

**(Re)Discovering “profile” HMMs**  
**i.e. apply/adapt HMM to multiple sequence alignment**

- **Q1: Could we use HMM to get multiple alignments?**
- **Q2: None of the previously exposed multiple alignment (MA) methods is supported by a fully probabilistic approach. Could we do better?**

Remark: If Q1 is positively answered, so is Q2!

- **Either**

directly answer Q1, i.e. design from scratch a HMM for MA

- **or (thinking of Q2...)**

we shouldn't really start from scratch...

(because profiles can be thought as being not far from the idea of emitting symbols: one state/table for each column in a MA profile)

Q2': What about inserts?

Q2'': What about gaps?

Q2''': Could we put all these together?

- **or**

Q3: could pair HMM be extended/adapted to do multiple alignments?

(because HMMs were successfully applied to pairwise alignment (PA), and MA is a generalisation of PA)

- **Q4: How should the probability parameters be set for a “profile” HMM?**
- **Q4': Are these all the parameters needed for a profile HMM?**
- **Q4'': If no, could we cope well with it?...**
- **Q5: Could we adapt (pair) HMM basic algorithms to the profile HMM model?**
- **Q6: Given a profile HMM and a new sequence, how should we proceed to align the sequence (to the model represented by the profile HMM)?**
- **Q7: Is it possible to get a profile HMM without starting from a profile (multiple alignment)?**
- **Q8: What should we do if the sequences in the initial MA (from which we built the profile HMM) are related? Could we ponder their relative importance by using some weights?**
- **Q8': How does this issue affect the profile HMM algorithms?**
- **Q8'': Where could we get these weights from (or how one compute them)?**
- **Q9: Could we get suboptimal alignments via probabilistic sampling/backtracing in profile HMM (as we did for HMM)?**
- **Q10: How could the pair HMM for global multiple alignment be modified so to do local multiple alignment?**