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Un enfoque para la compensación energética

An approach to energy compensation

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Resumen

La epistasis intramolecular, en el contexto de la compensación energética, describe cómo interactúan pares de residuos dentro de una proteína para preservar la estabilidad estructural ante perturbaciones. Este trabajo presenta un marco matemático derivado de principios termodinámicos para formalizar la compensación energética entre residuos. Al definir la función escalar Cpq e incorporar derivadas de primer y segundo orden, curvaturas locales y cruzadas, y coeficientes de sensibilidad, el modelo captura cómo se propagan las perturbaciones en los estados conformacionales a través de la red proteica. Se introduce la matriz hessiana para caracterizar la rigidez energética, la flexibilidad y el acoplamiento estructural, mientras que los coeficientes λpq cuantifican la eficiencia de la transmisión de energía y revelan condiciones de robustez, plasticidad, independencia, conflicto y resonancia destructiva. En conjunto, este enfoque proporciona una base conceptual y cuantitativa para mapear la geometría energética de las proteínas, identificar regiones críticas que actúan como amortiguadores, absorbentes o amplificadores de perturbaciones, y avanzar en la comprensión de cómo las proteínas mantienen la homeostasis y la estabilidad adaptativa.

Palabras clave: Epistasis intramolecular; Acoplamiento estructural; Mutaciones compensatorias

Abstract

Intramolecular epistasis, in the context of energy compensation, describes how pairs of residues within a protein interact to preserve structural stability under perturbations. This work presents a mathematical framework derived from thermodynamic principles to formalize energy compensation between residues. By defining the scalar function Cpq and incorporating first- and second-order derivatives, local and cross curvatures, and sensitivity coefficients, the model captures how perturbations in conformational states propagate through the protein network. The Hessian matrix is introduced to characterize energetic rigidity, flexibility, and structural coupling, while the coefficients λpq quantify the efficiency of energy transmission and reveal conditions of robustness, plasticity, independence, conflict, and destructive resonance. Altogether, this approach provides a conceptual and quantitative basis for mapping the energetic geometry of proteins, identifying critical regions that act as buffers, absorbers, or amplifiers of perturbations, and advancing the understanding of how proteins maintain homeostasis and adaptive stability.

Key words: Intramolecular epistasis; Structural coupling; Compensatory mutations

An approach to energy compensation

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Abstract

Intramolecular epistasis, in the context of energy compensation, describes how pairs of residues within a protein interact to preserve structural stability under perturbations. This work presents a mathematical framework derived from thermodynamic principles to formalize energy compensation between residues. By defining the scalar function C_{pq} and incorporating first- and second-order derivatives, local and cross curvatures, and sensitivity coefficients, the model captures how perturbations in conformational states propagate through the protein network. The Hessian matrix is introduced to characterize energetic rigidity, flexibility, and structural coupling, while the coefficients λ_{pq} quantify the efficiency of energy transmission and reveal conditions of robustness, plasticity, independence, conflict, and destructive resonance. Altogether, this approach provides a conceptual and quantitative basis for mapping the energetic geometry of proteins, identifying critical regions that act as buffers, absorbers, or amplifiers of perturbations, and advancing the understanding of how proteins maintain homeostasis and adaptive stability.

Keywords: Intramolecular epistasis, energy compensation, structural coupling, perturbations, adaptive stability.

Introduction

Intramolecular epistasis, in the context of energy compensation, refers to the interaction between two residues within the same protein that, together, influence its structural stability (1). This phenomenon can be illustrated by the case in which one mutation causes a detrimental effect on the protein's functionality, while a second mutation compensates for that effect, restoring the original functionality (2). In this process, the free interaction energy remains practically constant, reflecting a compensatory balance to the initial perturbation (4, 5). To understand this process, it is necessary to conceive of the protein as a network of internal interactions governed by energetic parameters that, in an abstract way, represent its capacity to perform the required biological work (6-9).

In this brief report, a mathematical approach is presented starting from the general equation of thermodynamics, with the purpose of defining energy compensation between two residues of a protein. Likewise, the use of the Hessian matrix is introduced as a tool to analyze the energetic curvature of the protein network, allowing the evaluation of how internal forces are modified under perturbations in the conformational states of those residues. All of this aims to understand local stability (whether a residue is in an energy minimum or in an unstable region), structural coupling (how two residues mutually influence each other when one is perturbed), rigidity and flexibility (regions of the protein more susceptible to deformations), and energetic resonance (compensation pathways that amplify or attenuate perturbations).

Mathematical approach

Starting from the fundamental equation of thermodynamics, $\Delta G = \Delta H - T\Delta S$, the equation was generalized to obtain a function that represents the energetic interaction between two residues in a protein, under the assumption that the protein behaves as an energy network.

$$G(x) = \sum_{i=1}^{N} [h(x_i) - Ts(x_i)] + \sum_{i<j} f(x_i, x_j) \qquad \text{Eq. 1}$$

Where $h(x_i) \simeq a_i x_i^2$ represents the local enthalpy for a harmonic energy system, $s(x_i) \simeq b_i log(x_i)$ represents Boltzmann entropy, and $f(x_i, x_j) \simeq c_{ij} x_i x_j$ represents the interaction force between two residues. By substituting into Eq. 1, the following was obtained:

$$G(x) = \sum_{i=1}^{N} [a_i x_i^2 - Tb_i ln(x_i)] + \sum_{i<j} c_{ij} x_i x_j$$

Then, for each residue x_k corresponding to local sensitivity.

$$\frac{\partial G}{\partial x_k} = \frac{da_k x_k^2}{dx_k} + \frac{d(-Tb_k log(x_k))}{dx_k} + \frac{d(c_{kj} x_k x_j)}{dx_k} + \frac{d(c_{ik} x_i x_k)}{dx_k} = 2a_k x_k - \frac{Tb_k}{x_k} + \sum_{j \neq k} c_{kj} x_j \qquad \text{Eq. 2}$$

Where $2a_k x_k$ becomes the structural anchor of the system, $-\frac{Tb_k}{x_k}$ the conformational freedom, and $\sum_{j\neq k} c_{kj}x_j$ (calculated from the sum $\sum_{j\neq k} c_{kj}x_j + \sum_{j\neq k} c_{ik}x_i$) is the net force on residue k, under a structural communication model.

By establishing a relationship of mutual sensitivity between two residues with conformational states "p" and "q," where x is a variable representing a physical or structural state of each residue as two nodes in a protein network (spatial position, torsion angle, rotation angle, degree of solvent exposure, bonding state, or any other parameter influencing energetic contribution), from Eq. 2 the first-order derivatives were calculated, where:

$$\frac{\partial G}{\partial x_p}=2a_p x_p - \frac{Tb_p}{x_p} + \sum_{j\neq p} c_{pj}x_j \qquad \text{Eq. 3}$$

$$\frac{\partial G}{\partial x_q}=2a_q x_q - \frac{Tb_q}{x_q} + \sum_{j\neq q} c_{qj}x_j \qquad \text{Eq.4}$$

Next, under the assumption that a perturbation generates compensation, the Taylor expansion is used.

$$\Delta G \simeq \frac{\partial G}{\partial x_q}\Delta x_p + \frac{\partial G}{\partial x_q}\Delta x_q \simeq 0$$

It was solved for Δx_q, with the purpose of obtaining an adjustment in x_q to compensate for a perturbation in x_p

$$\Delta x_q \simeq \frac{\frac{\partial G}{\partial x_p}}{\frac{\partial G}{\partial x_q}}\Delta x_p$$

Likewise, the scalar function of energy compensation $C_{pq}(x)$ was defined for residues x_p and x_q, , depending on the configuration of "x," as:

$$C_{pq}(x) = \frac{\Delta G/\partial x_p}{\Delta G/\partial x_q} \qquad \text{Eq. 5}$$

With this, (3) and (4) were substituted into (5), to obtain:

$$C_{pq}(x) = \frac{-2a_p x_p - Tb_p/x_p + \sum_{j\neq p} c_{pj} x_j}{2a_q x_q - Tb_q/x_q + \sum_{j\neq q} c_{qj} x_j} \qquad \text{Eq. 6}$$

In this way, the approximation can be evaluated for any conformation of the system, where constant C_{pq} implies that compensation is stable: if C_{pq} varies with x, there is energetic plasticity; if $C_{pq} \simeq 0$, the residues are energetically independent; and if C_{pq} changes sign, an energetic conflict arises.

Then, to address the question: *How does energy compensation vary when the conformational states* x_p and x_q*, are perturbed, in order to identify the regions of the protein where compensation is robust, fragile, or adaptive?*; the second-order derivatives were defined, first for the local curvature in the form of a diagonal Hessian representing the local energetic rigidity of each residue, where a local minimum is detected when $H_{pp}\ or\ H_{qq} > 0$, and zones of flexibility appear at small values of H_{pp} or H_{qq}.

$$H_{pp} = \frac{\partial^2 G}{\partial x_p^2} = 2a_p + \frac{Tb_p}{x_p^2} \qquad \text{Eq. 7}$$

$$H_{qq} = \frac{\partial^2 G}{\partial x_q^2} = 2a_q + \frac{Tb_q}{x_q^2} \qquad \text{Eq. 8}$$

And second, for the second-order cross curvature, establishing a direct structural coupling between residues “p” and “q,” under the assumption that the interaction term $f(x_p, x_q) = c_{pq} x_p x_q$, where c_{pq} represents the curvature of the energetic landscape between residues “p” and “q,” to construct a Hessian matrix $H_{pq} = \frac{\partial^2 G}{\partial x_p \partial x_q} = c_{pq}$ which describes the energetic geometry of the protein network. In this framework, it is possible to map functional interactions whenever $H_{pq} \neq 0$. Likewise, if the value of $c_{pq} > 0$, it implies that the residues energetically cooperate; if $c_{pq} < 0$, it implies that the residues compete or repel each other; and if $c_{pq} = 0$, the residues are energetically independent. In this way, the equation is described as follows:

$$\frac{\partial^2 G}{\partial x_p \partial x_q} = c_{pq}, \text{ for } \frac{\partial C_{pq}}{\partial x_p} \text{ y } \frac{\partial C_{pq}}{\partial x_q} \qquad \text{Eq. 9}$$

To address this question, for practical reasons and to simplify, the first-order derivatives were defined as: $A_p := \frac{\partial G}{\partial x_p}$ y $A_q := \frac{\partial G}{\partial x_q}$, with the purpose of deriving in terms of compensation starting from Eq. 1.

$$G(x) = \sum_{i=1}^{N} [h(x_i) - Ts(x_i)] + \sum_{i<j} f(x_i, x_j) \qquad \text{Eq. 10}$$

$$A_p = 2a_p x_p - Tb_p / x_p + \sum_{j \neq p} c_{pj} x_j \qquad \text{Eq. 11}$$

$$A_p = 2a_q x_q - Tb_q / x_q + \sum_{j \neq q} c_{qj} x_j \qquad \text{Eq. 12}$$

Then, these were represented as a quotient that measures how much variation in x_q is required to compensate for a perturbation in x_p while keeping the total free energy constant.

$$C_{pq}(x) = - \frac{A_p}{A_q} \qquad \text{Eq. 13}$$

Deriving for C as a function of “x”:

$$\frac{dC}{dx} = - \frac{A_q \frac{dA_p}{dx} - A_p \frac{dA_q}{dx}}{A_q^2} \qquad \text{Eq 14.}$$

Solving for x_q and x_p:

$$\frac{\partial C_{pq}}{\partial x_p} = - \frac{A_q \frac{\partial A_p}{\partial x_p} - A_p \frac{\partial A_q}{\partial x_p}}{A_q^2} \text{ y } \frac{\partial C_{pq}}{\partial x_q} = - \frac{A_q \frac{\partial A_p}{\partial x_q} - A_p \frac{\partial A_q}{\partial x_q}}{A_q^2} \qquad \text{Eq. 15}$$

By substituting into Eq. 15 the values $\frac{\partial A_p}{\partial x_p} = \frac{\partial^2 G}{\partial x_p^2} = 2a_p + Tb_p / x_p^2$, $\frac{\partial A_q}{\partial x_q} = \frac{\partial^2 G}{\partial x_q^2} = 2a_q + Tb_q / x_q^2$, $\frac{\partial A_p}{\partial x_q} = \frac{\partial^2 G}{\partial x_p \partial x_q} = c_{pq}$ y $\frac{\partial A_q}{\partial x_p} = \frac{\partial^2 G}{\partial x_p \partial x_q} = c_{pq}$, the following equations were obtained:

$$\frac{\partial C_{pq}}{\partial x_p} = - \frac{A_q (2a_p + Tb_p / x_p^2) - A_p c_{pq}}{A_q^2} \qquad \text{Eq. 16}$$

$$\frac{\partial C_{pq}}{\partial x_q} = -\frac{A_q c_{pq} - A_p(2a_q + Tb_q/x_q^2)}{A_q^2} \qquad \text{Eq. 17}$$

Where, if $\frac{\partial C_{pq}}{\partial x_p} \simeq 0$, compensation is insensitive to perturbations in x_p(the system exhibits robustness and can tolerate fluctuations in "p" without losing stability; residue "q" is well coupled and acts as a buffer or passive compensator). If $\frac{\partial C_{pq}}{\partial x_q} \simeq 0$ residue "q" absorbs the perturbation without altering compensation ("q" has energetic flexibility and acts as an absorber that redistributes energy without generating instability—in other words, it maintains the system's homeostasis). And if both derivatives are large, compensatory instability arises.

Finally, by reformulating the energy compensation from Eq. 6 with the elements of the Hessian matrix, a new function was obtained using the sensitivity coefficients λ_p, λ_q, λ_{pq}, λ_{qp} and δx_p, δx_q as perturbations of the conformational states, where $C_{pq}(x)$ comes to represent the net force on "p" due to its own local rigidity and coupling with "q," over the net force on "q" corrected by its own rigidity and by the influence of "p."

$$C_{pq}(x) = -\frac{A_p + \lambda_p H_{pp} \delta x_p + \lambda_{pq} H_{pq} \delta x_q}{A_q + \lambda_q H_{qq} \delta x_q + \lambda_{qp} H_{pq} \delta x_p} \qquad \text{Eq. 18}$$

Thus, if $\lambda_{pq} \neq 0$, "q" responds to perturbations in "p"; and if $\lambda_{pq} = 0$, compensation is passive.

Returning to the cross derivative of H_{pq}, this tells us that if $H_{pq} > 0$, a perturbation in x_p increases the force in x_q, if $H_{pq} < 0$, the perturbation in x_p reduces the force in x_q; and if $H_{pq} = 0$, there is no direct influence. Since this alone is not sufficient to calculate how much of that influence is conducted into functional compensation, the coefficient λ_{pq} is required. For this calculation, the following was first defined:

$$\lambda_{pq} := \frac{dx_q}{dx_p}\Big|_{compensation} \qquad \text{Eq. 19}$$

To express how much x_q must vary to compensate for a perturbation in x_p, while keeping $G(x)$ constant. Then, maintaining the compensation condition:

$$\delta G = \frac{\partial G}{\partial x_p}\delta x_p + \frac{\partial G}{\partial x_q}\delta x_q = 0 \Rightarrow \frac{dx_q}{dx_p} =- \frac{\partial G/}{\partial G/} \qquad \text{Eq. 20}$$

Next, by perturbing x_p so that x_q responds according to the curvature, it was defined:

$\lambda_{pq} := \frac{d^2 x_q}{dx_p^2}|_{compensation} \propto H_{pq}$, defining $\lambda_{pq} = \frac{H_{pq}}{H_{qq}}$ or $\lambda_{pq} = \frac{H_{pq}}{\sqrt{H_{pp}H_{qq}}}$ depending on whether a local or symmetric normalization is desired. Thus, λ_{pq} measures the efficiency of energetic transmission between “p” and “q”: if λ_{pq} is large, it implies that “q” actively responds to perturbations in “p”; if $\lambda_{pq} \simeq 0$, compensation is passive or null; and if $\lambda_{pq} < 0$, it corresponds to a possible destructive resonance. Where resonance refers to the phenomenon of propagation or amplification of a synchronized perturbation across the protein network, due to the geometry of the coupling and the curvature of the system.

Conclusions

The model developed makes it possible to understand how protein residues respond to conformational perturbations through a mathematical framework that integrates scalar compensation functions, first- and second-order derivatives, local and cross curvatures, as well as sensitivity coefficients. The definition of $C_{pq}(x)$, together with the Hessian matrix and the parameters λ_{pq}, provides a clear view of energy transmission within the protein network, distinguishing scenarios of robustness, plasticity, independence, and conflict. Compensation is shown to be stable when C_{pq} is constant, flexible when it varies with conformation, null when it tends to zero, and conflicting when it changes sign. Moreover, the interpretation of derivatives and sensitivity coefficients allows the identification of protein regions where compensation is robust, fragile, or adaptive, revealing that certain residues act as passive buffers, others as energetic absorbers, and some as active transmission nodes or even as sites of destructive resonance. Altogether, this theoretical and mathematical framework establishes a conceptual basis for mapping the energetic geometry of proteins and understanding how they maintain homeostasis under perturbations, opening the possibility of locating critical zones that determine their functional stability and adaptive capacity.

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