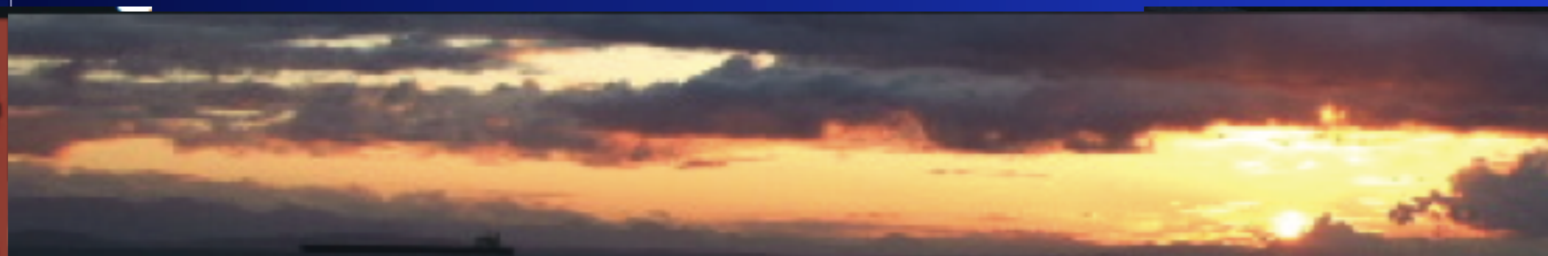
Mathematical Cell Biology Graduate Summer Course

University of British Columbia, May 1-31, 2012

Leah Edelstein-Keshet

Polymer size distributions Continued

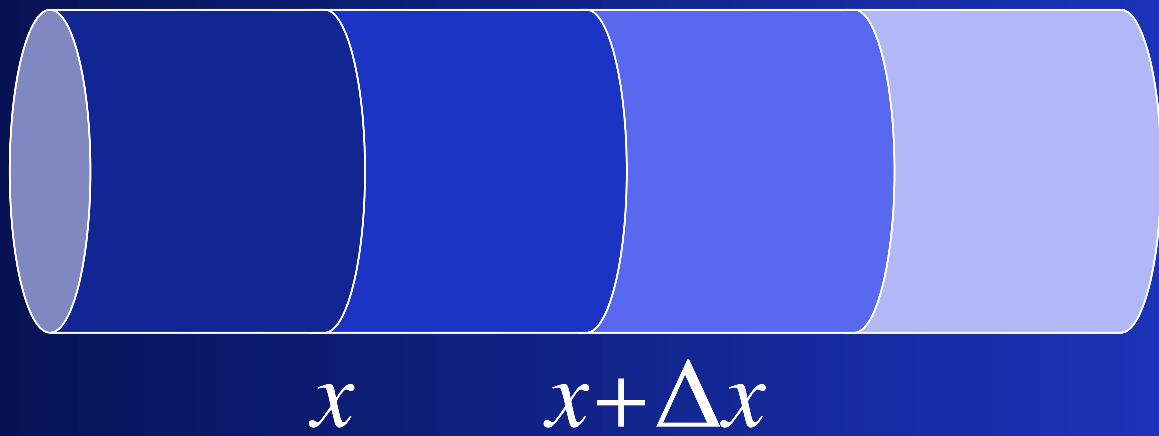


mprime

PIMS

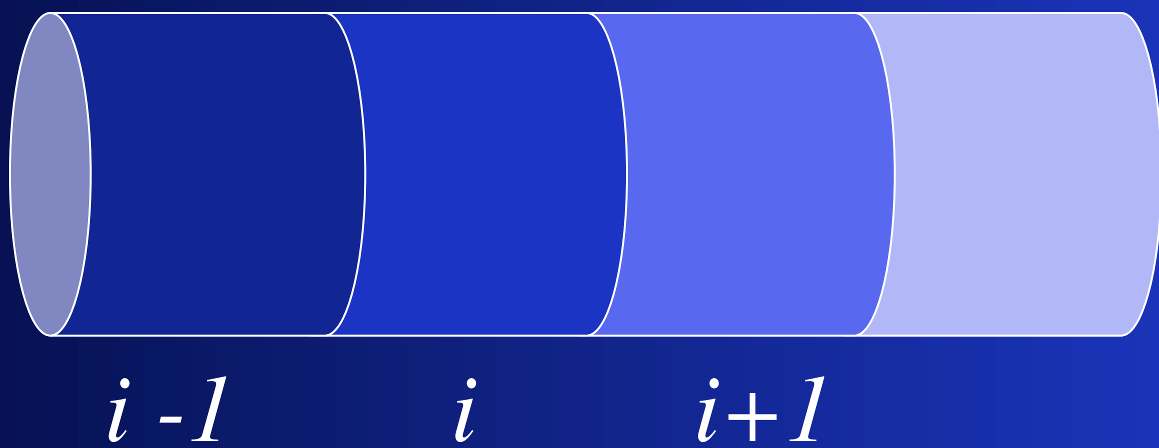
www.math.ubc.ca/~keshet/MCB2012/

Recall from last time: Discrete Diffusion Equation



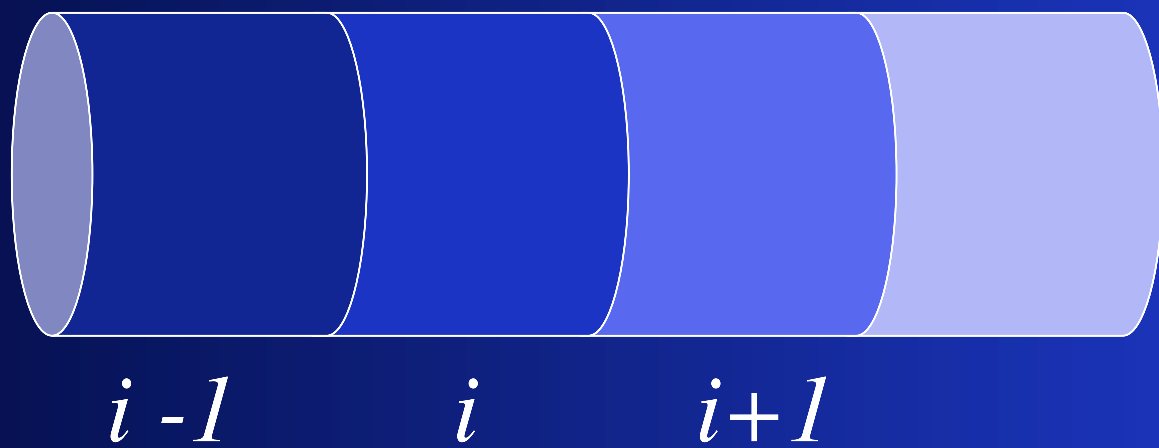
$$\frac{\partial c(x,t)}{\partial t} = \frac{D}{\Delta x^2}\left[c(x-\Delta x,t) - 2c(x,t) + c(x+\Delta x,t)\right]$$

Discrete Diffusion Equation



$$\frac{\partial c(x,t)}{\partial t} = \frac{D}{\Delta x^2}\left[c_{i-1} - 2c_i + c_{i+1}\right] + \sigma$$

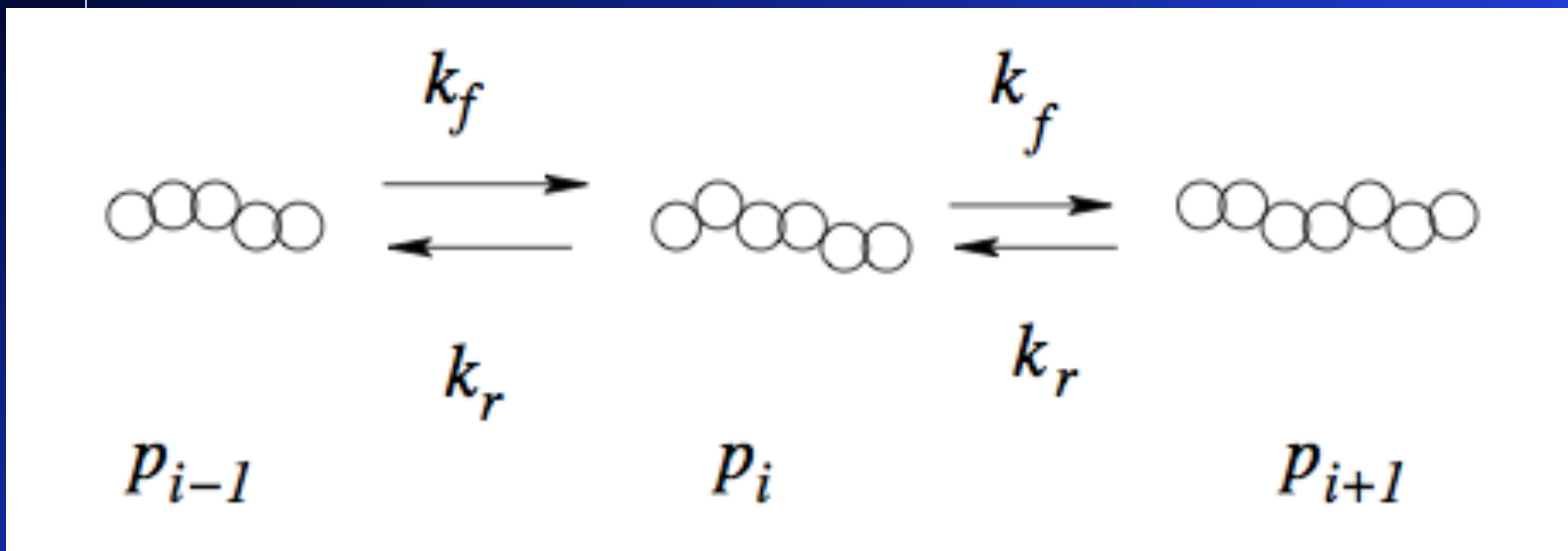
Discrete Diffusion Equation



$$\frac{\partial c(x,t)}{\partial t} = \frac{D}{\Delta x}\left(\left[\frac{c_{i+1} - c_i}{\Delta x}\right] - \left[\frac{c_i - c_{i-1}}{\Delta x}\right]\right)$$

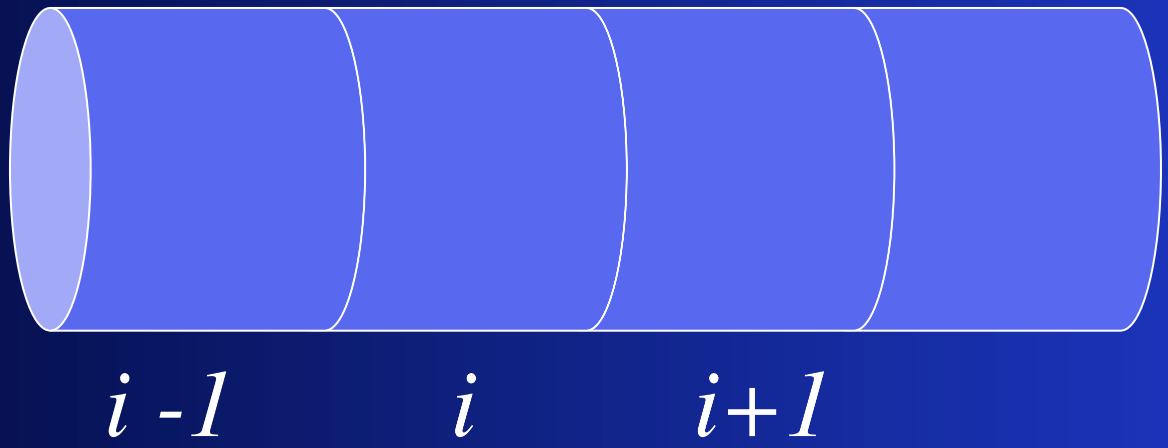
Polymer size distribution

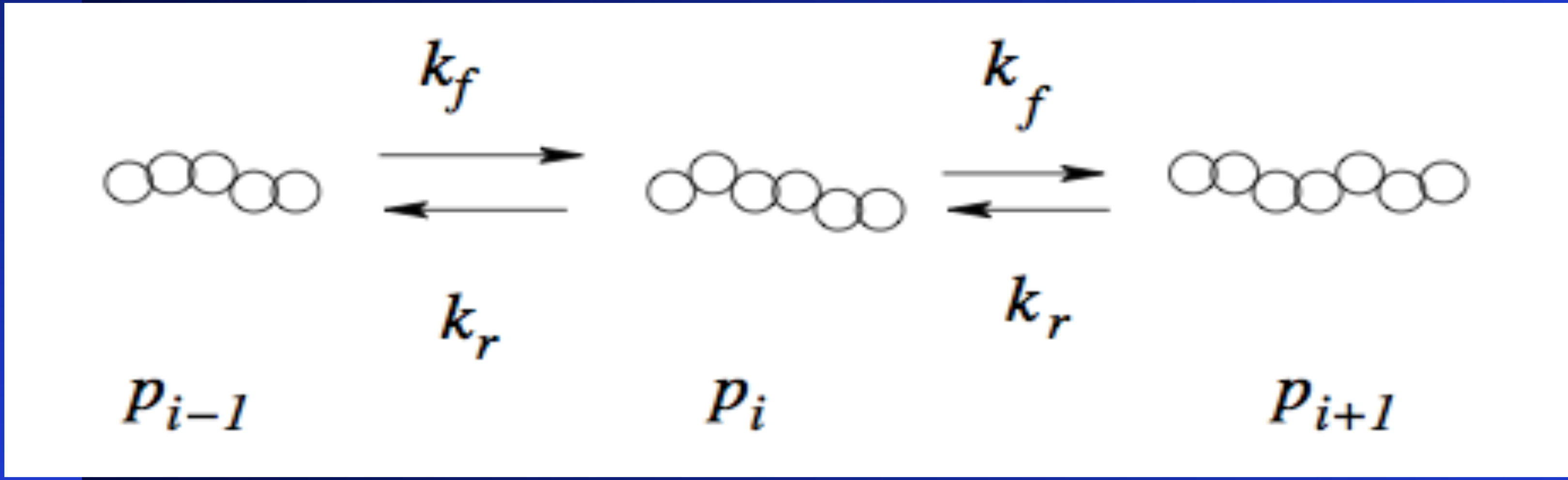
Size classes



$$k_f = k^+ a, \quad k_r = k^-$$

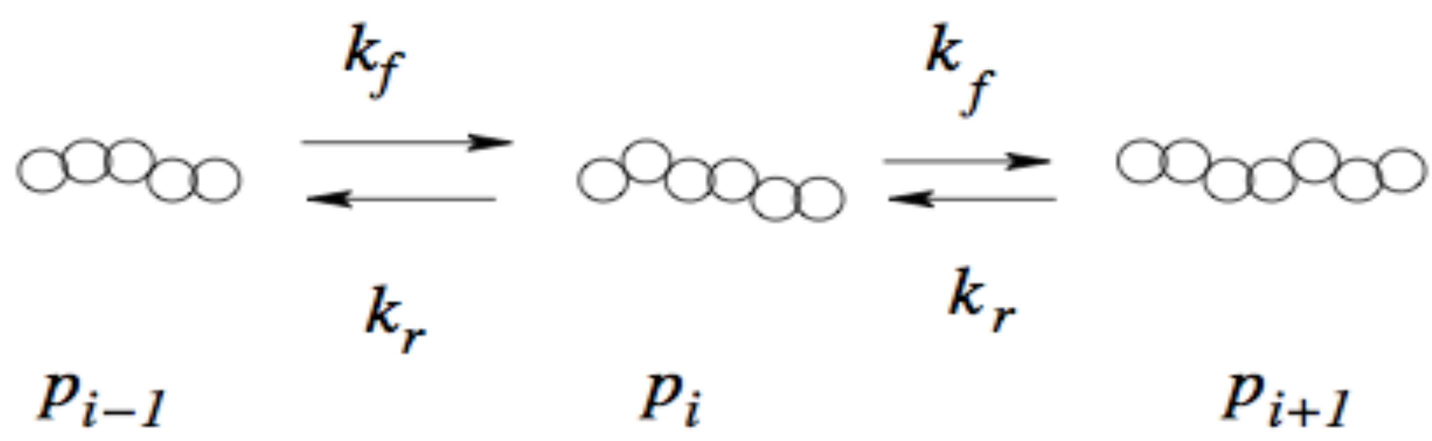
Discrete size classes





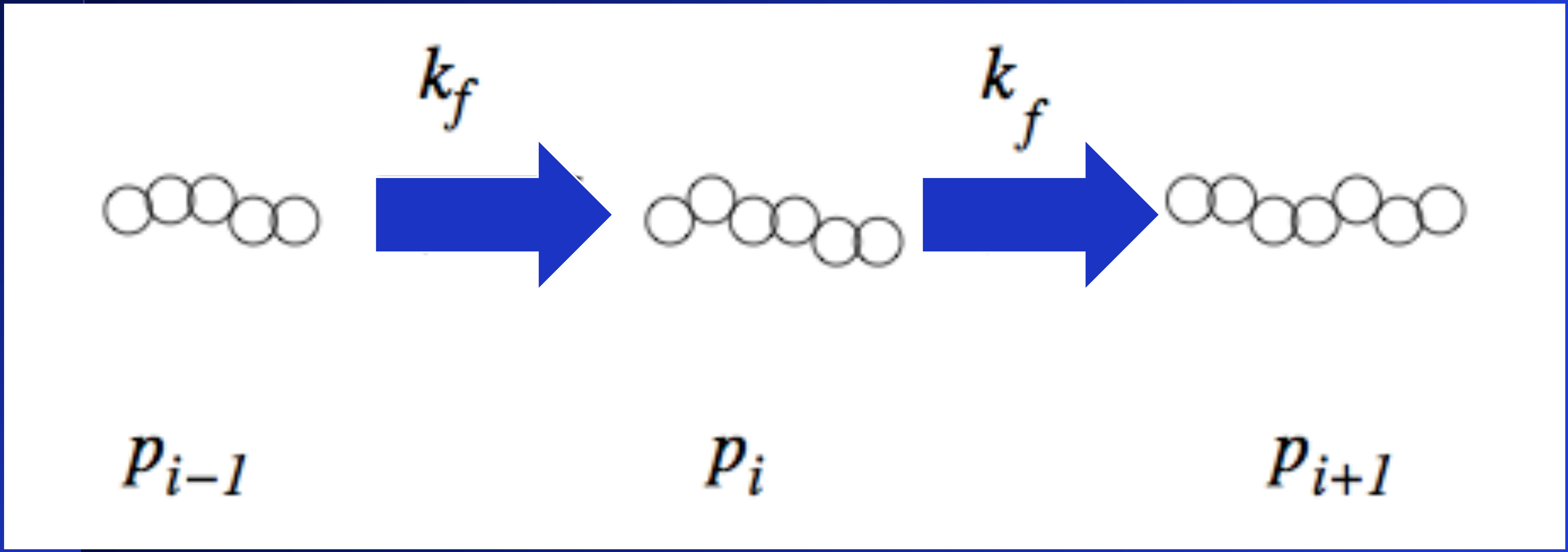
Balance equation

$$\frac{dp_i}{dt} = ck_f p_{i-1} - (ck_f + k_r)p_i + k_r p_{i+1}$$



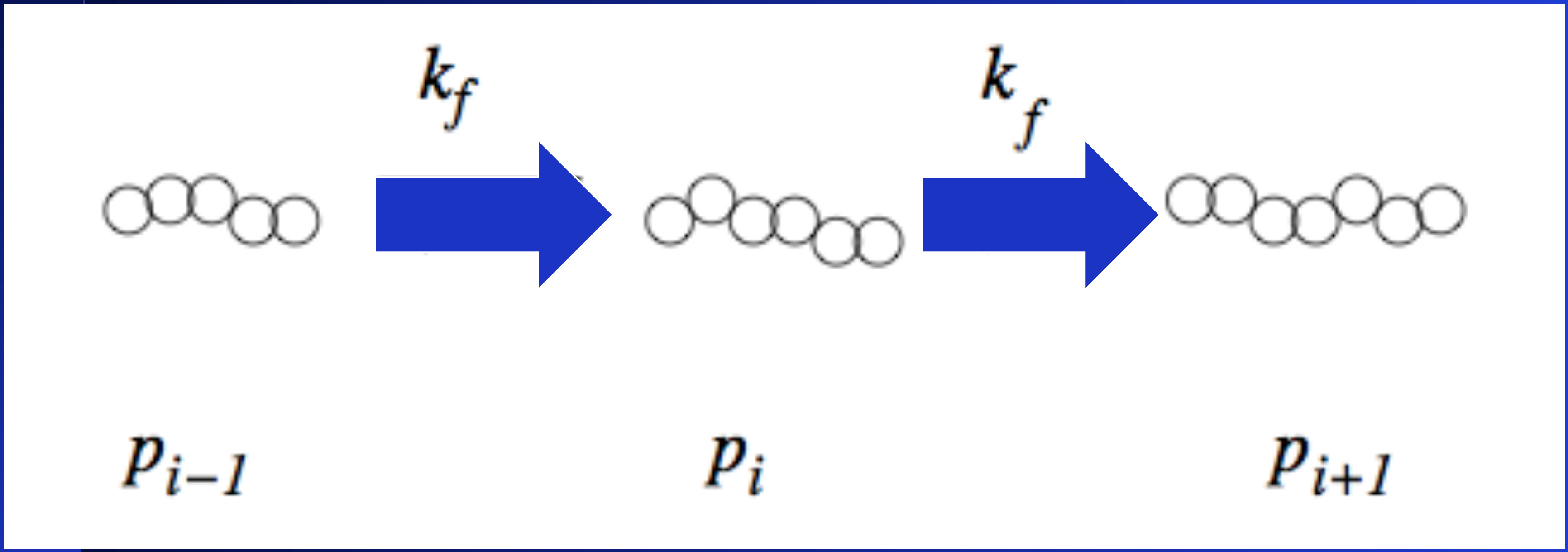
Intuition for limiting cases

$$k_f >> k_r$$



Intuition for limiting cases (1)

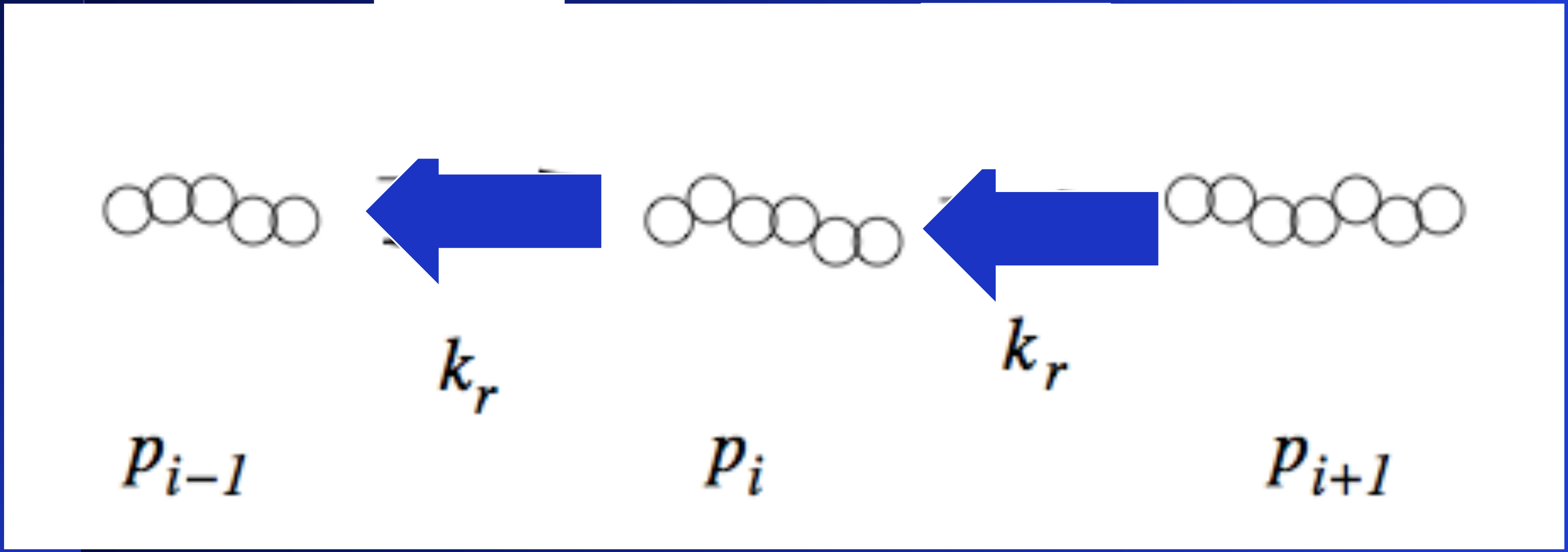
$$k_f >> k_r$$



Polymers just keep growing as long as monomer is available

Intuition for limiting cases (2)

$$k_r >> k_f$$



Polymers just keep shrinking

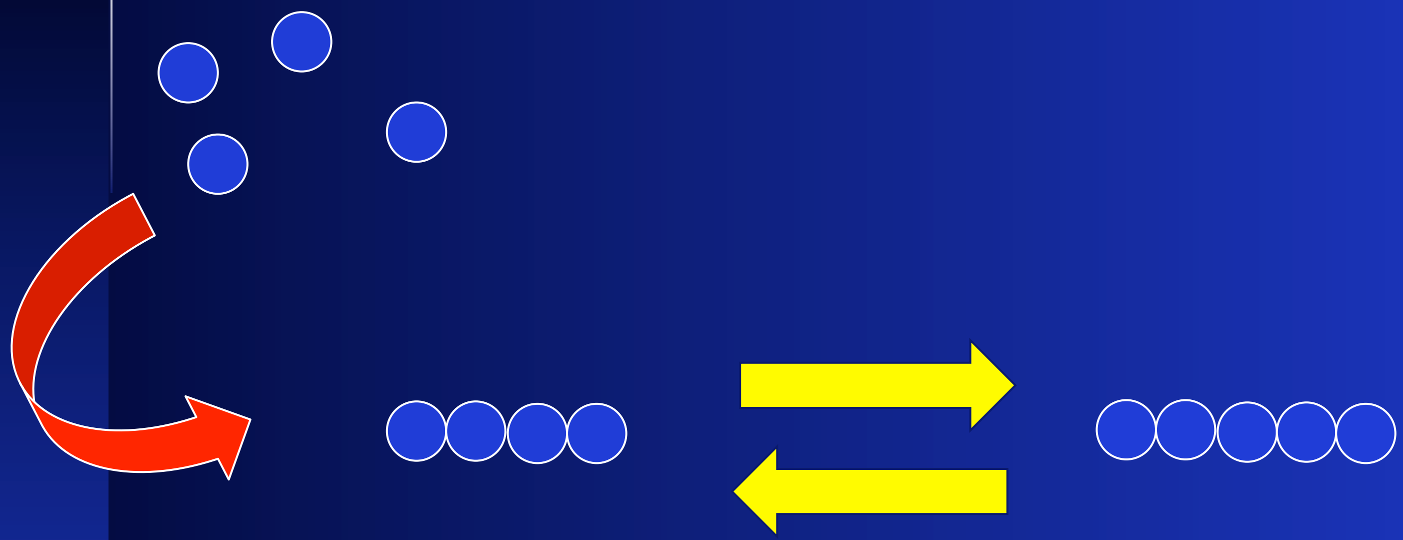
What happens afterwards?

- Consider case of monomer depletion

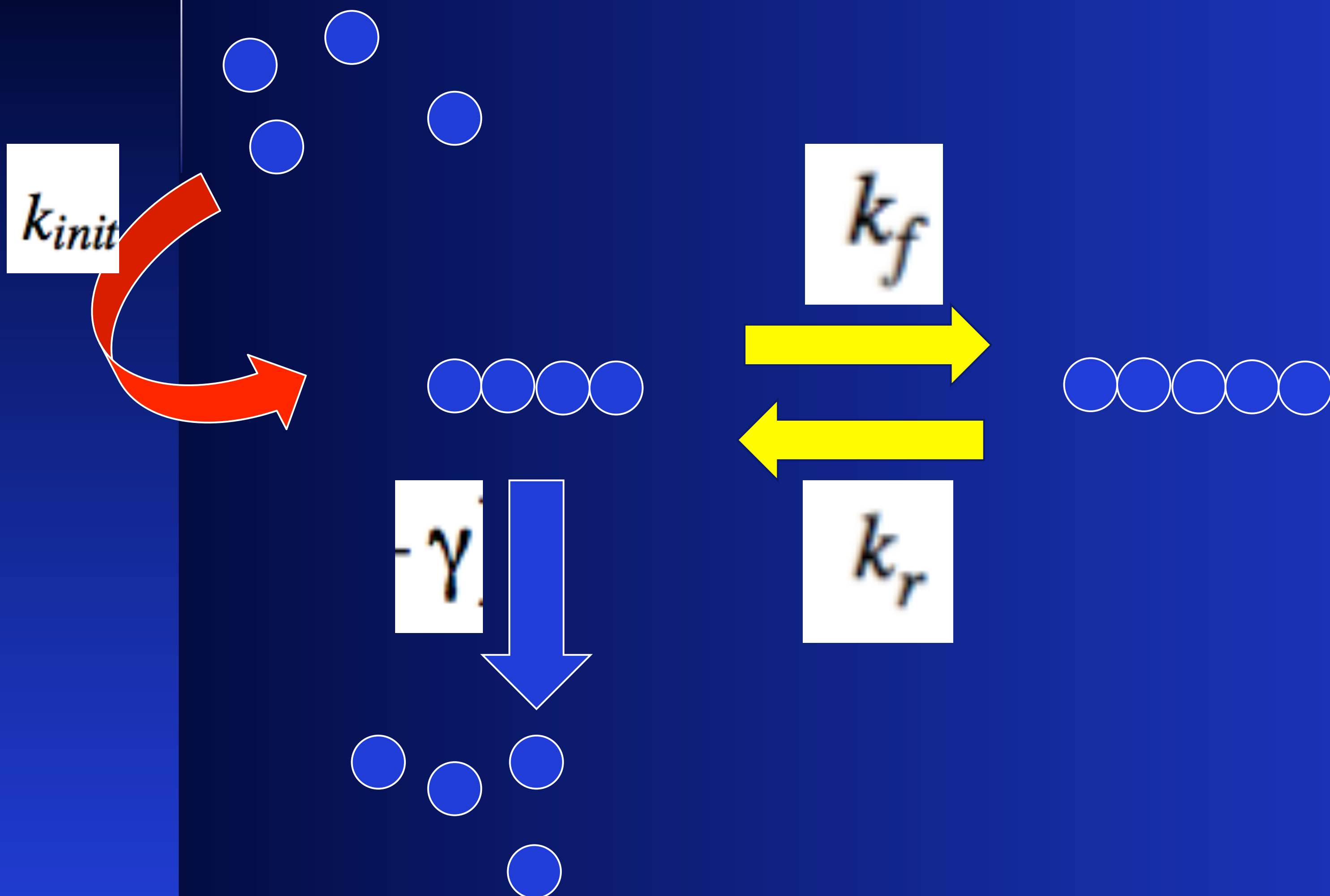
For i= smallest+1.. biggest

$$\frac{dp_i}{dt} = ck_f p_{i-1} - (ck_f + k_r)p_i + k_r p_{i+1}$$

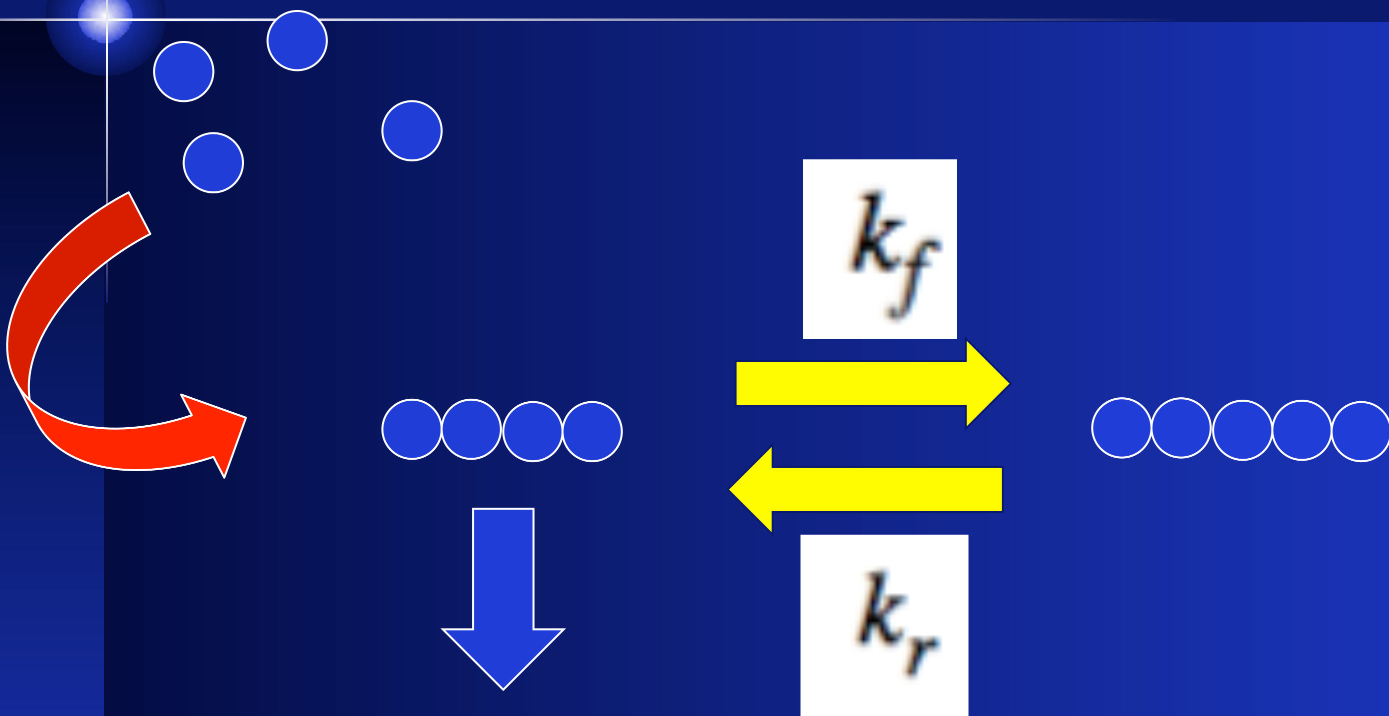
Need some rule for smallest size



Need some rule for smallest size



Need some rule for smallest size



$$\frac{dp_m}{dt} = k_{init}c^m - (ck_f + \gamma)p_m + k_r p_{m+1}$$

All pieces grow and use up the monomer pool

Number of pieces:

$$N_p = \sum p_i$$

$$\frac{dc}{dt} \approx a_{\text{depl}}(k_r - k_f c) N_p$$

NOTE: this equation holds after some time..

Actual monomer equation

- Obtained by enforcing mass balance
- (calculation given separately)

$$\frac{dc}{dt} = -\left[mk_{init}c^m - (m\gamma + k_r)p_m\right] - (ck_f - k_r)N(t)$$

- Formation and breakup of smallest size
- growth of all other polymers

NOTE: THIS SLIDE WAS ADDED AS A CORRECTION AFTER THE LECTURE

Monomer depletion

$$\frac{dc}{dt} \approx a_{\text{depl}}(k_r - k_f c)N_p$$

- As t $\longrightarrow$ ∞ Monomer level approaches

$$c \approx c_{crit} = k_r / k_f$$

Rewrite the polymer equation

$$\frac{dp_i}{dt} = ck_f p_{i-1} - (ck_f + k_r)p_i + k_r p_{i+1}$$

Rewrite the polymer equation

$$\frac{dp_i}{dt} = k_f\left(-c(p_i - p_{i-1}) + \frac{k_r}{k_f}(p_{i+1} - p_i)\right)$$

Rewrite the polymer equation

$$\frac{dp_i}{dt} = k_f\left(-c(p_i - p_{i-1}) + c_{crit}(p_{i+1} - p_i).\right)$$

$$k_r/k_f = c_{crit}.$$

Early time behaviour:

- Initially, a lot of monomer so $c >> c_{crit}$

$$\frac{dp_i}{dt} = k_f\left(-c(p_i - p_{i-1}) + c_{crit}(p_{i+1} - p_i).\right)$$

$$\frac{dp_i}{dt} \approx k_f\left(-c(p_i - p_{i-1})\right)$$

- "Transport to higher sizes at rate k_f"

Later time

- Monomer level approaches $c \approx c_{crit}$

$$\frac{dp_i}{dt} = k_f(-c(p_i - p_{i-1}) + c_{crit}(p_{i+1} - p_i).)$$

$$\Downarrow$$

$$\frac{dp_i}{dt} = k_f c_{crit}(-(p_i - p_{i-1}) + (p_{i+1} - p_i).)$$

- This is a discrete diffusion equation

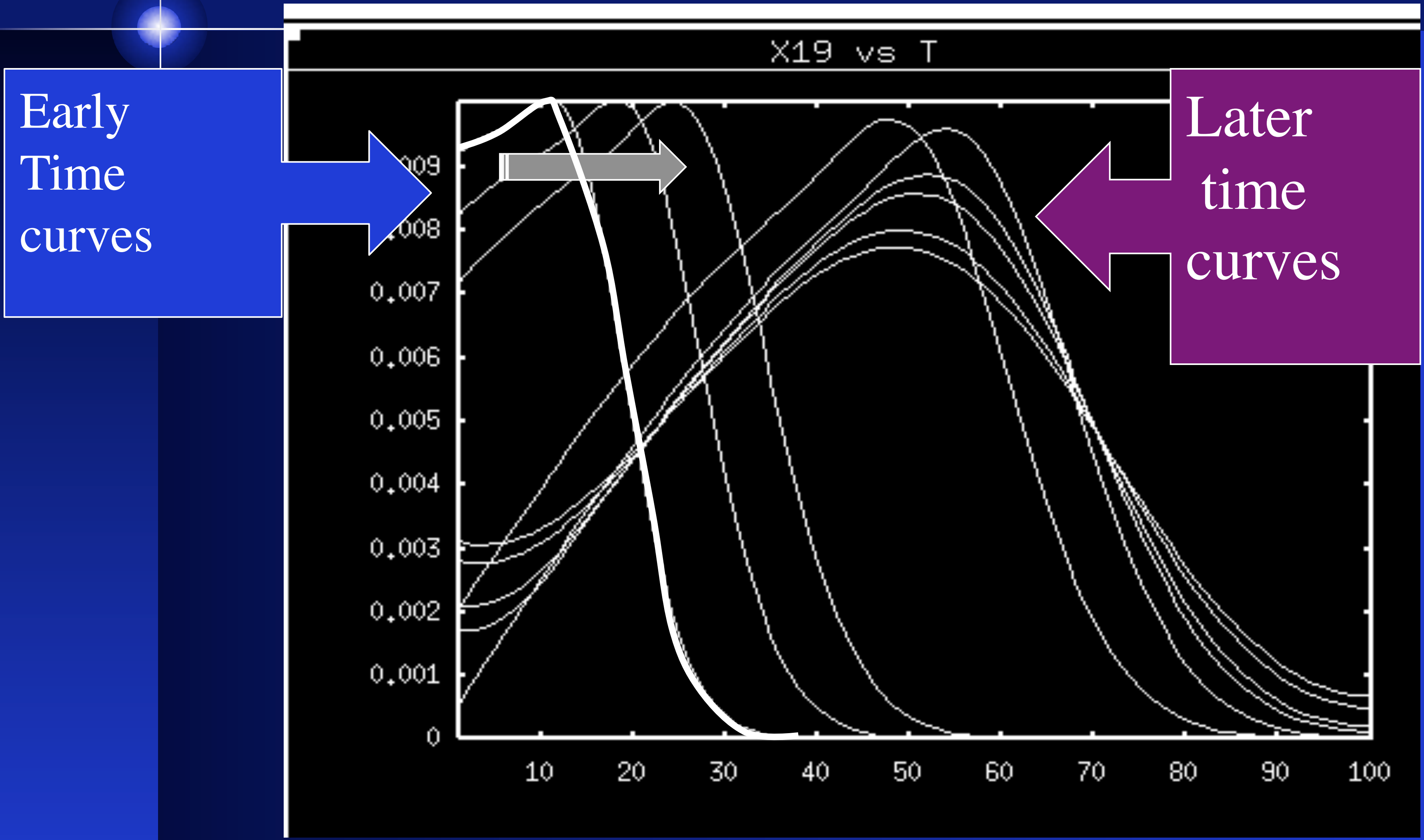
Simulations

- a' = adepl*(-kf*a*(sm2-x100+x2)+kr*(sm2+x2))

- # initialization from dimers
- x1'= kinit*a*a+kr*x2-kf*a*x1
- x[2..99]'= kf*a*(x[j-1]-x[j])+kr*(x[j+1]-x[j])
- x100' = -kr*x100+kf*a*x99

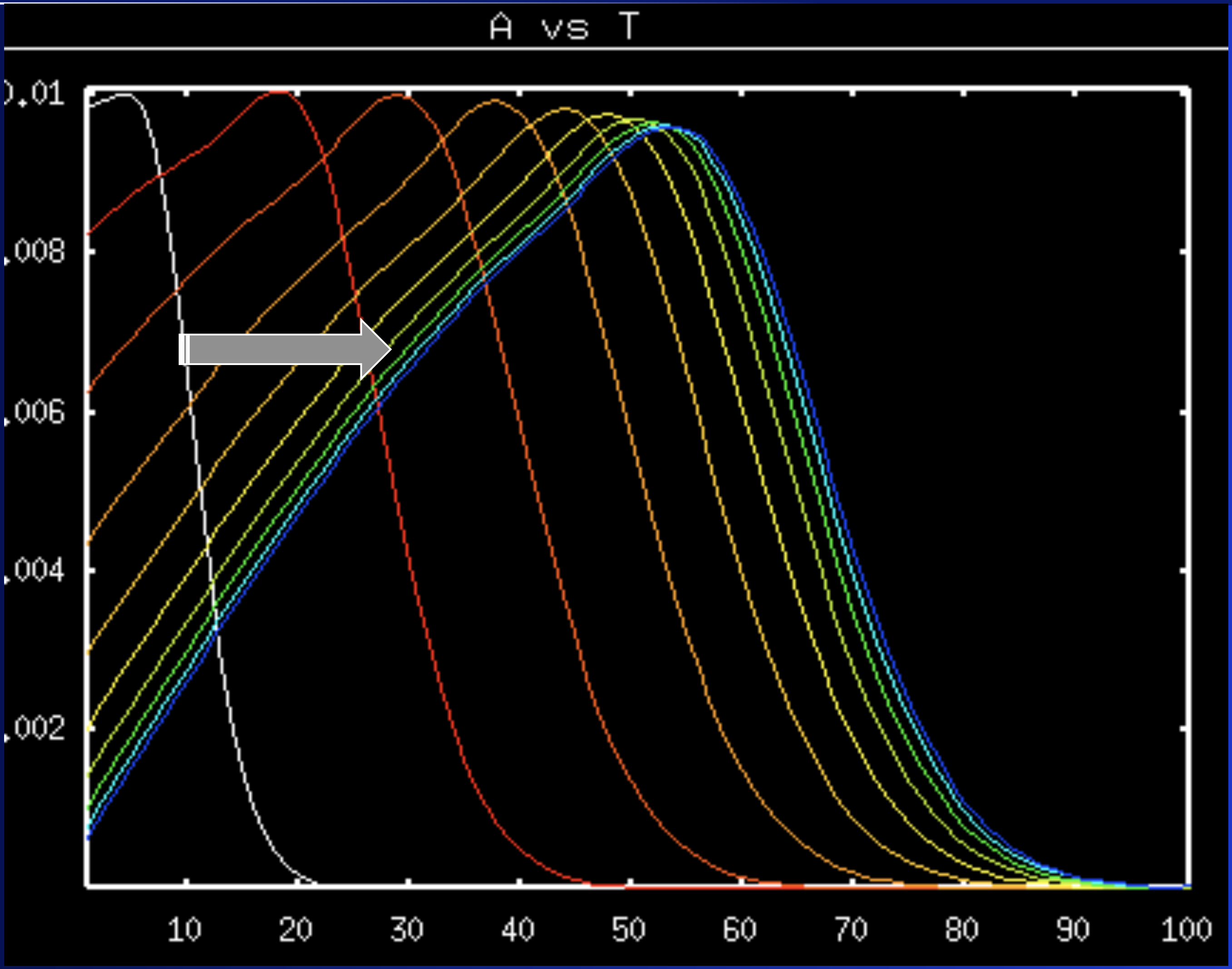
- #Computing the total number of fibers
- Nf=sm2+x2+x1
- aux Ntotal=Nf

Early “drift” then “diffusion”

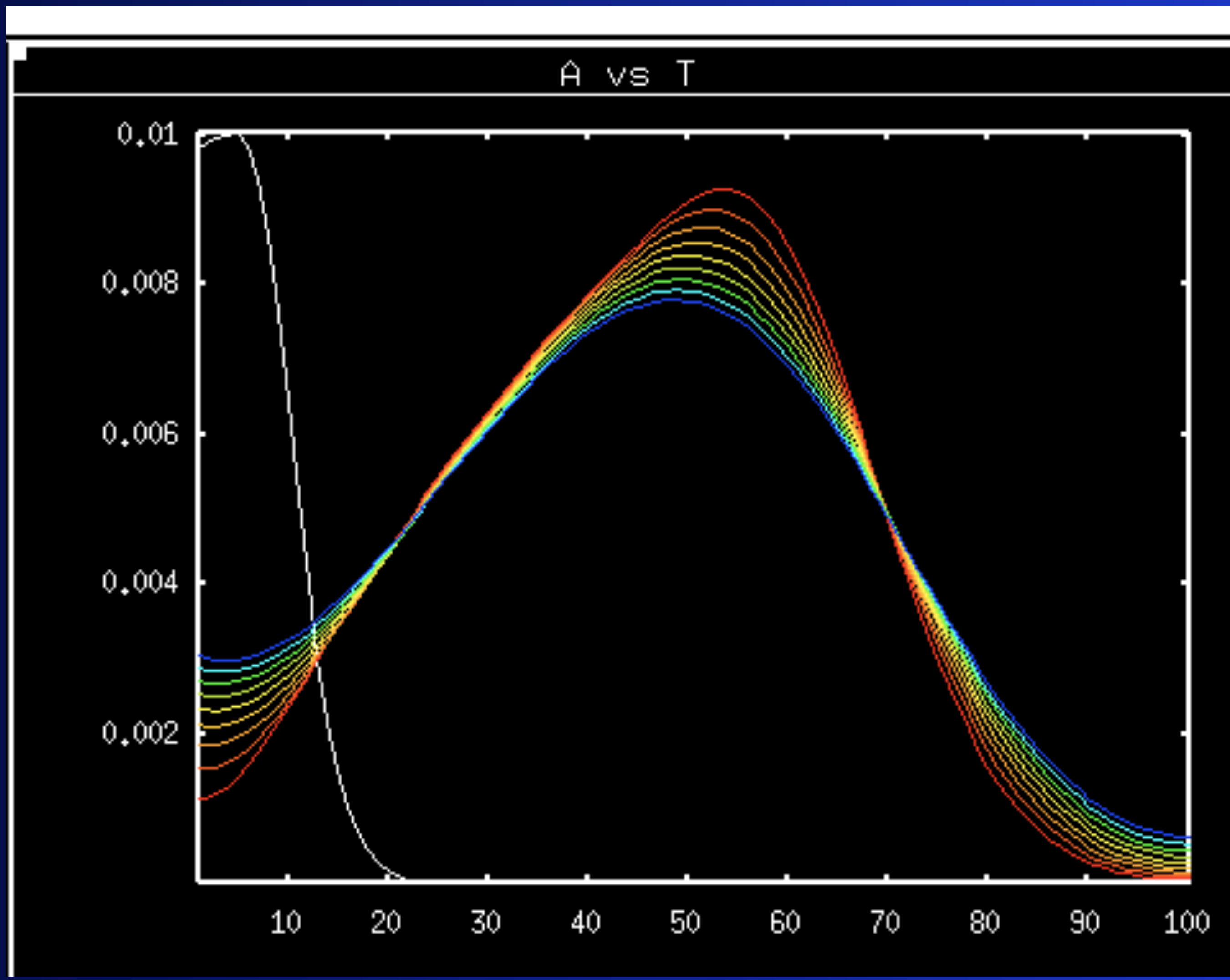


Polymer size (number of monomers)

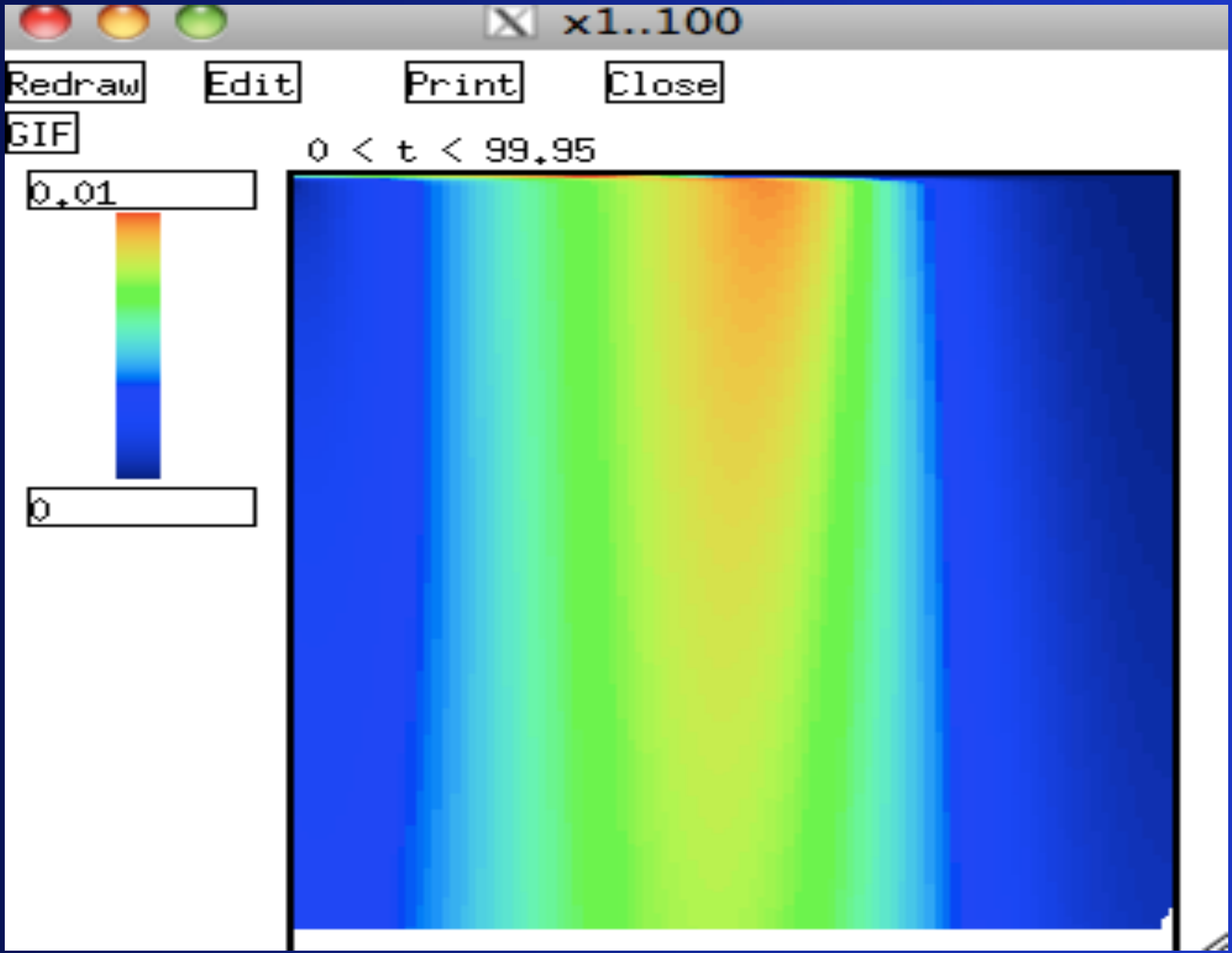
First Phase: growth to larger sizes



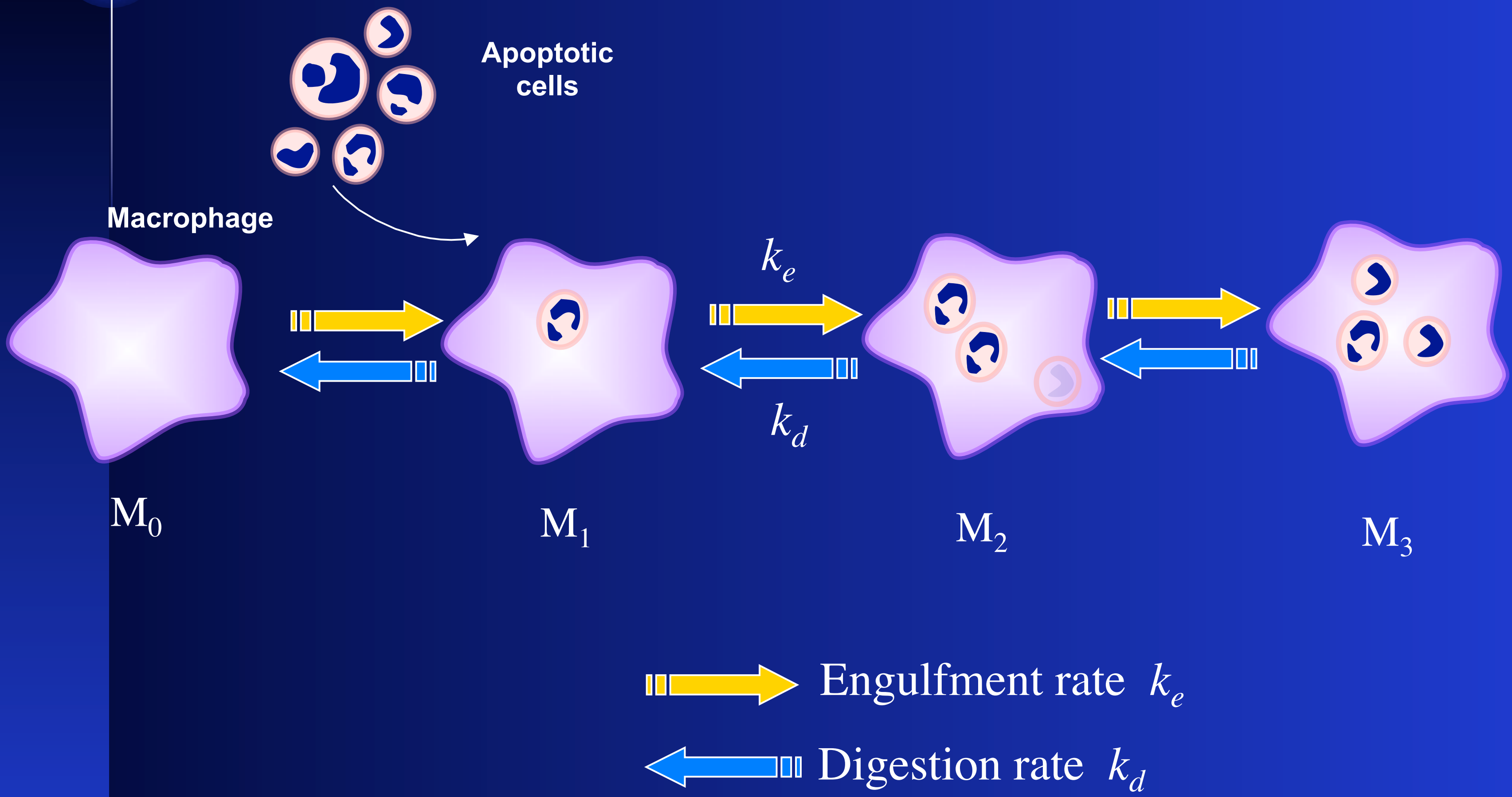
Second Phase: apparent "diffusion" in size space



Array plot

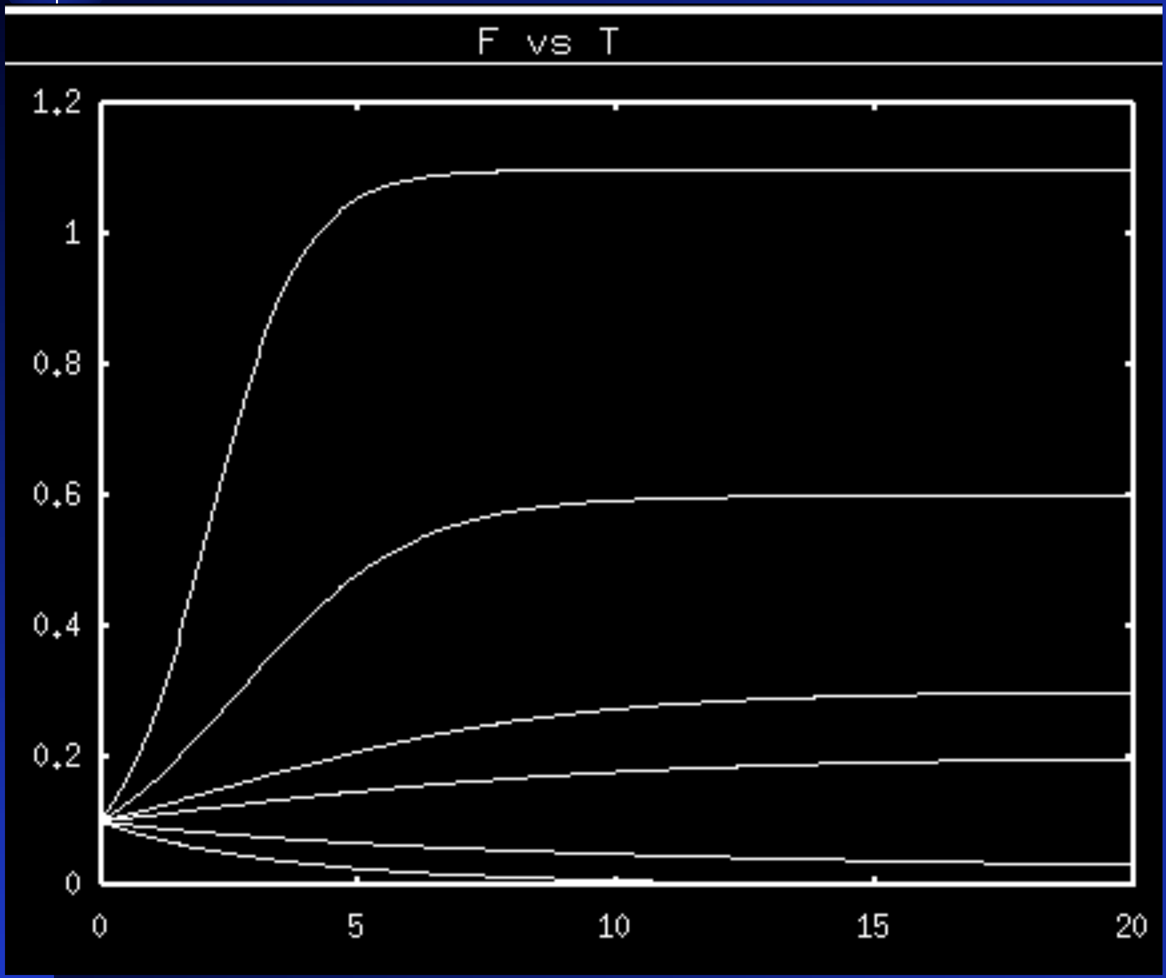


Other applications of same idea



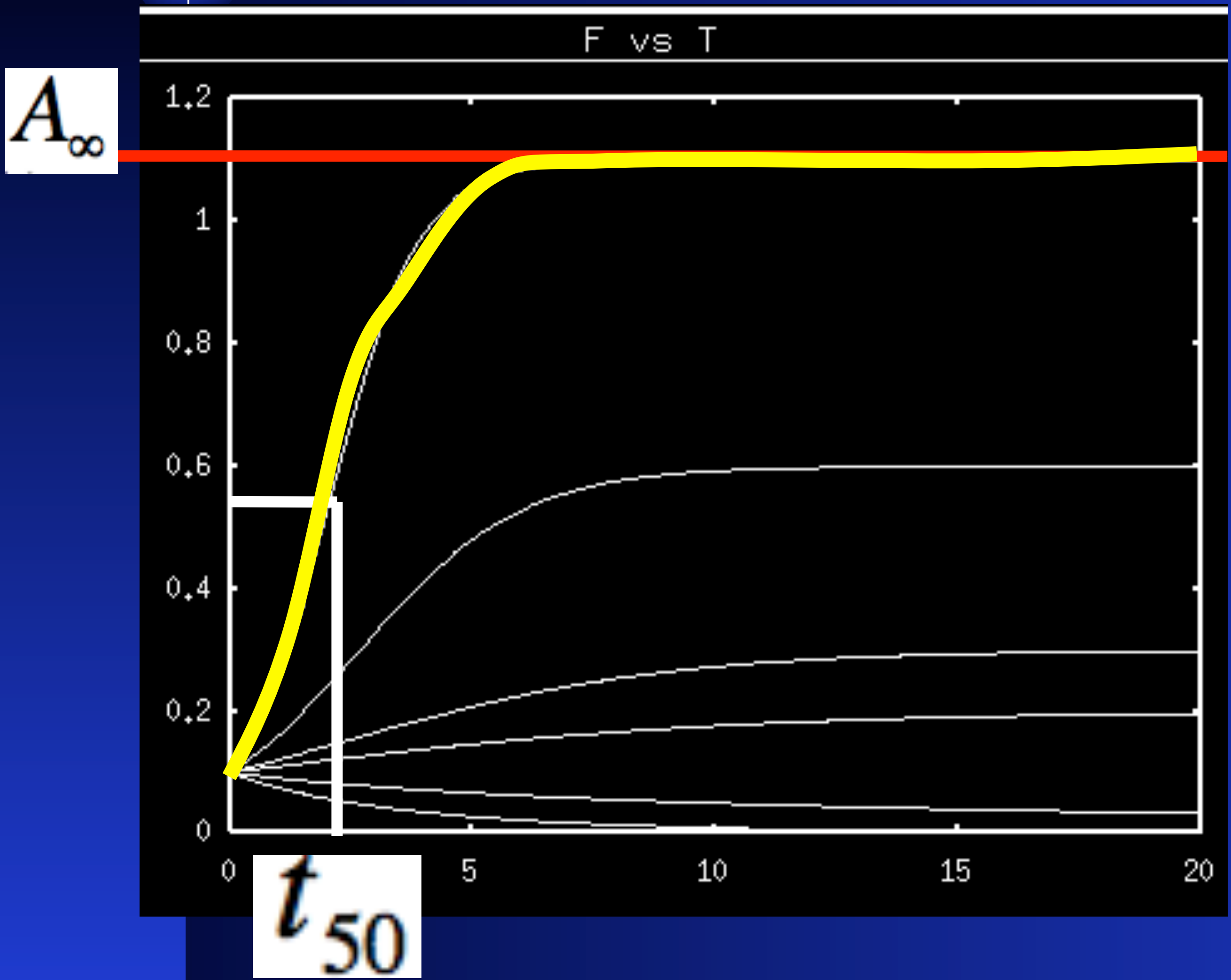
Generic polymerization behaviour

Recall: model → polymeriz vs t



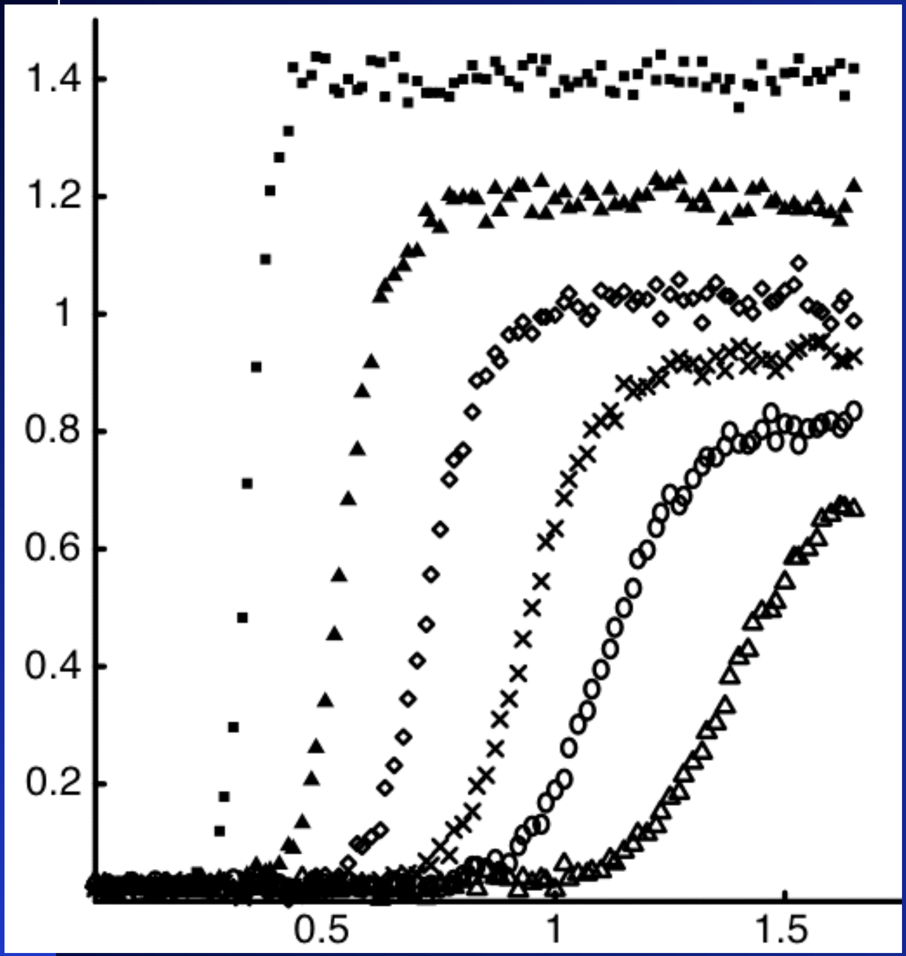
Curves for different initial monomer levels

Features of polymerization curves



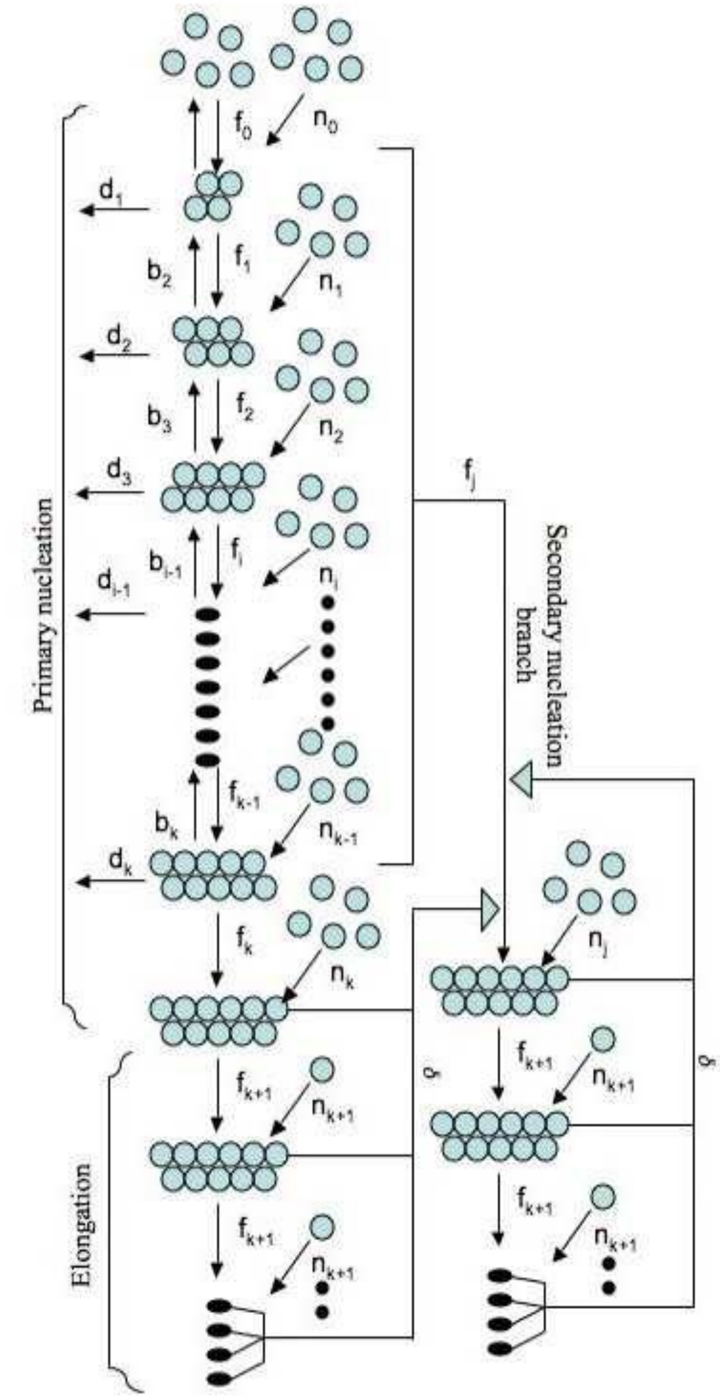
Curves for different initial monomer levels

Reverse direction: Data → model



Curves for different initial monomer levels

Figure credit: James Bailey, MSc UBC

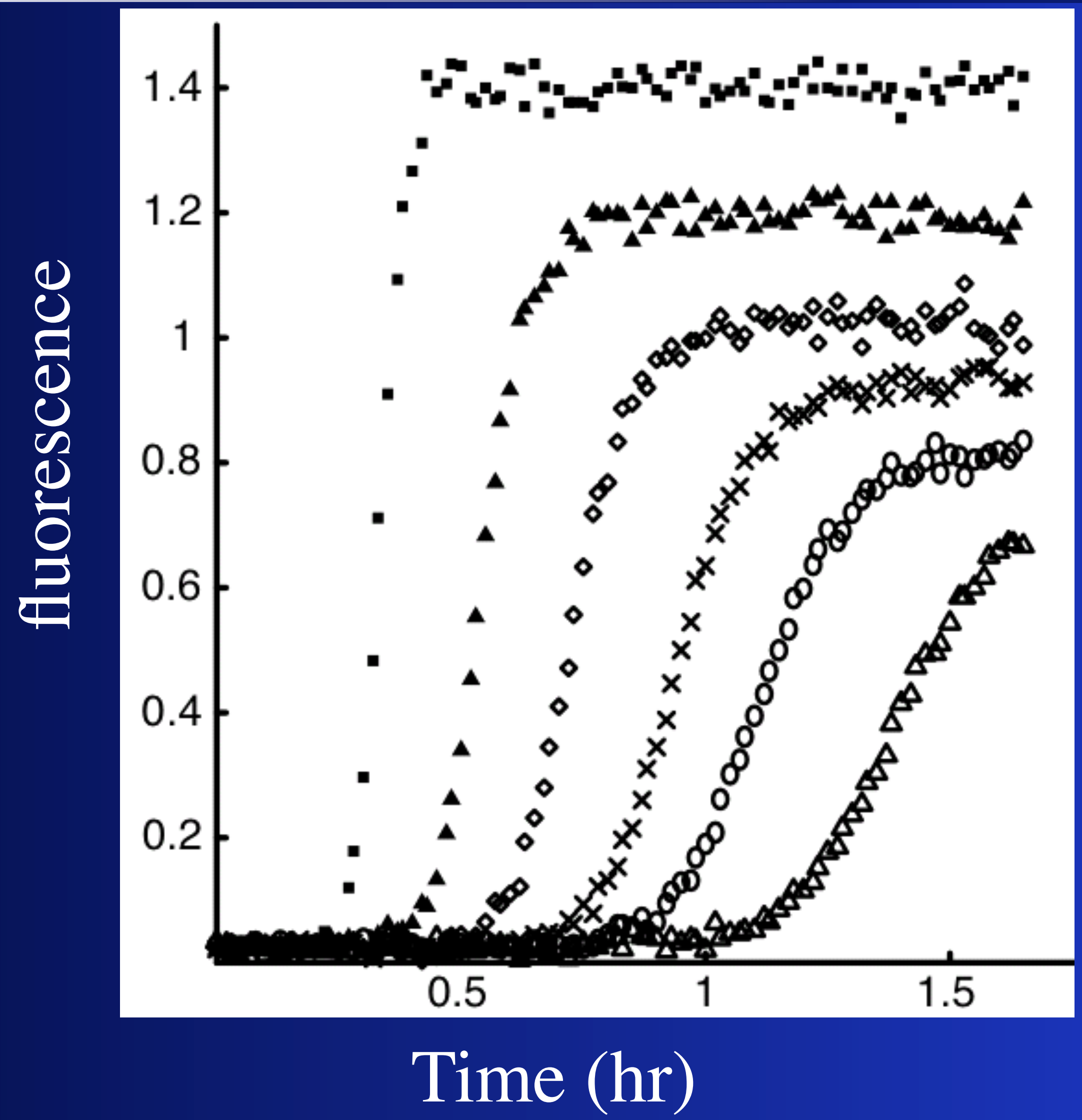


Possible steps

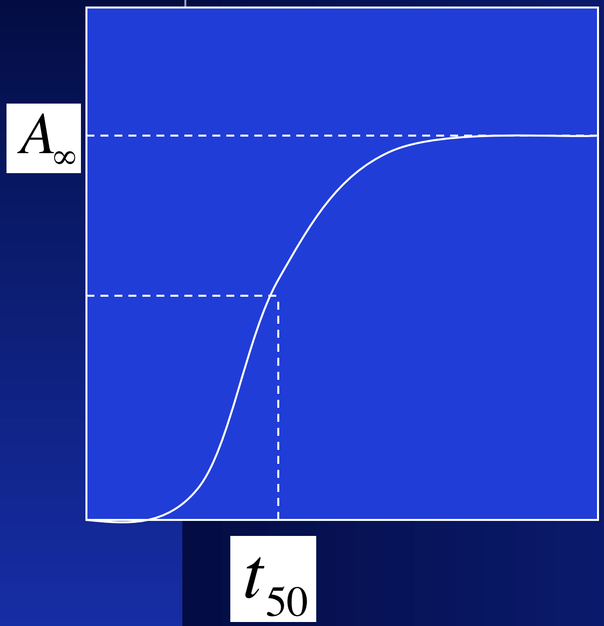
Initiation from multiple monomers, and addition/loss of many monomers or total disassembly at each early step.. until first stable nucleus.

Figure credit: James Bailey, MSc UBC

Experimental curves for various monomer levels



Scale the data:



Scale time: t/t_{50}

Scale fluorescence: $A(t)/A_\infty$

Scaling collapses the data

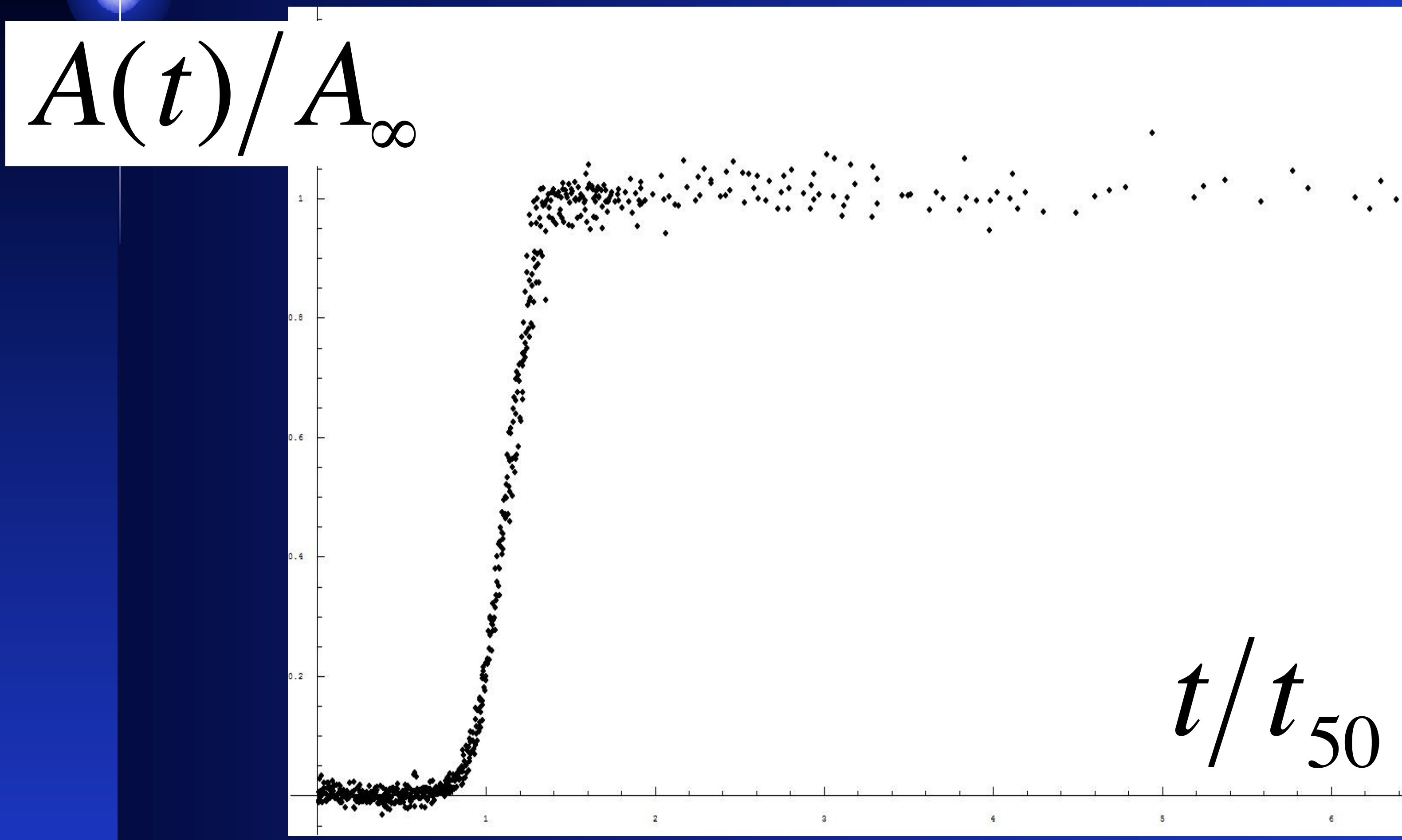
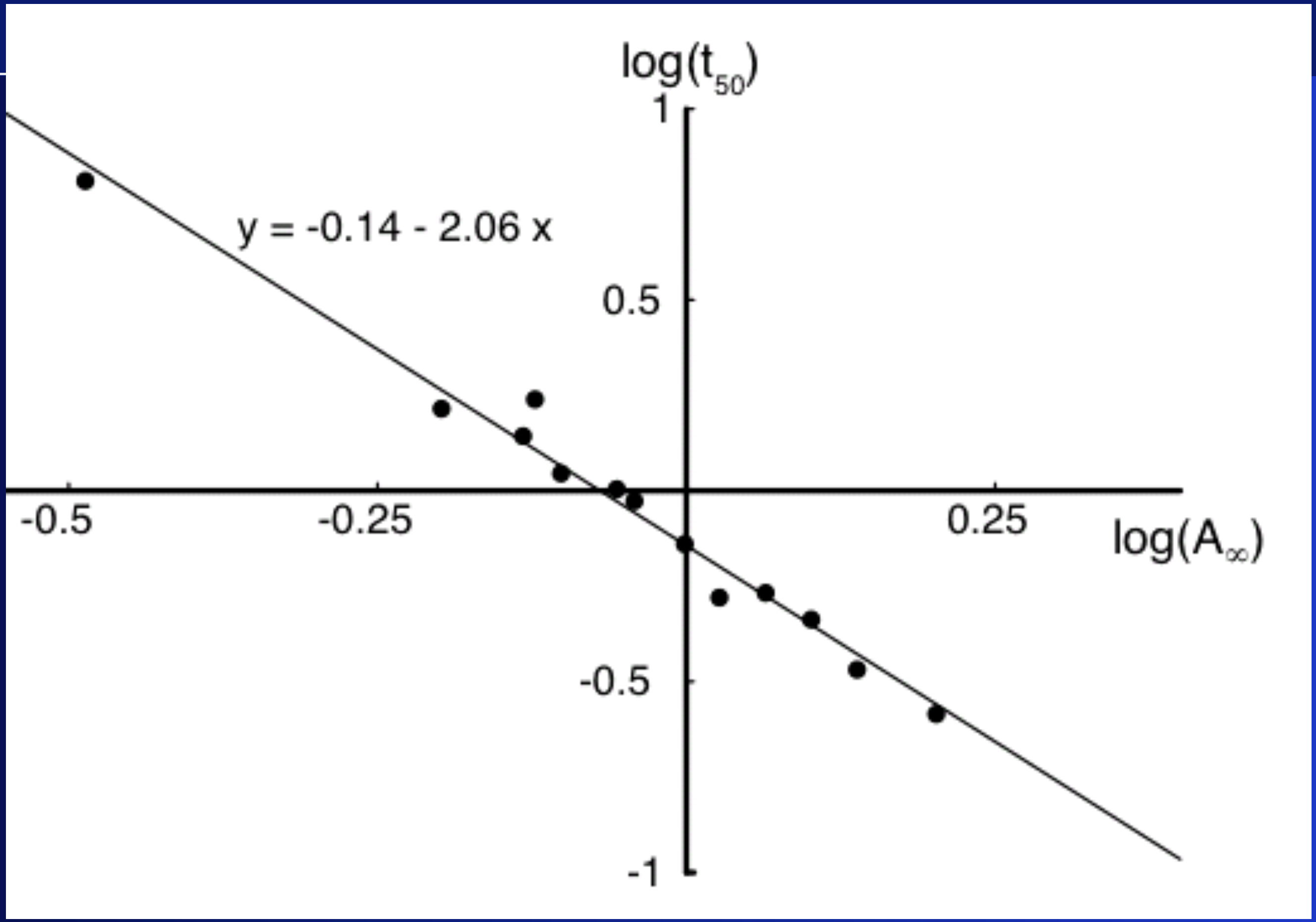


Figure credit: James Bailey, MSc UBC

Find a scaling law

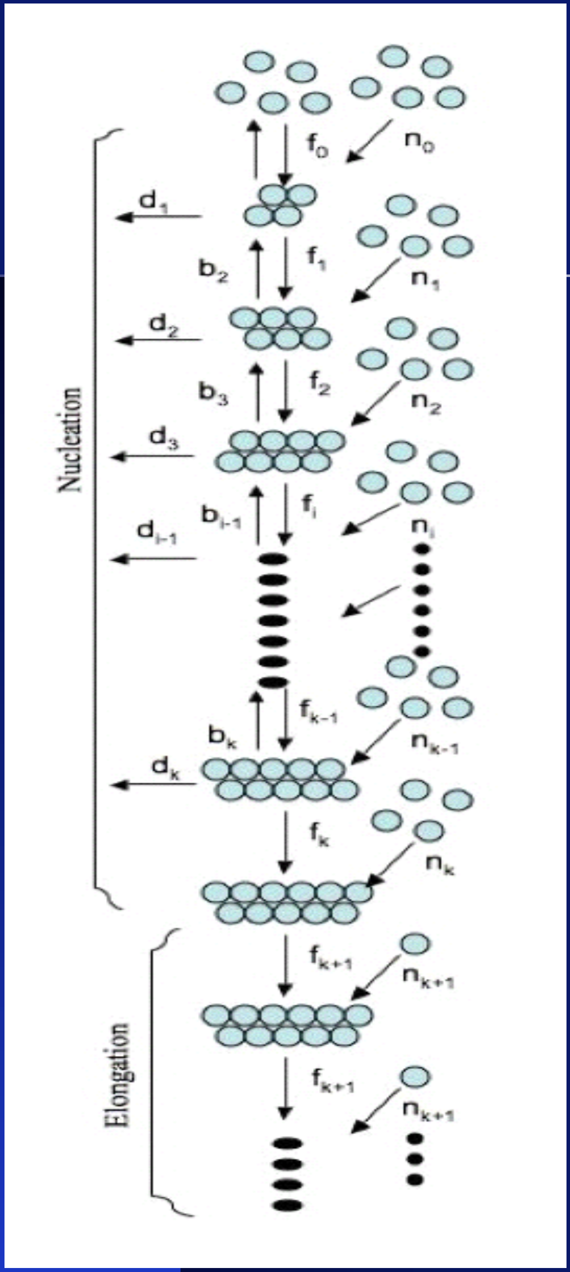


$$t_{50} \propto A_\infty^{-\gamma}$$

$$\gamma \approx 2$$

Figure credit: James Bailey, MSc UBC

Identify mechanism



Scaling and model

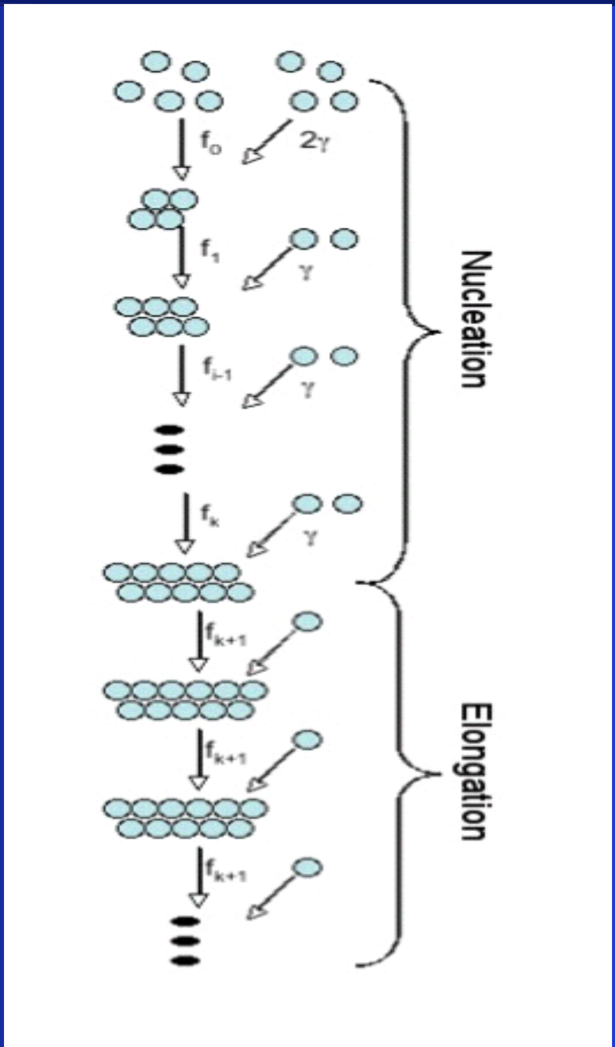
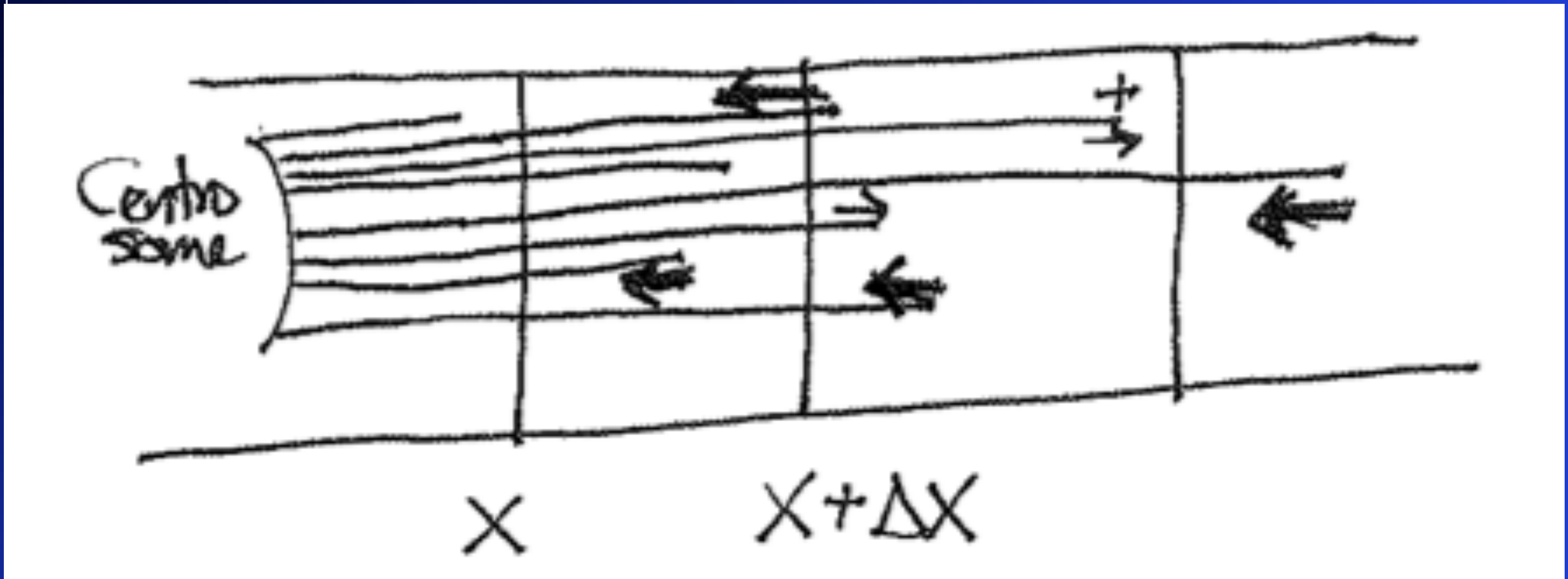


Figure credit: James Bailey, MSc UBC

Simulations of Microtubule (MT) dynamics using XPP

Growing and shrinking MT

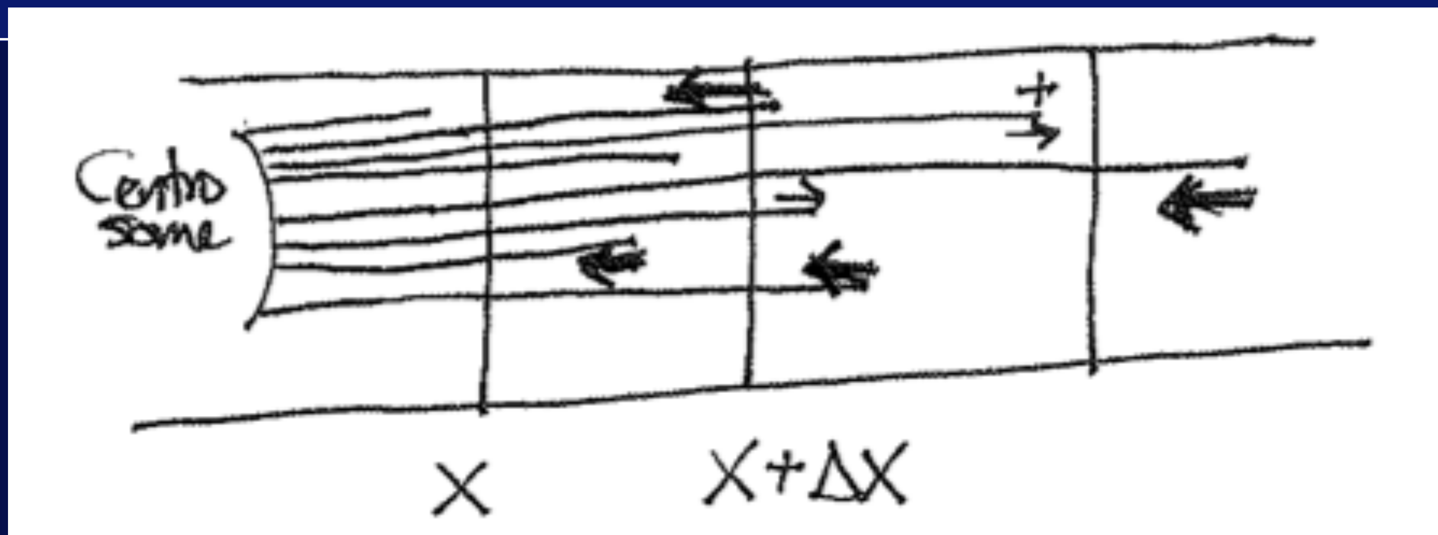


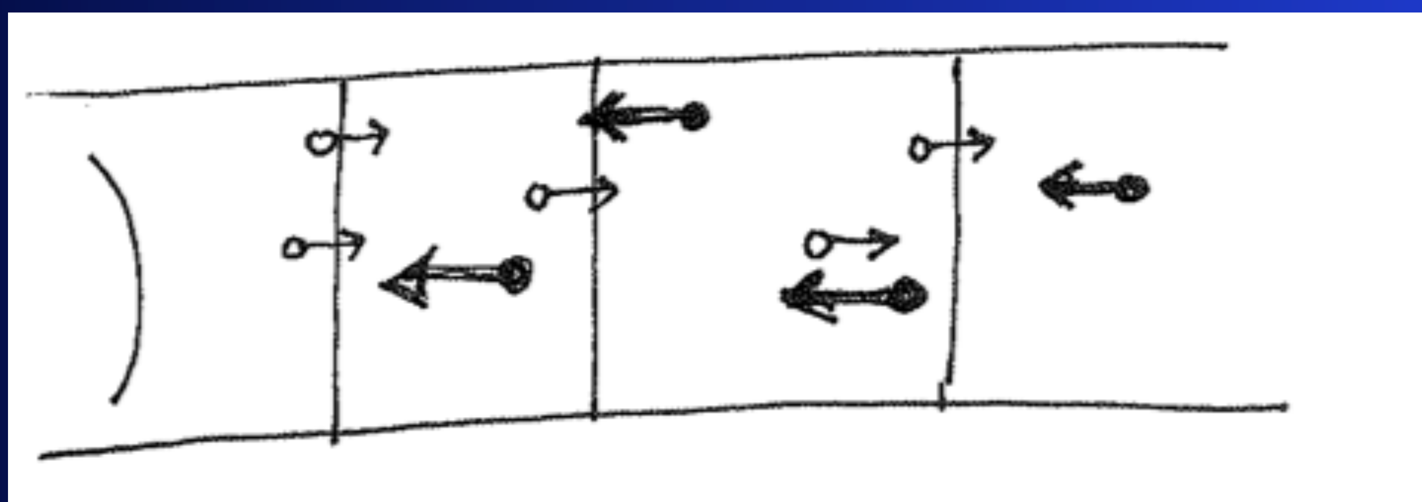
Some Movies…..

http://www.youtube.com/watch?v=9iXoXzgmEXw

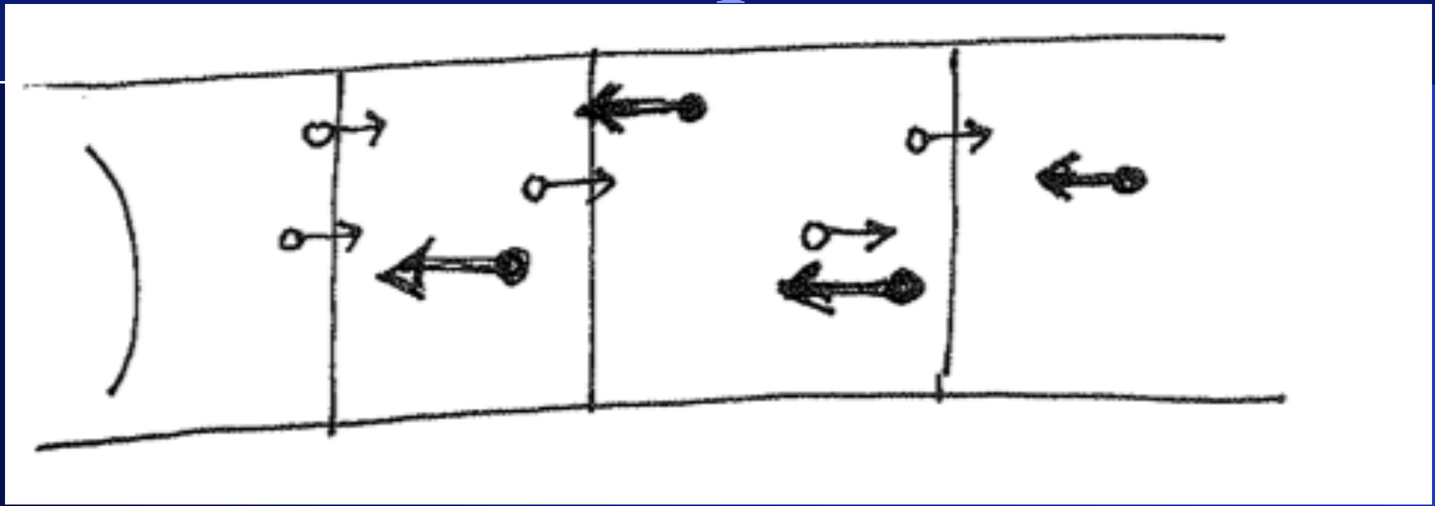
http://www.youtube.com/watch?v=PCI_GUHJJaY

Growing and shrinking tips





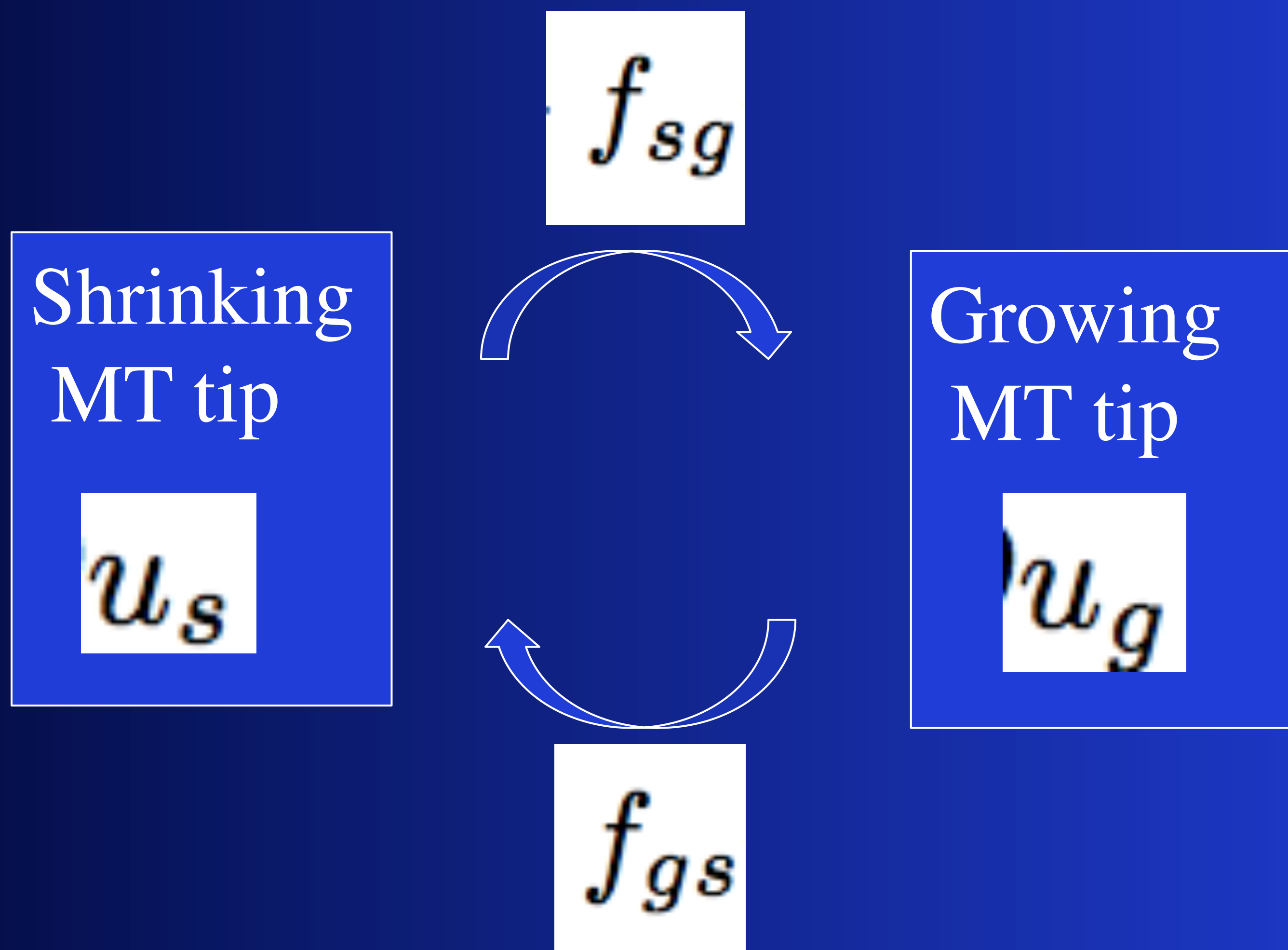
Balance equations



M. Dogterom and S. Leibler. Physical aspects of the growth and regulation of microtubule structures. *Phys. Rev Lett.*, 70:1347–1350, 1993.

M Dogterom, AC Maggs, and S Leibler. Diffusion and Formation of Microtubule Asters: Physical Processes Versus Biochemical Regulation. *PNAS*, 92(15):6683–6688, 1995.

Catastrophe and rescue



Balance equations

$$\frac{\partial u_g}{\partial t} = -v_g \frac{\partial u_g}{\partial x} - f_{gs} u_g + f_{sg} u_s,$$

$$\frac{\partial u_s}{\partial t} = v_s \frac{\partial u_s}{\partial x} + f_{gs} u_g - f_{sg} u_s,$$

Spatial terms

Exchange kinetics

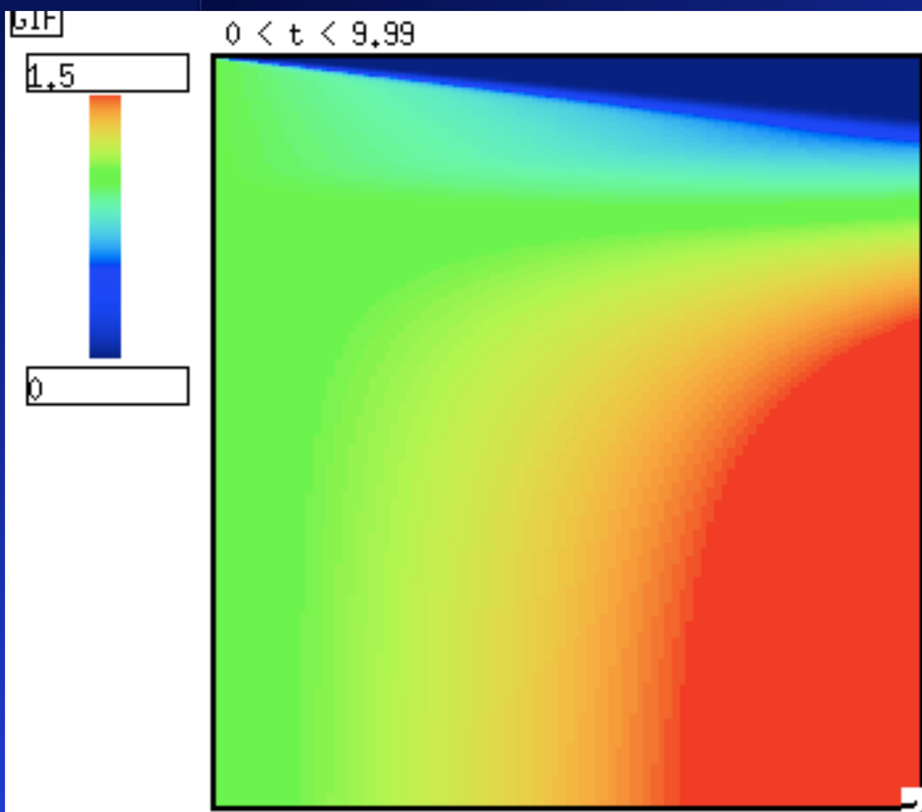
Steady state equations:

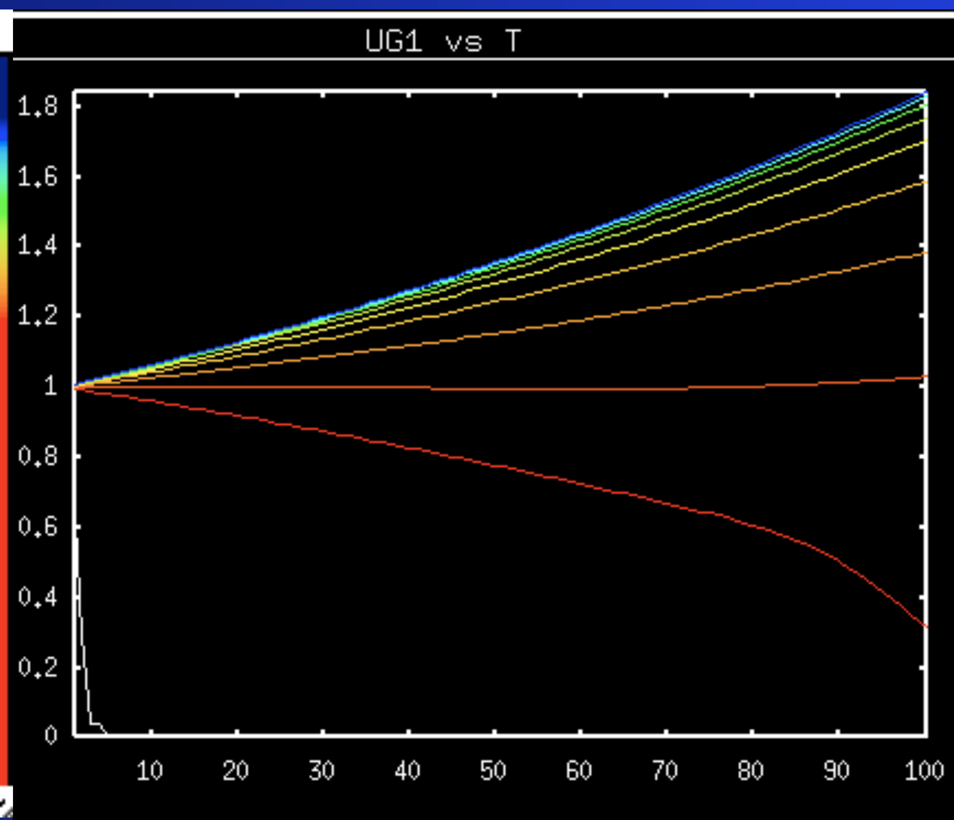
$$\frac{du_g}{dx} = \frac{1}{v_g}\left(-f_{gs}u_g + f_{sg}u_s\right),$$

$$\frac{du_s}{dx} = \frac{1}{v_s}\left(-f_{gs}u_g + f_{sg}u_s\right),$$

Growth regime

$$\frac{f_{sg}}{v_s} > \frac{f_{gs}}{v_g}$$





Shrinkage regime

$$\frac{f_{sg}}{v_s} < \frac{f_{gs}}{v_g}$$