RNA degradation

Model Implementation. The RNA decay sub-model encodes a molecular simulation of RNA degradation and occurs via two steps that represent RNase-mediated mechanisms. It is implemented in the `RNAdegradation` process (detailed in Algorithm 1).

Endo-nucleolytic Cleavage. First, the total counts of RNA degraded during a time step are computed as a fraction of the total capacity for endo-cleavage. Then, the total amount of RNA degraded is divided into different species (mRNA, tRNA, and rRNA) using known endoRNase::RNA affinities. Finally, non-functional RNA fragments are represented as an additional pseudo-metabolite in the `BulkMolecules` state.

Exo-nucleolytic Digestion. The exoRNase enzymatic capacity is used to determine the fraction of RNA fragments that can be digested and converted to individual nucleotides that can be recycled by the `Metabolism` process.

Difference from *M. genitalium* model. The *E. coli* model provides a more detailed, mechanistic representation in the `RNADegradation` process compared to the *M. genitalium* model. Unlike the previous model, the gene functionality of endoRNase and exoRNase is mechanistically integrated to evaluate: (1) rates of RNA degradation due to endo-nucleolytic cleavage, and (2) rates of nucleotides digested by exoRNases.

Associated files

wcEcoli Path	File	Type
wcEcoli/models/ecoli/processes	rna_degradation.py	process
wcEcoli/reconstruction/ecoli/dataclasses/process	rna_decay.py	data

Table 1: Table of files for RNA degradation.

Associated data

Parameter	Symbol	Units	Value	Reference
EndoRNase catalytic rate	$K_{cat,endo}$	non-functional RNA counts/s	0.10	See Source Code
ExoRNase catalytic rate	$K_{cat,exo}$	nt digested/s	50	See Source Code
mRNA half-lives[(1)]	τ_{mRNA}	min	[1.30, 31.40]	[1]
tRNA, rRNA half-lives	τ_{tRNA}, τ_{rRNA}	hour	48	[1]
Michaelis constant[(2)]	K_m	RNA counts	-	See Table 1
RNAse mechanism of action	-	endo-/exo-RNAse	-	See Source Code
EndoRNase specificity[(3)]	-	(mRNA, tRNA, rRNA)/RNase	Boolean	See Source Code

Table 2: Table of parameters for RNA degradation process.
[(1)]Non-measured mRNA half-lives were estimated as the average mRNA half-life (5.75 min).
[(2)]Michaelis constants were calculated by fitting the `RNADegradation` model to be equal to the first-order `RNADegradation` model, as follows:
$K_{cat,endo} \cdot c_{endo} \frac{c_{RNA,i}/K_{m,i}}{\sum_j c_{RNA,j}/K_{m,j}} = \frac{ln(2)}{\tau_{RNA,i}} \cdot c_{RNA,i}$
[(3)]Types of RNA that can be targeted by a given RNase.

Algorithm 1: Algorithm for RNA degradation: endo-cleavage for transcripts, and exo-nucleolytic digestion

Input : $K_{m,i}$ Michaelis constants of each mRNA transcript where $i = 1$ **to** n_{RNA}

Input : $K_{cat,endo}$, $K_{cat,exo}$ catalytic rate of endoRNase and exoRNase

Input : c_{endo}, c_{exo} count of endoRNase and exoRNase

Input : $c_{frag,i}$ count of non-functional RNA fragments where $i = 1$ **to** 4 for AMP, CMP, GMP, UMP

Input : c_{mRNA}, c_{tRNA}, c_{rRNA} count of each mRNA, tRNA and rRNA

Input : c_{molec} count of small molecules where $molec \rightarrow$ [H_2O, PPI, Proton, NMPs]

Input : `multinomial()` function that draws samples from a multinomial distribution

Input : `countNTs()` function that returns counts of AMP, CMP, GMP, and UMP for a given non-functional RNA fragment

Input : `lengthFragments()` function that returns the total number of bases of all RNA fragments

`/* Endo-nucleolytic cleveage */`

1. Calculate fraction of active endoRNases (f_i) that target each RNA where $i = 1$ **to** n_{gene}

$$f_i = \frac{\frac{c_{RNA,i}}{K_{m,i}}}{1+\sum \frac{c_{RNA}}{K_m}}$$

2. Calculate total counts of RNAs degraded (R)

$R_{mRNA} = \sum K_{cat,endo} \cdot c_{endo,mRNA} \cdot f_i$ where $i = 1$ **to** n_{mRNAs}

$R_{tRNA} = \sum K_{cat,endo} \cdot c_{endo,tRNA} \cdot f_i$ where $i = 1$ **to** n_{tRNAs}

$R_{rRNA} = \sum K_{cat,endo} \cdot c_{endo,rRNA} \cdot f_i$ where $i = 1$ **to** n_{rRNAs}

where $c_{endo,j}$: number of endoRNases targeting specific species considering endoRNase specificities, $j = 1$ **to** [mRNA, tRNA, rRNA]

3. Sample multinomial distribution D times weighted by endoRNase::RNA affinities to determine which RNAs are converted into non-functional RNAs (d_i)

$d_i = \texttt{multinomial}(R, \frac{f_i}{\sum f})$

4. Increase number of RNA fragments. Decrease RNA counts and amount of water required for RNA hydrolysis by endoRNases ($c_{H_2O,endo}$)

$c_{frag} = c_{frag} + \texttt{countNTs}(d_i)$

$c_{RNA} = c_{RNA} - d_{RNA}$

$c_{H_2O} = c_{H_2O} - c_{H_2O,endo}$

$c_{PPi} = c_{PPi} + D$

`/* Exo-nucleolytic digestion */`

5. Compute exoRNase capacity (E)

$$E = K_{cat,exo} \cdot c_{exo}$$

if $E > \sum c_{frag,i}$ **then**

Update NMPs, water and proton counts

$$c_{NMP} = c_{NMP} + c_{frag}$$

$$c_{H_2O} = c_{H_2O} - \texttt{lengthFragments}(c_{frag})$$

$$c_{proton} = c_{proton} + \texttt{lengthFragments}(c_{frag})$$

Set counts of RNA fragments equal to zero ($c_{frag,i} = 0$)

else

Sample multinomial distribution c_{frag} with equal probability to determine which fragments are exo-digested ($c_{fragDig}$) and recycled

$$c_{fragDig,i} = \texttt{multinomial}(E, \tfrac{c_{frag,i}}{\sum c_{frag}})$$

Update NMPs, water, proton counts, and RNA fragments

$$c_{NMP} = c_{NMP} + c_{fragDig}$$

$$c_{H_2O} = c_{H_2O} - \texttt{lengthFragments}(c_{fragDig})$$

$$c_{proton} = c_{proton} + \texttt{lengthFragments}(c_{fragDig})$$

$$c_{frag} = c_{frag} - c_{fragDig}$$

Result: RNAs are selected and degraded by endoRNases, and non-functional RNA fragments are digested through exoRNases. During the process water is consumed, and amino acids are released.

References

[1] Jonathan A Bernstein, Arkady B Khodursky, Pei-Hsun Lin, Sue Lin-Chao, and Stanley N Cohen. Global analysis of mrna decay and abundance in escherichia coli at single-gene resolution using two-color fluorescent dna microarrays. *Proceedings of the National Academy of Sciences*, 99(15):9697–9702, 2002.