Overview:

For our first session on transcription, we will jump right into our discussion paper, Schubert et al., which is a beautifully constructed analysis of the epigenetic switch that controls the development of bacteriophage λ. In order to appreciate this paper, you will need to familiarize yourself with the λ life cycle and the manner in which the phage genes are regulated. Please read the selections from the two Ptashne books (Genes & Signals and A Genetic Switch) first, which will provide you with the necessary background on gene regulation, in general, and the λ system, in particular. As many of you may know, the study of gene regulation had its origins in the 1950’s at the Pasteur Institute with the discovery of repression and derepression. These foundational studies involved the lac operon, on the one hand, and bacteriophage λ lysogeny, on the other hand. Although we will touch only briefly on the lac system in class, its regulation is described in the excerpt from Genes & Signals. The following is a brief preview of the λ lifecycle.

Bacteriophage λ is an example of a lysogenic phage that can enter two alternative developmental pathways upon infection of a naïve cell. If the lytic pathway prevails, then the phage replicates its genome, assembles new phage particles and induces cell lysis, liberating a crop of progeny phage. However, if the lysogenic pathway prevails, then the phage genome is integrated into the bacterial chromosome and ultimately all of the phage’s lytic genes are repressed under the control of a phage-encoded repressor called CI. A cell containing such an integrated “prophage” is referred to as a lysogen and it is immune to superinfection by other λ phage (due to the action of the CI repressor). In this quiescent state, the phage is propagated passively from cell division to cell division. Although lysogeny is extremely stable, certain environmental insults (such as UV irradiation) trigger a switch from lysogenic to lytic development in a process called prophage induction. The Lambda COSB review provides additional background for understanding the regulation of lysogeny by the CI and Cro proteins (note that Cro is a second phage-encoded repressor, which is produced during lytic growth); you need read only to the top of pg. 84 as we will not be discussing structure (Fig. 1 provides an overview).

For those of you who are interested, I have also included a historical essay (Gann) that describes how an enormously fruitful collaboration between Jacob and Monod uncovered the fundamental principles of gene regulation. This essay emphasizes the way in which a comparison between the two experimental systems provided critical insight, stimulating the formulation of essential hypotheses. Note the conceptual analogy between the Lac repressor and the repressor of lytic development (CI), uncovered by performing “zygotic induction” experiments*. (Of course, at the time the nature of the repressor was not known.) Note also the conceptual analogy between vir mutations and O′ mutations.

* In order to understand these experiments, you need to know the basics of bacterial conjugation (mating) and also how chromosomal markers can be mobilized during conjugation. For those of you who are not familiar with bacterial conjugation, please read the excerpt from the textbook (Griffiths, Introduction to Genetic Analysis, see below under “Extra”). This will be relevant for future classes, as well.
Our discussion paper is focused on the role(s) of the Cro protein during the λ life cycle. As we will see, the data establish a critical role for Cro during prophage induction. The proposal that Cro plays this role dates back to the 1970’s, but this 2007 study provides the first rigorous demonstration (and settles some controversy in the literature). I include here one additional piece of background information that you will need when reading this paper. Upon initial infection (which may lead either to lysogeny or to lytic development), the cl gene is expressed under the control of a promoter called P_{RE} (promoter for repressor establishment), which is located upstream of promoter P_{RM}. Once lysogeny is established, cl expression occurs exclusively under the control of P_{RM} (promoter for repressor maintenance). Whereas Cl itself activates transcription from P_{RM}, an activator called CII activates transcription from P_{RE}. (Note that CII is synthesized soon after infection under the control of the early lytic promoter P_{R}, but the cII gene is turned off in a lysogen.)

From a broader perspective, the focus of the discussion paper is a bistable (epigenetic) switch that is evidently conserved among temperate phages. Thus, the P_{RM}/P_{R} regulatory region is an example of a bistable switch. As extra reading, I have included a paper from Pam Silver’s lab that describes the use of the λ bistable switch to construct a genetic memory element that can detect transient environmental signals.

**Paper for Discussion:**


**Required Background:**

2. Ptashne M and Gann A (2002) Genes & Signals. I have scanned the following sections: Introduction, pgs 4-7; Chapter 1, pgs 11-39; Footnotes and Bibliography, pgs 53-57. The information on gene regulation in phage λ begins on pg 26.


4. Hochschild A and Lewis M (2009) The bacteriophage λ Cl protein finds an asymmetric solution. *Curr Opin Struct Biol* **19**: 79-86. Read only to top of pg. 84 (the introductory section); we will not be discussing structure.

**Extra:**

