mRNA translation rate modeling with an extended TASEP incorporating tRNAs modifications

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INTRODUCTION

Ribosome Elongation Rate

- There is a great ***variation in ribosomal velocity*** along even a single transcript
- What determines how fast a transcript is processed by a ribosome is not completely resolved [1]
- ***Changes in the local translation rate along mRNA have been implicated in health and disease [2]:***
  - ✓ Protein specific activity and folding
  - ✓ Correct localization of protein
  - ✓ Neurodegenerative diseases and cancers

Key Determinants of Elongation Rate

- ***Charged amino acids*** distribution in the nascent protein and ***electrostatic interaction with the ribosome exit tunnel (a)***
- Adaptation of ***codon usage*** to tRNA pool ***(b)***
- Codon ordering and ***tRNA recycling***
- ***tRNA wobble base*** enzymatic ***modifications (c)***
- ***Proline incorporation*** delay
- ***mRNA secondary structure*** melting delay
- Ribosomes resource pool

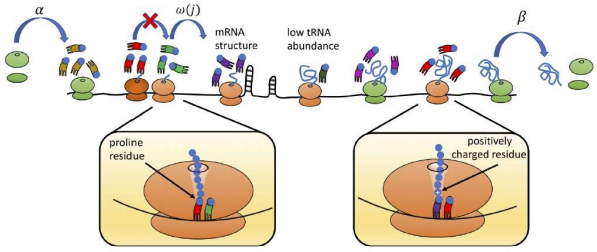
Aim of this study

- Adapt and extend ***TASEP (d)*** (Totally Asymmetric Simple Exclusion Process), a ***stochastic biophysical model of protein translation [3,4]***
- Predict ***protein levels relative abundance*** beyond RNA-seq proxy
- Better understand ribosome density profiles in ribosome fingerprinting experiments (***Ribo-Seq***)
- Shed light on the ***translational control dynamics and understand how codon usage and tRNA modifications impact on protein synthesis***

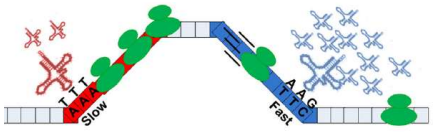
MATERIALS & METHODS

Computational biology modeling and proteomic data mining :

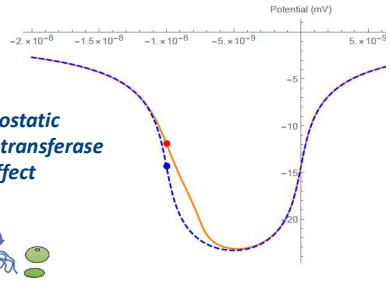
- ✓ Our approach is to study the interplay between the main determinants of elongation/translation rate
- ✓ ***Specifically, we test whether or not the exit tunnel electrostatic interaction constraints codon usage at the PTC (peptidyl transferase center) and if tRNA modifications might modulate this effect***



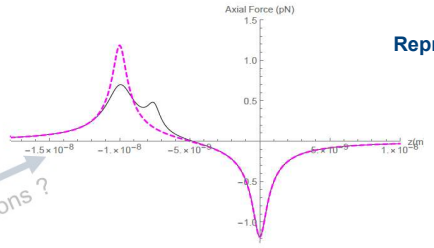
(d) TASEP biophysical stochastic model of translation [3,4]



Electrostatic potential model of ribosome exit tunnel (a)

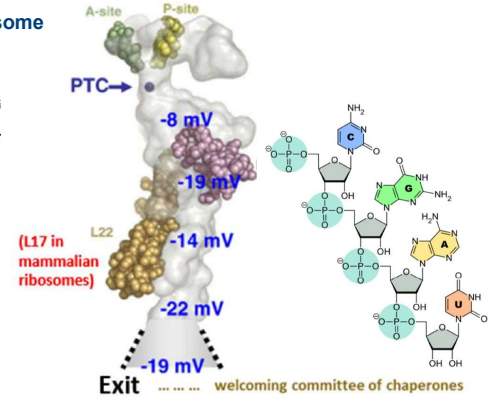


Electrostatic axial force $F_z(z)$ on a unit test charge

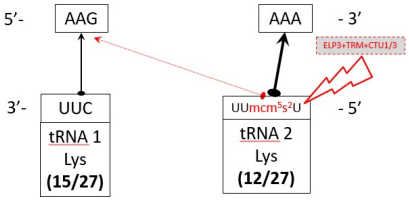


associations ?

Slow down effect [3] of non-preferred codons (b) modulated or not with tRNA modifications (c)



Representation of ribosome exit tunnel [5, 6]



FIRST RESULTS AND PERSPECTIVES

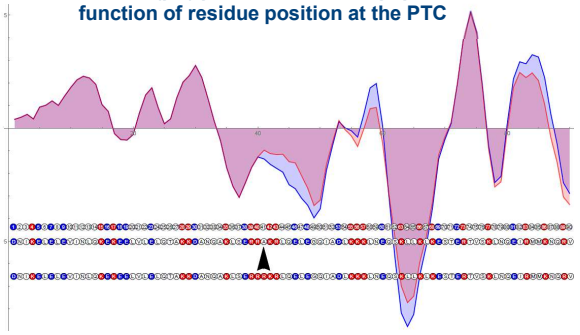
Bioinformatics and statistical analysis

- ✓ Associations are investigated between the sign of the axial forces acting on the peptide in the tunnel (slow down or speeding up) and the codon usage downstream in transcript's windows centered around the PTC.

Perspectives

- ✓ The ribosome exit tunnel electrostatic interaction model will ***improve TASEP*** input and provide ***better fitting to protein relative expression abundance*** levels and ***Ribo-Seq*** data results. Associations between electrostatic interaction and local codon usage can be incorporated and their strengths studied proteome wide and across species.
- ✓ We will ***test proteome wide*** and for particular cell lines whether a ***speeding up*** of the nascent protein in the exit tunnel ***requires simultaneous optimal codon local usage***.
- ✓ We will test whether a ***slow down*** of the nascent protein in the tunnel due to ***electrostatic braking axial forces*** must be ***compensated for by a higher turnover*** at the ribosomal decoding center.

Axial forces (pN) profile on nascent peptide as a function of residue position at the PTC



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[1] Charneski et al, 2013, PLoS Biol, 11(3) **[2] Rapino et al**, 2018, Nature, 558 **[3] Zur&Tuller**, 2016, Nucl. Acid Res., 44(19) **[4] Sharma et al.**, 2018, Phys. Rev. E; 97 **[5] Voss et al.**, 2006, J. Mol. Biol., 360(4) **[6] Lu et al**, 2007, J. Mol. Biol., 371(5)

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