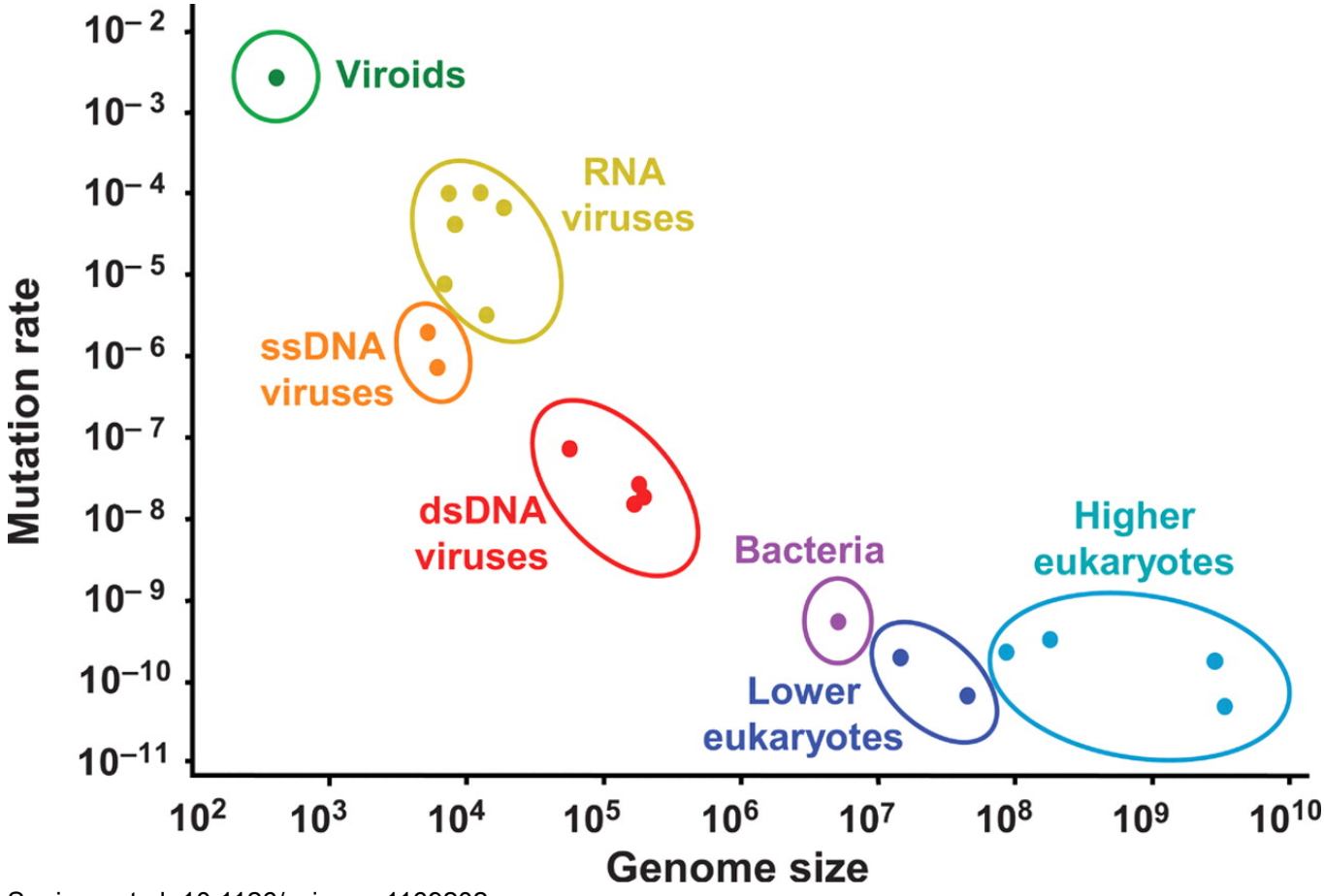
Why be accurate?

Many processes in biology rely on very accurate biochemical reactions. The importance of high accuracy is most evident in the replication of long chain molecules, that is

- genome replication: Need to copy millions of bases without mistake
- proteins: a single translation error can result in misfolded proteins
- tRNA synthesis

But these are not the only processes were accurate signal processing is critical. Detection systems that need to identify rare pathogens or chemicals need to be both sensitive and specific.

Mutation rates



Sanjuan et al. 10.1126/science.1169202

- Mutation rates scale (roughly) with inverse genome size!
- Mutation rates can be remarkably low: 10^{-10} per base and replication

Kinetic proofreading is a general mechanism to explain how such high fidelities can be achieved.

Why is high accuracy difficult? What are the fundamental limits?

- in the macroscopic world, accuracy is mostly about avoiding interference. Fidelity is often a problem of good engineering, not such much one of fundamental limitations
- in the nano- or microscopic world, accuracy is often limited by thermal fluctuations.
- Boltzmann statistics fundamentally limit the accuracy of (quasi-)equilbrium processes.

Boltzmann statistics

Different microstates of a system are realized with a probability that is proportional to

$$\sim e^{-\frac{E}{kT}}$$

Here, kT is the product of a constant and temperature which has dimensions of an energy. E is the energy of a system.

We typically don't consider an isolated system, but a system that is embedded in a larger system (for example at constant pressure). Furthermore, one usually can't specify a microstate exactly. Instead there are additional degrees of freedom such that the state we specify has "entropy". To account for these effects, one defines free energies G (or its variants H, F, etc) and the Boltzmann factor becomes

$$\sim e^{-\frac{G}{kT}}$$

Accuracy of Michaelis-Menten reactions

$$S + E \leftrightharpoons ES \rightarrow P + E$$

- Biochemical reactions typically go through intermediate states.
- Consider two substrates C and C': On rates are similar, limited by diffusion.
- Discrimination is via the off-rates
- Off-rates determine the life time of the intermediate.
- Off-rates are determined by the free energy of the transition state
- The ratio of off-rates is given by $e^{-\Delta G/kT}$ → Lower limit for error rate!

Energy of discrimination

$$C + E \underset{k_{on}}{\overset{k_{off}}{\rightleftharpoons}} EC \underset{w}{\rightarrow} P + E$$

$$C' + E \underset{k'_{on}}{\overset{k'_{off}}{\rightleftharpoons}} EC' \underset{w}{\rightarrow} P' + E$$

Assume for the moment $w = 0$. The population of the transition states are will be

$[EC] \sim [C]\frac{k_{on}}{k_{off}}$

$[EC'] \sim [C']\frac{k'_{on}}{k'_{off}}$

If we now assume that $k_{on} = k'_{on}$, we have

$$\frac{[EC']}{[EC]} = \frac{[C']k_{off}}{[C]k'_{off}} = \frac{[C']}{[C]}e^{-\Delta G/kT}$$

If the product formation rate w is low compared to the off-rates, the ratio of correct and incorrect product is roughly given by $e^{-\Delta G/kT}$, where ΔG is known as the **energy of discrimination**.

Fundamental limit on accuracy

- For many processes ΔG is small, just a few kT.
- Other mechanisms must exist to increase accuracy.
- Kinetic proofreading by Hopfield is the paradigm for such mechanisms.

Dig deeper

- how does the ratio between correct and incorrect substrate change as w increases?
- Why do you think there is this strong inverse relation between genome size and mutation rate?

In [ ]: