氏　　名	Kawashima, Kent Diel
学位(専攻分野)	博士(理学)
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論 文 審 査 委 員	主　査　准教授　池尾　一穂 教授　角谷　徹仁 教授　中村　保一 教授　木村　暁 教授　佐々木　顕 先導科学研究科　生命共生体進化学専攻

(Form 3)

Summary of Doctoral Thesis

Name in full Kawashima, Kent Diel

Title Network Models of Pathogen Evolution: Reconciling Population Genetics and Epidemiological Dynamics

Unlike free-living organisms, pathogenic viruses, bacteria, and fungi need to infect a host organism in order to reproduce and must continually transmit and colonize uninfected hosts to survive in the long run. This mode of survival creates reticulated evolutionary histories dependent on the network of hosts and incurs repeated population bottlenecks every time pathogens transmit from an infected host. In order to capture the complexity of pathogen evolution, processes occurring within the host and events happening between hosts in the population have to be considered. However, our current understanding of pathogen evolution is limited to observing evolution within single infections, or characterizing evolution over a host population. While these two views agree that pathogen evolution is largely driven by purifying selection, within-host studies have found little evidence to support the idea that positive selection of pathogens naturally occurs within hosts. Results from within-host studies appear to be at odds with finding of positive selection using sequences sampled from different individuals. If pathogens are rarely selected for their fitness advantage, how can we explain the signature of positive selection detected from host population samples?

In this study, I attempt to reconcile these conflicting observations using network model of pathogen evolution that integrates within-host processes of replication, mutation, and selection, with the between-host processes of transmission and host-host interactions. In combining processes that occur at different levels of biological organization, I was able to examine the effects of transmission and host network structure on the genetic evolution of pathogens. Due to the periodic infection and transmission pathogen lineages undergo, I found that these events dampen the effect of natural selection even at pathogens possess a large fitness. Two main factors impeded the effect of positive selection in pathogen evolution. First, the time it takes for selection to significantly raise the frequency of a new mutation is too long compared to the duration of acute infections. This means that new mutations remain at low

frequency throughout an infection unless the fitness advantage is extremely high, or the duration of the infection is significantly long. This explains why most findings of positive selection within hosts have been from pathogens that cause chronic infections. If beneficial mutations exist at low frequencies, the probability that these mutations are transmitted is slim, especially when the number of infectious units transmitted is low. The population bottleneck that occurs every transmission is the second reason positive selection cannot operate efficiently. Experimental studies have shown that transmissions tend to impose a harsh bottleneck on pathogens. Since pathogens transmits periodically, this means that bottlenecks recurrently occur over a short period of time. My results indicate pathogen evolution is not sensitive to fitness differences as the fixation probability of mutations tends to be flat up to moderate level of selective advantage. This indicates that the periodic expansion and reduction in population size in tandem with the short intervals between bottlenecks inhibit the role of positive selection in pathogens. This suggests that transmission parameters could play a bigger role in the evolution of pathogen than natural selection.

Placed in the context of a host network, both the density and the structure of the network influences the observed evolution of pathogens across the host population. Results from simulations on networks showed that diversity is significantly reduced when the host network is sparsely-connected than when it is densely-connected. However, any type of network used to condition the potential paths of transmission always showed lower levels of diversity compared to an unstructured population. While the network model saw reduced diversity, fixation probability is also diminished because the network structure promotes differentiation between pathogen lineages. Networks therefore make it hard for an advantageous genotype to sweep the entire population unless it is related to host immunity. When the new mutation changes the pathogen's immunological profile such that is create a new serotype, then these kinds of changes are expected spread rapidly as the pathogen is granted an effectively immunological naïve host population to infect.

In summary, this study revealed the underlying connection between epidemiological parameters of transmission and the duration of infection with the population genetics of pathogens within the host. Through computer simulations, I showed how why positive selection is so unlikely to be observed in pathogens and raises some concern about potential false-positive detection of positive selection.

Form8・Separate Sheet
(様式8・別紙)

Results of the doctoral thesis screening

博士論文審査結果

Name in Full
氏　　名　Kawashima, Kent Diel

Title
論文題目　Network Models of Pathogen Evolution: Reconciling Population Genetics and Epidemiological Dynamics

出願者は、病原体進化のネットワークモデルを用いて病原体の疫学的な動態と集団遺伝学的動態を理解することを目的に、宿主ー宿主相互作用を含む宿主間の感染過程と宿主内での病原体の集団遺伝学的振る舞いを統合する病原体進化のネットワークモデルを開発し、これらの異なる過程を統合して理解することを試みた。
その結果、異なるレベルの生物学的組織で起こるプロセスを組み合わせることで、病原体の遺伝的進化に対する、伝達と宿主のネットワーク構造の影響を調べることが可能であることを示し、病原体の進化において、定期的な宿主間感染と感染病原体の系列が原因となり病原体が大きな適応性を持っていても自然選択の効果を弱めることを見出した。第一に、新しい突然変異の頻度を著しく上げるために選択に要する時間は、急性感染の期間と比較して長すぎ、これは適応の強さが非常に高い場合や感染の期間が著しく長い場合を除いて新しい変異が低頻度で感染中に残ることを意味する。第二に、すべての感染過程で発生するボトルネックは正の選択が効率的に機能できない理由となる。
宿主ネットワークに関連した解析では、ネットワークの密度と構造の両方が、宿主集団全体の病原体において観察される進化に影響を及ぼすことを明らかにした。シミュレーションの結果、宿主のネットワークが密結合している場合は、多様性が大幅に低下しているが、宿主集団内に感染が拡大する経路を想定して生成したネットワークでは、非構造化集団と比較して常により低いレベルの多様性を示すことを明らかにした。
これらの解析結果から、病原体の免疫による新しい血清型を作り出す様な新しい突然変異が病原体に生じると、効果的に未感染の宿主集団に感染するので、これらの新しい変化が急速に広がると出願者は予想した。
以上の様に、出願者の研究は、数理モデルとシミュレーションによる病原性生物と宿主の相互作用による進化、特に病原性に対する正の淘汰の在りようを示す研究として意味を持つ。
本研究において開発された方法を組み込んだシミュレーションのためのプログラムは、GitHubを通じて既に公開されており、ひろく利用可能な状態にある。
解析結果は、今後の新規病原性の出現や流行に関する機構の基礎的な理解に貢献するとともに、今後、病原体進化に関する様々なパラメーターの在りようを明らかにしていくことで、病原性生物の進化の分野に貢献することが期待される成果である。
以上の理由により、審査委員会は、本論文が学位の授与に値すると判断した。