COMPUTATIONAL EXPLORATIONS OF THE PROPERTY SPACE OF BIOMOLECULES

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The objective of this lecture is to take a global view on molecular structure and to examine how it relates to the biological activity of drugs and other bioactive compounds [1]. The central concept in approaching molecular structure is that of property space, namely the ensemble of all distinct states a molecule can exist in. While the concept of conformational space is a well-known one, little has been done to date to explore molecular properties encoding recognition forces (e.g., lipophilicity) and their dependence on conformation. The molecule of the neurotransmitter acetylcholine will be used as an example to explore its property space, namely the range of values taken by conformation-dependent properties such as dipole moment and lipophilicity [2, 3]. Furthermore, the property space of molecules is strongly influenced by their molecular environment, in the sense that the environment constrains the molecule to occupy only a fraction of its potential property space [1, 4, 5]. This is true not only of the conformational space (a well-known fact), but also of the dynamics of intramolecular motions [2] and of recognition forces [3], as the lecture will illustrate.

Other, more drastic constraints are seen when comparing the behaviour of side-chains in amino acids and protein residues. Work in progress with the protein profilin Ib will be presented, showing that such constraints generate information as quantified by a decrease in Shannon entropy [6]. It will be hypothesized that this information increase is related to the emergent information generated when a complex adaptative system such as a drug-receptor complex is formed. This information emerges as a biochemical signal, which in turn is amplified downstream into a macroscopic response by the biological context.

[1] B. Testa, L.B. Kier, P.A. Carrupt. A systems approach to molecular structure, intermolecular recognition, and emergence-dissolvence in medicinal research. *Med. Res. Rev.* **1997**, *17*, 303-326.
[2] G. Vistoli, A. Pedretti, L. Villa, B. Testa. The solute-solvent system: Solvent constraints on the conformational dynamics of acetylcholine. *J. Amer. Chem. Soc.* **2002**, *124*, 7472-7480.
[3] G. Vistoli, A. Pedretti, L. Villa, B. Testa. Solvent constraints on the property space of acetylcholine. I. Isotropic solvents. *J. Med. Chem.* in press.
[4] B. Testa, L.B. Kier. Emergence and dissolvence in the self-organization of complex systems. *Entropy* **2000**, *2*, 1-25. http://www.mdpi.org/entropy/list00.htm
[5] B. Testa, A. Bojarski. Molecules as complex adaptative systems. Constrained molecular properties and their biochemical significance. *Eur. J. Pharm. Sci.* **2000**, *11*, S3-S14.
[6] A. Bojarski, M. Nowak, B. Testa. Conformational constraints on side chains in protein residues increase their information content. *Cell. Molec. Life Sci.* **2003**, *60*, 2526-2531.