Computing the optimal cocktail: formal methods and hybrid control for scheduling multiple treatments

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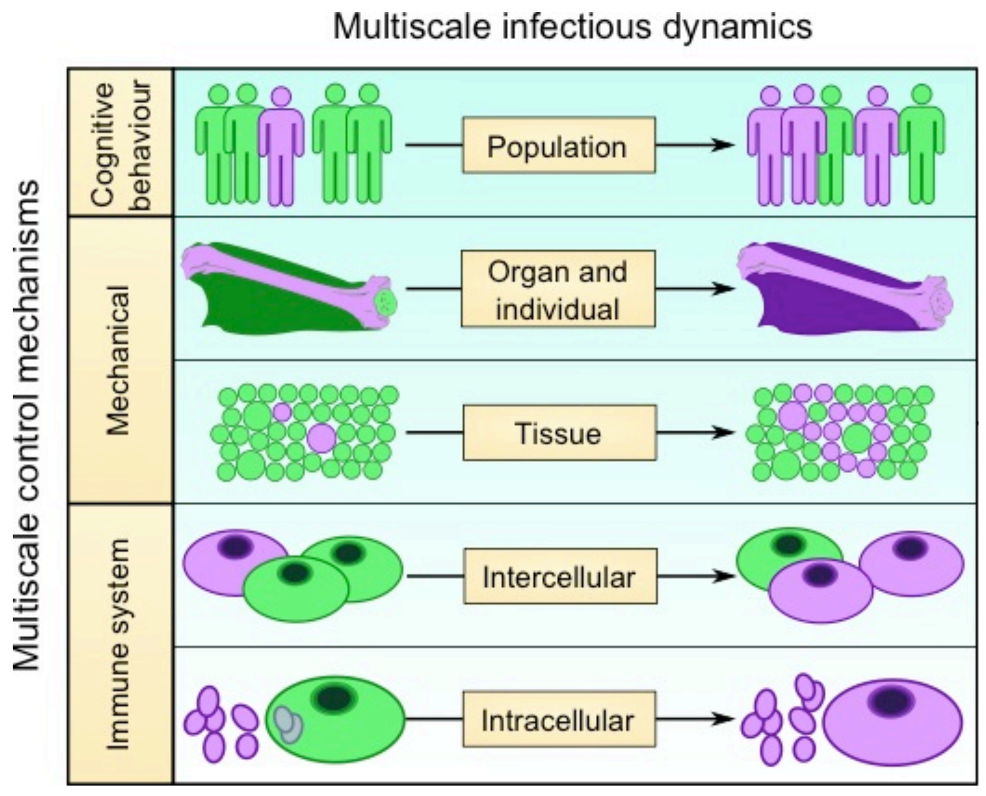
Background

Structured Therapy Interruption (**STI**), i.e. drug holiday, is the programmed interruption of a medication for a period of time. Like in HIV, **combinations of alternating therapies** are typically administered.

In a cocktail of therapies not just the ingredients make the difference, but also how they are dosed

STI Problem

Find an optimal scheduling of therapies over a complex disease model



Outline of the approach [1]

- **Quantitative process algebra,** the formal specification language
- **Hybrid semantics** (continuous diseases + discrete therapies)
- **Optimal control problem** for computing the optimal treatment strategy

Step 1 – Cook a modelling language

D-CGF (Disease CGF (Chemical Ground Form [2]))

D-CGF:: = (S,P,T,C)	a :: = t^r | ?x^r | !x^r
D-CFG model	*Rated actions (delay, input, output)*

Species (pathogens + hosts) — **Interpreted continuously**

S :: = 0 | X=I,S	I :: = 0 | a.P + I	P :: = 0 | (X || P)
Set of species definitions	*Individual species definition*	*Population*

$$S = t^{b}.(S||S) + t^{\mu}.\mathbf{0} + ?\,i^{\beta}.I + ?\,j^{p}.R$$
$$I = t^{b}.(I||S) + t^{\mu}.\mathbf{0} + !\,i^{\beta}.I + ?\,h^{k}.R + t^{v}.R$$
$$R = t^{b}.(R||S) + t^{\mu}.\mathbf{0}$$

Susceptible; Infected; Recovered; Birth of susceptible; Death; Infection of susceptible; "Vaccination" of susceptible by therapy 1; Infected recovers with therapy 2; Infected recovers "naturally"

Species definitions in the SIR epidemic model with therapies

Therapies — **Interpreted discretely**

T :: = 0 | U=R,T	R :: = 0 | a.C + R	C :: = 0 | (U || C)
Set of therapy definitions	*Therapy definition*	*Combination of therapies*

$$T1_{off} = t^{r1on}.T1_{on} \qquad T2_{off} = t^{r2on}.T2_{on}$$
$$T1_{on} = !\,j^{p}.T1_{on} + t^{r1off}.T1_{off} \qquad T2_{on} = !\,h^{k}.T2_{on} + t^{r2off}.T2_{off}$$

Therapy 1 inactive; Switch on T1; Therapy 1 active; Vaccination of susceptible; Switch off T2; Therapy 2 inactive; Switch on T2; Therapy 2 active; Vaccination of infected; Switch off T2

Therapy definitions in the SIR model

Step 2 – Distil a hybrid semantics

While the derivation of the continuous dynamics is quite standard [2], deriving the discrete part is a bit trickier. We need to identify **sets of processes acting as discrete switches**, i.e. where **exactly one term is active everytime**.

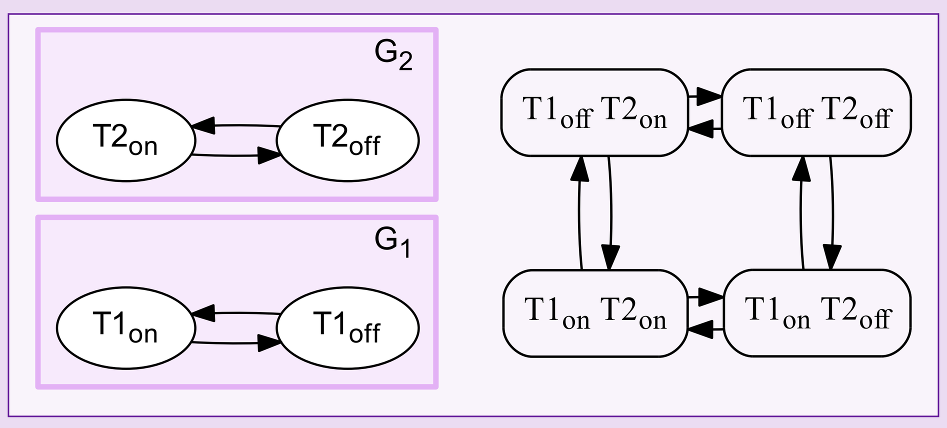


Figure 1. Structures for finding switches from processes

Controlled switched systems

A class of hybrid dynamical systems where the discrete operation mode **q** (a combination of on-off therapies) is given in input by an external controller (the therapist), based on observations **y** (e.g. patient data) of the piecewise smooth dynamics **x** (the disease model).

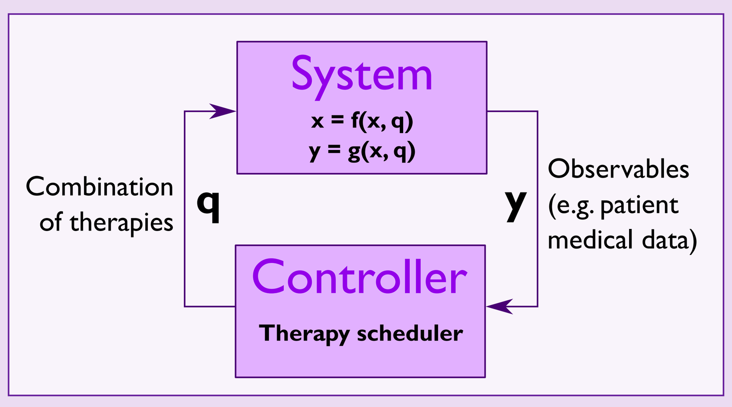


Figure 2. Control loop in a controlled switched system

Step 3 – Compute the optimal cocktail

Nonlinear hybrid optimal control

We define an optimal control problem over the hybrid semantics derived from the process-algebraic specification. Ideally, the control moves (i.e. the choice of a particular combination of therapies) are chosen to minimize the impact on the patient and to guarantee the success of the treatment.

Lack of efficient algorithms to solve optimal control problems on systems with both nonlinear and hybrid dynamics.

$$\min_{q} \int_{t}^{t_f} ||\boldsymbol{R}\boldsymbol{q}(t)||_p + ||\boldsymbol{Q}\boldsymbol{x}(t)||_p$$

sbj to
$$\dot{\boldsymbol{x}} = f(t, \boldsymbol{x}(t), \boldsymbol{q}(t))$$
$$\boldsymbol{x}(t) \in \mathbb{R}^n$$
$$\boldsymbol{q} \in \{0,1\}^m, \sum_i q_i = 1$$
$$\boldsymbol{x}(t_f) \in \mathcal{X}_f$$

R associates a weight (impact on the patient, cost, …) to each combination of therapies (discrete modes).

Q associates a weight to each state variable (e.g. high cost to pathogens).

Piecewise-smooth dynamics

Terminal constraints

Embedding approach [3]: the system is embedded into a larger family of systems (where discrete switches are relaxed). The relaxed problem can be solved with classical techniques for nonlinear optimization.

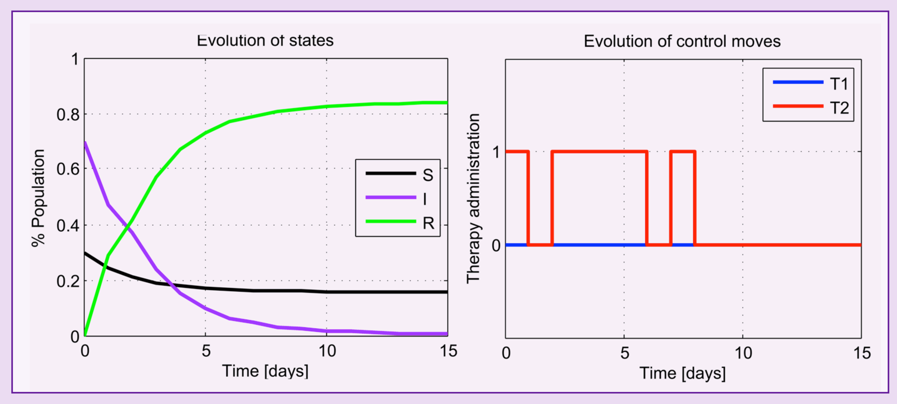


Figure 3. Optimal control of two therapies in the SIR epidemic model.

Future work

Playing games between the therapist and the disease

What if not just the therapist, but also the pathogen could play its moves? The most common case happens when the pathogen develops resistance to one or more therapies. Here, the therapist plays against an unpredictable, but somehow observable adversary.

We aim at using novel techniques in the **model checking of multi-player stochastic games** [4], for answering question like:

- *"What is the maximum impact on the patient of a **successful** treatment strategy, independently from pathogen's strategies?"*
- *"What is the probability that the pathogen has a strategy to survive, independently from therapist's strategies?"*

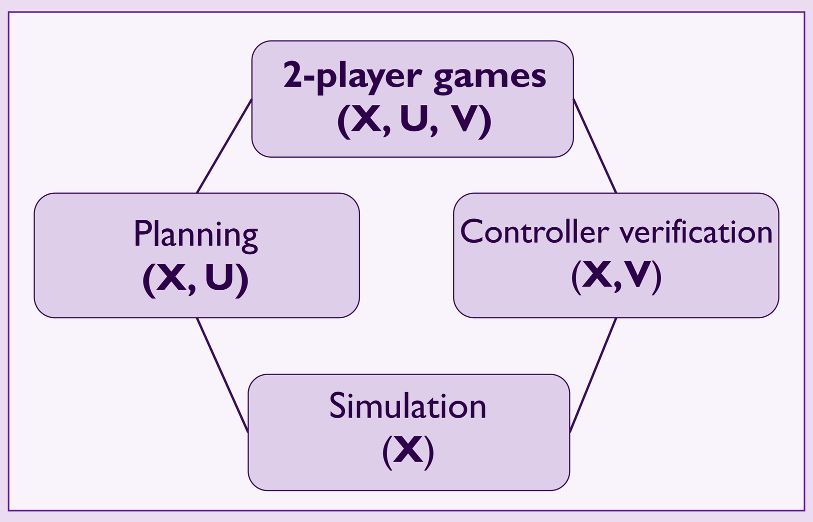


Figure 4. Games generalize a wide class of problems. **X** (system dynamics), **U** (controller), **V** (unpredictable environment).

References

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