

### Fitness, Polymers, & Coulomb Interactions

**1. Forward mutations:** Consider a fixed population of  $N$  diploid individuals. A particular allele  $A$ , can mutate to other forms (collectively indicated by  $\bar{A}$ ) as rate  $\mu$ , but there are no back mutations that revert to  $A$  from the mutated variants. Let us denote the fraction of unmutated alleles in the population by  $x = N_A/(2N)$ , starting with initial value  $x(t = 0) = x_0$  at time  $t = 0$ .

(a) Construct the drift–diffusion equation for  $p(x, t)$  (including binary drift but no selection).

(b) Construct a differential equation for  $\langle x \rangle(t) \equiv \int dx xp(x, t)$ , and find its solution.

(c) Construct a differential equation for the heterozygosity  $H(t) \equiv \langle x(1 - x) \rangle$ , and find its solution.

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**2. The Eigen model:** The quasi-species model (introduced by Manfred Eigen) considers a related group of genotypes (labelled by  $i = 1, \dots, M$ ) that mutate at rates  $\mu_{ji}$ , each reproducing at rate (fitness)  $f_i$ . Ignoring any competition for resources, the numbers  $\{N_i\}$  of different sub-populations grows as

$$\frac{dN_i}{dt} = f_i N_i + \sum_{j \neq i} (\mu_{ij} N_j - \mu_{ji} N_i).$$

Denote the fraction of each genotype by  $x_i(t) = N_i(t)/N(t)$  where  $N(t) = \sum_i N_i(t)$  is the total population at time  $t$ . These fractions can be used to define population averages  $\bar{O} = \sum_i O_i x_i$  for any property of the genotype.

(a) Construct equations for the growth rates  $dx_i/dt$  in terms of the mean fitness  $\bar{f} = \sum_i f_i x_i$ .

(b) *Fisher's fundamental equation:* What is the growth law  $d\bar{f}/dt$  for the mean fitness in the absence of mutations ( $\mu_{ij} = 0$ )?

(c) *Price's equation:* What is the growth rate  $d\bar{O}/dt$  of some other genotype property averaged over the population?

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**3. Error catastrophe:** Consider a wild-type RNA viral genome of  $N$  bases, with fitness  $f_w$ . Each base can mutate at rate  $\mu$ , and for simplicity assume that all mutant sequences (irrespective of the number of mutated bases) have fitness  $f_m$ .

(a) Neglecting back mutations to wild-type, write equations governing the growth of the two population numbers  $N_w$  and  $N_m$ .

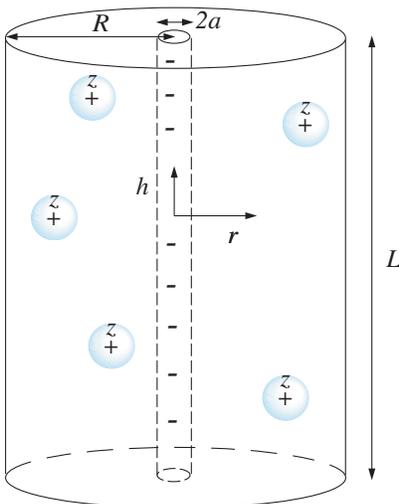
(b) What is the fraction of wild-type in the population in steady state?

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4. *The Manning Transition:* When ionic polymers (polyelectrolytes) such as DNA are immersed in water, the smaller charged *counter-ions* go into solution, leaving behind an oppositely charged polymer. Because of the electrostatic repulsion of the charges left behind, the polymer is stretched, and shall be modeled as a cylinder of radius  $a$  and length  $L$ , as depicted in the figure. While thermal fluctuations tend to make the ions wander about in the solvent, electrostatic attractions favor their return and condensation on the polymer. The potential due to a uniform linear charge density is logarithmic, and assuming that the counterions have valence  $z$  (charge  $ze$ ), their potential energy is given by

$$\mathcal{V} = 2ze^2n \sum_{i=1}^N \ln \left( \frac{r_i}{a} \right).$$

Here,  $n$  is the linear density and  $r_i$  is the radial coordinate of the  $i^{\text{th}}$  particle. Note that the Coulomb repulsions between the counter-ions have been left out.



(a) For a cylindrical container of radius  $R$ , show that at a temperature  $T$ , the canonical partition function  $Z$  has the form

$$Z = (\text{constant}) \left[ \frac{R^{2(1-\zeta)} - a^{2(1-\zeta)}}{2(1-\zeta)} \right]^N,$$

and give the value of  $\zeta$ .

(b) Calculate the probability distribution function  $p(r)$  for the radial position of a counter-ion, and its first moment  $\langle r \rangle$ , the average radial position of a counter-ion.

(c) The behavior of the results calculated above in the limit of  $R \gg a$  is very different at high and low temperatures. Identify the transition temperature, and characterize the nature of the two phases. In particular, how does  $\langle r \rangle$  depend on  $R$  and  $a$  in each case?

(d) Calculate the pressure exerted by the counter-ions on the wall of the container, in the limit  $R \gg a$ , at all temperatures.

(e) According to Manning, at low temperatures just enough counterions reattach to the polymer to reduce its charge density such that the value of  $\zeta$  stays at 1. Along a fully ionized double stranded DNA, unit (negative) charges occur at a separation of  $b = 1.7\text{\AA}$ . Use the Manning reasoning to calculate the fraction of this charge that is neutralized by salt counterions in solutions of either Na Cl or Mg Cl<sub>2</sub>. (The Bjerrum length in water is  $\ell_B = e^2/(\epsilon k_B T) \approx 7\text{\AA}$ .)

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**5. (Optional) Charged membranes:** In class, we solved the Poisson–Boltzmann for a flat membrane of uniform charge density  $\sigma$ , with a neutralizing background of counterions of charge  $e$ .

(a) Extend the solution to counterions of charge  $ze$ , and compute their density at a distance  $y$  from the membrane.

(b) There is an overall constant of proportionality that can be fixed by examining the electric field at the charged surface. Plot the electric field as a function of  $y$ .

(c) Check the overall neutrality of the system by integrating over the density of counterions.

(d) Calculate the self-consistent potential and charge density between two uniformly charged plates. (Each plate has uniform charge density  $\sigma$ , the neutralizing counterions have charge  $ze$ , and the plates are separated by  $L$ .)

(e) Solve the Poisson–Boltzmann equation around a cylinder of radius  $a$  and charge density  $n = e/b$ . (Hint: By changing variables to  $x = \ln(r/a)$  and  $\psi = \beta ze\phi - 2x$ , you should be able to reduce the two dimensional problem to the already solved one dimensional case.) Can you make connections to the results in problem 2 on Manning condensation?

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**6. Bending a charged polymer:** As indicated in the figure below, bending a polymer reduces the distances between its monomers.

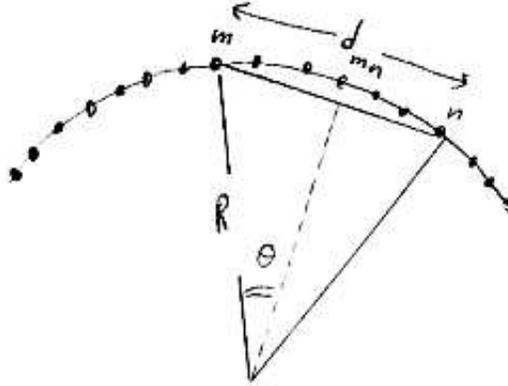
(a) For two monomers which are at a distance  $d_{mn} = b|m - n|$  when the polymer is straight, compute the change  $\delta d_{mn}(R)$ , when the polymer is bend into a circle of radius  $R \gg d_{mn}$ .

(b) Assume that unit charges at each monomer interact through the Debye potential

$$V(d) = k_B T \ell_B \frac{e^{-d/\lambda}}{d},$$

where  $\ell_B$  and  $\lambda$  and the Bjerrum and screening lengths, respectively. Compute the change in this pairwise energy if the distance is changed from  $d$  to  $d + \delta d$ .

(c) Show that bending increases the energy of the charged polymer by an amount proportional to  $L/R^2$ , where  $L = Nb$  is the total length of the polymer.



(d) The overall bending modulus for a charged polymer can be written as  $\kappa = \kappa_b + \kappa_e$ , where  $\kappa_b$  is the cost of deforming the backbone, while  $\kappa_e$  comes from the additional electrostatic energy. Compute  $\kappa_e$  using the model explored in the previous parts.

(e) Is electrostatic energy a significant component of the cost of bending a double stranded DNA? (For DNA in water,  $b \approx .17\text{nm}$ ,  $\ell_B \approx .7\text{nm}$ ,  $\lambda \approx 1\text{nm}$ , and  $\ell_P \approx 50\text{nm}$ . What about single-stranded DNA or RNA?)

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**7. Packaging DNA in a phage:** After an infected bacterium has duplicated the DNA and coat of an infecting phage, a new phage is assembled with the aid of protein motors. In the case of bacteriophage  $\phi 29$ , a 20,000 base pair dsDNA has to be packaged in a capsid, which is a cylinder of radius  $r = 42\text{nm}$  and height  $h = 47\text{nm}$ . Inside the capsid the DNA is arranged like a spool, first winding in a helical shell next to the wall, and then forming successively tighter shells moving inwards. A typical separation between strands in this structure is 2.3nm. Single molecule experiments have shown that the work required to pack the DNA in the capsid is approximately  $10^5 k_B T$  at room temperature ( $T = 300^\circ\text{K}$ ). In the following, *use order of magnitude estimates* to determine what sets this energy scale.

(a) Estimate the entropy of the DNA in solution, using a persistence length of  $\ell_P \approx 50\text{nm}$ . Can the loss of this entropic free energy account for the work of packaging?

(b) Estimate the energy cost of bending DNA into the helical form found in the capsid. (Express the rigidity parameter  $\kappa$  in terms of the persistence length  $\ell_P$ .) Is bending energy a significant fraction of the overall work of packaging?

(c) Estimate the electrostatic energy of DNA in the capsid: Assume unit charges along the DNA at a spacing of  $b \approx 0.17\text{nm}$ , which interact through a Debye–Hückel potential of screening length  $\lambda \approx 1\text{nm}$ , with charges on nearby strands (separations of around 2nm). Can electrostatic energies account for the work of packaging?

Here are a two articles on the packaging of DNA in a phage: *P. K. Purohit, M. M. Inamdar, P. D. Grayson, T. M. Squires, J. Kondev, and R. Phillips, Forces during Bacteriophage*

DNA Packaging and Ejection- *Biophys. J.*, February 1, 2005; 88(2): 851-866; and S. Tzllil, J. T. Kindt, W. M. Gelbart, and A. Ben-Shaul, Forces and Pressures in DNA Packaging and Release from Viral Capsids- *Biophys. J.*, March 1, 2003; 84(3): 1616-1627.

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**8. (Optional)** *Flory approximation*: The Coulomb energy of a ball of charge  $Q$  and dimension  $R$  in  $d$  spacial dimensions scales as

$$E_c \propto \frac{Q^2}{R^{d-2}}.$$

The proportionality coefficient depends on the exact shape and charge distribution; details that are not relevant to our intended scaling analysis.

(a) For a charged polymer of length  $N$ , estimate the dependence of  $R$  on  $Q$  and  $N$ , by balancing the above Coulomb energy with the entropy associated with confining the polymer to a size  $R$ . (Follow the Flory reasoning for self-avoiding polymers.)

(b) For a *polyelectrolyte* in which  $Q \propto N$ , find the Flory exponent  $\nu_F$  in the scaling relation  $R \propto N^{\nu_F}$ . Identify the upper critical dimension  $d_u$  above which  $\nu = 1/2$  (the Coulomb interaction is *irrelevant*), and the lower critical dimension  $d_u^F$  below which  $\nu_F = 1$  (the polymer is fully stretched).

(c) Unlike in the case of self-avoiding walks, the Flory estimate is a rather poor description for charged polymers. In fact, it can be shown that the exact value of the swelling exponent for uniformly charged polymers is  $\nu = 2/(d-2)$ . Identify the correct upper and lower critical dimensions from this formula. Note that a uniformly charged polymer in three dimensions is fully stretched.

(d) A *polyampholyte* is a heteropolymer with charged monomers of both signs. If the charges are randomly and independently chosen to be positive or negative, we expect  $\overline{Q^2} \propto N$ . What is the Flory estimate of the swelling exponent in this case?

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*Suggested reading*: Chapter 7 of *Biological Physics* by Philip Nelson.