

Yao H et al, 2020

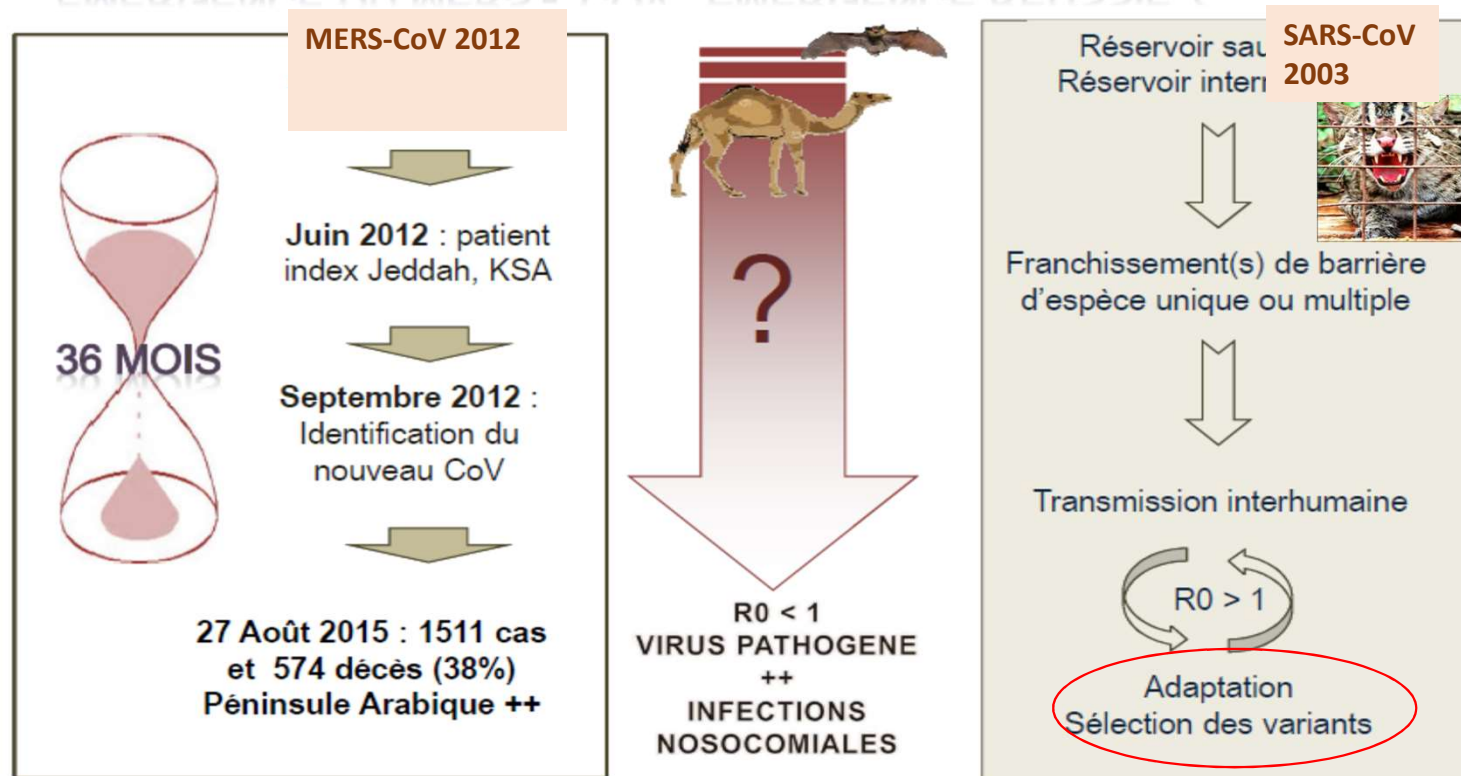
Laboratoire de virologie et crise sanitaire de la COVID-19

La COVID-19 ou l'émergence d'un virus à fort pouvoir adaptatif.

*Pr Evelyne Schvoerer – Septembre 2021
Virologie CHRU et laboratoire LCPME UMR 7564 CNRS-UL, Nancy*

COVID 19 - Le VIRUS, variabilité d'un coronavirus
cf MERS-CoV 2012, SARS-CoV-1 2003

EMERGENCE DU MERS - COV : EMERGENCE RÉUSSIE ?



Zaki AM, et al., NEJM 2012

From A Vabret

COVID 19 - Le VIRUS

- Coronavirinae, genre Beta, **ARN** , ~ **30kb** (*Corman 2020*)
- Hommes et animaux - Sélection de variants viraux, pouvoir **adaptatif**

- Virus SARS-CoV-2 : **VARIABILITE génétique**, quasi-espèces vira
(*Jary et al., 2020 ; Khatib et al., 2020*)

-> Dynamique évolutive du **virus chez les patients**
 Et de **l'épidémie de COVID-19 dans les populations**

-> Clinique polymorphe – cf Maladies infectieuses

-> **Diagnostic VIROLOGIQUE**

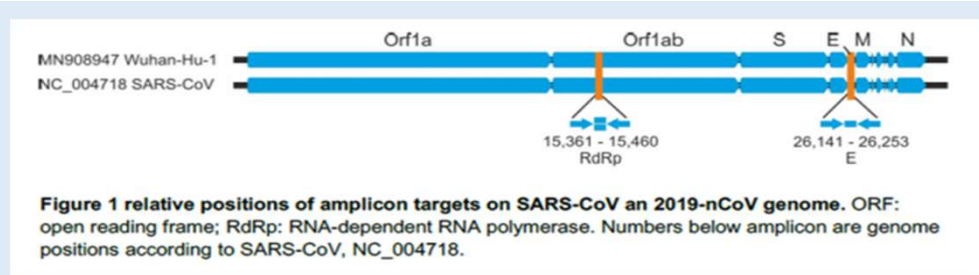
 outils moléculaires **évolutifs**



COVID 19 - Diagnostic de certitude = PCR

Diagnostic d'infection – et d'excrétion virale

Corman et al, Berlin / Rotterdam / Londres*
1^{ère} technique RT-PCR en ligne



Prélèvements respiratoires

Écouvillon nasopharyngé = ENP

Expectoration, LBA, aspiration trachéale

...



PCR sur (2) gènes viraux du CoV2 sur *ENP* : technique de reference

→ cinétiques des résultats PCR fonction de différents facteurs

→ Place des tests Ag du SARS-CoV2, des sérologies anti-SARS-CoV-2

Missions des CHRU

- En général, soins des patients hospitalisés + recherche 'translationnelle'
- En particulier contexte de l'aide à la gestion de la crise sanitaire COVID-19

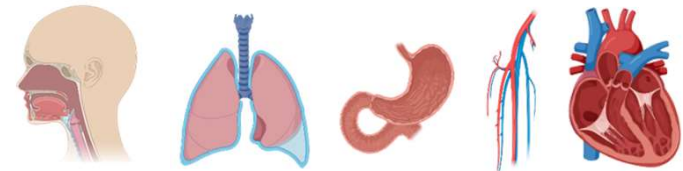
Virologie médicale : Exploration de la variabilité génétique du SARS-CoV-2

Variabilité temporelle

Vagues successives de la pandémie
en France

Variabilité tissulaire

COVID-19 polymorphe



Gène S codant la protéine **Spike**

Exemples de terrain, Virologie CHRU Nancy

Exemple 1 avec biopathologie et al

CHRU de Nancy

Case report

A 69-year-old man with a history of diabetes, hypertension, and ischemic heart disease, but without chronic heart failure, presented to the emergency room with fever, asthenia, and abdominal pain that had been progressing for a week. Physical examination was unremarkable. Initial blood analysis demonstrated high inflammatory markers and lymphopenia (white blood cell count, 14 460/mm³; neutrophils, 13710/mm³; lymphocytes, 540/mm³; C-reactive protein, 329 mg/L).

↓

were sterile. Reverse transcription polymerase chain reaction (RT-PCR) analysis for SARS-CoV-2 was negative on a nasal swab sample. A computed tomography (CT) scan showed no anomaly in the thoracic and abdominal areas. An electrocardiogram was performed and did not show signs of ischemia.



SARS-Cov-2 fulminant myocarditis: an autopsy and histopathological case study

Guillaume Gauchotte^{1,2,3,4} · Véronique Venard⁵ · Michaël Segondy² · Cyril Cadoz⁶ · Aude Esposito-Fava² · Damien Barraud⁶ · Guillaume Louis⁶

Received: 23 November 2020 / Accepted: 17 December 2020
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Severe myocardial dysfunction and severe hemodynamic compromise quickly led to implementation a veino-arterial extracorporeal membrane oxygenation (VA-ECMO). The patient deceased 6 days after admission, in a context of refractory shock and multi organ failure.

Case report

- *Viral proteins in cells*
- *SARS-CoV-2 genome in heart tissue*

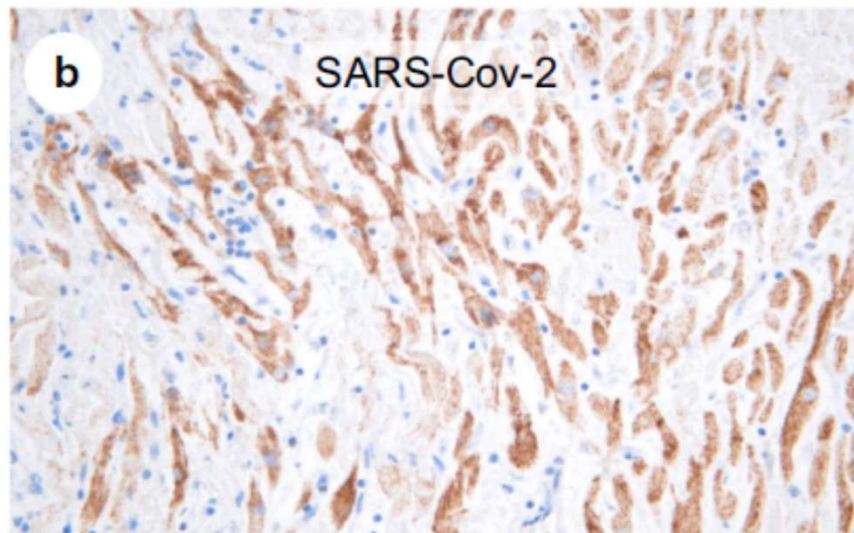


Fig. 1 (a) Abundant myocardium edema and interstitial inflammation, showing a predominance of mononucleated leucocytes, associated with cardiomyocytes dystrophies (hematoxylin, eosin, and saffron (HES), $\times 200$). (b) Strong granular cytoplasmic staining of cardiomyocytes for SARS coronavirus nucleocapsid protein (immunohistochemistry, $\times 200$)

Finally, RNA was extracted from formalin-fixed paraffin-embedded heart and lung tissue blocks, in order to perform RT-PCR, which allowed to detect SARS-CoV-2 (COVID-19) genome in heart tissue, but not in lung parenchyma. Analyses for influenzae (A and B) and parvovirus B19 were negative.

- ✓ SARS-CoV-2 : RT-PCR(-) in nasopharynx
- ✓ SARS-CoV-2 : RT-PCR(+) in cardiomyocytes, with viral protein
- ✓ Abundant T cell inflammation, TCD8+

Exemples de terrain, Virologie CHRU Nancy

Exemple 2 : Epidémiologie avec la Métropole du Grand Nancy

Exemple 2bis : Epidémiologie humaine et environnementale

Métropole Grand Nancy

Seroprevalence of SARS-CoV-2, symptom profiles and seroneutralization in a suburban area, France - *Viruses 2021*

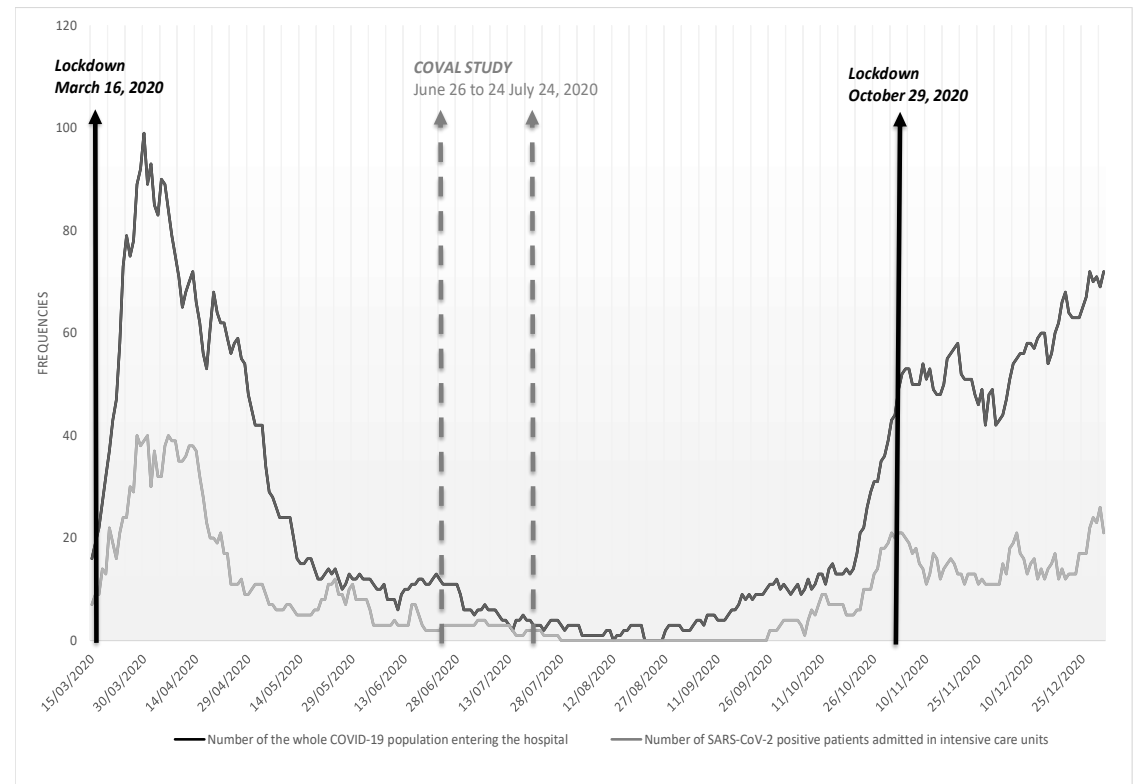
Anne GÉGOUT PETIT^{1†}; Hélène JEULIN^{2,3†*}; Karine LEGRAND⁴; Nicolas JAY⁵; Agathe BOCHNAKIAN⁴; Pierre VALLOIS¹; Evelyne SCHVOERER^{2,3 ††}; Francis GUILLEMIN^{4 ††}

Anticorps anti-SARS-CoV-2 IgT

IgA/IgG/IgM by using ELISA (SARS-CoV-2 Total Ab Assay, Bio-rad)

43/2006 participants séropositifs **2.1%**

- Aucun positif IgM anti-SARS-CoV-2 seulement
- 17 (39.5%) positifs anti-SARS-CoV-2 IgM et IgG
- 26 (60.5%) positifs anti-SARS-CoV-2 IgG seulement

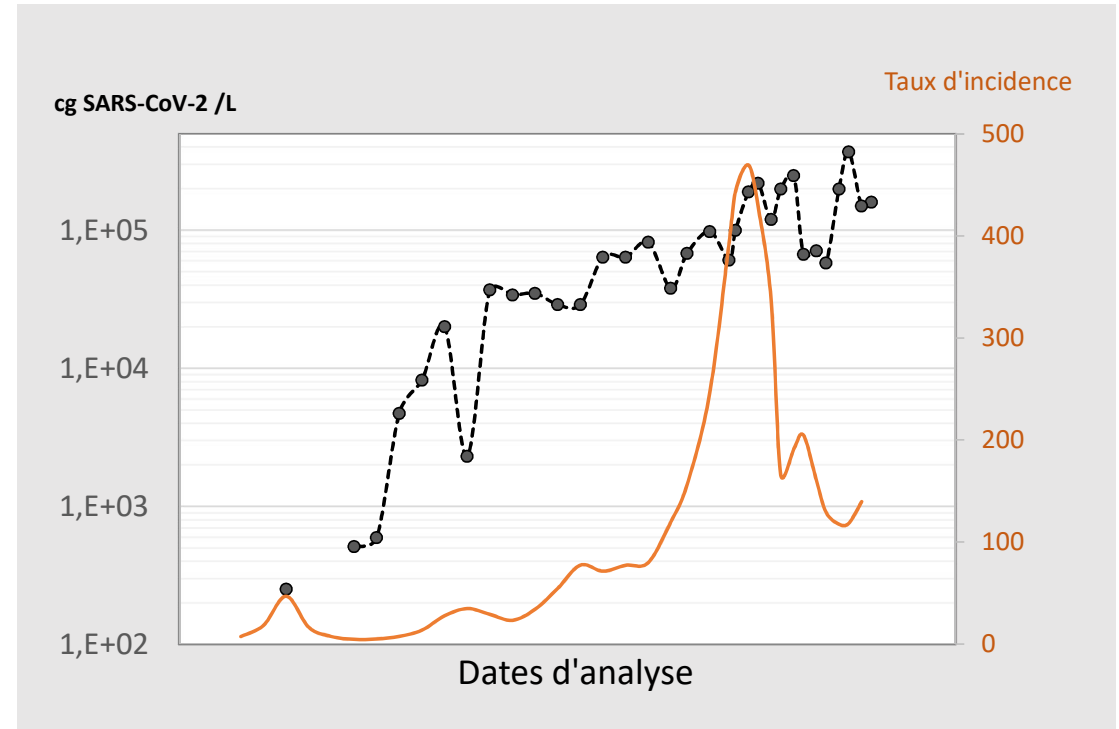
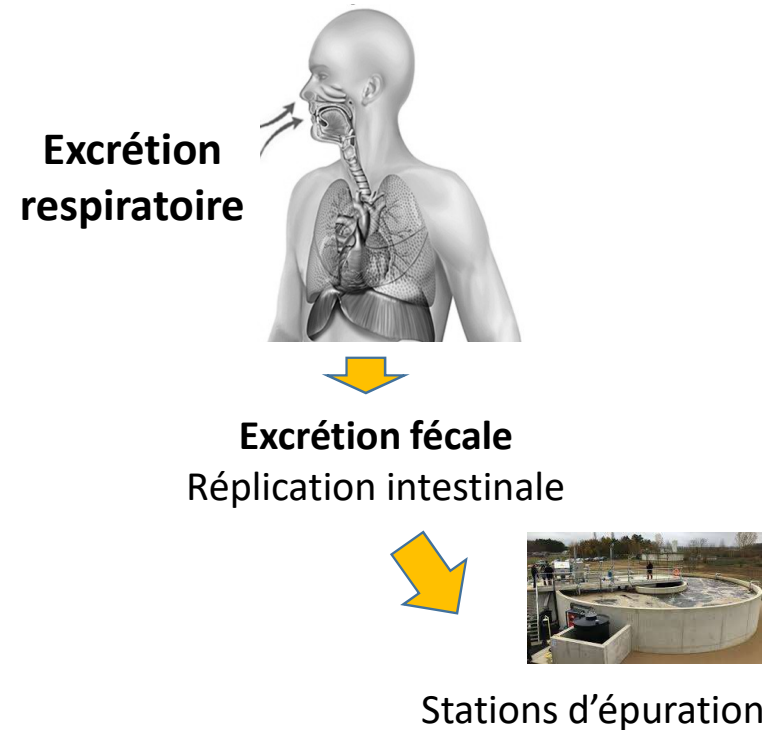


Présence environnementale du SARS-CoV-2



Diapositive Dr I Bertrand

Bertrand I et al, *Int J Hyg Environ Health* 2021



Analyse des eaux usées -> situation épidémiologique

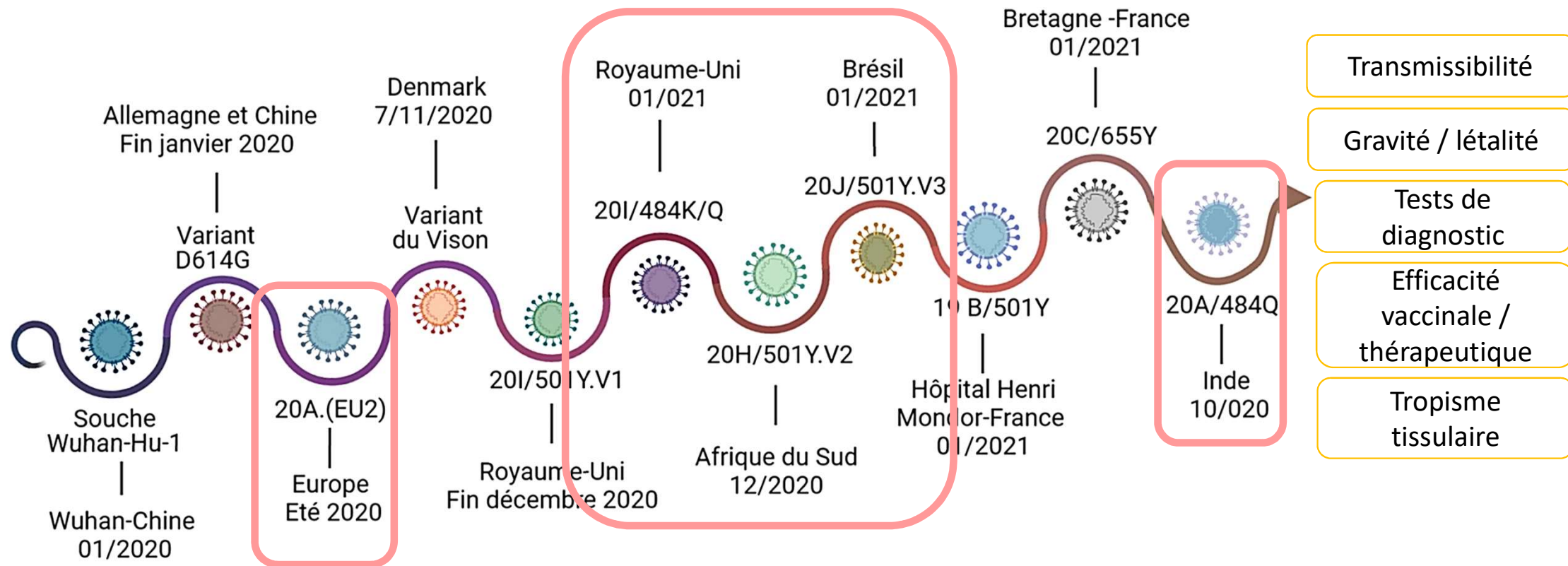
- **Evolution de l'épidémie et du virus ?**
- **Devenir des virus après leur excrétion fécale ?**
- **Outils d'évaluation du danger par rapport à la détection de génome viral ?**

Exemples de terrain, Virologie CHRU Nancy

Exemple 3 dans le réseau français de Virologues CHU

Problématique

Variabilité génétique → émergence de variants du SARS-CoV-2 et impact sur la circulation du virus et la maladie.



COVID 19 – Transmission/Pouvoir pathogène du Cov2

1^{ère} alerte Variabilité génomique virale et impact fonctionnel ? ‘bed ↔ bench’

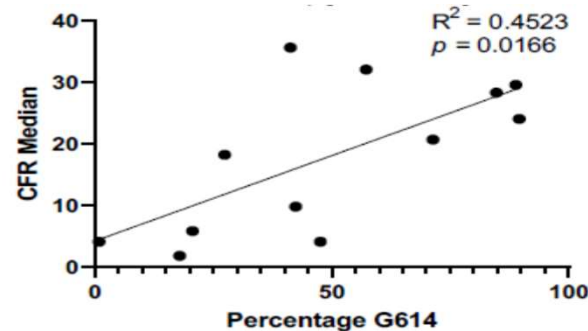
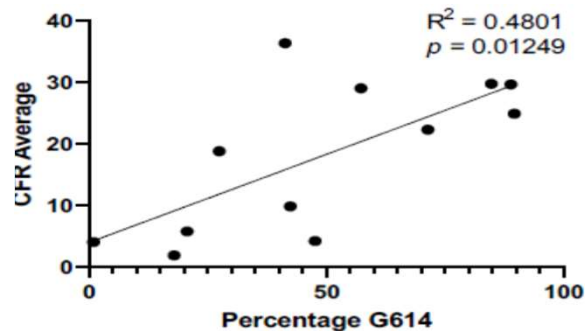
✓ Fitness viral et mutation D614G sur Spike

(IJCP, 2020)

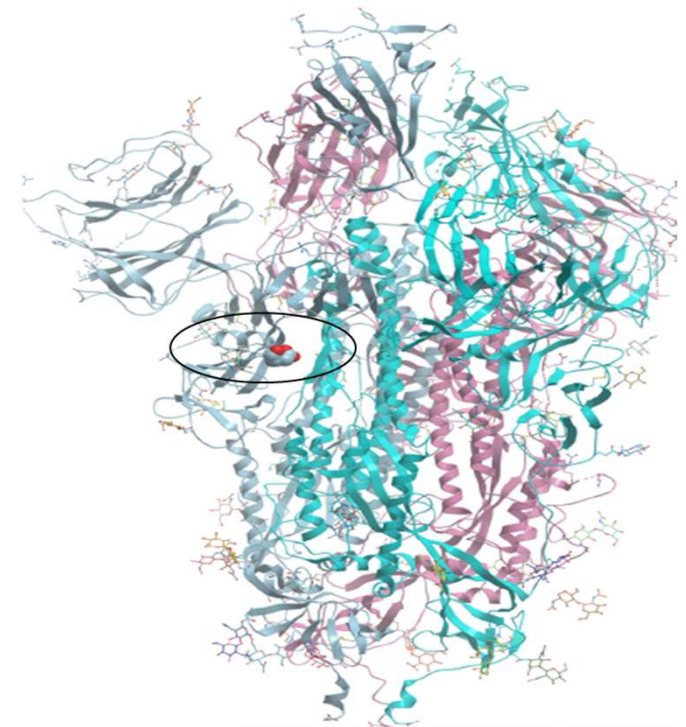
Glycine en 614 ⇒ Pouvoir pathogène viral

↓ production d’Acs neutralisants, RI délétère

Case Fatality Rate // pourcentage de virus avec Glycine en 614



Country	Percentage G614 Mutation	CFR Average	CFR Median
Belgium	88.89	29.73	29.57
France	84.82	29.83	28.32
China	0.89	4.07	4.07
Germany	47.62	4.25	4.08
Netherlands	57.30	29.07	32.07
Brazil	71.43	22.36	20.67
Canada	42.40	9.89	9.76
Italy	89.66	24.93	24.04
Australia	17.91	1.92	1.77
Japan	20.62	5.82	5.82
Spain	41.30	36.43	35.66
US	27.42	18.85	18.20



Variants SARS-CoV-2

Si RT-PCR SARS-CoV-2 positive



Recherche de mutations dans le gène Spike (S) – criblage **évolutif**

E484K-N501Y-del69/70-L452R (*ANRS-MIE Sondes Tib Mol Biol*)

Mutant	UK v1	Afr Sud	Brésil	Indien/ Delta
Del 69/70	x			
E484K	!	x	x	
N501Y	x	x	x	
L452R				x



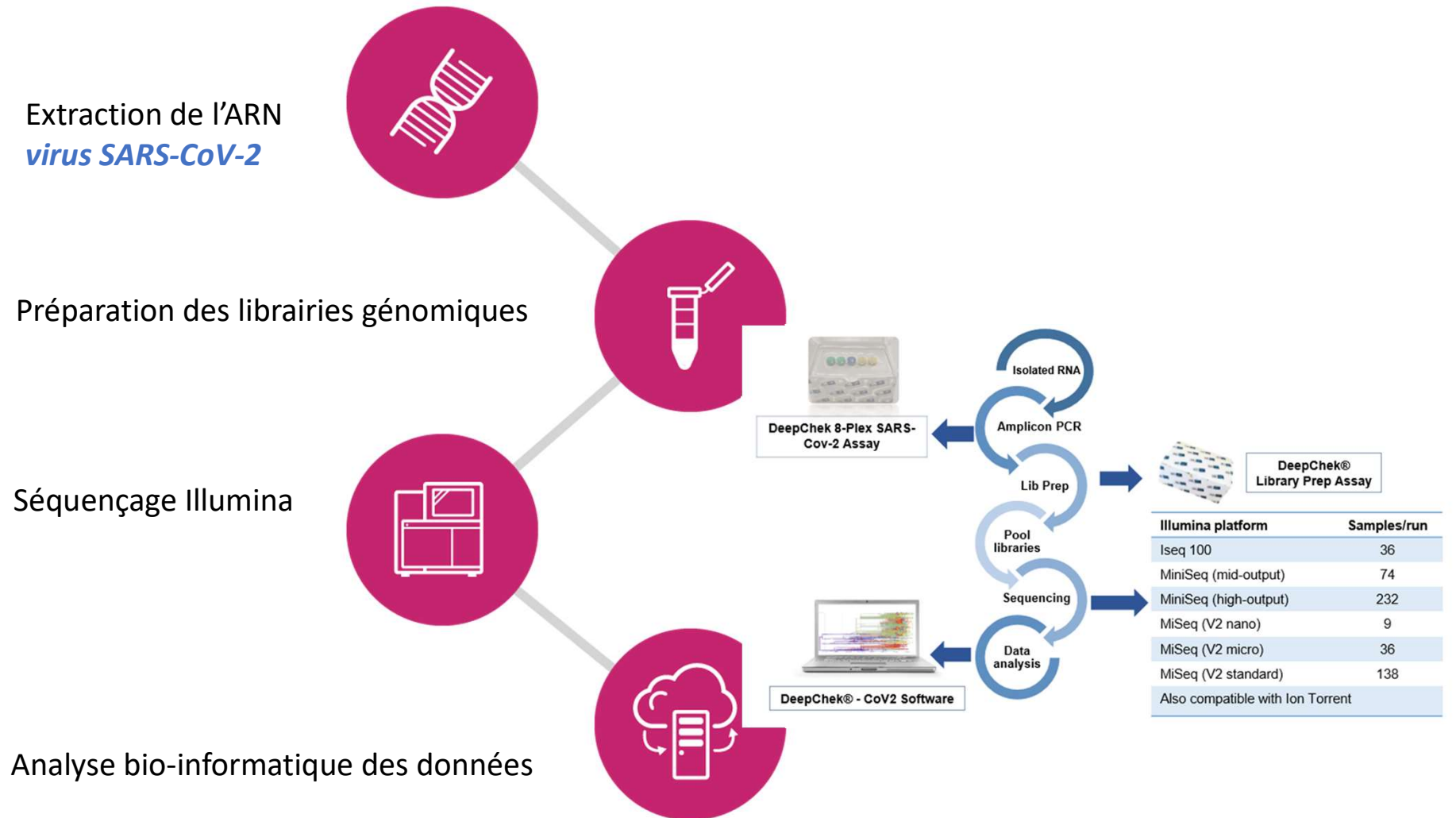
Pour exploration du génome viral

→ Séquençage du génome viral

Sanger S - WGS



Workflow pour séquençage SARS-CoV2



Stratégie de surveillance des variants SARS-CoV-2

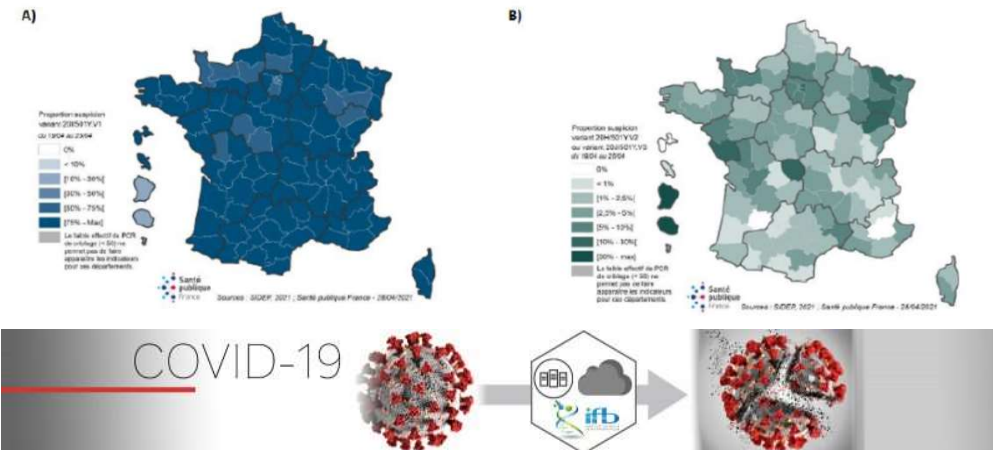
France



Flash#1	Sur prélèvements avec résultat de criblage suspectant la présence d'un variant	Prélèvements n=482	Laboratoires n=135	3,3% 20I/501Y.V1
Flash#2	Sur prélèvements avec résultat de criblage suspectant la présence d'un variant	1 528	234	13% 20I/501Y.V1
Flash#3	Sur sélection aléatoire	699	138	44,2% 20I/501Y.V1 6% 20H/501Y.V2 0,6% 20J/501Y.V3
Flash#4	Sur sélection aléatoire	1 656	107	68,6% 20I/501Y.V1 5,5% 20H/501Y.V2 0,1% 20J/501Y.V3
Flash#5	Sur sélection aléatoire	2 860	139	82,3% 20I/501Y.V1 6,4% 20H/501Y.V2 0,3% 20J/501Y.V3 0,1% 20I/484K
Flash#6	Sur sélection aléatoire	2 590	118	80,8% 20I/501Y.V1 7,8% 20H/501Y.V2 0,4% 20J/501Y.V3 0,5% 20I/484K

Santé publique France (SpF) et CNRs virus respiratoires

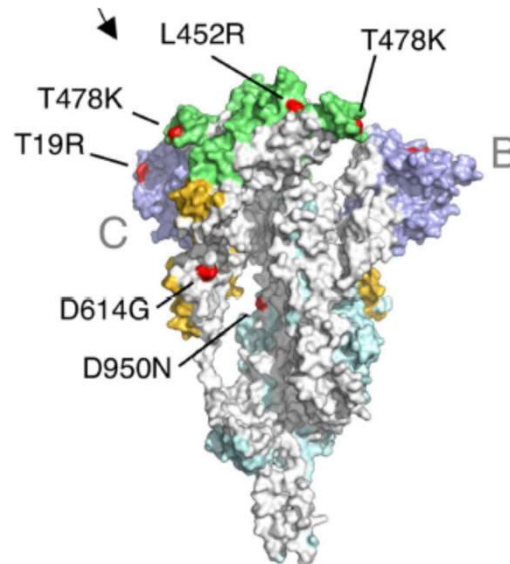
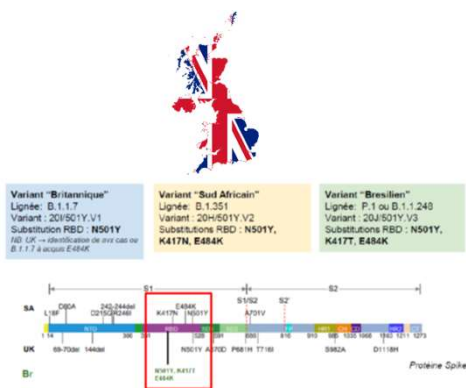
- Opérations Flash*, veille moléculaire
- Etudes locorégionales :
 - clusters, échappement immunitaire, COVID-19 sévères



VOC = 1^{ers} *variants of concern*

Août (2021)

Tendance variants détectés France :
mutations Delta majoritaires

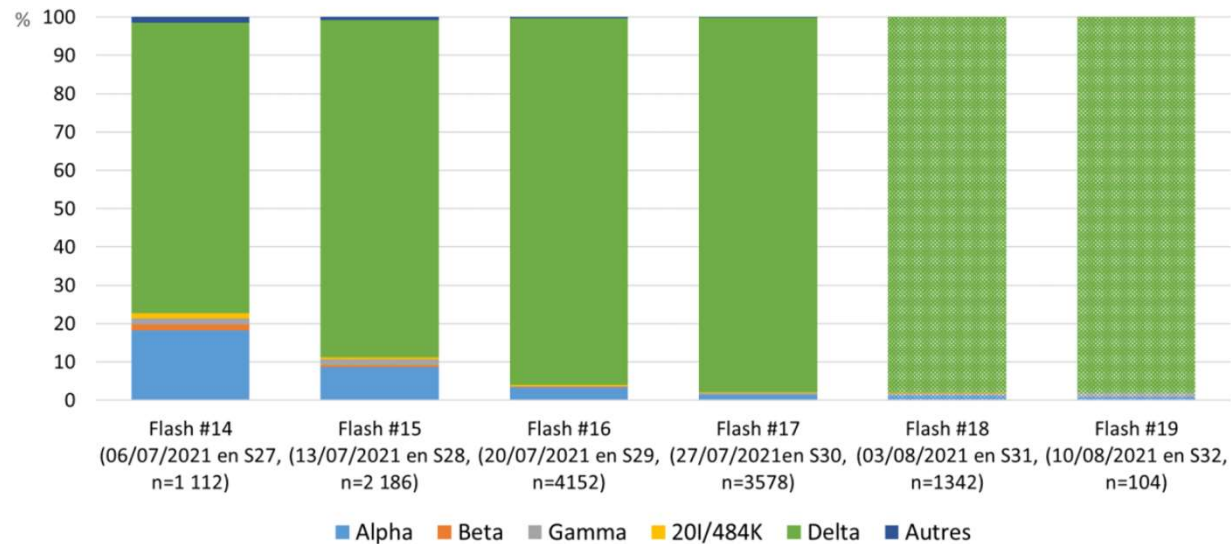


Delta SARS-CoV-2 variant, Planas et al, Nature 2021

Question de l'immunité anti-Delta ?

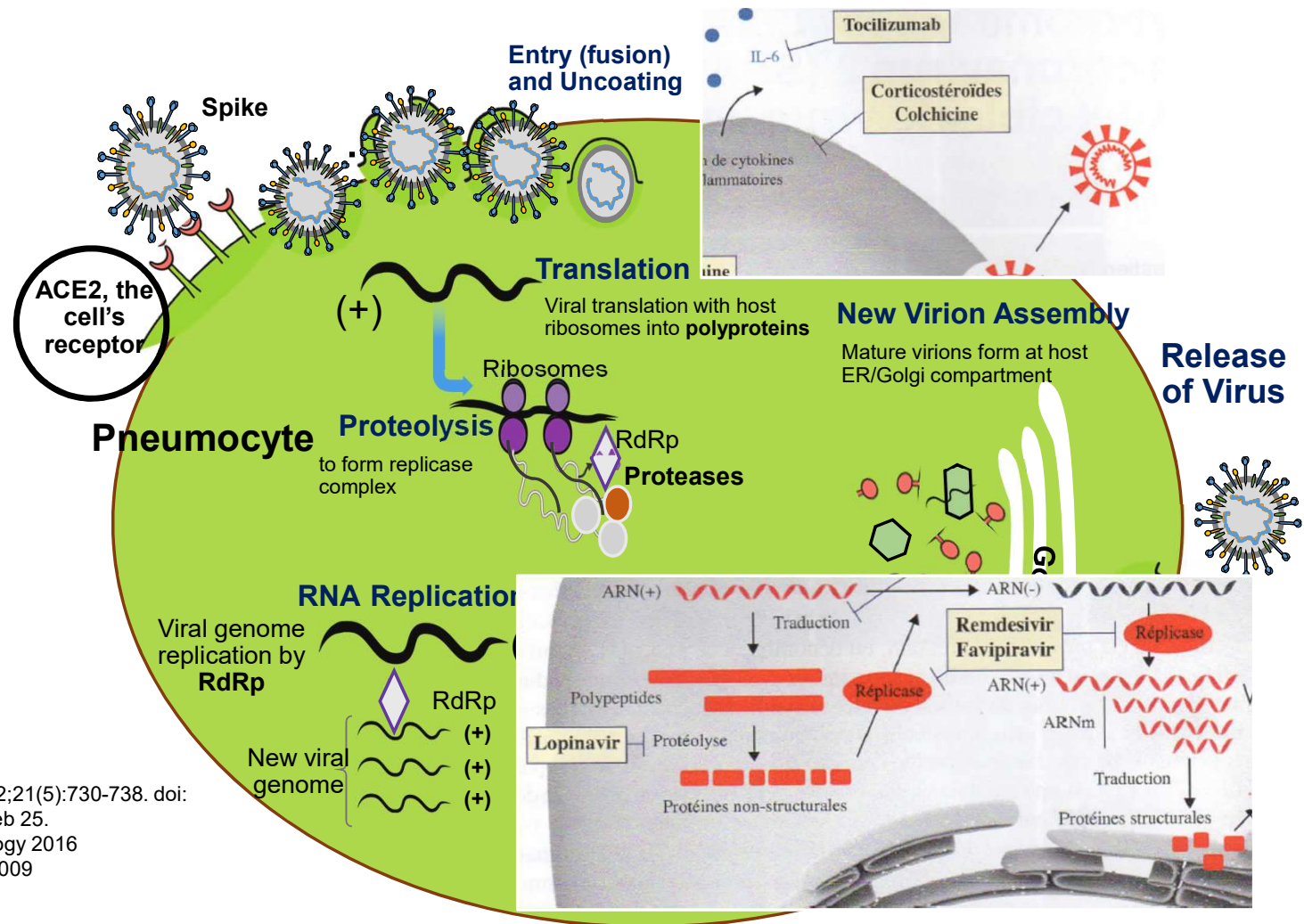
VOC = 1^{ers} *variants of concern*

Analyse de risques CNRs et SpF (dernier en date) ci-dessous



- *Prédominance du variant Delta Août 2021*
- *En cours : Question de l'immunité anti-Delta ?*

Multiplication du SARS-CoV-2 sur cellules



- Liu W, *et al.*, *ChemBiochem*. 2020 Mar 2;21(5):730-738. doi: 10.1002/cbic.202000047. Epub 2020 Feb 25.
- de Wit *et al.*, *Nature Reviews Microbiology* 2016
- Du *et al.*, *Nature review Microbiology*, 2009

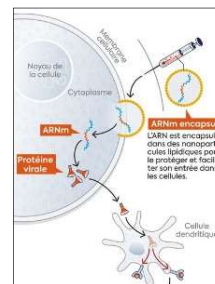
COVID 19 – Variabilité virale & questions

Potentiel de **mutation génomique** et **pouvoir adaptatif** du SARS-CoV-2 :

Homme, animaux, tropisme tissulaire, environnement

Pièges au diagnostic virologique

Vaccins* et traitements



Questions ?





Journée Scientifique 2021 Fédération Charles Hermite "COVID"

Using exoskeletons to assist medical staff during prone positioning of mechanically ventilated COVID-19 patients: a pilot study

Ivaldi, S.; Maurice, P.; Gomez, W.; Theurel, J.; Wioland, L.;
Atain-Kouadio, J.-J.; Claudon, L.; Hani, H.; Kimmoun, A.; Sellal, J.-M.;
Levy, B.; Paysant, J.; Malikov, S.; Chenuel, B.; Settembre, N.



Horizon 2020
European Union funding
for Research & Innovation

Prone Positioning in the ICU during COVID-19

- 15% of patients with SARS-CoV-2 infection developed severe hypoxemia eventually leading to acute respiratory distress syndrome (ARDS) and required ventilatory support
- Prone Positioning (PP) is used to improve oxygenation in patients with mechanical ventilatory support
- At the University Hospital of Nancy, in the first 10 days of COVID-19 outbreak, in one ICU department they executed the number of PP they usually do in one year (116). From 23/03 to 23/04 they executed 367 PP in a single department.
The doctors called that an “industrial situation”.

[Yang et al, Lancet Respir Med 2020; Grasselli et al, JAMA 2020]

[Guérin et al, N Engl J Med 2013]

[Kimmoun et al, Critical Care 2020]

Prone Positioning



Risk of extubation



Repositioning patient on the bed



Turning patient on the bed

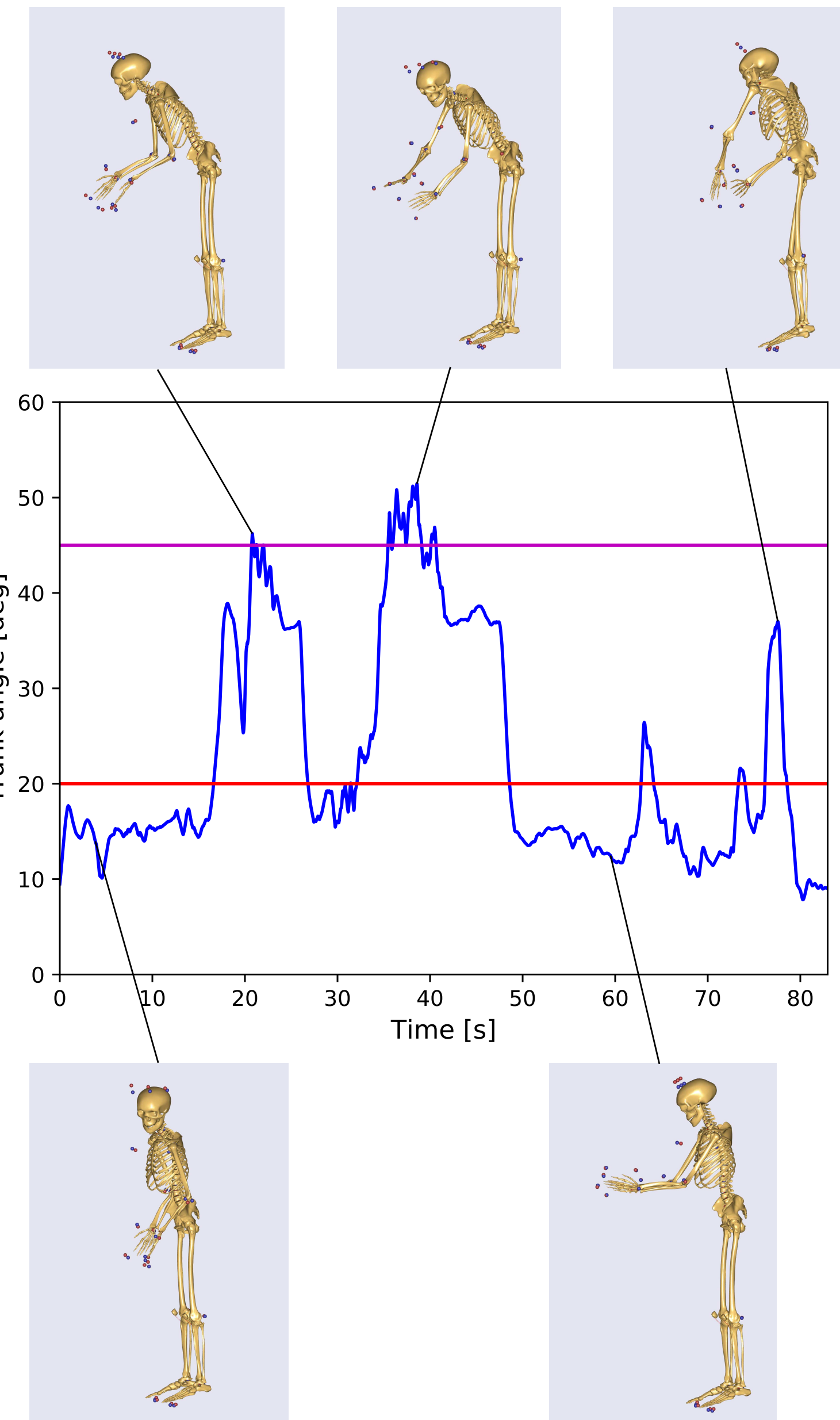
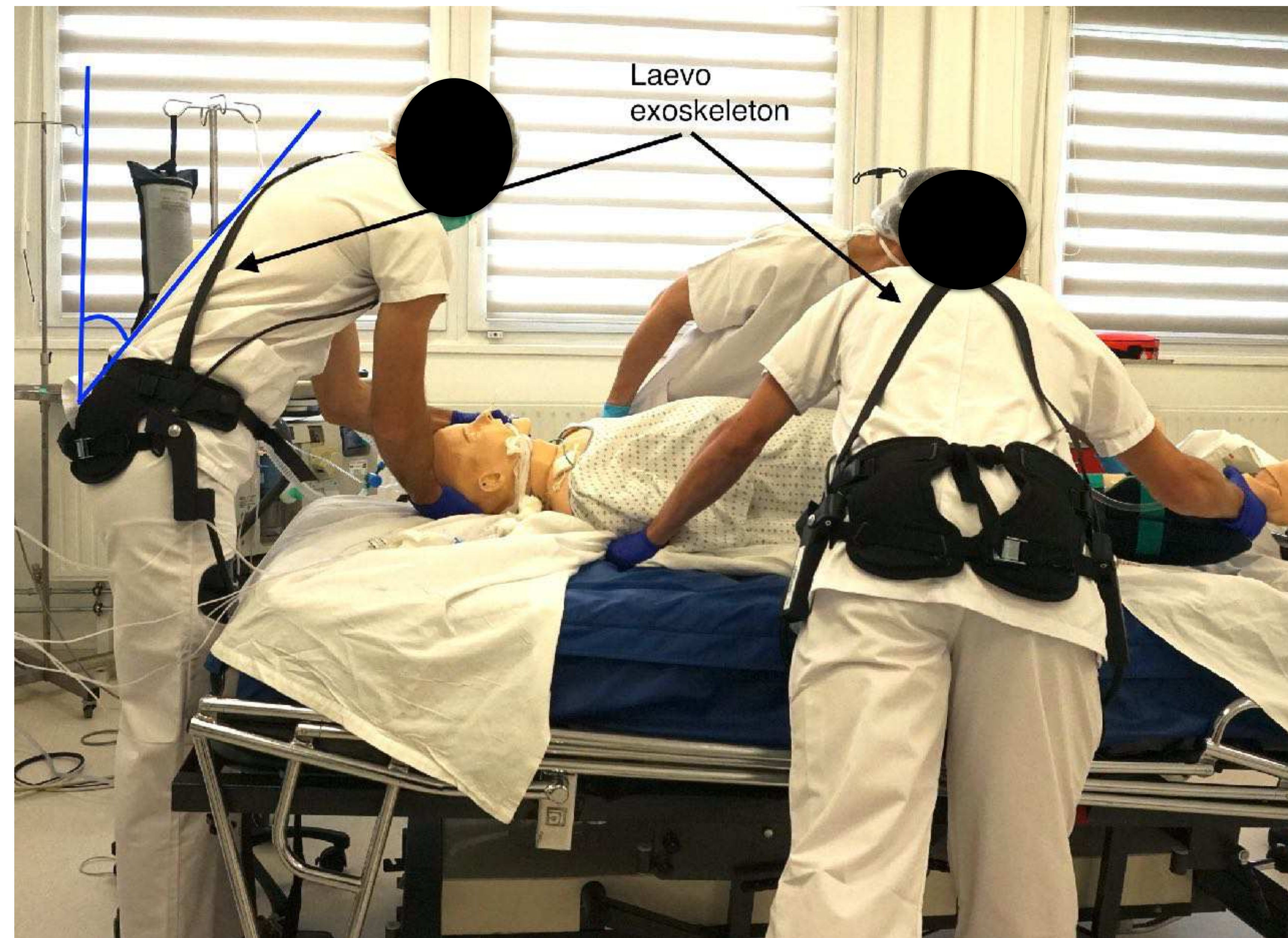


Positioning pillows, check “cables”

Innovation Un exosquelette pour aider les soignants

19/20 Lorraine

Why exoskeletons can help



Not only back pain: MSDs

60 %
European workers
experienced
musculoskeletal
diseases (MSDs) ¹

3.3 %
European GDP
spent on
occupational
Injuries ³

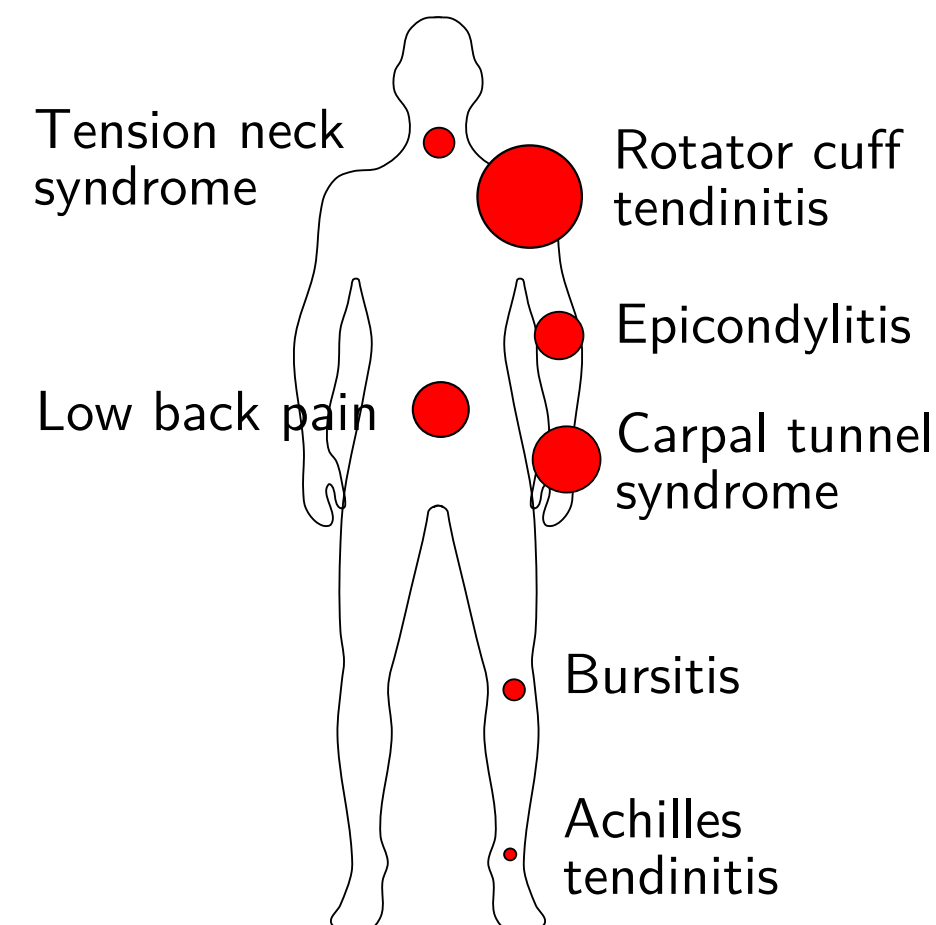
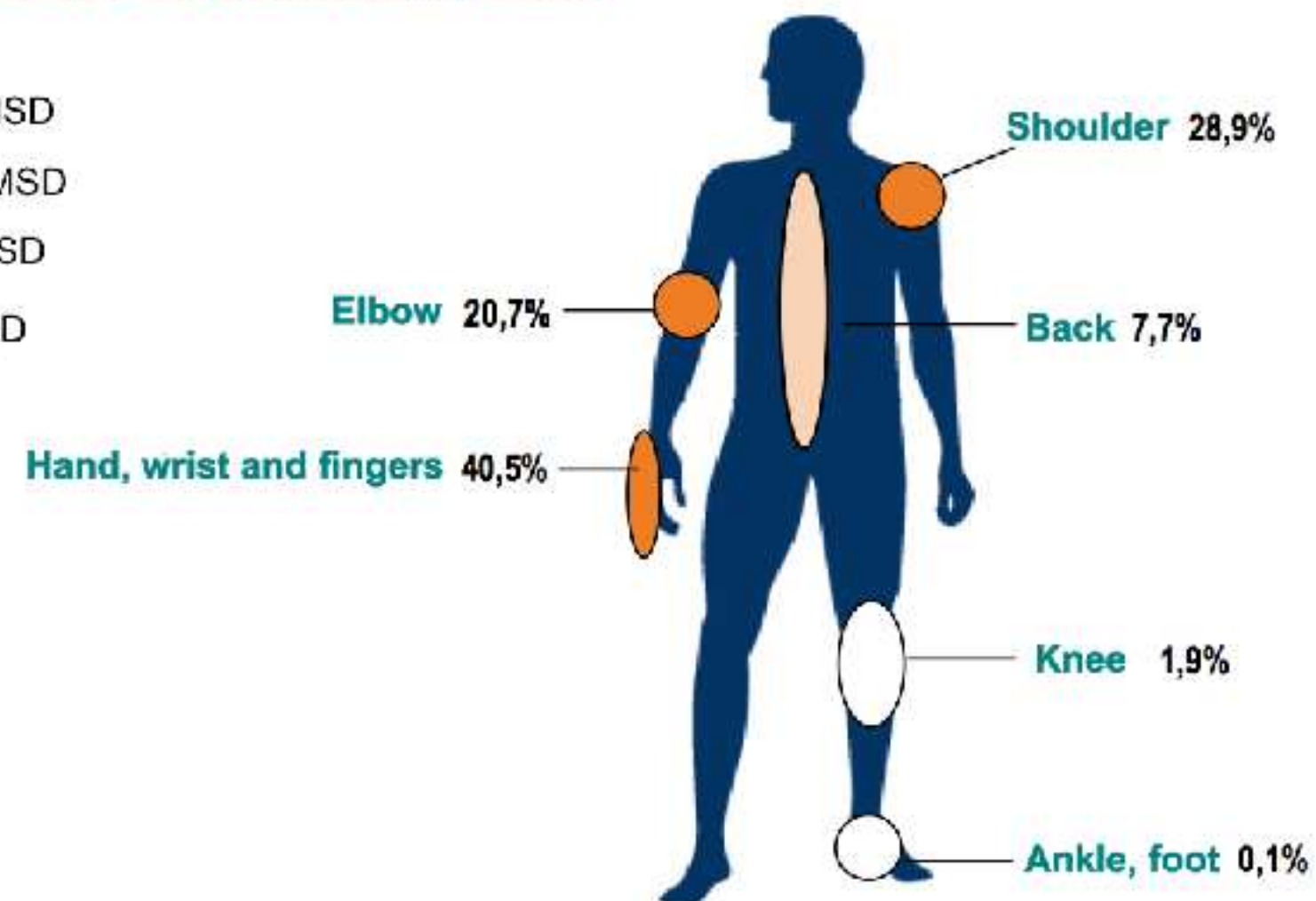
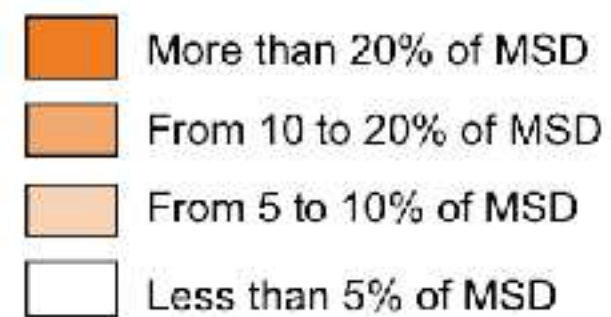
120 M
people
with chronic MSD
condition ²



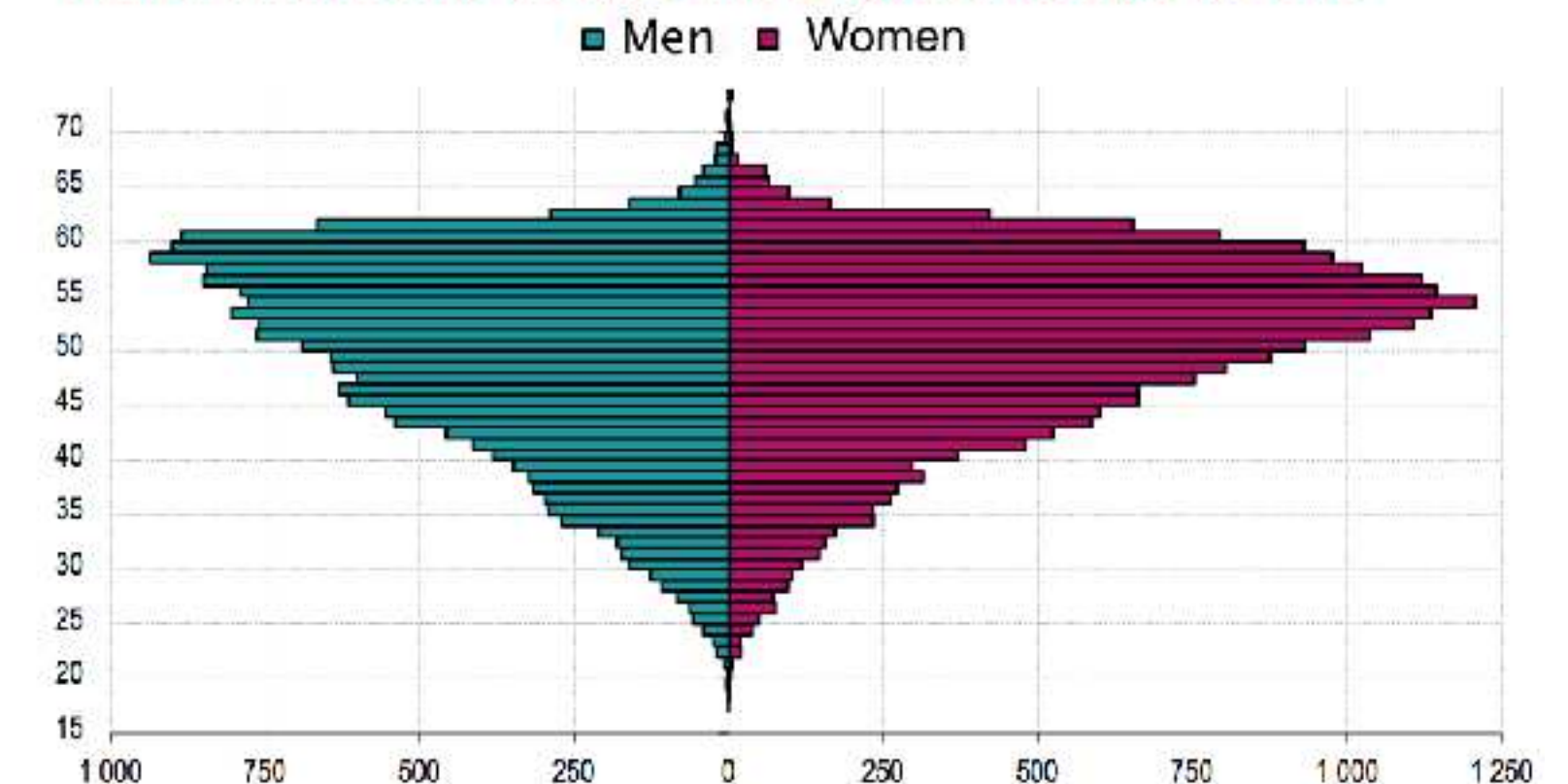
Main biomechanics risk factors:

- Awkward postures
- High efforts
- Static work
- Repetitive actions

Repartition of MSD syndromes per body part in 2014 (France)



Repartition of new victims of MSD by sex and age in 2014



Assisting physicians performing Prone Positioning in the ICU during COVID-19: timeline

- March 30th, 2020: Hospital of Nancy facing the peak of pandemic COVID-19 contacts us to receive help in the ICU, to assist the medical staff with Prone Positioning
- April 7th, 2020: pilot study in Hospital Simulation Center
- April 10th, 2020: 2 exoskeletons Laevo v1 used in ICU
- October 20th, 2020: 4 exoskeletons (2x Laevo v1, 2x Laevo v2.5) used in ICU
- January 25th, 2021: switching to an individual use of the exoskeletons (from a shared tool to individual tool)

Assisting physicians performing Prone Positioning in the ICU during COVID-19: timeline

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Pilot study



Candidates (what we had)

Corfor



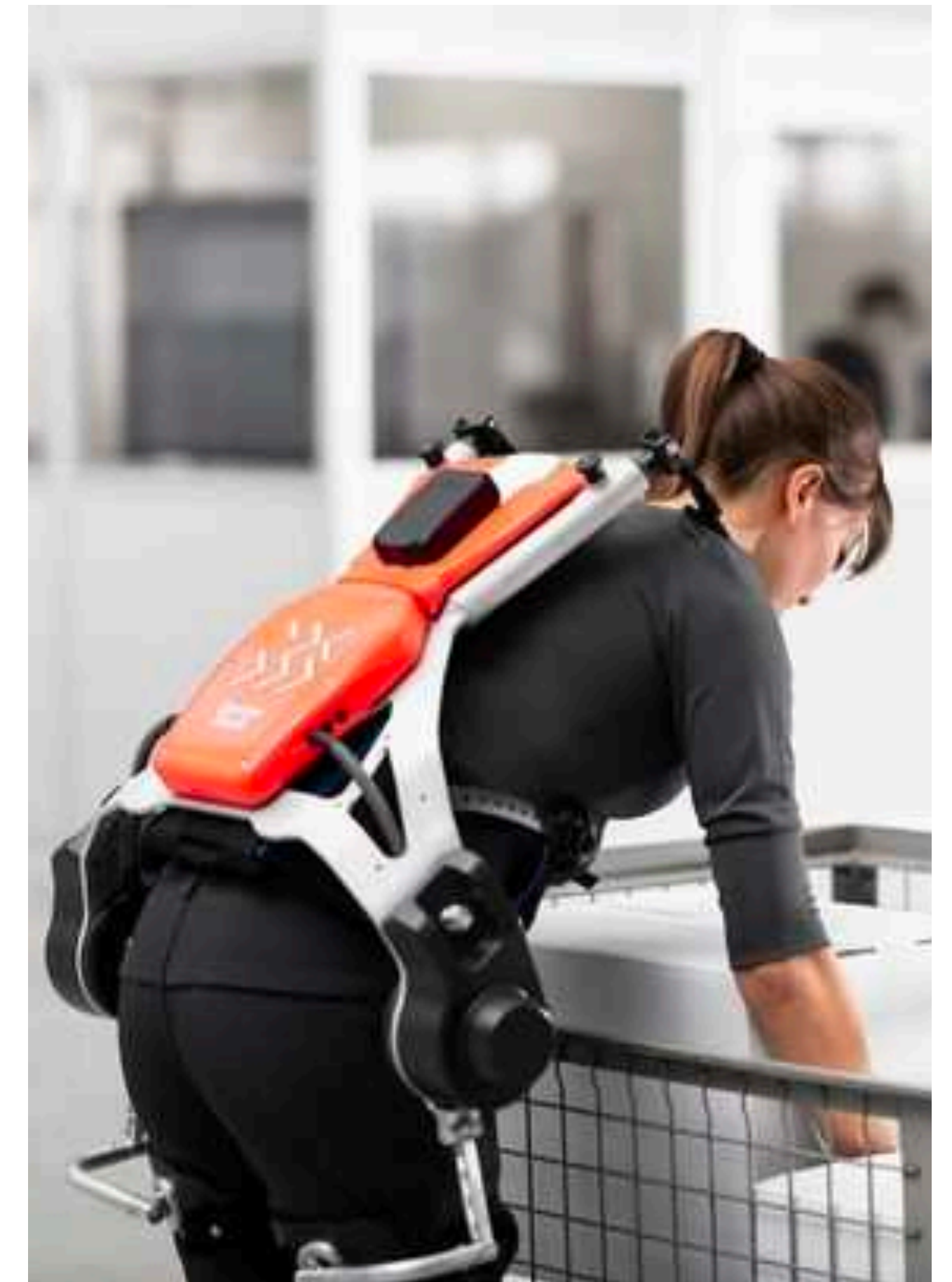
LAEVO



BackX



CrayX

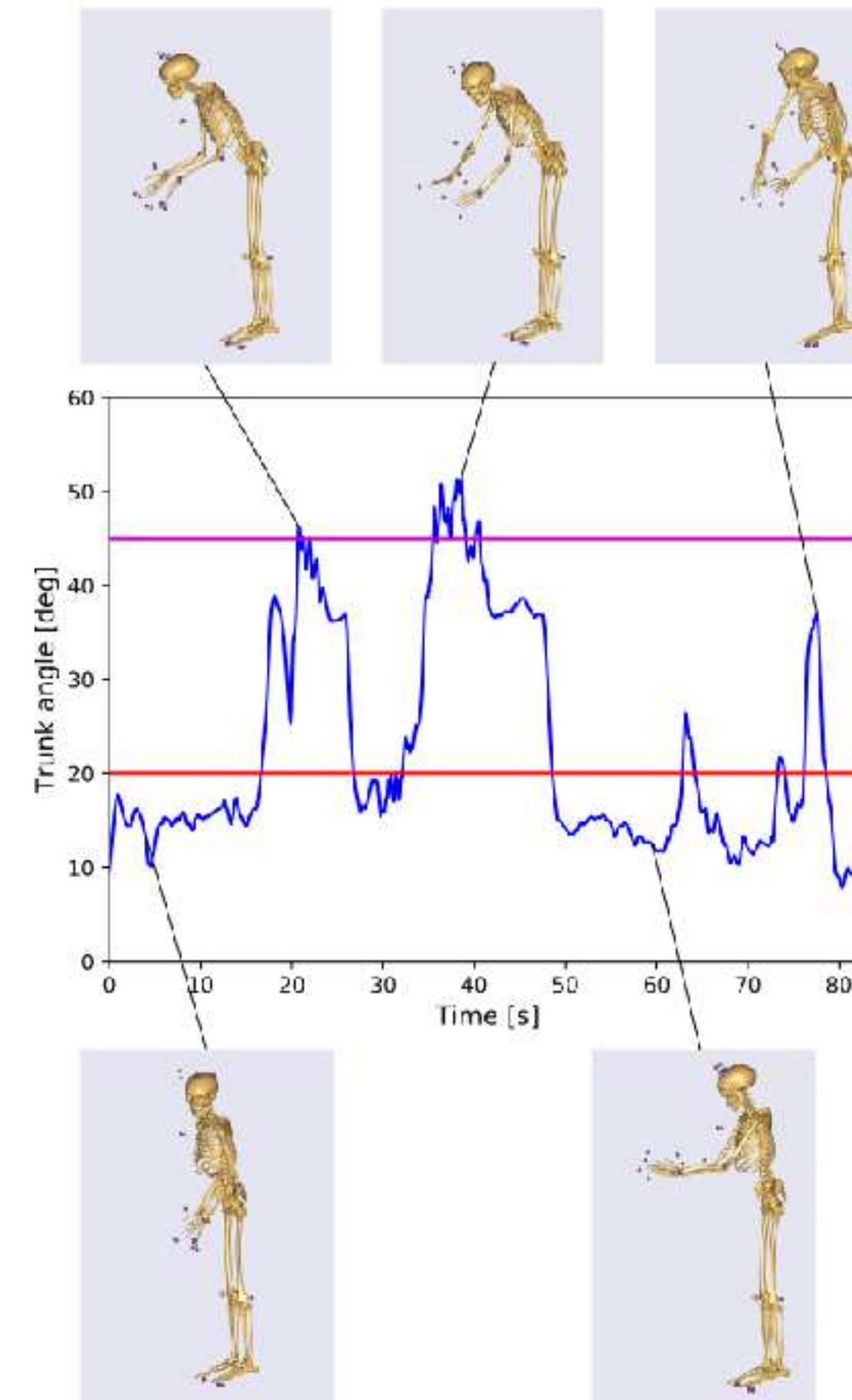


Kinematics analysis

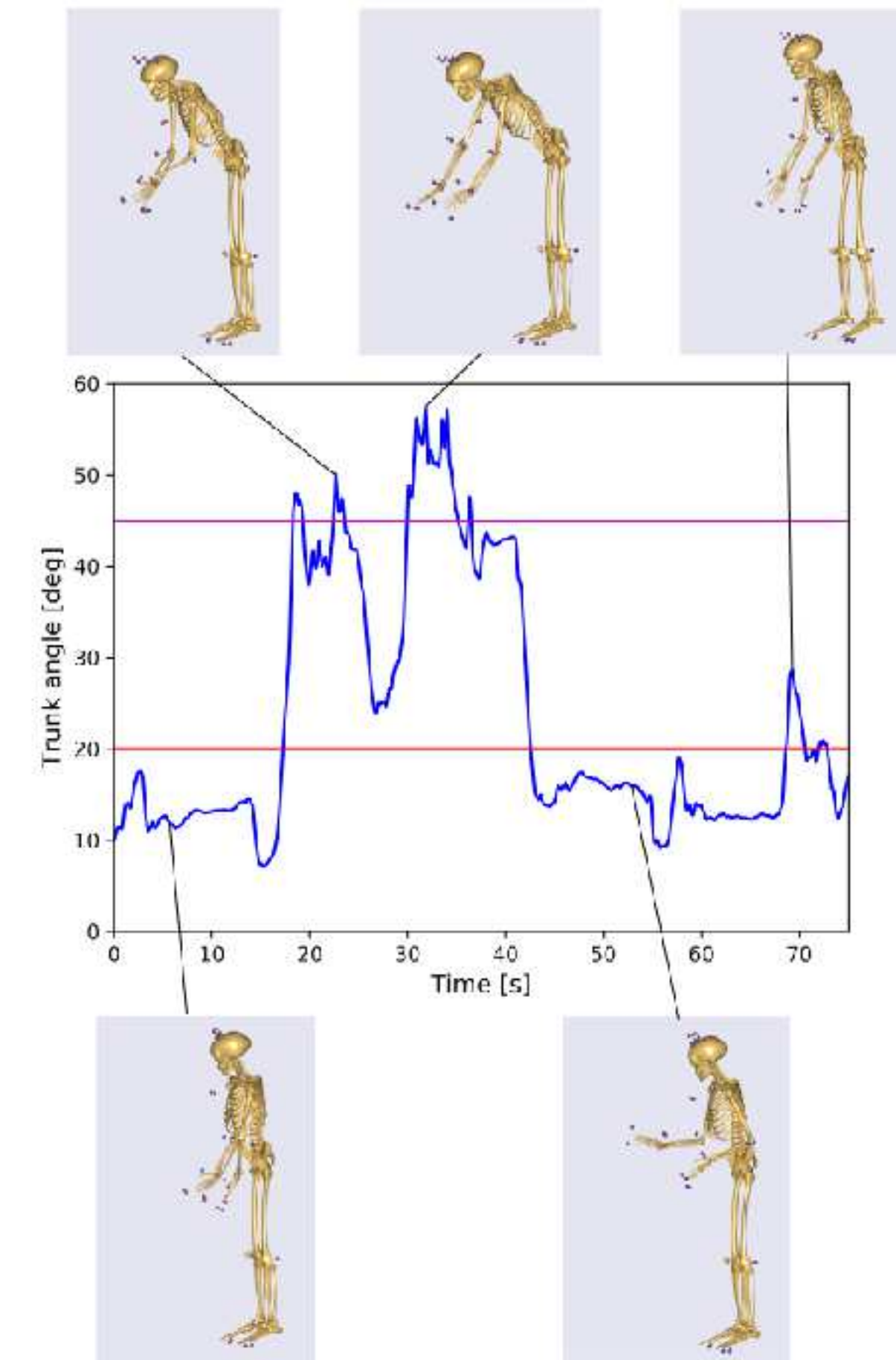


Xsens MVN suit

Without Exoskeleton

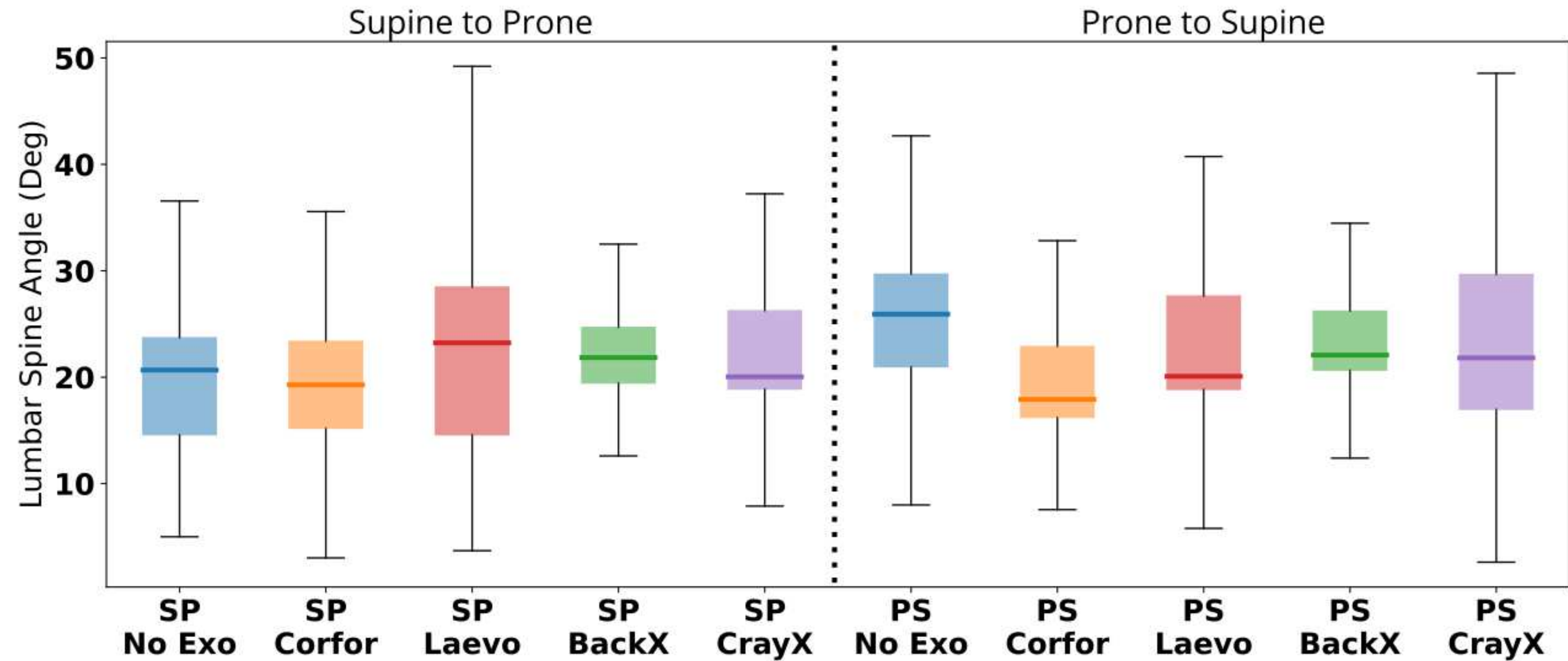


With Exoskeleton (Laevo)



(Anybody software for biomechanics)

Kinematics analysis



Selecting the candidate to use in the ICU

	Corfor	Laevo	BackX	CrayX
Physical effort	3	4	4	4
Perceived safety & comfort	4.37±0.7	4.5±0.5	4.0±1.1	3.8±1.0
Installation	3.5±2.1	4.5±0.7	1.5±0.7	1.5±0.7
Intention to use	3.0±0.0	4.5±0.7	2.5±0.7	3.0±0.0
Notes	Not helpful	Good compromise, freedom of movement	Hinders motions of the arms	Too cumbersome to wear, difficult to find a suitable setting

Settembre, N.; Maurice, P.; Paysant, J.; Theurel, J.; Claudon, L.; Kimmoun, A.; Levy, B.; Chenuel, B.; Ivaldi, S. (2020)
The use of exoskeletons to help with prone positioning in the intensive care unit during COVID-19.
 Annals of Physical and Rehabilitation Medicine. <https://doi.org/10.1016/j.rehab.2020.05.004>

Pilot study

- At the Hospital Simulation Center:
 - Compared 4 solutions => selected the LAEVO
 - Physiological evaluation of LAEVO

Letter to the editor

**The use of exoskeletons to help with prone positioning
in the intensive care unit during COVID-19**

ARTICLE INFO

Keywords:

COVID-19

Exoskeleton

Prone position

Ergonomy

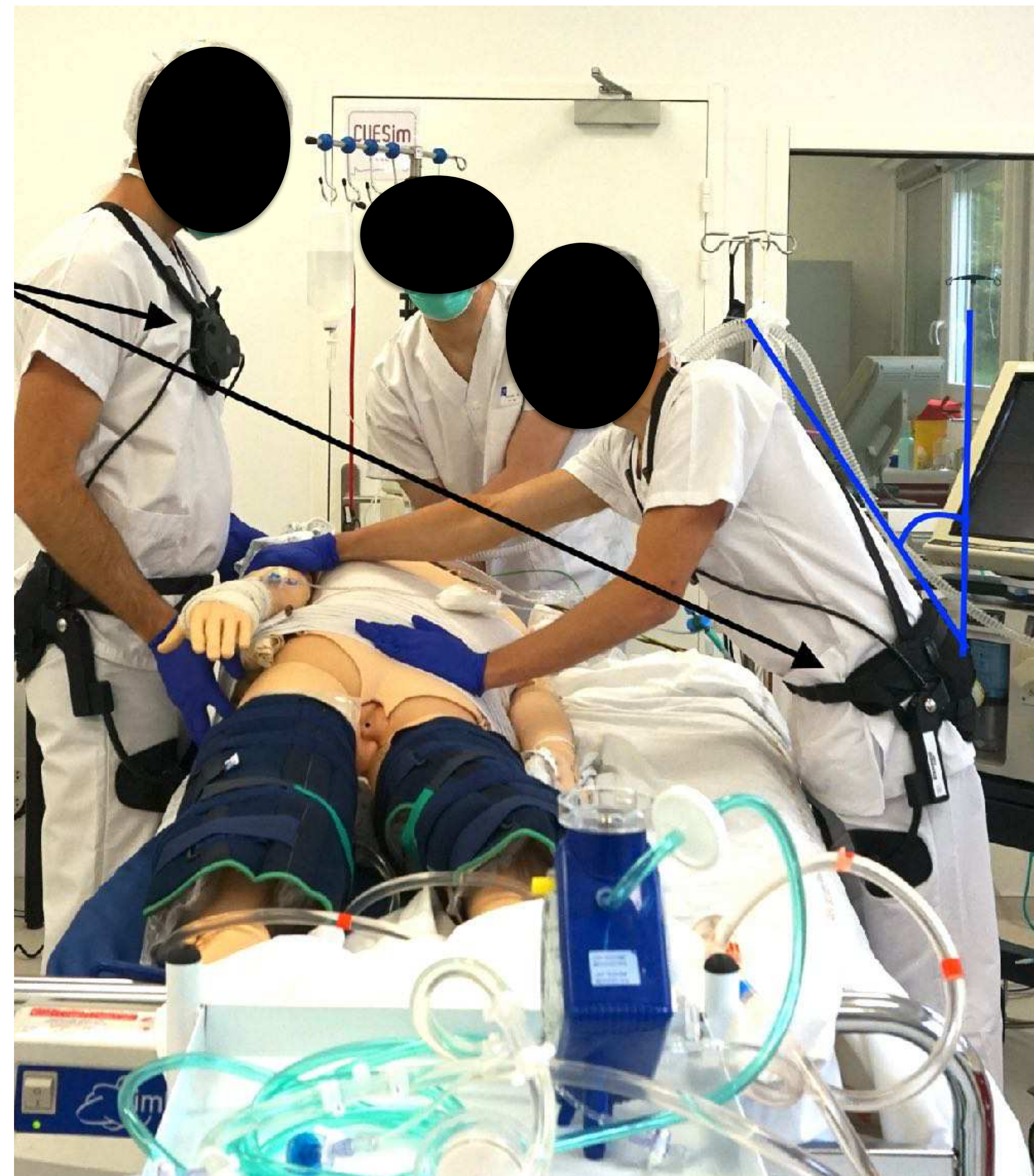
Simulation

Intensive care unit

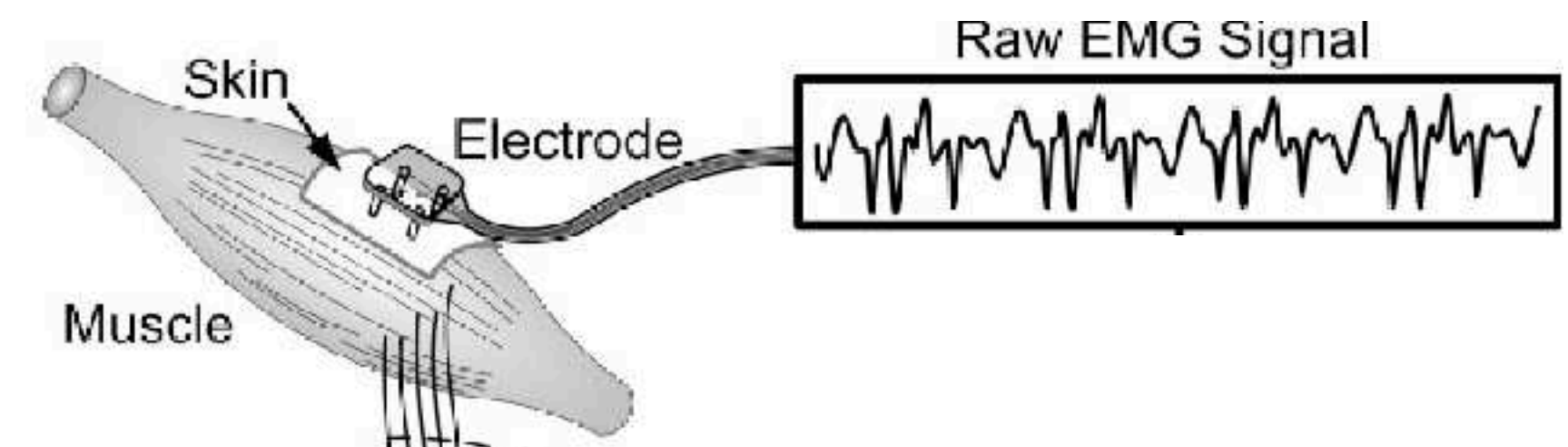
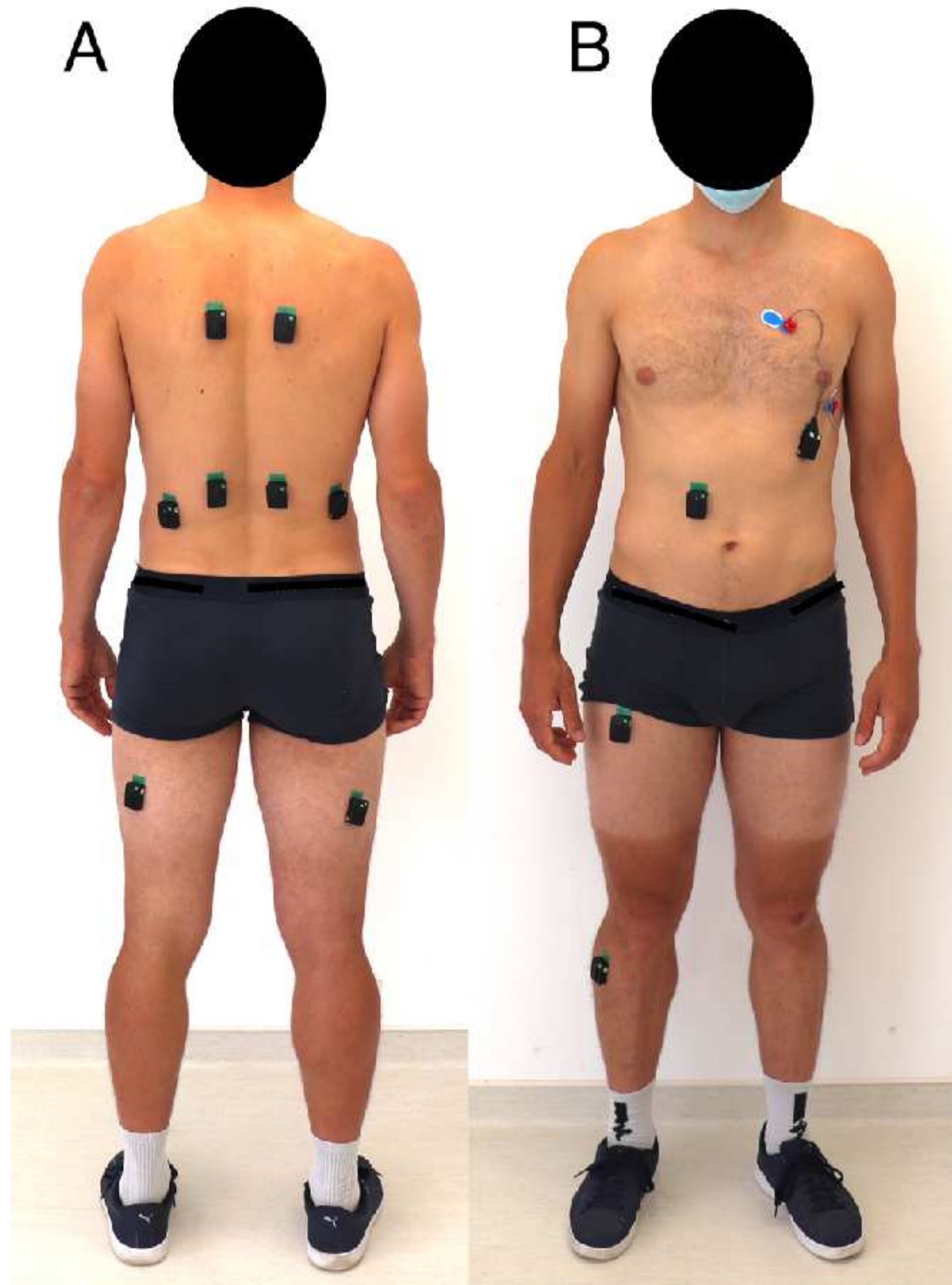
Dear Editor,

Many hospitals radically changed their organization during the COVID-19 pandemic to face the capacity and resources limitations of intensive care units (ICUs). Scheduled activities were suddenly stopped, allowing for massive reassignments of volunteers. At the University Hospital of Nancy, 15 specific medical teams (75 volunteers) were created to cope with the large number of patients with severe COVID-19-related acute respiratory distress syndrome (ARDS) and requiring prone positioning (PP).

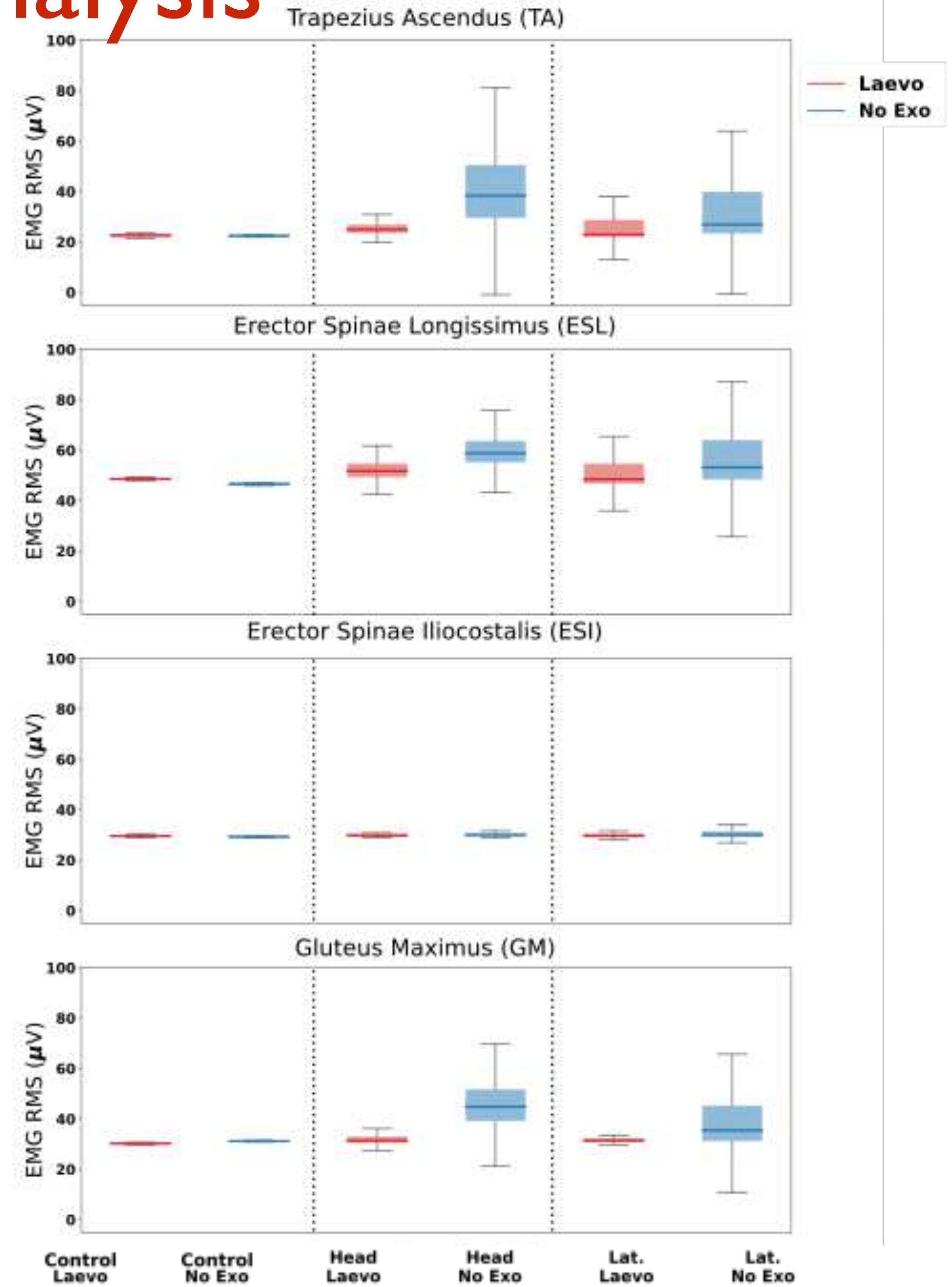
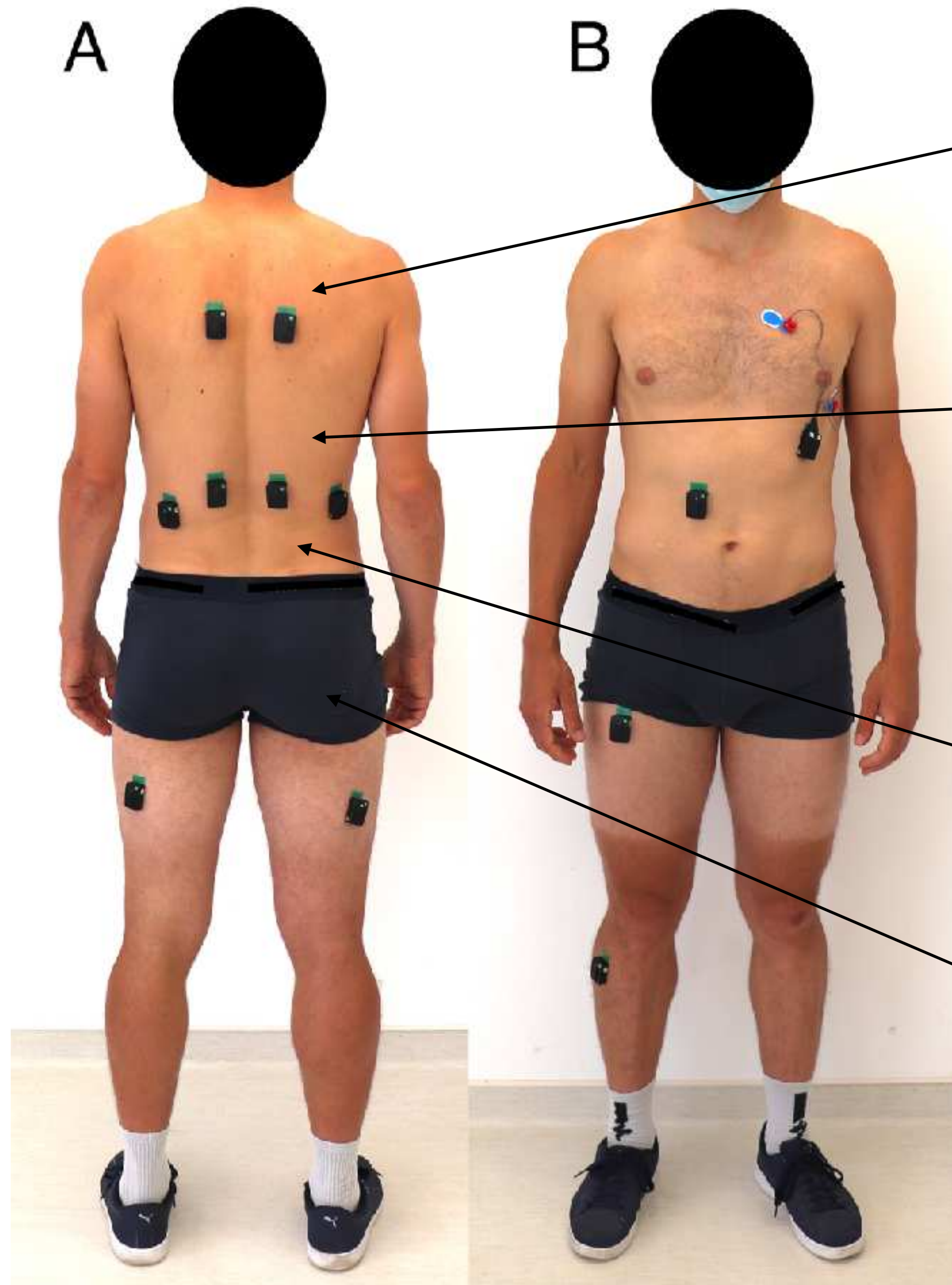
The PP procedure is of crucial importance for severe ARDS patients [1], especially when related to COVID-19 [2]. Although turning a patient into the prone position is not an invasive



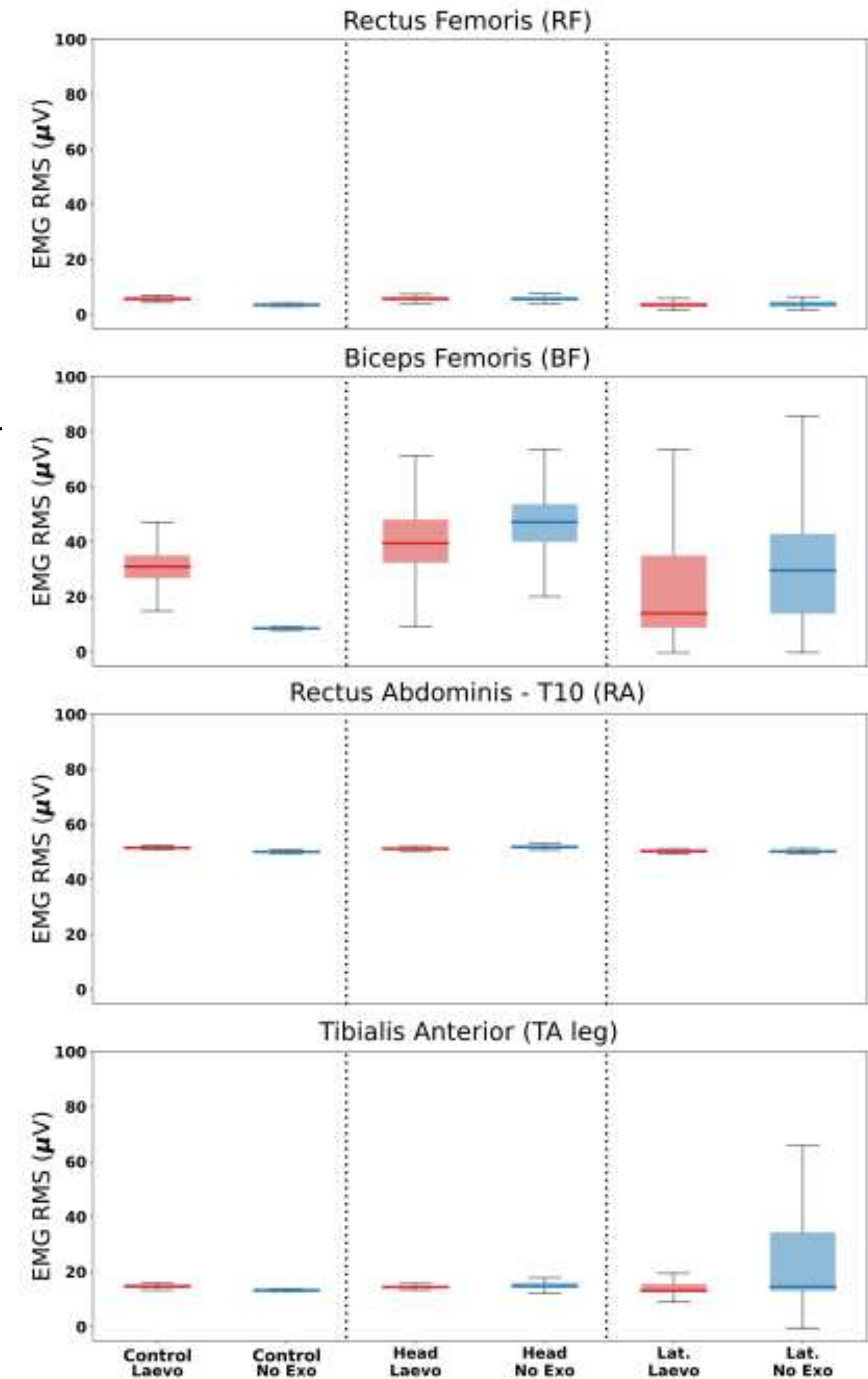
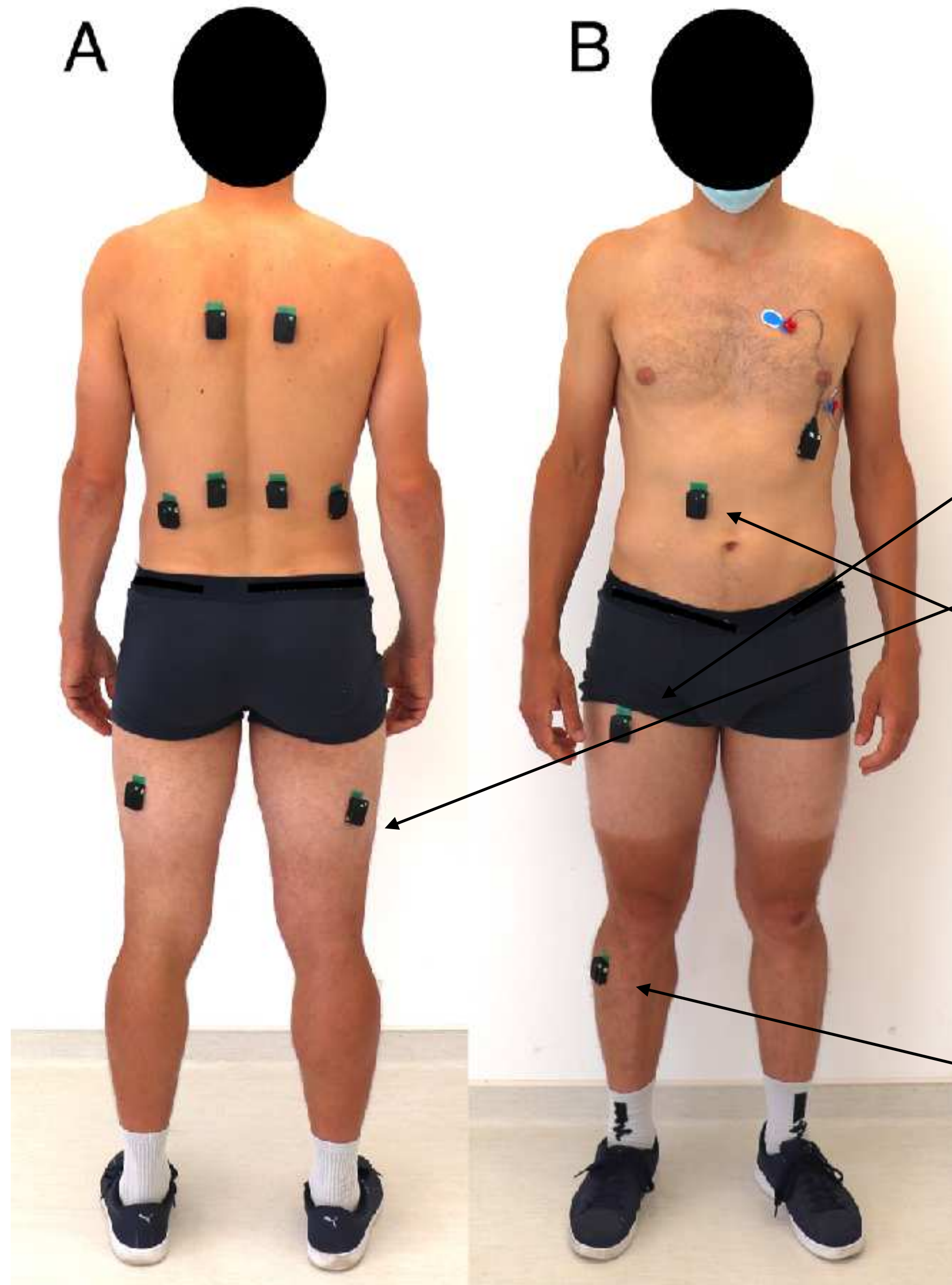
EMG analysis



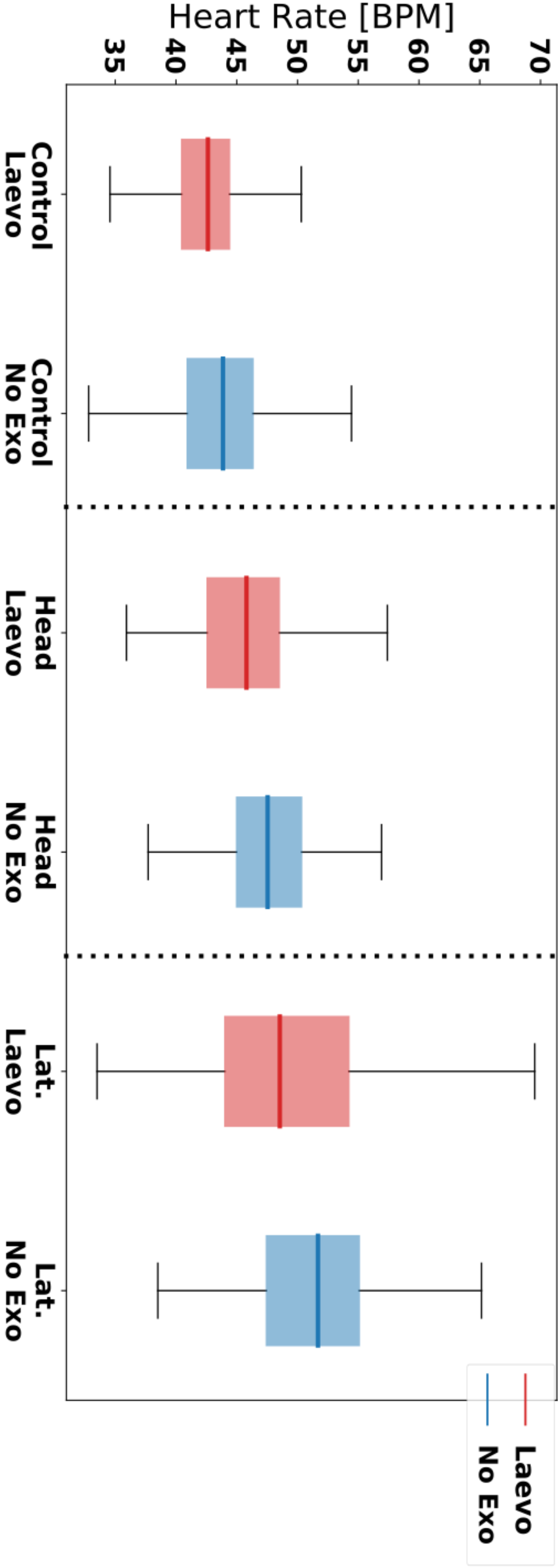
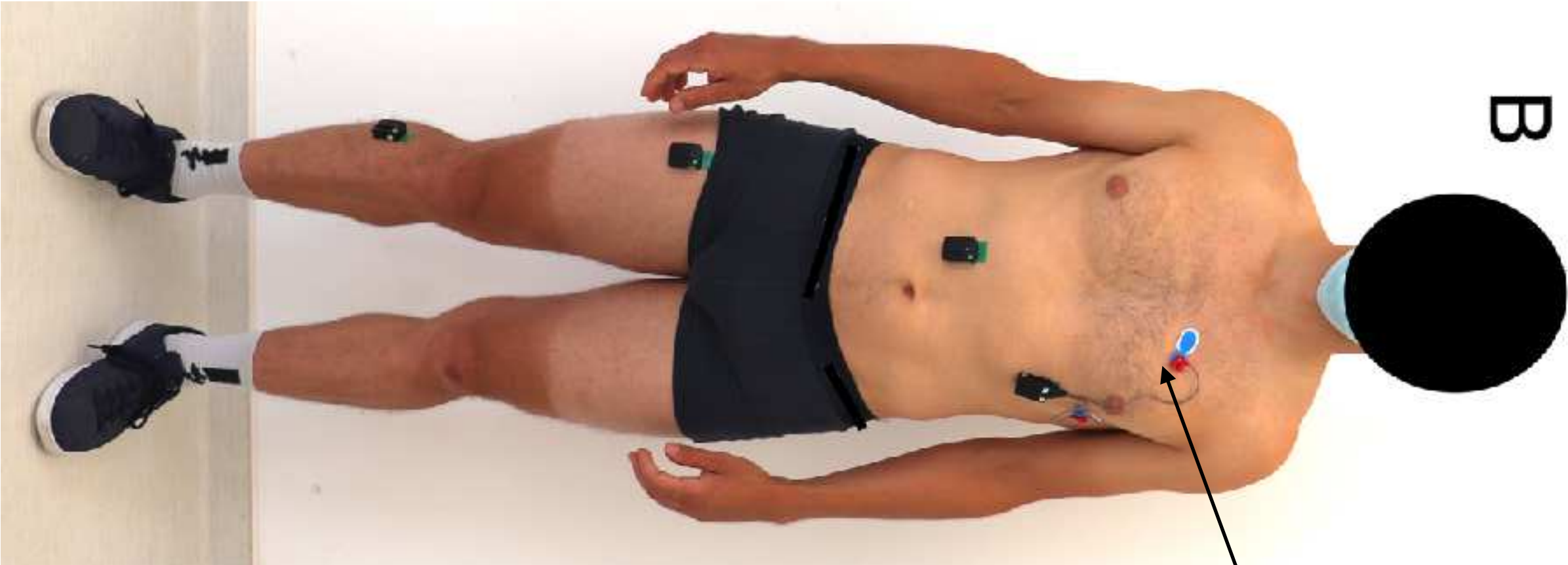
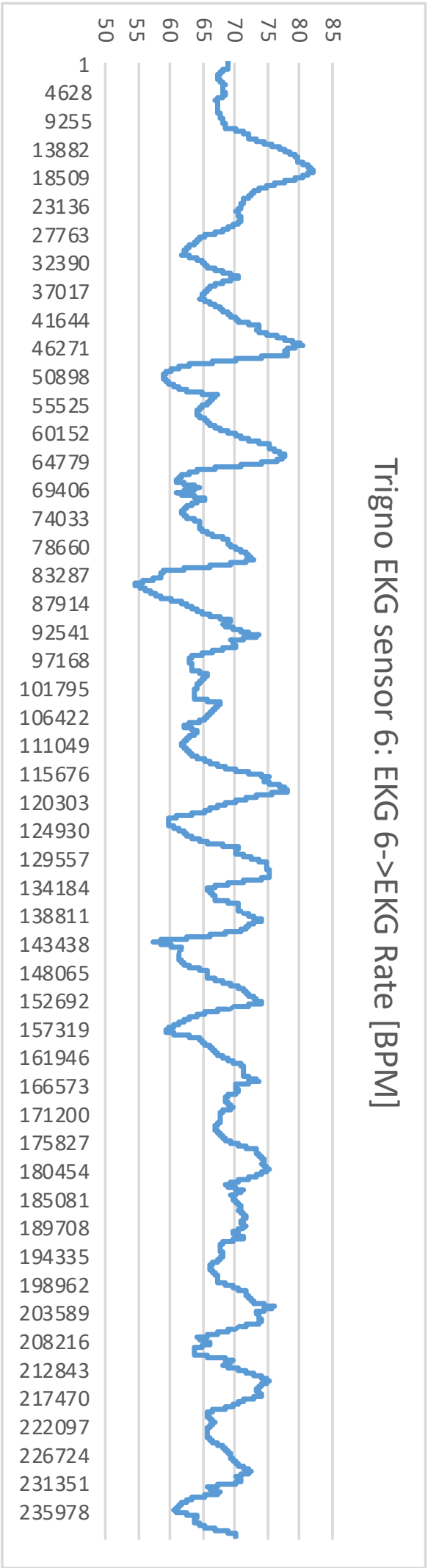
EMG analysis



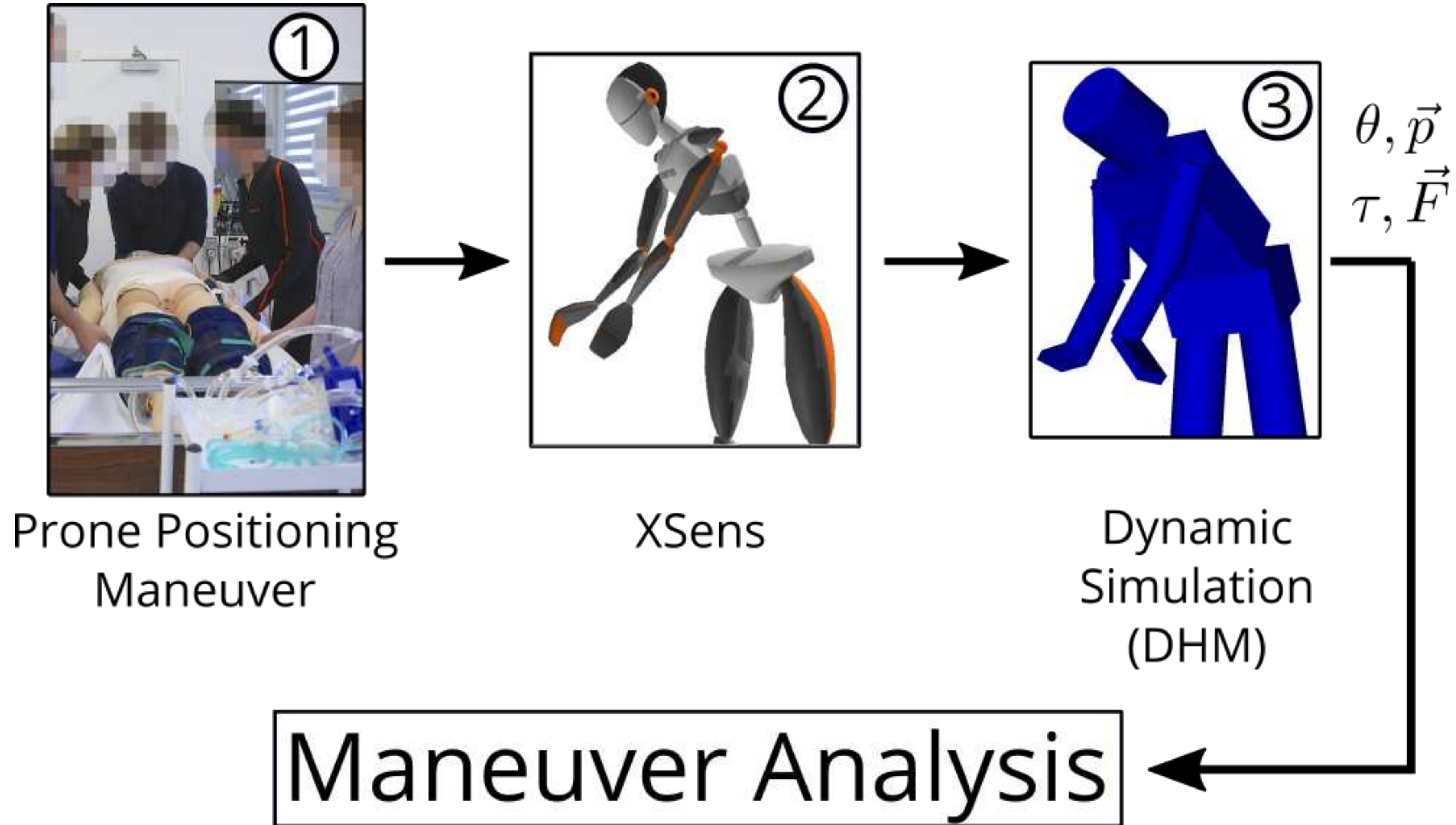
EMG analysis



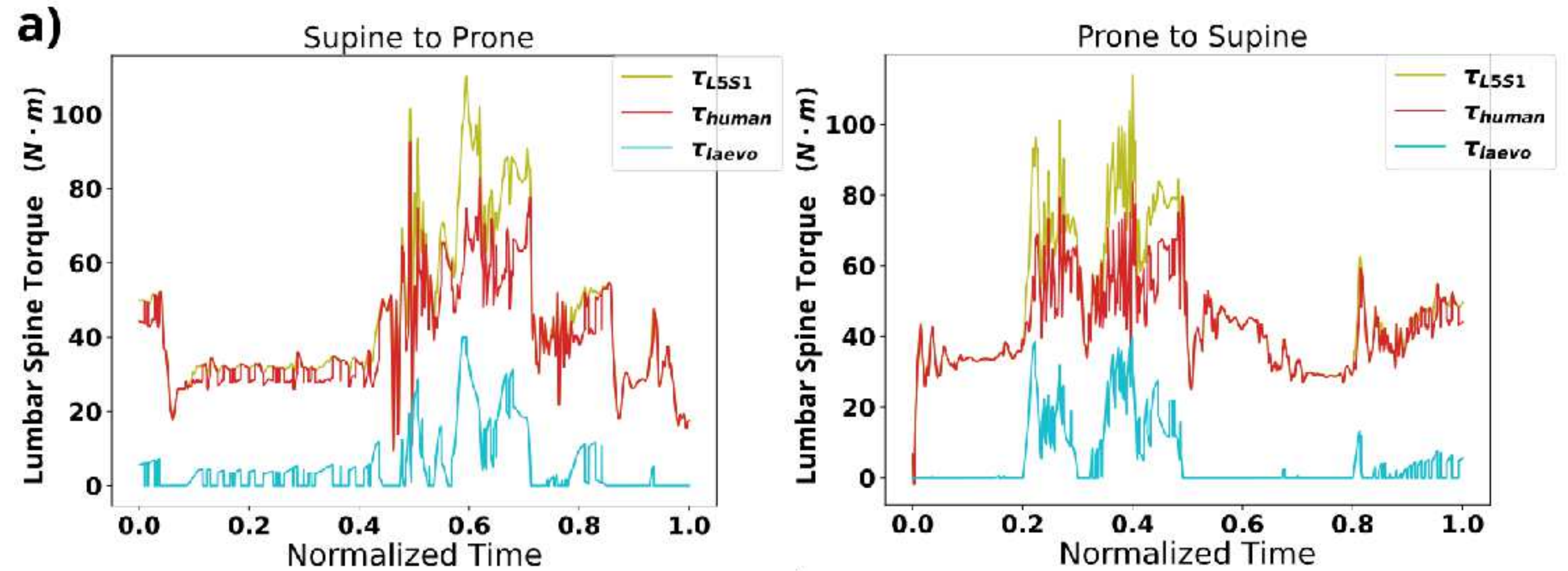
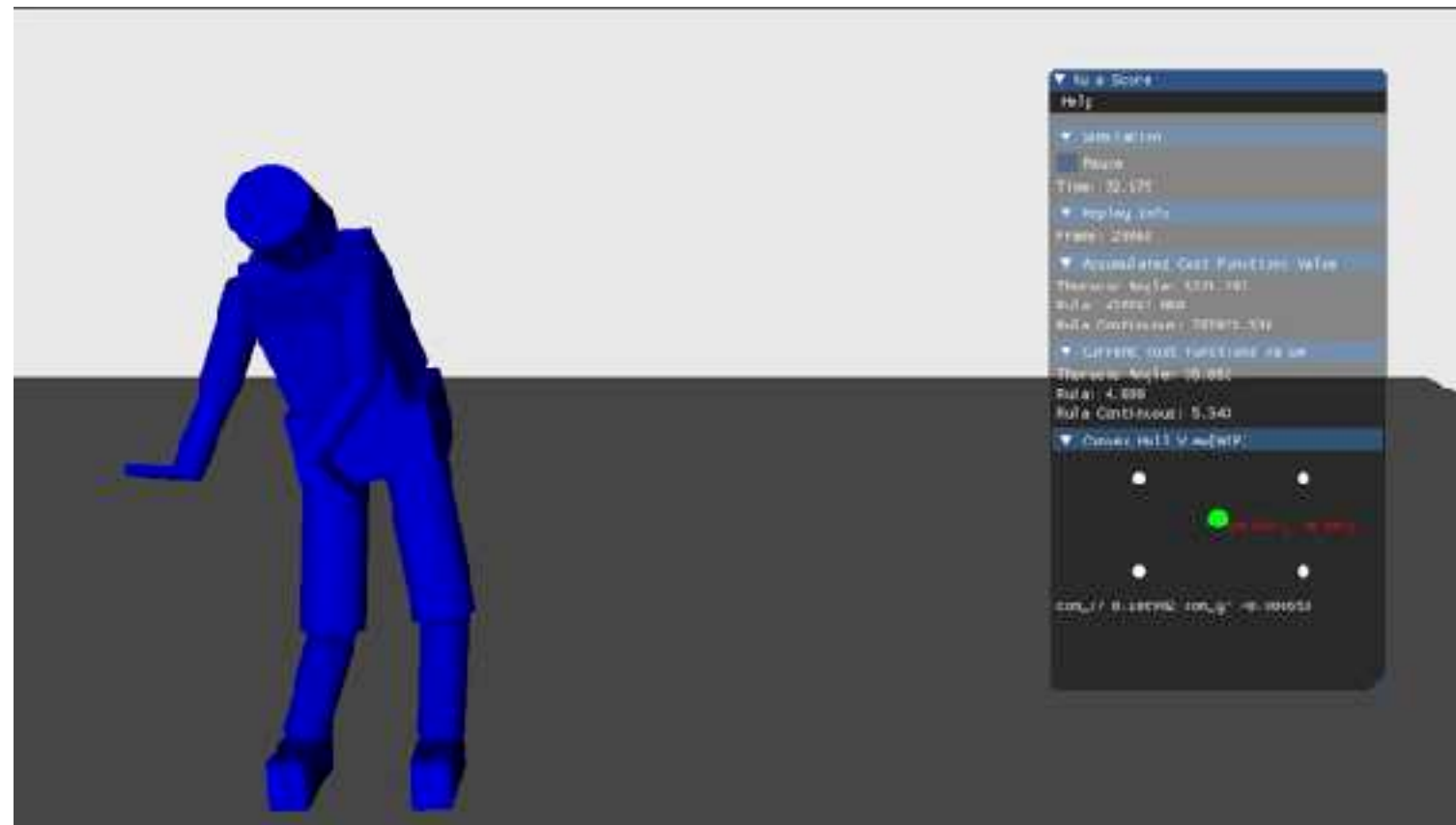
EKG analysis



Torque analysis



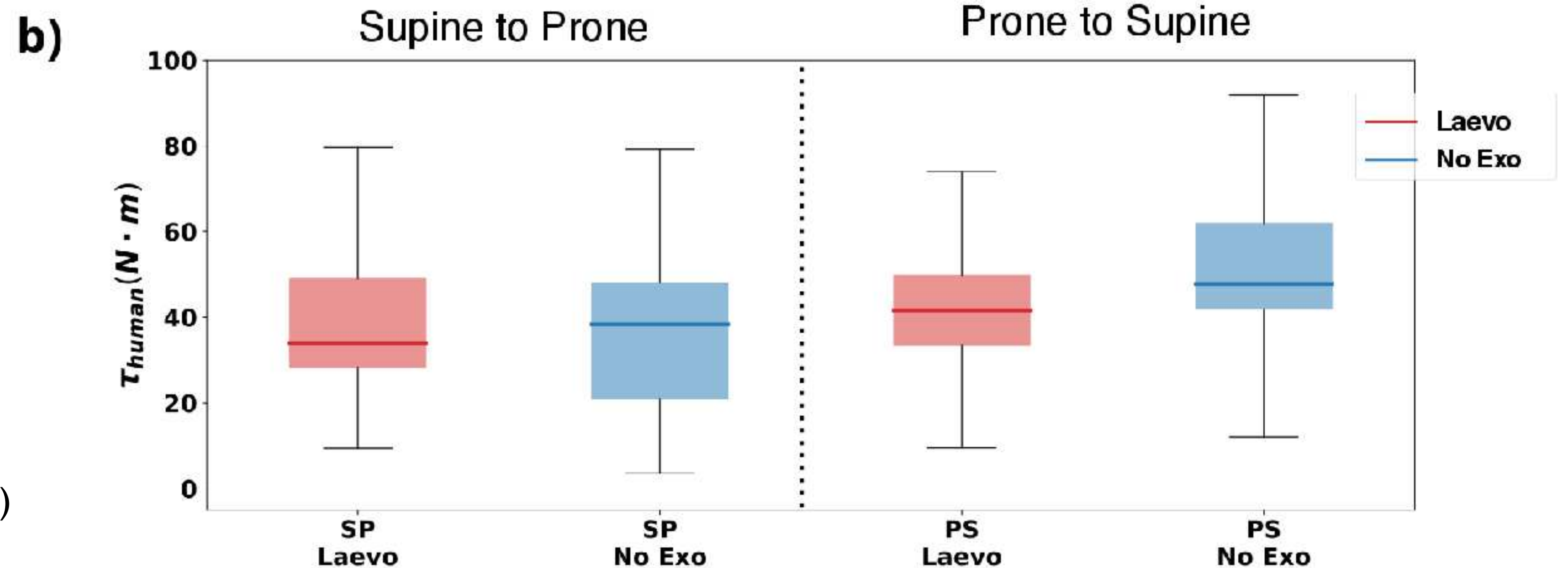
Torque analysis



$$\tau_{L5S1} = \tau_{human} + \tau_{exo}$$

$$\tau_{laevo} = \begin{cases} k_0 + k_1\theta & \dot{\theta} > 0 \\ k_0 + k_1\theta - k_{loss} & \dot{\theta} < 0 \end{cases}$$

K0, K1 and K_loss from Koopman et al. (2015)



Use of the exoskeleton in the ICU



Questionnaires

Participant (ID ou initiales)			
n. DV de la journée		Avec exo ?	Oui / Non

Veuillez noter pour chaque zone anatomique votre effort perçu lors de votre dernière manœuvre de DV (encercler le chiffre).

gauche

Cou

0 rien

0.5 très très léger

1 très léger

2 léger

3 modéré

4 un peu dur

5 dur

6

7 très dur

8

9

10 très très dur

Epaule/ Bras

0 rien

0.5 très très léger

1 très léger

2 léger

3 modéré

4 un peu dur

5 dur

6

7 très dur

8

9

10 très très dur

Lombes

0 rien

0.5 très très léger

1 très léger

2 léger

3 modéré

4 un peu dur

5 dur

6

7 très dur

8

9

10 très très dur

Avant-bras/ Main

0 rien

0.5 très très léger

1 très léger

2 léger

3 modéré

4 un peu dur

5 dur

6

7 très dur

8

9

10 très très dur

droite

Cou

0 rien

0.5 très très léger

1 très léger

2 léger

3 modéré

4 un peu dur

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8

9

10 très très dur

Avant-bras/ Main

0 rien

0.5 très très léger

1 très léger

2 léger

3 modéré

4 un peu dur

5 dur

6

7 très dur

8

9

10 très très dur

Échelle d'évaluation de l'effort perçu de Borg (CR10 de Borg)

Post-DV

Ce questionnaire est à compléter par les personnes équipées d'exosquelette à la fin de leur journée de travail pendant laquelle ils ont effectué des manœuvres de décubitus ventral (DV).

	Écrivez vos réponses dans cette colonne ⌵ ⌴
Participant ID (ou vos initiales)	
Type d'exosquelette	☐ LAEVO
Entre la prise de poste et maintenant, combien de fois avez-vous pratiqué la manœuvre de DV aujourd'hui ?	
Avez-vous systématiquement utilisé le LAEVO pour effectuer la manœuvre de DV ?	Oui / Non
Si non, pourquoi vous l'avez enlevé ?	Réponse :
Dans combien de manœuvres DV sur le total des manœuvres DV avez-vous utilisé le LAEVO ?	_____ (nombre) sur _____ (totale)
Au total, combien de temps l'avez-vous gardé ?	Réponse :
Avez-vous changé des réglages en cours d'utilisation ? Si oui, précisez à quel moment et pourquoi.	Réponse :

Le questionnaire suivant reprend celui que vous avez fait dans les tests à l'Hôpital Virtuel. Les réponses d'aujourd'hui seront comparées avec les précédentes pour voir la différence entre virtuel et réel.

Dans le questionnaire, vous trouverez une suite d'affirmations concernant votre expérience avec l'exosquelette. Pour **chaque** affirmation qui suit, veuillez donner votre avis en cochant la case correspondante sur une échelle de réponses en cinq points (exemple d'échelle : « **Pas du tout d'accord** » « **Plutôt pas d'accord** » « **Moyennement d'accord** » « **Plutôt d'accord** » « **Tout à fait d'accord** »).

La mise en place et les réglages de l'exosquelette (seulement la 1ere fois, sauf si vous avez fait à nouveau un réglage)

1. Je trouve que l'exosquelette est facile à mettre en place :

☐ Pas du tout d'accord

☐ Plutôt pas d'accord

☐ Moyennement d'accord

☐ Plutôt d'accord

☐ Tout à fait d'accord

L'utilisation de l'exosquelette

2. Globalement, je trouve que l'exosquelette est facile à utiliser :

☐ Pas du tout d'accord

☐ Plutôt pas d'accord

☐ Moyennement d'accord

☐ Plutôt d'accord

☐ Tout à fait d'accord

3. Je trouve que j'effectue mes mouvements facilement avec l'exosquelette :

☐ Pas du tout d'accord

☐ Plutôt pas d'accord

☐ Moyennement d'accord

☐ Plutôt d'accord

☐ Tout à fait d'accord

4. Je trouve que je me déplace facilement avec l'exosquelette :

☐ Pas du tout d'accord

☐ Plutôt pas d'accord

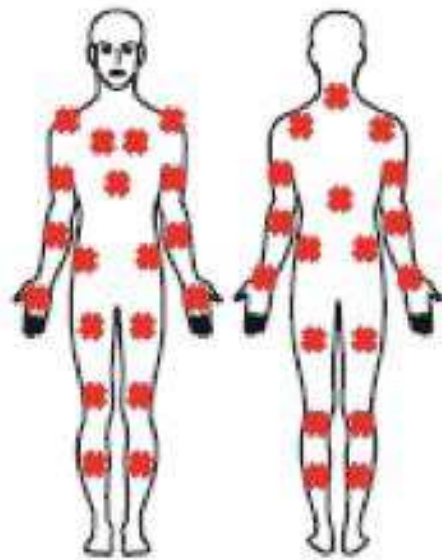
☐ Moyennement d'accord

☐ Plutôt d'accord

☐ Tout à fait d'accord

Évaluation globale de l'effort

Mettez un cercle sur cette image (recto-verso) sur les zones où vous avez ressenti de l'effort physique pendant les manœuvres DV avec l'exosquelette



Questionnaires

For users

Participant ID			
Exoskeleton type		☐ Laevo ☐ Corfor ☐ CrayX ☐ BackX	
Instructions: In the questionnaire you will find a series of statements about your experience with the exoskeleton. For each statement that follows, please give your opinion by checking the corresponding box on a five-point Likert scale. Scale A: 1. Strongly disagree 2. Disagree 3. Neither Agree nor Disagree 4. Agree 5. Strongly agree Scale B: 1. Much lower 2. Lower 3. Identical 4. Higher 5. Much higher			
N.	Reverse & ICU	Question	Scale
Exoskeleton setup and calibration			
1		I find the exoskeleton is easy to set up	A
The use of the exoskeleton			
2		Overall, I find the exoskeleton easy to use	A
3		I find that I can easily perform my movements with the exoskeleton	A
4		I find that I can easily move and walk with the exoskeleton	A
5		I find that I control my gestures as I wish with the exoskeleton	A
6	R	I find that the exoskeleton prevents me from working the way I want	A
7		I find that I easily got used to working with the exoskeleton	A
8	R	I find that using the exoskeleton requires an extra effort of concentration	A
My performance with the exoskeleton			
9		I find that the speed of my work with the exoskeleton is ...	B
10	*	I find that the quality of my	B

		work with the exoskeleton is ...	
11		I find that my effectiveness with the exoskeleton is ...	B
12		I find that the productivity of the team with the exoskeleton is ...	B
My health and safety			
13	R	Overall, I find that my physical efforts with the exoskeleton are ...	B
14	R	Overall, I find that with the exoskeleton, my fatigue is ...	B
15		I feel safe working with the exoskeleton.	A
My feeling with the exoskeleton			
16	R	I feel nervous when I use the exoskeleton.	A
17	R	I feel worried when I use the exoskeleton.	A
18		I feel confident when I use the exoskeleton.	A
19	R	I find I annoy my colleagues when I use the exoskeleton.	A
Future use			
20		If I have a choice, I am thinking of using or continuing to use the exoskeleton in the next months	A
21	*	I find that over the course of the day I have adapted to the exoskeleton	A
22	*	I find that using the exoskeleton during the day has been beneficial	A

For colleagues

2nd PART: FILL WHEN YOUR WORK WITH THE EXOSKELETON IS FINISHED	
Question	Answer
Participant ID	
Exoskeleton type	☒ LAEVO
Between when you started to work and now, how many times have you practiced the PP maneuver today?	
Have you systematically used the exoskeleton to perform the PP maneuver?	Yes / No
If not, why did you remove it?	
In how many of the total PP maneuvers out of the total PP maneuvers did you use the exoskeleton?	_____ (number) out of _____ (total)
In total, how long did you keep it?	
Did you change any settings during use? If yes, specify when and why.	
Did you change any settings after removing the system (for example, after using the restroom)? If so, specify when and why.	
Did you unhook the thighs pads to walk? If yes, how many times?	
Did the exoskeleton prevent you from making one or more movements? If yes, can you list them.	

You have worked with people wearing an exoskeleton.	
Did working next to a colleague with an exoskeleton make you nervous?	☐ 1 = not at all ☐ .. ☐ 10 = very nervous Answer: _____
Have you been annoyed by working next to people with exoskeletons?	☐ 1 = not at all ☐ .. ☐ 10 = very annoyed Answer: _____
Compared to the "normal" situation (no exoskeleton), did you find the new situation more physically demanding?	☐ 1 = much less ☐ ... ☐ 5 = identical ☐ ... ☐ 10 = much more Answer: _____
Compared to the "normal" situation (no exoskeleton), did you find the new situation more cognitively demanding (for example, you had to pay more attention...)?	☐ 1 = much less ☐ ... ☐ 5 = identical ☐ ... ☐ 10 = much more ☐ Answer: _____
If you had the choice, would you use an exoskeleton yourself in the next few months if the current sanitary situation continued?	☐ Strongly disagree ☐ Disagree ☐ Neither agree nor disagree ☐ Agree ☐ Strongly agree

Results & Takeaways

1st wave (March-April 2020):

- 1st step: study at the Hospital Simulation Center:
 - Compared 4 solutions => selected the LAEVO
 - Physiological evaluation of LAEVO
- 2nd step: 2 volunteers used the LAEVO in the ICU
 - **Acceptance: very helpful at the patient's head**

Task performance → No decrease in quality of prone positioning

Workload → Reduction of back effort and perceived effort + positive effect on morale

Acceptance → Positive attitude of medical staff

2nd wave (October 2020-May 2021):

- 4 exoskeletons used in ICU since end of October 2020
 - **Organisational issues: shared vs individual use**

Acceptance

- Positive attitude of medical staff, some users became ``regular'' users
- **60+ physicians used the 4 exoskeletons**

Using exoskeletons to assist medical staff during prone positioning of mechanically ventilated COVID-19 patients: a pilot study

Ivaldi, S.; Maurice, P.; Gomez, W.; Theurel, J.; Wioland, L.;
Atain-Kouadio, J.-J.; Claudon, L.; Hani, H.; Kimmoun, A.; Sellal, J.-M.;
Levy, B.; Paysant, J.; Malikov, S.; Chenuel, B.; Settembre, N.

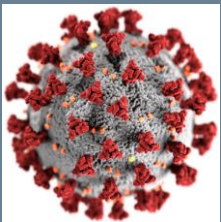


Horizon 2020
European Union funding
for Research & Innovation

3D simulation and deep learning for isolation of candidate inhibitors of SARS-CoV-2 infection and replication

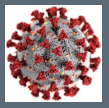
Marie-Dominique Devignes, on behalf of Bernard Maigret and the Capsid team.

In collaboration with IRIM (Montpellier) and LAMA (Chambéry)

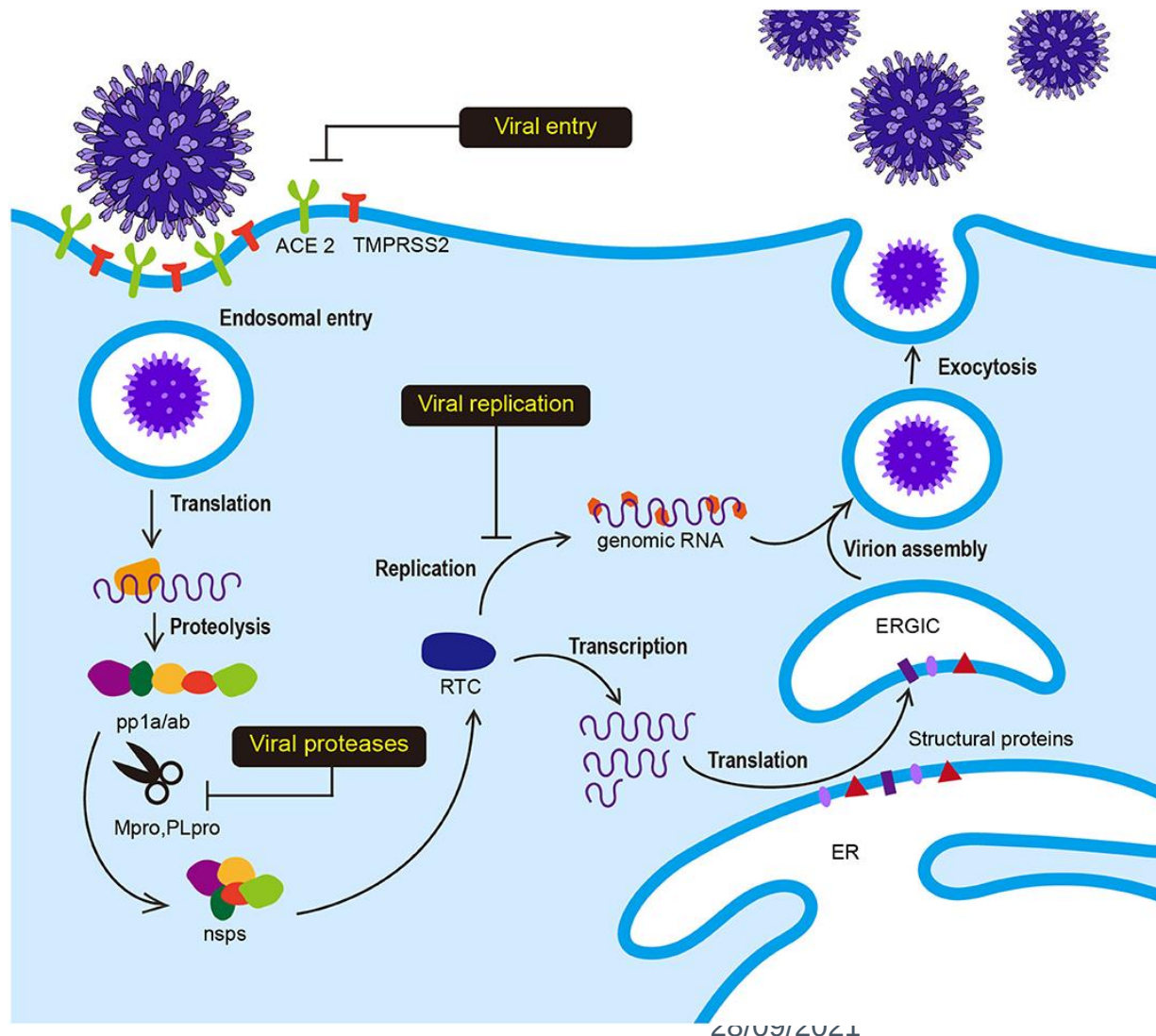


28/09/2021



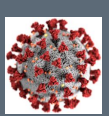


SARS-CoV-2 viral cycle



Jeong Gi Uk, et al. *Therapeutic Strategies Against COVID-19 and Structural Characterization of SARS-CoV-2: A Review.*

Frontiers in Microbiology, 11:1723, 2020.



Virus entry: Spike - ACE2 interaction

Covid-19 Disease Map project

(<https://covid.pages.uni.lu/>)

Mechanism 1 : Spike-ACE2 interaction

Species

Protein

Protein

Receptor

Receptor

Simple Molecule

Simple_Molecule

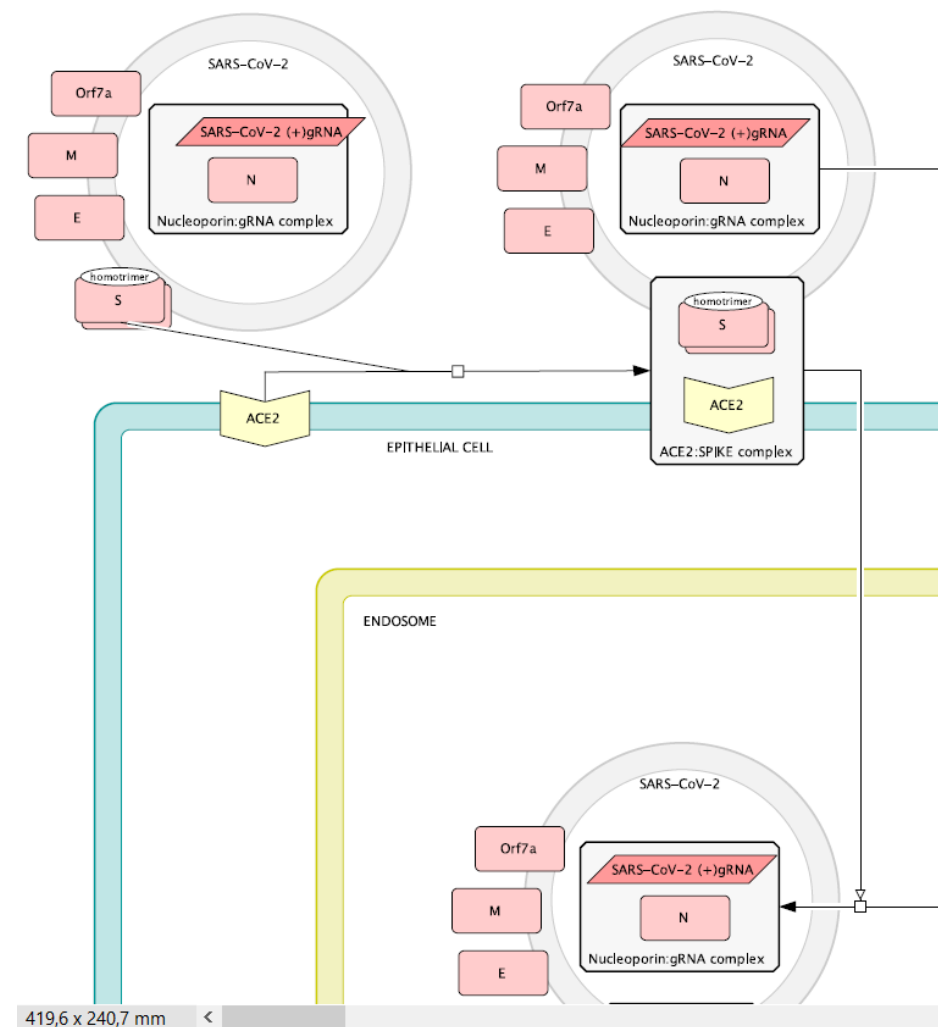
Gene

Gene

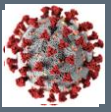
Compartments:

Compartment_Square

Ostaszewski M et al. Covid-19 Disease Map project, building a computational repository of SARS-CoV-2 virus-host interactions mechanisms. Scientific Data 7:136, 2020

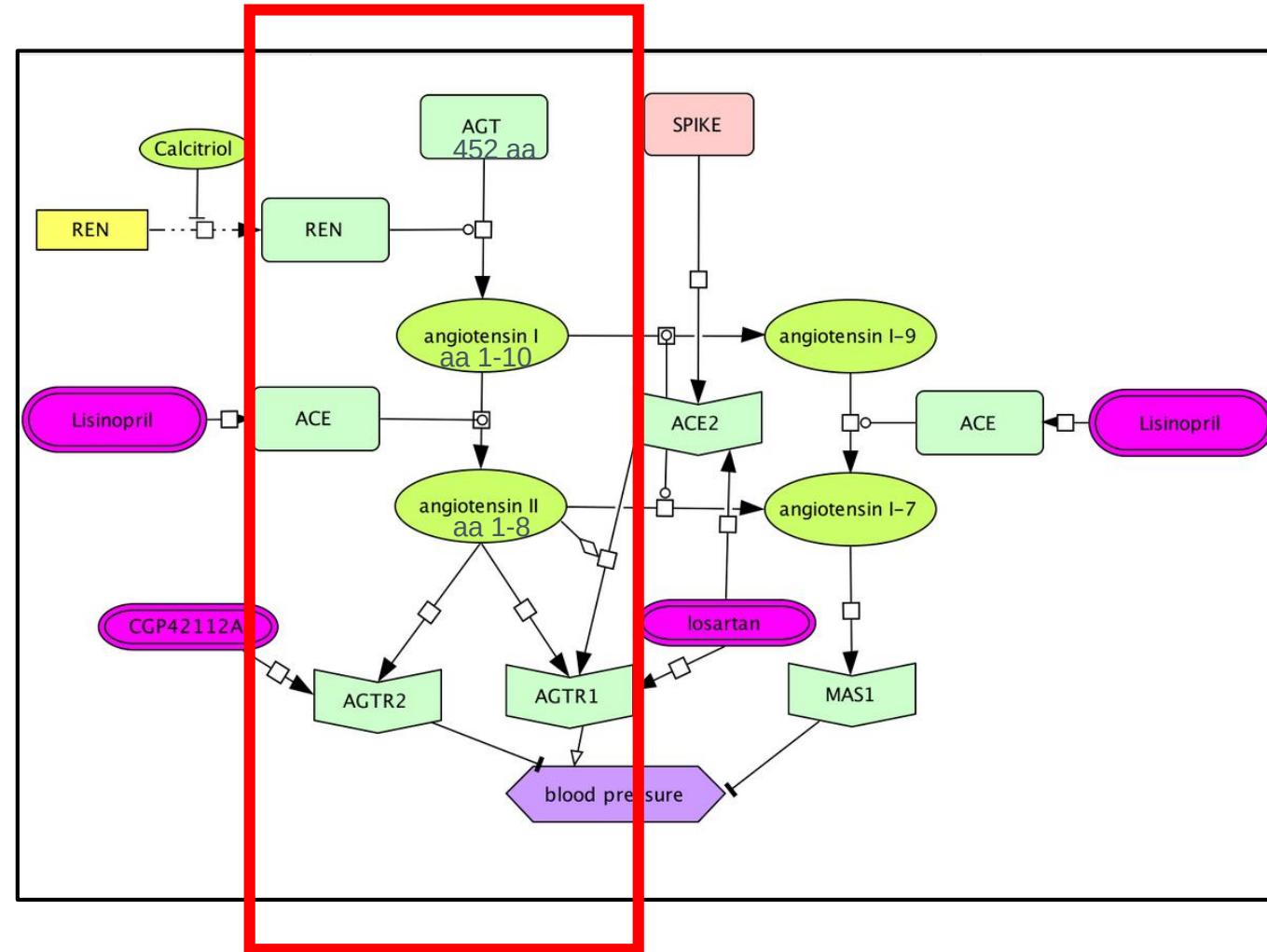
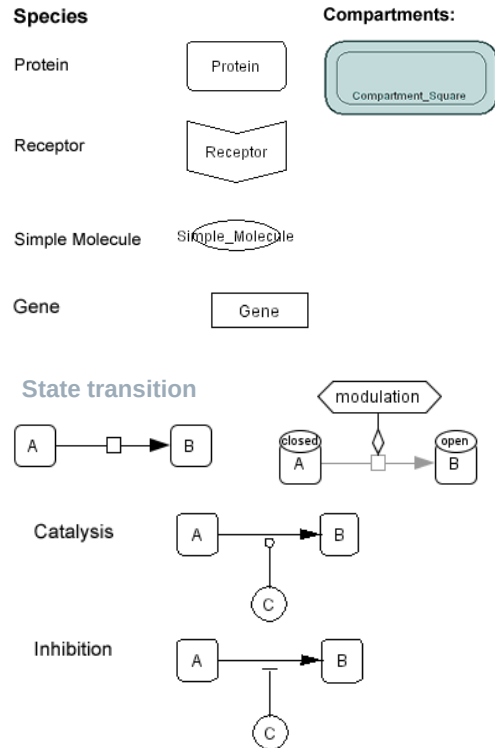


ACE2 : Angiotensin Converting Enzyme 2

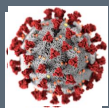


ACE2 is part of **RAAS : Renin Angiotensin Aldosterone System**

Model extracted
from [Covid19
disease map](#)
Built with [Cell Designer](#)

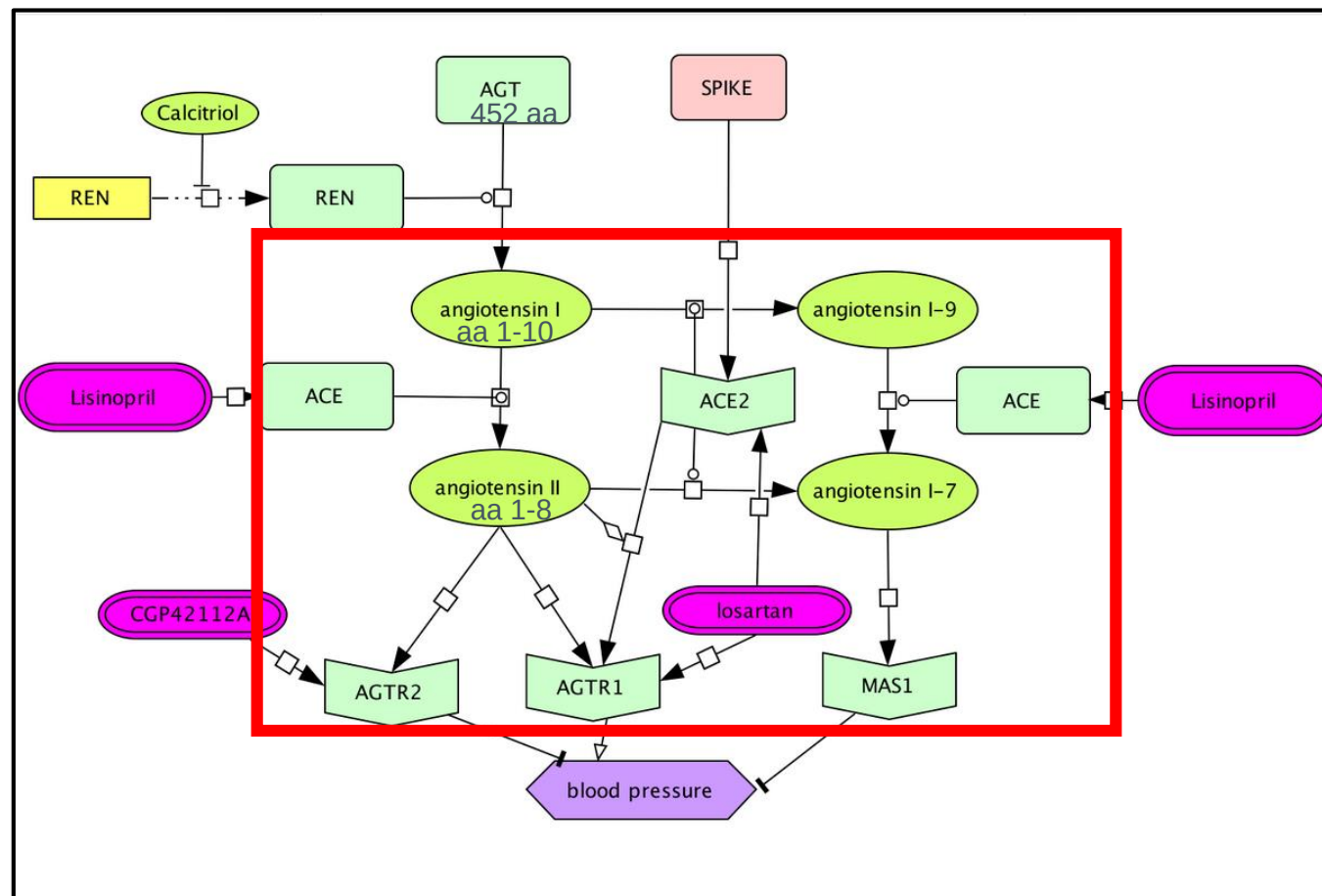
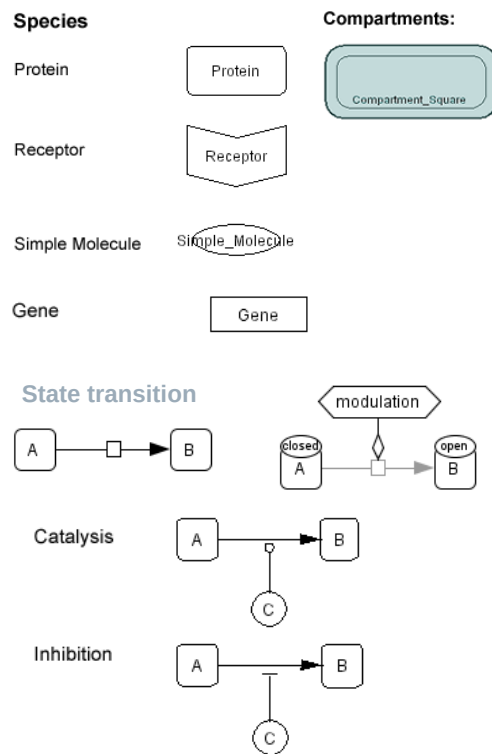


https://fairdomhub.org/models/709/model_images/91

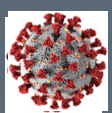


ACE2 counteracts ACE with respect to hypertension

Model extracted
from [Covid19
disease map](#)
Built with [Cell Designer](#)



https://fairdomhub.org/models/709/model_images/91

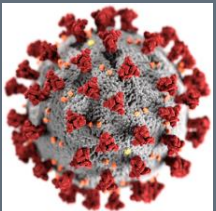


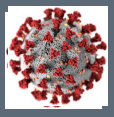
SARS-COV-2 mutants

Name	Country	Transmission	Characteristic mutation in RBD*	
Alpha	UK	+50%	N501Y	
Beta	South Africa	+50%	K417N E484K N501Y	
Gamma	Brazil	+50%	K417T E484K N501Y	
Epsilon	California	similar	L452R	
Delta	India	+80%	L452R T478K	
...				

RBD:
Receptor
Binding
Domain

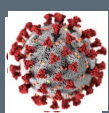
Methods





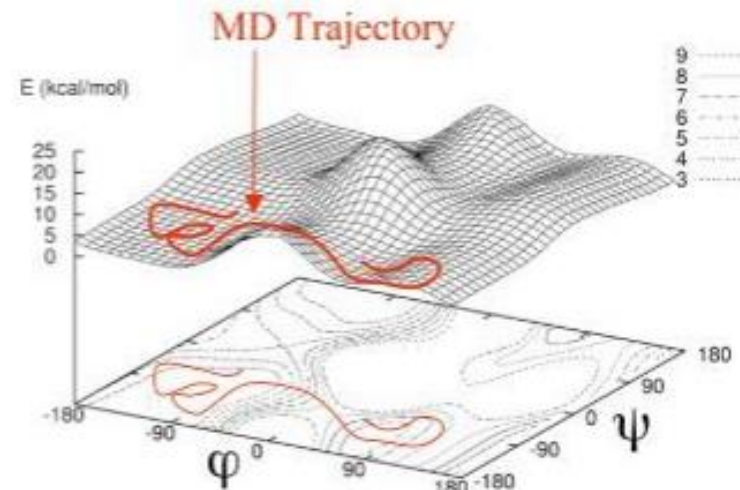
3D simulation in structural bioinformatics: Molecular Dynamics (MD)

- What for ?
 - Understand atomic and molecular interactions
 - Connection between macroscopic observations and microscopic world governed by the theory of statistical mechanics
- When ?
 - Experiment is impossible or too expensive or too dangerous
 - Replace with simulation
- Tools
 - Quantum Mechanics 10-100 atoms, 10-100 ps
 - **Classical Molecular Mechanics 10^4 - 10^5 atoms, 10-100 ns**
 - Mixed QM/MM 10^4 - 10^5 atoms, 10-100 ps
- Most popular software : NAMD (Nanoscale Molecular Dynamics)
 - Klaus Schutten, University Illinois at Urbana Champaign (1995)
 - Highly parallel, GPU version on NVIDIA using CUDA (NAMD3)



HPC for MD simulation

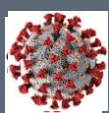
$$E = \sum_{\text{bonds}} K_b (r - r_0)^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_0)^2 + \sum_{\text{dihedrals}} K_\phi [1 + \cos(n\phi - \delta)] + \sum_{\text{impropers}} K_\psi (\psi - \psi_0)^2 + \sum_{i>j} \epsilon \left[\left(\frac{r_m}{r} \right)^{12} - 2 \left(\frac{r_m}{r} \right)^6 \right] + \sum_{i>j} \frac{q_i q_j}{4\pi\epsilon_0\epsilon r}$$



- Complex potential energy function
 - Computed at each step of the simulation for the whole set of atoms or particles
 - Using force-field parameters e.g. CHARMM (Karplus 1983)
 - Energy landscape -> minima = stable conformations
- Example of run time for a system 350,000 atoms simulated for 100 ns

	NAMD2 (CPU)	NAMD3 (GPU)
Jean Zay (IDRIS)	~ 9 days	~ 3 days
Grid5K (LORIA)	~70 days	~ 7 days

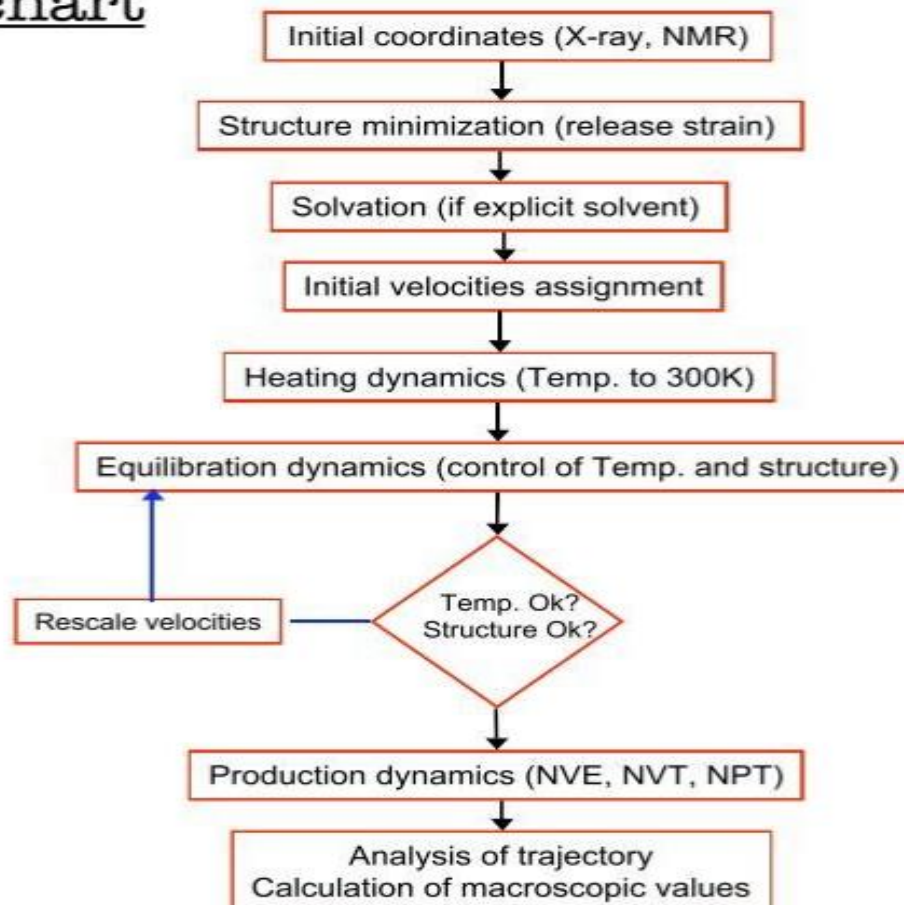
Bernard Maigret

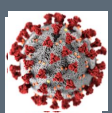


MD simulation in practice



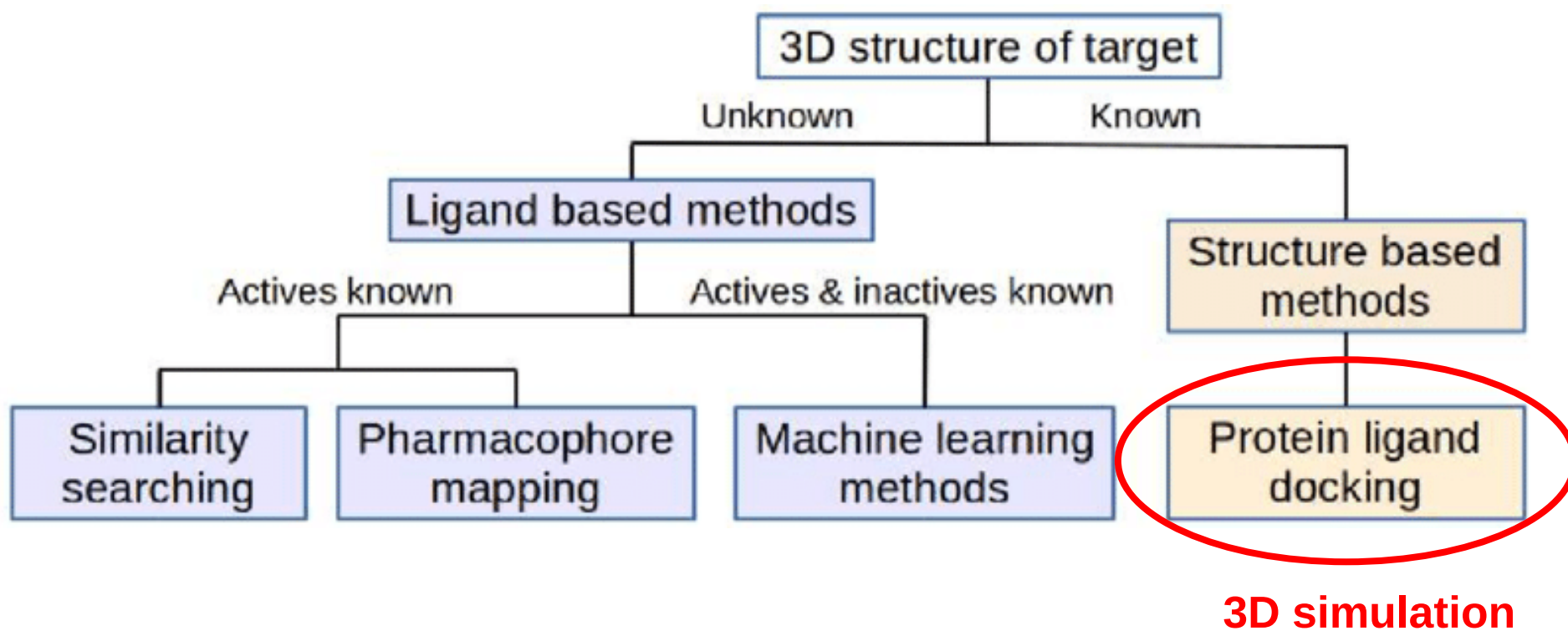
MD flowchart





Virtual screening methods

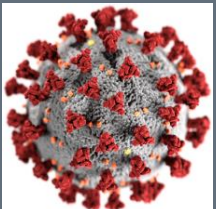
- Goal : *In silico* ranking and selection of best receptor-binding molecules

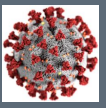


Source: PhD thesis Uttam Pal Interaction of Proteins with Small Molecules and Peptides. 10.13140/RG.2.2.17102.18240.

Searching SARS-CoV-2 binding inhibitors

Structure-based virtual screening





SARS-CoV-2 Spike protein

Trimeric spike 3D structure by CryoEM
(Wrapp D et al. Science 2020)

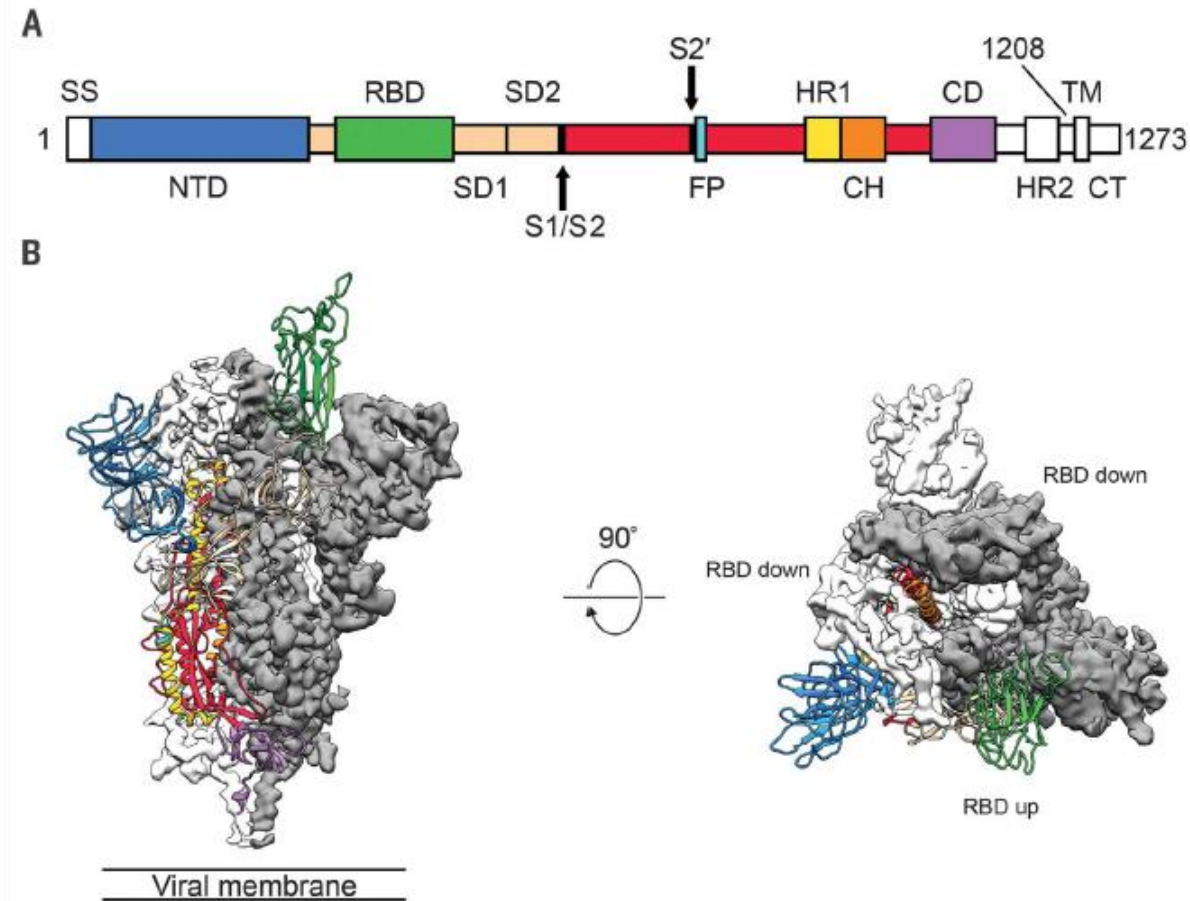
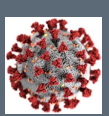
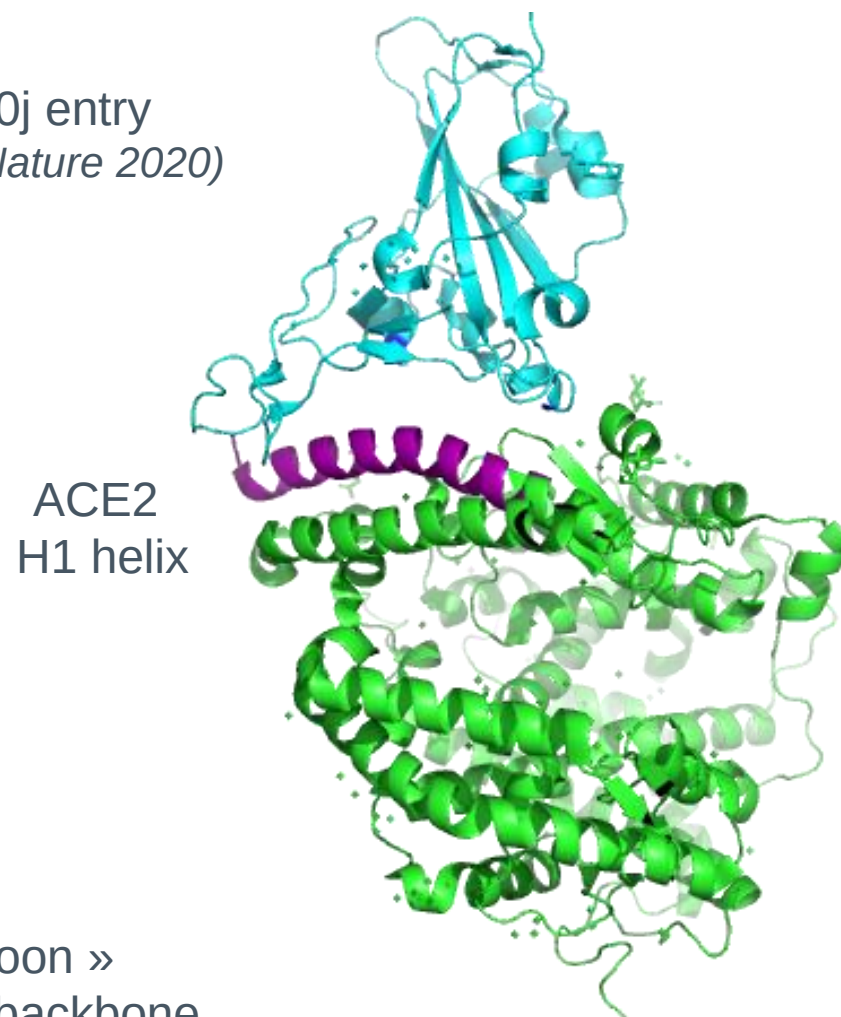


Fig. 1. Structure of 2019-nCoV S in the prefusion conformation. (A) Schematic of 2019-nCoV S primary structure colored by domain. Domains that were excluded from the ectodomain expression



RBD – ACE2 binding interface

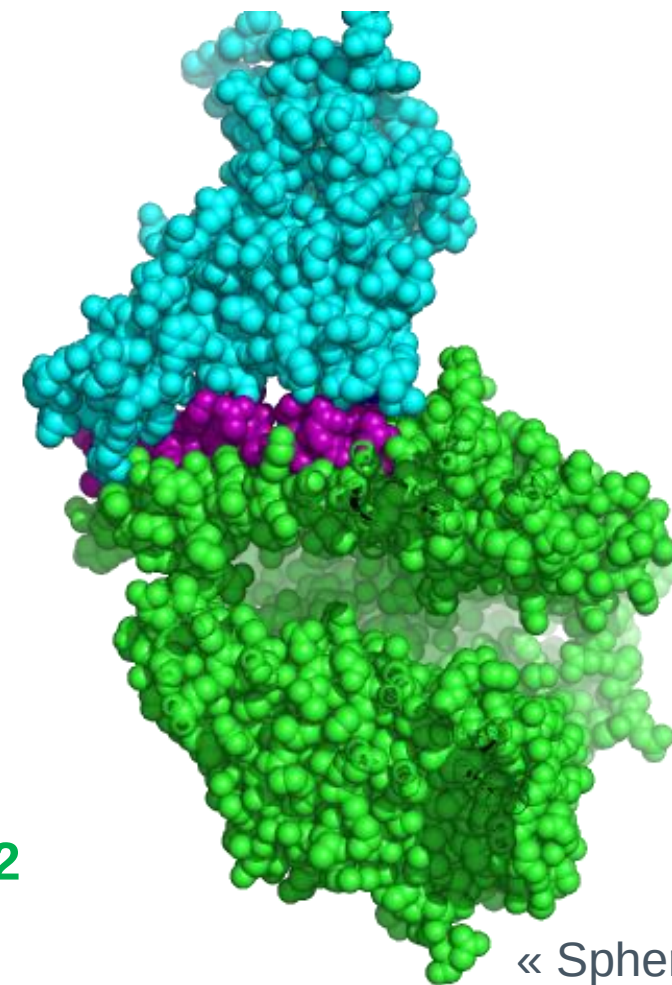
PDB 6m0j entry
(Lan J et al. Nature 2020)



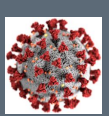
« Cartoon »
= protein backbone

RBD

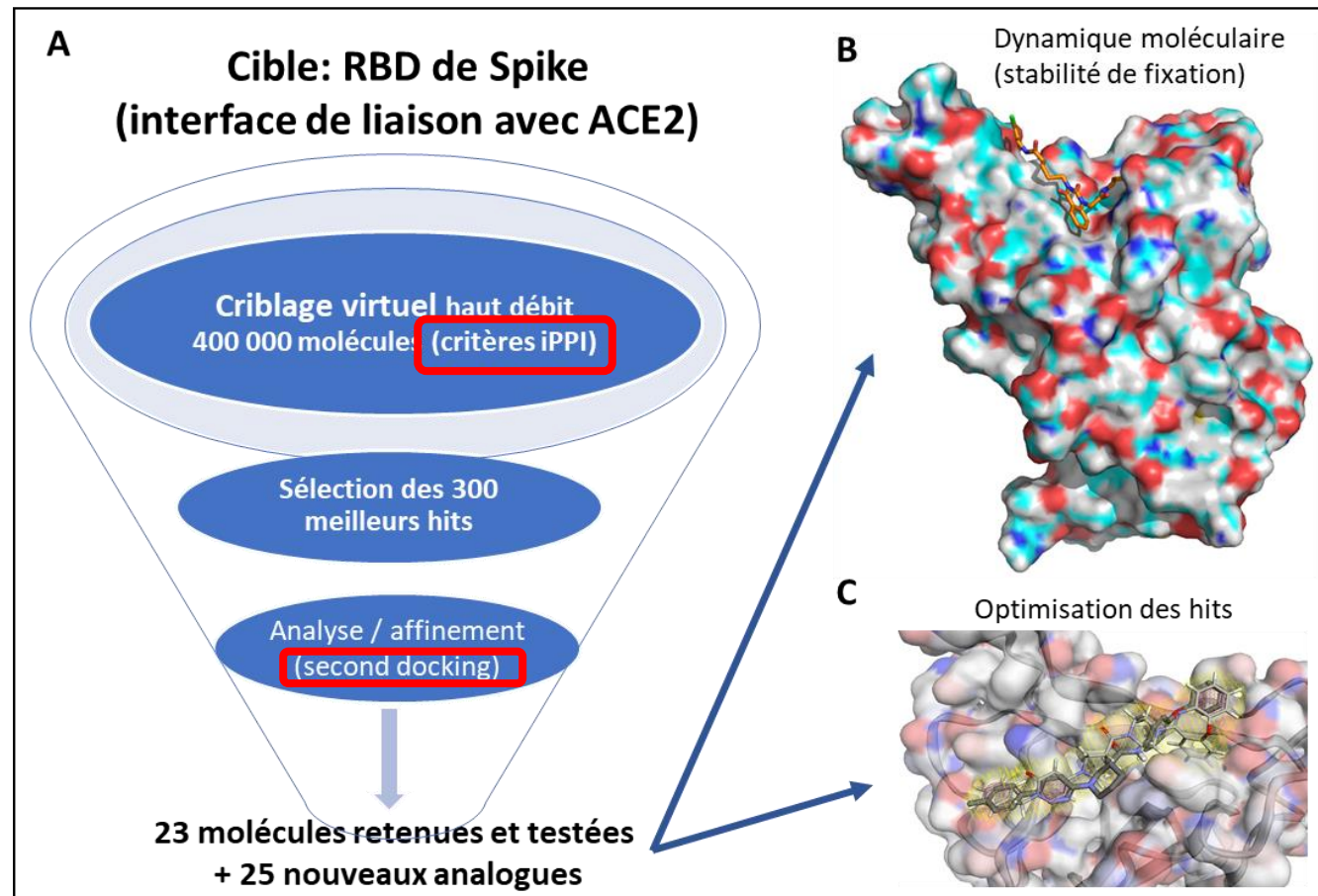
ACE2



« Spheres »
= backbone + side chains

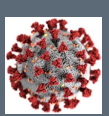


Structure-based virtual screening

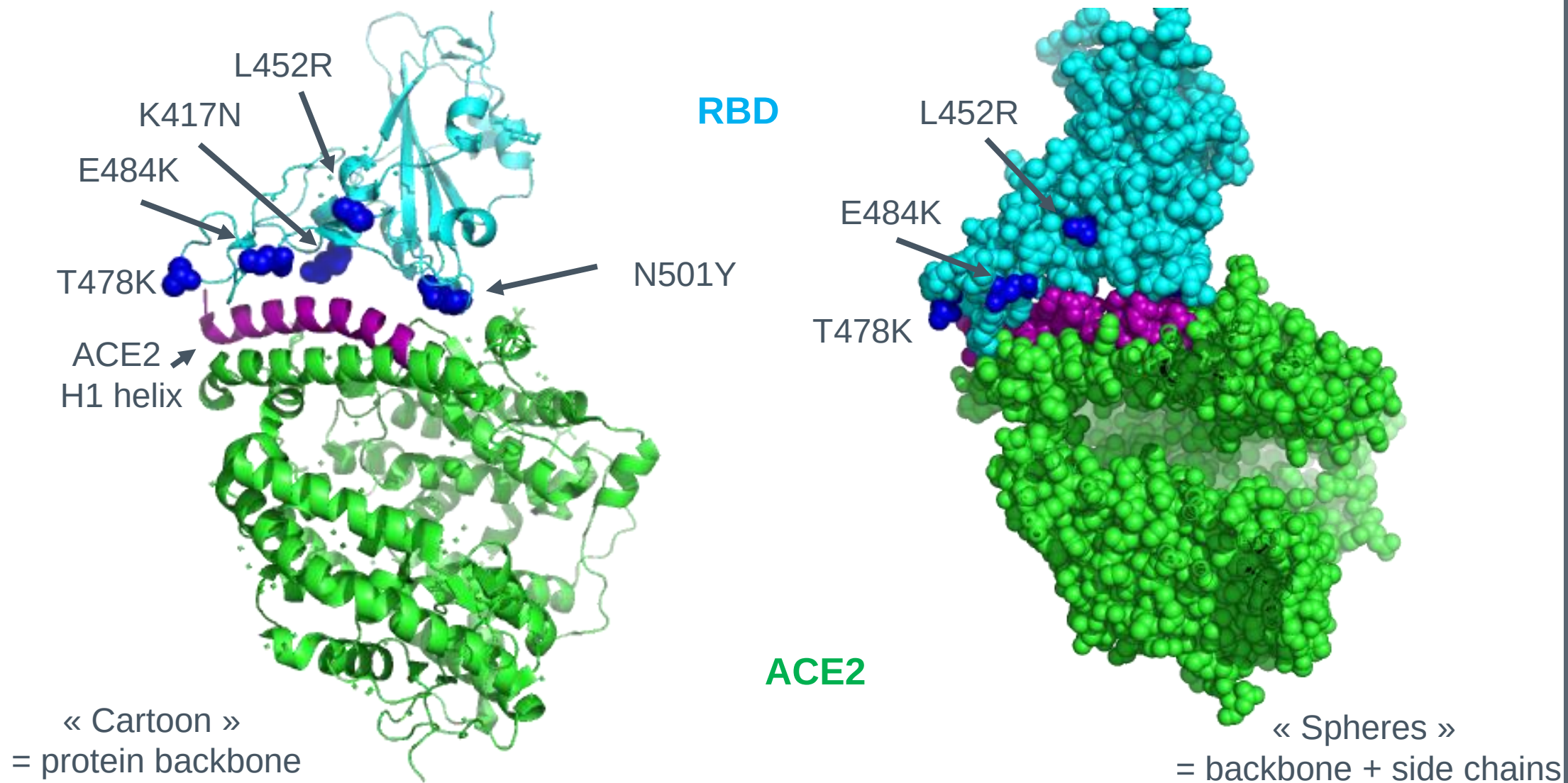


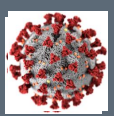
Tests biologiques sur cellules en culture infectées par le SARS- CoV2 :

- protection significative
contre l'effet cytopathique
par 2 composés (sur 23)
- inhibition de la prolifération
virale
- confirmé pour les
analogues de ces
composés



Position of variant residues in RBD





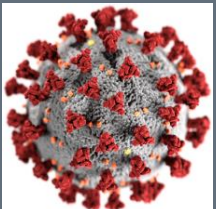
Roadmap for candidate interaction inhibitors

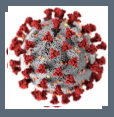
- › Detailed analysis of inhibitor binding to RBD
 - Affinity calculation
- › Chemical optimisation of the two hits
 - Improve affinity
 - Perform longer MD simulations
- › Impact of known mutations
- › ADME/tox study
 - Absorption, Distribution, Metabolism, and Excretion
 - Toxicity

*Laurent Chaloin (IRIM) Projet
Prématuration CNRS
22/01/2021*

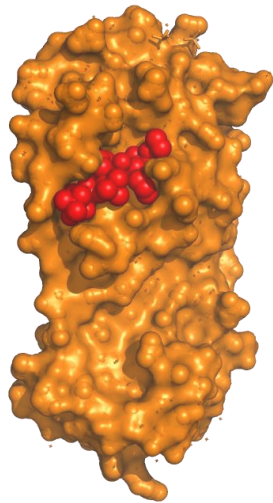
Searching for new SARS-CoV-2 anti-protease inhibitors

Ligand-based virtual screening

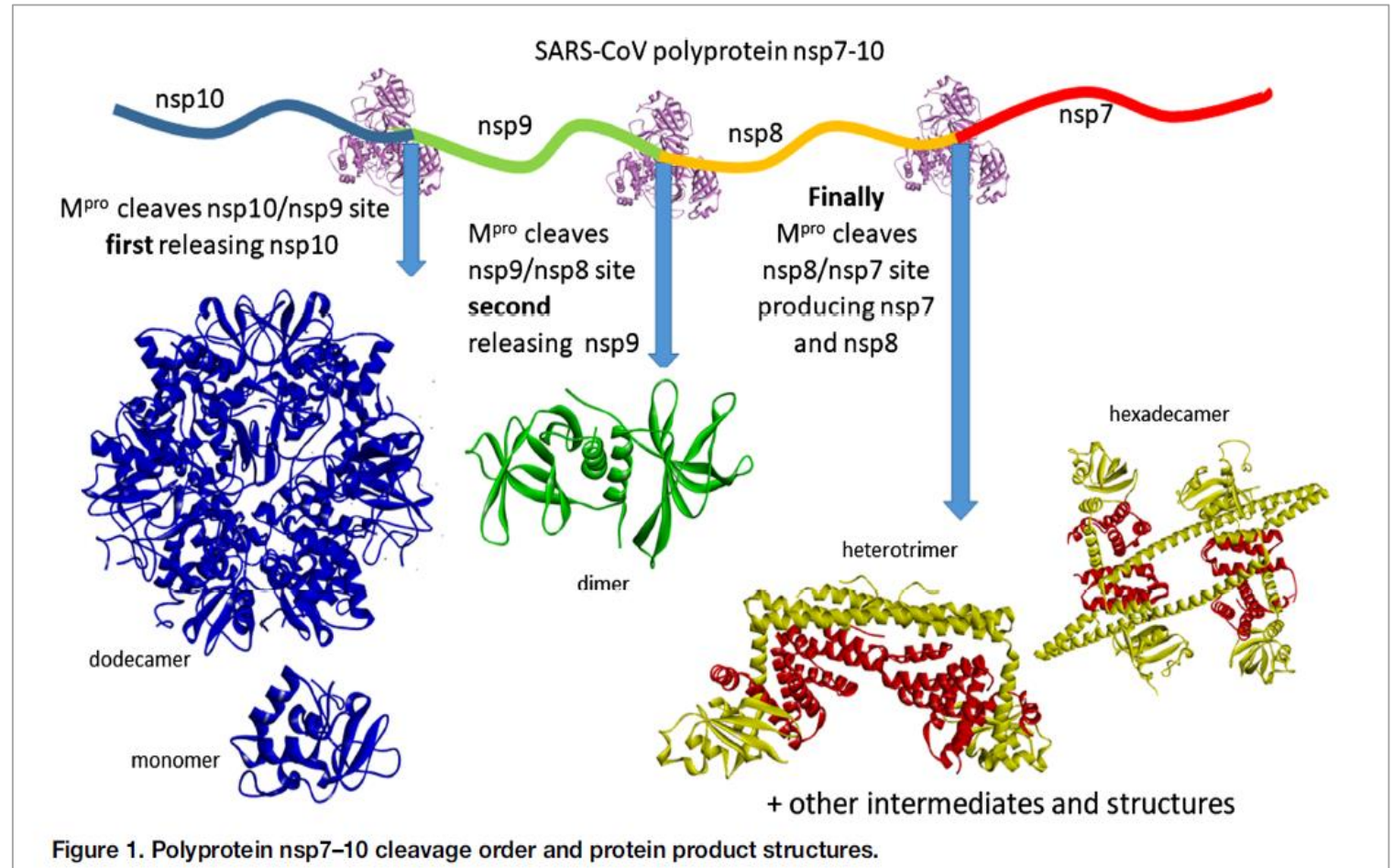


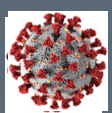


Target = SARS-CoV-2 main protease 3CLpro or Mpro (Nsp5)



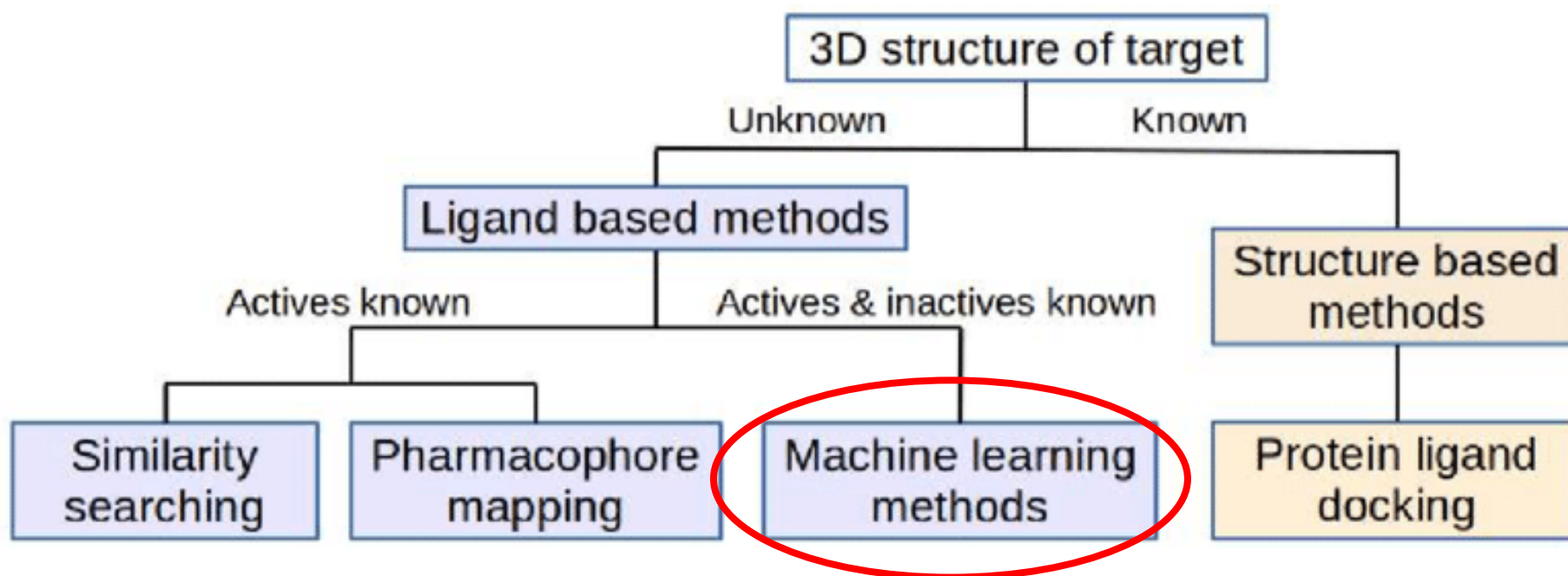
PDB entry 7jyc
Mpro with inhibitor
Narlaprevir





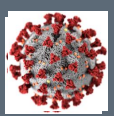
Virtual screening methods

- Goal : *In silico* ranking and selection of best receptor-binding molecules



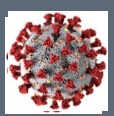
3D simulation

Source: PhD thesis Uttam Pal Interaction of Proteins with Small Molecules and Peptides. 10.13140/RG.2.2.17102.18240.



Ligand-based approach for Mpro inhibitors

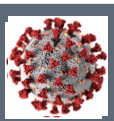
- › Collection of protease inhibitors (actives) and non inhibitor molecules (inactives)
- › Generate graph representation of molecules
- › Train a DL model to recognize active anti-protease molecules
- › Use this model with a chemical library



DL applied on graph representation of molecules

- › Inspired by multi-relational knowledge graph
- › To be used with DGL-KE framework (Deep Graph Library – Knowledge Embedding)
 - Amazon web services AWS-labs
 - <https://aws-dglke.readthedocs.io/en/latest/>
- › Experimentation during M1 internship in 2021

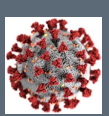




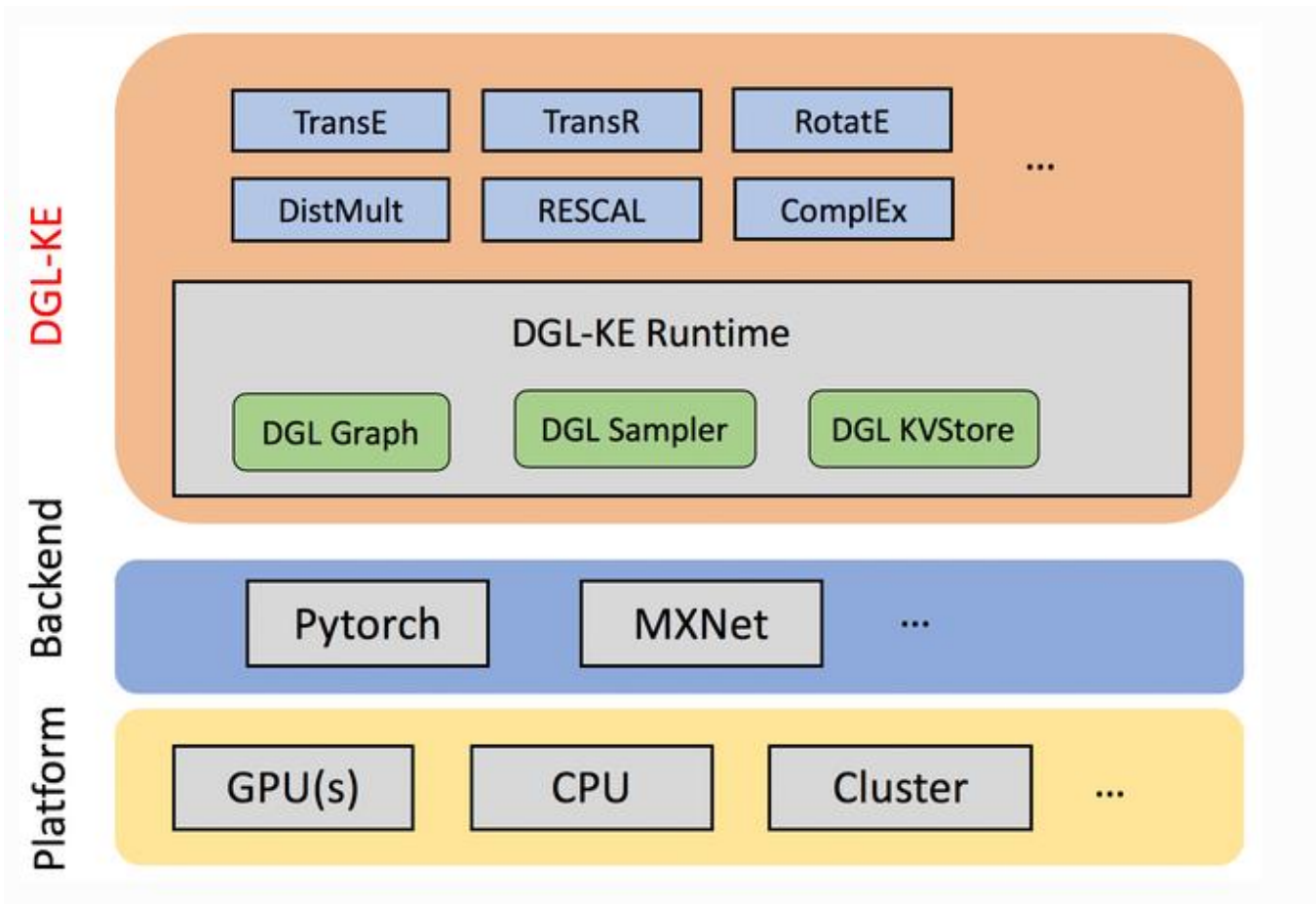
Graph representation of molecules

Chemical formule (SMILES format) of molecule 11234

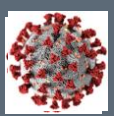
- CN(C)c(cc1)ccc1C(NC(Cc1ccccc1)C(Nc(ccc([N+])([O-])=O)c1)c1Cl)=O)=O
 - › Atome identifiers 11234_0, 11234_1, AA234_2, etc.
- › 5 types de relations : connected_to , double_connected_to, triple_connected_to , chemical_element , contains.
 - Instanciation for molecule 11234
 - › 11234, contains, 11234_0
 - › 11234, contains, 11234_1
 - › ...
 - › 11234_0, chemical_element, C
 - › 11234_2, chemical_element, N
 - › ...
 - › 11234_0 connected_to 11234_1
 - › ...
 - › 1123'_37, double_connected_to, 11234_38



DGL-KE framework

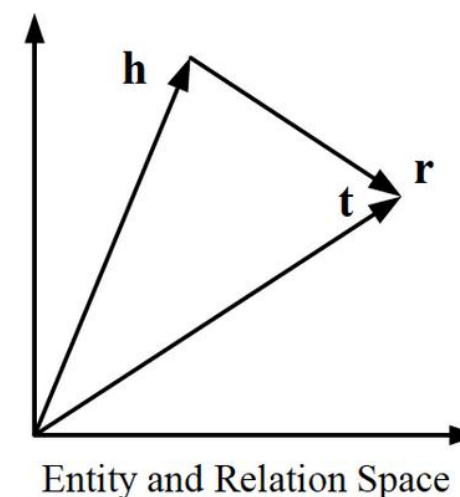


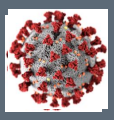
<https://aws-dglke.readthedocs.io/en/latest/>



Training the model for anti-protease activity

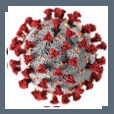
- › Active inhibitors: 206, inactive: 32
 - Graph representation -> graph embedding
- › hidden_dim = 40, regularization_coef = 1.00E-07, 24 threads (2 CPU 6 cores 12 threads each)
- › Calculation mode: Trans_E_L2
 - For a triplet (h, r, t) , $h + r \approx t$.
 - Score function $f = -\|h + r - t\|_{1/2}$
- › 800,000 epochs





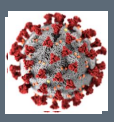
Testing with a collection of protease inhibitors

- › Repurposing strategy for 5000 protease inhibitors
- › Analyzed through the trained model
- › Repetition and comparison of Top-20 molecules
- › Further study on compounds often present in the Top-20 molecules



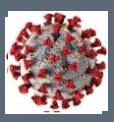
Roadmap for ligand-based candidate Mpro inhibitors

- › Test the binding with **MD simulation**
- › Analysis of binding and affinity to Mpro
- › Biological tests
- › Valorisation



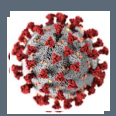
Conclusion and perspectives (1/2)

- › Two promising series of virtual screening
 - Structure-based for inhibiting RBD-ACE2 interaction
 - Ligand-based for inhibiting viral protease
 - Collaboration for biological tests and valorisation
- › DL-based approaches are more and more used in virtual screening
 - VSM-3G project on the MBI-DS4H platform (<http://mbi.loria.fr>)
- › 3D simulation using molecular dynamics is essential for virtual screening



Conclusion and perspectives (2/2)

- › 3D MD simulation also underway for two other projects
 - MD simulation for pairwise analyses
 - › Analysis of pair-wise atom interaction during MD trajectories
 - › Comparing native RBD + ACE2 with variant RBD and ACE2
 - › Collaboration with LAMA in Chambéry Université Savoie Mont-Blanc
 - MD simulation for studying Spike trimer kinetics
 - › Huge system : more than one million atom
 - › Targeted MD needed : post-doc project of Dominique Mias-Lucquin
 - › [Video mp4](#)
 - Currently, more than 100,000 hours requested from JeanZay super computer at IDRIS



› Capsid –LORIA

CNRS-Université de Lorraine

Bernard Maigret

Dominique Mias-Lucquin

Isaure C. de Beauchêne

Vincent Leroux (guest)

M1 interns : Ugo Cottin and
Nicolas Bombârde

› IDRIS (Jean-Zay)

CNRS-Université Paris-Sud

Thibaut Véry

Thanks !

› IRIM Infectious disease Research
Institute of Montpellier

CNRS-Université de Montpellier

Laurent Chaloin

Olivier Moncorgé

› LAMA Laboratory of Mathematics

CNRS - Université Savoie Mont-Blanc

Aria Gheeraert

Laurent Vuillon

Questions ?

COVAL NANCY

Étude épidémiologique de séroprévalence
contre le virus SARS-CoV-2 (COVID-19)
dans la population de la Métropole du
Grand Nancy

Anne Gégout-Petit, H. Jeulin, K. Legrand, A. Bochnakian, P.
Vallois, E. Schvoerer, F. Guillemin

28 septembre 2021
Journée FCH COVID

COVAL

1. Contexte
2. Protocole
3. Mise en oeuvre
4. Résultats
5. Discussion

Contexte

- Printemps 2020, pandémie, confinement
- Recommandation de l'OMS de réaliser des études de séroprévalence
- Appel-tribune du président de la SFdS de réaliser des sondages aléatoires
- Appel de nos tutelles : INSMI, INRIA, Université de Lorraine à participer à des actions « COVID »

Histoire du projet

- **07/04/20** : J. GARNIER, P. VALLOIS 😊, Laboratoire Atoutbio (privé), U de Lorraine, IPSOS
- **17/04/20** : Métropole du Grand Nancy financeur 😊, sondage à partir des listes électorales
- **Mi avril**: échange avec J.-M. MARIN P. CATTIAUX « RIPH2 » puis réunion 29/04
- **Début mai** : Contact avec F. GUILLEMIN 😊, (CIC Epidémiologie clinique CHRU NANCY)
- **mi mai** : CHRU de NANCY, E. SCHVOERER, H. JEULIN, virologues,
- **Prise en main du projet par le CIC** 😊,
- **04/06** : envoi des documents au CPP 😊, [protocole accéléré COVID](#)
- **17/06** : acceptation CPP,
- **22/06** : premier envoi de courriers
- **27/06** : Premiers prélèvements
- **24/07** : Inclusions terminées

COVAL

1. Contexte

2. *Protocole*

disponible sur clinicaltrials.gov

3. Mise en oeuvre

4. Résultats

5. Discussion

Protocole

- **Promoteur** : Centre Hospitalier Régional Universitaire de Nancy
- **Financier** : Métropole du Grand Nancy
- **Investigateur Principal** : Evelyne SCHVOERER ; Laboratoire de Virologie
- **Coordonnateur scientifique** : Pierre VALLOIS ; Université de Lorraine, Institut Elie Cartan
- **Méthodologie** :
 - Anne GEGOUT-PETIT ; Université de Lorraine, Institut Elie Cartan
 - Francis GUILLEMIN ; CIC 1433 Epidémiologie Clinique
- **Biologie** :
 - Hélène JEULIN ; Laboratoire de Virologie
- **Coordination de l'étude** : Francis GUILLEMIN ; CIC 1433 Epidémiologie Clinique
 - Coordinatrice d'étude : Karine LEGRAND
 - Data-manager : Jean Marc VIRION

Protocole

- ***Étude épidémiologique de séroprévalence contre le virus SARS-CoV-2 (COVID-19) dans la population de la Métropole du Grand Nancy (MGN)***

- **Objectif principal de l'étude**

Estimer la prévalence des sérologies positives anti-SARS-CoV-2, par détection d'anticorps IgT-totales (IgM/IgA/IgG) dans la population générale de la MGN

- **Objectifs secondaires**

- Symptômes : % d'asymptomatiques, profil
- Facteurs de susceptibilité à la COVID-19
- Ménages : séroprévalence, diffusion intra
- Protection (neutralisation) par des anticorps anti-Cov2
- Estimation pour mise en œuvre de Modèles mathématiques (SEIR)

Protocole données recueillies

- Auto-questionnaire
 - caractéristiques sociodémographiques, médicales,
 - contacts potentiels avec COVID-19 et symptômes,
 - Questionnaire EPICES, précarité sociale,
 - Questionnaires déclinés pour adolescents et enfants
- Variable environnementale
 - Score EDI (European Deprivation Index)
- Prélèvement sanguin
 - Séropositivité à IgT anti-SARS-CoV-2 (ELISA)
 - Si séropositif : recherche de séroneutralisation

Score EPICES

N°	Questions	Oui	Non
1	Rencontrez-vous parfois un travailleur social (assistante sociale, éducateur) ?	10,06	0
2	Bénéficiez-vous d'une assurance maladie complémentaire (mutuelle) ¹ ?	-11,83	0
3	Vivez-vous en couple ?	-8,28	0
4	Etes-vous propriétaire de votre logement (ou accédant à la propriété) ?	-8,28	0
5	Y-a-t-il des périodes dans le mois où vous rencontrez de réelles difficultés financières à faire face à vos besoins (alimentation, loyer, EDF...) ?	14,80	0
6	Vous est-il arrivé de faire du sport au cours des 12 derniers mois ?	-6,51	0
7	Etes-vous allé au spectacle (cinéma, théâtre...) au cours des 12 derniers mois ?	-7,10	0
8	Etes-vous parti en vacances au cours des 12 derniers mois ?	-7,10	0
9	Au cours des 6 derniers mois, avez-vous eu des contacts avec des membres de votre famille autres que vos parents ou vos enfants	-9,47	0
10	En cas de difficultés (financières, familiales, de santé...) y-a-t-il dans votre entourage des personnes sur qui vous puissiez compter pour vous héberger quelques jours en cas de besoin ?	-9,47	0
11	En cas de difficultés (financières, familiales, de santé...), y-a-t-il dans votre entourage des personnes sur qui vous puissiez compter pour vous apporter une aide matérielle (y compris un prêt) ?	-7,10	0
constante		75,14	

- Score >30 → précarité sociale

European Deprivation Index EDI

- Variable environnementale, associée au quartier (IRIS)
 - % logement surpeuplé,
 - % pas de chauffage,
 - % pas de voitures
 - % nationalité étrangère
 - % ouvriers non qualifiés
 - % Famille monoparentale, % ménage ≥ 6 personnes
 - % faible niveau d'étude
 - % chômage
 - % non-propriétaire
- Variable continue, regroupée en classes (quintiles) par l'INSEE

Protocole Sondage

- En grappe à partir des listes électorales
 - TAS sur les listes
 - Invitation de tous les membres du ménage
 - RDV questionnaire et prélèvement
- 2000 personnes contactées → 2000 participants

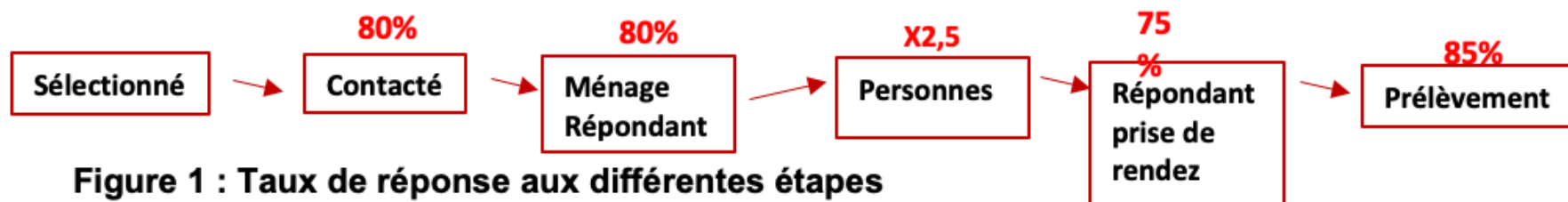


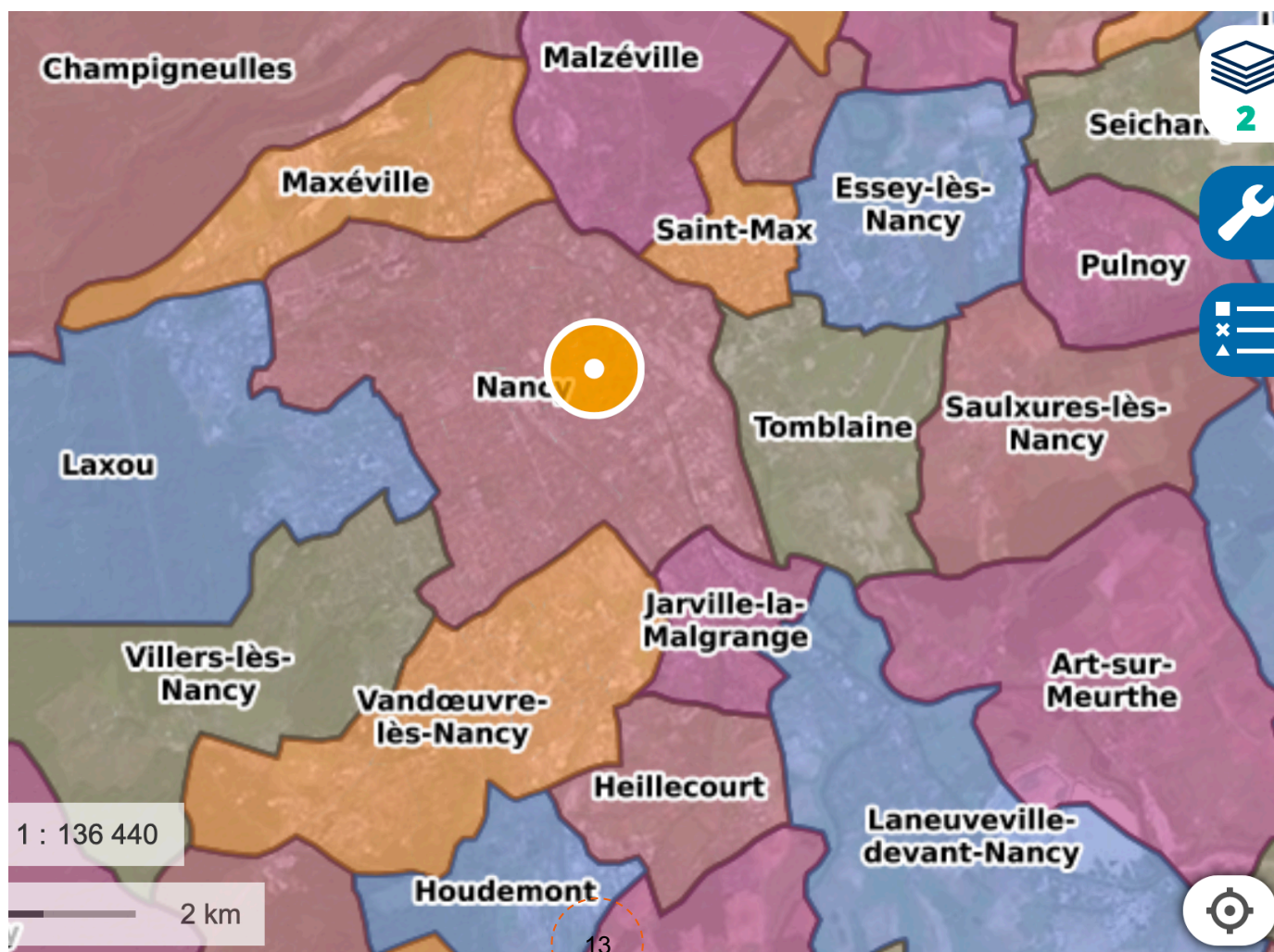
Figure 1 : Taux de réponse aux différentes étapes

COVAL

1. Contexte
2. Protocole
3. *Mise en œuvre*
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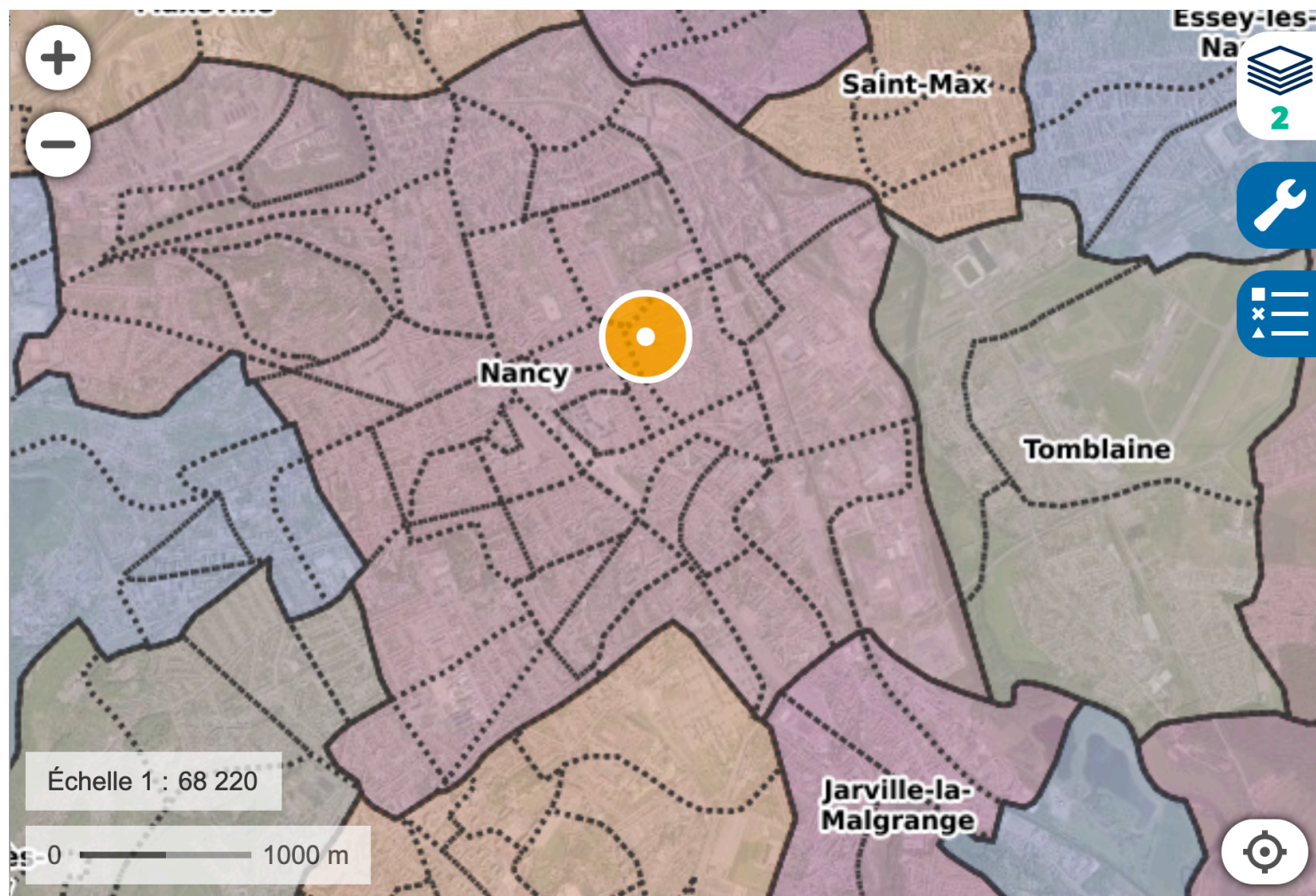
Tirage au sort

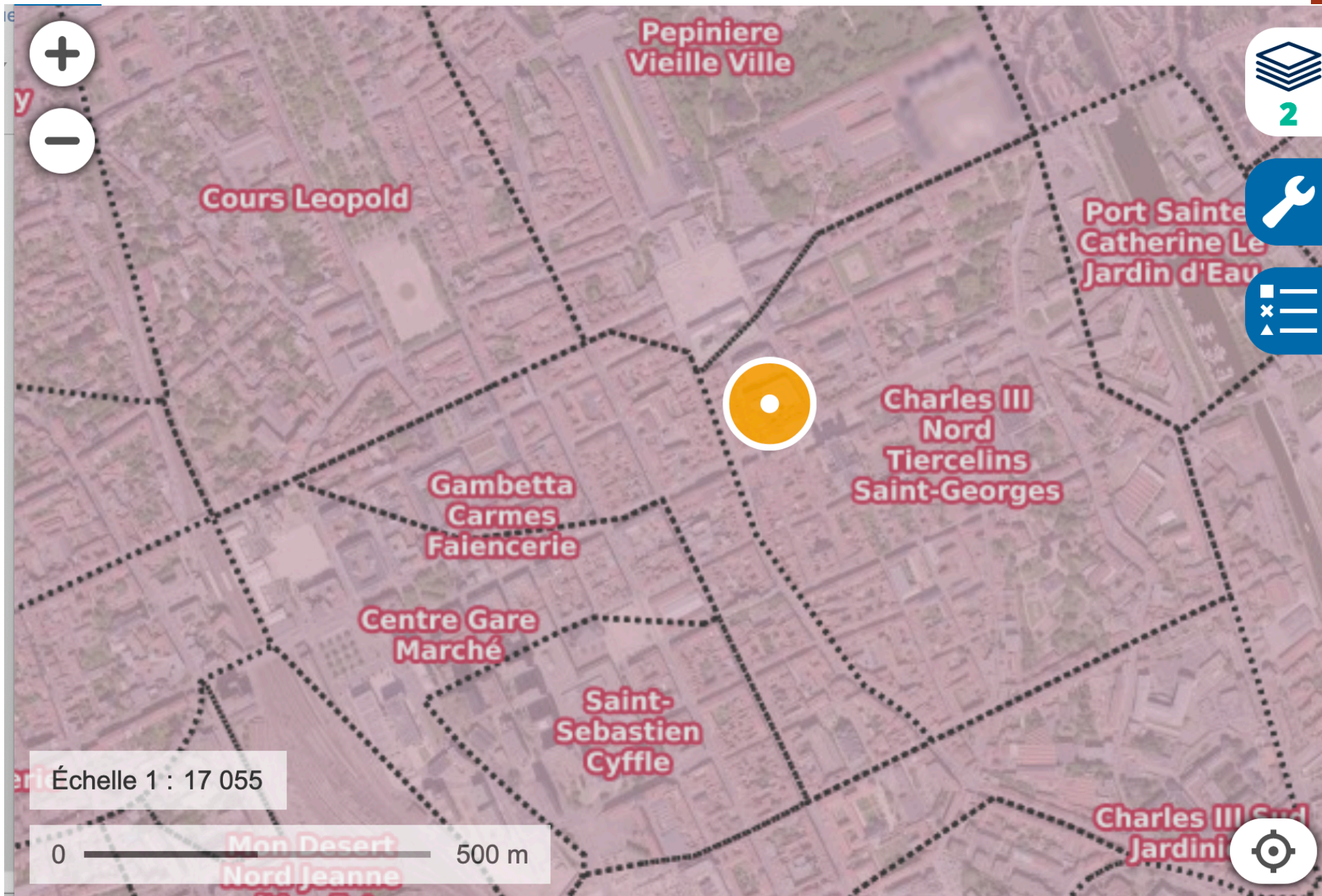
- MGN = 20 communes



Tirage au sort

- MGN = 20 communes = 110 zones IRIS





Données cartographiques : © FEDER, Préfecture de la région Grand-Est,

Tirage au sort (TAS)

- MGN = 110 zones IRIS (INSEE)
- Décision d'un TAS proportionnel au nombre de ménages par IRIS
- Pb de l'attribution de l'IRIS à chaque adresse (merci à Damien Garaud <https://gitlab.com/Oslandia/pyris>)
 - Sous échantillonnage de la base des 150 000 adresses à disposition
 - Attribution de l'IRIS
 - Sélection proportionnelle aux IRIS

Sollicitation des volontaires

- 2000 envois prévus
→ finalement 6094 courriers envoyés

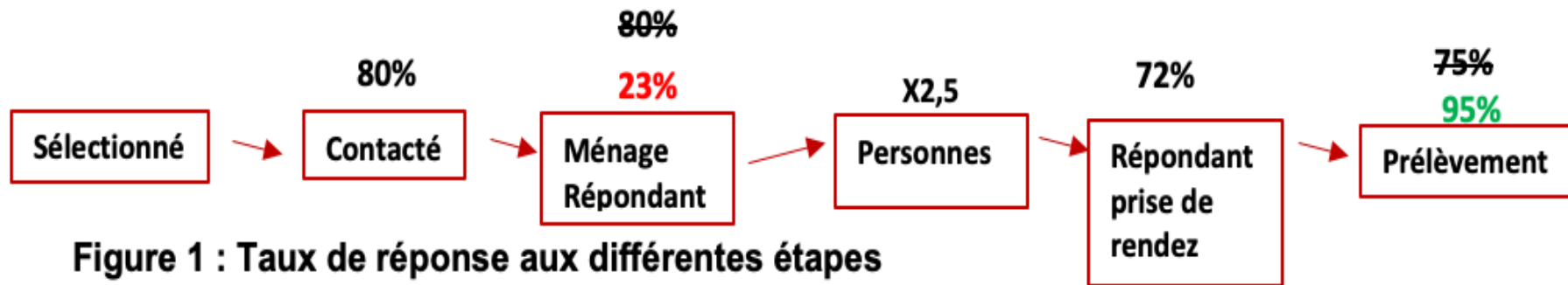


Figure 1 : Taux de réponse aux différentes étapes

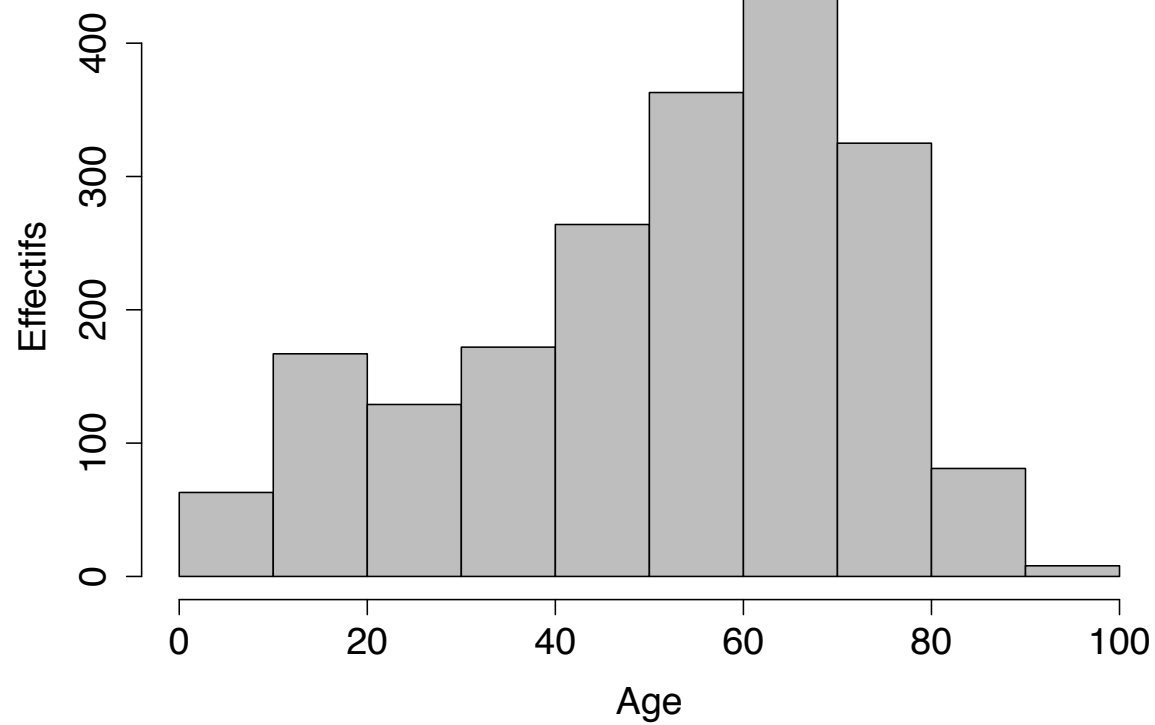
COVAL

1. Contexte
2. Protocole
3. Mise en œuvre
4. *Résultats*
 1. Echantillon
 2. Séroprévalence
 3. Symptômes
5. Discussion

Description échantillon

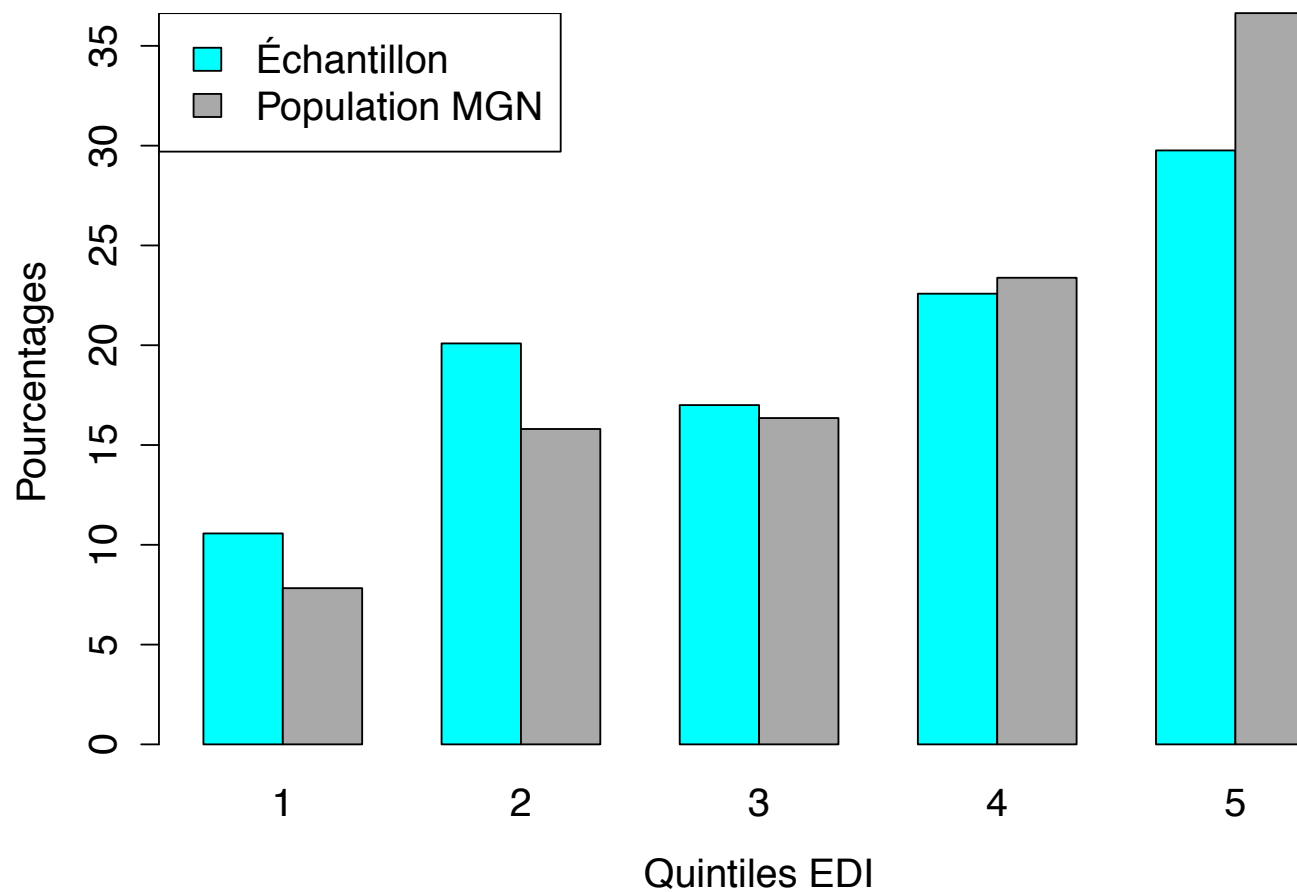
- **Participants**
 - 1111 ménages sur 108 des 110 IRIS
 - 2006 participants : questionnaires + prélèvements
 - 469 venues seules, 938 à deux, 599 en famille (≥ 3)
- **Caractéristiques**
 - De 5 à 95 ans !
 - 148 mineurs
 - 55% de femmes
 - 18 % fumeurs, 29% anciens fumeurs
- **Biais de participation**
 - Personnes plus âgées
 - CSP plus élevées
 - Favorisation sociale plus élevée

AGE



Répartition par classes d'âge, n=2006

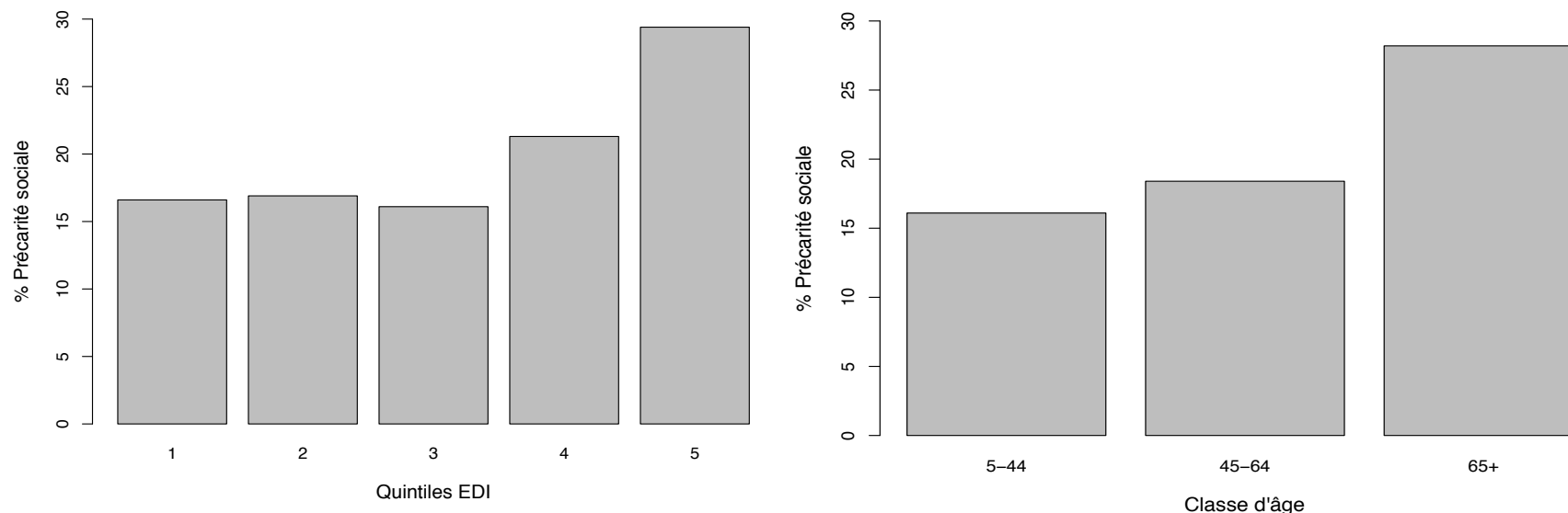
Quintile EDI



Représentativité par quintile EDI, (1: plus favorisé, ...
5 moins favorisé)

Précarité

- 21% des participants en précarité sociale
- Lien précarité avec EDI et AGE



Précarité sociale en fonction du quintile EDI (gauche) ou de la classe d'âge (droite)

Comorbidités

- 15 % ont une comorbidité pouvant induire une forme sévère du COVID
- Lien significatif avec la précarité sociale
 - 26% chez les précaires
 - 13% sinon

Histoire avec la COVID

- 13% pensaient avoir été infectés par la COVID
 - 86% ont ressenti des symptômes
 - 44% ont été en contact avec un malade
- 47% ont déclaré avoir ressenti au moins un des 18 symptômes depuis début février

Séroprévalence (en juillet)

- 43 individus séropositifs
- Séroprévalence brute 2,14 % (IC [1,5-2,8])
- Après redressement sur quintile EDI et standardisation sur Age et Sexe
 - MGN : 2,47%
 - France : 2,30%

Facteurs de susceptibilité

Modalities	Positive /Total	%	% CI	OR	OR CI	p-value
Age						
05-19	2/203	0.98	0.11 - 3.51	0.69	0.10 - 3.22	0.654
20-34	10/215	4.65	2.25 - 8.39	3.37	1.18 - 10.93	0.028*
35-49	5/350	1.43	0.47 - 3.30	ref		
50-64	16/553	2.89	1.66 - 4.66	2.06	0.80 - 6.33	0.163
65-79	9/573	1.57	0.72 - 2.96	1.10	0.38-3.61	0.864
80+	1/112	0.89	0.02 - 4.87	0.62	0.03 - 3.91	0.666
quintileEDI						
1-2	6/615	1.0	0.4 - 0.2	ref		
3-4-5	37/1391	2.66	1.88 - 3.65	2.77	1.25 - 7.34	0.0212

Séroprévalence (%) par groupe, OddsRatio (régression logistique), IC à 95%.

Non-significatif (manque de puissance ?)

Modalities	Positive /Total	%	% CI	OR	OR CI	p-value
Précarité						
EPICES<30	35/1428	2.45	1.71 - 3.39	ref		
EPICES>=30	4/388	1.03	0.28 - 2.62	0.40*	0.12 - 1.00	0.07
			*ajusté sur EDI			
Baccalauréat						
oui	33/1266	2.60	1.80 - 3.64	ref		
non	8/586	1.37	0.59 - 2.67	0.51*	0.22 - 1.06	0.09
missing	154		*ajusté sur EDI			
Smoking status						
Non-Smoker	38/1583	2.40	0.17 - 3.28	ref	ref	
Smoker	4/338	1.18	0.32 - 3.00	0.49	0.14 - 1.22	0.174
missing	85					

Séroprévalence (%) par groupe, OddsRatio (régression logistique), IC à 95%.

Séroprévalence des foyers

- 34 foyers positifs
 - 3.1% IC = [2,1 – 4,3]
- Diffusion intra-foyer significative
 - Test de permutations
 - RR= 30 IC=[11 – 78]

Taille Foyer	36	37	38	39	40	41	42	43
Effectifs	1	11	166	1 698	14 821	88 020	327 212	568 071

Distribution empirique du nombre de foyers positifs en cas de distribution aléatoire des cas

Symptômes

- **18 symptômes recensés** : fièvre, toux, rhino, douleurs poitrine, perte gout et/ou odorat, mal de gorge, douleurs musculaires, courbatures, fatigue, maux de tête, éruption cutanée, manque d'appétit, manque de souffle, diarrhée, perte d'équilibre, nausée, yeux irrités
- **3 degrés d'intensité** : léger, supportable, intense
- **Date de début des symptômes**

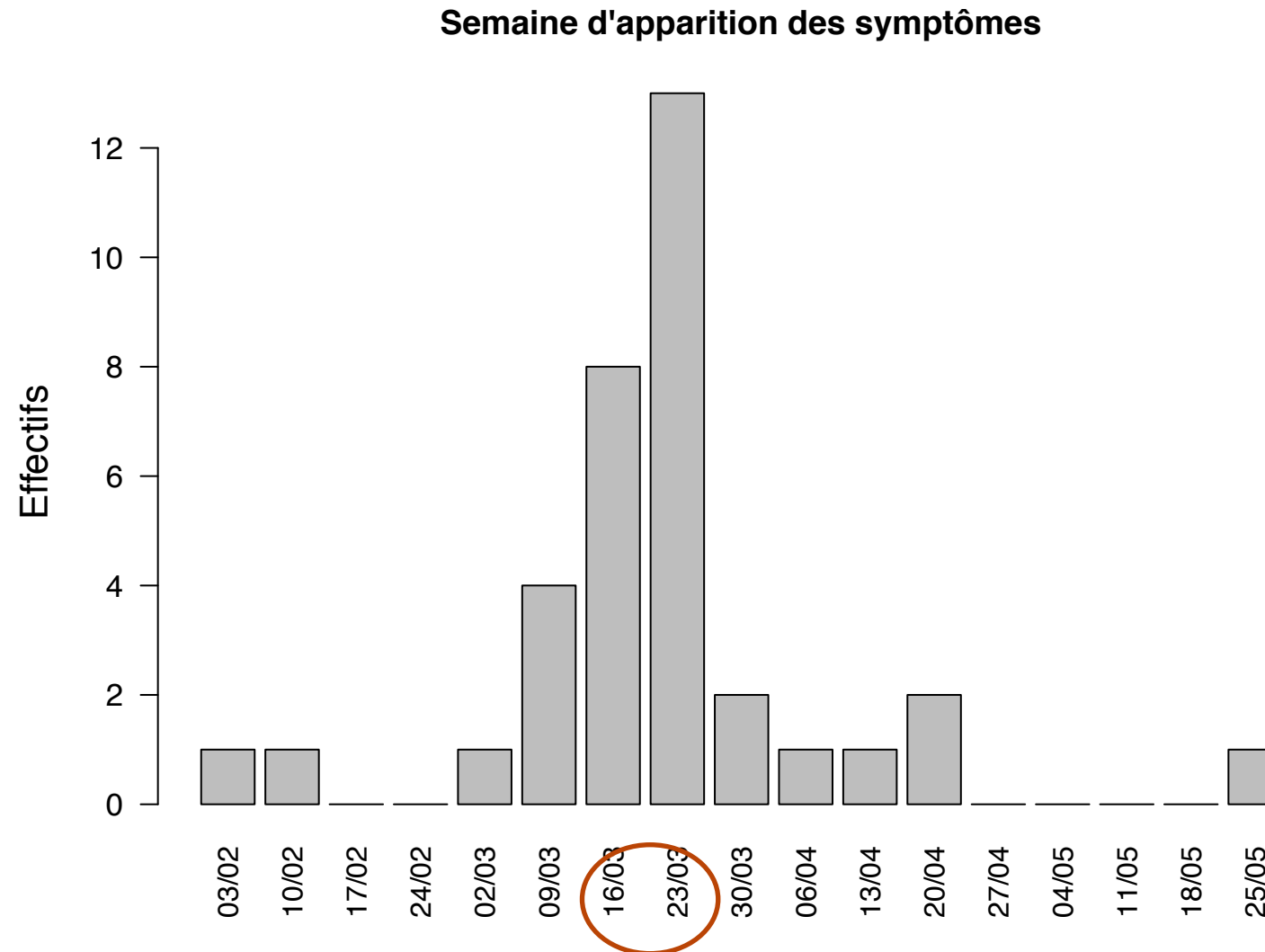
Expression des symptômes

	Positive	Negative	p-value
At least one symptom	83.7	47.6	1,25E-17
At least one intense sympto	60.5	13.1	1,27E-18
Fever	62.8	14.7	1,30E-17
Cough	53.5	12.1	1,20E-15
Fatigue	48.8	10.9	6,13E-11
Dyspnea	46.5	6.6	6,12E-23
Aches	41.9	8.2	2,22E-14
Anosmia/ageusia	39.5	2.3	4,60E-44
Muscle pain	37.2	10.4	2,97E-08
Sore throat	34.9	14.7	3,00E-04
Headaches	32.6	10.1	2,06E-06
Rhinorrhea	30.2	16.6	0,019
Chest pain	25.6	6.3	5,55E-17
Diarrhea	23.30	8.4	0,0006
Abdominal pain	20.9	6.8	0,0004
Loss of balance	14.0	4.0	0,001
Nausea	14.0	3.8	0,0009
Pas faim	11.6	1.1	1,52E-09
skin rashes	7.0	4.9	0,523
Irritated eyes	4.7 ³⁰	6.0	0,7

Symptômes des séro+

- Asymptomatiques : 16% (IC= [7– 31])

Date des symptômes chez les séro+



Etude COVAL

32

Séro-neutralisation

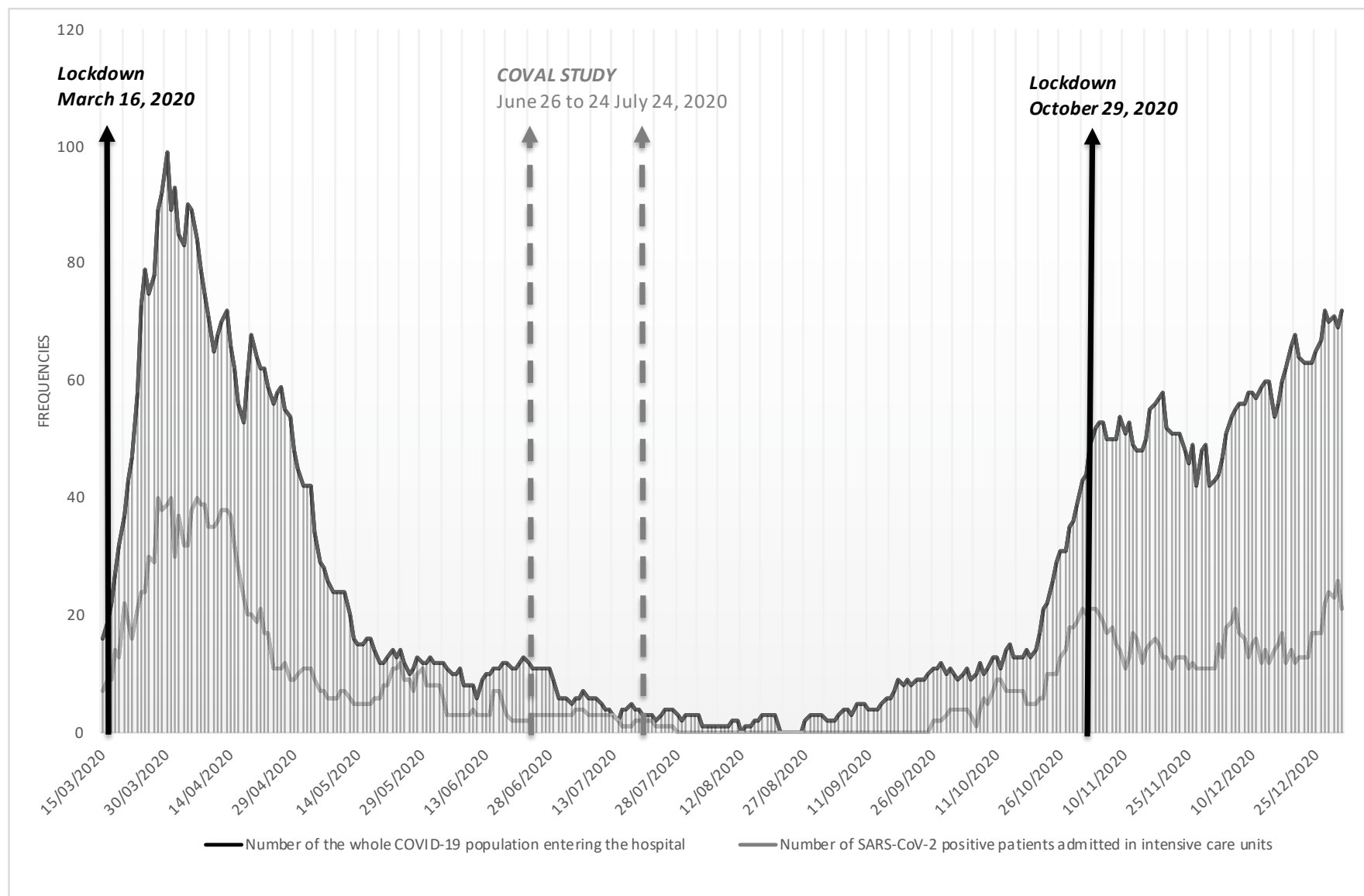
31 sur 43

COVAL

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Discussion

- Objectif premier : modélisation ... 2,1%, on fait quoi ?
- Limite du sondage sur les listes électorales
- Communication et politique
- Déposé sur MedRxiv et accepté pour publi dans Viruses

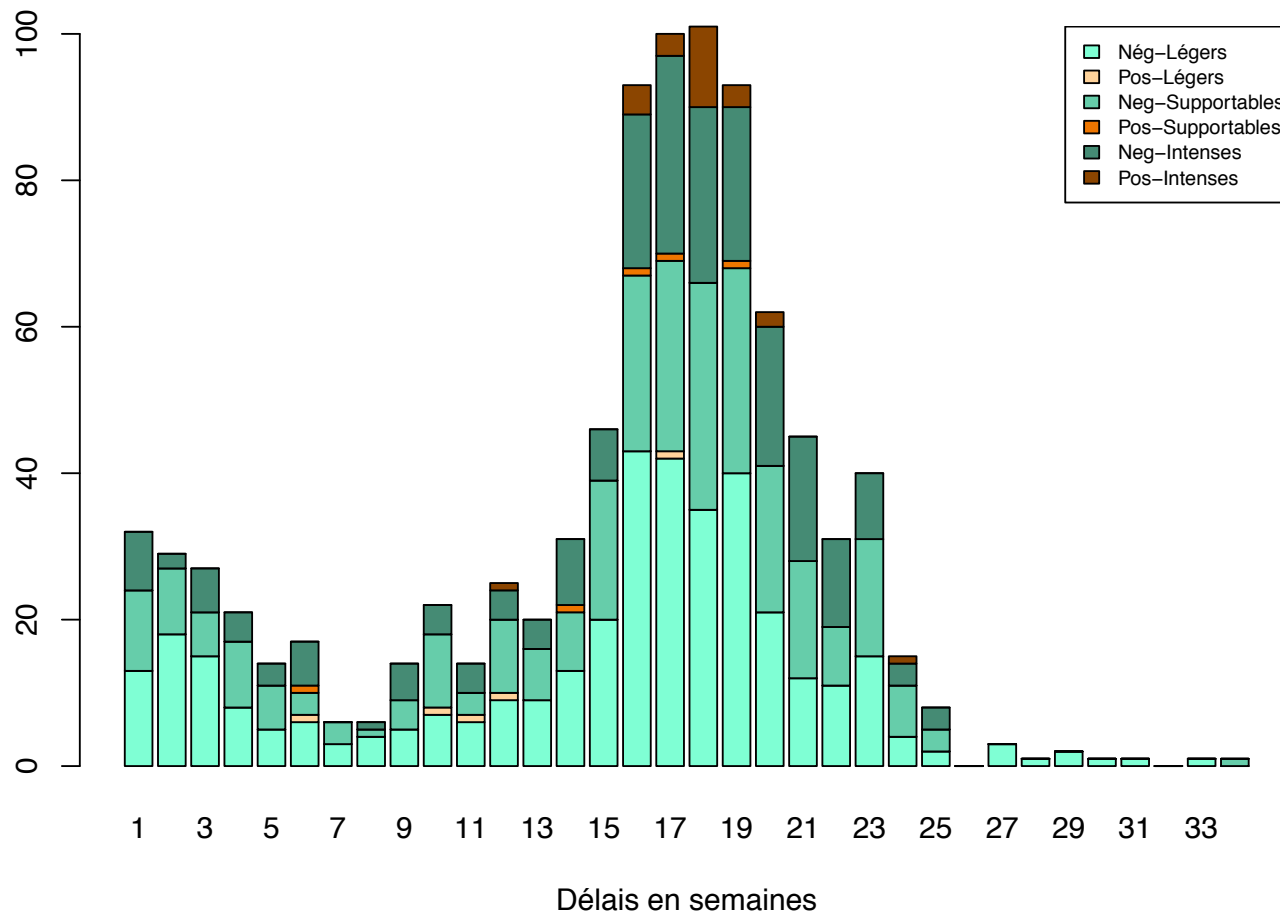


Discussion

Le Parisien

Le Pr Olivier Schwartz, de l'unité virologie et immunologie de l'Institut Pasteur, souligne ainsi qu'« en mai, entre 4% et 5% des Français étaient immunisés et 10% en Ile-de-France ».

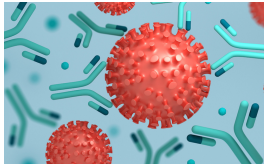
Symptômes : intensité et délais apparition-prélèvement



Etude COVAL

Séroprévalence des foyers

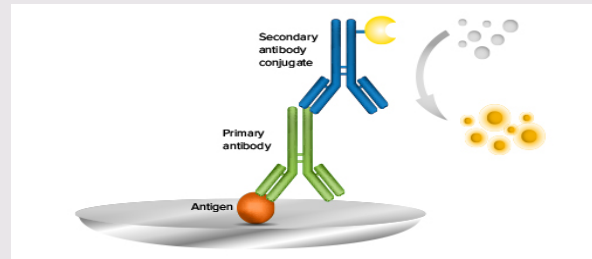
- 34 foyers positifs
 - 11 personnes venues seules
 - 17 foyers de 2 individus
 - 6 avec 2 séropositifs
 - 11 avec 1 séropositif
 - 4 foyers de 3 individus
 - 1 avec 3 séropositifs
 - 1 avec 2 séropositifs
 - 2 avec 1 ..
 - 2 foyers de + 1 de 4 individus
 - 1 seul séropositif
- Diffusion intra-foyer significative



Méthodes sérologiques

Méthode choisie

- Méthode ELISA (BioRad)
- Recherche d'Immunoglobulines totales (IgA, IgM, IgG)
- Spécificité : 100% ; Sensibilité : 100% (>21 jours)



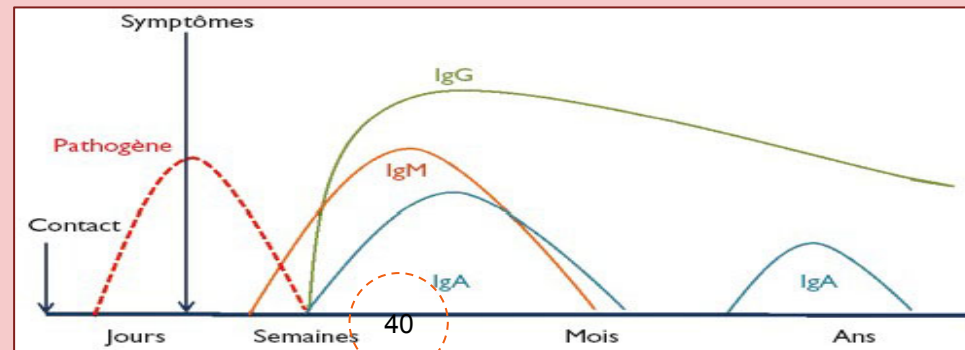
Analyses complémentaires

Si résultat positif, ou si membre foyer positif

→ confirmer le résultat

→ définir quel type d'Ac est présent & dater l'infection

- Recherche IgM (Automate Maglumi Snibe)
- Recherche IgG (Automate Maglumi Snibe)
- Recherche IgA (méthode ELISA EuroImmuno)



Herd immunity and Covid19

Abderrahman Iggridr

Inria and IECL University of Lorraine

Journée Scientifique Fédération Charles Hermite "COVID"
28 septembre 2021

Ongoing work with
G. Lallet (IECL), P.-M. Bliman (Inria-Paris),
J. Koiller (UFJ, Brazil), and M. Souza (UFF, Brazil)

Introduction

Simple SIR model

SIR model with permanent immunity and vaccination

SIR model with permanent immunity and with imperfect vaccine

Imperfect vaccine and waning immunity

Herd Immunity

We quote WHO to stress its importance.

'Herd immunity', also known as 'population immunity', is the indirect protection from an infectious disease that happens when a population is immune either through vaccination or immunity developed through previous infection. WHO supports achieving 'herd immunity' through vaccination.

A simple threshold theorem in [Dietz, 1975] and popularized by [Anderson and May, 1991] says that if the proportion p of immune individuals (by vaccination or recovered from the disease) satisfies

$$p > 1 - \frac{1}{\mathcal{R}_0}, \quad (1)$$

then the incidence of infection will decline and will finally disappear.

Here $\mathcal{R}_0$ is the now well known basic reproduction ratio, usually defined as the expected number of secondary cases produced by a typical infected individual during his entire period of infectiousness in a completely susceptible population.

A mathematical definition of $\mathcal{R}_0$ was given by [Diekmann and Heesterbeek, 1990], as the spectral radius of a positive linear operator "the next generation operator". A more computational method has been given by [van den Driessche and Watmough, 2002] for compartmental disease transmission model.

SIR model

$$\begin{cases} \dot{S} &= \mu N - \beta S I - \mu S \\ \dot{I} &= \beta S I - \gamma I - \mu I \\ \dot{R} &= \gamma I - \mu R. \end{cases} \quad (2)$$

$$\mathcal{R}_0 = \frac{\beta}{\mu + \gamma} N \quad (3)$$

Theorem

1. If $\mathcal{R}_0 \leq 1$, then $(N, 0, 0)$ is the only equilibrium of (2) (disease free equilibrium DFE). It is globally asymptotically stable.
2. If $\mathcal{R}_0 > 1$, the DFE is unstable, and there exists a unique endemic equilibrium (EE) of (2) EE is globally asymptotically stable.

SIR model with vaccination

Suppose now in addition that the susceptible are vaccinated with a vaccination rate ϕ . Denoting by V the immune individuals (either naturally or by vaccination), the corresponding model is now

$$\begin{cases} \dot{S} &= \mu N - \beta S I - \mu S - \phi S \\ \dot{I} &= \beta S I - \gamma I - \mu I \\ \dot{V} &= \gamma I - \mu V + \phi S. \end{cases} \quad (4)$$

The basic reproduction ratio for model (4) is

$$\mathcal{R}_{0,\text{vac}} = \frac{\mu}{\mu + \phi} \frac{\beta}{\mu + \gamma} N = \frac{1}{\left(1 + \frac{\phi}{\mu}\right)} \mathcal{R}_0. \quad (5)$$

The DFE is given by $(S^*, 0, V^*)$ with $S^* = \frac{\mu N}{\mu + \phi}$ and

$$V^* = \frac{\phi N}{(\mu + \phi)}.$$

Theorem

If $\mathcal{R}_{0,\text{vac}} \leq 1$ then the DFE $(S^*, I^*, V^*) = (\frac{\mu}{\mu + \phi} N, 0, \frac{\phi}{\mu + \phi} N)$ is globally asymptotically stable in the nonnegative orthant.

If $\mathcal{R}_{0,\text{vac}} > 1$ there exists a unique endemic equilibrium in the positive orthant and this endemic equilibrium is globally asymptotically stable in the nonnegative orthant minus the stable manifold of the DFE, i.e., in $\mathbb{R}_+^3 \setminus \{I = 0\}$.

The asymptotic proportion of vaccinated is

$$p = \frac{V^*}{N} = \frac{\phi}{\mu + \phi} = 1 - \frac{\mu}{\mu + \phi} = 1 - \frac{1}{1 + \phi/\mu}. \quad (6)$$

Thus $\mathcal{R}_{0,\text{vac}} = (1 - p) \mathcal{R}_0$. To eliminate the disease, the proportion p of vaccinated should satisfy the inequality

$$\mathcal{R}_{0,\text{vac}} = (1 - p) \mathcal{R}_0 < 1,$$

which is exactly the condition (1).

For COVID-19 with a $\mathcal{R}_0$ estimated at 3.3, the coverage of vaccination must be over 70%.

SIR Model with imperfect vaccine

The model now incorporates a vaccine efficiency

$$\varepsilon = 1 - \sigma. \quad (7)$$

The vaccine provides no protection to a fraction σ of the vaccinated.

$$\begin{cases} \dot{S} &= \mu N - \beta S I - \mu S - \phi S \\ \dot{I} &= \beta S I + \sigma \beta V I - \gamma I - \mu I \\ \dot{V} &= \phi S - \mu V - \sigma \beta V I \\ \dot{R} &= \gamma I - \mu R \end{cases} \quad (8)$$

For this model, The basic reproduction ratio is

$$\mathcal{R}'_{0,\text{vac}} = \frac{\beta}{\mu + \gamma} N [(1 - p) + \sigma p] = [1 - \varepsilon p] \mathcal{R}_0, \quad (9)$$

We still have: If $\mathcal{R}'_{0,\text{vac}} \leq 1$ then the DFE is GAS. Thus to eradicate the disease, p should satisfy

$$p > \frac{1}{\varepsilon} \left(1 - \frac{1}{\mathcal{R}_0} \right). \quad (10)$$

For COVID-19 with a $\mathcal{R}_0$ estimated at 3.3. Assuming permanent natural immunity and a vaccine efficacy $\varepsilon = 0.9$, the coverage of vaccination must be over 78%.

Imperfect vaccine and waning immunity

We will consider [here](#) a model for which the vaccine provides protection to a fraction $\varepsilon = (1 - \sigma)$ of the vaccinees and, in addition, the immunity [is waning, with a rate \$\theta\$ when it originates from the vaccine, and a rate \$\psi\$ when it ensues from natural infection.](#)

$$\left\{ \begin{array}{l} \dot{S} = \mu N - \beta S I - \mu S - \phi S + \theta V + \psi R \\ \dot{I} = \beta S I + \sigma \beta V I - \gamma I - \mu I \\ \dot{V} = \phi S - (\mu + \theta) V - \sigma \beta V I \\ \dot{R} = \gamma I - (\mu + \psi) R. \end{array} \right. \quad (11)$$

Using $R = N - S - I - V$,

$$\begin{cases} \dot{S} = (\mu + \psi) N - \beta S I - (\mu + \phi + \psi) S + (\theta - \psi) V - \psi I \\ \dot{I} = \beta S I + \sigma \beta V I - \gamma I - \mu I \\ \dot{V} = \phi S - (\mu + \theta) V - \sigma \beta V I \end{cases} \quad (12)$$

The Disease Free Equilibrium of System(12) is $E_0 = (S^*, 0, V^*)$ where

$$S^* = \frac{\mu + \theta}{\mu + \phi + \theta} N \quad \text{and} \quad V^* = \frac{\phi}{\mu + \phi + \theta} N = p' N$$

$$\mathcal{R}_{0,\text{vac}}'' = \frac{\beta N}{\mu + \gamma} \frac{\mu + \theta + \sigma \phi}{\mu + \theta + \phi} = \mathcal{R}_0 (1 - \varepsilon p'),$$

Theorem

The disease free equilibrium $(\frac{\mu + \theta}{\mu + \theta + \phi} N, 0, \frac{\phi}{\mu + \theta + \phi} N)$ is a globally asymptotically stable equilibrium for System (12) if

$$\mathcal{R}_{0,\text{vac}}'' \leq \frac{(\mu + \theta)(\mu + \phi + \text{Max}(\psi, \theta))}{(\mu + \phi + \theta)(\mu + \text{Max}(\psi, \theta))} := c^*, \quad (13)$$

or, equivalently

$$p' \geq \frac{\mathcal{R}_0 - 1}{\varepsilon \mathcal{R}_0 - \frac{\psi - \theta}{\mu + \psi}} \text{ and } \varepsilon > \frac{1}{\mathcal{R}_0} \frac{\psi - \theta}{\mu + \psi} + 1 - \frac{1}{\mathcal{R}_0} \quad (14)$$

- ▶ If $\psi \leq \theta$ then $c^* = 1$.
- ▶ If $\psi > \theta$ then $c^* < 1$.

Consequences of imperfect vaccine and waning immunity

If $\theta \geq \psi$, i.e., the natural immunization waning rate is smaller than the vaccine waning rate: the duration of "natural" immunization after recovering is larger than the period of acquired immunity by vaccine then the disease free equilibrium $((1 - p')N, 0, p'N)$ is a globally asymptotically stable equilibrium for System (12) iff $\mathcal{R}_{0,\text{vac}}'' \leq 1$ iff

$$p' \geq \frac{1}{\varepsilon} \left(1 - \frac{1}{\mathcal{R}_0} \right).$$

Consequences of imperfect vaccine and waning immunity

If $\theta < \psi$, then $c^* < 1$. In this case $\mathcal{R}_{0,\text{vac}}'' \leq 1$ is no more sufficient to eradicate the disease: a backward bifurcation may appear, it is possible to have existence of endemic equilibria (one of them is AS) even if $\mathcal{R}_{0,\text{vac}}'' < 1$.

Therefore, the DFE cannot be GAS. It is only AS. To prevent an outbreak, the initial condition must be in the basin of attraction of the DFE, a condition not easy to characterize.

Instead Theorem 3 gives a sufficient condition for eradication:

$$\varepsilon > \frac{1}{\mathcal{R}_0} \frac{\psi - \theta}{\mu + \psi} + 1 - \frac{1}{\mathcal{R}_0} \text{ and } p' \geq \frac{\mathcal{R}_0 - 1}{\varepsilon \mathcal{R}_0 - \frac{\psi - \theta}{\mu + \psi}}$$

For COVID-19 with a $\mathcal{R}_0$ estimated at 3.3. Assuming permanent natural immunity and a vaccine efficacy $\varepsilon = 0.9$, the coverage of vaccination must be over 78%.

Consequences of imperfect vaccine and waning immunity

We use a conservative value for the death rate

$$\frac{1}{\mu} = 75 \text{ years} = 75 \times 365 \text{ days which gives } \mu = 0.0000365 \text{ d}^{-1}.$$

The period of recovery is estimated between 4 to 12. We will use a conservative value of 10 days which gives $\gamma = 0.1 \text{ d}^{-1}$.

The period of vaccin-immunity is largely unknown since COVID-19 is a completely new disease. We will use a conservative value of 3 years: $\theta = 1/1095 = 0.0009 \text{ d}^{-1}$.

The duration of immunization after recovering is completely unknown. We will use a mean time of 180 days:

$$\psi = 1/180 = 0.005.$$

With these values we have $\theta < \psi$:

$$\varepsilon > 0.943 \text{ and } p' > 1.067!!! \text{ No herd immunity !}$$

With $\psi = 1/365$, we get

$$\varepsilon > 0.898 \text{ and } p' > 0.99$$

herd immunity possible by vaccinating the whole population

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-  O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz, *On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations*, J. Math. Biol., 28 (1990), pp. 365–382.
-  K. Dietz, *transmission and control of arbovirus diseases*, in SIMS 1974 Utah conference proceedings, D. Ludwig and K. Cooke, eds., 1975, pp. 104–121.
-  P. van den Driessche and J. Watmough, *reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission*, Math. Biosci., 180 (2002), pp. 29–48.

Detecting SARS-CoV-2 in wastewater

Wasted science?

Ulysse Herbach

28 septembre 2021

Introduction

« ***SARS** in **wastewater** : a **model** to predict an epidemic peak* »

Le projet « Siwam »

« *SARS in wastewater : a **m**odel to predict an epidemic peak* »

Christophe Gantzer (LCPME, Nancy) – 07/09/2020

« *à peu près 50% des infectés sécrètent du virus* »

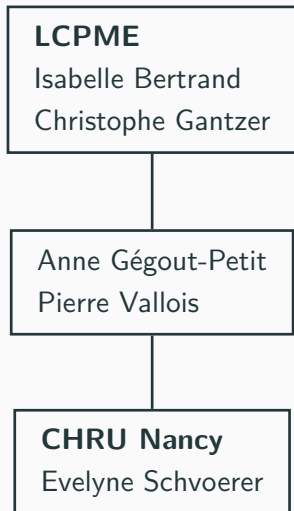
Le projet « Siwam »

« *SARS in wastewater : a **m**odel to predict an epidemic peak* »

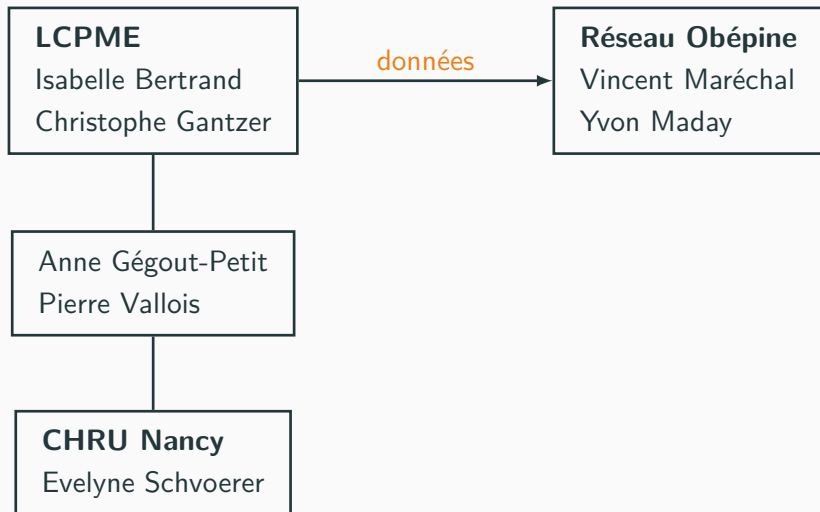
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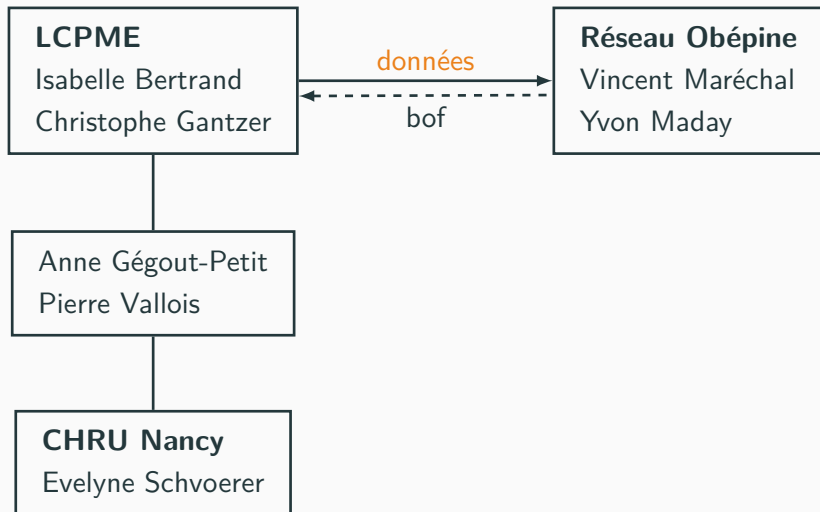
Un peu de contexte



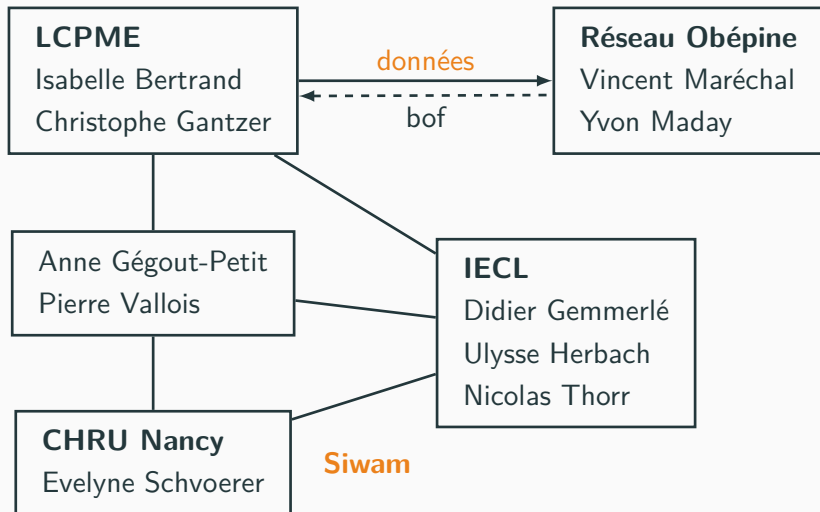
Un peu de contexte



Un peu de contexte

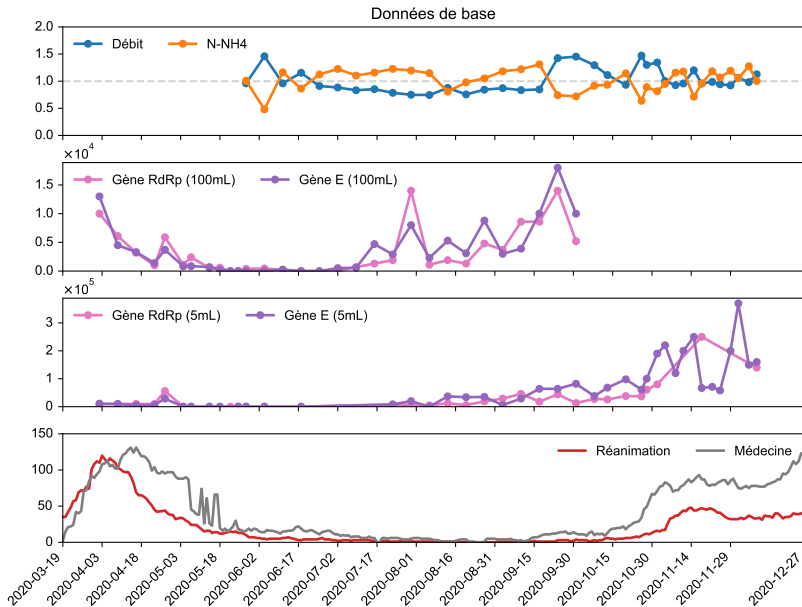


Un peu de contexte

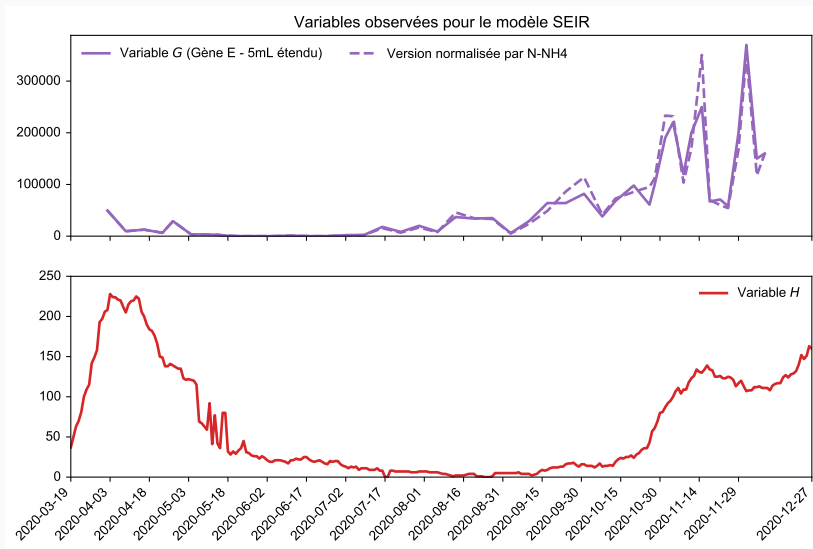


Les données

Données de base



Observables



Temps de séjour à l'hôpital

Médecine

Vague	Moyenne	Médiane
1	8.95	3
2	9.95	3

Réanimation

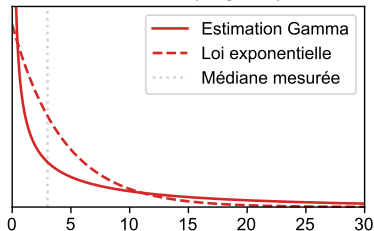
Vague	Moyenne	Médiane
1	15.5	7
2	12.1	8

Remarques

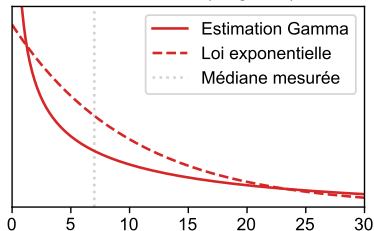
1. Pour la vague 2, tous les patients ne sont pas sortis : la moyenne est donc sous-estimée
2. Il vaut mieux prendre la médiane dans les deux cas

Loi du temps de séjour

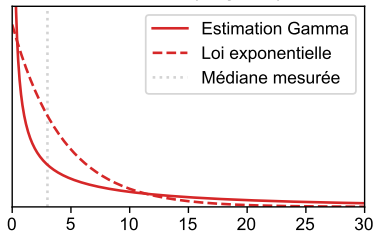
Médecine (Vague 1)



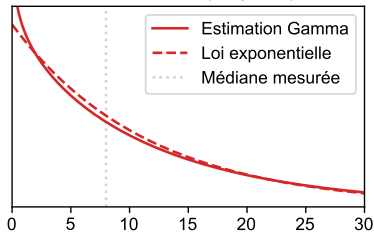
Réanimation (Vague 1)



Médecine (Vague 2)

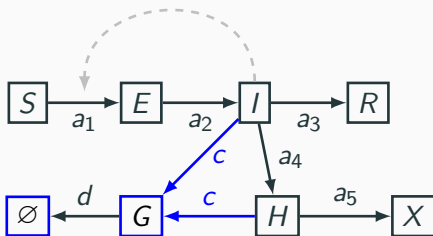


Réanimation (Vague 2)



Modélisation dynamique

Premier modèle



$$S' = -a_1 I \cdot S$$

$$E' = a_1 I \cdot S - a_2 E$$

$$I' = a_2 E - (a_3 + a_4) I$$

$$R' = a_3 I$$

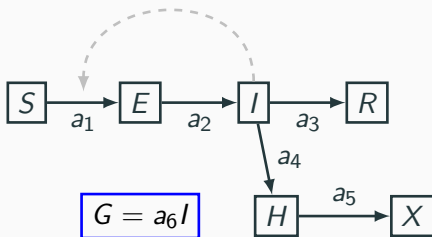
$$H' = a_4 I - a_5 H$$

$$X' = a_5 H$$

$$G' = c(I + H) - dG$$

- La somme des cases noires est constante au cours du temps
- Ce modèle est très similaire à celui d'ICUBAM
- On observe : $G(t)$, $H(t)$, $X(t)$

Premier modèle : version simplifiée



$$S' = -a_1 I \cdot S$$

$$E' = a_1 I \cdot S - a_2 E$$

$$I' = a_2 E - (a_3 + a_4) I$$

$$R' = a_3 I$$

$$H' = a_4 I - a_5 H$$

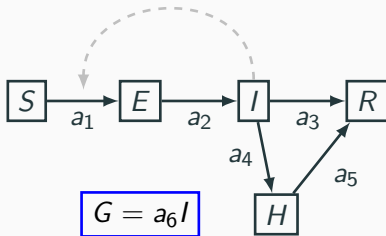
$$X' = a_5 H$$

$$G(t) = a_6 I(t)$$

Hypothèses

- $c, d \rightarrow \infty$ avec $c/d = a_6$ fixé
- $G' = 0$ **localement** (approx. de quasi-équilibre pour G)
- $I(t) \gg H(t)$ (pour tout $t \geq 0$) de sorte que $G(t) \approx a_6 I(t)$

Premier modèle : version sans flux



$$S' = -a_1 I \cdot S$$

$$E' = a_1 I \cdot S - a_2 E$$

$$I' = a_2 E - (a_3 + a_4) I$$

$$R' = a_3 I + a_5 H$$

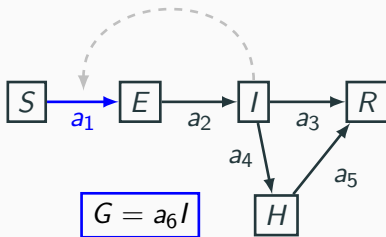
$$H' = a_4 I - a_5 H$$

$$G(t) = a_6 I(t)$$

Remarque

Les données de flux ne sont pas fiables, on oublie pour le moment

Premier modèle : version sans flux + linéaire



$$S' = 0 \quad (\text{conv. } S = 1)$$

$$E' = a_1 I - a_2 E$$

$$I' = a_2 E - (a_3 + a_4) I$$

$$R' = a_3 I + a_5 H$$

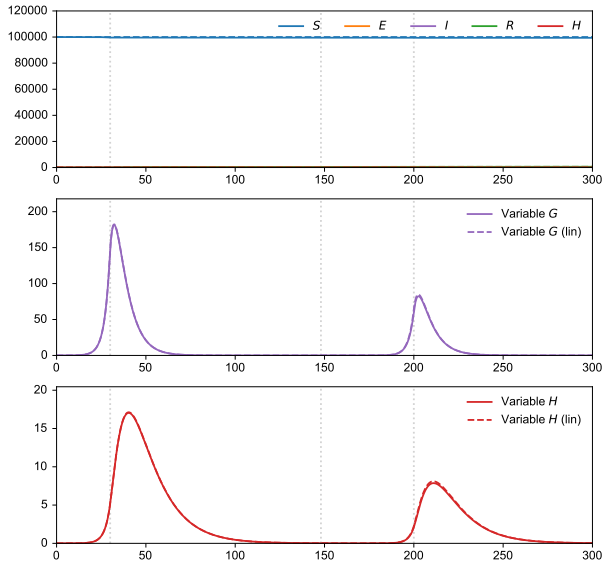
$$H' = a_4 I - a_5 H$$

$$G(t) = a_6 I(t)$$

Remarques

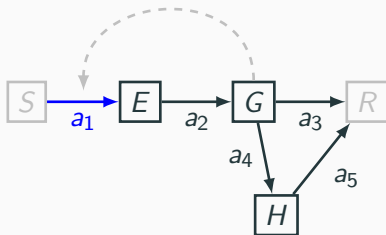
1. Très pertinent puisque le pic “naturel” est loin d’être atteint
2. On peut fixer $a_6 = 1$ puisque le système est linéaire (cf. après)
3. On peut ensuite considérer $a_1(t)$ qui correspond alors à $R_e(t)$

Exemple



Premier modèle : version finale

On reparamètre légèrement pour simplifier les notations :



$$E' = a_1 G - a_2 E$$

$$G' = a_2 E - a_3 G$$

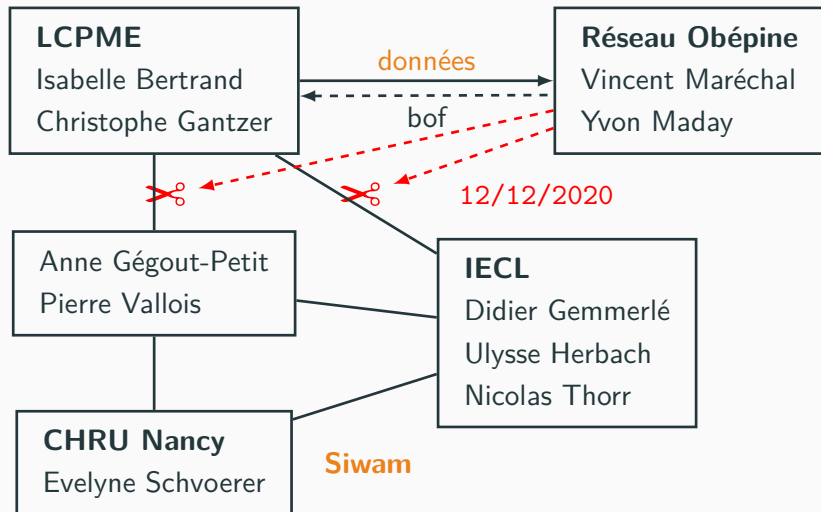
$$H' = a_4 G - a_5 H$$

Remarques

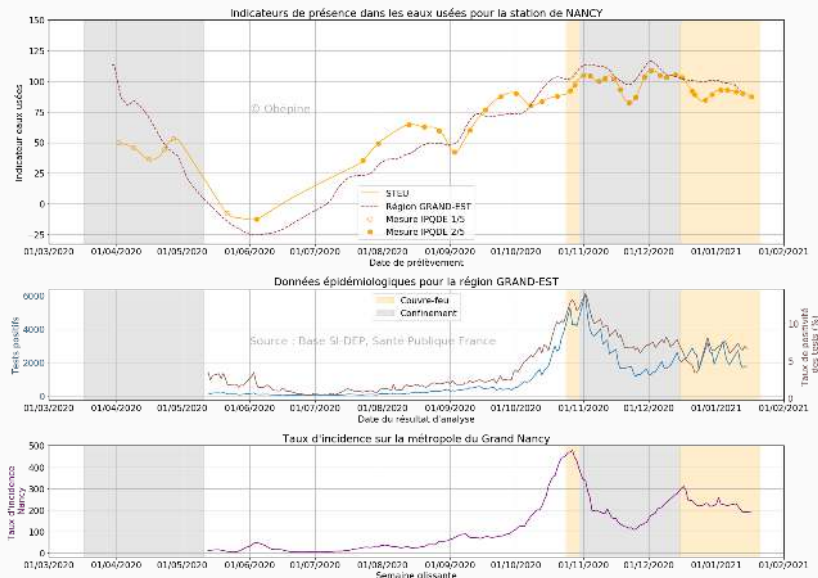
1. Plus précisément : $\tilde{E} \rightarrow E$ et $[a_4/a_6] \rightarrow a_4$ (et $G = a_6 I = \tilde{I}$)
2. Ici a_1 , a_2 , a_3 , a_4 et a_5 devraient être **identifiables**
3. On peut fixer a_5 (**donnée fiable CHRU Nancy**)
4. Il faut rajouter les paramètres $E(0)$, $G(0)$ et $H(0)$

Ça se gâte...

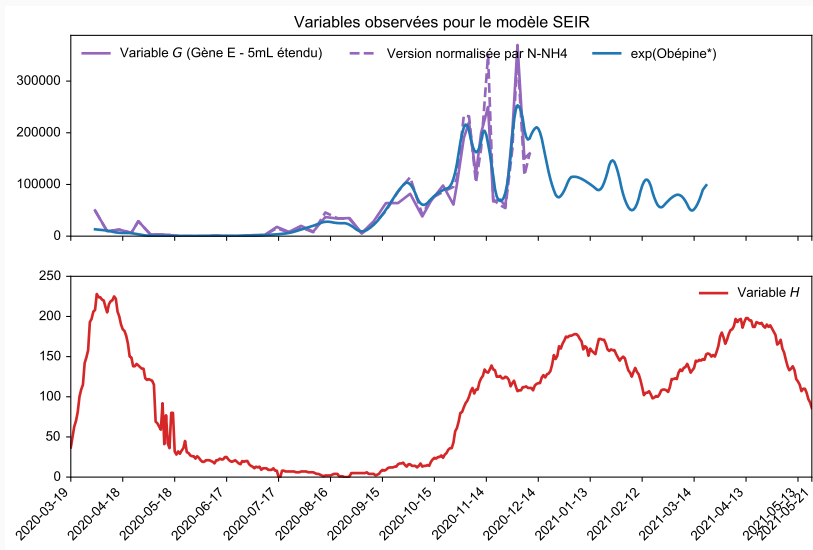
De l'eau (usée) dans le gaz



Les « données ouvertes »



Nouvelles observables



Conclusions

- La circulation du virus dans les eaux usées a tendance à **précéder de plusieurs semaines** la montée dans les hôpitaux, mais en l'état actuel les mesures sont **trop imprécises** pour avoir une puissance statistique suffisante en gardant l'avance

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- Les mesures dans les eaux usées sont potentiellement très utiles **lorsqu'on n'est pas dans un contexte de dépistage massif** (c'est BEAUCOUP moins cher, même en améliorant la précision !)

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- Ce genre d'approche n'est **pas spécifique au SARS-CoV-2 !**

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- Ce genre d'approche n'est **pas spécifique au SARS-CoV-2 !**
- **Attendre la fin du buzz** pour une science plus apaisée...

Nicolas Thorr & Didier Gemmerlé

Analyse automatique des données SPF (tests, hôpitaux)

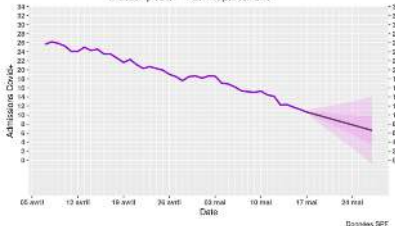
Prediction des admissions Covid+ en Meurthe-et-Moselle

Sur un horizon de 10 jours

Modèle basé sur l'évolution des cas détectés positifs

Lissage 14 jours glissants

Evolution prédite = - 26.7 % par semaine



Prediction des admissions Covid+ (REA) en Meurthe-et-Moselle

Sur un horizon de 10 jours

Prévision : sous l'hypothèse que le flux des admissions (REA) poursuive sa dynamique

Lissage 14 jours glissants

Evolution prédite = - 68.2 % par semaine



Remarque : Échanges réguliers avec un groupe de chercheurs lyonnais travaillant avec les Hospices Civils de Lyon (HCL)

- Site IECL (off) : <http://siwam.iecl.univ-lorraine.fr>
- Radio (France Bleu Isère, Pauline Tardy-Galliard 24/06/2021) :
« Covid-19, gérer l'urgence avec le numérique »
- <https://www.reseau-obepine.fr>

Gestion décentralisée d'une épidémie : efficacité globale et application au Covid-19

O. Lindamulage De Silva, S. Lasaulce, and C. Morarescu

CRAN - University of Lorraine and CNRS

Journée FCH/Covid-19
28 septembre 2021

Alone in the Dark : modéliser un début de pandémie sans données fiables

Bart LAMIROY

Pierre-Etienne MOREAU - LORIA

Contexte

31 mars 2020 – Pr. G. Karcher

Comme vous le savez un des problèmes majeurs de cette épidémie est la disponibilité des lits de réanimation.

Nous envisageons au CHU de développer rapidement un logiciel interactif de simulation pour **estimer le nombre de lits de rea nécessaires pour un établissement**

Il s'agit de mettre en entrée :

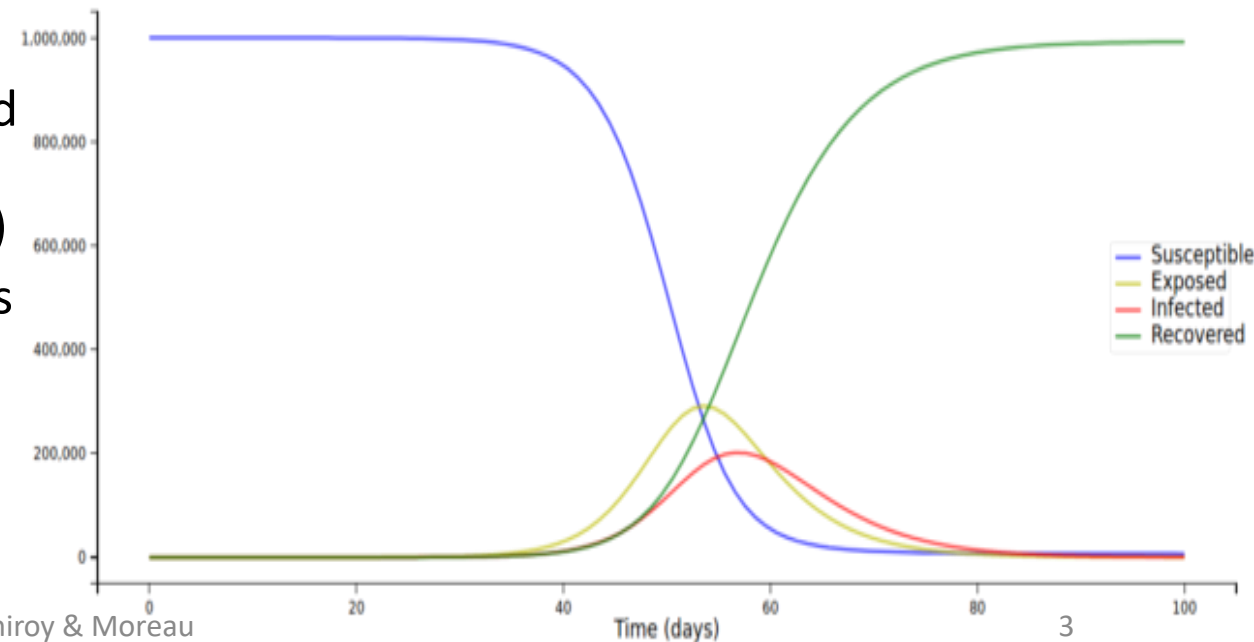
- les prévisions épidémiologiques (fournies par ailleurs)
- de **définir un modèle de durée de séjour en réa** des patients
- de mettre à jour quotidiennement le modèle en fonction de la réalité constatée

Le cahier des charges est à peu près clair. Ça marche sur excel (je l'ai fait en 2h) mais il faut le mettre au propre sur un logiciel robuste et créer les interfaces utilisateur

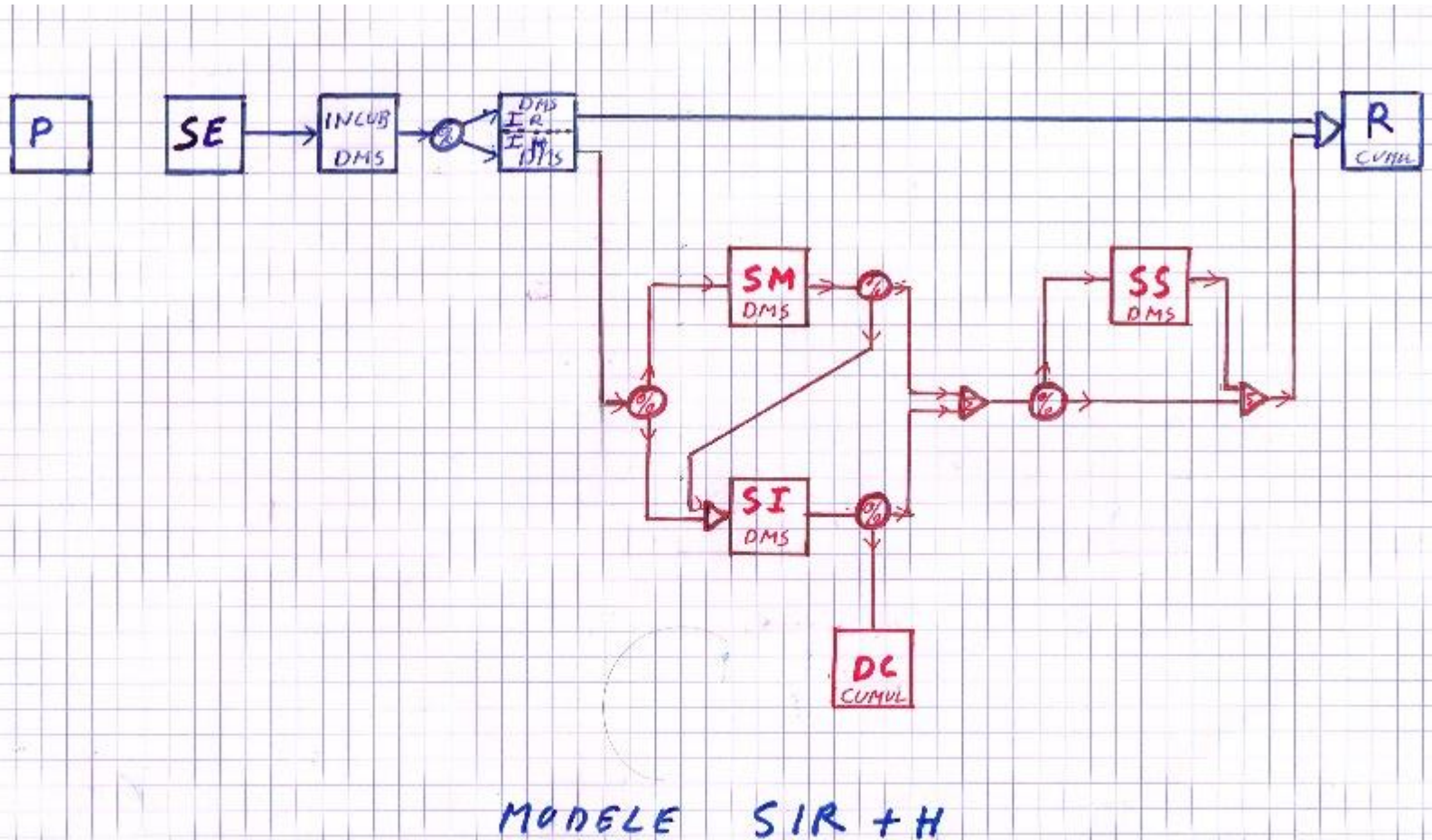
SEIR Model

- **S(t)**: number of people susceptible on day t
- **E(t)**: number of people exposed on day t
- **I(t)**: number of people infected on day t
- **R(t)**: number of people recovered on day t
- **N**: total population
- **β**: expected amount of people an infected person infects per day
- **D**: number of days an infected person has and can spread the disease
- **γ**: the proportion of infected recovering per day ($\gamma = 1/D$)
- **R₀**: the total number of people an infected person infects ($R_0 = \beta / \gamma$)

$$\begin{aligned}\frac{dS}{dt} &= -\beta \cdot I \cdot \frac{S}{N} \\ \frac{dE}{dt} &= \beta \cdot I \cdot \frac{S}{N} - \delta \cdot E \\ \frac{dI}{dt} &= \delta \cdot E - \gamma \cdot I \\ \frac{dR}{dt} &= \gamma \cdot I\end{aligned}$$



We need SIR+H Model



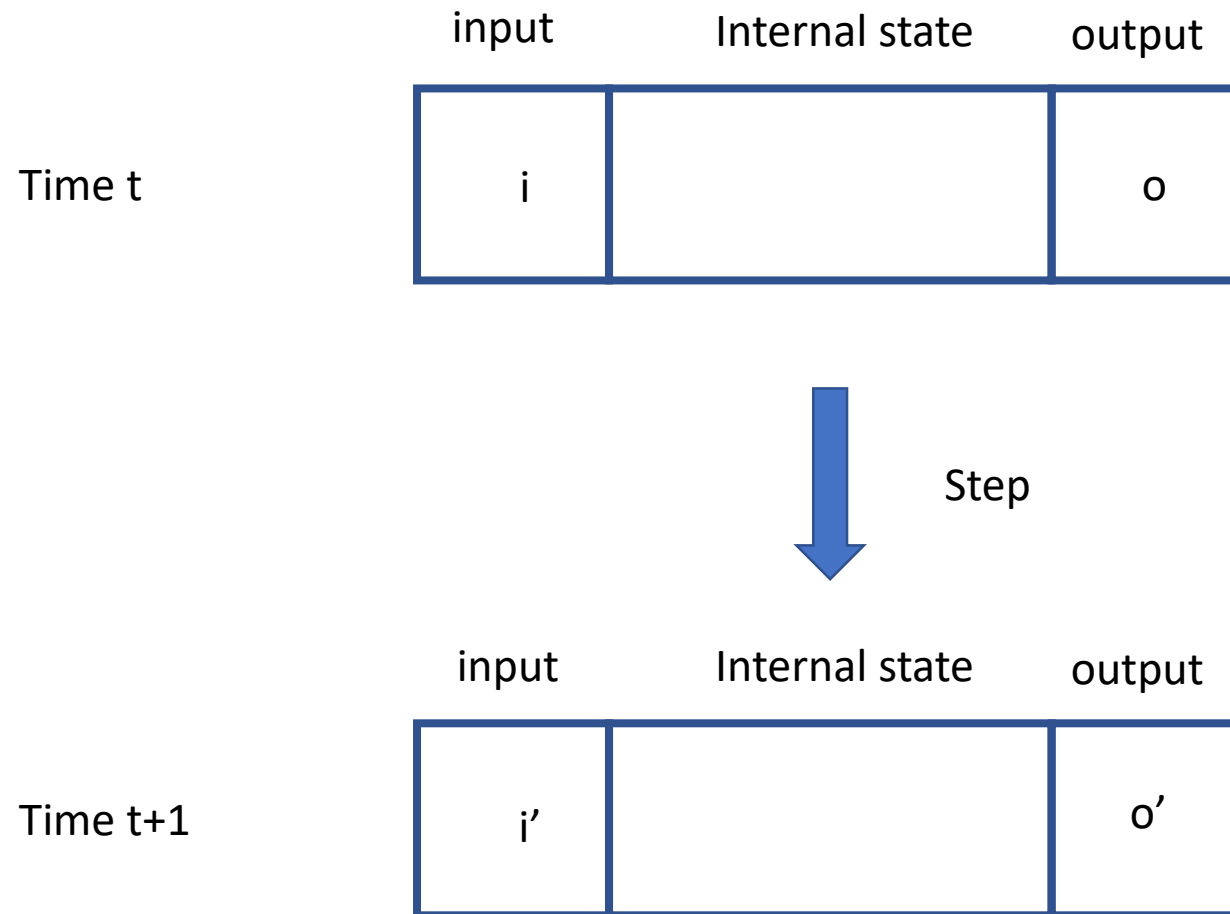
SEIR can be extended with new compartments (SM, SI, DC and SS)

But the continuous partial derivative model makes it difficult to

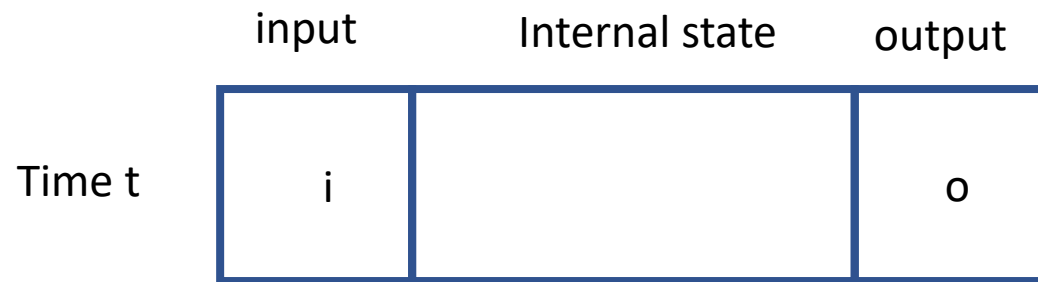
- precisely define the transition behavior of each compartment;
- model transfers and evacuations;
- experiment new configurations.

We have used a discrete model

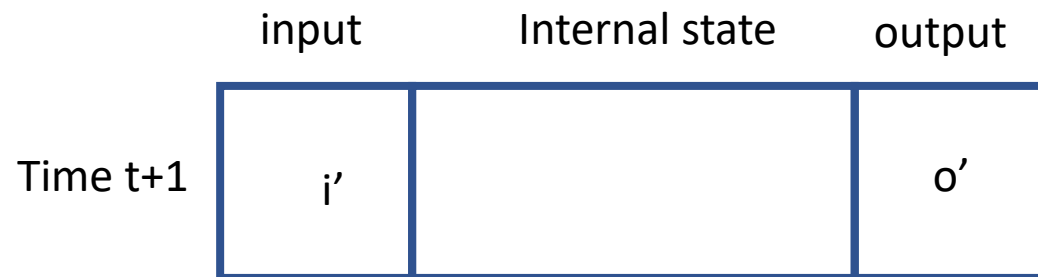
Box Model



Box Model



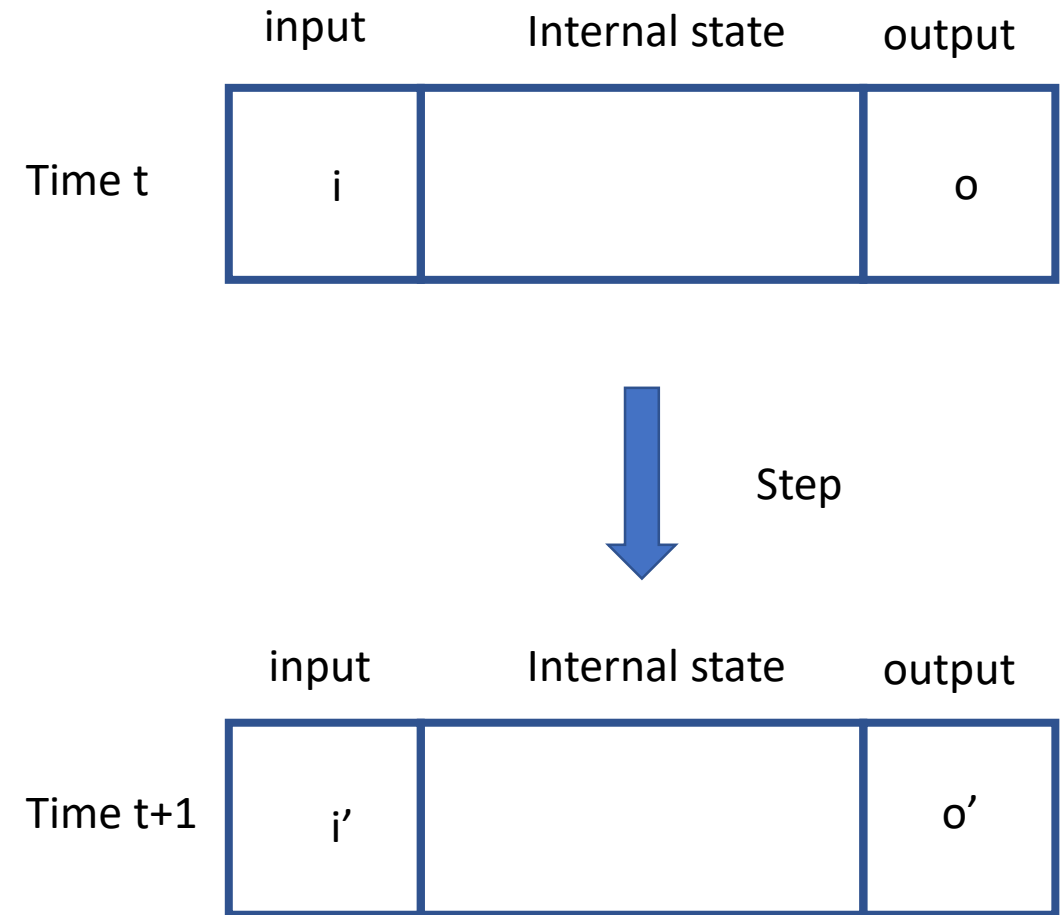
Step



- Given time t
 - $input(t)$ and $output(t)$ are floats (or integers)
- Given $0 \leq i \leq t$, we can access to past values:
 - $input(t - i)$
 - $output(t - i)$

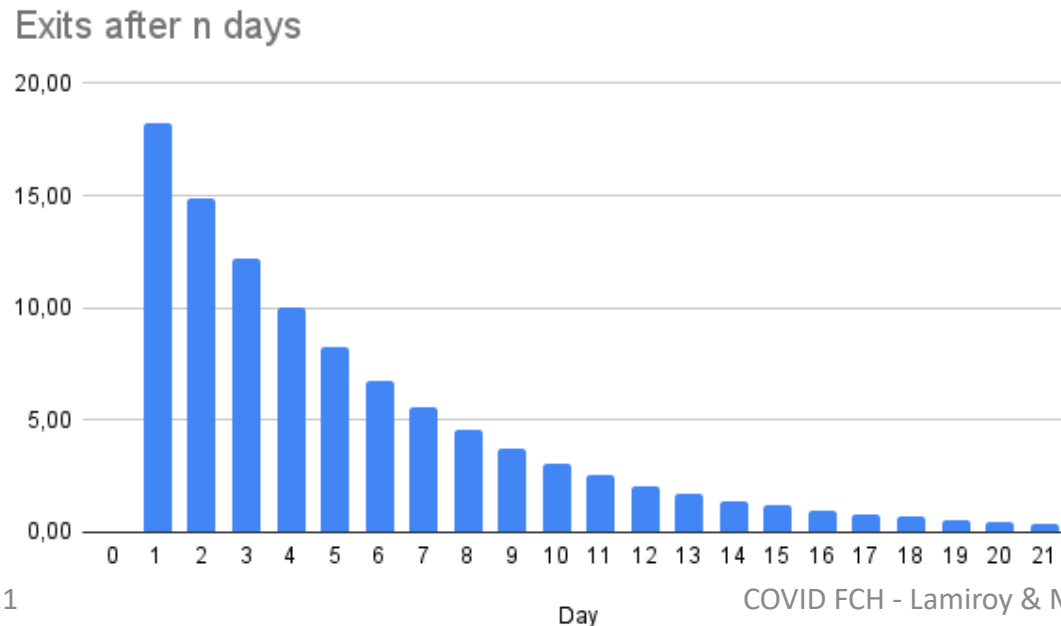
Convolution Box Model

- Given $k_1, \dots, k_n$ such that $\sum_{i=1}^n k_i = 1$
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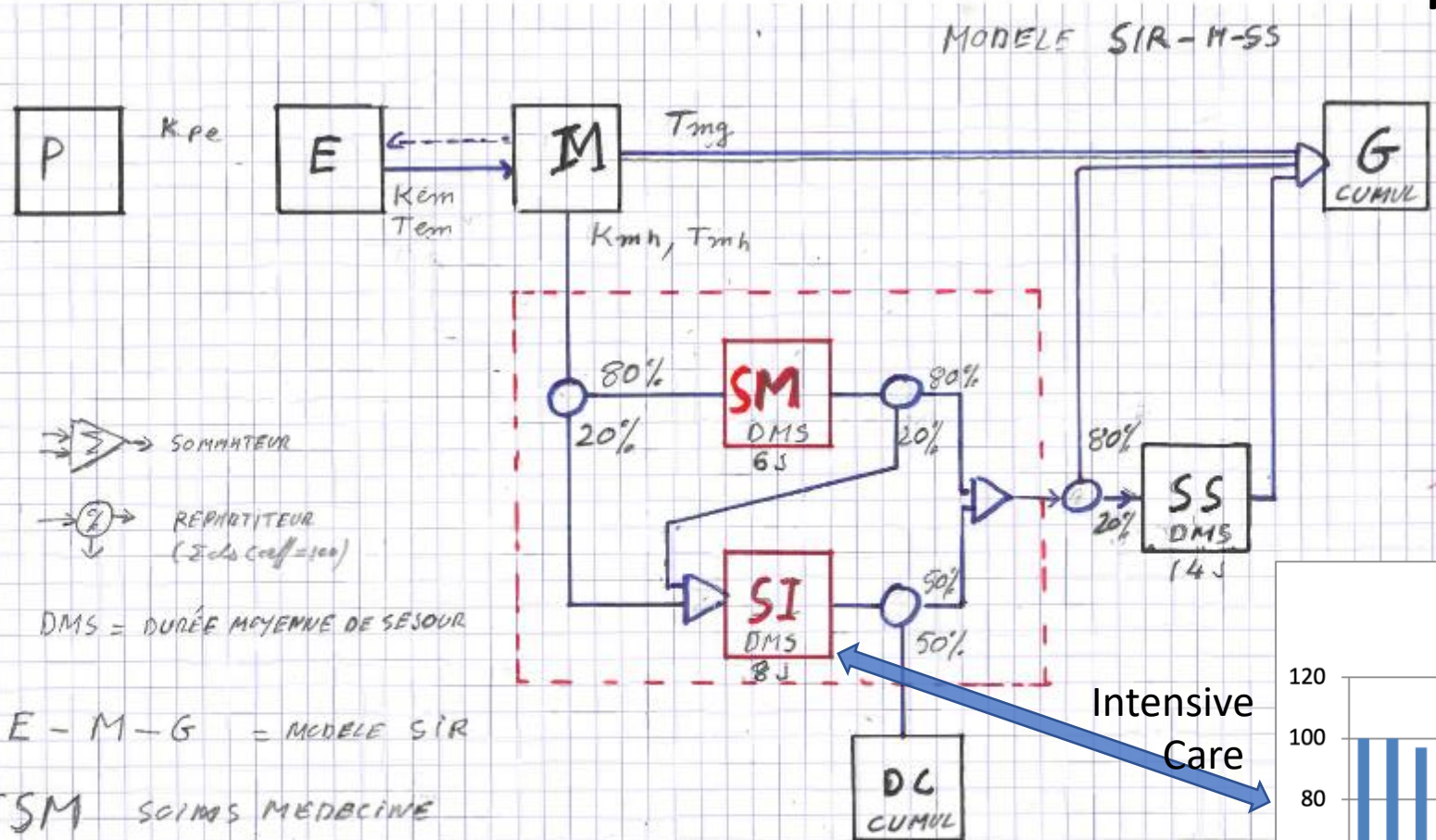


Convolution Box to model an Hospital Unit

- An Hospital Unit can be modeled by:
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 - For 100 persons admitted day-0 we have:



Convolution Box to model Hospital Services



- E: Exposed Subject
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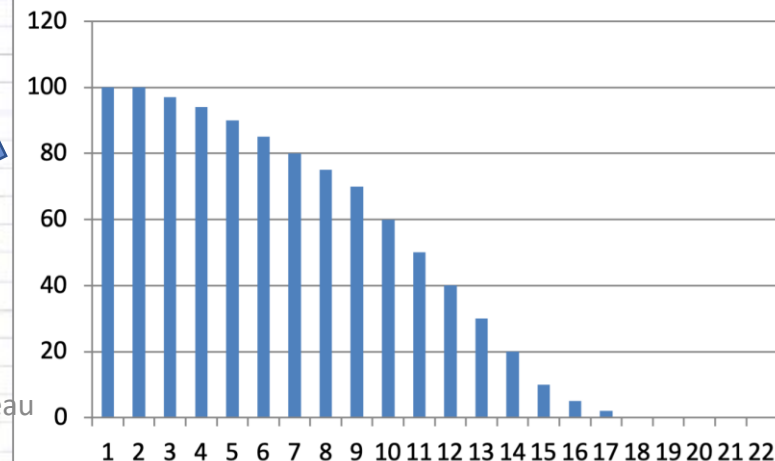
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$\begin{cases} SM & \text{SOINS MEDICINE} \\ SI & \text{SOINS INTENSIFS (= REA + SOINS CONTINUUS)} \end{cases}$

SS SOINS DE SUITE

Intensive Care

Patients Présents



Question 1: Finding Model Parameters

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- Few available data
- Unreliable data
- Delay in data generation and distribution
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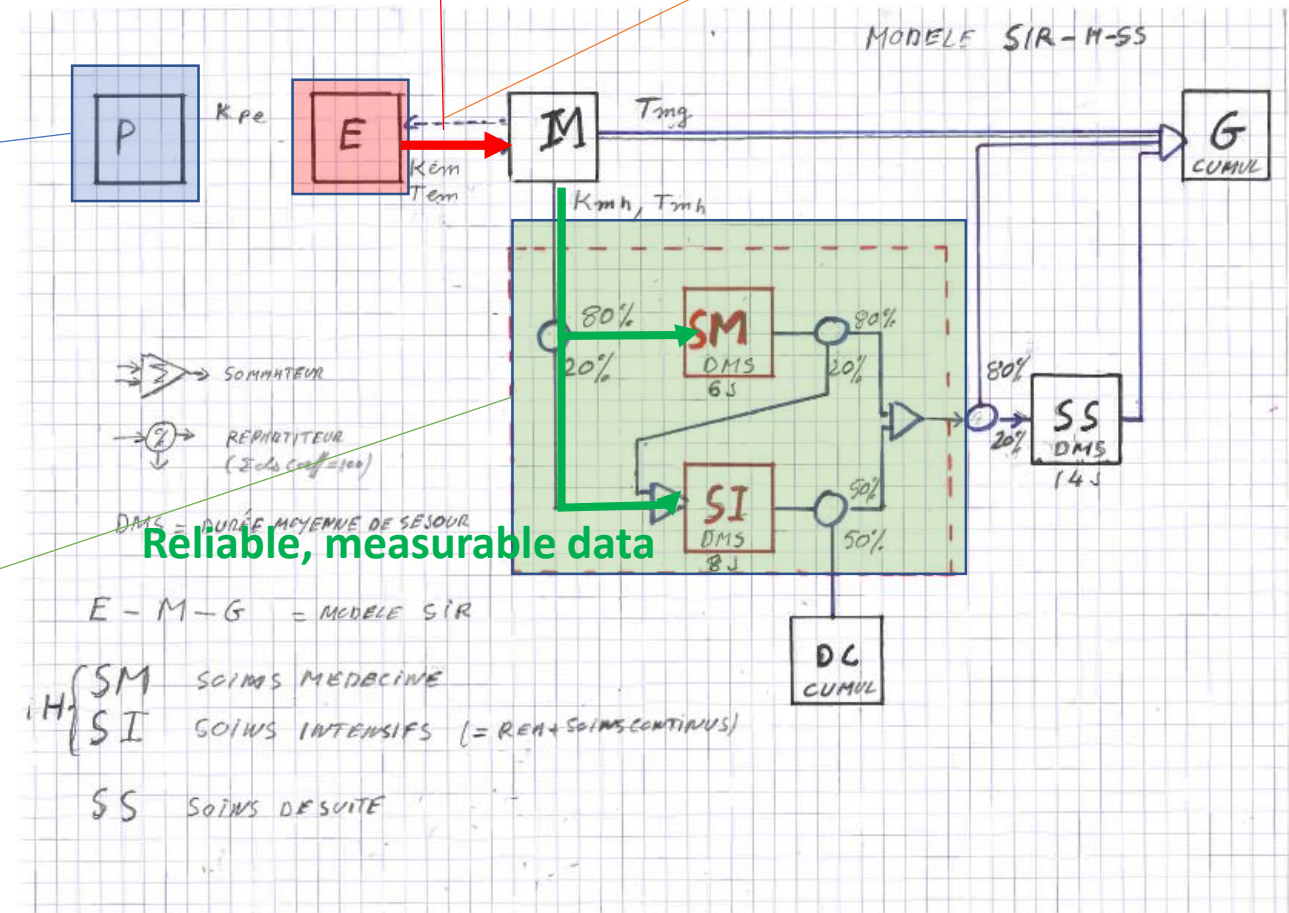
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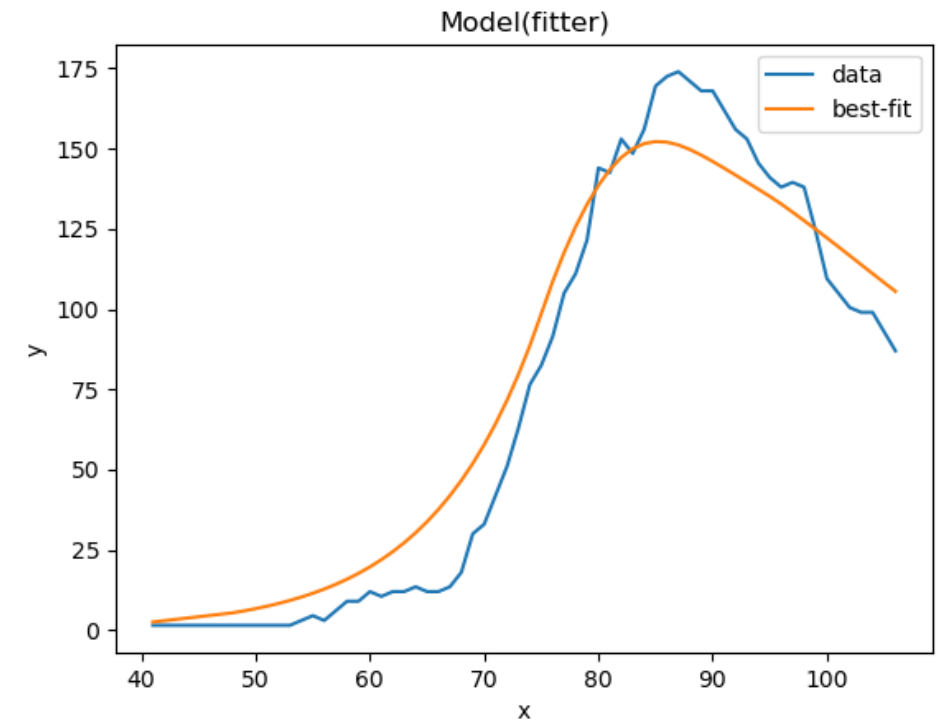
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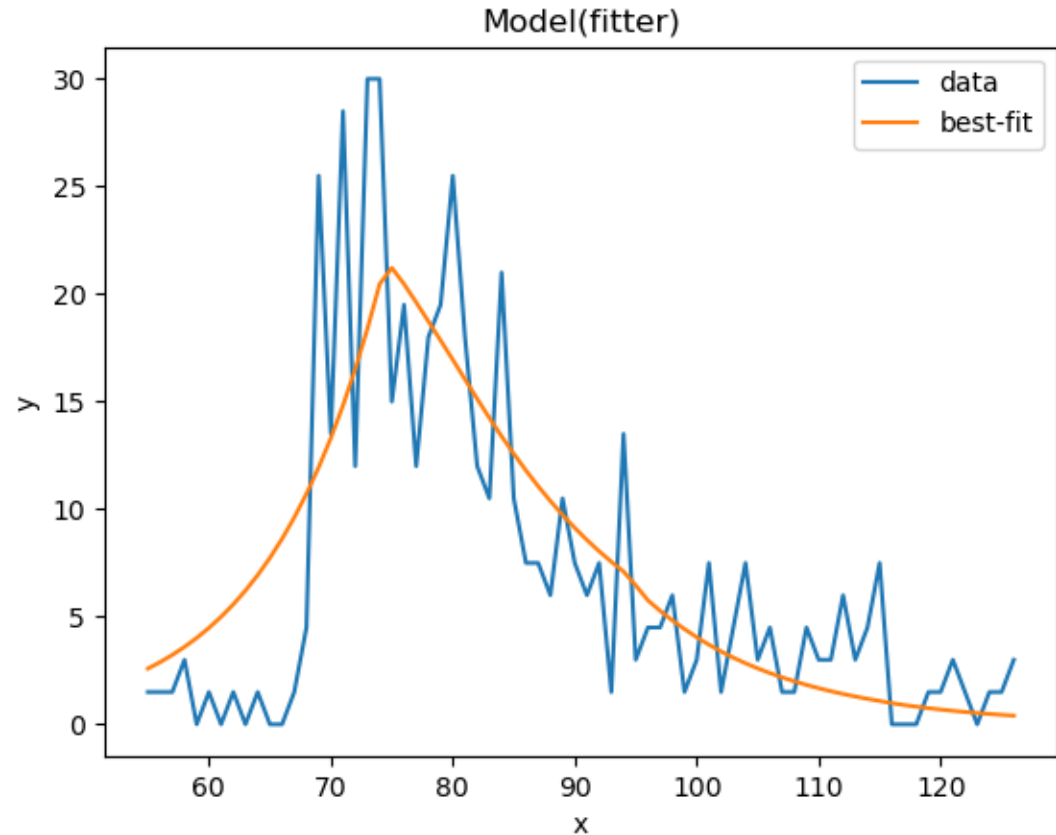
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- Real ICU admission data
- A posteriori estimated model

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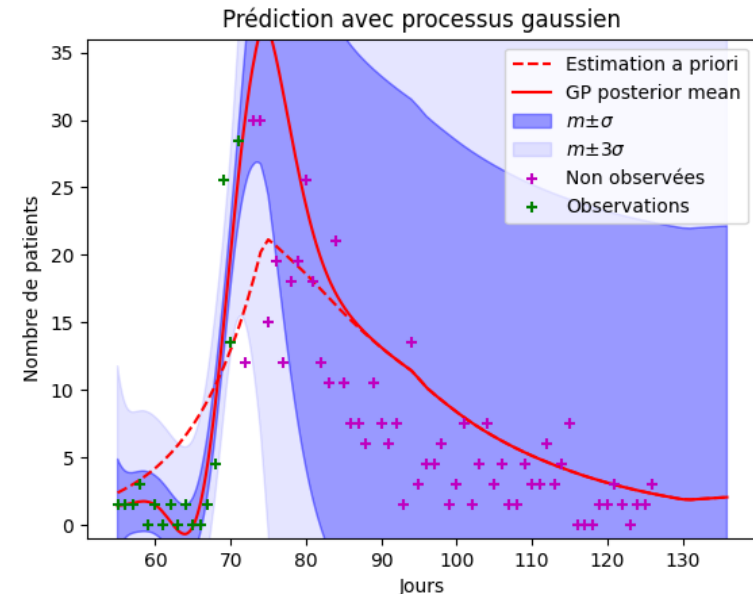
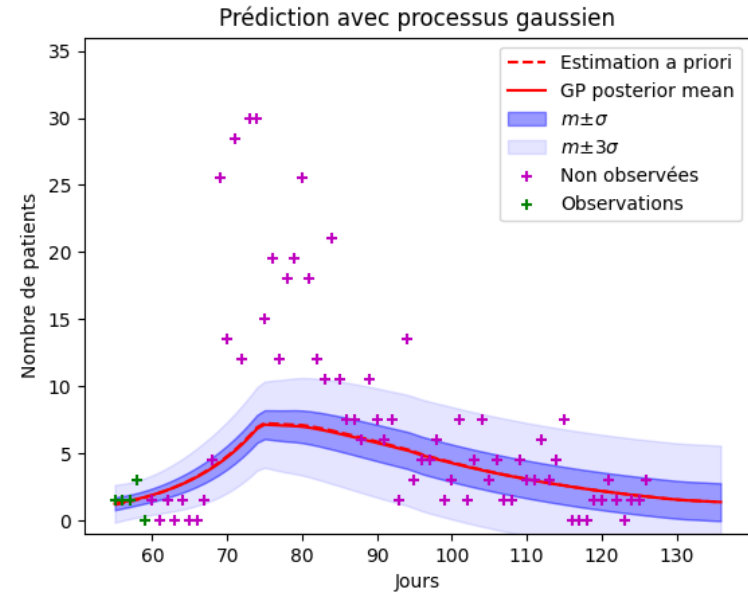
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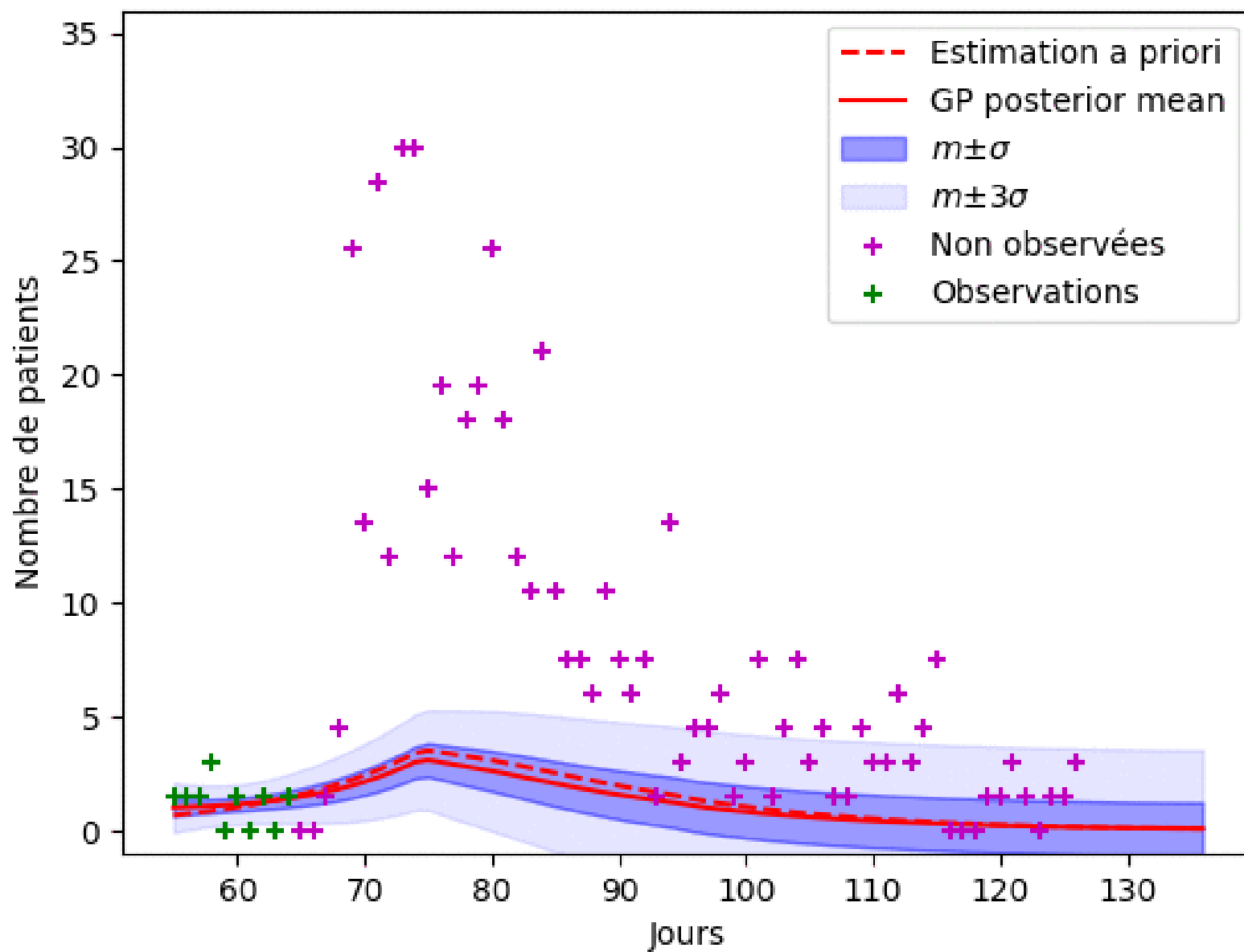
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Prédiction avec processus gaussien



Conclusion

- Fast and tuneable SEIR-XX model
(can be adapted to any range of transitional model simulation)
- Low-cost real-time parameter estimation
(as long as the model execution remains fast, plug-and-play `lmfit` compatibility)
- Low-cost real time micro-scale prediction process with confidence bounds

Further work

- Validation and evaluation of GPR limits
- Improve GPR kernel
- Improve optimisation and minimisation

Contributors

- Pr. G. Karcher (CHU)
- Pr. PE. Moreau (LORIA)
- Dr. B. Lamiroy (LORIA)
- P. Festor (Mines Nancy)
- A. Mozziconacci (Mines Nancy)
- R. Pajda (Mines Nancy)

<http://modsir19.nancyclotep.com/> (with Marmelab)



Main questions

- What is the **global optimality loss** induced by allowing the epidemic management to be decentralized?
- How to **measure** this loss?
- How to **model** the decision-making process and the interactions/interdependency between the different geographical areas?

Methodology

- Epidemic model: **SIR** model per geographical area + coupling
- Game theory: static game model where the players implement a tradeoff between health costs, economical costs, and freedom.
- Solution concept: **Nash equilibrium** (existence, uniqueness, efficiency, determination)
- Numerical analysis performed for Covid-19

Key notations

- Region index: $k \in \mathcal{K} := \{1, \dots, K\}$
- Time index: $t \in \mathbb{R}_{\geq 0}$
- Fraction of **S**usceptibles: $s_k \in [0, 1]$
- Fraction of **I**nfectious: $i_k \in [0, 1]$
- Fraction of **R**ecovered: $r_k \in [0, 1]$
- Endogenous transmission rates: $\beta_{kk} \geq 0$
- Inter-region transmission rates: $\beta_{k\ell}$ for all $k \neq \ell$
- Recovery transmission rates: $\gamma_k \geq 0$
- Individual control action: $u_k \in \mathcal{U}_k := [U_k^{\min}, U_k^{\max}] \subset [0, 1]$
- Action profile: $u := (u_1, \dots, u_K)$

Epidemic model

$$\left\{ \begin{array}{l} \frac{\partial s_k}{\partial t}(t, u) = -s_k(t, u) \left[(1 - u_k) \sum_{\ell=1}^K \beta_{k\ell} i_{\ell}(t, u) \right] \\ \frac{\partial i_k}{\partial t}(t, u) = -\frac{\partial s_k}{\partial t}(t, u) - \gamma_k i_k(t, u) \\ \frac{\partial r_k}{\partial t}(t, u) = \gamma_k i_k(t, u) \\ s_k(t, u) + i_k(t, u) + r_k(t, u) = 1 \end{array} \right.$$

The control action u_k is assumed to be constant over $[0, T]$, $T > 0$

Game model

Individual cost function:

$$J_k(u) := \underbrace{a_k u_k + b_k u_k^2}_{\text{socio-economic losses}} + \underbrace{c_k [s_k^0 - s_k(T, u)]}_{\text{health losses}}.$$

Strategic form:

$$\mathcal{G} := \left(\mathcal{K}, (\mathcal{U}_k)_{1 \leq k \leq K}, (J_k)_{1 \leq k \leq K} \right),$$

where:

- Players = regions/countries/states...
- $\mathcal{U}_k = [U_k^{\min}, U_k^{\max}] \subset (0, 1)$.
- Cost functions given by J_k

Global efficiency measures

Definition

An action profile u^{NE} is an NE if $\forall k, \forall u'_k, J_k(u^{\text{NE}}) \leq J_k(u'_k, u^{\text{NE}}_{-k})$.

Definition

The Price of Anarchy (PoA) is defined by:

$$\text{PoA} := \max_{u \in \mathcal{U}^{\text{NE}}} \sum_{k=1}^K J_k(u) / \min_{u \in \mathcal{U}} \sum_{k=1}^K J_k(u), \quad (1)$$

Definition

The Price of Connectedness (PoC) is defined as follows:

$$\text{PoC} := \max_{u \in \mathcal{U}^{\text{NE}}} \sum_{k=1}^K J_k(u) / \sum_{k=1}^K \min_{u_k \in \mathcal{U}_k} \tilde{J}_k(u_k), \quad (2)$$

where $\tilde{J}_k$ is the cost function of player $k \in \mathcal{K}$ when $\beta_{k\ell} = 0, \forall k \neq \ell$.

Nash equilibrium existence

Assumption

Let $\forall (k, \ell) \in \mathcal{K}^2, \rho_{k\ell} := \beta_{k\ell} / \gamma_\ell$.

Condition (i): The matrix $\hat{\mathbf{B}}$ whose entries are given by: $\hat{\mathbf{B}}_{k,\ell} = \beta_{k\ell}$, is non-singular.

Condition (ii): $\forall k, \forall u, \forall T \in \mathcal{T}$ one has that $s_k(T, u) > 0$.

Condition (iii): $\mathcal{T} = \mathbb{R}_{\geq 0}$ where

$$\mathcal{T} := \left\{ t \in \mathbb{R}_{\geq 0} : \forall k, \forall u, (1 - u_k) s_k(t, u) \leq \frac{1}{\sum_{\ell=1}^K \rho_{k\ell}} \right\}.$$

Condition (iii) is needed to characterize a bound for the inter-regions interactions i.e., to quantitatively describe the **WIR** with $\nu_{\beta,k} := \left(\frac{\min_{\ell \in \mathcal{K}} \gamma_\ell}{(1 - U_k^{\min}) s_k^0} - \beta_{kk} \right) / 4$.

Nash equilibrium existence: Continued

$$\mathcal{K}_{\text{NM}} := \left\{ k \in \mathcal{K} : J_k \text{ is not monotone w.r.t. } u_k \right\}.$$

Theorem

Let $T \in \mathcal{T}$. Suppose Assumption 1 holds and the less restrictive action profile $u_{\min} = (U_1^{\min}, \dots, U_K^{\min}) \in [0, 1)^K$ verifies that, $\forall k \in \mathcal{K}_{\text{NM}}$,

$$(1 - U_k^{\min})s_k(T, u_{\min}) \geq 1/(2\rho_{kk}).$$

Then, there is an NE.

Proof. Debreu-Fan-Glicksberg theorem. Implicit function theorem.

Numerical analysis (setting)

Motivated by a scenario which has been studied by the French government in May 2020, we assume that France is divided in $K = 5$ regions.

k	γ_k	β_{kk}	s_k^0	i_k^0	a_k	b_k	c_k
1	0.15	$3\gamma_1$	0.8	0.2	2	0	0
2	0.15	$2\gamma_2$	0.9	0.1	0.5	0	0
3	0.15	$1.5\gamma_3$	0.9	0.005	5	2	50
4	0.15	$1.2\gamma_4$	0.9	0.002	2	5	70
5	0.15	$1\gamma_5$	0.9	0.001	3	5	70

Table: Epidemic and Game parameters

Numerical analysis (PoA)

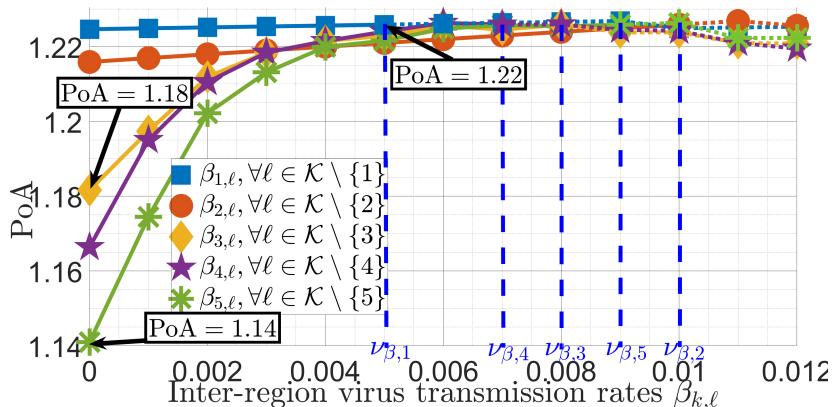


Figure: Interpolation of PoA by varying uniformly the incoming transmission rates of each Region k .

Numerical analysis (PoC)

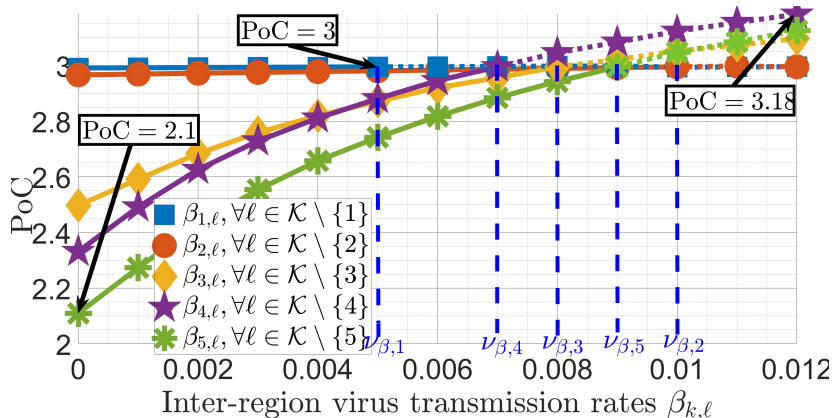


Figure: Interpolation of PoC by varying uniformly the incoming transmission rates of each Region k . The dotted curves do not fit into our theoretical setup.

Numerical analysis (epidemic evolution)

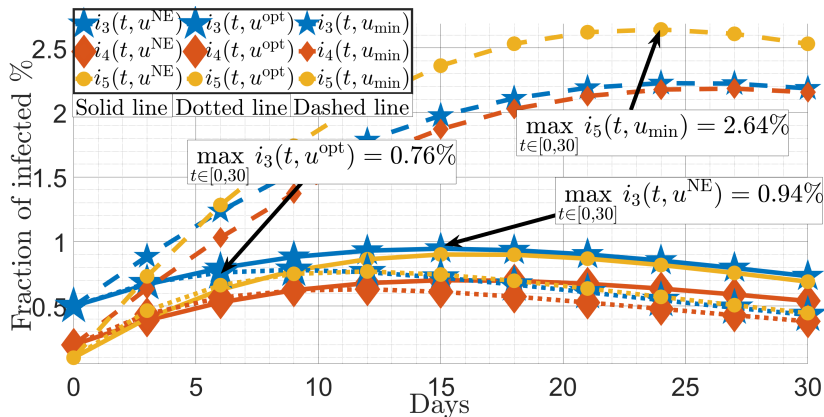


Figure: Interpolation of infected proportions in each Regions $k \in \{3, 4, 5\}$. u^{NE} = Nash equilibrium strategy; u^{opt} = optimal centralized strategy; u_{min} = less restrictive policy.

Work in Progress: Generalized Nash equilibrium problem (GNEP)

Let $i_{cu} := (i_{cu,1}, \dots, i_{cu,K}) > 0$,

$$C_k(u_{-k}) := \{u_k \in \mathcal{U}_k : (u_k, u_{-k}) \in \mathcal{C}\},$$

which is assumed to be non-empty with

$$\mathcal{C} := \left\{ u \in \mathcal{U} : g(u) := \begin{pmatrix} \sigma_1 \max_{t_1 \in \mathbb{R}_{\geq 0}} i_1(t_1, u) - i_{cu,1} \\ \vdots \\ \sigma_K \max_{t_K \in \mathbb{R}_{\geq 0}} i_K(t_K, u) - i_{cu,K} \end{pmatrix} \leq 0 \right\}$$

where $0 \leq \sigma_k \leq 1$ is the percentage of infected people requiring intensive care.

The strategic form of the generalized game under consideration is therefore given by:

$$\tilde{\mathcal{G}} := (\mathcal{K}, (\mathcal{U}_k)_{1 \leq k \leq K}, (J_k)_{1 \leq k \leq K}, (C_k)_{1 \leq k \leq K}),$$

with a jointly convex constraints formulation.

Related publications

- O. Lindamulage De Silva, S. Lasaulce, and C. Morarescu, "On the efficiency of decentralized epidemic management and application to Covid-19", IEEE Control Systems Letters (L-CSS), June 2021.
- S. Lasaulce, C. Zhang, V. Varma, and I.-C. Morarescu, "Analysis of the tradeoff between health and economic impacts of the Covid-19 epidemics", Frontiers in Public Health Infectious Diseases - Surveillance, Prevention, and Treatment, March 2021, pp. 1-13.
- S. Lasaulce, V. Varma, C. Morarescu, and S. Lin, "How efficient are the lockdown measures taken for mitigating the Covid-19 epidemic?", medRxiv, June 2020, <https://doi.org/10.1101/2020.06.02.20120089>

Thank You

Alone in the Dark : modéliser un début de pandémie sans données fiables

Bart LAMIROY

Pierre-Etienne MOREAU - LORIA

Contexte

31 mars 2020 – Pr. G. Karcher

Comme vous le savez un des problèmes majeurs de cette épidémie est la disponibilité des lits de réanimation.

Nous envisageons au CHU de développer rapidement un logiciel interactif de simulation pour **estimer le nombre de lits de rea nécessaires pour un établissement**

Il s'agit de mettre en entrée :

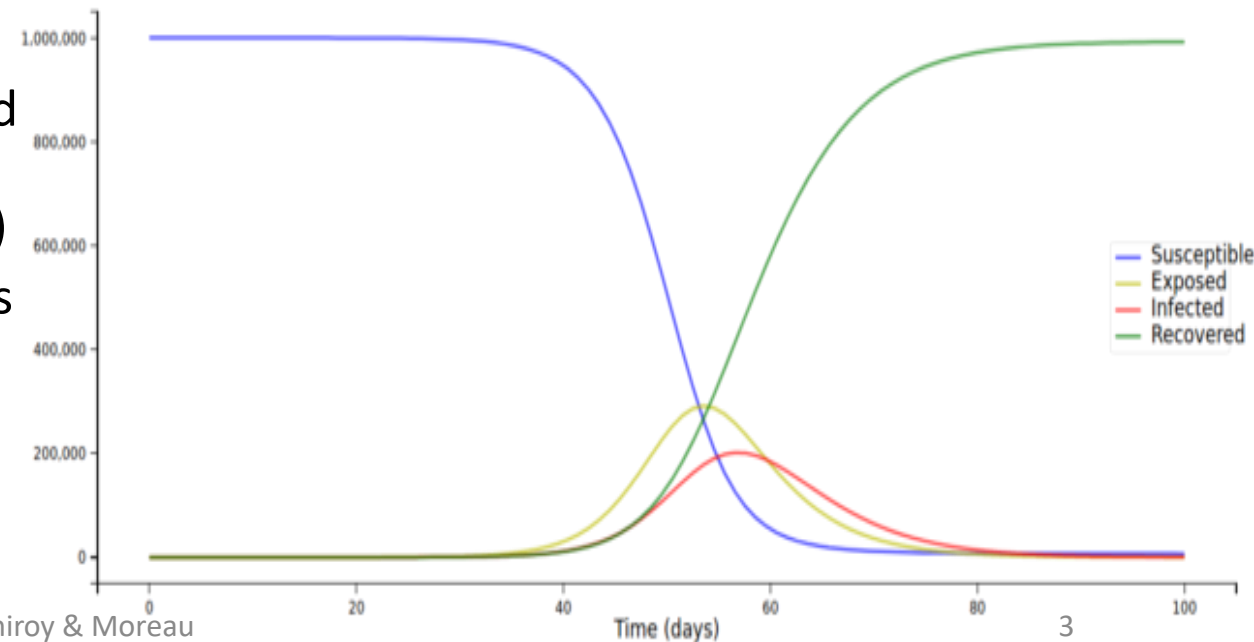
- les prévisions épidémiologiques (fournies par ailleurs)
- de **définir un modèle de durée de séjour en réa** des patients
- de mettre à jour quotidiennement le modèle en fonction de la réalité constatée

Le cahier des charges est à peu près clair. Ça marche sur excel (je l'ai fait en 2h) mais il faut le mettre au propre sur un logiciel robuste et créer les interfaces utilisateur

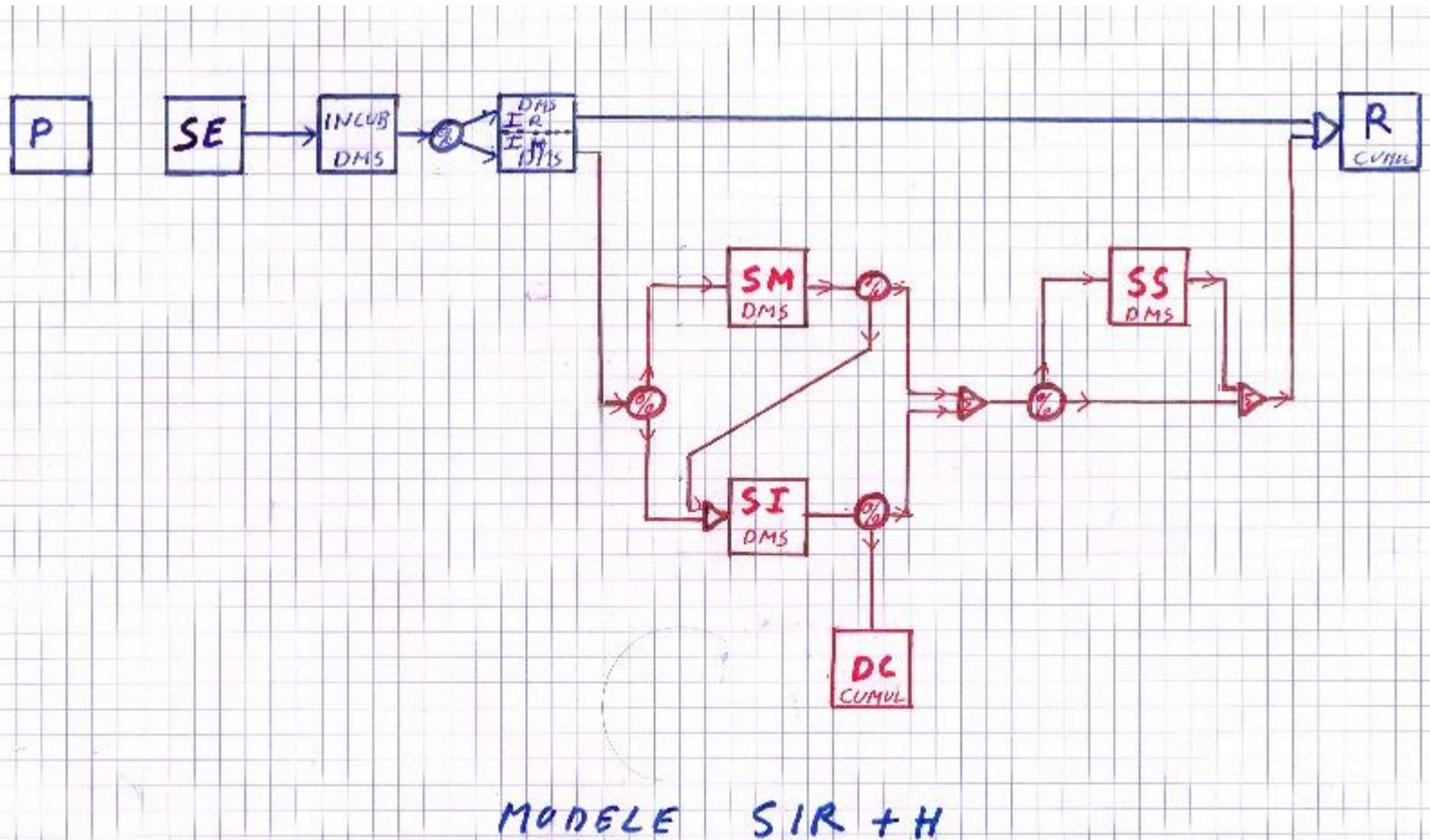
SEIR Model

- **S(t)**: number of people susceptible on day t
- **E(t)**: number of people exposed on day t
- **I(t)**: number of people infected on day t
- **R(t)**: number of people recovered on day t
- **N**: total population
- **β**: expected amount of people an infected person infects per day
- **D**: number of days an infected person has and can spread the disease
- **γ**: the proportion of infected recovering per day ($\gamma = 1/D$)
- **R₀**: the total number of people an infected person infects ($R_0 = \beta / \gamma$)

$$\begin{aligned}\frac{dS}{dt} &= -\beta \cdot I \cdot \frac{S}{N} \\ \frac{dE}{dt} &= \beta \cdot I \cdot \frac{S}{N} - \delta \cdot E \\ \frac{dI}{dt} &= \delta \cdot E - \gamma \cdot I \\ \frac{dR}{dt} &= \gamma \cdot I\end{aligned}$$



We need SIR+H Model



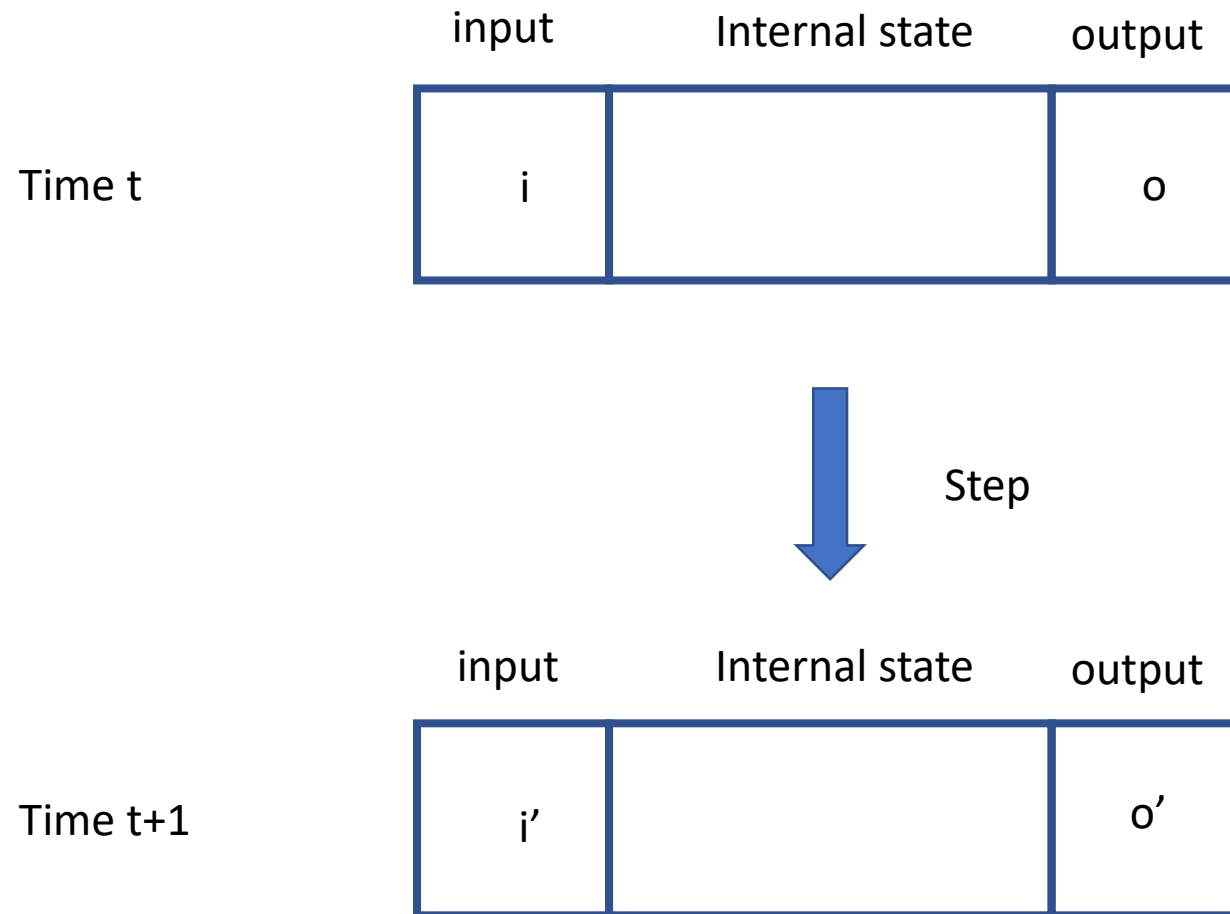
SEIR can be extended with new compartments (SM, SI, DC and SS)

But the continuous partial derivative model makes it difficult to

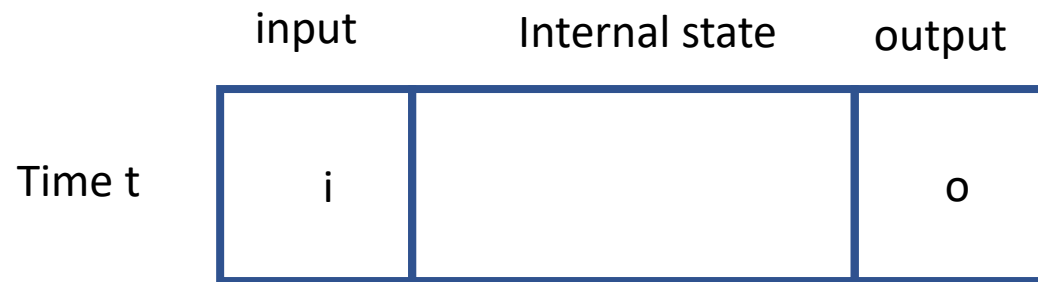
- precisely define the transition behavior of each compartment;
- model transfers and evacuations;
- experiment new configurations.

We have used a discrete model

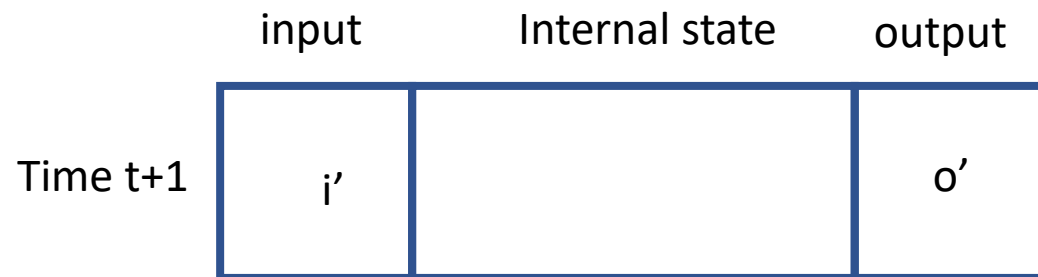
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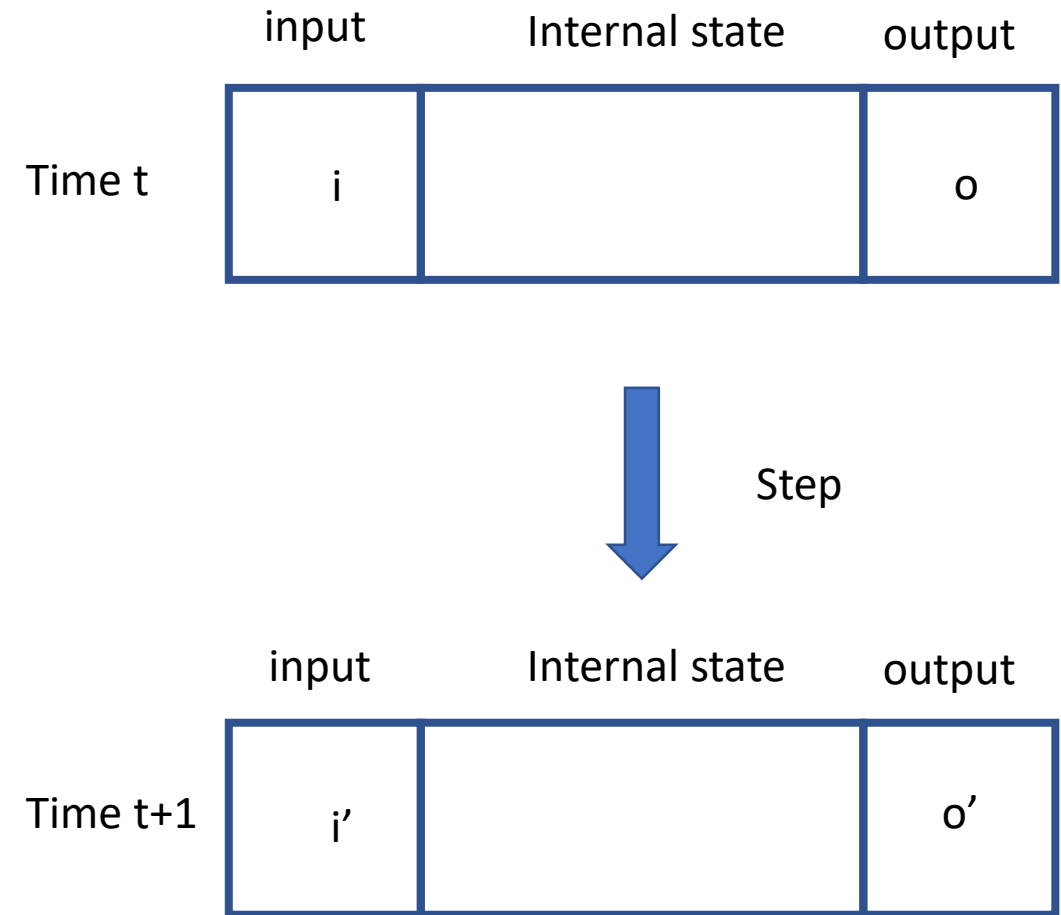
Step



- Given time t
 - $input(t)$ and $output(t)$ are floats (or integers)
- Given $0 \leq i \leq t$, we can access to past values:
 - $input(t - i)$
 - $output(t - i)$

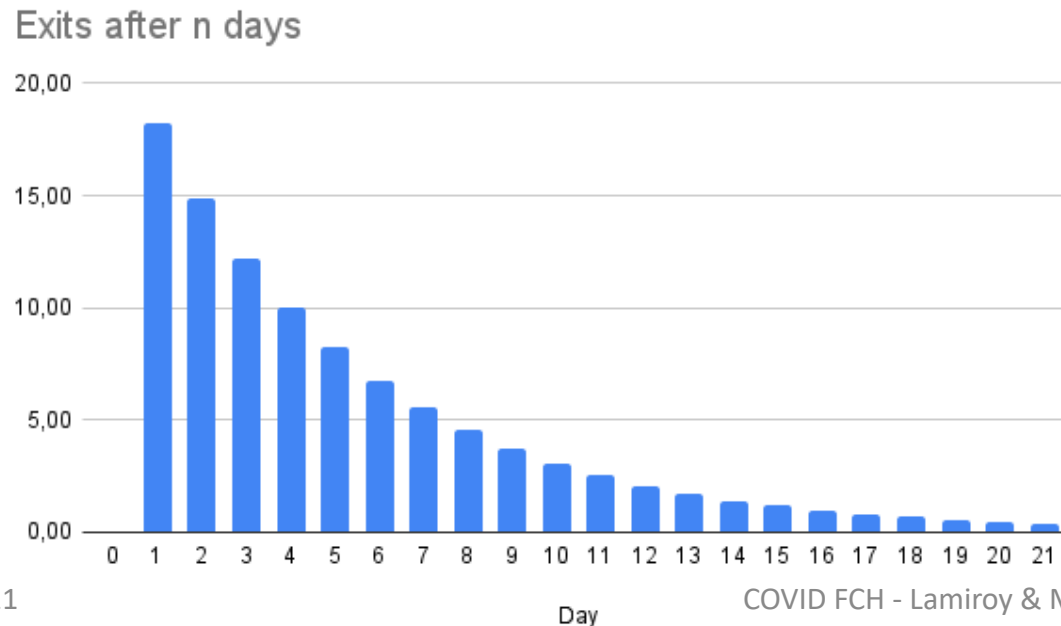
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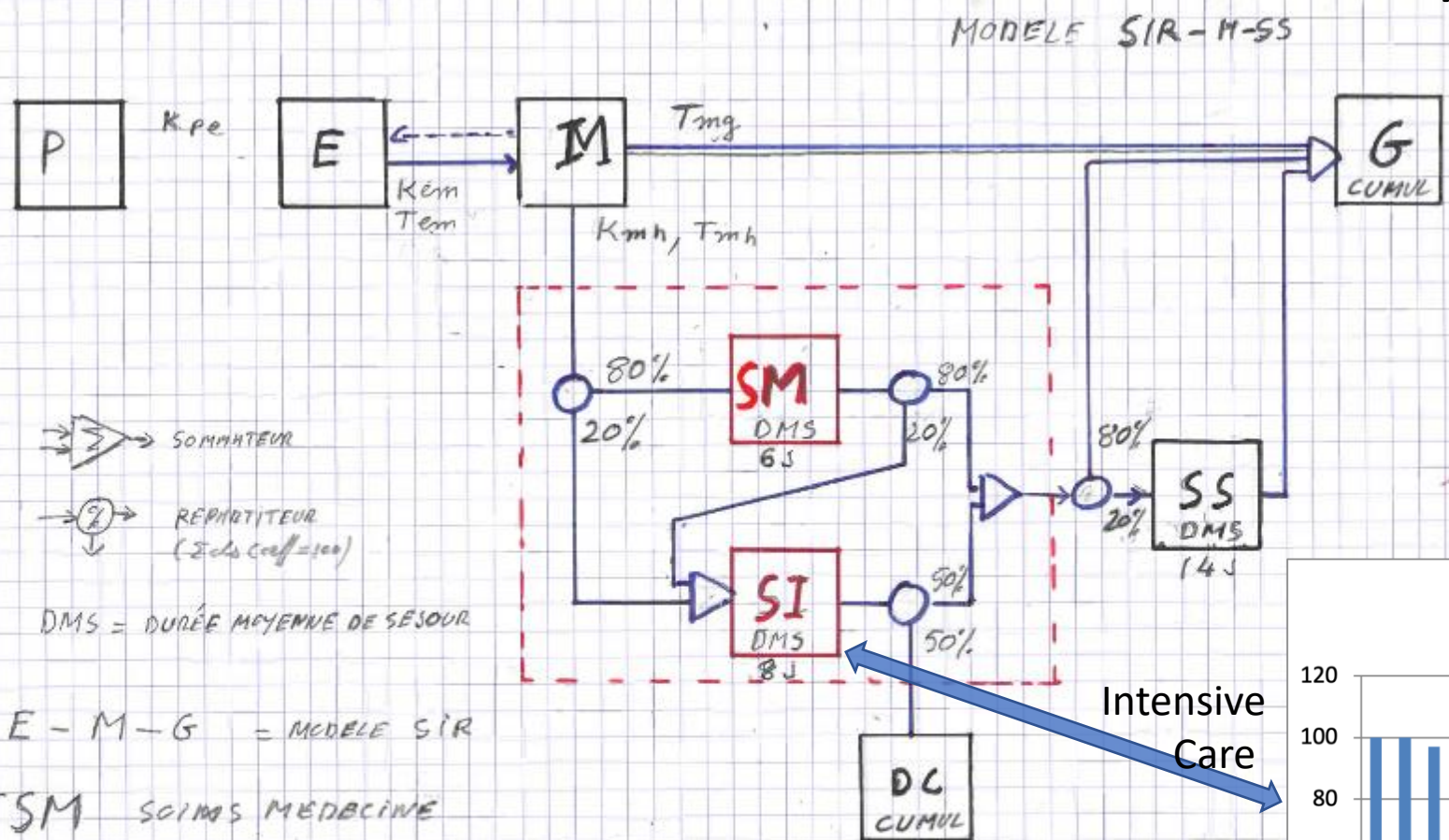


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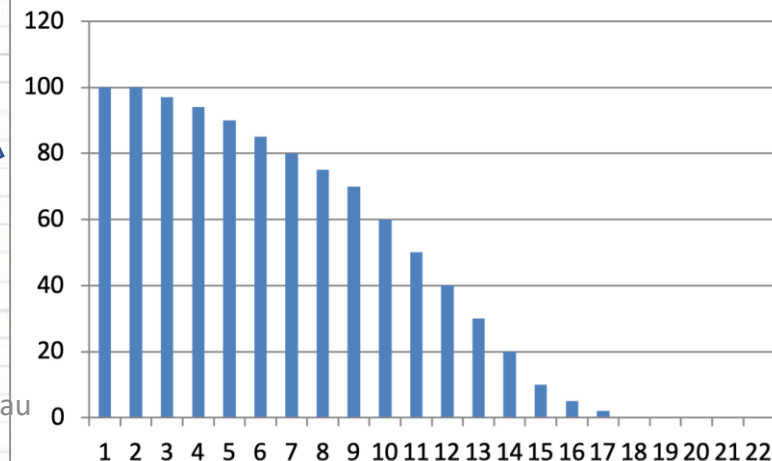
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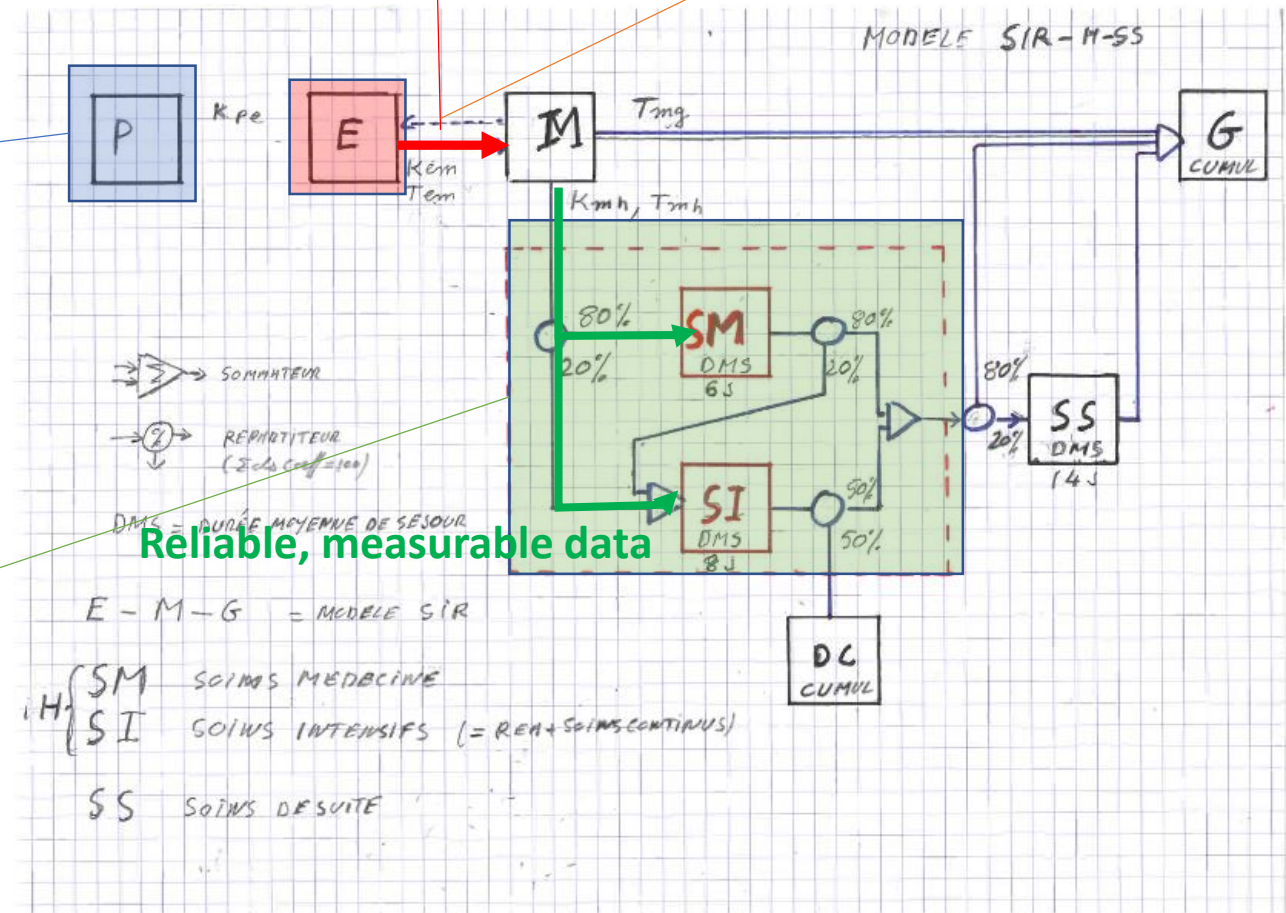
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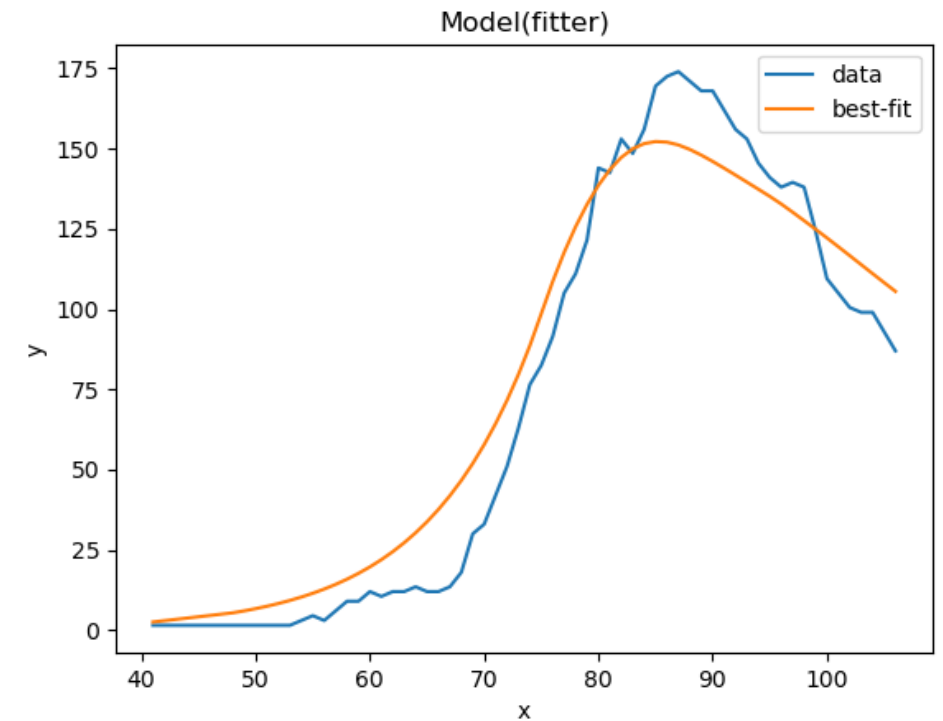
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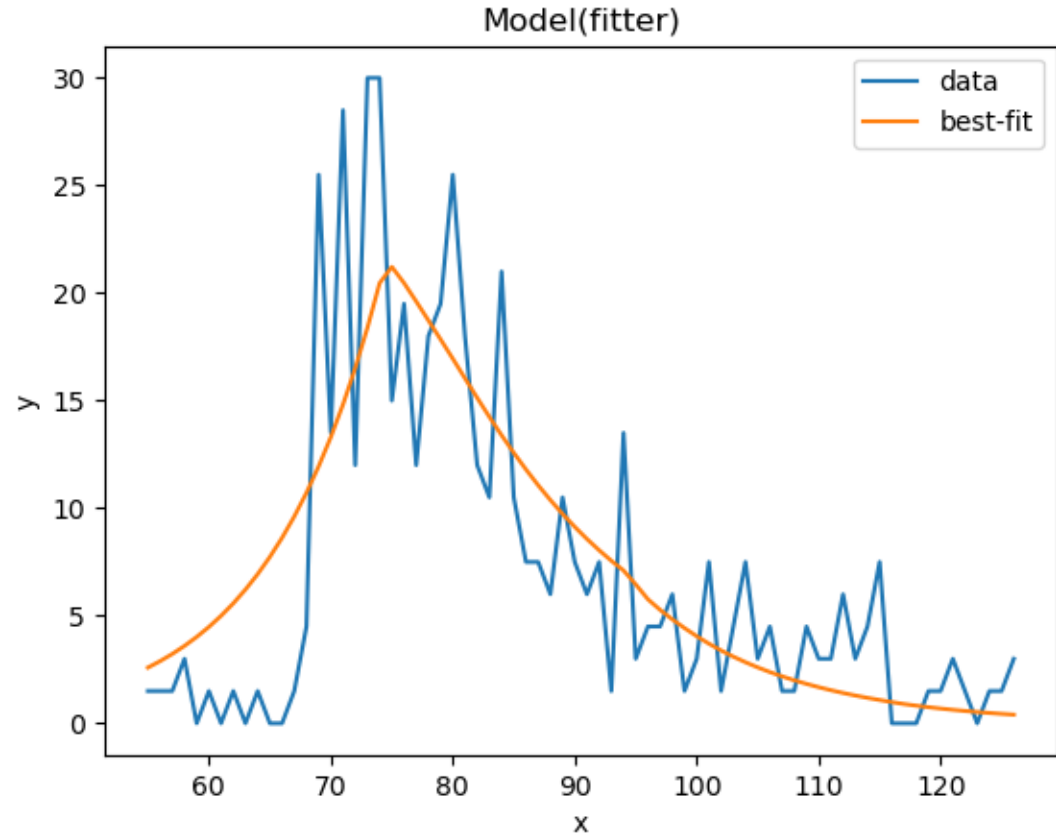
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- Real ICU admission data
- A posteriori estimated model

Problem:

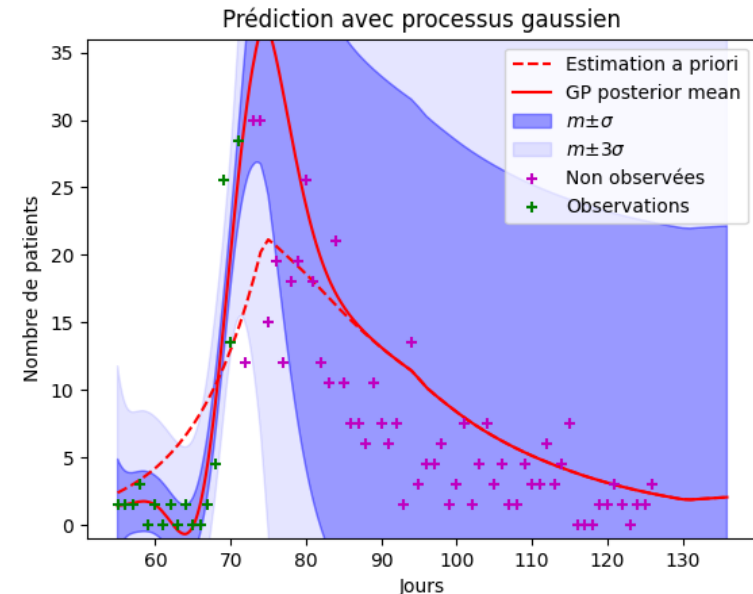
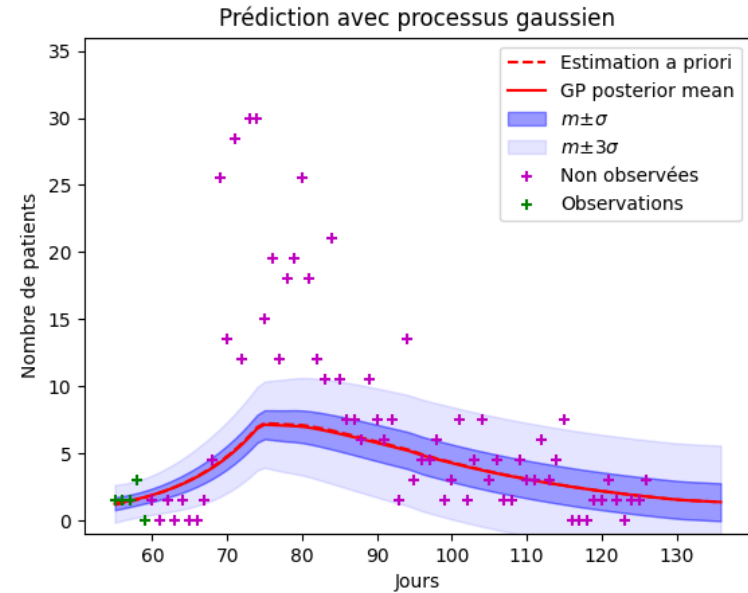
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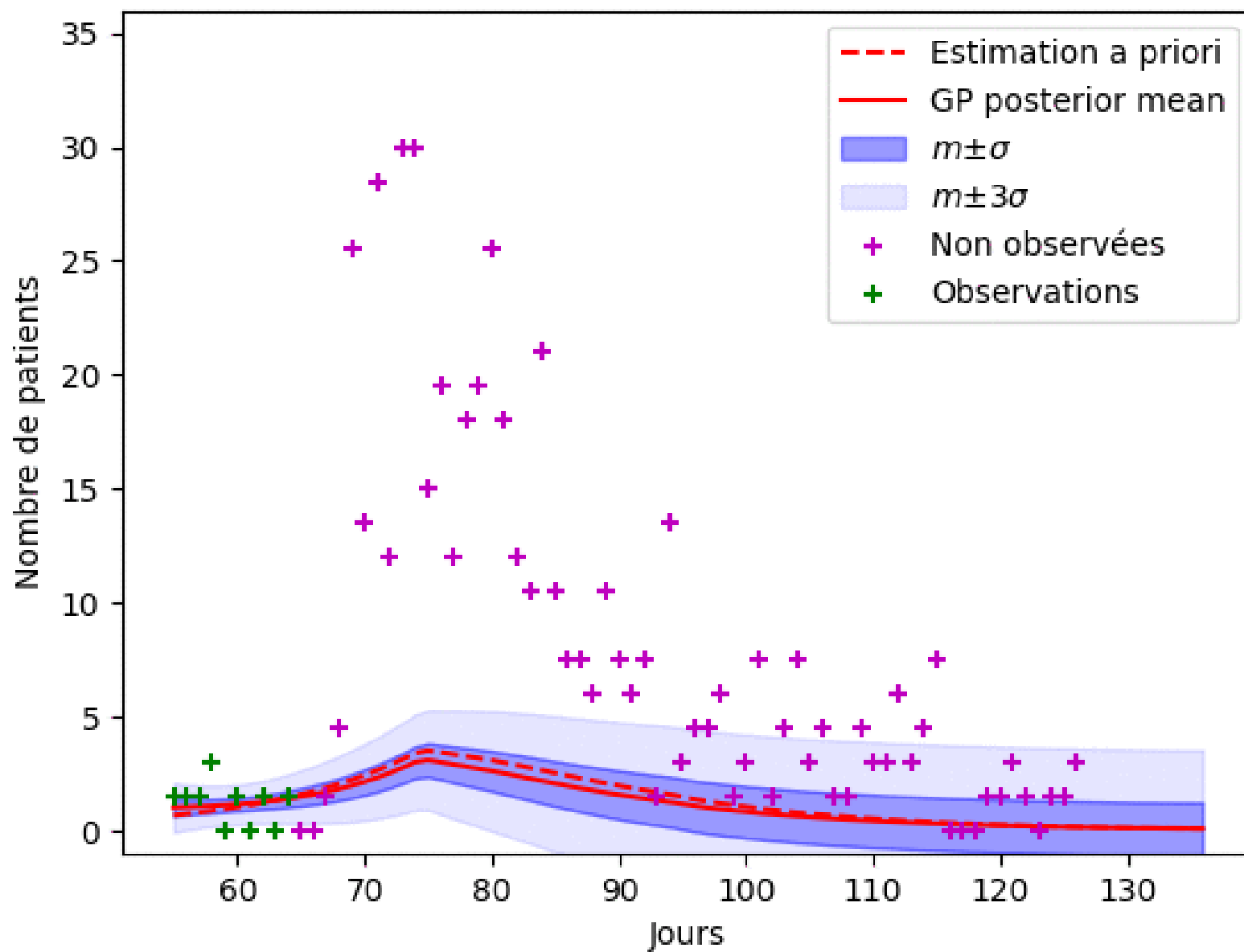
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Prédiction avec processus gaussien



Conclusion

- Fast and tuneable SEIR-XX model
(can be adapted to any range of transitional model simulation)
- Low-cost real-time parameter estimation
(as long as the model execution remains fast, plug-and-play `lmfit` compatibility)
- Low-cost real time micro-scale prediction process with confidence bounds

Further work

- Validation and evaluation of GPR limits
- Improve GPR kernel
- Improve optimisation and minimisation

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<http://modsir19.nancyclotep.com/> (with Marmelab)