Translation Initation Modeling

and its application in sRNA target prediction

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TBI

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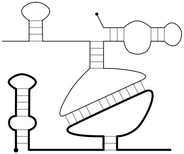

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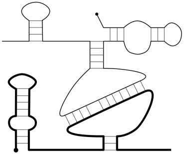

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- Many sRNAs are known (e.g. > 40 in e.coli).
- Just for a few of them targets are identified.

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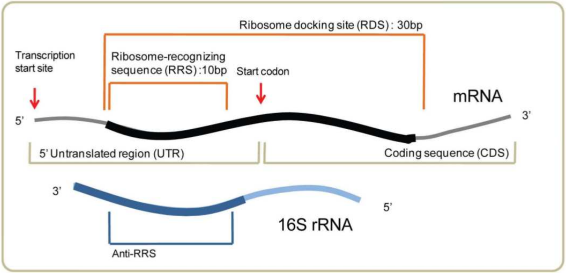
Solutions:

- model chaperon activity
- consider conservation
- model functional effect of the binding interaction

Modeling Translation Initiation



(Na et al., BMC Systems Biology, 2010)

- Ribosome-recognizing sequence (RRS) corresponds with Shine-Dalgarno sequence → ΔG_R
- *START*-Codon $tRNA^{fMet}$ anti-codon (3'-UAC-5') interaction → ΔG_R
- opening energy of the Ribosome docking site (RDS) → P_{Ex}

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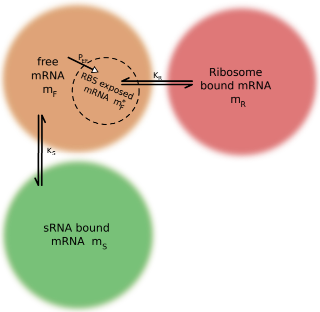
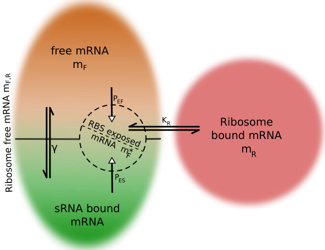
- $P_c = \frac{m_R}{m_T} = \frac{\alpha - \sqrt[2]{\alpha^2 - 4K_R^2 P_{Ex}^2 \frac{R_T}{n} m_T}}{2K_R P_{Ex} m_T}$

  with $\alpha = 1 + K_R \cdot P_{Ex} \cdot \frac{R_T}{n} + K_R \cdot P_{Ex} \cdot m_T$

Incorporating sRNA

overlap sRNA-BS and RDS	no overlap sRNA-BS and RDS





$$\frac{dm_s}{dt} = -k_r^s \cdot m_s + k_f^s \cdot m_F \cdot s_F = 0$$

$$\frac{dm_R}{dt} = -k_r^R \cdot m_R + k_f^R \cdot m_F^* \cdot R_F = 0$$

Incorporating sRNA

overlap sRNA-BS and RDS

$$m_F = m_T - m_R - m_s \tag{1}$$

$$m_F^* = P_{EF} m_F \tag{2}$$

no overlap sRNA-BS and RDS

$$m_{F,R} = m_T - m_R \tag{3}$$

$$m_{F,R}^* = P_{EF} \gamma m_{F,R} + P_{ES}(1-\gamma) m_{F,R} \qquad \text{with} \quad \gamma = \frac{m_{F,s}}{m_s} \tag{4}$$

Incorporating sRNA

overlap sRNA-BS and RDS

$$\begin{aligned}(m_R(-1+K_R(m_R-m_T)nP_{EF})+K_R(-m_R+m_T)P_{EF}R_T)\\(K_sm_R+K_RP_{EF}(-m_Rn+R_T))-K_RK_sm_RP_{EF}(-m_Rn+R_T)s_T=0\end{aligned} \tag{1}$$

no overlap sRNA-BS and RDS

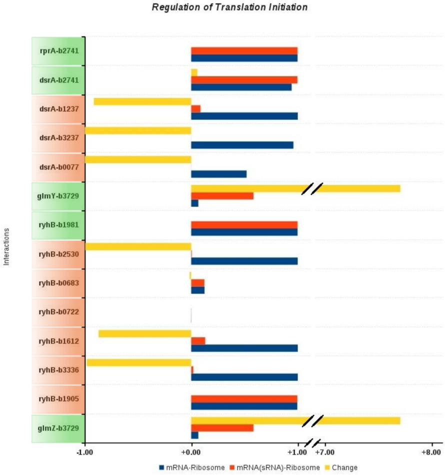
$$\begin{aligned}m_T(K_sm_R^2s_T+K_Rm_R(m_R-m_T)(m_Rn-R_T)(-(1+K_sm_T)(P_{EF}-P_{ES})+K_s(P_{EF}-3P_{ES})s_T)-\\K_R^2(m_R-m_T)^2(-m_Rn+R_T)^2((P_{EF}-P_{ES})(P_{EF}-(2+K_sm_T)P_{ES})+K_s(P_{EF}-2P_{ES})P_{ES}sT))=0\end{aligned} \tag{2}$$

Measure for Translation Initiation Rate

$$P_c=\frac{m_R}{m_T} \tag{3}$$

Results Positive Regulated Genes

- Example of calculated changes for some known Interactions



Results GcvB

Results known targets

Target	Change
b4208	-0.99
b1243	-0.71
b3544	-0.98
b0655	-0.99
b2310	-0.99
b3460	-0.96
b3458	-0.97
b3774	-0.95
b3203	-0.98

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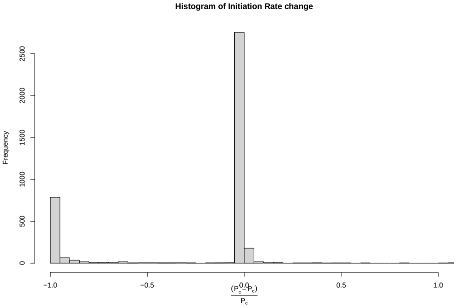
Distribution all genes



Target Prediction in Bordetella pertussis

- Bordetella pertussis (WT and Hfq-) in log and stat phase
- Illumina HiSeq Sequencing (total 932,115,202 reads in eight samples)

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- Translation Initiation Model applied to all this combinations

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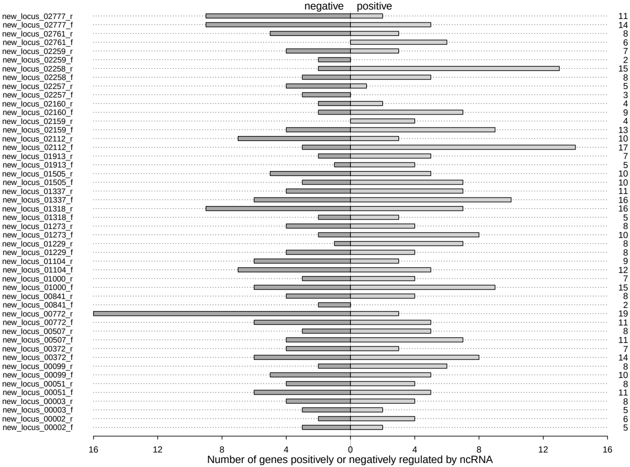

Summary

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- A mathematical model of translation initiation under the influence of sRNA binding.
- Using the information about thermodynamic binding properties sRNA-mRNA, mRNA-Ribosome (RNAplex, RNAup) and the stoichiometry of this reaction (RNAseq).
- Summarizing this integrated information in a comprehensible measure: the relative change of Translation Initiation.

Future
- Experimental validation (quantitative/qualitative) of calculated changes in Translation Initiation.

thx

Thanks to every body at the TBI for fruitful discussions and support.

And thank YOU for your attention.