frac{\Gamma_B - \Gamma_A}{(\Gamma_A + 1)(\Gamma_B + 1)} \log \frac{\Gamma_B}{\Gamma_A}, \end{aligned} \quad (13)$$

where R is the gas constant, and hereafter, we measure entropy in units of R and set $R = 1$. σ_{cpl} increases with both the difference between Γ_A and Γ_B and the product of currency pool sizes, $[A]_{\text{tot}}[B]_{\text{tot}}$. Intuitively, the EPR associated with currency coupling can be viewed as the effective “friction” between different currency metabolites [36] [Fig. 1(c)].

Examining the steady-state (housekeeping) EPR $\sigma_{\text{cpl}}^{\text{st}}$ in the strong coupling limit ($k_{\text{cpl}} \gg \kappa_X^{\pm}/[X]_{\text{tot}}$) provides further insight into the thermodynamic cost of currency coupling. In this limit, the housekeeping EPR of currency coupling is given by (see Appendix A for derivation)

$$\begin{aligned} \sigma_{\text{cpl}}^{\text{st}} &\simeq \frac{1}{k_{\text{cpl}}} \frac{(\kappa_A^- \kappa_B^+ - \kappa_A^+ \kappa_B^-)^2 [A]_{\text{tot}} [B]_{\text{tot}}}{([A]_{\text{tot}} \kappa_A^+ + [B]_{\text{tot}} \kappa_B^+)([A]_{\text{tot}} \kappa_A^- + [B]_{\text{tot}} \kappa_B^-)} \\ &\propto \frac{1}{k_{\text{cpl}}} \frac{\frac{[A]_{\text{tot}}}{[B]_{\text{tot}}}}{\left(\frac{[A]_{\text{tot}}}{[B]_{\text{tot}}} \kappa_A^+ + \kappa_B^+\right) \left(\frac{[A]_{\text{tot}}}{[B]_{\text{tot}}} \kappa_A^- + \kappa_B^-\right)}, \end{aligned} \quad (14)$$

which depends on the $[A]_{\text{tot}}/[B]_{\text{tot}}$ ratio, but is independent of the total abundance of currency metabolites, $[A]_{\text{tot}} + [B]_{\text{tot}}$. It is maximized at $[A]_{\text{tot}}/[B]_{\text{tot}} = \sqrt{\kappa_B^+ \kappa_B^-} / \sqrt{\kappa_A^+ \kappa_A^-}$ and decreases as the system deviates from this balanced $[A]_{\text{tot}}/[B]_{\text{tot}}$ ratio [Fig. 3(a)].

A similar approximation-based analysis also applies to the weak coupling limit ($k_{\text{cpl}} \ll \kappa_X^{\pm}/[X]_{\text{tot}}$), yielding a qualitatively consistent result: EPR $\sigma_{\text{cpl}}^{\text{st}}$ increases as the $[A]_{\text{tot}}/[B]_{\text{tot}}$ ratio approaches 1 (see Appendix A for details).

C. Tradeoff between elasticity and thermodynamic cost

With strong currency coupling, from Eqs. (9) and (14), the housekeeping EPR $\sigma_{\text{cpl}}^{\text{st}}$ and elasticity are related as

$$\sigma_{\text{cpl}}^{\text{st}} \simeq \frac{1}{k_{\text{cpl}}} \frac{(\kappa_A^- \kappa_B^+ - \kappa_A^+ \kappa_B^-)^2}{\sqrt{\kappa_A^+ \kappa_A^- \kappa_B^+ \kappa_B^-}} e^2. \quad (15)$$

This relation shows a tradeoff in which a higher (lower) mean elasticity is associated with a larger (smaller) EPR. We also

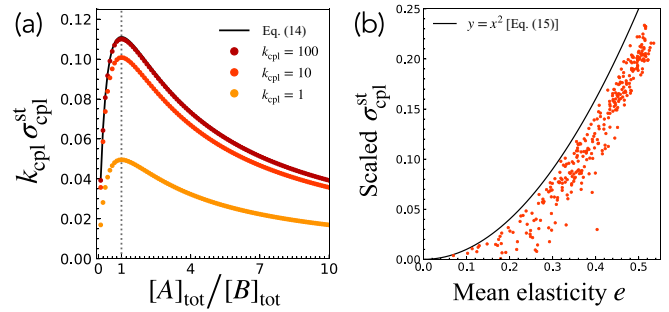


FIG. 3. Thermodynamic cost of currency coupling. (a) Dependence of $k_{\text{cpl}} \sigma_{\text{cpl}}^{\text{st}}$ on $[A]_{\text{tot}}/[B]_{\text{tot}}$ with relatively strong currency coupling. The black curve represents the strong coupling limit, Eq. (14). For a consistent comparison, the system size is kept constant by setting $[A]_{\text{tot}} + [B]_{\text{tot}} = 2$ while $[A]_{\text{tot}}/[B]_{\text{tot}}$ is varied; parameters are set as $\kappa_A^+ = 2/3$, $\kappa_A^- = 1/3$, $\kappa_B^+ = 1/3$, $\kappa_B^- = 2/3$. (b) Relationship between the scaled EPR of the coupling reaction, $\frac{k_{\text{cpl}} \sqrt{\kappa_A^+ \kappa_A^- \kappa_B^+ \kappa_B^-}}{(\kappa_A^- \kappa_B^+ - \kappa_A^+ \kappa_B^-)^2} \sigma_{\text{cpl}}^{\text{st}}$, and mean elasticity e . $k_{\text{cpl}} = 10$. The parameters $\kappa_X^{\pm}$ and $[X]_{\text{tot}}$ are randomly sampled from a uniform distribution within the range $[0, 1]$. The black curve represents the strong coupling limit, Eq. (15).

numerically confirmed a positive correlation between e and $\sigma_{\text{cpl}}^{\text{st}}$ even outside the strong coupling limit [Fig. 3(b)]; thus, this tradeoff could generally appear in systems with a coupling of different currency metabolites. In addition, the following tradeoff inequality holds for arbitrary k_{cpl} (see Appendix A for the derivation):

$$\frac{(\kappa_A^- \kappa_B^+ - \kappa_A^+ \kappa_B^-)^2}{k_{\text{cpl}} \sqrt{\kappa_A^+ \kappa_A^- \kappa_B^+ \kappa_B^-}} e^2 \geq \sigma_{\text{cpl}}^{\text{st}}. \quad (16)$$

The tradeoff suggests that greater uniformity in the currency metabolite pools could enhance the controllability of cellular metabolism and thus increase the effective degrees of freedom, at the expense of a higher thermodynamic cost [Fig. 1(c)]. Therefore, organisms inhabiting more complex environments, which require adaptive regulation of metabolic functions in response to higher-dimensional environmental cues, e.g., independent regulation of glycolysis via ATP, citric acid cycle via GTP, and pentose phosphate pathway via NADPH [24], are expected to favor more balanced currency pools during evolution and adaptation [Fig. 1(d)].

D. Influence of currency coupling on evolution of GC content

The above tradeoff has various biological implications, including a possible link between ATP-GTP coupling and an evolutionary trend in genomic GC content [see also Fig. 1(d)].

Genomic GC content refers to the percentage of guanine (G) and cytosine (C) in a genome. Interestingly, the GC content of bacterial genomes is highly diverse, ranging from 15 to 75% across species [37,38]. Although several factors have been proposed as contributing to this diversity, such as the differential stability due to the number of hydrogen bonds and sugar-acid preference arising from codon usage bias [39,40], the origin of this diversity remains unknown.

Here, we focus on the statistical relationship between genomic GC content and environmental complexity: GC content

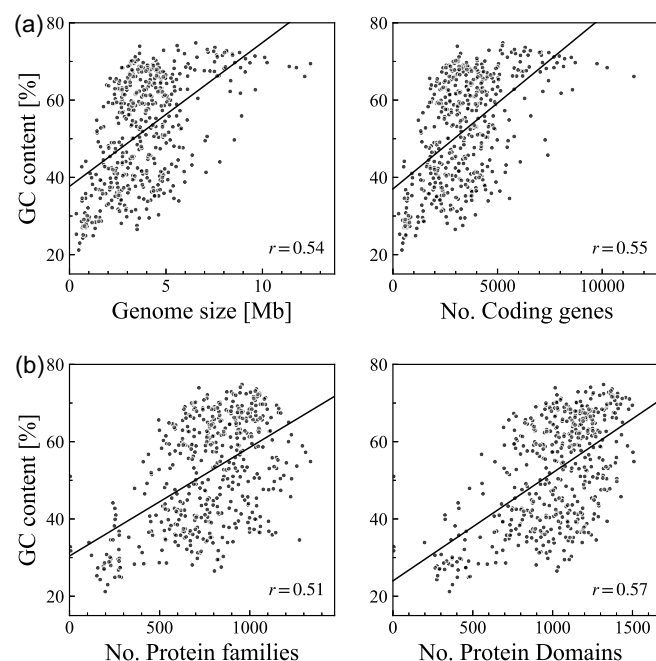


FIG. 4. Statistical relationship between organismal complexity and GC content. (a) Correlation between genomic properties (genome size or the number of coding genes) and GC content. (b) Correlation between proteomic properties (the number of protein families or domains) and GC content. In (a) and (b), the data are obtained from Ref. [38] and Pfam [41] for 496 bacteria and archaea.

is positively associated with various genomic and proteomic indicators of organismal or regulatory complexity (Fig. 4). Figure 4(a) shows a positive correlation between genomic GC content and the genome size or the number of coding genes—widely accepted indicators of organismal complexity, or the required complexity of physiological regulation [42,43]—across diverse microorganisms, as previously reported [44]. GC content also positively correlates with the number of protein families or domains, a recently proposed quantitative indicator of organismal complexity [45] [Fig. 4(b)]. More directly, insect endosymbionts, which inhabit relatively simple and stable host-associated environments, exhibit significantly lower GC content than their free-living relatives [Fig. 5(a)].

From an evolutionary perspective, it has been reported that organisms evolve to become GC-poor and AT-rich under simple environmental conditions [44,51]. Endosymbiotic organisms, which inhabit more stable and simplified environments compared to free-living species, evolve to become GC-poor [37,47,52]; similarly, mitochondria and chloroplasts typically have GC-poor genomes [53]. Notably, a phylogenetic analysis of insect endosymbionts in the genus *Sodalis* reported that an initial sharp reduction in genome size due to gene loss is followed by a progressive decrease in GC content [47]; in this regime, genome size and GC content are no longer correlated, but GC content continues to decrease as adaptation to relatively simple host-associated habitats proceeds. We found that a similar trend persists even when using updated data covering a broader range of insect endosymbionts [Fig. 5(b)]. These observations are consistent with the possibility that simple host-associated environments

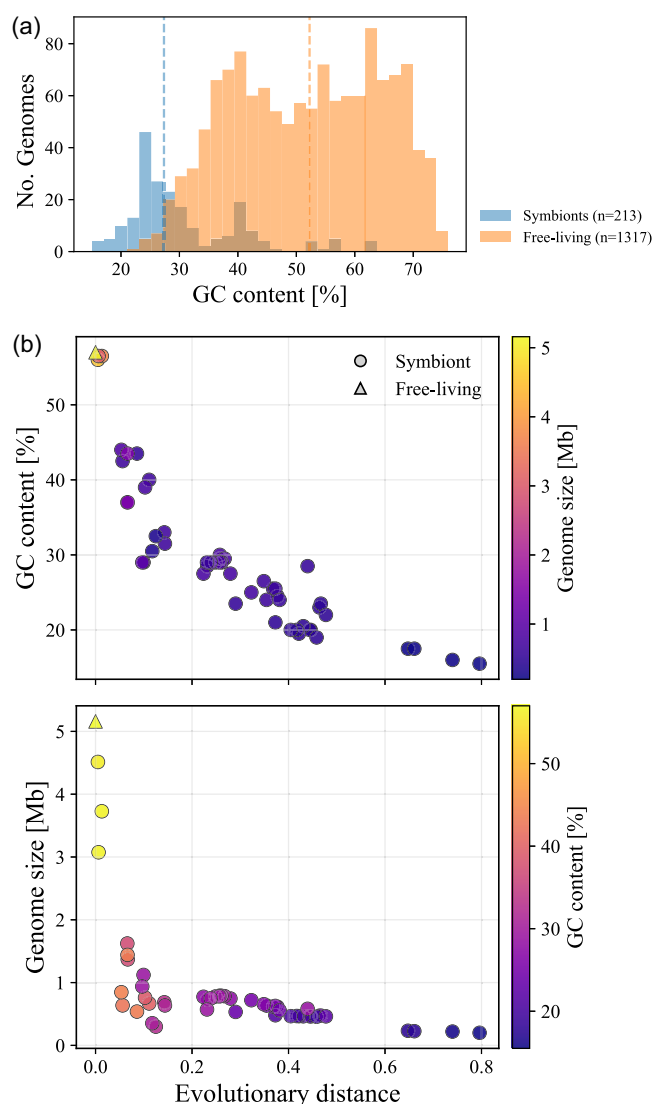


FIG. 5. GC-content decline and genome reduction in the evolution of insect endosymbionts. (a) Distribution of genomic GC content in insect endosymbionts (blue) and their free-living relatives (orange). The vertical dotted lines indicate the corresponding medians: 27.4% for symbionts and 52.3% for free-living relatives. Among the 267 symbionts compiled in Refs. [46,47], we analyzed the 213 genomes for which FASTA files were available from the NCBI database, along with 1317 free-living relatives. (b) Evolutionary distances of *Sodalis*-related insect endosymbionts, defined as tree branch lengths between symbiont lineages and their nearest free-living relative (*Sodalis praecaptivus*), are plotted against genome size (top) and GC content (bottom). Among the symbionts analyzed in (a), we extracted 55 symbiont genomes belonging to the same clade as the genera *Sodalis* and *Buchnera* in the GTDB bacterial reference tree [48,49] (downloaded from Ref. [50]).

evolutionarily favor lower GC content through mechanisms that are independent of genome-size reduction.

Our theory on metabolic currency coupling provides a possible explanation for the evolutionary tendency of microbes in simple environments to become GC-poor. NTPs are the building blocks of RNA, which is the second most abundant substance in cells after proteins [54]. Therefore, the intracellu-

lar ATP/GTP ratio may be negatively correlated with genomic GC content [55] (see also Appendix B). From the perspective of the above controllability-cost tradeoff due to currency coupling, GC-rich microbes should tend to have higher metabolic controllability but higher thermodynamic cost, and *vice versa*. Although GC content may be affected by many other factors, this suggests that microbes in complex habitats should evolve to increase their GC content to enhance metabolic controllability despite the added energetic burden, while microbes in simple habitats should reduce their GC content to lower thermodynamic cost at the expense of controllability [see also Fig. 1(d)].

IV. DISCUSSION

This work moves beyond the naïve view that distinct currency metabolites simply regulate distinct functions, instead providing a theoretical basis that quantitatively links the abundances and distributions of multiple currency metabolites to their physiological roles in managing controllability and energetic cost. By developing a minimal model of metabolic currency coupling that does not rely on specific molecules or reactions, we uncover a fundamental tradeoff between the metabolic controllability and the thermodynamic cost: greater controllability of cellular energetic states demands a higher thermodynamic cost, and *vice versa*.

This theory further applies to diverse contexts in both evolution and adaptation. As an evolutionary example, we have argued that metabolic currency coupling could influence the evolutionary trend toward more GC-rich microbes in more complex environments (Fig. 4). Comparisons between insect endosymbionts and their free-living relatives are consistent with this hypothesis: endosymbionts, which inhabit relatively stable host-associated environments, tend to evolve toward lower genomic GC content [Fig. 5(a)]. In particular, the phylogenetic analysis of insect endosymbionts suggests that GC-content reduction can continue even after substantial genome-size reduction has occurred, implying that the reduction in GC content is not merely a by-product of genome reduction [Fig. 5(b)]. This trend was first reported in a previous study (see Fig. 3 of Ref. [47]), while we show that the same trend is recapitulated using an expanded set of insect endosymbionts and a phylogenetic tree inferred by a different procedure [56], suggesting the robustness of this evolutionary trend.

At the level of nongenetic adaptation, our theoretical results could also be experimentally tested by manipulating currency-metabolite pool sizes. For example, adding guanosine, which is converted to GTP through the salvage pathway, can increase intracellular GTP levels [57]. Note here that, although our minimal model assumes a constant coupling strength k_{cpl} for simplicity, parameter values, including k_{cpl} , in reality vary dynamically, depending on enzyme and metabolite abundances or growth conditions. An order-of-magnitude estimation of the parameters in our model suggests that k_{cpl} and $\kappa_{\text{ATP}}^+ / [\text{ATP}]_{\text{tot}}$ are typically of comparable magnitude, both on the order of 10^3 – 10^4 [$\text{M}^{-1} \text{s}^{-1}$] under physiological conditions (see Appendix D for details); this, in turn, implies that both strong and weak currency-coupling regimes can arise in natural cells as well as in experimentally manipulated systems.

For analytical tractability, our model assumes local detailed balance and simple mass-action kinetics for the coupling reaction [Eq. (3)], as well as symmetry between currency metabolites $\Delta\mu_A^\circ = \Delta\mu_B^\circ$. However, our conclusions, including the cost-controllability tradeoff, persist even when we replace mass action by more general reversible enzyme-mediated kinetics (Appendix C1) or allow asymmetric coupling energetics or small dissipation in currency coupling (Appendix C2).

Our minimal model also coarse-grains substrates and anabolic products into a single quantity, $[F_X^+]$, to capture the essence of metabolic currency coupling. This leads to the unrealistic feature that the total EPR vanishes in the case without currency coupling ($k_{\text{cpl}}=0$). In addition, we treat $\kappa_X^\pm$ as constant parameters, reasonably assuming a separation of timescales in which coupling reactions relax sufficiently fast compared to other metabolic processes, particularly the rate-limiting steps in catabolism and anabolism. Such limitations could be resolved by introducing a more detailed and realistic model that incorporates the dynamic change in coupling strength k_{cpl} and distinguishes between catabolism and anabolism, without altering our core findings. For example, the present model can be easily extended to systems with the coupling of $n \geq 3$ currency metabolites, where a similar tradeoff between elasticity and EPR emerges (Appendix E).

The present study introduces the elasticity of the charged/uncharged ratios $e_{XY}^\pm$ [Eq. (7)] as a natural measure of metabolic controllability, based on economic theory [32]. This quantity is also closely related to concepts in metabolic control analysis (MCA) [58–60] (Appendix F). An interesting future direction is to establish further connections between classical MCA theorems and the concepts in our theory and nonequilibrium thermodynamics, particularly system-wide controllability (e_X and e), EPR, and the cost-controllability tradeoff.

The present study theoretically explores the monetary economics of energy metabolism, thereby revealing a key tradeoff between metabolic controllability and thermodynamic cost. Viewing biology through the lens of economics has already yielded valuable insights [61–64], and we anticipate further intersections between cellular metabolism and monetary economics. For example, the economic theory and observation that a new denomination of currency emerges to reduce temporal and spatial “friction” in the economy [65] seems consistent with the recent theory that the redundancy of currency metabolites (coenzymes) facilitates a parsimonious usage of the proteome [15]. We anticipate that further integrating nonequilibrium chemical thermodynamics, systems biology of metabolism, and mathematical economics will uncover universal constraints and design principles governing the economy of cellular metabolism.

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DATA AVAILABILITY

The data that support the findings of this article are openly available [38,41,46,47,50].

APPENDIX A: DERIVATION OF STEADY-STATE PROPERTIES

The steady state of the present model is calculated as

$$\begin{aligned} [A^*]^{\text{st}} &= \frac{k_{\text{cpl}}[A]_{\text{tot}}\kappa_A^+ + k_{\text{cpl}}[B]_{\text{tot}}\kappa_B^+ + \kappa_A^+\kappa_B}{k_{\text{cpl}}[A]_{\text{tot}}\kappa_A + k_{\text{cpl}}[B]_{\text{tot}}\kappa_B + \kappa_A\kappa_B} [A]_{\text{tot}}, \\ [A]^{\text{st}} &= \frac{k_{\text{cpl}}[A]_{\text{tot}}\kappa_A^- + k_{\text{cpl}}[B]_{\text{tot}}\kappa_B^- + \kappa_A^-\kappa_B}{k_{\text{cpl}}[A]_{\text{tot}}\kappa_A + k_{\text{cpl}}[B]_{\text{tot}}\kappa_B + \kappa_A\kappa_B} [A]_{\text{tot}}, \\ [B^*]^{\text{st}} &= \frac{k_{\text{cpl}}[A]_{\text{tot}}\kappa_A^+ + k_{\text{cpl}}[B]_{\text{tot}}\kappa_B^+ + \kappa_A\kappa_B^+}{k_{\text{cpl}}[A]_{\text{tot}}\kappa_A + k_{\text{cpl}}[B]_{\text{tot}}\kappa_B + \kappa_A\kappa_B} [B]_{\text{tot}}, \\ [B]^{\text{st}} &= \frac{k_{\text{cpl}}[A]_{\text{tot}}\kappa_A^- + k_{\text{cpl}}[B]_{\text{tot}}\kappa_B^- + \kappa_A\kappa_B^-}{k_{\text{cpl}}[A]_{\text{tot}}\kappa_A + k_{\text{cpl}}[B]_{\text{tot}}\kappa_B + \kappa_A\kappa_B} [B]_{\text{tot}}. \quad (\text{A1}) \end{aligned}$$

From Eq. (A1), we can calculate the steady-state charged/uncharged ratios of currency metabolites, Γ_A^{st} and Γ_B^{st} [Eq. (4) in the main text]. Equation (4) shows that $\Gamma_X^{\text{st}} := [X^*]^{\text{st}}/[X]^{\text{st}}$ and $1/\Gamma_X^{\text{st}}$ increase linearly with κ_X^+ and κ_X^- , respectively.

The EPR of the driving reaction for currency metabolite $X=A, B$ is given as follows [9]:

$$\begin{aligned} \sigma_X &:= (\kappa_X^- [X^*] - \kappa_X^+ [X]) \log \frac{\kappa_X^- [X^*]}{\kappa_X^+ [X]} \\ &= \frac{[X]_{\text{tot}}\kappa_X^-}{\Gamma_X + 1} (\Gamma_X - \Gamma_X^\kappa) \log \frac{\Gamma_X}{\Gamma_X^\kappa}, \end{aligned}$$

where $\Gamma_X^\kappa := \kappa_X^+/\kappa_X^-$. That is, the entropy production due to the driving reaction for X arises from the difference between the charged/uncharged ratios Γ_X of currency metabolite X and the bias $\Gamma_X^\kappa = \kappa_X^+/\kappa_X^-$ in the effective rate constants of forward and reverse driving reactions.

1. Weak currency coupling limit

In the limit of weak currency coupling ($k_{\text{cpl}} \ll \kappa_X^\pm/[X]_{\text{tot}}$), the present model is reduced to a linear dynamical system. The steady state, Eq. (A1), is then approximated as

$$\begin{aligned} [A^*]^{\text{st}} &\simeq [A]_{\text{tot}} \left[\frac{\kappa_A^+}{\kappa_A} + k_{\text{cpl}} \frac{[B]_{\text{tot}}}{\kappa_A} \left(\frac{\kappa_B^+}{\kappa_B} - \frac{\kappa_A^+}{\kappa_A} \right) \right], \\ [A]^{\text{st}} &\simeq [A]_{\text{tot}} \left[\frac{\kappa_A^-}{\kappa_A} + k_{\text{cpl}} \frac{[B]_{\text{tot}}}{\kappa_A} \left(\frac{\kappa_B^-}{\kappa_B} - \frac{\kappa_A^-}{\kappa_A} \right) \right], \\ [B^*]^{\text{st}} &\simeq [B]_{\text{tot}} \left[\frac{\kappa_B^+}{\kappa_B} + k_{\text{cpl}} \frac{[A]_{\text{tot}}}{\kappa_B} \left(\frac{\kappa_A^+}{\kappa_A} - \frac{\kappa_B^+}{\kappa_B} \right) \right], \\ [B]^{\text{st}} &\simeq [B]_{\text{tot}} \left[\frac{\kappa_B^-}{\kappa_B} + k_{\text{cpl}} \frac{[A]_{\text{tot}}}{\kappa_B} \left(\frac{\kappa_A^-}{\kappa_A} - \frac{\kappa_B^-}{\kappa_B} \right) \right]. \end{aligned}$$

Notably, the leading-order behavior of $[X^*]^{\text{st}}/[X]_{\text{tot}}$ and $[X]^{\text{st}}/[X]_{\text{tot}}$ exhibits no explicit dependence on $[X]_{\text{tot}}$. These are primarily governed by the pool size of the other currency metabolite, $[Y]_{\text{tot}}$ ($Y \neq X$), with the effect of $[X]_{\text{tot}}$ appearing only at second order.

The same holds for the charged/uncharged ratio and self-elasticity: e.g., in the case of currency metabolite B ,

$$\begin{aligned} \Gamma_B^{\text{st}} &\simeq \Gamma_B^\kappa + k_{\text{cpl}}[A]_{\text{tot}} \frac{\Gamma_B^\kappa + 1}{\Gamma_A^\kappa + 1} (\Gamma_A^\kappa - \Gamma_B^\kappa), \\ e_{BB}^\pm &= 1 - k_{\text{cpl}} \frac{[A]_{\text{tot}}\kappa_A^\pm}{\kappa_A\kappa_B^\pm} + O(k_{\text{cpl}}^2). \end{aligned}$$

This indicates that Γ_B^{st} is determined by a balance between the effective rate constants, $\kappa_B^\pm$, of the driving reaction for currency metabolite B and the driving strength, $k_{\text{cpl}}[A]_{\text{tot}}$, of the coupling reaction by the other currency metabolite A .

As a result, σ_i^{st} ($i = A, B, \text{cpl}$) are approximated as

$$\begin{aligned} \sigma_A^{\text{st}} &\simeq k_{\text{cpl}}^2 [A]_{\text{tot}} \frac{\kappa_A^+\kappa_A^-}{\kappa_A} \left[\frac{[B]_{\text{tot}}}{\kappa_B} \left(\frac{\kappa_B^+}{\kappa_A^+} - \frac{\kappa_B^-}{\kappa_A^-} \right) \right]^2, \\ \sigma_B^{\text{st}} &\simeq k_{\text{cpl}}^2 [B]_{\text{tot}} \frac{\kappa_B^+\kappa_B^-}{\kappa_B} \left[\frac{[A]_{\text{tot}}}{\kappa_A} \left(\frac{\kappa_A^+}{\kappa_B^+} - \frac{\kappa_A^-}{\kappa_B^-} \right) \right]^2, \\ \sigma_{\text{cpl}}^{\text{st}} &\simeq k_{\text{cpl}} [A]_{\text{tot}} [B]_{\text{tot}} \frac{\kappa_A^-\kappa_B^+ - \kappa_A^+\kappa_B^-}{\kappa_A\kappa_B} \log \frac{\kappa_A^-\kappa_B^+}{\kappa_A^+\kappa_B^-}. \quad (\text{A2}) \end{aligned}$$

The term in Eq. (A2), $\frac{\kappa_A^-\kappa_B^+ - \kappa_A^+\kappa_B^-}{\kappa_A\kappa_B} \log \frac{\kappa_A^-\kappa_B^+}{\kappa_A^+\kappa_B^-}$, is non-negative and quantifies the extent of asymmetry between the effective rate constants of driving reactions, $\kappa_A^\pm$ and $\kappa_B^\pm$. When normalized by the square of the total currency pool $C_{\text{tot}} := [A]_{\text{tot}} + [B]_{\text{tot}}$, the housekeeping EPR of currency coupling, $\sigma_{\text{cpl}}^{\text{st}}/C_{\text{tot}}^2 \propto k_{\text{cpl}}r/(1+r)^2$ with $r := [A]_{\text{tot}}/[B]_{\text{tot}}$, is maximized at $r = 1$. Note here that the total EPR, defined as $\sigma_{\text{tot}} := \sum_{i=A,B,\text{cpl}} \sigma_i$, satisfies $\sigma_{\text{tot}}^{\text{st}} = \sigma_{\text{cpl}}^{\text{st}} + O(k_{\text{cpl}}^2)$ and is primarily governed by the coupling reaction.

Figure 6 numerically shows that the above approximation (A2) holds well for small k_{cpl} . As k_{cpl} increases, the (scaled) EPR $\sigma_{\text{cpl}}^{\text{st}}/k_{\text{cpl}}$ decreases overall and deviates from Eq. (A2), but it is still maximized at $[A]_{\text{tot}}/[B]_{\text{tot}} = 1$.

2. Strong currency coupling limit

In the limit of strong currency coupling ($k_{\text{cpl}} \gg \kappa_X^\pm/[X]_{\text{tot}}$), the charged/uncharged ratios at the steady state are approximated as

$$\begin{aligned} \Gamma_A^{\text{st}} &= \Gamma_0 + \frac{\kappa_B(\kappa_A^+ - \Gamma_0\kappa_A^-)}{k_{\text{cpl}}([A]_{\text{tot}}\kappa_A^- + [B]_{\text{tot}}\kappa_B^-)} + O(k_{\text{cpl}}^{-2}), \\ \Gamma_B^{\text{st}} &= \Gamma_0 + \frac{\kappa_A(\kappa_B^+ - \Gamma_0\kappa_B^-)}{k_{\text{cpl}}([A]_{\text{tot}}\kappa_A^- + [B]_{\text{tot}}\kappa_B^-)} + O(k_{\text{cpl}}^{-2}). \end{aligned}$$

Accordingly,

$$\begin{aligned} \Gamma_B^{\text{st}} - \Gamma_A^{\text{st}} &\simeq (\kappa_A^-\kappa_B^+ - \kappa_A^+\kappa_B^-) \frac{1 + \Gamma_0}{k_{\text{cpl}}([A]_{\text{tot}}\kappa_A^- + [B]_{\text{tot}}\kappa_B^-)}, \\ \frac{\Gamma_B^{\text{st}}}{\Gamma_A^{\text{st}}} &\simeq 1 + \frac{([A]_{\text{tot}}\kappa_A + [B]_{\text{tot}}\kappa_B)(\kappa_A^-\kappa_B^+ - \kappa_A^+\kappa_B^-)}{k_{\text{cpl}}([A]_{\text{tot}}\kappa_A^+ + [B]_{\text{tot}}\kappa_B^+)([A]_{\text{tot}}\kappa_A^- + [B]_{\text{tot}}\kappa_B^-)}. \end{aligned}$$

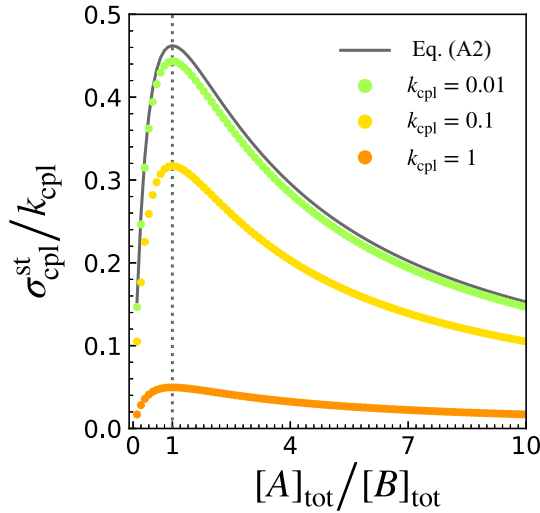


FIG. 6. Dependence of $\sigma_{\text{cpl}}^{\text{st}}/k_{\text{cpl}}$ on the $[A]_{\text{tot}}/[B]_{\text{tot}}$ ratio with relatively weak currency coupling (colored points). The gray curve represents Eq. (A2). For a consistent comparison, the system size is kept constant by setting $C_{\text{tot}} = [A]_{\text{tot}} + [B]_{\text{tot}} = 2$ while varying $[A]_{\text{tot}}/[B]_{\text{tot}}$; parameters are set as $\kappa_A^+ = 2/3$, $\kappa_A^- = 1/3$, $\kappa_B^+ = 1/3$, $\kappa_B^- = 2/3$.

With the definition of $\sigma_{\text{cpl}}^{\text{st}}$, this approximation leads to Eq. (14):

$$\sigma_{\text{cpl}}^{\text{st}} \simeq \frac{1}{k_{\text{cpl}}} \frac{(\kappa_A^- \kappa_B^+ - \kappa_A^+ \kappa_B^-)^2 [A]_{\text{tot}} [B]_{\text{tot}}}{([A]_{\text{tot}} \kappa_A^+ + [B]_{\text{tot}} \kappa_B^+)([A]_{\text{tot}} \kappa_A^- + [B]_{\text{tot}} \kappa_B^-)} \propto \frac{1}{k_{\text{cpl}}} \frac{\frac{[A]_{\text{tot}}}{[B]_{\text{tot}}}}{\left(\frac{[A]_{\text{tot}}}{[B]_{\text{tot}}} \kappa_A^+ + \kappa_B^+\right) \left(\frac{[A]_{\text{tot}}}{[B]_{\text{tot}}} \kappa_A^- + \kappa_B^-\right)}. \quad (\text{A3})$$

Moreover, from Eqs. (A3) and (10), $\sigma_{\text{cpl}}^{\text{st}}$ and $\tilde{\epsilon}_X$ are related as

$$\sigma_{\text{cpl}}^{\text{st}} \simeq \frac{(\kappa_A^- \kappa_B^+ - \kappa_A^+ \kappa_B^-)^2}{k_{\text{cpl}} \sqrt{\kappa_A^+ \kappa_A^- \kappa_B^+ \kappa_B^-}} \sqrt{\tilde{\epsilon}_A^+ \tilde{\epsilon}_A^-} \sqrt{\tilde{\epsilon}_B^+ \tilde{\epsilon}_B^-} \quad (\text{A4})$$

which leads to Eq. (15). This equation reveals a tradeoff: higher (lower) approximate elasticities are associated with larger (smaller) EPR. Given the constraint that the elasticities satisfy $\tilde{\epsilon}_A^+ + \tilde{\epsilon}_B^+ = 1$, the geometric mean $\tilde{\epsilon}_A \tilde{\epsilon}_B$ of the elasticities becomes larger when the elasticities $\tilde{\epsilon}_X$ are evenly distributed.

3. Tradeoff inequality

We here prove the inequality (16).

As $e = (e_{AA}^+ e_{AA}^- e_{BB}^+ e_{BB}^-)^{1/4} \geq (\tilde{\epsilon}_A^+ \tilde{\epsilon}_A^- \tilde{\epsilon}_B^+ \tilde{\epsilon}_B^-)^{1/4}$ holds from Eq. (10), the left-hand side of Eq. (16) satisfies

$$\begin{aligned} & \frac{(\kappa_A^- \kappa_B^+ - \kappa_A^+ \kappa_B^-)^2}{k_{\text{cpl}} \sqrt{\kappa_A^+ \kappa_A^- \kappa_B^+ \kappa_B^-}} e^2 \\ & \geq \frac{(\kappa_A^- \kappa_B^+ - \kappa_A^+ \kappa_B^-)^2}{k_{\text{cpl}} \sqrt{\kappa_A^+ \kappa_A^- \kappa_B^+ \kappa_B^-}} \sqrt{\tilde{\epsilon}_A^+ \tilde{\epsilon}_A^-} \sqrt{\tilde{\epsilon}_B^+ \tilde{\epsilon}_B^-} \\ & = \frac{[A]_{\text{tot}} [B]_{\text{tot}} (\kappa_A^- \kappa_B^+ - \kappa_A^+ \kappa_B^-)^2}{k_{\text{cpl}} ([A]_{\text{tot}} \kappa_A^+ + [B]_{\text{tot}} \kappa_B^+) ([A]_{\text{tot}} \kappa_A^- + [B]_{\text{tot}} \kappa_B^-)}. \quad (\text{A5}) \end{aligned}$$

Also, from $\log x \leq x - 1$, the right-hand side of Eq. (16) satisfies

$$\begin{aligned} \sigma_{\text{cpl}}^{\text{st}} &= k_{\text{cpl}} [A]_{\text{tot}} [B]_{\text{tot}} \frac{\Gamma_B^{\text{st}} - \Gamma_A^{\text{st}}}{(\Gamma_A^{\text{st}} + 1)(\Gamma_B^{\text{st}} + 1)} \log \frac{\Gamma_B^{\text{st}}}{\Gamma_A^{\text{st}}} \\ &\leq k_{\text{cpl}} [A]_{\text{tot}} [B]_{\text{tot}} \frac{\Gamma_B^{\text{st}} - \Gamma_A^{\text{st}}}{(\Gamma_A^{\text{st}} + 1)(\Gamma_B^{\text{st}} + 1)} \left(\frac{\Gamma_B^{\text{st}}}{\Gamma_A^{\text{st}}} - 1 \right) \\ &= k_{\text{cpl}} [A]_{\text{tot}} [B]_{\text{tot}} \frac{(\Gamma_B^{\text{st}} - \Gamma_A^{\text{st}})^2}{\Gamma_A^{\text{st}} (\Gamma_A^{\text{st}} + 1) (\Gamma_B^{\text{st}} + 1)}. \quad (\text{A6}) \end{aligned}$$

Noting that

$$\begin{aligned} \Gamma_B^{\text{st}} - \Gamma_A^{\text{st}} &= \frac{(\kappa_A^- \kappa_B^+ - \kappa_A^+ \kappa_B^-)}{(k_{\text{cpl}} [A]_{\text{tot}} \kappa_A^- + k_{\text{cpl}} [B]_{\text{tot}} \kappa_B^- + \kappa_A^- \kappa_B^-)} \\ &\quad \times \frac{(k_{\text{cpl}} [A]_{\text{tot}} \kappa_A^+ + k_{\text{cpl}} [B]_{\text{tot}} \kappa_B^+ + \kappa_A^+ \kappa_B^+)}{(k_{\text{cpl}} [A]_{\text{tot}} \kappa_A^- + k_{\text{cpl}} [B]_{\text{tot}} \kappa_B^- + \kappa_A^- \kappa_B^-)}, \quad (\text{A7}) \end{aligned}$$

it is sufficient to prove

$$\begin{aligned} & \frac{1}{k_{\text{cpl}}^2 ([A]_{\text{tot}} \kappa_A^+ + [B]_{\text{tot}} \kappa_B^+) ([A]_{\text{tot}} \kappa_A^- + [B]_{\text{tot}} \kappa_B^-)} \\ & \geq \frac{1}{(k_{\text{cpl}} [A]_{\text{tot}} \kappa_A^+ + k_{\text{cpl}} [B]_{\text{tot}} \kappa_B^+ + \kappa_A^+ \kappa_B^+)} \\ & \quad \times \frac{1}{(k_{\text{cpl}} [A]_{\text{tot}} \kappa_A^- + k_{\text{cpl}} [B]_{\text{tot}} \kappa_B^- + \kappa_A^- \kappa_B^-)}. \quad (\text{A8}) \end{aligned}$$

As Eq. (A8) is evident, we obtain Eq. (16).

4. Bounds on Γ_X modulation range

In addition to controllability in terms of elasticity, the achievable ranges of the charged/uncharged ratios Γ_X^{st} are fundamentally constrained by finite driving strength, $\kappa_X^{\pm}$. If the total driving strength $\kappa_X = \kappa_X^+ + \kappa_X^-$ has an upper bound κ_X^{max} , Γ_X^{st} is bounded as $\Gamma_X^{\text{max}} \geq \Gamma_X^{\text{st}} \geq \Gamma_X^{\text{min}}$ with

$$\begin{aligned} \Gamma_X^{\text{max}} &= \frac{\kappa_Y^+}{\kappa_Y^-} + \frac{k_{\text{cpl}} [X]_{\text{tot}} + \kappa_Y}{k_{\text{cpl}} [Y]_{\text{tot}} \kappa_Y^-} \kappa_X^{\text{max}}, \\ \Gamma_X^{\text{min}} &= \left(\frac{\kappa_Y^-}{\kappa_Y^+} + \frac{k_{\text{cpl}} [X]_{\text{tot}} + \kappa_Y}{k_{\text{cpl}} [Y]_{\text{tot}} \kappa_Y^+} \kappa_X^{\text{max}} \right)^{-1} \quad (Y \neq X). \end{aligned}$$

These upper and lower bounds are governed by the relative magnitudes of $[X]_{\text{tot}} \kappa_X^{\pm}$ and $[Y]_{\text{tot}} \kappa_Y^{\pm}$. When the currency metabolite pools are imbalanced ($[A]_{\text{tot}} \gg [B]_{\text{tot}}$), the charged/uncharged ratio Γ_B^{st} of the less abundant currency metabolite B is confined to a narrower range $\Gamma_B^{\text{max}}/\Gamma_B^{\text{min}}$ (Fig. 7), matching the trend observed in the elasticities.

Therefore, to achieve the wide range of charged/uncharged ratios observed *in vivo*, cells must regulate not only the bias κ_X^+/κ_X^- of the driving reactions for currency metabolite X but also the pool sizes $[X]_{\text{tot}}$ of currency metabolites.

APPENDIX B: CORRELATION BETWEEN THE INTRACELLULAR ATP/GTP RATIO AND GC CONTENT

The intracellular concentration $[NTP]$ of NTPs (i.e., ATP and GTP) is determined by the balance between their

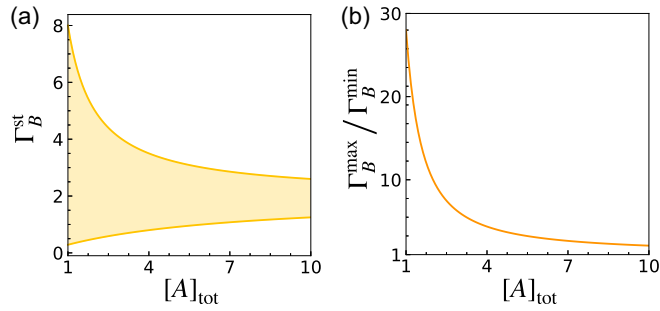


FIG. 7. Dependence of (a) the Γ_B^{st} modulation range, $[\Gamma_B^{\text{min}}, \Gamma_B^{\text{max}}]$, and (b) its width, $\Gamma_B^{\text{max}} / \Gamma_B^{\text{min}}$, on $[A]_{\text{tot}}$. $\kappa_B = 1$, $k_{\text{cpl}} = 1$, and $[B]_{\text{tot}} = 1$ are fixed.

production flux P_{NTP} and their conversion and dilution:

$$\frac{d}{dt}[\text{NTP}] = P_{\text{NTP}} - k_{\text{NTP}}[\text{NTP}].$$

Then, their steady-state concentration is

$$[\text{NTP}]^{\text{st}} = \frac{P_{\text{NTP}}}{k_{\text{NTP}}}.$$

One might reasonably expect the production flux of guanine nucleotides, including GTP, to increase with genomic GC content, as indirectly supported by experimental evidence [55]. We therefore assume that the production fluxes of ATP and GTP, P_{ATP} and P_{GTP} , positively correlate with the genomic AT and GC contents, respectively.

Furthermore, if P_{NTP} is decomposed into the flux used for RNA incorporation and that for *de novo* synthesis for currency metabolites, it is natural to assume that only the former is proportional to AT or GC content. Nevertheless, because the pool of free NTPs derived from RNA turnover can greatly exceed that from *de novo* synthesis, P_{ATP} and P_{GTP} are still expected to correlate positively with AT and GC content, respectively. According to Ref. [54], the weight of RNA per cell is about 60 fg, and thus that of ATP or GTP is about 15 fg. In contrast, the intracellular concentrations of ATP and GTP are about 3 and 1 mM, respectively [66–68]; because the molecular weights of ATP and GTP are 507 and 523 g/mol and the volume of a microbe such as *E. coli* is about $1 \mu\text{m}^3$,

the weights of (free) ATP and GTP are about 1.5 and 0.5 fg, respectively. That is, the intracellular amount of guanine molecules for RNA is more than an order of magnitude larger than the free intracellular GTP pool.

In contrast to the above causal direction, in which GC content influences NTP pool sizes, it has also been suggested that the GTP pool size [26] as well as the abundance of resources required for DNA/RNA synthesis, such as nitrogen sources [69], can bias genome GC content. In any case, some correlation between NTP pool sizes as currency metabolites and genomic GC content is expected.

APPENDIX C: ROBUSTNESS OF THE COST-CONTROLLABILITY TRADEOFF IN GENERALIZED CURRENCY COUPLING

1. Ping-pong bi-bi mechanism in currency coupling

In the main text, we assumed the mass-action kinetics for the coupling reaction: i.e., $J_{\text{cpl}} = k_{\text{cpl}}([A][B^*] - [A^*][B])$. This corresponds to an ideal-dilute, unsaturated approximation for the coarse-grained coupling reaction.

In general, this assumption is not necessarily realistic. For example, nucleoside diphosphate kinase (NDPK) catalyzes the coupling of NTPs via the so-called ping-pong bi-bi mechanism [70]. In this case, a more realistic functional form for J_{cpl} is represented as [71,72]

$$J_{\text{cpl}} = k_{\text{cpl}}([A][B^*] - [A^*][B]) / \left(\frac{[A]}{K_A} + \frac{[B^*]}{K_{B^*}} + \frac{[A][B^*]}{K_A K_{B^*}} + \frac{[A^*]}{K_{A^*}} + \frac{[B]}{K_B} + \frac{[A^*][B]}{K_{A^*} K_B} + \frac{[A][A^*]}{K_A K_{A^*}} + \frac{[B^*][B]}{K_{B^*} K_B} \right), \quad (\text{C1})$$

with parameters K_X and K_{X^*} ($X = A, B$).

Even with this more general reaction kinetics, the main results remain qualitatively unchanged, and the numerical calculations still exhibit a cost-controllability tradeoff (Fig. 8).

2. Stoichiometry mismatch and dissipation

In the main text, for simplicity, we assumed $\Delta\mu_A^{\circ} = \Delta\mu_B^{\circ}$, so that $k_{\text{cpl}}^+ = k_{\text{cpl}}^-$, and we considered a 1:1 coupling

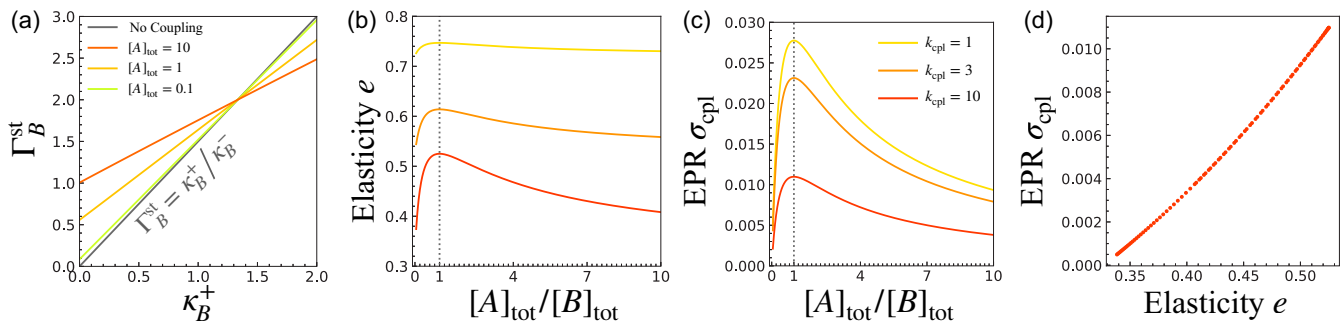


FIG. 8. Cost-controllability tradeoff in metabolic currency coupling with a ping-pong bi-bi mechanism: $J_{\text{cpl}} = k_{\text{cpl}} \frac{[A][B^*] - [A^*][B]}{[A][B^*] + [A][B] + [A^*][B] + [A^*][B^*] + [A][A^*] + [B][B^*] + [A][A^*][B] + [A^*][B][B^*]}$, where parameters in Eq. (C1), K_X and K_{X^*} , are set as unity. (a) Dependence of Γ_B^{st} on κ_B^+ . $[B]_{\text{tot}} = 1$, $k_{\text{cpl}} = 10$. (b) Dependence of mean elasticity e on $[A]_{\text{tot}}/[B]_{\text{tot}}$. (c) Dependence of EPR $\sigma_{\text{cpl}}^{\text{st}}$ on $[A]_{\text{tot}}/[B]_{\text{tot}}$. (d) Relationship between mean elasticity e and EPR $\sigma_{\text{cpl}}^{\text{st}}$. $k_{\text{cpl}} = 10$. In (b)–(d), $[A]_{\text{tot}} + [B]_{\text{tot}} = 1$ and $\kappa_B^+ = 1/3$ are fixed. In (a)–(d), the other parameters are set as $\kappa_A^+ = 2/3$, $\kappa_A^- = 1/3$, and $\kappa_B^- = 2/3$.

reaction in the form of $A + B^* \rightleftharpoons A^* + B$. These assumptions are reasonable for coupling within the same group of currencies, such as among NTPs or between NADPH and NADH. However, they do not necessarily hold for other currency couplings, including the electron transport chain (ETC), where the ATP/ADP and NADH/NAD couples are linked, and coupling between ATP/ADP and ADP/AMP.

Nevertheless, our main conclusions remain essentially unchanged for the more general case with $\Delta\mu_A^\circ \neq \Delta\mu_B^\circ$ and a stoichiometric exchange $\nu A + B^* \rightleftharpoons \nu A^* + B$. In this case, assuming the local detailed balance condition, the coupling rate constants satisfy

$$k_{\text{cpl}}^+ = k_{\text{cpl}}^- \exp\left(\frac{\Delta\mu_B^\circ - \nu\Delta\mu_A^\circ}{RT}\right), \quad (\text{C2})$$

where R is the gas constant and T is the temperature. The dynamics can then be written as

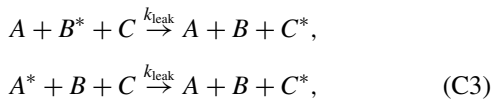
$$\begin{aligned} \frac{d}{dt}[A] &= -\nu(k_{\text{cpl}}^+[A][B^*] - k_{\text{cpl}}^-[A^*][B]) - \kappa_A^+[A] + \kappa_A^-[A^*], \\ \frac{d}{dt}[A^*] &= \nu(k_{\text{cpl}}^+[A][B^*] - k_{\text{cpl}}^-[A^*][B]) + \kappa_A^+[A] - \kappa_A^-[A^*], \\ \frac{d}{dt}[B] &= (k_{\text{cpl}}^+[A][B^*] - k_{\text{cpl}}^-[A^*][B]) - \kappa_B^+[B] + \kappa_B^-[B^*], \\ \frac{d}{dt}[B^*] &= -(k_{\text{cpl}}^+[A][B^*] - k_{\text{cpl}}^-[A^*][B]) + \kappa_B^+[B] - \kappa_B^-[B^*]. \end{aligned}$$

At steady state, this stoichiometry effectively rescales the driving reactions for currency metabolite A as $\kappa_A^\pm \rightarrow \kappa_A^\pm/\nu$. Aside from this rescaling and $k_{\text{cpl}}^+ \neq k_{\text{cpl}}^-$, the results in the main text remain unchanged.

Case with free-energy dissipation in the coupling reaction

In ETC-like settings, the proton-motive force is dissipated, and consequently the effective coupling between redox currencies (e.g., NADH/NAD) and phosphorylation currencies (ATP/ADP) can vary, even for the same amount of NADH oxidized. In such situations, the coupling step cannot be treated as microscopically reversible in isolation, and the local-detailed-balance condition Eq. (C2) need not apply directly at the coarse-grained level.

To incorporate such dissipation, we can additionally consider “leakage reactions” that effectively decrease the conversion stoichiometry in the coupling reactions between A and B :



where, for simplicity, we assume the concentrations of C and C^* are chemostated and denote the effective leakage rate constant by k_{leak} . Then, by assuming mass-action kinetics, $d := k_{\text{leak}}[C]/(k_{\text{leak}}[C] + k_{\text{cpl}})$ ($0 < d < 1$) parametrizes the degree of dissipation in the coupling reaction $A + B^* \rightleftharpoons A^* + B$. The resulting dynamics are

$$\begin{aligned} \frac{d}{dt}[A] &= -k_{\text{cpl}}[A][B^*] + \frac{1}{1-d}k_{\text{cpl}}[A^*][B] - \kappa_A^+[A] + \kappa_A^-[A^*], \\ \frac{d}{dt}[A^*] &= k_{\text{cpl}}[A][B^*] - \frac{1}{1-d}k_{\text{cpl}}[A^*][B] + \kappa_A^+[A] - \kappa_A^-[A^*], \end{aligned}$$

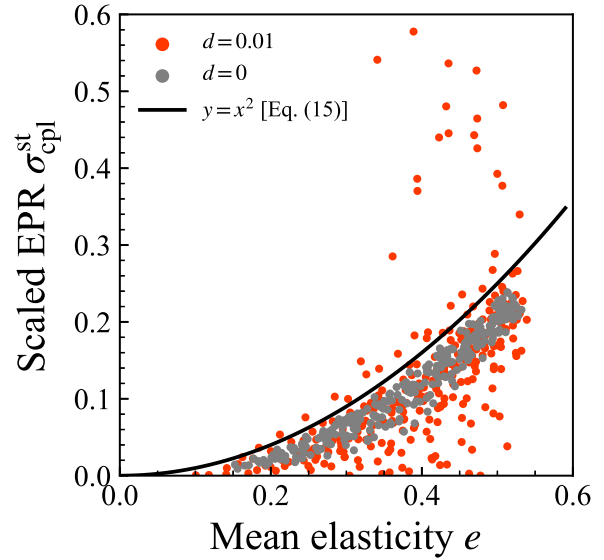


FIG. 9. Thermodynamic cost-controllability tradeoff with dissipation in currency coupling. The scaled EPR of the coupling reaction, $\frac{k_{\text{cpl}}\sqrt{\kappa_A^+\kappa_A^-\kappa_B^+\kappa_B^-}}{(\kappa_A^+\kappa_B^+ - \kappa_A^-\kappa_B^-)^2}\sigma_{\text{cpl}}^{\text{st}}$, is plotted against mean elasticity e for the dissipative case (orange; $d = 0.01$) and the nondissipative case [gray; $d = 0$; see also Fig. 3(b)]. The parameters $\kappa_X^\pm$ and $[X]_{\text{tot}}$ are randomly sampled from a uniform distribution within the range $[0, 1]$. $k_{\text{cpl}} = 10$. The black curve represents the strong coupling limit without dissipation, Eq. (15).

$$\begin{aligned} \frac{d}{dt}[B] &= \frac{1}{1-d}k_{\text{cpl}}[A][B^*] - k_{\text{cpl}}[A^*][B] - \kappa_B^+[B] + \kappa_B^-[B^*], \\ \frac{d}{dt}[B^*] &= -\frac{1}{1-d}k_{\text{cpl}}[A][B^*] + k_{\text{cpl}}[A^*][B] + \kappa_B^+[B] - \kappa_B^-[B^*]. \end{aligned}$$

Accordingly, the coupling reaction consumes $\frac{1}{1-d} (> 1)$ units of A^* to obtain 1 unit of B^* , and *vice versa*. Even in this dissipative case, as long as d is sufficiently small, the cost-controllability tradeoff qualitatively holds (Fig. 9).

APPENDIX D: ORDER ESTIMATION OF MODEL PARAMETER VALUES

It is thought that cells generally maintain substantial levels of enzymes responsible for metabolic currency coupling. NDPK, for example, is considered a housekeeping enzyme that is constitutively expressed in many types of cells to maintain nucleotide homeostasis [73].

To evaluate the biological relevance of our theory, particularly the controllability-EPR tradeoff relationship, we estimate typical values of relevant parameters and variables, using ATP-GTP coupling as an example (summarized in Table II).

1. Effective rate constant of the driving reaction

The total ATP synthesis flux in a microbe is estimated as [68]

$$\kappa_{\text{ATP}}^+[\text{ADP}] \simeq 10^{-2} [\text{M s}^{-1}],$$

TABLE II. Order estimation in the case of ATP-GTP coupling.

Symbol	Description	Estimated value	Refs.
$[\text{ATP}]_{\text{tot}}$	Pool size of ATP	1–5 (mM)	[66–68,74]
$[\text{GTP}]_{\text{tot}}$	Pool size of GTP	0.1–1 (mM)	[66–68]
k_{cpl}	Rate constant for the coupling reaction	$\sim 10^4$ ($\text{M}^{-1} \text{s}^{-1}$)	[75–77]
$\kappa_{\text{ATP}}^{\pm}$	Effective rate constant for the driving reaction $\text{ADP} \rightleftharpoons \text{ATP}$	$\sim 10^1$ (s^{-1})	[68,74]
Γ_{ATP}	$[\text{ATP}]/[\text{ADP}]$ ratio	1– 10^2	[80,81]
Γ_{GTP}	$[\text{GTP}]/[\text{GDP}]$ ratio	1– 10^2	[80,82]
r	$[\text{ATP}]_{\text{tot}}/[\text{GTP}]_{\text{tot}}$ ratio	1–10	[66]

and the intracellular ADP concentration in *E. coli* is measured as [74]

$$[\text{ADP}] \simeq 10^{-3} [\text{M}].$$

Therefore, the effective rate constant for the driving reaction, $\text{ADP} \leftrightarrow \text{ATP}$, should be estimated as

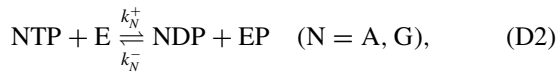
$$\kappa_{\text{ATP}}^+ \simeq 10^1 [\text{s}^{-1}].$$

Given that $[\text{ATP}]_{\text{tot}} \simeq 3 \times 10^{-3} [\text{M}]$ [74],

$$\kappa_{\text{ATP}}^+ / [\text{ATP}]_{\text{tot}} \simeq 10^3\text{--}10^4 [\text{M}^{-1} \text{s}^{-1}]. \quad (\text{D1})$$

2. Coupling constant k_{cpl} in the ping-pong mechanism

NDPK catalyzes the following reactions:



in the case of ATP-GTP coupling. Through this ping-pong mechanism, the charged/uncharged ratios, Γ_{ATP} and Γ_{GTP} , are driven toward equilibrium, providing an effective coupling between them.

Assuming that reaction (D2) follows mass-action kinetics, the steady-state concentrations of E and EP are calculated as

$$[\text{E}]^{\text{st}} = \frac{k_A[\text{ADP}] + k_G[\text{GDP}]}{k_A[\text{ATP}]_{\text{tot}} + k_G[\text{GTP}]_{\text{tot}}} E_{\text{tot}},$$

$$[\text{EP}]^{\text{st}} = \frac{k_A[\text{ATP}] + k_G[\text{GTP}]}{k_A[\text{ATP}]_{\text{tot}} + k_G[\text{GTP}]_{\text{tot}}} E_{\text{tot}},$$

where E_{tot} denotes the total amount of NDPK, and we assume $k_N := k_N^+ = k_N^-$.

Accordingly, we obtain the following dynamics of $[\text{ATP}]$:

$$\begin{aligned} \frac{d}{dt}[\text{ATP}] &= k_A[\text{ADP}][\text{EP}]^{\text{st}} - k_A[\text{ATP}][\text{E}]^{\text{st}} \\ &\quad + \kappa_A^+[\text{ADP}] - \kappa_A^-[\text{ATP}] \\ &= k_A E_{\text{tot}} \frac{k_G[\text{ADP}][\text{GTP}] - k_G[\text{ATP}][\text{GDP}]}{k_A[\text{ATP}]_{\text{tot}} + k_G[\text{GTP}]_{\text{tot}}} \\ &\quad + \kappa_A^+[\text{ADP}] - \kappa_A^-[\text{ATP}]. \end{aligned}$$

It follows that

$$k_{\text{cpl}} = \frac{k_A k_G E_{\text{tot}}}{k_A[\text{ATP}]_{\text{tot}} + k_G[\text{GTP}]_{\text{tot}}}. \quad (\text{D3})$$

From Refs. [75–77],

$$\begin{aligned} k_{\text{cat}} &\simeq 10^3 [\text{s}^{-1}], \\ K_{\text{M,ATP}} &\simeq 10^{-4}\text{--}10^{-3} [\text{M}], \end{aligned}$$

$$K_{\text{M,GDP}} \simeq 10^{-4} [\text{M}],$$

$$E_{\text{tot}} \simeq 10^{-6} [\text{M}],$$

and thus,

$$k_N \simeq k_{\text{cat}}/K_{\text{M,N}} \simeq 10^6\text{--}10^7 [\text{M}^{-1} \text{s}^{-1}]. \quad (\text{D4})$$

This is consistent with Ref. [78], which states that the second-order rate constants k_N for phosphorylation by natural NTPs are in the range $(0.7\text{--}13) \times 10^6 [\text{M}^{-1} \text{s}^{-1}]$.

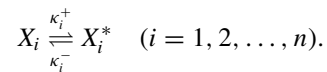
Finally, from Eq. (D3),

$$k_{\text{cpl}} \simeq 10^3\text{--}10^4 [\text{M}^{-1} \text{s}^{-1}]. \quad (\text{D5})$$

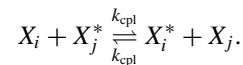
From Eqs. (D1) and (D5), k_{cpl} and $\kappa_{\text{ATP}}^+ / [\text{ATP}]_{\text{tot}}$ are typically in the same order of magnitude, while they depend largely on the amount of enzymes and the growth conditions. This order-of-magnitude estimation suggests that k_{cpl} and $\kappa_{\text{ATP}}^+ / [\text{ATP}]_{\text{tot}}$ are of comparable magnitude for typical NDPK concentrations, implying that both strong ($k_{\text{cpl}} \gg \kappa_{\text{ATP}}^+ / [\text{ATP}]_{\text{tot}}$) and weak ($k_{\text{cpl}} \ll \kappa_{\text{ATP}}^+ / [\text{ATP}]_{\text{tot}}$) currency coupling may occur in natural microbial systems. In particular, under nutrient-limited conditions, the strong coupling limit will be more likely.

APPENDIX E: COUPLING OF $n \geq 3$ CURRENCY METABOLITES

As an extension of the minimal model discussed in the main text, we consider a system with $n \geq 3$ currency metabolites, X_i ($i = 1, 2, \dots, n$). Each metabolite X_i is driven by a reaction with effective rate constants $\kappa_i^{\pm}$:



These currency metabolites are also assumed to be coupled through exchange reactions of the form [79]



Assuming mass-action kinetics, the rate equation is given by

$$\begin{aligned} [\dot{X}_i^*] &= \kappa_i^+ [X_i] - \kappa_i^- [X_i^*] + \sum_{i \neq j} k_{\text{cpl}} ([X_i][X_j^*] - [X_i^*][X_j]) \\ &= \kappa_i^+ [X_i]_{\text{tot}} - \kappa_i^- [X_i^*] \\ &\quad + \sum_{j \neq i} k_{\text{cpl}} ([X_i]_{\text{tot}} [X_j^*] - [X_i^*] [X_j]_{\text{tot}}), \end{aligned} \quad (\text{E1})$$

where $\kappa_i := \kappa_i^+ + \kappa_i^-$ ($i = 1, 2, \dots, n$).

1. Steady state

From Eq. (E1), the steady state $[X_i^*]^{\text{st}}$ satisfies

$$(\mathbf{D} + \mathbf{R})[\mathbf{X}^*]^{\text{st}} = \{\kappa_i^+ [X_i]_{\text{tot}}\}_i,$$

where a diagonal matrix $\mathbf{D}$ and a rank-1 matrix $\mathbf{R}$ are defined as

$$\mathbf{D} := \text{diag}(\kappa_i + k_{\text{cpl}} C_{\text{tot}})_i, \quad \mathbf{R} := -\{k_{\text{cpl}} [X_i]_{\text{tot}}\}_i \cdot \mathbf{1}^\top,$$

with $C_{\text{tot}} := \sum_j [X_j]_{\text{tot}}$.

Therefore, we have

$$[\mathbf{X}^*]^{\text{st}} = (\mathbf{D} + \mathbf{R})^{-1} \{\kappa_i^+ [X_i]_{\text{tot}}\}_i.$$

Here, the inverse can be evaluated using the matrix inversion lemma (Woodbury matrix identity):

$$\begin{aligned} (\mathbf{D} + \mathbf{R})^{-1} &= \mathbf{D}^{-1} + \mathbf{D}^{-1} \{k_{\text{cpl}} [X_i]_{\text{tot}}\}_i (1 - \mathbf{1}^\top \mathbf{D}^{-1} \{k_{\text{cpl}} [X_i]_{\text{tot}}\}_i)^{-1} \mathbf{1}^\top \mathbf{D}^{-1}. \end{aligned}$$

Accordingly, we obtain

$$\begin{aligned} [X_i^*]^{\text{st}} &= \frac{[X_i]_{\text{tot}}}{\kappa_i + k_{\text{cpl}} C_{\text{tot}}} \left(\kappa_i^+ + k_{\text{cpl}} \frac{\sum_j \frac{\kappa_j^+ [X_j]_{\text{tot}}}{\kappa_j + k_{\text{cpl}} C_{\text{tot}}}}{1 - \sum_j \frac{k_{\text{cpl}} [X_j]_{\text{tot}}}{\kappa_j + k_{\text{cpl}} C_{\text{tot}}}} \right), \\ [X_i]^{\text{st}} &= \frac{[X_i]_{\text{tot}}}{\kappa_i + k_{\text{cpl}} C_{\text{tot}}} \left(\kappa_i^- + k_{\text{cpl}} \frac{\sum_j \frac{\kappa_j^- [X_j]_{\text{tot}}}{\kappa_j + k_{\text{cpl}} C_{\text{tot}}}}{1 - \sum_j \frac{k_{\text{cpl}} [X_j]_{\text{tot}}}{\kappa_j + k_{\text{cpl}} C_{\text{tot}}}} \right), \\ \Gamma_i^{\text{st}} &:= \frac{[X_i^*]^{\text{st}}}{[X_i]^{\text{st}}} = \frac{\kappa_i^+ + k_{\text{cpl}} \sum_{j \neq i} \frac{(\kappa_j^+ - \kappa_i^+) [X_j]_{\text{tot}}}{\kappa_j + k_{\text{cpl}} C_{\text{tot}}}}{\kappa_i^- + k_{\text{cpl}} \sum_{j \neq i} \frac{(\kappa_j^- - \kappa_i^-) [X_j]_{\text{tot}}}{\kappa_j + k_{\text{cpl}} C_{\text{tot}}}}. \end{aligned} \quad (\text{E2})$$

In the strong coupling limit,

$$\begin{aligned} \Gamma_i^{\text{st}} &= \Gamma_0 + k_{\text{cpl}}^{-1} \frac{\sum_{j \neq i} \kappa_j [X_j]_{\text{tot}} [(\kappa_i^+ - \kappa_j^+) - \Gamma_0 (\kappa_i^- - \kappa_j^-)]}{C_{\text{tot}} \sum_j [X_j]_{\text{tot}} \kappa_j^-} \\ &\quad + O(k_{\text{cpl}}^{-2}), \end{aligned} \quad (\text{E3})$$

with

$$\Gamma_0 := \frac{\sum_j [X_j]_{\text{tot}} \kappa_j^+}{\sum_j [X_j]_{\text{tot}} \kappa_j^-}.$$

2. Elasticity

The dimensionless elasticity is defined as

$$e_{ij}^\pm := \pm \frac{\partial \log \Gamma_i^{\text{st}}}{\partial \log \kappa_j^\pm}.$$

Then,

$$\begin{aligned} e_{ii}^\pm &= 1 - \frac{k_{\text{cpl}} \sum_{l \neq i} \frac{\kappa_l^\pm [X_l]_{\text{tot}}}{\kappa_l + k_{\text{cpl}} C_{\text{tot}}}}{\kappa_i^\pm + k_{\text{cpl}} \sum_{l \neq i} \frac{(\kappa_l^\pm - \kappa_i^\pm) [X_l]_{\text{tot}}}{\kappa_l + k_{\text{cpl}} C_{\text{tot}}}}, \\ e_{ij}^\pm &= \frac{k_{\text{cpl}} \frac{\kappa_j^\pm [X_j]_{\text{tot}}}{\kappa_j + k_{\text{cpl}} C_{\text{tot}}}}{\kappa_i^\pm + k_{\text{cpl}} \sum_{l \neq i} \frac{(\kappa_l^\pm - \kappa_i^\pm) [X_l]_{\text{tot}}}{\kappa_l + k_{\text{cpl}} C_{\text{tot}}}} \quad (j \neq i). \end{aligned}$$

Accordingly, $\sum_j e_{ij}^\pm = 1$.

In the strong coupling limit,

$$e_{ij}^\pm \rightarrow \tilde{e}_j := \frac{[X_j]_{\text{tot}} \kappa_j^\pm}{\sum_l [X_l]_{\text{tot}} \kappa_l^\pm}.$$

3. EPR and tradeoff

The EPR of all coupling reactions is given by

$$\begin{aligned} \sigma_{\text{cpl}}^{(n)} &:= \sum_{i>j} \sigma_{(i,j)}^{\text{st}} \\ &= \sum_{i>j} k_{\text{cpl}} [X_i]_{\text{tot}} [X_j]_{\text{tot}} \frac{\Gamma_i^{\text{st}} - \Gamma_j^{\text{st}}}{(\Gamma_i^{\text{st}} + 1)(\Gamma_j^{\text{st}} + 1)} \log \frac{\Gamma_i^{\text{st}}}{\Gamma_j^{\text{st}}}. \end{aligned}$$

From Eq. (E3), in the strong coupling limit, each $\sigma_{(i,j)}^{\text{st}}$ can be approximated as

$$\begin{aligned} \sigma_{(i,j)}^{\text{st}} &\simeq \frac{k_{\text{cpl}}^{-1} [X_i]_{\text{tot}} [X_j]_{\text{tot}}}{(1 + \Gamma_0)^2 \Gamma_0} \left(\left. \frac{d\Gamma_i^{\text{st}}}{d\kappa_{\text{cpl}}^{-1}} \right|_{\kappa_{\text{cpl}}^{-1} \rightarrow 0} - \left. \frac{d\Gamma_j^{\text{st}}}{d\kappa_{\text{cpl}}^{-1}} \right|_{\kappa_{\text{cpl}}^{-1} \rightarrow 0} \right)^2 \\ &= \frac{[X_i]_{\text{tot}} [X_j]_{\text{tot}}}{k_{\text{cpl}} (\sum_l [X_l]_{\text{tot}} \kappa_l^+) (\sum_l [X_l]_{\text{tot}} \kappa_l^-)} \\ &\quad \times \left(\frac{\sum_l [X_l]_{\text{tot}} [(\kappa_l^+ - \kappa_j^+) \kappa_l^- - (\kappa_i^- - \kappa_j^-) \kappa_l^+]}{C_{\text{tot}}} \right)^2. \end{aligned}$$

That is,

$$\sigma_{(i,j)}^{\text{st}} \simeq \frac{[(\kappa_i^+ - \kappa_j^+) \kappa_l^- - (\kappa_i^- - \kappa_j^-) \kappa_l^+]^2}{k_{\text{cpl}} \sqrt{\kappa_i^+ \kappa_i^-} \sqrt{\kappa_j^+ \kappa_j^-}} \sqrt{\tilde{e}_i^+ \tilde{e}_i^-} \sqrt{\tilde{e}_j^+ \tilde{e}_j^-}, \quad (\text{E4})$$

where $\bar{\kappa}^\pm := (\sum_l [X_l]_{\text{tot}} \kappa_l^\pm) / (\sum_l [X_l]_{\text{tot}})$ is the average effective rate constant of all driving reactions. Therefore, a tradeoff between the EPR $\sigma_{\text{cpl}}^{(n)}$ and elasticity in the strong coupling limit [analogous to Eq. (15)] still holds, although it is biased by the driving reactions for currency metabolites other than X_i and X_j .

Noting the constraint $\sum_i \tilde{e}_i^\pm = 1$, Eq. (E4) implies that distributing the elasticities $\tilde{e}_i^\pm$ more evenly among the currency metabolites increases the total EPR contributed by the coupling reactions: i.e., an intrinsic tradeoff between system-wide controllability and thermodynamic cost.

The above results are consistent with the case of $n = 2$ in the main text.

APPENDIX F: RELATIONSHIP WITH METABOLIC CONTROL ANALYSIS

The dimensionless elasticity $e_{XY}^\pm$, defined in Eq. (7), is conceptually close to sensitivity measures in MCA. One key difference is that our elasticity concerns the susceptibility of a ratio of steady-state concentrations, not concentrations themselves.

In MCA, the concentration control coefficient (CCC) is defined as the dependence of a steady-state concentration of metabolite X on the activity of enzyme E_i :

$$C_{E_i}^X := \frac{\partial \log [X]}{\partial \log [E_i]}.$$

Thus, it is not directly equal to the dimensionless elasticity in Eq. (7):

$$e_{XY}^{\pm} := \pm \frac{\partial \log([X^*]/[X])}{\partial \log \kappa_Y^{\pm}}.$$

Rather, they are related via

$$e_{XY}^{\pm} = \pm (C_{\kappa_Y^{\pm}}^{X^*} - C_{\kappa_Y^{\pm}}^X), \quad (\text{F1})$$

where $\kappa_Y^{\pm}$ plays the role of an effective activity parameter for the coarse-grained driving reaction of currency metabolite Y . For clarity, note that the “elasticity” in MCA is typically defined as the dependence of a reaction flux J_i on metabolite X , $\epsilon_X^{J_i} := \frac{\partial \log J_i}{\partial \log [X]}$, which differs from CCC.

MCA provides fundamental theorems for CCCs, such as the summation theorem,

$$\sum_i C_{E_i}^X = 0,$$

and the connectivity theorems,

$$\sum_i C_{E_i}^X \epsilon_X^{J_i} = -1, \quad \sum_i C_{E_i}^X \epsilon_Y^{J_i} = 0 \quad (X \neq Y).$$

The summation theorem is somewhat related to our identity $e_{XA}^{\pm} + e_{XB}^{\pm} = 1$, which implies

$$e_{XA}^+ + e_{XB}^+ - (e_{XA}^- + e_{XB}^-) = 0 \quad (X = A, B).$$

From the perspective of MCA, the summation theorem yields the identical equality:

$$\sum_{E=\kappa_A^+, \kappa_A^-, \kappa_B^+, \kappa_B^-} C_E^{X^*} + \sum_{E=\kappa_A^+, \kappa_A^-, \kappa_B^+, \kappa_B^-} C_E^X = 0 \quad (X = A, B).$$

By contrast, it is not straightforward to apply the connectivity theorem to the elasticity $e_{XY}^{\pm} = \pm (C_{\kappa_Y^{\pm}}^{X^*} - C_{\kappa_Y^{\pm}}^X)$.

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