Modeling the homeostatic length of the rod outer segment in zebrafish

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Introduction

- Rods and cones are two retinal photoreceptor cells in the eye that enable vision by converting light energy into electrical signals perceived by the brain.
- Rods consist of rod outer segment (ROS), inner segment, cell body and synaptic terminal.
- The ROS, consisting of stacked, discrete membranous discs, undergoes a process of continuous renewal in which newly constructed discs are added at the base (growth) and oldest discs are shed from the top.
- The ROS maintains a homeostatic length by balancing growth and shedding. How this balance is controlled is unclear. ***[1,2,3]***

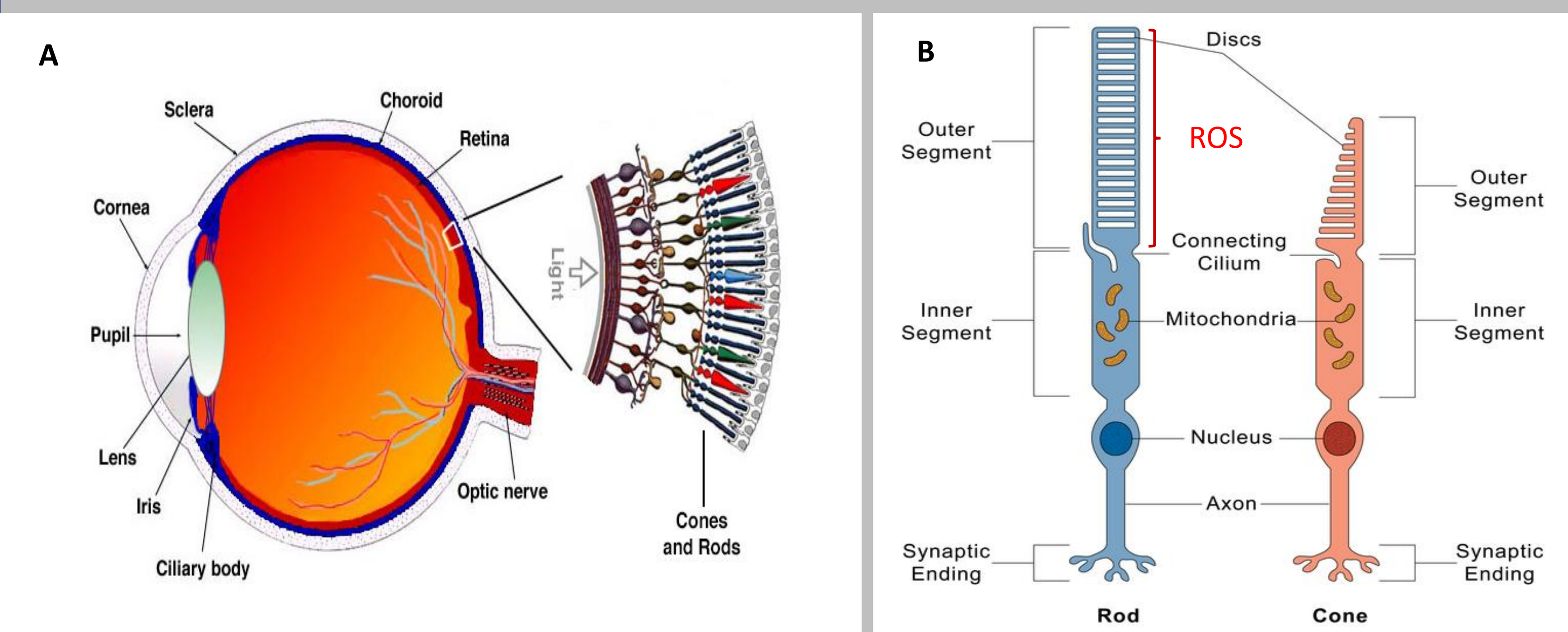

Figure 1

Source: BCM Families foundation

Objective

- Develop a mathematical model to describe the length of ROS and distribution of discs in the ROS over time
- Provide insight into balanced homeostatic ROS length by performing equilibrium analysis to determine the mechanistic balance between growth and shortening.
- Fit model to data from zebrafish where the ROS renewal is controlled experimentally. ***[4,5]***

ODE Model:

The ODE model describes the length of ROS over time

$$\frac{dx}{dt} = r - f_{shed}(x)$$

Rate of change in length of ROS

Growth rate

Shedding rate / function

We assume two forms of the shedding function, namely:

1.Linear function $f_{shed}(x) = \gamma x$ where some $\gamma > 0$

2.Sigmoid function $f_{shed}(x) = k_{max}\frac{x^n}{x^n + L_0^n}$, where k_{max} is the maximum shedding rate and L_0 is the value of x for which $f_{shed}(x) = \frac{1}{2}$

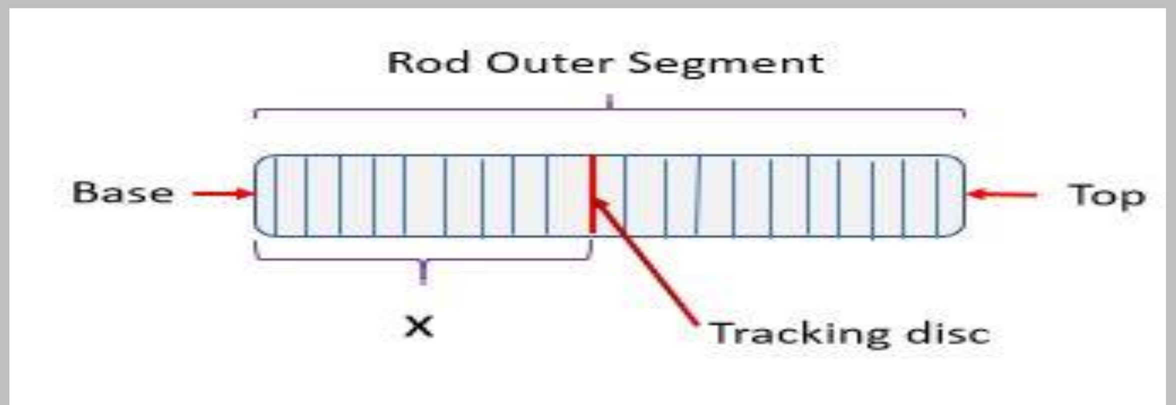

Figure 2

PDE Model

The PDE model describes the distribution of discs in the ROS

$$\frac{\partial u(x,t)}{\partial t} + v\frac{\partial u(x,t)}{\partial x} = -f_{shed}(x)u(x,t)$$

Rate of translocation of discs along the ROS. We assume v depends linearly on x (ie $v = k_{max}(1 - \frac{x}{L})$), since discs have been shown to crowd near the top of ROS

Removal of discs from the ROS through shedding (*the shedding function is the same for the ODE model*)

$$-v\frac{\partial u(x,t)}{\partial x}\Big|_{x=0} = r$$

Boundary condition (*constant flux*) describing addition of discs to the base of the ROS (growth)

Rate at which new discs are generated (growth)

Equilibrium result

Here, we increase the growth rate (r) and observe the corresponding change in the length of ROS

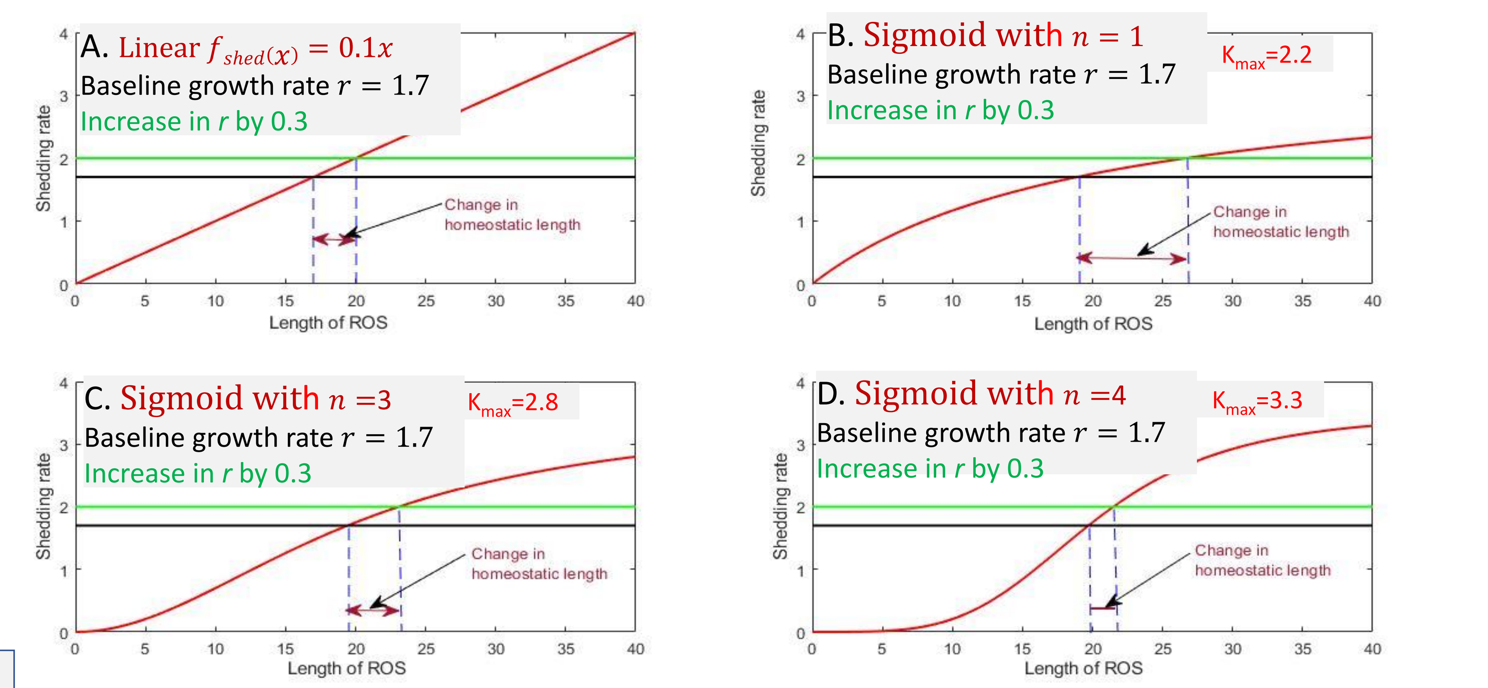

Figure 3

To maintain a homeostatic length, we hypothesized that increasing growth rate must trigger a corresponding increase in shedding rate. From figure 3D, a sigmoid function of order $n = 4$ seems to mimic our hypothesis, so we use that for the simulation

Result and discussion

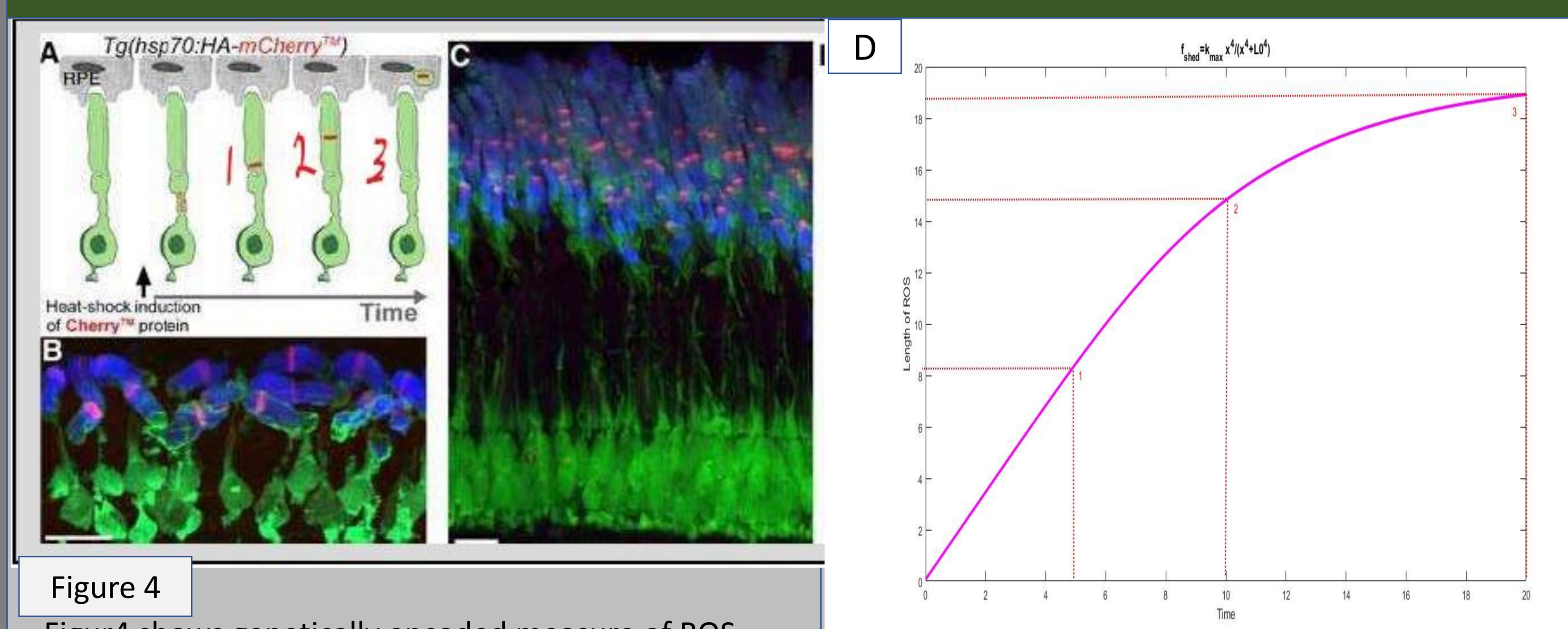

Figure 4

Figur4 shows genetically encoded measure of ROS renewal. Upon brief elevated temperature, the heat shock 70 (70hsp) promoter briefly turns on expression of mCherry protein that is incorporated into small number of newly generated ROS discs. As new unlabeled discs are added, mCherry is displaced distally. All rods express Green Fluorescent Protein (GFP) and the ROS labeled with antibodies to Rhodopsin (Blue). (B) is larval rods (C) Adult rods

Numerical result from the ODE model tracking the distance of a disc as it translocate from the base towards the top where shedding occurs. In the simulation we used $r = 1.7$ and $k_{max} = 3.3$ as predicted by figure 3D. The equilibrium length reached is $L^* = 19\mu m$.

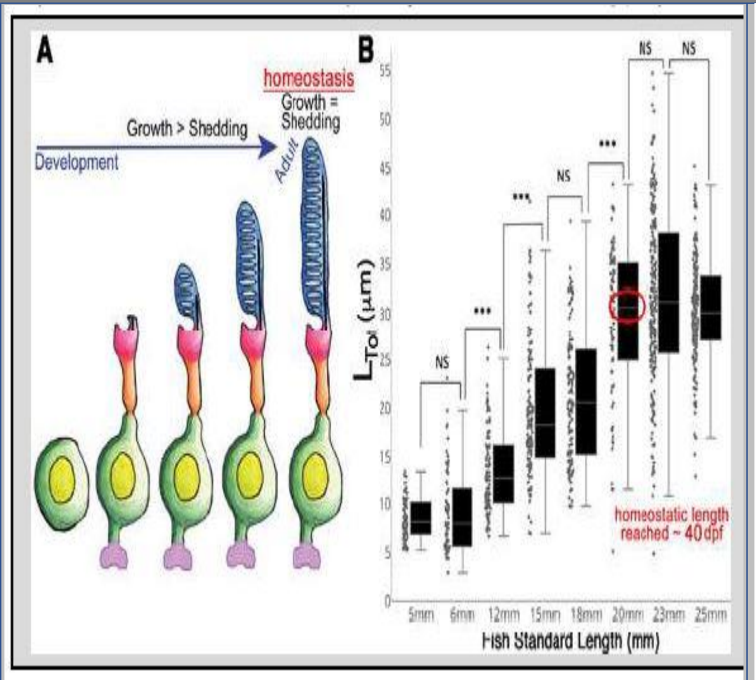

Figure 5

Development of ROS over time.

Figure (A) shows the elongation of ROS as new discs are added. Figure (B) shows the length of ROS for at least three different rods measured at various developmental times

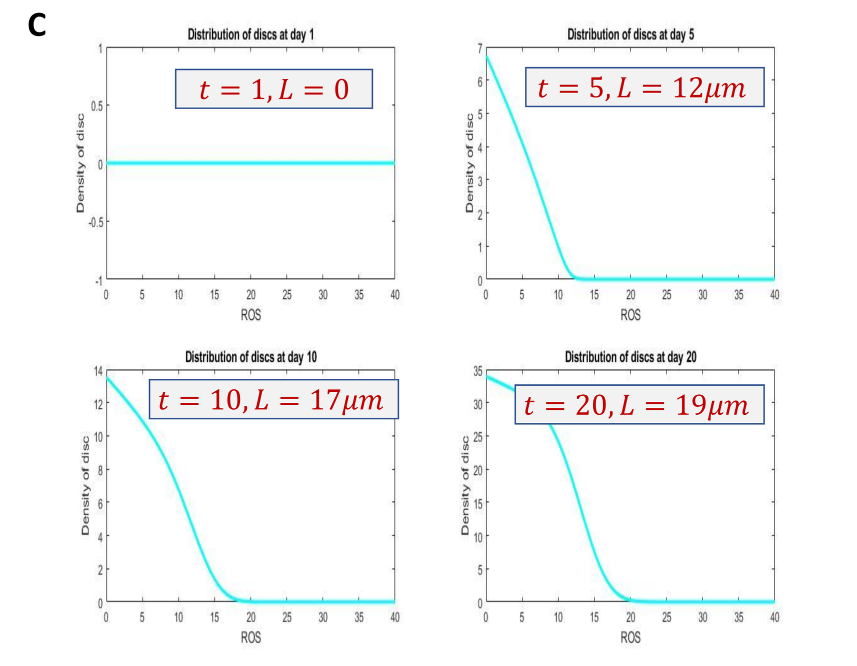

Figure 6

Distribution of discs along the ROS at specified times predicted by the PDE model. Initially, there was no disc at the ROS, but with time the ROS was filled with discs and the length continue to increase until a homeostatic length of $19\mu m$ was reached where shedding begin as predicted by the ODE model in figure 4D

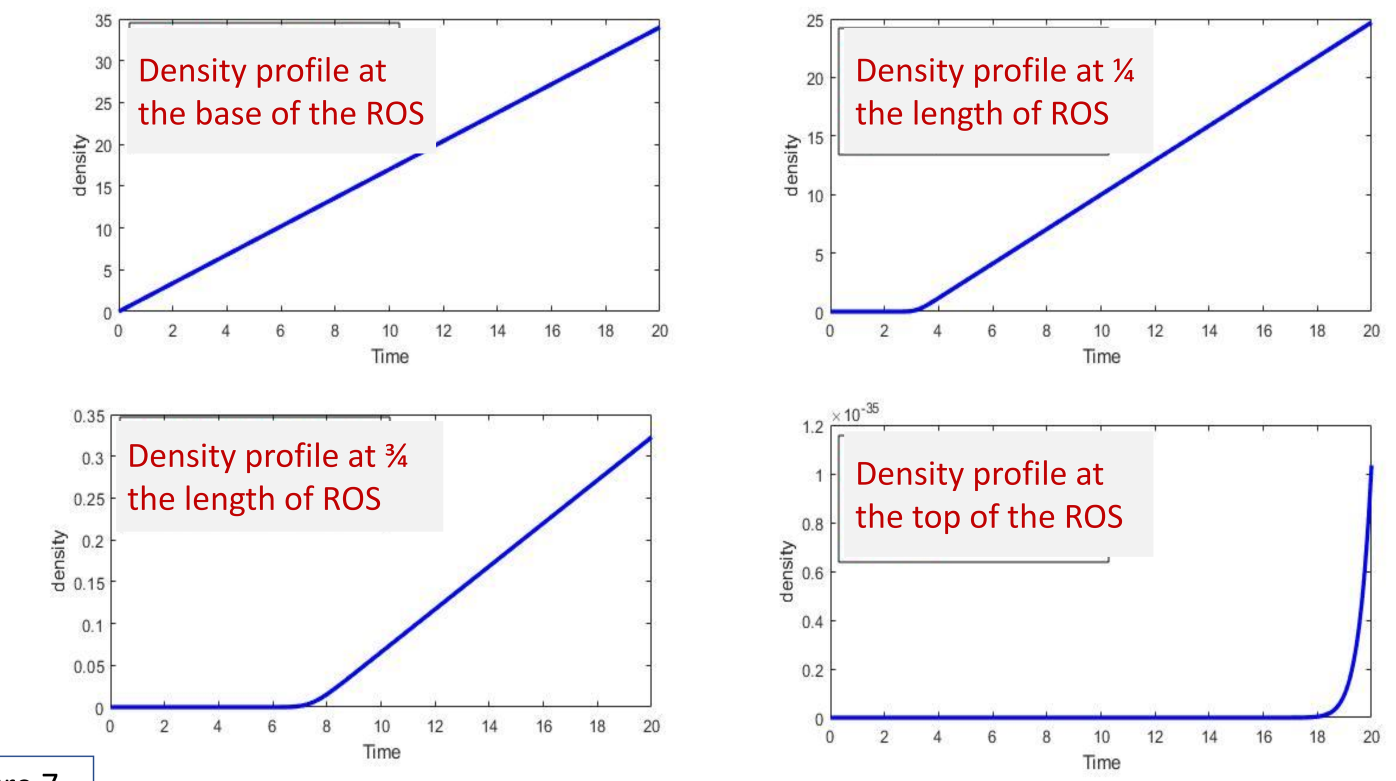

Figure 7

The figure shows the density profile at different sections along the ROS over time. Since newly generated discs are added to the base of the ROS, the lower section of the ROS is filled up first before the upper part. Also due to shedding at the top, the number of discs in the ROS always remain bound no matter how long we simulate.

Future work

- Use curve fitting to determine the appropriate values of the shedding rate r and the maximum shedding rate k_{max} .
- Be able to predict the length dynamics of ROS in healthy zebrafish and in those where the growth and shedding have been perturbed.

Reference

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