

DRAFT: NCT

RA

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1 NCT models

Abbreviations: FG-nups = FG-nucleoporins; NCT = nucleocytoplasmic transport; NPC = nuclear pore complex; ODE = ordinary differential equations.

1.1 GSR'03 model of NCT

Ran gradient. The Ran gradient, i.e. the nuclear accumulation of $\text{Ran} \cdot \text{GTP}$, is the base layer of nucleocytoplasmic transport. Thus we first implement the “minimal Ran gradient system” from [GSR03]. The equations are recapitulated in §2.1 and the constants are collected in Table 2. Following [GSR03], the “dynamic capacity” Ex is an optional maximal steady-state (positive) flux of nuclear $\text{Ran} \cdot \text{GTP}$ to cytoplasmic $\text{Ran} \cdot \text{GDP}$, which we determine using the additional equation (20). The fluxes are in units of concentration/time ($\mu\text{M}/\text{s}$). The ones across the nuclear boundary have positive sign when exiting the nucleus and are normalized to the nuclear volume. Thus, the *amount* exiting the nucleus per unit of time is $\text{flux} \times V_{\text{nuc}}$.

Simulating the ODE across the scenarios of [GSR03] we obtain results that are sufficiently close to the original, see Table 3. Importantly, an order of 1000-fold nuclear enrichment of $\text{Ran} \cdot \text{GTP}$ is sustained in steady-state.

Code #1.

Coupling to $\text{Imp}\beta$ -mediated transport. A coupling of the Ran gradient to importin-cargo transport was proposed in [GSR03, Fig. 6A]. We now formulate a version of it. The following equations comprise the handling of cargo by $\text{Imp}\beta$ in the cytoplasm,

$$\frac{d}{dt}[\text{Imp}\beta \cdot \text{Ran} \cdot \text{GTP}]_{\text{cyt}} = -R_{\text{cyt}} + F_{\text{Imp}\beta \cdot \text{Ran} \cdot \text{GTP}} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} - \text{GAP}_{\text{Imp}\beta} + \text{Knockoff}_{\text{cyt}} \quad (1a)$$

$$\frac{d}{dt}[\text{Imp}\beta]_{\text{cyt}} = +R_{\text{cyt}} + C_{\text{cyt}} + F_{\text{Imp}\beta} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} + \text{GAP}_{\text{Imp}\beta} \quad (1b)$$

$$\frac{d}{dt}[\text{Imp}\beta \cdot \text{Cargo}]_{\text{cyt}} = -C_{\text{cyt}} + F_{\text{Imp}\beta \cdot \text{Cargo}} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} - \text{Knockoff}_{\text{cyt}} \quad (1c)$$

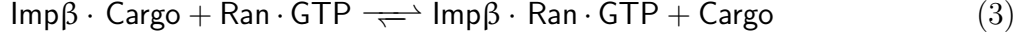
$$\frac{d}{dt}[\text{Cargo}]_{\text{cyt}} = +C_{\text{cyt}} + F_{\text{Cargo}} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} + \text{Knockoff}_{\text{cyt}} \quad (1d)$$

with the fluxes

$$R_{\text{cyt}} := -k_{\text{on}}^{\text{R}}[\text{Imp}\beta][\text{Ran} \cdot \text{GTP}]_{\text{cyt}} + k_{\text{off}}^{\text{R}}[\text{Imp}\beta \cdot \text{Ran} \cdot \text{GTP}]_{\text{cyt}} \quad (2a)$$

$$C_{\text{cyt}} := -k_{\text{on}}^{\text{C}}[\text{Imp}\beta][\text{Cargo}]_{\text{cyt}} + k_{\text{off}}^{\text{C}}[\text{Imp}\beta \cdot \text{Cargo}]_{\text{cyt}}. \quad (2b)$$

The forward flux of the reaction



is called **Knockoff**. It is modeled as a one-way reaction with forward rate k_{knockoff} . The GSR equations are modified accordingly:

$$\frac{d}{dt}[\text{Ran} \cdot \text{GDP}]_{\text{cyt}} = (14a) + \text{GAP}_{\text{Imp}\beta} \quad (14a')$$

$$\frac{d}{dt}[\text{Ran} \cdot \text{GTP}]_{\text{cyt}} = (14b) + R_{\text{cyt}} - \text{Knockoff}_{\text{cyt}} \quad (14b')$$

Analogous nuclear equations (without **GAP**) are implemented but are omitted here. Analogously to (18a)/(18b) we have the additional nuclear-to-cytoplasmic diffusion fluxes

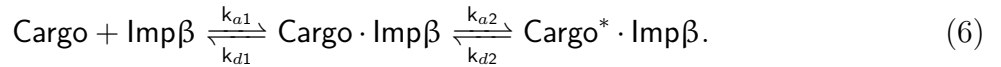
$$F_{\text{Imp}\beta \cdot \text{Ran} \cdot \text{GTP}}, \quad F_{\text{Imp}\beta}, \quad F_{\text{Imp}\beta \cdot \text{Cargo}}, \quad F_{\text{Cargo}} \quad (4)$$

with the permeability constants given in Table 1.

SPR experiments of [Cat+01] indicated that the IBB domain of importin- α binds importin- β and undergoes a conformational change,



We therefore assume the analogous reaction



Examples of the kinetic constants are available in [Cat+01, Table I], e.g.,

$$k_{a1} = 0.11 \mu\text{M}^{-1} \text{s}^{-1}, \quad k_{d1} = 0.024 \text{s}^{-1}, \quad k_{a2} = 0.024 \text{s}^{-1}, \quad k_{d2} = 7.4 \times 10^{-4} \text{s}^{-1}, \quad (7)$$

for an IBB domain binding to **Imp** β . The intermediate state in (5) is transient on a moderately relevant time-scale, see Fig. 1 (code #2). Therefore, in the present model we lump the complexed states together and take $k_{\text{on}}^{\text{C}} := k_{a1}$ and $k_{\text{off}}^{\text{C}} := k_{d1} \frac{k_{d2}}{k_{a2} + k_{d2}}$ as the effective kinetic constants for (2b), cf. Table 1.

With the constants from Table 1, the steady-state of the model (reached after some 10^4 s) is reported in Fig. 2. Nuclear accumulation of free cargo is 37-fold. Sensitivity analysis shows that, in relative terms, the final nuclear concentration of free cargo depends most strongly on k_{knockoff} . Doubling k_{knockoff} almost doubles the nuclear concentration. Code #3.

This model predicts a slight accumulation of **Imp** β in the nucleus, with **Imp** $\beta \cdot \text{Ran} \cdot \text{GTP}$ contributing most of the excess.

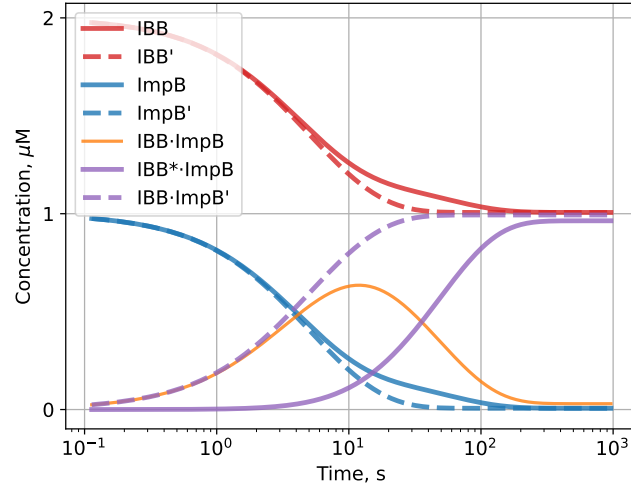


Figure 1: Stand-alone simulation of (5) starting with $2\text{ }\mu\text{M}$ IBB and $1\text{ }\mu\text{M}$ Imp β with the constants (7). The dashed counterpart is the effective system of the form $A + B \rightleftharpoons AB$, cf. §1.1.

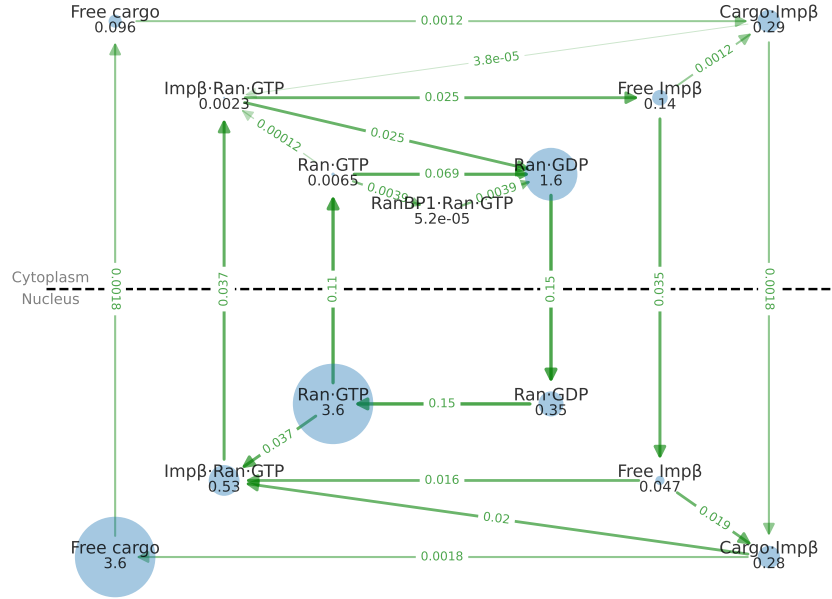


Figure 2: Steady-state of the transport system from §1.1 with conditions of Table 1. The free cargo shows 37-fold accumulation in the nucleus; total nuclear to total cytoplasmic cargo is 10-fold. Units are μM for species and $\mu\text{M s}^{-1}$ for fluxes. Initial conditions: $[\text{Ran} \cdot \text{GDP}]_{\text{cyt}} = 5\text{ }\mu\text{M}$, $[\text{Imp}\beta]_{\text{cyt}} = 1\text{ }\mu\text{M}$, $[\text{Cargo}]_{\text{cyt}} = 3\text{ }\mu\text{M}$, all else zero.

(2a)	$k_{\text{on}}^{\text{R}} = 0.096 \mu\text{M}^{-1} \text{s}^{-1}$, $k_{\text{off}}^{\text{R}} = 4.8 \times 10^{-6} \text{s}^{-1}$	[GSR03, Supp. Table A], [RM05, Table II]
(2b)	$k_{\text{on}}^{\text{C}} = 0.11 \mu\text{M}^{-1} \text{s}^{-1}$, $k_{\text{off}}^{\text{C}} = 7.2 \times 10^{-4} \text{s}^{-1}$	[Cat+01, Table I], [RM05, Table II]
(3)	$k_{\text{knockoff}} = 2 \times 10^{-2} \mu\text{M}^{-1} \text{s}^{-1}$	[RM05, Table II]
(4)	$D_{\text{Imp}\beta \cdot \text{Ran} \cdot \text{GTP}} = 0.07 \text{s}^{-1}$, $D_{\text{Imp}\beta} = 0.4 \text{s}^{-1}$ $D_{\text{Imp}\beta \cdot \text{Cargo}} = 0.25 \text{s}^{-1}$, $D_{\text{Cargo}} = 5 \times 10^{-4} \text{s}^{-1}$	[RM05, Table III]

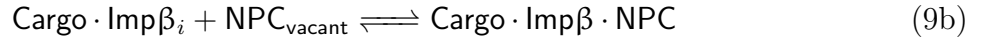
Table 1: Constants for the $\text{Imp}\beta$ -mediated transport from §1.1.

1.2 NPC as compartment

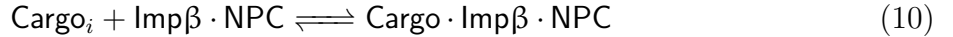
It has been observed **TODO(1): ref** that $\text{Imp}\beta$ accumulate inside the NPCs as they bind to the FG-nups, possibly shuttling the cargo across the pore without leaving themselves. To account for this we propose a three-compartment model with cytoplasm, nucleus and the nuclear envelope as the three compartments. Cytoplasmic and nuclear volume is as in Table 2. For the envelope volume (potentially including some perimembrane space) we take 10^{-3}pL . The unoccupied NPC space is called $\text{NPC}_{\text{vacant}}$, of which we take

$$1 \text{pL} \times 1 \mu\text{M} \approx 300 \times 2000 \text{ units}, \quad (8)$$

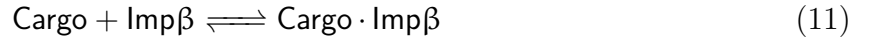
motivated by the estimated count of 2000 NPCs in the nuclear envelope **TODO(2): ref** and the capacity of about 300 Kaps each **TODO(3): ref**. The crux is now that the nuclear envelope, having small volume, has a high concentration of NPCs. At the nuclear envelope we posit the reactions



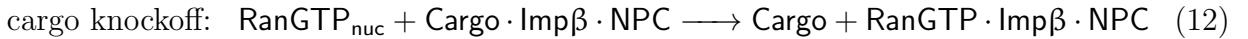
TODO(4): ref with $k_{\text{on}} = 10^{-3} \mu\text{M}^{-1} \text{s}^{-1}$ and $k_{\text{off}} = 10^{-4} \text{s}^{-1}$, as well as



with $k_{\text{on}}^{\text{C}} = 0.11 \mu\text{M}^{-1} \text{s}^{-1}$ and $k_{\text{off}}^{\text{C}} = 7.2 \times 10^{-4} \text{s}^{-1}$, where i can be “cytoplasmic” or “nuclear”. This envelope compartment is in diffusive exchange with cytoplasm ($i = \text{cyt}$) and nucleus ($i = \text{nuc}$) with the permeability constant $D = 1 \text{s}^{-1}$. In both, we also allow



with the same $k_{\text{on}}^{\text{C}}/k_{\text{off}}^{\text{C}}$. For simplicity, we assume $[\text{RanGTP}] = 3 \mu\text{M}$ and $[\text{RanGDP}] = 2 \mu\text{M}$ are maintained at fixed concentrations and are only relevant at the envelope, where we have



For hydrolysis we assume the reaction rate $v_{\text{GAP}}/(1+K_{\text{GAP}}/[\text{RanGTP} \cdot \text{Imp}\beta \cdot \text{NPC}])$, similarly to (19a). We take $v_{\text{GAP}} = 0.07 \mu\text{M} \text{s}^{-1}$ and $K_{\text{GAP}} = 0.1 \mu\text{M}$. This reaction rate about $100 \times$

smaller than in (19a) but in view of **TODO(5): ref**, this seems more realistic and has little effect on the course of the simulation.

Starting from $[\text{Cargo}]_{\text{cyt}} = 1 \mu\text{M}$ and $[\text{Imp}\beta]_{\text{cyt}} = [\text{Imp}\beta]_{\text{nuc}} = 0.5 \mu\text{M}$, this model predicts a 6-fold accumulation of total cargo in the nucleus in steady-state. Meanwhile, the concentration of $\text{Imp}\beta$ at the envelope is approximately $10^3 \mu\text{M}$.

Code [#4](#).

1.3 Role of RanBP1

According to [LM97, Fig. 4A], $\text{Imp}\beta$ blocks hydrolysis of $\text{Ran} \cdot \text{GTP}$ by RanGAP but RanBP1 rescues it for most part. Similarly, [BG97] showed that RanBP1 transiently detaches Ran from the complex $\text{Kap} \cdot \text{Ran} \cdot \text{GTP}$ (where Kap can be importin β , transportin or CAS), whereupon hydrolysis by RanGAP disassembles the complex; and that efficient disassembly of $\text{Imp}\beta \cdot \text{Ran} \cdot \text{GTP}$ required RanBP1 and $\text{Imp}\alpha$ [BG97, §3.2, cf. Fig. 4], [FBR97]. Importantly, Kaps and RanBP1 bind Ran at distinct sites [BG97, p.253].

Further, [See+03, Fig. 13] characterizes the kinetics of the formation of the complex between $\text{Ran} \cdot \text{GTP}$, RanBP1 and RanGAP and its hydrolysis. In particular, the release of the γ -phosphate, which is the rate-limiting step of hydrolysis by RanGAP , is barely influenced by RanBP1 , which instead stimulates the association of Ran with RanGAP .

In [RM05, p.1033], the initial rate of cargo import increased with co-addition of RanBP1 , disagreeing with their simulation (in which RanBP1 acts catalytically [RM05, Fig. S1]).

Crystal structure: [Sar+07]

Compartments: [Hof20]

Identification of CAS: [Kut+97]

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2 Appendix

2.1 Minimal Ran gradient system

Here we recapitulate the minimal Ran gradient system from [GSR03, Fig. 2], cf. §1.1. The following account for the cytoplasmic species. Here, [...] abbreviates the (cytoplasmic) concentration of the complex $\text{RanBP1} \cdot \text{Ran} \cdot \text{GTP}$. 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.

$$\frac{d}{dt}[\text{Ran} \cdot \text{GDP}]_{\text{cyt}} = F_{\text{Ran} \cdot \text{GDP}} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} + \text{GAP} + \text{GAP}_{\text{RanBP1}} + \text{Ex} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} \quad (14a)$$

$$\frac{d}{dt}[\text{Ran} \cdot \text{GTP}]_{\text{cyt}} = F_{\text{Ran} \cdot \text{GTP}} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} - \text{GAP} - k_{\text{on}}^{\text{rbp}}[\text{RanBP1}][\text{Ran} \cdot \text{GTP}]_{\text{cyt}} + k_{\text{off}}^{\text{rbp}}[\dots] \quad (14b)$$

$$\frac{d}{dt}[\text{RanBP1} \cdot \text{Ran} \cdot \text{GTP}] = -\text{GAP}_{\text{RanBP1}} + k_{\text{on}}^{\text{rbp}}[\text{RanBP1}][\text{Ran} \cdot \text{GTP}]_{\text{cyt}} - k_{\text{off}}^{\text{rbp}}[\dots] \quad (14c)$$

The following account for the nuclear species. As in [GSR03], E denotes free RCC1.

$$\frac{d}{dt}[\text{Ran} \cdot \text{GDP}]_{\text{nuc}} = -F_{\text{Ran} \cdot \text{GDP}} + r_8[\text{IntC}] - r_1[\text{E}][\text{Ran} \cdot \text{GDP}]_{\text{nuc}} \quad (15a)$$

$$\frac{d}{dt}[\text{Ran} \cdot \text{GTP}]_{\text{nuc}} = -F_{\text{Ran} \cdot \text{GTP}} + r_4[\text{IntA}] - r_5[\text{E}][\text{Ran} \cdot \text{GTP}]_{\text{nuc}} - \text{Ex} \quad (15b)$$

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.

$$\frac{d}{dt}[\text{IntA}] = -(r_4 + r_6)[\text{IntA}] + r_5[\text{E}][\text{Ran} \cdot \text{GTP}]_{\text{nuc}} + r_3[\text{GTP}][\text{IntB}] \quad (16a)$$

$$\frac{d}{dt}[\text{IntB}] = r_6[\text{IntA}] + r_2[\text{IntC}] - (r_3[\text{GTP}] + r_7[\text{GDP}])[\text{IntB}] \quad (16b)$$

$$\frac{d}{dt}[\text{IntC}] = -(r_2 + r_8)[\text{IntC}] + r_1[\text{E}][\text{Ran} \cdot \text{GDP}]_{\text{nuc}} + r_7[\text{GDP}][\text{IntB}] \quad (16c)$$

Constraints on the total concentration:

$$\text{Free RCC1 :} \quad [\text{E}] = \text{RCC1}_{\text{total}} - ([\text{IntA}] + [\text{IntB}] + [\text{IntC}]) \quad (17a)$$

$$\text{Free RanBP1 :} \quad [\text{RanBP1}] = \text{RanBP1}_{\text{total}} - [\text{RanBP1} \cdot \text{Ran} \cdot \text{GTP}] \quad (17b)$$

Gradient-driven fluxes from the nucleus to the cytoplasm:

$$F_{\text{Ran} \cdot \text{GTP}} = D_{\text{Ran} \cdot \text{GTP}} ([\text{Ran} \cdot \text{GTP}]_{\text{nuc}} - [\text{Ran} \cdot \text{GTP}]_{\text{cyt}}) \quad (18a)$$

$$F_{\text{Ran} \cdot \text{GDP}} = D_{\text{Ran} \cdot \text{GDP}} ([\text{Ran} \cdot \text{GDP}]_{\text{nuc}} - [\text{Ran} \cdot \text{GDP}]_{\text{cyt}}) \quad (18b)$$

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].

$$\text{GAP} = k_{\text{GAP}}[\text{RanGAP}]/(1 + K_{\text{GAP}}/[\text{Ran} \cdot \text{GTP}]_{\text{cyt}}) \quad (19a)$$

$$\text{GAP}_{\text{RanBP1}} = k'_{\text{GAP}}[\text{RanGAP}]/(1 + K'_{\text{GAP}}/[\text{RanBP1} \cdot \text{Ran} \cdot \text{GTP}]) \quad (19b)$$

To determine the dynamic capacity Ex at steady-state we introduce the additional equation:

$$\frac{d}{dt}\text{Ex} = k_{\text{Ex}}[\text{Ran} \cdot \text{GTP}]_{\text{nuc}}, \quad k_{\text{Ex}} := 10 \text{ s}^{-2}, \quad \text{initial} \quad \text{Ex} := 0 \text{ } \mu\text{M s}^{-1}. \quad (20)$$

(14a)	$V_{\text{nuc}} = 1.2 \text{ pl}, \quad V_{\text{cyt}} = 1.8 \text{ pl}$	[GSR03, Table II]
(14a)	initial condition $[\text{Ran} \cdot \text{GDP}]_{\text{cyt}} = 5 \mu\text{M}$	[GSR03, Table II]
(14b)–(14c)	$k_{\text{on}}^{\text{rbp}} = 0.3 \mu\text{M}^{-1} \text{ s}^{-1}, \quad k_{\text{off}}^{\text{rbp}} = 4 \times 10^{-4} \text{ s}^{-1}$	[GSR03, Supp. Table A]
(15a)–(16c)	$r_1 = 74 \mu\text{M}^{-1} \text{ s}^{-1}, \quad r_8 = 55 \text{ s}^{-1}$ $r_7 = 11 \mu\text{M}^{-1} \text{ s}^{-1}, \quad r_2 = 21 \text{ s}^{-1}$ $r_3 = 0.6 \mu\text{M}^{-1} \text{ s}^{-1}, \quad r_6 = 19 \text{ s}^{-1}$ $r_5 = 100 \mu\text{M}^{-1} \text{ s}^{-1}, \quad r_4 = 55 \text{ s}^{-1}$	[GSR03, Supp. Table A] [Kle+95, Fig. 6]
(16a)–(16c)	$[\text{GTP}] = 500 \mu\text{M}, \quad [\text{GDP}] = 1.6 \mu\text{M}$	[GSR03, Table II]
(17a)	$\text{RCC1}_{\text{total}} = 0.7 \mu\text{M}$	[GSR03, Supp. Table B]
(17b)	$\text{RanBP1}_{\text{total}} = 2 \mu\text{M}$	[GSR03, Fig. 4]
(18a)	$D_{\text{Ran} \cdot \text{GTP}} = 0.03 \text{ s}^{-1}$	[GSR03, Table II]
(18b)	$D_{\text{Ran} \cdot \text{GDP}} = 0.12 \text{ s}^{-1}$	
(19a)	$k_{\text{GAP}} = 10.6 \text{ s}^{-1}, \quad K_{\text{GAP}} = 0.7 \mu\text{M}$	[GSR03, Supp. Table A]
(19b)	$k'_{\text{GAP}} = 10.8 \text{ s}^{-1}, \quad K'_{\text{GAP}} = 0.1 \mu\text{M}$	[GSR03, Table I]
(19a)–(19b)	cytoplasmic $[\text{RanGAP}] = 0.7 \mu\text{M}$	[GSR03, Table II / ST B]

Table 2: Constants for the “standard simulation condition” of §1.1 at 25 °C. Except for (14a), 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].

2.2 List of codes

	page	https://github.com/numpde/nct1/tree/ ...
#1	p.1	main/code/20210225-GSR/v1
#2	p.2	main/code/20210407-Rearrangement
#3	p.2	main/code/20210225-GSR/v2
#4	p.5	main/code/20210403-StickyPore

3 TODO

TODOs:

1. p.4. ref
2. p.4. ref
3. p.4. ref
4. p.4. ref
5. p.5. ref