Modélisation et analyse de systèmes biologiques hybrides par les mesures d’occupations

Alexandre Rocca[1,2], Marcelo Forets[1], Victor Magron[1], Thao Dang[1], Eric Fanchon[2]

[1]Verimag, [2]TIMC-IMAG, Grenoble

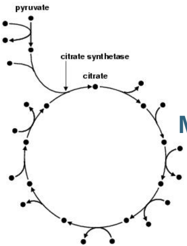
June 18, 2018

Context

- Biological systems

Context

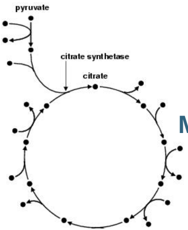
➢ Biological systems



Molecular level

Context

➢ Biological systems



Molecular level

. . .

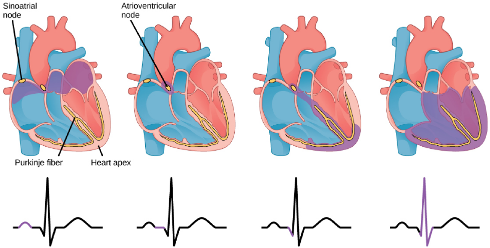
Population level

Context

- Biological systems
- Multi-stage behaviours

Context

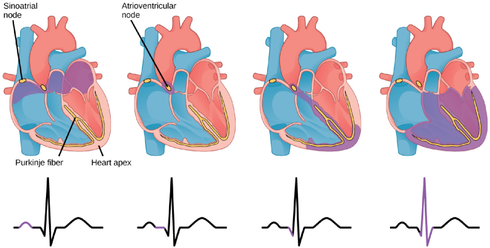
- ➢ Biological systems
- ➢ Multi-stage behaviours



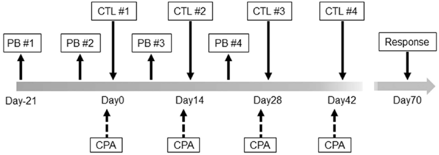
Multiple phase systems

Context

- ➢ Biological systems
- ➢ Multi-stage behaviours



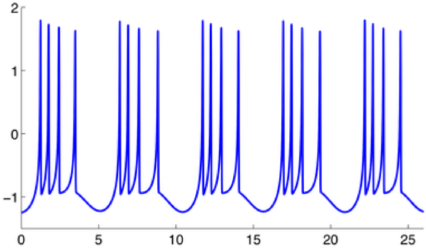
Multiple phase systems



Experimental protocols

Context

- Biological systems
- Multi-stage behaviours
- Slow/fast dynamics



Multiple time scale systems

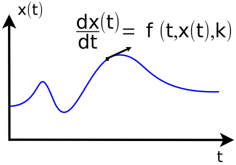
Context

- ➢ Biological systems
- ➢ Multi-stage behaviours
- ➢ Slow/fast dynamics

☞ Temporal evolution

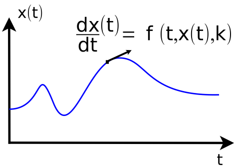
Modelling

➢ Continuous Time
- Ordinary differential equations (ODEs)

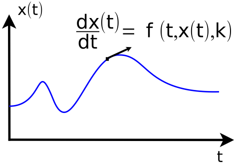


Modelling

- ➢ Continuous Time
  - Ordinary differential equations (ODEs)

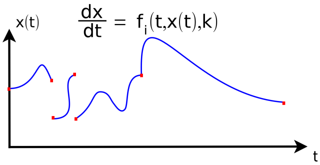


Modelling



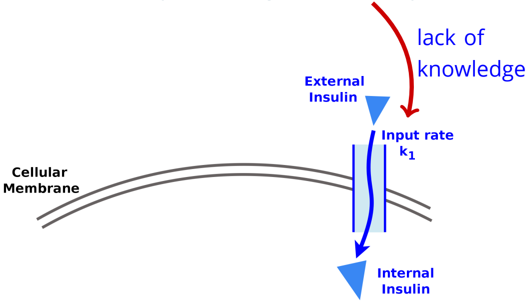
- Continuous Time
  - Ordinary differential equations (ODEs)

- Hybrid dynamics
  - Hybrid dynamical systems



Formal methods

- Efficiently handling **uncertainty** and **variability**



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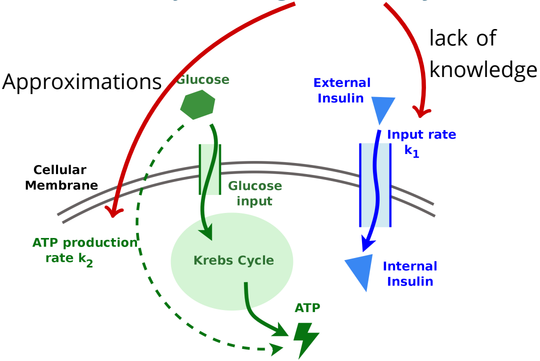
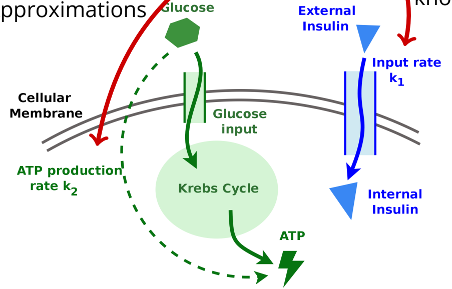


Formal methods

➢ Efficiently handling **uncertainty** and **variability**

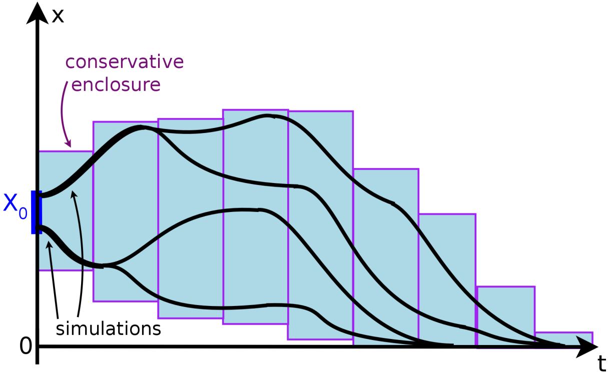
Approximations

lack of knowledge



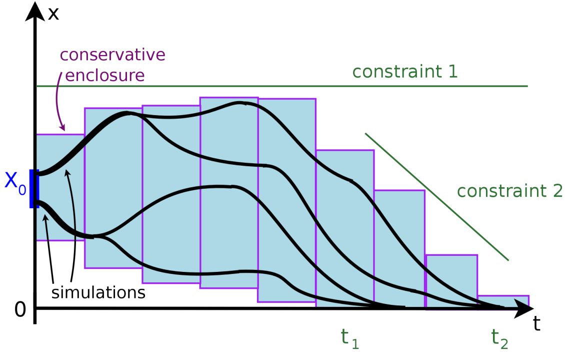
Formal methods

- Efficiently handling **uncertainty** and **variability**
- Providing **set-based** analysis



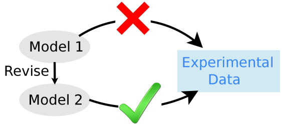
Formal methods

- Efficiently handling **uncertainty** and **variability**
- Providing **set-based** analysis
- Proving requirements and validating hypothesis



Contributions

1. Model revision



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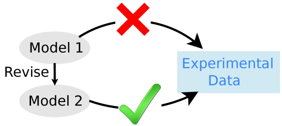

☞ Optimal control method based on occupation measures

- Haemoglobin production model

Contributions

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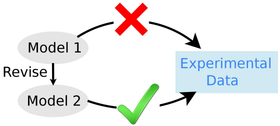
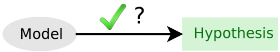


2. Hypothesis validation



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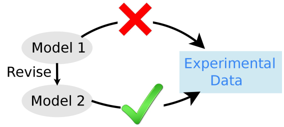

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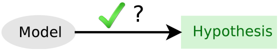

☞ Set-based analysis using Bernstein expansion or Krivine-Stengle representations
- Iron homeostasis model

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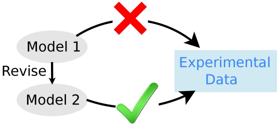

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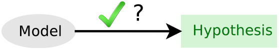

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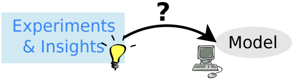
3. Model design



Contributions

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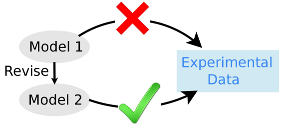

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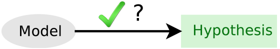

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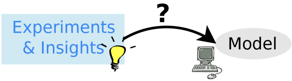

☞ Optimal control method based on occupation measures
- Haemoglobin production model

☞ Set-based analysis using Bernstein expansion or Krivine-Stengle representations
- Iron homeostasis model

☞ Hybrid automata to model experimental protocols
- Haemoglobin production model
- Generational Cadmium absorption study

Biological hybrid model revision using occupation measures

The Haemoglobin production model

- Erythroblasts: Differentiating red blood cells in bone marrow

The Haemoglobin production model

- Erythroblasts: Differentiating red blood cells in bone marrow
- Model of Haemoglobin production during the last 52 hours

- ODE system $\mathcal{F}_{norm}$

$$
\begin{cases}
\frac{d\mathrm{Fe}}{dt} = k_1 \mathrm{Fe}_{ex} - k_2 \mathrm{Fe} - k_3 \mathrm{Fe} \\
\frac{d\mathrm{H}}{dt} = k_3 \mathrm{Fe} - k_4 \mathrm{H} - 4\, k_5 \mathrm{H} \cdot \mathrm{G} \\
\frac{d\mathrm{G}}{dt} = k_6 \mathrm{H} - 4\, k_5 \mathrm{H} \cdot \mathrm{G} - k_7 \mathrm{G} \\
\frac{d\mathrm{Hb}}{dt} = k_5 \mathrm{H} \cdot \mathrm{G} - k_8 \mathrm{Hb}
\end{cases}
$$

The Haemoglobin production model

- ➢ Erythroblasts: Differentiating red blood cells in bone marrow
- ➢ Model of Haemoglobin production during the last 52 hours

- **Intra cellular Iron:** Fe

- ODE system $\mathcal{F}_{norm}$

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\end{cases}
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- **Intra cellular Iron:** Fe

$\mathrm{Fe}_{ex} \rightarrow \mathrm{Fe}$, Iron input rate: k_1

$\mathrm{Fe} \rightarrow \emptyset$, Iron degradation rate: k_2

- ODE system $\mathcal{F}_{norm}$

$$\begin{cases} \frac{d\mathrm{Fe}}{dt} = k_1 \mathrm{Fe}_{ex} - k_2 \mathrm{Fe} - k_3 \mathrm{Fe} \\ \frac{d\mathrm{H}}{dt} = k_3 \mathrm{Fe} - k_4 \mathrm{H} - 4 k_5 \mathrm{H} \cdot \mathrm{G} \\ \frac{d\mathrm{G}}{dt} = k_6 \mathrm{H} - 4 k_5 \mathrm{H} \cdot \mathrm{G} - k_7 \mathrm{G} \\ \frac{d\mathrm{Hb}}{dt} = k_5 \mathrm{H} \cdot \mathrm{G} - k_8 \mathrm{Hb} \end{cases}$$

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- **Intra cellular Iron:** Fe
- **Intra cellular (free) Heme:** H

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- **Intra cellular Iron:** Fe
- **Intra cellular (free) Heme:** H

$\mathrm{Fe} \to \mathrm{H}$, Heme production rate: k_3

$\mathrm{H} \to \emptyset$, Heme degradation rate: k_4

- ODE system $\mathcal{F}_{norm}$

$$\begin{cases} \dfrac{d\mathrm{Fe}}{dt} = k_1 \mathrm{Fe}_{ex} - k_2 \mathrm{Fe} - k_3 \mathrm{Fe} \\ \dfrac{d\mathrm{H}}{dt} = k_3 \mathrm{Fe} - k_4 \mathrm{H} - 4\, k_5 \mathrm{H} \cdot \mathrm{G} \\ \dfrac{d\mathrm{G}}{dt} = k_6 \mathrm{H} - 4\, k_5 \mathrm{H} \cdot \mathrm{G} - k_7 \mathrm{G} \\ \dfrac{d\mathrm{Hb}}{dt} = k_5 \mathrm{H} \cdot \mathrm{G} - k_8 \mathrm{Hb} \end{cases}$$

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- Model of Haemoglobin production during the last 52 hours

- **Intra cellular Iron:** Fe
- **Intra cellular (free) Heme:** H
- **Intra cellular Globin:** G

$\rightarrow \mathrm{G}$, Globin production rate: k_6 (accelerated by Heme)

$\mathrm{G} \rightarrow \emptyset$, Globin degradation rate: k_7

- ODE system $\mathcal{F}_{norm}$

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- **Intra cellular Iron:** Fe
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- **Intra cellular Globin:** G
- **Intra cellular Haemoglobin:** Hb

$4\mathrm{G} + 4\mathrm{H} \rightarrow \mathrm{Hb}$, Haemoglobin prodution rate: k_5

$\mathrm{Hb} \rightarrow \emptyset$, Haemoglobin degradation rate: k_8

- ODE system $\mathcal{F}_{norm}$

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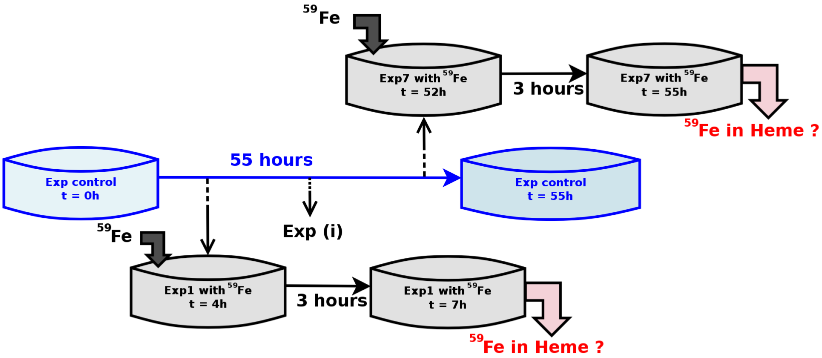
Associated experimental protocol



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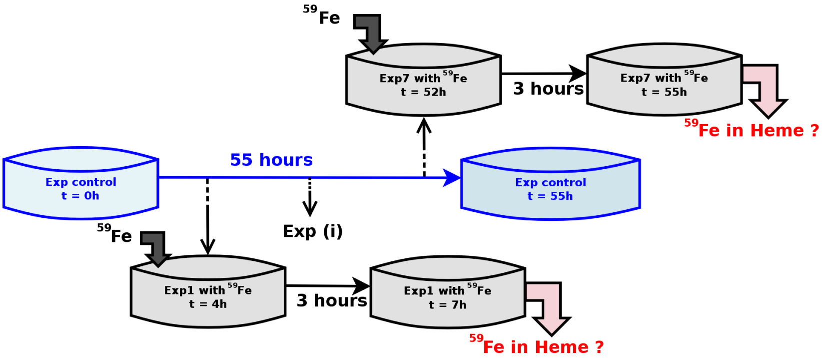
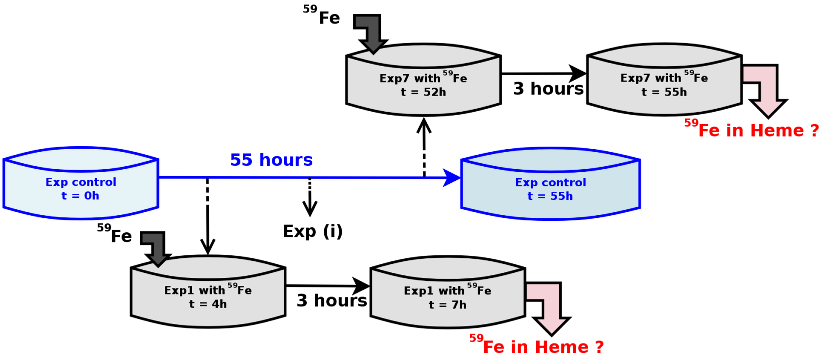


☞ ∼ Integration speed of iron in heme

Associated experimental protocol



- ∼ Integration speed of iron in heme
- ∼ Heme mainly in haemoglobin

Introducing new variables

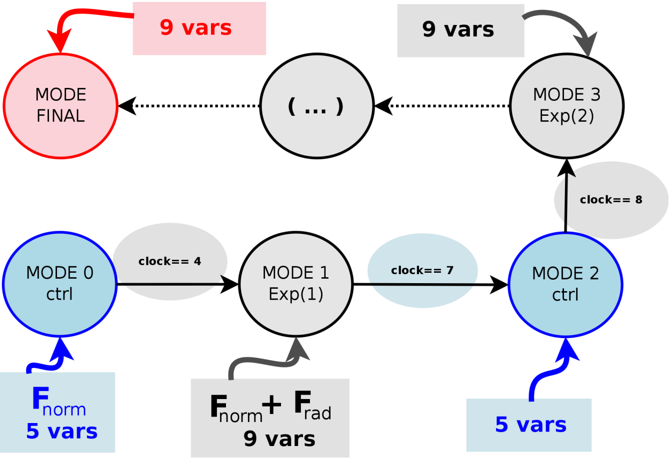
- $\mathcal{F}_{norm}$: System without radioactive species

$$\begin{cases} \frac{dFe}{dt} = k_1 Fe_{ex} - k_2 Fe - k_3 Fe \\ \frac{dH}{dt} = k_3 Fe - k_4 H - 4k_5 H \cdot G \\ \frac{dG}{dt} = k_6 H - 4k_5 H \cdot G - k_7 G \\ \frac{dHb}{dt} = k_5 H \cdot G - k_8 Hb \end{cases}$$

- $\mathcal{F}_{rad}$: System with (additional) radioactive species.

$$\begin{cases} \dots = \dots \\ \frac{d\,{}^{59}Fe}{dt} = k_1\,{}^{59}Fe_{ex} - k_2\,{}^{59}Fe - k_3\,{}^{59}Fe \\ \frac{d\,{}^{59}H}{dt} = k_3\,{}^{59}H - k_4\,{}^{59}H - 4k_5\,{}^{59}H \cdot G_{rad} \\ \frac{d\,G_{rad}}{dt} = k_6({}^{59}H + H) - 4k_5({}^{59}H + H)\,G_{rad} - k_7 G_{rad} \\ \frac{d\,{}^{59}Hb}{dt} = k_5\,{}^{59}H \cdot G_{rad} - k_8\,{}^{59}Hb \end{cases}$$

Associated hybrid automaton



Model revision: Haemoglobin model

We have:

- A hybrid automaton modelling a protocol

Model revision: Haemoglobin model

We have:

- A hybrid automaton modelling a protocol
- A parameter set obtained using simulations [Bouchnita et al., 2016]

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- To better reproduce the datasets

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Our approach:

- ☞ Transform a constant parameter into a time varying law

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- Transform a constant parameter into a time varying law
  - In the haemoglobin production model: $k_3 \Rightarrow k_3(t)$

$$\frac{\mathrm{dH}}{\mathrm{dt}} = k_3 \mathrm{Fe} - k_4 \mathrm{H} - 4k_5 \mathrm{H}\,\mathrm{G}$$

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  - In the haemoglobin production model: $k_3 \Rightarrow k_3(t)$

$$\frac{\mathrm{dH}}{\mathrm{dt}} = \underbrace{k_3}_{\text{Iron integration rate}} \mathrm{Fe} - k_4 \mathrm{H} - 4 k_5 \mathrm{H}\,\mathrm{G}$$

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We have:

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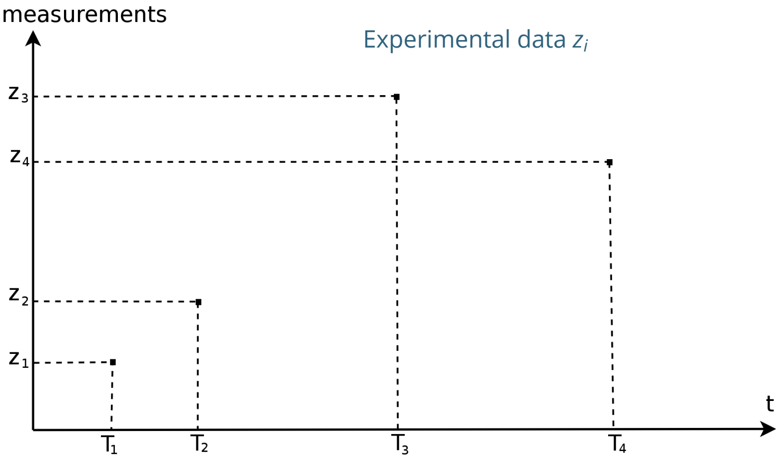
- Transform a constant parameter into a time varying law
  - In the haemoglobin production model: $k_3 \Rightarrow k_3(t)$

$$\frac{\mathrm{dH}}{\mathrm{dt}} = k_3(t)\mathrm{Fe} - k_4\mathrm{H} - 4k_5\mathrm{H}\,\mathrm{G}$$

Model revision: Cost function



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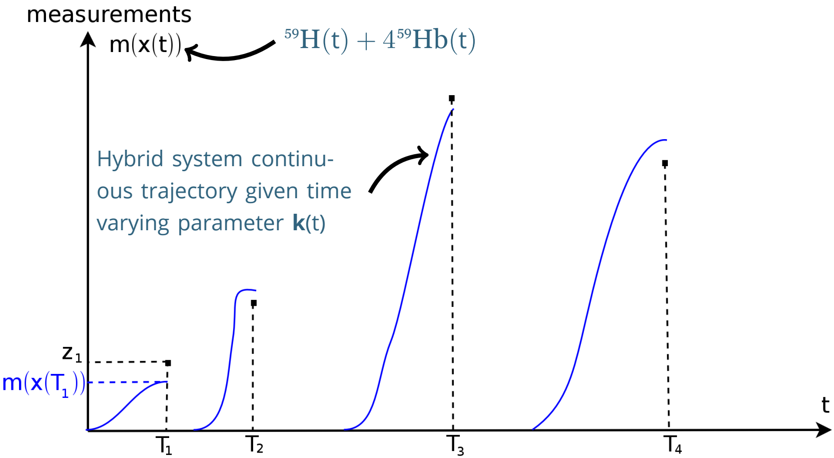
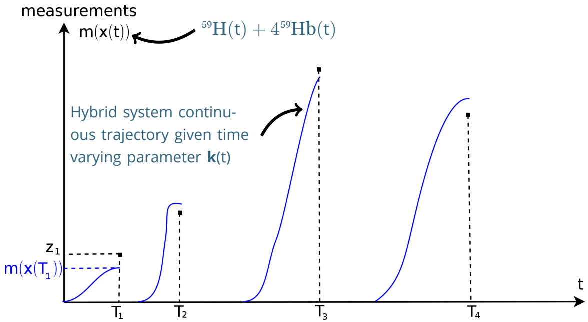


Model revision: Cost function



➢ We search for $\mathbf{k}(t)$ minimizing:

$$\sum_{j=1}^{n_{exp}} \|\mathbf{m}(\mathbf{x}(T_j)) - \mathbf{z}_j\|$$

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Model revision: Optimization problem

➢ $\min\limits_{(\mathbf{x},\mathbf{k})} \sum_{j=1}^{n_{exp}} \|\mathbf{m}(\mathbf{x}(T_j, \mathbf{k}(T_j))) - \mathbf{z}_j\|$

Model revision: Optimization problem

- $\min\limits_{(\mathbf{x},\mathbf{k})} \sum_{j=1}^{n_{exp}} \|\mathbf{m}(\mathbf{x}(T_j, \mathbf{k}(T_j))) - \mathbf{z}_j\|$
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  - ☞ $\mathbf{x}(0) \in X_0$: initial conditions

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- Optimal control problem (OCP)

The OCP method motivations

We want to solve an OCP with:

The OCP method motivations

We want to solve an OCP with:

- Hybrid dynamical system

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We want to solve an OCP with:

- Hybrid dynamical system
- Polynomial continuous dynamics

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The OCP method motivations

We want to solve an OCP with:

- ➢ Hybrid dynamical system
- ➢ Polynomial continuous dynamics
- ➢ Dimension varying between two modes
- ➢ Cost function on intermediate time points

☞ An appropriate approach using occupation measures reformulation
- [Zhao et al., 2017]

☞ Do not rely on sampling and numerous simulations

Measure intuition

Examples of measure:

- Volume (Lebesgue measure)
- Density measure
- Probability measure, ...

Occupation Measure Intuition

$$\dot{\mathbf{x}} = f(\mathbf{x}(t))$$

Occupation measure of $A \subset X$:

$$\mu(A|\mathbf{x}_0) := \int_0^T I_A(\mathbf{x}(t|\mathbf{x}_0)dt\,,$$

➢ **Indicator function:** $I_A(\mathbf{x}(t|\mathbf{x}_0))$ = 1 if $\mathbf{x}(t|\mathbf{x}_0) \in A$ else 0

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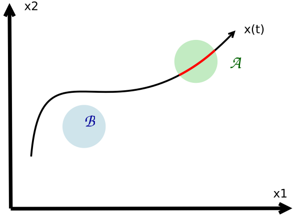

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- ➢ **Indicator function:** $I_A(\mathbf{x}(t|\mathbf{x}_0)) = 1$ if $\mathbf{x}(t|\mathbf{x}_0) \in A$ else 0
- ➢ occupation measure $\mu(\cdot|\mathbf{x}_0)$ on A: time spent by a trajectory $\mathbf{x}(t|\mathbf{x}_0)$ in A
- [Lasserre et al., 2008]
- ➢ The support of $\mu(\cdot|\mathbf{x}_0)$ is the trajectory in X

Liouville Equation

- Given an uncertain initial condition X_0 and final set X_T
- and associated initial and final measures μ_0 and μ_T:
  - μ_0 models the initial condition distribution
  - $\mu_T = \int_X I_{X_T}(\mathbf{x}(T|\mathbf{x}_0)d\mu_0$

$$\nabla \cdot (f\mu) = \mu_T - \mu_0$$

- Occupation measure Liouville equation
- Linear equation of the evolution of the occupation measure
- $\mathcal{L}'_f\mu = \nabla \cdot (f\mu)$: divergence of the measure under the effect of the vector field f

Liouville Intuition

- $\dot{\mathbf{x}} = f(\mathbf{x}(t))$
- $\mathbf{x}(0) \in X_0$
- $\mathbf{x}(T) \in X_T$

- $\mathcal{L}_f' \mu = \mu_T - \mu_0$
- $\mu, \mu_0, \mu_T \geq 0$
- X_0, X_T: supports of μ_0, μ_T

☞ Non-linear and differential constraint system on the phase space ...
☞ **Transformed into an infinite linear system** on the measure space

Hybrid Liouville

- Measure of **initial condition in mode** *i*: μ_0^i

Hybrid Liouville

- Measure of **initial condition in mode** i: μ_0^i
- **Evolution of the occupation measure** with flow f_i: $\mathcal{L}_i' \mu^i$

Hybrid Liouville

- Measure of **initial condition in mode** i: μ_0^i
- **Evolution of the occupation measure** with flow f_i: $\mathcal{L}_i' \mu^i$
- Measure of **trajectories entering the mode** i: $R_{(j,i)} \mu^{S_{j,i}}$
  - affected by a reset map associated with the transitions

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$$\mu_0^i + \mathcal{L}_i' \mu^i + \sum_{(j,i) \in \mathcal{E}} R_{(j,i)} \mu^{S_{j,i}} = \mu_T^i + \sum_{(i,j) \in \mathcal{E}} \mu^{S_{i,j}}$$

Optimal control solution

- Reformulation as an infinite dimensional linear optimisation problem
- Existing converging approximations using semi-definite programming relaxations
  - A control function $\mathbf{u}_i(t)$ associated to each mode (dynamics)
  - Each $\mathbf{u}_i(t)$ approximated by polynomials
  - For only one final time T

HOCP method: discussion

Advantages:

- ➢ Converge to the optimum

Limitations:

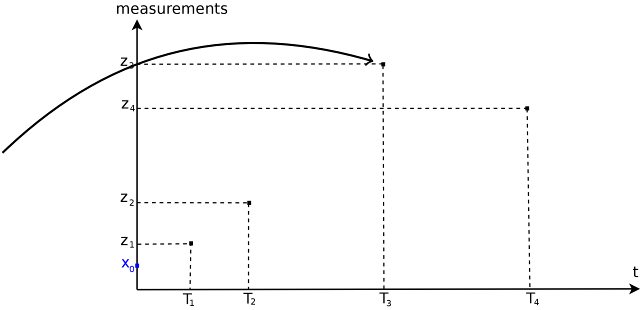
- ➢ Do not handle cost at fixed intermediate time
- ➢ Cannot be used in a dynamic programming scheme
- ➢ Piecewise polynomial control

Our proposal:

☞ HOCP applied in a greedy algorithm
☞ Smoothing of the control needed

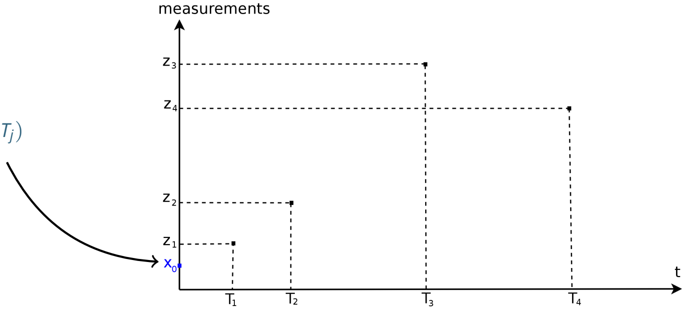
The model revision algorithm

➢ A set of data points (z_j, T_j)



The model revision algorithm

- ➢ A set of data points (z_j, T_j)
- ➢ An initial condition $\mathbf{x}_0$



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- ➢ A set of data points (z_j, T_j)
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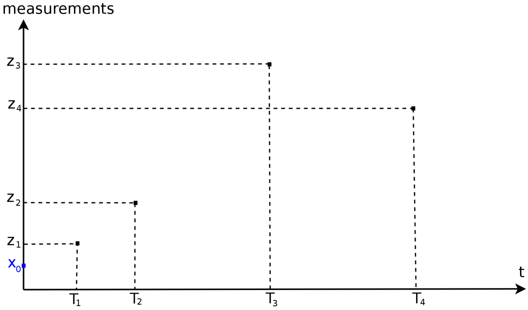
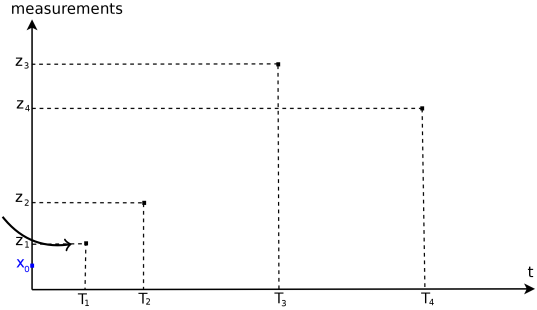
- ➢ Apply [Zhao et al., 2017] method with:



The model revision algorithm

- ➢ A set of data points (z_j, T_j)
- ➢ An initial condition $\mathbf{x}_0$
- ➢ Apply [Zhao et al., 2017] method with:
  - Final time $T = T_1$
  - cost to minimize: $H(T_1, \mathbf{x}(T_1), \mathbf{u}(T_1))$



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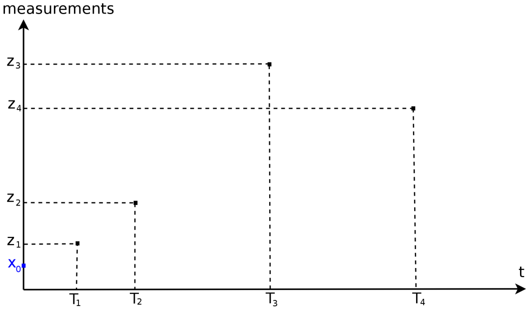
☞ Haemoglobin model:
$({}^{59}\mathrm{H}(T_1) + 4\,{}^{59}\mathrm{Hb}(T_1) - z_1)^2$



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- ➢ Apply [Zhao et al., 2017] method with:
  - Final time $T = T_1$
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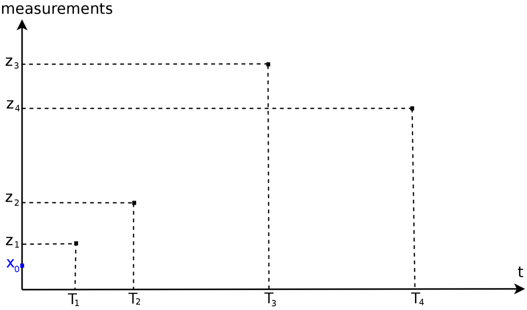
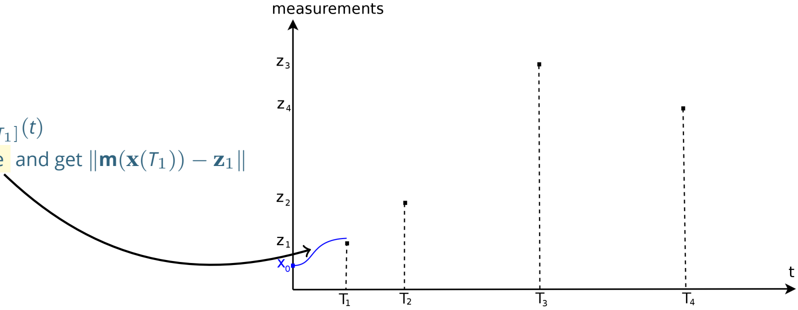
  - control $\mathbf{u}_{[0,T_1]}(t)$ Piecewise polynomial



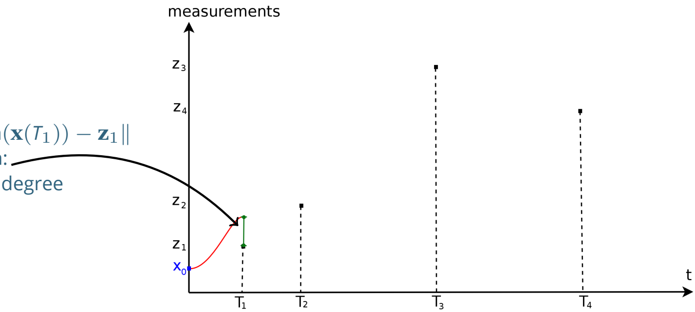
The model revision algorithm

- Given $\mathbf{u}_{[0,T_1]}(t)$
  - Simulate and get $\|\mathbf{m}(\mathbf{x}(T_1)) - \mathbf{z}_1\|$



The model revision algorithm

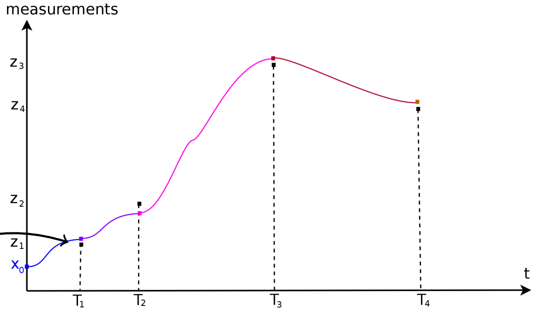
- Given $\mathbf{u}_{[0,T_1]}(t)$
  - Simulate and get $\|\mathbf{m}(\mathbf{x}(T_1)) - \mathbf{z}_1\|$
- If not accurate enough:
  - Increase polynomial degree



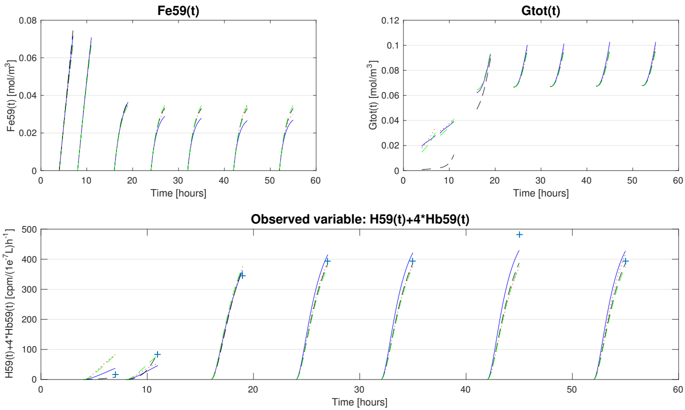
The model revision algorithm

Loop

- ➢ A set of data points (z_j, T_j)
- ➢ An initial condition $\mathbf{x}_0$
- ➢ Apply [Zhao et al., 2017] method with:
  - Final time $T = T_1$
  - cost to minimize: $H(T_1, \mathbf{x}(T_1), \mathbf{u}(T_1))$
  - control $\mathbf{u}_{[0,T_1]}(t)$ Piecewise polynomial
- ➢ Given $\mathbf{u}_{[0,T_1]}(t)$
  - ☞ Simulate and get $\|\mathbf{m}(\mathbf{x}(T_1)) - \mathbf{z}_1\|$
- ➢ New initial condition: $\mathbf{x}(T_1)$



Results on Haemoglobin case study



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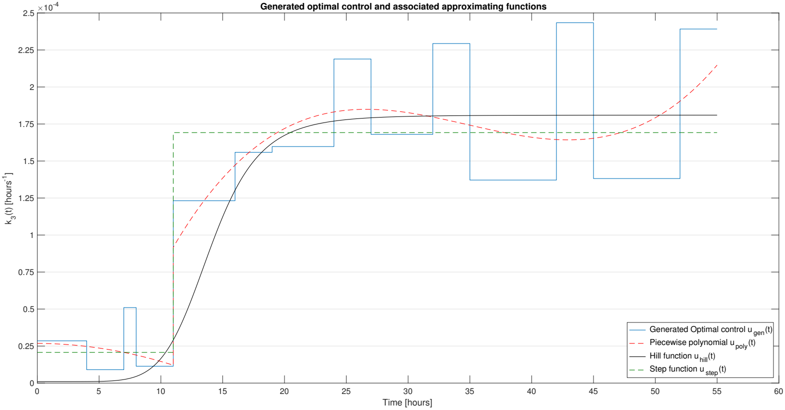

Results on Haemoglobin case study

☞ Implementation in Matlab

Control Type	ε_{total}
Sampling method [Bouchnita et al., 2016]	0.23
Generated control	0.096
Step function fit	0.12
Piecewise Polynomial fit	0.13
Hill function fit	0.075

$$\varepsilon_{total} = \sum_{1 \leq j \leq n_{exp}} \frac{\sqrt{H(\mathbf{x}(T_j))}}{\sum_{1 \leq j \leq n_{exp}} z_j}.$$

Conclusion

- Model revision of hybrid systems
  - Good trade-off performance/accuracy
  - Do not rely on numerous simulations

Future work:

- Synthesising sets of valid parameters for biological hybrid systems
  - Occupation measure formulation for parameter synthesis

Thank you for your attention !

Publications

- *Multi-scale Modelling of Erythropoiesis and Hemoglobin Production*, Journal of Inorganic and Organometallic Polymers and Materials, [Bouchnita et al., 2016]
- *Application of the Reachability Analysis for the Iron Homeostasis Study*, HSB2016, [Rocca et al., 2016]
- *Certified Roundoff Error Bounds using Bernstein Expansions and Sparse Krivine-Stengle Representations*, ARITH24 [Rocca et al., 2017b]
- *Occupation measure methods for modelling and analysis of biological hybrid systems*, ADHS2018, [Rocca et al., 2017a]
- *Certified Roundoff Error Bounds using Bernstein Expansions and Sparse Krivine-Stengle Representations*, submitted to Transaction on Computers [Magron et al., 2018]

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