

A Discrete Model for Simulating Eukaryotic Heat Shock Response

17.3.2006

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Reactions

Reaction

HSF + HSF --> HSF2

HSF2 + HSF --> HSF3

HSF3 + HSE --> HSF3:HSE

HSP:MFP --> MFP

HSP:HSF --> HSF

HSP --> NULL

HSP:MFP --> PROT + HSP

HSP:HSF --> HSP + HSF

HSP:HSF + MFP --> HSP:MFP + HSF

HSP + MFP --> HSP:MFP

HSP + HSF --> HSP:HSF

HSF2 --> HSF + HSF

HSF3 --> HSF2 + HSF

HSF2 + HSP --> HSP:HSF + HSF

Explanation

Two HSFs form an HSF dimer

An HSF dimer and a free HSF form an HSF trimer

An HSF trimer binds to an HSE

An HSP bound to an MFP dies

An HSP bound to an HSF dies

A free HSP dies

An HSP releases a refolded protein

An HSP:HSF bond spontaneously breaks

An HSP bound to an HSF gets released and binds to an MFP

A free HSP binds to an MFP

A free HSP binds to an HSF

An HSF dimer spontaneously breaks

An HSF trimer spontaneously breaks

An HSP breaks an HSF dimer and binds to one of the HSFs

Reactions (cont.)

Reaction

`HSF3 + HSP --> HSP:HSF + HSF + HSF`

`HSE:HSF3 + HSP --> HSP:HSF + HSE +
HSF + HSF`

`RNAHSP --> HSP`

`HSE:HSF3 --> RNAHSP`

`MFP --> NULL`

`HSP:MFP --> HSP + MFP`

Explanation

An HSP breaks an HSF trimer and binds to one of the HSFs

An HSP breaks an HSF trimer bound to an HSE and binds to one of the HSFs

The protein synthesis is complete and a new HSP is created

An HSF trimer bound to an HSE triggers the protein synthesis of a new HSP

A free MFP dies

An HSP releases an MFP before it has refolded

The discrete model

- Every molecule of interest is modeled independently
- Each of these molecules have variables describing their particular characteristics
- In a sense, each molecule "lives" independently
- Reactions between molecules are modeled using probabilities

Modeling reactions

- When an object of type A reacts with an object of type B, these disappear and an object of type C is created
- Reactions determined by probabilities

Implementation issues

- In every iteration, the probability of every object taking part in any reaction must be evaluated
 - quadratic complexity
- Quadratic complexity OK for smaller populations
- Large populations of HSPs and MFPs present problem

Implementation issues (cont.)

- $HSP + MFP \rightarrow HSP:MFP$ reaction becomes a significant bottleneck
- Solution: Reduce MFP to a counter
 - The complexity is reduced to linear
 - Problem: we lose the ability to track characteristics for individual MFPs

Implementation issues (cont.)

- The only characteristic needed for MFPs is the molecules' "Time-To-Live"
- We simulate the degradation of MFPs by a reaction with a specific rate (a real number)
- When the counter reaches 1, the MFP counter is decremented.

Deducing probabilities

- Goal: Homogeneous model
- Similar probabilities for similar reactions
- Some probabilities based on laboratory data and validating experiments
- **Example 1:** $\text{HSP} + \text{HSF} \rightarrow \text{HSP}:\text{HSF}$
 - Laboratory results indicate level of HSF between 1000 and 2000
 - We chose 1500

Deducing probabilities (cont.)

- The continuous model predicted the level of HSP in the absence of stress to be around 6000, which is the number we chose.
- The amount of free HSFs in the cell in the absence of stress needs to be minimal
- With this information, a probability was chosen that maintained the average of free HSFs at a sufficiently small level

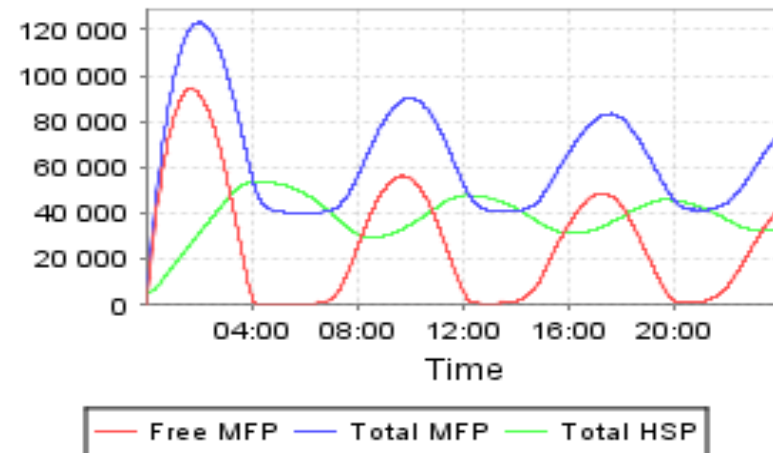
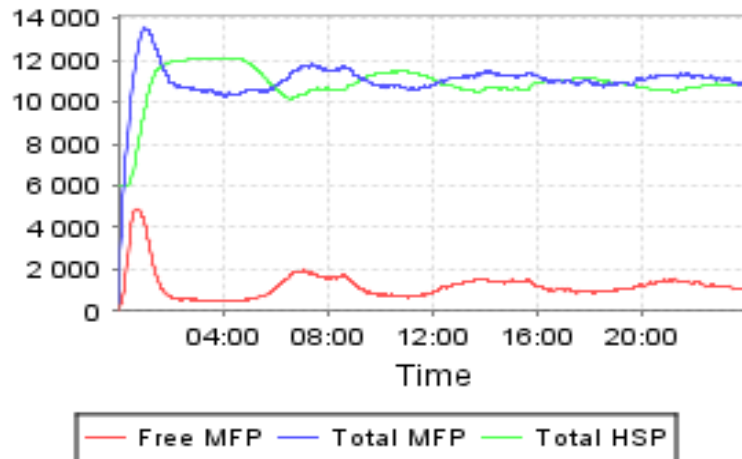
Deducing probabilities (cont.)

- **Example 2:** $\text{HSF} + \text{HSF} \rightarrow \text{HSF}_2$ and
 $\text{HSF} + \text{HSF}_2 \rightarrow \text{HSF}_3$
 - Laboratory observations indicate that very few HSF dimers are present at any given time
 - This suggests either that HSF dimers are very unstable, or that HSF trimers are formed directly from three HSFs.
 - In the model, both reactions are controlled by the same probability

Deducing probabilities (cont.)

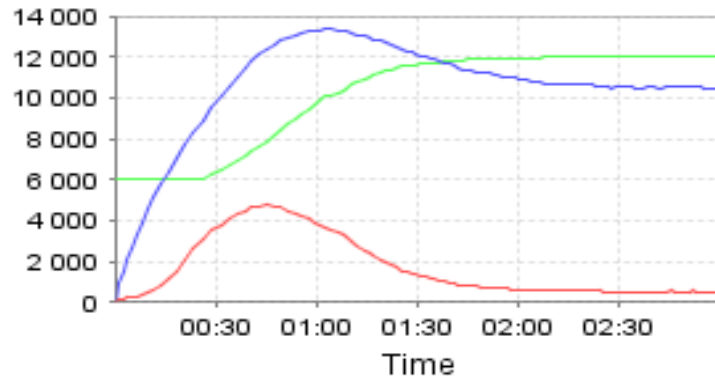
- Instead, the opposite reactions, $\text{HSF}_2 \rightarrow \text{HSF} + \text{HSF}$ and $\text{HSF}_3 \rightarrow \text{HSF}_2 + \text{HSF}$ are controlled by different probabilities
- HSF dimers break much more easily than HSF trimers

Simulations

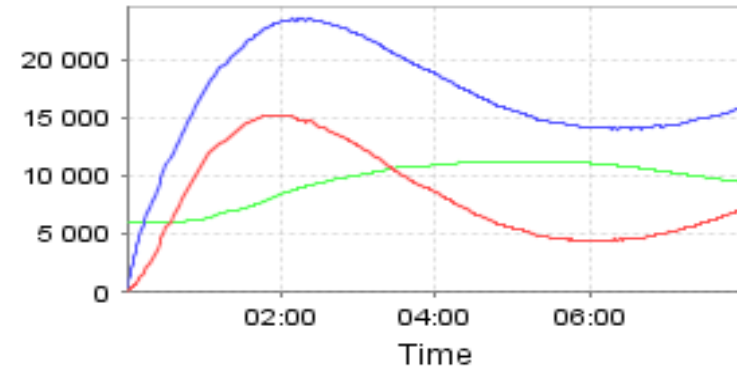


- Left: Normal simulation at 40 degrees for 24 hours
- Right: Normal simulation at 45 degrees for 24 hours

Test case 1, 40 degrees



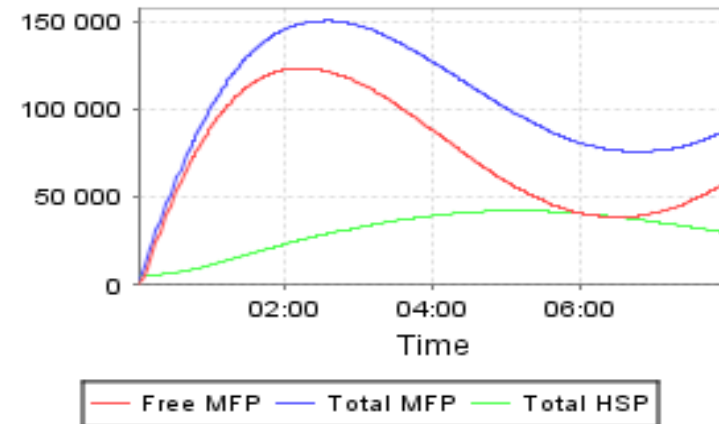
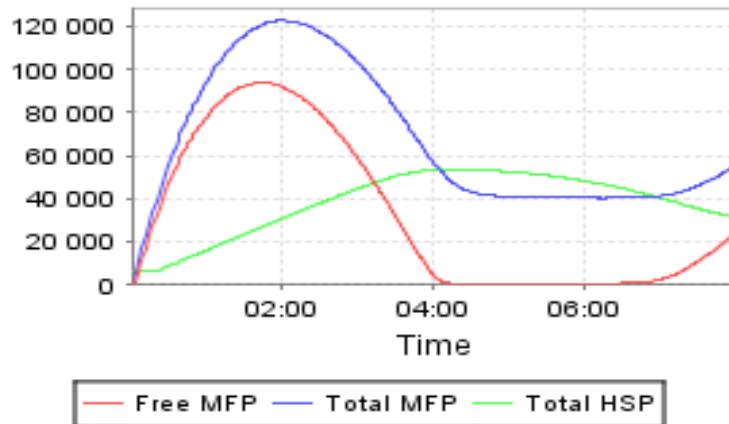
Free MFP Total MFP Total HSP



Free MFP Total MFP Total HSP

- Left: Normal behavior, 3 hours
- Right: The probabilities governing the breaking of bonds 100 times smaller, 8 hours

Test case 1, 45 degrees

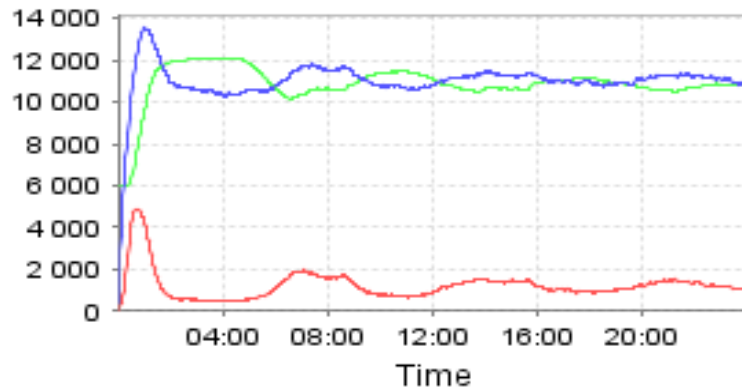


- Left: Normal behavior, 8 hours
- Right: The probabilities governing the breaking of bonds 100 times smaller, 8 hours

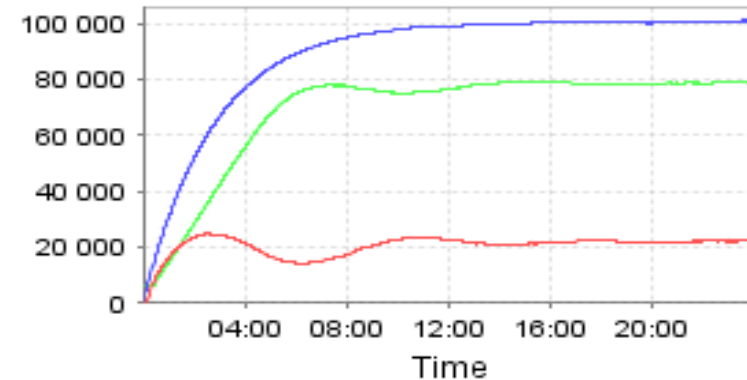
Test case 1, analysis

- Response slower, allowing the level of MFPs to peak at higher level
- The level of HSPs peak at a lower level
- Containment of MFPs not handled nearly as effectively

Test case 2, 40 degrees



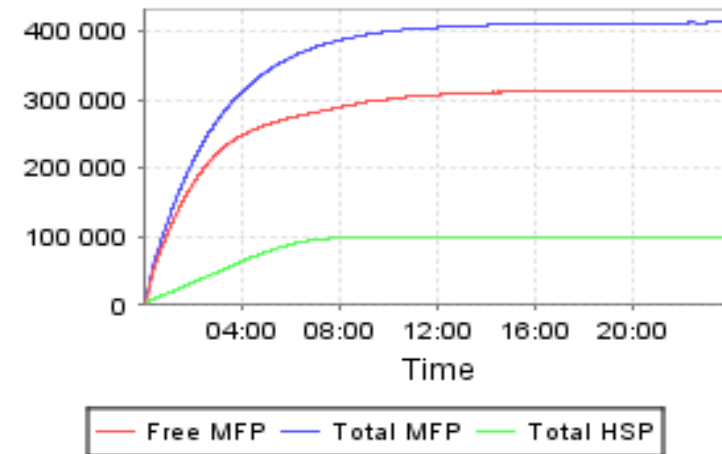
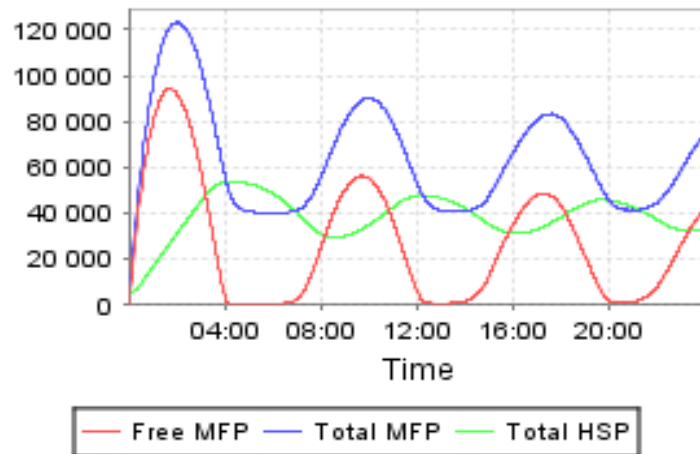
Free MFP Total MFP Total HSP



Free MFP Total MFP Total HSP

- Left: Normal behavior, 24 hours
- Right: The probability governing the refolding of chaperoned MFPs 10 times smaller, 24 hours

Test case 2, 45 degrees

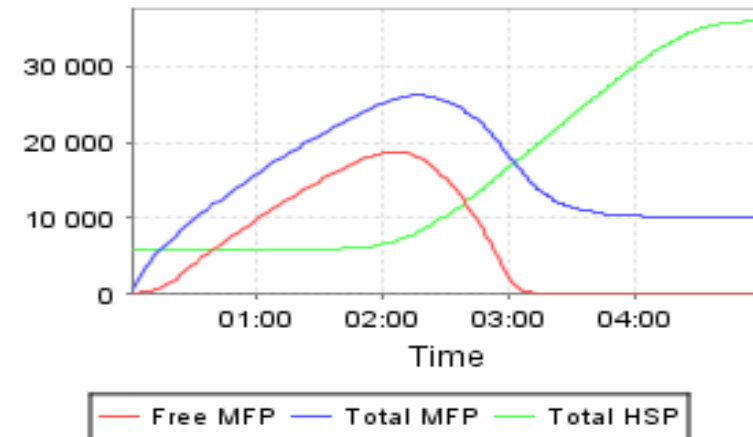
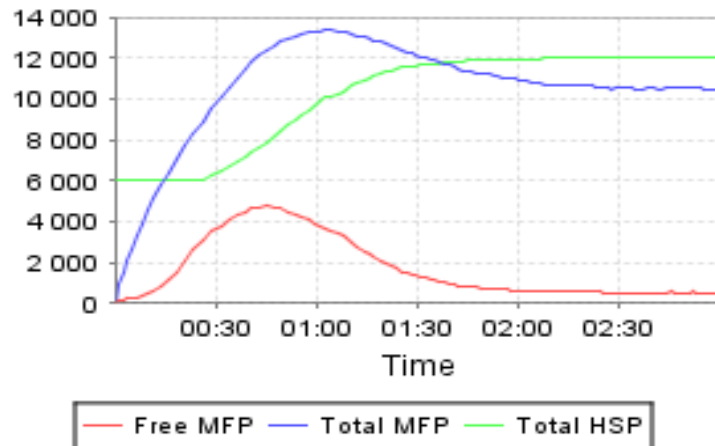


- Left: Normal behavior, 24 hours
- Right: The probability governing the refolding of chaperoned MFPs 10 times smaller, 24 hours

Test case 2, analysis

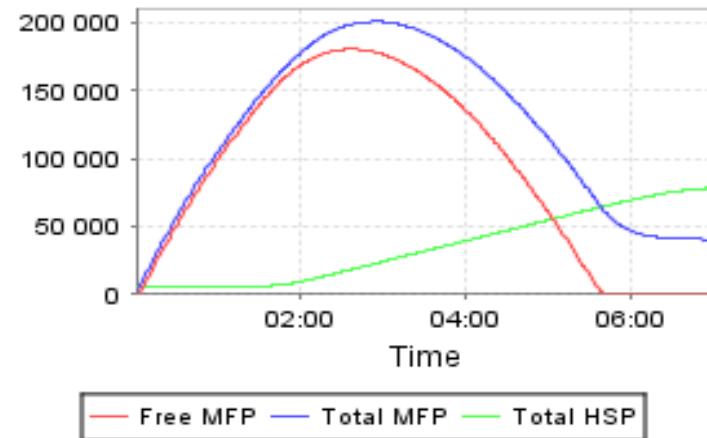
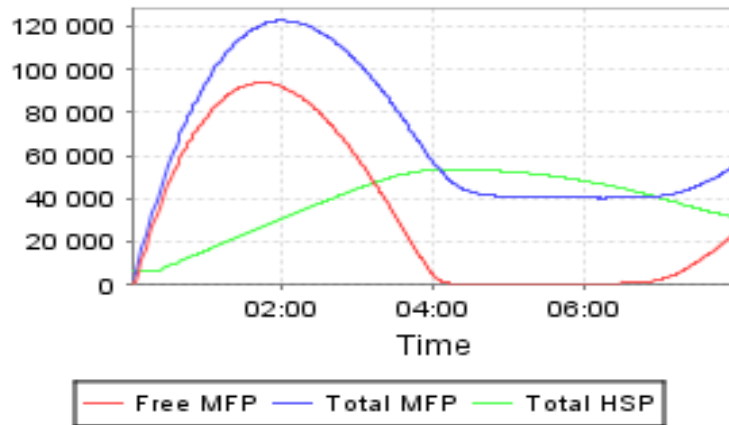
- Drastic effect on the behavior
- Peak of MFPs at 40 degrees about the same as at 45 degrees with normal values
- Much more HSPs created, but containment a lot worse
- Less fluctuation in level of HSPs due to large number of free MFPs

Test case 3, 40 degrees



- Left: Normal behavior, 3 hours
- Right: The creation time of HSPs 10 times longer, 5 hours

Test case 3, 45 degrees



- Left: Normal behavior, 8 hours
- Right: The creation time of HSPs 10 times longer, 8 hours

Test case 3, analysis

- Response takes longer: MFPs peak higher
- Slight over-production of HSPs because more HSPs are in the process of being created
- Back-regulation starts later
- Better containment of MFPs