A Systems Approach to Biology

MCB 195

Lecture 2
Tuesday, 8 Feb 2005

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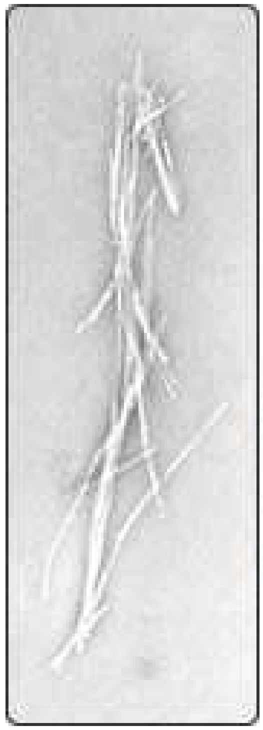
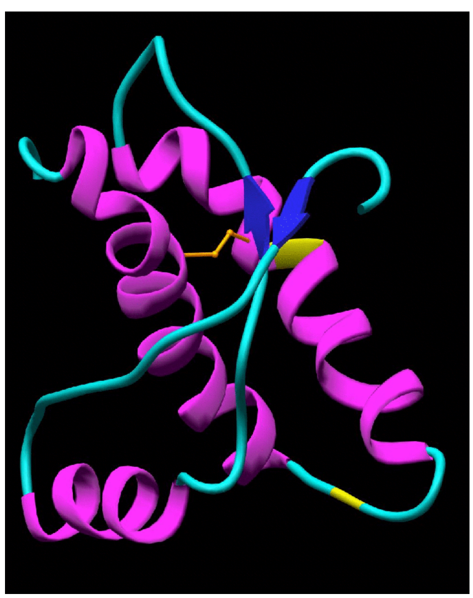
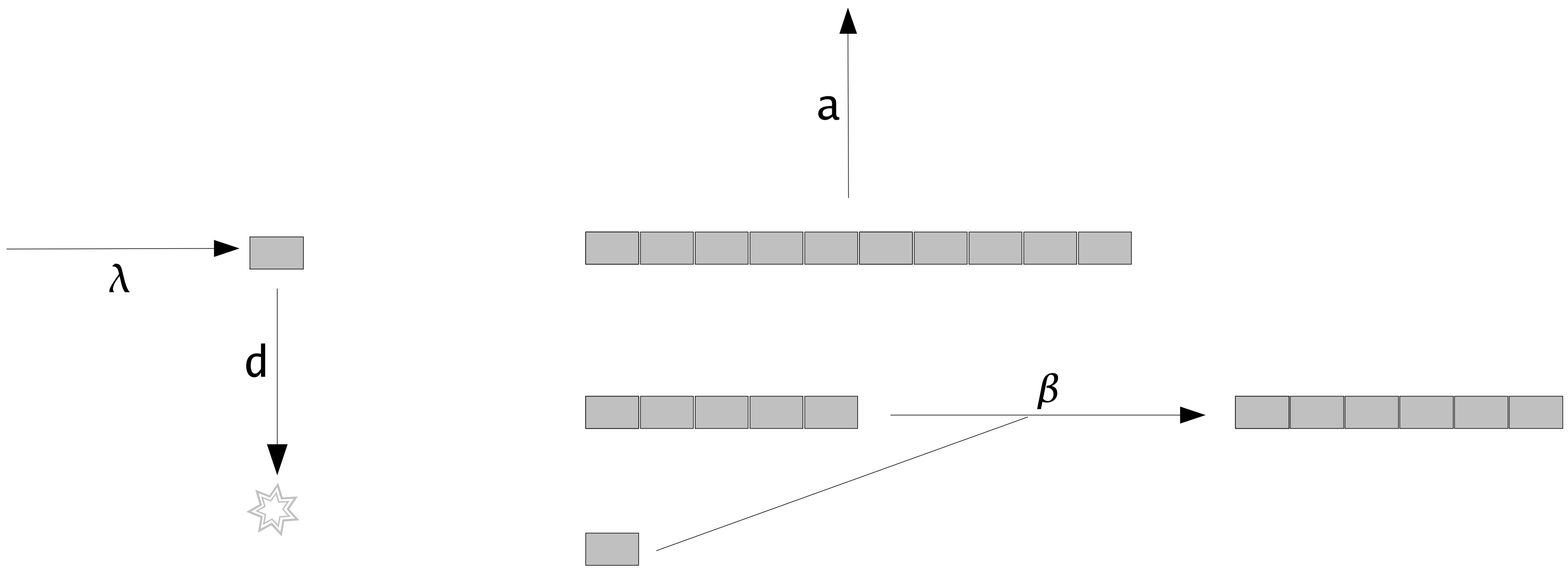
PRIONS CONTINUED

and then

DYNAMICAL SYSTEMS







monomer rates			**polymer rates**		
λ	production	(mols)(time)$^{-1}$	β	aggregation	(mols)$^{-1}$(time)$^{-1}$
d	degradation	(time)$^{-1}$	a	clearance	(time)$^{-1}$

J Masel, V Jansen & M Nowak, "Quantifying the kinetic parameters of prion replication" Biophysical Chemistry **77**:139-152 1999

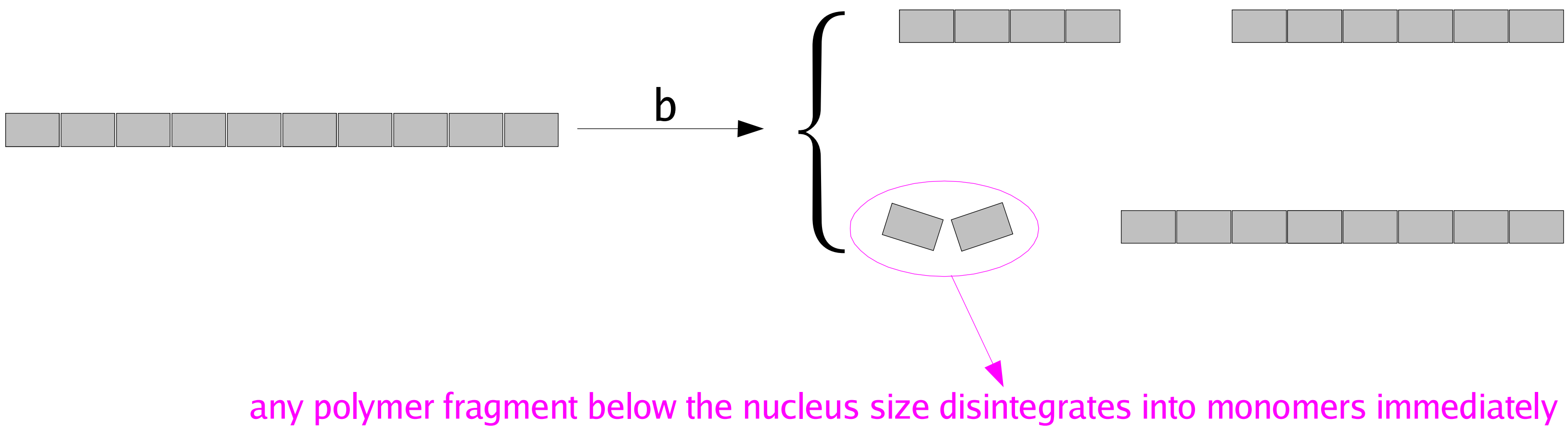
x amount of monomer

y_i amount of polymer with i monomer units

$$\frac{dx}{dt} = \lambda - dx - \sum_{i=n}^{\infty} \beta x y_i$$

$$\frac{dy_i}{dt} = \beta x y_{i-1} - \beta x y_i - a y_i \quad \text{for } i \geq n$$

$$y_i = 0 \quad \text{for } 1 \leq i < n$$



polymer rates

b breakage $(\text{time})^{-1}$

$$\frac{dx}{dt} = \lambda - dx - \sum_{i=n}^{\infty} \beta x y_i + \sum_{i=n}^{\infty} \sum_{j=1}^{n-1} 2bjy_i$$

$$\frac{dy_i}{dt} = \beta x y_{i-1} - \beta x y_i - a y_i - (i-1) b y_i + \sum_{j=i+1}^{\infty} 2b y_j \quad \text{for } i \geq n$$

$$y_i = 0 \quad \text{for } 1 \leq i < n$$

monomer rates

λ	production	(mols)(time)$^{-1}$
d	degradation	(time)$^{-1}$
n	nucleus size	

polymer rates

β	aggregation	(mols)$^{-1}$(time)$^{-1}$
a	clearance	(time)$^{-1}$
b	breakage	(time)$^{-1}$

3 state variables

x	amount of monomer
y	amount of polymer
z	mass of polymer (in monomer units)

6 parameters

n	nucleus size
λ	production
d	degradation
β	aggregation
a	clearance
b	breakage

time evolution

$$\begin{cases} \frac{dx}{dt} = \lambda - dx - \beta xy + bn(n-1)y \\ \frac{dy}{dt} = -ay + b(z+y) - 2nby \\ \frac{dz}{dt} = \beta xy - az - n(n-1)by \end{cases}$$

nonlinear terms (βxy)

3 dimensional, nonlinear dynamical system

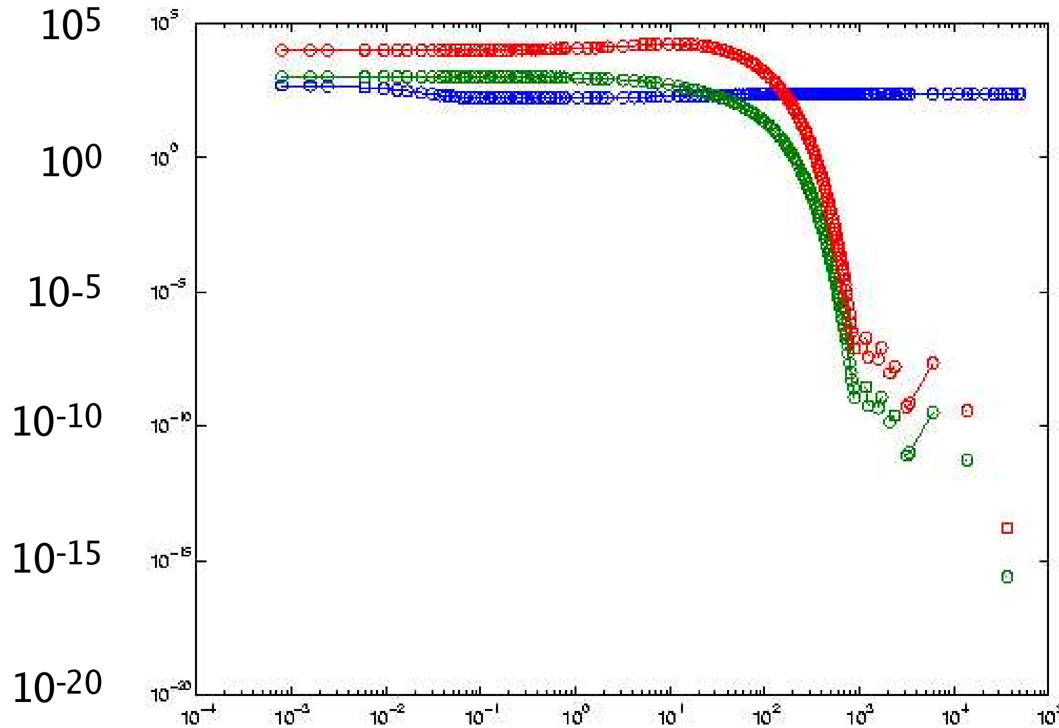
How do we work out the behaviour of this dynamical system?

1. choose reasonable parameter values and play with MATLAB

n	6	β	0.015
λ	9000	a	0.08
d	40	b	0.0009

initial conditions

x = 500
y = 1000
z = 10000



polymer disappears!

How do we work out the behaviour of this dynamical system?

2. determine the **steady states**, where

$$\frac{dx}{dt} = \frac{dy}{dt} = \frac{dz}{dt} = 0$$

$X_1 = \lambda/d$ depends only on monomer rates

$$X_2 = \frac{(a + (n-1)b)(a + nb)}{b\beta}$$ depends only on polymer rates

If $X_1 \leq X_2$ there is 1 steady state

$(X_1 , 0 , 0)$

If $X_1 > X_2$ there are 2 steady states

$(X_1 , 0 , 0)$ and $(X_2 , (X_1 - X_2)(d/as) , (X_1 - X_2)(d/a))$

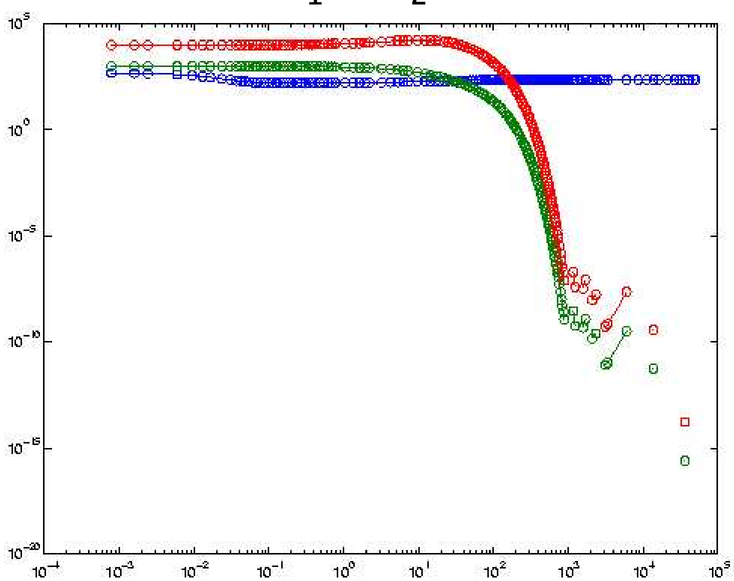
where $s = a/b + 2n-1$ is the average polymer length in the second steady state

n	6		
λ	9000	X_1	225
d	40	X_2	535
β	0.015		
a	0.08		
b	0.0009		

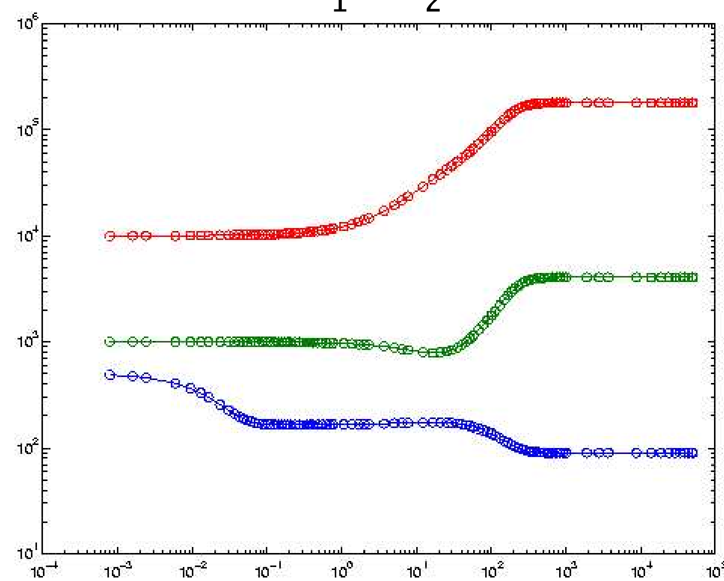
n	6		
λ	9000	X_1	225
d	40	X_2	90
β	0.015		
a	0.03		
b	0.0009		

x = 500
y = 1000
z = 10000

$X_1 \leq X_2$

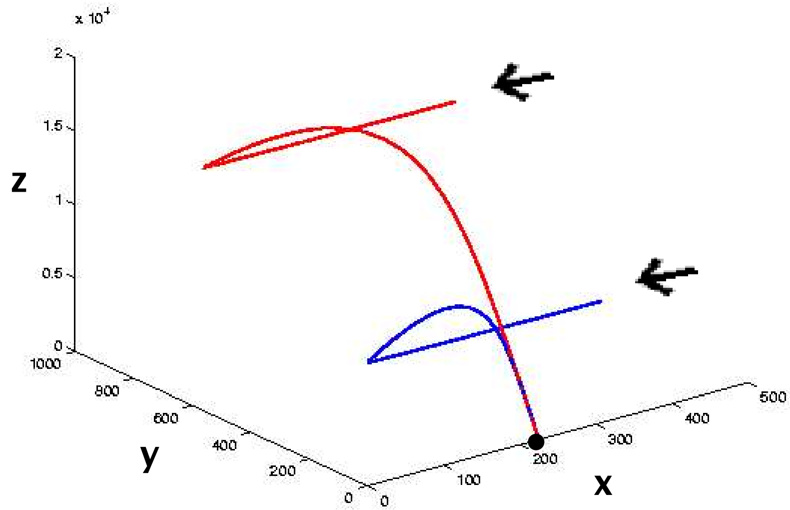


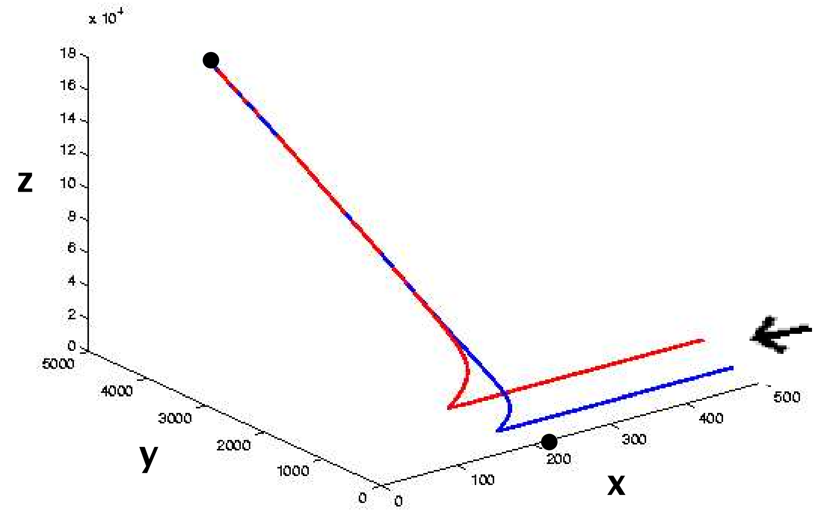
$X_1 > X_2$



BIFURCATION

a change in the qualitative ("topological") structure of steady states and trajectories as a result of changes in parameter values





a = 0.8 ⟶ a = 0.3

The moral of this story

changes in processes “outside” the system, like clearance or degradation, can have profound consequences on system behaviour

How do we work out the behaviour of this dynamical system?

3. determine the local **stability** of the steady states