

DRAFT: NCT

RA

2022-01-25

1 Introduction

TODO(1): intro

We are particularly interested in the nuclear-to-cytoplasmic contrast (henceforth, N:C contrast) of certain molecular species at steady state: $\text{Ran} \cdot \text{GTP}$, $\text{Imp}\beta$, CAS, and NLS.

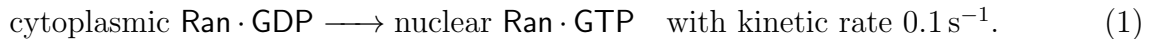
Abbreviations. FG-nups = FG-nucleoporins; NCT = nucleocytoplasmic transport; NPC = nuclear pore complex; NE = nuclear envelope; IBB = importin beta binding; ODE = ordinary differential equations; SPR = surface plasmon resonance;

2 NCT models

2.1 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. We implement it as the “minimal Ran gradient system” from [GSR03]. The equations are recapitulated in §4.1 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 (24). 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. Moreover, the dynamic capacity clocks in at around $0.6 \mu\text{M}/\text{s}$ in most cases, meaning the Ran gradient is established within seconds. Therefore, we will replace the whole Ran gradient layer by a virtual pump



This rate is chosen conservatively (a concentration of 1 μM of cytoplasmic $\text{Ran} \cdot \text{GDP}$ generates a flux of 0.1 $\mu\text{M/s}$) but will be sufficient for our purposes.

Code [#1](#).

Coupling to Imp β -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 Imp β in the cytoplasm,

$$\frac{d}{dt}[\text{Imp}\beta \cdot \text{Ran} \cdot \text{GTP}]_{\text{cyt}} = -R_{\text{cyt}} + F_{\text{Imp}\beta \cdot \text{Ran} \cdot \text{GTP}} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} - \text{GAP}_{\text{Imp}\beta} + \text{Knockoff}_{\text{cyt}} \quad (2a)$$

$$\frac{d}{dt}[\text{Imp}\beta]_{\text{cyt}} = +R_{\text{cyt}} + C_{\text{cyt}} + F_{\text{Imp}\beta} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} + \text{GAP}_{\text{Imp}\beta} \quad (2b)$$

$$\frac{d}{dt}[\text{Imp}\beta \cdot \text{Cargo}]_{\text{cyt}} = -C_{\text{cyt}} + F_{\text{Imp}\beta \cdot \text{Cargo}} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} - \text{Knockoff}_{\text{cyt}} \quad (2c)$$

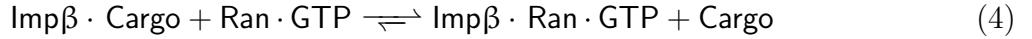
$$\frac{d}{dt}[\text{Cargo}]_{\text{cyt}} = +C_{\text{cyt}} + F_{\text{Cargo}} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} + \text{Knockoff}_{\text{cyt}} \quad (2d)$$

with the fluxes

$$R_{\text{cyt}} := -k_{\text{on}}^{\text{R}}[\text{Imp}\beta][\text{Ran} \cdot \text{GTP}]_{\text{cyt}} + k_{\text{off}}^{\text{R}}[\text{Imp}\beta \cdot \text{Ran} \cdot \text{GTP}]_{\text{cyt}} \quad (3a)$$

$$C_{\text{cyt}} := -k_{\text{on}}^{\text{C}}[\text{Imp}\beta][\text{Cargo}]_{\text{cyt}} + k_{\text{off}}^{\text{C}}[\text{Imp}\beta \cdot \text{Cargo}]_{\text{cyt}}. \quad (3b)$$

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:

$$\frac{d}{dt}[\text{Ran} \cdot \text{GDP}]_{\text{cyt}} = (18a) + \text{GAP}_{\text{Imp}\beta} \quad (18a')$$

$$\frac{d}{dt}[\text{Ran} \cdot \text{GTP}]_{\text{cyt}} = (18b) + R_{\text{cyt}} - \text{Knockoff}_{\text{cyt}} \quad (18b')$$

Analogous nuclear equations (without GAP) are implemented but are omitted here. Analogously to (22a)/(22b) we have the additional nuclear-to-cytoplasmic diffusion fluxes

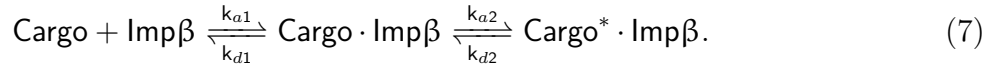
$$F_{\text{Imp}\beta \cdot \text{Ran} \cdot \text{GTP}}, \quad F_{\text{Imp}\beta}, \quad F_{\text{Imp}\beta \cdot \text{Cargo}}, \quad F_{\text{Cargo}} \quad (5)$$

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



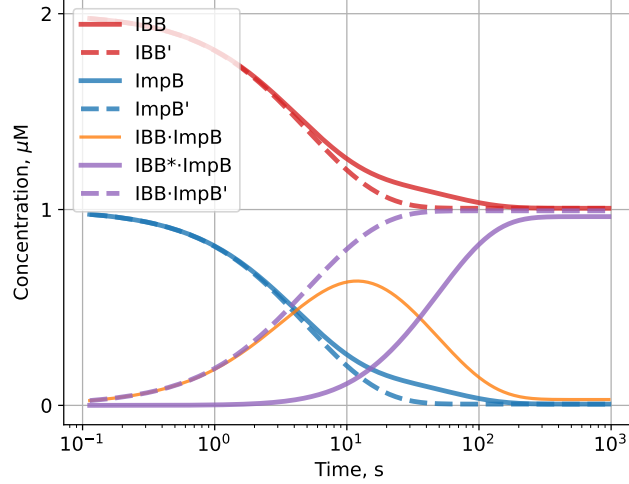


Figure 1: Stand-alone simulation of (6) starting with 2 μM IBB and 1 μM Imp β with the constants (8). The dashed counterpart is the effective system of the form $A + B \rightleftharpoons AB$, cf. §2.1.

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

Table 1: Constants for the Imp β -mediated transport from §2.1.

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

$$k_{a1} = 0.11 \mu\text{M}^{-1} \text{s}^{-1}, \quad k_{d1} = 0.024 \text{s}^{-1}, \quad k_{a2} = 0.024 \text{s}^{-1}, \quad k_{d2} = 7.4 \times 10^{-4} \text{s}^{-1}, \quad (8)$$

for an IBB domain binding to Imp β . The intermediate state in (6) 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 (3b), cf. Table 1.

With the constants from Table 1, the steady-state of the model (reached after some 10^4s) 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. We improve on it in §2.3.

2.2 Role of RanBP1

According to [LM97, Fig. 4A], Imp β blocks hydrolysis of Ran \cdot GTP by RanGAP but RanBP1 rescues it for most part. Similarly, [BG97] showed that RanBP1 transiently detaches Ran

2.3 NPC as compartment

Introduction. It has been observed [TODO\(2\): ref](#) that $\text{Imp}\beta$ accumulates inside the NPCs as they bind to the FG-nups, suggesting a regulatory role, and possibly shuttling the cargo across the pore repeatedly. To account for this we propose a model with cytoplasm, nucleus and the NPCs as three compartments. The following dual observation is essential (cf. [\[Hof20\]](#)):

1. cytoplasmic and nuclear species initially react with NPC components in proportion to the number of NPCs, and
2. the observed fluorescence signal from Kaps accumulating inside the NPCs correlates with the total volume or the capacity of the NPC channel (rather than their number).

The model includes the following main components:

- Generic NLS cargo. [TODO\(3\): on NLS](#)
- $\text{Imp}\alpha$ [TODO\(4\): on ImpA](#)
- $\text{Imp}\beta$ [TODO\(5\): on ImpB](#)
- CAS [TODO\(6\): on CAS](#)
- The NPCs are described as vacant NPC channel space, the cytoplasm-facing opening $\text{NPC}(c)$ and the nucleus-facing opening $\text{NPC}(n)$. To transition the nuclear pore, a species has to bind to the opening, transition into the channel, bind to the other opening, and unbind on the other side. This allows us to model the capacity of the NPC and the dwelling time (but we make no distinction between different transiting species). There is no directionality, i.e. a species currently residing in the channel is equally likely to bind to either opening next.
- $\text{Ran} \cdot \text{GTP}$ in the nucleus and $\text{Ran} \cdot \text{GDP}$ in the cytoplasm. The consumption of $\text{Ran} \cdot \text{GTP}$ that have transitioned to the cytoplasmic side by hydrolysis is compensated by an effective pump as in (1). The hydrolysis itself is described by one effective kinetic rate as in (9).

An overview of the model is shown in Fig. 3. The computational results for this model are summarized in Fig. 4. The code is found in Code [#5](#).

[TODO\(7\): Use a particular checkpoint throughout](#)

Main reactions. Here we comment on the main reactions of the model. For the complete set we refer to Fig. 3 as well as [TODO\(8\): Link to checkpoint on github.io](#).

The cytoplasmic NLS cargo associates with free $\text{Imp}\alpha \cdot \text{Imp}\beta$ before binding to the cytoplasmic side of the NPC, or with those already attached there. On the nuclear side, the “knockoff”

reaction releases the cargo (the suffix (n) is omitted):



TODO(9): More reactions

Baseline parameters. We estimate the total NPC channel capacity as 2000 NPCs per nuclear envelope times 300 Kaps per NPC TODO(10): refs for those numbers. Note that

$$1 \text{ pL} \times 1 \mu\text{M} \approx 300 \times 2000 \text{ units}, \quad (11)$$

which implies a concentration of 1 μM in a computational volume of 1 pL. The computation itself is performed in amounts (rather than concentration), so to convert apparent concentration of Kaps at the NE we estimate TODO(11): automate insertion of this volume

$$\text{the volume of apparent NE fluorescence as } 0.01 \text{ pL}. \quad (12)$$

TODO(12): complete section

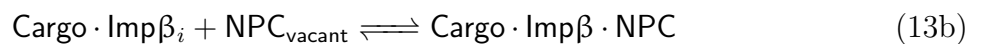
The definitive set of parameters is recorded in [TODO(13): Link to checkpoint base model].

Variants. We have defined a handful of scenarios to illustrate how parameter choice affects the steady-states. The results are shown in Fig. 4. All parameter changes are reported in [TODO(14): Link to the checkpoint parameter table].

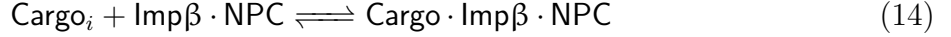
- Increase $\text{Imp}\beta$. TODO(15): Why
- Increase also the number of NPC. TODO(16): Why
- Decrease $\text{Imp}\alpha$. Starting from the baseline scenario, we decrease the initial concentration of $\text{Imp}\alpha$. In this scenario we obtain a clear N:C contrast for total CAS in the steady-state, in line with experimental evidence from [?] TODO(17): CAS contrast ref.
- Turn off $\text{Ran} \cdot \text{GTP}$ regeneration, starting from the baseline scenario. We obtain a breakdown of N:C contrast for all species, as expected.

3 Old stuff dump – ignore

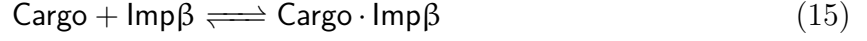
The crux is now that the nuclear envelope, having small volume, has a high concentration of NPCs. At the nuclear envelope we posit the reactions



TODO(18): 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 (23a). 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 (23a) but in view of **TODO(19): 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 [#6](#).

References

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4 Appendix

4.1 Minimal Ran gradient system

Here we recapitulate the minimal Ran gradient system from [GSR03, Fig. 2], cf. §2.1. 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.

$$\frac{d}{dt}[\text{Ran} \cdot \text{GDP}]_{\text{cyt}} = F_{\text{Ran} \cdot \text{GDP}} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} + \text{GAP} + \text{GAP}_{\text{RanBP1}} + \text{Ex} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} \quad (18a)$$

$$\frac{d}{dt}[\text{Ran} \cdot \text{GTP}]_{\text{cyt}} = F_{\text{Ran} \cdot \text{GTP}} \frac{V_{\text{nuc}}}{V_{\text{cyt}}} - \text{GAP} - k_{\text{on}}^{\text{rbp}}[\text{RanBP1}][\text{Ran} \cdot \text{GTP}]_{\text{cyt}} + k_{\text{off}}^{\text{rbp}}[\dots] \quad (18b)$$

$$\frac{d}{dt}[\text{RanBP1} \cdot \text{Ran} \cdot \text{GTP}] = -\text{GAP}_{\text{RanBP1}} + k_{\text{on}}^{\text{rbp}}[\text{RanBP1}][\text{Ran} \cdot \text{GTP}]_{\text{cyt}} - k_{\text{off}}^{\text{rbp}}[\dots] \quad (18c)$$

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

$$\frac{d}{dt}[\text{Ran} \cdot \text{GDP}]_{\text{nuc}} = -F_{\text{Ran} \cdot \text{GDP}} + r_8[\text{IntC}] - r_1[\text{E}][\text{Ran} \cdot \text{GDP}]_{\text{nuc}} \quad (19a)$$

$$\frac{d}{dt}[\text{Ran} \cdot \text{GTP}]_{\text{nuc}} = -F_{\text{Ran} \cdot \text{GTP}} + r_4[\text{IntA}] - r_5[\text{E}][\text{Ran} \cdot \text{GTP}]_{\text{nuc}} - \text{Ex} \quad (19b)$$

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.

$$\frac{d}{dt}[\text{IntA}] = -(r_4 + r_6)[\text{IntA}] + r_5[\text{E}][\text{Ran} \cdot \text{GTP}]_{\text{nuc}} + r_3[\text{GTP}][\text{IntB}] \quad (20a)$$

$$\frac{d}{dt}[\text{IntB}] = r_6[\text{IntA}] + r_2[\text{IntC}] - (r_3[\text{GTP}] + r_7[\text{GDP}])[\text{IntB}] \quad (20b)$$

$$\frac{d}{dt}[\text{IntC}] = -(r_2 + r_8)[\text{IntC}] + r_1[\text{E}][\text{Ran} \cdot \text{GDP}]_{\text{nuc}} + r_7[\text{GDP}][\text{IntB}] \quad (20c)$$

Constraints on the total concentration:

$$\text{Free RCC1 :} \quad [\text{E}] = \text{RCC1}_{\text{total}} - ([\text{IntA}] + [\text{IntB}] + [\text{IntC}]) \quad (21a)$$

$$\text{Free RanBP1 :} \quad [\text{RanBP1}] = \text{RanBP1}_{\text{total}} - [\text{RanBP1} \cdot \text{Ran} \cdot \text{GTP}] \quad (21b)$$

Gradient-driven fluxes from the nucleus to the cytoplasm:

$$F_{\text{Ran} \cdot \text{GTP}} = D_{\text{Ran} \cdot \text{GTP}} ([\text{Ran} \cdot \text{GTP}]_{\text{nuc}} - [\text{Ran} \cdot \text{GTP}]_{\text{cyt}}) \quad (22a)$$

$$F_{\text{Ran} \cdot \text{GDP}} = D_{\text{Ran} \cdot \text{GDP}} ([\text{Ran} \cdot \text{GDP}]_{\text{nuc}} - [\text{Ran} \cdot \text{GDP}]_{\text{cyt}}) \quad (22b)$$

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].

$$\text{GAP} = k_{\text{GAP}}[\text{RanGAP}]/(1 + K_{\text{GAP}}/[\text{Ran} \cdot \text{GTP}]_{\text{cyt}}) \quad (23a)$$

$$\text{GAP}_{\text{RanBP1}} = k'_{\text{GAP}}[\text{RanGAP}]/(1 + K'_{\text{GAP}}/[\text{RanBP1} \cdot \text{Ran} \cdot \text{GTP}]) \quad (23b)$$

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

$$\frac{d}{dt}\text{Ex} = k_{\text{Ex}}[\text{Ran} \cdot \text{GTP}]_{\text{nuc}}, \quad k_{\text{Ex}} := 10 \text{ s}^{-2}, \quad \text{initial} \quad \text{Ex} := 0 \text{ } \mu\text{M s}^{-1}. \quad (24)$$

(18a)	$V_{\text{nuc}} = 1.2 \text{ pl}, \quad V_{\text{cyt}} = 1.8 \text{ pl}$	[GSR03, Table II]
(18a)	initial condition $[\text{Ran} \cdot \text{GDP}]_{\text{cyt}} = 5 \mu\text{M}$	[GSR03, Table II]
(18b)–(18c)	$k_{\text{on}}^{\text{rbp}} = 0.3 \mu\text{M}^{-1} \text{ s}^{-1}, \quad k_{\text{off}}^{\text{rbp}} = 4 \times 10^{-4} \text{ s}^{-1}$	[GSR03, Supp. Table A]
(19a)–(20c)	$r_1 = 74 \mu\text{M}^{-1} \text{ s}^{-1}, \quad r_8 = 55 \text{ s}^{-1}$ $r_7 = 11 \mu\text{M}^{-1} \text{ s}^{-1}, \quad r_2 = 21 \text{ s}^{-1}$ $r_3 = 0.6 \mu\text{M}^{-1} \text{ s}^{-1}, \quad r_6 = 19 \text{ s}^{-1}$ $r_5 = 100 \mu\text{M}^{-1} \text{ s}^{-1}, \quad r_4 = 55 \text{ s}^{-1}$	[GSR03, Supp. Table A] [Kle+95, Fig. 6]
(20a)–(20c)	$[\text{GTP}] = 500 \mu\text{M}, \quad [\text{GDP}] = 1.6 \mu\text{M}$	[GSR03, Table II]
(21a)	$\text{RCC1}_{\text{total}} = 0.7 \mu\text{M}$	[GSR03, Supp. Table B]
(21b)	$\text{RanBP1}_{\text{total}} = 2 \mu\text{M}$	[GSR03, Fig. 4]
(22a)	$D_{\text{Ran} \cdot \text{GTP}} = 0.03 \text{ s}^{-1}$	[GSR03, Table II]
(22b)	$D_{\text{Ran} \cdot \text{GDP}} = 0.12 \text{ s}^{-1}$	
(23a)	$k_{\text{GAP}} = 10.6 \text{ s}^{-1}, \quad K_{\text{GAP}} = 0.7 \mu\text{M}$	[GSR03, Supp. Table A]
(23b)	$k'_{\text{GAP}} = 10.8 \text{ s}^{-1}, \quad K'_{\text{GAP}} = 0.1 \mu\text{M}$	[GSR03, Table I]
(23a)–(23b)	cytoplasmic $[\text{RanGAP}] = 0.7 \mu\text{M}$	[GSR03, Table II / ST B]

Table 2: Constants for the “standard simulation condition” of §2.1 at 25 °C. Except for (18a), 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].

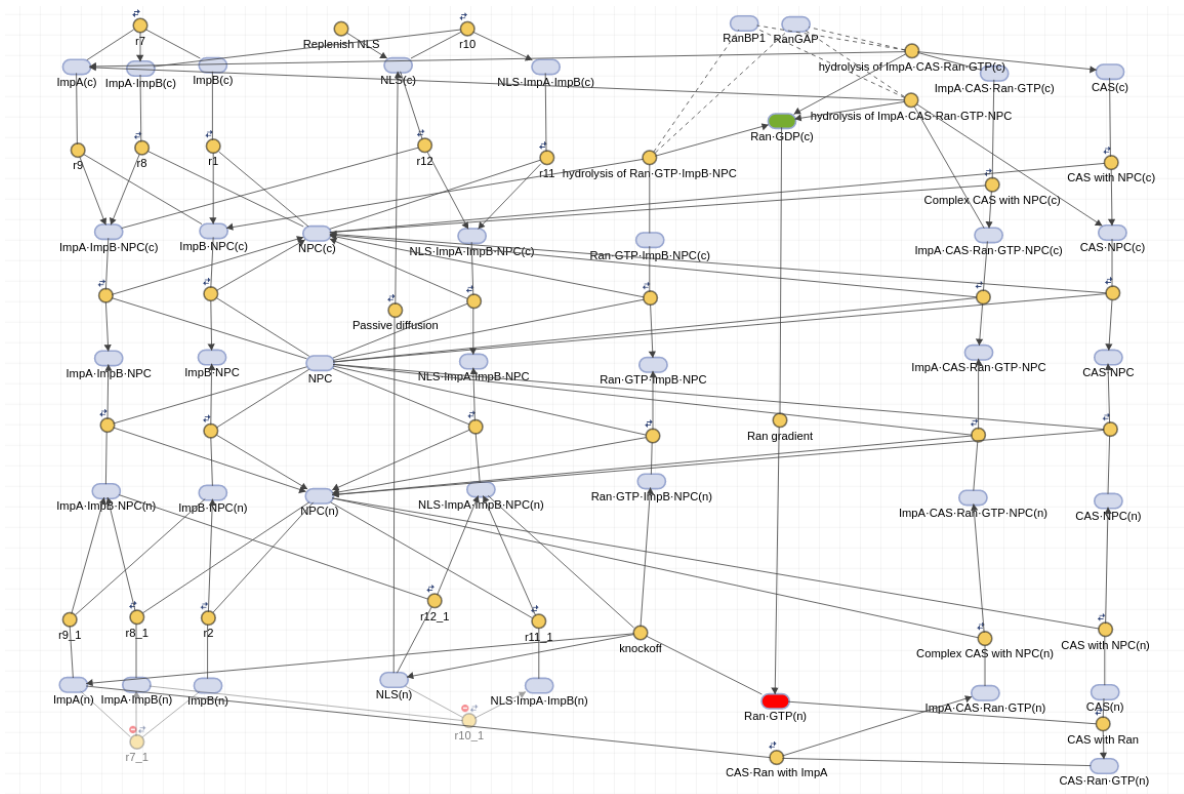


Figure 3: SimBiology diagram for the model “NPC as compartment” from §2.3.

Baseline condition (§2.3)			Low Imp α			No Ran · GTP regeneration		
Free ImpA, μ M			Free ImpA, μ M			Free ImpA, μ M		
Initial	0.5	0.5	Initial	0.1	0.1	Initial	0.5	0.5
Final	0.0362	0.432	Final	0.00162	0.000703	Final	0.441	0.509
(c)		(n)	(c)		(n)	(c)		(n)
Free ImpB, μ M			Free ImpB, μ M			Free ImpB, μ M		
Initial	0.05	0	Initial	0.05	0	Initial	0.05	0
Final	0.000876	0.00348	Final	0.0165	0.0235	Final	1.73e-06	1.61e-06
(c)		(n)	(c)		(n)	(c)		(n)
Free CAS, μ M			Free CAS, μ M			Free CAS, μ M		
Initial	1	0	Initial	1	0	Initial	1	0
Final	0.488	0.000716	Final	0.352	0.162	Final	0.488	0.488
(c)		(n)	(c)		(n)	(c)		(n)
Free NLS, μ M			Free NLS, μ M			Free NLS, μ M		
Initial	1	0	Initial	1	0	Initial	1	0
Final	0.0081	0.959	Final	0.00138	0.996	Final	0.475	0.475
(c)		(n)	(c)		(n)	(c)		(n)

TODO(20): More figures?
 TODO(21): Consider displaying in landscape

Figure 4: Initial states and steady-states for the model “NPC as compartment” from §2.3. For more full-size figures, see [TODO\(23\): Link to the full set](#)

4.2 NPC as compartment

4.3 List of codes

	page	https://github.com/numpde/nct1/tree/ ...
#1	p.2	main/code/20210225-GSR/v1
#2	p.3	main/code/20210407-Rearrangement
#3	p.3	main/code/20210225-GSR/v2
#4	p.4	main/code/20210403-StickyPore/c_rangap-sequence
#5	p.5	main/code/20211018-Appli
#6	p.7	main/code/20210403-StickyPore

5 TODO

TODOs:

1. p.1. intro
2. p.5. ref
3. p.5. on NLS
4. p.5. on ImpA
5. p.5. on ImpB
6. p.5. on CAS
7. p.5. Use a particular checkpoint throughout
8. p.5. Link to checkpoint on github.io
9. p.6. More reactions
10. p.6. refs for those numbers
11. p.6. automate insertion of this volume
12. p.6. complete section
13. p.6. Link to checkpoint base model
14. p.6. Link to the checkpoint parameter table
15. p.6. Why
16. p.6. Why
17. p.6. CAS contrast ref
18. p.7. ref

- 19. p.7. ref
- 20. p.12. More figures?
- 21. p.12. Consider displaying in landscape
- 22. p.???. Link to the full set
- 23. p.12. Link to the full set