Surges in latent infections: Mathematical analysis of viral blips

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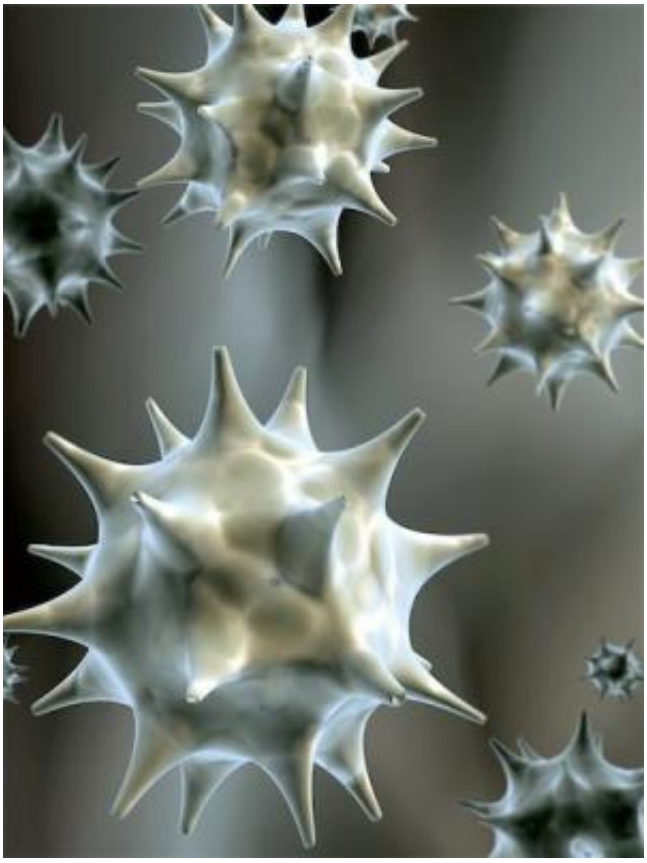

3d rendering of a colony of pathogen viruses. Photo Credit: © frenta / Masterfile

Recurrent infection is a common feature of persistent viral diseases. It includes episodes of high viral production interspersed by periods of relative quiescence. These quiescent or silent stages are hard to study with experimental models. Mathematical analysis can help fill in the

gaps.

In a paper titled Conditions for Transient Viremia in Deterministic in-Host Models: Viral Blips Need No Exogenous Trigger, published last month in the *SIAM Journal on Applied Mathematics*, authors Wenjing Zhang, Lindi M. Wahl, and Pei Yu present a model to study persistent infections.

In latent infections (a type of persistent infection), no infectious cells can be observed during the silent or quiescent stages, which involve low-level viral replication. These silent periods are often interrupted by unexplained intermittent episodes of active viral production and release. "Viral blips" associated with human immunodeficiency virus (HIV) infections are a good example of such active periods.

"Mathematical modeling has been critical to our understanding of HIV, particularly during the clinically latent stage of infection," says author Pei Yu. "The extremely rapid turnover of the viral population during this quiescent stage of infection was first demonstrated through modeling (David Ho, *Nature*, 1995), and came as a surprise to the clinical community. This was seen as one of the major triumphs of mathematical immunology: an extremely important result through the coupling of patient data and an appropriate modeling approach."

Recurrent infections also often occur due to drug treatment. For example, active antiretroviral therapy for HIV can suppress the levels of the virus to below-detection limits for months. Though much research has focused on these viral blips, their causes are not well understood.

Previous mathematical models have analyzed the reasons behind such viral blips, and have proposed various possible explanations. An early model considered the activation of T cells, a type of immune cell, in response to antigens. Later models attributed blips to recurrent activation

of latently-infected lymphocytes, which are a broader class of immune cells that include T-cells. Asymmetric division of such latently-infected cells, resulting in activated cells and latently-infected daughter cells were seen to elicit blips in another study.

These previous models have used exogenous triggers such as stochastic or transient stimulation of the immune system in order to generate viral blips.

In this paper, the authors use dynamical systems theory to reinvestigate in-host infection models that exhibit viral blips. They demonstrate that no such exogenous triggers are needed to generate viral blips, and propose that blips are produced as part of the natural behavior of the dynamical system. The key factor for this behavior is an infection rate which increases but saturates with the extent of infection. The authors show that such an increasing, saturating infection rate alone is sufficient to produce long periods of quiescence interrupted by rapid replication, or viral blips.

These findings are consistent with clinical observations where even patients on the best currently-available HIV therapy periodically exhibit transient episodes of viremia (high viral load in the blood). A number of reasons have been proposed for this phenomenon, such as poor adherence to therapy or the activation of a hidden reservoir of HIV-infected cells. "If adherence is the underlying factor, viral blips are triggered when the patient misses a dose or several doses of the prescribed drugs," explains Yu. "If activation is the cause, blips may be triggered by exposure to other pathogens, which activate the immune system. Our work demonstrates that viral blips might simply occur as a natural cycle of the underlying dynamical system, without the need for any special trigger."

The authors propose simple 2- and 3-dimensional models that can

produce viral blips. Linear or constant infection rates do not lead to blips in 2-, 3- or 4-dimensional models studied by the authors. However, a 5-dimensional immunological model reveals that a system with a constant infection rate can generate blips as well.

The models proposed in the paper can be used to study a variety of viral diseases that exhibit recurrent infections. "We are currently extending this approach to other infections, and more broadly to other diseases that display recurrence," says Yu. "For example, many autoimmune diseases recur and relapse over a timescale of years, and once again, the 'triggers' for episodes of recurrence are unknown. We would like to understand more fully what factors of the underlying dynamical system might be driving these episodic patterns."

More information: Conditions for Transient Viremia in Deterministic in-Host Models: Viral Blips Need No Exogenous Trigger, Wenjing Zhang, Lindi M. Wahl, and Pei Yu, *SIAM Journal on Applied Matematics*, 73(2), 853 (Online publish date: April 20, 2013). The source article is available for free access until August 31, 2013: epubs.siam.org/doi/abs/10.1137/120884535

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