

# Decoding the evolutionary record: What advanced models of sequence change reveal to us about proteins

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Nature has been performing ultra high throughput in vivo site-directed mutagenesis studies for the past few billion years. The resulting evolutionary record contains a wealth of information about proteins, their structure, function, and physiological context, and how proteins adapt to changing circumstances. Unfortunately, standard phenomenological models used to analyse sequence change generally assume the effects we are most interested in do not exist. By constructing more mechanistic models that explicitly consider the process of mutation and selection we can decipher the resulting patterns of sequence variation and conservation, providing us access to Nature's lab notebook. We use these models to represent the nature of the changing selective constraints acting on protein sequences.

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