Prediction of activation of metabolic pathways via dynamic optimization

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Introduction

- Genetic regulation of metabolic networks may be driven by optimality principles (Klipp et al, 2002; Zaslaver et al., 2004; Oyarzún et al, 2009).
- Dynamic optimization can be used to either **predict** (a priori) or **explain** (a posteriori) the activation profile of genes and/or enzymes in metabolic pathways.

Typical statement

Find the time-dependent profile of gene-expression or enzyme activation which minimizes a cost function, such as e.g. transition time from one steady state to another

Dynamic Optimization of metabolic pathways

Challenge: These dynamic optimization problems are **non-convex** (multimodal), so they can not be solved with standard optimization methods.

Our approach: We present the use of a suitable **dynamic optimization direct method** combined with adequate **global optimization solvers**.

Implementation: High-level scripts making use of the DOTcvpSB toolbox ((Hirmajer et al. 2009).

Advantage: (1) We can consider arbitrarily complex pathways, including branched ones.
(2) We avoid convergence to local solutions.

Simple linear pathway with N-steps

E_i : concentration of different enzymes;
 S : concentration of the substrate;
 X_{i-1} : concentrations of the metabolic intermediates.
 P : concentration of the final product.

Mathematical statement :

Find $u(t)$ over $t \in [t_0, t_f]$ to minimize

$$J = \frac{1}{C} \int_0^t (c - P) dt$$

Subjecto:

$$\frac{dS}{dt} = -k_1 \cdot E_1 \cdot S$$

$$\frac{dX_{i-1}}{dt} = -k_{i-1} \cdot E_{i-1} \cdot X_{i-1} - k_{i+1} \cdot E_{i+1} \cdot X_{i+1}$$

$$\frac{dP}{dt} = k_n \cdot E_n \cdot X_n$$

With the following path constraint:

$$\sum_{i=1}^n E_i \leq 1$$

The next end point constraint:

$$P(t_f) = 0.9$$

And this model Parameters

$$k_1 = 1, C = 1, S = 1, X_i = 0, P = 0$$

Solution:

Best result for different length pathways	
Pathway length (N)	Objective function (J)
2	2.29034
3	6.56399
4	10.4130
5	14.4268

Metabolic pathway with Michaelis-Menten kinetics

Mathematical statement :

Find $u(t)$ over $t \in [t_0, t_f]$ to minimize

$$J = \int_0^t \left(1 + \sum_{i=1}^{n-4} E_i \right) dt$$

Subjecto:

$$\frac{dX_{i-1}}{dt} = \left(\frac{k_{cat(i-1)} \cdot X_{i-1}}{K_{m(i-1)} + X_{i-1}} \right) \cdot E_{i-1} - \left(\frac{k_{cat(i)} \cdot X_{i-1}}{K_{m(i)} + X_{i-1}} \right) \cdot E_i$$

With four end point constraints:

$$\left(\frac{k_{cat i} \cdot X_i}{K_{m i} + X_i} \right) \cdot E_i = 0.2$$

The following path constraint:

$$\sum_{i=1}^4 E_i \leq E_T$$

And this model Parameters

$$k_{cat1} = 1, k_{cat2} = 2, k_{cat3} = 4, k_{cat4} = 3$$

$$K_{m1} = 1, S = 5, E_T = 1$$

Solution: Objective function (J): 4.75769954

Metabolic pathway with enzyme dynamics

Mathematical statement :

Find $u(t)$ over $t \in [t_0, t_f]$ to minimize

$$J = \int_0^t \left(1 + \sum_{i=1}^{n-4} E_i \right) dt$$

Subjecto:

$$\frac{dX_{i-1}}{dt} = \left(\frac{k_{cat(i-1)} \cdot X_{i-1}}{K_{m(i-1)} + X_{i-1}} \right) \cdot E_{i-1} - \left(\frac{k_{cat(i)} \cdot X_{i-1}}{K_{m(i)} + X_{i-1}} \right) \cdot E_i$$

$$\frac{dE_i}{dt} = u_i - \lambda \cdot E_i$$

With the following path constraint:

$$0 \leq E_i \leq E_T$$

$$0 \leq r_i \leq 1$$

The next end point constraints:

$$X_1(t_f) = 0.65, E_1(t_f) = 0.24$$

$$X_2(t_f) = 0.32, E_2(t_f) = 0.26$$

$$X_3(t_f) = 0.29, E_3(t_f) = 0.32$$

And this model Parameters

$$k_{cat1} = 1, k_{cat2} = 2, k_{cat3} = 4, k_{cat4} = 3$$

$$K_{m1} = 1, S = 5, E_T = 1, \lambda = 1$$

Solution: Objective function (J): 6.16467898

Conclusions

- Dynamic optimization as a way to predict/explain genetic regulation.
- Need of global optimization methods to properly solve these problems.
- DOTcvpSB: an excellent toolbox for efficient and robust solution of this class of problems

Selected References:

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