Turner lab research topic:­­­ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Summary of research:

Interesting or new information or ideas in research description:

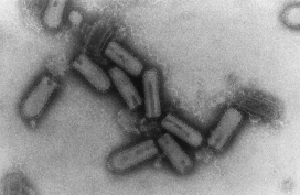
What was unclear to me and my group:

Fill this section out after meeting with other groups

If you were to join Dr. Turner’s Lab, which project would you like to work on?

Why?

**Vesicular Stomatitis Virus**

Electron micrograph of vesicular stomatitis virus particles

**Evolution of virus specialists and generalists**

Arthropod-borne viruses (arboviruses) are able to infect arthropods (insects, ticks) as well as other host organisms. For this reason, arboviruses typically encounter alternating host environments in the wild, and have evolved to feature very broad host ranges. We use the RNA arbovirus vesicular stomatitis virus (VSV) as a model to examine the evolutionary and molecular genetics of host adaptation.

One study allowed VSV to evolve on either of two novel hosts (selection for specialist viruses), or in environments where the two novel hosts fluctuated in time (selection for generalist viruses) ([Turner and Elena 2000, Genetics 156:1465-1470](http://www.yale.edu/turner/pdf/p007.pdf)). Specialists evolved increased performance on the novel host, at the expense of reduced performance in the alternate host. In contrast, generalists improved their fitness in both novel habitats. These findings contradict the idea that weaker response to selection causes generalists to be disadvantaged relative to specialists.

Current work examines the evolution of genetic architecture in our collection of derived specialists and generalists ([Remold et al. 2008, Mol Biol Evol 25:1138-1147](http://www.yale.edu/turner/pdf/p035.pdf)). How do these differing phenotypes map at the molecular level? Are genomic changes in each group highly conserved? Alternatively, do differing adaptive solutions to the same environmental challenges cause populations in each group to genetically diverge? Ongoing research examines the importance of spatially-structured environments in the evolution of VSV, and differing rates of adaptation in specialist and generalist viruses.

**Evolutionary Interactions between RNA Viruses and Cancer Cells**

Vesicular stomatitis virus (VSV) and other viruses are being developed as novel anti-cancer (oncolytic virus) therapies, where viruses target and destroy tumors. Our work showed that changes in the matrix protein of VSV coincided with evolutionary specialization of viruses on cancer-derived cells ([Remold et al. 2008, Mol Biol Evol 25:1138-1147](http://www.yale.edu/turner/pdf/p035.pdf)). We are currently using reverse genetics in VSV to determine whether these candidate beneficial mutations interact with other allele substitutions via epistasis. In addition, we are merging experimental evolution with systems biology to study how ecological history (evolution in presence vs. absence of cancer cells) affects VSV ability to control intracellular apoptotic networks and to resist innate cellular immunity. Other ongoing studies examine the effects of ecological history and genetic architecture (order of genes in the VSV genome), in the subsequent ability for VSV lineages to adapt to novel cancer-cell types.

**Evolution of Host Shifts and Emergence**

The emergence of RNA viruses in humans and other hosts presents increasing challenges in medicine, public health, agriculture and conservation biology. We are examining how prior ecological history (evolution on single vs. multiple hosts) affects the ability for viruses to emerge on novel hosts ([Turner et al. 2010, Evolution 64:3273-3286](http://www.yale.edu/turner/pdf/p044.pdf)). Ongoing projects concern the consequences of virus adaptation to new hosts, and how evolved host-use affects virus performance under radically different challenges, such as growth at extreme temperatures ([Alto and Turner, Evolutionary Ecology 24:299-315](http://www.yale.edu/turner/pdf/p040.pdf)). These empirical results can be combined with mathematical theory, to generally predict how current host-use breadth impacts the future probability that a virus will successfully emerge on a novel host ([Ogbunugafor et al. 2010. Phil. Trans. R. Soc. B 365:1919-1930](http://www.yale.edu/turner/pdf/p041.pdf" \t "_blank)).

**RNA Bacteriophage Φ6**

Colorized electron microscope image of herpesviruses (yellow and green spheres) coinfecting a single cell. During coinfection, sexual reproduction can produce viral progeny that contain a mixture of genes found in the coinfecting parents.

**Evolution of Thermotolerance and Life-History Trade-Offs**

We are using phage Φ6 as a model to study how segmented RNA viruses evolve increased stability (survival) under various environmental stressors ([McBride et al. 2008, BMC Evol Biol 8:231](http://www.yale.edu/turner/pdf/p036.pdf)). Challenges such as elevated heat, increased salinity and lowered acidity can cause virus particles to quickly degrade, and to lose their ability to subsequently infect host cells. Ongoing projects merge experimental evolution and structural biology, to examine how changes in virus proteins such as lytic enzymes explain increased virion stability in the face of heat shock ([Dessau et al. 2012, PLoS Genetics](http://www.yale.edu/turner/publications.htm)). This improved protein-stability may sometimes cause ‘life-history’ trade-offs, where increased virus survival evolves at the expense of reduced viral reproduction. We are studying whether compensatory mutations can alleviate trade-offs, and whether differences in genetic architecture among ancestor viruses affect the evolvability of their descendant lineages ([Ogbunugafor et al. 2009, CSH Symp Quant Biol 74:109-118](http://www.yale.edu/turner/pdf/p039.pdf" \t "_blank)).

**Evolution of Genetic Robustness and Evolvability**

We use RNA phage Φ6 as a model to examine the evolution of mutational robustness: phenotypic constancy in the face of underlying mutational change. Our work showed that selection to maintain robustness was relaxed under virus co-infection, because complementation between virus genotypes was a ‘built-in’ mechanism that buffered mutational effects ([Montville et al. 2005, PLoS Biology 3:1939](http://www.yale.edu/turner/pdf/p022.pdf)). Additional results showed that lineages founded by robust viruses can adapt faster than those initiated by brittle (non-robust) viruses, demonstrating a positive link between robustness and evolvability ([McBride et al. 2008, BMC Evol Biol 8:231](http://www.yale.edu/turner/pdf/p036.pdf)). Our ongoing studies continue to examine the relationship between robustness and evolvability, and generalized effects of robustness in the evolution of infectious diseases ([Ogbunugafor et al. 2010, Chaos 20:026108](http://www.yale.edu/turner/pdf/p045.pdf" \t "_blank)).

**Evolution of sex and its consequences**

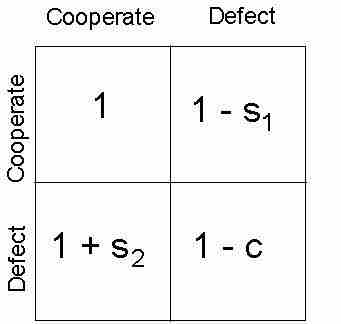
We use the RNA bacteriophage Φ6 as a model to study the costs and benefits of genetic exchange (sex). When multiple viruses co-infect the same host cell, sex produces hybrid progeny containing a mixture of genetic information from the co-infecting parents.

Sex may benefit viruses by promoting genetic variation, which might allow sexual populations to evolve faster than asexual ones. In contrast, sex requires co-infection and may exert a cost because it increases competition between viruses for limited intracellular resources.

One experiment allowed replicate populations of Φ6 to evolve in the presence and absence of sex for hundreds of viral generations ([Turner and Chao 1998, Genetics 150:523-532](http://www.yale.edu/turner/pdf/p004.pdf)). Unexpectedly, sex was costly because sexually-evolved viruses became attenuated (weakened) in their ability to infect the host alone. This indicates that the cost of intra-host competition can outweigh any of the potential benefits associated with sex.

Ongoing projects examine whether sex is advantageous in purging epistatic (interacting) mutations from the virus genome, whether sex is costly in terms of breaking apart co-adapted loci, and how reproductive system (sexuality versus asexuality) influences the rate of molecular evolution and prevalence for epistasis to evolve.

**Game theory and virus interactions**

**Expected fitness values for a game in which opponents utilize conflicting strategies of cooperation and defection. Entries in the payoff matrix represent the fitness to an individual adopting the strategy on the left, if the opponent adopts the strategy above. Defectors gain a fitness advantage (1 + s2) that allows them to invade a population of cooperators. If the cost of defection is too strong, (1 - c) < (1 - s1), cooperators may also invade and the two strategies are driven to a stable polymorphism. Prisoner's dilemma occurs if it always pays to be selfish, (1 - c) > (1 - s1); defection sweeps through the population despite the greater fitness payoff had all individuals cooperated.**

“Name me somebody that is not a parasite, and I’ll go out and say a prayer for him”  
– Bob Dylan (Visions of Johanna, 1966)

The manufacture of diffusible, and hence shared, intracellular products during virus co-infection allows for the conflicting strategies of cooperation and defection (selfishness). Whereas a viral genotype that synthesizes larger quantities of product is effectively a cooperator, a genotype that synthesizes less but specializes in sequestering a larger share of the products is a defector.

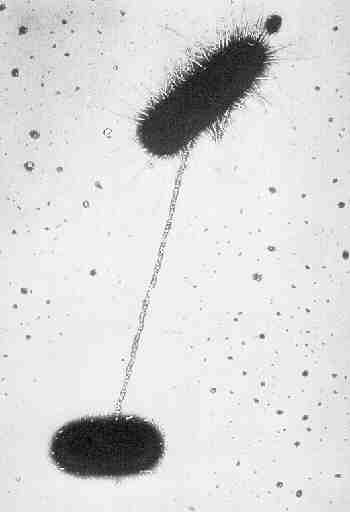
We use phage Φ6 to study the evolution of viral conflicts. One study showed that viruses cultured under high levels of co-infection evolve selfish strategies, but their fixation in the population causes mean fitness to decline ([Turner and Chao 1999, Nature 398:441-443](http://www.yale.edu/turner/pdf/p006.pdf)). These data conform to the prisoner’s dilemma of game theory, where selfishness evolves despite the greater fitness payoff if all players cooperate.

Ongoing projects examine the generality of the prisoner’s dilemma result in Φ6; for instance, evolved cooperator viruses can re-invade populations of defectors, allowing the two strategies to coexist in a stable polymorphism ([Turner and Chao 2003, American Naturalist 161:497-505](http://www.yale.edu/turner/pdf/p011.pdf)). Current research examines the molecular mechanism(s) that may afford selfish genotypes an advantage during intra-host competition. We are also examining whether viruses evolve specific mechanisms to exclude large numbers of viruses from co-infecting the same cell, in order to reduce intracellular competition ([Turner et al. 1999, Journal of Virology 73:2420-2424](http://www.yale.edu/turner/pdf/p005.pdf)).

**Evolutionary ecology of host shifts**

A virus’s ecological niche is governed in part by its host range, the hosts in which a virus can produce viable progeny. Viruses may expand their host range through mutations that facilitate entry into new host environments. Although host shifts allow a virus (or any other parasite) to expand its ecological niche, traits governing the infection of multiple host types can decrease fitness in the original or alternate host environments. We use phage Φ6 and Pseudomonas bacteria as a model to test basic questions relating to evolutionary ecology of host shifts. Ongoing projects include measuring the mutation spectrum associated with expanded host range, growth tradeoffs for host range mutants across host environments, and strength of selection resulting from simultaneous adaptation of viruses to multiple habitats.

**Escherichia Coli**

Two bacterial cells caught in the act of plasmid-mediated conjugation. Many plasmids are able to transfer horizontally from an infected donor (top) to an uninfected recipient (bottom) via conjugation. Conjugation is initiated by contact between donor and recipient cells via a plasmid-encoded protein appendage called a sex pilus. Conjugation results in the one-way transfer of a copy of the plasmid genome from donor to recipient.

**Evolution of horizontal transfer in E. coli plasmids**

For many parasites, a fundamental conflict should exist between modes of horizontal (infectious) and vertical (intergenerational) transmission. Parasite activities that increase infectious transmission are presumed to generally reduce host fitness (growth rate). In turn, reduced host fitness impedes vertical transmission of the parasite and thereby causes a tradeoff between transmission routes.

We use conjugative plasmids and their E. coli hosts as a model to examine the evolution of parasite transmission. One experiment allowed plasmids to evolve for hundreds of generations in environments that contained different densities of bacterial hosts ([Turner et al. 1998, Evolution 52:315-329](http://www.yale.edu/turner/pdf/p003.pdf)). The plasmid’s rate of conjugative (infectious) transfer increased at the expense of host fitness, indicating a tradeoff between horizontal and vertical modes of transmission. Surprisingly, susceptible host density had no significant effect on which mode of transfer was selectively favored. Continued research focuses on other environmental factors mediating the evolution of conjugation rates, epistatic interactions between genes for antibiotic-resistance and conjugative-transfer, and phenotypic plasticity in traits governing plasmid transmission.

**Evolution of E. coli-Phage Interactions**

Filamentous phages such as M13 generally do not kill their bacterial hosts. Rather, these viruses replicate within the cytoplasm, and can be inherited during cell division (vertical transfer) or can move between cells (horizontal transfer). Our ongoing work concerns effects of filamentous phage on the growth of their E. coli hosts, and whether their symbiotic interaction can switch from parasitism to mutualism depending on ecological conditions, such as presence of antibiotics. Also, we are using experimental evolution of E. coli-phage interactions to test whether viruses can move freely along the parasitism-mutualism continuum, versus being evolutionarily ‘locked-in’ to one type of symbiosis that prevents them from switching to a new evolved strategy.

Phage therapy is the use of bacteria-specific viruses to treat bacterial infections, rather than using antibiotic drugs. Widespread failure of antibiotics suggests that phage therapy and other alternatives may become increasingly important in combatting multi-drug resistant bacteria. We are using experimental evolution and molecular microbiology to determine how phage-therapy candidates may evolutionarily improve in their ability to attack deadly bacterial pathogens, such as E. coli O157:H7. In addition, we are using mathematical modeling to examine how virus characteristics such as mutation rate should affect abilities for phages to coevolve with bacterial pathogens ([Kysela and Turner 2007, J. Theor. Biol. 249:411-421](http://www.yale.edu/turner/p031.pdf" \t "_blank)).

**Evolution of mutualisms**

*“I get by with a little help from my friends”*  
– John Lennon and Paul McCartney (A Little Help from my Friends, 1967)

Mutualisms (cooperative interactions) have traditionally received less attention than parasitic interactions. This is surprising given that cooperation among individuals is extremely common in nature. For instance, the stability of bacterial communities may often rely upon cross-feeding, whereby certain bacteria excrete metabolites (nutrients) that are essential for the persistence of other strains in the local environment.

We are currently using E. coli bacteria to examine the ecology and evolution of mutualisms. In particular, an earlier study found that stable genetic polymorphisms can evolve even when bacteria are cultured in simple habitats containing only the single limiting resource glucose ([Turner et al. 1996, Ecology 77:2119-2129](http://www.yale.edu/turner/p001.pdf)). Ongoing projects concern the stability of the coexistence in different laboratory environments, the metabolites that contribute to the observed cross-feeding, and the vulnerability of mutualisms to invasion by exploitative genotypes and parasites.