Cell Growth Model - v0.8

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Model Overview

Features

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- Cell partition in 3 biomolecular species classes:
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    - Ribosome-associated
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    - 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	$\text{mod\_fnc\_a} = \left(\frac{a}{theta + a}\right)$ 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)	$\text{mod\_fnc\_txhsk} = \left(\frac{1}{1 + \left(\frac{p\_rib}{Krepr}\right)}\right)$		
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	m_x + ribo $\underset{ku}{\overset{kb\_x}{\leftrightarrow}}$ ic_x		
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)	$\text{mod\_fnc} = \left(\frac{1}{1 + \left(\frac{p\_rib}{Krepr} \right)} \right)$		
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	$\text{mod\_fnc\_gamma} = \left(\frac{a}{Kgamma + a}\right)$

Species	
ic_x	initiation complex of class x = {rib, met, hsk}
ec_x	elongation complex of class x = {rib, met, hsk}
m_x	RBS of class x = {rib, met, hsk}
a	Intracellular energy molecule

Parameters	Description	Value	Units
kc	rate constant of IC maturation		1/minutes
Kgamma	Threshold of half-maximal transpeptidation rate (based on energy levels)		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	$\text{mod\_fnc\_gamma} = \left(\frac{a}{Kgamma + a}\right)$

Species	
ec_x	elongation complex of class x = {rib, met, hsk}
a	Intracellular energy mollecule
p_x	protein of class x = {rib, met, hsk}

Parameters	Description	Value	Units
lenX {lenO,lenR,lenC}	Protein length {p_hsk, p_rib, p_met}		amino acids
Kgamma	Threshold of half-maximal transpeptidation rate (based on energy levels)		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	$\text{mod\_fnc\_gamma} = \left(\frac{a}{Kgamma + a}\right)$		
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	$\text{mod\_fnc\_gamma} = \left(\frac{a}{Kgamma + a}\right)$		
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}	Protein length {p_hsk, p_rib, p_met}		1/minute
Kgamma	Threshold of half-maximal transpeptidation rate (based on energy levels)		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	Minimal cell mass that is allowed for the cell to assume even in the absence of intracellular energy		amino acids
max_inf	Maximum inflation of cell size upon high levels of cell energy		amino acids
mid_inf	Energy levels inflection point of half maximal cell size inflation		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