DRAFT: NCT

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2021-04-06

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. 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. The "dynamic capacity" Ex is an optional maximal steady-state (positive) flux of nuclear $\mathsf{Ran} \cdot \mathsf{GTP}$ to cytoplasmic $\mathsf{Ran} \cdot \mathsf{GDP}$, which we determine using the additional equation (10). The fluxes are in units of concentration/time (µM/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 $\mathsf{flux} \times V_{\mathrm{nuc}}$.

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

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

With the constants from Table 5, the steady-state of the model (reached after some $10^4\,\mathrm{s}$) is reported in Fig. 1. Nuclear accumulation of free cargo is over 20-fold. Sensitivity analysis shows that, in relative terms, the final nuclear concentration of free cargo depends most strongly on k_{knockoff} (and the volume of the nucleus). Doubling k_{knockoff} almost doubles the nuclear concentration.

Code: 2a2199d/code/20210225-GSR/v2

TODO(1): ? [Cat+01] and [RM05] discuss the reaction $\mathsf{Imp}\beta \cdot \mathsf{Cargo} \rightleftharpoons \mathsf{Imp}\beta^* \cdot \mathsf{Cargo}$

1.2 NPC as compartments

It has been observed TODO(2): ref that certain transportins accumulate inside the NPCs as they bind to the FG-nups. They might potentially shuttle the cargo across the pore without leaving the pore themselves, like a conveyor belt. To account for this we propose a three-compartment model with cytoplasm, nucleus and the nuclear envelope (potentially including some perimembrane space) as the three compartments. The crux is that the nuclear envelope, having small volume, has a high concentration of NPCs. The unoccupied NPC space is called $\mathsf{NPC}_{\mathsf{vacant}}$. At the nuclear envelope we posit the reactions

$$\mathsf{Imp}\beta_i + \mathsf{NPC}_{\mathsf{vacant}} \rightleftharpoons \mathsf{Imp}\beta \cdot \mathsf{NPC} \tag{1a}$$
$$\mathsf{Cargo} \cdot \mathsf{Imp}\beta_i + \mathsf{NPC}_{\mathsf{vacant}} \rightleftharpoons \mathsf{Cargo} \cdot \mathsf{Imp}\beta \cdot \mathsf{NPC} \tag{1b}$$
$$\mathsf{Cargo}_i + \mathsf{Imp}\beta \cdot \mathsf{NPC} \rightleftharpoons \mathsf{Cargo} \cdot \mathsf{Imp}\beta \cdot \mathsf{NPC} \tag{1c}$$

where i can be "cytoplasmic" or "nuclear". This envelope compartment is in diffusive exchange with the cytoplasm (for i = cyt) and the nucleus (for i = nuc). In both, we also allow

$$\mathsf{Cargo} + \mathsf{Imp}\beta \rightleftharpoons \mathsf{Cargo} \cdot \mathsf{Imp}\beta. \tag{2}$$

For simplicity, we assume RanGTP and RanGDP are maintained at fixed concentrations and are only relevant at the envelope, where we have

$$\text{cargo knockoff:}\quad \mathsf{RanGTP}_{\mathsf{nuc}} + \mathsf{Cargo} \cdot \mathsf{Imp}\beta \cdot \mathsf{NPC} \longrightarrow \mathsf{Cargo} + \mathsf{RanGTP} \cdot \mathsf{Imp}\beta \cdot \mathsf{NPC} \tag{3a}$$
$$\text{GTP hydrolysis:}\quad \mathsf{RanGTP} \cdot \mathsf{Imp}\beta \cdot \mathsf{NPC} \longrightarrow \mathsf{RanGDP}_{\mathsf{cyt}} + \mathsf{P} + \mathsf{Imp}\beta \cdot \mathsf{NPC}. \tag{3b}$$

Under reasonable assumptions on the kinetic constants, the steady state of this model predicts some 10-fold accumulation of free cargo in the nucleus. Meanwhile, the concentration of total $\mathsf{Imp}\beta$ is roughly inversely proportional to the volume of the envelope compartment (keeping the total NPC amount constant).

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

$$\begin{aligned}
\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran} \cdot \mathsf{GDP}]_{\mathrm{cyt}} &= \mathsf{F}_{\mathsf{Ran{\cdot}GDP}} \tfrac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} + \mathsf{GAP} + \mathsf{GAP}_{\mathsf{RanBP1}} + \mathsf{Ex} \tfrac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} && \text{(4a)} \\
\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{cyt}} &= \mathsf{F}_{\mathsf{Ran{\cdot}GTP}} \tfrac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} - \mathsf{GAP} - k_{\mathrm{on}}^{\mathrm{rbp}} [\mathsf{RanBP1}][\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{cyt}} + k_{\mathrm{off}}^{\mathrm{rbp}} [\dots] && \text{(4b)} \\
\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{RanBP1} \cdot \mathsf{Ran} \cdot \mathsf{GTP}] &= -\mathsf{GAP}_{\mathsf{RanBP1}} \qquad\qquad + k_{\mathrm{on}}^{\mathrm{rbp}} [\mathsf{RanBP1}][\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{cyt}} - k_{\mathrm{off}}^{\mathrm{rbp}} [\dots] && \text{(4c)}
\end{aligned}$$

The following account for the nuclear species. Following [GSR03], E denotes free $\mathsf{RCC1}$.

$$\begin{aligned}
\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran} \cdot \mathsf{GDP}]_{\mathrm{nuc}} &= -\mathsf{F}_{\mathsf{Ran{\cdot}GDP}} + r_8[\mathsf{IntC}] - r_1[\mathsf{E}][\mathsf{Ran} \cdot \mathsf{GDP}]_{\mathrm{nuc}} && \text{(5a)} \\
\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{nuc}} &= -\mathsf{F}_{\mathsf{Ran{\cdot}GTP}} + r_4[\mathsf{IntA}] - r_5[\mathsf{E}][\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{nuc}} - \mathsf{Ex} && \text{(5b)}
\end{aligned}$$

The nucleotide-exchange reaction $\mathsf{Ran} \cdot \mathsf{GDP} + \mathsf{GTP} \rightleftharpoons \mathsf{Ran} \cdot \mathsf{GTP} + \mathsf{GDP}$ 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.

$$\begin{aligned}
\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{IntA}] &= -(r_4 + r_6)[\mathsf{IntA}] + r_5[\mathsf{E}][\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{nuc}} + r_3[\mathsf{GTP}][\mathsf{IntB}] && \text{(6a)} \\
\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{IntB}] &= r_6[\mathsf{IntA}] + r_2[\mathsf{IntC}] - (r_3[\mathsf{GTP}] + r_7[\mathsf{GDP}])[\mathsf{IntB}] && \text{(6b)} \\
\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{IntC}] &= -(r_2 + r_8)[\mathsf{IntC}] + r_1[\mathsf{E}][\mathsf{Ran} \cdot \mathsf{GDP}]_{\mathrm{nuc}} + r_7[\mathsf{GDP}][\mathsf{IntB}] && \text{(6c)}
\end{aligned}$$

Constraints on the total concentration:

$$\begin{aligned}
\text{Free } \mathsf{RCC1}: &\qquad [\mathsf{E}] = \mathsf{RCC1}_{\mathsf{total}} - ([\mathsf{IntA}] + [\mathsf{IntB}] + [\mathsf{IntC}]) && \text{(7a)} \\
\text{Free } \mathsf{RanBP1}: &\qquad [\mathsf{RanBP1}] = \mathsf{RanBP1}_{\mathsf{total}} - [\mathsf{RanBP1} \cdot \mathsf{Ran} \cdot \mathsf{GTP}] && \text{(7b)}
\end{aligned}$$

Gradient-driven fluxes from the nucleus to the cytoplasm:

$$\begin{aligned}
\mathsf{F}_{\mathsf{Ran.GTP}} &= D_{\mathsf{Ran} \cdot \mathsf{GTP}} \left([\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{nuc}} - [\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{cyt}}\right) && \text{(8a)} \\
\mathsf{F}_{\mathsf{Ran.GDP}} &= D_{\mathsf{Ran} \cdot \mathsf{GDP}} \left([\mathsf{Ran} \cdot \mathsf{GDP}]_{\mathrm{nuc}} - [\mathsf{Ran} \cdot \mathsf{GDP}]_{\mathrm{cyt}}\right) && \text{(8b)}
\end{aligned}$$

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

$$\begin{aligned}
\mathsf{GAP} &= k_{\mathsf{GAP}}[\mathsf{RanGAP}]/(1 + K_{\mathsf{GAP}}/[\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{cyt}}) && \text{(9a)} \\
\mathsf{GAP}_{\mathsf{RanBP1}} &= k'_{\mathsf{GAP}}[\mathsf{RanGAP}]/(1 + K'_{\mathsf{GAP}}/[\mathsf{RanBP1} \cdot \mathsf{Ran} \cdot \mathsf{GTP}]) && \text{(9b)}
\end{aligned}$$

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

$$\tfrac{\mathrm{d}}{\mathrm{d}t}\mathsf{Ex} = k_{\mathsf{Ex}} \, [\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{nuc}}, \quad k_{\mathsf{Ex}} := 10\,\mathrm{s}^{-2}, \quad \text{initial} \quad \mathsf{Ex} := 0\,\mu\mathrm{M}\,\mathrm{s}^{-1}. \tag{10}$$

Table 1: The minimal Ran gradient system from [GSR03, Fig. 2]. Ex is an additional potentially useful flux of nuclear $\mathsf{Ran} \cdot \mathsf{GTP}$ to cytoplasmic $\mathsf{Ran} \cdot \mathsf{GDP}$, set by default to zero.

(4a)	$V_{\text{nuc}} = 1.2\,\text{pl}, \quad V_{\text{cyt}} = 1.8\,\text{pl}$	[GSR03, Table II]
(4a)	initial condition $[\mathsf{Ran \cdot GDP}]_{\text{cyt}} = 5\,\mu\text{M}$	[GSR03, Table II]
(4b)–(4c)	$k_{\text{on}}^{\text{rbp}} = 0.3\,\mu\text{M}^{-1}\,\text{s}^{-1}, \quad k_{\text{off}}^{\text{rbp}} = 4 \times 10^{-4}\,\text{s}^{-1}$	[GSR03, Supp. Table A]
(5a)–(6c)	$r_1 = 74\,\mu\text{M}^{-1}\,\text{s}^{-1}, \quad r_8 = 55\,\text{s}^{-1}$ $r_7 = 11\,\mu\text{M}^{-1}\,\text{s}^{-1}, \quad r_2 = 21\,\text{s}^{-1}$ $r_3 = 0.6\,\mu\text{M}^{-1}\,\text{s}^{-1}, \quad r_6 = 19\,\text{s}^{-1}$ $r_5 = 100\,\mu\text{M}^{-1}\,\text{s}^{-1}, \quad r_4 = 55\,\text{s}^{-1}$	[GSR03, Supp. Table A] [Kle+95, Fig. 6]
(6a)–(6c)	$[\mathsf{GTP}] = 500\,\mu\text{M}, \quad [\mathsf{GDP}] = 1.6\,\mu\text{M}$	[GSR03, Table II]
(7a) (7b)	$\mathsf{RCC1}_{\mathsf{total}} = 0.7\,\mu\text{M}$ $\mathsf{RanBP1}_{\mathsf{total}} = 2\,\mu\text{M}$	[GSR03, Supp. Table B] [GSR03, Fig. 4]
(8a) (8b)	$D_{\mathsf{Ran \cdot GTP}} = 0.03\,\text{s}^{-1}$ $D_{\mathsf{Ran \cdot GDP}} = 0.12\,\text{s}^{-1}$	[GSR03, Table II]
(9a) (9b)	$k_{\mathsf{GAP}} = 10.6\,\text{s}^{-1}, \quad K_{\mathsf{GAP}} = 0.7\,\mu\text{M}$ $k'_{\mathsf{GAP}} = 10.8\,\text{s}^{-1}, \quad K'_{\mathsf{GAP}} = 0.1\,\mu\text{M}$	[GSR03, Supp. Table A] [GSR03, Table I]
(9a)–(9b)	cytoplasmic $[\mathsf{RanGAP}] = 0.7\,\mu\text{M}$	[GSR03, Table II / ST B]

Table 2: Constants for the "standard simulation condition" of §1.1 at 25 °C. Except for (4a), 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 2	4.26 (4.3)	7.75 (7.7)	0.59 (0.60)
Omission of RanBP1	$\mathsf{RanBP1}_{\mathsf{total}} := 0$	4.27 (4.3)	8.13 (8.1)	0.59 (0.60)
200% RCC1	$\mathsf{RCC1}_{\mathsf{total}}$	3.95 (4.0)	7.17 (7.1)	0.59 (0.60)
50% RCC1	$\mathsf{RCC1}_{\mathsf{total}}$	4.31 (4.3)	7.82 (7.7)	0.58 (0.60)
10% RCC1	$\mathsf{RCC1}_{\mathsf{total}}$	3.59 (3.6)	6.50 (6.4)	0.46 (0.48)
1% RCC1	$\mathsf{RCC1}_{\mathsf{total}}$	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	$D_{\mathsf{Ran \cdot GDP}} := 0.48\,\text{s}^{-1}$	5.12 (5.1)	9.32 (9.2)	2.18 (2.2)
No NTF2	$D_{\mathsf{Ran \cdot GDP}} := D_{\mathsf{Ran \cdot GTP}}$	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	$D_{\mathsf{Ran \cdot GTP}}$	4.91 (4.9)	4.44 (4.4)	0.59 (–)
200% permeability	$D_{\mathsf{Ran \cdot GTP}}$	3.41 (3.4)	12.4 (12.3)	0.59 (–)
400% permeability	$D_{\mathsf{Ran \cdot GTP}}$	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 $D_{\mathsf{Ran \cdot GDP}}$ is from [GSR03, Fig. 3].

The following equations comprise the handling of cargo by $\mathsf{Imp}\beta$ in the cytoplasm.

$$
\begin{align}
\mathsf{R}_{\mathsf{cyt}} &:= -k_{\mathrm{on}}^{\mathrm{R}}[\mathsf{Imp}\beta][\mathsf{Ran}\cdot\mathsf{GTP}]_{\mathrm{cyt}} + k_{\mathrm{off}}^{\mathrm{R}}[\mathsf{Imp}\beta\cdot\ \mathsf{Ran}\cdot\mathsf{GTP}]_{\mathrm{cyt}} \tag{11a}\\
\mathsf{C}_{\mathsf{cyt}} &:= -k_{\mathrm{on}}^{\mathrm{C}}[\mathsf{Imp}\beta][\mathsf{Cargo}]_{\mathrm{cyt}} + k_{\mathrm{off}}^{\mathrm{C}}[\mathsf{Imp}\beta\cdot\ \mathsf{Cargo}]_{\mathrm{cyt}} \tag{11b}\\
\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Imp}\beta\cdot\ \mathsf{Ran}\cdot\mathsf{GTP}]_{\mathrm{cyt}} &= -\mathsf{R}_{\mathsf{cyt}} + \mathsf{F}_{\mathsf{Imp}\beta\cdot\mathsf{Ran}\cdot\mathsf{GTP}}\tfrac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} - \mathsf{GAP}_{\mathsf{Imp}\beta} + \mathsf{Knockoff}_{\mathsf{cyt}} \tag{11c}\\
\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Imp}\beta]_{\mathrm{cyt}} &= +\mathsf{R}_{\mathsf{cyt}} + \mathsf{C}_{\mathsf{cyt}} + \mathsf{F}_{\mathsf{Imp}\beta}\tfrac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} + \mathsf{GAP}_{\mathsf{Imp}\beta} \tag{11d}\\
\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Imp}\beta\cdot\ \mathsf{Cargo}]_{\mathrm{cyt}} &= -\mathsf{C}_{\mathsf{cyt}} + \mathsf{F}_{\mathsf{Imp}\beta\cdot\mathsf{Cargo}}\tfrac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} - \mathsf{Knockoff}_{\mathsf{cyt}} \tag{11e}\\
\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Cargo}]_{\mathrm{cyt}} &= +\mathsf{C}_{\mathsf{cyt}} + \mathsf{F}_{\mathsf{Cargo}}\tfrac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} + \mathsf{Knockoff}_{\mathsf{cyt}} \tag{11f}
\end{align}
$$

The forward flux of the reaction

$$\mathsf{Imp}\beta\cdot\ \mathsf{Cargo} + \mathsf{Ran}\cdot\mathsf{GTP} \rightleftharpoons \mathsf{Imp}\beta\cdot\ \mathsf{Ran}\cdot\mathsf{GTP} + \mathsf{Cargo} \tag{12}$$

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

$$
\begin{align}
\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran}\cdot\mathsf{GDP}]_{\mathrm{cyt}} &= (4\mathrm{a}) + \mathsf{GAP}_{\mathsf{Imp}\beta} \tag{4a$'$}\\
\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran}\cdot\mathsf{GTP}]_{\mathrm{cyt}} &= (4\mathrm{b}) + \mathsf{R}_{\mathsf{cyt}} - \mathsf{Knockoff}_{\mathsf{cyt}} \tag{4b$'$}
\end{align}
$$

Analogous nuclear equations (without GAP) are implemented but are omitted here. Analogously to (8a)/(8b) we have the additional nuclear-to-cytoplasmic diffusion fluxes (cf. Table 5)

$$\mathsf{F}_{\mathsf{Imp}\beta\cdot\mathsf{Ran}\cdot\mathsf{GTP}},\quad \mathsf{F}_{\mathsf{Imp}\beta},\quad \mathsf{F}_{\mathsf{Imp}\beta\cdot\mathsf{Cargo}},\quad \mathsf{F}_{\mathsf{Cargo}}. \tag{13}$$

Table 4: Equations for the coupling of the minimal Ran gradient system from §1.1 to importin-mediated cargo transport.

(11a)	$k_{\mathrm{on}}^{\mathrm{R}} = 0.096\,\mu\mathrm{M}^{-1}\,\mathrm{s}^{-1}$, $k_{\mathrm{off}}^{\mathrm{R}} = 4.8\times10^{-6}\,\mathrm{s}^{-1}$	[GSR03, Supp. Table A], [RM05, Table II]
(11b)	$k_{\mathrm{on}}^{\mathrm{C}} = 0.49\,\mu\mathrm{M}^{-1}\,\mathrm{s}^{-1}$, $k_{\mathrm{off}}^{\mathrm{C}} = 0.017\,\mathrm{s}^{-1}$	[Cat+01, below Fig. 3], [RM05, Table II]
(12)	$k_{\mathrm{knockoff}} = 2\times10^{-2}\,\mu\mathrm{M}^{-1}\mathrm{s}^{-1}$	[RM05, Table II]
(13)	$D_{\mathsf{Imp}\beta\,\cdot\,\mathsf{Ran}\,\cdot\,\mathsf{GTP}} = 0.07\,\mathrm{s}^{-1}$, $D_{\mathsf{Imp}\beta} = 0.4\,\mathrm{s}^{-1}$ $D_{\mathsf{Imp}\beta\,\cdot\,\mathsf{Cargo}} = 0.25\,\mathrm{s}^{-1}$, $D_{\mathsf{Cargo}} = 5\times10^{-4}\,\mathrm{s}^{-1}$	[RM05, Table III]

Table 5: Constants for the $\mathsf{Imp}\beta$-mediated transport from §1.1 / Table 4.

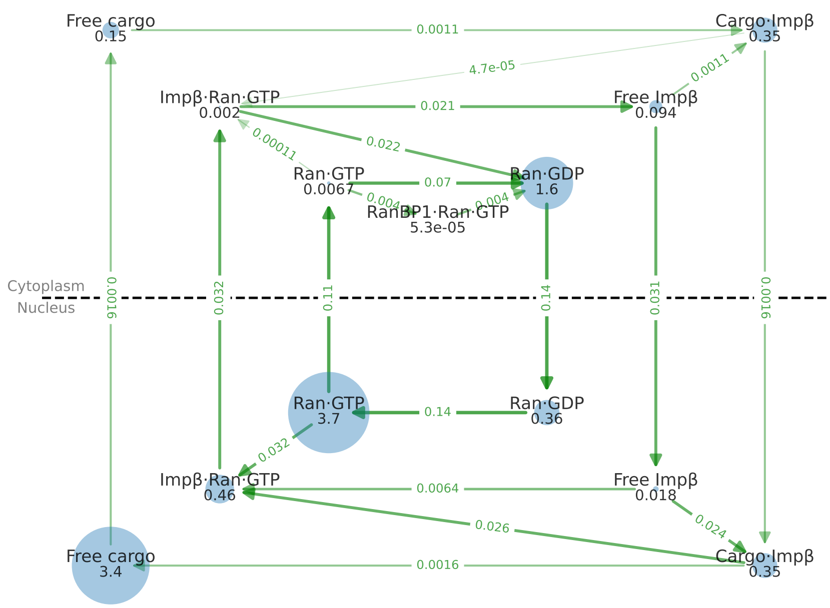

Figure 1: Steady-state of the transport system from §1.1 / Table 4 with conditions of Table 5. The free cargo shows a 20-fold accumulation in the nucleus. Units are µM for species and $\mu\mathrm{M}\,\mathrm{s}^{-1}$ for fluxes. Initial conditions: $[\mathsf{Ran} \cdot \mathsf{GDP}]_{\mathrm{cyt}} = 5\,\mu\mathrm{M}$, $[\mathsf{Imp}\beta]_{\mathrm{cyt}} = 1\,\mu\mathrm{M}$, $[\mathsf{Cargo}]_{\mathrm{cyt}} = 3\,\mu\mathrm{M}$, all else zero.

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. 3).

[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. 3, 4).

[Cat+01] B. Catimel, T. Teh, M. R. Fontes, I. G. Jennings, D. A. Jans, G. J. Howlett, E. C. Nice, and B. Kobe. “Biophysical Characterization of Interactions Involving Importin-α during Nuclear Import”. In: *Journal of Biological Chemistry* 276.36 (Sept. 2001), pp. 34189–34198. DOI: 10.1074/jbc.m103531200 (cit. on pp. 1, 5, 7).

[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, 3–5).

[RM05] G. Riddick and I. G. Macara. “A systems analysis of importin-α–β mediated nuclear protein import”. In: *Journal of Cell Biology* 168.7 (Mar. 2005), pp. 1027–1038. DOI: 10.1083/jcb.200409024 (cit. on pp. 1, 5, 7).

TODOs:

1. p.1. ? [Cat+01] and [RM05] discuss the reaction $\mathsf{Imp}\beta \cdot \mathsf{Cargo} \rightleftharpoons \mathsf{Imp}\beta^* \cdot \mathsf{Cargo}$
2. p.2. ref

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