

What we have done
in ANR STOCH-MC
Controlling Yeasts

Controlling a population

SM 2 : Real time yeast population control to a sine wave target profile

Long-term model predictive control of gene expression at the population and single-cell levels

J. Uhlendorf, A. Miermont, T. Delaveau, G. Charvin, F. Fages, S. Bottani, G. Batt* & P. Hersen*

✉ pascal.hersen@univ-paris-diderot.fr <http://tinyurl.com/TeamHersen>

✉ gregory.batt@inria.fr <http://www-rocq.inria.fr/~batt/>

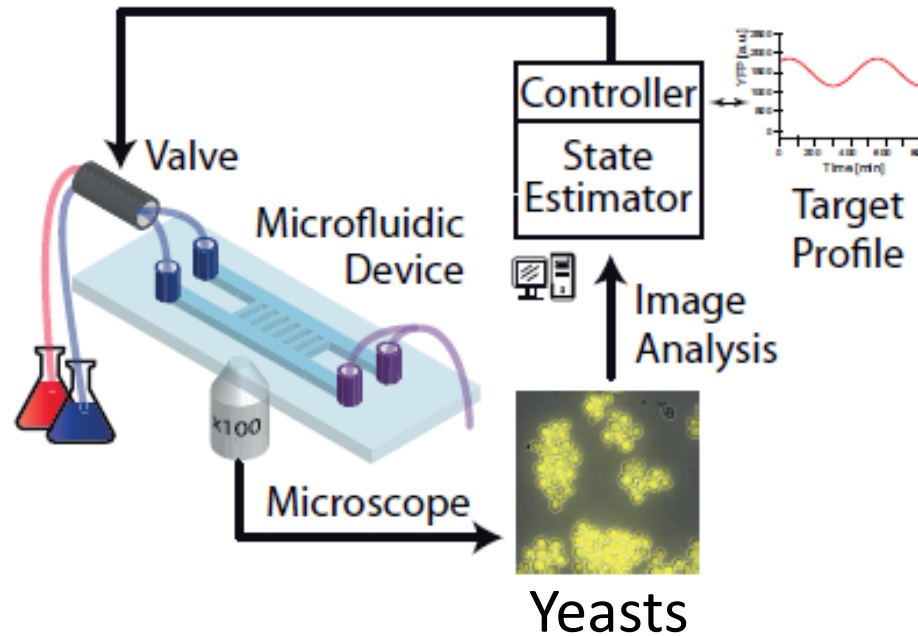
UNIVERSITÉ
PARIS
DIDEROT



Inria
INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

[Uhlendorf, Miermont, Delaveau, Charvin, [Fages](#), Bottani, Hersen, [Batt](#),
Chapter of *Computational Methods in Synthetic Biology, 2015*]

Population of cells



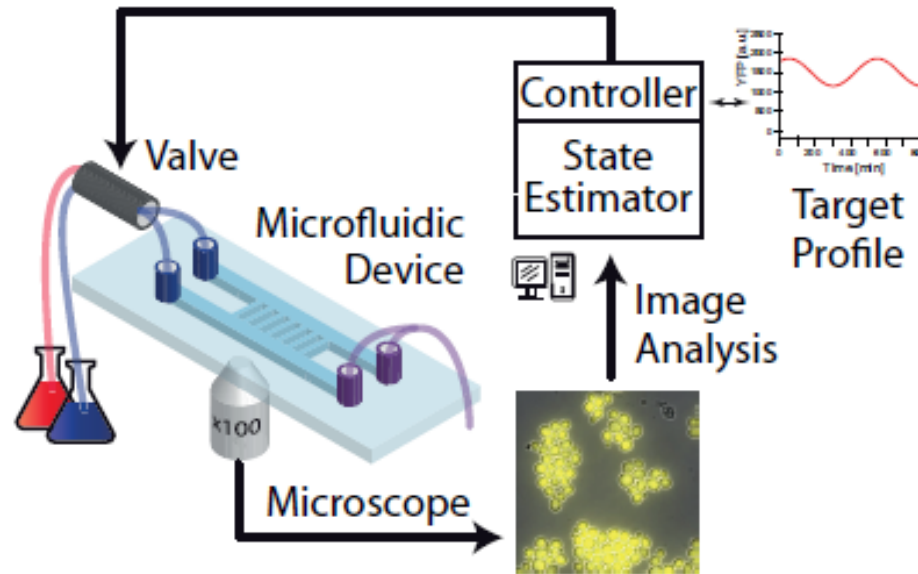
Setting: Many yeasts.

Image analysis: high concentration of protein X.

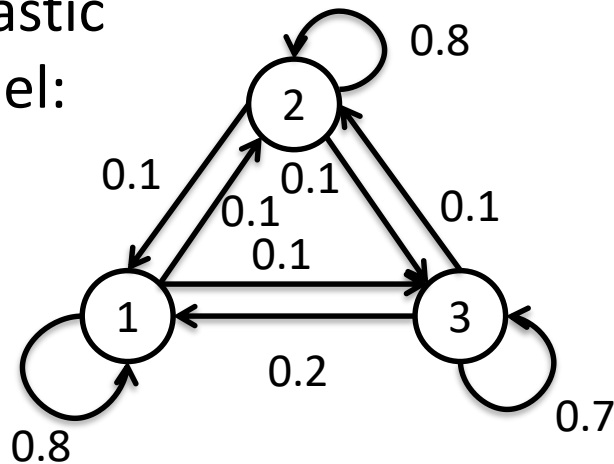
Control: sorbitol solution=> osmotic stress influencing X

What we have done
in ANR STOCH-MC
Theoretical Study

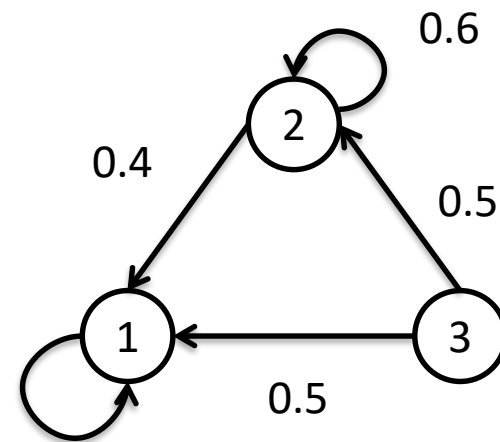
Simplistic Discrete Markovian Model



Simple
Stochastic
Model:



sorbitol on



sorbitol off

DTMC
modeling
of yeasts:
To do.

Fluid / Continuous Abstraction

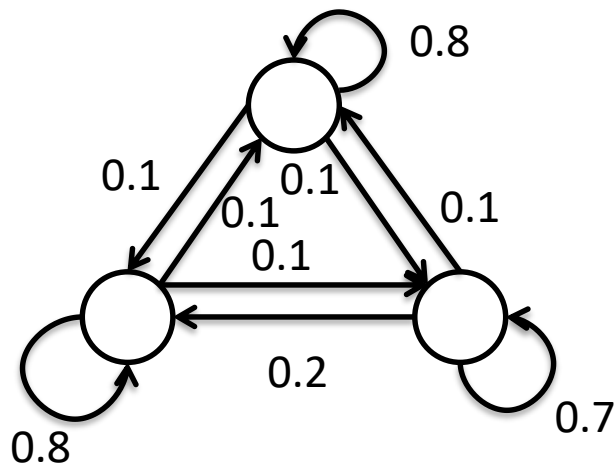
Assume enough yeasts => Proportion in state 1,2,3.

Configuration: Proportions

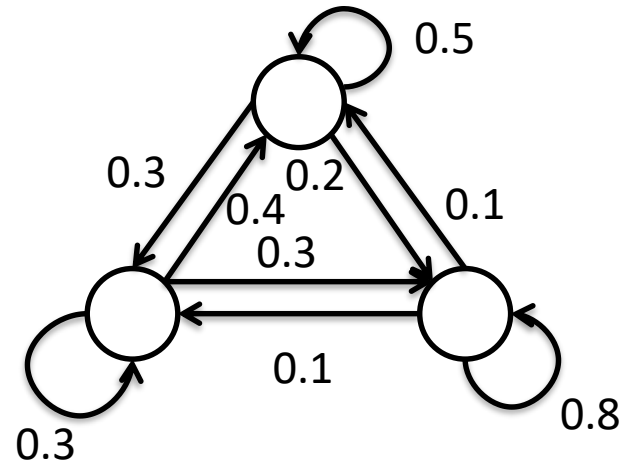
$$P = \begin{pmatrix} \frac{1}{3} & \frac{1}{2} & \frac{1}{6} \\ \frac{1}{3} & \frac{1}{2} & \frac{1}{6} \\ \frac{1}{3} & \frac{1}{2} & \frac{1}{6} \end{pmatrix}$$

In state 1 In state 2 In state 3

Actions:

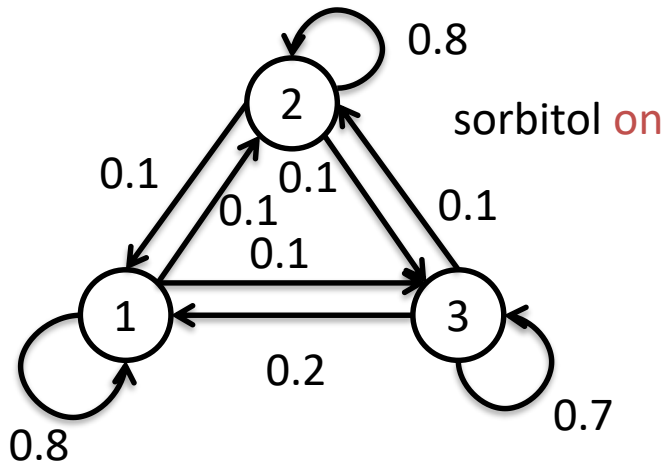


Saline solution



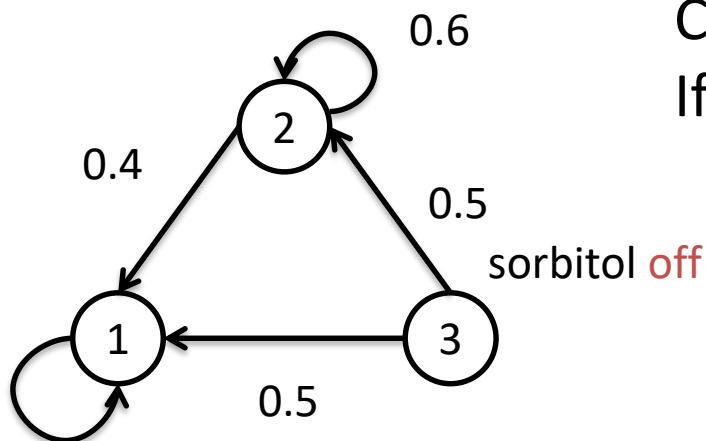
Sorbitol solution

Symbolic Population Model:



Configuration: (X,Y,Z) in \mathbb{N}^3

Can we control $N=X+Y+Z$ yeasts, for all N ?
If not for which N can we?



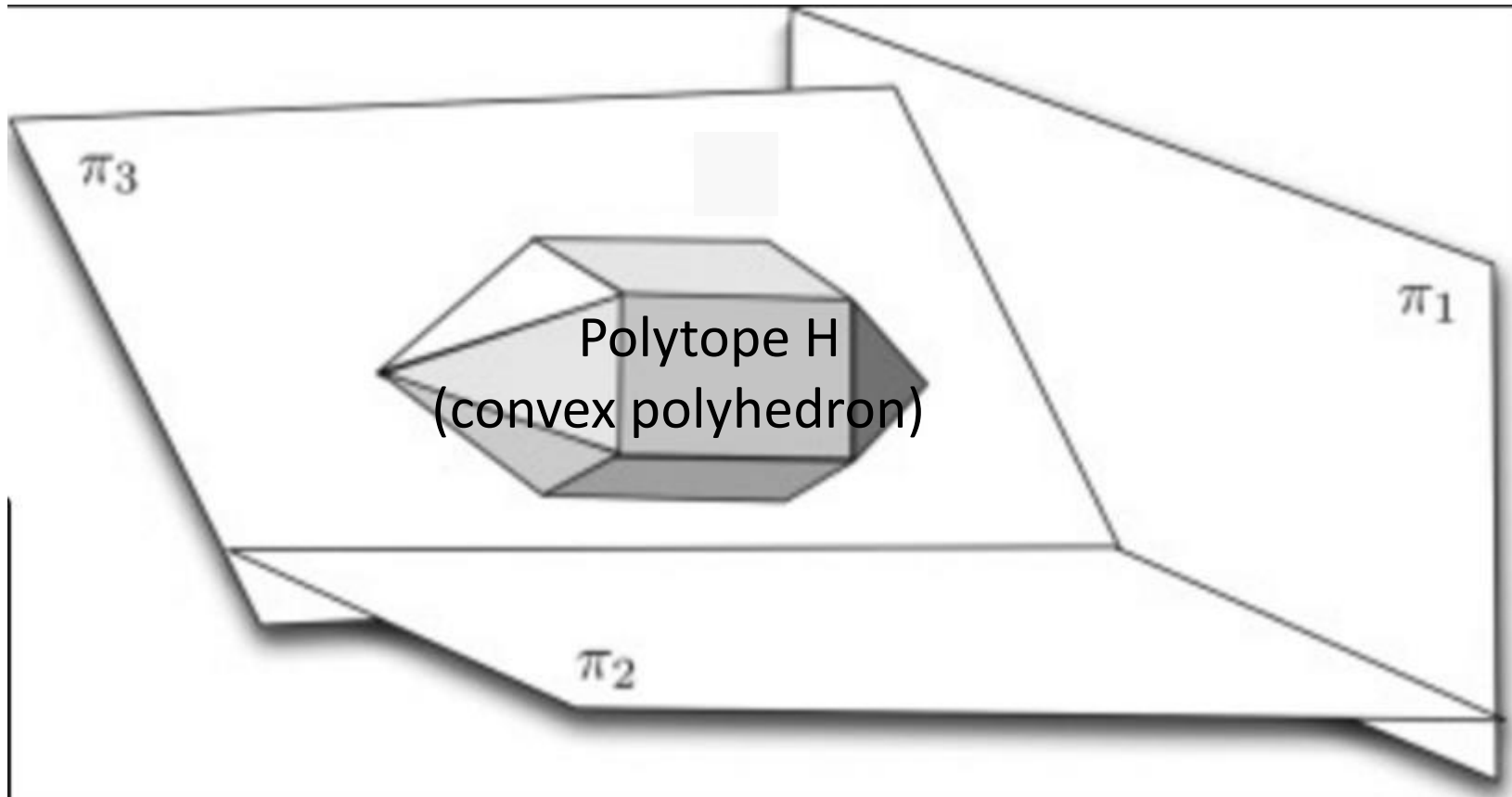
Parametric control question.

Note: up to now, mostly parametric **model-checking** question
(no synthesis of a controller)

Main Results

	Fluid abstraction ([0,1])	Symbolic model (in IN)
<p>1 fluid (sorbitol/saline) for the whole population</p> <p>Quantitative control: (bring 80% yeast ...)</p> <p>Undecidable (Rabbin's PFA).</p>	<p>Qualitative control: Sure and Almost-sure control to bring all yeasts to goal: decidable [JACM 2017]</p> <p>Quantitative Universal safety: (approximation of the prob) Decidable [LICS 2018]</p>	<p>Sure control to bring all yeasts to goal: decidable [CONCUR 2017]</p> <p>synchro N yeasts in time Polynomial in N [LMCS 201x]</p> <p>Almost sure to bring all yeasts in log(N) time: work in progress</p>
<p>Can put different fluids for every yeast (not the current experimental Setting)</p> <p>Quantitative problem: (bring 80% yeast ...)</p> <p>Skolem-hard (Linear Recc Sequence)</p>	<p>Region existentially safe: (approximation of the prob) decidable in P [LICS 2018], uses Kakutani fix point theorem.</p> <p>Skolem: work in progress</p>	<p>Not considered yet</p>

Safety Objectives



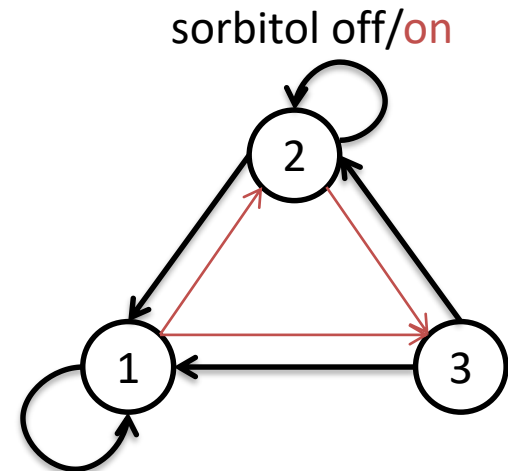
Simplest objective: keep the population proportions in polytope H
e.g.: $H := \{x_1 < 0.5\}$

Idealized Setting:

Question: $\exists?$ Controller to *surely* bring *all* yeasts to state 1 at the same time?

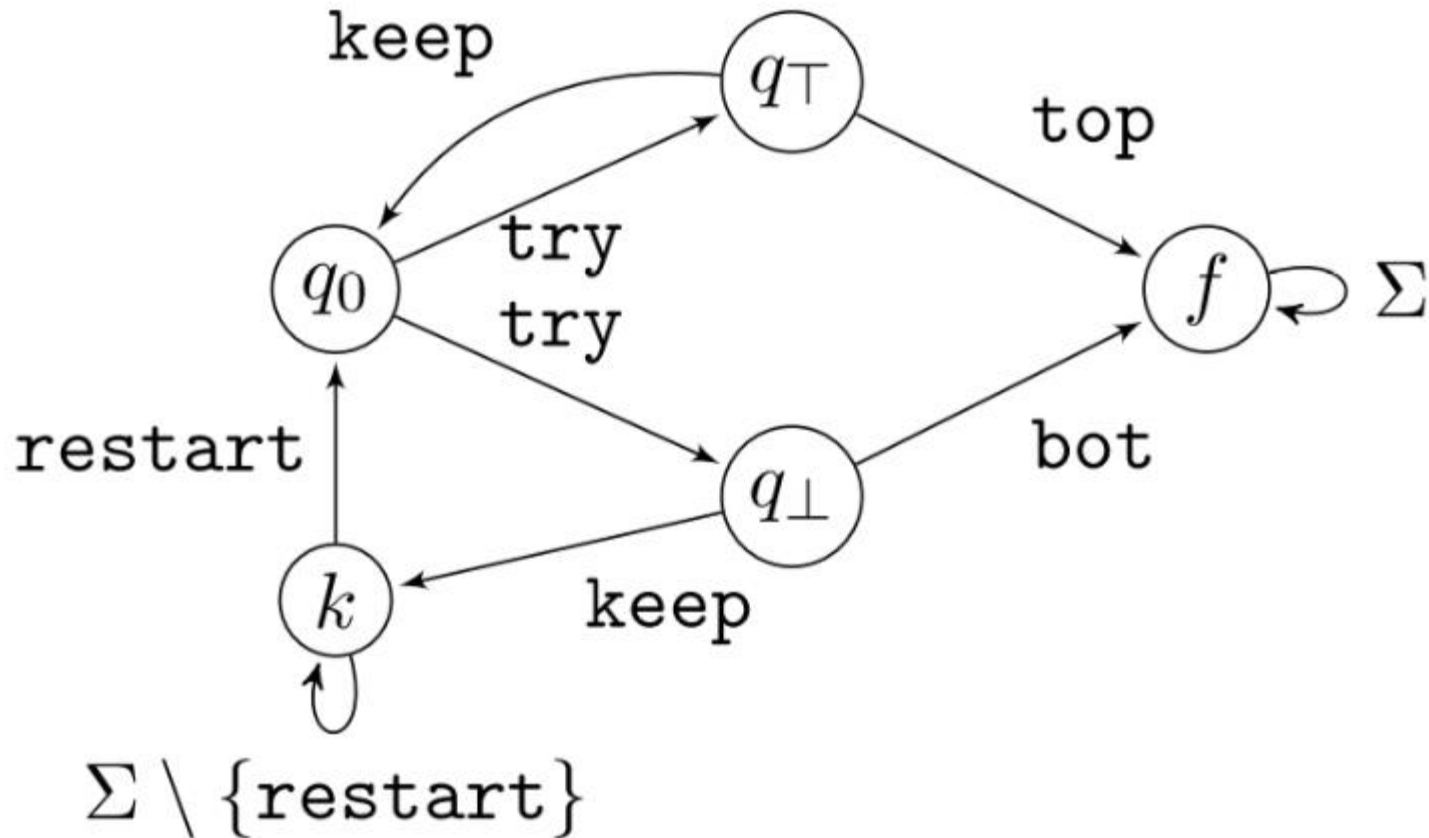
Control at each step:
same action for every yeast.

e.g.: sorbitol *off* for all yeasts,
sorbitol *on* for all yeasts



2 player game on NFA:
Controller player +
Agents resolving non det.

Symbolic Population Model:



Strategy: (try keep) till q_{top} or q_{bot} empty. Then top or bot.
Then restart and do it again with $n-1$ yeasts.
Takes time linear in the number n of yeasts.