Microeconomics of metabolism: Overflow metabolism as Giffen behavior

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Abstract

Living organisms optimize their survivability through evolutionary processes. In particular, intracellular metabolic systems are rationally regulated to maximize the cellular growth rate. Correspondingly, the field of microeconomics investigates the behavior of individuals assumed to act rationally to maximize their utility. Therefore, microeconomics can be applied to analyze the metabolic strategies of cells. Toward this end, we developed a microeconomics-based theory of cellular metabolism by precisely mapping the regulation of metabolic systems onto the theory of consumer choice in microeconomics. As a representative example, we focus on overflow metabolism, a seemingly wasteful strategy in which cells utilize fermentation instead of the more energetically efficient respiration (so-called Warburg effect in cancer). To resolve this apparent contradiction, we formulate overflow metabolism as an optimization problem of the allocation of carbon fluxes under the guidance of microeconomic theory. Accordingly, we demonstrate that overflow metabolism corresponds to Giffen behavior in economics, the strange consumer behavior by which greater amounts of goods are consumed as their price increases. We reveal the general conditions required for both overflow metabolism and Giffen goods: trade-off and complementarity, i.e., the impossibility of substitution for different goods, among multiple objectives. Based on the correspondence with Giffen behavior, a counterintuitive response of metabolism against the leakage and degradation of intermediate metabolites, which corresponds to the change in the price of a consumer good, is predicted. Overall, this demonstration highlights that application of microeconomics to metabolic systems will offer new predictions and potentially new paradigms for both biology and economics.

metabolic systems | theory of consumer choice | Warburg effect | optimization | trade-off

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Introduction

iving organisms are considered to optimize their survivability through evolutionary processes. In particular, the metabolic systems of cells need to be optimized to improve the growth rate or biomass yield. Indeed, several biological theories such as flux balance analysis (FBA) have succeeded in predicting the metabolic behavior under the assumption that cells rationally regulate their metabolism (1–5).

Correspondingly, microeconomics is the study of the behavior of individuals who are assumed to have perfect rationality to maximize their "utility" (6). However, in reality, humans do not behave completely rationally, and it is difficult to determine the precise forms of utility functions. Thus, microeconomics might actually be more applicable to understanding metabolism rather than human society.

Indeed, an analogy between biology and microeconomics has been sometimes argued (7–9). Here, we push beyond an analogy to exact mapping of metabolic systems onto the theory of consumer choice in microeconomics. Specifically, we reveal the conditions required for overflow metabolism and Giffen behavior, long-standing mysteries in biology and economics, respectively.

Overflow metabolism is a seemingly wasteful and yet ubiquitous behavior by which fermentation is favored over respiration even in the presence of abundant oxygen. This is an apparent contradiction, given that the respiratory pathway yields approximately 15-fold more ATP than the fermentation pathway, and yet aerobic organisms generally utilize the less energetically efficient fermentation strategy (10–16). This phenomenon is often observed in fast-growing cells with abundant carbon, resulting in the overflow of end products of the fermentation pathway, such as acetate and ethanol, leading to the designation of the term overflow metabolism. This behavior is ubiquitously observed across a variety of cells, ranging from bacteria to eukaryotes, e.g., yeasts (known as the Crabtree effect) (12) and mammalian cells, including cancer cells (known as the Warburg effect) (13, 14), stem cells (15), and immune cells (16). Many experimental and theoretical studies have proposed hypotheses to explain overflow metabolism. One of the main hypotheses put forward is that fermentation and respiration compete for limited resources such as the limited amount of proteome (11, 17–19), empty space on the cellular membrane (so-called "membrane real estate") (20, 21), and the volume of cytoplasm (13). Although a variety of mechanisms underlying overflow metabolism have been considered in specific organisms and surrounding environments, there is still little progress made to reveal the universal structure of this common phenomenon.

From a similar perspective in microeconomics, Giffen behavior represents the mysterious phenomenon by which the demand for a good increases when the price increases. This is in stark contrast to the general pattern of human economic activities in which demand decreases when the price of a normal good increases, and vice versa. Thus, Giffen behavior is also referred to as Giffen's paradox (6, 22). Although the existence of Giffen goods was theoretically predicted more than a century ago, their practical existence remains controversial. However, a few examples have recently been considered to represent Giffen goods in practice (22, 23).

In this study, we discovered a strong link between the above two biological and microeconomics phenomena. By mapping resource allocation models for metabolic systems

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on the theory of consumer choice in microeconomics, we formulated overflow metabolism as an optimization problem, and demonstrated that the utility function for overflow metabolism has the same universal structure required for Giffen behavior. Through this correspondence, we revealed two key conditions required for both overflow metabolism and Giffen behavior: (i) a trade-off and (ii) "complementarity" among multiple objectives. The latter is autonomously satisfied in metabolic systems due to the nature of stoichiometry. The correspondence also allows predicting a counter-intuitive response of metabolic systems to the leakage and degradation of intermediate metabolites. We further discuss the possibility of observing strange behaviors similar to overflow metabolism in other metabolic systems.

Model

The theory of consumer choice explains how the price p_i of goods and income I determine consumption behavior, i.e., how a consumer determines the demand for each good (x_i for the ith good) under the given utility function $u(x_1, x_2, \cdots, x_n)$. When the number of goods n is two, the utility function is represented as a curved surface (Fig. 1A). If the consumer is sufficiently rational in their decisions, the decision-making process can be mapped onto an optimization problem of the utility under the budget constraint $\sum_{i=1}^{n} p_i x_i \leq I$.

Changes in a good's price or the income of the consumer can both alter the consumption behavior so as to maximize utility (Fig. 1). To understand such changes intuitively, microeconomists usually use contours of the utility function, which are termed indifference curves, representing sets of demand from which the utilities take the same value (Fig. 1B). Then, the demand for each good is basically determined from a tangent point of the budget constraint line to the indifference curve on which the utility takes the largest value. When the price of either good changes, the budget constraint line tilts in the x_1-x_2 plane, and thus the optimal demand changes. In the example of the utility function $u(x_1, x_2) = \sqrt{x_1} + \sqrt{x_2}$ shown in Fig. 1, the demand for each good increases when its price decreases, and vice versa. Such goods are referred to as normal goods in microeconomics.

In this paper, we adopt the above framework for the theory of consumer choice to understand metabolic systems (see SI Appendix, Table S1). We consider a simple metabolic system that consists of a single flux to obtain a nutrient and multiple fluxes to metabolize the nutrient to energy molecules. If the rate of growth or biomass synthesis is given as a function of these fluxes, we can map the metabolic system onto a problem of consumer choice in which the intake flux of the nutrient is the income, and the multiple metabolic pathways correspond to multiple goods. Hence, the demand for goods are the rates to metabolize the nutrient in the pathways. In microeconomics, the price quantifies the inefficiency of conversion from money to goods; accordingly, the price of each metabolic pathway is interpreted as the inverse efficiency to metabolize the nutrient. For instance, when leakage and degradation of intermediate metabolites increases, the price

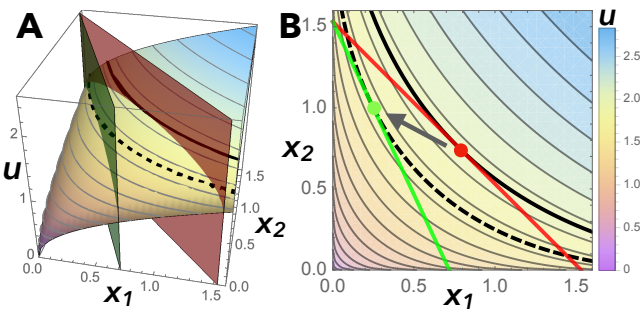

Fig. 1. Representation of optimization problems in microeconomics. (A) Landscape and (B) contour map of the utility function. Here we adopted $u(x_1, x_2) = \sqrt{x_1} + \sqrt{x_2}$ as the utility function, where x_1 and x_2 denote the demand for goods 1 and 2. The background color shows the value of $u(x_1, x_2)$. Gray lines are contour lines, which are known as indifference curves in microeconomics. Red and green lines are budget constraint lines, whose slopes depend on the price of each good. The optimal solution is determined from the tangent point of the budget constraint line to an indifference curve, and thus depends on the price of goods. Here, the optimal point moves from red to green points when the price p_1 increases.

of the metabolic pathways increases.

In the case of overflow metabolism, we consider the carbon source as the nutrient and the carbon fluxes allocated for respiration and fermentation, $J_{C,r}$ and $J_{C,f}$, respectively, as the demand of two goods. The budget constraint line is thus given by the carbon balance as

$$J_{C,in} = p_r J_{C,r} + p_f J_{C,f}, \tag{1}$$

where $J_{C,in}$ is the intake flux of the carbon source, and p_r and p_f are the inefficiencies of respiration and fermentation to metabolize the carbon source to downstream metabolites, especially ATP, respectively. For simplicity, we set p_r and p_f to 1 (i.e., assume that the carbon source is perfectly converted to the energy molecules with neither leakage nor degradation), unless otherwise stated.

The utility function is given by the growth rate, $\lambda(J_{C,r}, J_{C,f})$. For successful division, cells have to build their components from precursors of biomass and energy molecules. Hence, $\lambda(J_{C,r}, J_{C,f})$ is determined from the production rates of the energy molecules J_E and biomass precursors J_{BM}.

The energy production flux, J_E, is the sum of the fluxes of ATP synthesis via the respiratory and fermentation pathways, $J_{E,r}$ and $J_{E,f}$, which are proportional to $J_{C,r}$ and $J_{C,f}$ with different coefficients, respectively:

$$J_E\left(J_{C,r}, J_{C,f}\right) = J_{E,r} + J_{E,f} = \epsilon_r J_{C,r} + \epsilon_f J_{C,f}. \tag{2}$$

The positive constants satisfy $\epsilon_r > \epsilon_f$ because respiration can produce a greater amount of ATP than fermentation using the same amount of the carbon source (24).

In a cell, respiratory, fermentation, and biomass precursor production pathways compete for nutrients as well as other limited resources such as the total amount of proteins (11, 17–19) and empty space on the cellular membrane (20, 21). If we denote the total amount of a given resource allocated to growth by ρ_{tot}, competition for the limited resource can be described as $\rho_r + \rho_f + \rho_{BM} = \rho_{\mathrm{tot}}$, where ρ_r, ρ_f, and ρ_{BM} are the resources allocated to respiration,

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fermentation, and production of biomass precursors, respectively. For example, in the proteome allocation model (11), ρ_{tot} is the total fraction of enzymes allocated to growth. In the membrane real estate model (20, 21), ρ_{tot} is the total empty space in the cellular membrane, and ρ_r and ρ_f respectively correspond to the occupied membrane areas by membrane proteins used for respiration and fermentation; ρ_f is close to zero, and ρ_{BM} is the membrane area used to take in the compounds for building biomass precursors. Based on the law of mass action, each flux is proportional to the allocated resources: $J_{E,r} = \epsilon'_r \rho_r$, $J_{E,f} = \epsilon'_f \rho_f$, and $J_{BM} = \epsilon'_{BM} \rho_{BM}$. It follows that

$$J_{BM}\left(J_{C,r}, J_{C,f}\right) = \epsilon'_{BM}\rho_{\mathrm{tot}} - \epsilon'_{BM}\frac{\epsilon_r}{\epsilon'_r}J_{C,r} - \epsilon'_{BM}\frac{\epsilon_f}{\epsilon'_f}J_{C,f}. \quad \textbf{(3)}$$

Empirical observations have shown that respiration requires more resources than fermentation, e.g., enzymes for respiration function in bigger protein complexes than those used for fermentation (11, 13) and occupy a larger area of the cellular membrane (20, 21). That is, ϵ'_r is smaller than ϵ'_f. Since respiration is a much more efficient method of metabolizing ATP than fermentation, there is a trade-off between the production of energy molecules and occupancy of the limited resources.

Here, metabolic reactions, including biomass synthesis, follow the rules of stoichiometry. Each component of a cell is built by biochemical reactions involving multiple compounds whose amounts are determined by the law of mass conservation. In general, the compounds cannot be replaced by each other; thus, the total amount of the product is determined by the least abundant component. This property of stoichiometry is identical to the concept of (perfect) complementarity in microeconomics, in which perfect complementary utility is represented by a Leontief utility function, i.e., the least available element of all goods (22). Hence, the growth rate is represented by a Leontief utility function as

$$\lambda(J_{C,r}, J_{C,f}) = \min\left(\frac{1}{s_E}J_E, \frac{1}{s_{BM}}J_{BM}\right), \quad \textbf{(4)}$$

where s_E and s_{BM} are the stoichiometric coefficients for energy molecules and biomass precursors to synthesize biomass, respectively.

The biological meanings of the variables and parameters in the model, and their correspondence to microeconomics are summarized in Table 1.

Results

Overflow metabolism as Giffen behavior. In microeconomics, the effect of a change in price can be decomposed into two distinct effects (6, 25): a substitution effect and an income effect (see SI Appendix, Sec. S1 for details). The substitution effect is caused by relative changes in the combination of demand for goods, and is represented as a change of the tangent point along the indifference curve with the same utility value. The self-substitution effect, which is a special case of the substitution effect for a good due to a price change of the good itself, has to be non-negative (25); i.e., the demand for a good cannot be increased by the substitution effect when its price increases. By contrast, a change in the price of a good affects the budget to spend freely; that is, an increase in a good's price can be interpreted as an effective decrease in the consumer's income. Such an effective change in the income alters the demand for each good, which is termed the income effect. The income effect of a good can be either positive or negative, by which an increase in the income increases or reduces the demand for the good, respectively. The goods with a negative income effect are known as inferior goods. The overall change in the demand for goods according to a price change is given by the sum of the substitution and income effects (see SI Appendix, Eq. [S1]).

A Giffen good, which is a particular type of inferior good, shows a negative income effect that is larger than its substitution effect (see SI Appendix, Sec. S1 for details).

Indifference curves can allow for considering both the substitution and income effects. If the growth rate takes the value $\tilde{\lambda}$, the indifference curve is given as a two-valued function from Eqs. (2)-(4), as shown in Fig. 2A and 2B:

$$J_{C,f} = \begin{cases} -\frac{\epsilon_r}{\epsilon_f}J_{C,r} + \frac{s_E}{\epsilon_f}\tilde{\lambda}, & \text{if } \frac{1}{s_E}J_E \leq \frac{1}{s_{BM}}J_{BM} \\ -\frac{\epsilon_r}{\epsilon_f}\frac{\epsilon'_f}{\epsilon'_r}J_{C,r} + \frac{\epsilon'_f}{\epsilon_f}\left(\rho_{\mathrm{tot}} - \frac{s_{BM}}{\epsilon'_{BM}}\tilde{\lambda}\right). & \text{if } \frac{1}{s_E}J_E \geq \frac{1}{s_{BM}}J_{BM} \end{cases}$$

The growth rate is maximized at the tangent point of the budget constraint line (Eq. (1)) to an indifference curve.

If the influx of carbon sources $J_{C,in}$ is lower than $r_0 = \rho_{\mathrm{tot}}/(\frac{s_{BM}\epsilon_r}{\epsilon'_{BM}s_E} + \frac{\epsilon_r}{\epsilon'_r})$, the budget constraint line has no tangent point to any indifference curve, and the maximum growth rate is achieved at $(J_{C,r}, J_{C,f}) = (J_{C,in}, 0)$ (see the light-blue area in Fig. 2C and 2D). In this regime, the occupancy of the limited resources does not limit cell growth, and cells only use respiration to produce energy molecules more efficiently. When the intake $J_{C,in}$ is sufficiently high, the budget constraint line has a tangent point to an indifference curve. The set of such tangent points with various $J_{C,in}$ is given as the line on which $\frac{1}{s_E}J_E = \frac{1}{s_{BM}}J_{BM}$ (see the ridgeline in Fig. 2A and 2B represented by the dashed lines):

$$J_{C,f} = -\frac{f_0}{r_0}J_{C,r} + f_0, \quad \textbf{(5)}$$

where $f_0 = \rho_{\mathrm{tot}}/(\frac{s_{BM}\epsilon_f}{\epsilon'_{BM}s_E} + \frac{\epsilon_f}{\epsilon'_f})$. Thus, the growth rate is maximized at the intersection between the above ridgeline and the budget constraint line (Eq. (1)).

The slope of this ridgeline is negative, as the growth rate rises when $J_{C,f}$ increases and $J_{C,r}$ decreases along the ridgeline because of the trade-off between the efficiency of energy production and resource occupancy. Accordingly, with greater amounts of carbon sources a cell takes in, there will be more flux flowing to the fermentation pathway, and less flowing to the respiratory pathway (see the light-green area in Fig. 2C and 2D). That is, overflow metabolism occurs. In other words, the income effect for respiration is negative. Here, the Leontief utility function has no substitution effect (26, 27),

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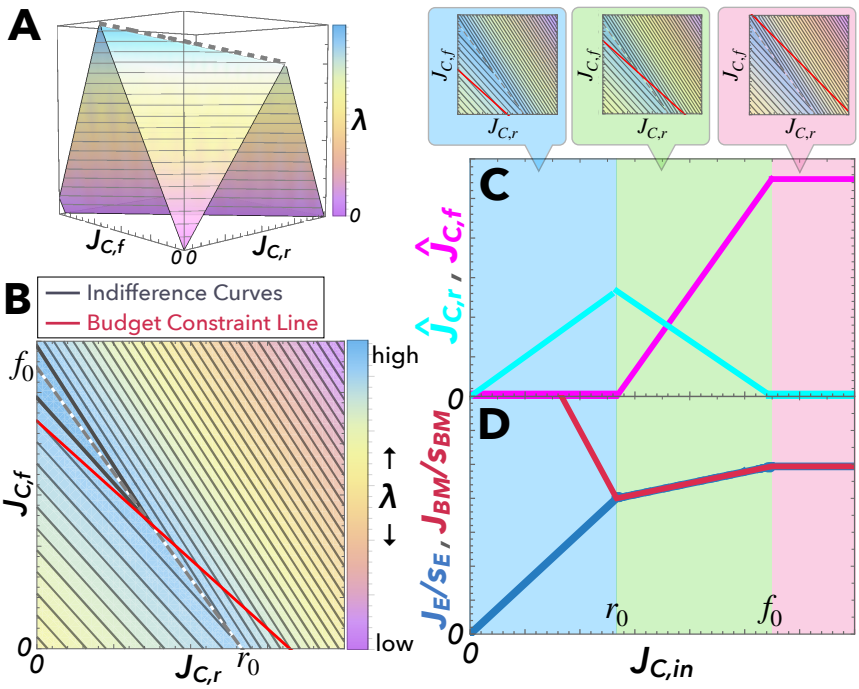

Fig. 2. Overflow metabolism and Giffen behavior as an optimization problem. (A) Landscape of the growth rate $\lambda(J_{C,r}, J_{C,f})$ and (B) corresponding contour map. Indifference curves (Eq. (4)) and a budget constraint line (Eq. (1)) are represented by black and red solid lines, respectively. The gray dashed line is the ridgeline of the utility function (Eq. (5)). The background color represents the growth rate $\lambda(J_{C,r}, J_{C,f})$. (C) Dependence of the optimal strategy $(\hat{J}_{C,r}, \hat{J}_{C,f})$ on $J_{C,in}$ (Engel curve; Eq. (6)). $J_{C,r}$ (cyan line) and $J_{C,f}$ (magenta line) in the optimal solutions are plotted against $J_{C,in}$. (D) J_E/s_E (blue line) and J_{BM}/s_{BM} (dark-red line) in the optimal solutions are plotted against $J_{C,in}$; $\lambda(\hat{J}_{C,r}, \hat{J}_{C,f})$ also corresponds to the blue line. Top panels depict the contour maps for the cases $J_{C,in} \leq r_0$ (light-blue area), $f_0 \geq J_{C,in} \geq r_0$ (light-green area), and $J_{C,in} \geq f_0$ (pink area).

and thus overflow metabolism immediately corresponds to Giffen behavior in which the respiratory pathway is a Giffen good.

When the carbon intake increases further and exceeds f_0, the $J_{C,f}$-intercept of the ridgeline, $(J_{C,r}, J_{C,f})$ in the optimal solution always takes the value $(0, f_0)$ (see the pink area in Fig. 2C and 2D) because the global maximum of the utility function is achieved at this point. In this scenario, the efficiency of producing energy molecules is no longer a primary concern given the excess carbon sources available, and occupancy of the limited resources is the only selection criterion for the two metabolic pathways. Hence, cells allocate the carbon intake to only fermentation until reaching the upper bound determined by the available resources.

Based on these results, we calculated the dependence of the optimal strategy $(\hat{J}_{C,r}, \hat{J}_{C,f})$ on $J_{C,in}$, called the Engel curve in microeconomics, as shown in Fig. 2C:

$$\left(\hat{J}_{C,r}, \hat{J}_{C,f}\right) = \begin{cases} (J_{C,in}, 0), & \text{if } J_{C,in} \leq r_0 \\ \left(\frac{r_0}{f_0 - r_0}(f_0 - J_{C,in}), \frac{f_0}{f_0 - r_0}(J_{C,in} - r_0)\right), & \\ \qquad\qquad \text{if } f_0 \geq J_{C,in} \geq r_0 & \\ (0, f_0). & \text{if } J_{C,in} \geq f_0 \end{cases} \quad \textbf{(6)}$$

This Engel curve is in good agreement with experimental observations (10, 11). We also calculated the dependence of the optimal growth rate λ on $J_{C,in}$ (see the blue curve in Fig. 2D). When the intake of carbon sources increases, the growth rate λ increases linearly on $J_{C,in}$ initially, and then the slope of the increase in λ becomes gentle at $J_{C,in} = r_0$ due to the trade-off between the energy efficiency and resource occupancy, where overflow metabolism is observed. Finally, the growth rate reaches the maximum due to the resource limitation.

Note that if there is no trade-off, i.e., both $\epsilon_r > \epsilon_f$ and $\epsilon'_r > \epsilon'_f$ hold, the maximal point of the utility function is not $(J_{C,r}, J_{C,f}) = (0, f_0)$ but rather $(J_{C,r}, J_{C,f}) = (r_0, 0)$. Hence, when the intake of carbon sources increases, only $J_{C,r}$ increases and saturates at $J_{C,r} = r_0$, while $J_{C,f}$ remains at zero; namely, overflow metabolism cannot be observed. A trade-off is thus required for overflow metabolism and Giffen behavior.

Leakage of intermediate metabolites drastically influence overflow metabolism. This clear correspondence between overflow metabolism and Giffen behavior leads to a new prediction. Although we have considered the case $p_r = p_f = 1$, the price p_r and p_f can be larger than 1 due to inefficiencies in carbon metabolization, i.e., the leakage and degradation of intermediate metabolites will increases the price of metabolic pathways. For example, leakage in the tricarboxylic acid cycle or electron transport chain will increase p_r.

Such changes in price alter the slope of the budget constraint line (1) along with its intersection with the ridgeline (5). Since the property of each metabolic pathway depends on how the budget constraint line intersects with the indifference curves, the form of the Engel curve (Eq. (6)) is modified when the price p_r or p_f is not equal to 1 (SI Appendix, Sec. S2).

We here set an initial condition at a point where overflow metabolism is observed (i.e., $f_0 \geq J_{C,in} \geq r_0$ holds), and consider the influence of increases in p_r. Notably, the property of the optimal carbon allocation qualitatively changes depending on whether the price ratio p_r/p_f is higher or lower than ϵ_r/ϵ_f.

(I) $p_r/p_f < \epsilon_r/\epsilon_f$ (the green and blue areas in Fig. 3): the

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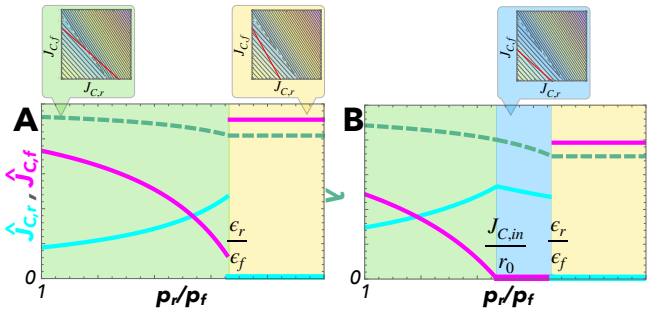

Fig. 3. Dependence of the optimal strategy $(\hat{J}_{C,r}, \hat{J}_{C,f})$ on the price of respiration p_r. Here p_f is set to 1. (A) $J_{C,in} > \frac{\epsilon_r}{\epsilon_f} r_0$ and (B) $J_{C,in} < \frac{\epsilon_r}{\epsilon_f} r_0$. The cyan, magenta, and green curves depict $\hat{J}_{C,r}$, $\hat{J}_{C,f}$, and $\lambda(\hat{J}_{C,r}, \hat{J}_{C,f})$, respectively. Top panels depict the contour maps of the utility function for the cases $J_{C,in} \geq p_r r_0$ and $p_r < \epsilon_r/\epsilon_f$ (light-green area), $J_{C,in} \leq p_r r_0$ and $p_r < \epsilon_r/\epsilon_f$ (light-blue area), and $p_r > \epsilon_r/\epsilon_f$ (yellow area). Indifference curves and the budget constraint line are represented by black and red solid lines, respectively.

budget constraint line intersects with the ridgeline, and the respiratory pathway behaves as a Giffen good, i.e., the demand $J_{C,r}$ increases along with the price p_r. In other words, if there is more leakage and degradation of intermediates in respiration pathways, i.e., the carbon metabolization efficiency for respiration decreases, the carbon flux toward respiration will increase counterintuitively. Note that in the case of $J_{C,in} < \epsilon_r r_0/\epsilon_f$, the carbon flux toward fermentation goes to zero at $p_r/p_f = J_{C,in}/r_0$, and thus respiration decreases against an increase in p_r (see the blue area in Fig. 3B).
(II) $p_r/p_f > \epsilon_r/\epsilon_f$ (yellow areas in Fig. 3): the budget constraint line does not intersect with the ridgeline, and the point $(J_{C,r}, J_{C,f}) = (0, J_{C,in}/p_f)$ is optimal in terms of the growth rate. In this regime, considering the imbalance in price, the fermentation pathway becomes more efficient for both J_E and J_{BM}, and there is no longer a trade-off (see also SI Appendix, Sec. S3 for details). Hence, the carbon intake is allocated to only fermentation and not respiration.
The optimal allocation of carbon fluxes shows a jump from regime (I) to (II) in a discontinuous manner when p_r increases (see the cyan and magenta curves in Fig. 3). Nevertheless, the optimal growth rate changes continuously (see the green dashed curves in Fig. 3).

Discussion

We here developed the microeconomics of metabolism, which revealed the clear correspondence between overflow metabolism in biology and Giffen behavior in economics as a prominent example. Such correspondence indicates their common requirements: (i) a trade-off and (ii) complementarity among multiple objectives. In metabolism, cells have to produce biomass from precursors and energy molecules, which introduces a trade-off: higher efficiency for ATP production places a heavier burden on biomass precursor production. Complementarity between biomass precursors and energy molecules is autonomously achieved because of the law of mass conservation. Hence, although respiration has higher efficiency for ATP production, cells also use fermentation to catabolize carbon sources in a nutrient-enriched environment. The metabolic systems satisfying these two conditions generally show overflow metabolism and Giffen behavior regardless of the origin of the trade-off (e.g., protein allocation and membrane allocation).

Of note, another mechanism of overflow metabolism has been proposed in terms of the Warburg effect in cancer, which hypothesizes that overflow metabolism is caused by a trade-off between the production efficiencies of ATP and some other metabolites required for growth such as nucleosides and amino acids (14). However, this mechanism is also formulated as an optimization problem with the same universal structure as shown in Fig. 2 (see SI Appendix, Fig. S1 and Sec. S3). Hence, the systems satisfying the two conditions, i.e., trade-off and complementarity, generally show Giffen behavior even if the precise mechanism is different from that based on limited resource allocation.

Although our study was based on the spirit inherited from constraint-based modeling in that evolutionary processes force metabolic systems to become optimized (1–4), we here adopted a reductionist approach. We considered a model with only a few variables so as to best uncover the universal and essential structure, whereas FBA comprises numerous variables with the aim of predicting the metabolic states of actual cells. Recent studies have successfully reproduced overflow metabolism with FBA modified in an ad hoc manner (19, 29, 30). We believe that such modified versions of FBA could be reduced to the universal structure we have revealed herein. Moreover, our framework will provide a design principle for constraint-based modeling to handle overflow metabolism across various species.

The analogy between overflow metabolism and Giffen goods offers new predictions on the relationship between optimal carbon allocation and the inefficiency of carbon metabolism. Specifically, we demonstrated that if the carbon metabolism efficiency of respiration decreases due to leakage of the intermediates, the carbon allocation for respiration will counterintuitively increase, as in Giffen goods. Indeed, a shift from fermentation to respiration was reported in a line of cancer cells that dissipates energy by leakage of proton required to produce ATP (31). We expect that more quantitative experiments will further prove our predictions by increasing the price of respiration. For example, uncouplers of oxidative phosphorylation such as 2,4-dinitrophenol and CCCP promote the dissipation of the proton gradient (32).

Besides overflow metabolism, Giffen behavior will be observed in a variety of metabolic systems as long as the two requirements are satisfied. Since perfect complementarity should hold in metabolic systems owing to the law of mass conservation, metabolic systems with a trade-off are generally expected to show Giffen behavior. One representative example is the Embden-Meyerhoff-Parnass (EMP) and Entner-Doudoroff (ED) pathways for the glycolytic strategy. The EMP pathway is more efficient for ATP production but requires a greater amount of enzymes than the ED pathway (19, 33, 34), which imposes a heavier burden for the production of biomass precursors. As this is the same trade-off that occurs in overflow metabolism, the EMP pathway is expected to behave as a Giffen good. Indeed, at high growth rates, the

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ED pathway is utilized to catabolize glucose (33, 34). Moreover, an identical trade-off can be observed with respect to the usage of the mixed-acid or lactic-acid fermentation pathways (35, 36).

Furthermore, different types of trade-offs are present in a wide range of metabolic systems, including trade-offs for the production of different metabolites from resources taken up by extracellular carbon, nitrogen, and phosphorus-acquiring enzymes (37); a trade-off between carbon fixation and light harvesting in nitrogen allocation toward rubisco and chlorophyll (38, 39); a trade-off between energy production and resistance to external stresses in nitrogen allocation toward photosynthesis and cell walls (40); and a trade-off between ATP synthesis and occupancy of the biomembrane in the co-utilization of photosynthesis and glycolysis (41). We expect that these examples in metabolism can also be described by the same universal utility landscape and will show Giffen behavior.

From the perspective of microeconomics, we have provided a concrete example of Giffen goods. These results are consistent with and contribute toward resolving the mechanism for an economic experiment (23) in which Giffen behavior occurs when the income is not high, but cannot be observed in the case of extreme poverty. In our model, Giffen behavior was observed when the income was in the intermediate range at which point the trade-off is operating (see Fig. 2). However, when the income is too low, a good (e.g., the respiratory pathway) behaves as a perfect substitute. Although one can construct other types of utility functions that are plausible for economic behavior, which will show the similar Engel curve and Giffen behavior, they are reduced into the same optimization problem as formulated herein (see SI Appendix, Sec. S3). Note that although perfect complementarity does not always exist outside of metabolic systems, Giffen behavior can still be observed without perfect complementarity as long as a trade-off exists and the form of the utility landscape is similar to that of the Leontief type (see SI Appendix, Sec. S4 and Fig. S2).

We have paved the road for the field of the microeconomics of metabolism using overflow metabolism and Giffen behavior as stepping stones. We hope that close links will be revealed for a variety of other metabolic phenomena and theories in microeconomics, as shown in this paper, and we expect that further development in the microeconomics of metabolism will bring about a deeper understanding of both biology and economics.

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Table 1. Biological and economic meanings of symbols.

Symbol	Biological meaning	Economic meaning
$J_{C,in}$	Intake flux of carbon source	Income
$J_{C,r}, J_{C,f}$	Fluxes of carbon in respiratory and fermentation pathways	Demand for goods
p_r, p_f	Inefficiency of carbon metabolism in respiration and fermentation	Price of goods
λ	Growth rate	Utility
J_E	Total flux of ATP production	An objective
$J_{E,r}, J_{E,f}$	Flux of ATP production by respiration and fermentation	
J_{BM}	Total flux of biomass precursors production	Another objective
ρ_{tot}	Total amount of the limited resource	
$\rho_r, \rho_f, \rho_{BM}$	Fraction of the limited resource used for respiration, fermentation, and biomass synthesis	
ϵ_r, ϵ_f	Efficiency of ATP production in respiration and fermentation	
$\epsilon'_r, \epsilon'_f, \epsilon'_{BM}$	Occupancy rate of the limited resource for respiration, fermentation, and biomass synthesis	
s_E, s_{BM}	Stoichiometric constants	

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Supporting Information Text

S1. Substitution Effect and Income Effect

The influence of a change in price on the demand for goods can be decomposed into an income effect and a substitution effect, as mentioned in the main text. This is known as Hicksian decomposition or the Slutsky equation (1).

We here define $x_i(\mathbf{p}, I)$ as the (optimal) demand for good i as a function of the price of goods $\mathbf{p}$ and income I. $E(\mathbf{p}, u)$ represents the minimum income required for a given utility value u under price $\mathbf{p}$, and thus $h_i(\mathbf{p}, u) \equiv x_i(\mathbf{p}, E(\mathbf{p}, u))$ is the smallest demand for good i necessary to achieve the given utility value u. We can differentiate this with respect to p_j and obtain

$$\frac{\partial h_i(\mathbf{p}, u(\mathbf{p}, I))}{\partial p_j} = \frac{\partial x_i(\mathbf{p}, I)}{\partial p_j} + \frac{\partial x_i(\mathbf{p}, I)}{\partial I} \frac{\partial E(\mathbf{p}, u(\mathbf{p}, I))}{\partial p_j},$$

where $u(\mathbf{p}, I)$ is the maximal utility with given price $\mathbf{p}$ and income I. Note that the last term, $\partial E(\mathbf{p}, u(\mathbf{p}, I))/\partial p_j$, is simply equal to the demand x_j under price $\mathbf{p}$ and income I.

Accordingly, the change in $x_i(\mathbf{p}, I)$ due to a change in p_j is given by the Slutsky equation:

$$\frac{\partial x_i(\mathbf{p}, I)}{\partial p_j} = \frac{\partial h_i(\mathbf{p}, u(\mathbf{p}, I))}{\partial p_j} - x_j(\mathbf{p}, I) \frac{\partial x_i(\mathbf{p}, I)}{\partial I}. \quad \text{[S1]}$$

The first term, $\partial h_i(\mathbf{p}, u)/\partial p_j$, is the substitution effect, which is caused by relative changes in the combination of the price values (2). The case of $i = j$ represents the self-substitution effect, which is proven to be always non-positive (1), i.e., the substitution effect never increases the demand for a good when its own price increases. In contrast, the second term, $x_j(\mathbf{p}, I) \frac{\partial x_i(\mathbf{p}, I)}{\partial I}$, is the income effect, which can be either positive or negative. This effect reflects the change in the demand for goods due to the effective decrease of the income that is caused by increasing the price of a good. According to Eq. [S1], these two effects determine the dependence of the demand for goods on the price (Table S2).

The substitution effect is represented as movement of the combination of the demand for goods along an indifference curve to a point at which the tangent line has a slope that is equal to the ratio of the altered price of goods. Hence, if the utility is given as a Leontief utility function, the substitution effect is zero within a certain range of the price change due to the indifferentiability of each indifference curve at the kink. It follows that the substitution effect of the utility is zero in the case of metabolic systems. Consequently, whether or not a metabolic pathway is a Giffen good depends only on the sign of its income effect; namely, a metabolic pathway behaves as a Giffen good if its income effect is negative. In the case of overflow metabolism, when the budget constraint line intersects with the ridgeline (Eq. (5) in the main text), the income effect is negative for the utility $\lambda(J_{C,r}, J_{C,f})$ (Eq. (4) in the main text), and thus Giffen behavior is observed.

Note that although the demand for branded goods also increase with their price, they are not Giffen goods. This is because the demand for branded goods increase when the income increase, in other words, their income effect is positive. Such goods are called Veblen goods in microeconomics (3, 4).

S2. Dependence of the optimal strategy on the price

The optimal strategy depends on the price p_r and p_f as well as on the income $J_{C,in}$. This is because changes in price alter the demand for goods, as described above. Accordingly, if the price p_r or p_f takes a value larger than 1, the Engel curve (Eq. (6) in the main text) is modified as follows.

$$\left(\hat{J}_{C,r}, \hat{J}_{C,f}\right) = \begin{cases} (J_{C,in}/p_r, 0), & \text{if } J_{C,in} \leq p_r r_0 \\ \left(\left(f_0 - \frac{J_{C,in}}{p_f}\right) \Big/ \left(\frac{f_0}{r_0} - \frac{p_r}{p_f}\right), \left(\frac{J_{C,in}}{p_r} - r_0\right) \Big/ \left(\frac{p_f}{p_r} - \frac{r_0}{f_0}\right)\right), & \text{if } p_f f_0 \geq J_{C,in} \geq p_r r_0 \\ (0, f_0), & \text{if } J_{C,in} \geq p_f f_0 \end{cases} \quad \text{[S2]}$$

with $r_0 = \rho_{\text{tot}}/(\frac{s_{BM}\epsilon_r}{\epsilon'_{BM} s_E} + \frac{\epsilon_r}{\epsilon'_r})$ and $f_0 = \rho_{\text{tot}}/(\frac{s_{BM}\epsilon_f}{\epsilon'_{BM} s_E} + \frac{\epsilon_f}{\epsilon'_f})$. Here, the optimal $(J_{C,r}, J_{C,f})$ for the case $p_f f_0 \geq J_{C,in} \geq p_r r_0$ is obtained from the intersecting point of the budget constraint line with the ridgeline (Eq. (5) in the main text). Note that Eq. [S2] is identical to Eq. (6) in the main text if $p_r = p_f = 1$.

S3. Generalization of the theory of consumer choice for overflow metabolism

Generalization of the proposed model elucidates the necessary and sufficient conditions for Giffen behavior, which is applicable to a variety of biological and economic phenomena. Let us define a Leontief utility function

$$u(x_1, x_2) \equiv \min(A, B), \quad \text{[S3]}$$

where

$$\begin{cases} A(x_1, x_2) = a_1 x_1 + a_2 x_2 + A_0, \\ B(x_1, x_2) = b_1 x_1 + b_2 x_2 + B_0. \end{cases}$$

The demand for and price of two goods are represented by x_1, x_2 and p_1, p_2, respectively. The budget constraint line is thus $I = p_1x_1 + p_2x_2$.

With respect to the utility [S3], the model proposed for overflow metabolism in the main text corresponds to the case where the signs of the parameters are given as $\mathrm{sgn}\begin{pmatrix} a_1 & a_2 \\ b_1 & b_2 \end{pmatrix} = \begin{pmatrix} + & + \\ - & - \end{pmatrix}$, while other sets of parameters also evoke overflow metabolism and Giffen behavior. For instance, a trade-off between the production efficiencies of ATP and other molecules required for growth (5) can cause overflow are given by $\mathrm{sgn}\begin{pmatrix} a_1 & a_2 \\ b_1 & b_2 \end{pmatrix} = \begin{pmatrix} + & + \\ + & + \end{pmatrix}$ (Fig. S1). Indeed, the Leontief utility function with $\mathrm{sgn}\begin{pmatrix} a_1 & a_2 \\ b_1 & b_2 \end{pmatrix} = \begin{pmatrix} + & + \\ + & 0 \end{pmatrix}$ was recently reported to demonstrate Giffen behavior in the context of microeconomics (6, 7), which is a special case of the utility function [S3].

In this section, we demonstrate that the optimization problem of the above utility [S3] with every set of parameters will always be reduced into the optimization problem with an identical structure to that shown in the main text, as long as it shows Giffen behavior. Hence, the two conditions, i.e., complementarity and trade-off, are required in all cases. Moreover, we expand the trade-off to include the effect of the price.

First, we consider the simple case where $p_1 = p_2 = 1$. We here assume a trade-off between goods 1 and 2 as $a_1 > a_2$ and $b_1 < b_2$, whereas without the trade-off, the optimal strategy is to use either good 1 or 2 only. Owing to the trade-off, the utility is maximized on the rigeline

$$x_2 = -\frac{a_1 - b_1}{a_2 - b_2}x_1 - \frac{A_0 - B_0}{a_2 - b_2} \qquad \text{[S4]}$$

where $A(x_1, x_2) = B(x_1, x_2)$ holds. Giffen behavior can be observed when this rigeline has a negative slope and exists on the first quadrant, i.e., when $-(a_1 - b_1)/(a_2 - b_2) < 0$ and $(B_0 - A_0)/(a_2 - b_2) > 0$ hold.

From symmetry between $A(x_1, x_2)$ and $B(x_1, x_2)$, it is sufficient to consider the situation where

$$a_1 > b_1, \quad a_2 > b_2, \quad B_0 > A_0 \qquad \text{[S5]}$$

are satisfied. Note that this is the condition for a comparative advantage (8).

If both b_1 and b_2 are non-positive and a_1 and a_2 are positive, the condition [S5] is autonomously satisfied. Then, the income effect is negative and Giffen behavior is observed, as shown in the main text (see Fig. 2).

Even if b_1 or b_2 is positive, the condition [S5] can be satisfied as long as the condition $\mathrm{sgn}(a_1 - b_1) = \mathrm{sgn}(a_2 - b_2)$ is satisfied, as in Fig. S1. As discussed below, even such cases can be reduced to an optimization problem with the same universal structure as demonstrated in the main text.

When Giffen behavior can occur (i.e., the condition [S5] is satisfied), we can take a real number c such that $a_2 > c > b_2$, and the utility [S3] can be represented as

$$\begin{aligned} u(x_1, x_2) = \min(A, B) &= c(x_1 + x_2) + A_0 + \min\left((a_1 - c)x_1 + (a_2 - c)x_2, (b_1 - c)x_1 + (b_2 - c)x_2 + B_0 - A_0\right) \\ &= cI + A_0 + \min(A', B'), \end{aligned} \qquad \text{[S6]}$$

where

$$\begin{cases} A'(x_1, x_2) = (a_1 - c)x_1 + (a_2 - c)x_2 = a'_1x_1 + a'_2x_2, \\ B'(x_1, x_2) = (b_1 - c)x_1 + (b_2 - c)x_2 + B_0 - A_0 = b'_1x_1 + b'_2x_2 + B'_0. \end{cases}$$

Here, $a'_1 = a_1 - c > a_2 - c = a'_2$, $b'_1 = b_1 - c < b_2 - c = b'_2 < 0$, and $B'_0 = B_0 - A_0 > 0$ are satisfied from the condition [S5]. Because only the last term, $\min(A', B')$, depends on allocation of the income to goods, the generalized model is reduced to the same optimization problem as proposed in the main text as long as it shows Giffen behavior.

A similar argument remains valid even when considering changes in the price, although in this case the definition of trade-offs needs to be expanded to include the effect of the price. In this case, a real number c can be taken such that $a_2/p_2 > c > b_2/p_2$. Then, the utility [S3] can be represented as

$$\begin{aligned} u(x_1, x_2) &= c(p_1x_1 + p_2x_2) + A_0 + \min\left((a_1 - cp_1)x_1 + (a_2 - cp_2)x_2, (b_1 - cp_1)x_1 + (b_2 - cp_2)x_2 + B_0 - A_0\right) \\ &= cI + A_0 + \min(A', B'), \end{aligned} \qquad \text{[S7]}$$

where

$$\begin{cases} A'(x_1, x_2) = (a_1 - cp_1)x_1 + (a_2 - cp_2)x_2 = a'_1x_1 + a'_2x_2, \\ B'(x_1, x_2) = (b_1 - cp_1)x_1 + (b_2 - cp_2)x_2 + B_0 - A_0 = b'_1x_1 + b'_2x_2 + B'_0. \end{cases}$$

If $a_1/a_2 > p_1/p_2 > b_1/b_2$ holds, $a'_1 = a_1 - cp_1 > a_2 - cp_2 = a'_2$, $b'_1 = b_1 - cp_1 < b_2 - cp_2 = b'_2 < 0$, and $B'_0 = B_0 - A_0 > 0$ are satisfied. Again, the generalized models showing Giffen behavior are reduced to the optimization problem with the same universal structure as demonstrated in the main text.

Of note, if the difference of the price between goods 1 and 2 is so large that p_1/p_2 is larger than a_1/a_2 or smaller than b_1/b_2, Giffen behavior disappears even when the condition [S5] and the trade-off of efficiencies to produce A and B (i.e., $a_1 > a_2$ and $b_1 < b_2$) hold. In this case, we need to consider a trade-off including the price. If p_1/p_2 is larger than a_1/a_2, a unit of demand for good 2 produces more A than that for good 1 even when a_1 is higher than a_2. That is, there is no longer a trade-off

between the production of A and B. Hence, the condition for a trade-off is rewritten as $a_1/p_1 > a_2/p_2$ and $b_1/p_1 < b_2/p_2$ (or $a_1/p_1 < a_2/p_2$ and $b_1/p_1 > b_2/p_2$).

Intuitively, the trade-off including the price corresponds to rescaling of the utility landscape so that the slope of the budget constraint line, $-\frac{p_1}{p_2}$, becomes equal to -1. If there is a trade-off between A and B in the rescaled landscape (i.e., $a_1/p_1 > a_2/p_2$ and $b_1/p_1 < b_2/p_2$, or $a_1/p_1 < a_2/p_2$ and $b_1/p_1 > b_2/p_2$), Giffen behavior can be observed.

S4. Giffen behavior requires complementarity but not perfect complementarity

Based on biological considerations, we introduced the Leontief utility function $\lambda(J_{C,r}, J_{C,f})$ (Eq. (4) in the main text) that has perfect complementarity. However, Giffen behavior can be observed with utility functions showing only partial complementarity as long as the substitution effect is sufficiently small.

An example of such utility functions is

$$u(x_1, x_2) \equiv \left[s_E / \left(\epsilon_r x_1 + \epsilon_f x_2 \right) + s_{BM} / \left(\rho_{\mathrm{tot}} - \frac{\epsilon_r}{\epsilon'_r} x_1 - \frac{\epsilon_f}{\epsilon'_f} x_2 \right) \epsilon'_{BM} \right]^{-1}. \qquad \text{[S8]}$$

The landscape of this utility function (Fig. S2A) is similar to that of $\lambda(J_{C,r}, J_{C,f})$ (Fig. 2B in the main text). As shown in Fig. S2B, x_1 with the utility [S8] shows Giffen behavior within a range of the price of good 1, p_1.

Another example of utility functions showing Giffen behavior is $u(J_{C,r}, J_{C,f}) \equiv J_E H(J_{BM} - J_{BM,min})$, where $H(\cdot)$ is the Heaviside step function.

Table S1. General correspondence between metabolism and microeconomics

Metabolism	Microeconomics
Intake of nutrient	Income
Metabolic pathways	Goods
Nutrient allocation	Demand for goods
Loss of intermediate metabolites	Price of goods
(inefficiency of metabolism from nutrient to products)	(inefficiency of conversion from income to goods)
Growth rate (Biomass synthesis rate)	Utility

Table S2. Microeconomic properties of goods.

Type of goods	Self-substitution effect	Income effect	Income ↑	Price ↑
Normal good	non-positive	positive	Demand ↑	Demand ↓
Inferior good	non-positive	(slightly) negative	Demand ↓	Demand ↓
Giffen good	non-positive	negative	Demand ↓	Demand ↑

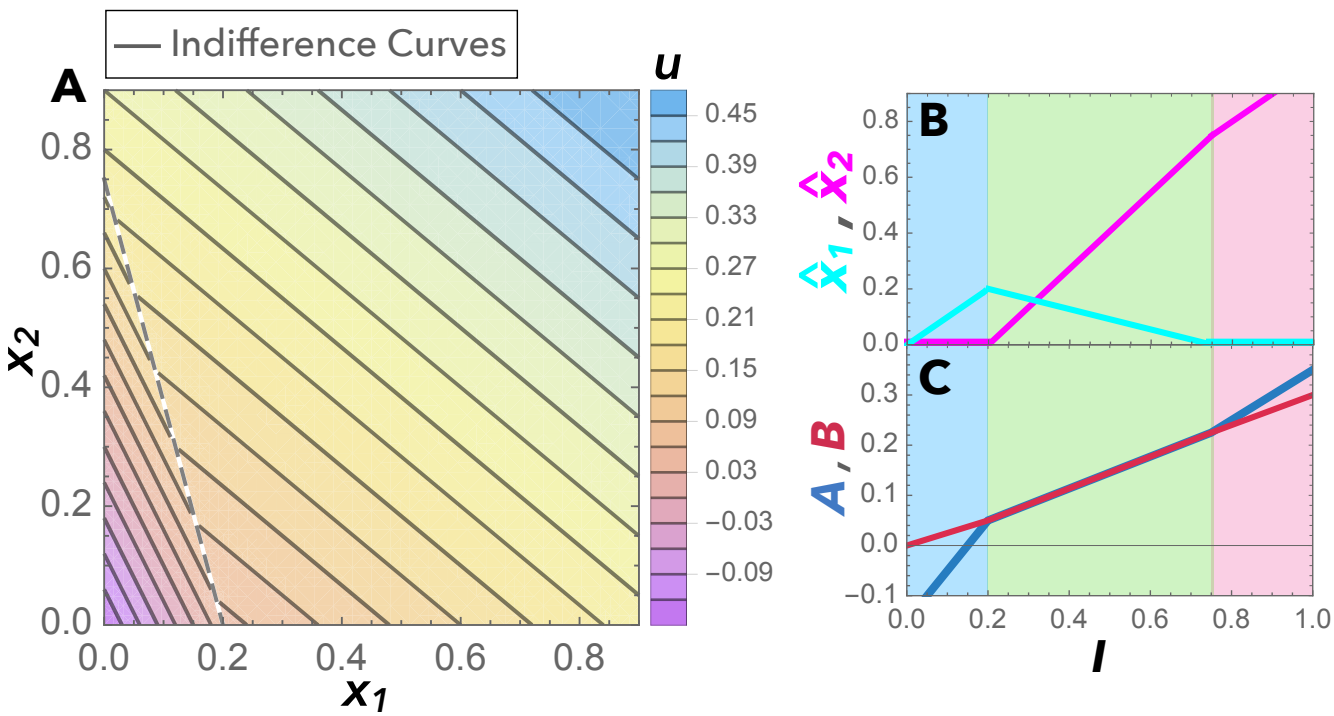

Fig. S1. Example of a generalized model with the coefficients $a_1, a_2, b_1, b_2 > 0$. (A) Contour map. Indifference curves are shown as gray lines, and the dashed line depicts the ridgeline [S4] on which $A(x_1, x_2) = B(x_1, x_2)$ holds. The background color exhibits the value of the Leontief-type utility $u(x_1, x_2) = \min(A, B) = \min(a_1x_1 + a_2x_2 + A_0, b_1x_1 + b_2x_2 + B_0)$ (Eq. [S3]). (B) The Engel curve: x_1 (cyan line) and x_2 (magenta line) in the optimal solutions are plotted against the income I. (C) A (blue line) and B (dark-red line) in the optimal solutions are plotted against the income I. In (B-C), the price p_1 and p_2 are set at unity. In this example, the coefficients are set such that $a_1 > a_2 > b_2 > b_1$ and $B_0 > A_0$: $a_1 = 1, a_2 = 0.5, b_1 = 0.25, b_2 = 0.3, A_0 = -0.15, B_0 = 0$. Since there is a tradeoff between the production efficiencies of A and B and the condition [S5] is satisfied, Giffen behavior is observed.

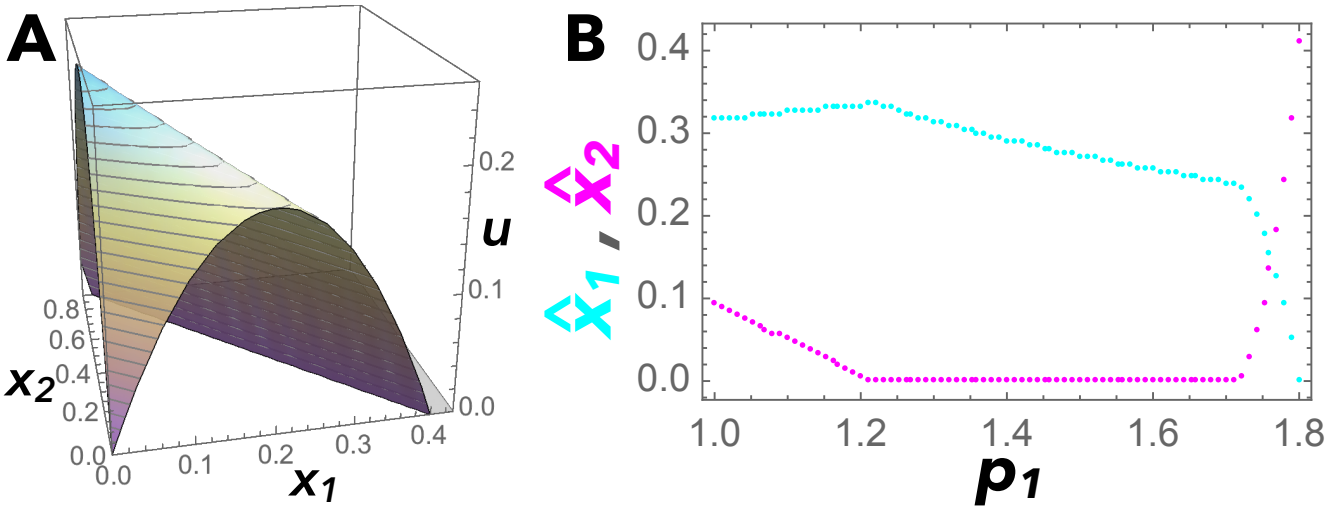

Fig. S2. Example of utility functions showing Giffen behavior without perfect complementarity. The utility function $u(x_1, x_2)$ is given by Eq. [S8]. (A) Utility landscape of $u(x_1, x_2)$ and (B) demand curves for goods 1 (light-blue dots) and 2 (pink dots). The optimal strategies $(\hat{x}_1, \hat{x}_2)$ were numerically calculated with the parameters $\epsilon_r = 0.75, \epsilon_f = 0.4, \epsilon'_r = 0.5, \epsilon'_f = 1, J_{C,in} = 0.4$; all other parameters (i.e., $\rho_{\rm tot}$, ϵ'_{BM}, s_E, s_{BM}, and p_2) were set at unity.

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