Seeing the Wood for the Trees with Mathematical Modelling

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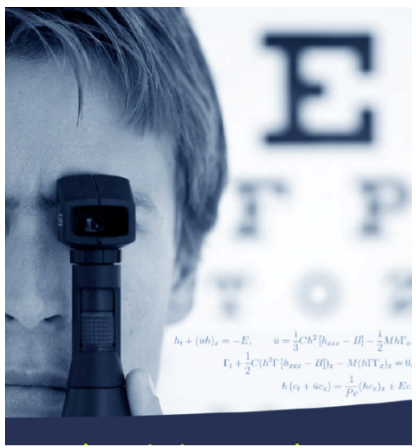

The University of Nottingham

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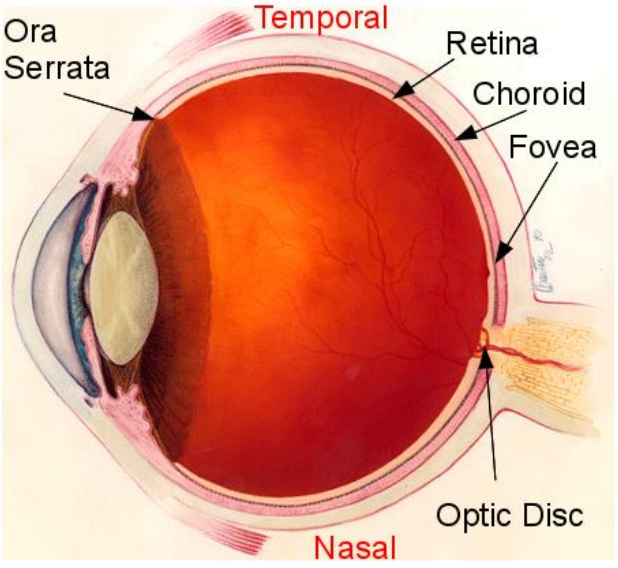
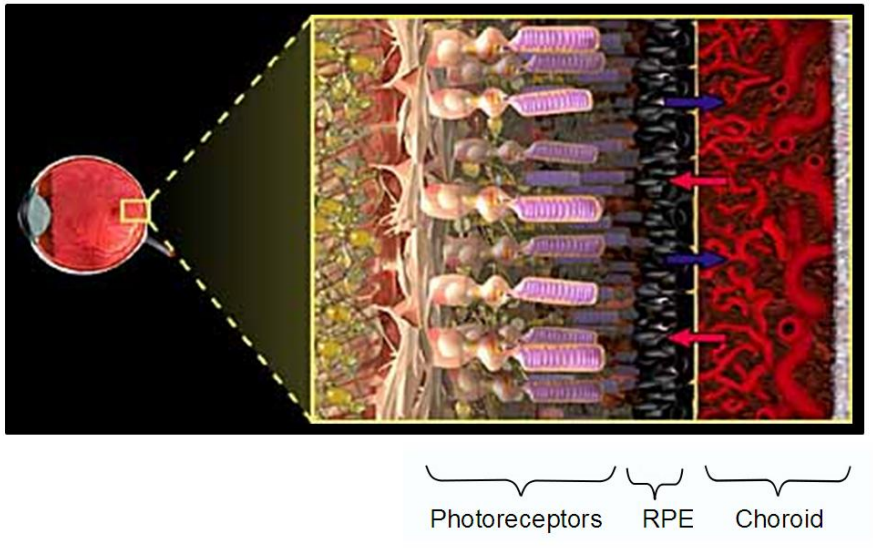
Talk Outline



The human eye (transverse plane)



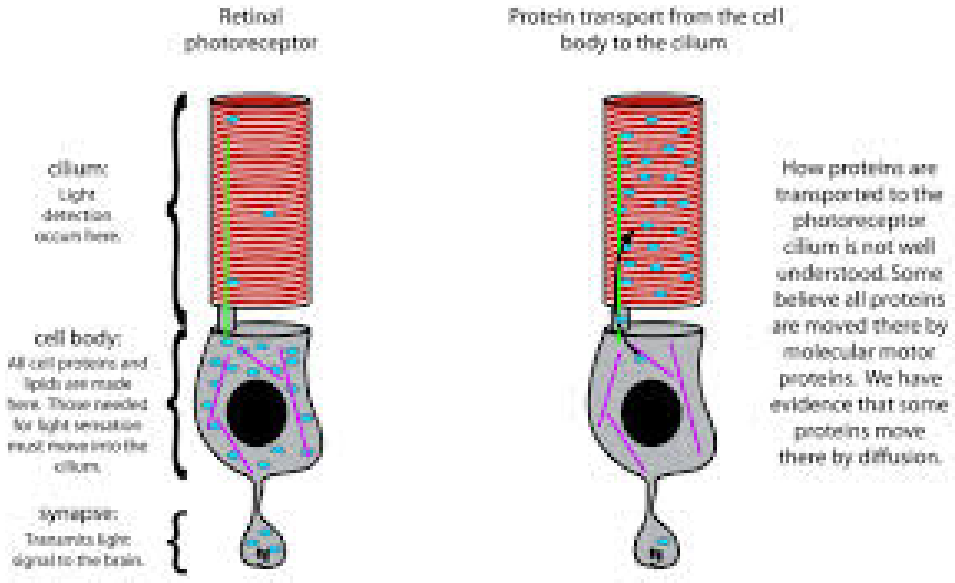
The structure of the retina

- Micro: metabolism as a determinant of diurnal variations in rod photoreceptor length
- Macro: hyperoxia as a driver of retinitis pigmentosa

Length Variation in Rod Photoreceptors

Aim

- Establish whether changes in metabolism can explain diurnal variations in rod photoreceptor length

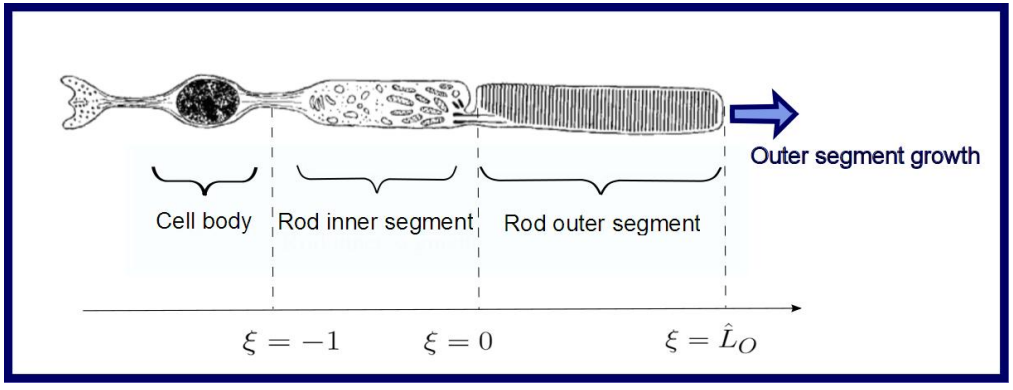


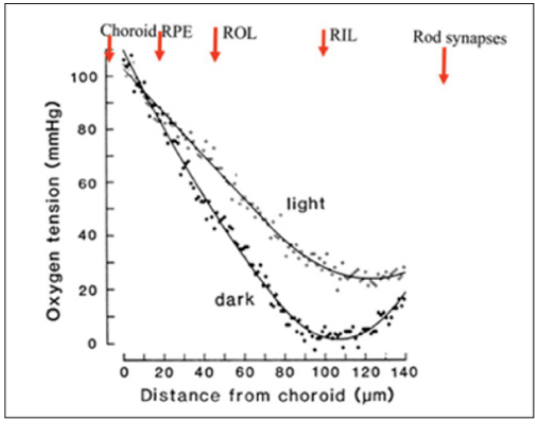
Acknowledgements

- **Lindsey MacDougall**, Markus Owen, Alex Foss, Nottingham

Rod Photorecptor Metabolism

Discs in outer segment continously turned over





- Dark conditions $\Rightarrow$ net growth of outer segment (OS)
- Light conditions $\Rightarrow$ net decrease in OS length
- **Question:** changes in metabolism regulate OS length?
  - **Hypothesis 1:** oxygen regulates outer segment length.
  - **Hypothesis 2:** phosphocreatine shuttle regulates OS length

Dimensionless Model Equations

$$\frac{\partial [O_2]}{\partial \tau} + \frac{\partial}{\partial \xi}(v[O_2]) = D_O \frac{\partial^2}{\partial \xi^2}[O_2] - \underbrace{\gamma_{\text{mito}} H(-\xi)[O_2]}_{\text{mito. consumptn}} - \underbrace{\gamma_{\text{decay}}[O_2]}_{\text{nat. decay}}$$

where $\gamma_{\text{mito}}^{\text{dark}} = 2\gamma_{\text{mito}}^{\text{light}}$ (i.e. more energy needed in dark)

$$\frac{\partial [O_2]}{\partial \xi}(-1, \tau) = 0, \quad [O_2](L_O, \tau) = 1,$$

$$\frac{\partial v}{\partial x} = r([O_2]|_{\xi=-1} - [O_2]^*)\delta(x), \quad v(-1, \tau) = 0$$

$$\frac{dL_O}{d\tau} = v(L_O, \tau) = r\left([O_2]|_{\xi=-1} - [O_2]^*\right)$$

Dimensionless Model Equations

$$\frac{\partial [O_2]}{\partial \tau} + \frac{\partial}{\partial \xi}(v[O_2]) = D_O \frac{\partial^2}{\partial \xi^2}[O_2] - \underbrace{\gamma_{\text{mito}} H(-\xi)[O_2]}_{\text{mito. consumptn}} - \underbrace{\gamma_{\text{decay}}[O_2]}_{\text{nat. decay}}$$

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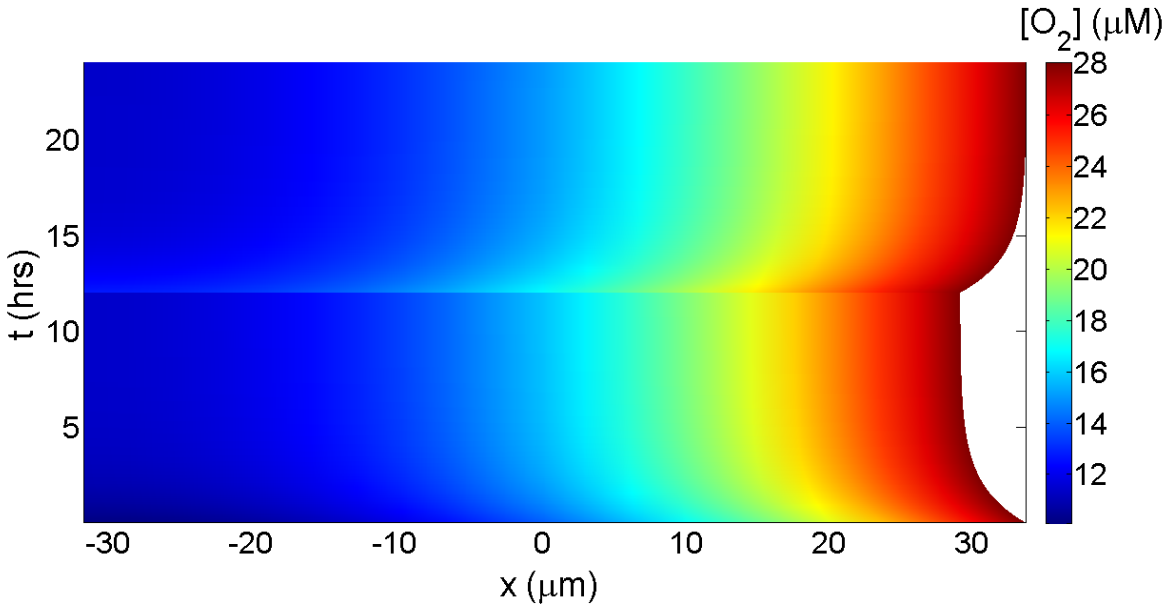
$$\frac{dL_O}{d\tau} = v(L_O, \tau) = r\left([O_2]|_{\xi=-1} - [O_2]^*\right)$$

Simulation Results



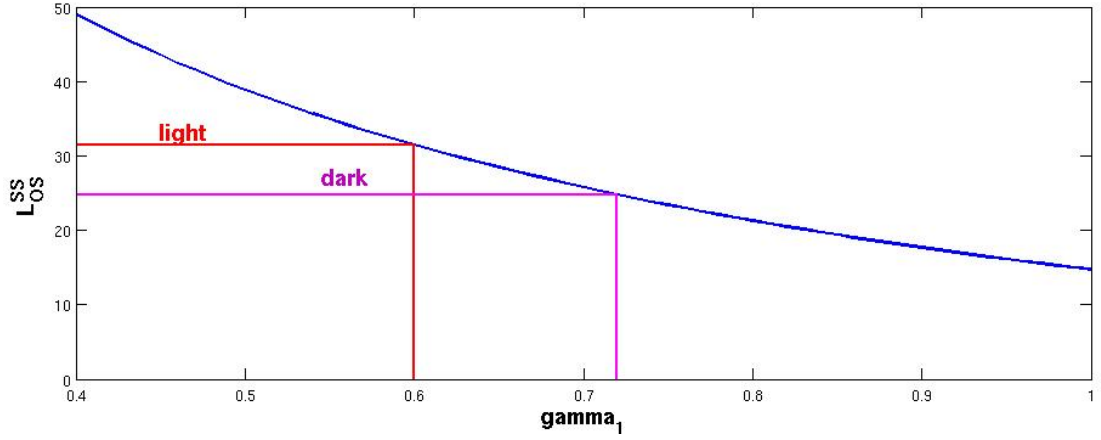
Typical simulation showing oxygen distribution (M).

- **Light conditions:** outer segment **grows**
- **Dark conditions:** outer segment **shrinks**
- **Wrong way round!**
- Oxygen **not** limiting in light but **could be** in dark

Steady State Analysis

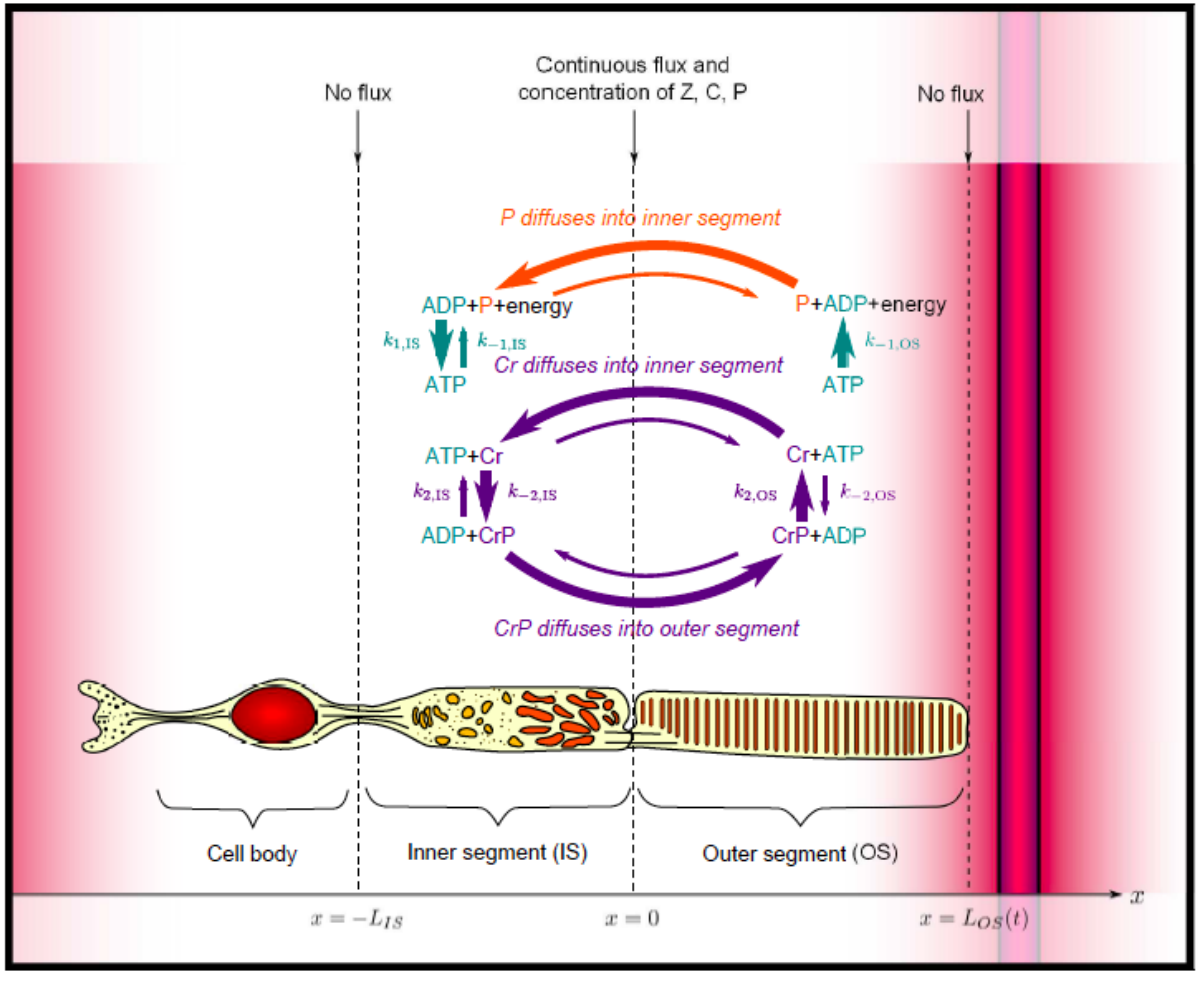
$$\frac{\partial[O_2]}{\partial t} = 0 = \frac{dL_0}{dt} \Rightarrow L_O = \frac{1}{\sqrt{\gamma_2}} \ln\left\{\frac{1}{[O_2]^*}\left(1+\sqrt{1+[O_2]^{*2}(\beta^2-\alpha^2)}\right)\right\}$$

where $\alpha = \cosh\sqrt{\gamma_1}$, $\beta = \sqrt{\gamma_1/\gamma_2}\sinh\sqrt{\gamma_1}$, $\gamma_1 = \gamma_{mito}+\gamma_{decay} > \gamma_2 = \gamma_{decay}$



Dependence of L_O at steady state on γ_1, $[O_2]$ consumption rate in IS.
$L_O^{dark} < L_O^{light}$ because $\gamma_1^{dark} > \gamma_1^{light}$: contradicts biology

The phosphocreatine shuttle



Phosphocreatine Shuttle Model

Inner segment (IS)	Outer segment (OS)
$\frac{D[CrP]}{D\tau} = D_{CrP}\frac{\partial^2[CrP]}{\partial\xi^2} + S([CrP],[Cr],[P])$ $\frac{D[Cr]}{D\tau} = D_{Cr}\frac{\partial^2[Cr]}{\partial\xi^2} - S([CrP],[Cr],[P])$ $\frac{D[P]}{D\tau} = D_{P}\frac{\partial^2[P]}{\partial\xi^2} - S([CrP],[Cr],[P])$	$\frac{\partial[CrP]}{\partial\tau} = D_{CrP}\frac{\partial^2[CrP]}{\partial\xi^2} - E([CrP])$ $\frac{D[Cr]}{D\tau} = D_{Cr}\frac{\partial^2[Cr]}{\partial\xi^2} + E([CrP])$ $\frac{D[P]}{D\tau} = D_{P}\frac{\partial^2[P]}{\partial\xi^2} + E([CrP])$
$S = \frac{k_1 k_{-2}[Cr][P] - k_2 k_{-1}[CrP]}{k_1[P] + k_2[CrP] + k_{-1} + k_{-2}[Cr]}$	$E = \frac{-k_2 k_{-1}[CrP]}{k_2[CrP] + k_{-1} + k_{-2}[Cr]}$
Law of Mass Action With fast kinetics for $[ATP]$ and $[ADP]$	$k_1 = 0$ (no ATP produced in OS) Saturating demand for CrP (dark conditions $\Rightarrow$ $k_{-1} = 0$)

where $\frac{Df}{D\tau} = \frac{\partial f}{\partial\tau} + \frac{\partial}{\partial\xi}(vf)$

Phosphocreatine Shuttle Model

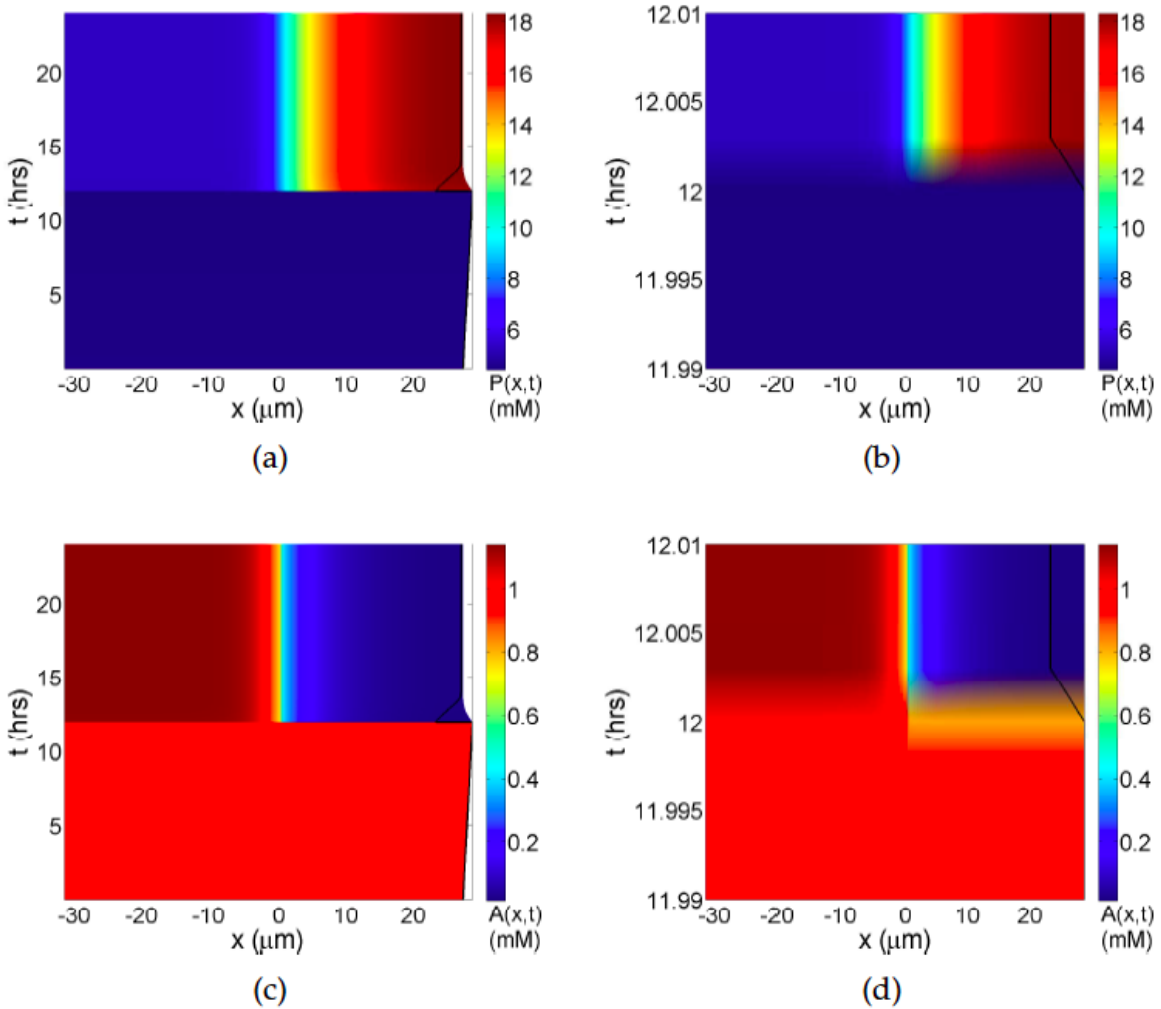
- Assume discs shed where ATP low (i.e., where $[A] < [A^*]$)
- Define internal free boundary, $\xi = \hat{L}_O^*$, implicitly:

$$[ATP] = \frac{k_1[P] + k_2[CrP]}{k_1[P] + k_2[CrP] + k_{-1} + k_{-2}[CrP]} = \begin{cases} > [A^*] & \text{for } \xi < \hat{L}_O^* \\ = [A^*] & \text{for } \xi = \hat{L}_O^* \\ < [A^*] & \text{for } \xi > \hat{L}_O^* \end{cases}$$

- Assume outer segment grows such that

$$\frac{d\hat{L}_O}{d\tau} = v(L_O, \tau) = K_{\text{grow}} - \alpha\left(\hat{L}_O - \hat{L}_O^*\right) \mathrm{H}\left(\hat{L}_O - \hat{L}_O^*\right)$$

Phosphocreatine Shuttle Model



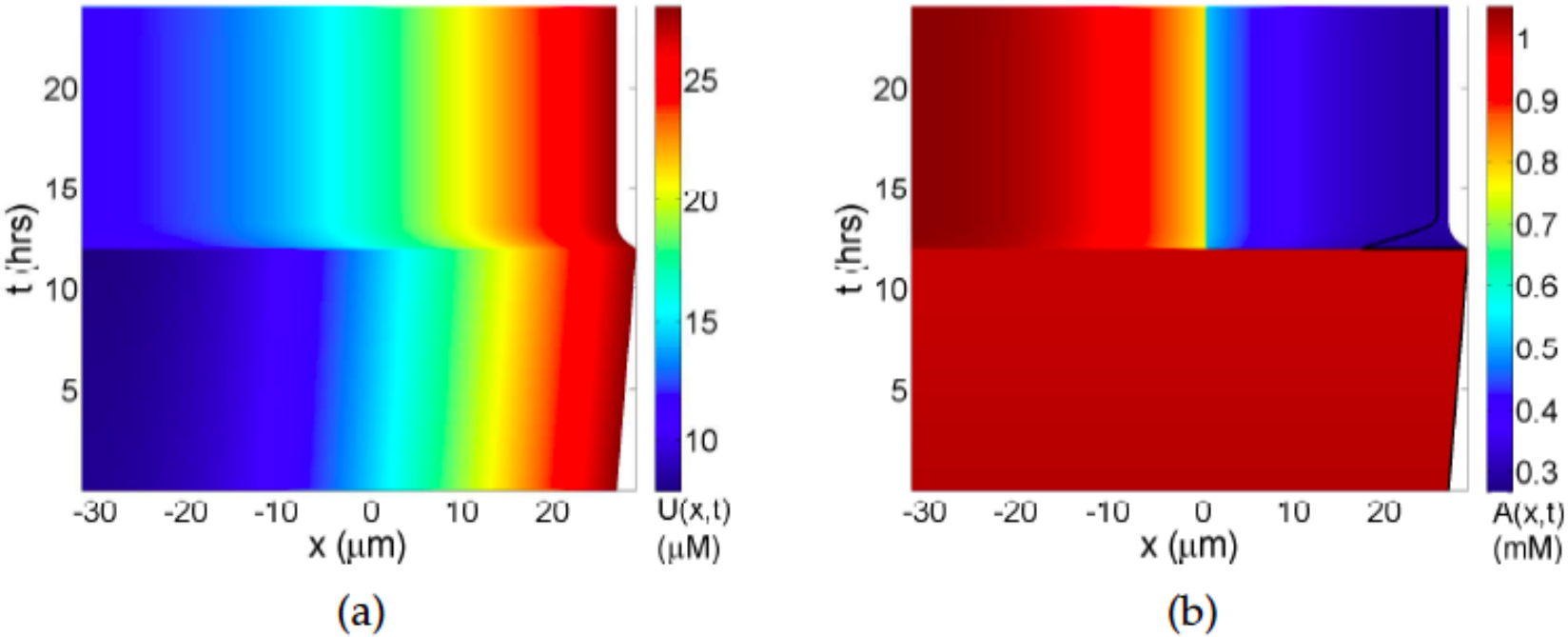
- **Light conditions:** outer segment shrinks
- **Dark conditions:** outer segment grows indefinitely
- Shuttle **not** growth-rate limiting in dark but **could be** in light

Combined Model

- PDEs for $[O_2]$, $[Cr]$, $[P]$, $[CrP]$ as before
- Coupling via growth of outer segment:

$$\frac{d\hat{L}_O}{d\tau} = r\left([O_2]|_{\xi=-1} - [O_2]^*\right) - \alpha\left(\hat{L}_O - \hat{L}_O^*\right)\mathrm{H}\left(\hat{L}_O - \hat{L}_O^*\right)$$

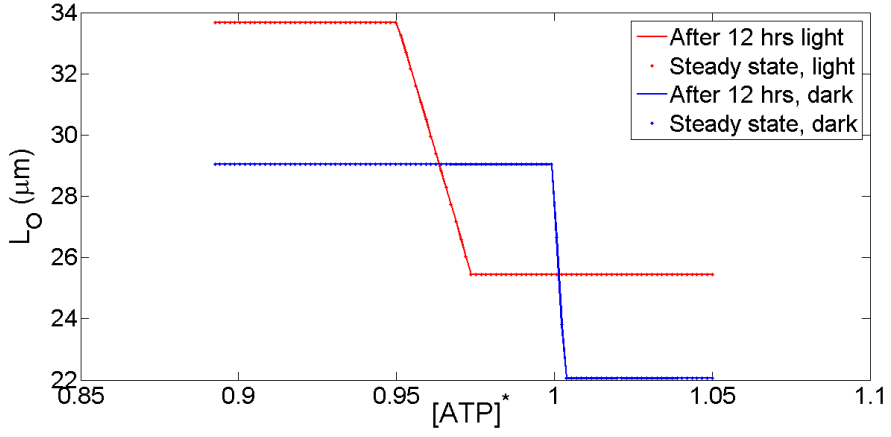
Combined Model: Numerical Results

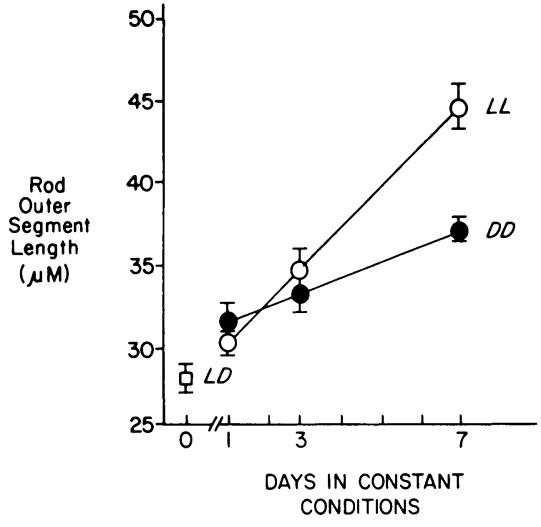


Conclusions

- **Light conditions:** outer segment shrinks
- **Dark conditions:** outer segment grows
- Growth and shedding regulated under light and dark conditions!
- Need combined model to obtain observed behaviour

Combined Model: Compare with Experimental Results



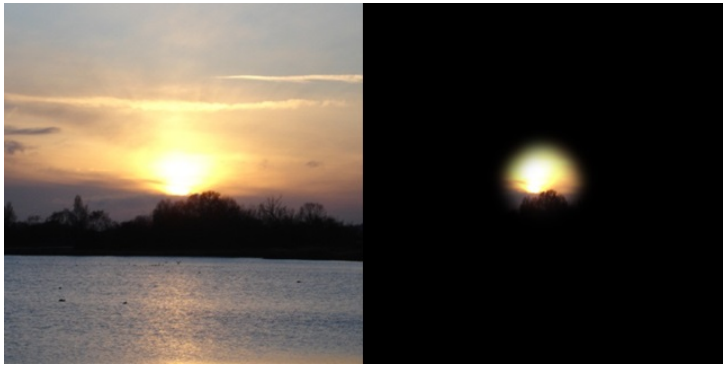


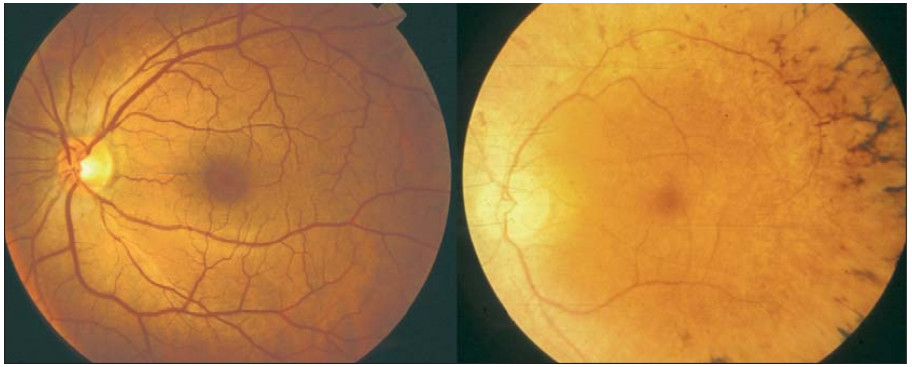
Left: variation with A^* of L_{OS} at steady state
Right: experimental results for goldfish

Conclusions

- Good qualitative agreement between theoretical and experimental results
- Shortening of photoreceptors predicted under ageing (metabolism less efficient)

Retinitis Pigmentosa

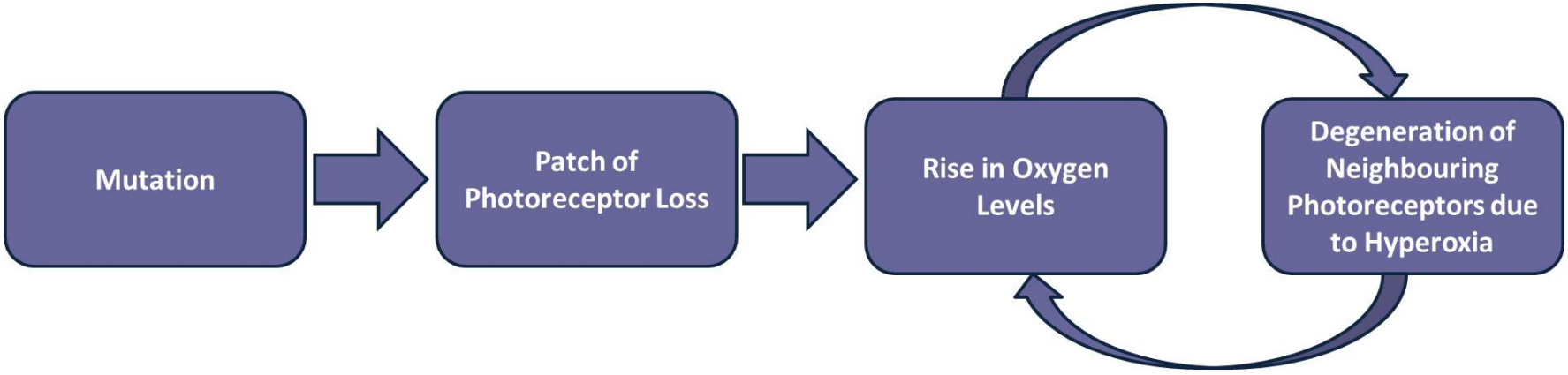




Hartong *et al.*, Lancet (2006)

- Genetically mediated retinal degenerative disease
- Rod-cone dystrophy
- Night blindness, tunnel vision and loss of central vision
- A leading cause of blindness worldwide
- No effective treatments available

The Oxygen Toxicity Hypothesis



Questions

- What is the critical width of a patch of photoreceptor loss needed to induce a wave of degeneration?
- How does pattern of degeneration depend upon eccentricity?

Acknowledgements

- **Paul Roberts**, Eamonn Gaffney, Oxford;
- Alex Foss, Nottingham; Phil Luthert, UCL.

1D Model Formulation I

Oxygen:
$$0 = \underbrace{\frac{D}{\sin(\Theta\theta)}\frac{\partial}{\partial\theta}\left(\sin(\Theta\theta)\frac{\partial c}{\partial\theta}\right)}_{\text{diffusion}} - \underbrace{\frac{Qpc}{\gamma + c}}_{\text{uptake}} + \underbrace{\beta(1-c)}_{\substack{\text{exchange with}\\ \text{choriod}}}$$

Photoreceptors:
$$\frac{\partial p}{\partial t} = \underbrace{\mu p\left(1 - \frac{p}{\tilde{p}(\theta)}\right)\lambda_1(c)}_{\text{regrowth (normoxia)}} - \underbrace{\lambda_2(c)p}_{\substack{\text{degeneration}\\ \text{(hyperoxia)}}}$$

where
$$\tilde{p}(\theta) = \underbrace{B_1 e^{-b_1\theta} + B_2 e^{-b_2\theta}}_{\text{Cones}} + \underbrace{B_3\theta e^{-b_3\theta}}_{\text{Rods}}$$

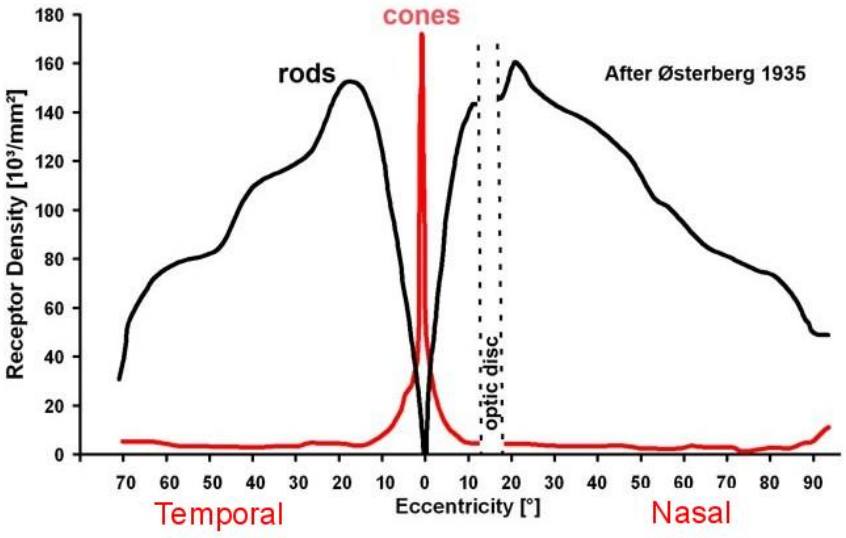
$$\lambda_1(c) = H(c_{crit} - c), \quad \lambda_2(c) = H(c - c_{crit}) = \begin{cases} 0 & \text{if } c < c_{crit} \\ 1 & \text{if } c \geq c_{crit} \end{cases}$$

1D Model Formulation III

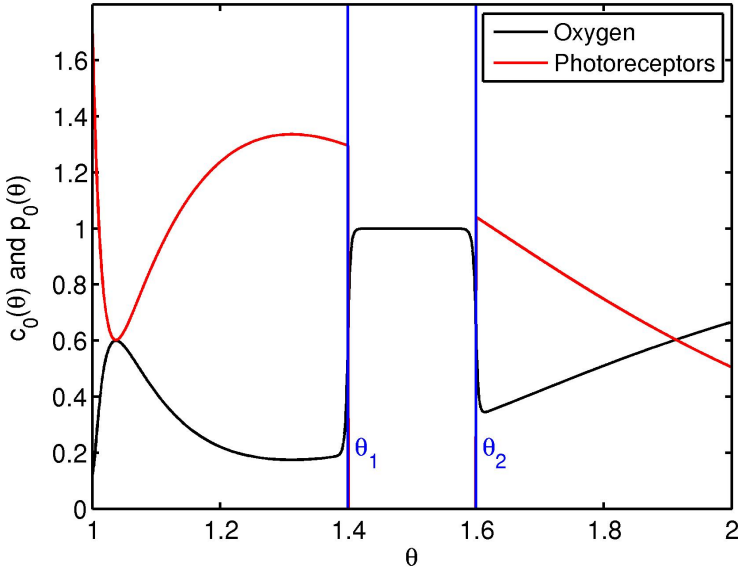
Initial conditions:

$$p(\theta, 0) = (B_1 e^{-b_1\theta} + B_1 e^{-b_2\theta} + B_3\theta e^{-b_3\theta})(H(\theta - \theta_2) + H(\theta_1 - \theta))$$

i.e. remove patch of photoreceptors from $\theta \in [\theta_1, \theta_2]$



Photoreceptor distribution

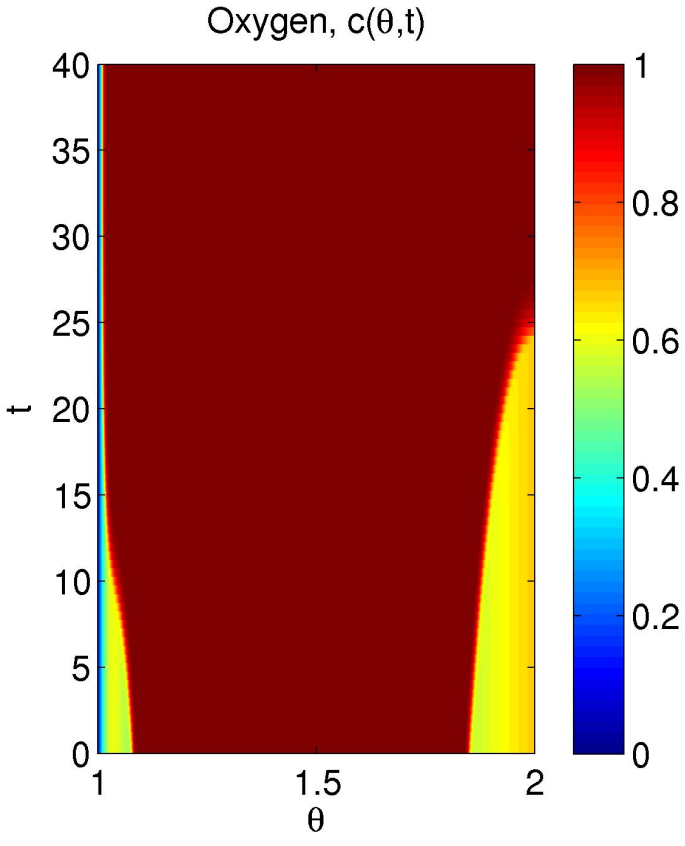


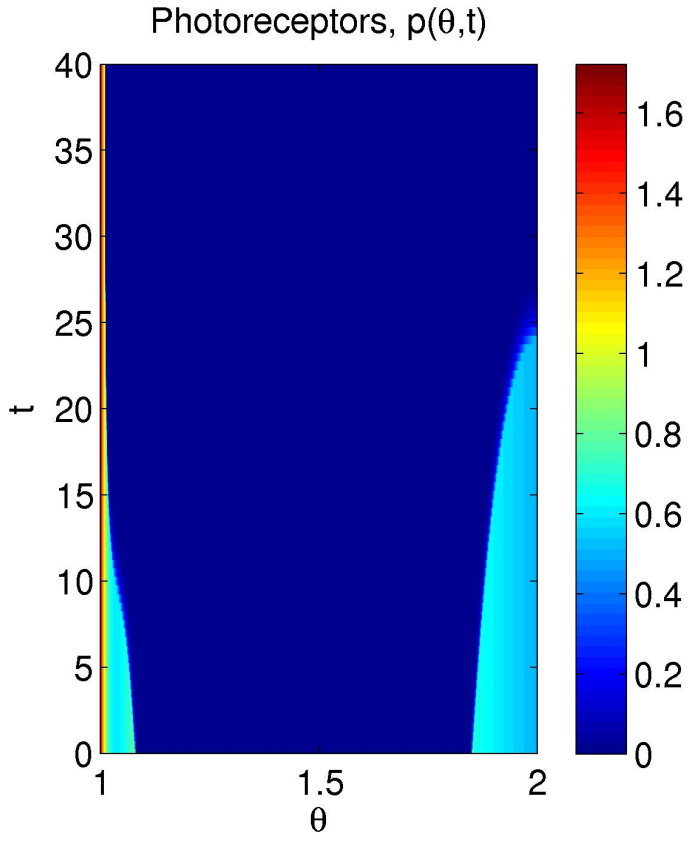
Curcio *et al.*, J.Comp.Neurol (1990)

Zero-flux boundary conditions: $\frac{\partial c}{\partial \theta}(1, t) = 0 = \frac{\partial c}{\partial \theta}(2, t)$

Motivating Simulations

$(\theta_1, \theta_2) = (1.08, 1.85)$

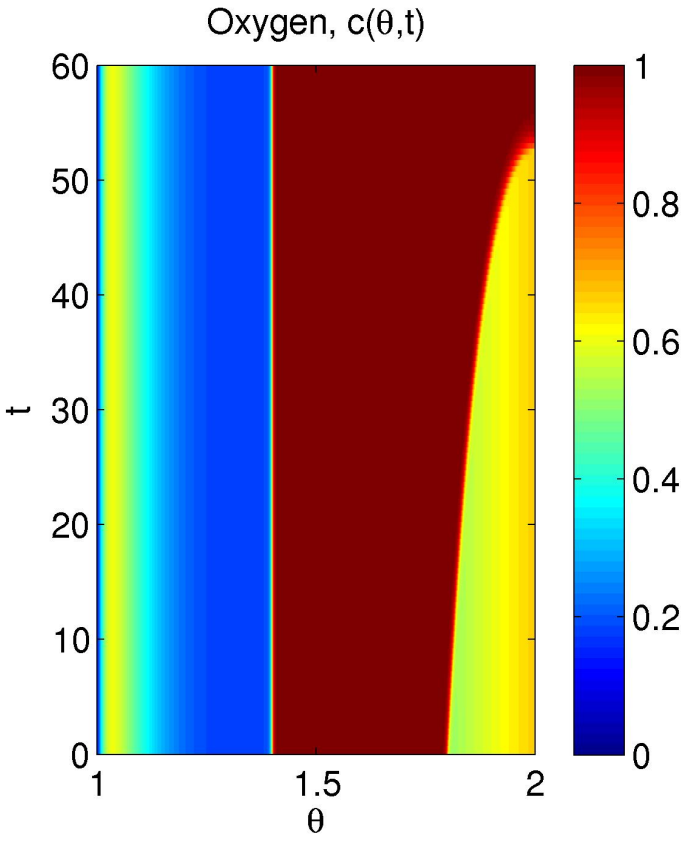


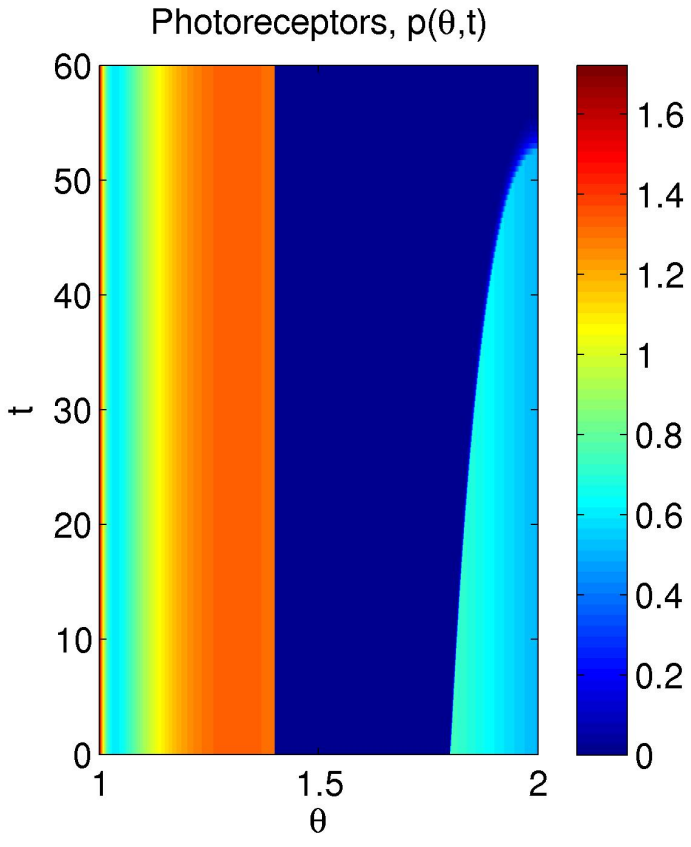


Large patch removed: degeneration spreads in both directions

Motivating Simulations

$(\theta_1, \theta_2) = (1.40, 1.80)$

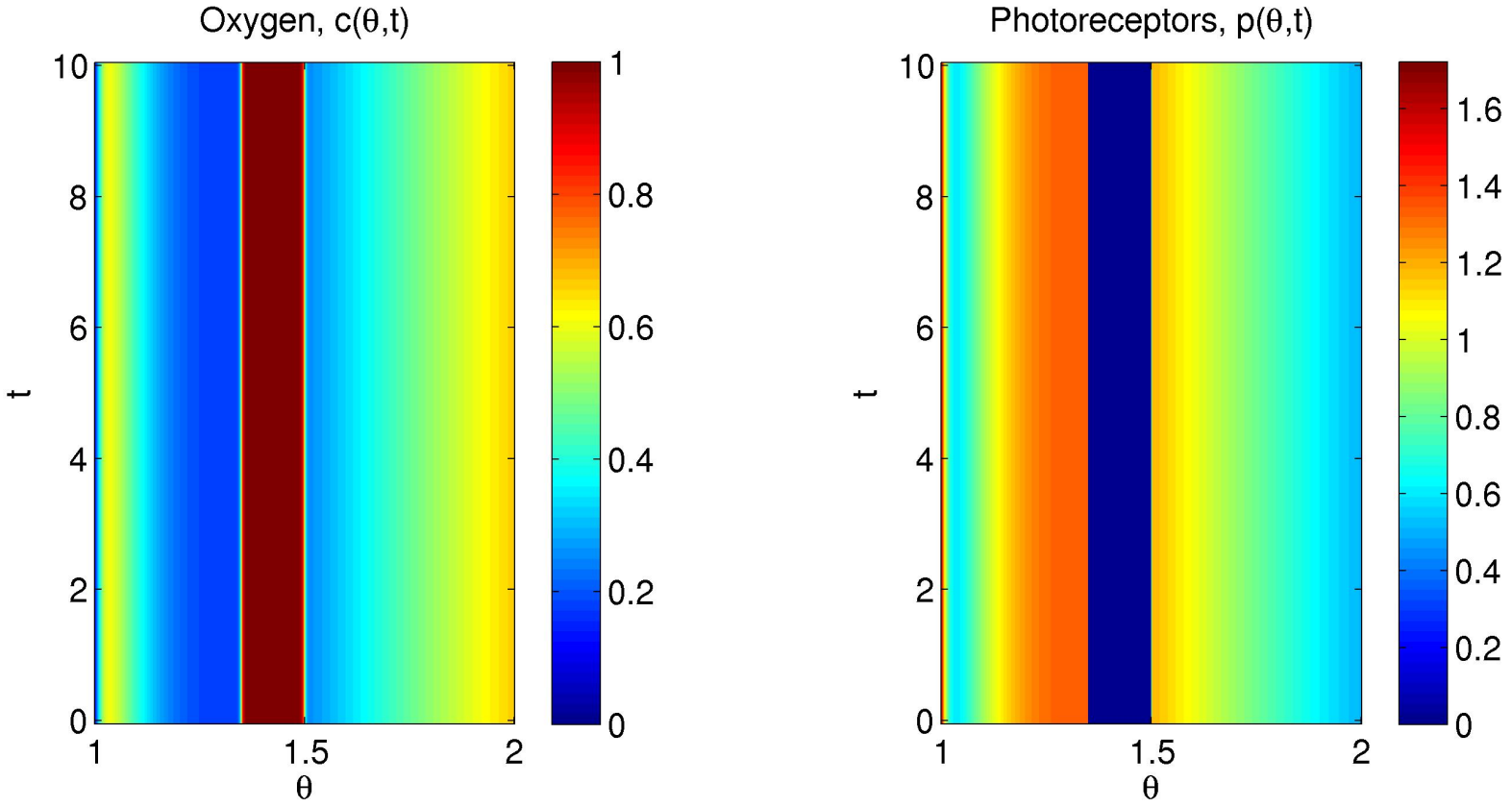




Smaller, right-skewed patch: degeneration spreads to the right only

Motivating Simulations

$(\theta_1, \theta_2) = (1.35, 1.50)$



Small, central patch removed: no degeneration

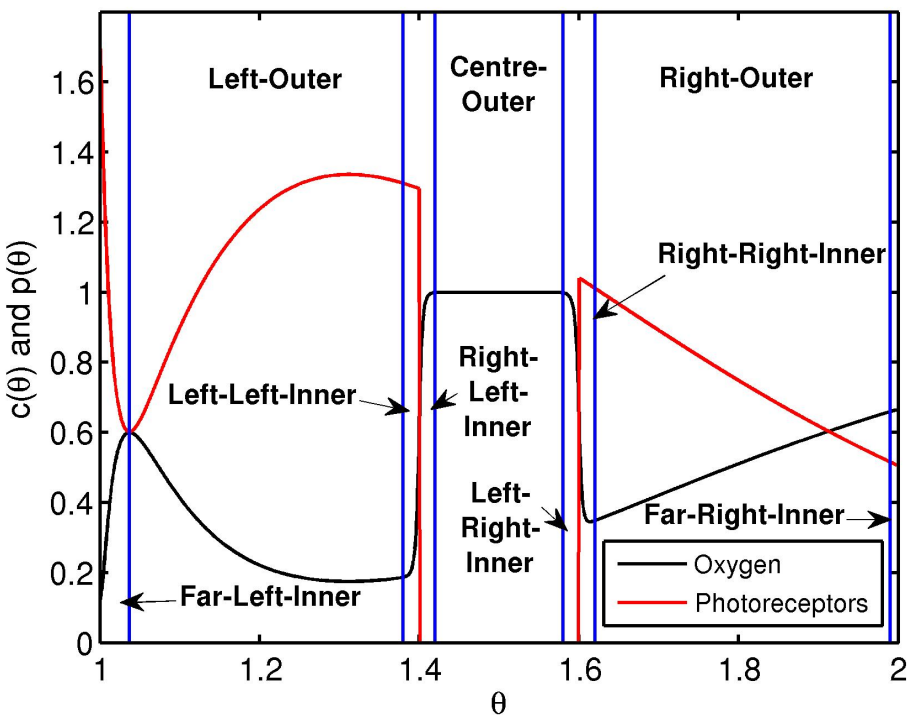
Quasi-Steady Asymptotic Analysis

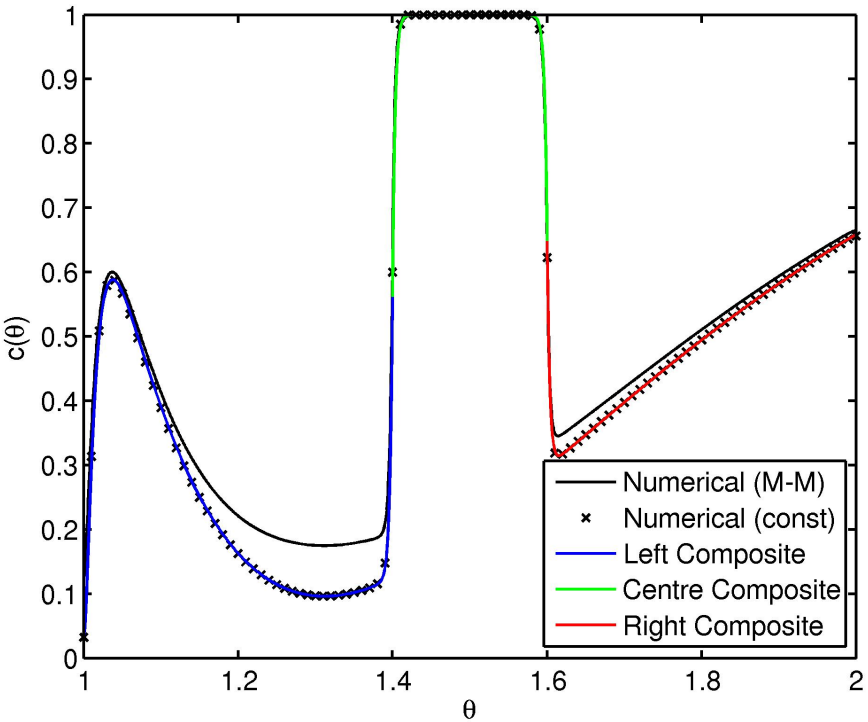
Consider quasi steady-state with $p = \tilde{p}(\theta)(H(\theta - \theta_2) + H(\theta_1 - \theta))$

$$D^* = \epsilon D,\ Q^* = \epsilon^3 Q,\ \beta^* = \epsilon^3 \beta,\ \gamma^* = \epsilon^{-1}\gamma,\ b_1^* = \epsilon b_1$$

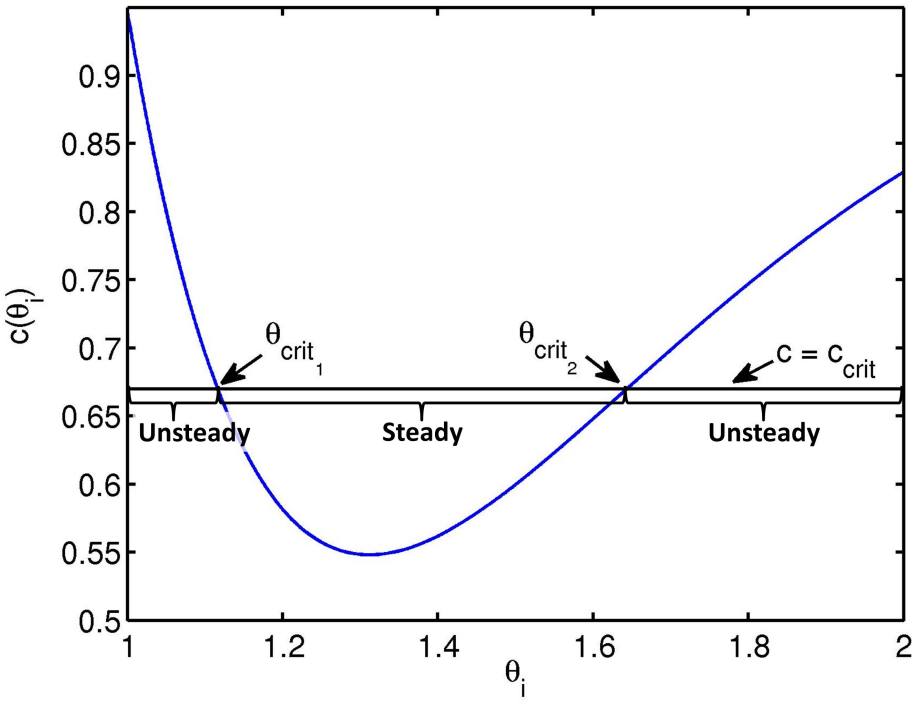
where $0 < \epsilon \ll 1$. Seek trial solutions of the form

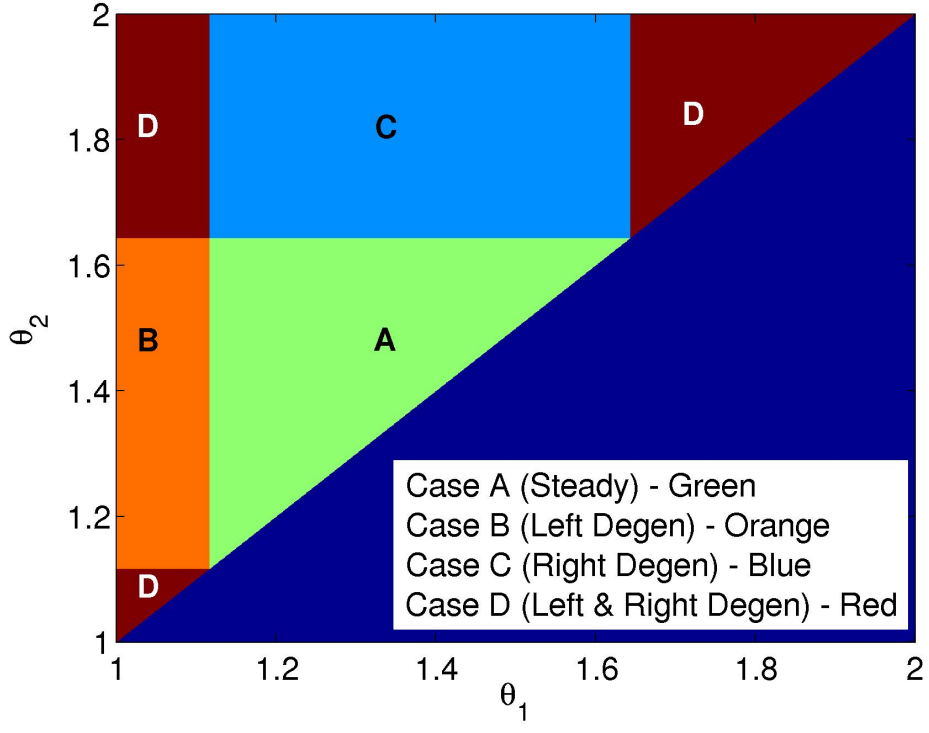
$$c(\theta) = c_0(\theta) + \epsilon c_1(\theta) + O(\epsilon^2) \qquad p(\theta) = p_0(\theta) + \epsilon p_1(\theta) + O(\epsilon^2)$$





Steady and Unsteady Regions



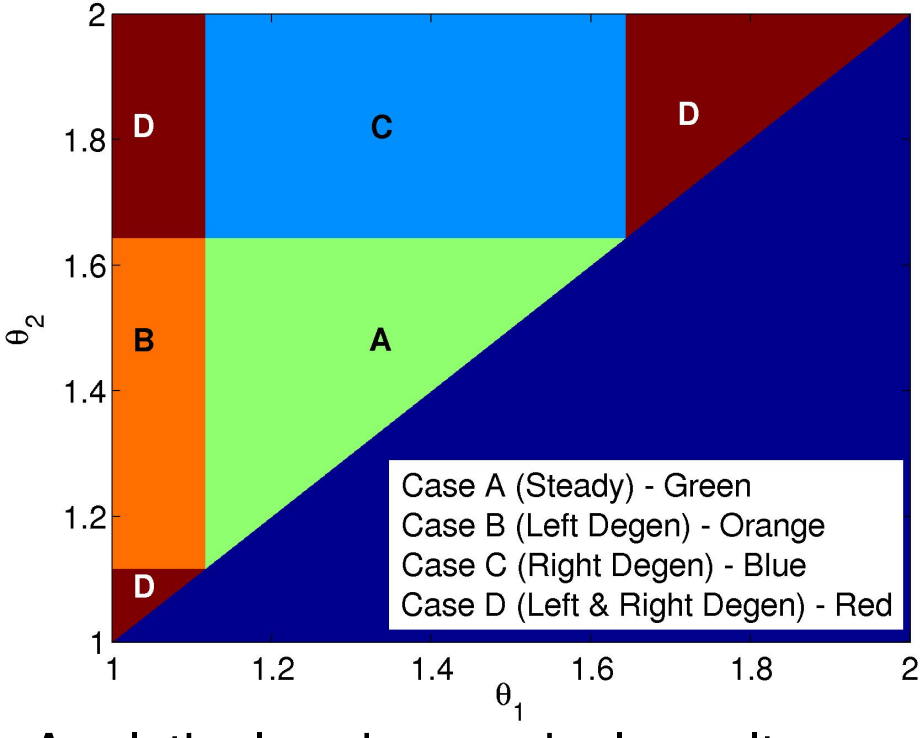


Boundaries of the 'steady region' ($0 < \theta_1 = \theta_{crit_1} \leq \theta_2 = \theta_{crit_2}$) solve

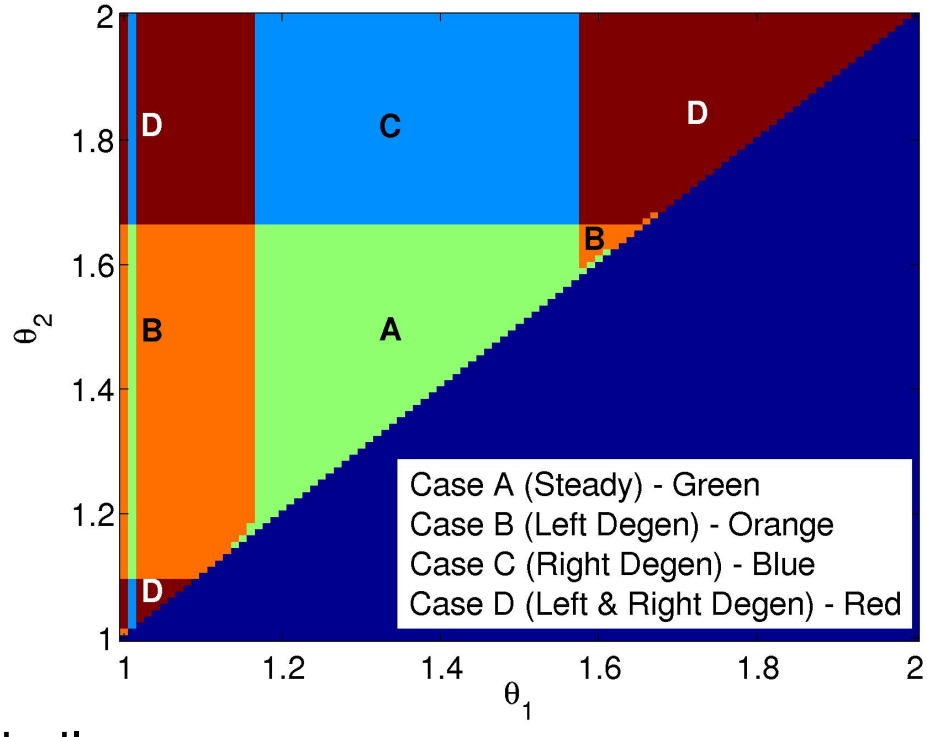
$$0 = (1 - c_{crit}) - \frac{Q}{2\beta}\left[B_2 e^{-b_2(\theta_{crit_i}-1)} + B_3(\theta_{crit_i}-1)e^{-b_3(\theta_{crit_i}-1)}\right] \quad (i = 1, 2)$$

Steady and Unsteady Regions – Comparison with Numerics

Analytical Approximation

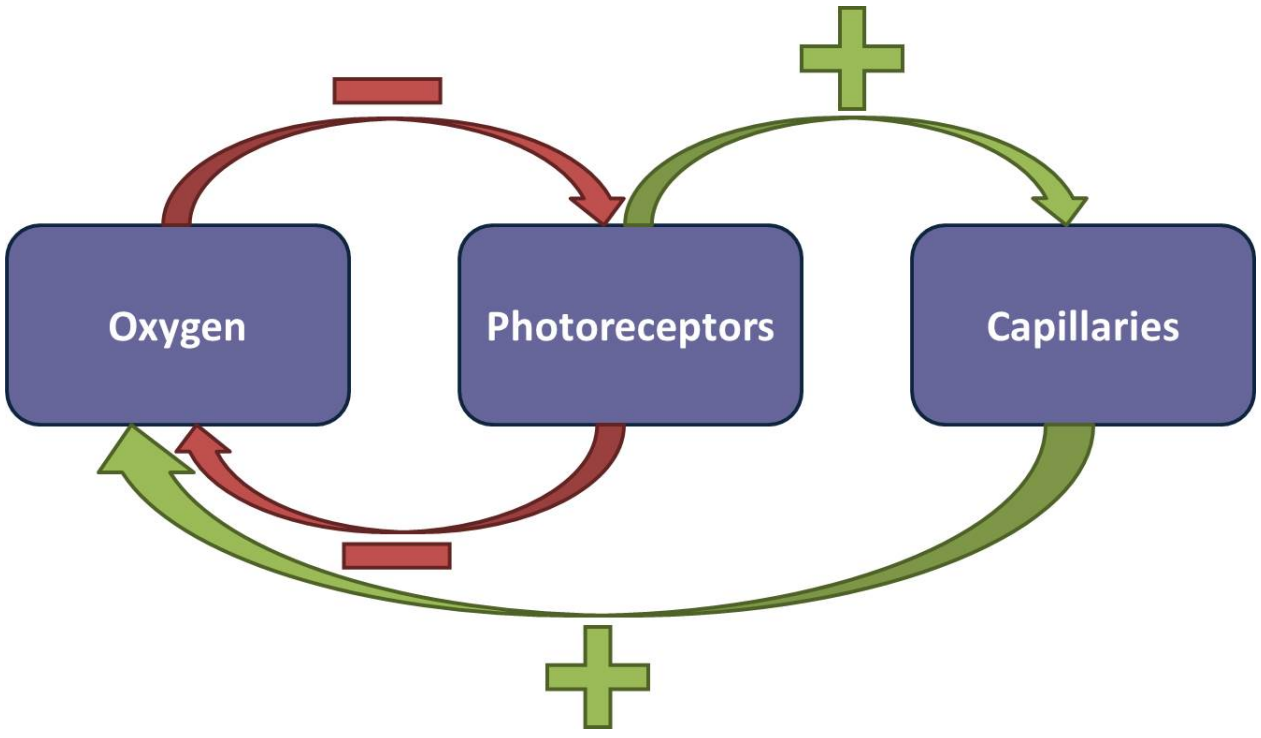


Numerical Result



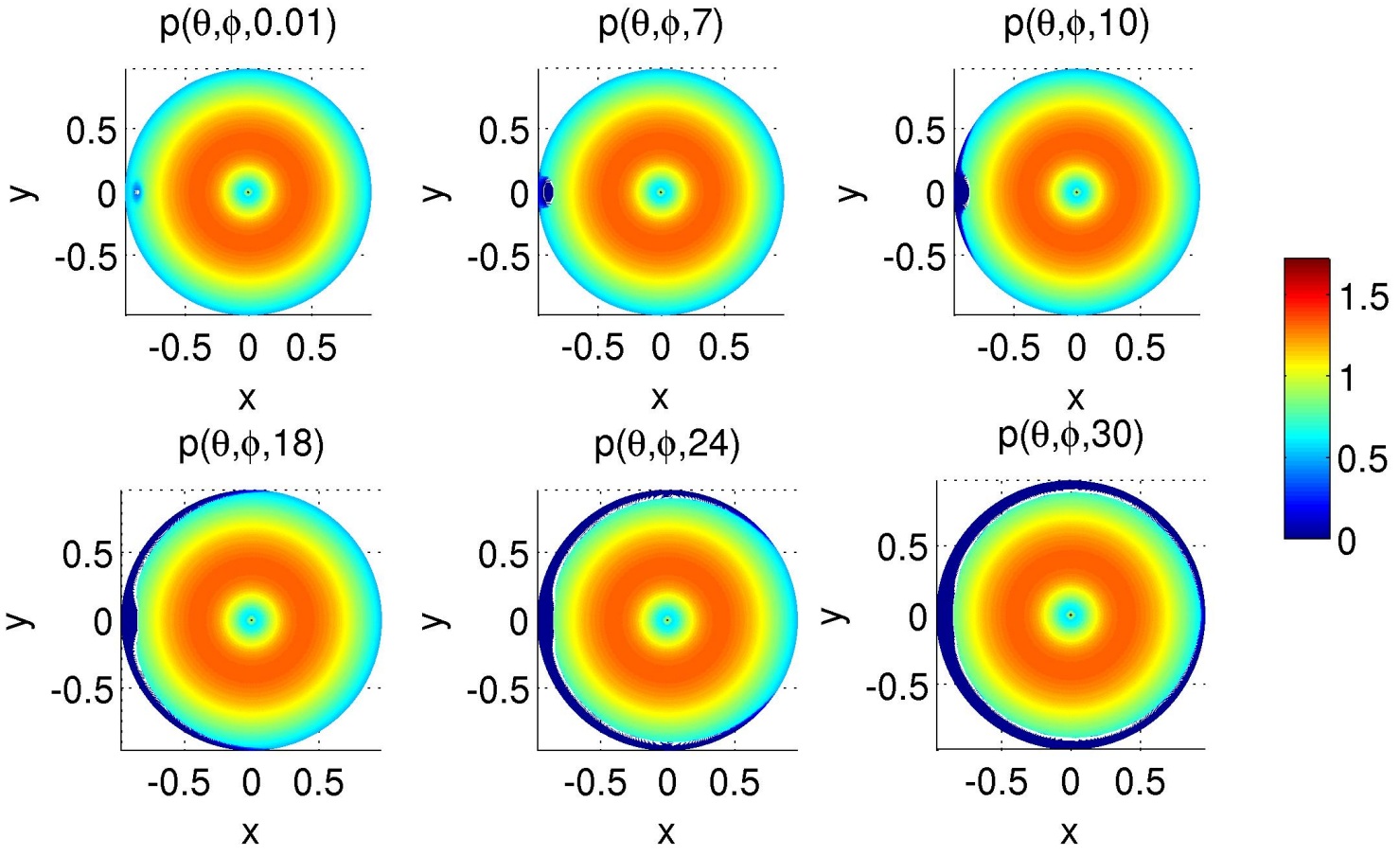
Analytical and numerical results are similar

Model Extensions



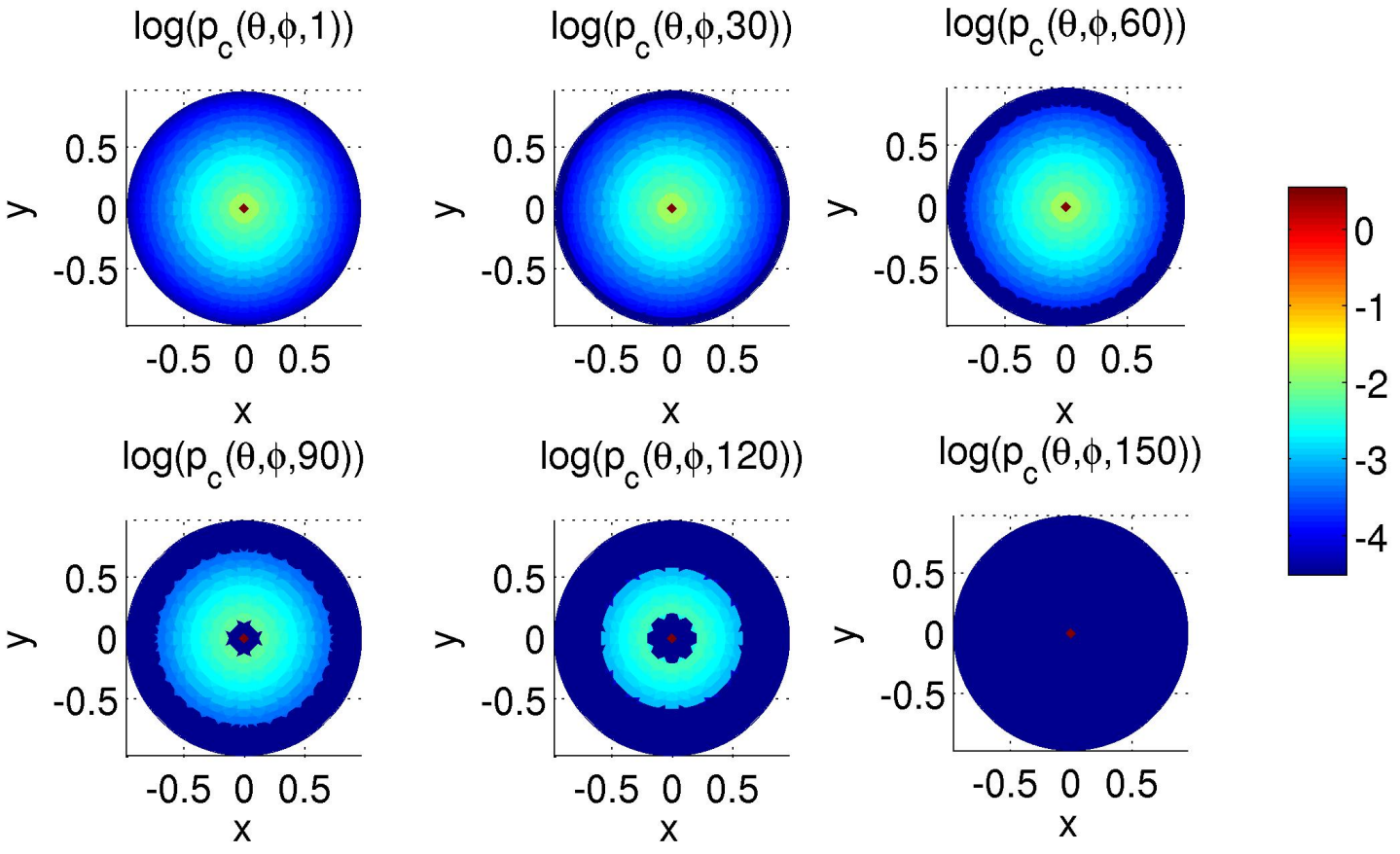
- Degeneration of the choroid (=supporting vasculature)
- 2D simulations, with patch of photoreceptors removed at $t = 0$

Patterns of Degneration I



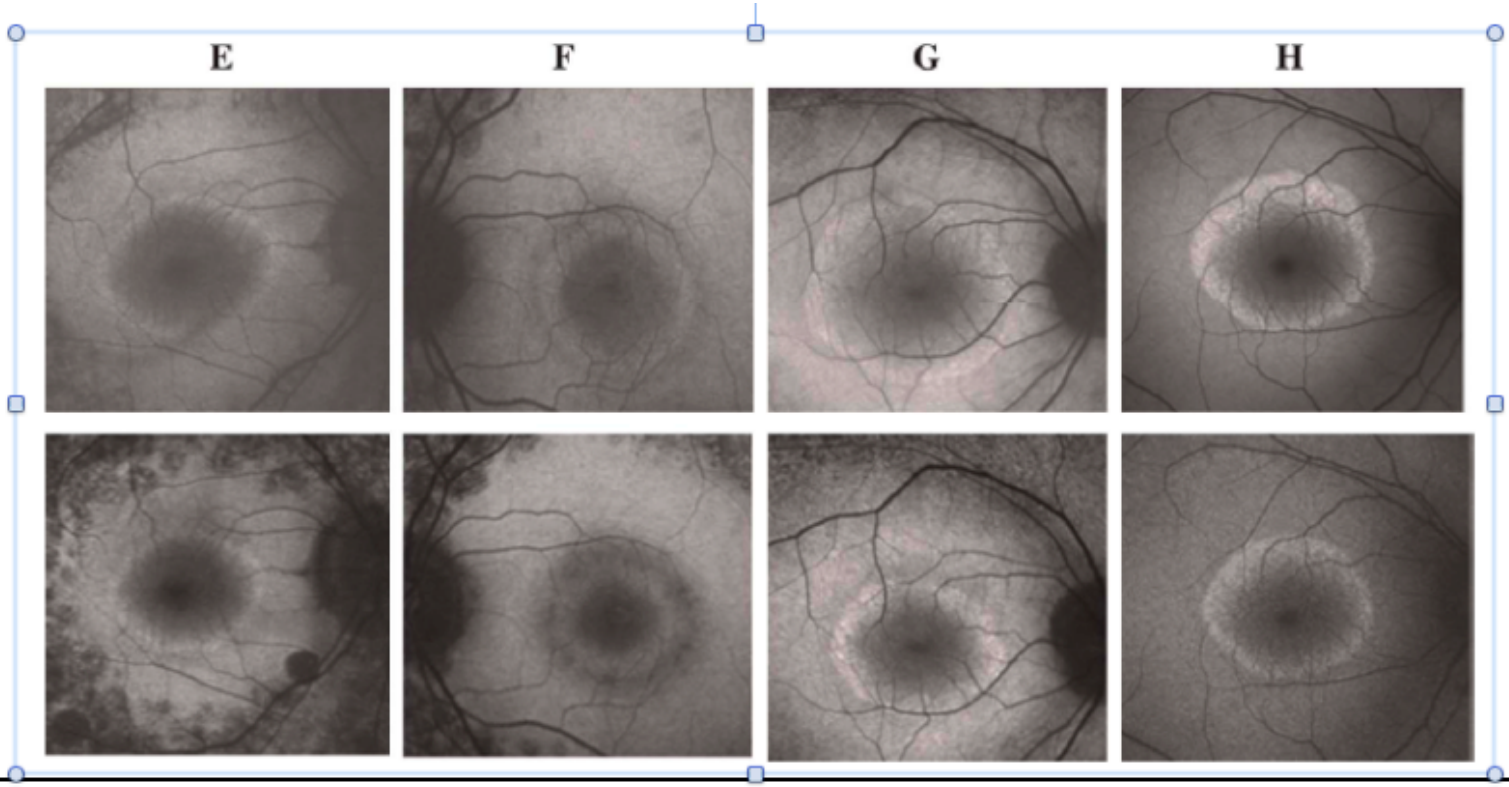
Degenerate patch of photoreceptors expands radially outwards and then extends around outer boundary of retina before propagating radially inwards.

Patterns of Degneration II



Mutant rods degenerate, stimulating hyperoxia and subsequent cone degeneration

Patterns of Photoreceptor Degeneration

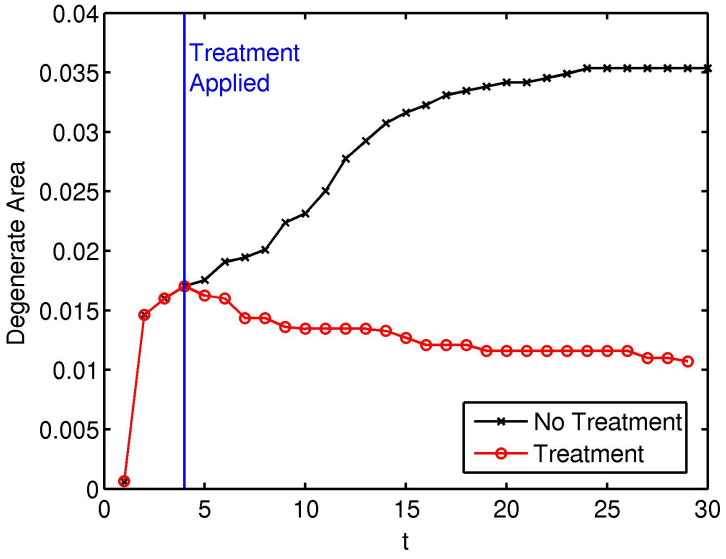


Pairs of autofluorescence images from 4 individual patients. The time intervals between the upper and lower frames are (E) 79, (F) 64, (G) 37 and (H) 12 months.

- Model reproduces two patterns associated with RP
- What about therapy?

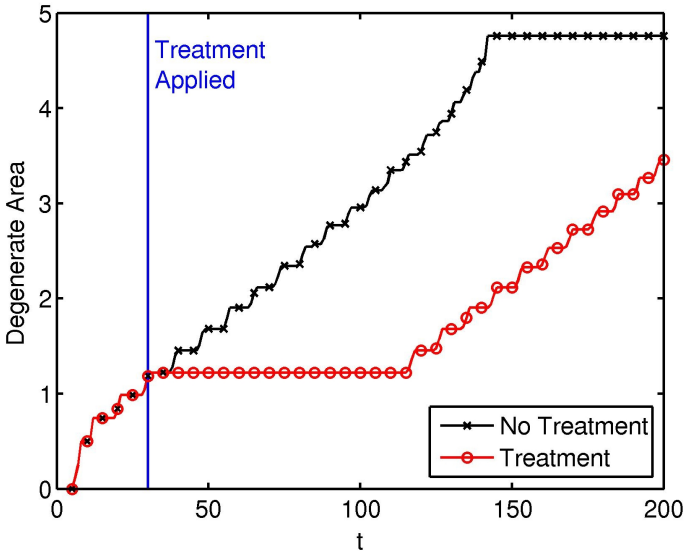
In Silico Treatment (Increases Hyperoxic Threshold)

Disc Loss



Partial recovery

Mutation-Induced Rod Loss



Delayed degeneration

Summary:

- Simple model for hyperoxia-driven photoreceptor degeneration
- Analysis of 1D model provides insight into disease progression
- Patterns of degeneration consistent with retinitis pigmentosa
- Compared possible treatments

Conclusions

- The eye is a fascinating organ, ideal for math investigation
- Simple models can provide mechanistic insight into its behaviour