Controlling complex systems
challenges and opportunities

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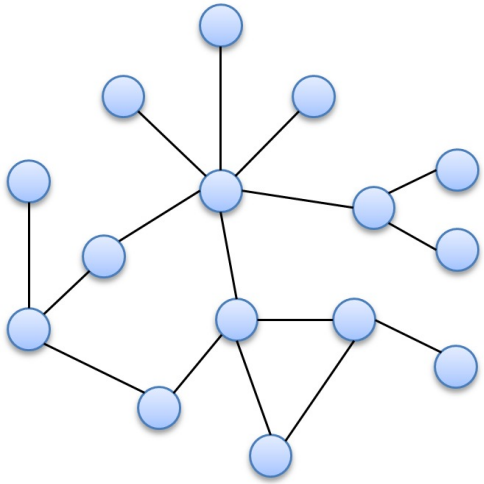
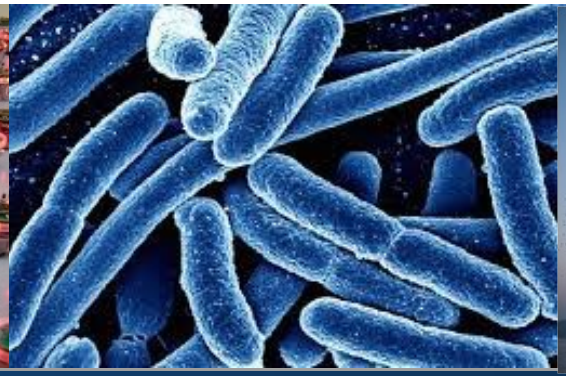
Outline

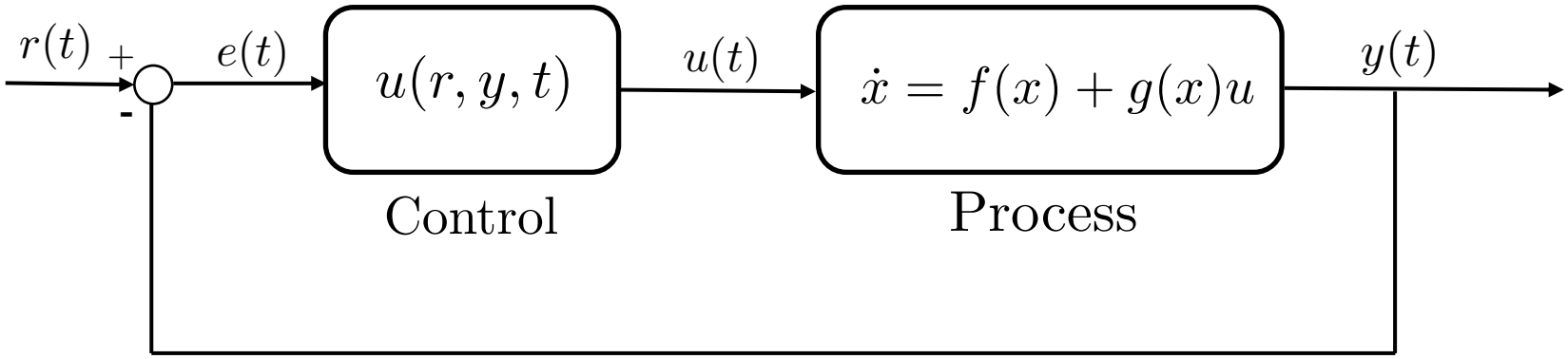
- Control theory in a nutshell
- Controlling complex systems: why and how
- The challenge of large scale systems
- Applications:
  synthetic biology and epidemic control
- A pressing open problem
- Conclusions





Control theory in a nutshell

Feedback Control = Sense + Compute + Actuate



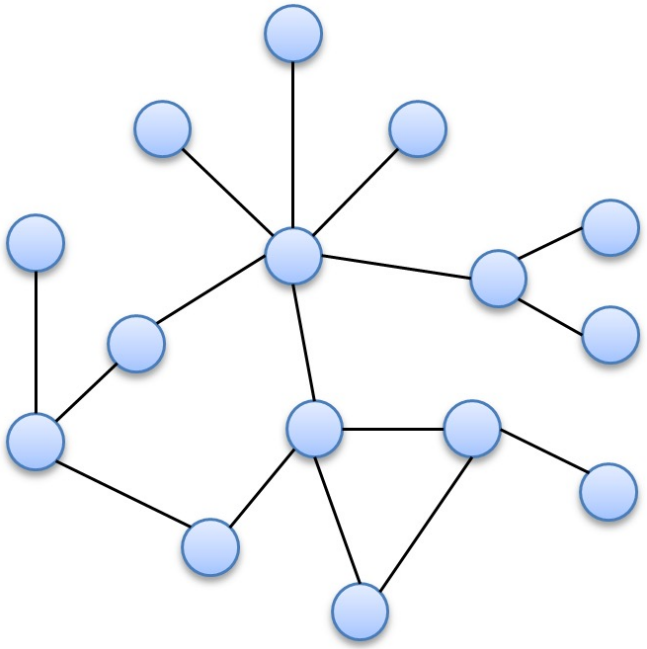
Goal = Stability + Performance + Robustness

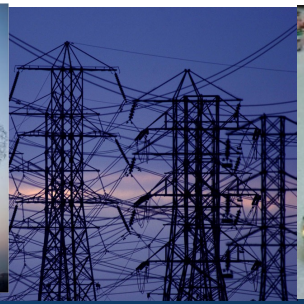
Complex systems: from one to many

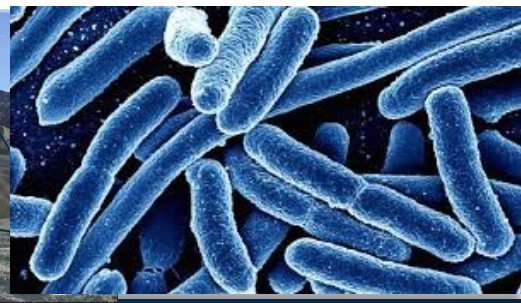
- Complex systems from applications have been constantly challenging the classical control paradigm

$$\dot{x}_i = f_i(t, x_i) + u_i(t, X_i)$$

$$u_i = \sigma \sum_{j=1}^{N} a_{ij} \left[h(x_j) - h(x_i) \right]$$



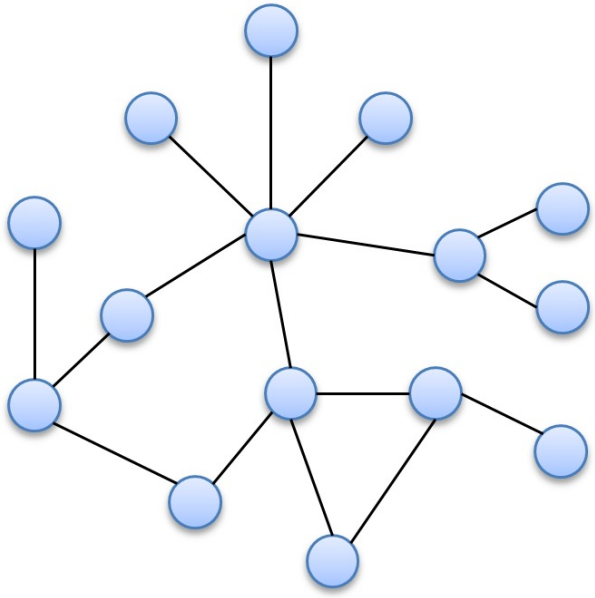



Controlling complexity

- How can we orchestrate in real-time the collective behaviour of a large-scale multiagent system?

Feedback Control = Sense + Compute + Actuate

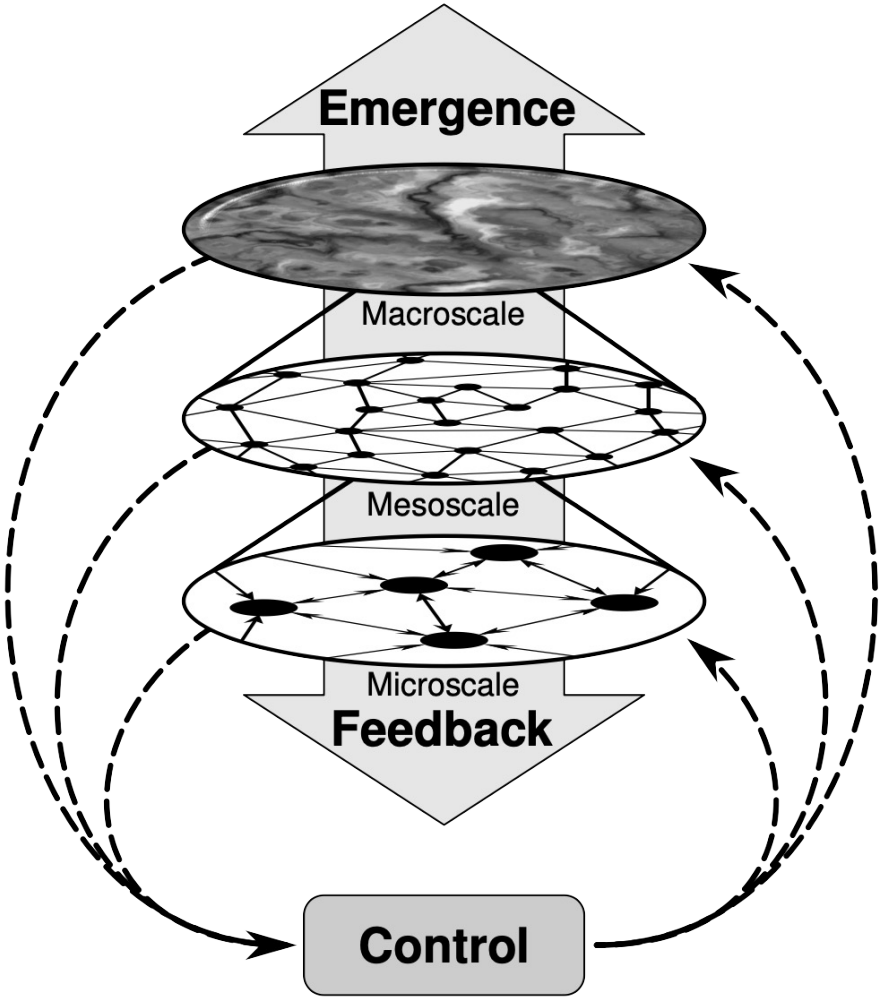
1. Whom do we sense?
2. Whom do we control?
3. What do we compute?



- We want the control to be distributed, and to be computed **on-line**

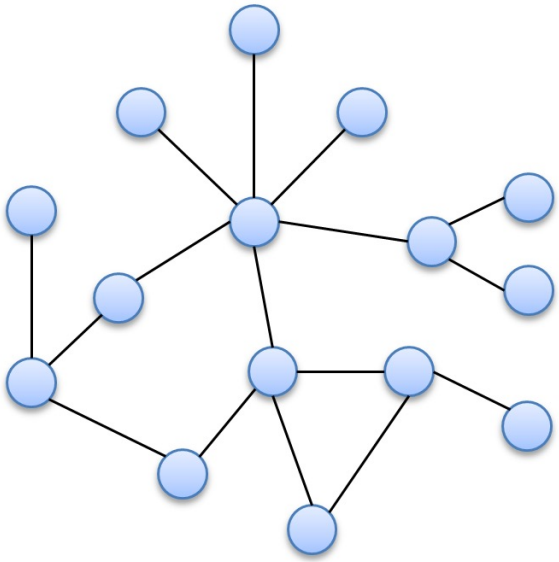
A multi-scale problem

- We need to “close the loop” across *different scales*



How to control

- To achieve this goal we can act on
  1. the agents
  2. the links interconnecting them
  3. the topology of the network structure itself

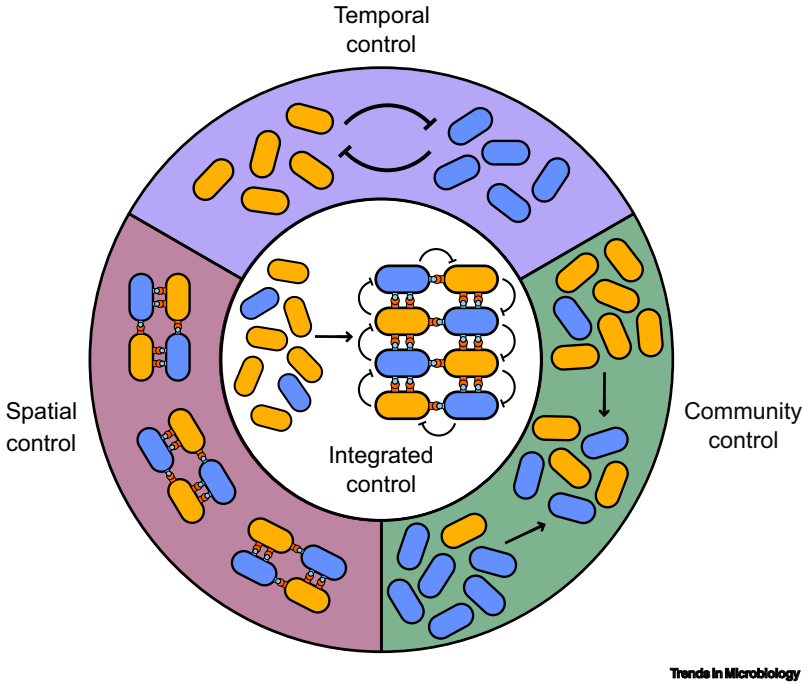


$$\dot{x}_i = f_i(x_i, t) + \sigma(t) \sum_j \mathcal{L}_{ij}(t) h(x_j, t)$$

- Each of these approaches yields different types of problems
- e.g. *controllability, observability, proving stability and convergence, control design etc.*

Applications

- Let’s have a look at two representative applications



Controlling the pandemic in Italy

- Following the COVID-19 outbreak in Lombardy a strict national lockdown was enforced in March 2020
- All regions were shut down independently of their epidemic status
- A hot debate ensued..

What intervention strategies?

A hot national debate!

18th April 2020

Coronavirus, De Luca: 'Pronto a chiudere i confini della Campania'

Coronavirus, scontro Nord-Sud sulla riapertura differenziata. Zaia: "Noi trattati da untori, ma la Campania fa meno tamponi del Veneto"

la Repubblica 19th April 2020

"Piano nazionale omogeneo per tutte le regioni", dice il premier.

21st April 2020

LA FASE 2

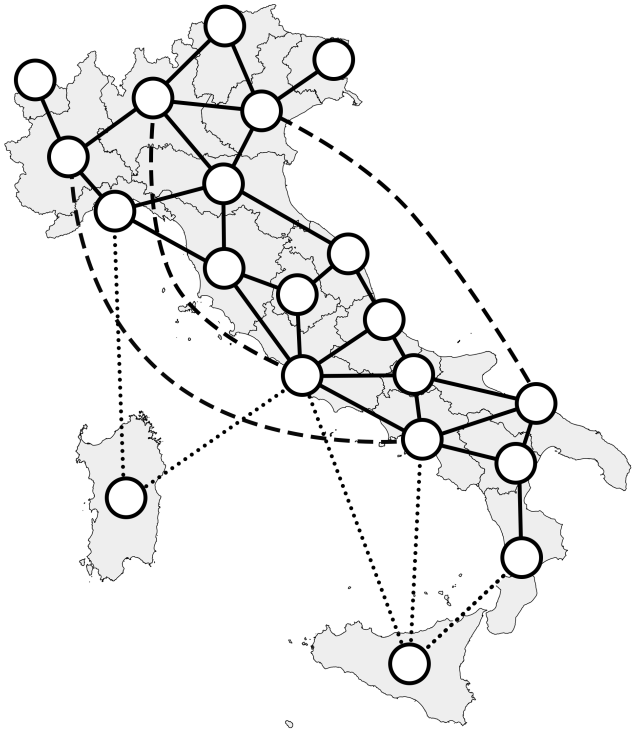
Conte annuncia: «In Italia riaperture dal 4 maggio, entro domenica un piano differenziato per zone»

• **Le reazioni** Fontana: "Dannosa una ripartenza per regioni". E lancia i Lombard bond

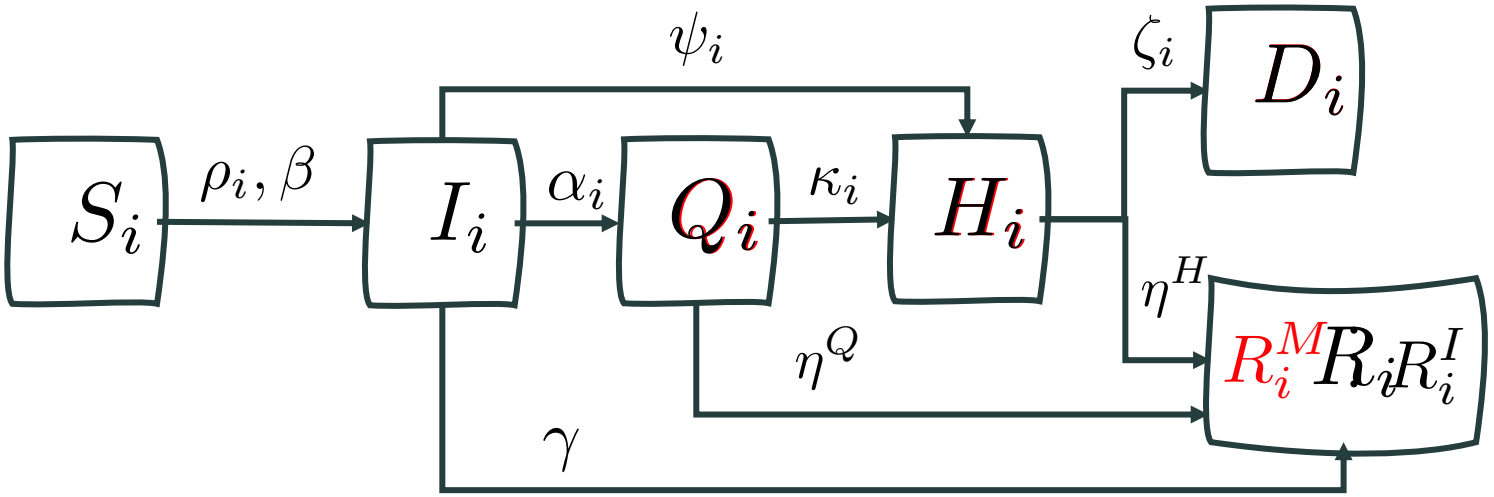
Our research questions back then

- **Do we need to shut down all regions concurrently independently from their epidemic status?**
- Can we envisage *regional* lockdown strategies to mitigate the COVID19 epidemic…
- … where each region automatically enforces or releases mitigating measures according to some indicators?
- Are such regional measures effective and do they cause lesser economic costs?

Modeling Italy as a complex system



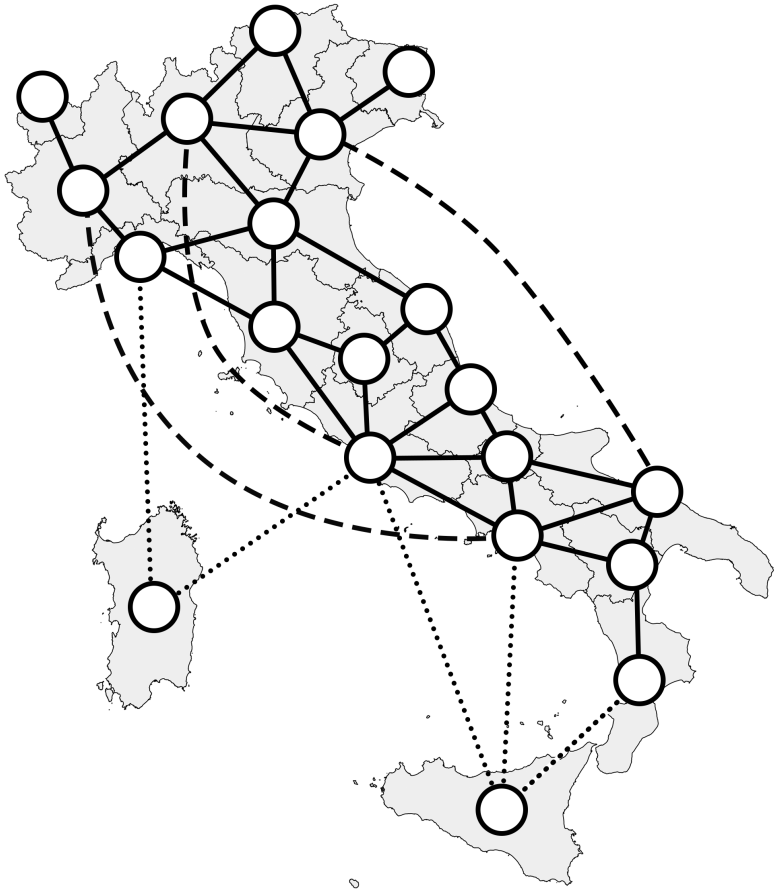
Regional models (nodes)

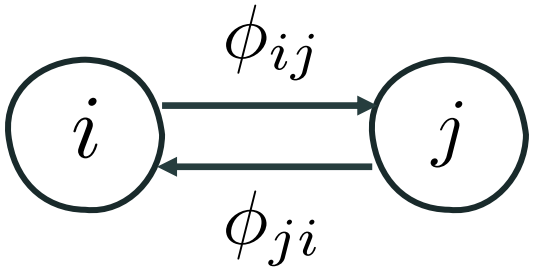


- Links among compartments suggested from data analysis
- We set $\beta = 1/2, \gamma = 1/14$
- **Ansatz:** parameters constant over time intervals T_k (no duration fixed *a priori*)
- We want to find parameters' values and when they change

Modeling the edges

- Once each region has been modelled and identified we introduced fluxes among regions and their effects





$$\sum_j \phi_{ij} = 1$$

The resulting network model

$$\dot{S}_i = -\sum_{j=1}^{M}\sum_{k=1}^{M} \rho_j(t)\beta\phi_{ij}(t)S_i\frac{\phi_{kj}(t)I_k}{N_j^p}$$

$$\dot{I}_i = \sum_{j=1}^{M}\sum_{k=1}^{M} \rho_j(t)\beta\phi_{ij}(t)S_i\frac{\phi_{kj}(t)I_k}{N_j^p} - \gamma I_i - \alpha I_i - \psi I_i$$

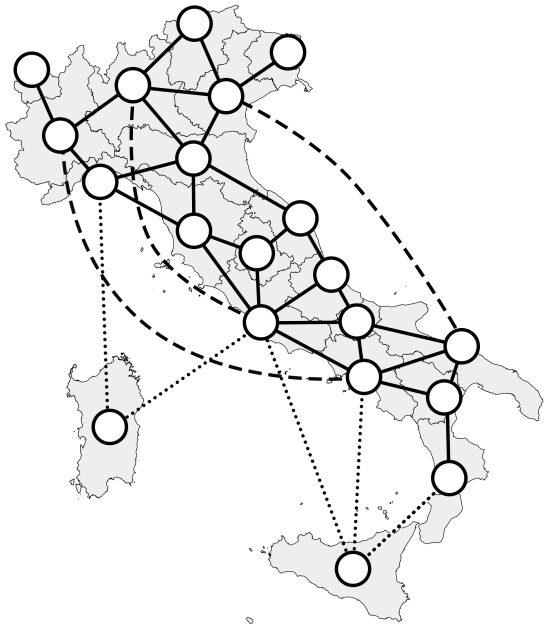
$$\dot{Q}_i = \alpha I_i - \kappa Q_i - \eta^Q Q_i$$

$$\dot{H}_i = \psi I_i - \eta^H H_i + \kappa Q_i - \zeta(H_i/T_i^H)H_i$$

$$\dot{R}_i = \gamma I_i + \eta^Q Q_i + \eta^H H_i$$

$$\dot{D}_i = \zeta(H_i/T_i^H)H_i$$

$$N_i^p = \sum_{k=1}^{M}\phi_{ki}(t)N_k$$



Data-driven parameterization

$$C_i := Q_i + H_i + R_i^M + D_i$$

$$\dot{S}_i = -\hat{\rho}_i \beta \overline{S_i I_i}, \qquad S_i(0) = N_i - I_i(0) - C_i(0)$$
$$\dot{I}_i = \hat{\rho}_i \beta \overline{S_i I_i} - (\hat{\tau} + \gamma) I_i, \qquad I_i(0) = \hat{I}_{i,0}$$
$$\dot{C}_i = \hat{\tau} I_i, \qquad C_i(0) = C_{i,0}$$

Ad hoc identification algorithm

$$\hat{\rho}_i, \hat{\tau}, \hat{I}_i, T_k$$

$$\dot{H}_i = \hat{\psi}_i \hat{I}_i - \hat{\eta}^H H_i + \hat{\kappa}_i Q_i - \hat{\zeta}_i H_i \qquad H_i(0) = H_{i,0}$$
$$\dot{R}_i^M = \hat{\eta}^Q Q_i + \hat{\eta}^H H_i \qquad R_i^M(0) = R_{i,0}^M$$
$$\dot{D}_i = \hat{\zeta}_i \; H_i \qquad D_i(0) = D_{i,0}$$

Least-squares identification

$$\hat{\psi}_i, \hat{\kappa}_i, \hat{\zeta}_i, \hat{\eta}^{Q,H}$$

Estimating the fluxes

- For fluxes not much freely available data [ISTAT 2011]
- Since then, high-speed train travel increased substantially
- We estimated fluxes by using publicly available data on trains, air traffic and capacity, key ferries routes
- We used a simple mobility model to estimate missing data

TRENITALIA
GRUPPO FERROVIE DELLO STATO ITALIANE

MINISTERO DELL'INTERNO

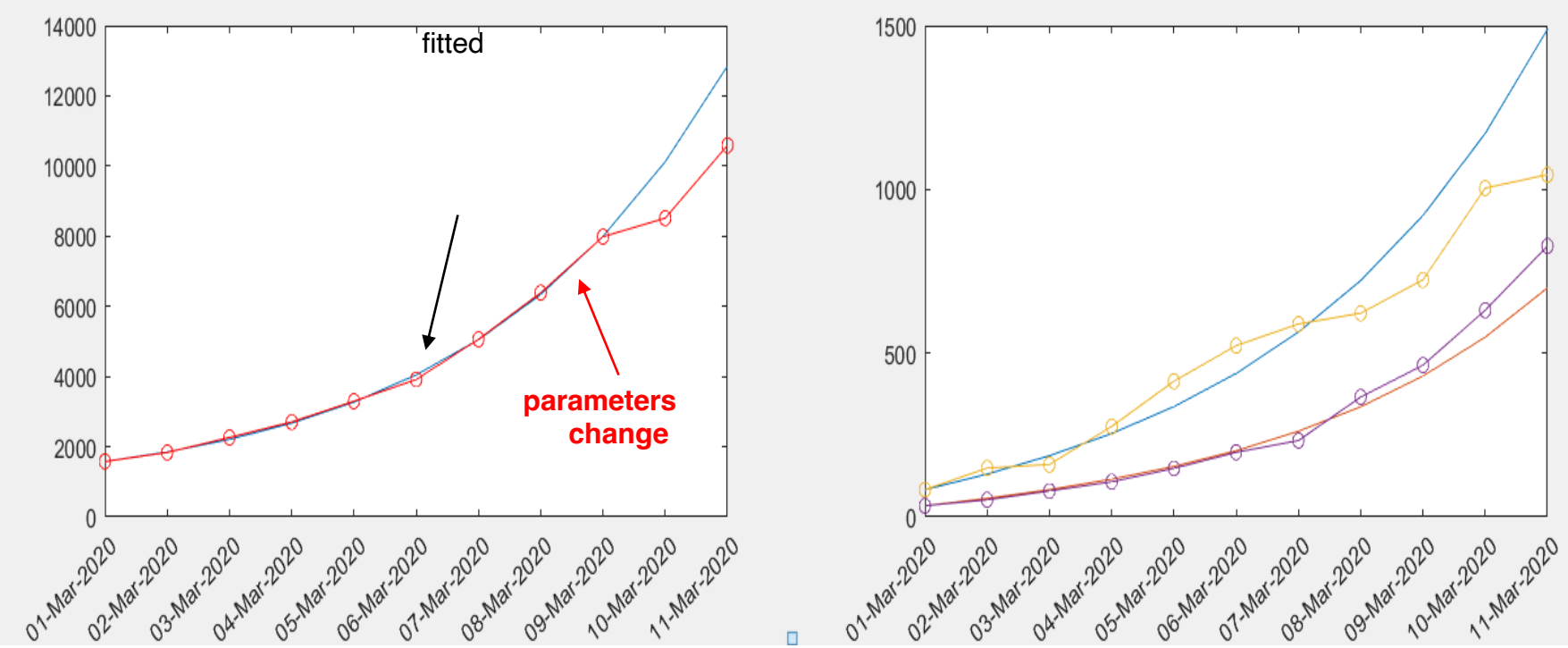
PORTMOBILITY
VIAGGI DA MARE

Skyscanner

ENAC
ENTE NAZIONALE PER L'AVIAZIONE CIVILE

Automatic breakpoint detection

- We identify automatically timepoints where parameters significantly change



Example 1: Lombardy

$\rho\beta$	α	ψ	ζ	T	$H\%$
0,499	0,020	0,050	0,026	27 Feb – 2 Mar	0,15
0,268	0,038	0,032	0,034	2 Mar – 21 Mar	1,23
0,081	0,043	0,027	0,030	21 Mar – 8 Apr	1,21
0,047	0,052	0,018	0,019	13 Apr - 21 Apr	0,63

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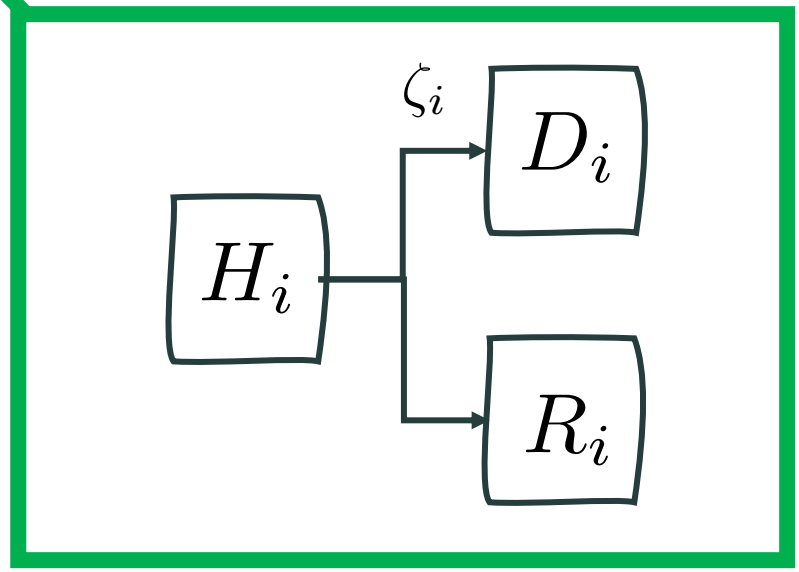
8/03/2020



Example 2: Campania

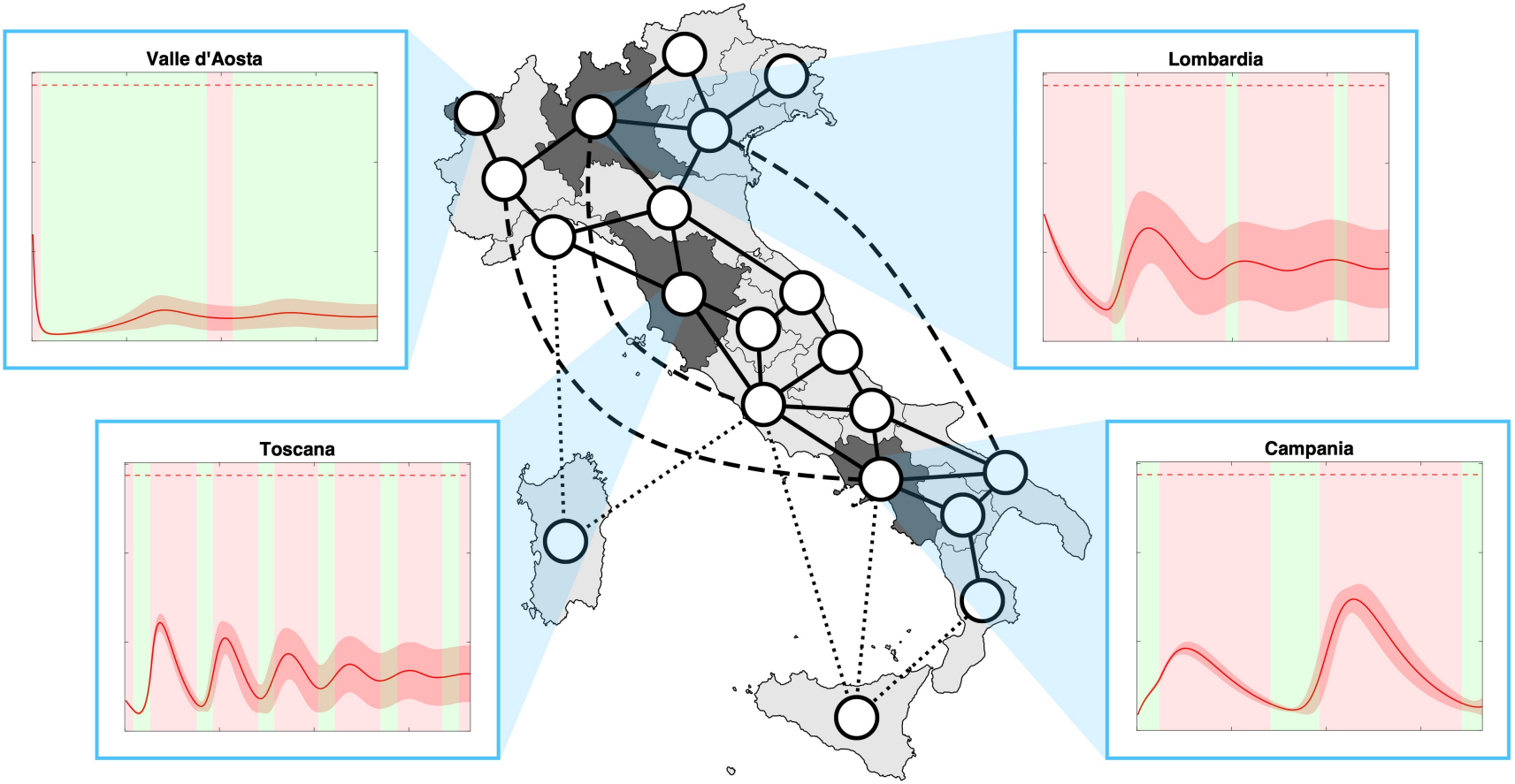
$\rho\beta$	α	ψ	ζ	T
0,009	0,070	0,000	0,014	27 Feb – 2 Mar
0,231	0,007	0,000	0,020	2 Mar – 21 Mar
0,061	0,057	0,013	0,013	21 Mar – 22 Apr

North -> South Flux

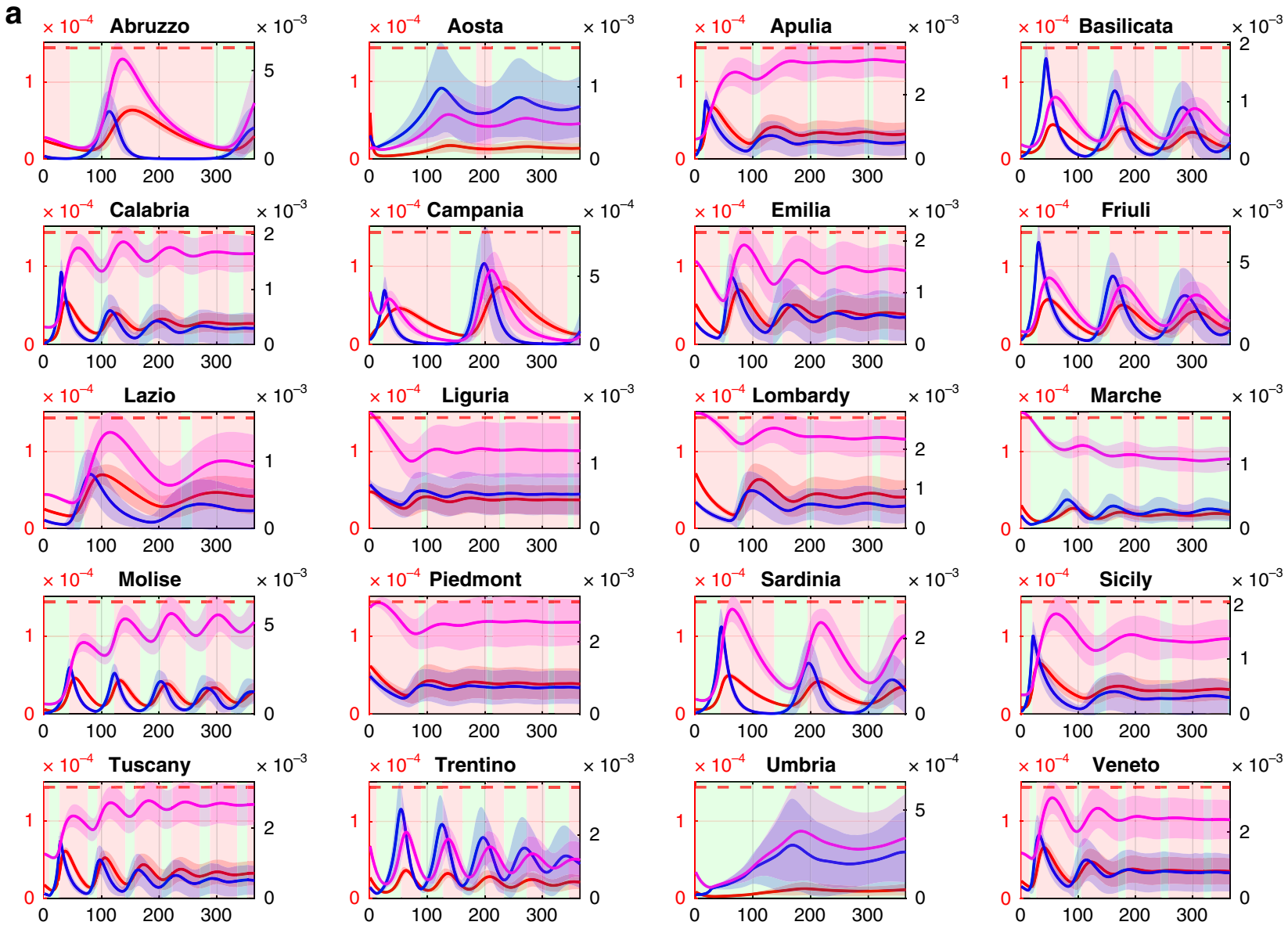
Controlling the epidemic spread

- **Goal:** introduce automatic *feedback* measures to avoid saturation of the regional health services while mitigating the epidemic spread
- *When its regional health system becomes under pressure*, a region enforces a lockdown and prevents travel to/from other regions
- e.g. when the number of patients requiring ICU treatment crosses a certain threshold (we set to 20%)

A distributed regional strategy



A distributed regional strategy



Comparison with nationwide lockdown

Table 2 Comparison of each of the simulated scenarios.

Simulation	Total cases	Total deaths	Maximum hospitalized	Days over hospital's capacity (nation)	Regions over hospital's capacity	Economic cost [M€]
All regions but Lombardy are locked down (Fig. 2)	10,550,000 ± 146,084	1,196,063 ± 97,122	137,640 ± 10,249	75.8 ± 2.7	3	503,355 ± 0
Intermittent regional measures (Fig. 3a, b)	1,986,601 ± 76,184	173,637 ± 3911	2801 ± 170	0 ± 0	0	509,142 ± 6606
Intermittent national measure (Fig. 3c, S4)	2,162,539 ± 194,929	205,261 ± 10,854	4481 ± 277	0 ± 0	3	562,373 ± 12,809
Intermittent regional measures with increased testing (Fig. 4)	1,590,459 ± 69,118	128,644 ± 2690	2057 ± 102	0 ± 0	0	366,514 ± 12,258

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-18827-5 OPEN

Check for updates

A network model of Italy shows that intermittent regional strategies can alleviate the COVID-19 epidemic

Fabio Della Rossa[1,2,5], Davide Salzano[2,5], Anna Di Meglio[2,5], Francesco De Lellis[2,5], Marco Coraggio[2], Carmela Calabrese[2], Agostino Guarino[2], Ricardo Cardona-Rivera[2], Pietro De Lellis[2], Davide Liuzza[3], Francesco Lo Iudice[2], Giovanni Russo[4] & Mario di Bernardo[2]✉

CORRIERE DELLA SERA

PUBBLICATO SU «NATURE COMMUNICATIONS»

Studio italiano: un nuovo modello (matematico) per gestire la pandemia

Gli autori suggeriscono di attivare lockdown intermittenti a livello regionale per controllare la diffusione dell'epidemia e contenerne l'impatto economico

di Redazione Salute

11 Ottobre 2020
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Gli esperti
Federico II, lo studio «Chiudere a zona»

Mariagiovanna Capone

C'è uno studio che ha verificato che attivare lockdown intermittenti a livello regionale per controllare la diffusione dell'epidemia è efficace tanto quanto un lockdown nazionale. Gli autori appartengono al gruppo di ricerca Sincro dell'Università di Napoli Federico II e la ricerca dimostra l'efficacia di chiusura di 15-20 giorni per evitare che gli ospedali vano in tilt con costi ridotti per la collettività rispetto al lockdown totale.

A pag. 23

Stop a macchia di leopardo, gli esperti «Possono bastare solo quindici giorni»

LO STUDIO

Mariagiovanna Capone

In Campania crescono i positivi al Covid-19, e con essi i timori di un possibile nuovo lockdown, come ipotizzato dal presidente della Regione Vincenzo De Luca che ha definito: «Questo fine settimana sarà una prova della responsa-

cesso aperto che pubblica ricerche di alta qualità che rappresentano progressi significativi per gli specialisti in ciascun campo. Gli autori appartengono al gruppo di ricerca SINCRO (Sistemi Nonlineari, Controllo di Reti e Processi) dell'Università di Napoli Federico II coordinato da Mario di Bernardo, docente di Automatica al Dieti e coordinatore del phD in Modeling and Engineering

La Galleria durante il lockdown della scorsa primavera

attuare o revocare misu-
kdown o distanziamento
n base al livello di satura-
i propri sistemi sanitari
li, si può contenere il dif-
i dell'epidemia in manie-
alente se non migliore di
possa fare un lockdown
le». Secondo lo studio,

UN'INDAGINE DELLA FEDERICO II PREVEDE L'INTERRUZIONE DELLE ATTIVITÀ PER SINGOLE AREE

Covid:Federico II,lockdown intermittenti a livello regionale

Modello matematico per contenimento del contagio da coronavirus

Redazione ANSA

NAPOLI

09 ottobre 2020
17:13
NEWS

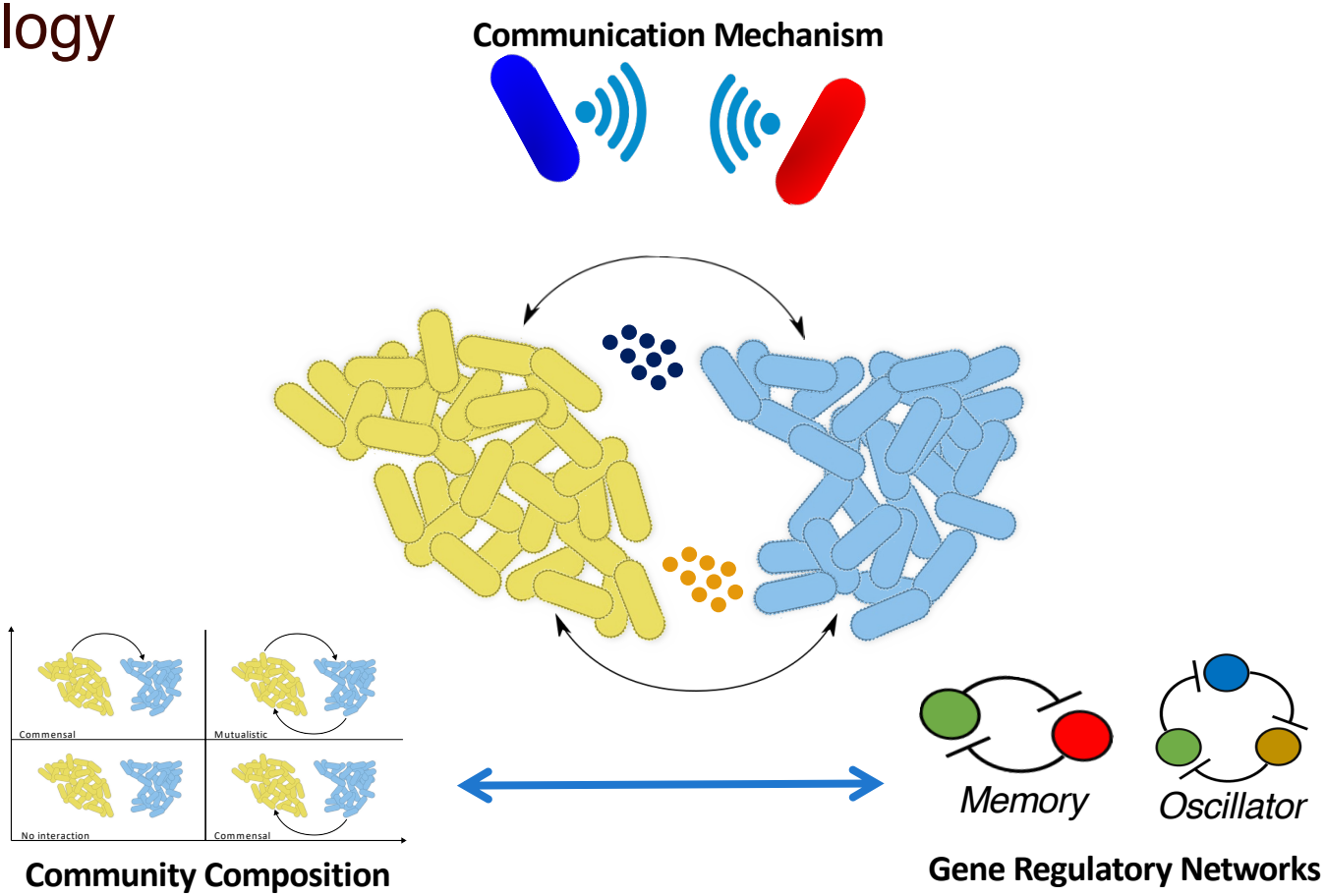
(ANSA) - NAPOLI, 09 OTT - Strategie di lockdown a livello regionale, anche per brevi periodi di tempo, per evitare e/o contenere, nuovi picchi epidemici riducendo gli enormi costi economici di un lockdown nazionale.

Remarks

- Our work convincingly showed the benefits of regional rather than national NPIs to deal with the pandemic
- This is precisely the idea behind the strategy adopted in Italy since 3rd November 2020
- In this problem, a set of local control actions deployed on the nodes and edges is used to reach a desired target state
- The resulting strategy can be seen as a distributed nonlinear switched feedback control action
- All sorts of open problems (local vs global, controllability, observability, distributed optimization, adaptivity, robustness etc)

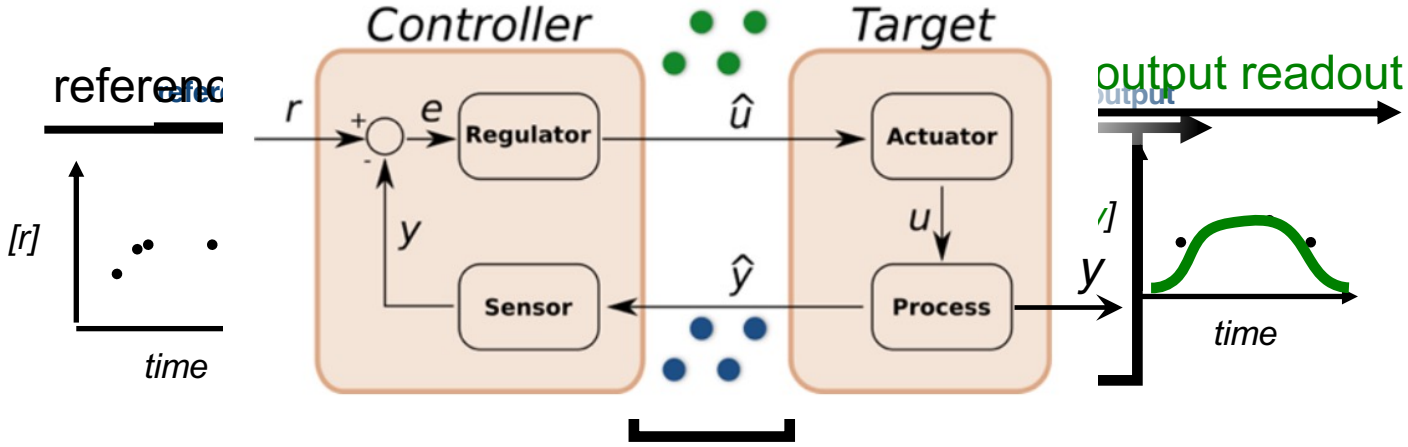
Multicellular Control

- Complex systems are often large-scale
- E.g. engineering controlled cell consortia in Synthetic Biology



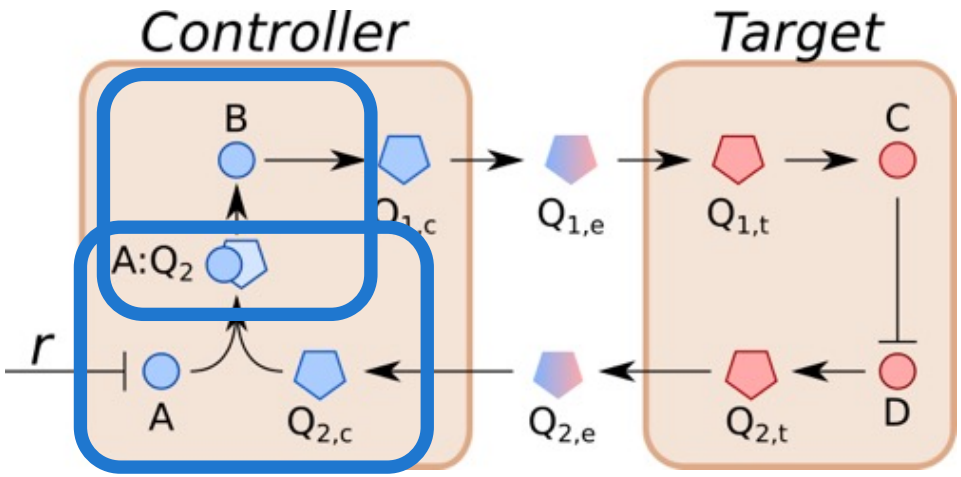
Controlled microbial consortia

- We proposed the use of engineered cellular consortia to achieve the control of a phenotype of interest
- The idea is to achieve modularity by splitting the feedback control loop across multiple cells



Fiore, G. et al, *ACS synthetic biology,* 2017; Shannon et al, *ACS synthetic biology,* 2020*;* Salzano et al, IEEE Control Systems Letters 2021

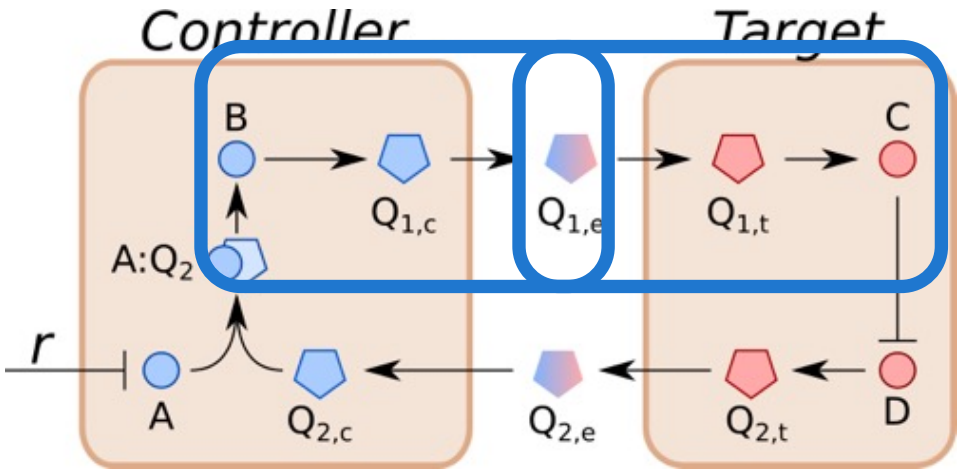
Multicellular Control Strategy



$$\frac{d[A{:}\,Q_2]}{dt} = \left(\chi_{A:Q,r,0} + \chi_{A:Q,r}\frac{K_r^{n_r}}{K_r^{n_r} + [r]^{n_r}}\right)\cdot\left(\chi_{A:Q,a,0} + \chi_{A:Q,a}\frac{[Q_{2,c}]_r^{n_r}}{K_q^{n_r} + [Q_{2,c}]^{n_r}}\right) - \gamma_{A:Q}[A{:}\,Q_2]$$

$$\frac{d[B]}{dt} = \chi_{B,0} + \chi_B\frac{[A{:}\,Q_{2,c}]^{n_r}}{K_r^{n_r} + [A{:}\,Q_{2,c}]^{n_r}} - \gamma_B[B]$$

Modelling the Signalling To Targets

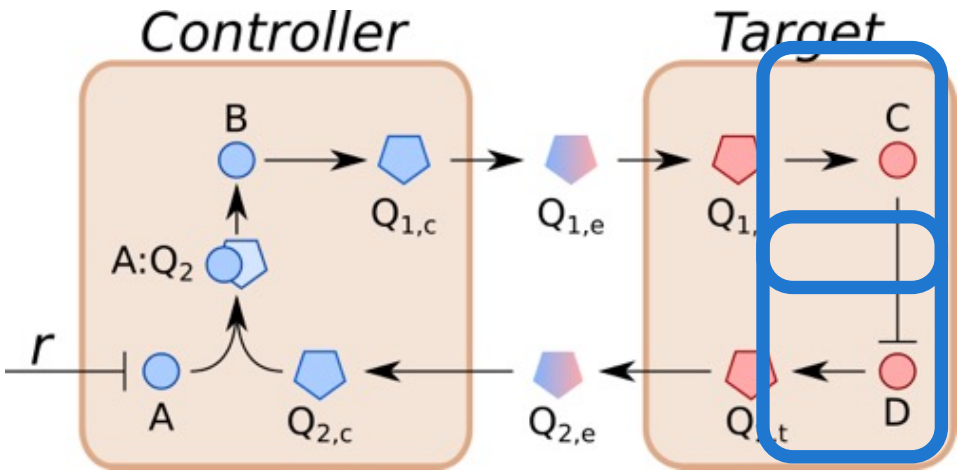


$$\frac{d[Q_{1,c}]}{dt} = K_{Q_1}[B] + \eta([Q_{1,e}] - [Q_{1,c}]) - \gamma_i[Q_{1,c}]$$

$$\frac{\partial[Q_{1,e}]}{\partial t} = \eta([Q_{1,c}] - [Q_{1,e}]) + \eta([Q_{1,t}] - [Q_{1,e}]) - \gamma_e[Q_{1,e}] + \Theta\nabla^2[Q_{1,e}]$$

$$\frac{d[Q_{1,t}]}{dt} = \eta([Q_{1,e}] - [Q_{1,t}]) - \gamma_i[Q_{1,t}]$$

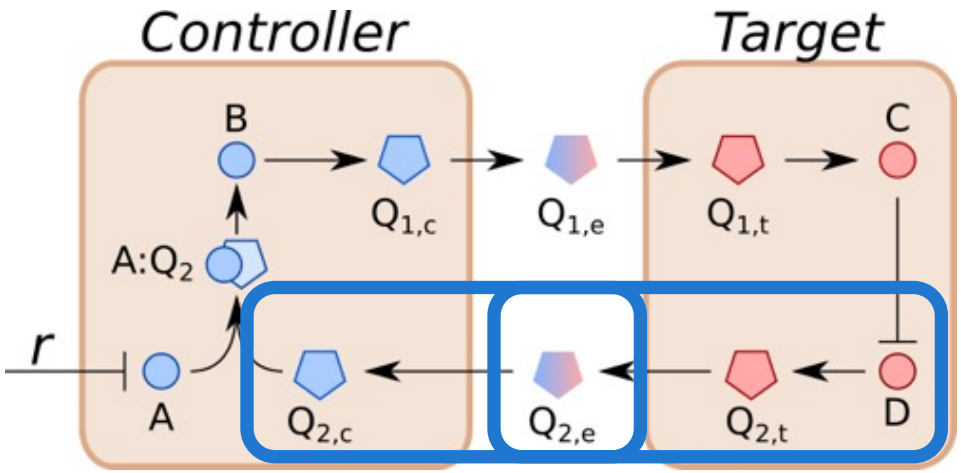
Modelling Target cells



$$\frac{d[C]}{dt} = \chi_{c,0} + \chi_c \frac{[Q_{1,t}]^{n_c}}{K_c{}^{n_c} + [Q_{1,t}]^{n_c}} - \gamma_C[C]$$

$$\frac{d[D]}{dt} = \chi_{d,0} + \chi_d \frac{K_d{}^{n_d}}{K_d{}^{n_d} + [C]^{n_d}} - \gamma_D[D]$$

Modelling the Signalling To Controllers

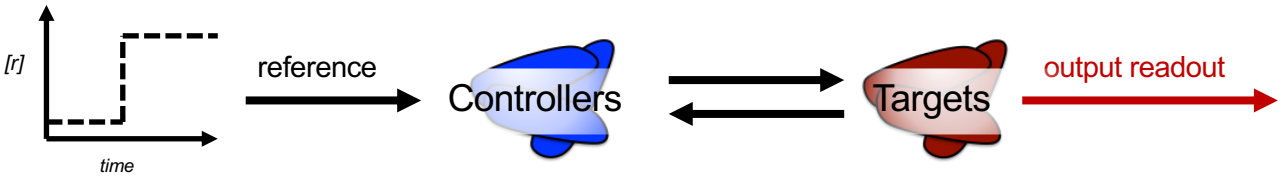


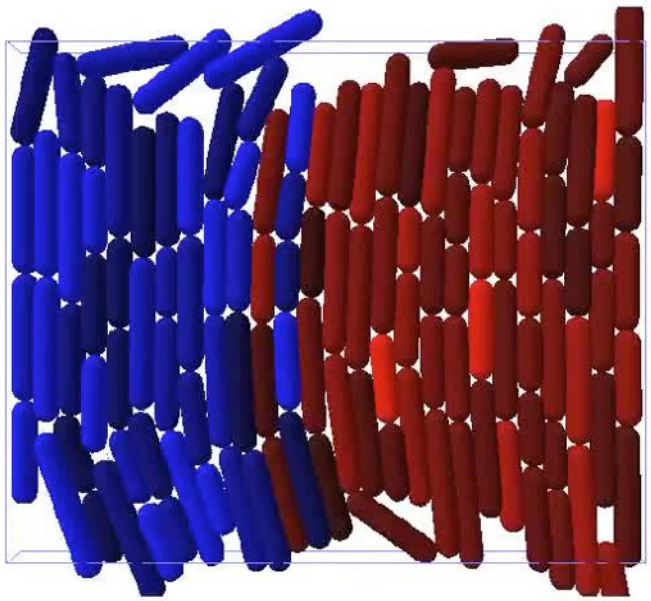
$$\frac{d[Q_{2,t}]}{dt} = K_{Q_2}[D] + \eta([Q_{2,e}] - [Q_{2,t}]) - \gamma_i[Q_{2,t}]$$

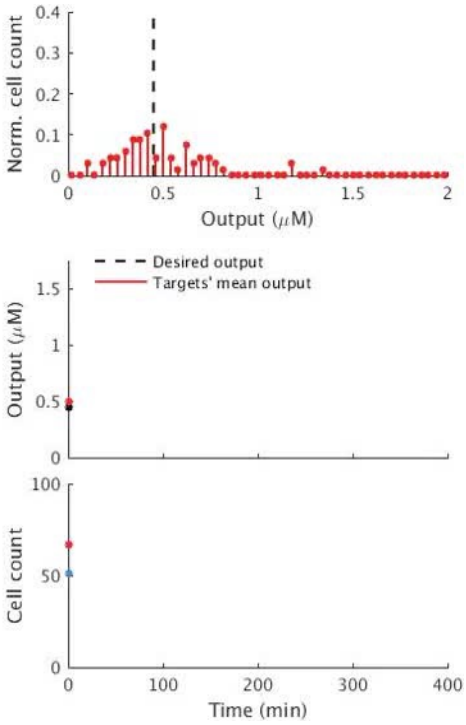
$$\frac{\partial[Q_{2,e}]}{\partial t} = \eta([Q_{2,c}] - [Q_{2,e}]) + \eta([Q_{2,t}] - [Q_{2,e}]) - \gamma_e[Q_{2,e}] + \Theta\nabla^2[Q_{2,e}]$$

$$\frac{d[Q_{2,c}]}{dt} = \eta([Q_{2,e}] - [Q_{2,c}]) - \gamma_i[Q_{2,c}]$$

Multicellular Regulation



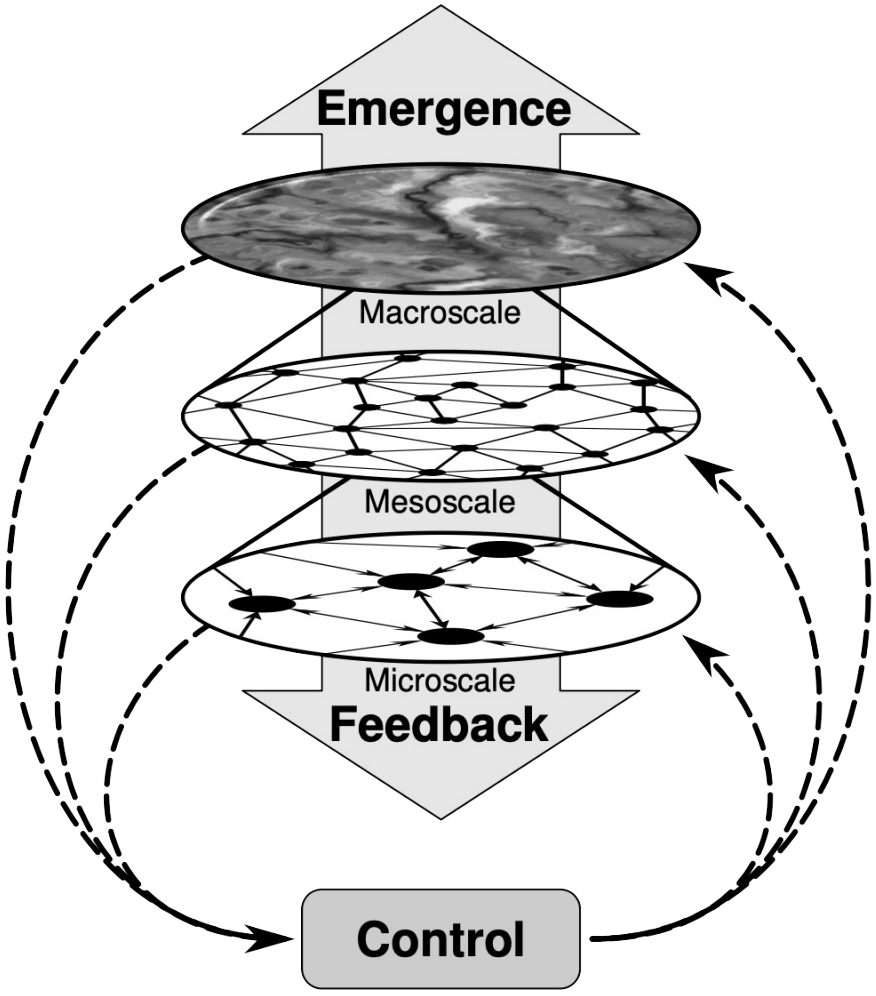




Matyjaszkiewicz A. et al, *ACS synthetic biology,* 2017l Gorochowski, T. et al*, PLoS One*, 2012

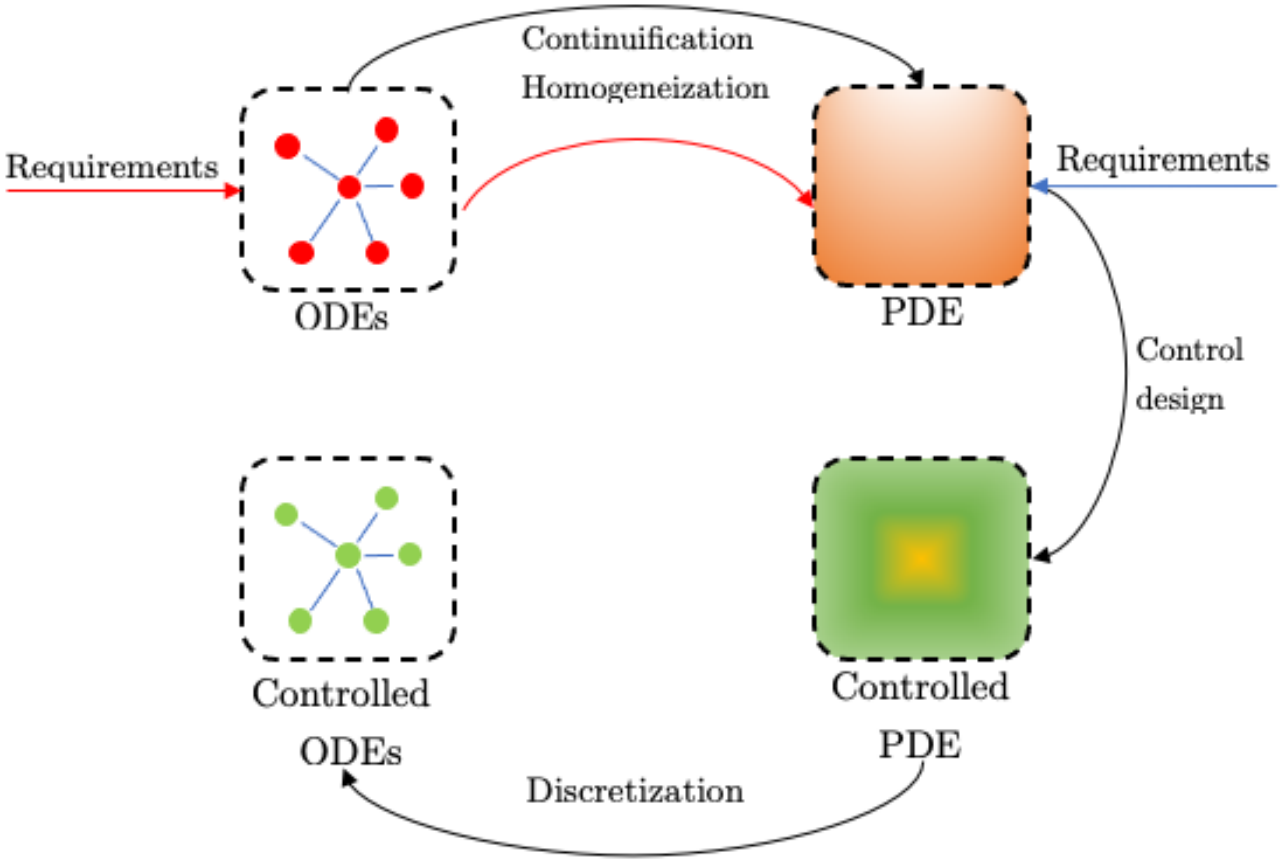
Large-scale complex systems

- Cells are just an example of large-scale complex systems
- How can we go beyond the state-of-the-art..
- .. and devise strategies to orchestrate the collective behaviour of large ensembles of interacting agents?



From ODEs to PDEs and back

- Using tools from statistical mechanics such as mean-field methods might be the key to close the loop across scales…



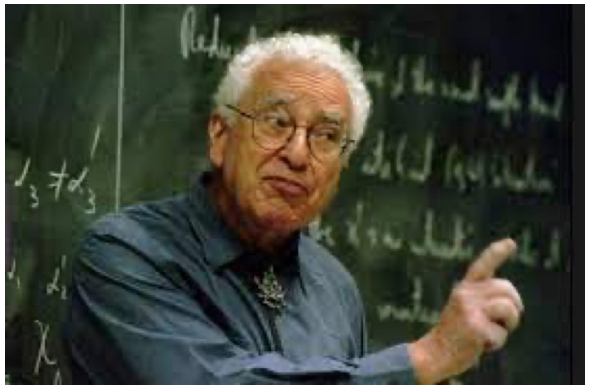
D. Nitikin et al, *Automatica,* 2021

A crucial problem

- Finding ways to merge PDEs/Stochastic Control with methods from statistical Physics to achieve the control of large-scale complex systems
- But…

> "*if particles could think Physics would be much harder*"
> M. Gell-Man (1969 Physics Nobel Laureate)

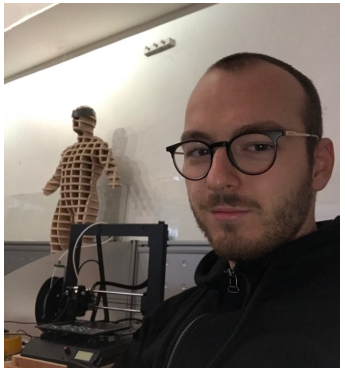
- Controlling some of the agents in real-time does precisely that…
- Lots of opportunites for exciting research



Conclusions

- We discussed the problem of controlling complex systems
- We looked at two different application examples
- In both cases the problem becomes that of devising strategies at the microscopic level able to induce desired collective properties at the macroscopic level
- The crucial problem is how to close the loop across these two scales
- A promising solution might be to look at ways of using methods from statistical physics but the very presence of control makes existing methods not always viable




Thank
you

PICASSO