COMSOL CONFERENCE 2017 SINGAPORE

3D hydrodynamics and mass transport simulations of ocular drug delivery considering segmental aqueous humor outflow phenomenon in the human eye

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What is GLAUCOMA?

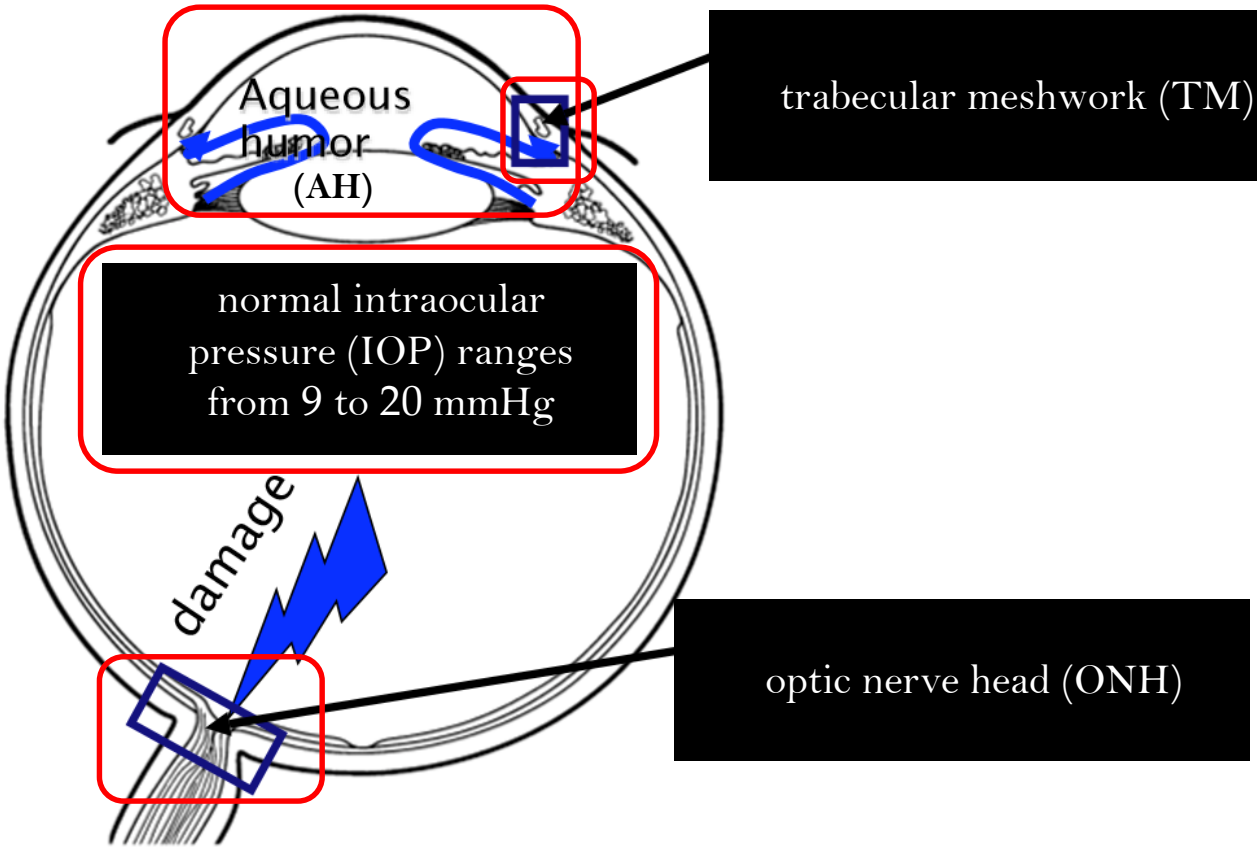


Figure 1
Pathogenesis of glaucoma (Murgatroyd *et al.*, 2008).

RESEARCH BACKGROUND

The anterior segment of the human eye: anatomy and physiology

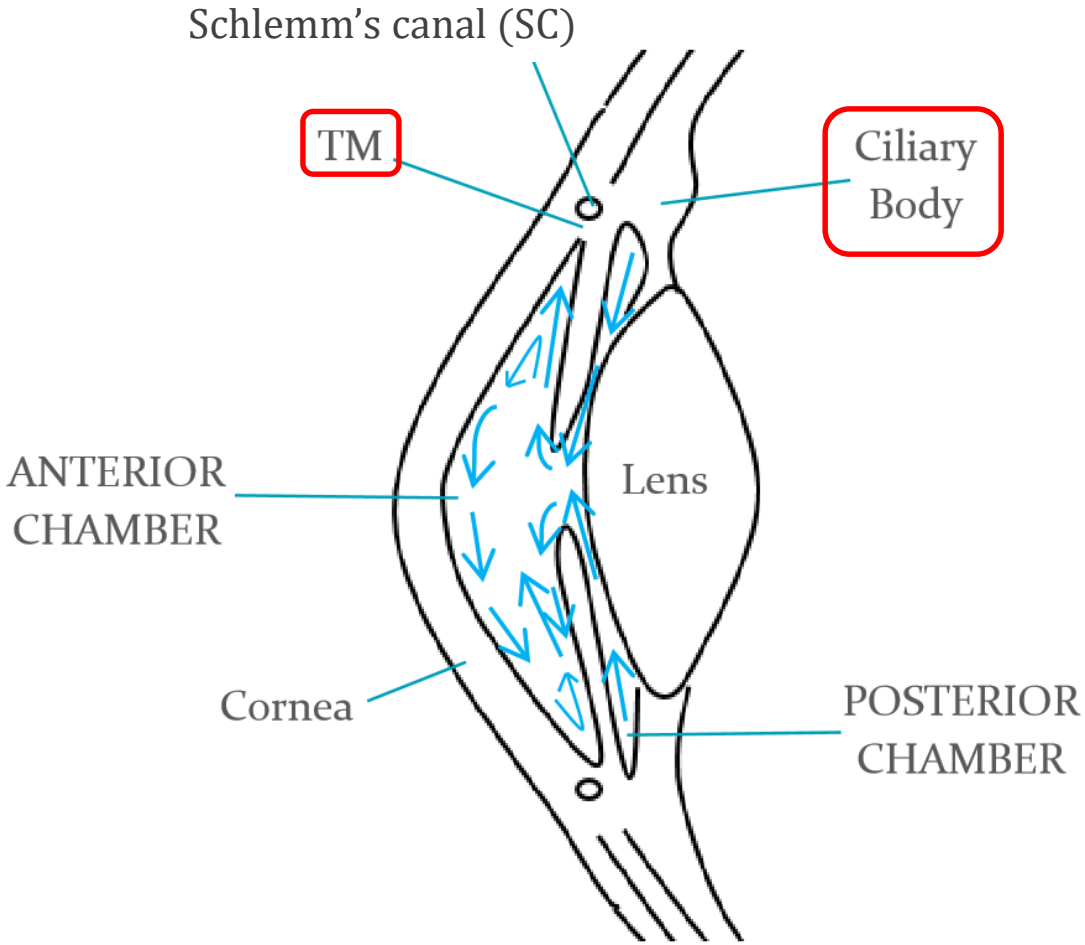
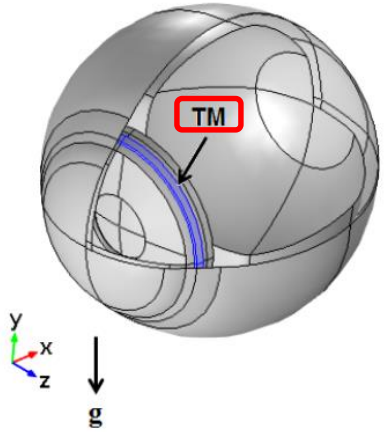


Figure 2
Production and drainage of the AH.

Circulation of the aqueous humor (AH)

1. Production and drainage of AH
2. Thermal-induced buoyant forces



RESEARCH BACKGROUND

The segmental outflow phenomenon

✓ heterogeneity in the TM outflow facility (Chang *et al.*, 2014): active and inactive outflow regions

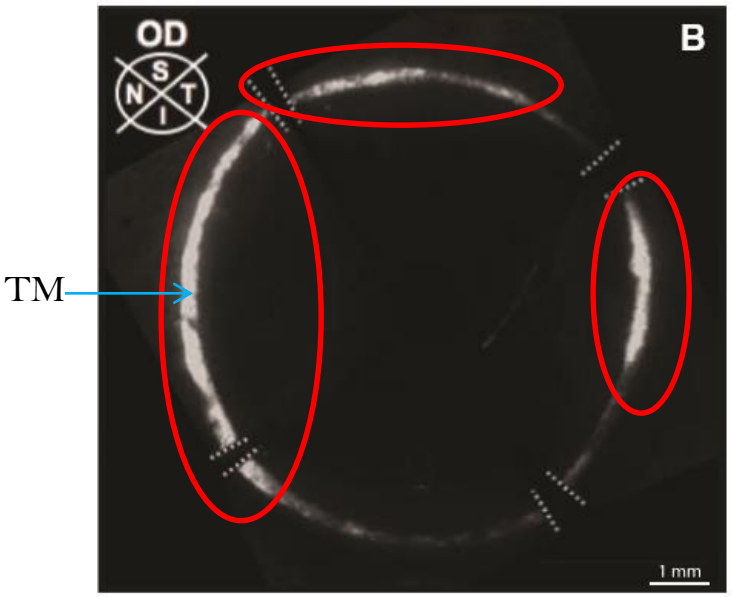


Figure 3
The non-uniformity of AH outflow across the TM in previous fluorescent tracer distribution study (Chang *et al.*, 2014)

Questions

✓ how does it affect the AH flow?

✓ does it limit the efficacy of the anti-glaucoma drugs delivery?

Research objective

✓ to investigate the response of the AH flow to outflow segmentation and its influence towards treatment of glaucoma

HYPOTHESIS

Segmental outflow : Effects on the ocular drug delivery system

✓ hypothesis: it limits the efficacy of the anti-glaucoma drugs delivery

Major concerns

'over-treating' and 'under-treating' conditions

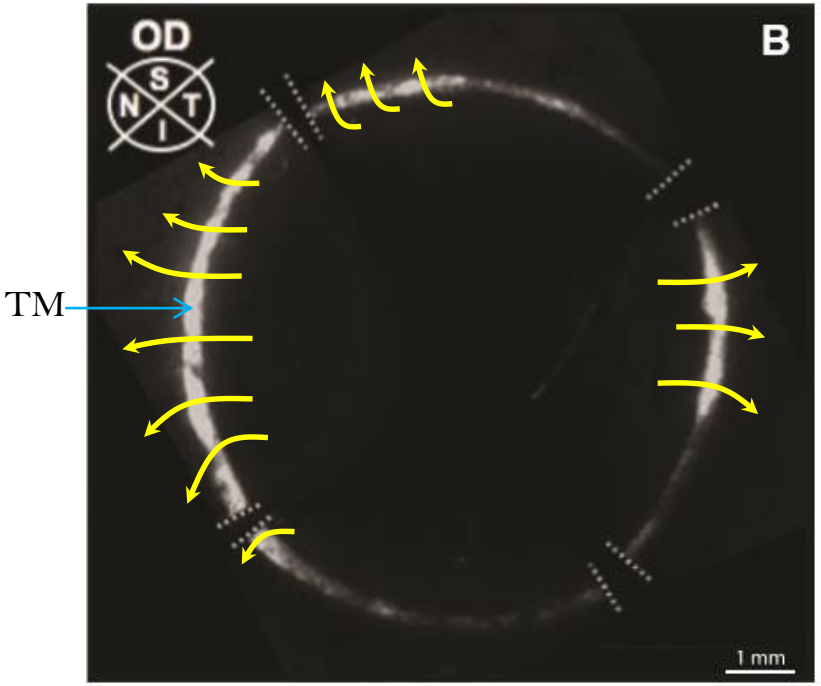


Figure 4
Hypothesized outflow behavior of the AH and the ocular drugs.

METHODS & MATERIALS

The geometry

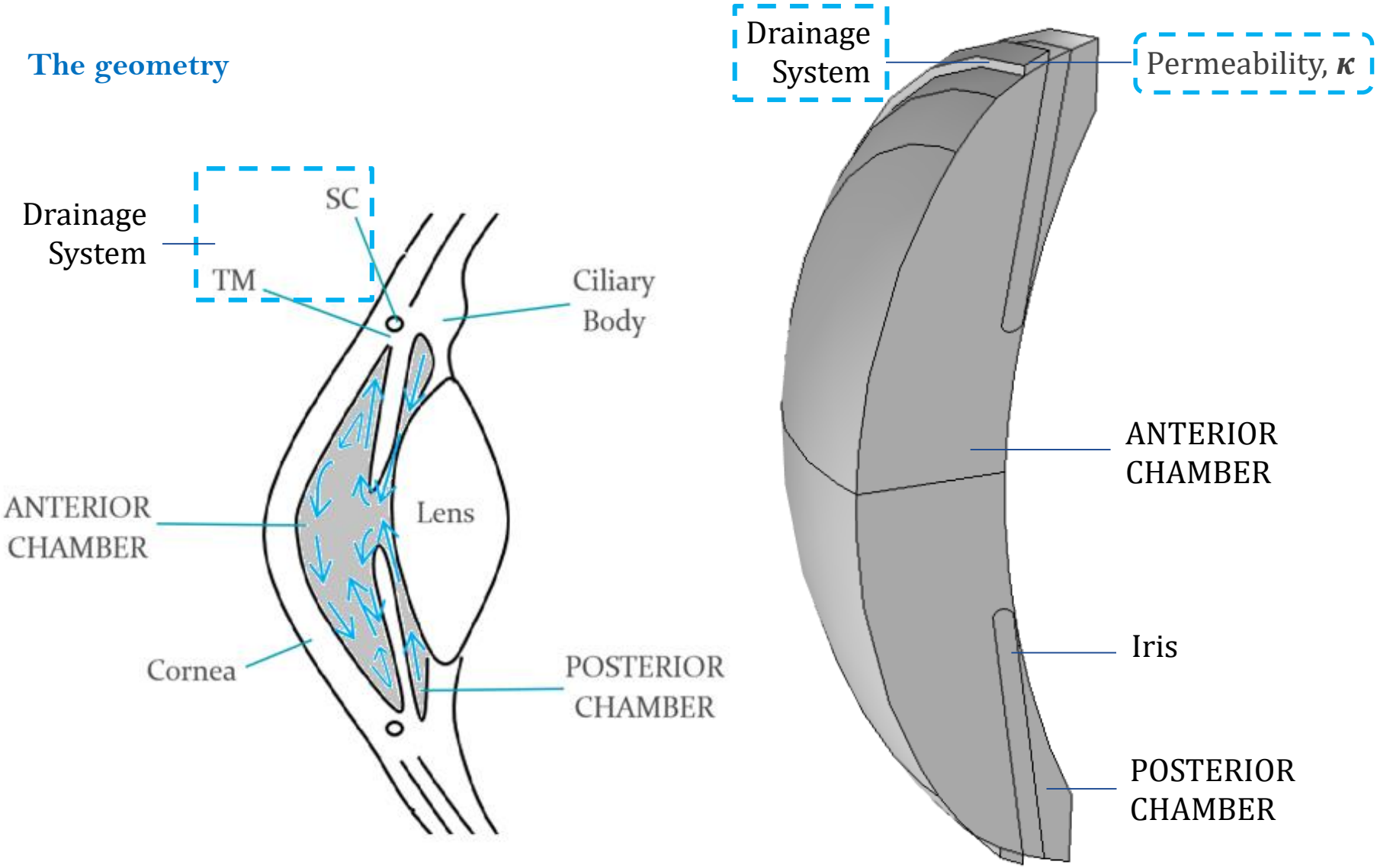


Figure 5
Illustration of the 3D model in COMSOL MULTIPHYSICS 5.3.

METHODS & MATERIALS

Free and porous media flow

Navier-Stokes equation coupled with Boussinesq Approximation,

$$\rho(\mathbf{v} \cdot \nabla \mathbf{v}) = -\nabla p + \mu \nabla^2 \mathbf{v} + \rho_0 \mathbf{g}[1 - \beta(T - T_{ref})]$$

$$\nabla \cdot \mathbf{v} = 0$$

Stokes-Brinkmann equation,

$$\mu \nabla^2 \mathbf{v} - \nabla p - \frac{\mu}{\boldsymbol{\kappa}}$$

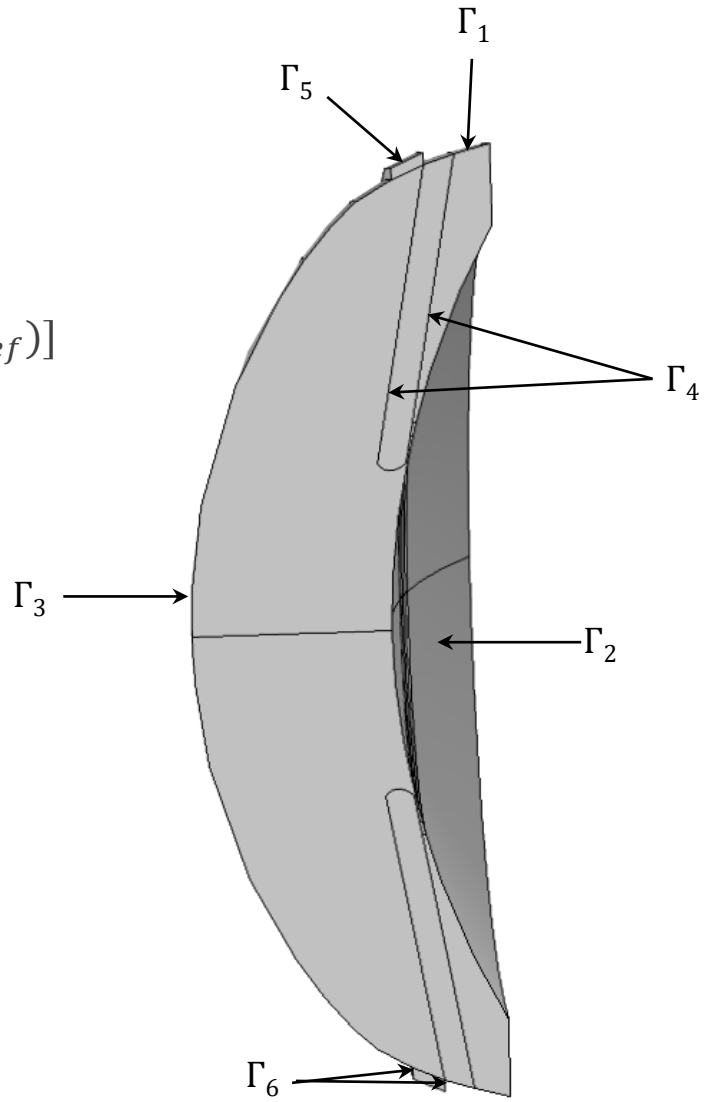


Table 1
Hydraulic boundary conditions.

Boundary	Boundary Conditions
Γ_1	AH inlet
Γ_2	Non-slip/wall condition
Γ_3	Non-slip/wall condition
Γ_4	Non-slip/wall condition
Γ_5	AH outlet
Γ_6	Non-slip/wall condition

METHODS & MATERIALS

Thermal and hydraulic boundary conditions

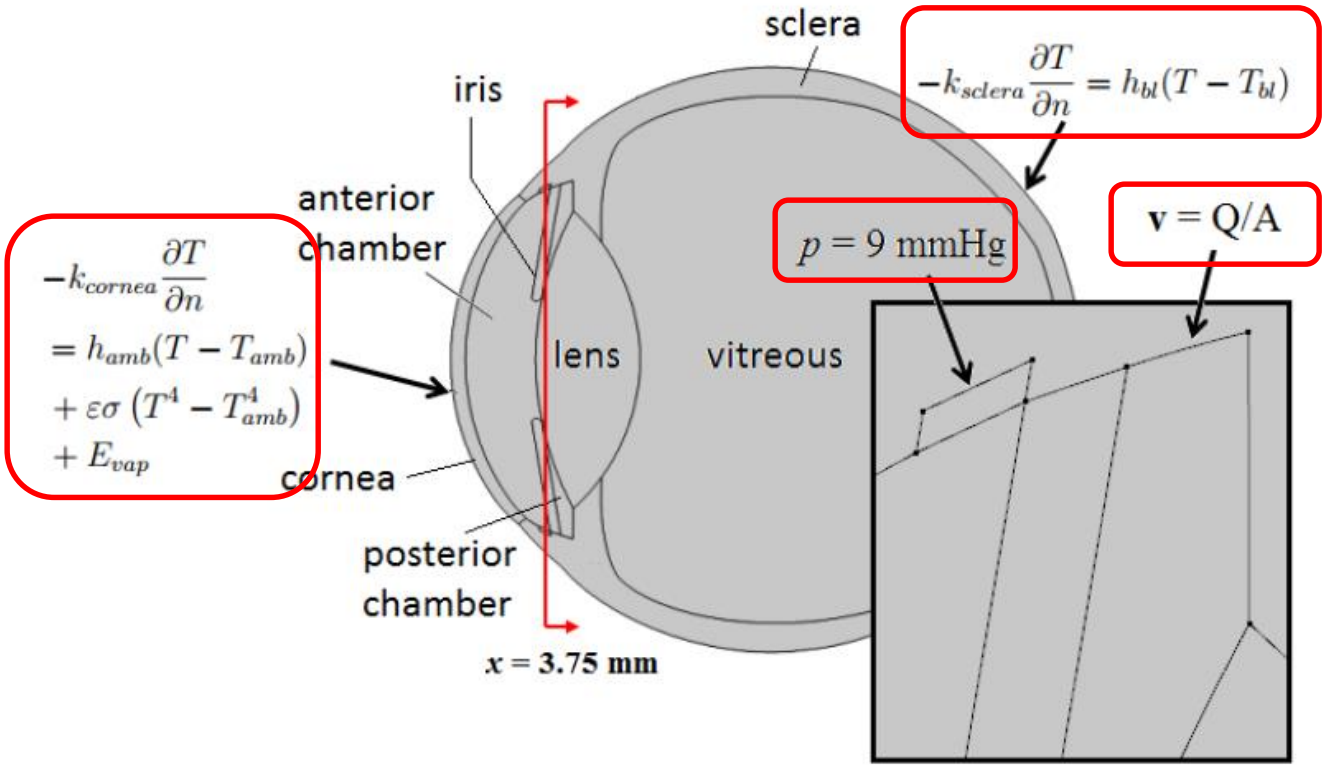


Figure 6
Thermal and hydraulic boundary conditions employed.

The drug transport model

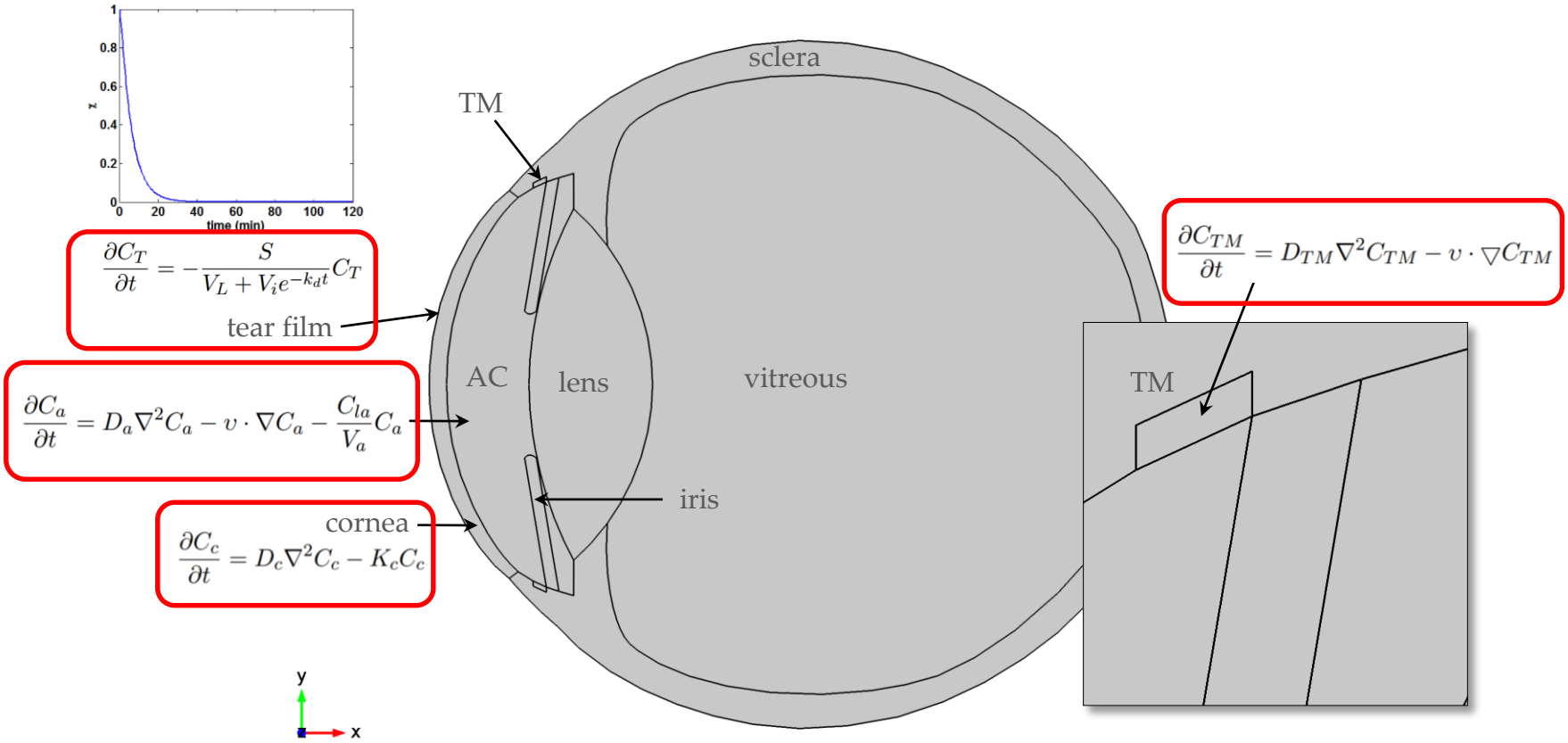


Figure 7
Boundary conditions employed on the drug transport model.

METHODS & MATERIALS

The segmental outflow model

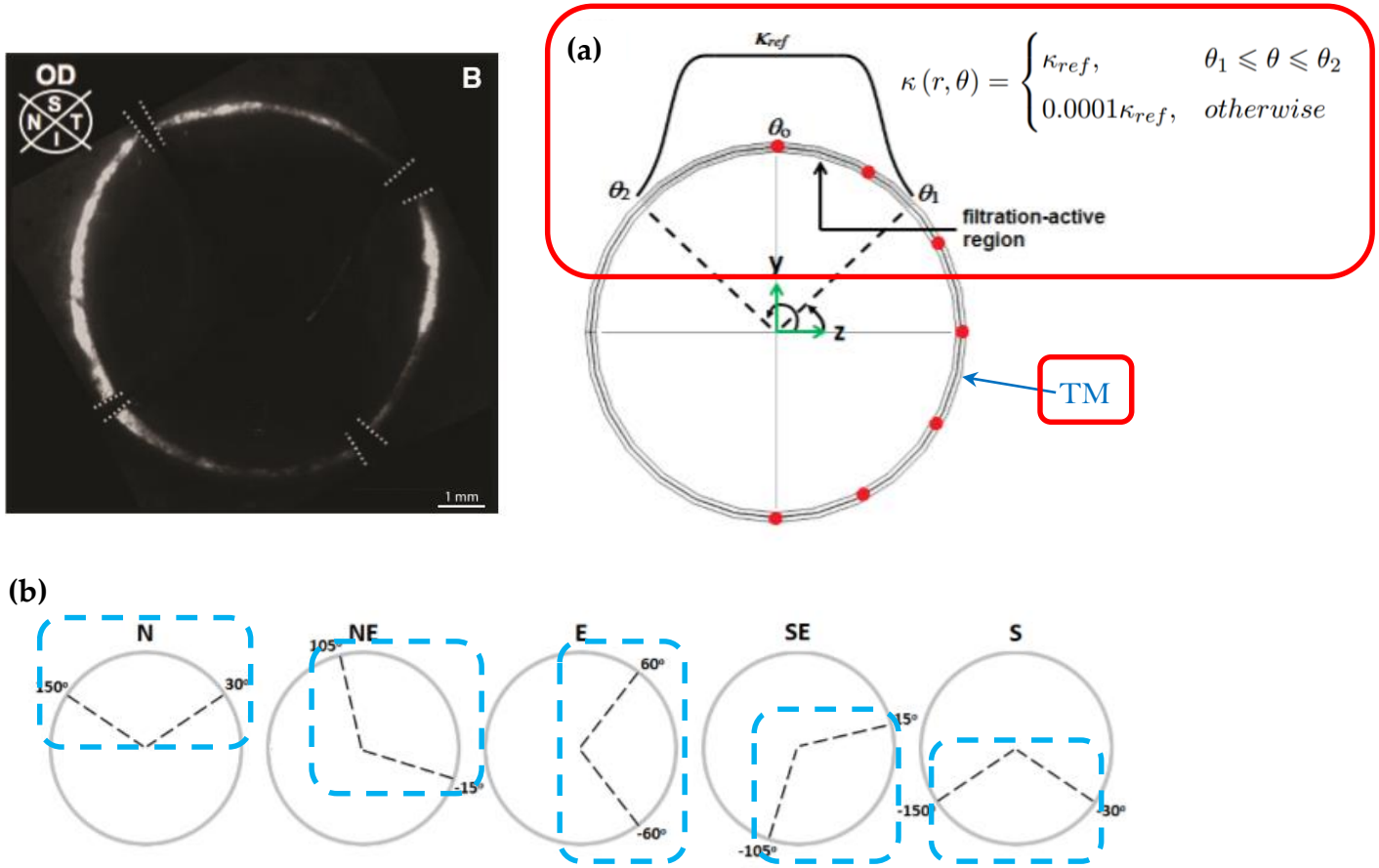


Figure 8

(a) The spatially defined TM permeability in rectangular function, expressed in terms of θ_0, θ_1 and θ_2; (b) the schematic diagrams illustrating active outflow regions on the TM at N, NE, E, SE and S.

METHODS & MATERIALS

Material properties

Table 2 The thermal, hydraulic and transport properties.

Parameter	Values	Source
Thermal conductivity, k (W/(m·K))		
Cornea	0.58	Ooi and Ng, 2008
AC & PC	0.58	Emery *et al.*, 1975
Iris and sclera	1.0042	Cicekli, 2003
Lens	0.40	Lagendijk, 1982
Vitreous	0.603	Assumed as water
Diffusion coefficient, D (m^2/s)		
Cornea	5.74×10^{-9}	Ferreira *et al.*, 2014
AC & PC	5×10^{-11}	Ferreira *et al.*, 2014
TM[a]	1.62×10^{-11}	Ferreira *et al.*, 2014
AH		
Thermal expansion coefficeint, β (K^{-1})	3.37×10^{-4}	Assumed as water
Dynamic viscosity, μ (Pa·s)	7×10^{-4}	Assumed as water
Specific heat, C_p (J/(kg·K))	3997	Scott, 1988
Density, ρ (kg/m^3)	996	Scott, 1988
Baseline permeability of TM, κ_{ref} (m^2/s)	2×10^{-15}	Johnson, 2006

[a] Estimated using the Stokes-Einstein equation for 0.95nm particle radius

METHODS & MATERIALS

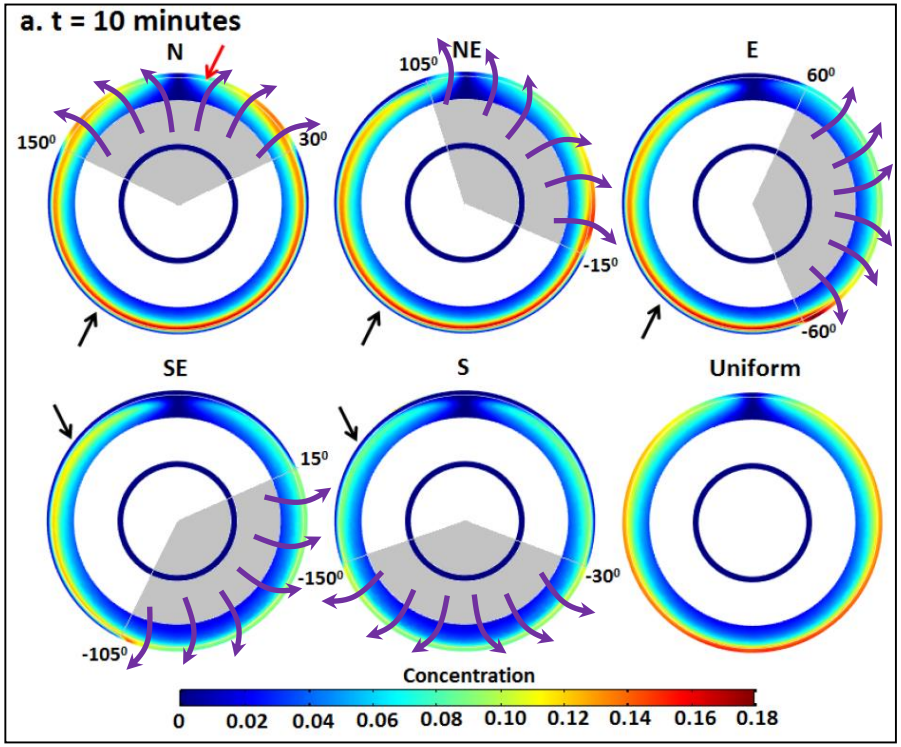
Material properties

Table 3 The baseline values for different model parameters.

Parameter	Values	Source
Ambient convection coefficient, h_{amb} (W/(m^2·K))	10	Ooi and Ng, 2008
Ambient temperature, T_{amb} (K)	298	Ooi and Ng, 2008
Blood convection coefficient, h_{bl} (W/(m^2.K))	65	Ooi and Ng, 2008
Blood temperature, T_{bl} (K)	310	Ooi and Ng, 2008
Corneal surface emissivity, ε	0.95	Ooi and Ng, 2008
Reference temperature, T_{ref} (K)	310	Ooi and Ng, 2008
Tears evaporation rate, E_{vap} (W/m^2)	40	Ooi and Ng, 2008
Lacrimal secretion rate, S (μl/min)	1.2	Ferreira *et al.*, 2014
Normal lacrimal volume, V_L (μl)	7	Ferreira *et al.*, 2014
Initial tear volume of eye drop instillation, V_i (μl)	10	Ferreira *et al.*, 2014
Tear drainage constant, k_d (min^{-1})	1.45	Ferreira *et al.*, 2014
Corneal metabolic consumption rate, K_c (min^{-1})	1.0713×10^{-5}	Ferreira *et al.*, 2014
Transference coefficient, λ (s^{-1})	2×10^{-4}	Ferreira *et al.*, 2014
Drug clearance rate from AC, C_{la} (μl/min)	30	Ferreira *et al.*, 2014

RESULTS & DISCUSSIONS

Standing position



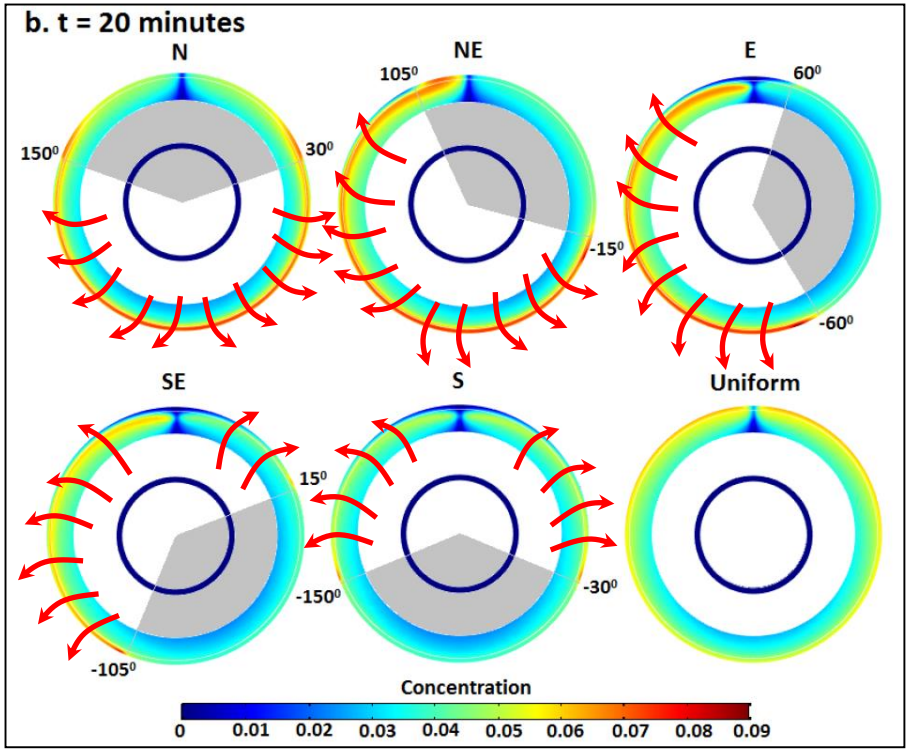
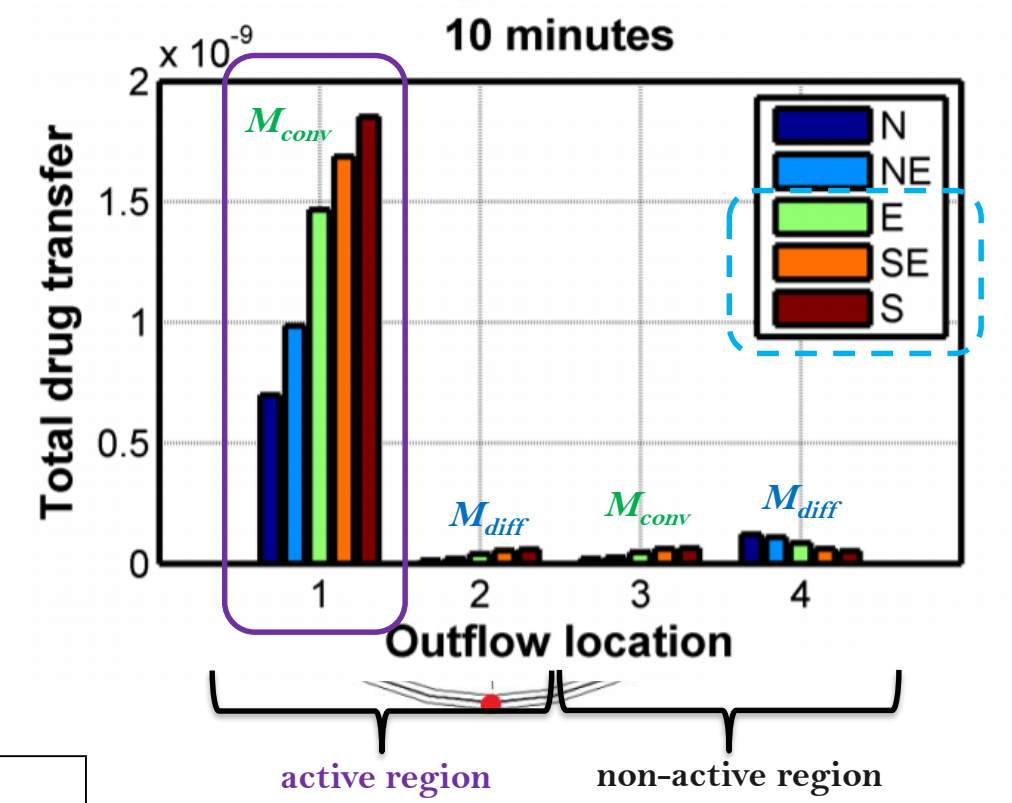


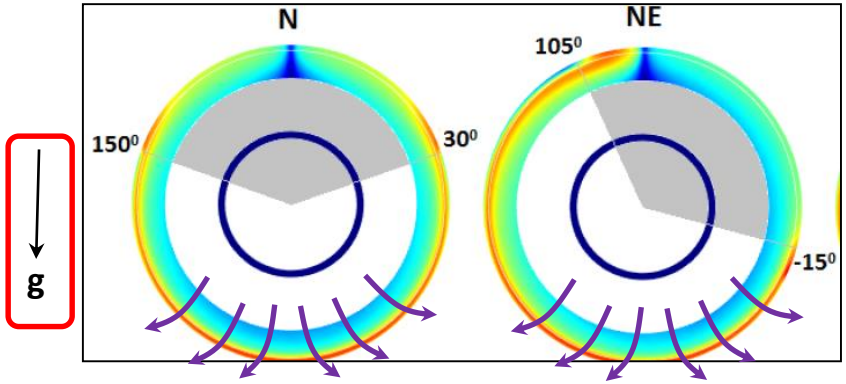
Figure 10
Normalized drug concentration across the plane $x = 3.75$ mm at (a) 10 minutes; (b) 20 minutes after eye drop instillation at a standing position.

RESULTS & DISCUSSIONS

Standing position

Figure 11
Values of mass transport by convection, M_{conv} and mass transport by diffusion, M_{diff} across the active and non-active region of the TM for the eye in the standing position, after 10 minutes upon eye drop instillation.





Hypothesis

the direction of the acting gravitational contributes to the preferential outflow of the drugs through the bottom half of the eye.

RESULTS & DISCUSSIONS

Supine position

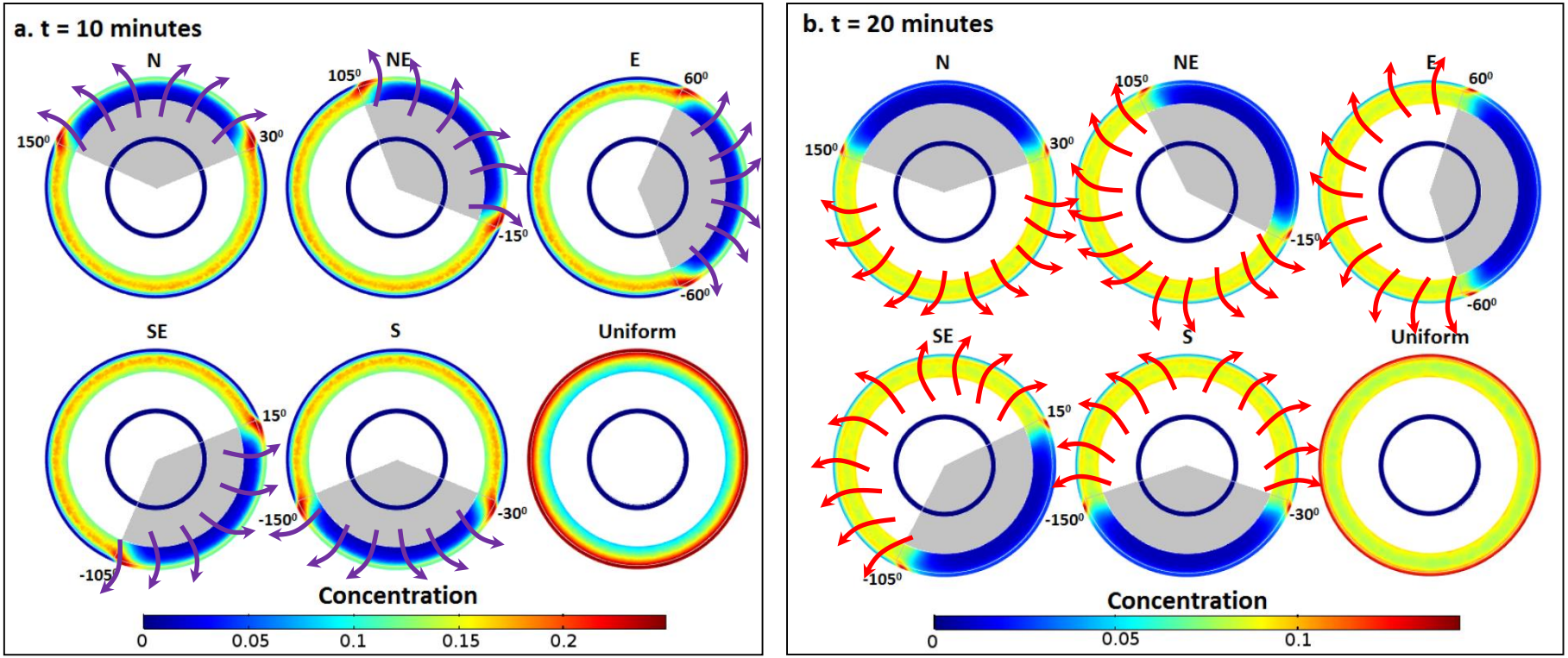


Figure 13

Normalized drug concentration across the plane $x = 3.75$ mm at (a) 10 minutes; (b) 20 minutes after eye drop instillation at a supine position.

RESULTS & DISCUSSIONS

Total mass transport through the TM by convection & diffusion

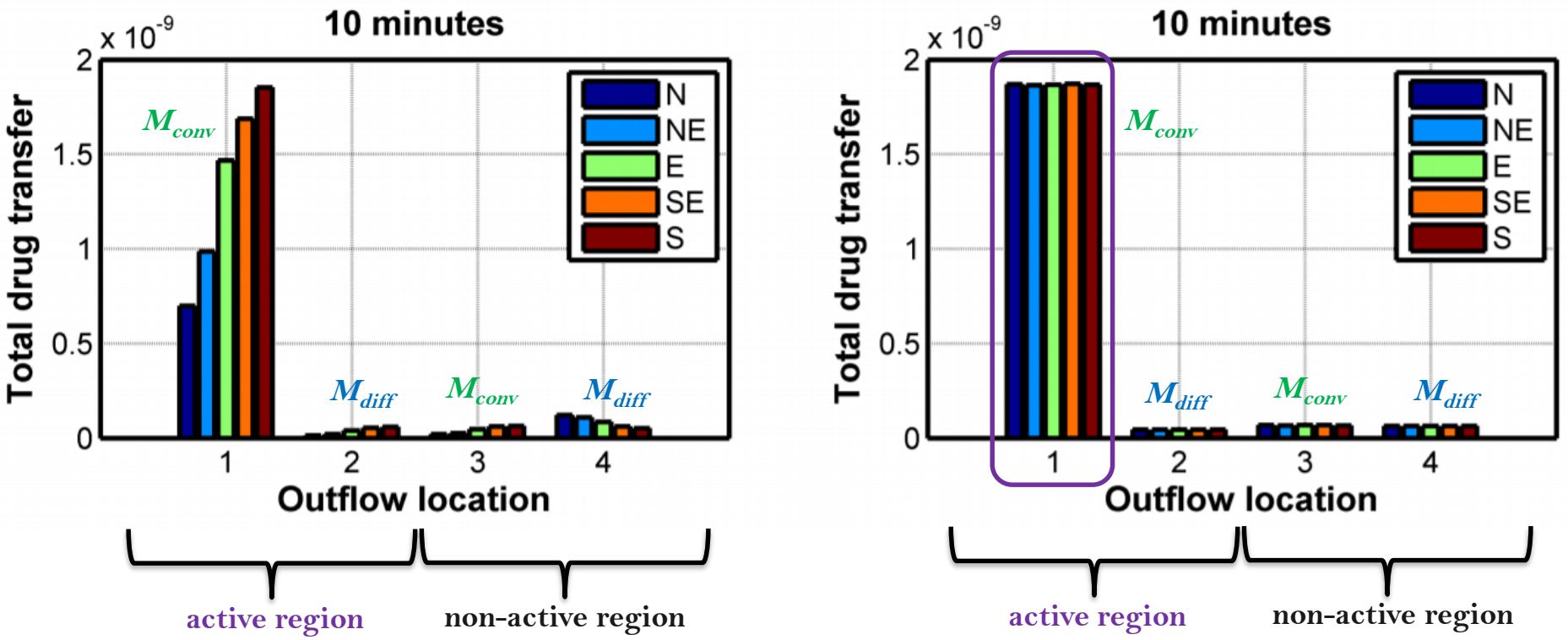


Figure 14

Values of M_{conv} and M_{diff} across the active and non-active region of the TM for the eye in the (a) standing and (b) supine position, after 10 minutes upon eye drop instillation.

RESULTS & DISCUSSIONS

Total mass transport through the TM by convection & diffusion

Table 4 Convective and diffusive drug transport through the active and non-active regions of the TM in (a) the standing position; and (b) the supine position, for the first 15 minutes upon eye drop instillation.

(a) **standing position**

	Total amount of drugs ($\times 10^{-9}$)				
	Active	Non-active	Clearance	Remaining	Total
15 minutes					
N	3.3569	0.3627	5.2816	5.9899	14.9911
NE	3.3538	0.3609	5.2790	5.9860	14.9797
E	3.3537	0.3624	5.2847	5.9943	14.9951
SE	3.3630	0.3617	5.2853	5.9960	15.006
S	3.3561	0.3606	5.2795	5.9866	14.9827

(b) **supine position**

	Total amount of drugs ($\times 10^{-9}$)				
	Active	Non-active	Clearance	Remaining	Total
15 minutes					
N	18.7560	2.9638	57.7310	61.4594	140.9100
NE	19.9471	2.7575	57.3550	62.2207	142.2800
E	24.7065	2.5230	55.9910	60.7867	144.0070
SE	26.6866	2.1509	55.7410	61.1961	145.7750
S	28.8066	2.0337	54.9460	59.2568	145.0430

CONCLUSION

- ✓ the hypothesis of ‘over-treated’ and 'under-treated' conditions are tenable
- ✓ treatment at a supine position may lead to higher drug efficacy

THANK YOU