From Contagion to in-host Dynamics of a Mutating Virus

A multi-scale active particles approach

Nicola Bellomo,

Universitad de Granada, Spain, and Politecnico, Torino, Italy

In collaboration with

Mark Chaplain, St. Andrews University, UK

Diletta Burini University of Perugia, Italy

Nisrine Outada, Cadi Ayyad, Morocco and IRD-Sorbonne, France

Understanding the Generation Time for COVID–19,
Newton Gateway to Mathematics, 28th–30th July 2021

Index - Part 1

1. Modelling objectives and strategy: *Design a rationale towards the modeling of large living, hence complex, systems. Derivation of general structure suitable to capture the main complexity features of living systems.*

2. Multiscale models from contagion to in-host dynamics: *Models consider immune competition, onset of variants, vaccination.*

1.2. Modelling objectives and strategy

Main Sources

• **Rapid Assistance in Modelling the Pandemic: RAMP** A call for assistance, addressed to the scientific modelling community *Coordinated by the **Royal Society**, In-host modeling, coordinated by **Mark Chaplain**.* https://epcced.github.io/ramp/

• N. Bellomo, R. Bingham, M. A. J. Chaplain, G. Dosi, G. Forni, D. A. Knopoff, J. Lowengrub, R. Twarock, and M. E. Virgillito, **A multi-scale model of virus pandemic: Heterogeneous interactive entities in a globally connected world**, *Math. Models Methods Appl. Sci.*, 30, 1591–1651, (2020). (Open source)

• N. Bellomo, D. Burini, and N. Outada, Multiscale Models of Covid-19 with Mutations and Variants, Preprint, (2021).

• N. Bellomo, D. Burini, and N. Outada, Pandemics of Mutating Virus and Society: A multi-scale active particles approach, Preprint, (2021).

1.3. Modelling objectives and strategy

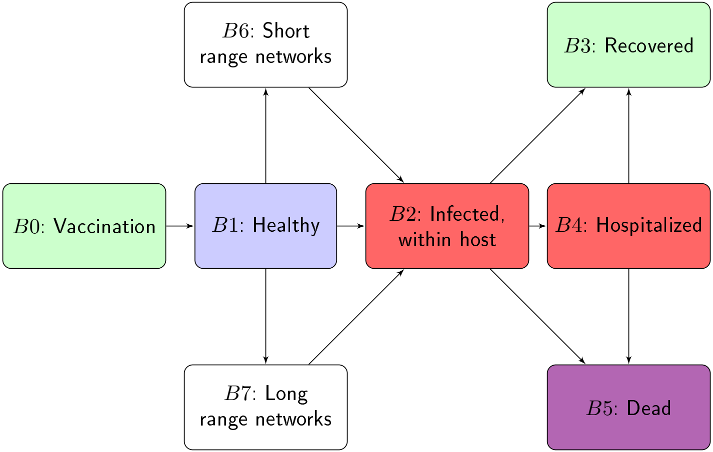
• Applied mathematicians cannot tackle the modeling problem by a stand-alone approach. The scope of such a research project should not be confined only to biological and medical sciences: An interdisciplinary vision is necessary, including economists and sociologists.

• Modeling approach should go far beyond deterministic population dynamics: Individual reactions to the infection and pandemic are heterogeneously distributed over the population. Spatial dynamics is generated by nonlocal interactions and transportation devices.

• The modeling ought to be developed within a multiscale approach: The macro-scale and the micro-scale which constantly interact. Heterogeneity appears at both scales.

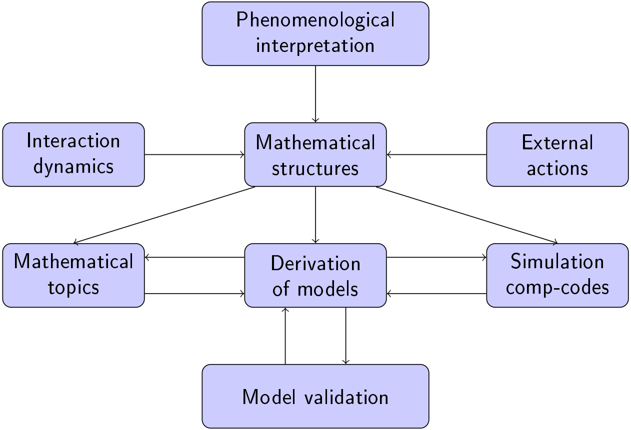
Once refined and informed by empirical data, **mathematical models can produce insightful provisional simulations which can even uncover dynamics which were not previously observed** (cf. emergent behavior).

1.4. Modelling objectives and strategy



Dynamics and of the Objectives of the Research Program

1.5. A strategy towards mathematical tools



The strategy consists in replacing the field theory by a mathematical structure (say mathematical theory - conceptual framework) suitable to capture the complexity features of living systems.

2.1. Multiscale contagion and in-host dynamics

1. The approach is multiscale, i.e. the macro-scale corresponds to individuals who might be infected or not-infected and the micro-scale of in-host entities, within infected individuals.

2. Contagion probability depends on the level of the infection, i.e. on the *viral charge*, as well as on the *social distance* between individuals.

3. Within each infected individual, a competition occurs between the *proliferative virus* and the *immune system*. The level of infection can progress (or regress) due to a prevalence (or lack of prevalence) of the virus over the immune defence ending up with full recovery or death.

4. Mutations and selection up to the onset of new variants of the virus are modeled by a post-Darwinist dynamics. The probability of mutations increases with increasing viral charge and with frequency of interactions.

5. Vaccination is applied by inducing a higher defence ability over the immune system. Vaccinated individuals can, however, become infected, although by lower levels of the viral charge.

2.2. Multiscale models of contagion and in-host dynamics

• $\alpha = \alpha(t) \in [0, 1]$ defines the level of confinement. It is also a locking parameter $\alpha_\ell < 1$ (social distance). The awareness of risk of contagion induces a "locking" action α_ℓ. Subsequently to a decay of the number of infected, a de-locking action may be applied by α_d with $\alpha_\ell < \alpha_d < 1$.

• w is the defence ability of the immune system with levels $w_1 < \beta < w_v = \beta(1 + \gamma)$ corresponding, respectively, to the innate immunity, activated within host immunity, and immunity activated by vaccines, where γ models the intensity of the action of the vaccine.

• κ_j, with $j = 1, \ldots, m$, defines the level of pathology corresponding to the level of proliferative activity of the virus. κ_j is related to u_j as follows: $\kappa_j = \kappa\, u_j$.

• $\lambda > 0$ models the increase of proliferative activity of a variant with respect to the primary virus: $\kappa_j(\lambda) = \kappa_j(1 + \lambda)$.

• μ ia a parameter which models the vaccination program which may also depend on time by a function $\varphi = \varphi(t)$.

2.3. Multiscale models of contagion and in-host dynamics

We define eight FSs labeled by the subscripts $i = 1, \ldots, 7$, while the abbreviation i-FS is used to denote the i-th FS. i-FSs, which are carrier of a pathological state, include an additional micro-state corresponding to the level of the pathology labeled by the superscript $j = 1, \ldots, m$:

$i = 1$: *healthy* with state $f_1(t; w_1)$.

$i = 2$: *vaccinated* with state $f_2(t; w_v)$.

$i = 3$: *infected individuals by the primary virus* $f_3^j(t, \kappa_j, \beta)$, with $j > 1$.

$i = 4$: *infected individuals by a variant* $f_4^j(t, \kappa_j(1 + \lambda), \beta)$, with $j > 1$.

$i = 5$: *individuals who after vaccination are infected by a variant* $f_5^j(t, \kappa_j(1 + \lambda), \beta(1 + \gamma))$, with $j > 1$.

$i = 6$: *recovered individuals* $f_6 = f_6(t)$ for past-infected who succeed to go back to the state $j = 1$.

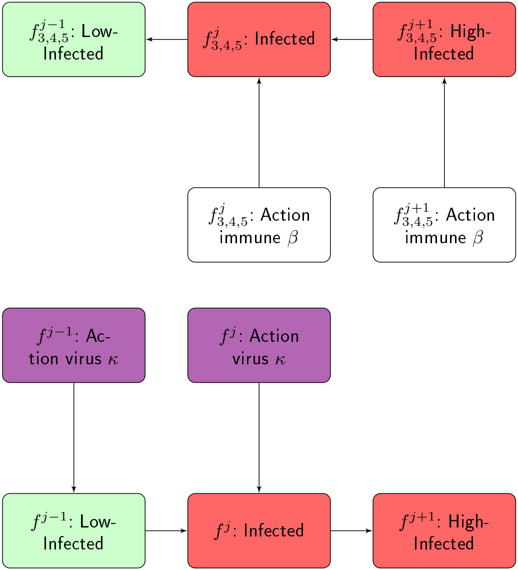
$i = 7$: *death individuals* $f_7 = f_7(t)$ for infected who reach the state $j = m$.

All dependent variables, which represent the state of the system, are referred (divided) to N_0.

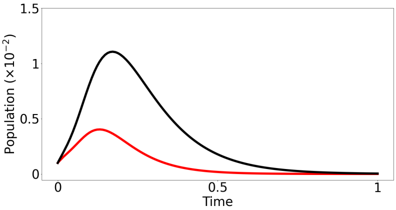
2.4. Multiscale models of contagion and in-host dynamics

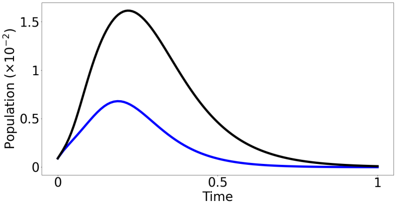
$$
\begin{cases}
\partial_t f_1(t) = -\alpha(t) \displaystyle\sum_{j=2}^{m-1} \kappa\, u_j\, f_1(t) \big[f_3^j(t) + (1+\lambda)(f_4^j(t) + f_5^j(t)) \big] - \mu\, \varphi(t), \\
\partial_t f_2(t) = \mu\, \varphi(t), \\
\partial_t f_3^j(t) = \alpha(t)\, \kappa\, u_2\, f_1(t)\, f_3^2(t) \;+\; \kappa\, u_{j-1}\, f_3^{j-1}(t) + \beta\, f_3^{j+1}(t) \\
\qquad\qquad - \kappa\, u_j\, f_3^j(t) - \beta\, f_3^j(t), \\
\partial_t f_4^j(t) = \alpha(t)\, \kappa\, u_2 (1+\lambda)\, f_1(t)\, f_4^2(t) \;+\; \kappa\, u_{j-1}(1+\lambda)\, f_4^{j-1}(t) + \beta\, f_4^{j+1}(t) \\
\qquad\qquad - \kappa\, u_j (1+\lambda)\, f_4^j(t) - \beta\, f_4^j(t), \\
\partial_t f_5^j(t) = \alpha(t)\, \kappa\, u_2 (1+\lambda)\, f_1(t)\, f_5^2(t) \;+\; \kappa\, u_{j-1}(1+\lambda)\, f_5^{j-1}(t) \\
\qquad\qquad + \beta(1+\gamma)\, f_5^{j+1}(t) - \kappa\, u_j (1+\lambda) f_5^j(t) - \beta(1+\gamma)\, f_5^j(t), \\
\partial_t f_6(t) = \beta \left(f_3^2(t) + f_4^2(t) \right) + \beta(1+\gamma) f_5^2(t), \\
\partial_t f_7(t) = \kappa\, u_{m-1}\, f_3^{m-1}(t) + \kappa\, u_{m-1}(1+\lambda) \left(f_4^{m-1}(t) + f_5^{m-1}(t) \right).
\end{cases}
$$

2.5. Multiscale models of contagion and in-host dynamics



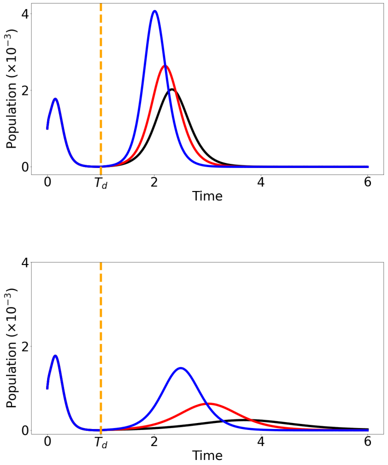
2.6. Locking, de-locking, perspectives





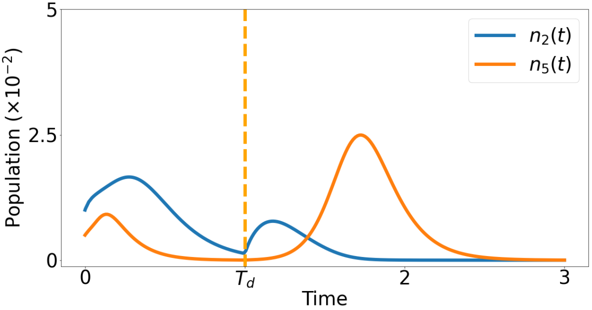
Up: Infected n_3 : $\varepsilon = 0.001$, $\kappa = 0.16$, $\alpha_\ell = 0.2$ (red) and $\alpha_\ell = 0.3$ (black).
Down: n_3 : $\varepsilon = 0.001$, $\alpha_\ell = 0.3$, $\kappa = 0.1$ (blue), $\kappa = 0.2$ (black).

2.7. Locking, de-locking, perspectives



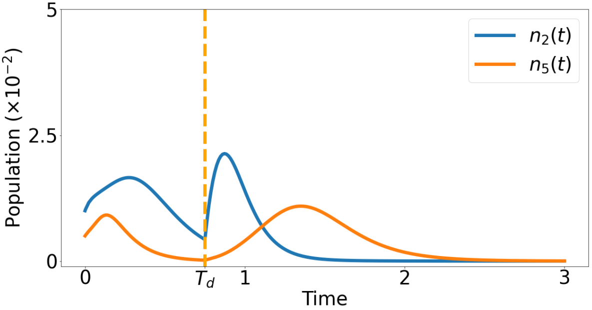
Up: n_3 for $\varepsilon = 0.001$, $\kappa = 0.1$, $T_d = 1$, $\alpha_\ell = 0.1$, $\alpha_d = 0.40$ (black), $\alpha_d = 0.45$ (red), and $\alpha_d = 0.50$ (blue). **Down:** n_3 for $\varepsilon = 0.001$, $\kappa = 0.1$, $T_d = 1$, $\alpha_\ell = 0.1$, $\alpha_d = 0.20$ (black), $\alpha_d = 0.25$ (red), and $\alpha_d = 0.30$ (blue).

2.8. Locking, de-locking, perspectives



$n_3(t)$ and $n_4 = n_4(t)$ for $\varepsilon = 0.01$, $\varepsilon_v = 0.005$, $\kappa = 0.1$, $\lambda = 1.5$, $T_d = 1$, $\alpha_\ell = 0.1$, $\alpha_d = 0.50$.

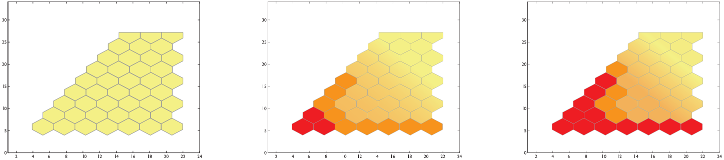
2.9. Locking, de-locking, perspectives



Infected population $n_3 = n_3(t)$ and $n_4 = n_4(t)$ for $\varepsilon = 0.01$, $\varepsilon_v = 0.005$, $\kappa = 0.1$, $\lambda = 1.5$, $T_d = 0.75$, $\alpha_\ell = 0.1$, $\alpha_d = 0.50$.

Study of the role of vaccination programs

In-host and lung dynamics should be coupled. The picture of damages contributes to focus therapeutical actions.



Simulations of the Lung Parenchima for different times.

2.11. Closure

Thanks to a multidisciplinary team

- Richard Bingham, University of York, U.K.,
- Diletta Burini, Univ. Perugia, Italy
- Mark A.J. Chaplain, University of St Andrews, Scotland, U.K.,
- Giovanni Dosi, Scuola Superiore Sant'Anna, Pisa, Italy,
- Guido Forni, Accademia Nazionale dei Lincei, Roma, Italy,
- Livio Gibelli, University of Edinburgh, Scotland, U.K.,
- Damian A. Knopoff, BCAM, Bilbao, Spain,
- John Lowengrub, University California Irvine, USA,
- Nisrine Outada, IRD-Sorbonne, France; Cadi Ayyad Univ., Morocco,
- Pietro Terna, University of Torino, Italy,
- Reidun Twarock, University of York, U.K.,
- Maria Enrica Virgillito, Scuola Superiore Sant'Anna, Pisa, Italy.

THANKS TO ORGANIZERS
THANKS TO THE AUDIENCE

B. Avishai, *The pandemic isn't a black swan but a portent of a more fragile global system*, The New Yorker, April 21, (2020).

https://www.newyorker.com/news/daily-comment/the-pandemic-isnt-a-black-swan-but-a-portent-of-a-more-fragile-global-system