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## Mutations go tick, tock

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The rate of mutations in certain types of DNA sequences are the same no matter the species, according to a paper in this week's [Proceedings of the National Academy of Sciences USA](#), and suggest the presence of a molecular clock that operates in DNA, say the authors (*Proc Natl Acad Sci USA* 2004, DOI:10.1073/pnas.0404142101).

The [molecular clock hypothesis](#) resulted from studying how beta-globin proteins from different organisms appeared to be changing at a fairly constant rate, no matter which lineage was studied, [Philip Green](#), one of the authors, told us. But prior to the findings described in the paper, scientists had believed that such a clock - due to changes that occur as the result of errors during replication - could not hold at the DNA level.

Green and Dick G. Hwang, both of the [Department of Genome Sciences](#) at the University of Washington, applied a Bayesian Markov chain Monte Carlo sequence analysis - "a statistical model for a complicated situation where you can write down the mathematical equations but you can't solve them explicitly," said Green - to neutral mutations that have no consequence for an organism because they occur in noncoding regions. They incorporated the effect of neighboring sequences into the model, examining noncoding sequences from a 1.7-megabase genomic region in 19 mammalian species.

Looking at mammalian evolution and at the pattern of changes at CpG dinucleotides and comparing them to other types of changes that occur at other nucleotide positions revealed much more clock-like behavior at CpG dinucleotides, Green said. "You do actually have something like a molecular clock, even though people had pretty much given up hope of having one at the nucleotide level," he said.

CpG dinucleotides have a high mutation rate relative to other nucleotides in the genome, because the mutations are caused by a chemical change, Green said. "The type of mutation does not involve an error at replication - it's a chemical change that can happen at any time - and so it makes sense that you would not have a generation time effect for this type of mutation," he said.

Most statistical models of DNA evolution have not taken into account the effects of neighboring nucleotides, to the dismay of most biologists, said [Nick Goldman](#), who heads a research group at the European Bioinformatics Institute, Cambridge, UK. But Goldman, who was not involved in the study, told us that it had been a very important assumption made for many years, because it simplified the data analysis.

Adding such features as neighboring sequence to the so-called traditional methods caused the analysis of the data not to work any more, Goldman said. Some ideas of how neighboring nucleotides might be incorporated into statistical models had been around for some time, "and this... approach is one of them - but nobody's really got very far with doing it, because computationally it's horrible," he said.

"You need the computers; you need to be brave to wade in there and write the software that will do it," Goldman said. "This is the first one that I've seen that does it in this way to this data."

"If we understand the neutral evolution process as well as possible, then we should be able to do a better job of picking out parts of the genome sequence that are not changing neutrally and inferring that those are likely to have some important function," Green said.

There is a lot of controversy about the molecular clock, according to [Ron C. Woodruff](#), research professor in the Department of Biological Sciences at Bowling Green State University, Ohio, because some say there is so much variation in it that it cannot be relied on. "There will continue to be controversy about this, I think... they [Hwang and Green] still end up with all kinds of things that can modify this rate [of evolution of CpG dinucleotides]."

"So really, what they're saying is, yes there's a molecular clock, but you've got to take into consideration that there may be a lot of things that come into play here that keep it from being precise. But that's not too surprising," added Woodruff, who was not involved in the study.

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