- many biochemical reactions are extremely accurate?
- DNA replication as low as 1 in 10^{10}
- how is such accuracy achieved?
- what are the costs?

![Graph showing error rates vs. genome size with labels for viruses, bacteria, and eukaryotes.]

- rough scaling: $\mu = \frac{1}{L}$
- necessary to enable error-free replication with high prob.
- $e^{-nL}$
- other wise, Muller's Ratchet kicks in....
- how is high accuracy achieved?

**Energy of discrimination**

consider a set of competing reactions

$$C + c \xrightleftharpoons[k_c^0]{k_c} C_c \rightarrow \text{correct}$$

$$D + c \xrightleftharpoons[k_c^0]{k_c^0} D_c \rightarrow \text{wrong}$$

diffusion limited on rate:

$$k = k_c + k_c^0$$

polymerisation independent of identity ( $W$ )
Transition state population

\[ [C_c](W + k_c) = [C_3]k_c \]

Product formation: \( W[C_c] = W \frac{[C_3]k_c}{W + k_c} \)

Ratio of correct to wrong product:

\[
\frac{W[C_c]}{W[C_D]} = \frac{[C_3](k_0 + W)}{[C_3](k_0 + W)} \rightarrow \frac{[C_3]k_0}{[C_3]k_c} = \frac{[C_3]}{[C_3]} e^{-\Delta G/kT}
\]

\( \Delta G \) is the difference in binding free energy of C/D state

Wrong nucleotide pairings only cost \( 2-5kT \) \( e^{-5} \approx 0.01 \gg 10^{-8} \)

How do cells achieve high accuracy?

Intermediate states

\[ X + c \Rightarrow X_c \xrightarrow{W} X_c^* \xrightarrow{V} \text{product} \]

\[ \text{II} \]

\[ X + c \]

Just adding an intermediate doesn't work

\( \Rightarrow \) if \( X_c \not\leftrightarrow X_c^* \) is an equilibrium reaction, nothing is gained

\( \Rightarrow \) discrimination is still \( e^{-\Delta G/kT} \)

Need irreversible step?
\[ X + C \xrightarrow{\text{irreversible}} X_c \xrightarrow{\text{small}} X + C \]

- can be achieved by coupling to ATP hydrolysis
- often trigger conformational transitions
- now \( X_c \) is already biased towards \( C \)
- \( X_c \rightarrow X^* \) can achieve another factor \( \exp(-\Delta G/kT) \)
  \[ \Rightarrow \text{enrichment of correct product by } e^{-\Delta G/kT} \]
  \( \Rightarrow \) more intermediate steps increase accuracy even further

Effectively a delay

- consider freshly formed \( X_c \) complex
- probability of still being present
  \[ \frac{dp}{dt} = -(k_x + W)p(t) \Rightarrow p(t) = e^{-(k_x + W)t} \]

- second intermediate is populated by \( p(t) \)

\[ \frac{dq(t)}{dt} = Wp(t) - Vq(t) = We^{-(k_x + W)t} - Vq(t) \]

\[ q(t) = We^{-(k_x + W)t} \int_0^t e^{-(V-W-k_x)t} dt \]

\[ = \frac{We^{-Vt}}{W+k_x-V} \left[t - e^{-(W+k_x-V)t} \right] \]
shifted away from 0

$\Rightarrow$ delay gives more time to discriminate $e^{-(ko-k_0)t}$

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**Museum metaphor**

- consider the challenge: "Identify Holbein fans in the Kunstmuseum".

- Holbein fans stay 10 min
- others stay 1 min
- but there are only 10% Holbein fans

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$\frac{1}{10}$

$\frac{1}{100}$