Cell Growth Model - v0.8

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# Model Overview

## Features

Phenotypes

* Cell partition in 3 biomolecular species classes:
  + Metabolic
  + Ribosome-associated
  + Housekeeping
* Cell mass
  + Phenomenological model/Logistic function shaped
  + Variable mass dependent on intracellular energy levels
* Growth rate
  + Function of protein mass growth rate & cell mass size

Cell processes

* Translation models:
  + Initiation Complex formation
  + Elongation Complex maturation
  + Protein Synthesis
* Elongation complex maturation model:
  + Allows polysomes formation implicitly
  + Maturation dependent on cell energy levels
* Energy production & utilisation models
  + Simple one-step energy production model
  + Energy Utilised by Protein Synthesis & Elongation Complex Maturation
* Ribosome Assembly model
  + Ribosome formation from ribosome-associated proteins
  + No rRNA species involved
  + Allows for realistic numbers of ribosomes in cell

## Version Modifications

* Derived from model v0.7
* Ribosome Assembly model
* Removed rRNA species

# Processes Models

## Transcription

|  |  |  |  |
| --- | --- | --- | --- |
| Assumptions | | | |
| * Transcription is an energy dependent process, but it is not made to consume any energy as its consumption rate is small compared to the translation processes (Weiße et al., 2015) * The threshold value for half-maximal activation of transcription occurs at higher intracellular energy levels for ribosomal protein gene expression, as it has been demonstrated that intracellular effector molecules inhibit transcription of ribosome-associated genes at poor intracellular metabolic environment (Barker et al., 2001; Lemke et al., 2011). | | | |
| Reaction | | | |
| Forward rate  Reverse rate | wx\*mod\_fcn\_a  🡪 m\_x | | |
| Energy modulating function | theta for hsk & met = thetax  theta for rib = thetar | | |
| Species | | | |
| m\_x  a | RBS of class x = {rib, met, hsk}  Intracellular energy molecule | | |
| Parameters | Description | Value | Units |
| wx | transcription rate |  | molecules/minutes |
| Modifications to basic Model | | | |
| Assumptions | | | |
| * For hsk class:   + For rbs/mRNA of housekeeping class, the transcription rate is inhibited by a modulation function based on the number of hsk proteins in the cell, as previous research suggests the existence of an autoregulation mechanism so that their relative proteome abundance is maintained across different growth conditions (Hwa et al., 2010) | | | |
| Modulating function (hsk class) |  | | |
| Parameters/Species | Description | Value | Units |
| p\_rib  Krepr | ribosomal proteins  repression threshold |  | molecules  molecules |
| Fluxes | | | |
| d(m\_rib)/dt = +wr\*mod\_fcn\_a  d(m\_met)/dt = +wr\* mod\_fcn\_a\* mod\_fnc\_txhsk  d(m\_hsk)/dt = +wr\*mod\_fcn\_a | | | |

## mRNA degradation

|  |  |  |  |
| --- | --- | --- | --- |
| Assumptions | | | |
| * Only the free form of the mRNA is degraded (RBS) * Degradation rate is the same for all mRNA classes | | | |
| Reaction | | | |
| Forward rate  Reverse rate | dm  m\_x 🡪 null | | |
| Species | | | |
| m\_x | RBS of class x = {rib, met, hsk} | | |
| Parameters | Description | Value | Units |
| dm | mRNA degradation rate |  | 1/minute |
| Fluxes | | | |
| d(m\_rib)/dt = -dm\* m\_rib    d(m\_met)/dt = -dm\* m\_met  d(m\_hsk)/dt = -dm\* m\_hsk | | | |

## Translation Initiation Complex formation

|  |  |  |  |
| --- | --- | --- | --- |
| Assumptions | | | |
| * The association rate constant between ribosomes and rbs\_mRNAs is variable, while all classes exhibit the same dissociation kinetics. This simplification does not represent reality as experimental observation show both constant values can vary within an interval of 3 orders of magnitude (Gualerzi & Pon, 2015) but its implementation was necessary to reduce the search space and the number of dimensions in parameter fitting. | | | |
| Reaction | | | |
| Forward rate  Reverse rate | kb\_x  m\_x + ribo 🡨🡪 ic\_x  ku | | |
| Species | | | |
| m\_x  ribo  ic\_x | RBS of class x = {rib, met, hsk}  Ribosomes  Translation Initiation complex of class x = {rib, met, hsk} | | |
| Parameters | Description | Value | Units |
| kb\_x  ku | RBS/ribosome association rate  Initiation Complex dissociation rate |  | 1/(molecules\*minutes)  1/minute |
| Modifications to basic Model | | | |
| Assumptions | | | |
| * For rib class:   + The association rate of rbs\_mRNA with ribosome for the formation of ic\_rib is inhibited by a modulating function based on the amount of free ribosomal protein molecules in the cell, as negative feedback regulation at translation initiation stage is well established for the control of ribosomal protein expression (Nomura et al., 1980) | | | |
| Modulating function (rib class) |  | | |
| Parameters/Species | Description | Value | Units |
| p\_rib  Krepr | ribosomal proteins  repression threshold |  | molecules  molecules |
| Fluxes | | | |
| d(ic\_rib)/dt = +kb\_ribo \*ribo \*r\_rib \* ( 1 / ( 1 + ( ***p\_rib*** / Krepr ) ) )  -ku\*ic\_rib    d(ic\_met)/dt = +kb\_met \*ribo \* r\_cat  -ku\*ic\_cat  d(ic\_hsk)/dt = +kb\_others\*ribo \*r\_hsk  -ku\*ic\_hsk | | | |

## Translation Elongation Complex formation

|  |  |  |  |
| --- | --- | --- | --- |
| Assumptions | | | |
| * The maturation rate of IC to EC is energy dependent with an activating modulating function that depends on the cell energy levels. The modulating function half-activation threshold is set at the same value as that of translation elongation process. This parameter value can be independently modified but only towards a higher value to prevent ribosome overcrowding on the mRNA molecule. * 1 energy molecule is consumed per maturation event a GTP molecule is utilised by IF2 in the pathway for 70SIC formation (Gualerzi & Pon, 2015). | | | |
| Reaction | | | |
| Forward rate  Reverse rate | kc \* mod\_fcn\_gamma  ic\_x + a 🡪 ec\_x + m\_x | | |
| Energy modulating function |  | | |
| Species | | | |
| ic\_x  ec\_x  m\_x  a | initiation complex of class x = {rib, met, hsk}  elongation complex of class x = {rib, met, hsk}  RBS of class x = {rib, met, hsk}  Intracellular energy molecule | | |
| Parameters | Description | Value | Units |
| kc  Kgamma | rate constant of IC maturation  Threshold of half-maximal transpeptidation rate (based on energy levels) |  | 1/minutes  molecules |
| Fluxes | | | |
| d(ic\_rib)/dt = -ic\_rib \* kc \* mod\_fcn\_gamma  d(ic\_met)/dt = -ic\_met \* kc \* mod\_fcn\_gamma  d(ic\_hsk)/dt = -ic\_hsk \* kc \* mod\_fcn\_gamma  d(a)/dt = -ic\_rib \* kc \* mod\_fcn\_gamma  -ic\_met \* kc \*mod\_fcn\_gamma  -ic\_hsk \* kc \*mod\_fcn\_gamma  d(ec\_rib)/dt = +ic\_rib \* kc \* mod\_fcn\_gamma  d(ec\_met)/dt = +ic\_met \* kc \*mod\_fcn\_gamma  d(ec\_hsk)/dt = +ic\_hsk \* kc \* mod\_fcn\_gamma  d(m\_rib)/dt = +ic\_rib \* kc \*mod\_fcn\_gamma  d(m\_met)/dt = +ic\_met \* kc \* mod\_fcn\_gamma  d(m\_hsk)/dt = +ic\_hsk \* kc \*mod\_fcn\_gamma | | | |

## Translation Protein Synthesis

|  |  |  |  |
| --- | --- | --- | --- |
| Assumptions | | | |
| * Simplified translation elongation model developed in (Weiße et al., 2015). In short, the net rate is dependent on the amino acid length of the protein molecule and is controlled by a modulating function that is activated by increased cellular energy levels. | | | |
| Reaction | | | |
| Forward rate  Reverse rate | gmax \* mod\_fcn\_gamma  ec\_x + a\*lenX 🡪 p\_x | | |
| Energy modulating function |  | | |
| Species | | | |
| ec\_x  a  p\_x | elongation complex of class x = {rib, met, hsk}  Intracellular energy mollecule  protein of class x = {rib, met, hsk} | | |
| Parameters | Description | Value | Units |
| lenX {lenO,lenR,lenC}  Kgamma | Protein length {p\_hsk, p\_rib, p\_met}  Threshold of half-maximal transpeptidation rate (based on energy levels) |  | amino acids  molecules |
| Fluxes | | | |
| d(ec\_rib)/dt = -ec\_rib \* gmax / lenR \*mod\_fcn\_gamma  d(ec\_met)/dt = -ec\_met \* gmax / lenC \*mod\_fcn\_gamma  d(ec\_hsk)/dt = -ec\_hsk \* gmax / lenO \*mod\_fcn\_gamma  d(a)/dt = -ec\_rib \* gmax \*mod\_fcn\_gamma  -ec\_met \* gmax \*mod\_fcn\_gamma  -ec\_hsk \* gmax \*mod\_fcn\_gamma  d(p\_rib)/dt = + ec\_rib \* gmax /lenR \*mod\_fcn\_gamma  d(p\_met)/dt = + ec\_met \* gmax /lenC \*mod\_fcn\_gamma  d(p\_hsk)/dt = +ec\_hsk \* gmax /lenO \*mod\_fcn\_gamma | | | |

## Ribosome Assembly

|  |  |  |  |
| --- | --- | --- | --- |
| Assumptions | | | |
| * Ribosomal proteins instantaneously form sets of ribosomal proteins of size equal to the total amino acid mass of an assembled ribosome * Ribosome Assembly is a single association event where a ribosomal proteins set forms an assembled ribosome | | | |
| Reaction | | | |
| Forward rate  Reverse rate | k\_form  p\_rib\_set 🡪 ribo | | |
| Species | | | |
| p\_rib  p\_rib\_set  ribo | Free ribosomal proteins  p\_rib\_set = ribosomal proteins / (lenRibo/lenR)  Ribosomes | | |
| Parameters | Description | Value | Units |
| lenRibo  lenR  k\_form | Size of ribosome with all its ribosomal proteins  Size of ribosomal protein  Rate constant for ribosome assembly |  | aa  aa  molecules/minute |
| Fluxes | | | |
| d(rib)/dt = - k\_form \* [p\_rib\_set] \* (lenRibo/lenR)  d(Ribo)/dt = + k\_form \* [p\_rib\_set] | | | |

## Energy production

|  |  |  |  |
| --- | --- | --- | --- |
| Assumptions | | | |
| * Energy production is limited by a single bottleneck enzyme in the metabolic pathway and is modelled based on Michaelis-Menten reaction rate model * Efficiency of energy generation is dictate by the quality of the media (ns). The ns variable linearly scales the effectiveness by which energy molecules are produced by the metabolic sector. This simplification has also been used by others (Weiße et al., 2015) and is necessary as the true relationship between media composition/quality and energy molecules production would be very hard to calculate * The production rate flux is determine by protein molecules that are able to carry out a series of chemical reactions that facilitate the conversion of an extracellular nutrient molecule to an intracellular energy molecule. Thus, the Vmax, Km, and ns values are not meant to represent any “real” values but adjustable quantities that facilitates the devotion of amino acid mass to the metabolic proteome sector for the needs of resources allocations | | | |
| Reaction | | | |
| Forward rate  Reverse rate | ns\* ((Vmax \*s0)/(Km + s0))  p\_ met 🡪 a + met | | |
| Species | | | |
| a  p\_met | Intracellular energy  Proteins metabolic class | | |
| Parameters | Description | Value | Units |
| ns  Vmax  s0  Km | Nutrient quality  Catalytic rate of nutrient utilisation  Extracellular concentration of nutrients  Half-maximal threshold of nutrient levels utilisation |  | No units  1/minute  molecules  molecules |
| Fluxes | | | |
| d(a)/dt = +p\_met \* ns\* ((Vmax \*s0)/(Km + s0)) | | | |

## Energy consumption

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Assumptions | | | | |
| * One energy molecule is consumed by each Elongation Complex maturation event * One energy molecule is consumed by each transpeptidation event in protein synthesis, where the consumption of each protein synthesis event is determined by the aa length of the synthesized protein | | | | |
| Process 1 | | | | |
| Forward rate  Reverse rate | kc \* mod\_fcn\_gamma  ic\_x + a 🡪 ec\_x + m\_x | | | |
| Energy modulating function | |  | | |
| Species | | | | |
| ic\_x  ec\_x  m\_x  a | initiation complex of class x = {rib, met, hsk}  elongation complex of class x = {rib, met, hsk}  RBS of class x = {rib, met, hsk}  Intracellular energy molecule | | | |
| Parameters | Description | | Value | Units |
| kc  Kgamma | rate constant of EC formation from IC  transpeptidation elongation rate threshold for translation based on energy levels | |  | 1/minute  molecules |
| Process 2 | | | | |
| Forward rate  Reverse rate | gmax \* mod\_fcn\_gamma  ec\_x + a\*lenX 🡪 p\_x | | | |
| Energy modulating function | |  | | |
| Species | | | | |
| ec\_x  a  p\_x | elongation complex of class x = {rib, met, hsk}  Intracellular energy mollecule  protein of class x = {rib, met, hsk} | | | |
| Parameters | Description | | Value | Units |
| lenX {lenO,lenR,lenC}  Kgamma | Protein length {p\_hsk, p\_rib, p\_met}  Threshold of half-maximal transpeptidation rate (based on energy levels) | |  | 1/minute  molecules |
| Fluxes | | | | |
| tinitrate = - (ic\_rib + ic\_met + ic\_hsk) \* kc \* mod\_fcn\_gamma  ttrate = - (ec\_rib + ec\_met + ec\_hsk) \* gmax \* mod\_fcn\_gamma  d(a)/dt = - tinitrate - ttrate | | | | |

# Phenotypes

## Cell size

|  |  |  |  |
| --- | --- | --- | --- |
| Assumptions | | | |
| * Phenomenological model based on a logistic function * Cell size is increases with increasing availability of intracellular energy (metabolic precursors) * Cell size is equal to an intracellular amino acid count, while other biomolecules are not considered (ex. Lipids, carbohydrates, DNA, RNA etc). This is because the model here aims to describe the competition between various cellular processes for proteome space and protein based biomolecules. * facilitates the dilution of intracellular species and redistribution of cellular content according to the reaction fluxes. | | | |
| Phenotype Equation | | | |
| cell size | minimal\_mass +  ( max\_inf / (1 + exp(- inlation\_gradient \* ( a – mid\_inf) ) ) ) | | |
| Species | | | |
| a | Intracellular energy molecule | | |
| Parameters | Description | Value | Units |
| min\_mass  max\_inf  mid\_inf | Minimal cell mass that is allowed for the cell to assume even in the absence of intracellular energy  Maximum inflation of cell size upon high levels of cell energy  Energy levels inflection point of half maximal cell size inflation |  | amino acids  amino acids  molecules |

## Growth rate

|  |  |  |  |
| --- | --- | --- | --- |
| Assumptions | | | |
| * Growth of the system is defined as the number of transpeptidation (amino acid incorporation in protein molecules) events per unit of time. * Normalised to 1 cell unit set by cell mass variable. * facilitates the dilution of intracellular species and redistribution of cellular content according to the reaction fluxes. | | | |
| Phenotype Equation | | | |
| Cell growth rate | lam = ttrate / cell size  where:  ttrate = (ec\_rib + ec\_met + ec\_hsk) \* gmax \* mod\_fcn\_gamma | | |
| Species | | | |
| ec\_x | Elongation complexes of class x = {rib, met, hsk} | | |
| Parameters | Description | Value | Units |
| Kgamma | Threshold of half-maximal transpeptidation rate (based on energy levels) |  | molecules |