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Fractals and self-organized criticality in anti-inflammatory drugs

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HIGHLIGHTS

- There are two kinds of aspirin; both act by inhibiting a certain catalytic activity.
- Large medical differences are unexplained at the molecular level.
- Fractals quantify bicyclic imbalances of large-scale hydropathic forces.
- Success made possible by a new record of 25 decades for fractal content.
- Natural surface mutations can modify bicyclic imbalances.

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) act through inhibiting prostaglandin synthesis, a catalytic activity possessed by two distinct cyclooxygenase (COX-1 and COX-2) isozymes encoded by separate genes. The discovery of COX-2 launched a new era in NSAID pharmacology, resulting in the synthesis, marketing, and widespread use of COX-2 selective inhibitors. Extensive structural studies of the biology of prostaglandin synthesis and inhibition have explained some of the differences between COX-1 and COX-2 functionality, but others are still unexplained. Notably these include molecular differences that cause COX-1 inhibitors to produce a slight decrease, and COX-2 inhibitors to induce a significant increase, in heart attacks and strokes. These differences were unexpected because of the 60% overall COX-1 and COX-2 sequence similarity and the 1–2 conservation of catalytic sites. Hydropathic analysis shows important bicyclic differences between COX-1 and COX-2 on a large scale outside the catalytic pocket. These differences involve much stronger amphiphilic interactions in COX-2 than in COX-1, and may explain the selective antiplatelet effectiveness of COX-2. Success of the non-Euclidean structural analysis is the result of using the new Brazilian hydropathicity scale based on self-organized criticality (SOC) of universal protein modules.

1. Introduction

Aspirin (acetylsalicylic acid or ASA) is probably the oldest drug (its uses stretch back to antiquity, though pure ASA has been manufactured and marketed only since 1899), see Wiki on history of aspirin. In 1971 Vane discovered the mechanism by which aspirin exerts its anti-inflammatory, analgesic and antipyretic actions. Aspirin and other non-steroid anti-inflammatory drugs (NSAIDs) inhibit the activity of cyclooxygenase (COX) which leads to the formation of prostaglandins

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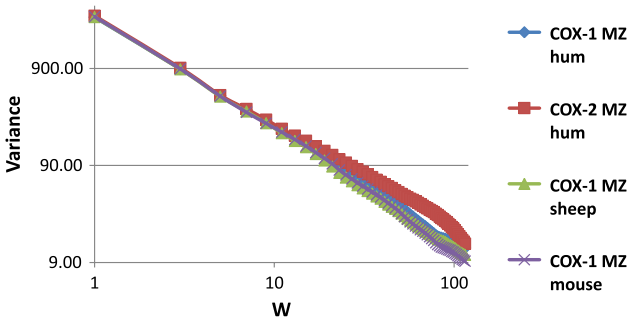

Fig. 1. Variances $\mathcal{R}(W)$ for COX-1 for several species and COX-2 human. For large W the differences are larger, and the evolutionary trends (mouse–sheep–human) of COX-1 become monotonic. The small differences shown here are enhanced in Fig. 2 by comparing variance ratios. Ratios can also be applied successfully to monitoring evolutionary advances in functionality, and identifying optimal values of W [6,7].

(PGs) that cause inflammation, swelling, pain and fever. However, by inhibiting this key enzyme in PG synthesis, the aspirin-like drugs also prevent the production of physiologically important PGs which protect the stomach mucosa from damage by hydrochloric acid, maintain kidney function and aggregate platelets when required. This conclusion provided a unifying explanation for the therapeutic actions and shared side effects of the aspirin-like drugs. Daniel Simmons discovered the COX-2 enzyme in 1988, and Harvey Herschman discovered a COX-2 gene in 1991. The constitutive isoform, COX-1, supports the beneficial homeostatic functions, whereas the inducible isoform, COX-2, becomes upregulated by inflammatory mediators [1].

COX-2 inhibitors became attractive when it was realized that they could have the same anti-inflammatory, anti-pyretic, and analgesic activities as nonselective inhibitors NSAIDs, with little or none of the gastrointestinal side-effects [2]. However, the most important difference between COX-1 and COX-2 inhibitors is the appearance of significant cardiovascular toxicity associated with chronic use (2%–4% of patients after 3 years) of COX-2. This difference remains unexplained, although there are few enzymes of lipid biochemistry for which there is such a wealth of structural and functional information [3]. However, this structural information is limited to COX complexed with inhibitors, which are known to strain the wild structures [4].

Given that only 50% sequence identity is enough to make the backbone coordinates of chicken and human lysozyme *c* superposable to 1.5 A [5], the larger 60%–65% sequence identity of COX-1 and COX-2 should be enough to prevent elucidation of their functional differences from structural data alone [2]. However, Ref. [5] found that the evolutionary trends from chicken to human of compensating enzymatic and lytic properties of lysozyme *c* were explicable from analysis of their amino acid (aa) sequences alone, by evaluating their hydroanalytic profiles and modular correlations. These new methods extract a wealth of information from (aa) sequences alone, by using scaling to obtain amino acid hydropathicities. The latter describe water–protein interactions in a quasi-one-dimensional non-Euclidean space quite different from conventional Euclidean three-dimensional structural models. Because the description has both evolutionary and thermodynamic aspects, it yielded many accurate results both for amyloid precursor A4 (770 aa) [6] and amyloid beta (40 aa) [7] unobtainable from conventional Euclidean structural models alone.

Here we use similar hydroanalytic methods to analyze functional differences between COX-1 and COX-2 in terms of the human amino acid sequences Uniprot P23219 COX-1, 599 aa, and COX-2, 604 aa, P35354. In earlier work we found that the best single descriptor of small differences between similar proteins is given by their roughnesses $\mathcal{R}(W)$ or variances of $\psi(\text{aa}, W)$, where $\psi(\text{aa}, W)$ is $\psi(\text{aa}, 1)$ averaged over a sliding window of length W centered on consecutive aa. Here $\psi(\text{aa}, 1)$ is a hydropathicity value from one of two scales, the KD scale [8], which corresponds to complete (water–air) unfolding, and has first-order thermodynamic character, and the Brazilian MZ scale based on modular surface areas obtained from Voronoi partitioning [9], which has second-order character and reflects both evolutionary and thermodynamic aspects of protein optimization. The MZ scale has yielded consistently much more accurate sequence-functional results [5, 6.7], which is not surprising, as it is ideally suited to describing conformational changes and how these change protein packing.

2. Optimizing the length scale *W*

Because of the large sequence identity of COX-1 and COX-2, it may appear difficult to analyze their differences quantitatively. However, their similarity can be turned to advantage by comparing their overall roughnesses or sequence variances $\mathcal{R}(W)$ in Fig. 1. We see that the $\mathcal{R}(W)$ differences are small for small W, but increase with increasing W, finally peaking at $W = 79$. The meaning of this large value of W will be made clear below, but for the moment we can interpret it as an average spacing between the centers of modules that are involved in critical large-scale conformational changes that distinguish COX-1 from COX-2.