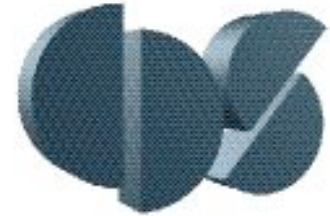# APh 161, Lecture 7: Biological Circuit (Design)

Richard M. Murray
Control and Dynamical Systems
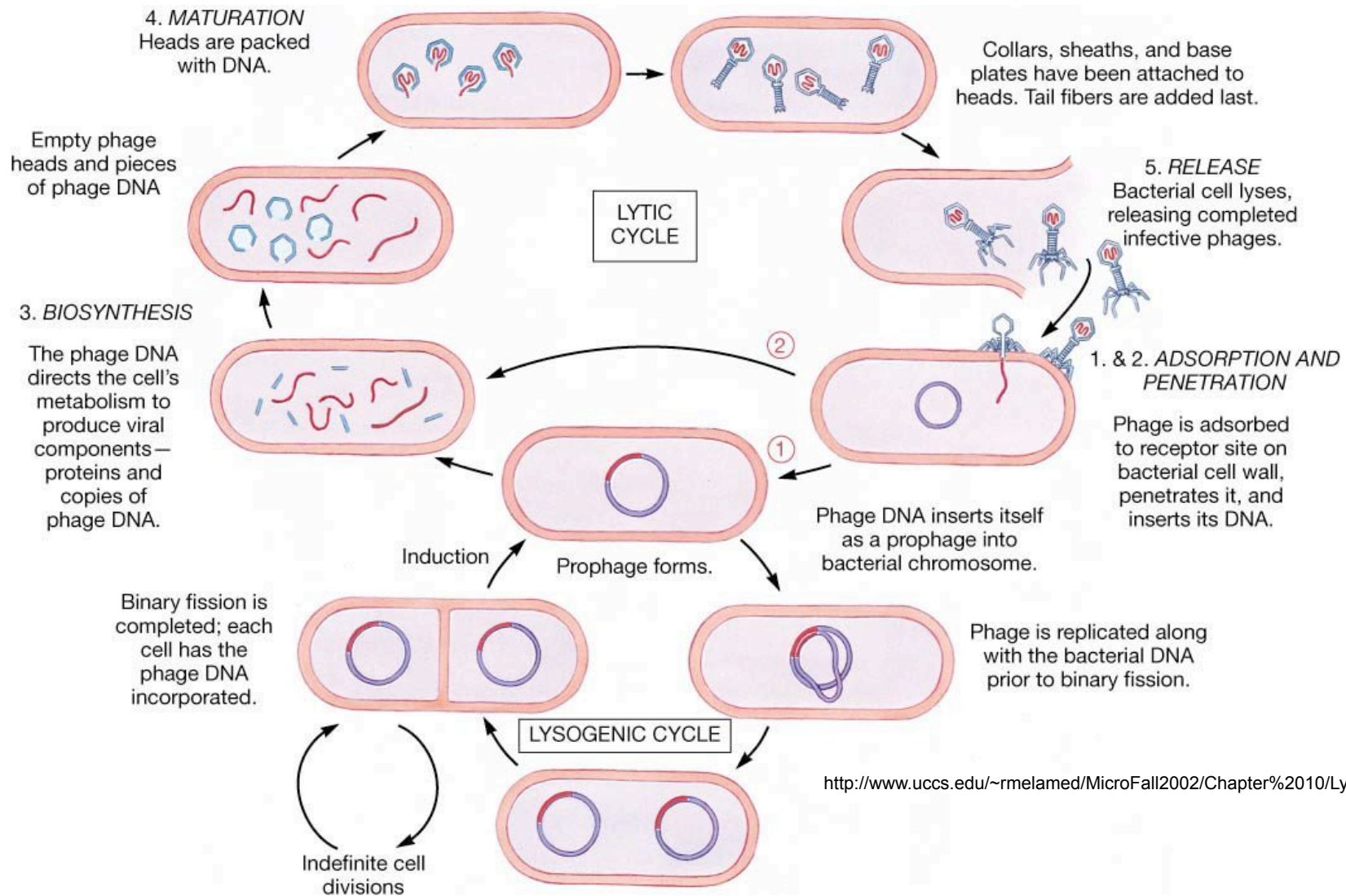
25 January 2007

Goals:

- Talk about the role of switches as an example of a biological circuit
- Walk through "stick in the sand" calculation of switch dynamics
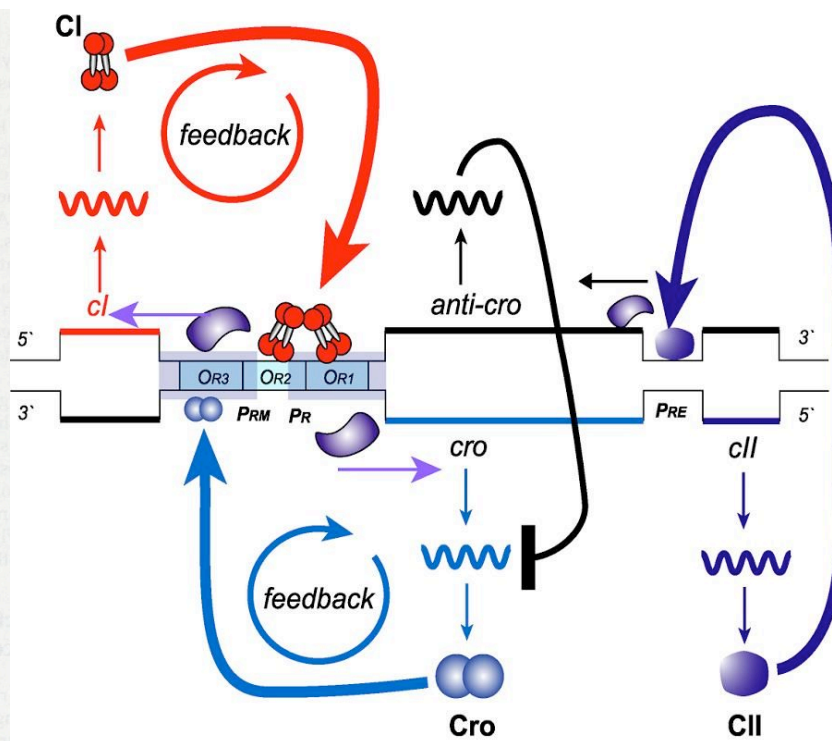- Walk through "fingers on the keyboard" calculation of oscillator circuit
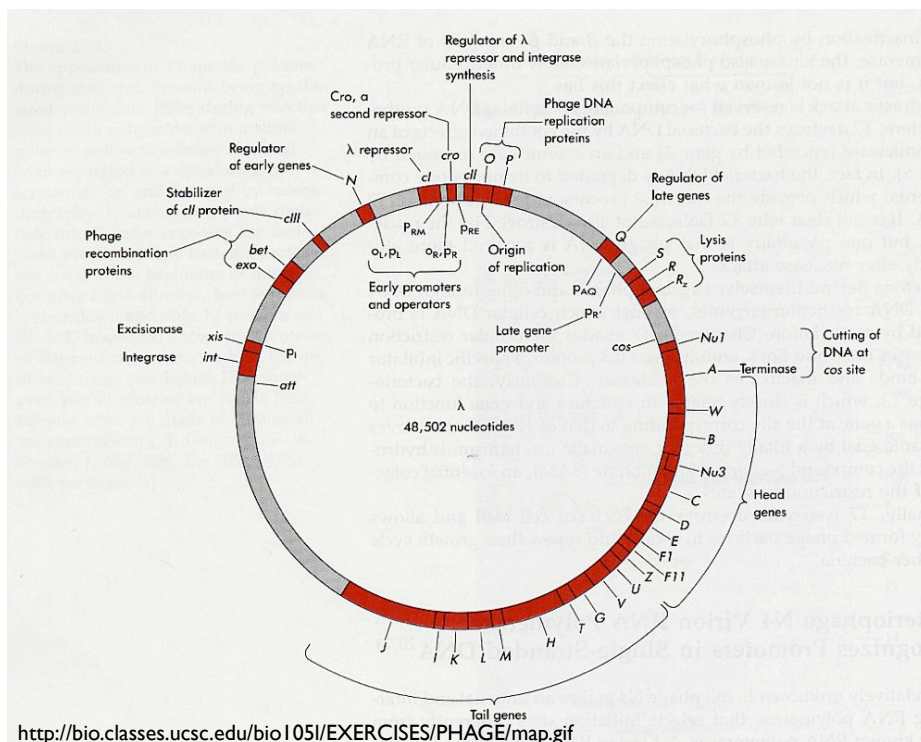
Reading

- Kondev, Phillips and Theriot, Physical Biology of the Cell, Chapter 19
- Gardner et al, "Construction of a genetic toggle switch...", Nature 2000
- Cherry and Adler, "How to make a biological switch", J. Theor Bio, 2000
- Elowitz and Leibler, A synthetic oscillatory network of transcriptional regulators, Nature, 2000

Phage λ

4. MATURATION Heads are packed with DNA.

Collars, sheaths, and base plates have been attached to heads. Tail fibers are added last.

Empty phage heads and pieces of phage DNA

LYTIC CYCLE

5. RELEASE Bacterial cell lyses, releasing completed infective phages.

3. BIOSYNTHESIS

The phage DNA directs the cell's metabolism to produce viral components— proteins and copies of phage DNA.

②

①

1. & 2. ADSORPTION AND PENETRATION

Phage is adsorbed to receptor site on bacterial cell wall, penetrates it, and inserts its DNA.

Phage DNA inserts itself as a prophage into bacterial chromosome.

Induction

Prophage forms.

Binary fission is completed; each cell has the phage DNA incorporated.

Phage is replicated along with the bacterial DNA prior to binary fission.

LYSOGENIC CYCLE

http://www.uccs.edu/~rmelamed/MicroFall2002/Chapter%2010/Lysogeny.jpg

Indefinite cell divisions

Phage λ Circuit

http://bio.classes.ucsc.edu/bio105I/EXERCISES/PHAGE/map.gif

Control logic

- Set of operator regions controls expression of both *cl* and *cro* genes
- Cooperativity (multiple copies of repressor bound to operator region) plays important role
- As in *lac* operon, multiple feedback loops interacting with each other => complex to analyze

Gardner, Cantor and Collins (Nature, 2000)

T. S. Gardner, C. R. Cantor and J. J. Collins
Construction of a genetic toggle switch in *Escherichia coli*
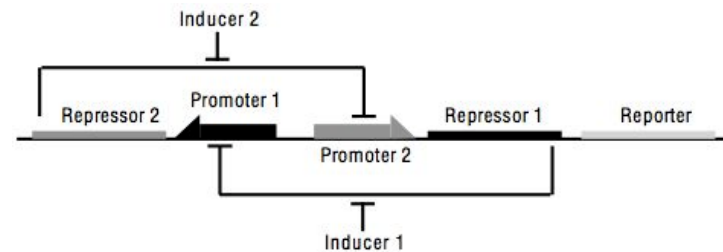Nature, 2000
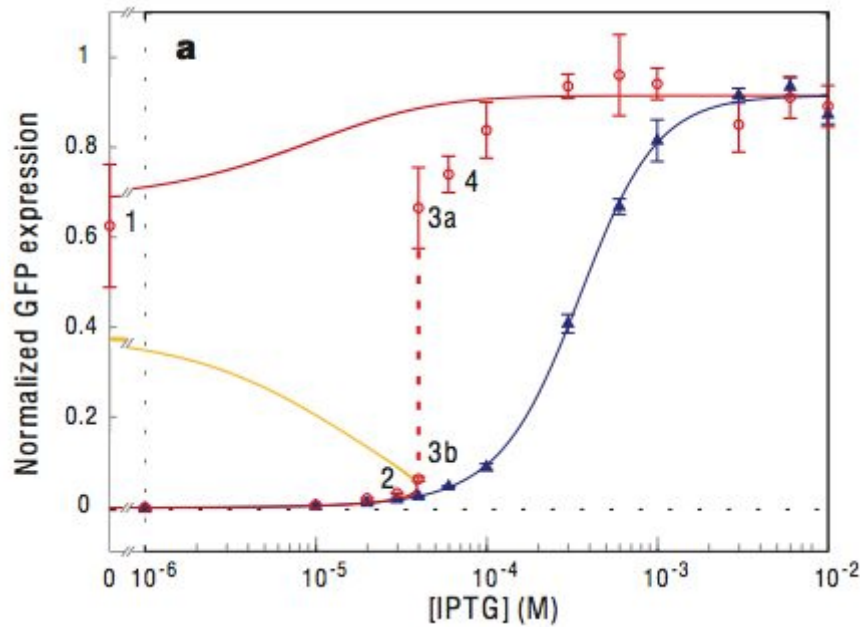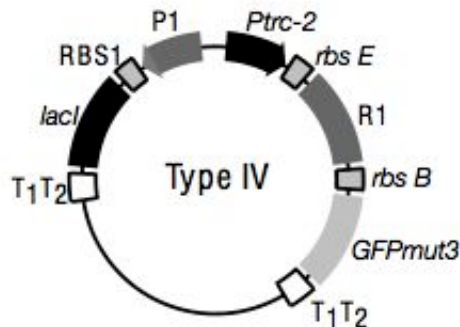
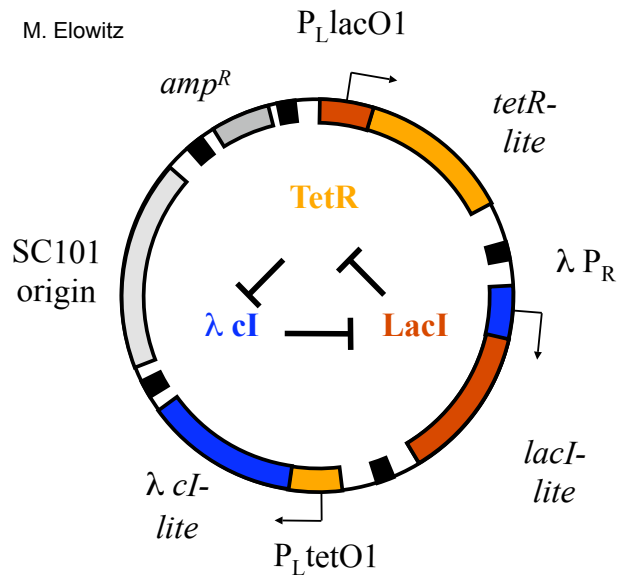
Method: interconnect lacI, λ genes
- *lacI*: gene for repressor from *lac* operon
  - Can be repressed through IPTG
- *cI* from λ
  - Can be repressed using temperature
- Also tried *tetR* (regulates resistance to tetracycline)

Results
- Where able to show they could induce a change from one state to the other through inducers

Repressilator

M. Elowitz

$P_L$lacO1

amp^R

tetR-lite

TetR

SC101 origin

λ P_R

λ cI   LacI

λ cI-lite

lacI-lite

$P_L$tetO1

Basic idea

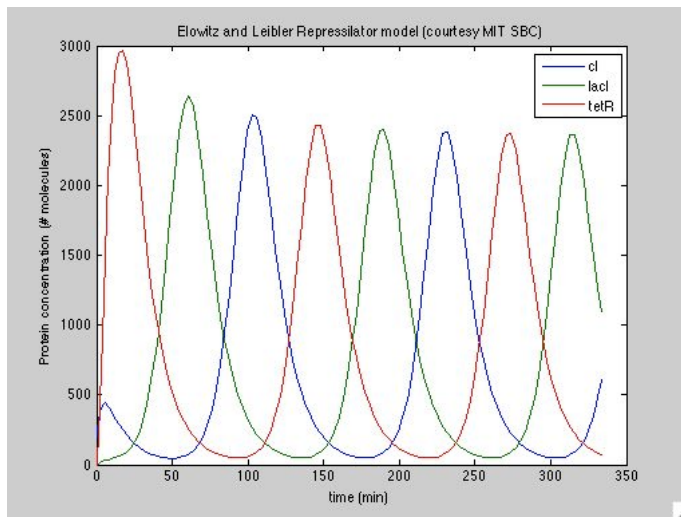- Three genes whose proteins are each repressors of the next gene in the sequence

Model:

$$\frac{dm_i}{dt} = -K_m m_i + \frac{\gamma}{1 + K_b p_{i-1}^n} + \gamma_0$$
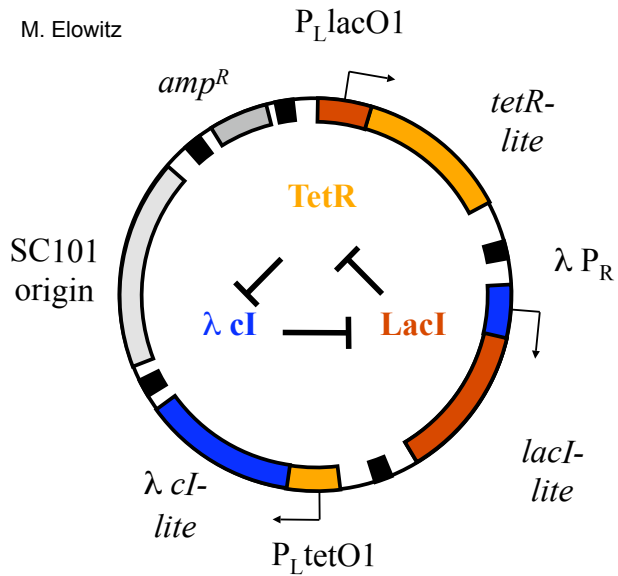
$$\frac{dp_i}{dt} = -K_p p_i + T m_i$$

- 6 states: m_tetR, m_cI, m_LacI, p_tetR, p_cI, p_laci
- "Stick in the sand" calculations are hard, but "fingers on the keyboard" works well
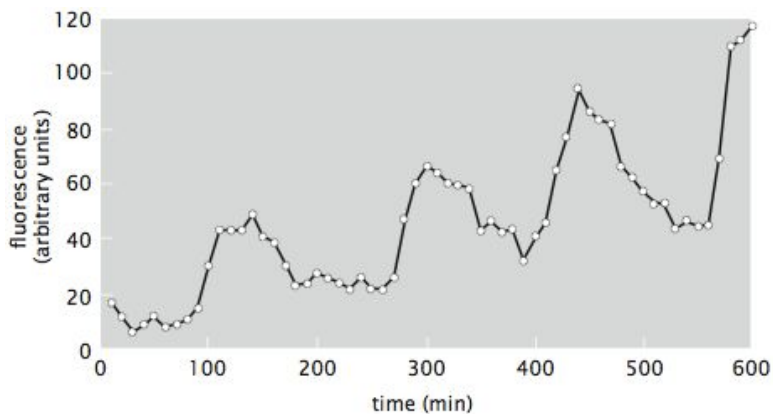
MATLAB implementation

- repressilator.m - file with dynamics
- repressilator_plot.m - commands to run simulation and generate plots
- Also: geneticswitch.m for Gardner et al switch

Repressilator

M. Elowitz

P$_L$lacO1

amp^R

tetR-
lite

TetR

SC101
origin

λ P$_R$

λ cI

LacI

λ cI-
lite

lacI-
lite

P$_L$tetO1

A synthetic oscillatory network of transcriptional regulators
Michael B. Elowitz and Stanislas Leibler
Nature 403, 335-338 (20 January 2000)

Basic idea

- Three genes whose proteins are each repressors of the next gene in the sequence

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- "Stick in the sand" calculations are hard, but "fingers on the keyboard" works well