Preliminary investigations into multiple-model input design for controlling intracellular signaling dynamics

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Abstract

The complex nature of intracellular signaling pathways and their abstracted mathematical models complicates the design of control inputs for obtaining desired responses. The most effective control input design may be derived considering several mathematical models of a given signaling pathway with differing structures and parameter values. These preliminary investigations design open loop control inputs for an intracellular signaling system to reach a desired system behavior based on predictions from multiple models. The method utilizes sparse grids for rapid and efficient screening of the input space to identify a set of controller inputs that are robust to the effects of model structure and parameter uncertainties. This approach to multiple-model predictive controller design will be demonstrated in mock experiments utilizing ordinary differential equation models of the mitogen-activated protein kinase (MAPK) pathway.

Goal

Design open loop control inputs using model predictive control (MPC) selection of robust inputs based on multiple model predictions to reduce structural uncertainty

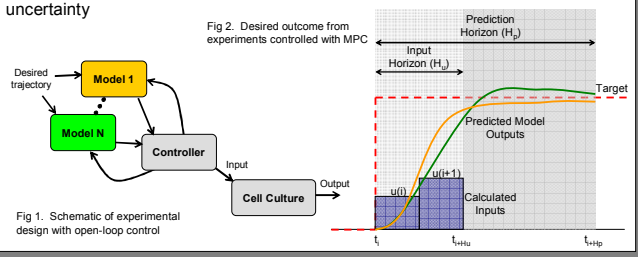


Fig 1. Schematic of experimental design with open-loop control

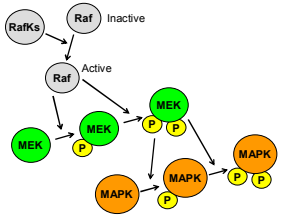
Fig 2. Desired outcome from experiments controlled with MPC

Background

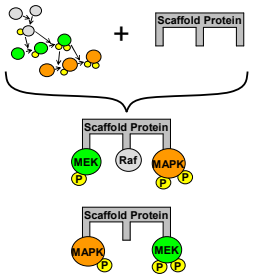
Multiple models can represent the same system:

- Ex: MAPK pathway for activating extracellular-signal-regulating kinase (ERK)
- Pathway regulates cell differentiation, proliferation and survival

Model 1) MAPK pathway *without* scaffold protein interactions



Model 2) MAPK pathway *with* scaffold protein interactions



Form of Model Equations:

Nonlinear ODEs

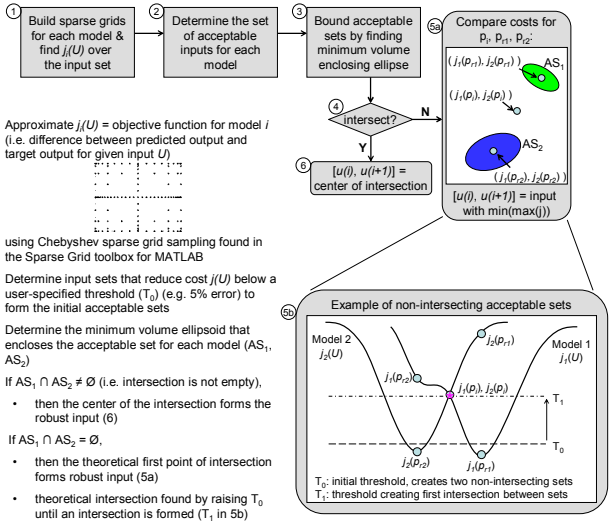
$$\dot{x} = f(x,u) \qquad x(t_0) = x_0$$
$$y = g(x)$$

- Scaffold proteins have binding slots for each Raf, MEK and MAPK that modulate reaction kinetics
- Model 2 includes pathway illustrated in Model 1, and all possible scaffold binding combinations
- Reactions follow Michaelis-Menten kinetics

Controller Design

Open loop controller utilizing sparse grids for input sampling

- Controller procedure (two models shown, $H_u = 2$)



1) Approximate $j_i(U)$ = objective function for model i (i.e. difference between predicted output and target output for given input U)

using Chebyshev sparse grid sampling found in the Sparse Grid toolbox for MATLAB

2) Determine input sets that reduce cost $j(U)$ below a user-specified threshold (T_0) (e.g. 5% error) to form the initial acceptable sets

3) Determine the minimum volume ellipsoid that encloses the acceptable set for each model (AS_1, AS_2)

4) If $AS_1 \cap AS_2 \neq \emptyset$ (i.e. intersection is not empty),

- then the center of the intersection forms the robust input (6)

If $AS_1 \cap AS_2 = \emptyset$,

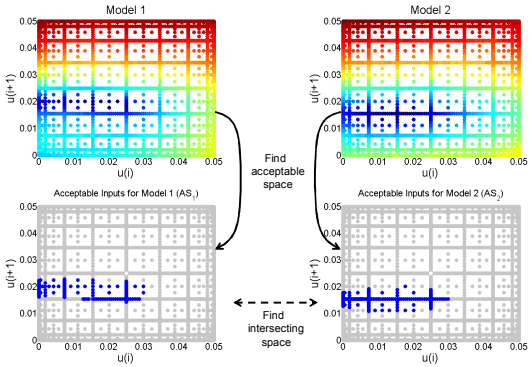
- then the theoretical first point of intersection forms robust input (5a)
- theoretical intersection found by raising T_0 until an intersection is formed (T_1 in 5b)

Annotated Methods

Demonstration of the input selection process based on the models described in the Background section:

- Input: Raf Kinases (RafKs)
- Output: doubly phosphorylated MAPK (ppMAPK)

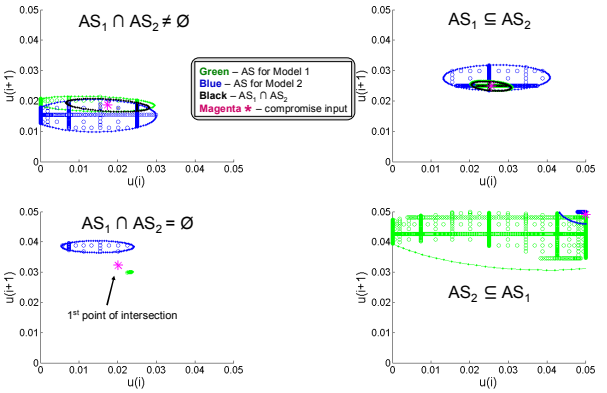
To find input $u(i)$, evaluate $j(U)$ for each model:



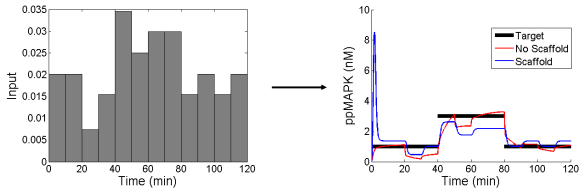
Select compromise input $u(i)$, then repeat process using $u(i+1)$ and $u(i+2)$ as predictors of next input $u(i+1)$

Simulated Results

1) Input selection for possible model dynamics simulated by modulating acceptable set (AS) characteristics



2) Simulated model responses after input selection



Summary

- This algorithm applies MPC to identify compromise inputs using multiple models to inform predictions
- Efficient control designs using sparse grids are robust in the face of model uncertainty

Future Work

- Apply to T Cell signaling models to direct *in vitro* experiments
- Extend control algorithm to handle multiple objectives and inputs

Acknowledgements

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