DRAFT: NCT

RA

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1 NCT models

1.1 GSR'03 model of NCT

In the first step we implement the "minimal Ran gradient system" from [GSR03].

References

[Bis+95] F. R. Bischoff, H. Krebber, E. Smirnova, W. Dong, and H. Ponstingl. "Co-activation of RanGTPase and inhibition of GTP dissociation by Ran–GTP binding protein RanBP1". In: *The EMBO Journal* 14.4 (Feb. 1995), pp. 705–715. DOI: 10.1002/j.1460-2075.1995.tb07049.x (cit. on p. 2).

[Kle+95] C. Klebe, H. Prinz, A. Wittinghofer, and R. S. Goody. "The Kinetic Mechanism of Ran-Nucleotide Exchange Catalyzed by RCC1". In: *Biochemistry* 34.39 (Oct. 1995), pp. 12543–12552. DOI: 10.1021/bi00039a008 (cit. on pp. 2, 3).

[GSR03] D. Görlich, M. J. Seewald, and K. Ribbeck. "Characterization of Ran-driven cargo transport and the RanGTPase system by kinetic measurements and computer simulation". In: *The EMBO Journal* 22.5 (Mar. 2003), pp. 1088–1100. DOI: 10.1093/emboj/cdg113 (cit. on pp. 1–3).

TODOs:

1. p.3. (**??**)

The following account for the cytoplasmic species. Here, $[\dots]$ abbreviates the (cytoplasmic) concentration of the complex $\mathsf{RanBP1 \cdot Ran \cdot GTP}$.

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran \cdot GDP_{cyt}}] = \mathsf{F_{Ran \cdot GDP}} \frac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} + \mathsf{GAP} + \mathsf{GAP_{RanBP1}} + \mathsf{Ex} \frac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} \tag{1a}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran \cdot GTP_{cyt}}] = \mathsf{F_{Ran \cdot GTP}} \frac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} - \mathsf{GAP} - k_{\mathrm{on}}^{\mathrm{rbp}}[\mathsf{RanBP1}][\mathsf{Ran \cdot GTP_{cyt}}] + k_{\mathrm{off}}^{\mathrm{rbp}}[\dots] \tag{1b}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{RanBP1 \cdot Ran \cdot GTP}] = -\mathsf{GAP_{RanBP1}} + k_{\mathrm{on}}^{\mathrm{rbp}}[\mathsf{RanBP1}][\mathsf{Ran \cdot GTP_{cyt}}] - k_{\mathrm{off}}^{\mathrm{rbp}}[\dots] \tag{1c}$$

The following account for the nuclear species. E denotes free $\mathsf{RCC1}$.

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran \cdot GDP_{nuc}}] = -\mathsf{F_{Ran \cdot GDP}} + r_8[\mathsf{IntC}] - r_1[\mathsf{E}][\mathsf{Ran \cdot GDP_{nuc}}] \tag{2a}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran \cdot GTP_{nuc}}] = -\mathsf{F_{Ran \cdot GTP}} + r_4[\mathsf{IntA}] - r_5[\mathsf{E}][\mathsf{Ran \cdot GTP_{nuc}}] - \mathsf{Ex} \tag{2b}$$

The nucleotide-exchange reaction $\mathsf{Ran \cdot GDP + GTP} \rightleftharpoons \mathsf{Ran \cdot GTP + GDP}$ is catalyzed by $\mathsf{RCC1}$. It is modeled as in [Kle+95, Fig. 6] / [GSR03, Fig. 1] with three intermediates. Note that it depends on the availability of GDP and GTP.

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{IntA}] = -(r_4 + r_6)[\mathsf{IntA}] + r_5[\mathsf{E}][\mathsf{Ran \cdot GTP_{nuc}}] + r_3[\mathsf{GTP}][\mathsf{IntB}] \tag{3a}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{IntB}] = r_6[\mathsf{IntA}] + r_2[\mathsf{IntC}] - (r_3[\mathsf{GTP}] + r_7[\mathsf{GDP}])[\mathsf{IntB}] \tag{3b}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{IntC}] = -(r_2 + r_8)[\mathsf{IntC}] + r_1[\mathsf{E}][\mathsf{Ran \cdot GDP_{nuc}}] + r_7[\mathsf{GDP}][\mathsf{IntB}] \tag{3c}$$

Constraints on the total concentration:

$$\text{Free } \mathsf{RCC1}: \quad [\mathsf{E}] = \mathsf{RCC1_{total}} - ([\mathsf{IntA}] + [\mathsf{IntB}] + [\mathsf{IntC}]) \tag{4a}$$

$$\text{Free} \quad [\mathsf{RanBP1}] = \mathsf{RanBP1_{total}} - [\mathsf{RanBP1 \cdot Ran \cdot GTP}] \tag{4b}$$

Gradient-driven fluxes from the nucleus to the cytoplasm:

$$\mathsf{F_{Ran.GTP}} = D_{\mathsf{Ran \cdot GTP}} \left([\mathsf{Ran \cdot GTP_{nuc}}] - [\mathsf{Ran \cdot GTP_{cyt}}]\right) \tag{5a}$$

$$\mathsf{F_{Ran.GDP}} = D_{\mathsf{Ran \cdot GDP}} \left([\mathsf{Ran \cdot GDP_{nuc}}] - [\mathsf{Ran \cdot GDP_{cyt}}]\right) \tag{5b}$$

RanGAP hydrolyzes the γ-phosphate of $\mathsf{Ran \cdot GTP}$. This is more efficient when $\mathsf{Ran \cdot GTP}$ is bound to $\mathsf{RanBP1}$ [Bis+95], reducing the IC50 seven-fold [GSR03, Table I, p. 1091].

$$\mathsf{GAP} = k_{\mathsf{GAP}}[\mathsf{RanGAP}]/(1 + K_{\mathsf{GAP}}/[\mathsf{Ran \cdot GTP_{cyt}}]) \tag{6a}$$

$$\mathsf{GAP_{RanBP1}} = k'_{\mathsf{GAP}}[\mathsf{RanGAP}]/(1 + K'_{\mathsf{GAP}}/[\mathsf{RanBP1 \cdot Ran \cdot GTP}]) \tag{6b}$$

Figure 1: From [GSR03, Fig. 2]. Ex is additional potentially useful flux of nuclear $\mathsf{Ran \cdot GTP}$ to cytoplasmic $\mathsf{Ran \cdot GDP}$, set by default to zero.

(1a)	$V_{\text{nuc}} = 1.2\,\text{pl}, \quad V_{\text{cyt}} = 1.8\,\text{pl}$	[GSR03, Table II]
(1a)	initial condition $[\mathsf{RanGDP_{cyt}}] = 5\,\mu\text{M}$	[GSR03, Table II]
(1b)–(1c)	$k_{\text{on}}^{\text{rbp}} = 0.3\,\mu\text{M}^{-1}\,\text{s}^{-1}, \quad k_{\text{off}}^{\text{rbp}} = 4 \times 10^{-4}\,\text{s}^{-1}$	[GSR03, Supp. Table A]
(2a)–(3c)	$r_1 = 74\,\mu\text{M}^{-1}\,\text{s}^{-1}, \quad r_8 = 55\,\text{s}^{-1}$ $r_7 = 11\,\mu\text{M}^{-1}\,\text{s}^{-1}, \quad r_2 = 21\,\text{s}^{-1}$ $r_3 = 0.6\,\mu\text{M}^{-1}\,\text{s}^{-1}, \quad r_6 = 19\,\text{s}^{-1}$ $r_5 = 100\,\mu\text{M}^{-1}\,\text{s}^{-1}, \quad r_4 = 55\,\text{s}^{-1}$	[GSR03, Supp. Table A] [Kle+95, Fig. 6]
(3a)–(3c)	$[\mathsf{GTP}] = 500\,\mu\text{M}, \quad [\mathsf{GDP}] = 1.6\,\mu\text{M}$	[GSR03, Table II]
(4a)	$\mathsf{RCC1_{total}} = 0.7\,\mu\text{M}$	[GSR03, Supp. Table B]
(4b)	$\mathsf{RanBP1_{total}} = 2\,\mu\text{M}$	[GSR03, Fig. 4]
(5a) (5b)	$D_{\mathsf{RanGTP}} = 0.03\,\text{s}^{-1}$ $D_{\mathsf{RanGDP}} = 0.12\,\text{s}^{-1}$	[GSR03, Table II]
(6a)	$k_{\mathsf{GAP}} = 10.6\,\text{s}^{-1}, \quad K_{\mathsf{GAP}} = 0.7\,\mu\text{M}$	[GSR03, Supp. Table A]
(6b)	$k'_{\mathsf{GAP}} = 10.8\,\text{s}^{-1}, \quad K'_{\mathsf{GAP}} = 0.1\,\mu\text{M}$	[GSR03, Table I]
(6a)–(6b)	cytoplasmic $[\mathsf{RanGAP}] = 0.7\,\mu\text{M}$	[GSR03, Table II / ST B]
TODO(1): (??)	$K_R = 5 \times 10^{-4}\,\mu\text{M}$	[GSR03, Supp. Table A]

Table 1: Constants for the "standard simulation condition" at 25 °C. Except for (1a), all species are initialized to zero at $t = 0$.

Condition	Affected parameters	Nuclear RanGTP, µM	Cytoplasmic RanGTP, nM	Dynamic capacity, µM/s
"Standard"	See Table 1	4.26 (4.3)	7.75 (7.7)	0.59 (0.60)
Omission of RanBP1	$\mathsf{RanBP1_{total}} := 0$	4.27 (4.3)	8.13 (8.1)	0.59 (0.60)
200% RCC1	$\mathsf{RCC1_{total}}$	3.95 (4.0)	7.17 (7.1)	0.59 (0.60)
50% RCC1	$\mathsf{RCC1_{total}}$	4.31 (4.3)	7.82 (7.7)	0.58 (0.60)
10% RCC1	$\mathsf{RCC1_{total}}$	3.59 (3.6)	6.50 (6.4)	0.46 (0.48)
1% RCC1	$\mathsf{RCC1_{total}}$	1.40 (1.4)	2.52 (2.5)	0.075 (0.08)
GTP:GDP = 500:0	$[\mathsf{GDP}] := 0\,\mu\text{M}$	4.80 (4.8)	8.72 (8.6)	0.59 (0.60)
GTP:GDP = 500:50	$[\mathsf{GDP}] := \frac{1}{10}[\mathsf{GTP}]$	0.98 (0.8)	1.76 (1.5)	0.57 (0.58)
GTP:GDP = 500:500	$[\mathsf{GDP}] := [\mathsf{GTP}]$	0.12 (0.12)	0.22 (0.21)	0.34 (0.34)
Saturating NTF2	$D_{\mathsf{RanGDP}} := 0.48\,\text{s}^{-1}$	5.12 (5.1)	9.32 (9.2)	2.18 (2.2)
No NTF2	$D_{\mathsf{RanGDP}} := D_{\mathsf{RanGTP}}$	2.55 (2.5)	4.60 (4.5)	0.15 (0.16)
200% RanGAP	$[\mathsf{RanGAP}]$	4.27 (4.3)	3.95 (3.9)	0.59 (0.60)
50% RanGAP	$[\mathsf{RanGAP}]$	4.26 (4.3)	14.9 (14)	0.59 (0.60)
50% permeability	D_{RanGTP}	4.91 (4.9)	4.44 (4.4)	0.59 (–)
200% permeability	D_{RanGTP}	3.41 (3.4)	12.4 (12.3)	0.59 (–)
400% permeability	D_{RanGTP}	2.46 (2.5)	18.0 (17.8)	0.59 (–)

Table 2: Steady-state concentrations for the simulation scenarios from [GSR03, Table II/III], with their results shown in brackets. Value for D_{RanGDP} is from [GSR03, Fig. 3].