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A multi-reservoir model of influenza evolution

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Objectives

The work by Koelle et al [1] introduced the idea that the influenza virus type A (IVA) may evolve on neutral networks. A neutral network is a collection of genotypes that map (in some way) to the same phenotype even if there may be significant evolutionary change in the genotype. The virus experiences no evolutionary pressure until it enters a new neutral network. This allows the IVA genotype to diffuse over the entire neutral network. This diffusion can bring the current IVA cluster (phenotype) in contact with many other neutral networks (phenotypes). Upon entering a new network, the phenotype can change either moderately or significantly. The model can be seeded with strains from an (unmodeled) external reservoir via migration events. The phylogenetic trees emerging from the neutral network model are visually stunning.

Subsequent investigations by Shih et al [2] and Suzuki [3] have cast doubt on whether IVA evolves on a neutral network. Their work suggests that IVA experiences continuous evolutionary pressure.

This raises the obvious question whether neutral network–based theory of IVA evolution in humans can be constructed in such a way that the IVA still experiences continuous positive selection. One conceivable way for this to happen is to allow IVA evolution to occur in several reservoirs. The evolution within each reservoir will be subjected to positive evolutionary pressure. On occasion, new genotypes arising in these other reservoirs could be (re)introduced to the human population. From the perspective of the human reservoir, significant evolutionary change can occur in IVA. However, this evolution is occurring in other populations.

Methods

The phenotypes of the IVA strains are determined by constructing a neutral network for each of 8 RNA strands comprising the IVA genome, similar to what was done in reference [1], restricted for IVA hemagglutinin gene. Every IVA genotype is assigned to these networks. Every neutral network has associations with certain class(es) of reservoir(s) that it

can infect. In our model, the use of the neutral networks is restricted to assigning IVA strains to reservoirs. All of the populations are treated as well mixed, so there is no network structure within any reservoir. That is, any agent in a given reservoir is equally likely to contact any other agent. The reservoirs are connected by weighted edges, where the weight of an edge determines how strongly the IVA strains can be passed between the different reservoirs. Each population is assigned characteristics such as birth and death rates, transmission rates, and seasonal effects. Within each population, we model every individual as an agent, where on the order of 10^5 agents are currently being simulated. Each agent retains a history of all previous IVA infections as well as the strains with which it is currently infected. Agents are added and removed from the populations. The trans-reservoir transmissions are done between specific agents. Two main types of evolutionary processes are incorporated in our model. The first is point mutations of the IVA strains' genotypes. Here we conceptualize each of the 8 genes to have a certain number of loci. This allows the strains to evolve over a particular reservoir's neutral network. If a strain evolves onto a network that can infect multiple reservoirs, we can have trans-reservoir infections. The second evolutionary process is the reassortment of 2 IVA strains within an agent. The genome of IVA is composed of 8 individual strands of RNA. If an agent is currently infected by more than a single strain, the RNA strands can be reassorted, allowing for the rise of novel strains.

Results

We hope to demonstrate that using a multi-reservoir model can reproduce the effects of using neutral networks. In this way, the model will reproduce the phylodynamics of the IVA. We have also included the important features of multiple different species and strain reassortment for IVA evolution.

Conclusions

We have examined an agent-based model of IVA evolution and epidemiology. The model includes multiple interacting reservoirs (eg, avian, swine and human) of agents. Each reservoir is assigned IVA strains by which it can be infected. One of the reservoirs acts as a bridge between other reservoirs. In this, trans-reservoir transmission is allowed. In addition, IVA can evolve within each reservoir through the processes of mutation and reassortment.

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