Didactic Material: Lens Growth Model

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Harvard University
#1 in Best Medical Schools: Research

Johns Hopkins University
#2 in Best Medical Schools: Research

Stanford University
#3 in Best Medical Schools: Research (tie)

University of Pennsylvania (Perelman)
#3 in Best Medical Schools: Research (tie)

University of California--San Francisco
#5 in Best Medical Schools: Research

Columbia University
#6 in Best Medical Schools: Research (tie)

University of California--Los Angeles (Geffen)
#6 in Best Medical Schools: Research (tie)

Washington University in St. Louis
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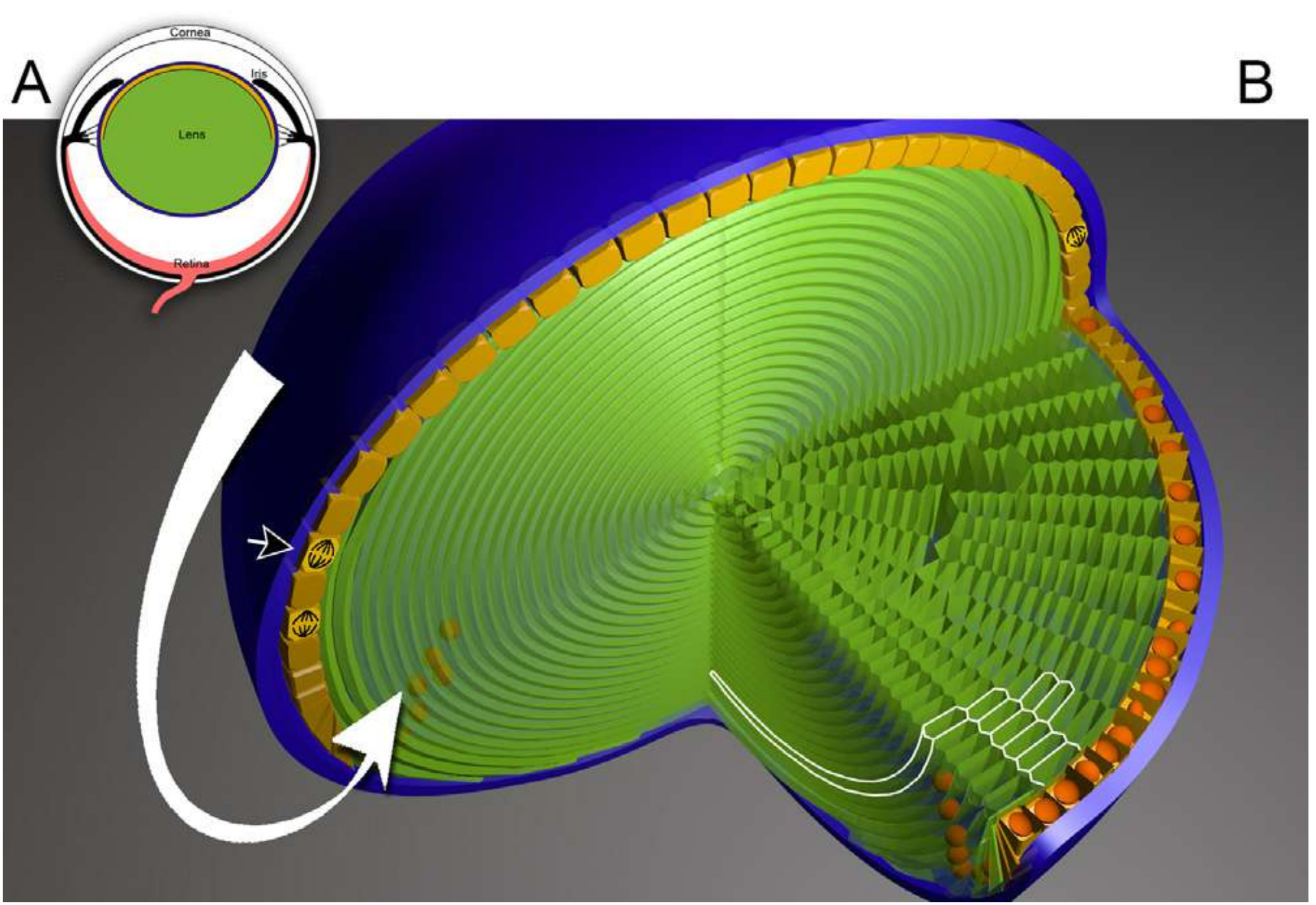
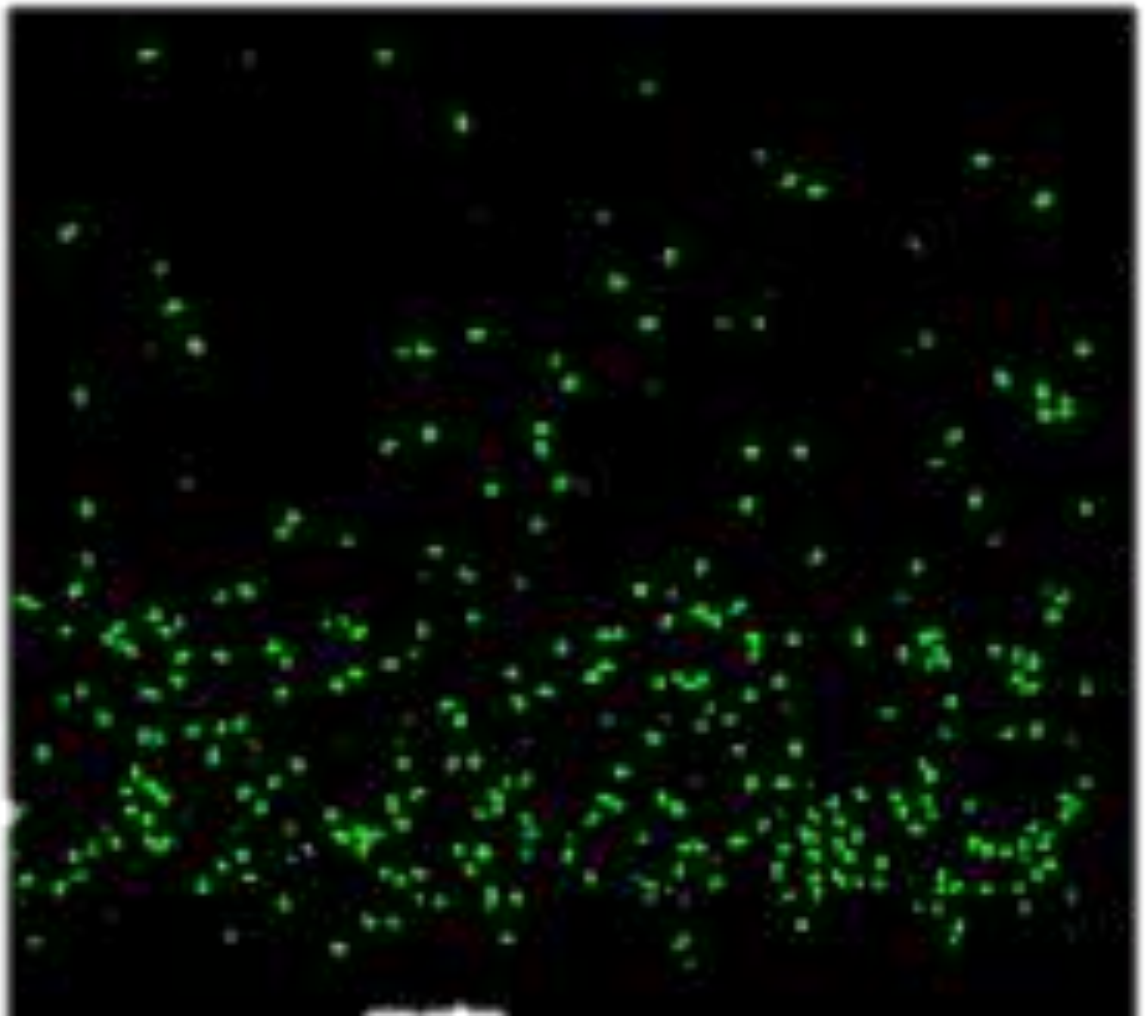
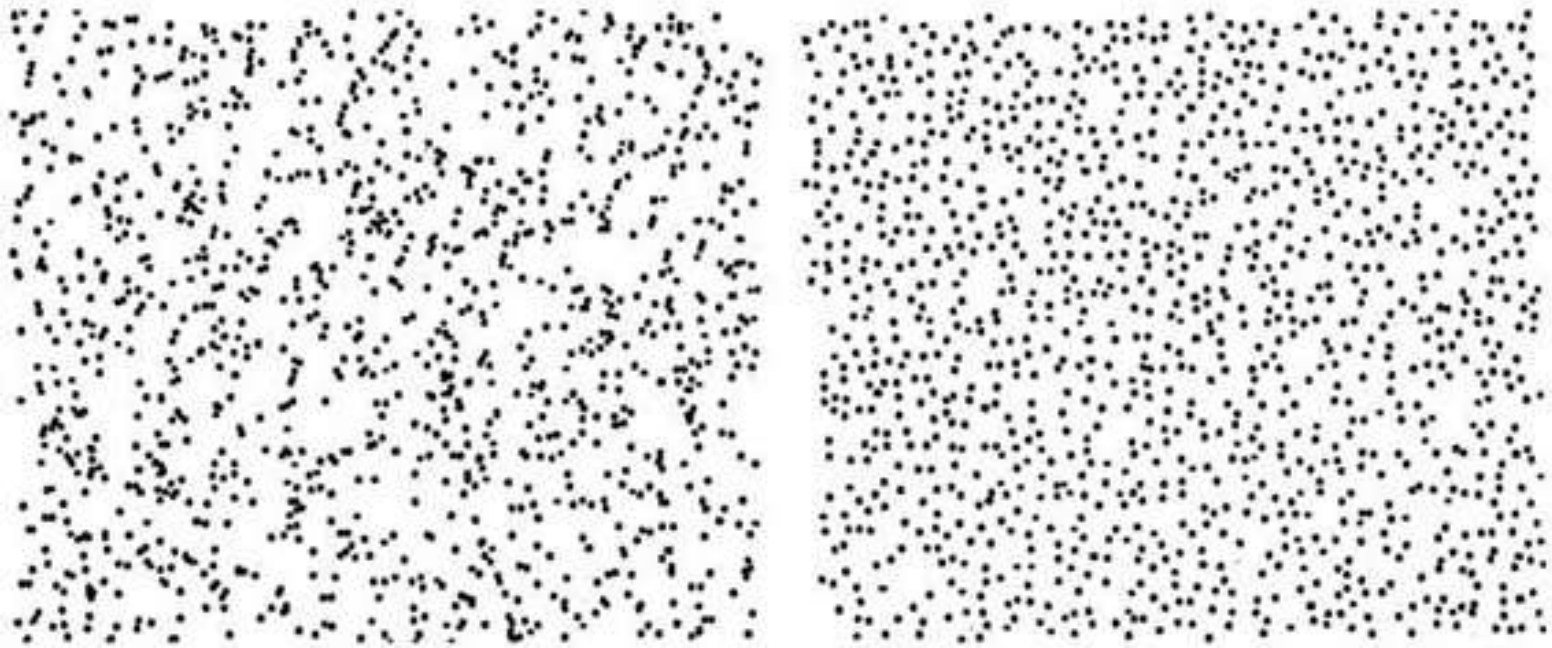

A
Cornea
Iris
Lens
Retina
B



How does this look like to you? Are the dots random?



Only one of this is random. Which one?

What is randomness?

- Very difficult question!
- Common sense – lack of “order” or pattern or predictability
- Information theory (mathematical) – string of zeroes and ones is random if it is shorter than any computer program that can produce it
- Probability theory – repeatable conceptual experiment with uncertain outcomes

Remark. The word uncertain means that an observer (us in this case) does not have enough knowledge to predict an outcome, i.e., what may look random to us today, may not be random tomorrow…..

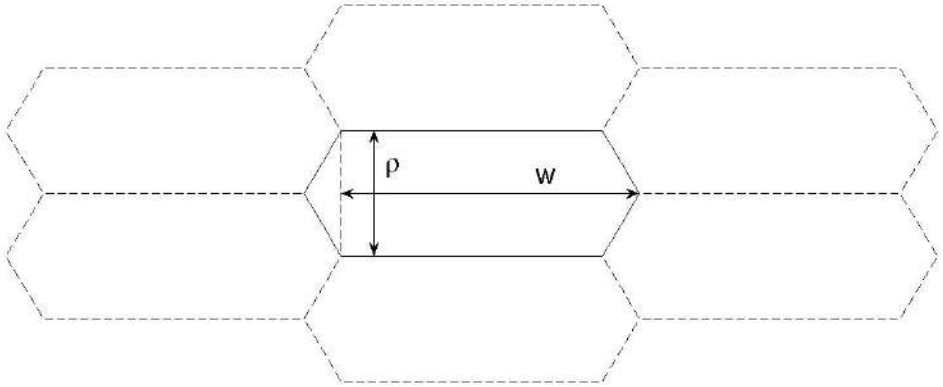
For example, string of numbers is selected between 0 and 1.

We could plot its distribution and its going to be a perfectly nice uniform distribution. So, it is random and we can model it completely well via a stochastic process. However……

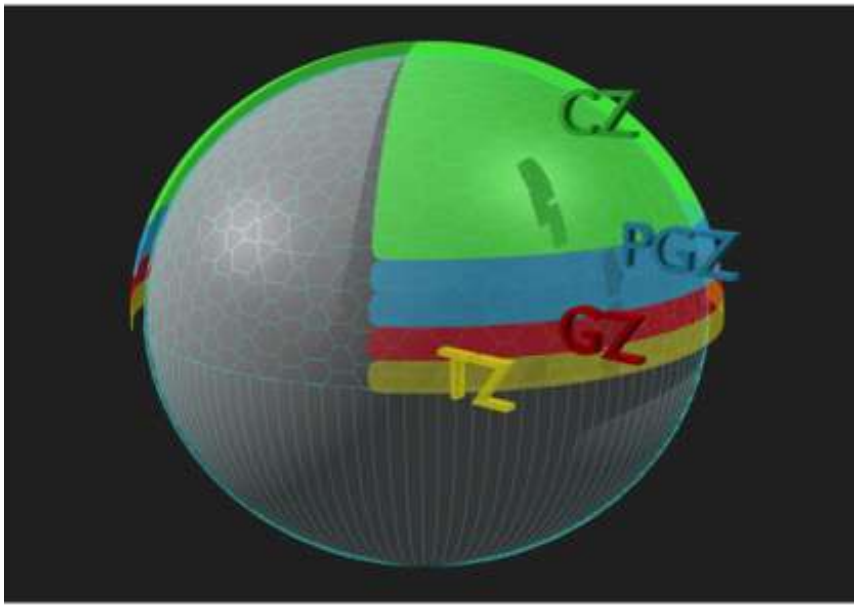
$$x_{n+1} = [1103515245\, x_n + 12345\,] \bmod 2^{31}$$

Basic Assumptions

Randomness – stochastic processes describe the number of cells, radius etc
Time – we opt for discrete time parameter
Shape – some three dimensional geometric shape with axes of symmetry
Surface area – of the epithelium and of individual cells
Interior – simplify into two-dimensional intersection areas



We start with the limited time frame: from 4 to 12 weeks in the life of a mouse.



How much evidence do we have for various Zones? Observe that the zones are established based on different division properties of the cells.

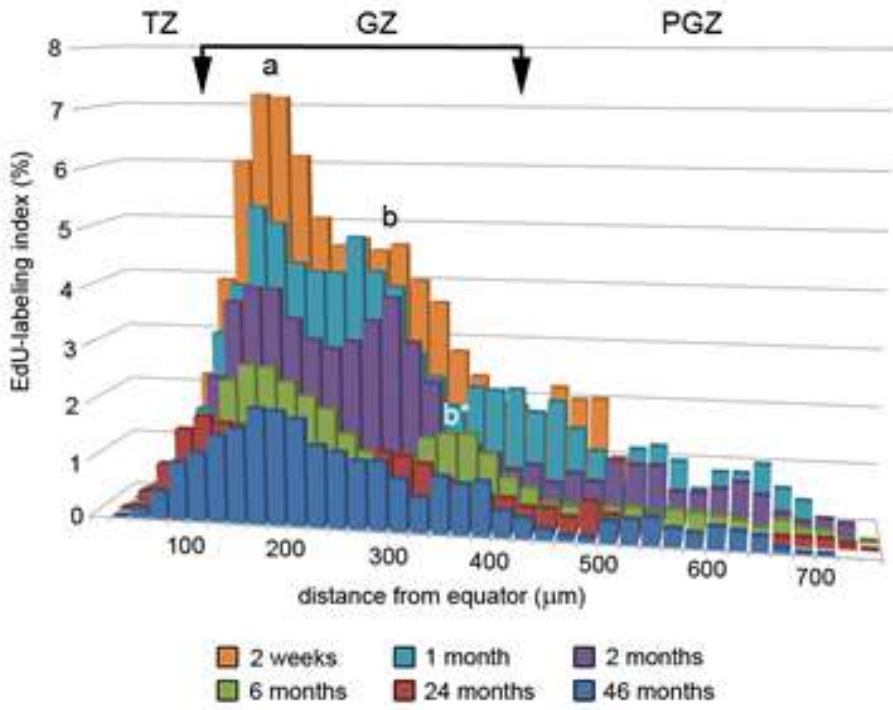
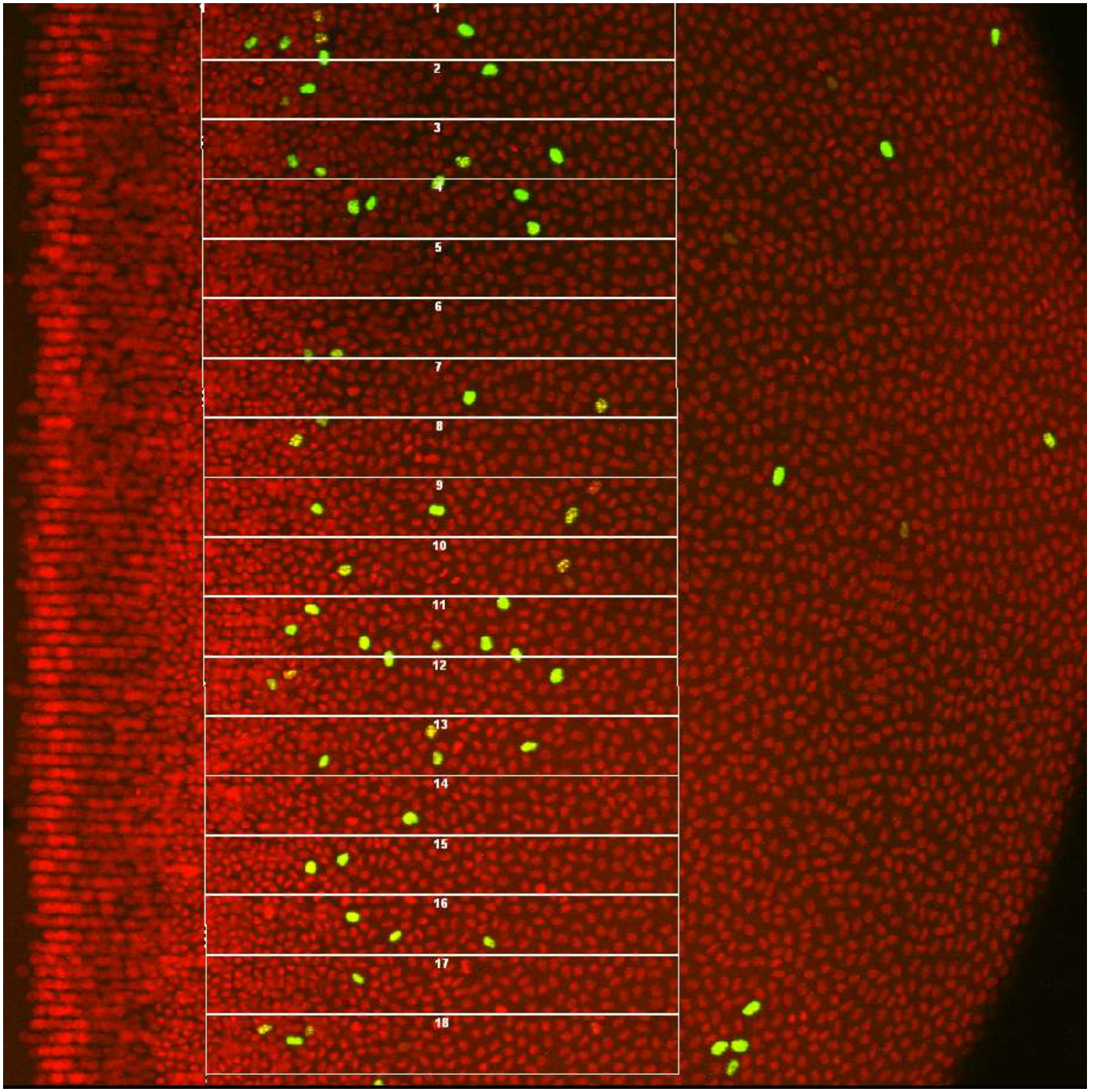
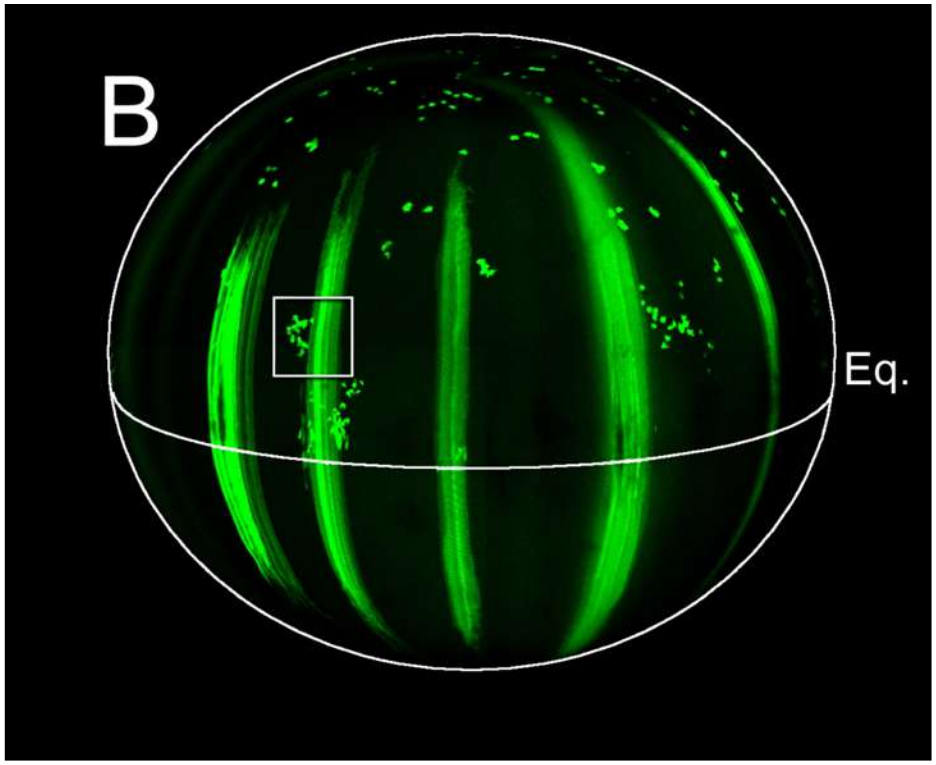


Figure 4. Distribution of EdU-labeled cells as a function of age and distance from the lens equator. TZ, transition zone; GZ, germinative zone; PGZ, pre-germinative zone. Data represent mean values of >6 determinations at each age. Error bars have been omitted for clarity but are similar in magnitude to those shown in Figure 3C. Within the GZ two labeling peaks, a and b, are apparent. At later stages


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18

No of "green cells" per box (total 72 boxes)	Expected No. of boxes (Poisson with λ = 2.8333)	Actual No. of boxes
0	4.235	5
1	11.999	13
2	16.998	15
3	16.054	14
4	11.371	11
5	6.443	9
6+	4.9	5

Chi-square test for Poisson does not reject the null-hypothesis with the very high p-value of 88.3%.

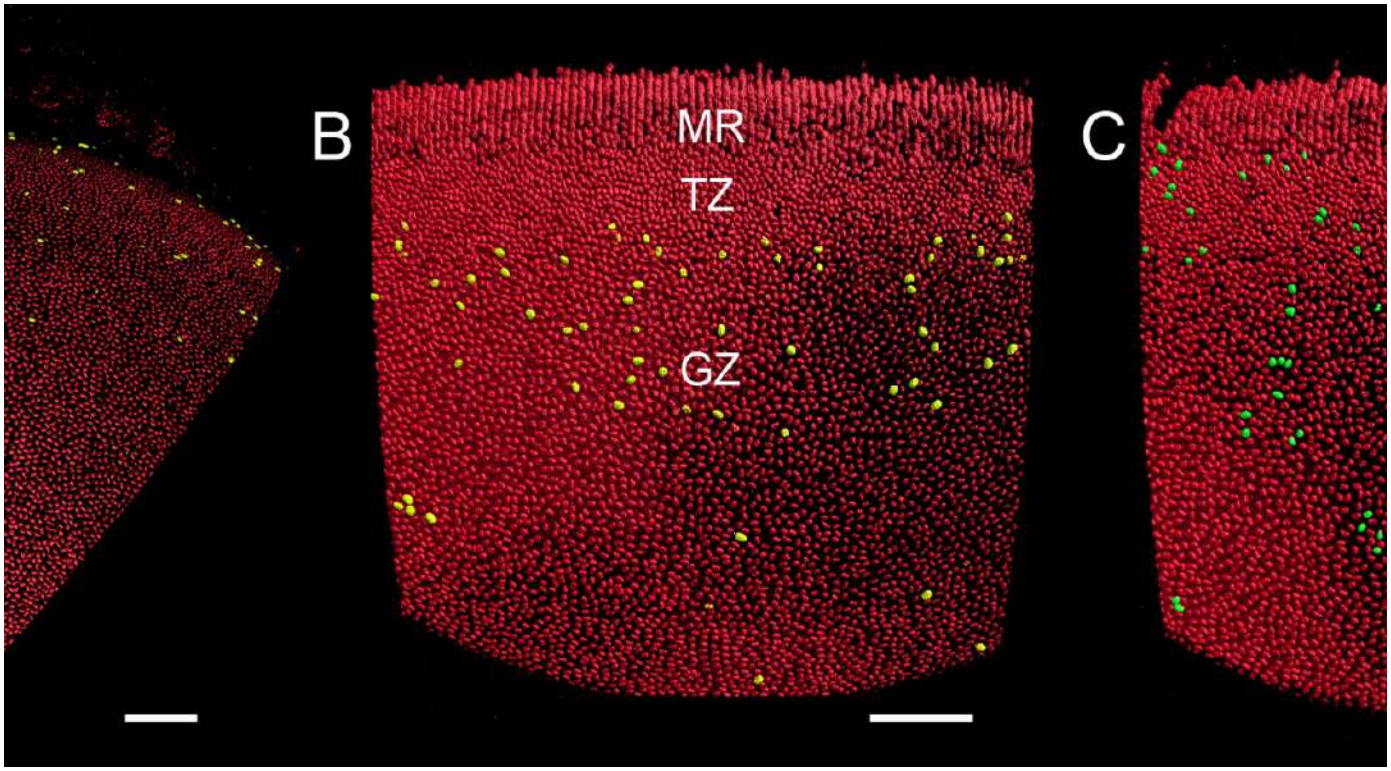


Clustering (Poisson)

Independence

Markov Branching Process

Implies the “Penny Pusher concept” (tennis balls)


B
MR
TZ
GZ
C

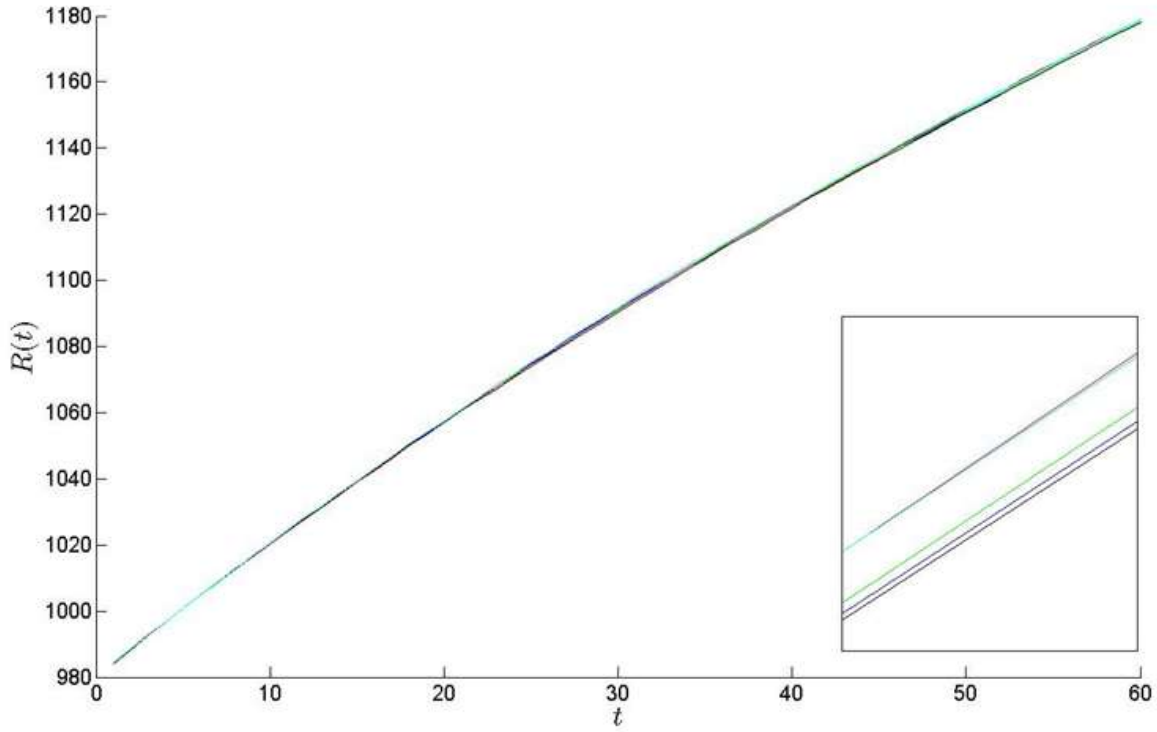


Figure 6. Change in mouse lens radius modeled over the sixty-day interval between 4- and 12-weeks-of-age. Results of five independent model simulations are shown. Note that growth is smooth and that, even at the end of the 60-day period, fluctuations between runs are negligible. In the inset, the y-axis scale has been expanded greatly so that individual simulation curves can be discriminated.

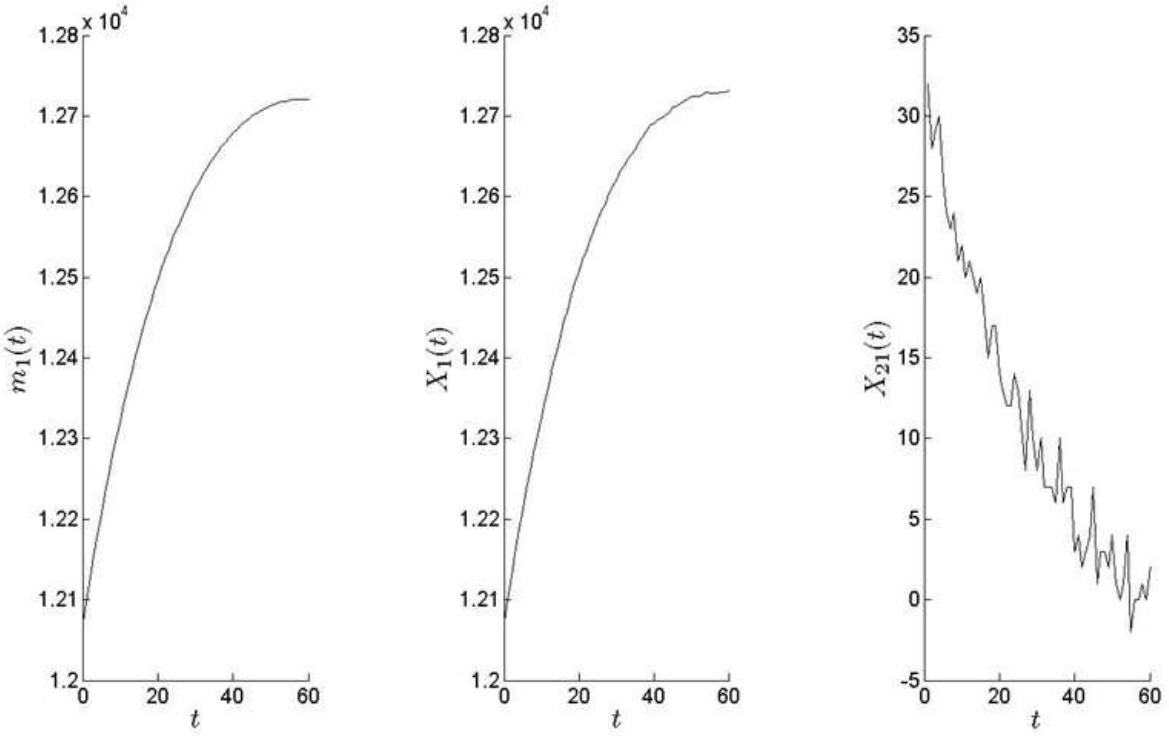
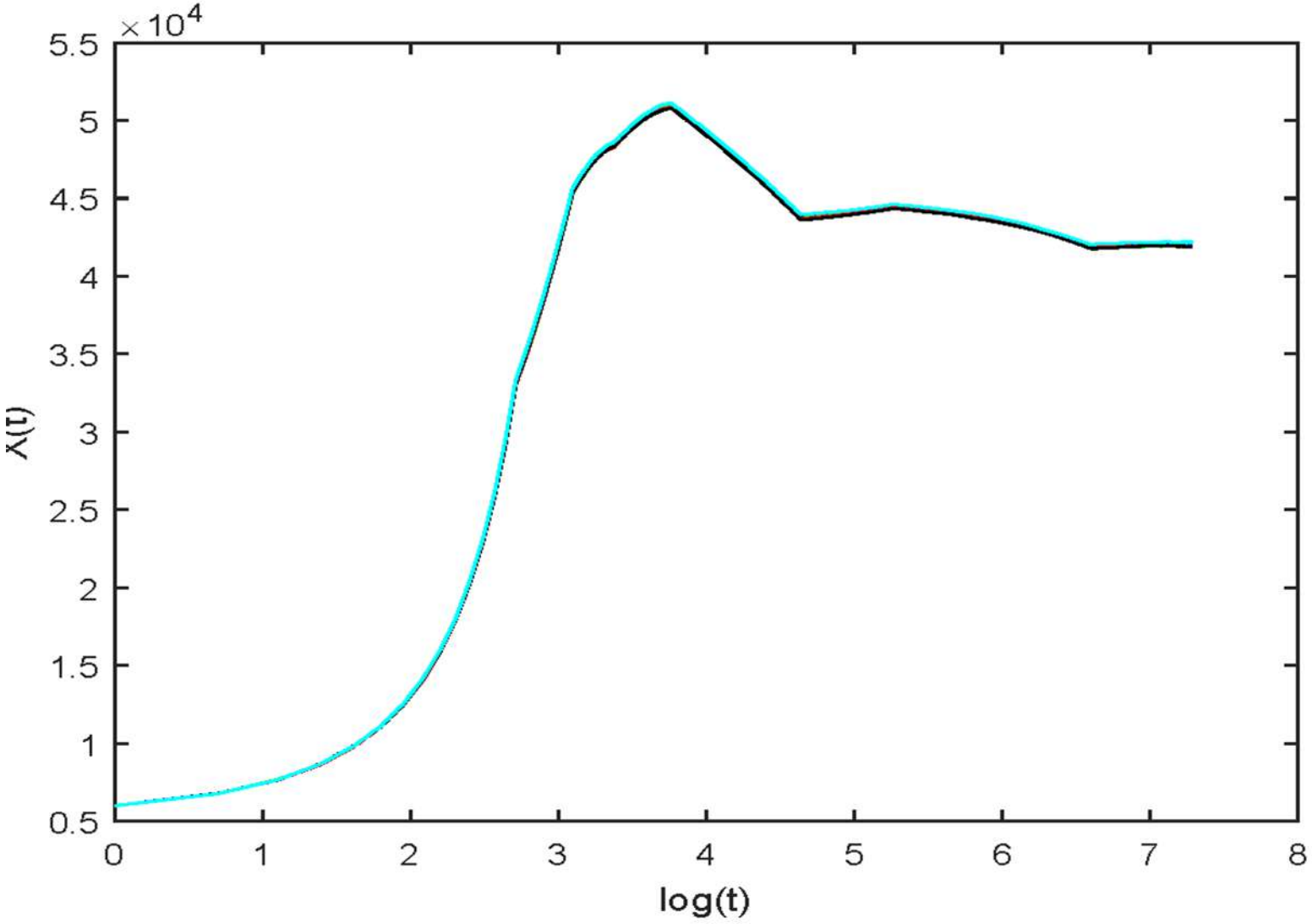
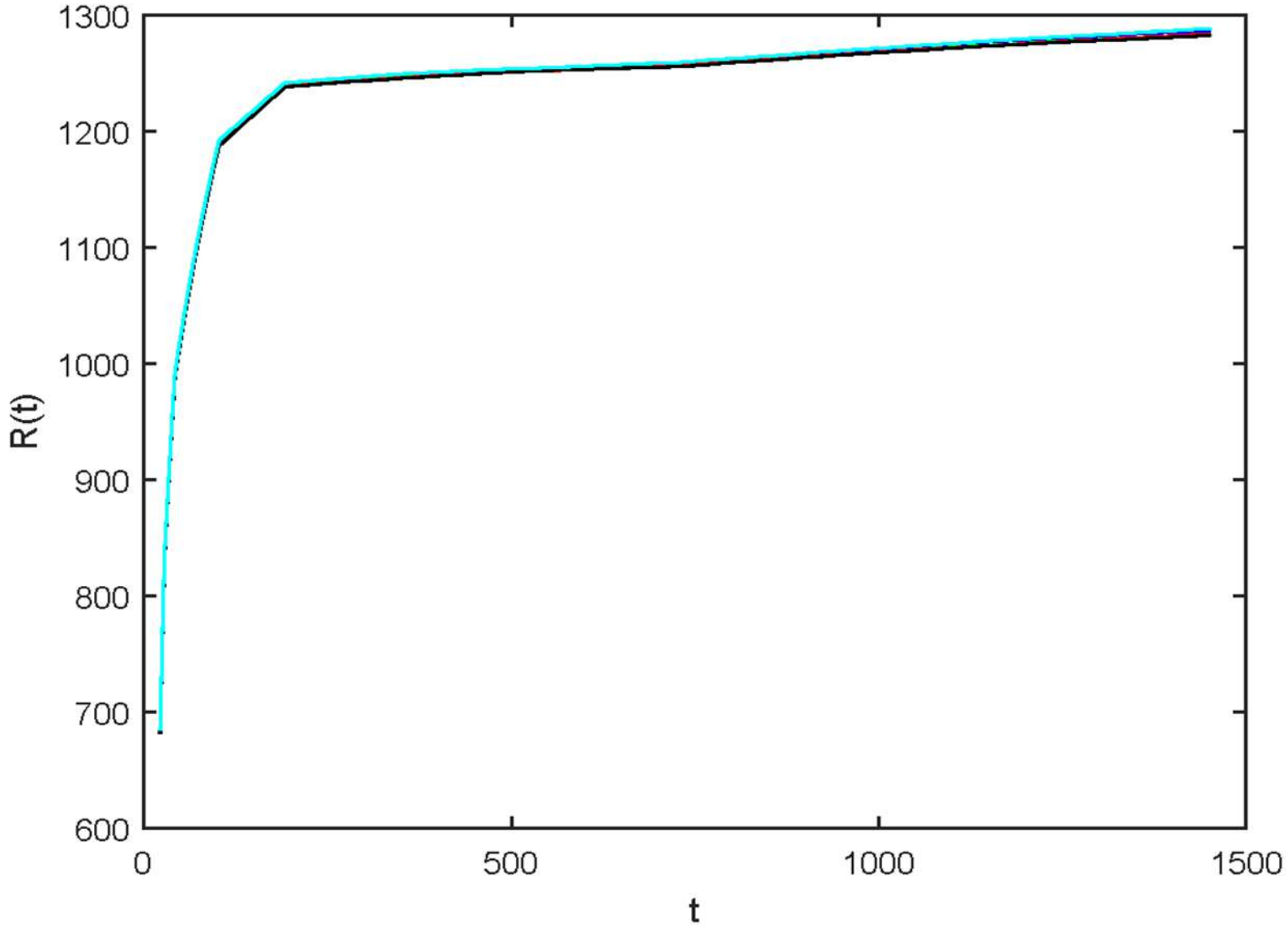


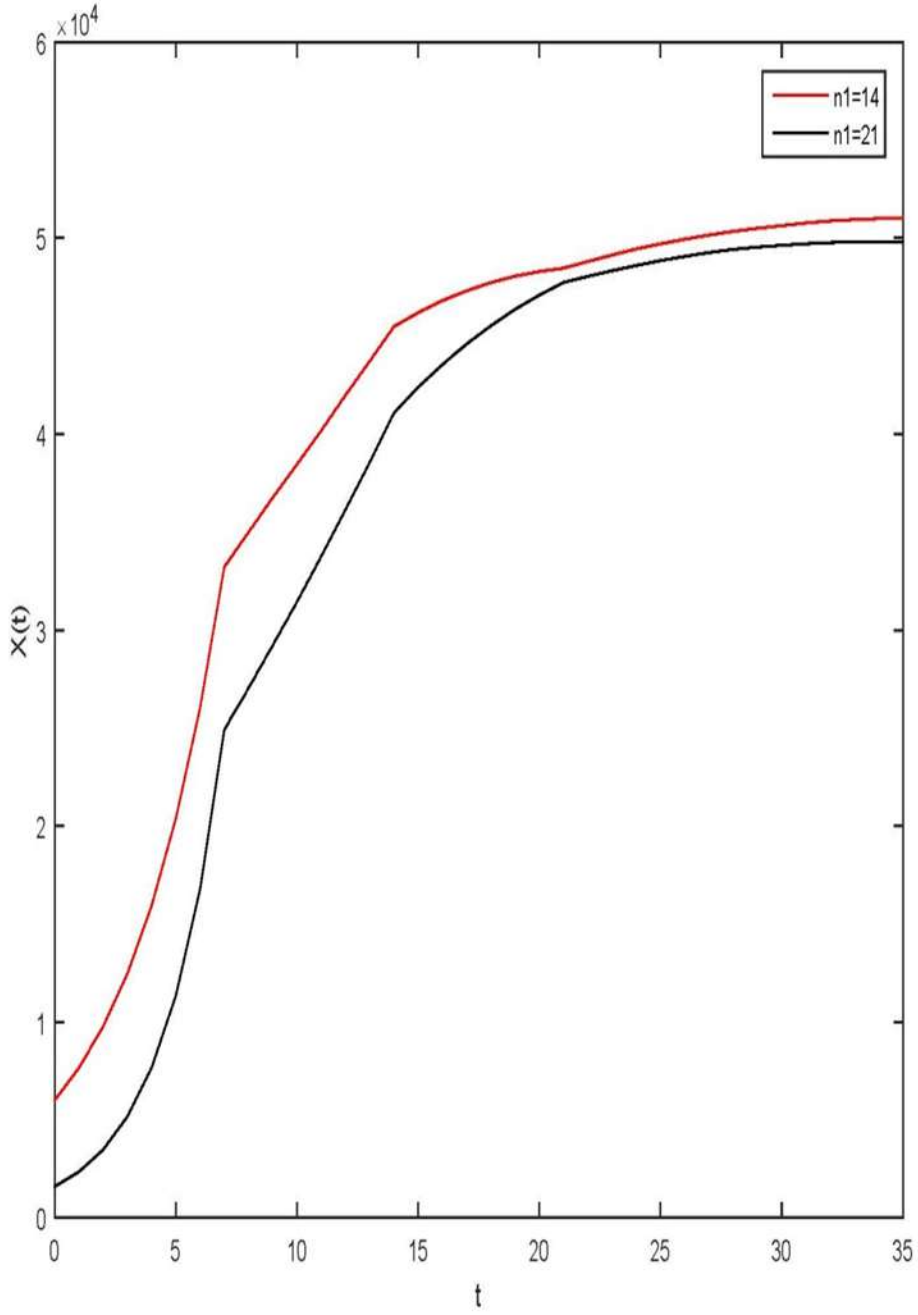
Figure 8. Cell population dynamics in the CZ. A. The theoretical mean of the number of cells in CZ. The number of cells in the CZ increases over time. B. Simulation results for the number of cells in CZ. C. The rate at which cells emigrate from the PGZ into the CZ shows marked stochastic fluctuations but generally declines.

Entire life graph.




1300
1200
1100
1000
900
800
700
600
R(t)
0
500
1000
1500
t

Early life comparison graph.



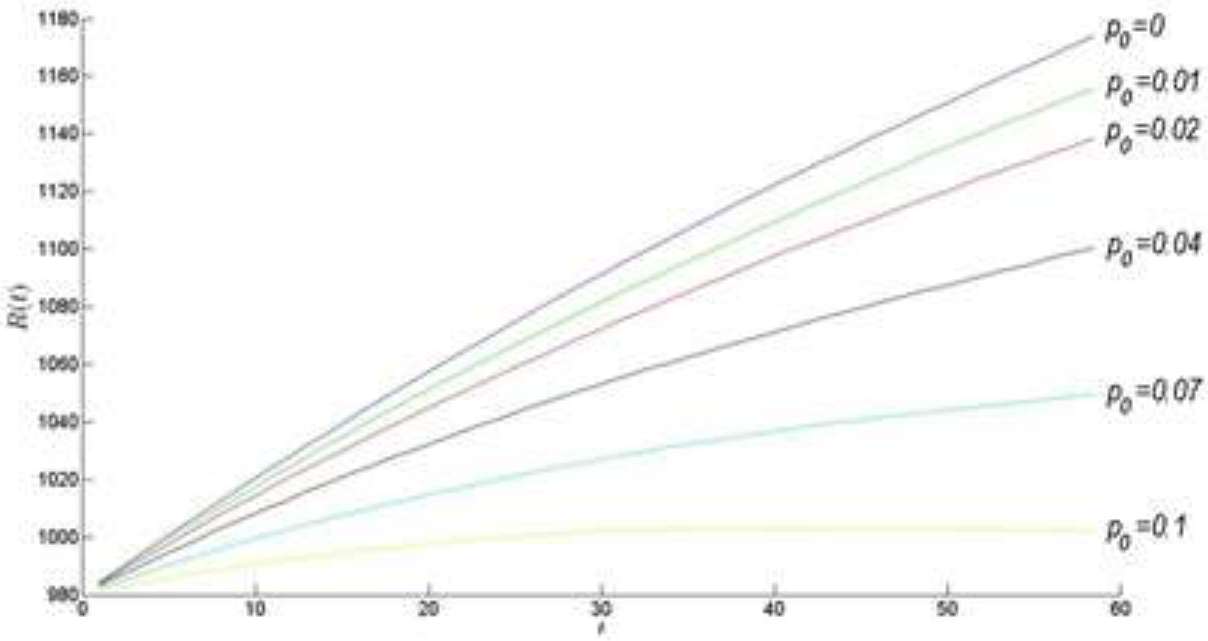
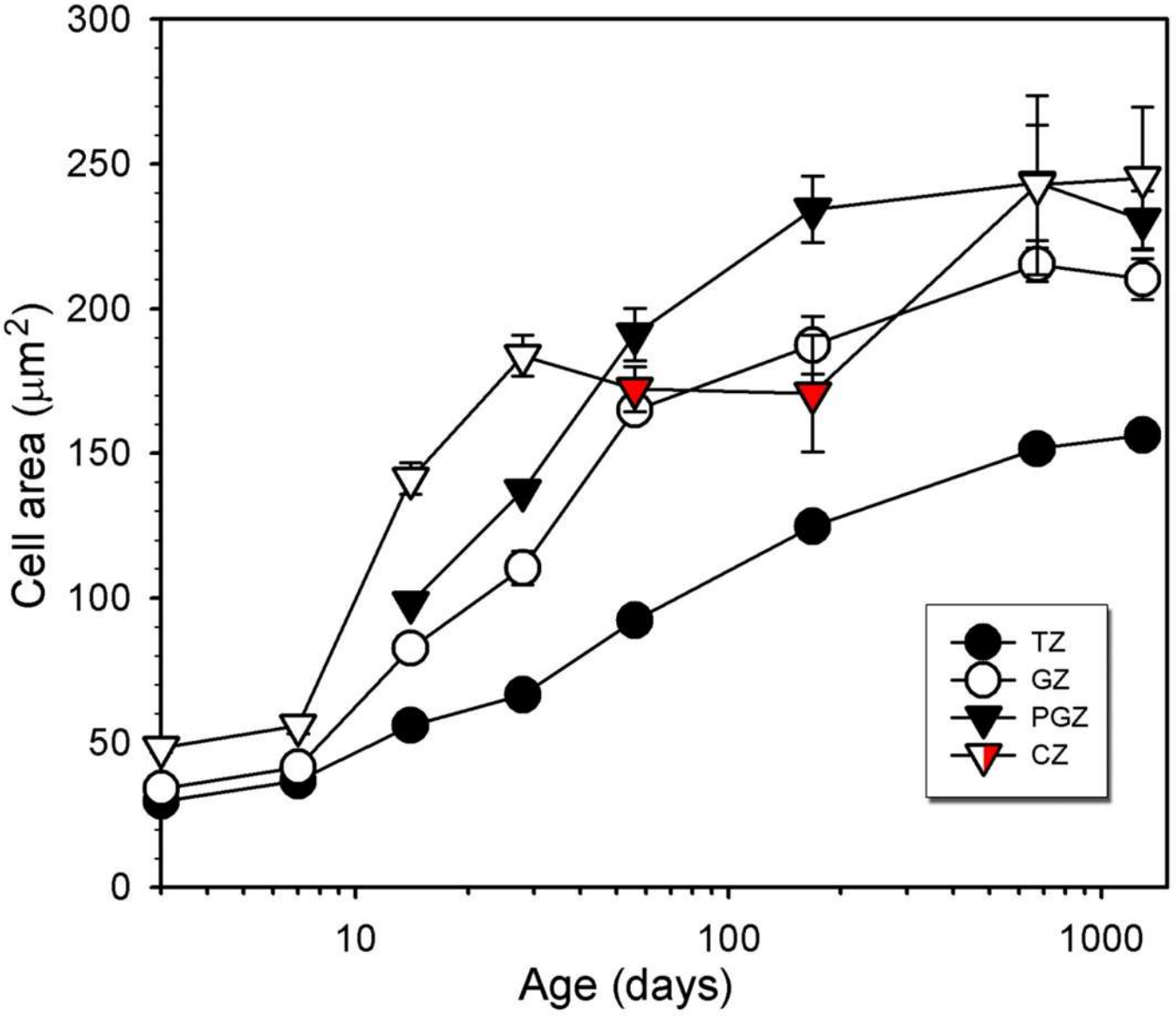


Figure 14. The growth of the radius of the lens for various values of the death rate in CZ.


300
250
200
150
100
50
0
Cell area (μm²)
10
100
1000
Age (days)
TZ
GZ
PGZ
CZ

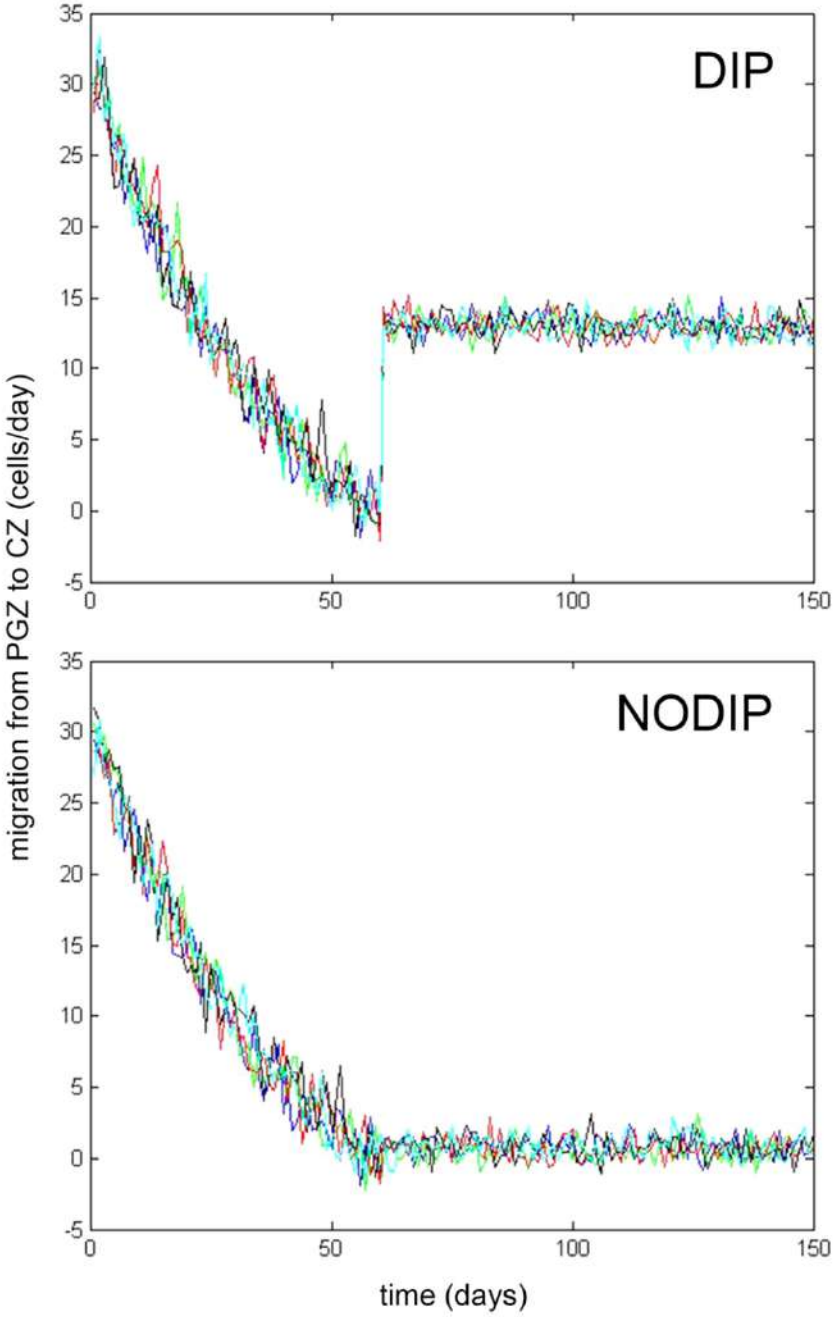


Figure. Flow of cells between the PGZ and CZ compartments. The figures shows the results of 5 independent model runs. The variance between runs reflects the stochastic nature of the model. Under the DIP conditions, cell migration remains positive throughout the simulation. Thus, despite the fact that the CZ cell population increases during the model period and the PGZ cell population declines, CZ cells do not migrate into the PGZ. In contrast, under the NODIP conditions, the net flow of cells between the compartments was approximately zero at day 60 of the model run. Under such circumstances there are inevitably days when small numbers of CZ cells enter the PGZ because of stochastic fluctuations near the border between the two zones.

Add 2. The lens growth model provides additional control feature; both the CZ and the fiber-department produce "pressure-valve" effect. It is a mathematical calculation.

Consider parameter $0 < \lambda < 1$. It turns out that in our model we have the following rule (our $\lambda \approx 1/10$).

If $(1 - \lambda)$ – fraction of offspring cells is stored in the "spillway zone" (combined CZ and fiber-dept in our case), then

$$\frac{\text{cell number variance with spillway zone}}{\text{cell number mean with spillway zone}} \approx$$

$$\lambda \frac{\text{cell number variance without spillway zone}}{\text{cell number mean without spillway zone}}$$