Aligning knowledge: A hands-on approach to teaching basic biological sequence analysis

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Introduction

Engaging students in active learning is a key goal in science education. Experiential learning activities promote deeper understanding by building knowledge through hands-on experience (Kolb, 1984). Although hands-on, activities using scientific software often face the challenge that students struggle to connect theoretical principles with the software's processes because much happens "under the hood". This can result in software exercises becoming "hands-on, mind-off" (Dolin, 2019), where outputs are generated without a conceptual understanding.

Biological sequence alignment is a clear example of this challenge. As a key technique in comparative DNA, RNA, and protein analysis, it is widely taught in biology. Pairwise or multiple sequence alignments match individual "letters" of biological sequences across individuals or species, and optimal alignments are inferred by dedicated software. Yet, these processes happen in a black box, students may not

understand the underlying processes and how parameter choices impact the results.

To address this problem, this paper describes a pedagogical exercise for a bachelor-level *Molecular Ecology* course at the University of Copenhagen. Through hands-on activities, students construct their own understanding of sequence alignment before formal instruction and software use. This approach aligns with discovery learning, where students uncover principles through guided exploration rather than passive absorption (Alfieri et al., 2011). The exercise aims to strengthen understanding of this key element of biological sequence analysis.

Approach

The activity aims to break the alignment process into individual steps, which are done manually, before moving to software-based alignment. This scaffolding helps students deduce alignment logic in manageable units, leading to deeper understanding of the overall process.

Identifying the major processes of sequence alignment. Students work in groups with two words of different lengths (representing a "sequence", Fig. **1a**), and their task is to align them in the best way. Using words instead of biological sequences provides a familiar context without the complexity of genetic data. After discussing their process in plenum,

the teacher relates their description to the lingo of sequence alignment. For example, students align shared letters between the two words, representing "matches". Unique letters can be either paired with another letter as "mismatches" or unpaired, introducing a "gap" in the other sequence (Fig. **1b**). This exercise helps students deduce the core processes used by alignment software.
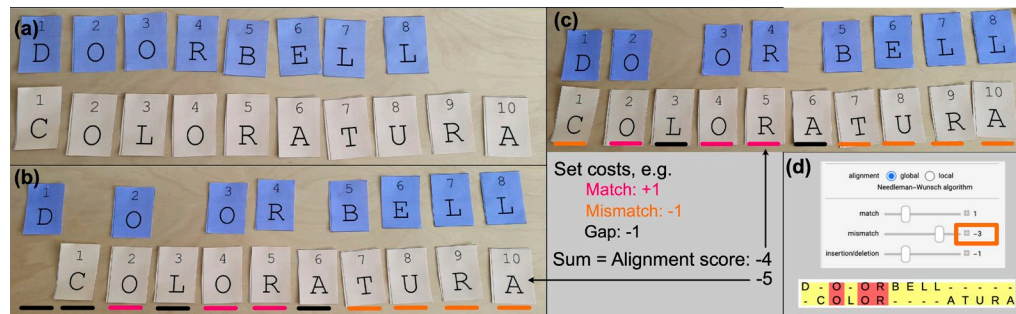

Fig. 1. (**a**) Example of two words given to students for alignment. (**b**) After discussions, students arrive at their best solution. (**c**) They can then compute an alignment score by assigning costs**,** allowing to rank one alignment relative to another. (**d**) Using a webserver, students experiment with modifying the costs and their effects on the alignment.

Finding the best alignment. The teacher makes one change to each group's alignment and asks students to evaluate whether the new

alignment is better or worse. To justify their reasoning, students often proposed to assign "costs" to different types of changes, such as penalizing gaps and mismatches or rewarding matches. They recognize that some alignments are objectively better based on these cost considerations. Hence, they have discovered the notion of an "alignment score" that sums the costs for a given alignment, which can be compared to alternative alignments (Fig. **1c**). The teacher explains that alignment software follows the same principles.

Exploring the impact of modifying costs. The students now align their words with an online alignment tool ([link]) to observe how altering costs for matches, mismatches and gaps affect the optimal alignment (Fig. **1d**).

Applying the concepts with software. Finally, students perform alignments using two popular software implementations (muscle, clustal) on their computers. They compare results and experiment with modifying costs for gaps from default settings.

The exercise applies a progressive formalization framework (Nathan, 2012) by first engaging students in a hands-on activity before gradually introducing terminology and computational implementations of sequence alignment. This allowed students to develop a stepwise

understanding of biological sequence alignment that builds on their initial insights using the words.

Student reception and Outlook

Students were engaged in exercises and actively participated in discussions. During the software-based portion, they referenced the hands-on experience, indicating a stronger connection between theory and software implementation. Discussions also raised important biological considerations, such as whether all mismatches should have equal costs. This suggests that students made connections between the exercise and broader molecular biology concepts.

This exercise aims to improve student comprehension of a common computational method. The manual alignment makes computational algorithms more accessible, while discovery-based learning allows developing an intuitive understanding before formal instruction. A deeper understanding of these fundamental concepts of biological sequence analysis better prepares students to critically engage with software, both in academic and applied settings.

References

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