DRAFT: NCT

RA

2021-04-07

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 (12). 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.

Code: d56d16f/code/20210225-GSR/v1

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.

SPR experiments of [Cat+01] indicated that the N-terminal IBB domain of importin-α (TODO(1): fused to ?) binds importin-β followed by a conformational change, $\mathsf{A}+\mathsf{B}\rightleftharpoons\mathsf{AB}\rightleftharpoons\mathsf{AB}^{\mathsf{*}}$. Thus, in our case we expect

$$\mathsf{Imp}\beta+\mathsf{Cargo}\underset{\mathsf{k}_{d1}}{\overset{\mathsf{k}_{a1}}{\rightleftharpoons}}\mathsf{Imp}\beta\cdot\mathsf{Cargo}\underset{\mathsf{k}_{d2}}{\overset{\mathsf{k}_{a2}}{\rightleftharpoons}}\mathsf{Imp}\beta^{*}\cdot\mathsf{Cargo}. \tag{1}$$

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

$$k_{a1}=0.11\,\mu\mathrm{M}^{-1}\,\mathrm{s}^{-1},\quad k_{d1}=0.024\,\mathrm{s}^{-1},\qquad k_{a2}=0.024\,\mathrm{s}^{-1},\quad k_{d2}=7.4\times10^{-4}\,\mathrm{s}^{-1}, \tag{2}$$

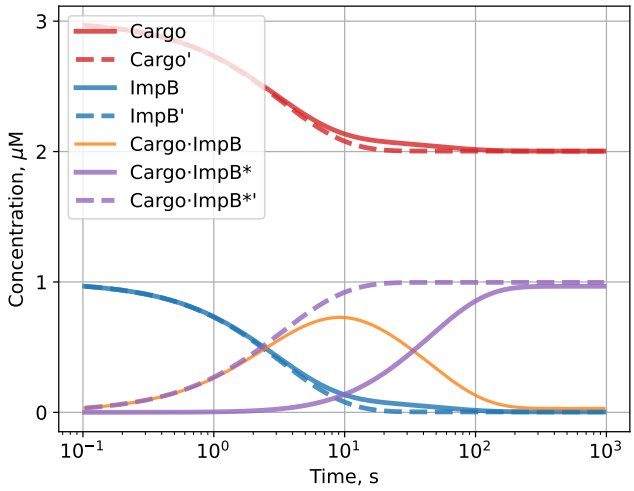

Figure 1: Stand-alone simulation of (1) starting with 3 µM Impβ and 1 µM Cargo with the constants (2). The dashed counterpart is the effective system of the form $\mathsf{A} + \mathsf{B} \rightleftharpoons \mathsf{AB}^*$, cf. §1.1. Code: here

TODO(2): code ref

for Impβ binding to the IBB domain (see [Cat+01]). The intermediate state in (1) is transient on a moderately relevant time-scale, see Fig. 1. Therefore, in the present model we ignore the second reaction and take $k_{\text{on}}^{\text{C}} := k_{a1}$ and $k_{\text{off}}^{\text{C}} := \frac{k_{d1}}{k_{a2}} k_{d2}$ as the effective kinetic constants for (13b), cf. Table 5.

With the constants from Table 5, 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} (and the volume of the nucleus). Doubling k_{knockoff} almost doubles the nuclear concentration.

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1.2 NPC as compartments

It has been observed TODO(3): ref that certain transportins accumulate inside the NPCs as they bind to the FG-nups. They might shuttle the cargo across the pore without leaving the pore themselves. 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

$$\mathsf{Imp}\beta_i + \mathsf{NPC}_{\mathsf{vacant}} \rightleftharpoons \mathsf{Imp}\beta \cdot \mathsf{NPC} \tag{3a}$$

$$\mathsf{Cargo} \cdot \mathsf{Imp}\beta_i + \mathsf{NPC}_{\mathsf{vacant}} \rightleftharpoons \mathsf{Cargo} \cdot \mathsf{Imp}\beta \cdot \mathsf{NPC} \tag{3b}$$

$$\mathsf{Cargo}_i + \mathsf{Imp}\beta \cdot \mathsf{NPC} \rightleftharpoons \mathsf{Cargo} \cdot \mathsf{Imp}\beta \cdot \mathsf{NPC} \tag{3c}$$

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

$$\mathsf{Cargo} + \mathsf{Imp}\beta \rightleftharpoons \mathsf{Cargo} \cdot \mathsf{Imp}\beta. \tag{4}$$

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

$$\text{cargo knockoff:} \quad \mathsf{RanGTP}_{\mathsf{nuc}} + \mathsf{Cargo} \cdot \mathsf{Imp}\beta \cdot \mathsf{NPC} \longrightarrow \mathsf{Cargo} + \mathsf{RanGTP} \cdot \mathsf{Imp}\beta \cdot \mathsf{NPC} \tag{5a}$$

$$\text{GTP hydrolysis:} \quad \mathsf{RanGTP} \cdot \mathsf{Imp}\beta \cdot \mathsf{NPC} \longrightarrow \mathsf{RanGDP}_{\mathsf{cyt}} + \mathsf{P} + \mathsf{Imp}\beta \cdot \mathsf{NPC}. \tag{5b}$$

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 Impβ is roughly inversely proportional to the volume of the envelope compartment (keeping the total NPC amount constant).

Code: here

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

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran} \cdot \mathsf{GDP}]_{\mathrm{cyt}} = \mathsf{F}_{\mathsf{Ran} \cdot \mathsf{GDP}} \frac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} + \mathsf{GAP} + \mathsf{GAP}_{\mathsf{RanBP1}} + \mathsf{Ex} \frac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} \tag{6a}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{cyt}} = \mathsf{F}_{\mathsf{Ran} \cdot \mathsf{GTP}} \frac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} - \mathsf{GAP} - k_{\mathrm{on}}^{\mathrm{rbp}}[\mathsf{RanBP1}][\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{cyt}} + k_{\mathrm{off}}^{\mathrm{rbp}}[\dots] \tag{6b}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{RanBP1} \cdot \mathsf{Ran} \cdot \mathsf{GTP}] = -\mathsf{GAP}_{\mathsf{RanBP1}} + k_{\mathrm{on}}^{\mathrm{rbp}}[\mathsf{RanBP1}][\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{cyt}} - k_{\mathrm{off}}^{\mathrm{rbp}}[\dots] \tag{6c}$$

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

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran} \cdot \mathsf{GDP}]_{\mathrm{nuc}} = -\mathsf{F}_{\mathsf{Ran} \cdot \mathsf{GDP}} + r_8[\mathsf{IntC}] - r_1[\mathsf{E}][\mathsf{Ran} \cdot \mathsf{GDP}]_{\mathrm{nuc}} \tag{7a}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{nuc}} = -\mathsf{F}_{\mathsf{Ran} \cdot \mathsf{GTP}} + r_4[\mathsf{IntA}] - r_5[\mathsf{E}][\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{nuc}} - \mathsf{Ex} \tag{7b}$$

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

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{IntA}] = -(r_4 + r_6)[\mathsf{IntA}] + r_5[\mathsf{E}][\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{nuc}} + r_3[\mathsf{GTP}][\mathsf{IntB}] \tag{8a}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{IntB}] = r_6[\mathsf{IntA}] + r_2[\mathsf{IntC}] - (r_3[\mathsf{GTP}] + r_7[\mathsf{GDP}])[\mathsf{IntB}] \tag{8b}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}[\mathsf{IntC}] = -(r_2 + r_8)[\mathsf{IntC}] + r_1[\mathsf{E}][\mathsf{Ran} \cdot \mathsf{GDP}]_{\mathrm{nuc}} + r_7[\mathsf{GDP}][\mathsf{IntB}] \tag{8c}$$

Constraints on the total concentration:

$$\text{Free RCC1}: \qquad [\mathsf{E}] = \mathsf{RCC1}_{\mathsf{total}} - ([\mathsf{IntA}] + [\mathsf{IntB}] + [\mathsf{IntC}]) \tag{9a}$$

$$\text{Free RanBP1}: \qquad [\mathsf{RanBP1}] = \mathsf{RanBP1}_{\mathsf{total}} - [\mathsf{RanBP1} \cdot \mathsf{Ran} \cdot \mathsf{GTP}] \tag{9b}$$

Gradient-driven fluxes from the nucleus to the cytoplasm:

$$\mathsf{F}_{\mathsf{Ran.GTP}} = D_{\mathsf{Ran} \cdot \mathsf{GTP}} \left([\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{nuc}} - [\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{cyt}}\right) \tag{10a}$$

$$\mathsf{F}_{\mathsf{Ran.GDP}} = D_{\mathsf{Ran} \cdot \mathsf{GDP}} \left([\mathsf{Ran} \cdot \mathsf{GDP}]_{\mathrm{nuc}} - [\mathsf{Ran} \cdot \mathsf{GDP}]_{\mathrm{cyt}}\right) \tag{10b}$$

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

$$\mathsf{GAP} = k_{\mathsf{GAP}}[\mathsf{RanGAP}]/(1 + K_{\mathsf{GAP}}/[\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{cyt}}) \tag{11a}$$

$$\mathsf{GAP}_{\mathsf{RanBP1}} = k'_{\mathsf{GAP}}[\mathsf{RanGAP}]/(1 + K'_{\mathsf{GAP}}/[\mathsf{RanBP1} \cdot \mathsf{Ran} \cdot \mathsf{GTP}]) \tag{11b}$$

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathsf{Ex} = k_{\mathsf{Ex}}\,[\mathsf{Ran} \cdot \mathsf{GTP}]_{\mathrm{nuc}}, \quad k_{\mathsf{Ex}} := 10\,\mathrm{s}^{-2}, \quad \text{initial} \quad \mathsf{Ex} := 0\,\mu\mathrm{M}\,\mathrm{s}^{-1}. \tag{12}$$

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.

(6a)	$V_{\text{nuc}} = 1.2\,\text{pl}, \quad V_{\text{cyt}} = 1.8\,\text{pl}$	[GSR03, Table II]
(6a)	initial condition $[\mathsf{Ran}\cdot\mathsf{GDP}]_{\text{cyt}} = 5\,\mu\text{M}$	[GSR03, Table II]
(6b)–(6c)	$k_{\text{on}}^{\text{rbp}} = 0.3\,\mu\text{M}^{-1}\,\text{s}^{-1}, \quad k_{\text{off}}^{\text{rbp}} = 4\times10^{-4}\,\text{s}^{-1}$	[GSR03, Supp. Table A]
(7a)–(8c)	$r_1 = 74\,\mu\text{M}^{-1}\,\text{s}^{-1}, \quad r_8 = 55\,\text{s}^{-1}$ $r_7 = 11\,\mu\text{M}^{-1}\,\text{s}^{-1}, \quad r_2 = 21\,\text{s}^{-1}$ $r_3 = 0.6\,\mu\text{M}^{-1}\,\text{s}^{-1}, \quad r_6 = 19\,\text{s}^{-1}$ $r_5 = 100\,\mu\text{M}^{-1}\,\text{s}^{-1}, \quad r_4 = 55\,\text{s}^{-1}$	[GSR03, Supp. Table A] [Kle+95, Fig. 6]
(8a)–(8c)	$[\mathsf{GTP}] = 500\,\mu\text{M}, \quad [\mathsf{GDP}] = 1.6\,\mu\text{M}$	[GSR03, Table II]
(9a)	$\mathsf{RCC1}_{\mathsf{total}} = 0.7\,\mu\text{M}$	[GSR03, Supp. Table B]
(9b)	$\mathsf{RanBP1}_{\mathsf{total}} = 2\,\mu\text{M}$	[GSR03, Fig. 4]
(10a) (10b)	$D_{\mathsf{Ran}\cdot\mathsf{GTP}} = 0.03\,\text{s}^{-1}$ $D_{\mathsf{Ran}\cdot\mathsf{GDP}} = 0.12\,\text{s}^{-1}$	[GSR03, Table II]
(11a) (11b)	$k_{\mathsf{GAP}} = 10.6\,\text{s}^{-1}, \quad K_{\mathsf{GAP}} = 0.7\,\mu\text{M}$ $k'_{\mathsf{GAP}} = 10.8\,\text{s}^{-1}, \quad K'_{\mathsf{GAP}} = 0.1\,\mu\text{M}$	[GSR03, Supp. Table A] [GSR03, Table I]
(11a)–(11b)	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 (6a), 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	$D_{\mathsf{Ran}\cdot\mathsf{GDP}} := 0.48\,\text{s}^{-1}$	5.12 (5.1)	9.32 (9.2)	2.18 (2.2)
No NTF2	$D_{\mathsf{Ran}\cdot\mathsf{GDP}} := D_{\mathsf{Ran}\cdot\mathsf{GTP}}$	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	$D_{\mathsf{Ran}\cdot\mathsf{GTP}}$	4.91 (4.9)	4.44 (4.4)	0.59 (–)
200% permeability	$D_{\mathsf{Ran}\cdot\mathsf{GTP}}$	3.41 (3.4)	12.4 (12.3)	0.59 (–)
400% permeability	$D_{\mathsf{Ran}\cdot\mathsf{GTP}}$	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 $D_{\mathsf{Ran}\cdot\mathsf{GDP}}$ is from [GSR03, Fig. 3].

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

$$\mathsf{R}_{\mathsf{cyt}} := -k^{\mathrm{R}}_{\mathrm{on}}[\mathsf{Imp}\beta][\mathsf{Ran}\cdot\mathsf{GTP}]_{\mathrm{cyt}} + k^{\mathrm{R}}_{\mathrm{off}}[\mathsf{Imp}\beta\cdot\ \mathsf{Ran}\cdot\mathsf{GTP}]_{\mathrm{cyt}} \tag{13a}$$

$$\mathsf{C}_{\mathsf{cyt}} := -k^{\mathrm{C}}_{\mathrm{on}}[\mathsf{Imp}\beta][\mathsf{Cargo}]_{\mathrm{cyt}} + k^{\mathrm{C}}_{\mathrm{off}}[\mathsf{Imp}\beta\cdot\ \mathsf{Cargo}]_{\mathrm{cyt}} \tag{13b}$$

$$\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Imp}\beta\cdot\ \mathsf{Ran}\cdot\mathsf{GTP}]_{\mathrm{cyt}} = -\mathsf{R}_{\mathsf{cyt}} + \mathsf{F}_{\mathsf{Imp}\beta\cdot\mathsf{Ran}\cdot\mathsf{GTP}}\tfrac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} - \mathsf{GAP}_{\mathsf{Imp}\beta} + \mathsf{Knockoff}_{\mathsf{cyt}} \tag{13c}$$

$$\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Imp}\beta]_{\mathrm{cyt}} = +\mathsf{R}_{\mathsf{cyt}} + \mathsf{C}_{\mathsf{cyt}} + \mathsf{F}_{\mathsf{Imp}\beta}\tfrac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} + \mathsf{GAP}_{\mathsf{Imp}\beta} \tag{13d}$$

$$\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Imp}\beta\cdot\ \mathsf{Cargo}]_{\mathrm{cyt}} = -\mathsf{C}_{\mathsf{cyt}} + \mathsf{F}_{\mathsf{Imp}\beta\cdot\mathsf{Cargo}}\tfrac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} - \mathsf{Knockoff}_{\mathsf{cyt}} \tag{13e}$$

$$\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Cargo}]_{\mathrm{cyt}} = +\mathsf{C}_{\mathsf{cyt}} + \mathsf{F}_{\mathsf{Cargo}}\tfrac{V_{\mathrm{nuc}}}{V_{\mathrm{cyt}}} + \mathsf{Knockoff}_{\mathsf{cyt}} \tag{13f}$$

The forward flux of the reaction

$$\mathsf{Imp}\beta\cdot\ \mathsf{Cargo} + \mathsf{Ran}\cdot\mathsf{GTP} \rightleftharpoons \mathsf{Imp}\beta\cdot\ \mathsf{Ran}\cdot\mathsf{GTP} + \mathsf{Cargo} \tag{14}$$

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

$$\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran}\cdot\mathsf{GDP}]_{\mathrm{cyt}} = (6\mathrm{a}) + \mathsf{GAP}_{\mathsf{Imp}\beta} \tag{6a$'$}$$

$$\tfrac{\mathrm{d}}{\mathrm{d}t}[\mathsf{Ran}\cdot\mathsf{GTP}]_{\mathrm{cyt}} = (6\mathrm{b}) + \mathsf{R}_{\mathsf{cyt}} - \mathsf{Knockoff}_{\mathsf{cyt}} \tag{6b$'$}$$

Analogous nuclear equations (without GAP) are implemented but are omitted here. Analogously to (10a)/(10b) we have the additional nuclear-to-cytoplasmic diffusion fluxes (cf. Table 5)

$$\mathsf{F}_{\mathsf{Imp}\beta\cdot\mathsf{Ran}\cdot\mathsf{GTP}},\quad \mathsf{F}_{\mathsf{Imp}\beta},\quad \mathsf{F}_{\mathsf{Imp}\beta\cdot\mathsf{Cargo}},\quad \mathsf{F}_{\mathsf{Cargo}}. \tag{15}$$

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

(13a)	$k^{\mathrm{R}}_{\mathrm{on}} = 0.096\,\mu\mathrm{M}^{-1}\,\mathrm{s}^{-1}$, $k^{\mathrm{R}}_{\mathrm{off}} = 4.8\times10^{-6}\,\mathrm{s}^{-1}$	[GSR03, Supp. Table A], [RM05, Table II]
(13b)	$k^{\mathrm{C}}_{\mathrm{on}} = 0.11\,\mu\mathrm{M}^{-1}\,\mathrm{s}^{-1}$, $k^{\mathrm{C}}_{\mathrm{off}} = 7.4\times10^{-4}\,\mathrm{s}^{-1}$	[Cat+01, Table I], [RM05, Table II]
(14)	$k_{\mathrm{knockoff}} = 2\times10^{-2}\,\mu\mathrm{M}^{-1}\mathrm{s}^{-1}$	[RM05, Table II]
(15)	$D_{\mathsf{Imp}\beta\cdot\ \mathsf{Ran}\cdot\mathsf{GTP}} = 0.07\,\mathrm{s}^{-1}$, $D_{\mathsf{Imp}\beta} = 0.4\,\mathrm{s}^{-1}$ $D_{\mathsf{Imp}\beta\cdot\ \mathsf{Cargo}} = 0.25\,\mathrm{s}^{-1}$, $D_{\mathsf{Cargo}} = 5\times10^{-4}\,\mathrm{s}^{-1}$	[RM05, Table III]

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

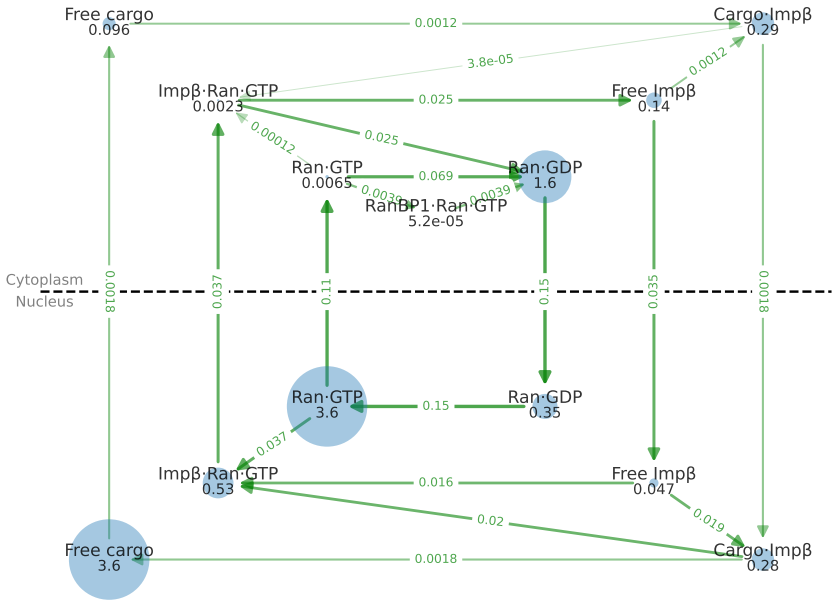

Figure 2: Steady-state of the transport system from §1.1 / Table 4 with conditions of Table 5. The free cargo shows 37-fold accumulation in the nucleus; total nuclear to total cytoplasmic cargo is 10-fold. Units are µM for species and $\mu\mathrm{M\,s^{-1}}$ for fluxes. Initial conditions: $[\mathsf{Ran}\cdot\mathsf{GDP}]_{\mathrm{cyt}} = 5\,\mu\mathrm{M}$, $[\mathsf{Imp}\beta]_{\mathrm{cyt}} = 1\,\mu\mathrm{M}$, $[\mathsf{Cargo}]_{\mathrm{cyt}} = 3\,\mu\mathrm{M}$, all else zero.

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TODOs:

1. p.1. fused to ?
2. p.2. code ref
3. p.2. ref