LECTURE 8: SIGNALLING SYSTEMS

Introduction to cellular system modelling

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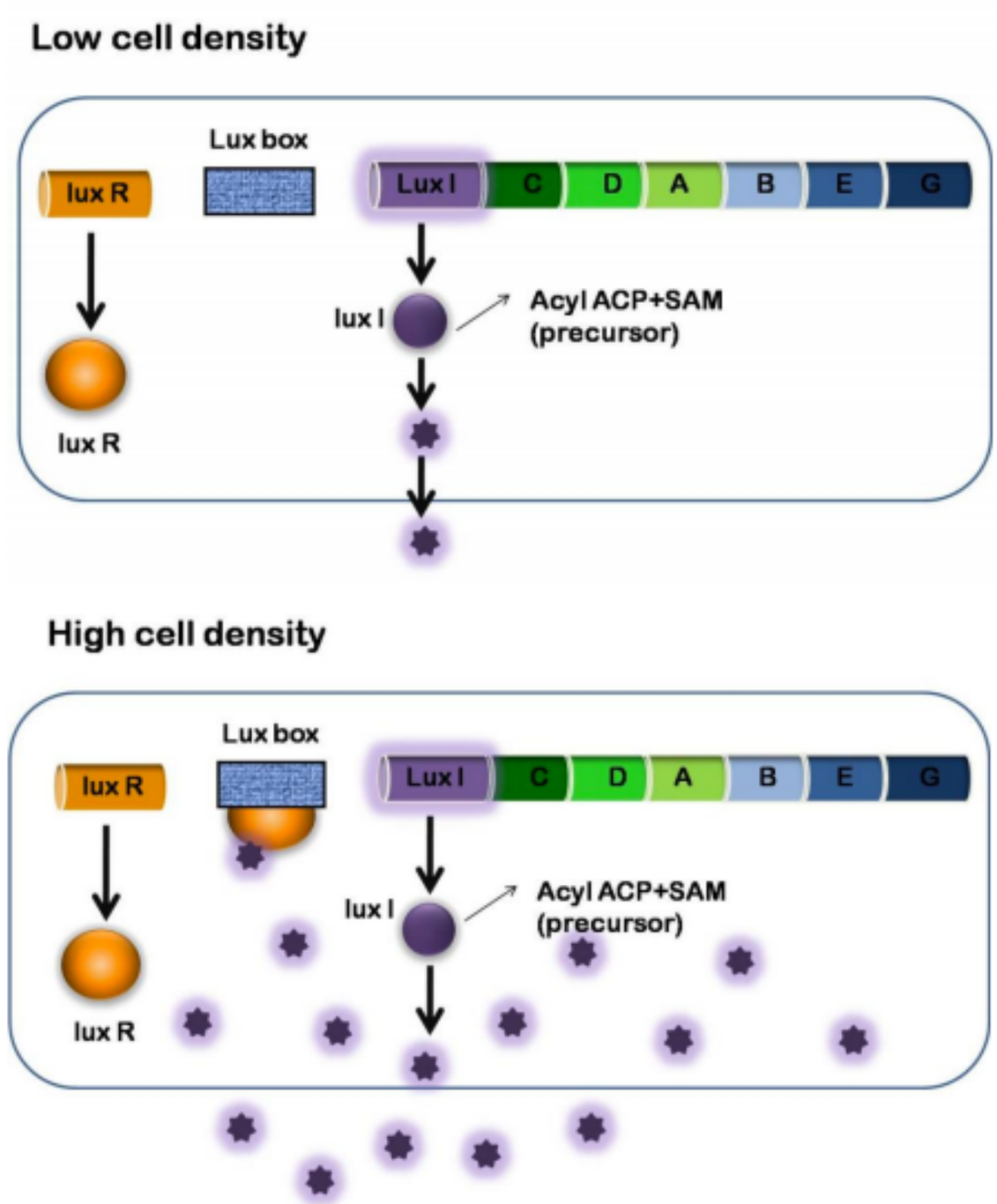
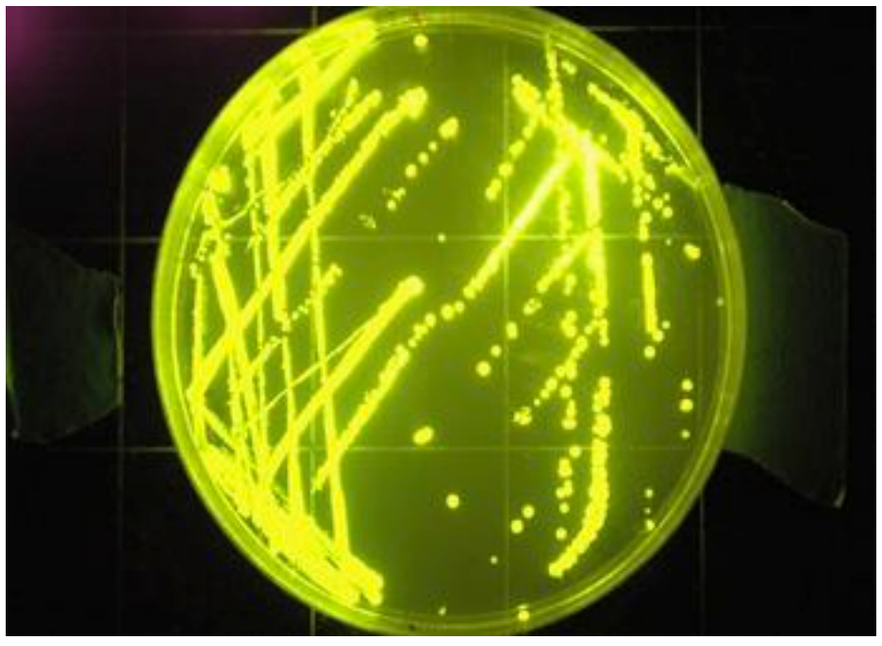
OUTLINE

- Quorum sensing
- AHL signalling
- LuxR - AHL receptor
- LuxI - AHL synthase
- Enzymatic reactions
- Signal transduction of extracellular signals
- Two component system
- Phosphorelays
- MAPK cascades
- Multi-layered perceptrons
- Kinetic proofreading

QUORUM SENSING - VIBRIO FISCHERI:



QUORUM SENSING - BIOLUMINESCENCE:

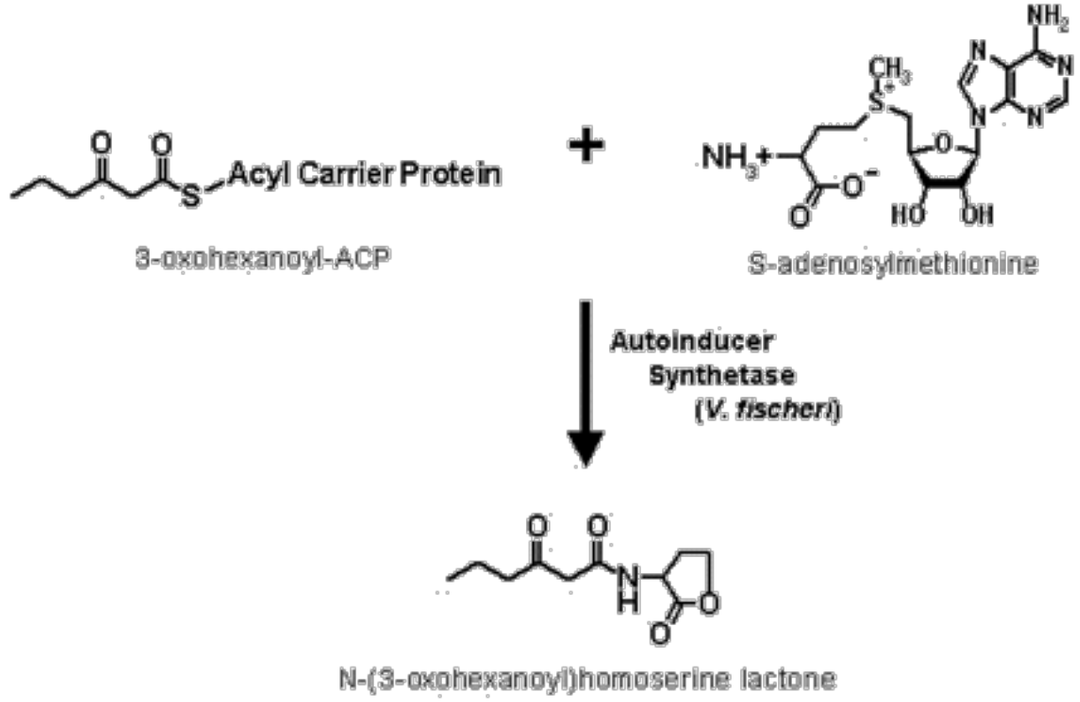


AHL INTRACELLULAR RECEPTOR - LUXR

$$\mathrm{LuxR} + 2\,\mathrm{AHL} \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} \mathrm{LuxR}^*$$

$$\mathrm{LuxR}^* + \mathrm{luxO} \underset{k_2^-}{\overset{k_2^+}{\rightleftharpoons}} \mathrm{luxO}^*$$

LUXI GENE AND AHL



MICHAELIS-MENTEN REACTION

$$E + S \underset{k_3}{\overset{k_1}{\rightleftharpoons}} ES \overset{k_2}{\rightleftharpoons} E + P$$

QUORUM SENSING - GRAM-POSITIVE BACTERIA

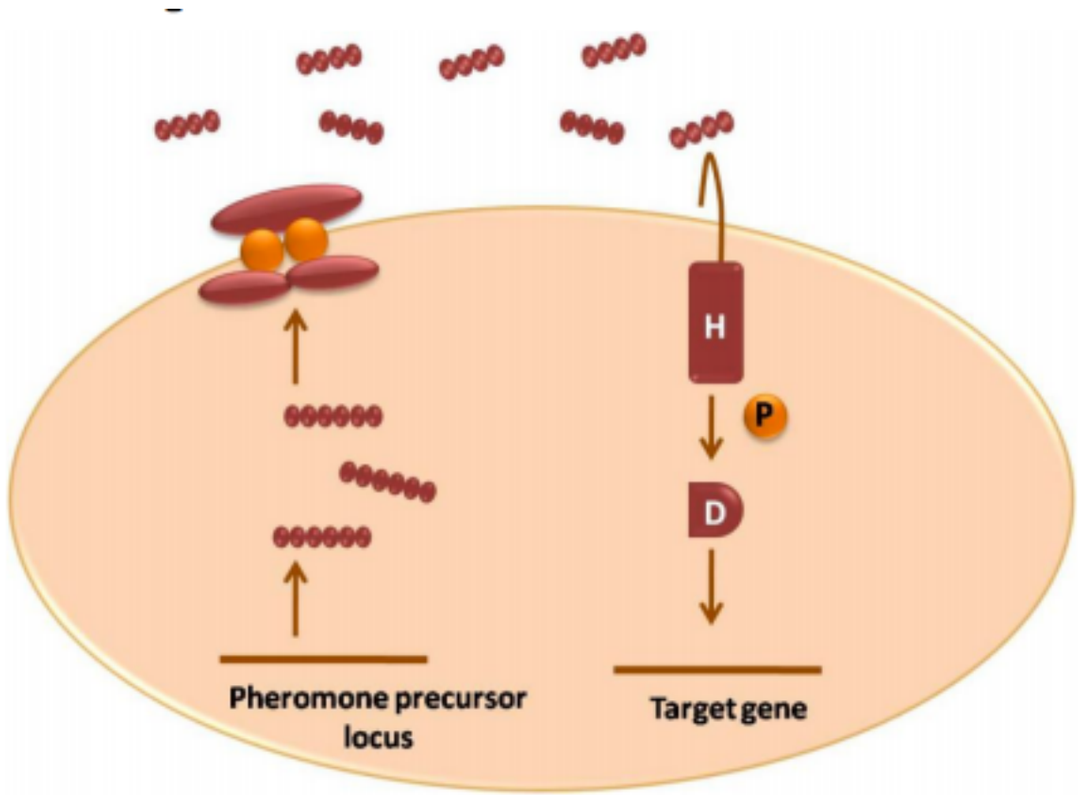
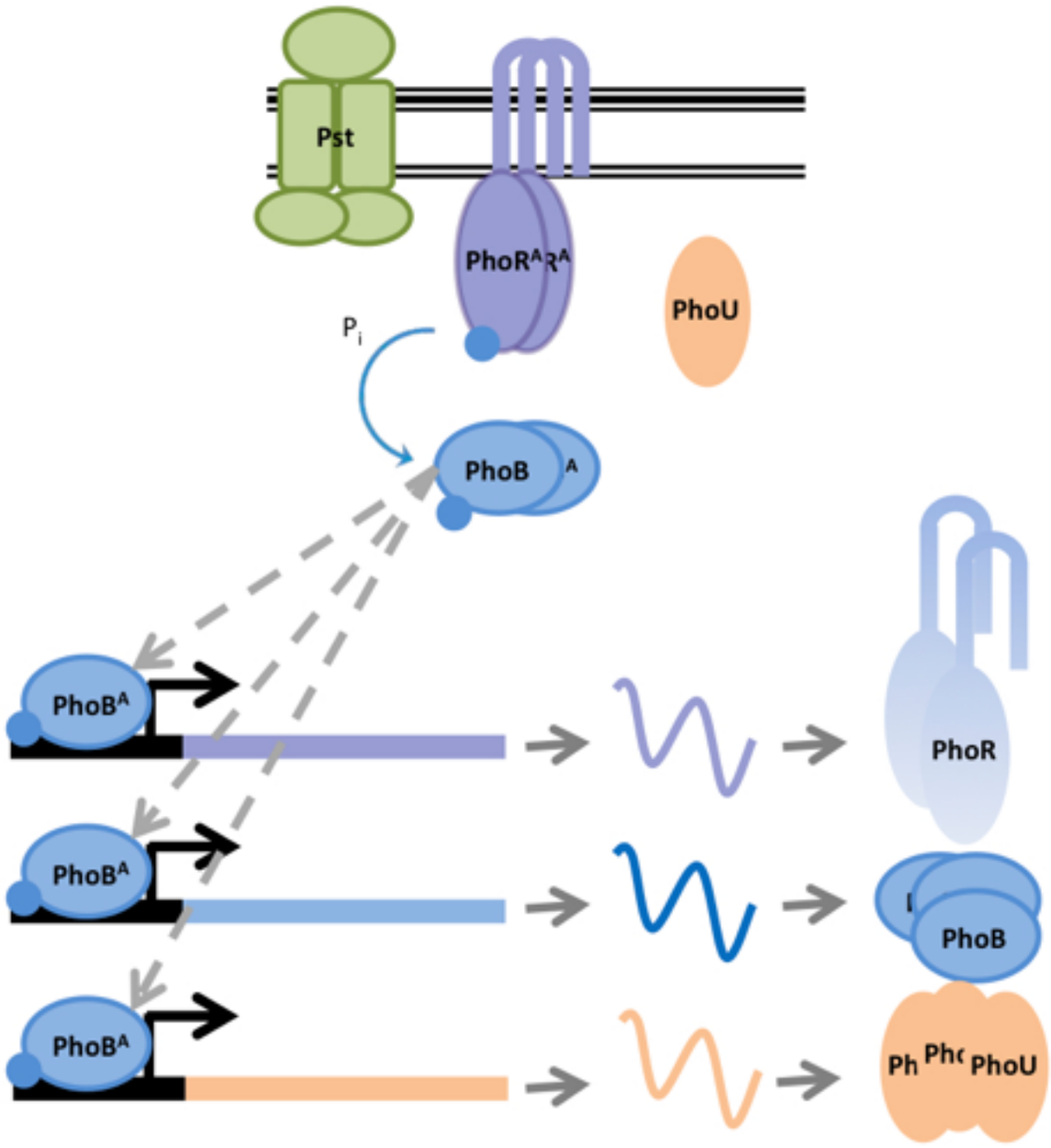
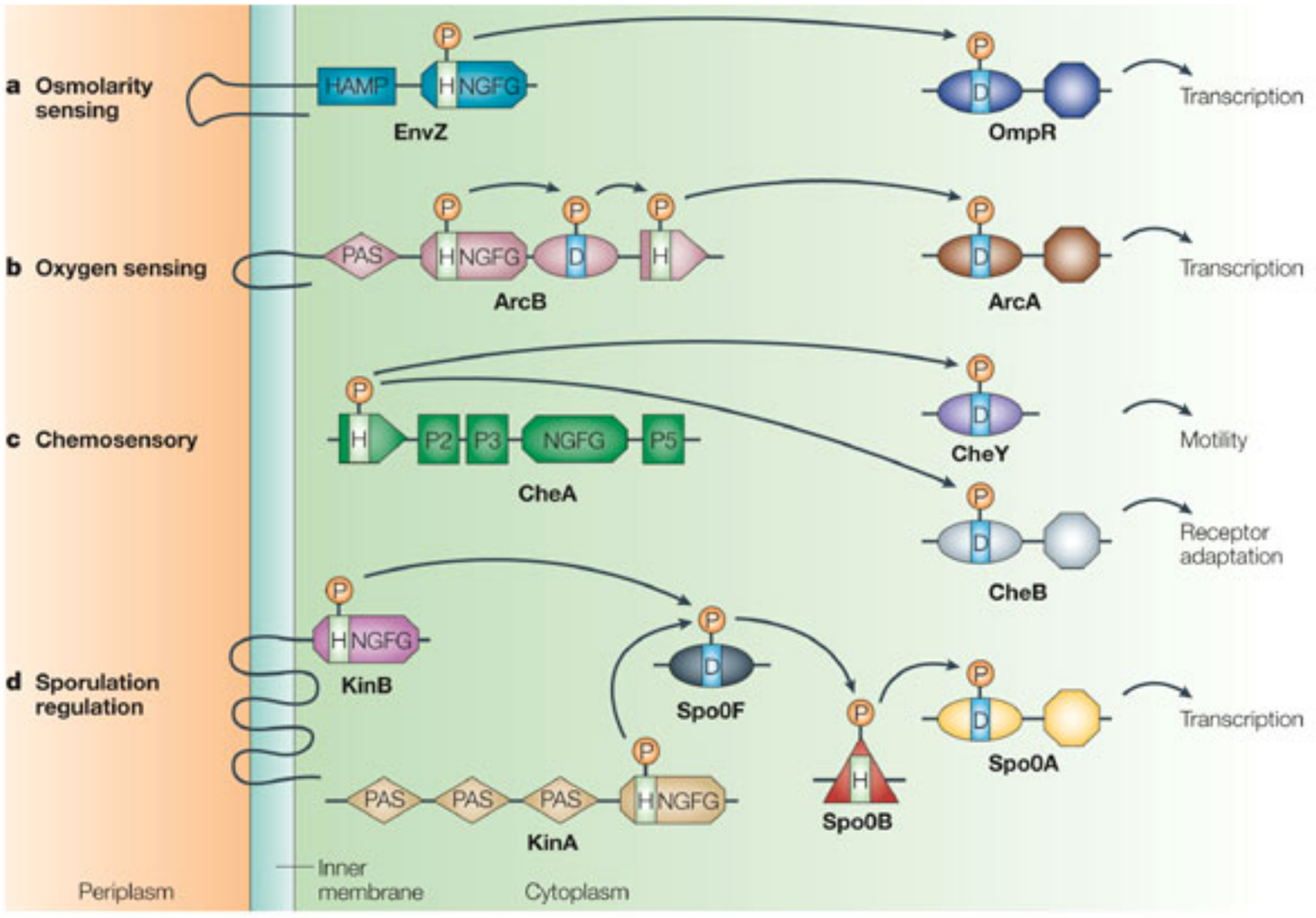


Fig 3. Quorum sensing in Gram-positive bacteria

SIGNAL TRANSDUCTION - TWO-COMPONENT SYSTEM

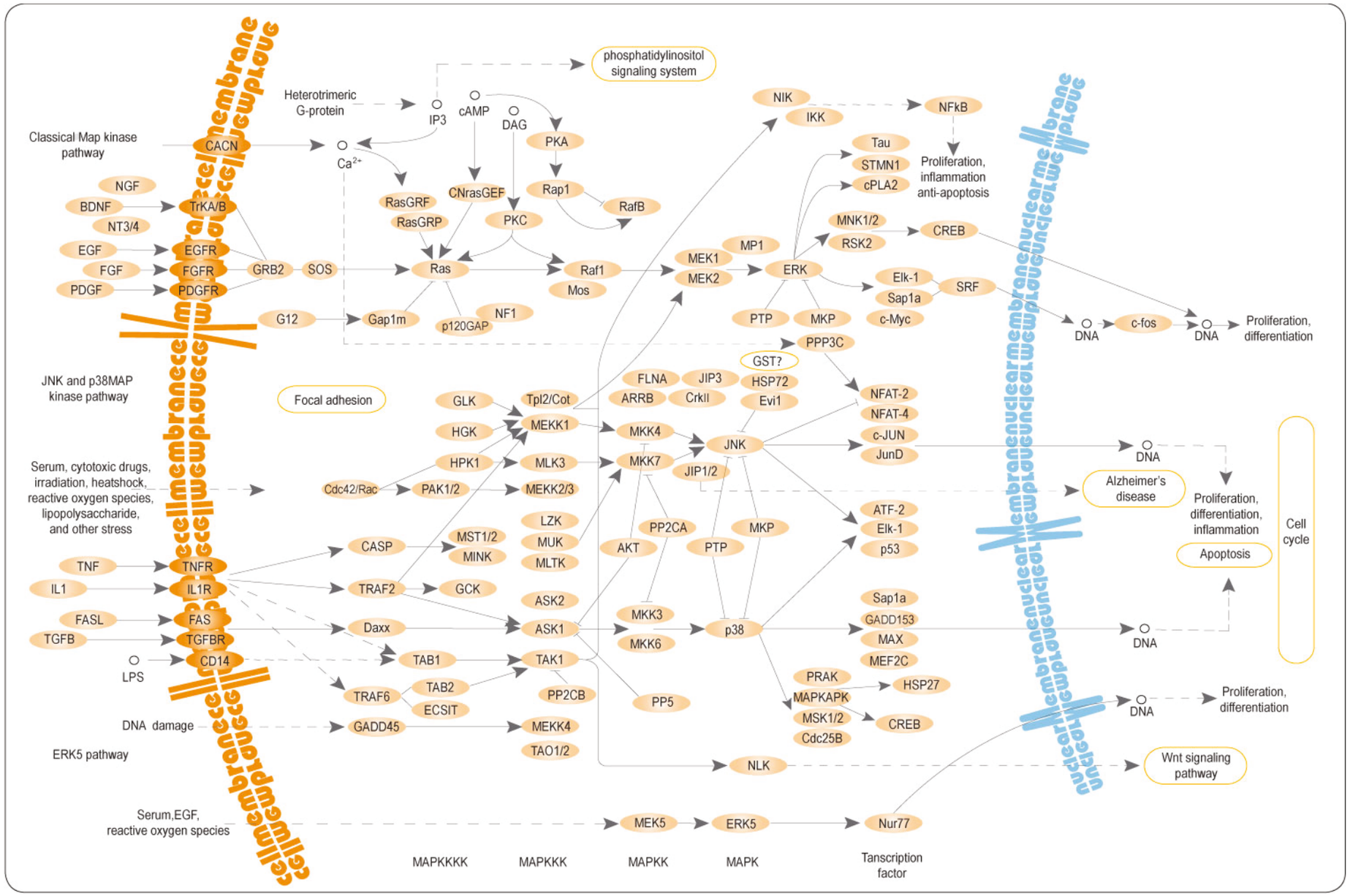


SIGNAL TRANSDUCTION - TCS PHOSPHORELAYS

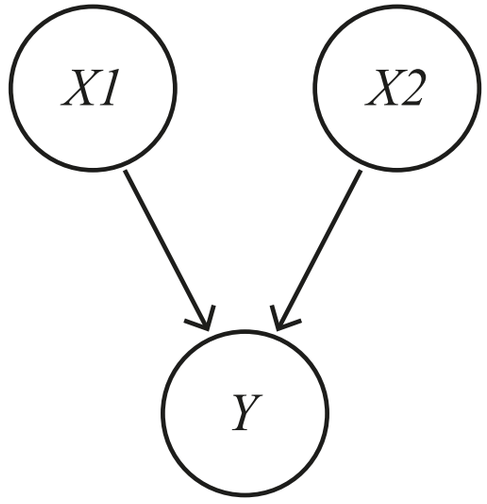


Nature Reviews | Molecular Cell Biology

SIGNAL TRANSDUCTION - MAPK CASCADES

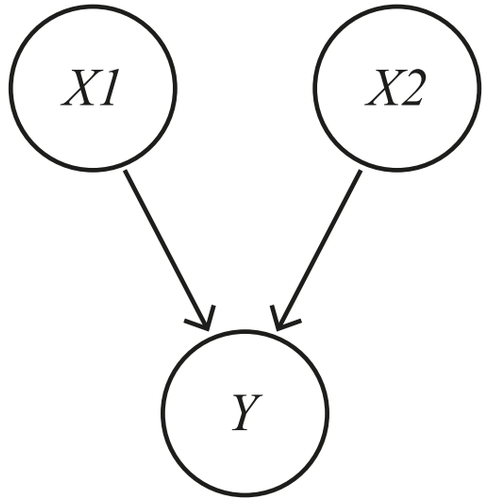


KINASE CASCADES - PERCEPTRONS



$$\frac{dY^*}{dt} = k_1 X_1 Y + k_2 X_2 Y - \alpha Y$$

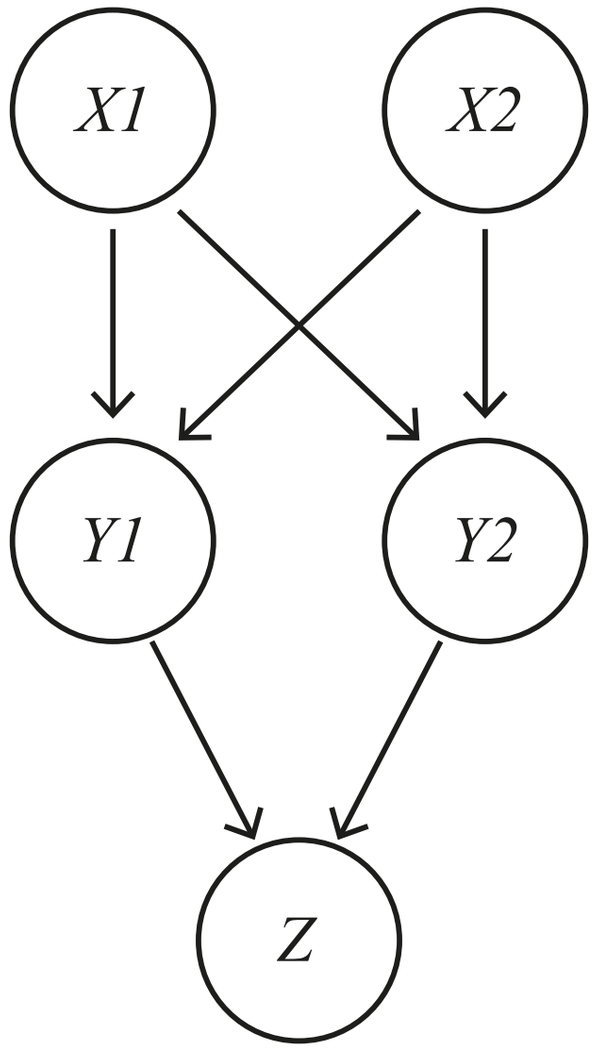
PERCEPTRONS - EQUILIBRIUM ANALYSIS



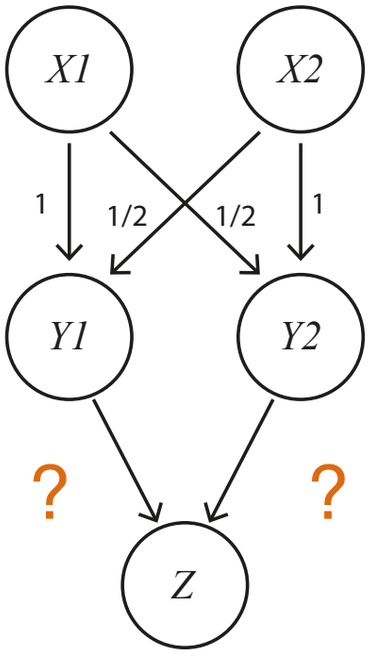
$$0 = k_1 X_1 Y + k_2 X_2 Y - \alpha Y$$

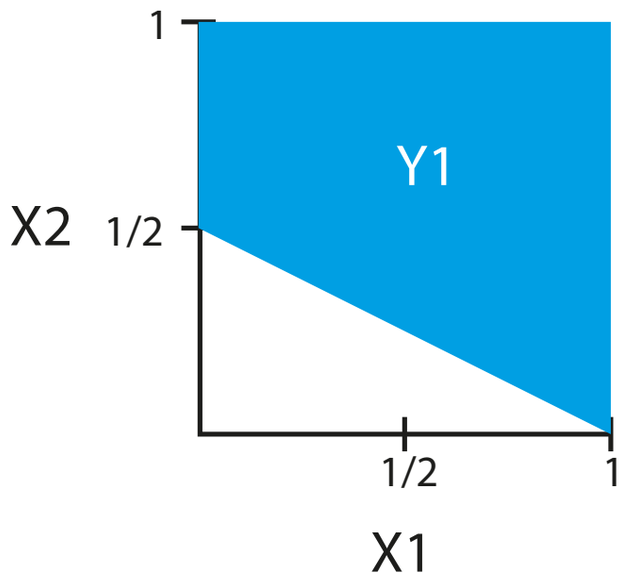
$$\frac{Y}{Y_T} = f\left(w_1 \frac{X_1}{X_{1T}} + w_2 \frac{X_2}{X_{2T}}\right), f(u) = \frac{u^n}{1+u^n}$$

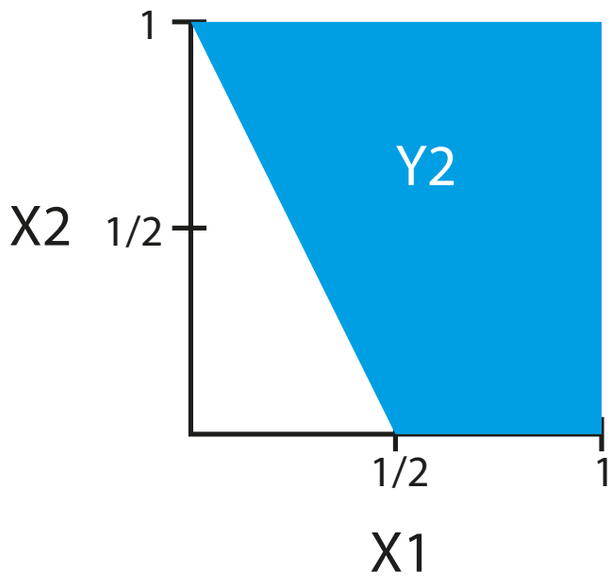
MULTI-LAYERED PERCEPTRONS



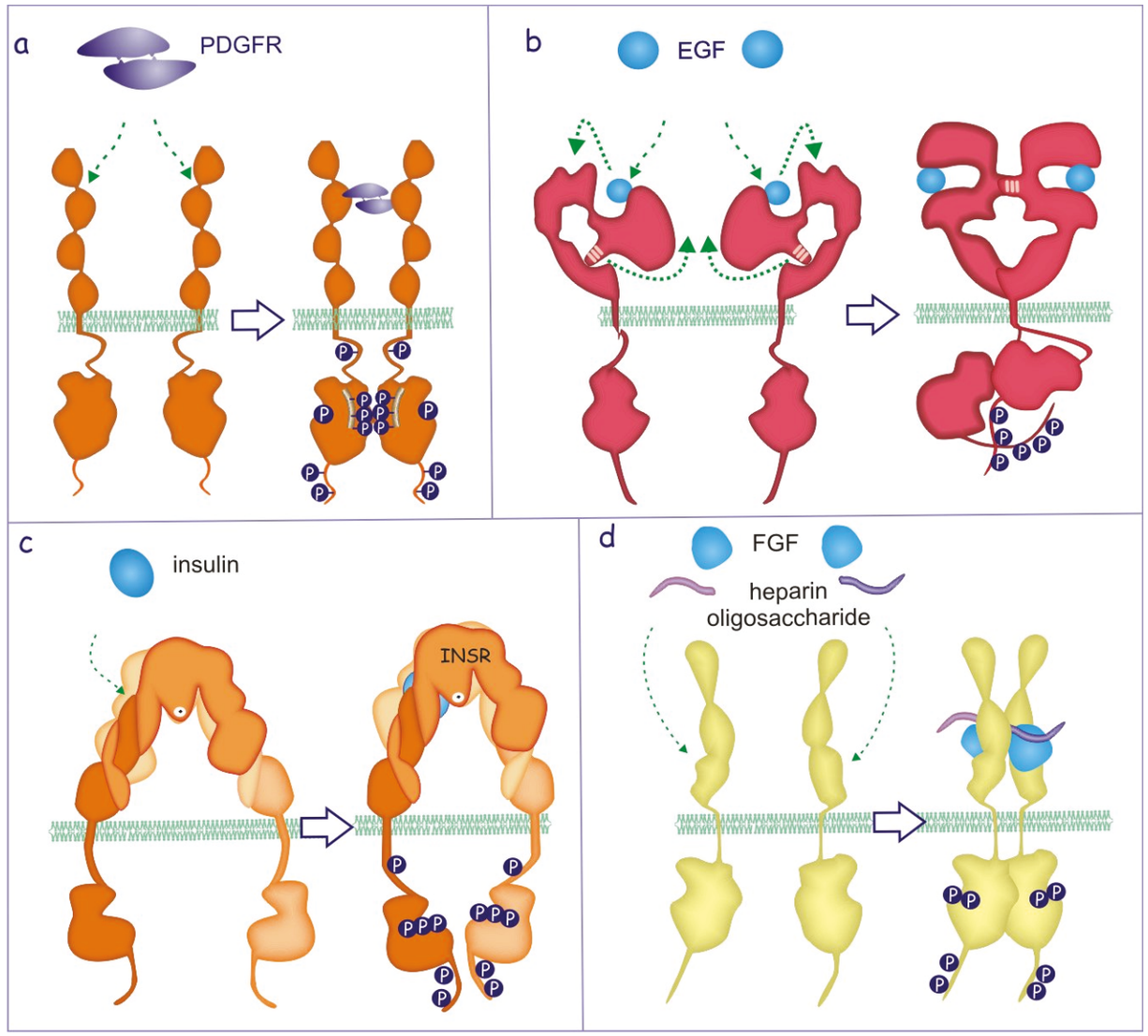
MULTI-LAYERED PERCEPTRONS … MANY POSSIBILITIES





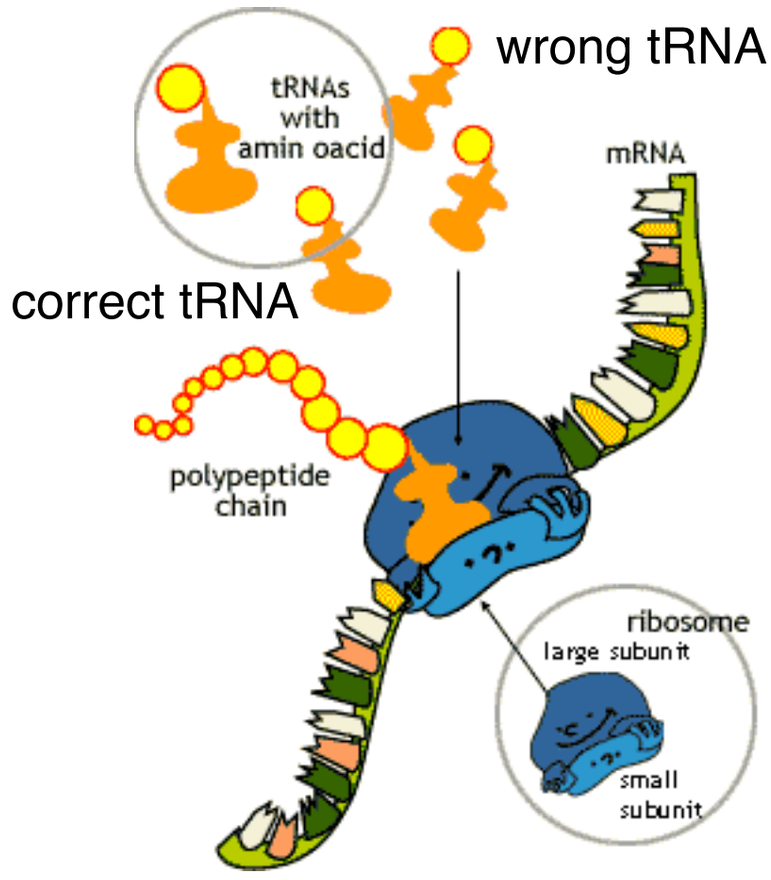


RECEPTOR KINETICS



TRANSLATION ACCURACY

TRANSLATION CAN CAUSE ERRORS:
Error rate = 1/10,000
For a short protein (100 AAs) 99% chance of being totally right
For a long protein (1000 AAs) 90.5% chance of being totally right



EQUILIBRIUM BINDING MODEL

$$c + C \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} cC \xrightarrow{v} \text{correct aa}$$

$$d + C \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} dC \xrightarrow{v} \text{incorrect aa}$$

$$R_c = \frac{vc \cdot C}{K_c}$$

$$R_d = \frac{vd \cdot C}{K_c}$$

EQUILIBRIUM BINDING MODEL - PREDICTION

$$\frac{R_d}{R_c} \approx \frac{K_c}{K_d}$$

$$= \frac{1}{100} << \frac{1}{10000}$$

Proc. Nat. Acad. Sci. USA
Vol. 71, No. 10, pp. 4135–4139, October 1974

Kinetic Proofreading: A New Mechanism for Reducing Errors in Biosynthetic Processes Requiring High Specificity

(protein synthesis/DNA replication/amino-acid recognition)

J. J. HOPFIELD

Department of Physics, Princeton University, Princeton, New Jersey 08540; and Bell Laboratories, Murray Hill, New Jersey 07974

Contributed by John J. Hopfield, August 6, 1974

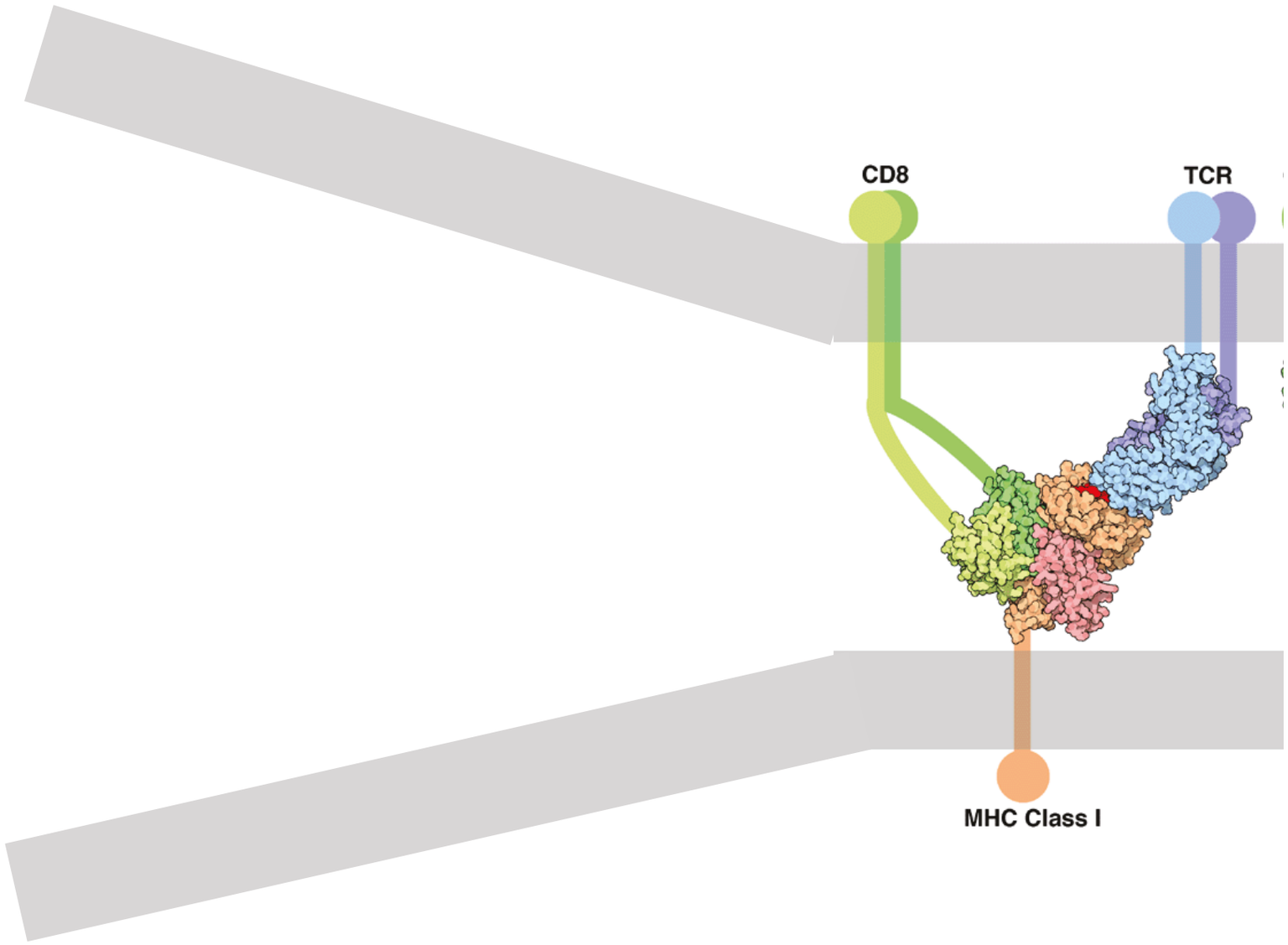
$$c + C \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} cC \overset{m}{\rightarrow} c^*C \overset{v}{\rightarrow} \text{correct aa}$$

$$d + C \underset{k_2^-}{\overset{k_2^+}{\rightleftharpoons}} dC \overset{m}{\rightarrow} d^*C \overset{v}{\rightarrow} \text{incorrect aa}$$

$$c^*C \overset{k_1^-}{\rightarrow} c^* + C$$

$$d^*C \overset{k_2^-}{\rightarrow} d^* + C$$

KINETIC PROOFREADING - IMMUNE RESPONSE



IMMUNE RESPONSE - EQUILIBRIUM MODEL

$$\frac{A_d}{A_c} \approx \frac{K_c d}{K_d c}$$

$$= \frac{1}{10} << 10^{-6}$$

IMMUNE RESPONSE - KINETIC PROOFREADING MODEL

$$P(t) = \mathrm{e}^{k^- t}$$

$$\frac{A_d}{A_c} \approx \mathrm{e}^{-\left(k_d^- - k_c^-\right)\tau}$$

$$k_d^- = 10/\,\mathrm{sec}$$

$$k_c^- = 1/\,\mathrm{sec}$$

$$\tau = 1.5\,\mathrm{sec}$$

$$\frac{A_d}{A_c} \approx \mathrm{e}^{-(10-1)1.5} \approx 10^{-6}$$