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# Low-frequency resonance and cooperativity of hemoglobin

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contributing important work on biosynthesis and the role of *polyamines* in cell functions and neoplastic growth. An International Symposium on Polyamines is organized biannually in Naples, where the role of methyladenosine phosphorylase in polyamine biosynthesis and polyamines of thermophiles are studied by E. Zappia's group. Regulation of ornithine-decarboxylase is investigated in Bologna (C. M. Caldarera). The metabolism of polyamines in different tissues is investigated in Rome (B. Mondovi), in Turin (N. Bargoni and M. A. Grillo) and in Modena (B. Barbiroli).

Italy has a tradition for studies on *Marine Biochemistry*. There are groups working in genetics and enzymology of sea organisms at the University of Bari (M. N. Gadaleta), Bologna (R. Viviani) and Messina (G. Cuzzucra), others are interested in possible exploitation of the marine environment for economical purposes. There are post-graduate schools specializing in Marine Biochemistry at the Universities of Bologna and Messina.

Limitation in the space available makes it impossible to describe in detail the achievements of biochemical research in Italy and to mention the names of many distinguished bio-

chemists. For this reason, only senior investigators of the various groups have been quoted. We apologize for these as well as for other unintentional omissions. However, a further up-to-date appraisal of current biochemical research in Italy can be obtained by glancing through the abstracts of the numerous contributions presented by Italian investigators at the 19th FEBS Meeting in Rome this July.

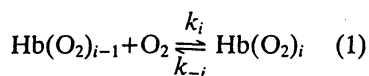
Italian biochemists are truly pleased with the opportunity they have to host the 19th FEBS Meeting and extend a most cordial welcome to colleagues coming to the 'Eternal City' from all over the world.

## Letters

### Low-frequency resonance and cooperativity of hemoglobin

The recent article by Gill *et al.* in *TIBS* raises a good question: Why are triply ligated species of hemoglobins so low in population? This question is certainly not answered fully and satisfactorily by the conventional theory of cooperativity. Actually, the issue can also be raised from a different point of view, as follows.

Consider the following positive cooperative reactions



where Hb denotes hemoglobin, O<sub>2</sub> the oxygen molecule, and  $k_i$  and  $k_{-i}$  ( $i = 1-4$ ) are the eight rate constants, based on which the four stepwise equilibrium constants can be written as:

$$K_i = \frac{k_i}{k_{-i}}$$

The experiments indicate that, rather than  $K_4 > K_3 > K_2 > K_1$  as expected according to the general positive cooperativity, we instead have<sup>2</sup>

$$K_4 > K_2 > K_1 \approx K_3 \quad (2)$$

Again, rather than  $k_4 > k_3 > k_2 > k_1$ , we instead have<sup>2</sup>

$$k_4 \approx k_2 > k_1 > k_3 \quad (3)$$

Why is this so? The conventional cooperativity theories<sup>3,4</sup> haven't given any explanation on these phenomena, especially as here  $K_3$  is between one

and two orders of magnitude less than  $K_2$ . These phenomena, however, can be elucidated quite naturally from the viewpoint of low-frequency resonance. Permit me to demonstrate this by addressing the following points.

(1) A hemoglobin molecule consists of two  $\alpha$ -subunits and two  $\beta$ -subunits, each having a binding site separated by 25–40 Å from the others. Although the low-frequency spectra of an  $\alpha$ -subunit are different from those of a  $\beta$ -subunit, the two  $\alpha$ - or two  $\beta$ -subunits have the same low-frequency spectra<sup>5,6</sup>.

(2) When two subunits have the same intrinsic frequency and are coupled with each other as in an oligomer, the energy transfer between them can take place via feedback<sup>7,8</sup>, and hence bears the feature of high efficiency and rapidity<sup>5,6</sup> in comparison with thermal exchange through collisions.

(3) According to the general theory of positive cooperativity in oligoproteins, once a subunit has bound to a ligand, the energy released will somehow be transferred to the next subunit, triggering there a conformational change from the T state (i.e. low-affinity state<sup>4</sup> or inactivated state<sup>5,6</sup>) to the R state (i.e. high-affinity state<sup>4</sup> or activated state<sup>5,6</sup>), so as to increase its binding constant with ligand. Now if this kind of energy is transmitted through the resonance-coupled channel, then the energy transfer between two  $\alpha$ -subunits or between two  $\beta$ -subunits is much more efficient than that between an  $\alpha$ -subunit and a  $\beta$ -subunit. Conse-

quently, the induced activation will proceed much more favorably between two like subunits than between two unlike subunits. This rationalizes the observed facts that  $k_2 > k_1$  and  $k_4 > k_3$  but  $k_3 < k_2$  and that  $K_2 > K_1$  and  $K_4 > K_3$  but  $K_3 < K_2$ , as indicated by Eqns 2–3.

The above demonstration also provide at a different angle some insight into the question why the population of triply ligated species is so small for hemoglobin, as discussed by Gill *et al.*<sup>1</sup>

In writing this letter I share the feelings of Gill *et al.* that the case in the study of hemoglobin is far from being closed. New volumes will be written, especially in the aspect of revealing the intrinsic relations between allosterism and energy transmission, as well as between cooperativity and internal collective motion.

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