Pandemics of SARS-CoV-2 and Society:

A multi-scale active particles systems approach

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1.1. Towards a Mathematical Theory of Virus Pandemics

The pandemic of COVID19 has affected our minds, health and wellbeing. However, we have learned that science is a primary wealth to respect and preserve all that we leave in a complex and interconnected world.

This Lecture is devoted to the modeling, within a multiscale vision, of the in-host dynamics of mutating-proliferating viruses contrasted by the immune system and by therapeutical actions. The objective consists in providing tools for decision making by artificial intelligence methods.

1.2. Part 1 - Index

Part 1. Mathematical frameworks towards modeling: *Introduction to modeling within a multiscale vision of living systems.*

Part 2. Multiscale models from contagion to in-host dynamics: *Immune competition, onset of variants, and vaccination programs.*

Part 3. Perspectives: *Towards mathematical tools to support crisis managers*

1.3. Part 1: Mathematical frameworks towards modeling

Main Sources

• 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 access)

• N. Bellomo, D. Burini, G. Dosi, L. Gibelli, D. Knopoff, N. Outada, P. Terna, and M.E. Virgillito, **What is life? A perspective of the mathematical kinetic theory of active particles**, *Math. Models Methods Appl. Sci.*, **31(9)**, 1821–1866, (2021). (Open access)

• N. Bellomo, D. Burini, and N. Outada, **Multiscale Models of Covid-19 with Mutations and Variants**, *Networks Heter. Media*, **17(3)**, 293–310, (2022).

• N. Bellomo, D. Burini, and N. Outada, **Pandemics of Mutating Virus and Society: A multi-scale active particles approach**, *Philosophical Transactions, Royal Society*, **380**, 20210161, (2022).

1.4. Selected recent articles

The selection in the following presents research papers where the pandemics if referred to complex environments. The selection is not exhaustive, but it is representative of Brazil and Argentina.

• M. Aguiar, G. Dosi, D.A. Knopoff, and M.E. Virgillito, A multiscale network-based model of contagion dynamics: Heterogeneity, spatial distancing and vaccination, *Math. Models and Methods Appl. Sci.*, 31, (2021), 2425–2454.

• J. F. Fontanari, A stochastic model for the influence of social distancing on loneliness,*Physica A*, 584 (2021) 126367.

• M. Gravea, A. Viguerieb, G.F. Barrosc, A. Reali, R.F.S. Andradee, A.L.G.A. Coutinho, Modeling nonlocal behavior in epidemics via a reaction-diffusion system incorporating population movement along a network, *Computer Methods Appl. Mech. Engrg.*, (2022).

• N.L. Kontorovsky, C.G. Ferrari, J.P. Pinasco and N. Saintier, Kinetic modeling of coupled epidemic and behavior dynamics. The social impact of public policies, *Math. Models and Methods Appl. Sci.*, 32, (2023).

1.5. Mathematical frameworks towards modeling

• Applied mathematicians cannot tackle the modeling problem by a stand-alone approach. An interdisciplinary vision is necessary, including biologists, clinicians, 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, should be considered, while heterogeneity appears at both scales.

• Mathematical models can produce insightful provisional simulations supporting researchers and crisis managers by artificial intelligence tools. Simulations can even uncover, not previously observed, emergent behaviors.

1.6. Mathematical frameworks towards modeling

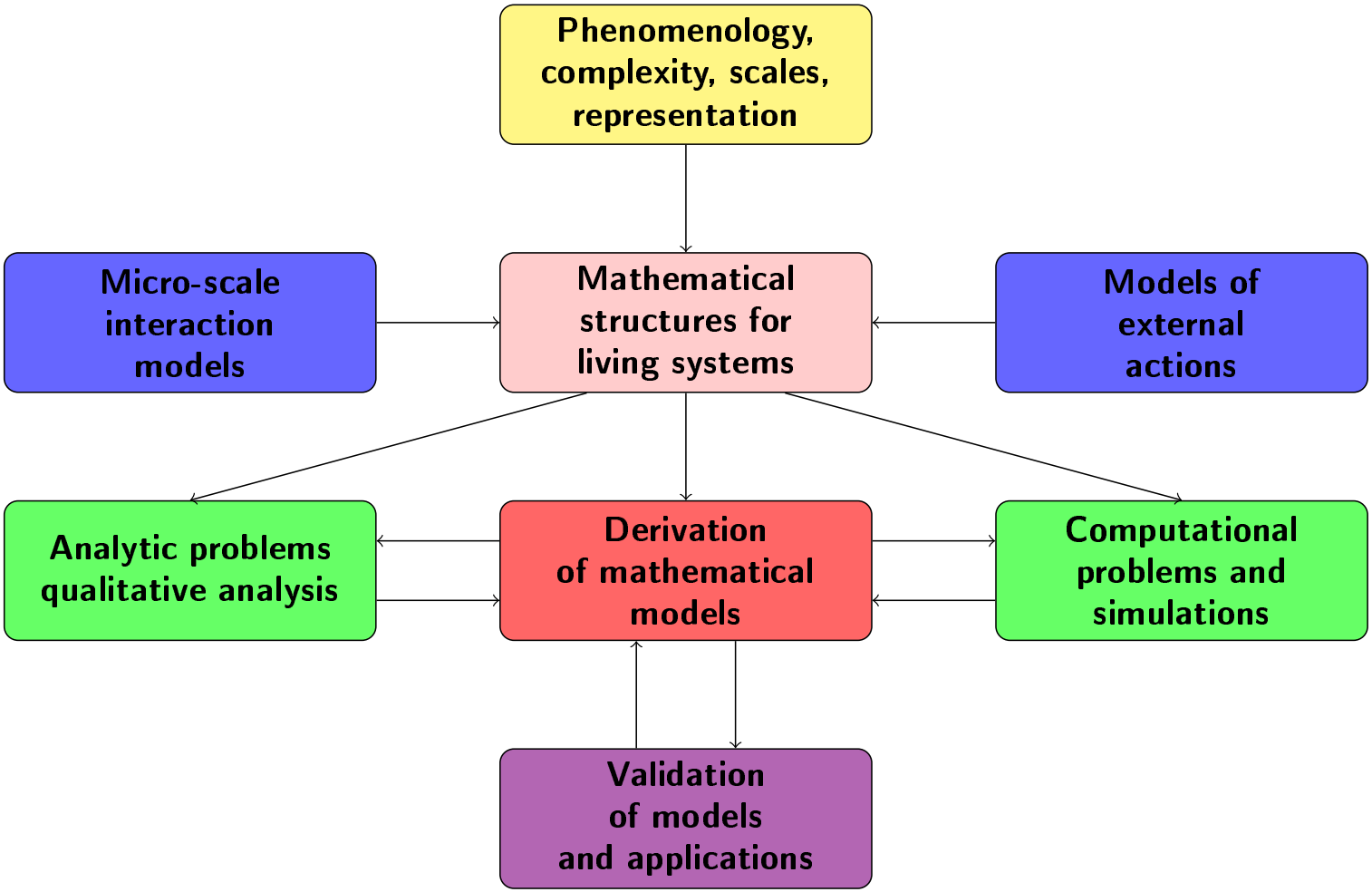


Figure 1 - Strategy towards the derivation of models of living systems

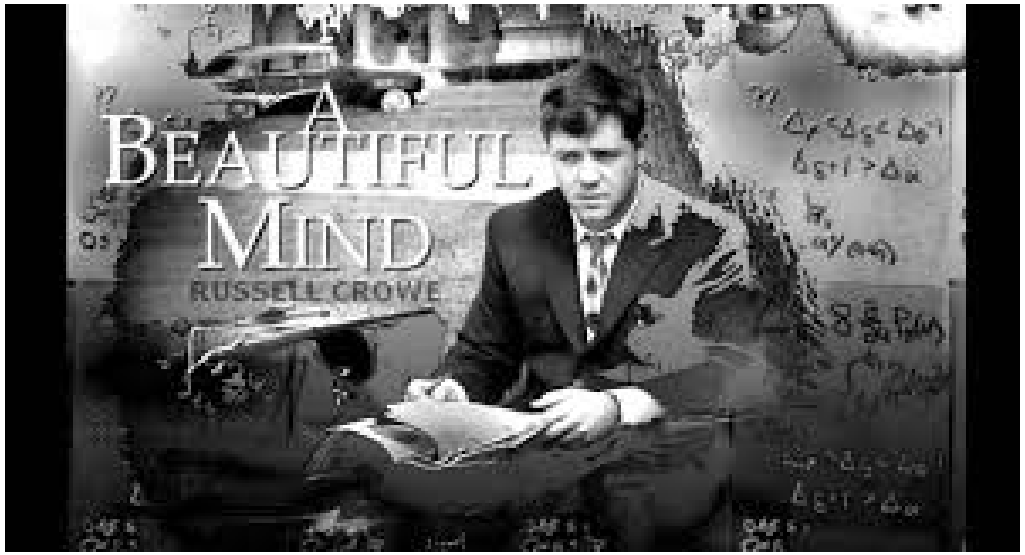
1.7. On the kinetic theory of active particles

Stochastic game theory towards a mathematical theory of living systems

- *Stochastic game theory deals with an entire population of players, where strategies with higher payoff might spread over the population.*
- *The strategy expressed by individuals, i.e., active particles, is heterogeneously distributed over players.*
- *Players are modeled as random variables linked to a distribution function over the activity variable.*
- *The pay-off is heterogeneously distributed over players and it can be motivated by "rational" or even "irrational" strategies.*
- *The payoff depends on the actions of the co-players, as well as on the frequencies of interactions.*

* N. Bellomo, A. Bellouquid, L. Gibelli, and N. Outada, ***A Quest Towards a Mathematical Theory of Living Systems***, Birkhäuser-Springer, New York, (2017).

Forward look: Applied mathematicians, **although if beautiful minds**, cannot tackle the modeling problem by a stand-alone approach



End Part 1

Part 2. Multiscale models from contagion to in-host dynamics.
Models consider immune competition, onset of variants, vaccination.
Towards a mathematical theory of SARS-CoV-2 epidemics.

2.1. Multiscale contagion and in-host dynamics

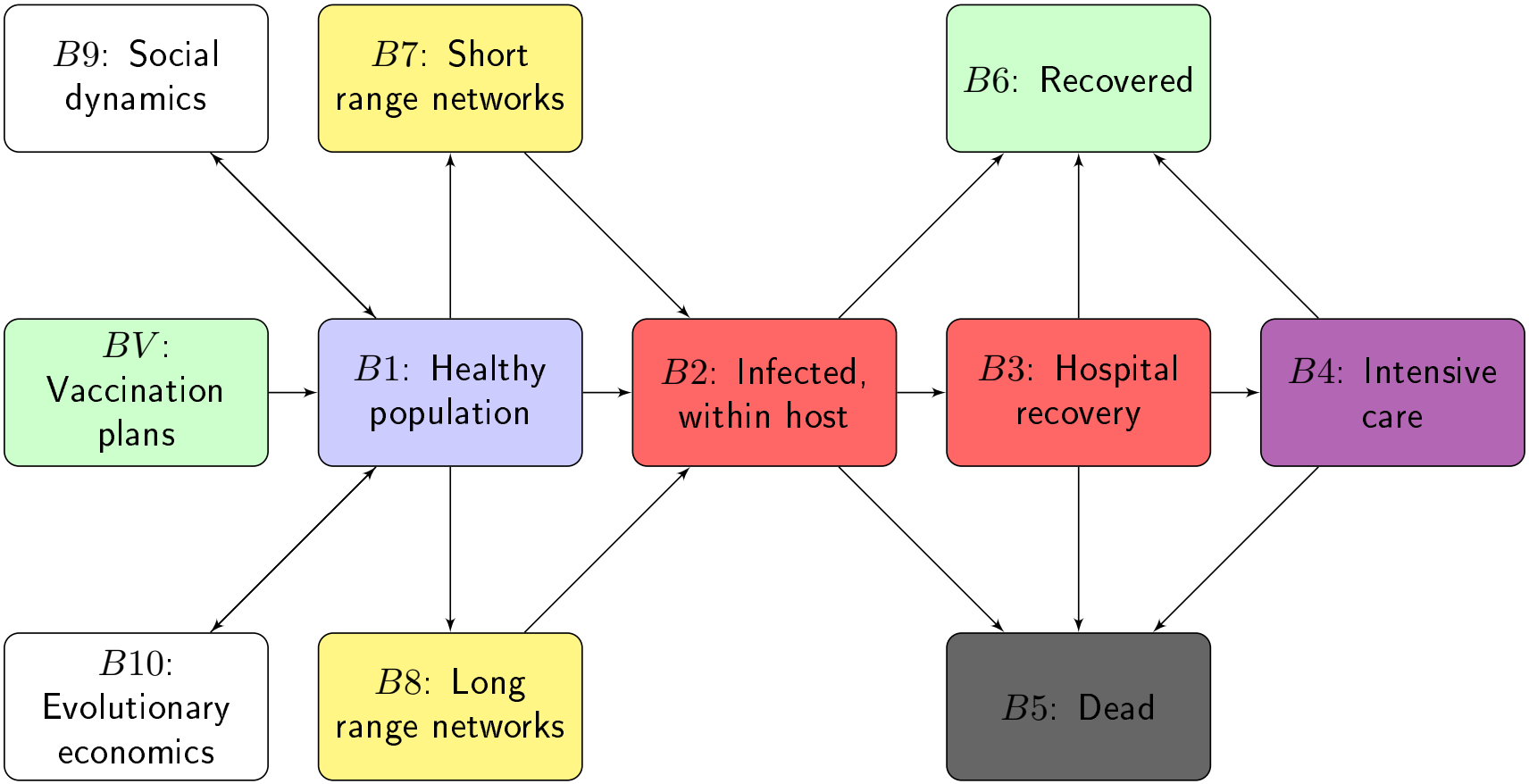


Figure 2 - Flow chart of the systems approach to the global dynamics

2.2. Multiscale models of contagion and in-host dynamics

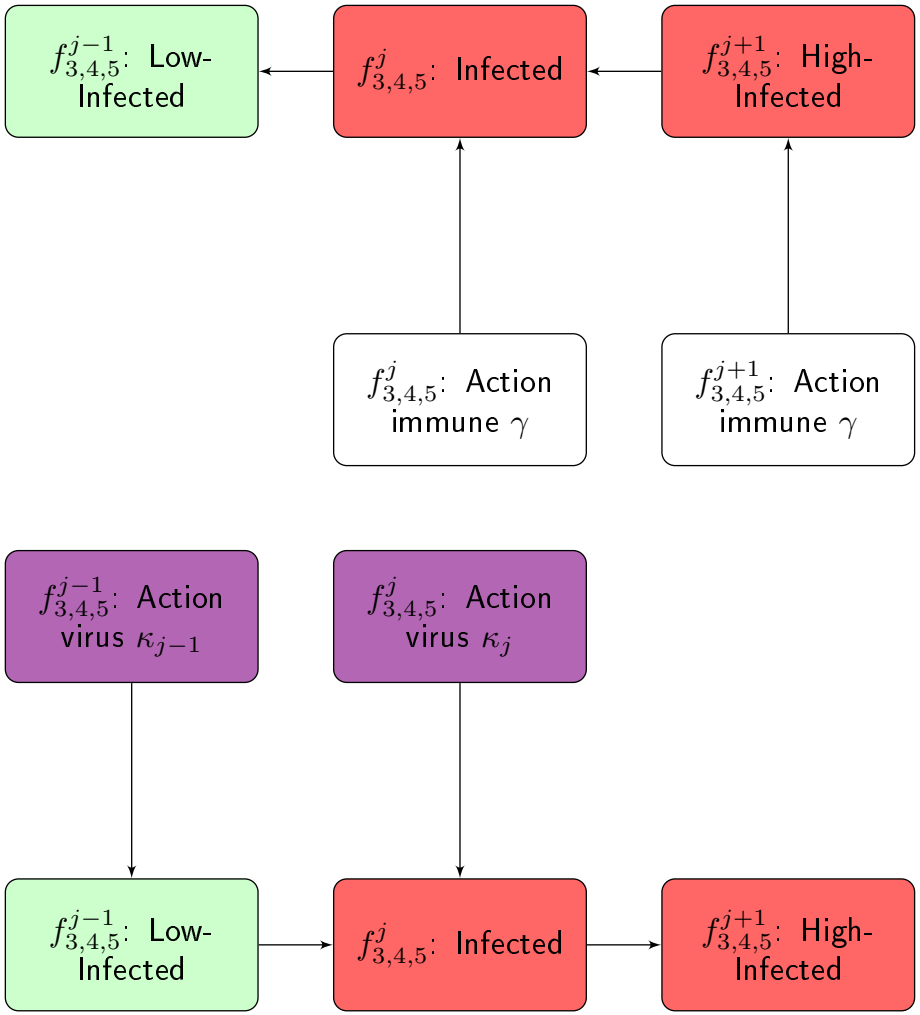


Figure 3. Up: Dynamics of f^j under the action of immune system; Down: Dynamics of f^j under the action of the virus.

2.3. Multiscale models of contagion and in-host dynamics

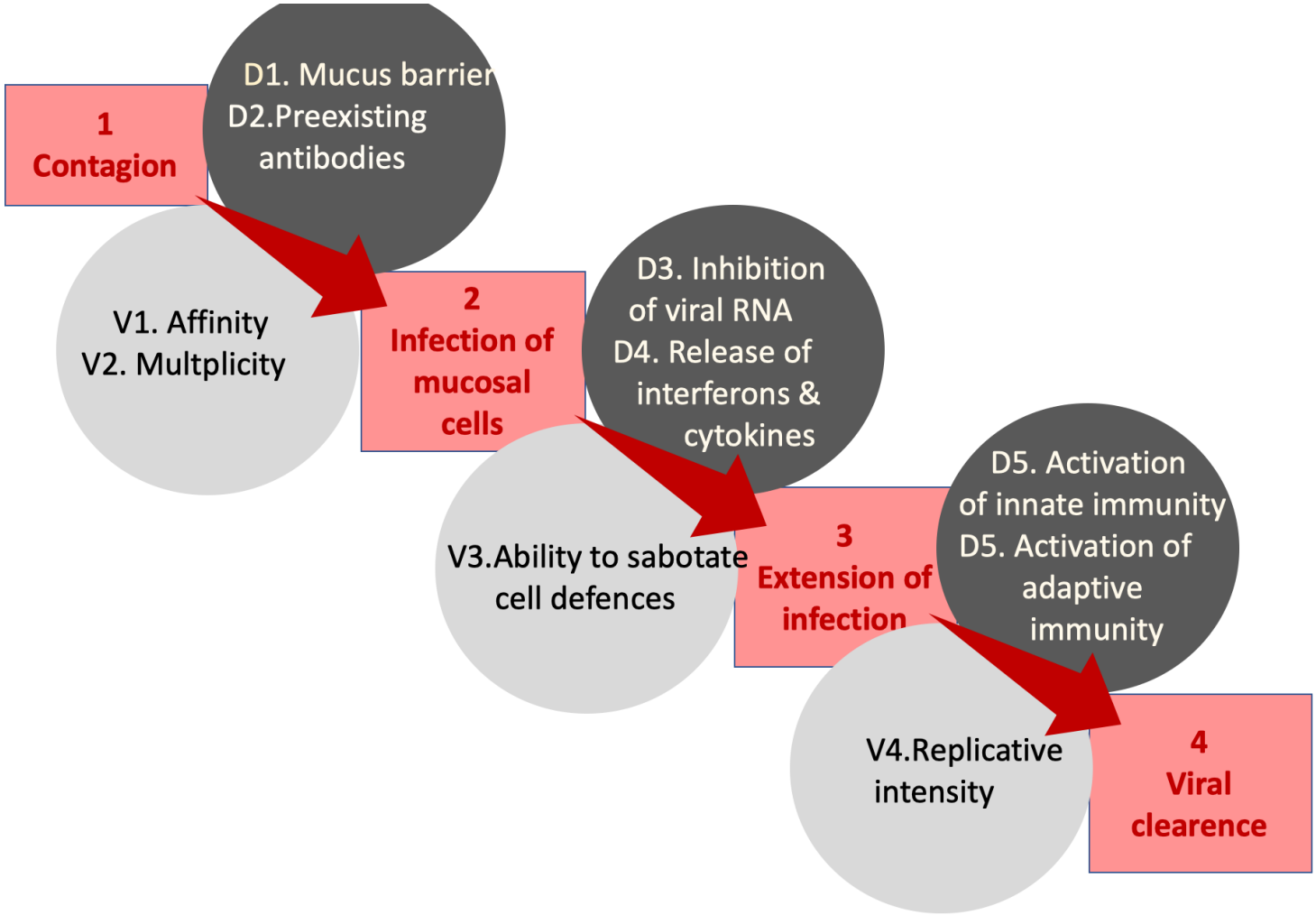


Figure 4. Representation of the in-host dynamics of the virus and of the immune reaction.

2.4. Multiscale contagion and in-host dynamics

1. The approach is multiscale, where the macro-scale corresponds to individuals who might be infected or not-infected, while the micro-scale to 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.

2.5. Multiscale models of contagion and in-host dynamics

Parameters

• $\alpha = \alpha(t) \in [0, 1]$ defines the level of social distance. It includes the "locking" action $0 < \alpha_\ell < 1$ and the de-locking action α_d with $\alpha_\ell < \alpha_d < 1$.

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

• κ_j, with $j = 1, \ldots, m$, defines the levels of pathology corresponding to the level of proliferative activity of the virus u_j. 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: $\kappa_j(\lambda) = \kappa_j(1 + \lambda)$.

• $\mu = \mu(t; \cdot)$ models the vaccination program which may depend on time as well as on the overall state of the system.

2.6. Multiscale models of contagion and in-host dynamics

Seven FSs labeled by the subscripts $i = 1, \ldots, 7$ 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 final state $j = m$.

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

Models in absence of variants and vaccination: $\varphi(\cdot) = 0$ **and** $f_2 = f_4 = f_5 = 0$

$$
\begin{cases}
\partial_t f_1(t) = -\alpha(t) \displaystyle\sum_{j=2}^{m-1} k_j f_1(t) f_3^j(t), \\
\partial_t f_3^j(t) = \alpha(t) \displaystyle\sum_{s=2}^{m-1} \kappa_s f_1(t) f_3^s(t) \delta_{2j} + \kappa \left(u_{j-1} f_3^{j-1}(t) - u_j f_3^j(t) \right) \\
\qquad\qquad + \gamma \left(f_3^{j+1}(t) - f_3^j(t) \right), \\
\partial_t f_6(t) = \gamma f_3^2(t), \\
\partial_t f_7(t) = \kappa u_{m-1} f_3^{m-1}(t).
\end{cases}
$$

Variants, in absence of vaccination: $\varphi(\cdot) = 0, f_2 = f_5 = 0$

$$
\begin{cases}
\partial_t f_1(t) = -\alpha(t) \sum_{j=2}^{m-1} k_j f_1(t) \left(f_3^j(t) + (1+\lambda) f_4^j \right), \\
\partial_t f_3^j(t) = \alpha(t) \sum_{s=2}^{m-1} \kappa_s \, f_1(t) \, f_3^s(t) \, \delta_{2j} + \kappa \left(u_{j-1} \, f_3^{j-1}(t) - \, u_j \, f_3^j(t) \right) \\
\qquad + \gamma \left(f_3^{j+1}(t) - f_3^j(t) \right), \\
\partial_t f_4^j(t) = \alpha(t) \sum_{s=2}^{m-1} \kappa_s (1+\lambda) \, f_1(t) \, f_4^s(t) \, \delta_{2j} \\
\qquad + \kappa(1+\lambda) \left(u_{j-1} \, f_4^{j-1}(t) - \, u_j \, f_4^j(t) \right) + \gamma \left(f_4^{j+1}(t) - f_4^j(t) \right), \\
\partial_t f_6(t) = \gamma \left(f_3^2(t) + f_4^2(t) \right), \\
\partial_t f_7(t) = \kappa \, u_{m-1} \, f_3^{m-1}(t) + \kappa \, u_{m-1} (1+\lambda) \left(f_4^{m-1}(t) \right).
\end{cases}
$$

2.9. Multiscale models of contagion and in-host dynamics

$$
\begin{cases}
\partial_t f_1(t) = -\alpha(t) \displaystyle\sum_{j=2}^{m-1} k_j f_1(t) \left(f_3^j(t) + (1+\lambda) f_4^j \right) - \varphi(t; f_1) H(x), \\
\partial_t f_2(t) = -\alpha(t) \displaystyle\sum_{j=2}^{m-1} k_j (1+\lambda) f_2(t) \left(f_4^j(t) + f_5^j(t) \right) + \varphi(t; f_1) H(x), \\
\partial_t f_3^j(t) = \dots \\
\partial_t f_4^j(t) = \dots \\
\partial_t f_5^j(t) = \alpha(t) \displaystyle\sum_{s=2}^{m-1} k_s (1+\lambda) f_2(t) (f_4^s(t) + f_5^s(t)) \delta_{2j} \\
\qquad + \kappa(1+\lambda) \left(u_{j-1} f_5^{j-1}(t) - u_j f_5^j(t) \right) + \gamma(1+\mu) \left(f_5^{j+1}(t) - f_5^j(t) \right) \\
\partial_t f_6(t) = \gamma \left(f_3^2(t) + f_4^2(t) \right) + \gamma(1+\mu) f_5^2(t), \\
\partial_t f_7(t) = \kappa\, u_{m-1}\, f_3^{m-1}(t) + \kappa\, u_{m-1} (1+\lambda) \left(f_4^{m-1}(t) + f_5^{m-1}(t) \right).
\end{cases}
$$

2.10. Multiscale models of contagion and in-host dynamics

Plan of the simulations referred to the sequence of two consecutive waves.

Simulation 1: Absence of variants and vaccination programs.

Simulation 2: On the role of the onset of variants and their dominance over the primary virus.

Simulation 3: On the role of vaccination programs over the dynamics with variants.

Remark 1. Simulations are deemed to develop a parameter sensitivity analysis for key parameters reported for each type of simulation.

Remark 2. Dimensionless variables are used referring time to the time-interval of the first wave and the densities to the initial number if individuals.

Simulations 1, Absence of variants and vaccination programs. Parameters:

• $\alpha \in [0,1]$ models the level of social distance, where defines $\alpha = 0$ and $\alpha = 1$ correspond, respectively, to full locking and absence of locking.

• α_ℓ and α_d correspond to the social distance, kept constant, during the locking and de-locking wave. $\Theta = \alpha_d/\alpha_\ell$.

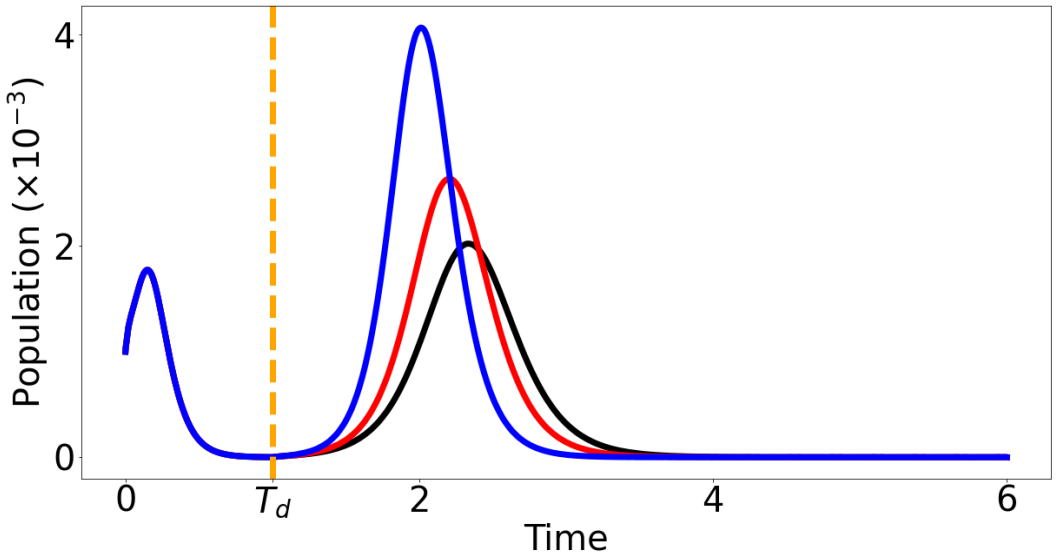
• γ defence ability of the immune system.

• k_j proliferative ability of the virus corresponding to the levels $u_j, \;\; j = 1, \ldots, m$. A simple model is $k_j = \kappa \cdot u_j$, where κ is referred to γ.

• T_d Is the time at which the locking action is replaced by the de-locking action.

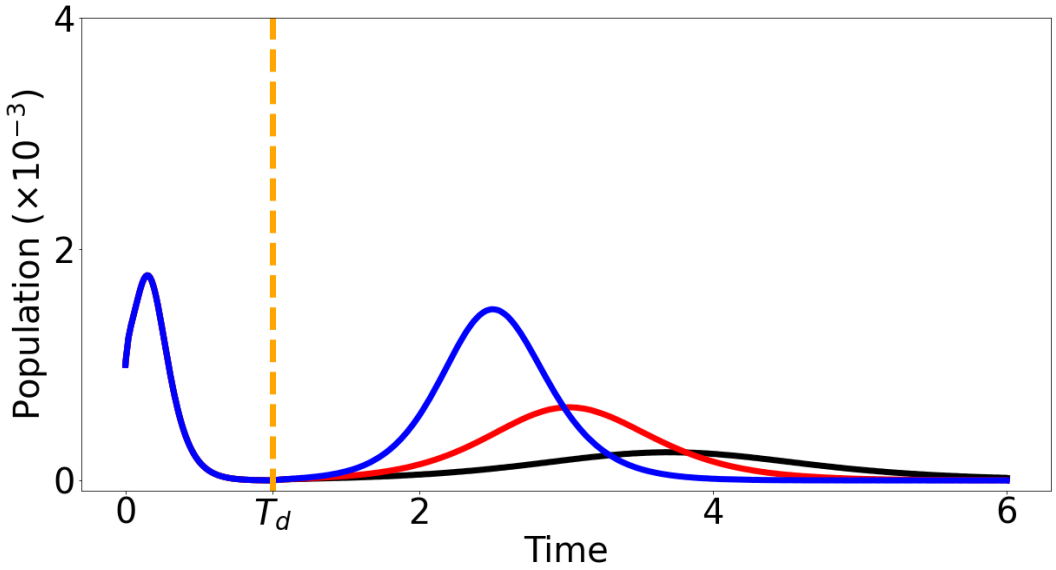
• ε Initial number, referred to the total number N of the population, of infected individuals.

Simulations 1: *The peaks of the second wave are higher than those of the first wave due to the too permissive de-locking action.*



$n_3 = n_3(t)$ for $\varepsilon = 0.001$, $\kappa = 0.1$, $T_d = 1$, $\alpha_\ell = 0.1$, $\Theta = 4.0$ (black), $\Theta = 4.5$ (red), and $\alpha_d = 5.0$ (blue).

Simulations 1: *The peaks of the second wave are lower than those of the first wave due to the low de-locking action.*



$n_3 = n_3(t)$ for $\varepsilon = 0.001$, $\kappa = 0.1$, $T_d = 1$, $\alpha_\ell = 0.1$, $\Theta = 2.0$ (black), $\Theta = 2.5$ (red), and $\alpha_d = 3.0$ (blue).

Simulations 2, variants and their dominance over the primary virus. Parameters:

- Al parameters of Simulation 1, see Slide 2.14.

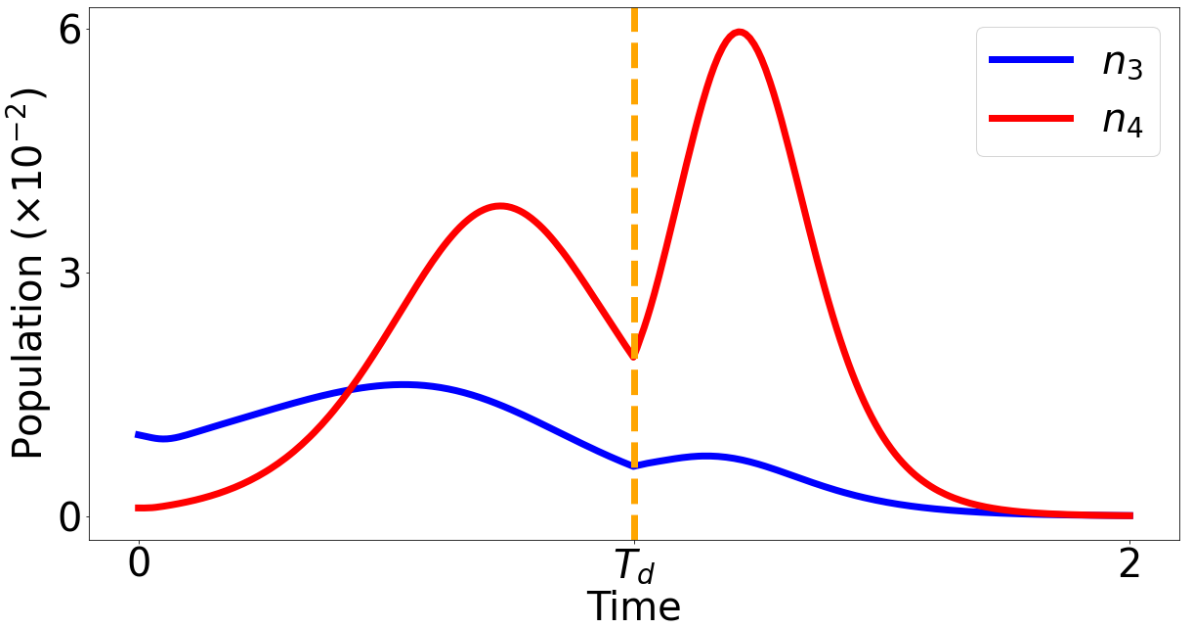
- λ models the increase of the virus proliferative ability of the variant with respect to the primary virus.

- ε Initial number, referred to the total number N of the population, of infected individuals.

- ε_v Initial number, referred to the total number N of the population, of infected individuals.

2.15. Multiscale models of contagion and in-host dynamics

Simulations 2: *Infected by the primary virus $n_3 = n_3(t)$ (blue) and by the variant $n_4 = n_4(t)$ (red). Simulations show how the dominance of the variant appears already during the locking period, and become more effective during the second wave.*



$$\varepsilon = 0.01,\ \varepsilon_v = 0.001,\ \lambda = 1.0,\ \kappa = 0.20,\ \alpha_\ell = 0.2,\ \Theta = 2.0,$$

Simulations 3: Dynamics of the primary virus and variants under the action of a vaccination program. Parameters:

- All parameters of Simulations 1 and 2, see Slides 2.14 and 2.16.

- $\varphi(t; f_1)$ models the vaccination program, namely the external action to vaccinate individuals along time accounting for the time depending number of the whole population.

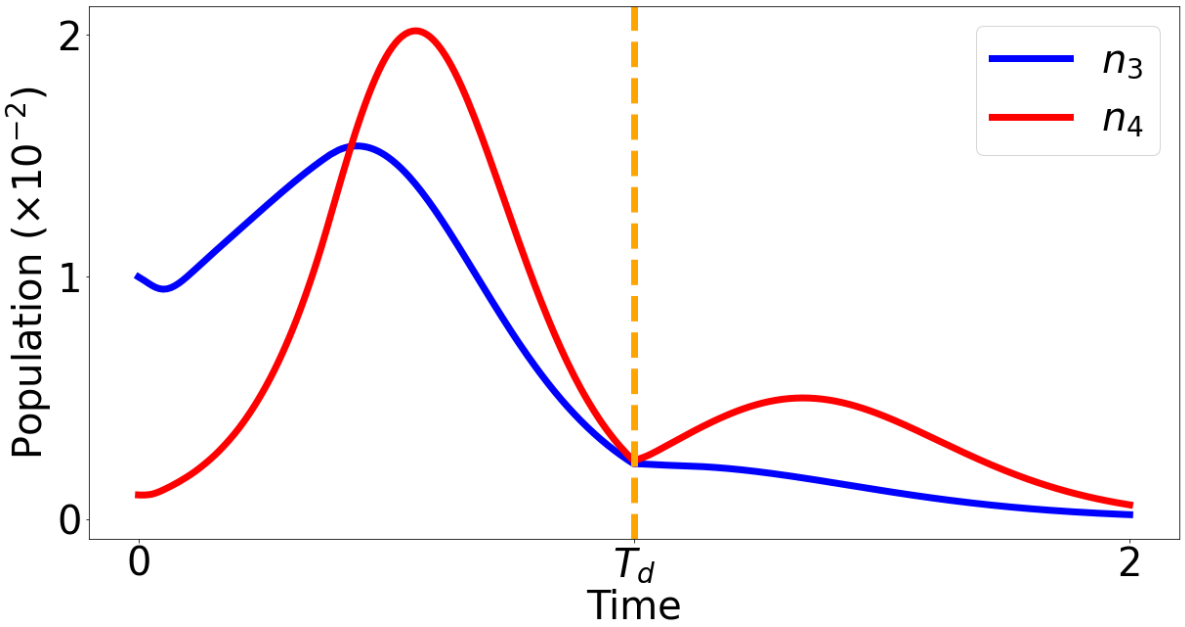
- σ models the intensity of the vaccination program.

- μ models the efficacy of the vaccine to activate the immune system.

Remark 3. Real dynamics suggest to include in the overall vaccination program also the resilient number of no-vax individual and the individual decay of the vaccines, which affects the structure of the term μ.

2.17. Multiscale models of contagion and in-host dynamics

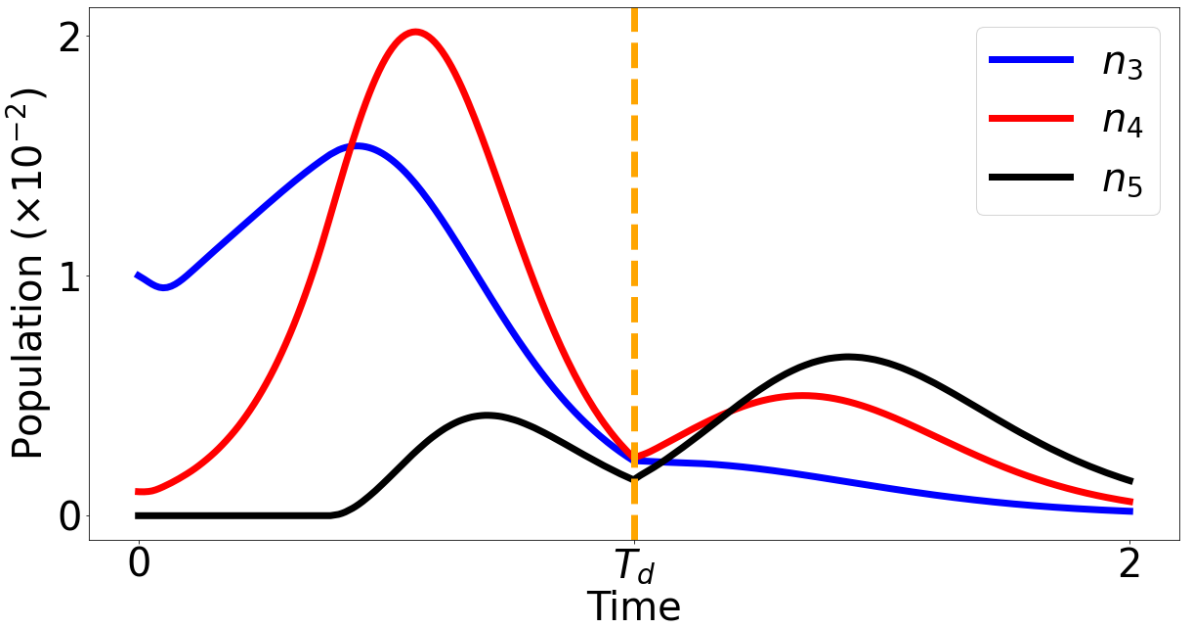
Simulations 3: *Simulations are developed with the same parameters of slide 2.17, plus those modeling the vaccination program. The figure shows how the program weakens the number of infected both for the primary virus and of the variant.*



$$\sigma = 0.25,\ \mu = 2,\ \delta = 0.1.$$

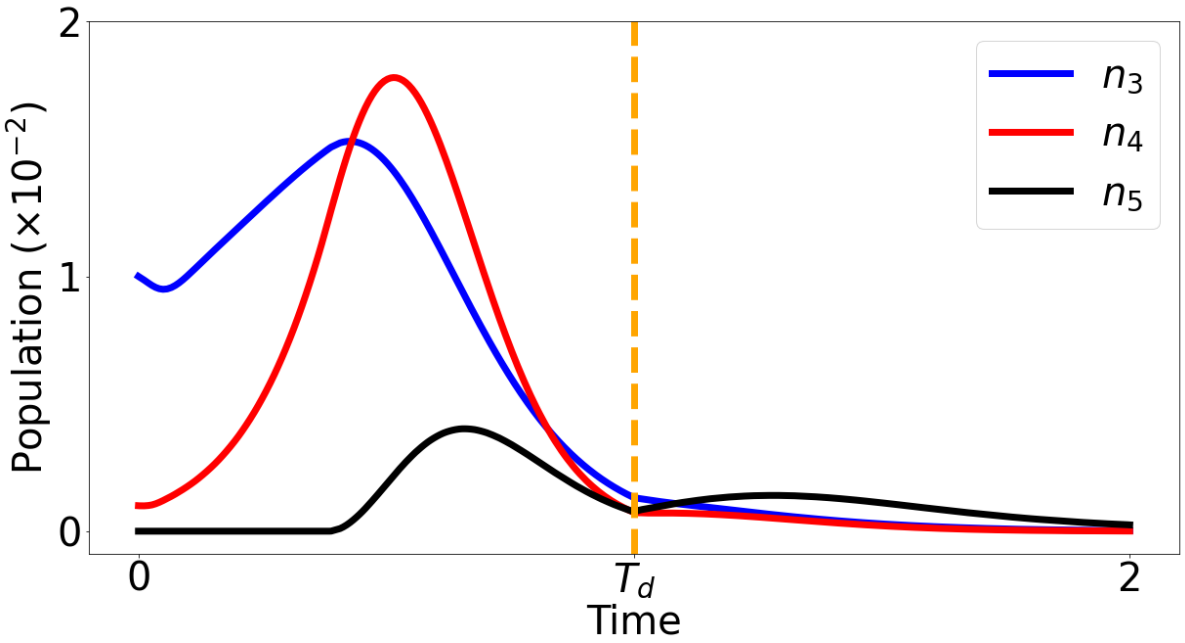
2.18. Multiscale models of contagion and in-host dynamics

Simulations 3: *Parameters are those of slide 2.17. The figure reports also the number of contagion of vaccinated which becomes greater than that of the non vaccinated as the number of vaccinated increases. But the relative number is lower and the risk of death is lower.*



$\sigma = 0.25,\ \mu = 2,\ \delta = 0.1.$

Simulations 3: *Parameters are those of slide 2.19. The figure reports also the risk of contagion of vaccinated which becomes greater than that of the non vaccinated as the number of vaccinated increases.*



$$\sigma = 0.25,\ \mu = 3,\ \delta = 0.1.$$

Summary

- The variant becomes prevalent already during the first wave, while during the second wave it fully dominates over the primary virus. This behavior is enhanced by λ and it depends also on the parameters of α_ℓ and α_d. For instance, it is enhanced by α_d.

- Simulations show how the vaccine decreases the number of infected individuals. The action already appears during the locking time and enhanced after the down-locking.

- Increasing values of vaccination action, i.e. μ, leads to decreasing values of the infected individuals.

2.21. Multiscale models of contagion and in-host dynamics

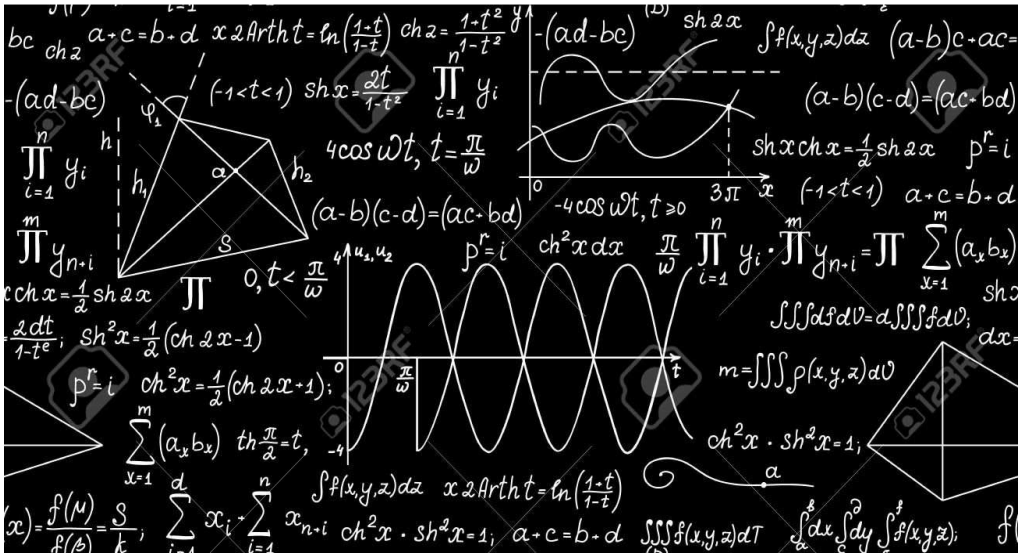
- Increasing values of α_d, corresponding to the de-locking action, leads to a second wave with high values of the density of infected individuals thus reducing the benefit of the vaccination program. In addition, the presence of vaccinated, but re-infected cannot be neglected.

- Infected individuals increase their defence against the virus, as the immune systems learns toward adaptative immunity. However, both the action of vaccination and of infection decay in time.

- Simulations show existence, for populations, of endemic states which might turn to infection waves whenever the social distance is reduced. The presence of non vaccinated individuals contributes to make permanent the aforementioned endemic states.

2.22. Multiscale models of contagion and in-host dynamics

Forward look: Mathematical tools should be further developed towards a dialogue with the society.

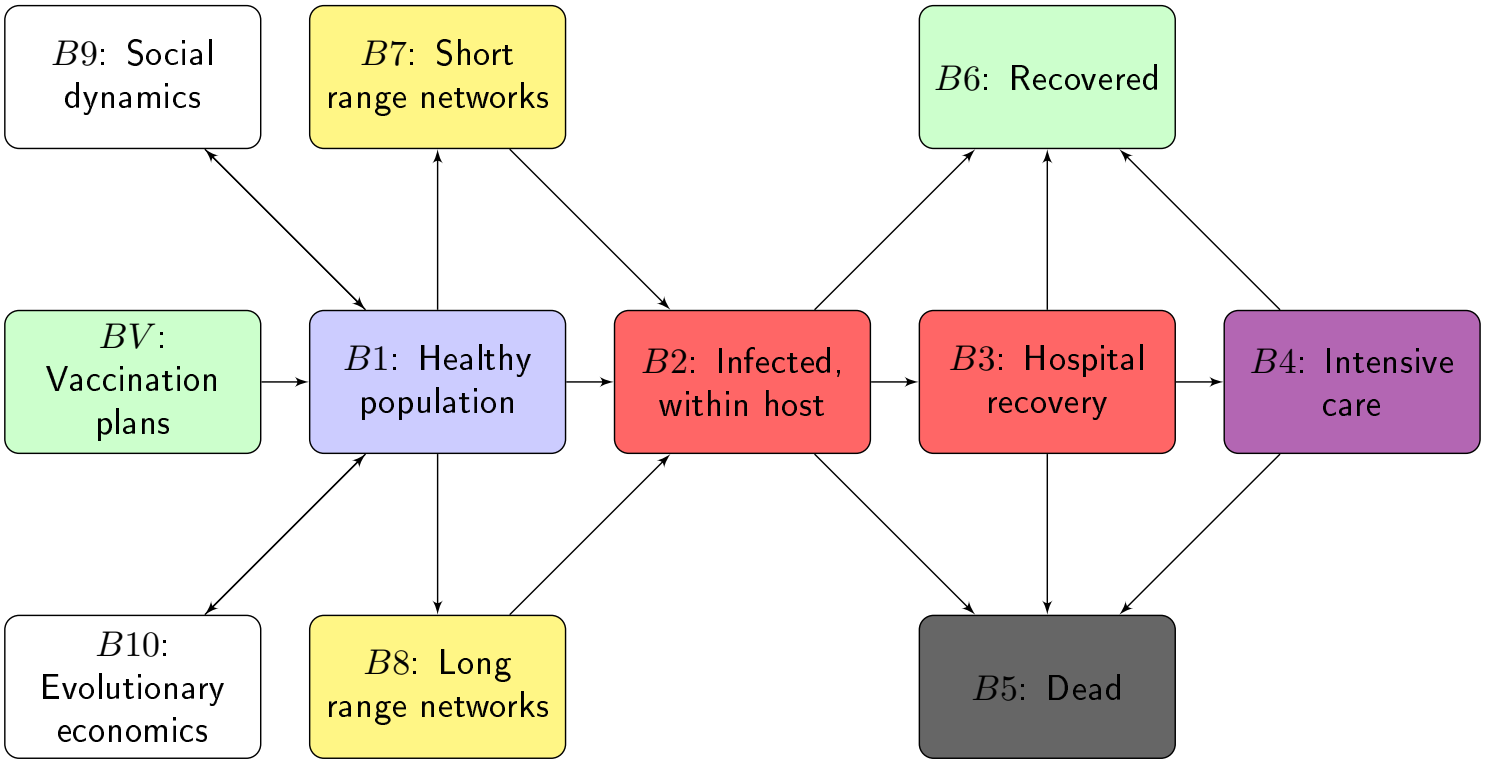


End Part 2

Part 3. Perspectives: Towards mathematical tools to support crisis managers. *Research activity in the field towards a dialogue with the Society.*

3.1. Perspectives

Key Target: *The key target consists in organizing a Research Team suitable to update the research activity and present achievements towards the needs of our society within a framework designed in collaboration with by crisis managers.*



3.2. Perspectives

A Strategy to chase this target is as follows:

1. Systems approach: *Updating the systems approach by accounting for all blocks of the flow chart in a globally connected world. In more detail, a mathematical theory of SARS-CoV-2 epidemics which should consider a deeper interpretation of the immune competition and onset of variants accounting for the dynamics at the lower molecular scale.*

2. Extended study of vaccination programs: *Modeling and simulations should consider different projects of vaccination strategies, no-vax resilience, and natural decay in time of immunity induced by vaccines.*

3. Dialogue with the society and governments: *Open a dialogue with crisis managers to inquire the whole information they need to organize actions to tackle crisis situations.*

4. Design of an interactive platform *The platform should provide simulations and artificial intelligence algorithms to support decision making.*

3.3. Lectures Open Access

Five Lectures Open Access

Five Lectures on Covid19 and Mathematics are available Open Access

https://www.carloalberto.org/cca-events/collegioaperto/six-lectures-in-the-time-of-covid-19/

After registration the contents can be downloaded.

Just published Nicola Bellomo and M. A.J. Chaplain Eds., **Predicting Pandemics in a Globally Connected World, Volume 1.** *Toward a Multiscale, Multidisciplinary Framework through Modeling and Simulation.* Springer-Birkhauser, (2022).

3.4. Closure

Thanks to a multidisciplinary team

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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