

DRAFT: NCT

RA

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1 NCT models

Abbreviations: ODE = ordinary differential equations.

1.1 GSR’03 model of NCT

First we implement the “minimal Ran gradient system” from [GSR03]. The equations are shown in Table 1 and the constants are collected in Table 2. Simulating the ODE across the scenarios of [GSR03] we obtain results that are fairly close to the original, see Table 3.

A coupling of the Ran gradient to importin–cargo transport was proposed in [GSR03, Fig. 6A]. We formulate (part of) it in Table 4.

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

$$\frac{d}{dt}[\text{Ran} \cdot \text{GDP}]_{\text{cyt}} = F_{\text{Ran} \cdot \text{GDP}} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} + \text{GAP} + \text{GAP}_{\text{RanBP1}} + \text{Ex} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} \quad (1a)$$

$$\frac{d}{dt}[\text{Ran} \cdot \text{GTP}]_{\text{cyt}} = F_{\text{Ran} \cdot \text{GTP}} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} - \text{GAP} - k_{\text{on}}^{\text{rbp}}[\text{RanBP1}][\text{Ran} \cdot \text{GTP}]_{\text{cyt}} + k_{\text{off}}^{\text{rbp}}[\dots] \quad (1b)$$

$$\frac{d}{dt}[\text{RanBP1} \cdot \text{Ran} \cdot \text{GTP}] = -\text{GAP}_{\text{RanBP1}} + k_{\text{on}}^{\text{rbp}}[\text{RanBP1}][\text{Ran} \cdot \text{GTP}]_{\text{cyt}} - k_{\text{off}}^{\text{rbp}}[\dots] \quad (1c)$$

The following account for the nuclear species. E denotes free RCC1.

$$\frac{d}{dt}[\text{Ran} \cdot \text{GDP}]_{\text{nuc}} = -F_{\text{Ran} \cdot \text{GDP}} + r_8[\text{IntC}] - r_1[\text{E}][\text{Ran} \cdot \text{GDP}]_{\text{nuc}} \quad (2a)$$

$$\frac{d}{dt}[\text{Ran} \cdot \text{GTP}]_{\text{nuc}} = -F_{\text{Ran} \cdot \text{GTP}} + r_4[\text{IntA}] - r_5[\text{E}][\text{Ran} \cdot \text{GTP}]_{\text{nuc}} - \text{Ex} \quad (2b)$$

The nucleotide-exchange reaction $\text{Ran} \cdot \text{GDP} + \text{GTP} \rightleftharpoons \text{Ran} \cdot \text{GTP} + \text{GDP}$ is catalyzed by 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.

$$\frac{d}{dt}[\text{IntA}] = -(r_4 + r_6)[\text{IntA}] + r_5[\text{E}][\text{Ran} \cdot \text{GTP}]_{\text{nuc}} + r_3[\text{GTP}][\text{IntB}] \quad (3a)$$

$$\frac{d}{dt}[\text{IntB}] = r_6[\text{IntA}] + r_2[\text{IntC}] - (r_3[\text{GTP}] + r_7[\text{GDP}])[\text{IntB}] \quad (3b)$$

$$\frac{d}{dt}[\text{IntC}] = -(r_2 + r_8)[\text{IntC}] + r_1[\text{E}][\text{Ran} \cdot \text{GDP}]_{\text{nuc}} + r_7[\text{GDP}][\text{IntB}] \quad (3c)$$

Constraints on the total concentration:

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

$$\text{Free } [\text{RanBP1}] = \text{RanBP1}_{\text{total}} - [\text{RanBP1} \cdot \text{Ran} \cdot \text{GTP}] \quad (4b)$$

Gradient-driven fluxes from the nucleus to the cytoplasm:

$$F_{\text{Ran} \cdot \text{GTP}} = D_{\text{Ran} \cdot \text{GTP}} ([\text{Ran} \cdot \text{GTP}]_{\text{nuc}} - [\text{Ran} \cdot \text{GTP}]_{\text{cyt}}) \quad (5a)$$

$$F_{\text{Ran} \cdot \text{GDP}} = D_{\text{Ran} \cdot \text{GDP}} ([\text{Ran} \cdot \text{GDP}]_{\text{nuc}} - [\text{Ran} \cdot \text{GDP}]_{\text{cyt}}) \quad (5b)$$

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

$$\text{GAP} = k_{\text{GAP}}[\text{RanGAP}]/(1 + K_{\text{GAP}}/[\text{Ran} \cdot \text{GTP}]_{\text{cyt}}) \quad (6a)$$

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

Table 1: The minimal Ran gradient system from [GSR03, Fig. 2]. Ex is an additional potentially useful flux of nuclear $\text{Ran} \cdot \text{GTP}$ to cytoplasmic $\text{Ran} \cdot \text{GDP}$, 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 $[\text{Ran} \cdot \text{GDP}]_{\text{cyt}} = 5 \mu\text{M}$	[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)	$[\text{GTP}] = 500 \mu\text{M}, \quad [\text{GDP}] = 1.6 \mu\text{M}$	[GSR03, Table II]
(4a)	$\text{RCC1}_{\text{total}} = 0.7 \mu\text{M}$	[GSR03, Supp. Table B]
(4b)	$\text{RanBP1}_{\text{total}} = 2 \mu\text{M}$	[GSR03, Fig. 4]
(5a)	$D_{\text{Ran} \cdot \text{GTP}} = 0.03 \text{ s}^{-1}$	[GSR03, Table II]
(5b)	$D_{\text{Ran} \cdot \text{GDP}} = 0.12 \text{ s}^{-1}$	
(6a)	$k_{\text{GAP}} = 10.6 \text{ s}^{-1}, \quad K_{\text{GAP}} = 0.7 \mu\text{M}$	[GSR03, Supp. Table A]
(6b)	$k'_{\text{GAP}} = 10.8 \text{ s}^{-1}, \quad K'_{\text{GAP}} = 0.1 \mu\text{M}$	[GSR03, Table I]
(6a)–(6b)	cytoplasmic $[\text{RanGAP}] = 0.7 \mu\text{M}$	[GSR03, Table II / ST B]
TODO(1): Eq	$K_R = 5 \times 10^{-4} \mu\text{M}$	[GSR03, Supp. Table A]

Table 2: 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, $\mu\text{M/s}$
“Standard”	See Table 2	4.26 (4.3)	7.75 (7.7)	0.59 (0.60)
Omission of RanBP1	$\text{RanBP1}_{\text{total}} := 0$	4.27 (4.3)	8.13 (8.1)	0.59 (0.60)
200% RCC1	$\text{RCC1}_{\text{total}}$	3.95 (4.0)	7.17 (7.1)	0.59 (0.60)
50% RCC1	$\text{RCC1}_{\text{total}}$	4.31 (4.3)	7.82 (7.7)	0.58 (0.60)
10% RCC1	$\text{RCC1}_{\text{total}}$	3.59 (3.6)	6.50 (6.4)	0.46 (0.48)
1% RCC1	$\text{RCC1}_{\text{total}}$	1.40 (1.4)	2.52 (2.5)	0.075 (0.08)
GTP:GDP = 500:0	$[\text{GDP}] := 0 \mu\text{M}$	4.80 (4.8)	8.72 (8.6)	0.59 (0.60)
GTP:GDP = 500:50	$[\text{GDP}] := \frac{1}{10} [\text{GTP}]$	0.98 (0.8)	1.76 (1.5)	0.57 (0.58)
GTP:GDP = 500:500	$[\text{GDP}] := [\text{GTP}]$	0.12 (0.12)	0.22 (0.21)	0.34 (0.34)
Saturating NTF2	$D_{\text{Ran} \cdot \text{GDP}} := 0.48 \text{ s}^{-1}$	5.12 (5.1)	9.32 (9.2)	2.18 (2.2)
No NTF2	$D_{\text{Ran} \cdot \text{GDP}} := D_{\text{Ran} \cdot \text{GTP}}$	2.55 (2.5)	4.60 (4.5)	0.15 (0.16)
200% RanGAP	$[\text{RanGAP}]$	4.27 (4.3)	3.95 (3.9)	0.59 (0.60)
50% RanGAP	$[\text{RanGAP}]$	4.26 (4.3)	14.9 (14)	0.59 (0.60)
50% permeability	$D_{\text{Ran} \cdot \text{GTP}}$	4.91 (4.9)	4.44 (4.4)	0.59 (–)
200% permeability	$D_{\text{Ran} \cdot \text{GTP}}$	3.41 (3.4)	12.4 (12.3)	0.59 (–)
400% permeability	$D_{\text{Ran} \cdot \text{GTP}}$	2.46 (2.5)	18.0 (17.8)	0.59 (–)

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

$$R_{\text{cyt}} := -k_{\text{on}}^{\text{R}}[\text{Imp}\beta][\text{Ran} \cdot \text{GTP}]_{\text{cyt}} + k_{\text{off}}^{\text{R}}[\text{Imp}\beta \cdot \text{Ran} \cdot \text{GTP}]_{\text{cyt}} \quad (7\text{a})$$

$$C_{\text{cyt}} := -k_{\text{on}}^{\text{C}}[\text{Imp}\beta][\text{Cargo}]_{\text{cyt}} + k_{\text{off}}^{\text{C}}[\text{Imp}\beta \cdot \text{Cargo}]_{\text{cyt}} \quad (7\text{b})$$

$$\frac{d}{dt}[\text{Imp}\beta \cdot \text{Ran} \cdot \text{GTP}]_{\text{cyt}} = -R_{\text{cyt}} + F_{\text{Imp}\beta \cdot \text{Ran} \cdot \text{GTP}} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} \quad (7\text{c})$$

$$\frac{d}{dt}[\text{Imp}\beta]_{\text{cyt}} = +R_{\text{cyt}} + C_{\text{cyt}} + F_{\text{Imp}\beta} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} \quad (7\text{d})$$

$$\frac{d}{dt}[\text{Imp}\beta \cdot \text{Cargo}]_{\text{cyt}} = -C_{\text{cyt}} + F_{\text{Imp}\beta \cdot \text{Cargo}} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} \quad (7\text{e})$$

$$\frac{d}{dt}[\text{Cargo}]_{\text{cyt}} = +C_{\text{cyt}} + F_{\text{Cargo}} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} \quad (7\text{f})$$

TODO(2): Analogous equations for *nuclear*

TODO(3): Diffusion eqn

TODO(4): Add R to Ran · GTP eqn

TODO(5): Need $\text{Imp}\beta \cdot \text{Ran} \cdot \text{GTP} + \text{Cargo} \rightleftharpoons \text{Imp}\beta \cdot \text{Cargo} + \text{Ran} \cdot \text{GTP}?$

Table 4: Eq

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](https://doi.org/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](https://doi.org/10.1021/bi00039a008) (cit. on pp. 2, 3).
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TODOs:

1. p.3. Eq
2. p.4. Analogous equations for *nuclear*
3. p.4. Diffusion eqn
4. p.4. Add R to Ran · GTP eqn
5. p.4. Need $\text{Imp}\beta \cdot \text{Ran} \cdot \text{GTP} + \text{Cargo} \rightleftharpoons \text{Imp}\beta \cdot \text{Cargo} + \text{Ran} \cdot \text{GTP}$?