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Modeling How Tamiflu Treatment Affects the Immune Response to Influenza in PhysiCell

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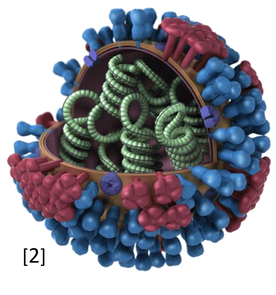
PEPPERDINE Summer Undergraduate Research in Biology

Introduction

Influenza presents a major public health issue, and complications result in about 114,000 hospitalizations and 20,000 deaths each year in the U.S. [1]. The best way to avoid serious flu complications is to get the annual flu vaccine. Once infected, treatments are limited and include antiviral drugs like Tamiflu (oseltamivir phosphate). Tamiflu inhibits neuraminidase to prevent viral secretion by infected cells.

This study aims to adapt a PhysiCell computational model of the immune response to influenza within the body to investigate the effects of antiviral treatment on various immune/disease metrics. PhysiCell is a multiscale agent-based model that tracks both viral replication inside cells and individual immune cell interactions within lung tissue. This project adds new treatment functionality to the PhysiCell Tissue Immune Submodel and allows for investigation of the behavior of neuraminidase inhibition on multiple aspects of the immune response. Through modeling we can gain crucial insights to better understand the dynamics of immune-drug interactions during a viral infection.



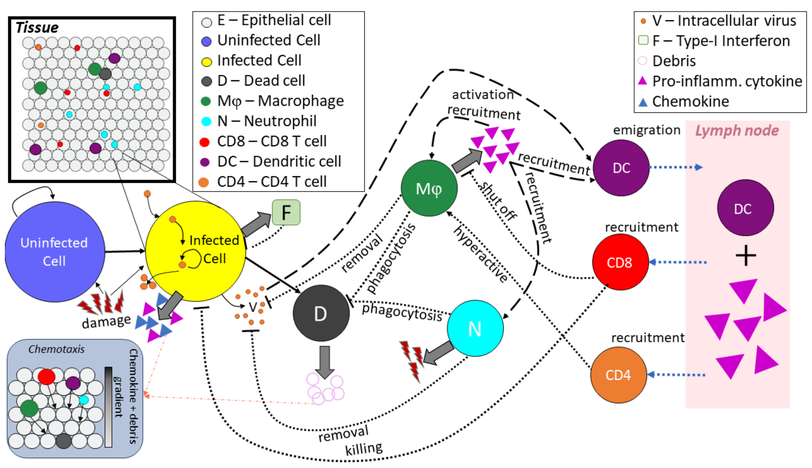
[2]

Influenza:
- Enveloped RNA virus
- Surface proteins: hemagglutinin and neuraminidase (HxNx)
- Causes respiratory symptoms
- Tamiflu is a neuraminidase inhibitor, preventing influenza viral release from infected cells

[1]

PhysiCell:
- Agent-based, multi-scale, spatial computational model of host tissue
- High performance computing, written in C++ and XML
- Open source and continuously enhanced:
  - 2018: Cancer model [3]
  - 2020: COVID-19 model with immune submodel [4]
  - 2021: Influenza tissue immune submodel [5]

PhysiCell Tissue Immune Submodel [4]



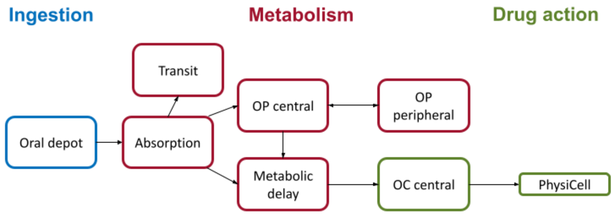
Biological questions:

We investigate the relationships between the antiviral treatment Tamiflu, influenza virus, and the immune system, such as:

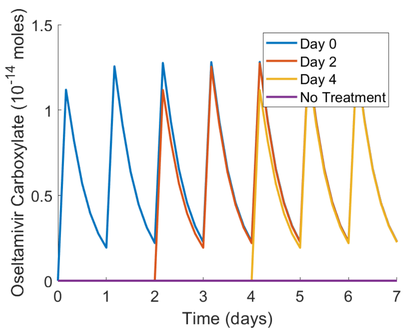
1. How does the presence or absence of treatment impact influenza virus-immune interactions and outcomes?
1. How well does Tamiflu control infection at different doses and administration times, such as upon exposure and once symptomatic?

Pharmacokinetic modeling of Tamiflu

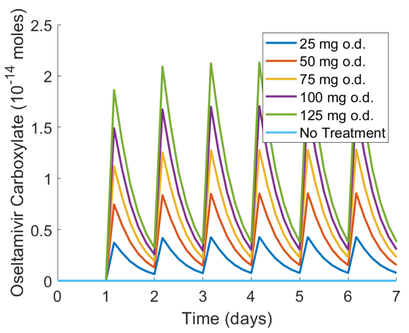
- Pharmacokinetics (PK): movement of drugs through the body
- We employ a 7-compartment model of PK dynamics of Tamiflu [5]
- Oseltamivir phosphate (OP) is the ingested form of Tamiflu, which is then converted to the active form oseltamivir carboxylate (OC)



Varying initial dose time



Varying dose



Model OC concentrations are converted to appropriate PhysiCell units (moles/μm³), exported to a .bin file, and read into PhysiCell.

PhysiCell code and parameters

Code implementing the effect of Tamiflu on viral release in relation to its IC_{50} value.

```
if(pCell->phenotype.molecular.internalized_total_substrates[vtest_external]*Vvoxel>8e3 && PhysiCell_globals.current_time>pCell->custom_data["eclipse_time"])
{
    double treatment_concentration = pCell->nearest_density_vector()[treatment];
    if(treatment_concentration>0)
    {
        pCell->phenotype.secretion.secretion_rates[vtest_external] = parameters.doubles("kRel")*(1-(treatment_concentration/(tIC50+treatment_concentration)));
        // std::cout<< (1-(treatment_concentration/(tIC50+treatment_concentration))) << std::endl;
    }
```

Parameter	Description	Value	Units	Ref
$D_{treatment}$	Diffusion rate of Tamiflu	420	μm²/min	[7]
$\lambda_{treatment}$	Decay rate of Tamiflu	1.7×10^{-3}	1/min	[8]
TR_0	Initial concentration of Oseltamivir Carboxylate (OC)	1.2×10^{-21}	moles/μm³	[9]
tIC50	IC_{50} value of Tamiflu	7.77×10^{-23}	moles/μm³	[9]

Acknowledgements

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References

[1] McClellan K, Perry C. Drugs 61(2): 263-283 (2001)
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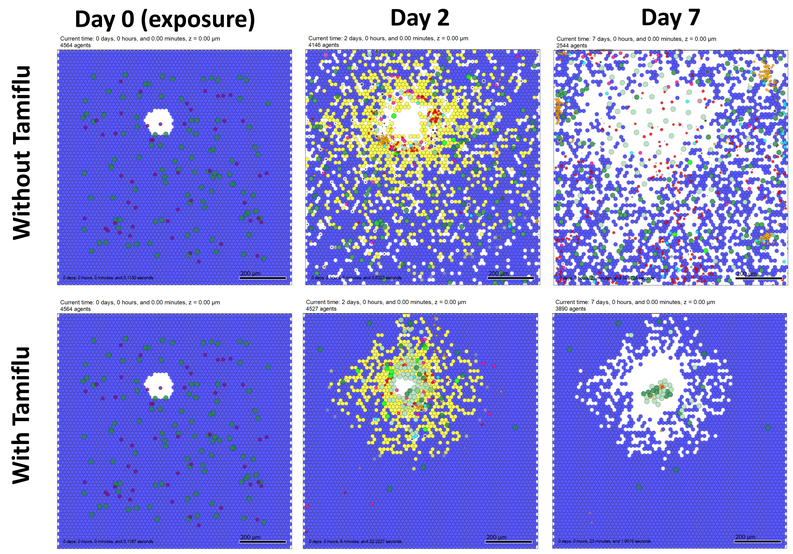
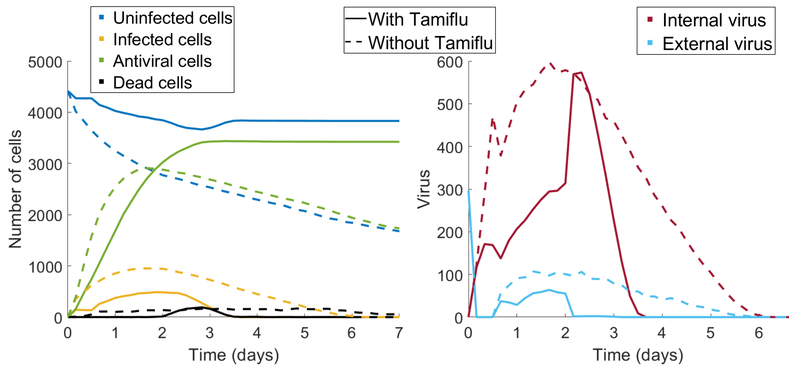
[3]Ghaffarizadeh A et al. PLoS Computational Biology 14: e1005991 (2018)
[4]Getz M et al. Iterative community-driven development of a SARS-CoV-2 tissue simulator. bioRxiv preprint (Nov. 2020)
[5] Jenner A et al. Unpublished (2021)
[6] Gibiansky L et al. Journal of Pharmacokinetics and Pharmacodynamics 42: 225-236 (2015)
[7] Hawles M et al. Molecular Pharmaceutics 15: 1534-1547 (2018)
[8] Jullien V et al. Antimicrobial Agents and Chemotherapy 55(9): 4183-4187 (2011)
[9] Widmer N et al. Clinical Pharmacokinetics 49: 741–765 (2010)

Infection with and without Tamiflu



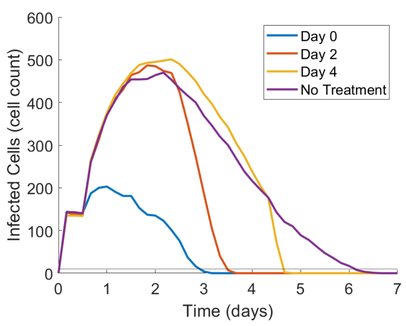
75 mg dose of Tamiflu taken daily beginning 2 days after exposure.
Legend: See flowchart for simulation color key.



Internal virus accumulates because Tamiflu reduces viral secretion. Tamiflu results in fewer infected cells for a shorter duration.

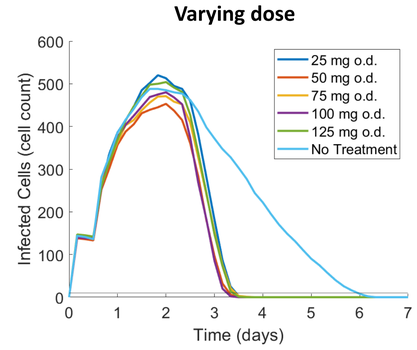
Sensitivity analysis

Varying initial dose time



75 mg o.d. dose administered beginning at time of exposure (day 0), two days after exposure, 4 days after exposure.

Varying dose



Various dose sizes administered beginning 2 days after exposure.

Initiating Tamiflu treatment earlier results in shorter infection time, whereas dose amount does not substantially affect infection length.

Conclusions and Future Directions

- We built antiviral treatment functionality into a computational immune model that can be generalized to other RNA viruses.
- Tamiflu shortens infection time compared to infection time without treatment.'
- Administering treatment earlier shortens infection.
- When Tamiflu treatment begins at day two, effectiveness does not depend heavily on dosage.

Future directions:
- Include different subtypes of influenza virus, particularly those causing pandemic versus seasonal influenza.
- Model other antiviral drug mechanisms of action such as viral replication or viral entry.
- Adapt the model to analyze the effects of simultaneous drug treatment.