Within Host Modeling of SARS-CoV-2

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SARS-CoV-2

From SARS-CoV-2 by the numbers  Bar-On et al. eLife 2020

The virus infects cells

Research suggests the SARS-CoV-2 virus has an array of adaptations that help it break into human cells — the first step in causing COVID-19 disease. Scientists are still debating many of the details.

1. The spike proteins that stud the exterior of the virus have receptor binding domains that are extremely efficient at latching onto ACE2 receptors on human cells.

2. Furin or another enzyme, such as TMPRSS2, on the exterior of the host cell are thought to break the spike protein at one or more cleavage sites.

3. That exposes fusion peptides — small chains of amino acids — that fuse the viral membrane with the membrane of the host cell.
The period from virus binding and infecting a cell until new viruses are released is called the eclipse phase of infection.
Picture is showing only one part of the surface of an infected cell ciliated cell.
Infected cell - SARS-CoV-2 (yellow)
Acute Infection

- Why are some infections acute while others are chronic?
  - Target cell limited
  - Innate response clears the infection
  - Adaptive response clears the infection

- Examples:
  - Influenza, Zika, SARS-CoV-2 – acute
  - HIV, CMV, HCV, HBV – chronic
Model of Acute Infection

\[
\frac{dT}{dt} = -\beta VT \\
\frac{dI}{dt} = \beta VT - \delta I \\
\frac{dV}{dt} = pI - cV
\]

Model with infection delay

\[ \frac{dT}{dt} = -\beta VT \]
\[ \frac{dI_1}{dt} = \beta VT - kI_1 \]
\[ \frac{dI_2}{dt} = kI_1 - \delta I_2 \]
\[ \frac{dV}{dt} = pI - cV - \beta VT \]

Target cells
Eclipse phase
Productively infected
Virus

Initial conditions: \( T=T_0, I_1=0, I_2=0, V=V_0 \)

$R_0$ : Basic Reproductive Ratio

Number of secondary infections caused by one infected cell in a wholly susceptible population of uninfected cells

Objective : $R_0 < 1$

$$R_0 = \frac{p\beta T_0}{\delta(c+\beta T_0)}.$$
Look for longitudinal data to compare with models.
Experimental Data + Model Fit

Model assumes 5 d incubation period
Parameters

- Data from all 13 subjects was fit simultaneously using a population approach (mixed-effects model)

- $R_0 \sim 8.6$ 95%CI 1.9 – 17.6

- Death rate of infected cells, $\delta \sim 0.6$ d$^{-1}$
  - (95% CI 0.22 d$^{-1}$ – 0.97 d$^{-1}$)

- $t_{1/2}$ of productively infected cell $\sim 1.2$ d
Effect of Therapy

- Antiviral drugs with effectiveness $0 < \varepsilon < 1$
  - block infection, i.e. reduce $\beta$, $(1-\varepsilon)\beta$
    - e.g. hydroxychloroquine, neutralizing Ab
  - block viral replication, i.e. reduce $p$, $(1-\varepsilon)p$
    - e.g. remdesivir, new Merck drug

Antibodies (convalescent plasma, Lilly, Regeneron mAbs, vaccines)
  - increase viral clearance $c/(1-\varepsilon)$
  - increase infected cell death $\delta/(1-\varepsilon)$
# Use drug PK to estimate $\bar{\varepsilon}$

<table>
<thead>
<tr>
<th>Drug</th>
<th>PK parameter</th>
<th>EC$_{50}$</th>
<th>Dosing regimen</th>
<th>$\bar{\varepsilon} = \frac{1}{7} \times \int_{0}^{7} \frac{C(u)}{C(u) + EC_{50}} , du$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Wang et al. [12]</td>
<td>5.2 μM (unpublished)</td>
<td>400/100 BID</td>
<td>66%</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Morita et al [13]</td>
<td>4.2 μM [17]</td>
<td>400 mg BID at D0, followed by 400 mg QD</td>
<td>6%</td>
</tr>
<tr>
<td>IFN-β-1a</td>
<td>Hu et al. [14]</td>
<td>175 IU/mL [19]</td>
<td>12 MIU at D0, D2, D5</td>
<td>18%</td>
</tr>
<tr>
<td>Remdesivir</td>
<td>EMEA guidelines [15]</td>
<td>1 μM [16]</td>
<td>200 mg QD at D0, followed by 100 mg QD</td>
<td>87%</td>
</tr>
</tbody>
</table>

Drug conc likely lower in vivo as protein binding and ability to penetrate tissues ignored.

*Goncalves et al. CPT: Pharmacometrics & Syst Pharmacology 9, 509-514.*
Effect of drug on peak VL

If treatment is initiated at day of infection (DI)

If treatment is initiated at day of symptoms (DS)

Effect of drug on viral dynamics

A
B

No treatment

Early initiation

Late initiation

Medium decay

Viral load

Days post symptom onset

D.L.

60% inhibition

99% inhibition

Viral load

Days post symptom onset

D.L.

Treatment

D.L.
Predictions of Model

- None of these drugs with the possible exception of remdesivir, an RNA polymerase inhibitor, will have a noticeable antiviral effect.
- Most benefit will be achieved if drug is given as soon as possible after infection, preferably before the viral load peak, or used for prophylaxis.
- Lowering the peak VL or flattening the curve can extend the time to viral negativity.
Hospitalized pts treated with remdesivir exhibited faster viral decay from blood and other compartments (NP swaps and sputum) combined.

Also, virus was detected systemically in blood in all tested individuals.
Effect of drugs

- Drugs with an effectiveness lower than the critical effectiveness can “flatten” the viral load curve.
- This can extend the time to viral clearance and allow more time for viral evolution unless immune responses develop and enhance the rate of viral decay beyond that predicted by this simple model.
Combo therapy

Yellow – both drugs 50% effective given d1
Blue – 95% effective given d4, Black no drug
## Merck drug Molnupirivar

### Time to SARS-CoV-2 Viral RNA Negativity

<table>
<thead>
<tr>
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<th>200 mg</th>
<th>400 mg</th>
<th>800 mg</th>
<th>Placebo</th>
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<tr>
<td></td>
<td>Molnupiravir</td>
<td>Molnupiravir</td>
<td>Molnupiravir</td>
<td></td>
</tr>
<tr>
<td>Participants with Response, n/N (%)</td>
<td>21/23 (91.3)</td>
<td>48/61 (78.7)</td>
<td>49/53 (92.5)</td>
<td>49/61 (80.3)</td>
</tr>
<tr>
<td>Median time to response (95% CI), days</td>
<td>22.0 (15.0, 28.0)</td>
<td>27.0 (15.0, 28.0)</td>
<td>14.0 (13.0, 14.0)</td>
<td>15.0 (15.0, 27.0)</td>
</tr>
</tbody>
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### Percentage of Participants Positive for Infectious SARS-CoV-2 Virus

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<td></td>
</tr>
<tr>
<td>Day 1, n/N (%)</td>
<td>11/22 (50.0)</td>
<td>18/43 (41.9)</td>
<td>20/52 (38.5)</td>
<td>25/53 (47.2)</td>
</tr>
<tr>
<td>Day 3, n/N (%)</td>
<td>4/22 (18.2)</td>
<td>5/43 (11.6)</td>
<td>1/53 (1.9)</td>
<td>9/54 (16.7)</td>
</tr>
<tr>
<td>Day 5, n/N (%)</td>
<td>1/22 (4.5)</td>
<td>0/42 (0.0)</td>
<td>0/53 (0.0)</td>
<td>6/54 (11.1)</td>
</tr>
</tbody>
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medRxiv preprint doi: https://doi.org/10.1101/2021.06.17.21258639
Use drugs for prophylaxis to prevent infection

- Give drugs before infection with hope of preventing infection in
  - Health care workers
  - Ambulance drivers, police
  - Household members after one member tests positive
  - Nursing home residents after someone tests positive
  - Unvaccinated individuals
Stochastic Version of Within Host Model

\[ \begin{align*}
V + T & \xrightarrow{\beta} I_1, & \text{infection of target cells,} \\
I_1 & \xrightarrow{k} I_2, & \text{end of eclipse phase,} \\
I_2 & \xrightarrow{\delta} \emptyset, & \text{infected cell death,} \\
I_2 & \xrightarrow{p} I_2 + V, & \text{virus production,} \\
V & \xrightarrow{c} \emptyset, & \text{virus clearance.}
\end{align*} \]

Interested in early events, so set \( T = T_0 \)
Can solve analytically

- Solve for probability of extinction
  - Multidimensional analogue of classic gambler’s ruin problem
- Probability of establishment = 1 - P(extinction)

\[
\varphi = \begin{cases} 
1 - \left(1 - \frac{R_0 - 1}{N}\right)^{V_0}, & \text{if } R_0 \geq 1, \\
0, & \text{if } R_0 < 1.
\end{cases}
\]

\[R_0 = \frac{\beta T_0}{c + \beta T_0} \frac{p}{\delta},\]

\[N=\text{burst size} = \frac{p}{\delta}\]

Pearson, Krapivsky, Perelson  Plos Comp Biol 2011
Conway et al. SIAM J Appl Math 2013
Drugs reduce establishment probability

- For drugs that reduce infectivity

\[
\varphi_\beta = 1 - \left( 1 - \frac{(1 - f(\varepsilon_\beta)) R_0 - 1}{N} \right)^{V_0}.
\]

\[
1 - f(\varepsilon_\beta) = 1 - \frac{c\varepsilon_\beta}{c + (1 - \varepsilon_\beta) \beta T_0}.
\]

For drugs that reduce viral production

\[
\varphi_p = 1 - \left( 1 - \frac{(1 - \varepsilon_p) R_0 - 1}{(1 - \varepsilon_p) N} \right)^{V_0}.
\]

Effects of drug therapy

Orange – reduce infectivity $\beta$ by $(1-\epsilon)$
Blue - reduce viral production $p$ by $(1-\epsilon)$
Low N $\sim$ 20; High N = $\sim$200 infect. virions

Critical efficacy $\epsilon_c$: $\epsilon > \epsilon_c$ est. prob = 0
Viral load data from NBA bubble

- Individuals (NBA players and staff) were tested frequently in the NBA bubble in 2020. Viral loads were measured from nasal swabs longitudinally using RT-PCR. Data from 68 individuals who became infected is available in Kissler et al.

- We analyzed longitudinal viral load measurements from 9 newly infected individuals (where more than one pre-peak VL was measured).

- We fit the target cell limited model to the data plus an additional model with an innate immune response.

Kissler et al. medRxiv.
Viral dynamic model incorporating an innate immune response proved better than the target cell limited models

T: Target cells
R: Refractory cells
E: Eclipse cells
I: Productively infected cells
V: Viruses
F: Interferons

\[
\frac{dT}{dt} = -\beta VT - \Phi FT + \rho R \\
\frac{dR}{dt} = \Phi FT - \rho R \\
\frac{dE}{dt} = \beta VT - kE \\
\frac{dl}{dt} = kE - \delta I \\
\frac{dV}{dt} = \pi I - cV \\
\frac{dF}{dt} = qI - dF
\]
Model fit the data well

Blue dashed – innate response  Black – target cell limited model
Profiles similar to other respiratory infections – eg influenza
2349 and 3491 showed symptoms others did not
The NBA data was combined with data from another study in which dates of infection were known as well as data from the lower respiratory tract.
Fits of innate response model to the data

A) German data,  B) NBA data  
Vertical line = symptom onset
Summary of results

- Death rate of productively infected cells is $1.7 \text{ d}^{-1}$ so ave lifespan $\sim 14 \text{ hrs}$

- Ave. eclipse phase length $\sim 6 \text{ hrs}$

- Ave. infected cell lifetime $\sim 20 \text{ hrs}$

- $R_0$ mean = 7.4; range 2.6 – 14.9
During a typical contact of length $\tau$, of the order of minutes to hrs, the VL in the donor is $\sim$constant. To infect someone one or more infectious viruses must be transmitted during the contact. Assume the ave. number of infectious viruses shed per unit of time is $\mu V_i$, where $V_i$ is the number of infectious viruses in the donor. Of these shed viruses a fraction $\varphi$ reach the recipient. Thus on average a total of $n = \varphi \mu \tau V_i$ reach the recipient. Assume the actual number, $X$, is Poissonly distributed with parameter $n$. Assume each infectious virus then has probability $\nu$ to successfully infect and the number that infect is $\text{Bin} (X, \nu)$. Since $X$ is Poissonly distributed the distribution of viruses that successfully infect is Poisson with parameter $n \nu$ and prob of one or more successfully infecting is $p(t) = 1 - \exp(-\alpha V_i)$, $\alpha = \varphi \mu \tau \nu$. 
How is the number of infectious viruses related to the viral load?

- $V_i$ is a constant fraction of $V$ – linear
- $V_i$ is related to $V$ by a power law $\sim V^h$, $h<1$
- $V_i$ is a saturating function of $V$, e.g. Hill function $\sim V^h / (K^h + V^h)$

Can test these relationships by comparing to experimental data
P(culture positive) = 1 – exp(-V_i \rho), then use Binomial

\rho is prob an infectious virus establishes infection

- Simple linear model assuming a fixed fraction of virus is infectious fits poorly
- Saturation (Hill function) and power law models both fit equally well until VL is very high \sim 10^9/ml or more
Probability of successful transmission

Saturation model: \( p(t) = 1 - e^{-\frac{\theta V(t)^h}{V(t)^h + K_m^h}}. \)

Power function model: \( p(t) = 1 - e^{-\omega V(t)^h}. \)

\( P(t) \): the probability of a successful transmission event given a typical contact at time \( t \).

From fitting experimental data we estimated \( h=0.51 \) and \( K_m = 8.8 \times 10^6 \) RNA copies/ml for the saturation model and \( h=0.45 \), \( \omega = 0.0001 \) and \( \eta = 0.45 \) for the power-law model. For the saturation model the max infectiousness is \( 1 - \exp(-\theta) \sim \theta \) for small \( \theta \). Multiple epidemiological studies suggest that prob of transmission is typically < 20%, so we set \( \theta = 0.20 \).
Probability of infection

Prob of transmission for a typical contact

Infectious profiles $p(t)$ based on $V(t)$ of each individual
Presymptomatic transmission

- For the German dataset the time of symptom onset is known and we calculated the probability of presymptomatic transmission as the fraction of AUC of $p(t)$ that occurs before symptom onset.
- This fraction varied from 0 to 20% and correlated with the time from infection to symptom onset, i.e. the incubation period, for both the saturation model (left) and power law model (right).
Predicting the epidemiological R0

- Estimates from several European countries have suggested that there are on average 13.4 typical contacts per day. Then and averaging over the 17 individuals we modeled we estimate $R_0$ is $\sim 5$, which is in the range predicted from epidemiological data, esp for the early infection in Wuhan.
Modeling URT and LRT infection
Fit of model to the German data

Red = URT data and model fit, Blue = LRT
Conclusions

- Tried to show that models can give insights into the viral infection dynamics underlying SARS-CoV-2 and the possible effects of innate immune responses.
- Models with more detailed adaptive immune responses are under development as well as models of the later stages of disease that involve the inflammatory response.
- Modeling of this type is very data limited especially for humans so animal studies are also being done in parallel.
- Studying the effects of therapy is important and in June the US govt announced it will invest $3.2B to speed development and testing of “antiviral pills”.