Lecture 3
Towards a Mathematical Theory of Virus Pandemics

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Five Lectures

by *N. Bellomo, D. Burini, D. A. Knopoff, N. Outada and P. Terna*

From a Mathematics of Living Systems to Modeling Virus Pandemics

3.0. Plan of the Lectures

Nicola Bellomo **Lecture 1. A Quest Towards a Mathematical Theory of Living Systems**

Diletta Burini **Lecture 2. Mathematical Tools of the Kinetic Theory of Active Particles**

Nicola Bellomo, Diletta Burini and Nisrine Outada **Lecture 3. Towards a Mathematical Theory of Virus Pandemics - Models with Mutations, Variants and Vaccination Programs**

Damian Knopoff **Lecture 4. Heterogeneity and Networks**

Pietro Terna **Lecture 5. Agent Methods to Modeling Virus Pandemics - A quick reference to complexity**

Pietro Terna **Closure, Description of the material support to the Lectures, Acknowledgments**

3.1. Towards a Mathematical Theory of Virus Pandemics

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

This Lecture is devoted to the derivation of a mathematical theory, consistent with the strategy proposed in Lectures 1 and 2, of mutating virus pandemics within a multi scale vision. Applications to within host dynamics follow in the second part of the Lecture

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, 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 App. Sci.*, 31, 1821–1866, (2021). (Open source)

3.3. Towards a Mathematical Theory of Virus Pandemics

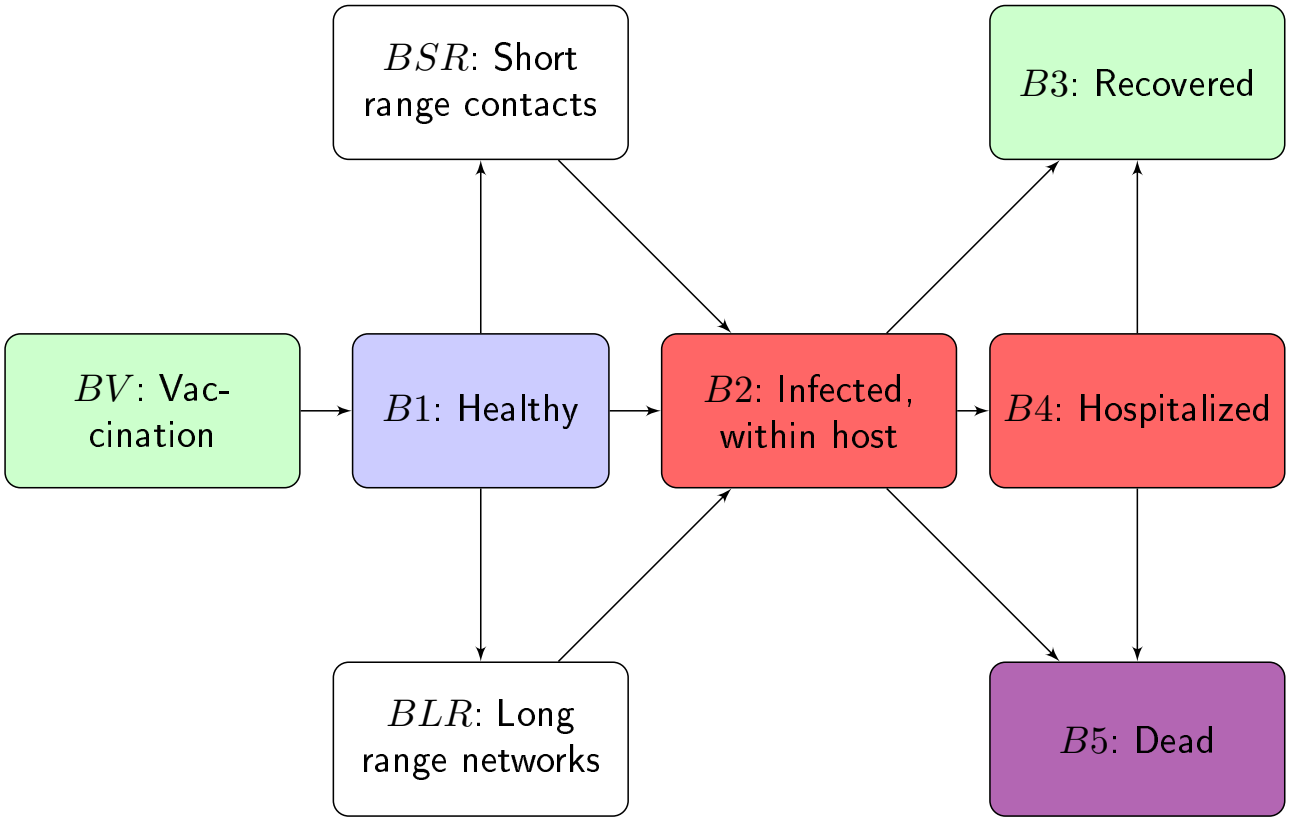
Some preliminary reasonings

• Applied mathematicians cannot tackle the modeling problem by a stand-alone approach: The scope of a research project in the field should not be confined only to the interaction of mathematics with biological and medical sciences. A global 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 constantly interact. Heterogeneity appears at both scales. Below the micro-scale the molecular scale at the level of genes should be considered.

On a Systems Approach



3.5. Towards a Mathematical Theory of Virus Pandemics

Blocks of the system approach: Slide 3.5 has described a systems approach towards a mathematical theory of a pandemics of a mutating (evolutionary) virus. A mathematical theory suitable to consider all interactions in the flow chart of Slide 3.5 is not yet available. The interpretation of each block can contribute, as preliminary step, to the said mathematical theory.

Block 1 - Dynamics of healthy people due to contagion: An heterogeneous populations should be considered. Heterogeneity may include differences in the immune defence ability, social state, type of employment, etcetera. The dynamics refers, for each subpopulation, to the number and defence ability of healthy people considering: (i) Decay to contagion by short range interactions and inlet-outlet flows due to transportation over networks; (ii) Improved defence ability of vaccinated individuals; (iii) Recovery after contagion.

3.6. Towards a Mathematical Theory of Virus Pandemics

Block BSR - Contagion by short range interactions: The contagion depends on the physical and social distance between individuals, i.e. both the protective devices and the physical distance. Contagion probability depends on the level of the infection, i.e. on the *viral charge*, as well as on the *social distance* between individuals. Contagion can even affect vaccinated individuals although they possess a stronger immune defence.

Studies on crowd dynamics lead to compute trajectories of pedestrian motion under awareness of contagion risk:

***** Daewa Kim and A. Quaini, **Coupling kinetic theory approaches for pedestrian dynamics and disease contagion in a confined environment**, *Math. Models Methods in App. Sci.*, 30(10), 1893–1915, (2020).

3.7. Towards a Mathematical Theory of Virus Pandemics

Block BLR - Inlet and outlet related to networks connection: The movement in the territory due to transportation networks can contribute to the spread in space of the infection. Two types, at least, of networks should be considered. I.E. short distance networks for daily inlet-outlet dynamics and long distance network for aperiodic. It is an important feature as already put in evidence in the second $*$ of the Slide 3.2.

Block BV - Vaccination program: The vaccination program may be planned as a function of time and it might depend on the number of non-vaccinated people. A vaccine increases the defence ability of of the immune system of each individual. Therefore vaccination acts at the low scale within each individual.Vaccinated individuals can, however, become infected, although by lower levels of the viral charge.

3.8. Towards a Mathematical Theory of Virus Pandemics

Block 2 - In-host dynamics of infected individuals: A micro-scale competition occurs in the lungs of infected individuals. Virus particles proliferate feeded by lung tissues and increase their aggressiveness which is contrasted by immune system. 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.

Block Hospitalization: Infected individuals may need home care or, depending on the level of the pathology, different levels of hospitalization up the resuscitation actions. The modeling should consider different levels of pathology as well as medical care strategies.

Block - Recovery/Death: *Recovery* is reached if the level of progression of the virus is reduced to zero. *Death* if the action of the immune system and medical care do not succeed to reduce the progression of the virus which reaches a limit value for survivance.

3.9. In-host Dynamics: Mutations, Variants, Vaccination

A general structure provides the conceptual framework: The structure is delivered by the mathematical theory presented in Lectures 2, 3:

$$\begin{aligned}\frac{d}{dt}f_{ij}^r &= G_{ij}^r(\mathbf{f}) - L_{ij}^r(\mathbf{f}) \\ &= \sum_{s=1}^{m}\sum_{h,k,p,q=1}^{n} \eta_{hk}^{pq}(r,s)(\mathbf{f})\mathcal{A}_{hk}^{pq}(hk \to ij)(\mathbf{f}) f_{hk}^r\, f_{pq}^s \\ &\quad - f_{ij}^r \sum_{s=1}^{m}\sum_{p,q=1}^{n} \eta_{ij}^{pq}(\mathbf{f})\, f_{pq}^s\end{aligned}$$

The subscripts h, k and p, q denote, respectively, the micro-states corresponding to the FSs which by interactions lead to the dynamics of f^r; η_{hk}^{pq}, η_{ij}^{pq}, denote the interaction rates, and $\mathcal{A}_{hk}^{pq}$ the transition rate into the micro-state i, j of the r-FS.

3.10. In-host Dynamics: Mutations, Variants, Vaccination

From contagion and in-host dynamics. Parameters

• $\alpha = \alpha(t) \in [0, 1]$ 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 models the level of the efficacy of the vaccine.

3.11. In-host Dynamics: Mutations, Variants, Vaccination

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 $j = 1, \ldots, m$. All dependent variables are referred (divided) to N_0.

$i = 1$: *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 reaching $j = m$.

In-host dynamics: The action of the immune system

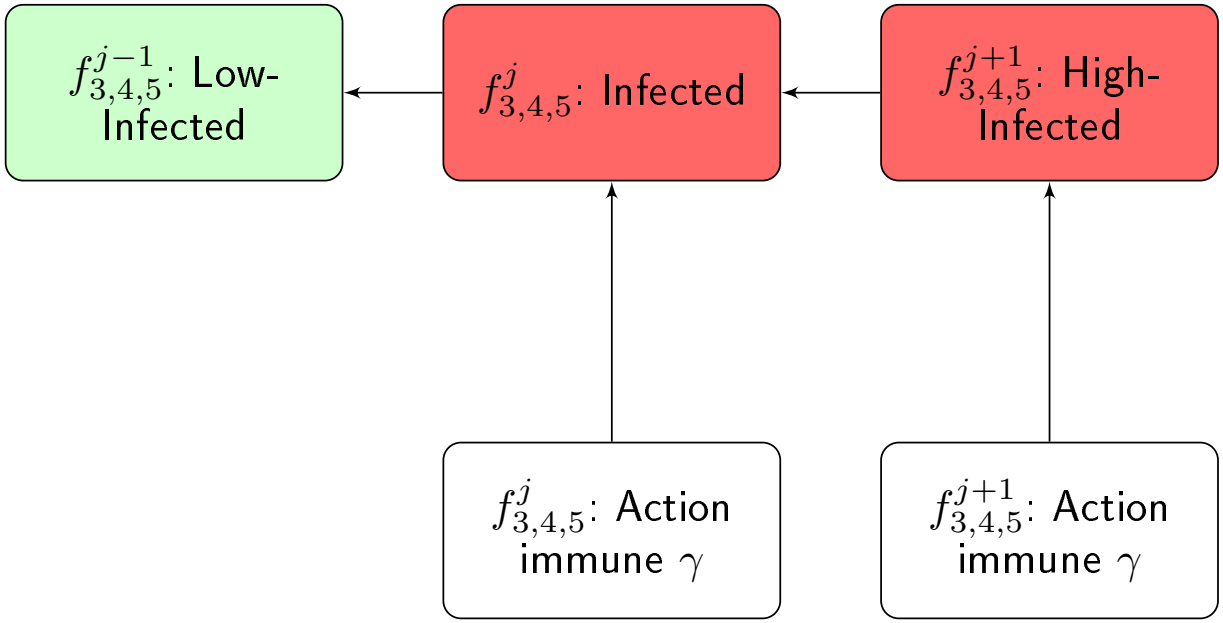


Figure – Dynamics of f^j under the action of immune system

In-host dynamics: The action of the virus

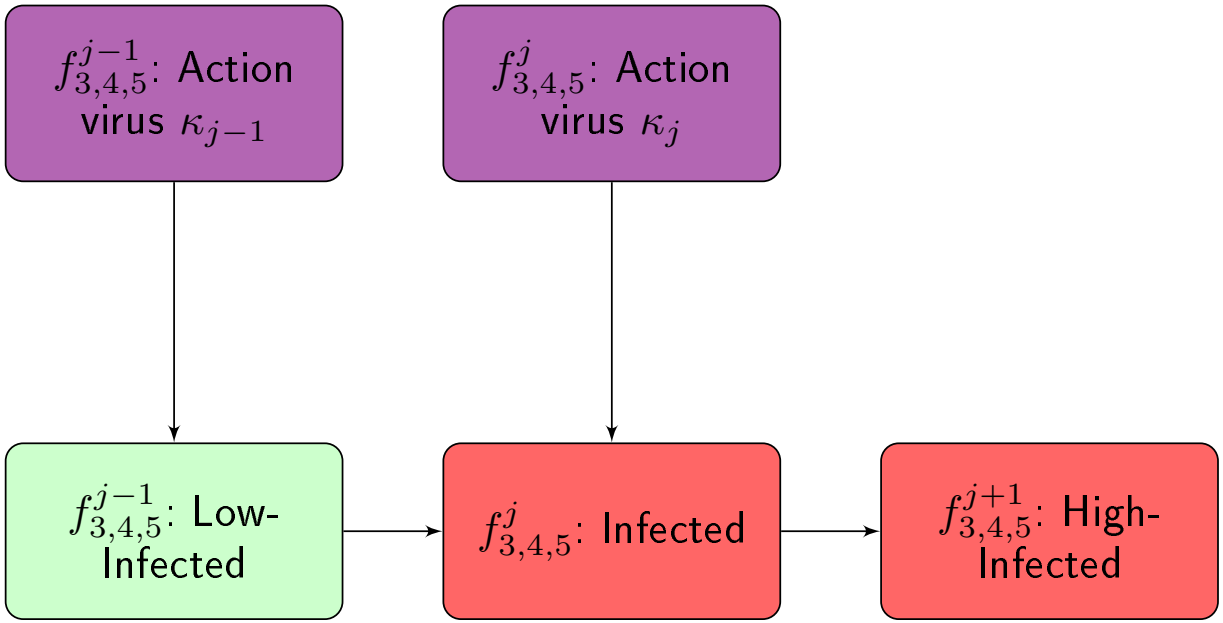


Figure – Dynamics of f^j under the action of the virus.

3.14. In-host Dynamics: Mutations, Variants, Vaccination

Vaccination program: It can depend on time. A specific program is:

$$\varphi(t; f_1) > 0, \quad \text{if} \quad f_1 < 1 - \delta; \quad \varphi(t; f_1) = 0 \quad \text{if} \quad f_1 \geq 1 - \delta,$$

where δ denotes a sentinel fraction of infected individuals which induces the start of vaccination program. The action increases γ to $\omega_v = \gamma(1 + \mu)$. Then, $f_2 = f_2(t, \gamma(1 + \mu))$.

Dynamics of vaccinated individuals: Let $x = f_1 + \delta - 1$, where H is the heaviside function, $H(x) = 1$ for $x > 0$, and $H(x) = 0$ for $x \leq 0$. Then

$$\partial_t f_2(t) = -\alpha(t) \sum_{j=2}^{m-1} k_j (1 + \lambda) f_2(t) \left(f_4^j(t) + f_5^j(t) \right) + \varphi(t; f_1) H(x),$$

Dynamics of healthy people: The dynamics refers to the decay of $f_1(t)$ due to contagion interactions ruled by α and by the vaccination program:

$$\partial_t f_1(t) = -\alpha(t) \sum_{j=2}^{m-1} k_j f_1(t) \left(f_3^j(t) + (1 + \lambda) f_4^j(t) \right) - \varphi(t; f_1) H(x).$$

3.15. In-host Dynamics: Mutations, Variants, Vaccination

In-host dynamics: The virus proliferates by feeding lung tissues and increase the level of the pathology from j- to $(j+1)$-level depending on κ_j and, on the level by λ, of the new variant. The immune system decreases j- to $(j-1)$-level of the virus depending on the parameter w.

$$\partial_t f_3^j(t) = \alpha(t) \sum_{s=2}^{m-1} \kappa_s \, f_1(t) \, f_3^s(t) \, \delta_{2j} \; + \; \kappa_{j-1} \, f_3^{j-1}(t) + \gamma \, f_3^{j+1}(t) \\ -\kappa_j \, f_3^j(t) - \gamma \, f_3^j(t).$$

The infection by the variants refers to f_1 and by infected ε_v in f_4.

$$\partial_t f_4^j(t) = \alpha(t) \sum_{s=2}^{m-1} \kappa_s(1+\lambda) \, f_1(t) \, f_4^s(t) \, \delta_{2j} \; + \; \kappa_{j-1}(1+\lambda) \, f_4^{j-1}(t) \\ +\gamma \, f_4^{j+1}(t) - \kappa_j(1+\lambda) \, f_4^j(t) - \gamma \, f_4^j(t),$$

where δ denotes the Dirac delta function, while the proliferative ability of the variant is modeled by the factor $(1+\lambda)$.

Follows Block 2

The contagion dynamics of individuals who have been vaccinated involves vaccinated individuals of the population f_2, who possess now a stronger ability in the immune defence, and f_4 that might infect vaccinated individuals.

$$\partial_t f_5^j(t) = \alpha \sum_{s=2}^{m-1} \kappa_s(1+\lambda) f_2(t) \left(f_4^s(t) + f_5^s(t)\right) \delta_{2j} + \kappa_{j-1}(1+\lambda) f_5^{j-1}(t)$$
$$+\gamma(1+\mu)\, f_5^{j+1}(t) - \kappa_j(1+\lambda)\, f_5^j(t) - \gamma(1+\mu)\, f_5^j(t).$$

Block 3 - Trend to recover: The dynamics consider the inflow,of healthy people, of individuals from 3-FS, 4-FS and 5-FS, with state $j = 2$ into 1-FS, corresponding to $j = 1$, due to the action of the immune system:

$$\partial_t f_6(t) = \gamma \left(f_3^2(t) + f_4^2(t)\right) + \gamma(1+\mu) f_5^2(t).$$

3.17. In-host Dynamics: Mutations, Variants, Vaccination

Block 4 - Hospitalization: The dynamics related to need of hospitalization is modeled by the variables $f^j_{3,4,5}$ with $2 < j < m-1$. As an example, for $m = 6$, $j = 2, 3, 4, 5$ may correspond to asymptomatic, symptomatic needing home care, hospital care, and advanced care, respectively. The model derived in this subsection do not consider this specific refinement which is, however critically analyzed in the last subsection.

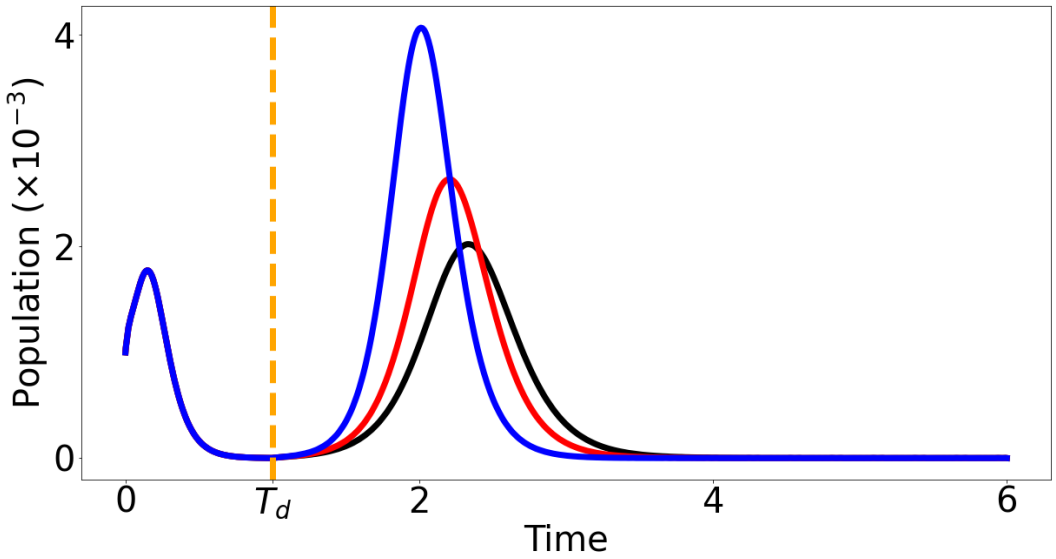
Block 5 - Trend to death: The dynamics are caused by the inflow from 3-FS, 4-FS and 5-FS in $j = m-1$, into 7-FS, corresponding to $j = m$, due to the action of the virus proliferation:

$$\partial_t f_7(t) = \kappa_{m-1}\, f_3^{m-1}(t) + \kappa_{m-1}(1+\lambda)\left(f_4^{m-1}(t) + f_5^{m-1}(t)\right).$$

The mathematical model is obtained by all interconnected equations modeling the dynamics of the system

3.18. Multiscale models of contagion and in-host dynamics

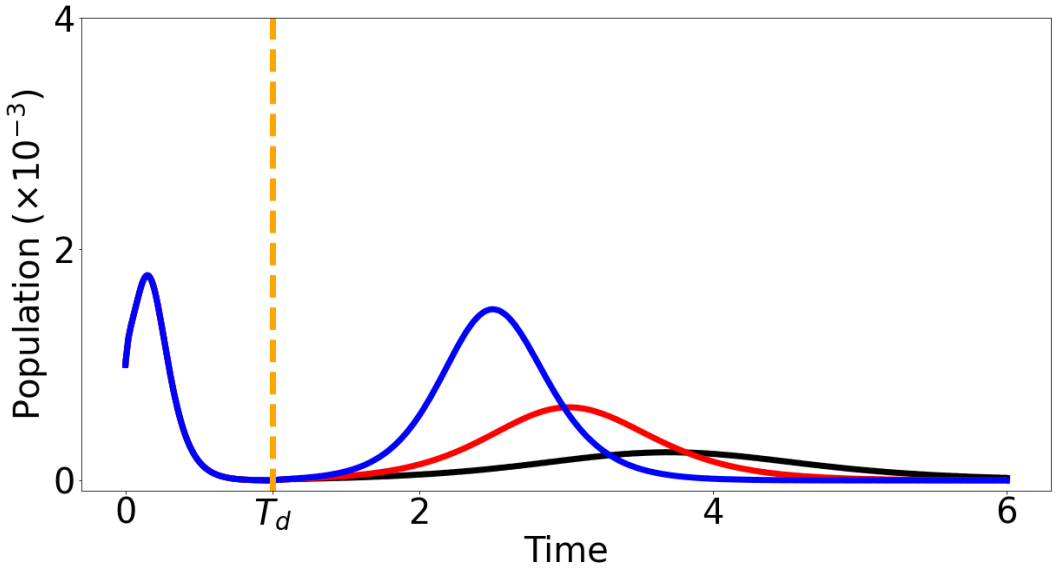
Second wave: decreasing the social distance, i.e. increasing the parameter α, decreases the number of infected. The second wave can show infections higher than the first wave.



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).**

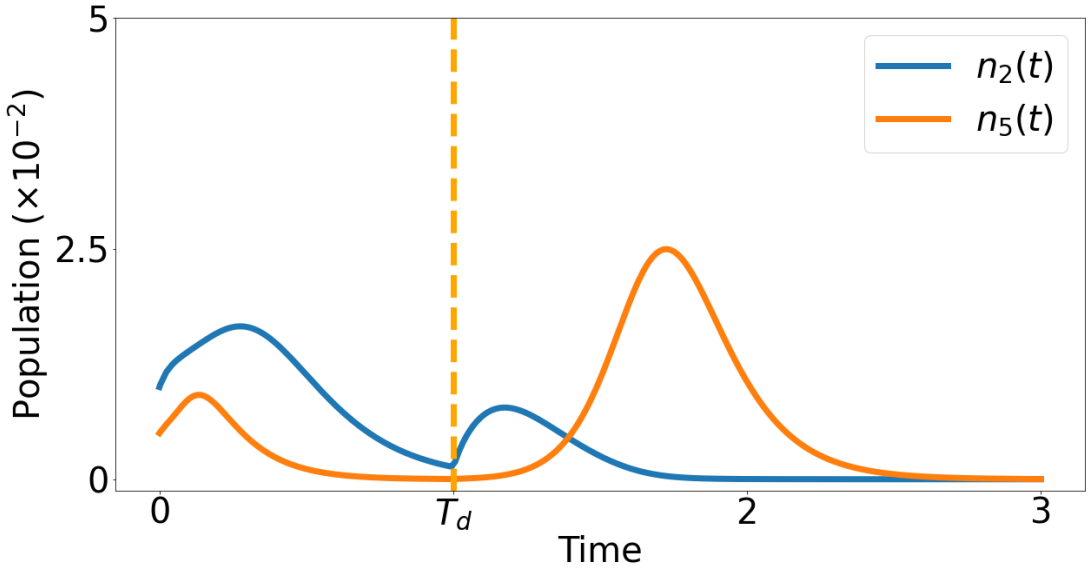
Second wave: Further decrease of the confinement parameter decreases the peaks of the second wave.



n_3 **for** $\varepsilon = 0.001$, $\kappa = 0.1$, $T_d = 1$, $\alpha_\ell = 0.1$,

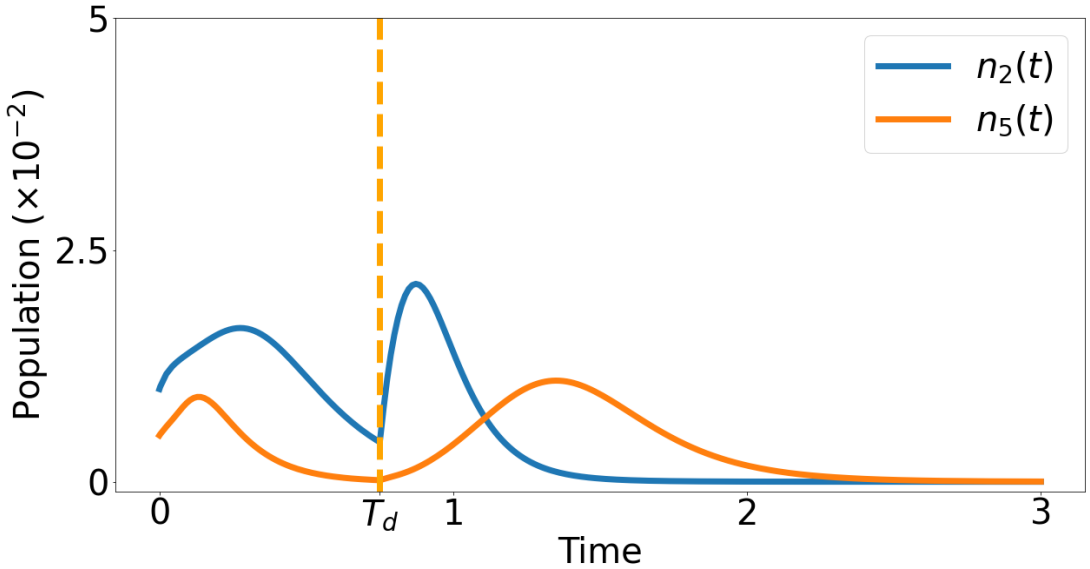
$\alpha_d = 0.20$ **(black),** $\alpha_d = 0.25$ **(red), and** $\alpha_d = 0.30$ **(blue).**

Dynamics with variants: The variant become predominant during the second wave



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

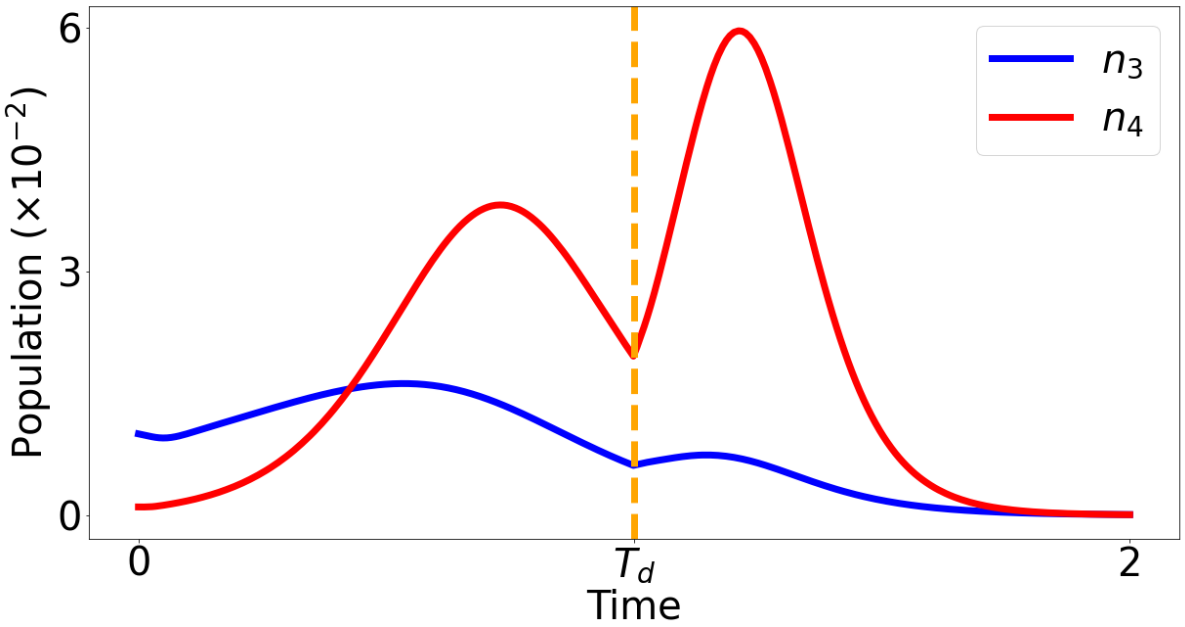
Dynamics with variants: Reducing the de-locking time modifies the dynamics



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

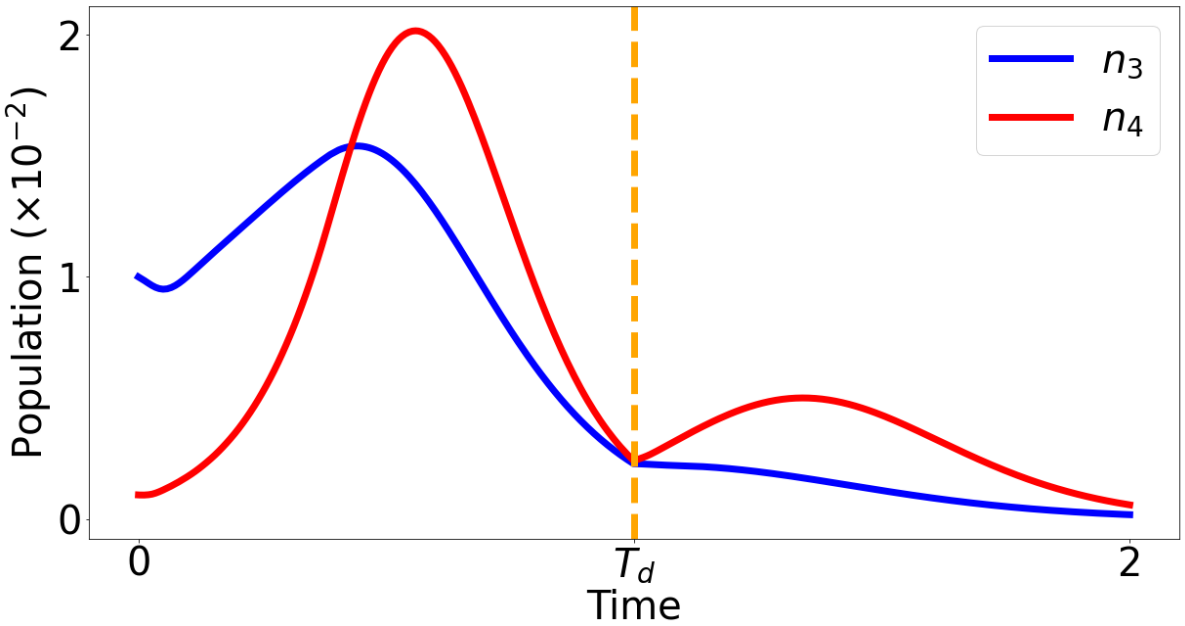
3.22. Multiscale models of contagion and in-host dynamics

n_3 (infected by the primary virus) and n_4 (infected by the variant) versus time under a locking and de-locking actions



3.23. Multiscale models of contagion and in-host dynamics

n_3 and n_4 versus time under a locking and de-locking actions and under a under vaccination program



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 the locking and de-locking action. 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 μ, lead to decreasing values of the infected individuals.
- Increasing values of α_d, 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.

3.25. Closure

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