In-Silico Drug Design and the Molecular Classification of Local Anaesthetics

Torrens F[(1)], Castellano G[(2)]

[(1)] Institut Universitari de Ciencia Molecular, Universitat de Valencia, Valencia, Spain
[(2)] Instituto Universitario de Medio Ambiente y Ciencias Marinas,
Universidad Catolica de Valencia San Vicente Martir, Valencia, Spain

Motivation

Algorithms for classification and taxonomy based on criteria, e.g., information entropy and its production are proposed. As an example, the feasibility of replacing a given anaesthetic by similar ones in the composition of a complex drug is studied.

Methods

Some local anaesthetics currently in use are classified using characteristic chemical properties of different portions of their molecules. Many classification algorithms are based on information entropy. When applying the procedures to sets of moderate size, an excessive number of results appear compatible with data, and this number suffers a combinatorial explosion. However, after the equipartition conjecture, one has a selection criterion between different variants resulting from classification between hierarchical trees. According to this conjecture, for a given charge or duty, the best configuration of a flowsheet is the one in which the entropy production is most uniformly distributed.

Results

Information entropy and principal component analyses agree. Provisional conclusions follow:
1) Several criteria, selected to reduce the analysis to a manageable quantity of structures from the large set of local anaesthetics, refer to the structural parameters related with the lipophilic portion, etc. Many algorithms for classification are based on information entropy. For sets of moderate size, an excessive number of results appear compatible with data, and the number suffers a combinatorial explosion. However, after the equipartition conjecture, one has a selection criterion between different variants resulting from classification between hierarchical trees. According to the conjecture, the best configuration of a flowsheet is the one in which the entropy production is most uniformly distributed. The method avoids the problem of other methods of continuum variables, because for the four compounds with constant <11111> vector, the null standard deviation always causes a Pearson correlation coefficient of r = 1. The lower level classification processes show lower entropy and may be more parsimonious.
2) Program MolClas, is a simple, reliable, efficient and fast procedure for molecular classification based on the equipartition conjecture of entropy production.
3) The good comparison of our classification results with other taken as good confirm the adequacy of the property vector selected for the molecular structures of the local anaesthetics. Information entropy and principal component analyses permit classifying the local anaesthetics and agree. The ester- and amide-type local anaesthetics are grouped in different classes. The agents of low potency and short duration are separated from those of high potency and long duration. The final classification is shown more precise and with lower bias. The classification model calculates in each case the contribution of signal and noise. MolClas has been written not only to analyze the equipartition conjecture of entropy production, but also to explore the world of molecular classification.
4) Topical anaesthetics remain a powerful, new advancement for minimizing pain during cutaneous procedures. While several new topical anaesthetic agents have been released that claim increased efficacy and faster onset, EMLA remains the most widely used topical anaesthetic given its proven efficacy and safety by several clinical trials. As the options for the practitioner continue to grow, the need for studies comparing onset of action, efficacy and safety continues to be of paramount importance. MolClas provides a way to classify the local anaesthtics for difficult cases that are hard to sort a priori, e.g., the relationship between procaine and ice. Both EMLA and ice decrease the discomfort associated with needle injection. Although EMLA performs better in pain control, ice has advantages in easy of use, fast action and is less expensive than EMLA. Both EMLA and ice are good topical anaesthetics, each with advantages and disadvantages in clinical use.

Contact : Francisco.Torrens@uv.es