Model of Viral Tissue Infection

Release 0.0.1

J. Aponte-Serrano, T.J. Sego, J. F. Gianlupi, J. A. Glazier

Apr 13, 2020

Note: To cite this model please use the following:

Josua Aponte-Serrano, T.J. Sego, Juliano F. Gianlupi, James A. Glazier, "Model of Viral Tissue Infection", https://github.com/covid-tissue-models/covid-tissue-response-models/tree/master/CC3D/Models/BiocIU/SARSCoV2MultiscaleVTM

Model Description

This model describes select interactions between generalized epithelial and immune cells and their extracellular environment associated with viral infection and immune response at the cellular and intracellular levels, and in the context of spatiotemporal dynamics. While at the moment, the model is a generic viral infection model our hope is to collaboratively develop it into a model of SARS-CoV-2 tissue infection and Covid-19 progression. As such, it is intended to serve as a base model for constructing and implementing more advanced models of targeted cellular- and intracellular-level phenomena in tissue after initial exposure. In its current state, it has not been formally peer-reviewed, and should not be used for patient diagnostics or predicting clinical outcomes. Rather, the model and its implementation can be used to develop and interrogate mechanistic hypotheses about the spread of a virus and how the interplay between viral spreading and immune response determine the outcome of the disease, such as:

- Why does the progression of the disease seem to be dependent on the initial viral exposure level?
- Why is the start time of symptoms and immune response so variable?
- What is the role of cytokine signaling in explaining immune response variability?
- What are the specific factors determining early immune response? What are the key players on early immune response?
- Does the collapse observed in individuals who develop complications result from viral replication in a secondary location or is it primarily a delayed hyper-inflammatory response?
- Could we build a personalized model for immune response to predict who is likely to develop immune complications and use it to design a personalized immunosuppressive therapy to determine timing and dosage of an immunosuppressive regime?

Some factors to be included in future developments of the model are:

- How is the virus transported in the extracellular environment and mucus?
- What is the role of the humoral immune response in controlling the viral spreading?

The model includes a representation of extracellular virus in the mucus, epithelial cells and immune cells. It also includes the processes of epithelial cell infection by extracellular virus, viral replication and cell damage inside epithelial

cells, release of viruses by epithelial cells, immune cell response to infected epithelial cells and immune cell killing of infected and non-infected epithelial cells.

At the epithelial cell level, the model accounts for internalization, replication, release and clearance of viral particles, as well as for induced cell apoptosis by either viral damage or immune cytotoxicity.

- **Viral internalization**: model of viral binding to cell receptors, endocytosis and release of genetic material into the cytoplasm
- **Viral replication**: model of replication of viral genetic material, transcription, translation and virion packing
- **Viral release**: model of the release of newly assembled virions into the extracellular environment
- **Viral damage:** model of accumulated damage to the cell due to viral load
- **Cell death:** model of cell death due to accumulated damage from viral infection or by cytotoxicity from immune response

At the immune cell level, the model accounts for recruitment and chemotaxis of immune cells due to cytokine signaling, the cytotoxic effect on infected epithelial cells as well as the clearance of immune cells.

- **Immune cell recruitment**: model of immune cell recruitment and infiltration into the tissue by signaling molecules produced in response to viral insult on infected cells
- **Immune cell chemotaxis**: model of immune cell movement guided by the difference in concentration of a signal represented as a chemical field
- **Immune cell cytotoxicity**: model of cell-dependent cytotoxic effect of immune cells on infected cells
- **Immune cell clearance**: model of immune cell-accumulated damage, cell death and clearance from the tissue
- **Immune activation**: model of immune cells changing behaviour based on lung tissue status (amount of cytokine in the environment).

At the tissue level, the model accounts for the extracellular transport of viral particles, cytokine transport, and an oxidative burst agent. It can be extended to incorporate recovery by reepithelialization.

- **Viral transport**: model of diffusion and spreading of viral particles in the extracellular environment
- **Cytokine transport**: model of transport of small immune signaling molecules in the extracellular environment (to be included)
- **Tissue recovery**: model of recovery of the tissue by reepithelialization following cell death (to be included)

Model Implementation

Epithelial cells can adopt one of three different phenotypes: uninfected, infected and dead. Uninfected cells can absorb viral particles from the extracellular environment but do not release newly assembled particles until a critical viral load is reached. Once the critical viral load is reached, uninfected cells change their cell type to become infected cells. Infected cells both absorb and release viral particles from the extracellular environment. Infected cells can become uninfected cells by clearing their viral load. Infected cells can also trigger apoptosis and become dead cells either by reaching a critical viral load or by cytotoxic interaction with immune cells.

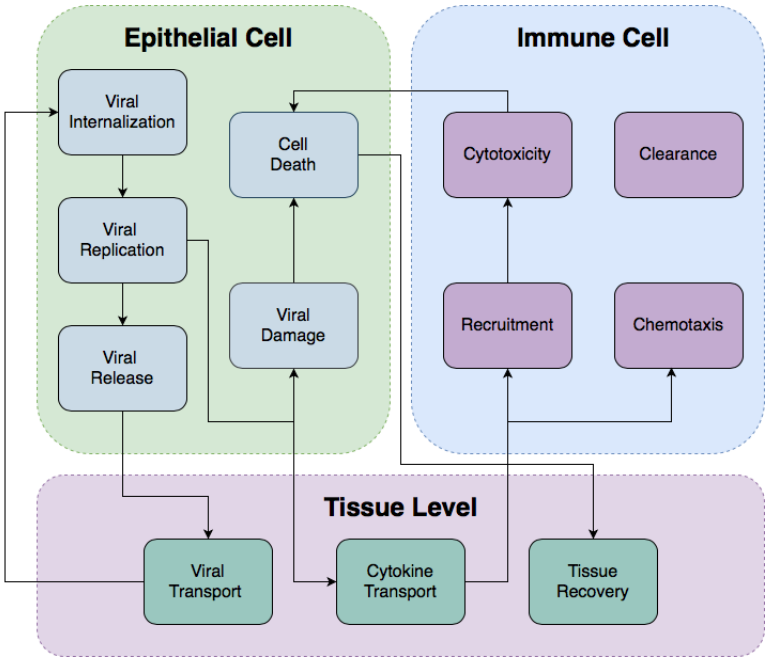

Fig. 1: Conceptual Model

Intracellular state models

The submodels governing the intracellular state of uninfected and infected cells associated with viral infection are implemented as follows.

Viral internalization

Uninfected and infected cells have the ability of absorbing diffusive viral particles from the extracellular viral field. The uptake probability $\Pr\left(\text{Uptake}\left(\text{cell}\right) > 0\right)$ for each cell occurs according to a Hill equation of the total amount of diffusive viral particles in the domain of the cell $V\left(\text{cell}\right)$.

$$\Pr\left(\text{Uptake} > 0\right) = \frac{V\left(\text{cell}\right)^{h}}{V\left(\text{cell}\right)^{h} + V_{\text{half}}}$$

Where h is a Hill coefficient and V_{half} is the local amount of the viral field at which $\Pr\left(\text{Uptake} > 0\right) = 0.50$. When uptake occurs, the uptake rate is proportional to the local amount of the viral field and a prescribed uptake efficiency r_e, and saturates at a prescribed threshold $U_{\text{threshold}}$,

$$\text{Uptake} = \begin{cases} r_e V\left(\text{cell}\right) & V\left(\text{cell}\right) < U_{\text{threshold}} \\ U_{\text{threshold}} & V\left(\text{cell}\right) > U_{\text{threshold}} \end{cases}$$

The amount absorbed by each cell is subtracted from the viral field and passed to the cell's instance of the viral replication model according to conservation of species.

Viral replication

A system of ordinary differential equations modeling the viral replication process is assigned to each uninfected and infected cell. The model contains four variables representing different states of the viral replication process: unpacking U, replicating R, packing P, and assembly of new virion capsids A.

$$\frac{\mathrm{d}U}{\mathrm{d}t} = \text{Uptake} - r_u U$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = r_u U + r_{\max}\frac{R}{R + r_{\text{half}}} - r_t R$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = r_t U - r_p P$$

$$\frac{\mathrm{d}A}{\mathrm{d}t} = r_p P - \text{Secretion}$$

Here r_u is the unpacking rate, $r_{\max}$ is the maximum replication rate, r_t is the translation rate and r_p is the packing rate. The regulation of replication is represented by a Michaelis-Menten function of the amount of replicating viral material $\frac{R}{R + r_{\text{half}}}$, where r_{half} is the amount of R at which the replicating rate is $\frac{r_{\max}}{2}$. The viral replication model is specified as a readily sharable Antimony string that can be implemented as a standalone using the Tellurium package. The number of newly assembled virion capsids is passed to the cell's instance of the viral release model.

Viral release

Infected cells have the ability to secrete diffusive viral particles into the extracellular viral field. The total amount released is proportional to the state variable for assembled virions from the viral replication model.

$$\text{Secretion} = r_s A$$

Here r_s is the secretion rate of viral particles. The amount released by each cell is subtracted from the cell's state variable for assembled virions and passed to the source term of the extracellular viral field according to conservation of species.

Virally induced apoptosis

Each infected cell is assigned a survival probability. Once the state variable for assembled virions from the viral replication model reaches a prescribed critical threshold in a cell, the probability of cell survival is evaluated against a uniformly distributed random variable. Surviving cells remain infected and their survival is not re-evaluated. Dying cells change cell type to dead cell and their instances of the viral internalization, replication and release models are disabled.

Immune response models

Immune cells infiltrate the tissue and move up the gradient of the extracellular viral field. The viral field is used as a proxy for cytokines. Immune cells can induce cytotoxicity in infected cells and trigger apoptosis. Immune cells are cleared out from the tissue. Submodels of immune response are implemented as follows.

Immune cell recruitment

The total immune cell population is governed by an ordinary differential equation of a state variable S that represents immune response due to local conditions and long-distance signaling. Our convention is that when $S > 0$, immune cells are recruited to the simulation domain; likewise, immune cells are removed from the simulation domain when $S < 0$. We accomplish this by imposing probability functions describing the likelihood of immune cell seeding and removal,

$$\Pr\left(\text{add immune cell}\right) = \text{erf}\left(\alpha_{\text{immune}} S\right), \quad S > 0,$$

$$\Pr\left(\text{remove immune cell}\right) = \text{erf}\left(-\alpha_{\text{immune}} S\right), \quad S < 0.$$

Here the coefficient α_{immune} controls the sensitivity of immune cell addition and removal to the state variable S. The dynamics of S are cast such that, in a homeostatic condition, a typical number of immune cells can be found in the simulation domain, and production of cytokine in the simulation domain results in additional recruitment via long-distance signaling (i.e., with some delay). We accomplish this by using the feedback mechanisms of the total number of immune cells N_{immune} in the simulation domain and a fraction of the total amount of decayed cytokine $\alpha_{\text{sig}}\delta$. Here δ is the total amount of decayed cytokine in the simulation domain and $0 < \alpha_{\text{sig}} < 1$ models signaling by transmission of cytokine to some far-away source of immune cells. With these mechanisms, we write the rate of S as such,

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \beta_{\text{add}} - \beta_{\text{sub}} N_{\text{immune}} + \beta_{\text{delay}} \alpha_{\text{sig}} \delta - \beta_{\text{decay}} S$$

Here β_{add} and β_{sub} control the number of immune cells in the simulation domain under homeostatic conditions, β_{delay} controls the delay between transmission of the cytokine and immune response, and β_{decay} controls the return of S to an unperturbed state (i.e., $S = 0$).

At each simulation step the seeding probability is evaluated against a uniformly distributed random variable. To determine the seeding location, the simulation space is randomly sampled, and immune cells are seeded at the unoccupied location with the highest amount of the viral field. If no location is unoccupied, then the immune cell is not seeded. The removal probability is evaluated against a uniformly distributed random variable for each immune cell at each simulation step.

Immune cell chemotaxis

Immune cells experience a motile force as a response to a signaling field. Currently, the viral field is used as a proxy of cytokine signaling molecules. The chemotactic function measures the local gradient of the viral field and computes the effective energy $E_{\text{chemotaxis}}$ associated with the gradient according to a prescribed chemotactic sensitivity parameter chemotaxis. The chemotactic effective energy term is saturated by normalizing the chemotactic sensitivity parameter by the local concentration $V\left(\text{cell}\right)$.

$$E_{\text{chemotaxis}} = \frac{\lambda_{\text{chemotaxis}} \nabla V}{1 - V\left(\text{cell}\right)}$$

Immune cell cytotoxicity

Immune cells kill infected cells by direct contact. At each simulation step, neighbors of infected cells are evaluated. Apoptosis is triggered in an infected cell if it has an immune cell as one of its neighbors. The infected cell changes its cell type to dead cell and its instances of the viral internalization, replication and release models are disabled.

Immune cell oxidative burst

Immune cells when detecting a high cytokine concentration will release a short-range oxidative agent. The agent kills any tissue cells when in contact (there is a minimum concentration for death).

Immune cell clearance

Each infected immune cell is assigned a dying probability. For each simulation step, the dying probability is evaluated against a uniformly distributed random variable for every infected cell. Clearance is achieved by setting the immune cell volume constraint to zero.

Transport models

The extracellular viral field is used to represent the transport of viral particles across the tissue over time. Rates of secretion into the viral field are determined by the output of the viral release model. Rates of absorption from the viral field are determined by the viral internalization model.

Viral transport

The change in concentration of the viral field at each location is calculated using a partial differential equation solver of a reaction-diffusion equation.

$$\frac{\partial V\left(x\right)}{\partial t} = D\Delta V - cV\left(x\right) - \text{Uptake}\left(\text{Cell}\left(x\right)\right) + \text{Secretion}\left(\text{Cell}\left(x\right)\right)$$

Transport parameters such as the diffusion constant D and decay rate c are estimated from the literature. Conversion factors are used to translate experimental parameter values to internal simulation parameters.

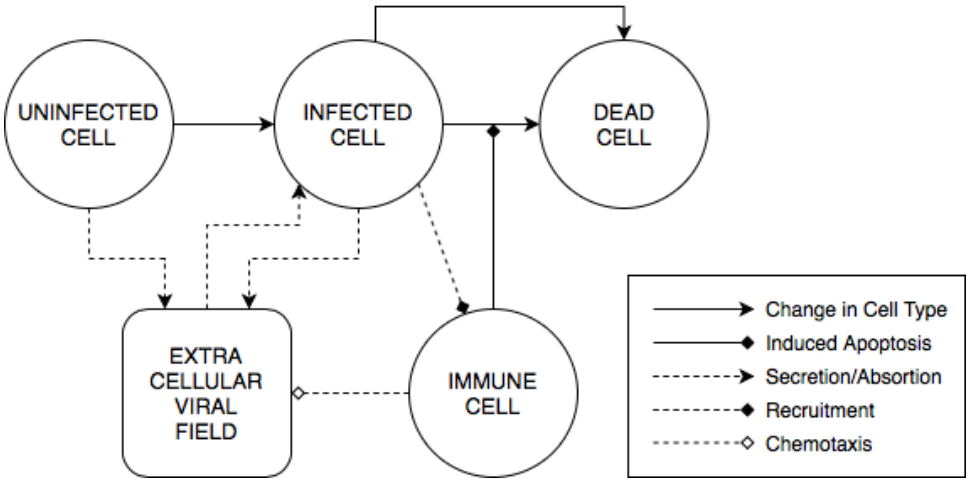

Fig. 2: Interactions in the Tissue Model

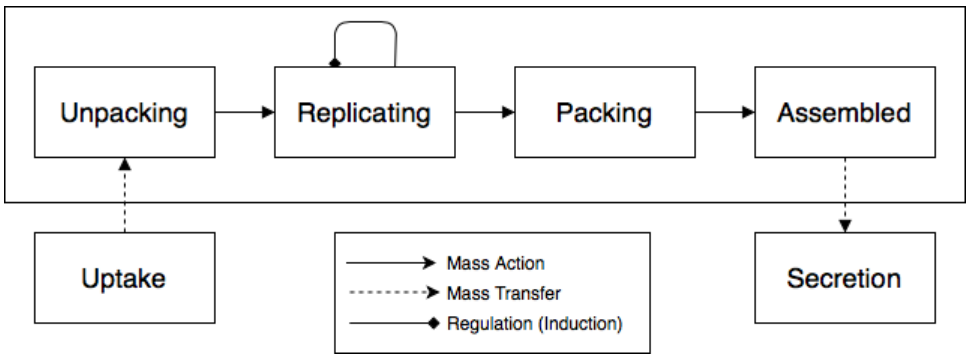

Fig. 3: Interactions in the Viral Replication Model