Piecewise smooth hybrid systems as models for networks in molecular biology Application to cell cycle models

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200



- Cell cycle
- Cell cycle control
- Cell cycle models
- Hybrid model approach
 - Why using Smooth Hybrid Models ?
 - Non linear modes
 - Transitions
 - Discrete interactions
 - Definition
 - Algorithm
- 3 A simple exemple
 - Goldbeter model
 - Modes
 - Hybrid model parameters
 - Transition matrix
 - Results

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• Regulating cell proliferation

• Tumors are result of uncontrolled cell proliferation

• A need to understand exactly how it happen



- Multiple phases and checkpoints
- A complex regulation
- Links with signaling pathways remain unclear

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Cell cycle models



- A lot of different models
- Extremely difficult to build
- A few names : Tyson, Novak, Goldbeter
- Need to be linked with signaling pathways



• Some of the components act like switchs, according to thresholds

• Cell cycle models need to describe the dynamic of interactions

• Need to combine continuous and discrete interactions

• A way to simplify, and help model dynamics analysis

Non linear modes



• Trajectories can be divided into phases, or modes

• A mode is a subset of the model between two transitions, which has simpler non linear dynamics

• Understanding how a model can switch from one mode to another is also important

7 / 17

Finding transitions

• Transitions are fast changes in reaction flows



- We can extract this information from the second derivative of trajectories
- Found transitions correspond to transitions between cell cycle phases

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Discrete interactions

During modes, some interactions can be activated or inactivated

• Activity of reaction CycB-Cdk1 + p27 -> CycB-Cdk1-p27 :



 Activity of reactions CycA-Cdk2 + p27 -> CycA-Cdk2-p27, CycD-Cdk4/6 + p27 -> CycD-Cdk4/6-p27, CycE-Cdk2 + p27 -> CycE-Cdk2-p27 :



• Helps to understand the specificity of each mode

Mathematical Framework

Hybrid dynamical systems (HDS) consist of two components
a continuous part, u, defined by

$$\frac{du_i}{dt} = f_i(u(t), s(t)), \quad t > 0, \tag{1}$$

where $u = (u_1, u_2, ..., u_n) \in \mathbf{R}^n$

• and a discrete part $s(t) \in S$, where S is a finite set of states. $s = (s_1(t), s_2(t), ..., s_m(t))$, where $s_j \in \{0, 1\}$

$$\frac{du_{i}}{dt} = \sum_{k=1}^{N} s_{k} P_{ik}(u) + P_{i}^{0}(u) - \sum_{l=1}^{M} \tilde{s}_{l} Q_{il}(u) - Q_{i}^{0}(u),$$

$$s_{j} = H(\sum_{k=1}^{n} w_{jk} u_{k} - h_{j}), \quad \tilde{s}_{l} = H(\sum_{k=1}^{M} \tilde{w}_{lk} u_{k} - \tilde{h}_{l}), \quad (2)$$

The goal of this algorithm is to generate an hybrid model from a continuous model.

Identify transitions

• Build modes by identifying discrete reactions

Parameter fitting

• Finding transition conditions

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• A minimal cell cycle model

- Only three components : Cyclin, Cdk (Cyclin dependant kinase), and a Protease (degrading the cyclin)
- We observe 2 transitions, on Cyclin and Cdk

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12 / 17

• In this exemple, we will only consider the transition on Cyclin



• The Cyclin degradation by the protease is a discrete interaction

• Two modes, one with cyclin degradation by protease, and one without

Hybrid model definition :

$$\frac{dC}{dt} = k_1 - \tilde{k}_1 CH(X - \tilde{h}_1) - \tilde{k}_1^0 C$$

$$\frac{dM}{dt} = (k_2 MC + k_1^0) - \tilde{k}_2^0 M$$

$$\frac{dX}{dt} = (k_3 M + k_2^0) - \tilde{k}_3^0 X$$
(3)

- The continous part will be multivariate monomials, plus some basal terms
- The discrete part acts on the cyclin degradation by the kinase
- Then, to find all model parameters , we use a global optimisation algorithm (simulated annealing) based on trajectories distance.

Once we have all the model parameters, we need to compute the transition matrix, to find transition conditions.

• For mode 1, degradation activated :

$$\sum_{j}(w_{j}u_{j}(t)-h_{j})>=0$$
 for all $t\in T_{k1}$

• For mode 2, degradation desactivated :

$$\sum_{j} (w_j u_j(t) - h_j) < 0$$
 for all $t \in T_{k2}$

To find transition conditions, we solve this system of inequations





• Good dynamical approximation

• Condition to activate/desactivate protease degradation :

$$-5.1588 * [C] + 5.1688 * [M] + 2.5325 * [X] >= 1$$
(4)

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16 / 17

- We need to automatize the way we define modes
- The algorithm must be adapted for large number of variables
- We have to include signaling pathways

$$s_{j} = H(\sum_{k=1}^{n} w_{jk}u_{k} + w_{jm}i_{m} - h_{j}),$$

$$\tilde{s}_{l} = H(\sum_{k=1}^{M} \tilde{w}_{lk}u_{k} + \tilde{w}_{jn}i_{n} - \tilde{h}_{l})$$
(5)

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