Introduction

- Genetic regulation of metabolic networks may be driven by optimality principles (Klipp et al, 2002; Zaslaver et al., 2004; Oyarzun 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

Mathematical statement:

Find $a(t)$ over $[0,T]$ to minimize

$$ J = \frac{1}{2} \int_{0}^{T} (a(t) - P dt)^2 $$

Subject to:

$$ \frac{dX}{dt} = \sum_{i=1}^{n} a_{i} X^i $$

With the following path constraint:

$$ \sum_{i=1}^{n} a_{i} = 1 $$

And this model parameters:

$$ a_{i} \geq 0, \ c_{i} \geq 0, \ X_{i} \geq 0, \ P = 0 $$

Solution:

Best result for different length pathways

<table>
<thead>
<tr>
<th>Pathway length</th>
<th>Objective function</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td>2.29504</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>6.54399</td>
</tr>
</tbody>
</table>
| 4             |                   | 10.41300
| 5             |                   | 14.4268 |

No. 5

Metabolic pathway with Michaelis-Menten kinetics

Mathematical statement:

Find $a(t)$ over $[0,T]$ to minimize

$$ J = \int_{0}^{T} \left( \sum_{i=1}^{n} \frac{a_{i} S X^i}{K_{m} + X^i} - \frac{a_{i} E_{i}}{K_{m} + X^i} \right)^2 dt $$

Subject to:

$$ \frac{dX}{dt} = \sum_{i=1}^{n} a_{i} X^i $$

With the following path constraint:

$$ \sum_{i=1}^{n} a_{i} = 1 $$

The next end point constraint:

$$ X(T) = 0 $$

And this model parameters:

$$ a_{i} \geq 0, \ c_{i} \geq 0, \ X_{i} \geq 0, \ P = 0 $$

Solution:

Objective function ($J$): 4.75769954

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.