S2: Half-life model of adaptive gene product activity

Assume that the adaptive gene product requires readthrough at the primary stop codon, but not at any subsequent “backup” stop codons in the 3'UTR. The relevant adaptive expression levels \( E^b_i \) of the \( Agp^+_i \) products are now \( \delta_j (1-\delta_j) \) for \( agp^+_{i'/} / agp^+_{i''} \) genotypes, \( (1-\delta^2_j)/2 \) for \( agp^+_{i''} / agp^+_{i'} \) genotypes and \( (1-\delta_j) \) for \( agp^-_{i'/} / agp^-_{i''} \) genotypes for \( i \in \{1,2\} \) and \( j \in \{psi^-_i, PSI^+ \} \). Let \( F^b_1 \) and \( F^b_2 \) give the portions of total gene product levels \( E^b_i \) and \( E^b_2 \) that are free rather than contained in a dimer. Let \( k_+ \) and \( k_- \) be the rate constants of dimer assembly and disassembly respectively. Heterodimer formation is now described by

\[
\frac{dF^b_1}{dt} = k_+ [\text{dimer}] - k_+ F^b_1 F^b_2 \\
\frac{dF^b_2}{dt} = k_+ [\text{dimer}] - k_+ F^b_1 F^b_2 \\
\frac{d[\text{dimer}]}{dt} = k_+ F^b_1 F^b_2 - k_- [\text{dimer}].
\]

Assuming that translation and protein degradation determine constant values for \( E^b_i \) and hence that \( E^b_i = F^b_i + [\text{dimer}] \), we obtain

\[
[dimer]_{eq} = \frac{1}{2} \left( \frac{k_+}{k_-} + E^b_1 + E^b_2 - \left( \frac{k_+}{k_-} + E^b_1 + E^b_2 \right)^2 - 4E^b_1 E^b_2 \right). \tag{S2.1}
\]

To calculate the homodimer case, we simply set \( E^b_1 = E^b_2 \). In either case,

\[
t_{1/2} = \ln(2)/\left(k_+ [\text{dimer}]_{eq} \right) \tag{S2.2}
\]

where \( k_1 \) is the rate constant for the reaction catalyzed by the dimer. We use the parameter value \( k_- / k_+ = 10^{-3} \) in expression units, so that when stop codon readthrough is 100% and hence \( E=1 \) expression unit, dimer formation is realistically stable such that dimers are 31 times as frequent as monomers. Our choice of the parameter value \( k_1 = 50 \) per unit concentration, together with our choice of the selective advantage \( s_2 \) of \( [PSI^+] \), affects the relative fitnesses in our model. As shown in Figure S1, larger values of \( k_1 \) mean that optimal expression \( E_{opt} \) is lower than complete readthrough \( E=1 \). Larger \( k_1 \) would therefore be an inappropriate choice, since our model posits readthrough to be unconditionally adaptive in environment 2. Smaller values of \( k_1 \) mean that optimal expression levels are unrealistically high. \( k_1=50 \) corresponds to optimal expression of the readthrough product a few fold greater than 100% readthrough at existing levels of gene expression. This represents the fact that the adaptive readthrough product is unlikely to
have a fully optimized sequence when first expressed, a defect that can be overcome by
moderate overexpression relative to the typical expression level of a gene defined as $E=1$. 