

Information Transduction Capacity of Mitochondrial Retrograde Signaling

Abstract:

Mitochondrion is the powerhouse of eukaryotic cells, which participates in crucial cellular processes such as ATP production and intermediate metabolism. Though mitochondria possess their own genomes, most of the mitochondrial proteins are encoded in nucleus. Therefore, the retrograde response between mitochondria and nucleus is essential for the mitochondrial quality control which includes removing damaged mitochondria and fission-fusion dynamics. However, all the mitochondria use the same biological pathway to interact with nucleus genome, and it is still unclear that how this multiplexing problem reduces the information transduction capacity of mitochondrial retrograde signaling. In this project, the differential equation-based model is used to simulate the information transmission rate under the influences of mitochondrial dynamics.

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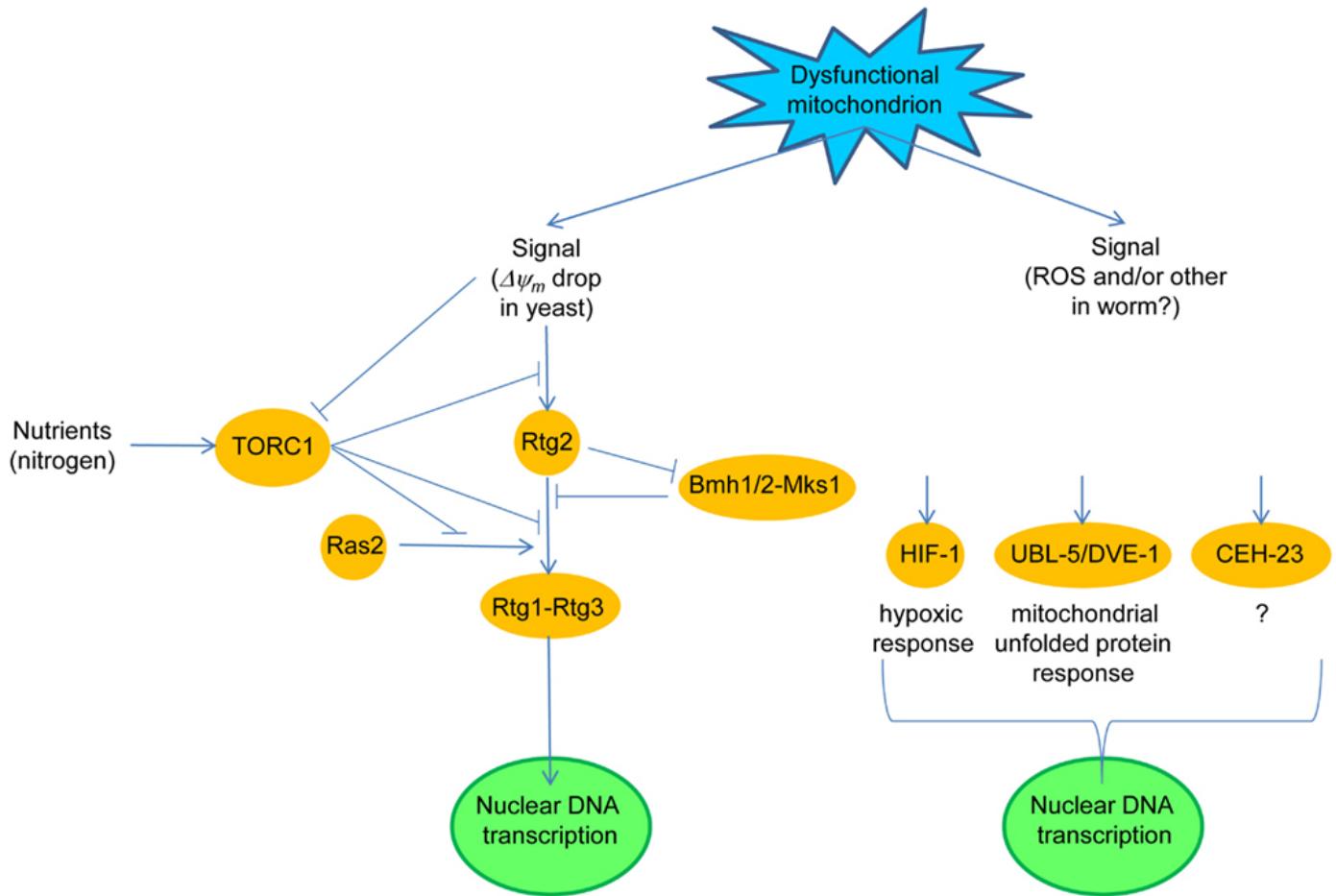
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Review of retrograde model

Title: The yeast retrograde response as a model of intracellular signaling of mitochondrial dysfunction

Abstract: Mitochondrial dysfunction activates intracellular signaling pathways that impact yeast longevity, and the best known of these pathways is the retrograde response. More recently, similar responses have been discerned in other systems, from invertebrates to human cells. However, the identity of the signal transducers is either unknown or apparently diverse, contrasting with the well-established signaling module of the yeast retrograde response. On the other hand, it has become equally clear that several other pathways and processes interact with the retrograde response, embedding it in a network responsive to a variety of cellular states. An examination of this network supports the notion that the master regulator NF κ B aggregated a variety of mitochondria-related cellular responses at some point in evolution and has become the retrograde transcription factor. This has significant consequences for how we view some of the deficits associated with aging, such as inflammation. The support for NF κ B as the retrograde response transcription factor is not only based on functional analyses. It is bolstered by the fact that NF κ B can regulate Myc-Max, which is activated in human cells with dysfunctional mitochondria and impacts cellular metabolism. Myc-Max is homologous to the yeast retrograde response transcription factor Rtg1-Rtg3. Further research will be needed to disentangle the pro-aging from the anti-aging effects of NF κ B. Interestingly, this is also a challenge for the complete understanding of the yeast retrograde response.



keynotes in retrograde response

Reference: The yeast retrograde response as a model of intracellular signaling of mitochondrial dysfunction

Abstract

1. Mitochondrial dysfunction activates intracellular signaling pathways that impact yeast longevity.
 1. The best known one is the retrograde response
 2. It is also discerned in invertebrates to human cells
 3. NF κ B is a retrograde response transcription factor.
 1. discovered not only by functional analysis
 2. NF κ B can regulate Myc-Max, which is activated in human cells with dysfunctional mitochondria and impacts cellular metabolism
2. Myc-Max is homologous to the yeast retrograde response transcription factor Rtg1-Rtg3.

Keynotes

1. Mitochondrial dysfunction
 1. Mitochondrial encephalomyopathy
 2. cardiac hypertrophy
 3. Parkinson's disease
 4. cancer
 5. May determine life span
 1. *Caenorhabditis elegans*, *Drosophila melanogaster*, mouse, yeast
2. Identify retrograde response in bioinformatics approach
3. Yeast retrograde response
 1. rho⁰ vs. rho⁺
 1. Lost TCA cycle → lost glutamate synthesis, due to compromised activity of succinate dehydrogenase
 2. Still possess first three reactions
 1. Metabolic adaptation: α -ketoglutarate → glutamate. If citrate is provided by the activation of glyoxylate cycle
 3. No active electron transport chain
4. Retrograde response
 1. translocation of Rth1/3 heterodimer
 1. helix-loop-helix/leucine zipper proteins

2. bind to the sequence GTCAC (R box)

3. Rtg1 is atypical, there is no apparent transcriptional activation domains

4. Requires: Rtg2 protein

1. Rtg2 has no known homologs in higher organism

2. Rtg2 promotes the dephosphorylation of Rtg3 by binding Mk1 and preventing Mk1 from forming a complex with the 14-4-4 protein Bmh1 or Bmh2 ([minor isoform](#)), a complex which maintain in a hyperphosphorylated state.

3. Mks1 is removed by ubiquitin-mediated degradation promoted by the ubiquitin ligase component Grr1.

1. Grr1 → positive regulator

2. Mks1 → Negative regulator

4. TORC1 negatively regulate both upstream and downstream of Rtg2

1. Genetic studies:

1. WD-protein Lst8/ mutation of Lst8

2. When glutamate and nutrient are plentiful, TORC1 downregulates pathway

3. TORC1 <-> negative feedback from dysfunctional mitochondria

1. mediate phosphorylation of Sch9 (AGC protein kinase) is downregulated

2. Phosorylated Sch9

1. Antagonize stress responses

5. Reactions

1. Rtg2 + Mks1 ↔ Rtg2-Mks1

2. Mks1 + Bmh ↔ Bmh-Mks1

3. Bmh-Mks1 + *-Rtg3^{hyper-p_i} ↔ Bmh-Mks1-Rtg3^{hyper-p_i} → Bmh-Mks1 + Rtg3^{partial-p_i}

4. Mks1 + Grr1 ↔ Mks1-Grr1 → Mks1^{ubi} + Grr1

5. Mks1^{ubi} →

where [*-Rtg3^{hyper-p_i}] = Rtg3^{hyper-p_i} + Rtg1-Rtg3^{hyper-p_i}

2. only Rtg3 can bind to Rbox and activate transcription

3. Rtg1 is in the top layer. abundant, long-lived, and noisy.

4. Osmotic stress can recruit Rtg1-Rtg3

5. Ras2: unclear, relate to cAMP-dependent pathway. Positive regulator

1. ↑ lifespan via cAMP-dependent pathway

6. Rtg2 functions

1. Positive regulator of retrograde response

1. ↑ dephosphorylation of Rtg3 in cytoplasm

2. Integral cofactor of transcriptional co-activator SAGA-like complex, which is required for the induction of the retrograde response target gene CIT2, and it binds to CIT2 promoter

3. Genome stability (unknown mechanism)

4. Sense dysfunctional mitochondria- possible mechanisms

1. ↓ of Δψ_m

1. When yeast ages, Δψ_m ↓, loses mtDNA, progressive activation of retrograde response.

2. Necessary and sufficient to induce retrograde response

3. how Rtg2 read Δψ_m: unclear

2. ROS scavenger doesn't block signal

3. ATP↓ doesn't involve

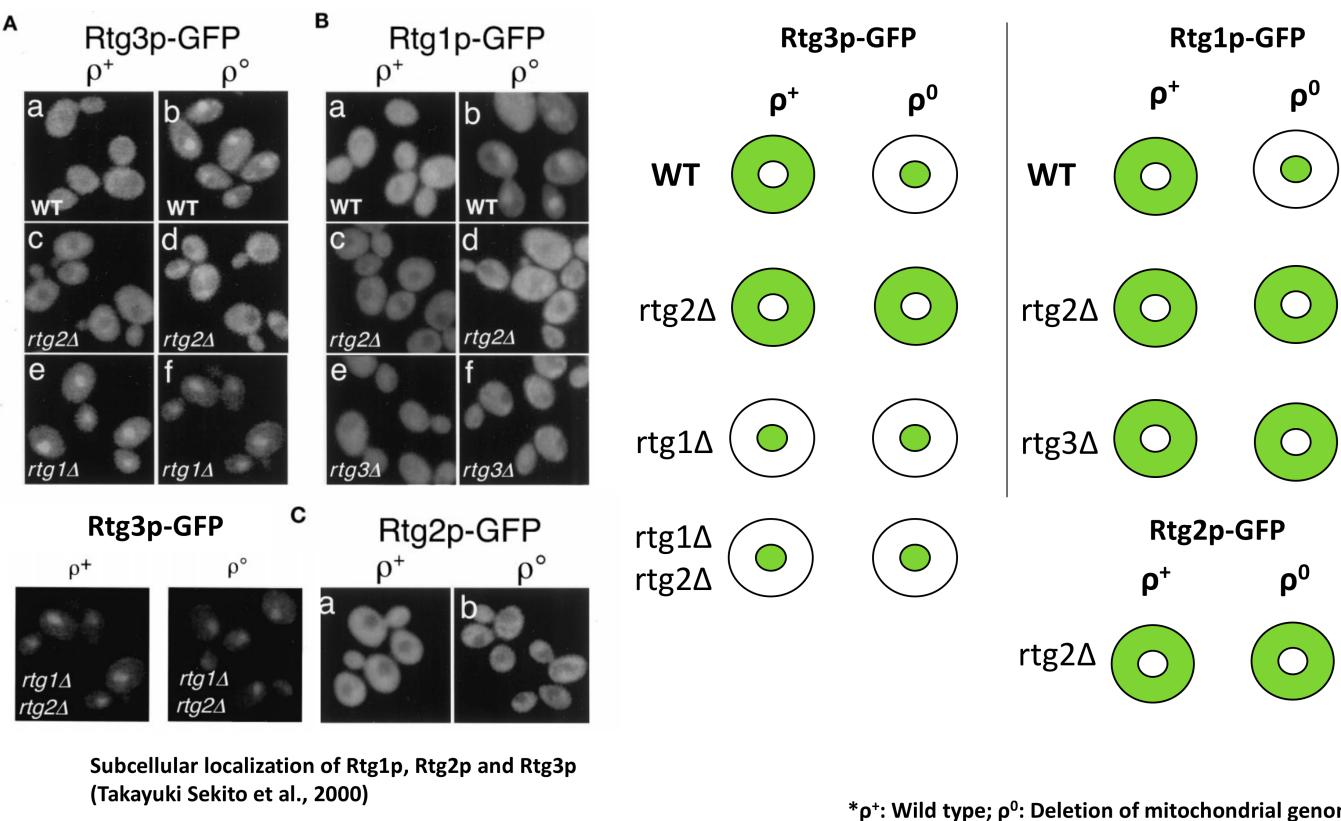
Table of RTG-associated Proteins

Reagents	function
Rtg1-Rtg3	activate retrograde response
Rtg2	promote Rtg1-Rtg3: cytosol → nucleus; binding with Mks1
Mks1	phospholayte Rtg3; downregulate RTG pathway
Bmh1 or Bmh2	form Bmh1/2-Mks1 to phosphate Rtg3
Grr1	degrade Mks1
TORC1	negative regulator of the retrograde response; act both upstream and downstream of Rtg2

Review of retrograde signaling

Title: Mitochondria to Nuclear Signaling Is Regulated by the Subcellular Localization of the Transcription Factors Rtg1p and Rtg3p

Abstract: Cells modulate the expression of nuclear genes in response to changes in the functional state of mitochondria, an interorganelle communication pathway called retrograde regulation. In yeast, expression of the CIT2 gene shows a typical retrograde response in that its expression is dramatically increased in cells with dysfunctional mitochondria, such as in respiratory competent (r1+) cells in which CIT2 expression is low, Rtg1p and Rtg3p exist as a complex largely in the cytoplasm, and in respiratory incompetent (r1-) cells in which CIT2 expression is high, they exist as a complex predominantly localized in the nucleus. Cytoplasmic Rtg3p is multiply phosphorylated and becomes partially dephosphorylated when localized in the nucleus. Rtg2p, which is cytoplasmic in both r1+ and r1- cells, is required for the dephosphorylation and nuclear localization of Rtg3p. Interaction of Rtg3p with Rtg1p is required to retain Rtg3p in the cytoplasm of r1+ cells; in the absence of such interaction, nuclear localization and dephosphorylation of Rtg3p is independent of Rtg2p. Our data show that Rtg1p acts as both a positive and negative regulator of the retrograde response and that Rtg2p acts to transduce mitochondrial signals affecting the phosphorylation state and subcellular localization of Rtg3p.



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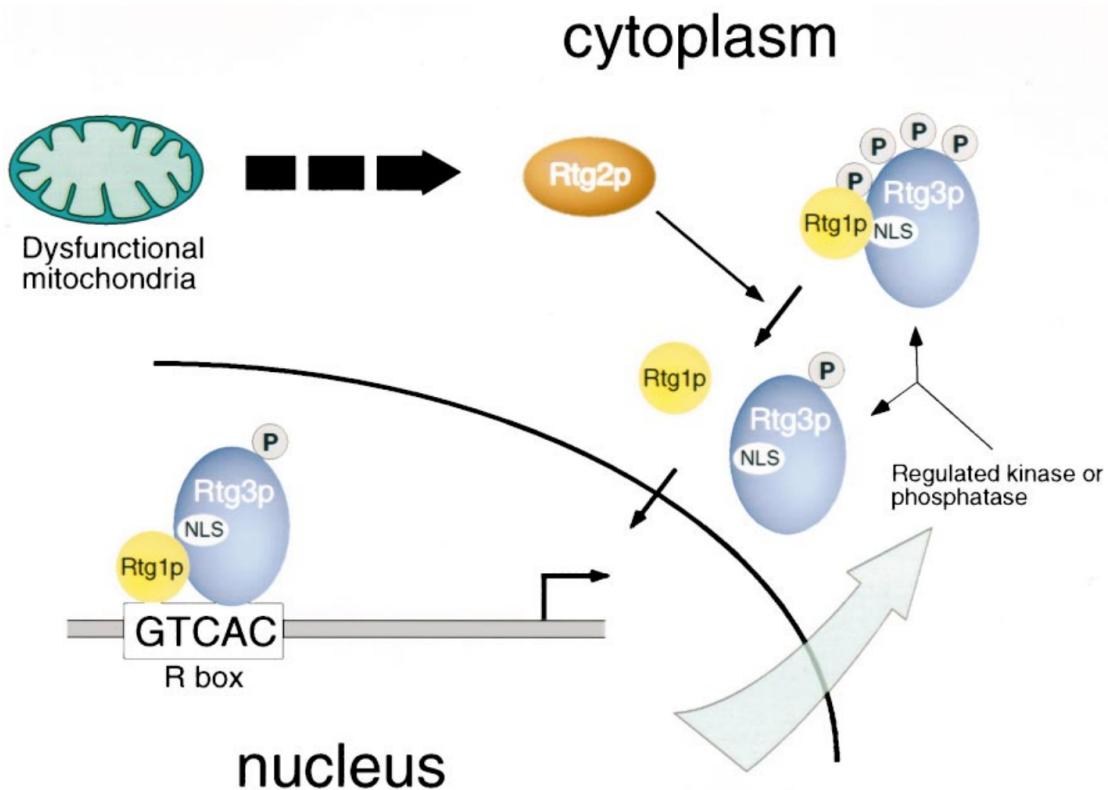


Figure 8. Model of the control of mitochondria-to-nuclear signaling. In cells with dysfunctional mitochondria, one or more signals, one of which is possibly the level of glutamate produced from the TCA cycle, are transmitted from mitochondria (bold, dashed arrow) via Rtg2p to a cytoplasmic complex between Rtg1p and a highly phosphorylated form of Rtg3p. This complex, which may include other factors not indicated, becomes transiently dissociated along with a dephosphorylation of Rtg3p. Rtg1p and Rtg3p then translocate to the nucleus and assemble for transcriptional activation at target gene R box sites, GTCAC. The phosphorylation state of cytoplasmic Rtg3p is sensitive to a feedback response, indicated by the light green arrow, in that the absence of Rtg1p–Rtg3p-dependent transcription in the nucleus activates further dephosphorylation and nuclear translocation of cytoplasmic Rtg3p. It is not known whether dephosphorylation of cytoplasmic Rtg3p is caused by inactivation of a kinase or activation of a phosphatase.

Reminders

Review of transcription factor translocation

Title: Tunable Signal Processing Through Modular Control of Transcription Factor Translocation

Notes:

- Functional Domains for translocation signaling
 - Nucleus Export Sequence (NES)
 - Nucleus Localization Sequence (NLS)
- Signal

Functional Domain	P-phosphorylated	U-unphosphorylated
NES	→ Nucleus	→ Cytosol
NLS	→ Cytosol	→ Nucleus

Mathematical model of NLS-only translocation

Because there is only NLS site in RTG3, I consider the case of *NLS only*

Ordinary differential equation:

$$\begin{aligned}\frac{dPr_C^U}{dt} &= -(k_{in}' + k_{pc})Pr_C^U + (k_{dpC})Pr_C^P + (k_{out})Pr_N^U + 0 \times Pr_N^P \\ \frac{dPr_C^P}{dt} &= (k_{pc})Pr_C^U - (k_{in} + k_{dpC})Pr_C^P + 0 \times Pr_N^U + (k_{out})Pr_N^P \\ \frac{dPr_N^U}{dt} &= (k_{in}')Pr_C^U + 0 \times Pr_C^P - (k_{pN} + k_{out})Pr_N^U + (k_{dpN})Pr_N^P \\ \frac{dPr_N^P}{dt} &= 0 \times Pr_C^U + (k_{in})Pr_C^P + (k_{pN})Pr_N^U - (k_{out} + k_{dpN})Pr_N^P\end{aligned}$$

Matrix form:

$$\frac{d}{dt} \begin{bmatrix} Pr_C^U \\ Pr_C^P \\ Pr_N^U \\ Pr_N^P \end{bmatrix} = \begin{bmatrix} -(k_{in}' + k_{pc}) & k_{dpC} & k_{out} & 0 \\ k_{pc} & -(k_{in} + k_{dpC}) & 0 & k_{out} \\ k_{in} & 0 & -(k_{pN} + k_{out}) & k_{dpN} \\ 0 & k_{in} & k_{pN} & -(k_{out} + k_{dpN}) \end{bmatrix} \begin{bmatrix} Pr_C^U \\ Pr_C^P \\ Pr_N^U \\ Pr_N^P \end{bmatrix}$$

Notation	Content
P	Phosphorylated
U	Unphosphorylated
C	cytoplasmic
N	nuclear
$Pr_{\{C,N\}}^{\{U,P\}}$	Protein with NLS only
k_{in}	normal output rate for Pr_C^P
k_{in}'	enhanced input rate for Pr_C^U
k_{pc}	Cytoplasmic phosphorylation rate
k_{pN}	Nucleus phosphorylation rate
k_{dpC}	Cytoplasmic dephosphorylation rate
k_{dpN}	Nucleus dephosphorylation rate
k_{out}	Export rate. Same value for NLS-only transcription factor

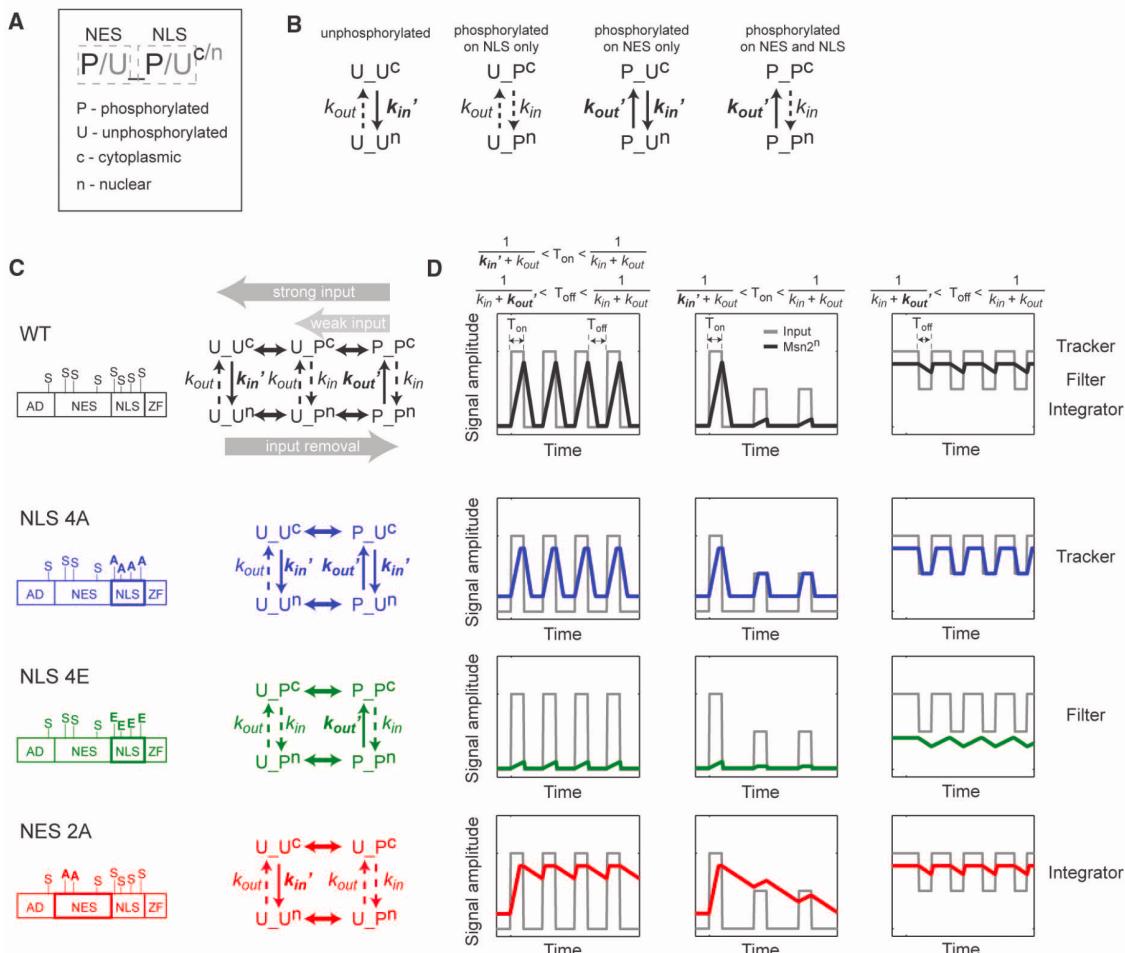


Fig. 2. A theoretical analysis of TF translocation. (A) Nomenclature used to define the status of phosphorylation and localization of the TF: for example, the first "P/U": the NES is phosphorylated (P) or unphosphorylated (U); "c/n": superscript shows location in the cytoplasm (c) or nucleus (n). (B) Phosphorylation states determine the rate constants of nucleocytoplasmic transport. Unphosphorylated or phosphorylated NES has slow (dashed line) or fast (solid line) nuclear export rates (k_{out} , k_{out}'), respectively; unphosphorylated or phosphorylated NLS has fast (solid line) or slow (dashed line) nuclear import rates (k_{in} ', k_{in}), respectively. Thus, each phosphoform has a specific combination of nuclear import and export rates. (C) The translocation model. (Left) Schematic of WT and phosphosite mutants; (right) model structures and reaction flows (gray arrows) in response to strong or weak inputs and input removal. First row: WT; second row: NLS 4A at S582A, S620A, S625A,

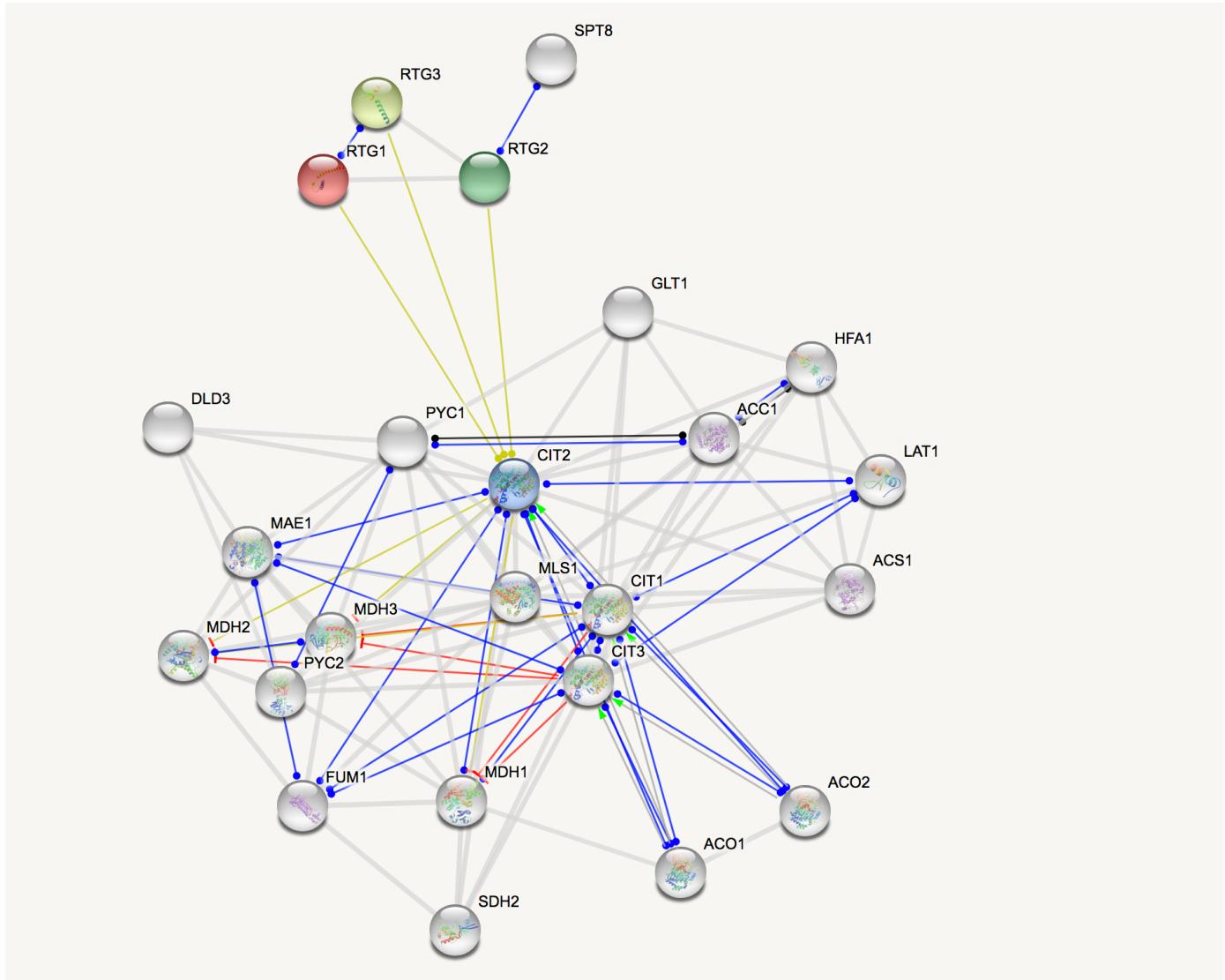
and S633A; third row: NLS 4E at S582E, S620E, S625E, and S633E; fourth row: NES 2A at S288A and S304A. We did not specifically study the case in which the NES sites are constitutively phosphorylated because Ser-to-Glu mutants of the NES sites behaved similarly to Ser-to-Ala mutants, which suggests that Glu cannot mimic phosphorylation on NES sites (fig. S2A). (D) Predicted responses to various dynamic inputs—first column: oscillatory high-amplitude input, second column: fluctuating input with varied amplitudes, third column: input fluctuating between high and low amplitudes. Color key—black: responses of WT, blue: NLS 4A, green: NLS 4E, red: NES 2A. The ranges of input time scales necessary to generate the predicted responses are determined by the fast and slow time scales of transport rates and are listed above each column. Model output was generated by a steady-state analysis of the translocation system (supplementary materials).

RTG Network Analysis

from STRING

Conclusion:

1. Bottleneck effect in RTG-to-CIT2 pathway



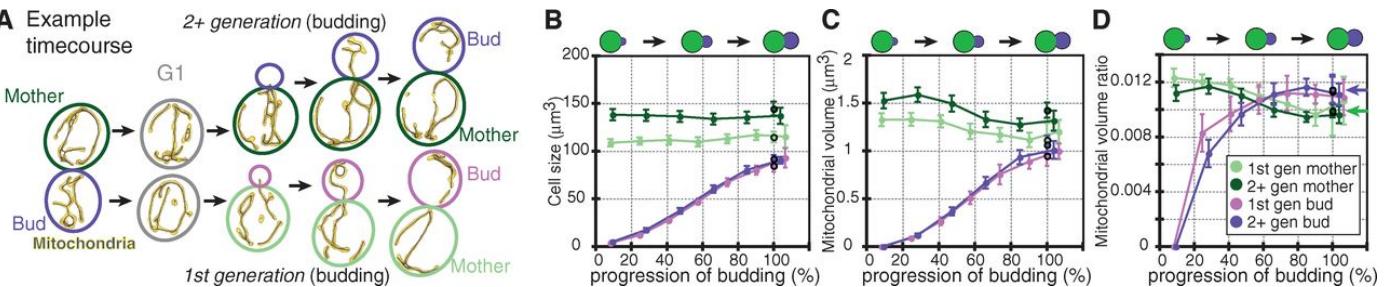
Review of Mitochondrial network scaling

Title: Mitochondrial Network Size Scaling in Budding Yeast

Abstract: Mitochondria must grow with the growing cell to ensure proper cellular physiology and inheritance upon division. We measured the physical size of mitochondrial networks in budding yeast and found that mitochondrial network size increased with increasing cell size and that this scaling relation occurred primarily in the bud. The mitochondria-to-cell size ratio continually decreased in aging mothers over successive generations. However, regardless of the mother's age or mitochondrial content, all buds attained the same average ratio. Thus, yeast populations achieve a stable scaling relation between mitochondrial content and cell size despite asymmetry in inheritance.

Conclusion:

1. Yeast mitochondrial volume = [0.3, 4] μm^2

**Fig. S18**

Mitochondrial volume to cell size scaling relation is the same for wild-type and mutant $\Delta ypt11$ cells. Mitochondrial content asymmetry is abolished in $\Delta ypt11$ cells, generating a population in which the mitochondrial volume ratio is evenly maintained in both compartments. We compared the mitochondrial to cell size scaling in $\Delta ypt11$ cells with symmetric inheritance to wild-type cells with asymmetric inheritance. **(A)** Mitochondrial volume vs. cell size for wild-type cells (gray; $n = 200$) and **(B)** for $\Delta ypt11$ cells (orange; $n=164$), including budding and non-budding cells. Pearson's correlation coefficient, r , and significance value, p , are shown. Thick lines indicate rolling average. Inset in **(B)** shows both rolling average lines plotted together. The volume ratio in newborn mothers (Fig. 4), and thus the mitochondrial to cell size scaling relation, are maintained in $\Delta ypt11$ mutant cells (see inset). The main difference between these populations is that $\Delta ypt11$ buds attain the proper final volume ratio much closer to the time of division than wild-type buds (Fig. 4). This could make the mutant population more sensitive to fluctuations in the timing of division. The result would be newborn mothers with greater divergence in their mitochondrial volume ratios, which in turn would generate a population with higher variation in mitochondrial to cell size scaling. Intriguingly, we do find that the population-wide mitochondrial to cell size scaling of $\Delta ypt11$ cells is more variable than that of wild-type cells.

Mathematical Model of Retrograde Response

Biochemical Network component:

1. Input \vec{MT} with N species:

$$\vec{MT} := MT_1, \dots, MT_N$$

where N is the total number of mitochondria

1. Input coding:

$$S = \sum_{i=1}^N Volume_{MT_i} \times Damaged_{MT_i}$$

$$Volume_{MT_i} \propto size_i n_2 D$$

Distributions of $Volume_{MT_i}$ and $Damaged_{MT_i}$ can be derived from Mitochondrial-netlogo-model

1. $Volume_{MT_i} := \{0, V_{max}\}$

$$V_{max} = \frac{4}{3} h \times Area_{MT_i}$$

yeast mitochondria volume = [0.3, 4] μm^2

2. $Damaged_{MT_i} := \{0, 1\}$ where 0 represents healthy state, and 1 represents damaged state of mitochondrion i (MT_i)

3. Channel ν with M species:

1. Components:

$$V_1, \dots, V_M$$

where M is the total number of proteins involved in network

2. Label (in input-to-output order):

1. $V_1 := Rtg2_C^{ina}$
2. $V_2 := Rtg2_C^{act}$
3. $V_3 := Rtg3_C^P$
4. $V_4 := Rtg3_C^U$
5. $V_5 := Rtg3_N^P$
6. $V_6 := Rtg3_N^U$
7. $V_7 := Rtg1_C$
8. $V_8 := Rtg1_N$
9. $V_9 := Rtg1 - 3_C^P$
10. $V_{10} := Rtg1 - 3_C^U$
11. $V_{11} := Rtg1 - 3_N^P$
12. $V_{12} := Rtg1 - 3_N^U$
13. $V_{13} := Bmh_C$
14. $V_{14} := Bmh - Mks1_C$
15. $V_{15} := Mks1 - Rtg2_C^{ina}$
16. $V_{16} := Mks1 - Rtg2_C^{act}$

Note: Protein $_{\#}^*$, the notations represent *:{modification state}; #: {Location}

3. $Rtg1 - 3_{\#}^*$: hereodimer can activate CIT2 expression, then start retrograde response.

1. *: {p, u} (phosphptate, partially dephosphated)
2. #: {n,c} {nucleus, cytoplasm}

4. $Rtg2^*$:

1. a sensor of mitochondrial dysfunction.
2. *: {inactivated (ina), activated (a)}

5. TORC1 effect is ignored, for it is nutrient-dependent

6. Ras2 is ignored and combined to the process of TORC1 inhibition

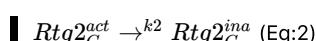
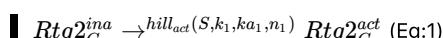
4. Output X with 1 component:

1. $X_1 = Rtg1/3_n^*$
2. $[Rtg1/3_n^*] = [Rtg1/3_n^p] + [Rtg1/3_n^u]$

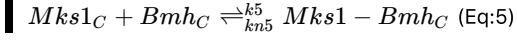
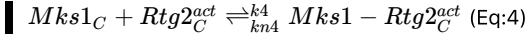
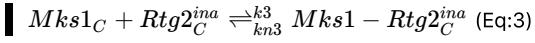
Reactions of RTG pathway

The following displays all reactions mentioned in review1 and review2:

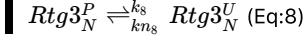
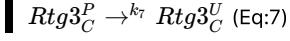
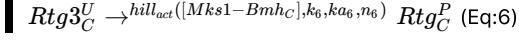
RTG2 and S: **Input layer**



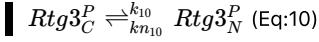
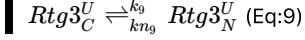
RTG2, BMH AND MKS1: **Switch layer**



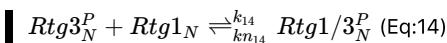
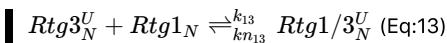
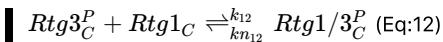
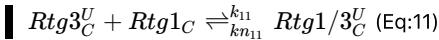
RTG3: Phosphorylation (P) and partially dephosphorylation (U)



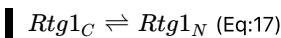
RTG3: Translocation



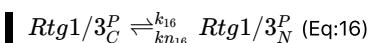
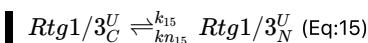
RTG1 and RTG3



Rtg1: Translocation



RTG1/3: Output layer



Differential Equation-based Framework

$$\frac{d}{dt} V_1 := \frac{d}{dt} [Rtg2_C^{ina}] = -k_1 \frac{S^{n_1}}{ka_1 + S^{n_1}} + k_2 [Rtg2_C^{act}] - k_3 [Rtg2_C^{ina}] [Mks1_C] + kn_3 [Rtg2^{ina} - Mks1_C]$$

$$\frac{d}{dt} V_2 := \frac{d}{dt} [Rtg2_C^{act}] = k_1 \frac{S^{n_1}}{ka_1 + S^{n_1}} - k_2 [Rtg2_C^{act}] - k_4 [Rtg2_C^{act}] [Mks1_C] + kn_4 [Rtg2^{act} - Mks1_C]$$

$$\frac{d}{dt} V_3 := \frac{d}{dt} [Rtg3_C^P] = k_6 \frac{[Bmh - Mks1_C]^{n_6}}{ka_6 + [Bmh - Mks1_C]^{n_6}} - k_7 [Rtg3_C^P] - k_{10} [Rtg3_C^P] + kn_{10} [Rtg3_N^P] - k_{12} [Rtg3_C^P] [Rtg1_C] + kn_{12} [Rtg1/3_C^P]$$

$$\frac{d}{dt} V_4 := \frac{d}{dt} [Rtg3_C^U] = -k_6 \frac{[Bmh - Mks1_C]^{n_6}}{ka_6 + [Bmh - Mks1_C]^{n_6}} + k_7 [Rtg3_C^P] - k_9 [Rtg3_C^U] + kn_9 [Rtg3_N^U] - k_{11} [Rtg3_C^U] [Rtg1_C] + kn_{11} [Rtg1/3_C^U]$$

$$\frac{d}{dt} V_5 := \frac{d}{dt} [Rtg3_N^P] = -k_8 [Rtg3_N^P] + kn_8 [Rtg3_N^U] + k_{10} [Rtg3_C^P] - kn_{10} [Rtg3_N^P] - k_{14} [Rtg_N^P] [Rtg1_N] + kn_{14} [Rtg1/3_N^P]$$

$$\frac{d}{dt} V_6 := \frac{d}{dt} [Rtg3_N^U] = k_8 [Rtg3_N^P] - kn_8 [Rtg3_N^U] + k_9 [Rtg3_C^U] - kn_9 [Rtg3_N^U] - k_{13} [Rtg_N^U] [Rtg1_N] + kn_{13} [Rtg1/3_N^U]$$

$$\frac{d}{dt} V_7 := \frac{d}{dt} [Rtg1_C] = -k_{11} [Rtg3_C^U] [Rtg1_C] + kn_{11} [Rtg1/3_C^U] - k_{12} [Rtg3_C^P] [Rtg1_C] + kn_{12} [Rtg1/3_C^P] - k_{17} [Rtg1_C] + k_{17} [Rtg1_N]$$

$$\frac{d}{dt} V_8 := \frac{d}{dt} [Rtg1_N] = -k_{13} [Rtg3_N^U] [Rtg1_N] + kn_{13} [Rtg1/3_N^U] - k_{14} [Rtg3_N^P] [Rtg1_N] + kn_{14} [Rtg1/3_N^P] + k_{17} [Rtg1_C] - k_{17} [Rtg1_N]$$

$$\frac{d}{dt} V_9 := \frac{d}{dt} [Rtg1/3_C^P] = k_{12} [Rtg3_C^P] [Rtg1_C] - kn_{12} [Rtg1/3_C^P] - k_{16} [Rtg1/3_C^P] + kn_{16} [Rtg1/3_N^P]$$

$$\frac{d}{dt} V_{10} := \frac{d}{dt} [Rtg1/3_C^U] = k_{11} [Rtg3_C^U] [Rtg1_C] - kn_{11} [Rtg1/3_C^U] - k_{15} [Rtg1/3_C^U] + kn_{15} [Rtg1/3_N^U]$$

$$\frac{d}{dt} V_{11} := \frac{d}{dt} [Rtg1/3_N^P] = k_{14} [Rtg3_N^P] [Rtg1_N] - kn_{14} [Rtg1/3_N^P] + k_{16} [Rtg1/3_C^P] - kn_{16} [Rtg1/3_N^P]$$

$$\frac{d}{dt} V_{12} := \frac{d}{dt} [Rtg1/3_N^U] = k_{13} [Rtg3_N^U] [Rtg1_N] - kn_{13} [Rtg1/3_N^U] + k_{15} [Rtg1/3_C^U] - kn_{15} [Rtg1/3_N^U]$$

$$\begin{aligned}\frac{d}{dt}V_{13} &:= \frac{d}{dt}[Bmh_C] = -k_5[Mks1_C][Bmh_C] + kn_5[Mks1 - Bmh_C] \\ \frac{d}{dt}V_{14} &:= \frac{d}{dt}[Mks1 - Bmh_C] = k_5[Mks1_C][Bmh_C] - kn_5[Mks1 - Bmh_C] \\ \frac{d}{dt}V_{15} &:= \frac{d}{dt}[Mks1 - Rtg2_C^{ina}] = k_3[Mks1_C][Rtg2_C^{ina}] - kn_3[Mks1 - Rtg2_C^{ina}] \\ \frac{d}{dt}V_{16} &:= \frac{d}{dt}[Mks1 - Rtg2_C^{act}] = k_4[Mks1_C][Rtg2_C^{act}] - kn_4[Mks1 - Rtg2_C^{act}]\end{aligned}$$

Necessary requirements:

From [review2](#), GFP experiments describes 14 localizton patterns by deletions of Rtg1, Rtg2, and Rtg3. The derived mathematical model has to fulltil all of the requirements that found in real world.

1. Properties of Rtg3p-GFP localization

Property	$[* - Rtg1_*]$	$[Rtg2_C]$	s
$[* - Rtg3_C^*] > [* - Rtg3_N^*]$	>0	>0	=0
$[* - Rtg3_C^*] > [* - Rtg3_N^*]$	>0	=0	=0
$[* - Rtg3_C^*] > [* - Rtg3_N^*]$	>0	=0	=high
$[* - Rtg3_C^*] < [* - Rtg3_N^*]$	>0	>0	=high
$[* - Rtg3_C^*] < [* - Rtg3_N^*]$	=0	>0	=0
$[* - Rtg3_C^*] < [* - Rtg3_N^*]$	=0	>0	=high
$[* - Rtg3_C^*] < [* - Rtg3_N^*]$	=0	=0	=0
$[* - Rtg3_C^*] < [* - Rtg3_N^*]$	=0	=0	=high

where

$$\begin{aligned}[* - Rtg3_C^*] &= [Rtg1 - Rtg3_C^P] + [Rtg1 - Rtg3_C^U] + [Rtg3_C^U] + [Rtg3_C^P] \\ [* - Rtg3_N^*] &= [Rtg1 - Rtg3_N^P] + [Rtg1 - Rtg3_N^U] + [Rtg3_N^U] + [Rtg3_N^P] \\ [* - Rtg1_*] &= [Rtg1_C] + [Rtg1_N] + [Rtg1 - Rtg3_C^P] + [Rtg1 - Rtg3_C^U] + [Rtg1 - Rtg3_N^P] + [Rtg1 - Rtg3_N^U]\end{aligned}$$

2. Properties of Rtg1p-GFP localization

Properties	$[Rtg3_\#]$	$[Rtg2_C]$	s
$[* - Rtg1_C] > [* - Rtg1_N]$	>0	>0	=0
$[* - Rtg1_C] > [* - Rtg1_N]$	>0	=0	=0
$[* - Rtg1_C] > [* - Rtg1_N]$	>0	=0	=high
$[* - Rtg1_C] > [* - Rtg1_N]$	=0	>0	=0
$[* - Rtg1_C] > [* - Rtg1_N]$	=0	>0	=high
$[* - Rtg1_C] < [* - Rtg1_N]$	>0	>0	=high

where

$$\begin{aligned}[* - Rtg1_C] &= [Rtg1_C] + [Rtg1 - Rtg3_C^P] + [Rtg1 - Rtg3_C^U] \\ [* - Rtg1_N] &= [Rtg1_N] + [Rtg1 - Rtg3_N^P] + [Rtg1 - Rtg3_N^U] \\ [Rtg3_\#] &= [* - Rtg3_C^*] + [* - Rtg3_N^*]\end{aligned}$$

Truth Table and Karnaugh Map

In order to display these properties, I used boolean funtion to model input-output relation, and applied [Karnaugh map](#) to find the simplest boolean formula of RTG pathway.

Rtg3p Translocation

Definition

Condition	Mapping to Boolean Space
$[* - Rtg3_C^*] < [* - Rtg3_N^*]$	1
$[* - Rtg3_C^*] > [* - Rtg3_N^*]$	0
$[* - Rtg1_*] > 0$	1
$[* - Rtg1_*] = 0$	0
$[Rtg2_C] > 0$	1
$[Rtg2_C] = 0$	0
$S = \text{high}$	1
$S = 0$	0

$$\text{Translocation}_{Rtg3} := \begin{cases} 1 & \text{if } [* - Rtg3_C^*] < [* - Rtg3_N^*] \\ 0 & \text{if } [* - Rtg3_C^*] > [* - Rtg3_N^*] \end{cases}$$

Truth Table:

Bool($[* - Rtg1_*]$)	Bool($[Rtg2_C]$)	S	Translocation _{Rtg3} (Output)
0	0	0	x
0	0	1	1
0	1	0	1
0	1	1	1
1	0	0	0
1	0	1	0
1	1	0	0
1	1	1	1

Result:

$$\text{Translocation}_{Rtg3} = \sim \text{Bool}([* - Rtg1_*]) + \text{Bool}([Rtg2_C]) \times S$$

This model expects (0,0,0,1)

Rtg1p Translocation

Definition

Condition	Mapping to Boolean Space
$[* - Rtg1_C] > [* - Rtg1_N]$	0
$[* - Rtg1_C] < [* - Rtg1_N]$	1
$[Rtg3_{\#}^*] > 0$	1
$[Rtg3_{\#}^*] = 0$	0
$[Rtg2_C] > 0$	1
$[Rtg2_C] = 0$	0
$S = \text{high}$	1
$S = 0$	0

$$\text{Translocation}_{Rtg1} := \begin{cases} 1 & \text{if } [* - Rtg1_C] < [* - Rtg1_N] \\ 0 & \text{if } [* - Rtg1_C] > [* - Rtg1_N] \end{cases}$$

Truth table

Bool($[Rtg3_{\#}^*]$)	Bool($[Rtg2_C]$)	S	Translocation _{Rtg1} (Output)
0	0	0	x
0	0	1	x

		S		(Output)
0	1	0	0	
0	1	1	0	
1	0	0	0	
1	0	1	0	
1	1	0	0	
1	1	1	1	

where x is "don't care term", for some relations aren't verified in [review2](#)

Result:

$$\text{Transduction}_{Rtg1} = \text{Bool}([Rtg3^*_{\#}]) \times \text{Bool}([Rtg2_C]) \times S$$

This model expects (0,0,0,0), (0,0,1,0)

Construct a communication channel of RTG pathway

$$x_1 = \text{channel}(\vec{MT}, \vec{V})$$

where $x_1 := Rtg1/3_N^* = Rtg1/3_N^U + Rtg1/3_N^P$

Question: How to achieve maximum information transmission under known \vec{MT} :

The model

$$[MT_1, MT_2, \dots, MT_N] \rightarrow S_1 \rightarrow \nu \rightarrow X_1$$

In order to decode X_1 , the output needs to one-to-one mapping to all possibilities of input array, that is, \vec{MT} , there are 2^N possible combination.

Frequency Response

Lemma:

A system can be linearized by the following equations:

$$\begin{aligned} \frac{d}{dt}\mathbf{x} &= f(\mathbf{x}(t), \mathbf{u}(t)) = \mathbf{A}\mathbf{x}(t) + \mathbf{B}\mathbf{u}(t) \\ y(t) &= h(\mathbf{x}(t), \mathbf{u}(t)) = \mathbf{C}\mathbf{x}(t) + \mathbf{D}\mathbf{u}(t) \end{aligned}$$

where

Symbol	Content	Property
x	System state	Vector
u	Input	Vector
y	output	value
A	System Jacobian	Matrix
B	Input maps	Matrix
C	Output Maps	Matrix
D	Feed-forward term	Matrix

Then

$$H(\omega) = \mathbf{C}(i\omega\mathbf{I} - \mathbf{A})^{-1}\mathbf{B} + \mathbf{D}$$