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On the implementation of quantitative model refinement

Turku Centre *for* Computer Science

Summary

- Model building
- Quantitative model refinement
- The heat shock response (HSR)
- The role of protein acetylation within HSR
- Data refinement of the HSR model
- Implementations in RuleBender, Snoopy and Prism
- Conclusions

Model building

- The level of abstraction of the model
  - An abstraction of the real biological process is a biochemical reaction system
    - The *biochemical network* consists of a finite set of reactions the process to be analysed translates into
- The mathematical model
  - The framework
  - The dynamics of the system
  - The numerical setup

Why model refinement?

- Re-fitting the model causes several difficulties:
  - time consuming
  - computationally-intensive
  - non-unique solution

Model formulation

- Consider model M consisting of a list of m species $\Sigma = \{A_1, A_2, \ldots, A_m\}$, and n reactions r_i, $1 \leq i \leq n$:

$$r_i\colon S_{i,1}A_1 + S_{i,2}A_2 + \cdots + S_{i,m}A_m \xrightarrow{k_i} S'_{i,1}A_1 + S'_{i,2}A_2 + \cdots + S'_{i,m}A_m$$

where:

  - $S_{i,1}, S_{i,2}, \ldots, S_{i,m}$; $S'_{i,1}, S'_{i,2}, \ldots, S'_{i,m}$ are the stoichiometric coefficients
  - $k_i \geq 0$ are the kinetic rate constants

- The framework - an ODE-based, mass-action formulation:
  - A time-dependent function is associated to each variable corresponding to each species, representing its concentration level at a specific moment in time: $[A_i]\colon \mathbb{R}_+ \rightarrow \mathbb{R}_+$

Model refinement

- In systems biology:
  - The *starting point* is an abstract, high-level model of a biological system
  - The *aim* is to gradually add details concerning model's reactants and/or reactions so that certain numerical properties are preserved
- We distinguish two types of refinement:
  - *data refinement*: replacing one (or more) species with several subspecies
  - *process refinement*: replacing a generic reaction describing a particular process with several reactions, elaborating on intermediate steps of the process

Quantitative model refinement (1)

- A reaction in the refined model M′ has the following form:

$$r_{i,j}:\ ({T_{i,1}}^{j}B_1+\ldots+{T_{i,l}}^{j}B_l)+S_{i,2}{A'}_2+\cdots+S_{i,m}{A'}_m \xrightarrow{k_{i,j}}$$
$$({T'}_{i,1}{}^{j}B_1+\ldots+{T'}_{i,l}{}^{j}B_l)+{S'}_{i,2}{A'}_2+\cdots+{S'}_{i,m}{A'}_m$$

where: $k_{i,j}$ is the kinetic rate constant and $({T_{i,1}}^{j}, \ldots, {T_{i,l}}^{j}, {T'}_{i,1}{}^{j}, \ldots, {T'}_{i,l}{}^{j})$ are nonnegative integers such that :

$${T_{i,1}}^{j}+\ldots+{T_{i,l}}^{j}=S_{i,1} \text{ and } {T'}_{i,1}{}^{j}+\ldots+{T'}_{i,l}{}^{j}={S'}_{i,1}.$$

Quantitative model refinement (2)

- Model M’ is a quantitative refinement of model M on variable A_1 if it satisfies the following conditions $\forall\, 2 \leq i \leq m, t \geq 0$:
  - $[A_i](t)=[A'_i](t)$
  - $[A_1](t)=[B_1](t)+\ldots+[B_l](t)$

Our focus

- The focus - the implementation of quantitative model refinement in different frameworks:
  - Petri nets (with Snoopy);
  - Rule based modelling (with Bionetgen);
  - Guarded command languages (with PRISM).

- Some modelling frameworks are more suitable for the implementation of quantitative model refinement with respect to the compact representation of the refined model.

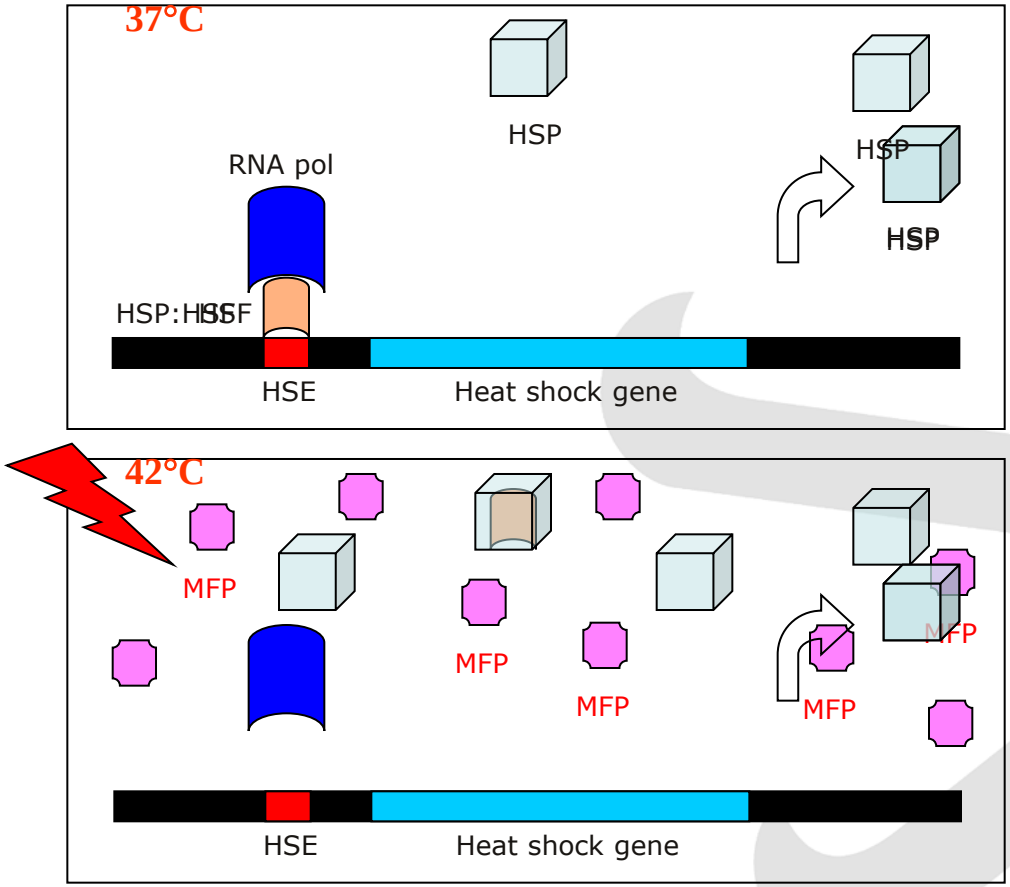
The heat shock response

- Cell's response to elevated temperatures
  - The cell reacts rapidly to elevated temperatures

- Major actors in HSR:
  - **Heat shock proteins(HSP)**: assist misfolded proteins in their refolding process
  - **Heat shock elements(HSE):** act as promoter sites of the gene
  - **Heat shock factors(HSF):** mediate gene transcription, they trimerize and bind to **HSEs**, activating **HSP** synthesis

We consider here the heat shock response model proposed in I. Petre et al., 2009.

The molecular model for HSR



Courtesy of
Ion PETRE

Petre et al., A simple mass-action model for the eukaryotic heat shock response and its mathematical validation, Natural Computing, 10(1), 595-612, 2011.

The molecular model

Transcription

1. $HSF+HSF <-> HSF_2$
2. $HSF+HSF_2 <-> HSF_3$
3. $HSF_3+HSE <-> HSF_3:HSE$
4. $HSF_3:HSE -> HSF_3:HSE+HSP$

Backregulation

5. $HSP+HSF <-> HSP:HSF$
6. $HSP+HSF_2 -> HSP:HSF+HSF$
7. $HSP+HSF_3 -> HSP:HSF+2HSF$
8. $HSP+HSF_3:HSE -> HSP:HSF+2HSF+HSE$

Petre et al., A simple mass-action model for the eukaryotic heat shock response and its mathematical validation, Natural Computing, 10(1), 595-612, 2011.

Response to stress

9. PROT->MFP
10. HSP+MFP<->HSP:MFP
11. HSP:MFP->HSP+PROT

Protein degradation

12. HSP→0

By courtesy of Ion PETRE

Protein aceytlation

- Substituting an acetyl group for a hydrogen atom in a chemical compound

- Types:
  - N-terminal acetylation occurs at the α-amino group and is irreversible.
  - Lysine acetylation occurs at the ε-amino group on the lysine residues. It influences gene regulation by changing the charge of histone tails.

- The role of protein acetylation:
  - Acetylation diminishes hsf's DNA binding activity (Westerheide et al., 2009)

Data refinement of the HSR model

- All species and complexes involving hsf are refined to include two subtypes of hsf:
  - First, where its K80 residue is acetylated
  - Second, where it is not acetylated

- Data refinement of the HSR model:

$$\text{hsf} \rightarrow \{\text{rhsf},\ \text{rhsf}^{(1)}\}$$

$$\text{hsf}_2 \rightarrow \{\text{rhsf}_2,\ \text{rhsf}_2{}^{(1)}, \text{rhsf}_2{}^{(2)}\}$$

$$\text{hsf}_3 \rightarrow \{\text{rhsf}_3,\ \text{rhsf}_3{}^{(1)}, \text{rhsf}_3{}^{(2)}, \text{rhsf}_3{}^{(3)}\}$$

$$\text{hsf}_3\text{:hse} \rightarrow \{\text{rhsf}_3\text{:rhse},\ \text{rhsf}_3{}^{(1)}\text{:rhse}, \text{rhsf}_3{}^{(2)}\text{:rhse}, \text{rhsf}_3{}^{(3)}\text{:rhse}\}$$

$$\text{hsp:hsf} \rightarrow \{\text{rhsp:rhsf},\ \text{rhsp:rhsf}^{(1)}\}$$

Data refinement - example

- Dimerization

Initial reaction :

$$2\mathrm{hsf} \leftrightarrow \mathrm{hsf}_2$$

Refined reactions:

$$\mathrm{rhsf} + \mathrm{rhsf} \leftrightarrow \mathrm{rhsf}_2$$

$$\mathrm{rhsf} + \mathrm{rhsf}^{(1)} \leftrightarrow \mathrm{rhsf}_2{}^{(1)}$$

$$\mathrm{rhsf}^{(1)} + \mathrm{rhsf}^{(1)} \leftrightarrow \mathrm{rhsf}_2{}^{(2)}$$

Numerical setup of the refined model

- The initial values of the refined variables are set so as to fulfill the data refinement relations
  - Example:

$$[\mathrm{hsf}_3](0)=[\mathrm{rhsf}_3](0)+[\mathrm{rhsf}_3{}^{(1)}](0)+[\mathrm{rhsf}_3{}^{(2)}](0)+[\mathrm{rhsf}_3{}^{(3)}](0)$$
$$[\mathrm{hse}](0)=[\mathrm{rhse}](0)$$

- The setup:
  - The systems of ODEs of the initial and the refined model are identical modulo a variable renaming.
  - Both the refined and the initial model have identical initial conditions.
  - The refined model is a quantitative refinement of the original one.

Refining HSR

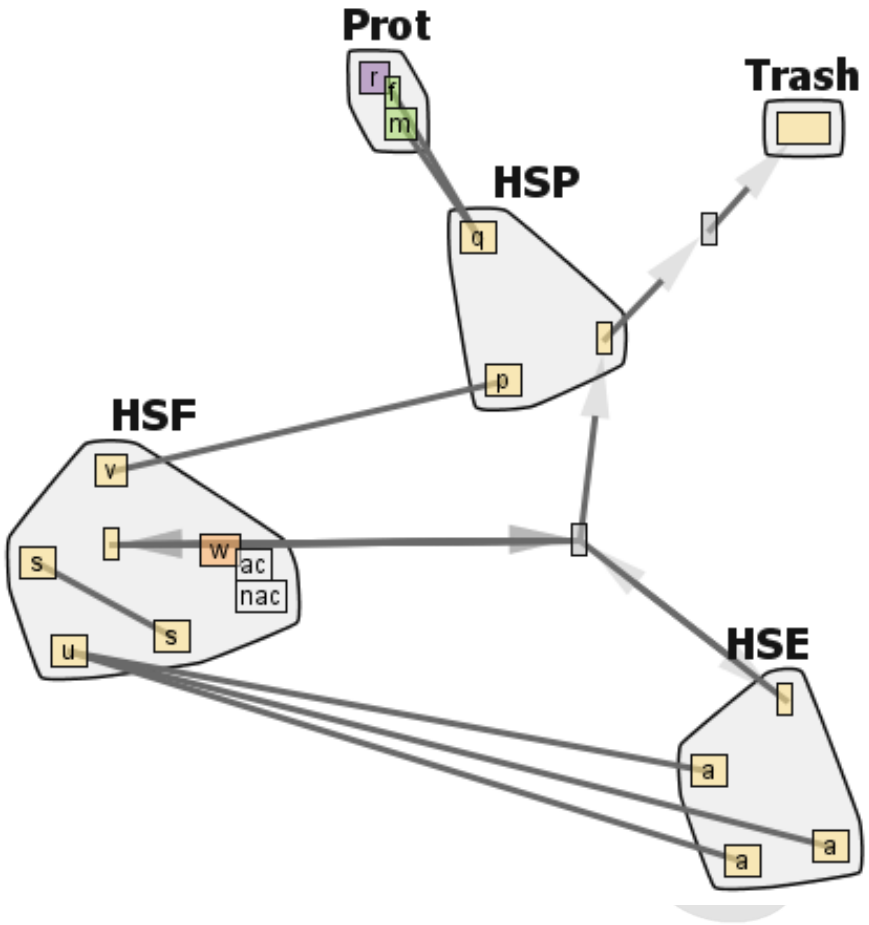
- The number of reactions and reactants augmented considerably:
  - The initial model consists of: 12 reactions involving 10 different species and 16 kinetic rate constants.
  - The refined model comprises: 39 reactions, 20 species and 54 kinetic rate constants.

- Fitting a model like the refined one for the HSR is time consuming and requires a lot of computational resources.
  - The proposed approach allowed building a model with a satisfactory behavior, avoiding any supplementary model fit.

Refining HSR – frameworks

- Four different frameworks for the implementation of the heat shock response:
  - ODE-based implementation
  - Rule-based modelling
  - Petri nets
  - Model checking
- Tools and software:
  - ODEs: Copasi.
  - Rule-based modelling: Bionetgen and Rulebender.
  - Petri nets: Snoopy.
  - Model checking: Prism.

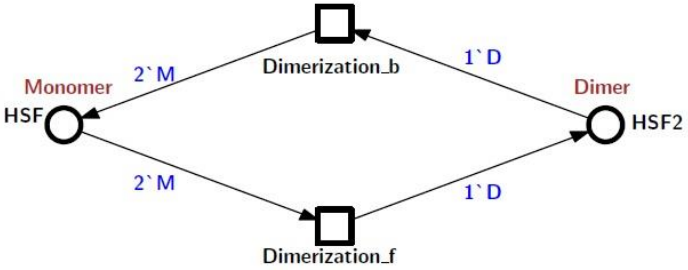
HSR- a rule-based implementation – Contact map



Model refinement with colored Petri nets

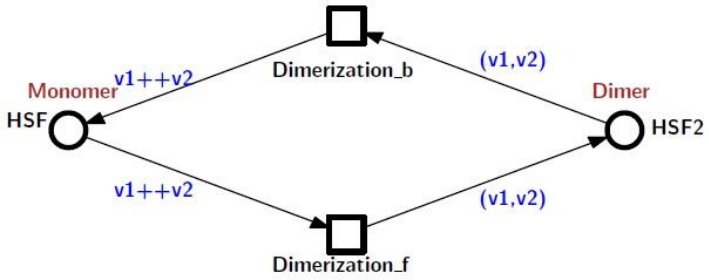
Dimerization

Initial model

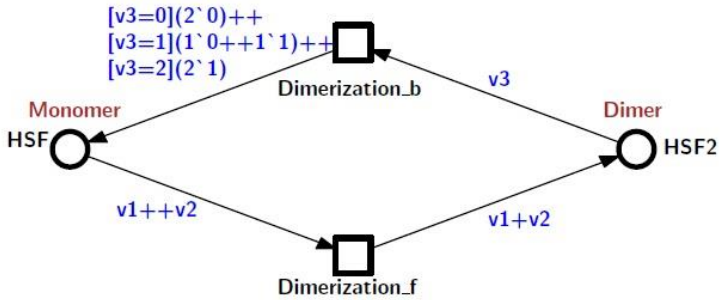


Monomer = enumeration with M;
Dimer = enumeration with D;

Refined model



Monomer = enumeration with 0, 1;
Dimer = product Monomer×Monomer;
VAR v1, v2:Monomer;



Monomer = int 0..1;
Dimer = int 0..2;
VAR v1, v2:Monomer;
VAR v3:Dimer;

The Prism implementation

- The representation of all possible configurations for acetylated species:
  - The implementation required defining separate variables for the representation of all possible acetylation-refined configurations of hsf.
- Verification of two basic properties of the model:
  - The validity of the mass-conservation relations.
  - The level of DNA binding return to basal values, both at 37℃ and at 42℃.

Discussion

- Our aim: studying the capabilities of four different frameworks with regards to the implementation of quantitative model refinement: ODEs, rule-based modelling, Petri nets and guarded command languages.

- Rule-based modelling:
  - The compact representation is based on partial presentation of the details of the refined model.
- Petri nets:
  - The complexity of the refinement can be tackled by the use of colored Petri nets.
- Guarded command languages:
  - The implementation of the refinement required an explicit description.

Advantages and future work

- Advantage:
  - Model refinement is more efficient computationally in setting up a large model.
- The acetylation refined heat shock response model:
  - The initial model consists of: 12 reactions involving 10 different species.
  - The refined model comprises: 39 reactions, 20 species.
- The refinement of the ErbB signalling pathway:
  - The initial model consists of: 148 reactions involving 103 different.
  - The refined model comprises: 936 reactions, 416 species.
- Future work:
  - Building up a software for the automatic construction of refined models;
  - Add the concept of process refinement to the current framework.

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