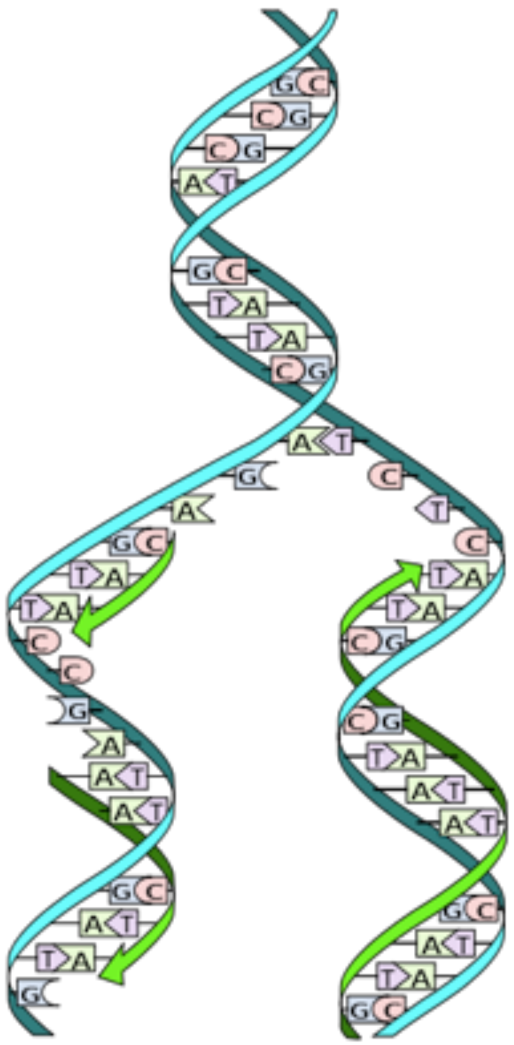
Thermodynamics of biological copying

Simone Pigolotti (UPC, Barcelona)
Roma, 24/9/2013

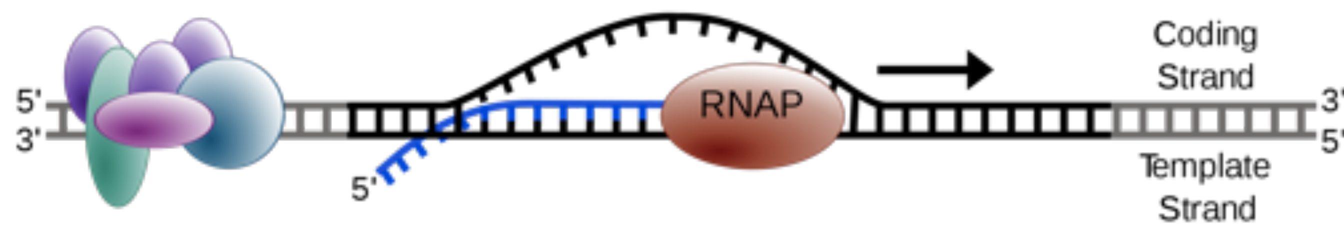
with: Pablo Sartori (MPIPKS, Dresden)

Biological copying



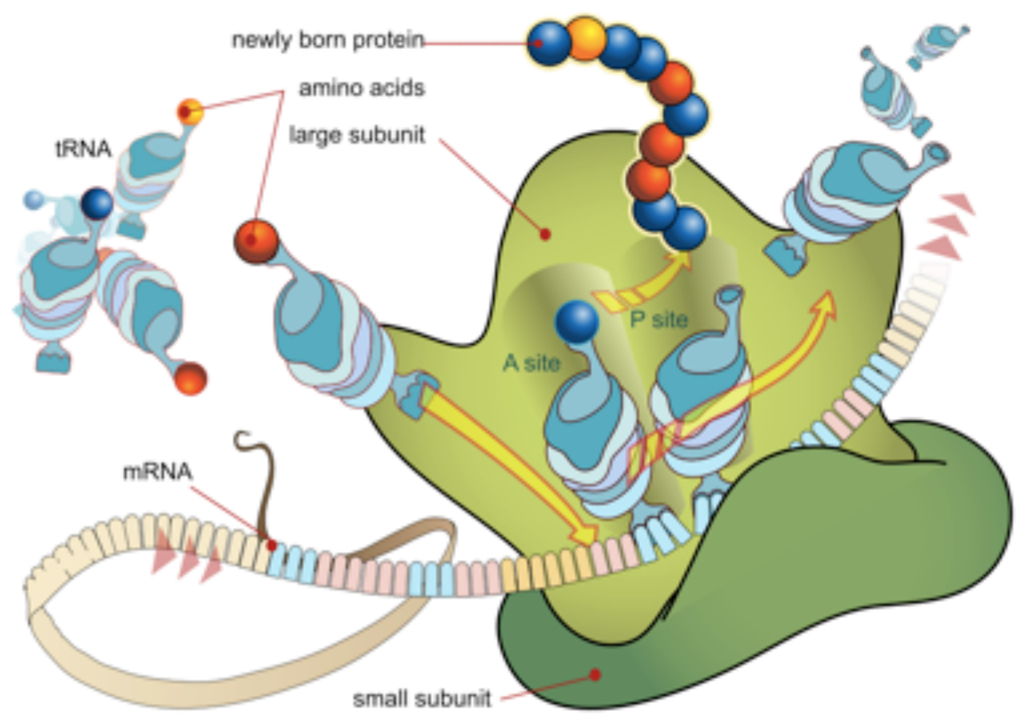
DNA duplication

error rate ~ 10^{-9}



transcription

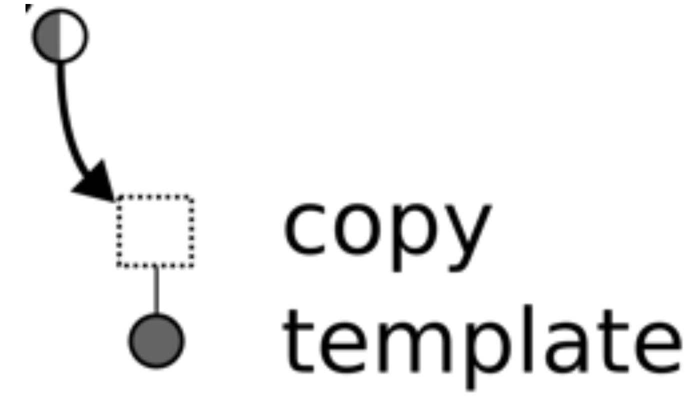
error rate ~ 10^{-4}



translation

error rate ~ 10^{-4}

Enzymatic copying model



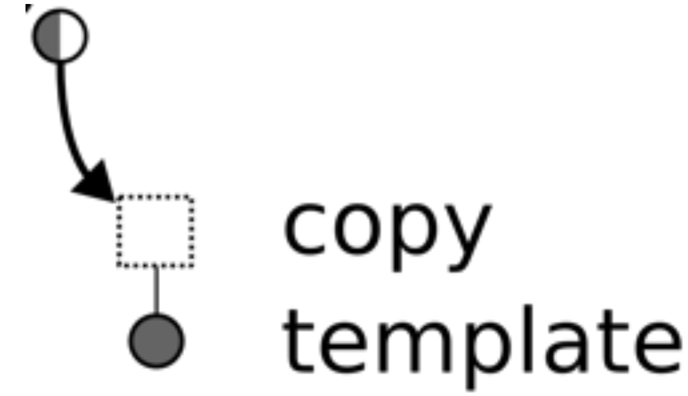
$$E + R \rightleftharpoons ER \longrightarrow \text{right product}$$

$$E + W \rightleftharpoons EW \longrightarrow \text{wrong product}$$

error rate $> e^{-\beta \Delta G}$ where $\Delta G = G_{EW} - G_{ER}$

minimum error achieved in quasi-equilibrium -> very slow reaction

Enzymatic copying model



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error rate $> e^{-\beta \Delta G}$ where $\Delta G = G_{EW} - G_{ER}$

minimum error achieved in quasi-equilibrium -> very slow reaction

DNA duplication:

kT ~ 2.479 kJ/mol

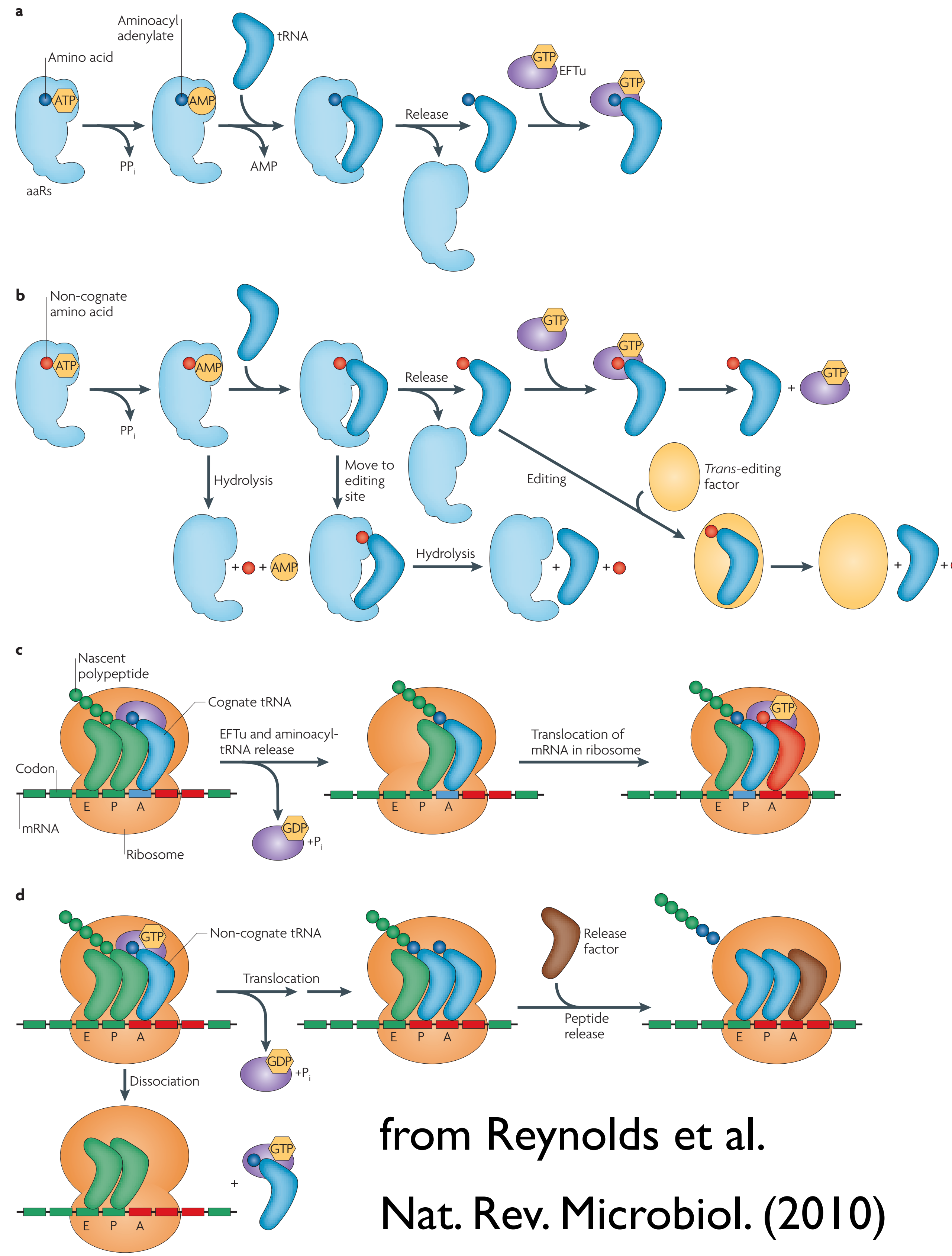
ΔG ~ 1 -- 16 kJ/mol

minimum error from binding energies > 0.01

incompatible with observed value = 10^{-9}

Proofreading

example: translation



high fidelity is achieved via complex multi-step reactions

from Reynolds et al. Nat. Rev. Microbiol. (2010)

Kinetic Proofreading

$$E + R \rightleftharpoons ER \longrightarrow ER^* \longrightarrow \text{right product}$$

$$E + W \rightleftharpoons EW \longrightarrow EW^* \longrightarrow \text{wrong product}$$

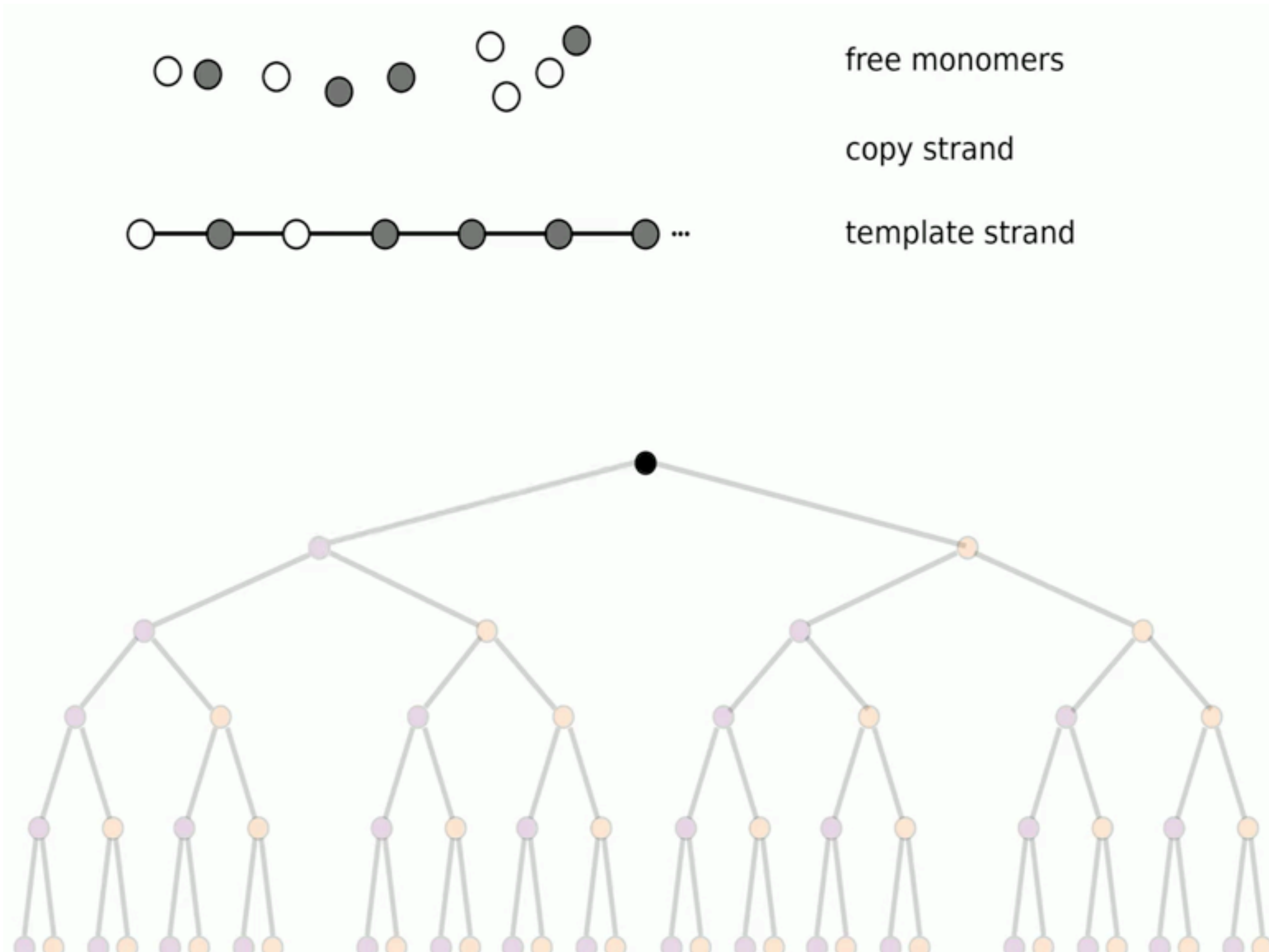
proofreading step is non-discriminating but reduces the error

error rate $> \left(e^{-\beta \Delta G}\right)^2$

proofreading is intrinsically dissipative

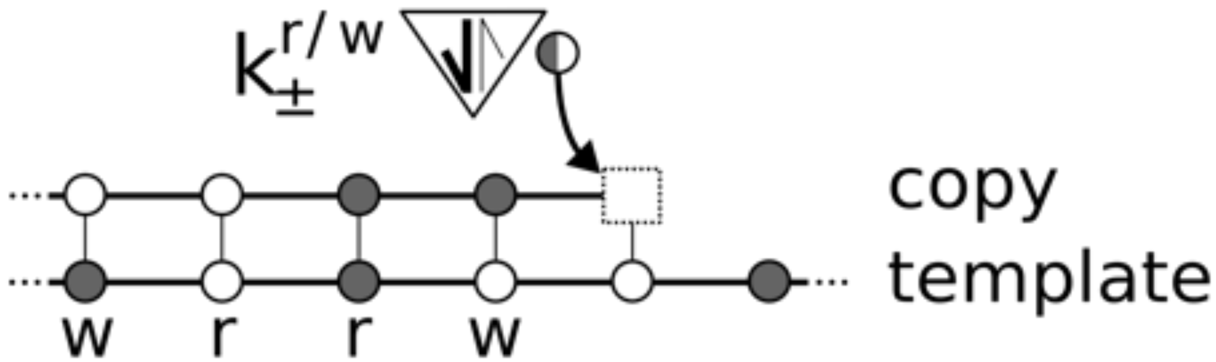
Hopfield, *PNAS* (1974)

Bennett's copolymerization model



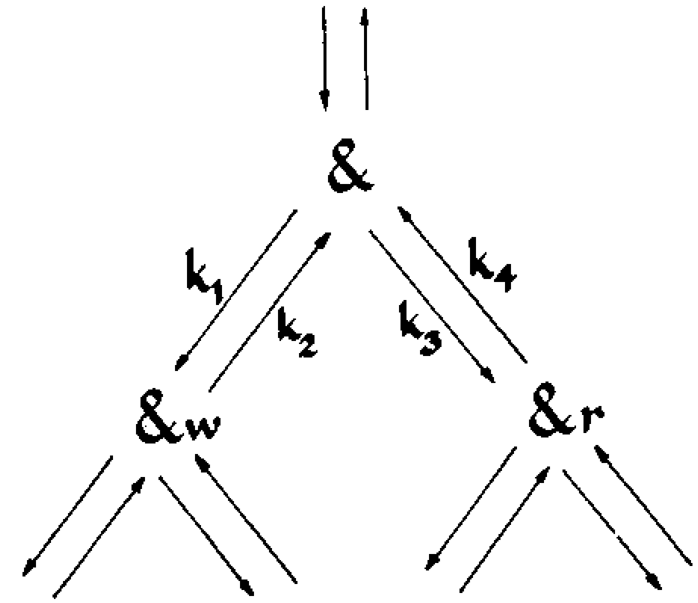
Bennett, *Biosystems* (1979)

Copolymerization model

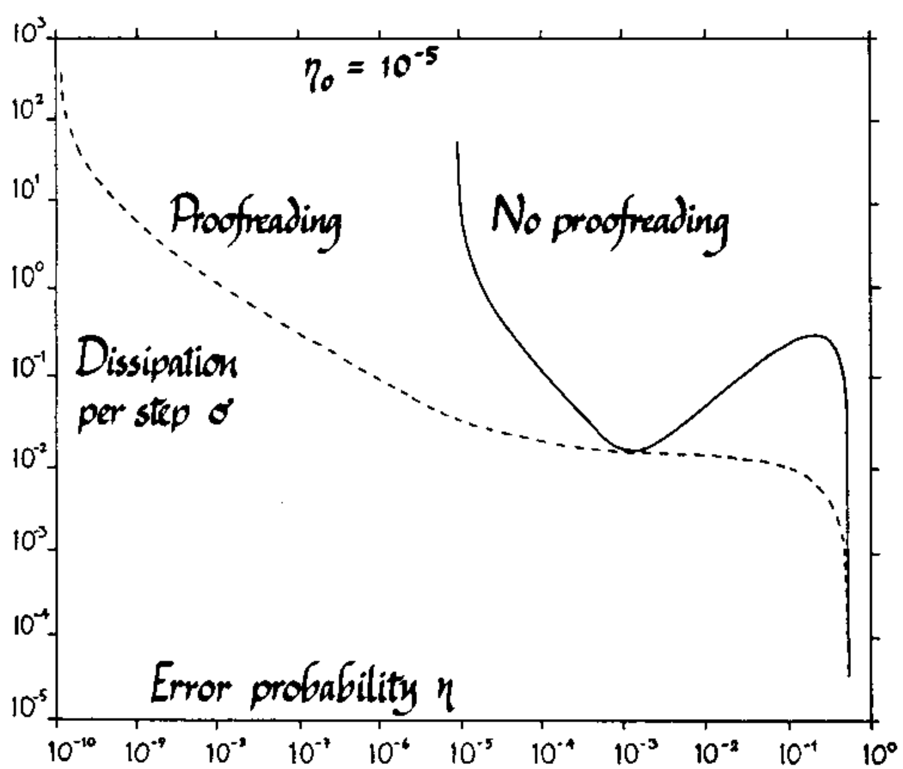


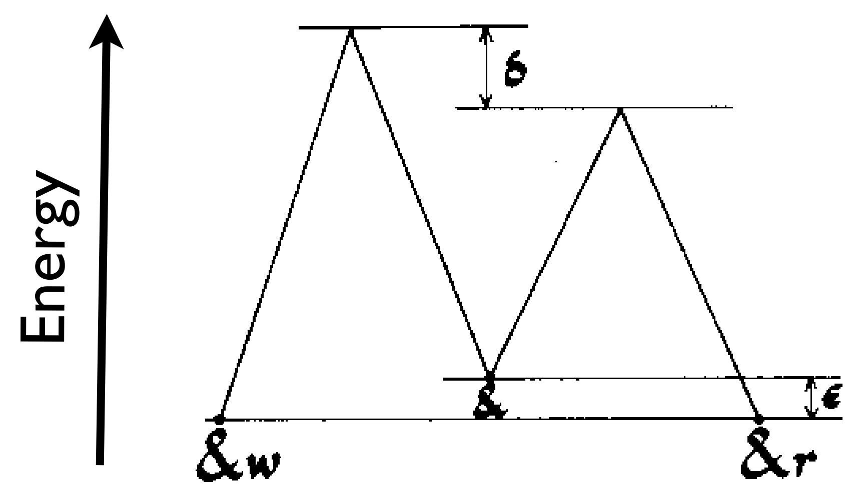
Copying of a long polymer

$k_{\pm}^{r/w}$ rates of binding/unbinding of right/wrong monomers



transition diagram





energy diagram - isoenergetic strains

Bennett, *Biosystems* (1979)
Andrieux and Gaspard, PNAS (2008), Esposito et al. JSTAT (2010)

Enzymatic copy vs. copolymerization

	enzymatic copy	copolymerization
ΔG	yes, determines minimum error	no, copies are isoenergetic
minimum error limit	adiabatic	$\dot{S} \to \infty$
proofreading	only dissipative step	less dissipation with proofreading than without

P. Sartori and S. Pigolotti, PRL (2013)

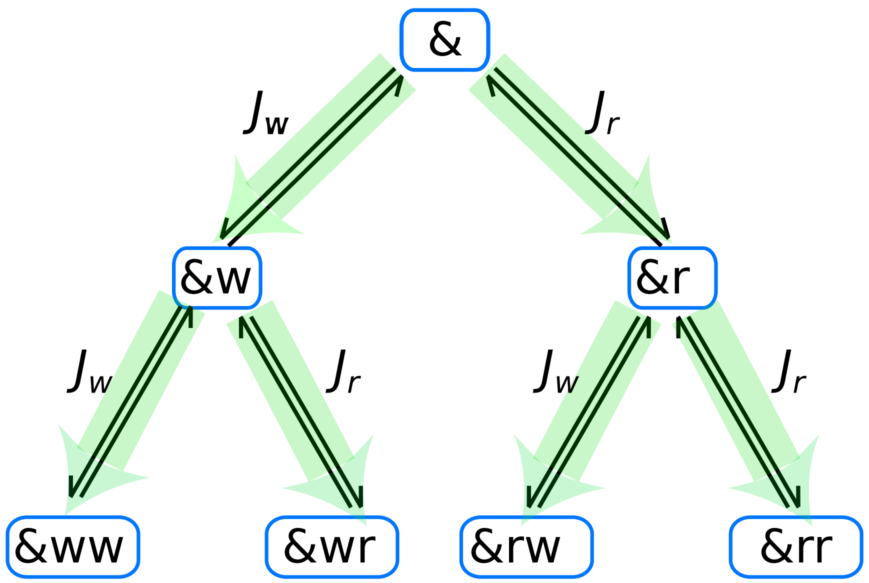
The bigger picture

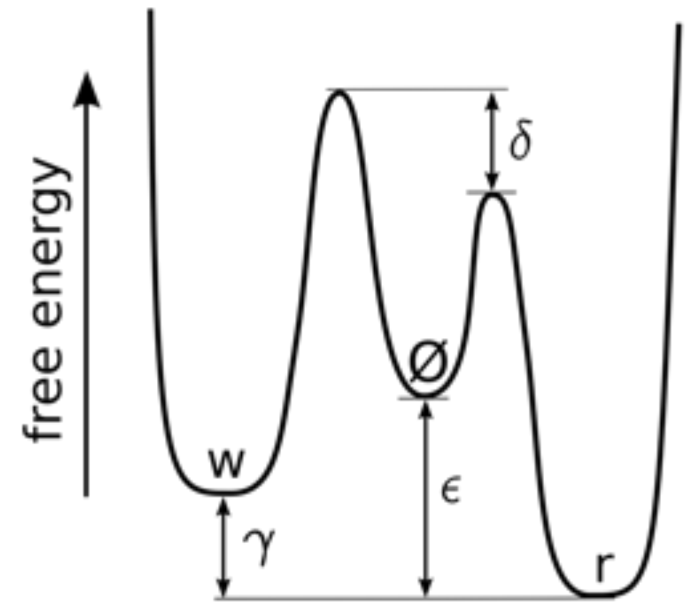
I want a copying pathway with

- low error
- low dissipation
- high copying velocity

How should I design it?

Copolymerization





write rates as Kramers rates: $k_+^r = \omega e^{\epsilon+\delta}$ $\quad k_-^r = \omega e^{\delta}$

$$k_+^w = \omega e^{\epsilon} \qquad k_-^w = \omega e^{\gamma}$$

master equation:

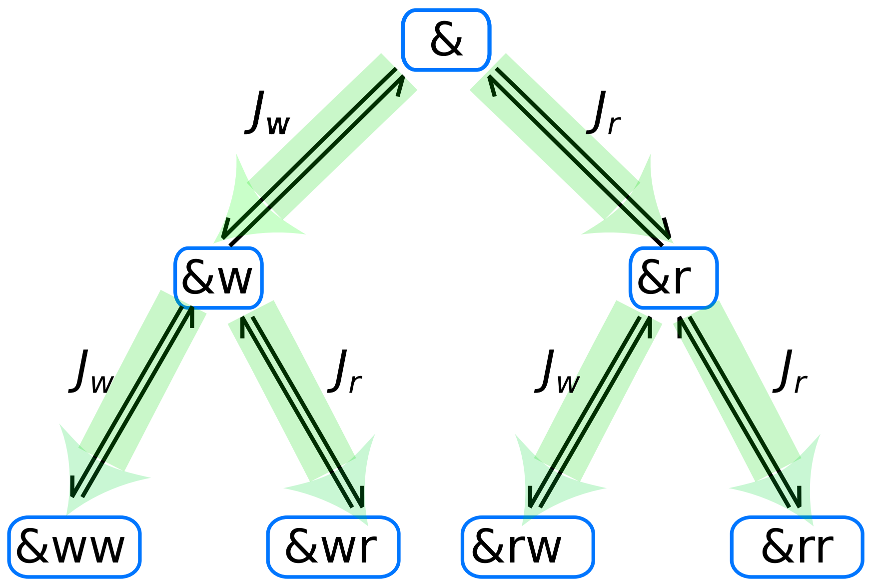
$$\frac{d}{dt}P(\cdots r) = k_+^r P(\cdots) + k_-^w P(\cdots rw) + k_-^r P(\cdots rr) - (k_-^r + k_+^w + k_+^r)P(\cdots r)$$

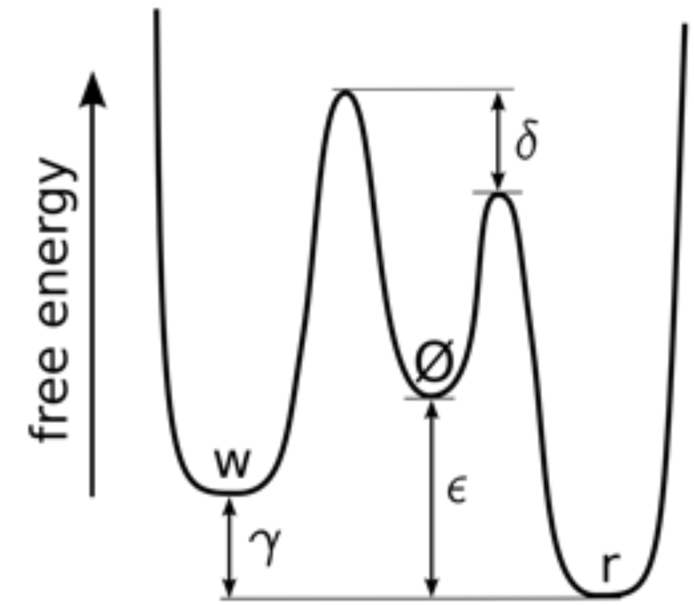
$$\frac{d}{dt}P(\cdots w) = k_+^w P(\cdots) + k_-^w P(\cdots ww) + k_-^r P(\cdots wr) - (k_-^w + k_+^w + k_+^r)P(\cdots w)$$

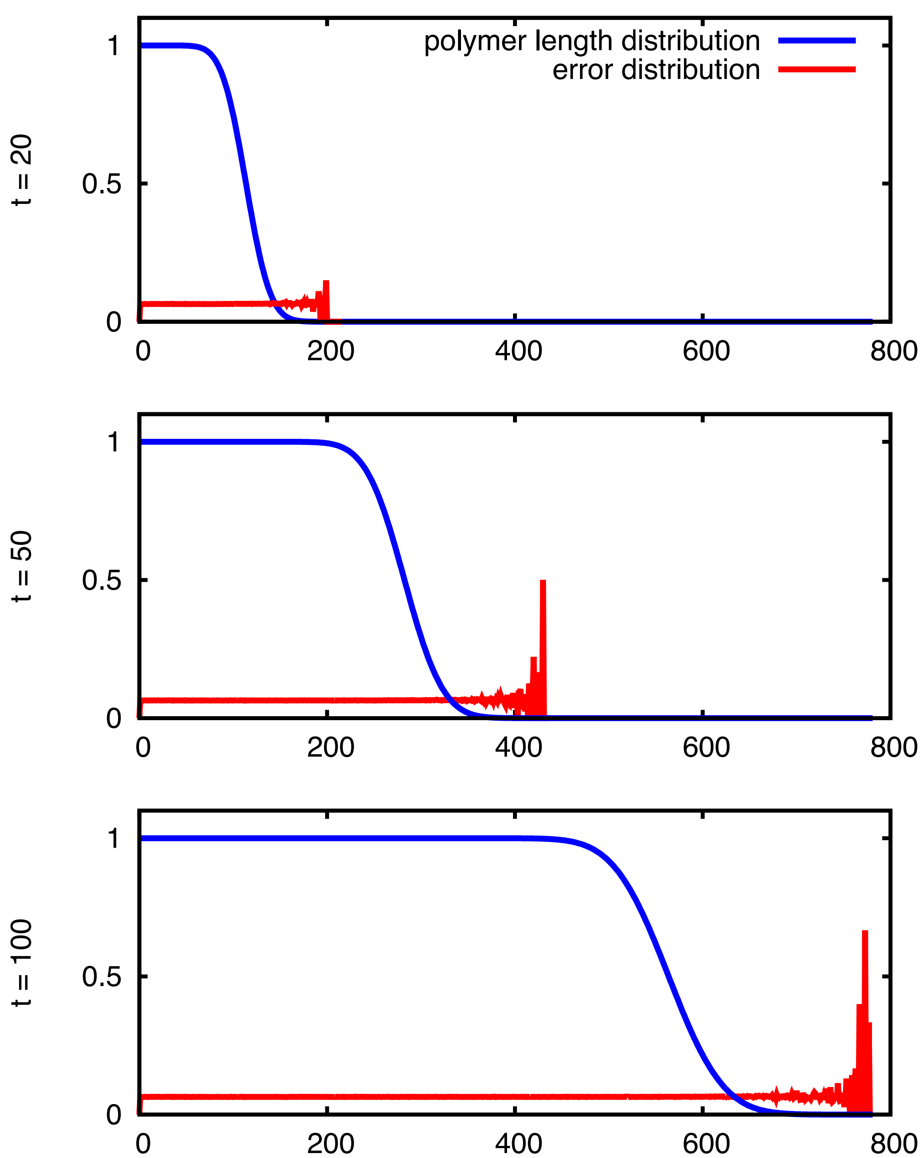
mean field solution:

$$\frac{\eta}{1-\eta} = \frac{\text{net increase wrong monomers}}{\text{net increase right monomers}} = \frac{k_+^w - k_-^w \eta}{k_+^r - k_-^r(1-\eta)}$$

Copolymerization







the ansatz

$$P(rwwrw\dots) \propto (1-\eta)^{N_r}\eta^{N_w}$$

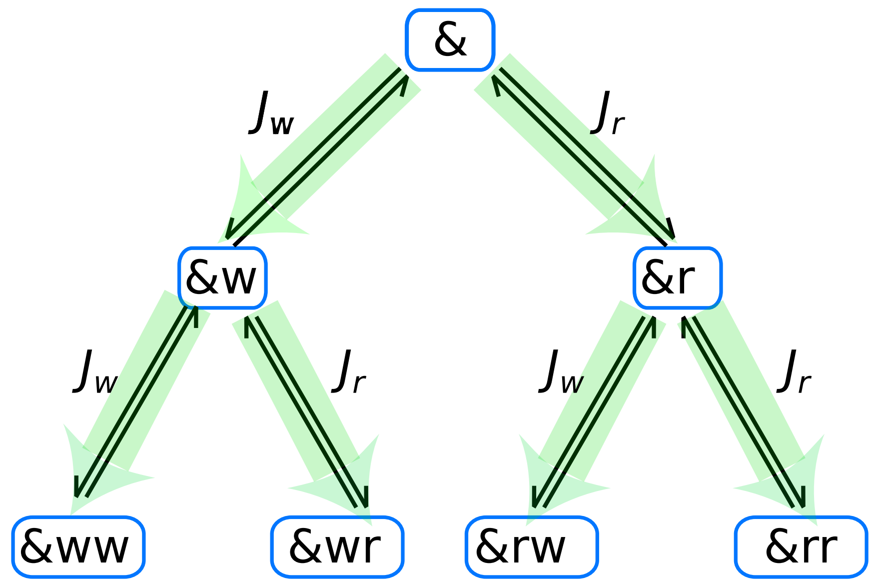
solves the model

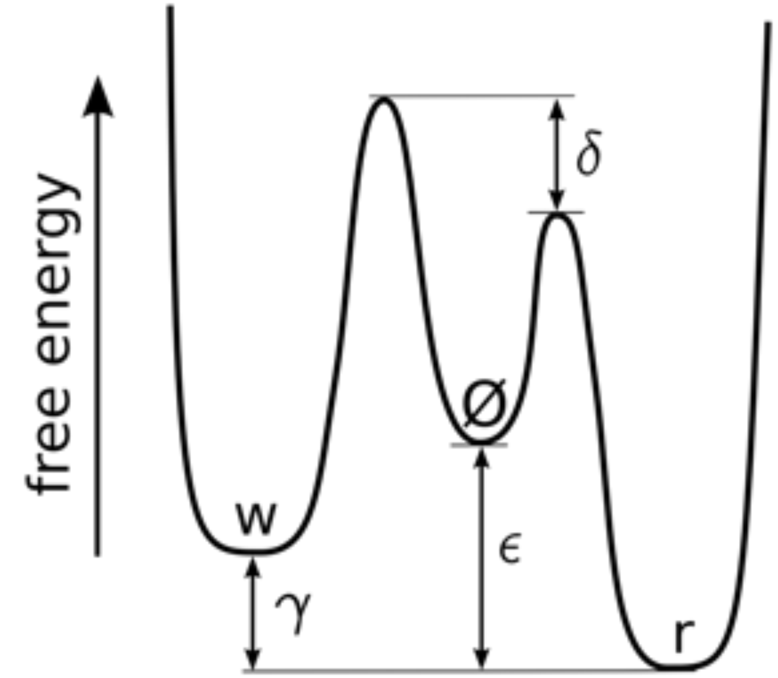
-> mean field solution is exact

stochastic simulations

$$\delta = 2 \quad \gamma = 3 \quad \epsilon = 0.5$$

Results





$$\boxed{\dot{S} = v\Delta S = v[(1-\eta)\epsilon + \eta(\epsilon - \gamma) + H(\eta)]}$$

$\dot{S}$ entropy production

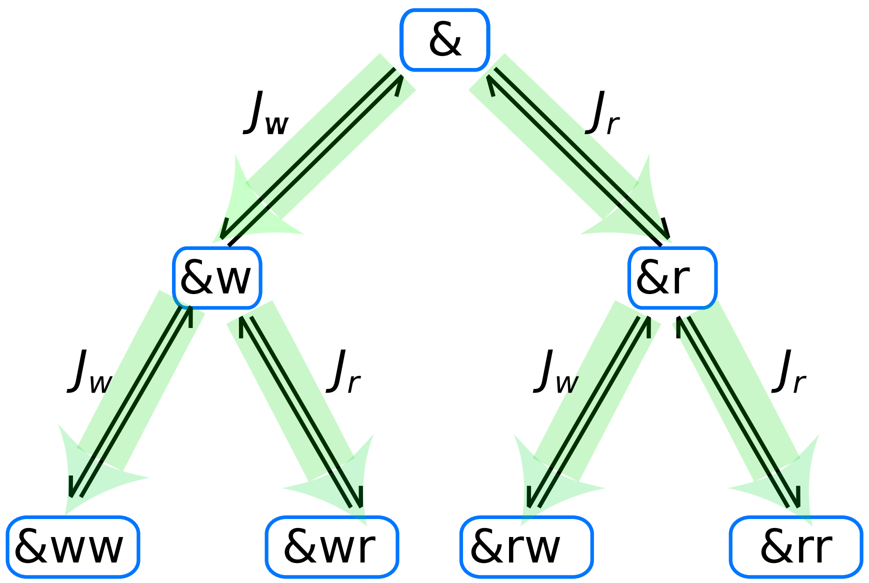
ΔS entropy production per copied base

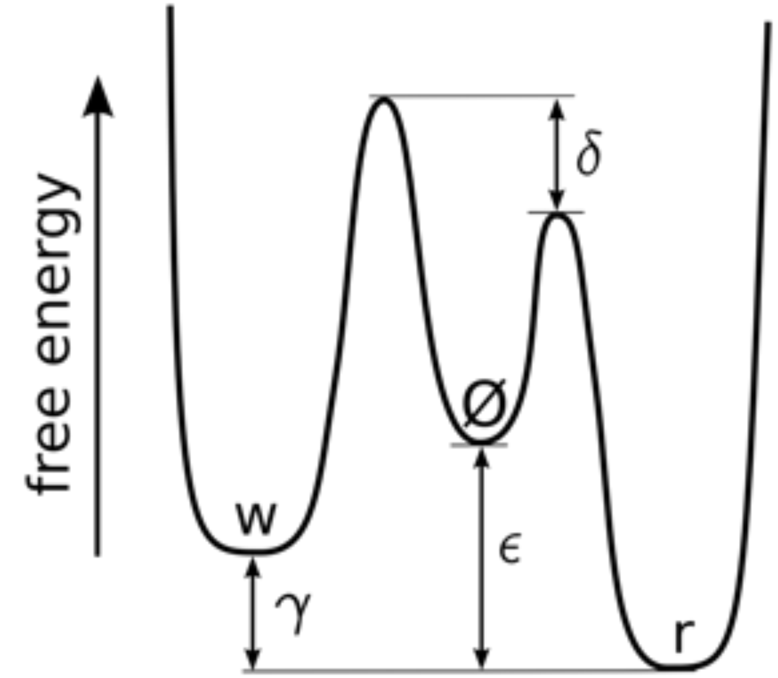
v average copying velocity

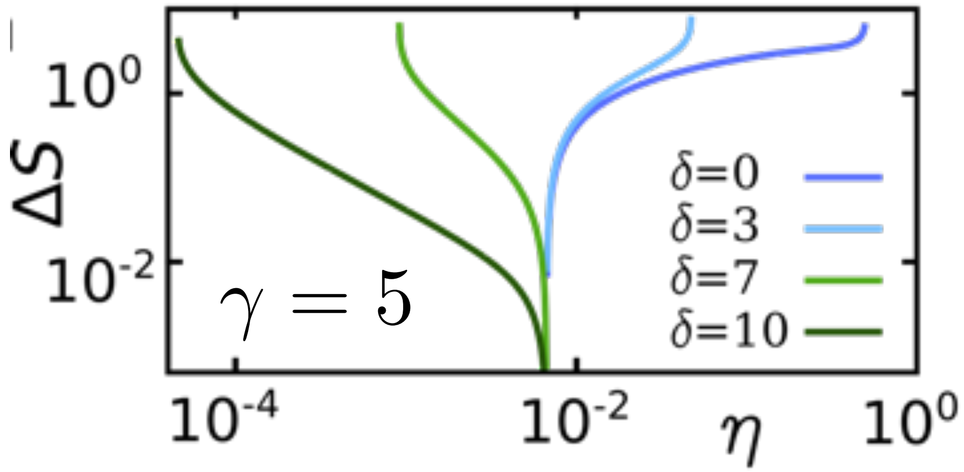
$$H(\eta) = -\eta\ln(\eta) - (1-\eta)\ln(1-\eta)$$

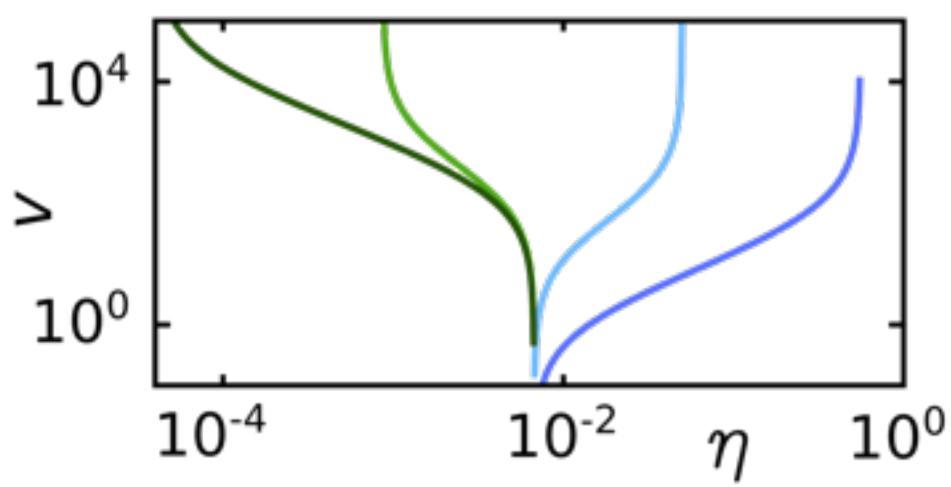
P. Sartori and SP, PRL (2013)

Results









adiabatic limit:

$$\eta \to e^{-\gamma}$$

dissipation per step and velocity vanish

highly dissipative limit:

$$\eta \to e^{-\delta}$$

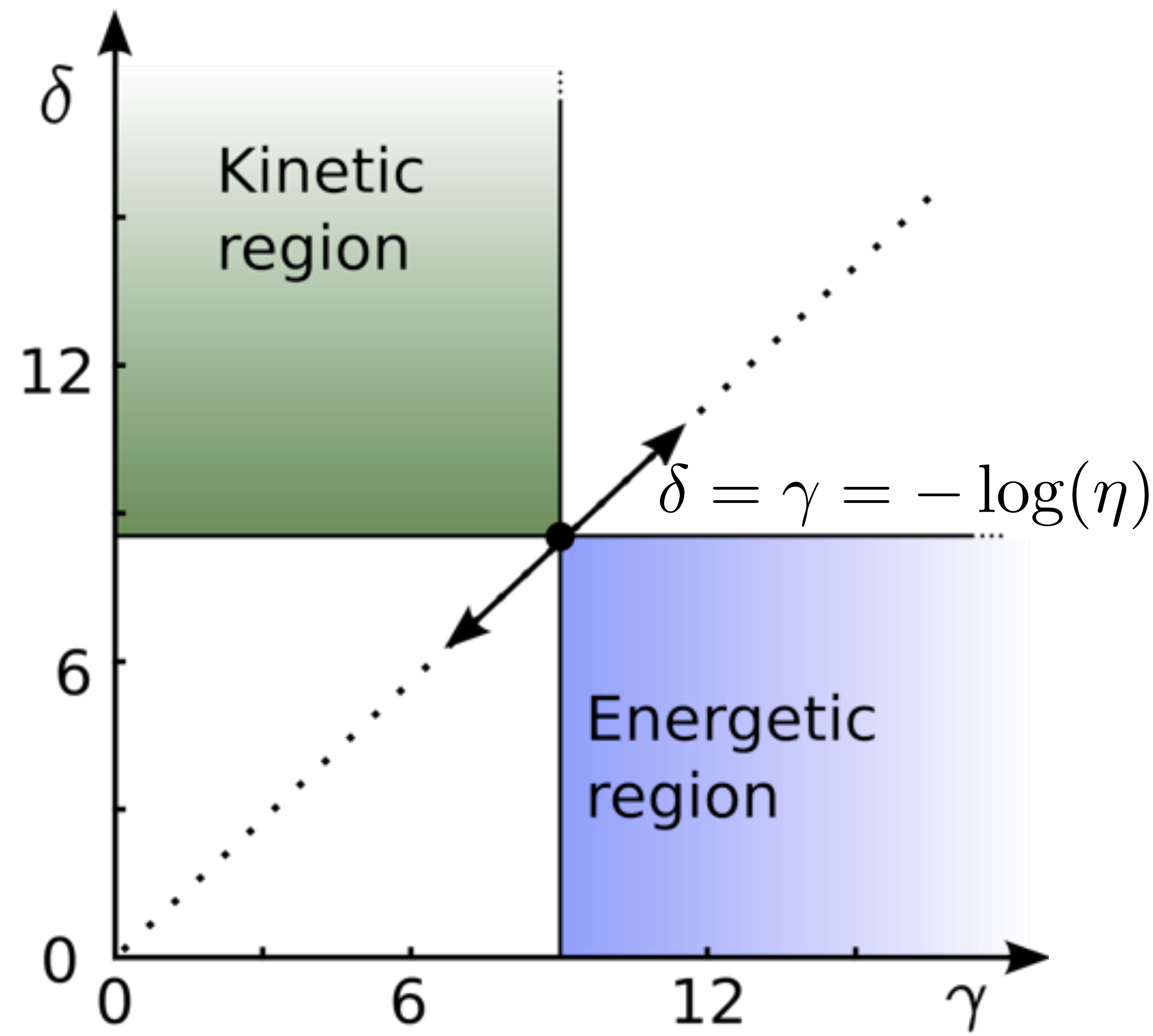
dissipation per step and velocity diverge

physical region:

$$\min[e^{-\delta}, e^{-\gamma}] < \eta < \max[e^{-\delta}, e^{-\gamma}]$$

Two distinct copying strategies

	Kinetic region	Energetic region
η	$\downarrow$	$\downarrow$
ϵ	$\uparrow$	$\downarrow$
ΔS	$\uparrow$	$\downarrow$
v	$\uparrow$	$\downarrow$

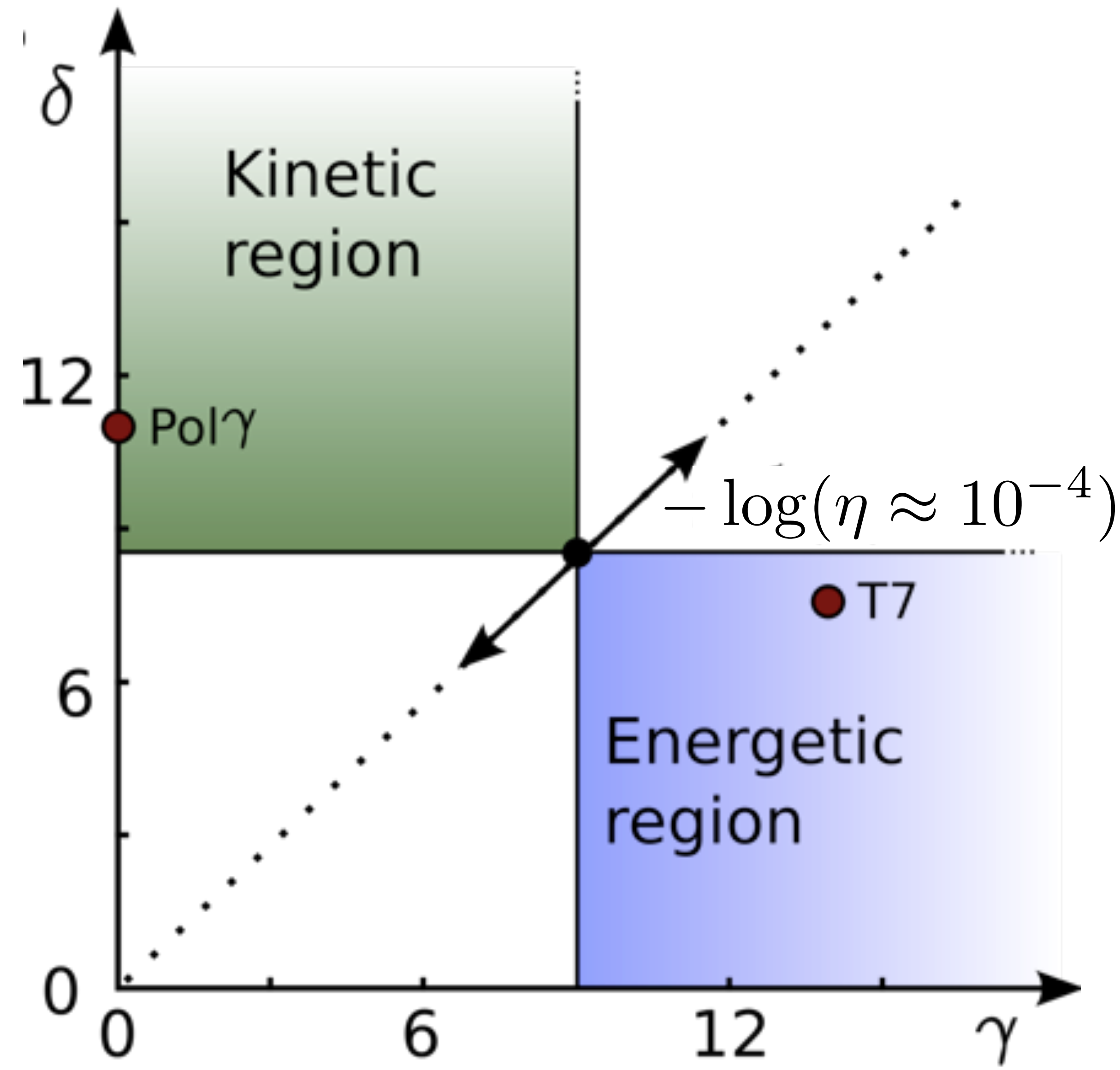


$$\boxed{\min[e^{-\delta}, e^{-\gamma}] < \eta < \max[e^{-\delta}, e^{-\gamma}]}$$

different tradeoffs in the two regions

Experimental comparison

Polγ human DNA polymerase
studied in (Andrieux and Gaspard, 2008)
assuming isoenergetic strains ($\gamma = 0$)
result: $\delta \approx 11$



T7 phage DNA polymerase

Correct nucleotide - dCTP

(Tsai and Johnson 2006)

$$E\cdot D_n + dCTP \overset{28\ \mu M}{\rightleftharpoons} ED_n\cdot dCTP \underset{1.6\ s^{-1}}{\overset{660\ s^{-1}}{\rightleftharpoons}} \underset{aligned}{FD_n\cdot dCTP} \overset{360\ s^{-1}}{\rightleftharpoons} FD_{n+1}\cdot PP_i$$

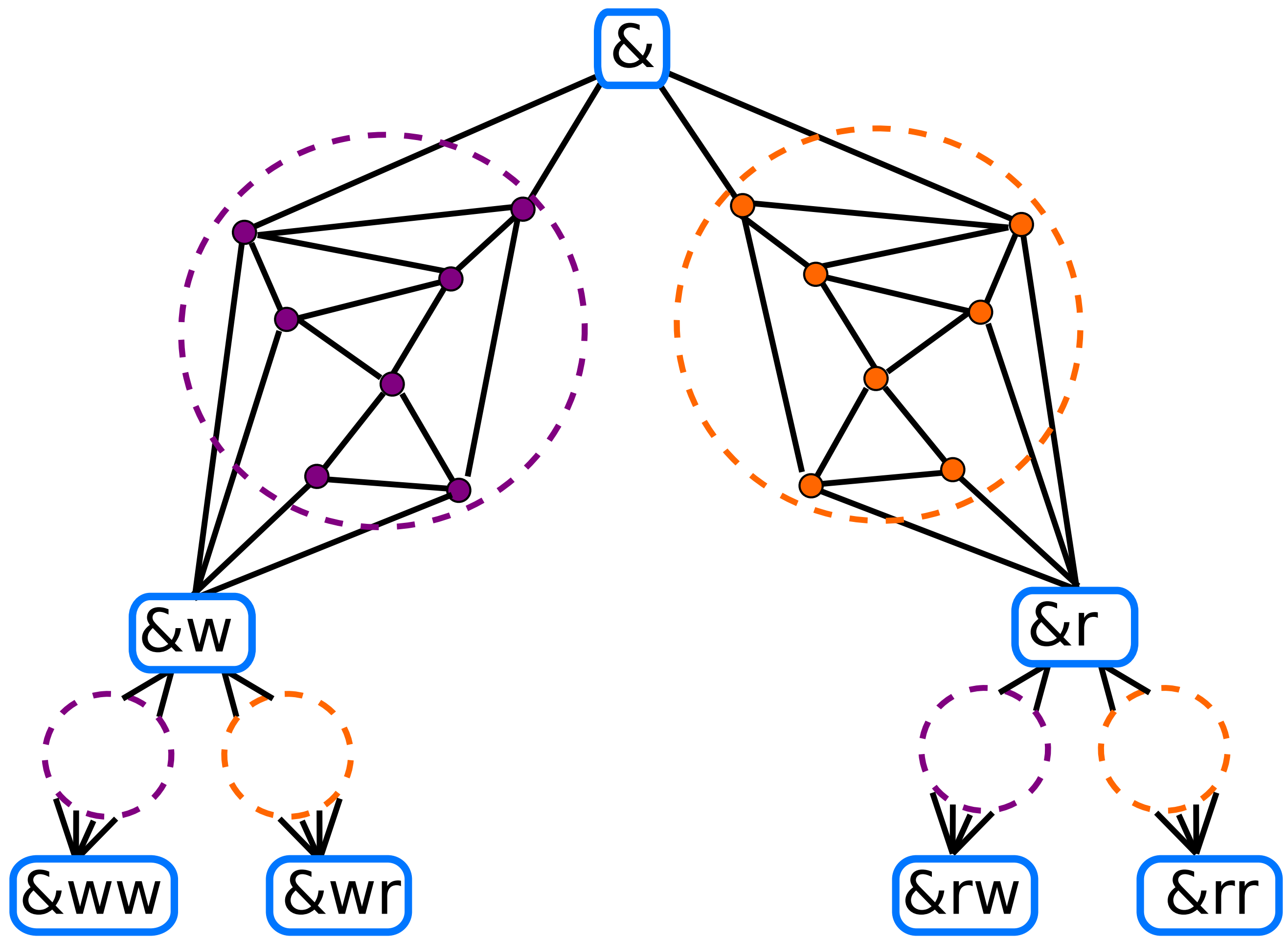
Incorrect nucleotide - dGTP

$$E\cdot D_n + dGTP \overset{200\ \mu M}{\rightleftharpoons} ED_n\cdot dGTP \underset{420\ s^{-1}}{\overset{220\ s^{-1}}{\rightleftharpoons}} \underset{misaligned}{HD_n\cdot dGTP} \overset{0.3\ s^{-1}}{\rightleftharpoons} HD_{n+1}\cdot PP_i$$

$$\gamma \approx 14 \quad \delta \approx 8$$

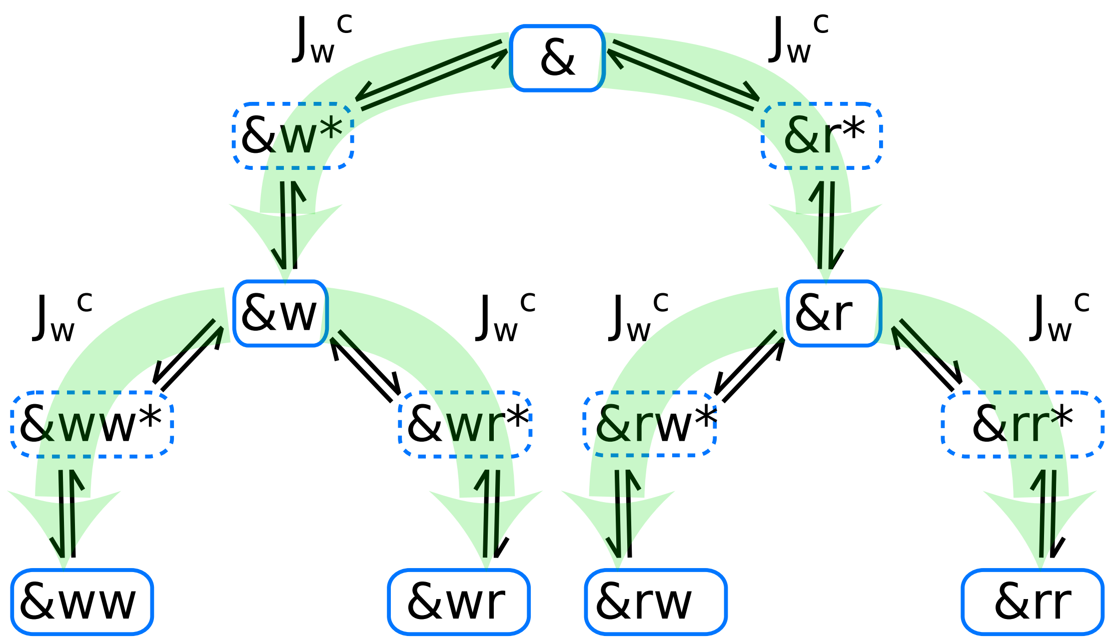
the two copying machines operate in different regions

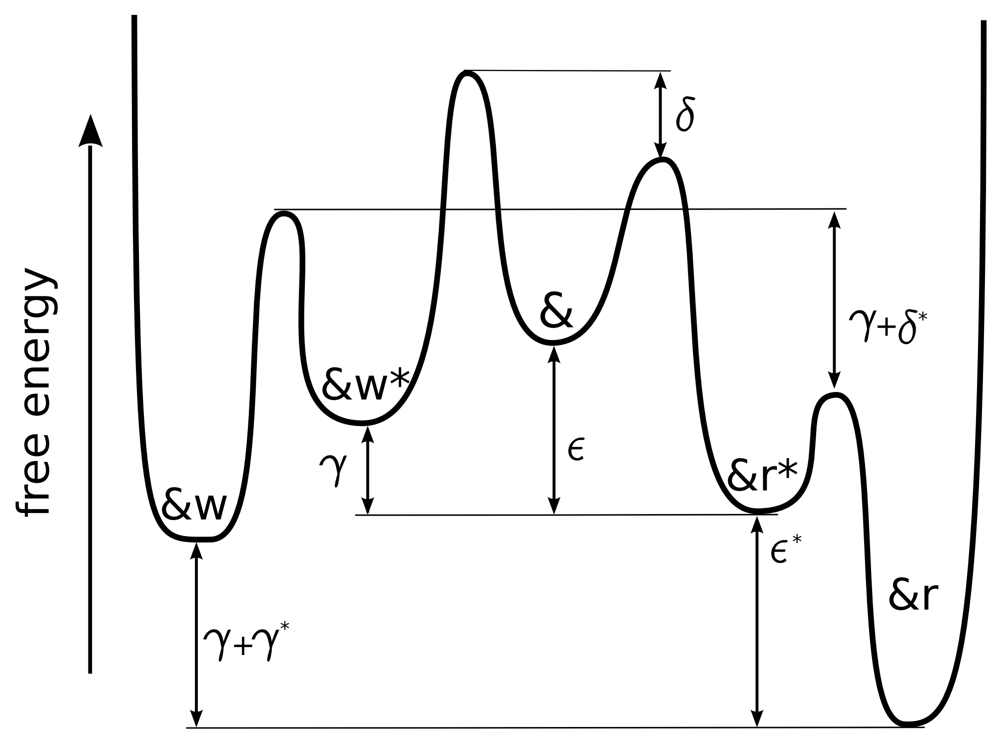
Intermediate states



1) eliminate intermediate states via steady-state condition
2) same ansatz as before

Example: two-steps copy



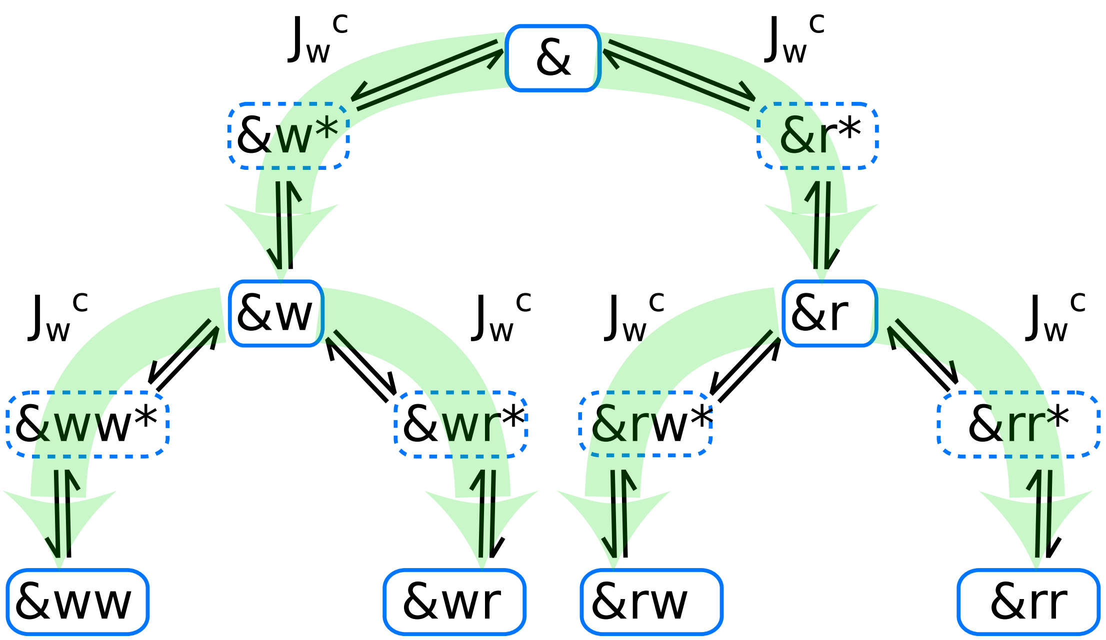


Solution:

$$\frac{\eta}{1-\eta} = \frac{(\mathrm{e}^{\delta} + \omega \mathrm{e}^{\bar{\epsilon}+\bar{\delta}})(\mathrm{e}^{\epsilon+\bar{\epsilon}} - \eta \mathrm{e}^{\gamma+\bar{\gamma}})}{(\mathrm{e}^{\gamma} + \omega \mathrm{e}^{\bar{\epsilon}})[\mathrm{e}^{\epsilon+\delta+\bar{\epsilon}+\bar{\delta}} - (1-\eta)\mathrm{e}^{\delta+\bar{\delta}}]}$$

P. Sartori and SP, in preparation

Example: two-steps copy

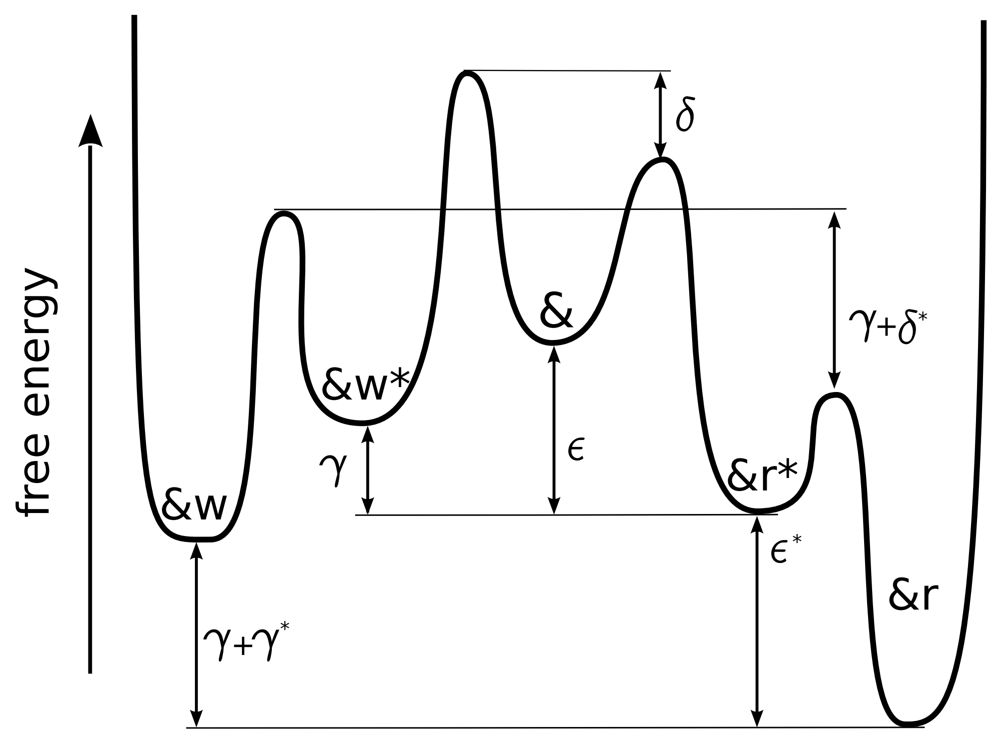


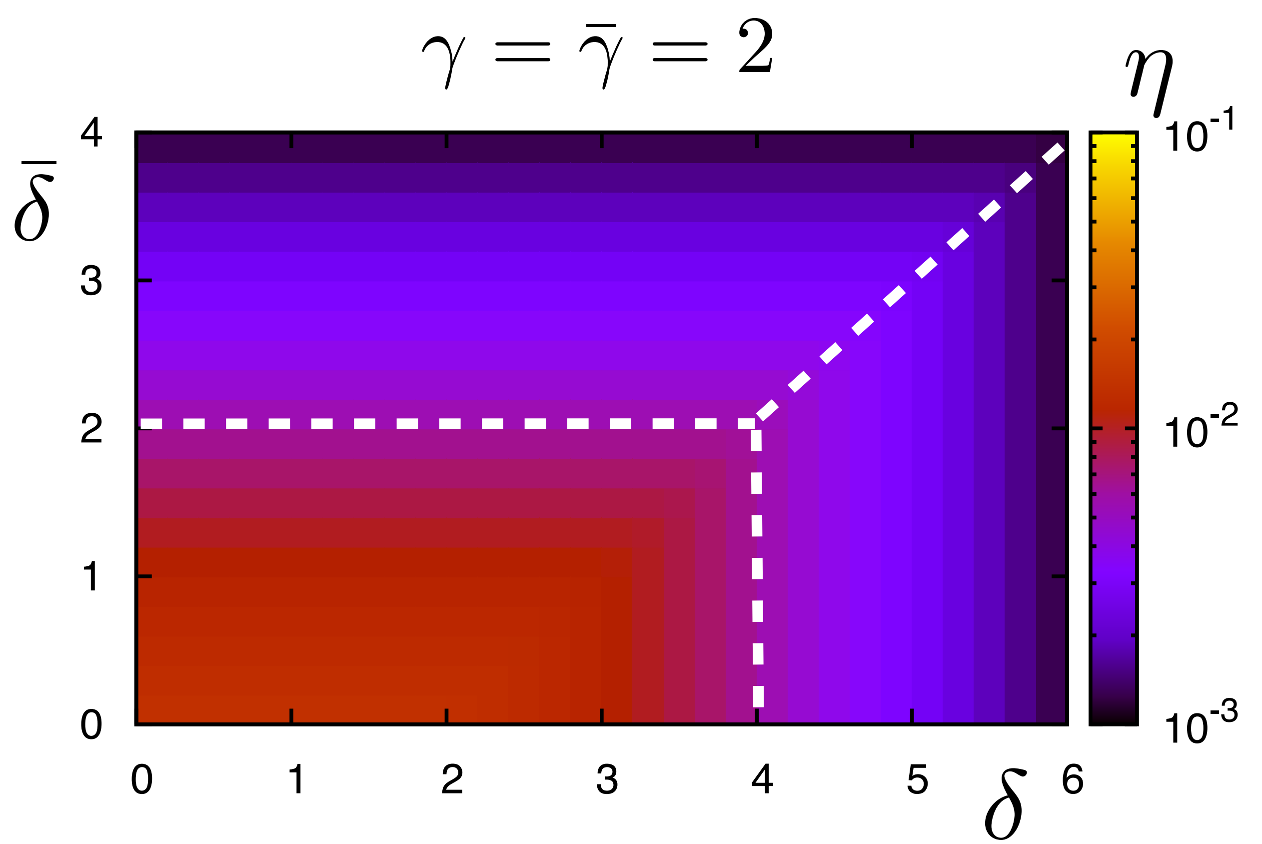
3 regions:

1) adiabatic: $\eta_{min} = e^{-\gamma-\bar{\gamma}}$

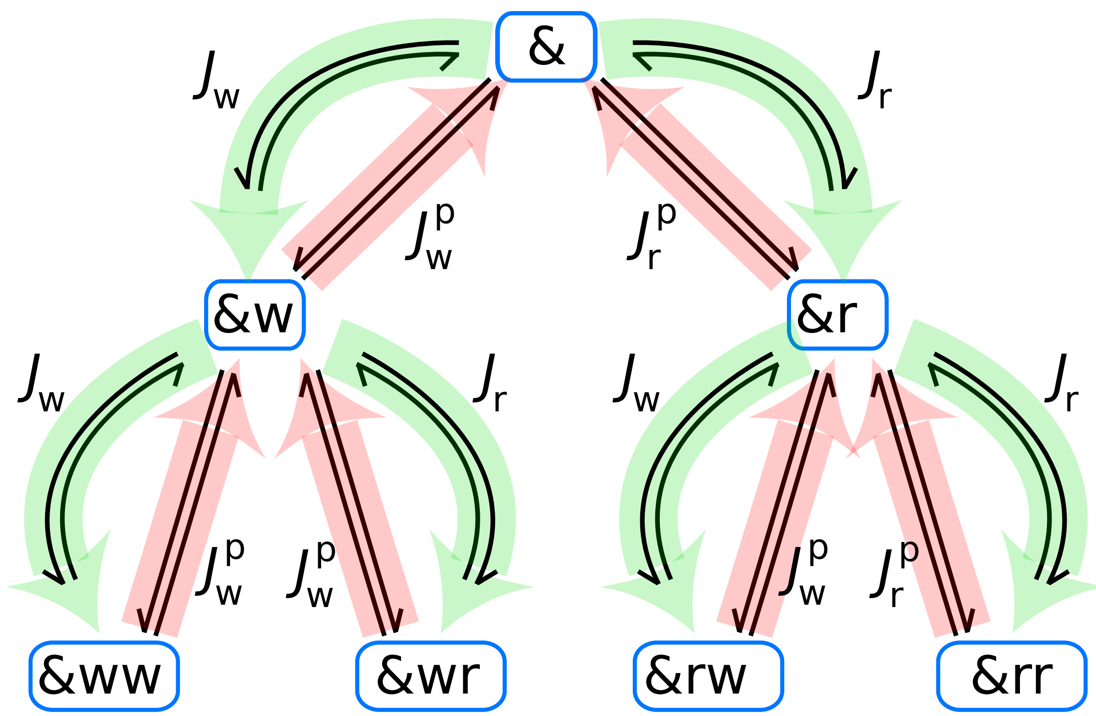
2) fast: $\eta_{min} = e^{-\delta}$

3) "forward proofreading": $\eta_{min} = e^{-\gamma-\bar{\delta}}$

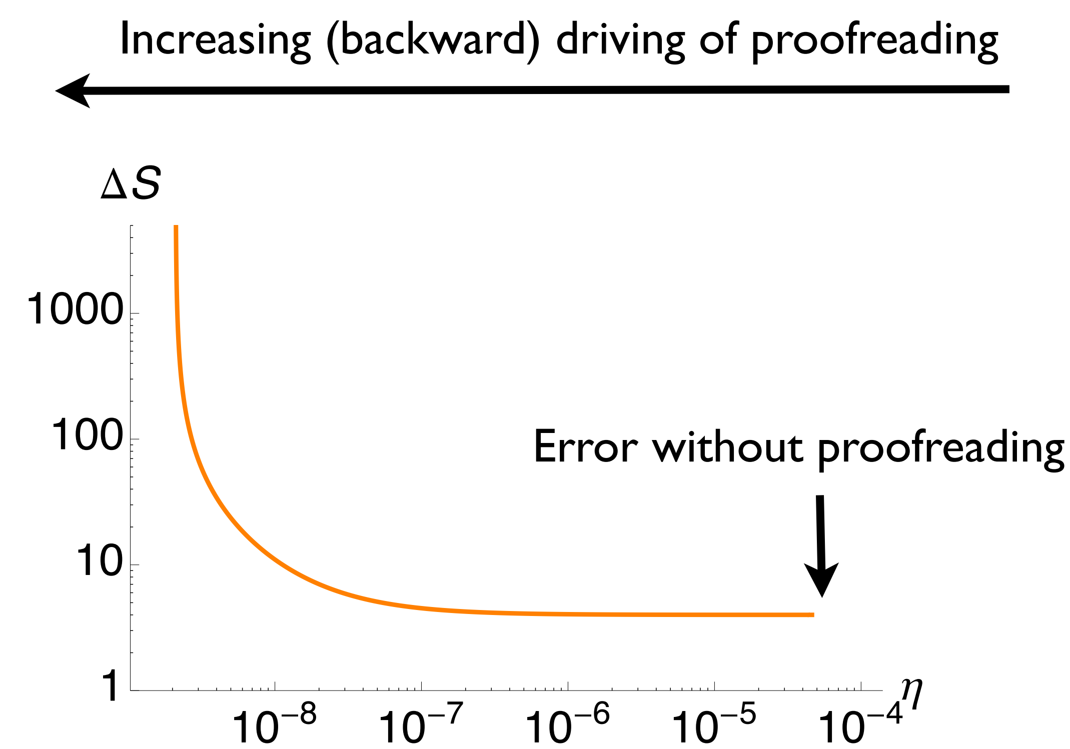


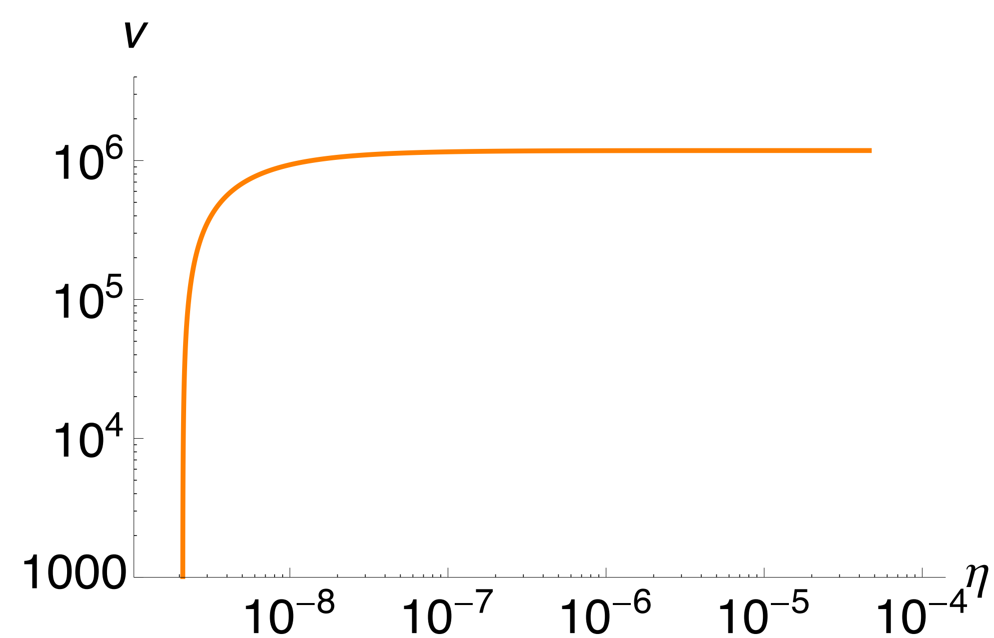


Proofreading



parallel reaction with a backward driving
(preferencially removing wrong monomers)

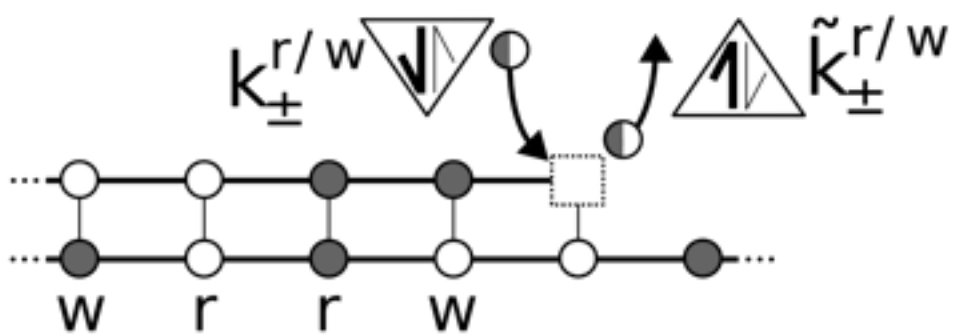




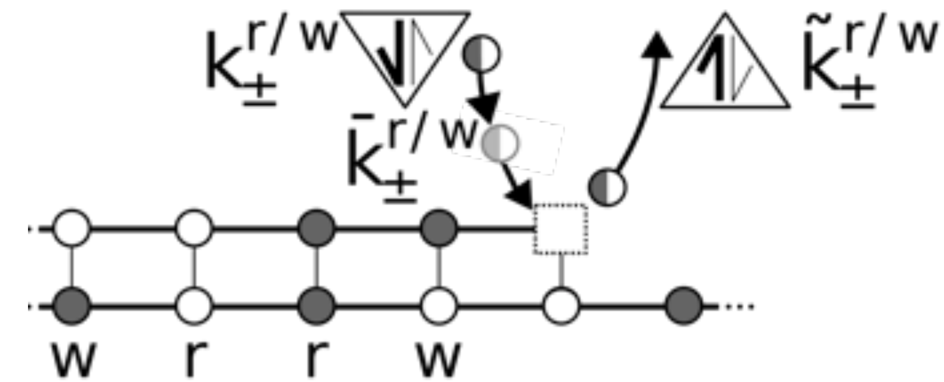
low error limit of proofreading:
high dissipation per step, vanishing velocity

P. Sartori and SP, in preparation

Proofreading



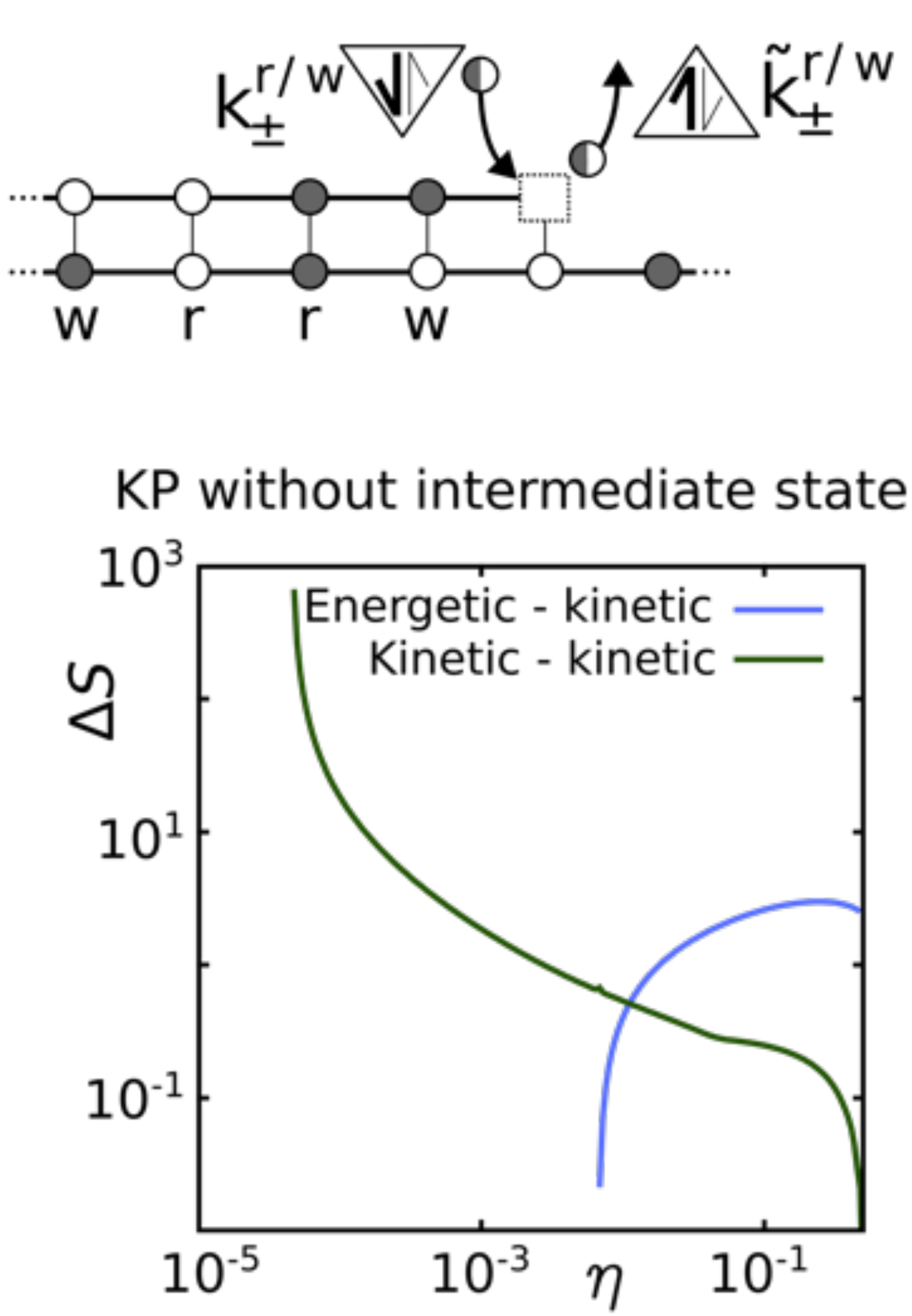
two one-step parallel reactions

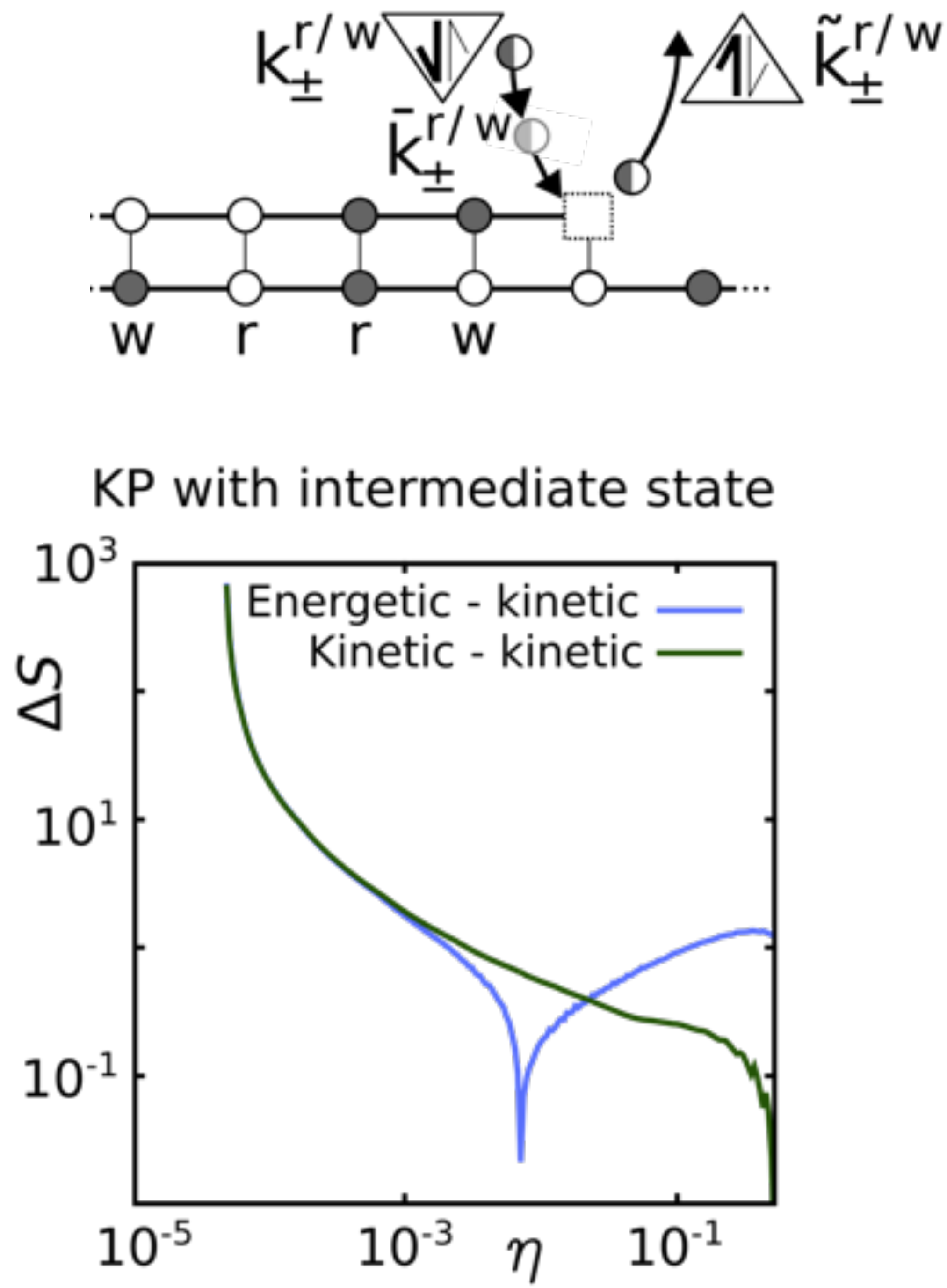


copying with an intermediate step + proofreading

- the proofreading rates are characterized by δ_p and γ_p
- numerical minimization of the dissipation over the remaining parameters

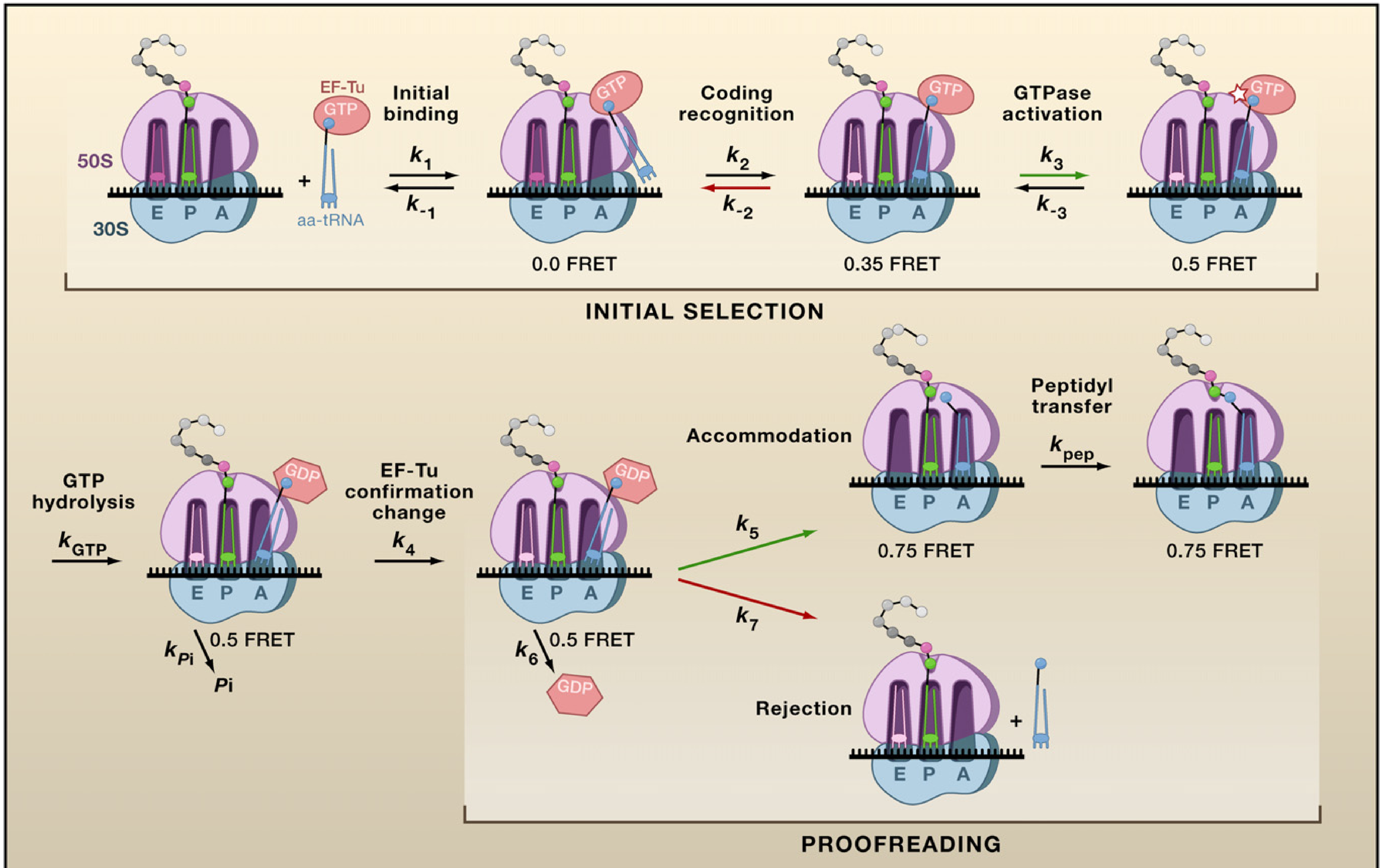
Proofreading models





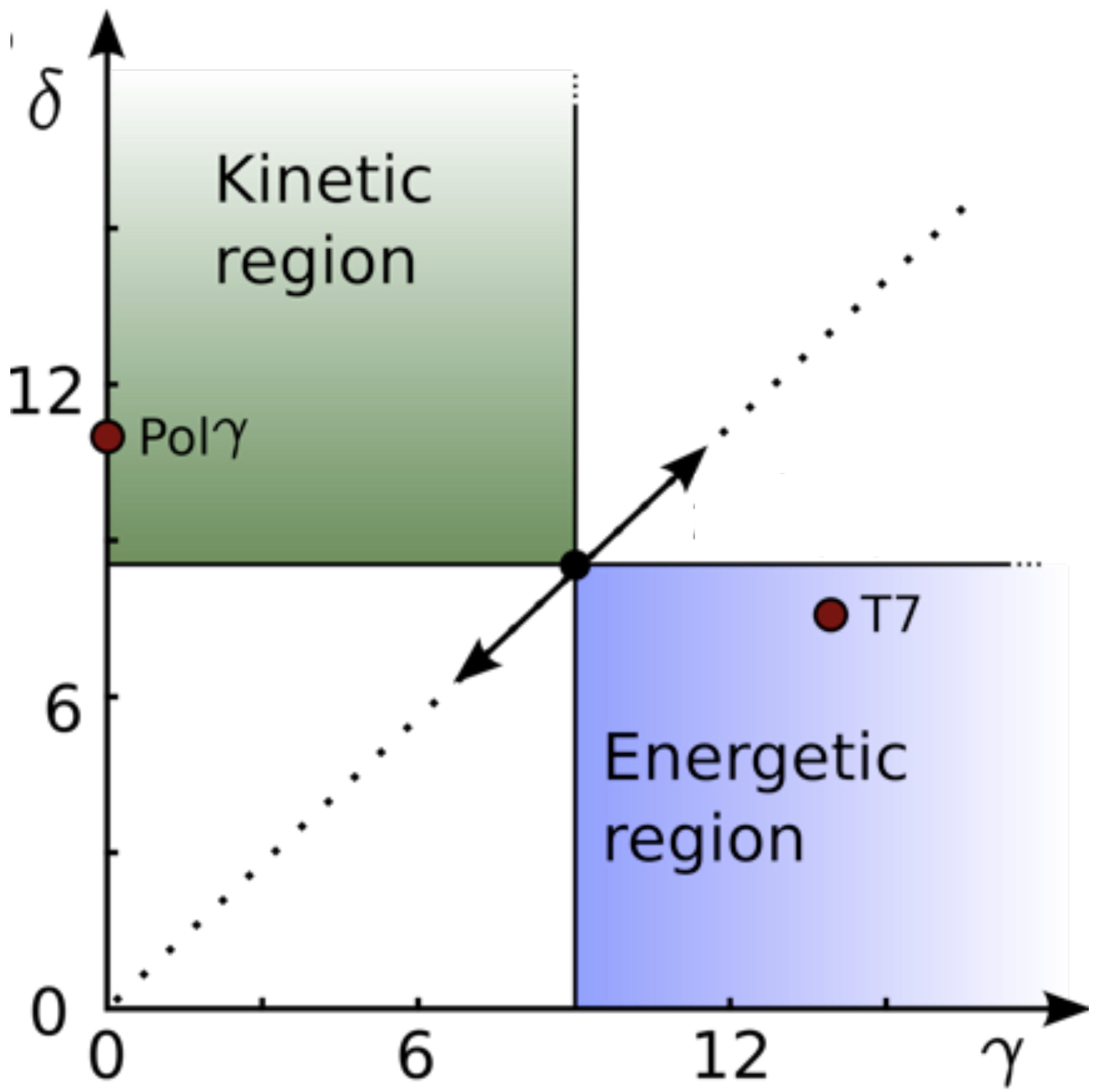
1) proofreading is always kinetic
2) energetic copy + kinetic proofreading requires intermediate state

tRNA selection pathway



Zaher and Green, Cell (2009)

Conclusions



- There are two different and *separated* regimes in stochastic copying: one based on energy barriers and one based on energy differences

- Reducing the error rate in the two regimes has different costs (more dissipation or less velocity)

- Experimental data suggest that both copying strategies are adopted in biology

- An analysis of more complex schemes shows how the strategies can be combined. Getting closer to realistic models