Variability and suppression of variability in the photoresponse in the mouse rod

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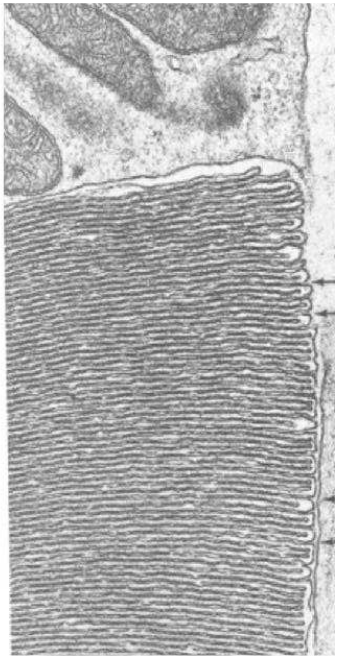
Outline

Outline

The Rod Outer Segment (ROS)



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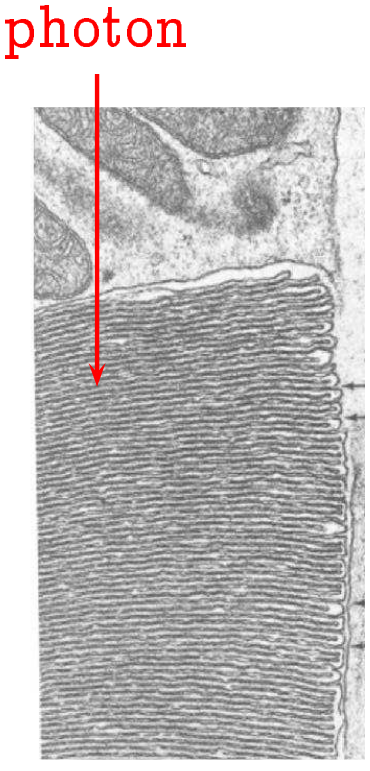

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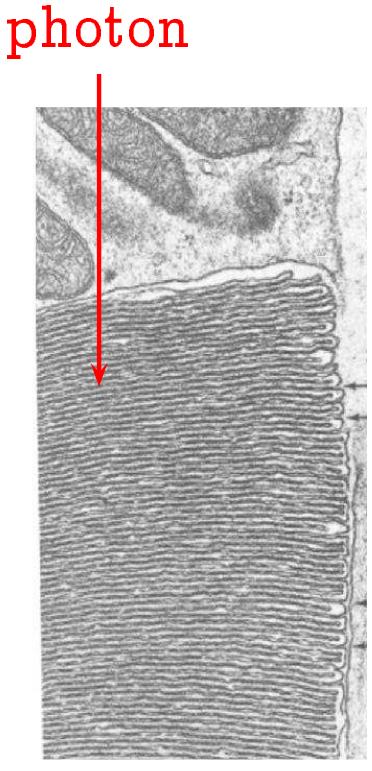

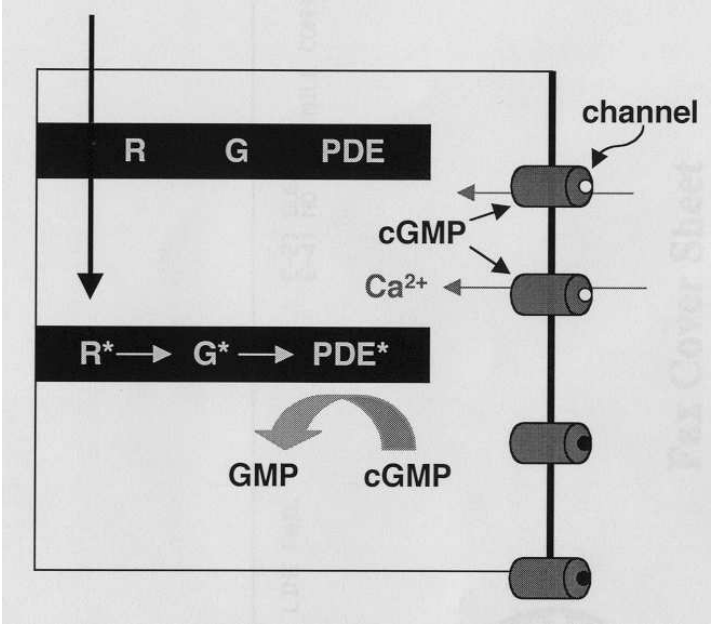

On disc: $\mathrm{R}^* \rightarrow \mathrm{G}^* \rightarrow \mathrm{PDE}^*$

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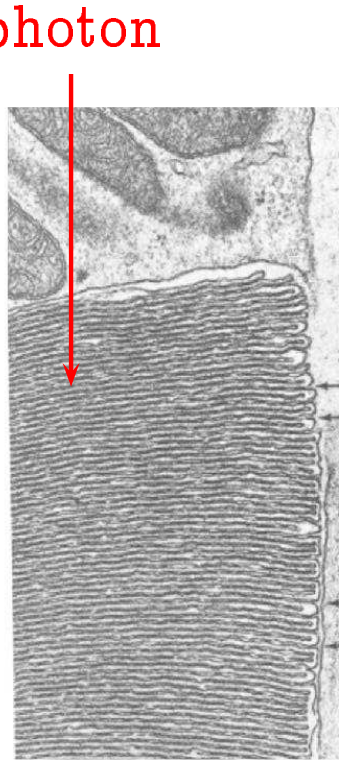

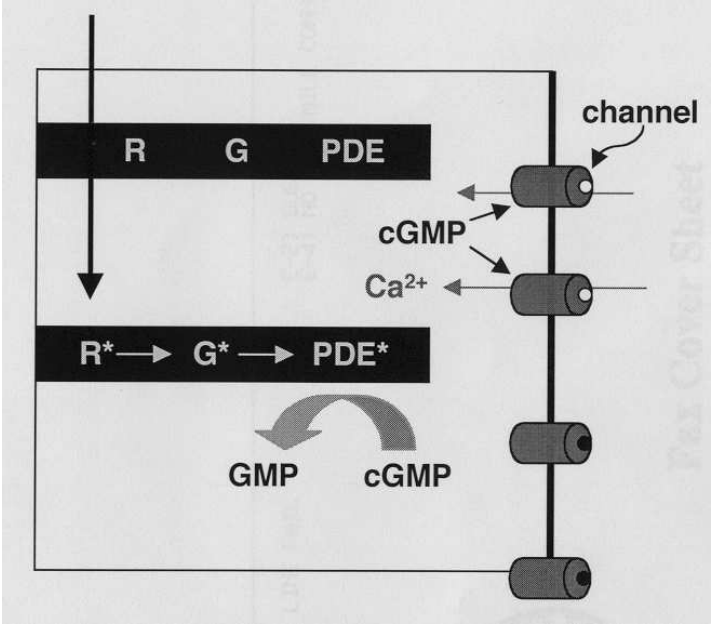

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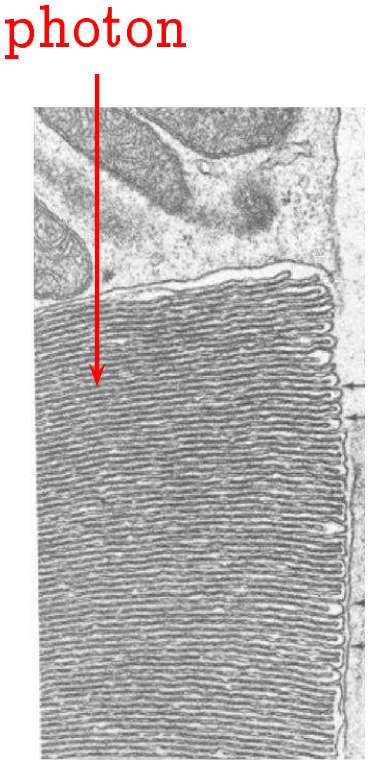

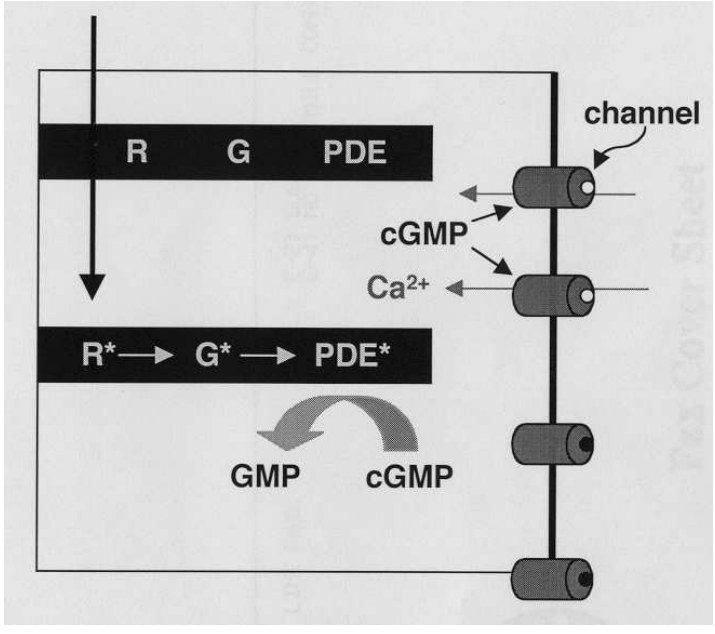

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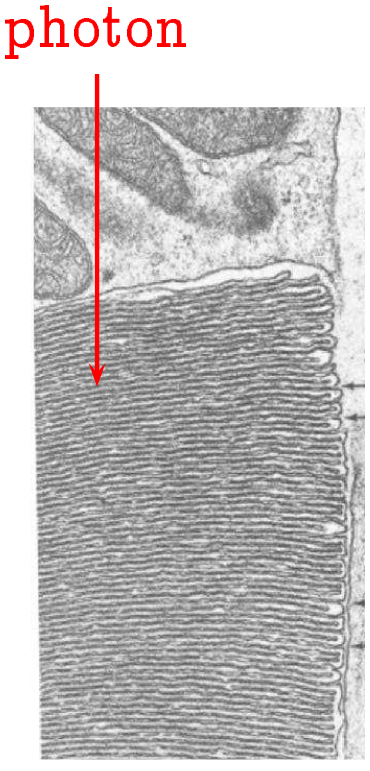
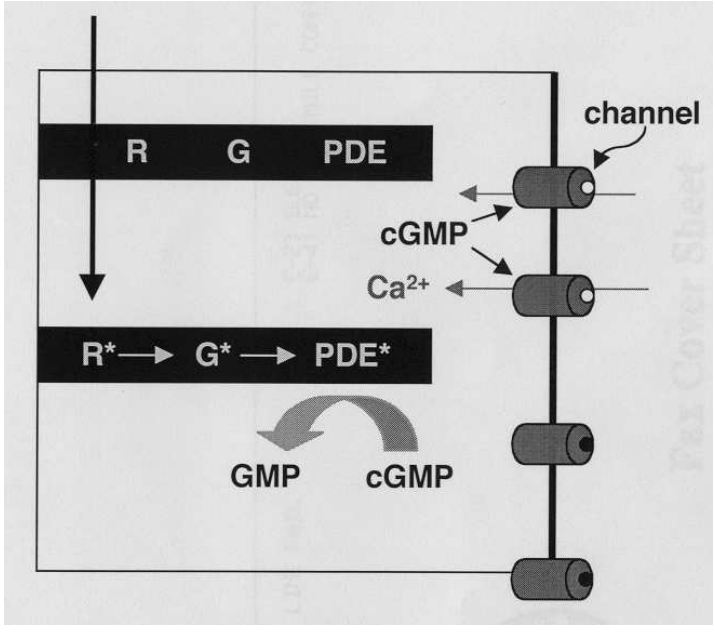
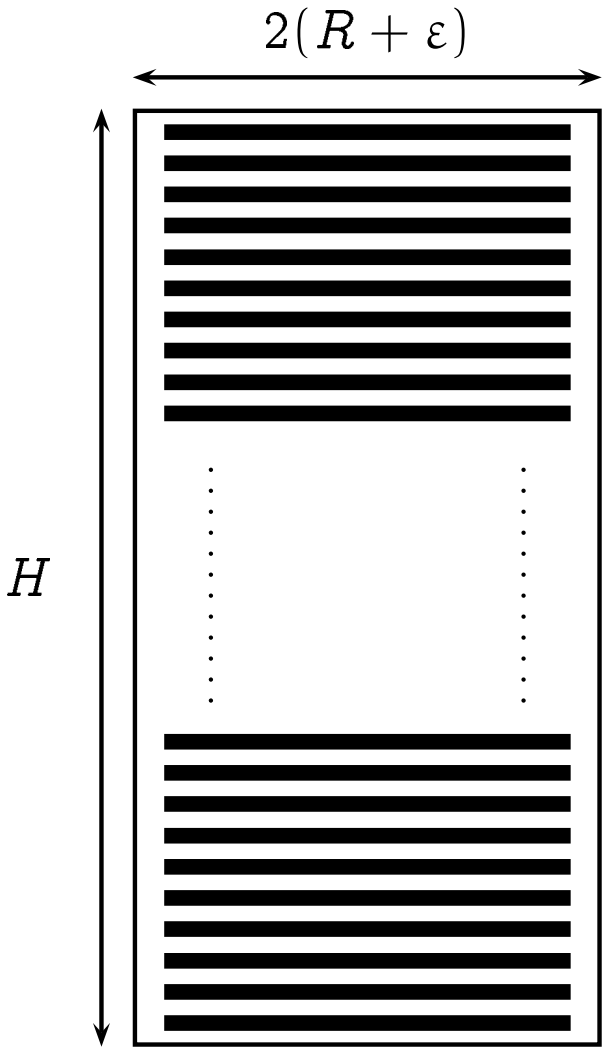




In cytosol: PDE* depletes cyclic guanosine monophosphate (cGMP) ... the lowering of concentration of cGMP causes the closure of ion channels in the cell membrane.
This unbalance in the flux of Ca^{2+} ions causes the current drop which triggers the electrical signal.

The Mouse Rod Outer Segment: Geometry



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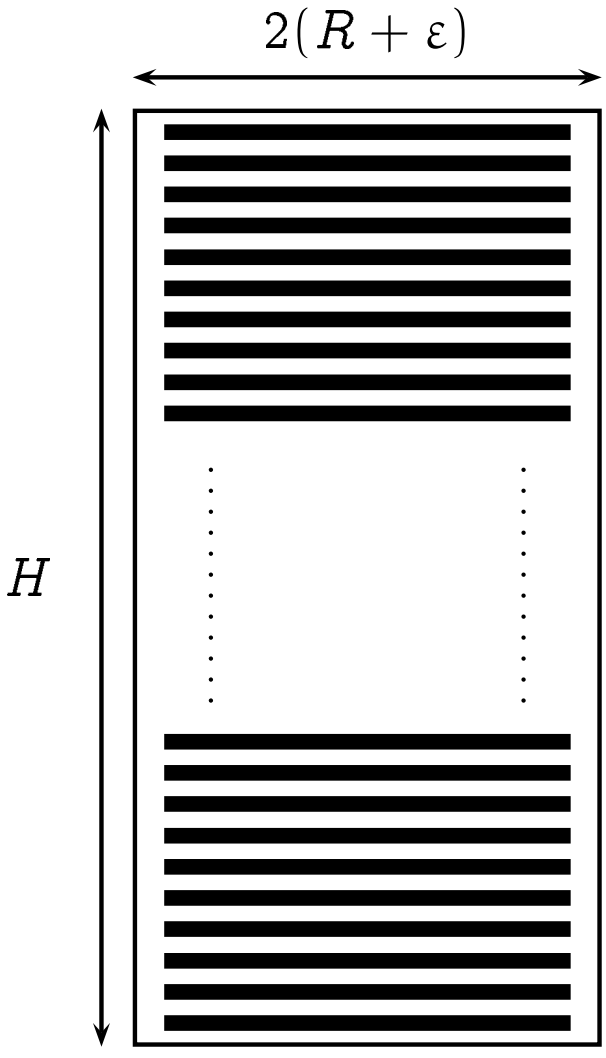

Dimensions:
$H = 23.6\mu\text{m}$, $R = 0.7\mu\text{m}$;
$\varepsilon = 0.014\mu\text{m}$ width of:

- disc;
- gap between discs;
- outer shell;

Number of discs: $n_{discs} = 800$–1000.

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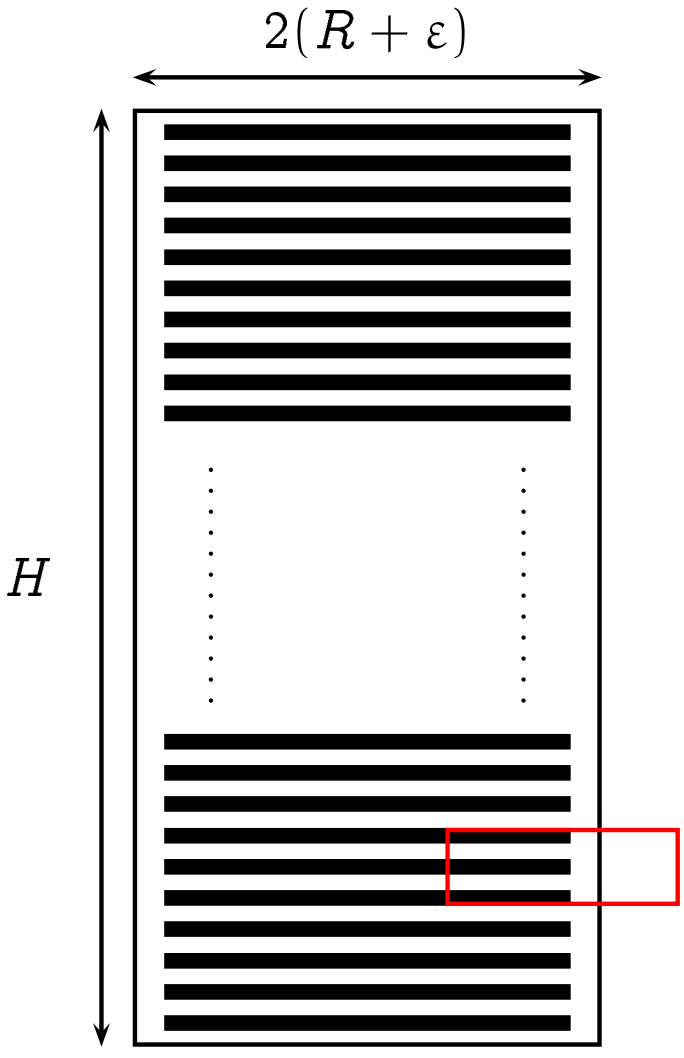

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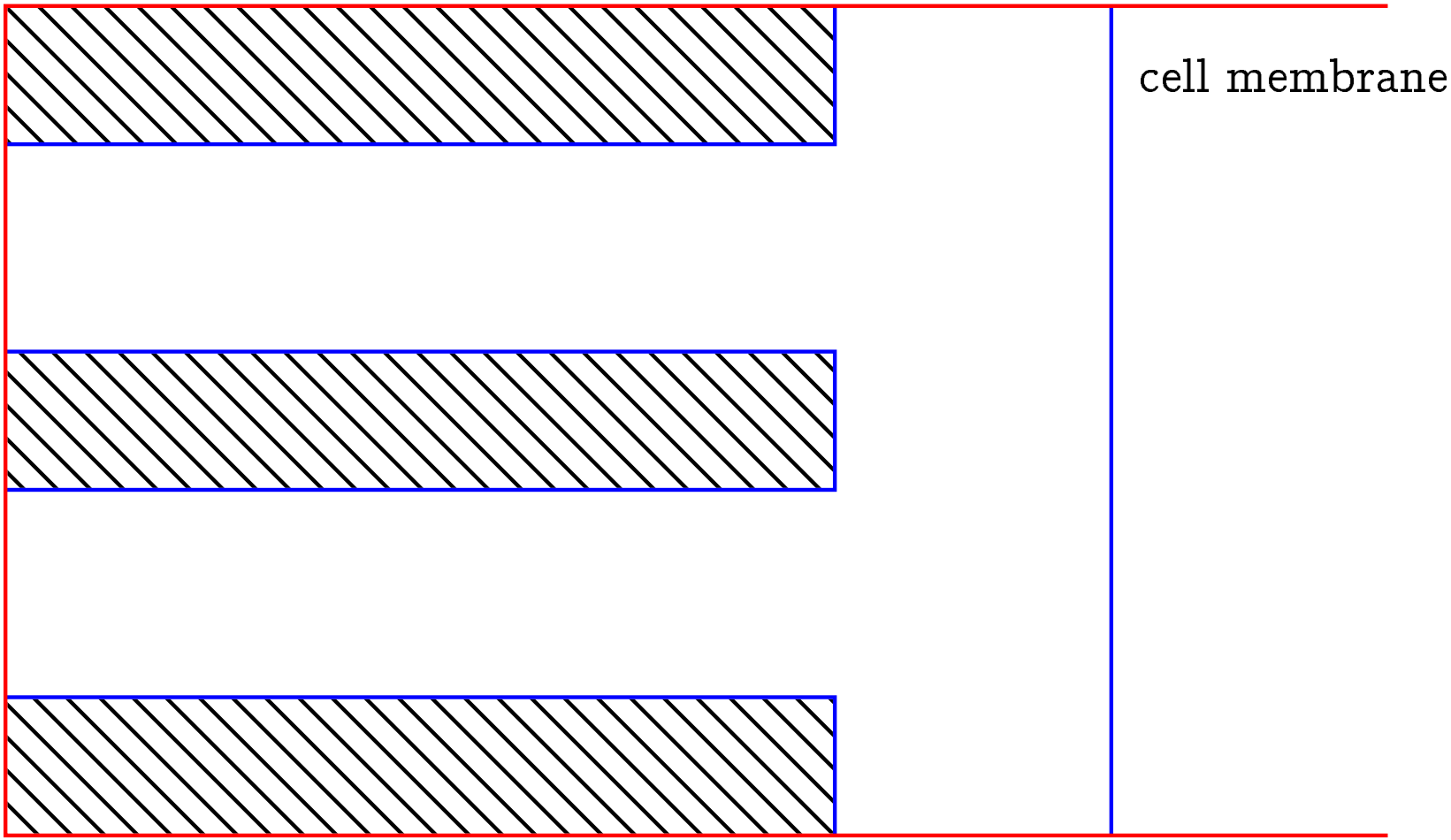

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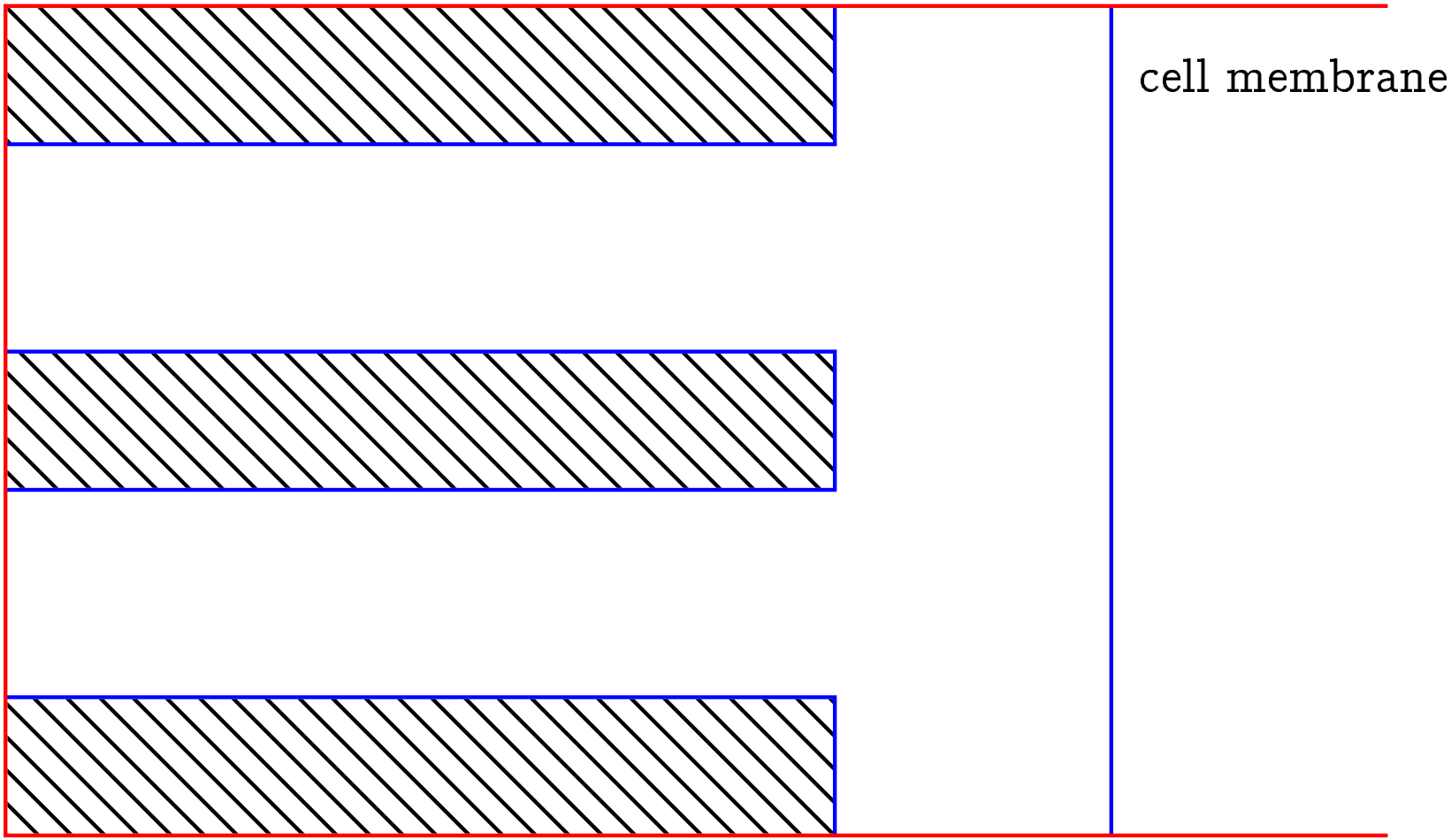

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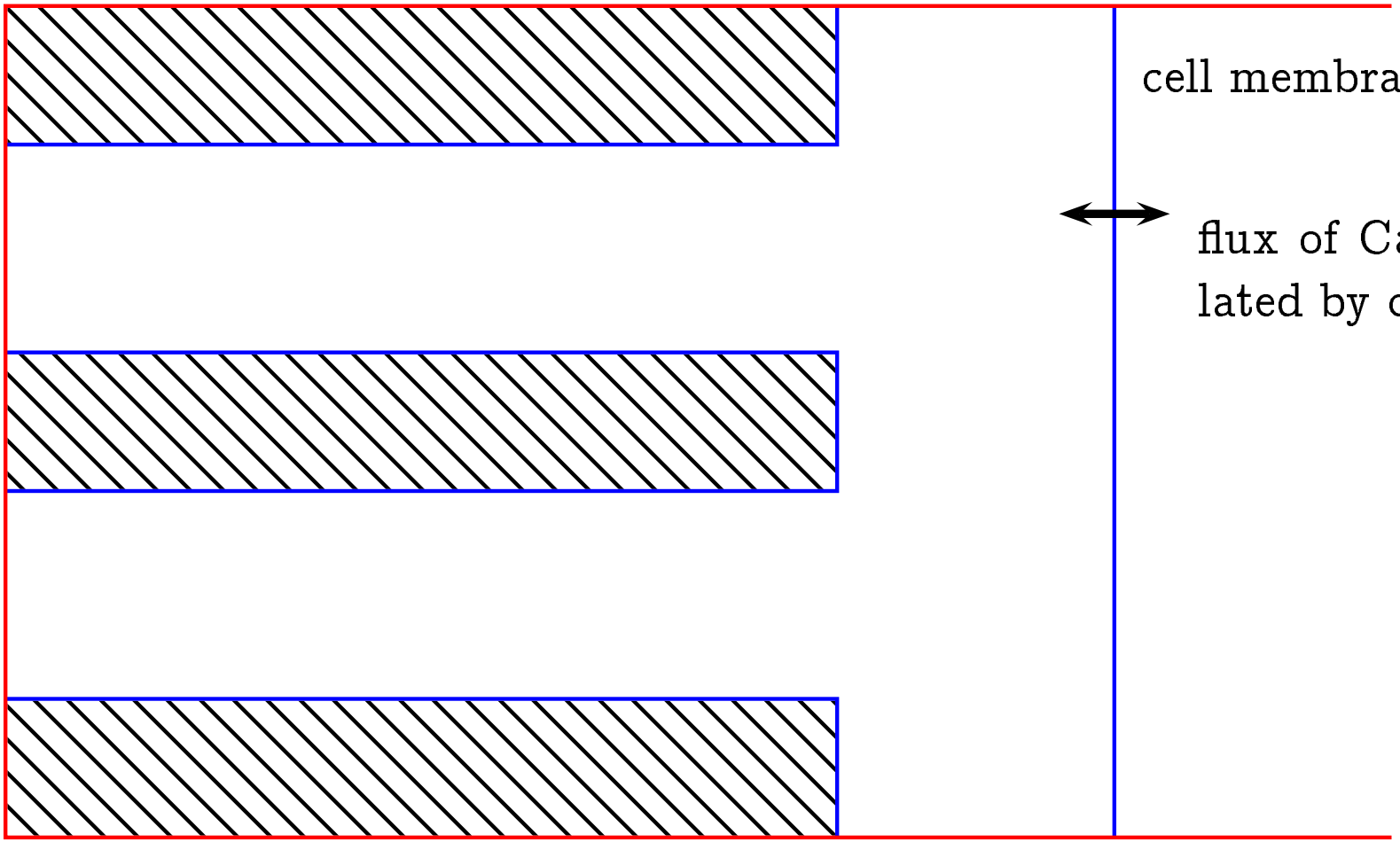

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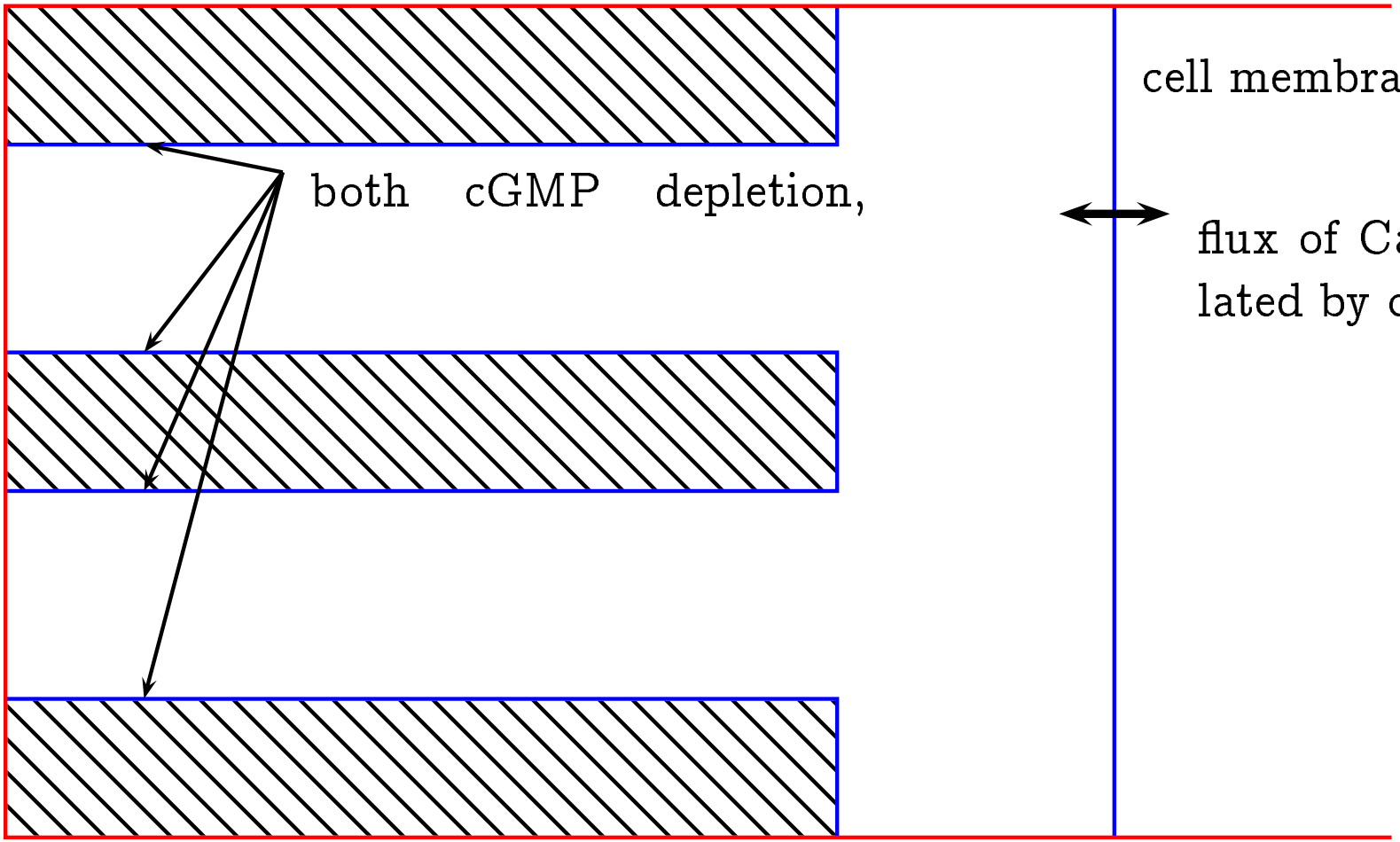

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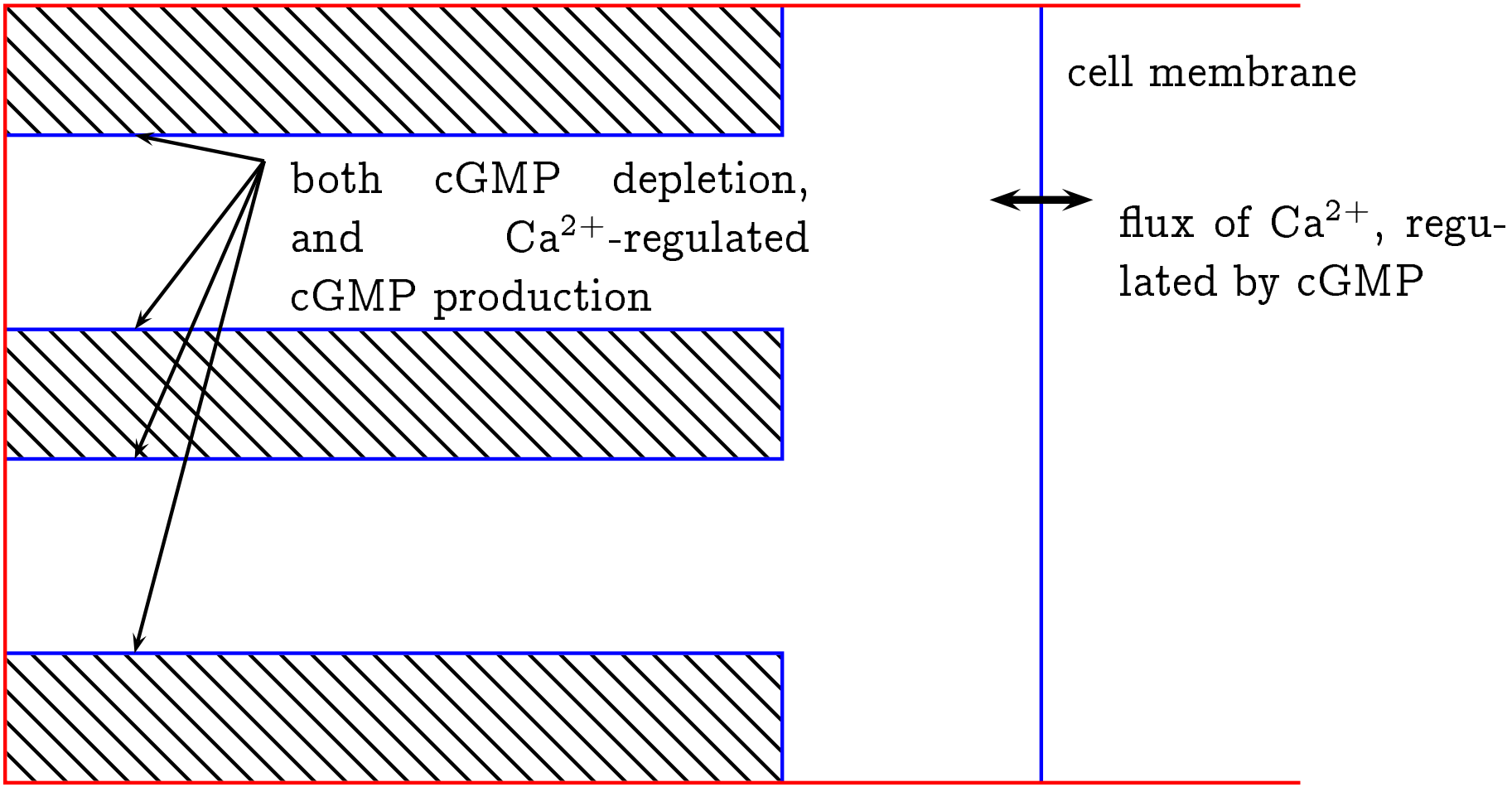

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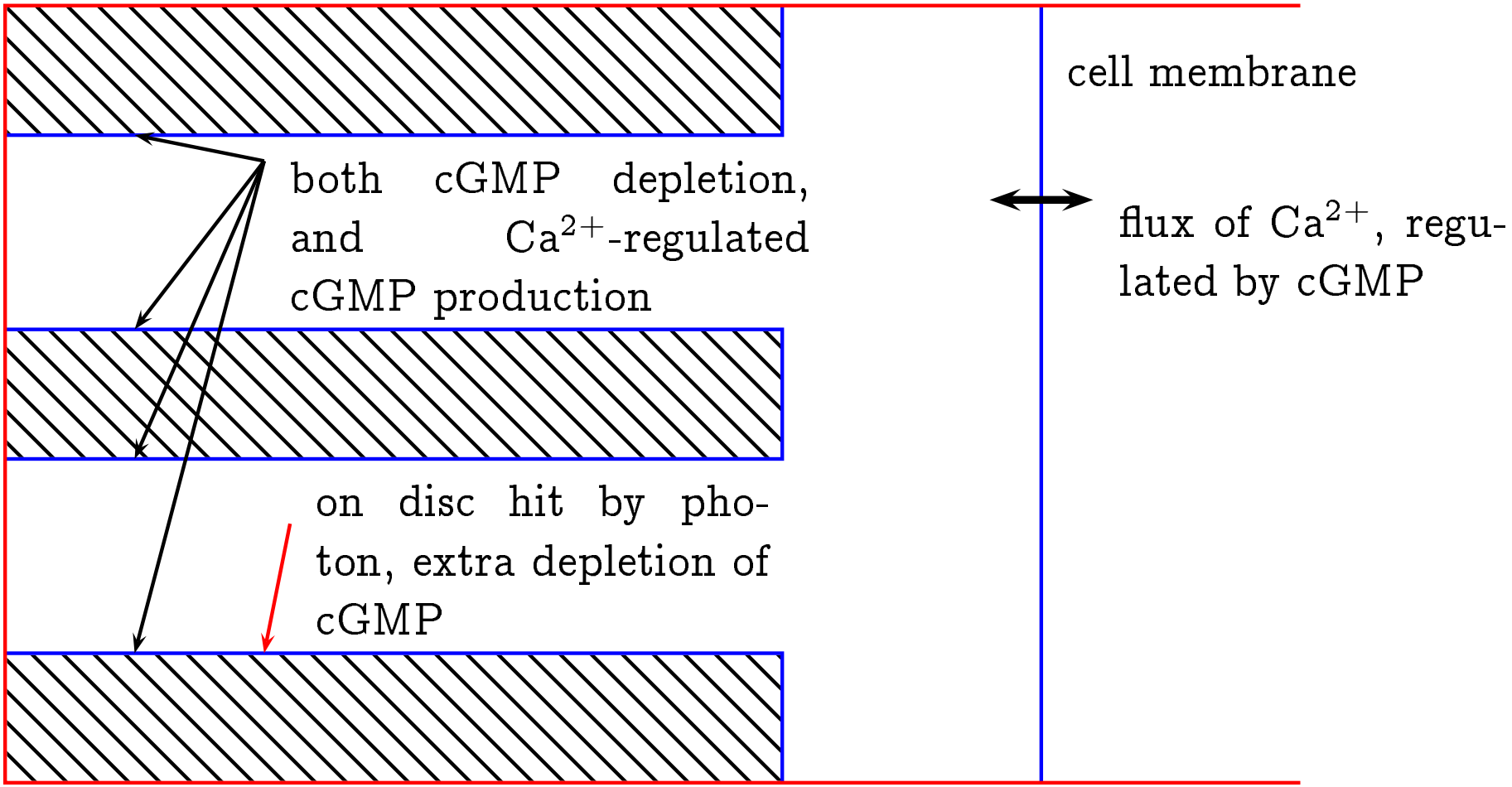

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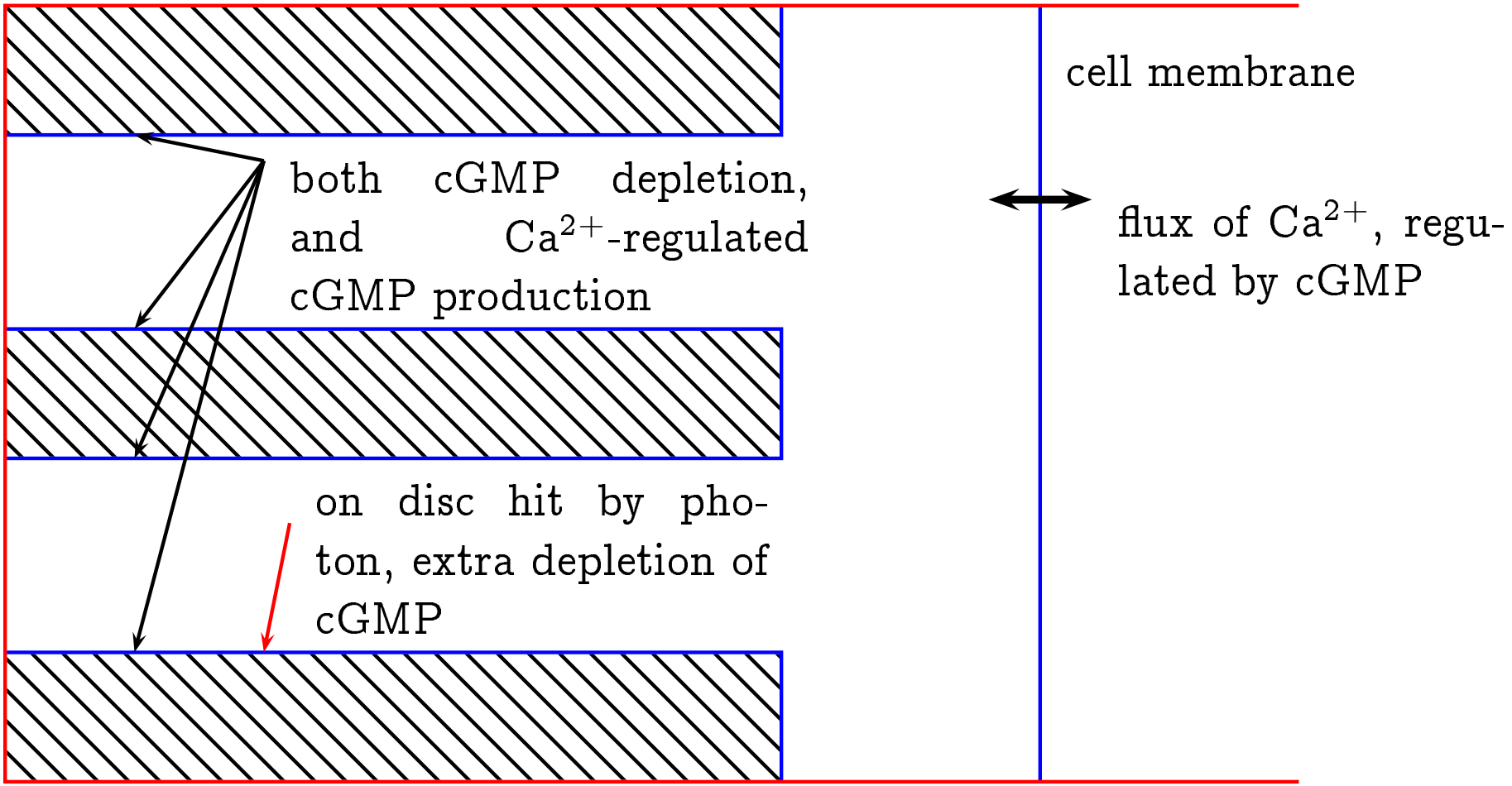

Assume for simplicity that the photon hits the center of the rod outer segment.

The problem: the cytosol compartment

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Here, we investigate the effect of the cytosol compartment.

Outline

The complete model: diffusion equations

In the case of Mouse, we adopt a transversally well stirred model (only the longitudinal spatial dependence is preserved).

$$\frac{\partial u}{\partial t} - D_u \frac{\partial^2 u}{\partial z^2} = -\beta u + \frac{\alpha_{\max} K^m + \alpha_{\min} v^m}{K^m + v^m}, \qquad 0 < z < H/2,$$

$$\frac{\partial v}{\partial t} - D_v \frac{\partial^2 v}{\partial z^2} = -\frac{j_1}{V_{\text{cyto}}} \frac{v}{K_1 + v} + \frac{j_2}{V_{\text{cyto}}} \frac{u^n}{K_2^n + u^n}, \qquad 0 < z < H/2.$$

u: [cGMP]; v: [Ca^{2+}].

The model has been obtained from the 3-D scheme through homogenization, concentration of capacity ... E.g., D_u, D_v are *effective* diffusivities, taking into account the geometry of the domain.

The complete model: initial and boundary data

Initial Data: At time $t = 0$, we have

$$u(z,0) = u_{\text{dark}} \qquad 0 < z < H/2\,,$$
$$v(z,0) = v_{\text{dark}} \qquad 0 < z < H/2\,.$$

Here u_{dark}, v_{dark} are the equilibrium concentrations at dark.

The complete model: initial and boundary data

Boundary Data at $z = 0$, $H/2$: null flux conditions at $z = H/2$; at $z = 0$ we have for u the photon-activated depletion:

$$D_u \frac{\partial u}{\partial z}(0,t) = K^*[\mathrm{PDE}]^*_\sigma u(0,t)\,,$$
$$D_v \frac{\partial v}{\partial z}(0,t) = 0\,.$$

Here $[\mathrm{PDE}]^*_\sigma$ is the surface concentration of activated Phosphodiesterase ...

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Here $[\mathrm{PDE}]^*_\sigma$ is the surface concentration of activated Phosphodiesterase ... and the source of variability.

The complete model: current drop functionals

The response of the ROS is evaluated essentially through the variation of the current exchanged through its boundary.

The complete model: current drop functionals

We define the total averaged current $J(t)$, and the drop $I(t)$

$$J(t) = \frac{2}{H} \int_0^{H/2} \left[j_{\mathrm{ex}}^{\mathrm{sat}} \frac{v(z,t)}{K_1 + v(z,t)} + j_{\mathrm{cG}}^{\mathrm{max}} \frac{u(z,t)^n}{K_2^n + u(z,t)^n} \right] \mathrm{d}z \,,$$

$$I(t) = 1 - \frac{J(t)}{J_{\mathrm{dark}}} \,, \qquad J_{\mathrm{dark}} = J(0) \,.$$

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We look at the CV = s.d./mean of two functionals

$$I_{\text{int}} = \int_0^{\infty} I(t)\, \mathrm{d}t \,, \qquad \text{CV}_{\text{exp}}(I_{\text{int}}) \simeq .25 - .35 \,,$$

$$I_{\text{peak}} = \max_{t \geq 0} I(t) \,, \qquad \text{CV}_{\text{exp}}(I_{\text{peak}}) \simeq .20 \,.$$

Three factors suppressing variability

We investigate the effects of three factors:

$$\frac{\partial u}{\partial t} - D_u \frac{\partial^2 u}{\partial z^2} = -\beta u + \frac{\alpha_{\max} K^m + \alpha_{\min} v^m}{K^m + v^m}, \qquad 0 < z < H/2,$$

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Omitting nonlinearity

The DFn model, where equations are linearized:

$$\frac{\partial u}{\partial t} - D_u \frac{\partial^2 u}{\partial z^2} = A_{11}(u - u_{\mathtt{dark}}) + A_{12}(v - v_{\mathtt{dark}}),$$
$$\frac{\partial v}{\partial t} - D_v \frac{\partial^2 v}{\partial z^2} = A_{21}(u - u_{\mathtt{dark}}) + A_{22}(v - v_{\mathtt{dark}}).$$

Omitting diffusion

The dFN model, stipulating a globally well-stirred assumption:

$$\frac{\mathrm{d}u}{\mathrm{d}t} = -\beta u + \frac{\alpha_{\max} K^m + \alpha_{\min} v^m}{K^m + v^m} - \frac{2K^*}{H}[\mathrm{PDE}]^*_\sigma u\,,$$
$$\frac{\mathrm{d}v}{\mathrm{d}t} = -\frac{j_1}{V_{\mathrm{cyto}}}\frac{v}{K_1 + v} + \frac{j_2}{V_{\mathrm{cyto}}}\frac{u^n}{K_2^n + u^n}\,.$$

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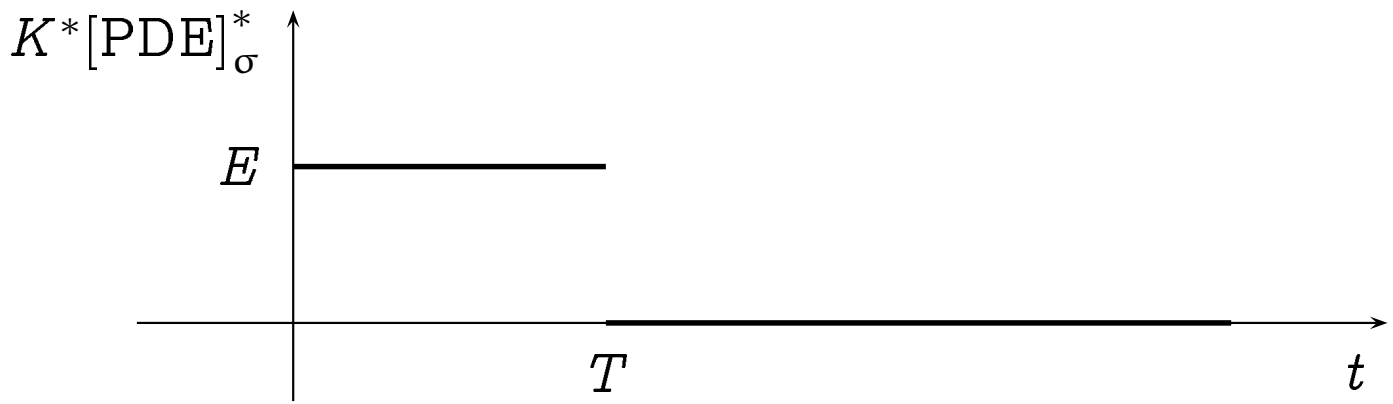
The random simplified input

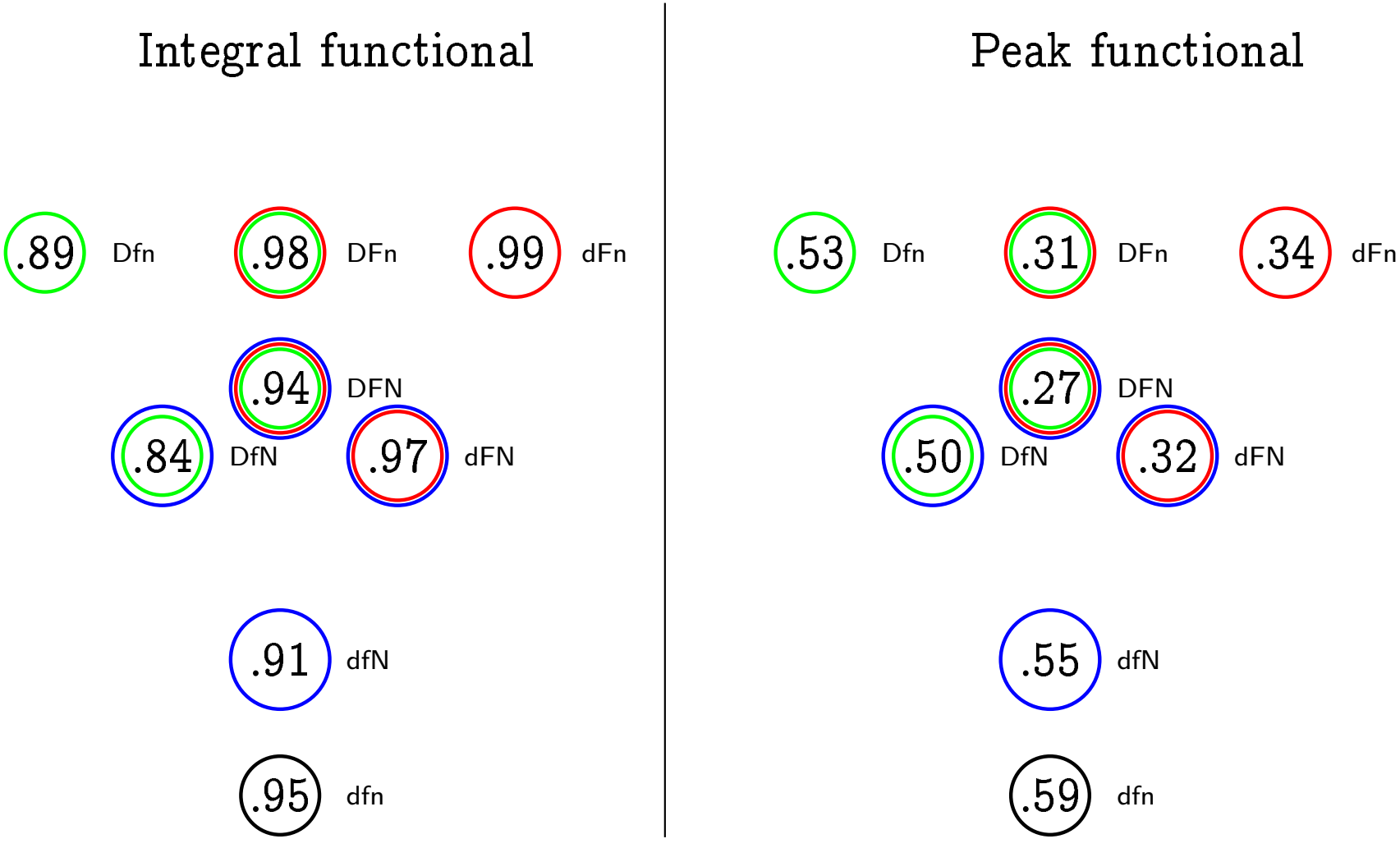
We simplify the random behaviour of $[\mathrm{PDE}]^*_\sigma$ as follows:

$$K^*[\mathrm{PDE}]^*_\sigma = \begin{cases} E & 0 < t < T\,, \\ 0 & t > T\,, \end{cases}$$

where $E > 0$, and T an exponentially distributed random time, with average $1/\lambda$.

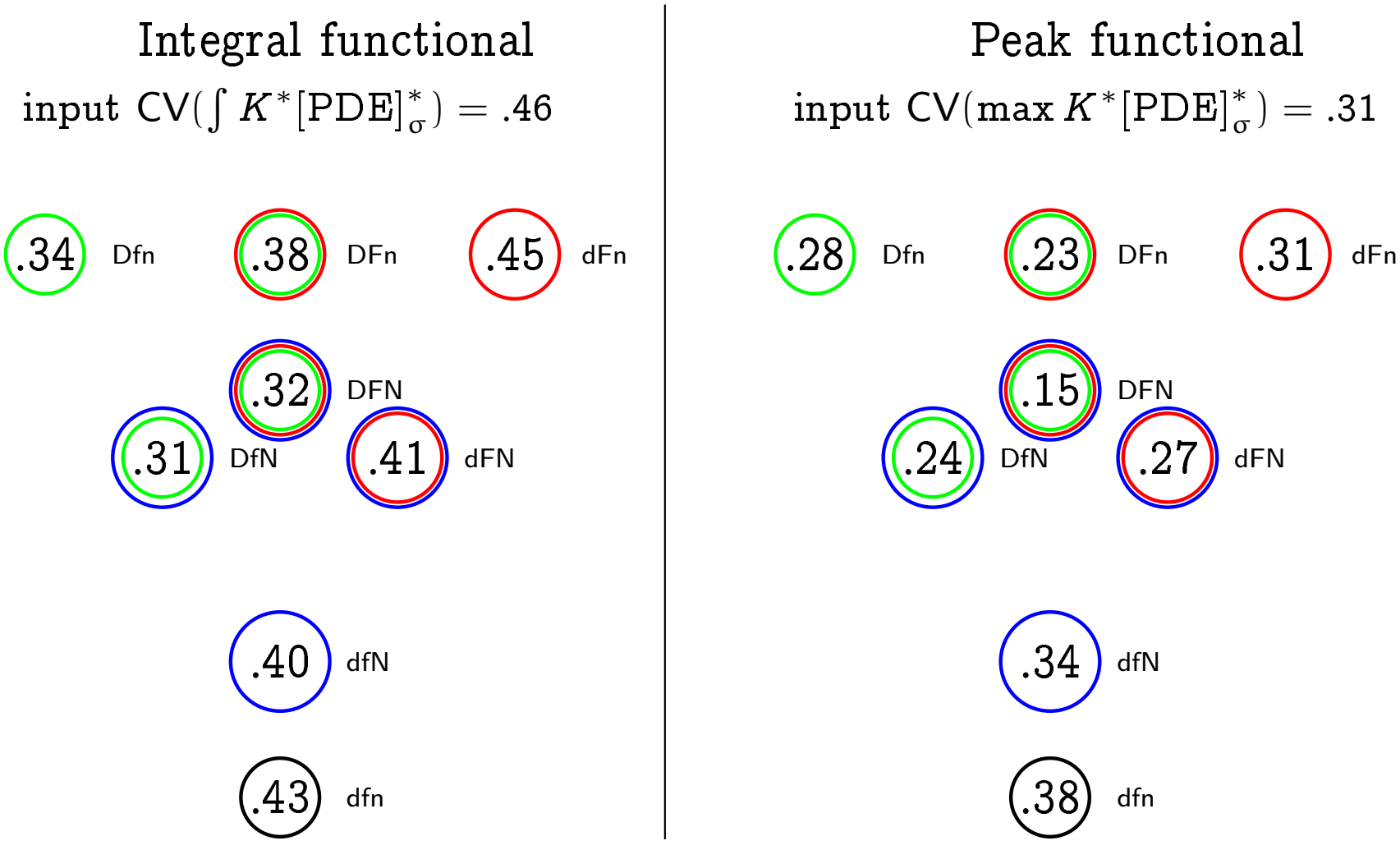


The effects on CV: simplified input



• Diffusion; • Feedback; • Nonlinearity.

The effects on CV: realistic input



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  - We considered both an idealized activation mechanism, and (just numerically) a realistic model of the biochemistry: they reveal the same trend.
- Diffusion and nonlinearity have a comparable effect in reducing variability. This comparable role is played in both the functionals.
- On the contrary the effects of feedback are opposite in the two functionals: feedback reduces variability of the supremum, and increases variability of the integral.

Collaborators & refs

Joint work with: P.Bisegna, G.Caruso, E.DiBenedetto, H.Hamm, L.Shen.

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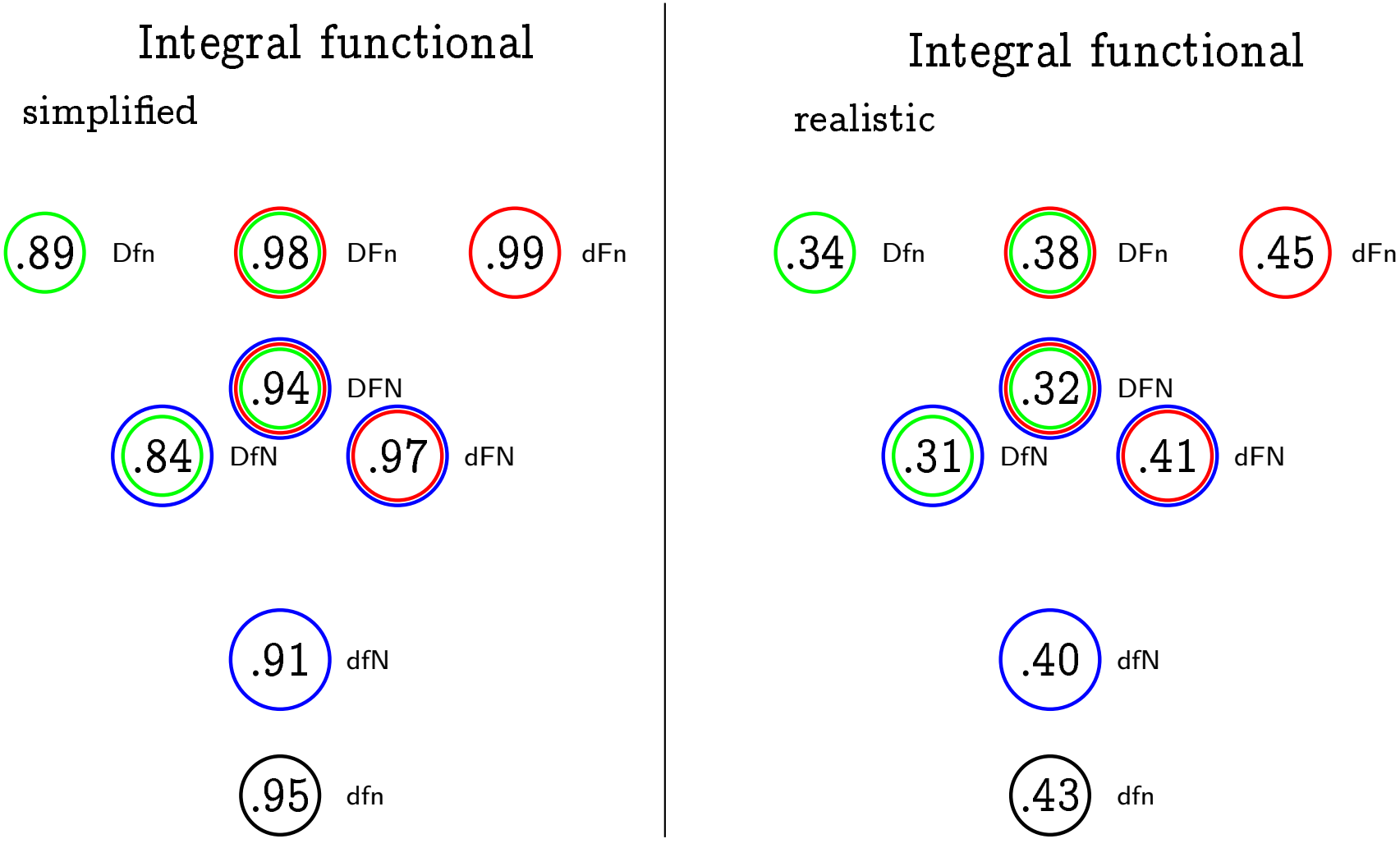
Funding: NIH

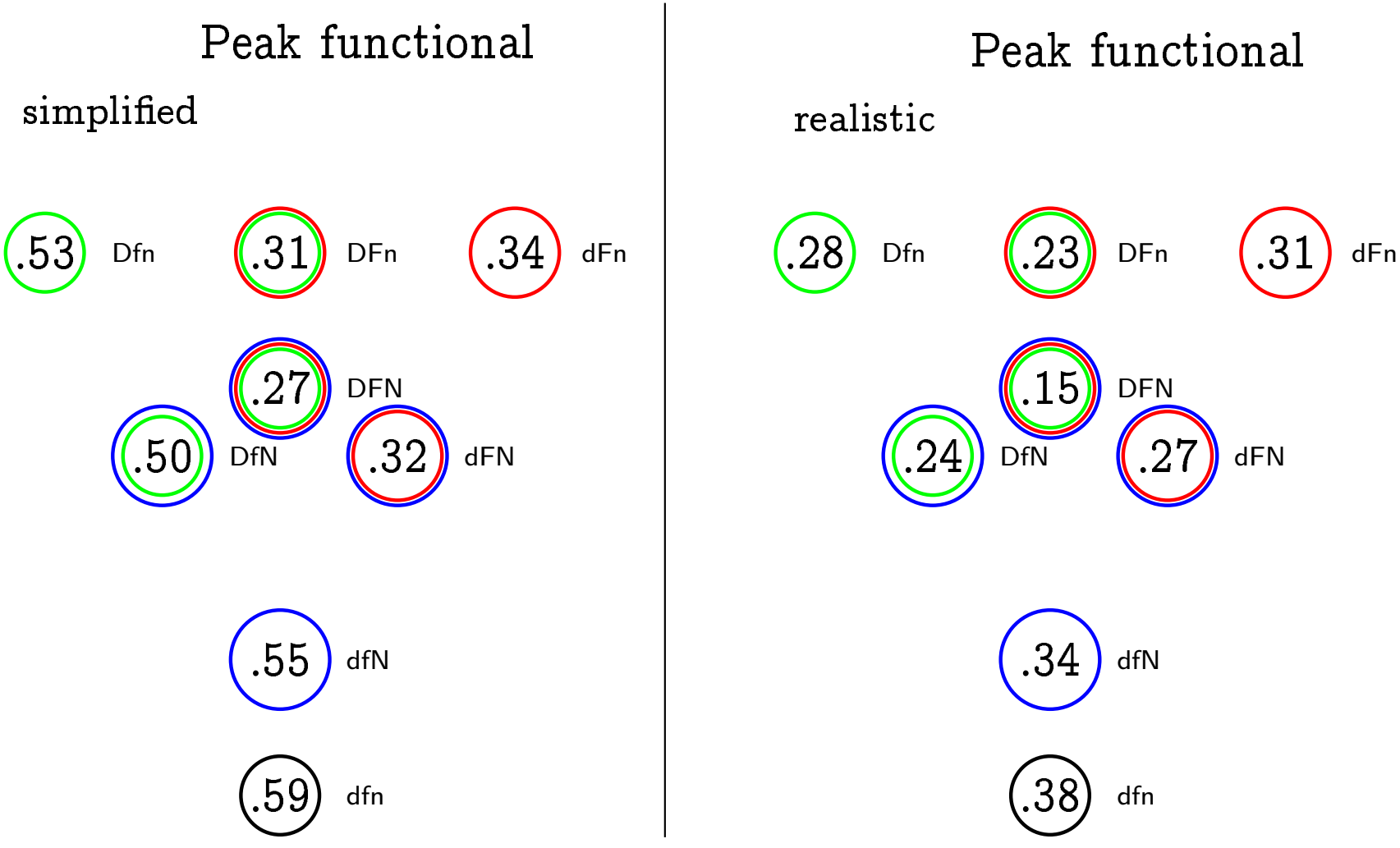
Outline

The effects on $\mathrm{CV}(I_{\mathrm{int}})$: simplified vs realistic



● Diffusion; ● Feedback; ● Nonlinearity.

The effects on $\mathrm{CV}(I_{\mathrm{peak}})$: simplified vs realistic



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Diffusion Feedback Nonlinearity

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$$\frac{\partial u}{\partial t} - D_u \frac{\partial^2 u}{\partial z^2} = -\beta u + \frac{\alpha_{\max} K^m + \alpha_{\min} v^m}{K^m + v^m}\,, \qquad 0 < z < H/2\,,$$

$$\frac{\partial v}{\partial t} - D_v \frac{\partial^2 v}{\partial z^2} = -\frac{j_1}{V_{\text{cyto}}} \frac{v}{K_1 + v} + \frac{j_2}{V_{\text{cyto}}} \frac{u^n}{K_2^n + u^n}\,, \qquad 0 < z < H/2\,,$$

plus initial and boundary conditions, e.g.,

$$D_u \frac{\partial u}{\partial z}(0,t) = K^* [\text{PDE}]^*_\sigma u(0,t)\,,$$

$$D_v \frac{\partial v}{\partial z}(0,t) = 0\,.$$

Diffusion Feedback Nonlinearity

The DFn model:

$$\frac{\partial u}{\partial t} - D_u \frac{\partial^2 u}{\partial z^2} = A_{11}(u - u_{\text{dark}}) + A_{12}(v - v_{\text{dark}}),$$
$$\frac{\partial v}{\partial t} - D_v \frac{\partial^2 v}{\partial z^2} = A_{21}(u - u_{\text{dark}}) + A_{22}(v - v_{\text{dark}}),$$

and the current functional is also linearized.

The dFN model:

$$\frac{\mathrm{d}u}{\mathrm{d}t} = -\beta u + \frac{\alpha_{\max} K^m + \alpha_{\min} v^m}{K^m + v^m} - \frac{2K^*}{H}[\mathrm{PDE}]^*_\sigma u\,,$$
$$\frac{\mathrm{d}v}{\mathrm{d}t} = -\frac{j_1}{V_{\mathrm{cyto}}}\frac{v}{K_1 + v} + \frac{j_2}{V_{\mathrm{cyto}}}\frac{u^n}{K_2^n + u^n}\,.$$

Diffusion Feedback Nonlinearity

The DfN model:

$$\frac{\partial u}{\partial t} - D_u \frac{\partial^2 u}{\partial z^2} = -\beta u + \frac{\alpha_{\max} K^m + \alpha_{\min} v_{\text{dark}}^m}{K^m + v_{\text{dark}}^m} ,$$

plus initial and boundary conditions, e.g.,

$$D_u \frac{\partial u}{\partial z}(0,t) = K^* [\text{PDE}]_\sigma^* u(0,t) .$$

The differential equation is actually linear but the current functional is not linearized.

The Dfn model:

$$\frac{\partial u}{\partial t} - D_u \frac{\partial^2 u}{\partial z^2} = -\beta u + \frac{\alpha_{\max} K^m + \alpha_{\min} v_{\text{dark}}^m}{K^m + v_{\text{dark}}^m} ,$$

plus initial and boundary conditions, e.g.,

$$D_u \frac{\partial u}{\partial z}(0,t) = K^* [\text{PDE}]_\sigma^* u(0,t) ,$$

and the current functional is also linearized.

The dFn model:

$$\frac{\mathrm{d}u}{\mathrm{d}t} = -\frac{2K^*}{H}[\mathrm{PDE}]^*_\sigma u + A_{11}(u - u_{\mathrm{dark}}) + A_{12}(v - v_{\mathrm{dark}})\,,$$
$$\frac{\mathrm{d}v}{\mathrm{d}t} = A_{21}(u - u_{\mathrm{dark}}) + A_{12}(v - v_{\mathrm{dark}})\,.$$

The current functionals are also linearized.

The dfN model:

$$\frac{\mathrm{d}u}{\mathrm{d}t} = -\frac{2K^*}{H}[\mathrm{PDE}]^*_\sigma u - \beta u + \frac{\alpha_{\max} K^m + \alpha_{\min} v_{\mathrm{dark}}^m}{K^m + v_{\mathrm{dark}}^m}\,.$$

The differential equation is actually linear but the current functional is not linearized.

The dfn model:

$$\frac{\mathrm{d}u}{\mathrm{d}t} = -\frac{2K^*}{H}[\mathrm{PDE}]^*_\sigma u - \beta u + \frac{\alpha_{\max} K^m + \alpha_{\min} v_{\mathrm{dark}}^m}{K^m + v_{\mathrm{dark}}^m}\,.$$

The current functionals are also linearized.

$$\mathrm{CV}\left(\frac{H}{2}\int_0^\infty (u(t) - u_{\mathrm{dark}})\,\mathrm{d}t\right) = \left[\frac{1 + \frac{2EH^{-1}}{|A_{11}|(1+\lambda(2|A_{11}|)^{-1})(1+\lambda|A_{11}|^{-1})^2}}{1 + \frac{2EH^{-1}}{|A_{11}|(1+\lambda(2|A_{11}|)^{-1})}}\right]^{\frac{1}{2}},$$

$$\mathrm{CV}\left(\sup_{0<t<\infty} |u(t) - u_{\mathrm{dark}}|\right) = \frac{1}{\sqrt{1 + 2|A_{11}|\lambda^{-1} + 4EH^{-1}\lambda^{-1}}}\,.$$

Multistep shutting off

Denote by $\chi_{(t_{j-1},t_j]}$ the characteristic function of the interval $(t_{j-1}, t_j]$. Then the rate equations for G (G-protein) and E (Phosphodiesterase) are

$$G_t = \sum_{j=1}^{n} \nu_j \chi_{(t_{j-1},t_j]}(t) - k_1 GE \,,$$

$$E_t = k_1 GE - k_2 E \,,$$

with initial data

$$G(0) = E(0) = 0 \,.$$

Parameters

Symbol	Units	Definition	Value
a_{int}	$\mu\mathrm{m}^2$	interior transversal area of the ROS	$\pi R^2 \nu/(1+\nu)$
a_{inc}	$\mu\mathrm{m}^2$	area of the incisure	0.0367
a_{tot}	$\mu\mathrm{m}^2$	total transversal area of the ROS	$2\pi R\sigma\varepsilon + a_{\mathrm{int}} + a_{\mathrm{inc}}$
a_{pat}	$\mu\mathrm{m}^2$	patent transversal area of the ROS	$2\pi R\sigma\varepsilon + a_{\mathrm{inc}}$
α_{max}	$\mu\mathrm{Ms}^{-1}$	maximum rate of cGMP synthetization	76.5
$\alpha_{\mathrm{max}}/\alpha_{\mathrm{min}}$		suppression rate of cGMP synthetization	13.9
β	s^{-1}	rate of cGMP hydrolisis by dark act. PDE	2.9
B_{Ca}		buffering power of cytoplasm for Ca^{2+}	20
D_{cG}	$\mu\mathrm{m}^2\mathrm{s}^{-1}$	diffusivity of cGMP	150
D_u	$\mu\mathrm{m}^2\mathrm{s}^{-1}$	effective axial diffusivity of cGMP	$D_{\mathrm{cG}}\frac{a_{\mathrm{pat}}}{a_{\mathrm{tot}}}$
D_{Ca}	$\mu\mathrm{m}^2\mathrm{s}^{-1}$	diffusivity of Ca^{2+}	15
D_v	$\mu\mathrm{m}^2\mathrm{s}^{-1}$	effective axial diffusivity of Ca^{2+}	$D_{\mathrm{Ca}}\frac{a_{\mathrm{pat}}}{a_{\mathrm{tot}}}$
E	$\mu\mathrm{ms}^{-1}$	amplitude of act. in simplified model Dfn	6.96
ε	$\mu\mathrm{m}$	disk thickness	0.0145
$\mathcal{F}$	Cmol^{-1}	Faraday's constant	96500
f_{Ca}		frac. of current carried by Ca^{2+}	0.06
H	$\mu\mathrm{m}$	height of ROS	23.6

Parameters

Symbol	Units	Definition	Value
j_1	$\mu M s^{-1} \mu m^3$	coefficient in eq. for v	$j_{ex}^{sat}/(B_{Ca}\mathcal{F})$
j_2	$\mu M s^{-1} \mu m^3$	coefficient in eq. for v	$j_{cG}^{max} f_{Ca}/(2B_{Ca}\mathcal{F})$
j_{cG}^{max}	pA	maximum cGMP-gated channel current	3550
j_{ex}^{sat}	pA	saturated exchanger current	1.8
K_{hyd}	$\mu m^3 s^{-1}$	surface hydrolisis rate by dark-act. PDE	$2.8 \cdot 10^{-5}$
k^*	$\mu m^3 s^{-1}$	surface hydrolisis rate by light-act. PDE	0.9
K	μM	half-saturating v for GC activity	0.129
K_2	μM	u for half-max cGMP-gated channel opening	20
K_1	μM	v for half-max exchanger channel opening	1.6
λ	s^{-1}	parameter in the simplified model Dfn	3.60
n_{discs}		number of discs	814
m		Hill coefficient for the effect of GC	2.45
n		Hill coefficient for the cGMP-gated channels	3
R	μm	radius of disk	0.7
V_{cyto}	μm^3	cytoplasmic volume	$a_{tot} H$
u_{dark}	μM	concentration of cGMP in the dark	3.0750
v_{dark}	μM	concentration of Ca^{2+} in the dark	0.4363