Formalising the law of diminishing returns in metabolic networks using an electrical analogy

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Abstract

The way biological systems respond to changes in parameter values caused by mutations is a key issue in evolution and quantitative genetics, as it affects fundamental aspects such as adaptation, selective neutrality, robustness, optimality, evolutionary equilibria, etc. We address this question using the enzyme-flux relationship as a model of the genotype-phenotype relationship. Applying an analogy between electrical circuits and metabolic networks, we show that a behaviour of diminishing returns, which is commonly observed at various phenotypic levels, is inevitable, irrespective of the complexity of the system.

Introduction

As reviewed and discussed in various papers [1, 2], the genotype-phenotype (GP) relationship, as well as the relationship between adjacent or distant phenotypic levels, often seems to follow a law of diminishing returns: as the value of a given parameter increases, the gain in value of the phenotypic output becomes increasingly smaller, and the curve reaches a horizontal asymptote. This type of response may account in part for the selective neutrality of many molecular polymorphisms [3], the predominance of antagonistic epistasis between deleterious mutations [2] and the pervasive robustness in living systems [4].

The archetypal behaviour of diminishing returns in systems biology is displayed by the relationship between enzyme activity and flux, which has been comprehensively analysed during the past 50 years within the framework of the Metabolic Control Analysis (MCA) [5, 6, 7, 8]. However, the MCA formalism has been mainly developed for linear pathways and not for networks. The way the total flux through a network changes in response to variations in enzyme parameters is a central question in quantitative and evolutionary genetics. In principle, this question can be addressed with systems of ordinary differential equations. However, most of the time we do not have a sufficient knowledge of the *in vivo* parameter values, and furthermore, this approach is not informative regarding possible general behaviours: beyond the specific responses of particular networks, is there a shape of the enzyme-flux relationship that would be *qualitatively* valid for a majority of situations? Intuitively, a behaviour of diminishing returns makes sense: irrespective of the complexity of a network, the effect of increasing a particular parameter value is limited by the fixed values of the other parameters. The purpose of this brief communication is to examine the validity of this idea.

An electrical analogy for metabolism

We tackled this question using the analogy between electrical circuits and metabolic networks. There are several more or less sophisticated versions of this analogy [9, 10, 11, 12, 13, 14]. In most cases, enzymes are considered to be analogous to resistors and metabolites to nodes.

In electricity, the current across a dipole is written as:

$$I = \frac{U}{R} \tag{1}$$

where U is the potential difference and R the resistance. The ratio $\frac{1}{R}$ is the conductance of the dipole.

In enzymology, the rate of a reaction catalysed by a Michaelian enzyme that is far from saturation is written as [15, 5]:

$$v \approx [E]\frac{k_{\text{cat}}}{K_{\text{M}}}\left(X_S - \frac{X_P}{K_{\text{eq}}}\right) \tag{2}$$

where $[E]$, k_{cat} and K_{M} are respectively the concentration, the catalytic constant and the Michaelis constant of the enzyme, X_S and X_P are respectively the concentration of the substrate and concentration of the product of the reaction and K_{eq} is the equilibrium constant of the reaction.

If we compare the forms of equations 1 and 2, we see that the reaction rate v is analogous to the electrical current I, the enzyme efficiency $F = [E]\frac{k_{\text{cat}}}{K_{\text{M}}}$ is analogous to the conductance $\frac{1}{R}$ and the difference $X_S - \frac{X_P}{K_{\text{eq}}}$ is analogous to the potential difference U.

The total flux through a metabolic network of any complexity is dependent on the enzyme efficiencies and the topology of the network, in the same way that the total current through an electrical circuit is dependent on the conductances and the topology of the circuit.

The concept of equivalent conductance

An important characteristic of an electrical circuit is its *equivalent resistance*, R_{E}, defined as the resistance of a single resistor that, if it replaced all resistors in the circuit, would result in the same total current. Thus, the *equivalent conductance* of the circuit is:

$$\sigma_{\text{E}} = \frac{1}{R_{\text{E}}}$$

Because the total current through the circuit is

$$I = \sigma_{\text{E}} U$$

where U is the potential difference at the circuit terminals, the equivalent conductance σ_{E} is proportional to the total current I, U being the proportionality constant.

In the same way, we can define the *equivalent enzyme efficiency*, F_{E}, of a metabolic network, whereby X_{S} is metabolised into X_{P} through a single pseudo-reaction. The total flux through the network is then written as:

$$J = F_{\text{E}}\left(X_S - \frac{X_P}{K_{\text{E}}}\right)$$

where K_{E} is the equivalent equilibrium constant that depends on all individual equilibrium constants. The equivalent enzyme efficiency F_{E} is proportional to the total metabolic flux J, $(X_S - \frac{X_{\text{P}}}{K_{\text{E}}})$ being the proportionality constant.

Therefore, characterising the relationship between the conductance σ_{ij} between nodes i and j and the equivalent conductance $\sigma_E \propto I$ in an electrical circuit of any complexity can help answer the question of the relationship between a particular enzyme efficiency F_{ij} and the equivalent efficiency $F_E \propto J$ in a metabolic network of any complexity.

Simple circuits

If the resistors in the electrical circuit are exclusively in series and/or in parallel, the equivalent resistance and the equivalent conductance can be easily calculated by applying the rule of additivity for resistances and conductances, respectively. For instance, the circuit in figure 1a has resistor R1 in series with a bypass loop containing resistors R2 and R3 in parallel. Summing the conductances σ_2 and σ_3 of R2 and R3, respectively, then summing the resistances $\frac{1}{\sigma_1}$ and $\frac{1}{\sigma_2 + \sigma_3}$, we get

$$\sigma_{\text{E}} = \frac{\sigma_1(\sigma_2 + \sigma_3)}{\sigma_1 + \sigma_2 + \sigma_3}$$

or, using a notation where the conductances are indexed according to the node numbers flanking each resistor (see figure 1):

$$\sigma_{\mathrm{E}} = \frac{\sigma_{12}\sigma_{23}}{\sigma_{12} + \sigma_{23}}$$

where $\sigma_{12} = \sigma_1$ and $\sigma_{23} = \sigma_2 + \sigma_3$. All the conductances are positive, thus it is easy to show that the relationship between σ_{E} and any of the conductances is a concave hyperbole (figure 1b).

This reduction method of successively grouping resistances can be applied to circuits of any size provided they only contain resistors in series and in parallel.

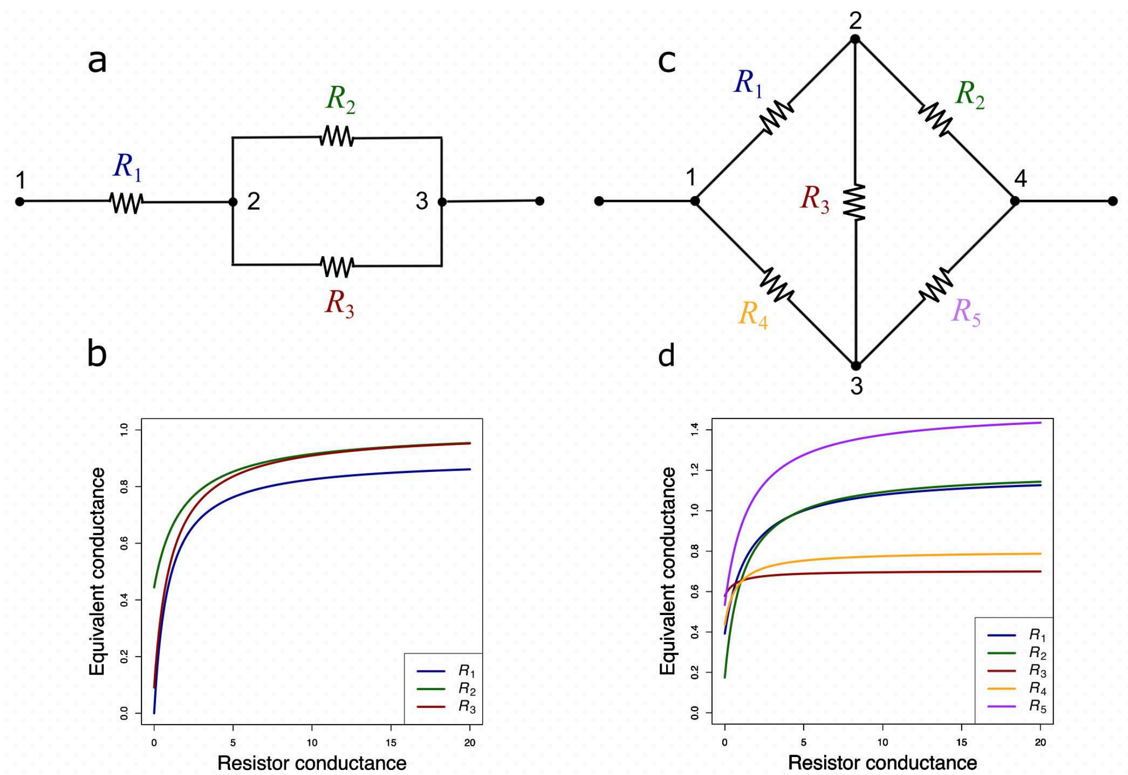

Figure 1: **Two basic types of electrical circuits.** **a.** A circuit with resistors exclusively in series and in parallel. **b.** Relationship between the equivalent conductance σ_{E} and the individual conductances in circuit **a** (same colour code as in **a**). For each curve, one conductance increased from 0 to 20, the other conductances being fixed. The fixed conductance values are $1/R_1 = 1$, $1/R_2 = 10$ and $1/R_3 = 1.25$. **c.** A wheatstone bridge. **d.** Relationship between the equivalent conductance σ_{E} and the individual conductances in the Wheatstone bridge in **c**. The fixed conductance values are $1/R_1 = 0.43$, $1/R_2 = 1$, $1/R_3 = 1.25$, $1/R_4 = 1$ and $1/R_5 = 5$.

Complex circuits

For circuits that do not contain resistors only in series and/or in parallel, the rule of additivity for resistances and conductances cannot be used directly. Consider for instance a Wheatstone bridge, which represents the simplest case of a complex circuit (figure 1c): it is easy to show that the additivity rule does not apply. More sophisticated techniques, such as the *nodal potential method* [16] or the *Delta-Y method* that relies on the Kennelly's theorem [17], have to be used.

Generalising these approaches, Kagan [16] showed that in an n-node circuit ($n > 2$) of any topology, the relationship between σ_{E} and σ_{ij} is:

$$\sigma_{\mathrm{E}} = \frac{A\sigma_{ij} + B}{C\sigma_{ij} + D} \quad (3)$$

where A, B, C et D are constants that depend on the conductances of the circuit out of σ_{ij}. For instance, the relationship between σ_{E} and the conductances in a Wheatstone bridge is:

$$\sigma_{\mathrm{E}} = \frac{\sigma_{12}\sigma_{24}(\sigma_{23}+\sigma_{13}+\sigma_{34}) + \sigma_{24}\sigma_{23}\sigma_{13} + \sigma_{12}\sigma_{23}\sigma_{34} + \sigma_{13}\sigma_{34}(\sigma_{12}+\sigma_{24}+\sigma_{23})}{\sigma_{23}(\sigma_{12}+\sigma_{24}+\sigma_{13}+\sigma_{34}) + (\sigma_{12}+\sigma_{24})(\sigma_{13}+\sigma_{34})},$$

If the variable conductance is, say, σ_{12}, we have:

$$\begin{aligned}
A &= \sigma_{24}\sigma_{34} + (\sigma_{13}+\sigma_{23})(\sigma_{24}+\sigma_{34}) \\
B &= \sigma_{13}(\sigma_{23}\sigma_{24} + \sigma_{24}\sigma_{34} + \sigma_{23}\sigma_{34}) \\
C &= \sigma_{13} + \sigma_{23} + \sigma_{34} \\
D &= \sigma_{23}\sigma_{24} + (\sigma_{13}+\sigma_{34})(\sigma_{23}+\sigma_{24})
\end{aligned}$$

We used Kagan's developments [16] to further analyse the relationship between σ_{E} and individual conductances σ_{ij}'s in a circuit. Equation 3 being the quotient of two affine functions, it is a hyperbola equation (unless $C = 0$, in which case the function is strictly linear, but this could only be obtained by choosing *ad hoc* conductance values). Using the theory of concave functions and Jacobi's theorem, we show in the Supplementary Information that the relationship between σ_{ij} and σ_{E} is necessarily concave for all σ_{ij}, and tends toward a horizontal asymptote with a value of A/C. Figure 1d shows the curves in the case of a Wheatstone bridge with arbitrary conductance values. Simulations of circuits with different topologies were carried out with LTSpice® [18] and gave consistent results: we observed in all cases increasing hyperbolae with horizontal asymptotes (not shown).

From electric circuits to metabolic networks

The previous developments can be applied to metabolic networks, but are more laborious to write due to the presence of equilibrium constants of the reactions that have no equivalent term in electrical circuits (see the case of a Wheatstone-like metabolic network in Appendix C4 of [19]). However, since these additional parameters are necessarily positive and act only as multiplicative factors of enzyme efficiencies, they do not alter the structure of the equations and hence the conclusions drawn from them. Therefore, in any network of unimolecular reactions catalysed by Michaelian enzymes that are far from saturation, the relationship between an enzyme parameter (kinetic parameter or concentration) and the flux is an increasing concave function with a horizontal asymptote (with the exception of the unrealistic case where $C = 0$ [see above]).

Discussion

The law of diminishing returns is valid for every enzyme of such metabolic networks, irrespective of their topology. As a consequence, the concavity of the enzyme-flux relationship is expected to increase with the number of enzymes in the network. Indeed, the summation property of the flux control coefficients states that $C^J_{F_k} = \sum_{k=1}^{n} \frac{\partial \ln J}{\partial \ln F_k} = 1$, where n is the total number of enzymes [5, 20]. Thus, the average control coefficient is $1/n$: the more enzymes there are in the network, the smaller the control of the enzymes on the flux, on average. Smaller control means that enzyme efficiencies are at or near a plateau, which corresponds to a highly concave enzyme-flux relationship, *i.e.* robustness to mutations of metabolic genes [21, 22].

Interestingly, several studies have reported that the robustness of gene expression patterns increases as the number of connections and regulatory factors increases [discussed in 23]. These results suggests a widespread link between robustness – a consequence of diminishing returns – and network complexity, a link that is possibly valid for any network of transportation of matter and energy (*e.g.* metabolic networks, gene regulatory networks, signal transduction pathways, etc.). Thus, in addition to the numerous "local" mechanisms of robustness that are assumed to result from natural selection (feedback loops, kinetic proofreading, modularity, redundancy, etc. [reviewed in 24, 23, 4, 25]), there would be an intrinsic robustness, precluding any selective advantage, which emerges from the complexity of the global cellular network.

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Supplementary information

Relationship between the conductance of a resistor and the total current in an electrical circuit

Relationship between an individual conductance and the equivalent conductance The junction equations for all node potentials in an electrical circuit of n nodes ($n > 2$) can be expressed as:

$$\Sigma \mathbf{U} = \mathbf{I}$$

where $\mathbf{U} = (U_1, U_2, \ldots, U_n)^{\mathrm{T}}$ is the vector of the potentials, $\mathbf{I} = (I_{out}, 0, \ldots, 0, I_{in})^{\mathrm{T}}$ is the vector of the currents and Σ the conductance matrix in the electrical circuit,

$$\Sigma = \begin{pmatrix} c_1 & -\sigma_{12} & -\sigma_{13} & -\sigma_{14} & \cdots & -\sigma_{1,n} \\ -\sigma_{21} & c_2 & -\sigma_{23} & -\sigma_{24} & \cdots & -\sigma_{2,n} \\ -\sigma_{31} & -\sigma_{32} & c_3 & -\sigma_{34} & \cdots & -\sigma_{3,n} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ -\sigma_{n,1} & -\sigma_{n,2} & -\sigma_{n,3} & -\sigma_{n,4} & \cdots & c_n \end{pmatrix}$$

with $c_i = \sum_{\substack{j \neq i \\ i=1}}^{n} \sigma_{ij}$. Note that $\sigma_{ij} = 0$ for non-connected nodes.

Kagan[16] derived the formula for the equivalent conductance in a generic non-simplifiable circuit and, by posing $U_1 = \varepsilon$ and $U_n = 0$, showed that

$$\sigma_{\mathrm{E}} = \frac{\det \Sigma'}{\det \Sigma''}$$

where Σ' is the upper left sub-matrix $(n-1) \times (n-1)$ of the conductance matrix Σ

$$\Sigma' = \begin{pmatrix} c_1 & -\sigma_{12} & -\sigma_{13} & -\sigma_{14} & \cdots & -\sigma_{1,n-1} \\ -\sigma_{21} & c_2 & -\sigma_{23} & -\sigma_{24} & \cdots & -\sigma_{2,n-1} \\ -\sigma_{31} & -\sigma_{32} & c_3 & -\sigma_{34} & \cdots & -\sigma_{3,n-1} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ -\sigma_{n-1,1} & -\sigma_{n-1,2} & -\sigma_{n-1,3} & -\sigma_{n-1,4} & \cdots & c_{n-1} \end{pmatrix}$$

and Σ'' is the lower right sub-matrix $(n-2) \times (n-2)$ of Σ'

$$\Sigma'' = \begin{pmatrix} c_2 & -\sigma_{23} & -\sigma_{24} & \cdots & -\sigma_{2,n-1} \\ -\sigma_{32} & c_3 & -\sigma_{34} & \cdots & -\sigma_{3,n-1} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ -\sigma_{n-1,2} & -\sigma_{n-1,3} & -\sigma_{n-1,4} & \cdots & c_{n-1} \end{pmatrix}$$

Kagan [16] showed that each term in $\det \Sigma'$ and $\det \Sigma''$ is positive. Thus, the equivalent conductance is a ratio of two polynomials of degree $(n-1)$ and $(n-2)$, respectively, with only positive terms. Thus, it is possible to express σ_{E} as:

$$\forall \sigma_{ij} \quad \sigma_{\mathrm{E}} = \frac{A\sigma_{ij} + B}{C\sigma_{ij} + D} \tag{4}$$

were A, B, C and D are non-negative terms that depend on all conductances other than σ_{ij}.

Proof of concavity A real-valued function $f : \mathbb{R} \to \mathbb{R}$ is said to be concave if, $\forall x, y \in \mathbb{R}$ and $\forall \alpha \in [0, 1]$,

$$f((1-\alpha)x + \alpha y) \geq (1-\alpha) f(x) + \alpha f(y) \tag{5}$$

The function f is given here by eq. 4, so by substituting it in eq. 5 we have:

$$\frac{((1-\alpha)\sigma_{ij}^x + \alpha \sigma_{ij}^y)A + B}{((1-\alpha)\sigma_{ij}^x + \alpha \sigma_{ij}^y)C + D} \geq (1-\alpha)\frac{\sigma_{ij}^x A + B}{\sigma_{ij}^x C + D} + \alpha \frac{\sigma_{ij}^y A + B}{\sigma_{ij}^y C + D}$$

We have to prove that this inequality is valid $\forall ij$.

Taking the least common denominator and denoting $\sigma^* = ((1-\alpha)\sigma^x_{ij} + \alpha\sigma^y_{ij})$, the above equation can be written as

$$\frac{(\sigma^* A + B)(\sigma^x_{ij} C + D)(\sigma^y_{ij} C + D)}{(\sigma^* C + D)(\sigma^x_{ij} C + D)(\sigma^y_{ij} C + D)} \geq \frac{(1-\alpha)(\sigma^x_{ij} A + B)(\sigma^* C + D)(\sigma^y_{ij} C + D) + \alpha(\sigma^y_{ij} A + B)(\sigma^* C + D)(\sigma^x_{ij} C + D)}{(\sigma^* C + D)(\sigma^x_{ij} C + D)(\sigma^y_{ij} C + D)} \quad (6)$$

Given that $\forall \sigma_{ij}$, $\sigma_{ij} \geq 0$ and $A, B, C, D \geq 0$, eq. 6 is satisfied if and only if

$$(\sigma^* A + B)(\sigma^x_{ij} C + D)(\sigma^y_{ij} C + D) \geq (1-\alpha)(\sigma^x_{ij} A + B)(\sigma^* C + D)(\sigma^y_{ij} C + D) + \alpha(\sigma^y_{ij} A + B)(\sigma^* C + D)(\sigma^x_{ij} C + D)$$

Thus,

$$(\sigma^* A + B)(\sigma^x_{ij} C + D)(\sigma^y_{ij} C + D) \geq (\sigma^* C + D)(AD\sigma^* + \sigma^x_{ij}\sigma^y_{ij} AC + ((1-\alpha)\sigma^y_{ij} + \alpha\sigma^x_{ij})BC + BD)$$

$$ACD(\sigma^* - \sigma^y_{ij})(\sigma^x_{ij} - \sigma^*) + BCD(\sigma^x_{ij} + \sigma^y_{ij} - \sigma^* - ((1-\alpha)\sigma^y_{ij} + \alpha\sigma^x_{ij})) + BC^2(\sigma^x_{ij}\sigma^y_{ij} - \sigma^*((1-\alpha)\sigma^y_{ij} + \alpha\sigma^x_{ij})) \geq 0 \quad (7)$$

Noting that

$$(\sigma^* - \sigma^y_{ij})(\sigma^x_{ij} - \sigma^*) = (\sqrt{\alpha(1-\alpha)}\sigma^x_{ij} - \sqrt{\alpha(1-\alpha)}\sigma^y_{ij})^2$$
$$\sigma^x_{ij} + \sigma^y_{ij} - \sigma^* - ((1-\alpha)\sigma^y_{ij} + \alpha\sigma^x_{ij}) = 0$$

and

$$\sigma^x_{ij}\sigma^y_{ij} - \sigma^*((1-\alpha)\sigma^y_{ij} + \alpha\sigma^x_{ij}) = -(\sqrt{\alpha(1-\alpha)}\sigma^x_{ij} - \sqrt{\alpha(1-\alpha)}\sigma^y_{ij})^2$$

eq. 7 can be simplified to

$$AD - BC \geq 0 \quad (8)$$

Thus, this inequality must be satisfied to verify the concave relationship between a particular conductance, all others being constant, and the equivalent conductance.

Without loss of generality, we can focus on σ_{12}. We set $c'_1 = c_1 - \sigma_{12}$, $c'_2 = c_2 - \sigma_{12}$ and $n - 1 = k$. So we have

$$A = \begin{vmatrix} c'_1 + c'_2 & -(\sigma_{13} + \sigma_{23}) & \dots & -(\sigma_{1,k} + \sigma_{2,k}) \\ -(\sigma_{31} + \sigma_{32}) & c_3 & \dots & -\sigma_{3,k} \\ \vdots & \vdots & \ddots & \vdots \\ -(\sigma_{k,1} + \sigma_{k,2}) & -\sigma_{k,3} & \dots & c_k \end{vmatrix}$$

$$B = \begin{vmatrix} c'_1 & c'_1 & -\sigma_{13} & \dots & -\sigma_{1,k} \\ c'_1 & c'_1 + c'_2 & -(\sigma_{13} + \sigma_{23}) & \dots & -(\sigma_{1,k} + \sigma_{2,k}) \\ -\sigma_{31} & -(\sigma_{31} + \sigma_{32}) & c_3 & \dots & -\sigma_{3,k} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ -\sigma_{k,1} & -(\sigma_{k,1} + \sigma_{k,2}) & -\sigma_{k,3} & \dots & c_k \end{vmatrix}$$

$$C = \begin{vmatrix} c_3 & \dots & -\sigma_{3,k} \\ \vdots & \ddots & \vdots \\ -\sigma_{k,3} & \dots & -c_k \end{vmatrix}$$

$$D = \begin{vmatrix} c'_2 & -\sigma_{23} & \dots & -\sigma_{2,k} \\ -\sigma_{32} & c_3 & \dots & -\sigma_{3,k} \\ \vdots & \vdots & \ddots & \vdots \\ -\sigma_{k,2} & -\sigma_{k,3} & \dots & c_k \end{vmatrix}$$

Now, we need to verify eq. 8 to demonstrate the concave relationship between a particular conductance, all others being fixed, and the equivalent conductance. To this end we used the Jacobi's theorem.

Let M denotes the determinant of a matrix $M = \|m_{ij}\|_1^n$, M^c denotes the determinant of the matrix of its cofactors $M^c = \|M_{ij}\|_1^n$, $1 \leq p < n$ and $\sigma\binom{i_1 \dots i_n}{j_1 \dots j_n}$ denotes an arbitrary permutation of the n rows and columns of M. Then

$$\begin{vmatrix} M_{i_1 j_1} & \dots & M_{i_1 j_p} \\ M_{i_2 j_1} & \dots & M_{i_2 j_p} \\ \vdots & \ddots & \vdots \\ M_{i_p j_1} & \dots & M_{i_p j_p} \end{vmatrix} = (-1)^\sigma \begin{vmatrix} m_{i_{p+1} j_{p+1}} & \dots & m_{i_{p+1} j_n} \\ m_{i_{p+2} j_{p+1}} & \dots & m_{i_{p+2} j_n} \\ \vdots & \ddots & \vdots \\ m_{i_n j_{p+1}} & \dots & m_{i_n j_n} \end{vmatrix} \cdot M^{p-1}$$

Now, note that C is a minor of B obtained by deleting the first two rows and columns of B. Using Jacobi's theorem, with $p = 2$, $n = k$, $i_l = l$ and $j_l = l \ \forall l \in 1, \dots k$, we can express BC as

$$\begin{vmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{vmatrix} = (-1)^\sigma C B^{2-1} = CB \tag{9}$$

since $\sigma = 0$ (there are no permutations).

Using the sum property of the determinants, we can rewrite B as

$$B = \begin{vmatrix} c_1' & 0 & -\sigma_{13} & \dots & -\sigma_{1,k} \\ 0 & c_2' & -\sigma_{23} & \dots & -\sigma_{2,k} \\ -\sigma_{31} & -\sigma_{32} & c_3 & \dots & -\sigma_{3,k} \\ \vdots & \vdots & \ddots & \vdots & \\ -\sigma_{k,1} & -\sigma_{k,2} & -\sigma_{k,3} & \dots & c_k \end{vmatrix}$$

and give an explicit expression of the cofactors in eq. 9 :

$$B_{11} = D$$

$$B_{12} = - \begin{vmatrix} 0 & -\sigma_{23} & \dots & -\sigma_{2,k} \\ -\sigma_{31} & c_3 & \dots & -\sigma_{3,k} \\ \vdots & \vdots & \ddots & \vdots \\ -\sigma_{k,1} & -\sigma_{k,3} & \dots & c_k \end{vmatrix} = -B^{**}$$

$$B_{21} = - \begin{vmatrix} 0 & -\sigma_{13} & \dots & -\sigma_{1,k} \\ -\sigma_{32} & c_3 & \dots & -\sigma_{3,k} \\ \vdots & \vdots & \ddots & \vdots \\ -\sigma_{k,2} & -\sigma_{k,3} & \dots & c_k \end{vmatrix} = -B^{*}$$

$$B_{22} = \begin{vmatrix} c_1' & -\sigma_{13} & \dots & -\sigma_{1,k} \\ -\sigma_{31} & c_3 & \dots & -\sigma_{3,k} \\ \vdots & \vdots & \ddots & \vdots \\ -\sigma_{k,1} & -\sigma_{k,3} & \dots & c_k \end{vmatrix}$$

Thus,

$$BC = \begin{vmatrix} D & -B^{**} \\ -B^* & B_{22} \end{vmatrix} = DB_{22} - (B^*)^2$$

where $B^* = B^{**}$ since the respective matrices are a transpose of each other.

On the other hand, we can rewrite A as a function of D, B^* and B_{22}. Using the properties of determinants, we get

$$A = 2B^* + D + B_{22}$$

We can now substitute all this information in eq. 8:

$$AD - BC = (2B^* + D + B_{22})D - (B_{22}D - (B^*)^2) = 2B^*D + D^2 + (B^*)^2 = (D + B^*)^2$$

which is always equal to or greater than zero. Thus eq. 8 is always satisfied, meaning that the relationship between any conductance and the equivalent conductance is concave for any electrical circuit, the limits of the hyperbola being

$$\lim_{\sigma_{ij} \to 0} \sigma_{\mathrm{E}} = B/D \quad \text{and} \quad \lim_{\sigma_{ij} \to +\infty} \sigma_{\mathrm{E}} = A/C$$

As the equivalent conductance is proportional to the total current through the circuit, we have shown that the law of diminishing returns applies to the relationship between any conductance and the total current, irrespective of the topology of the circuit.