

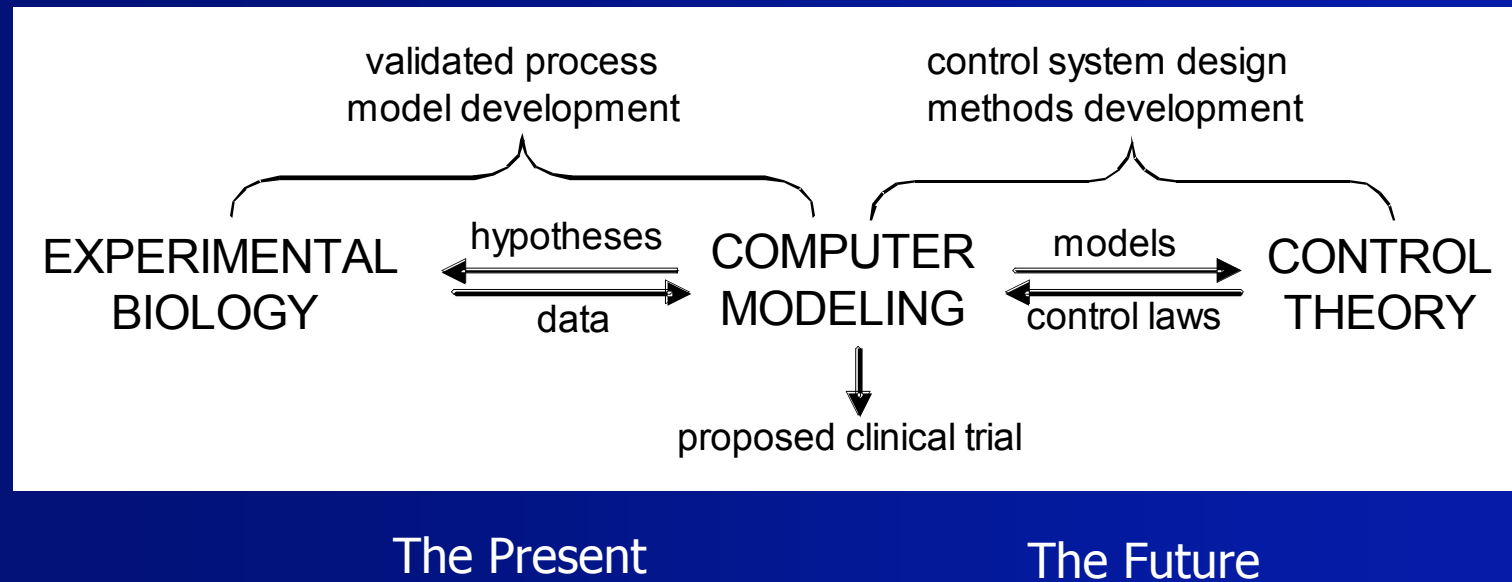
Integrative Cancer Biology

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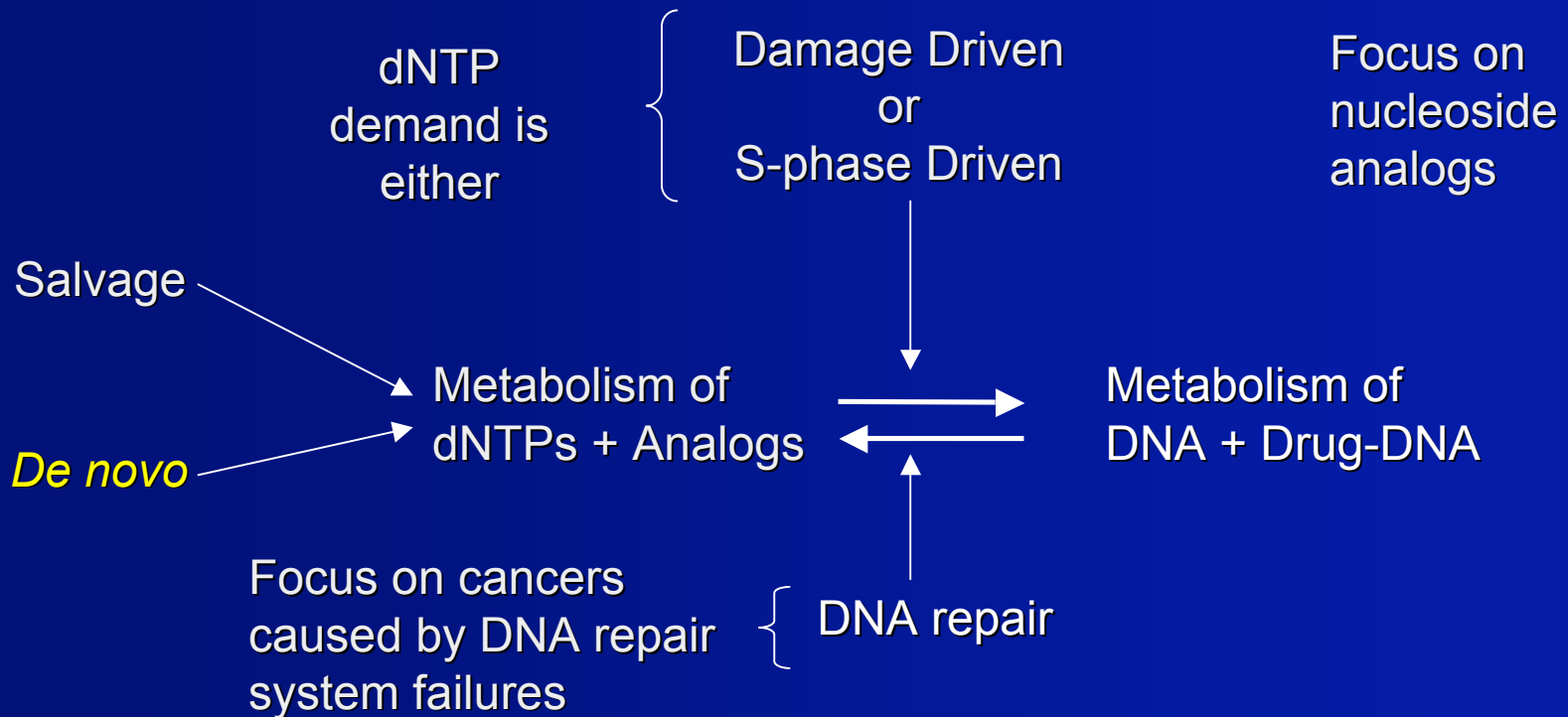
ICB Goals



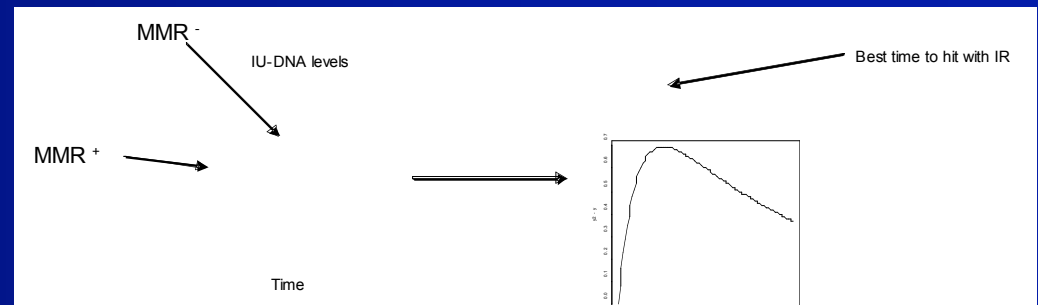
Ultimate Goal: individualized, state feedback based clinical trials

CASE ICBP

Problem Statement



For Example:



ICB Model-Based Approaches to Therapeutic Gain

■ Direct approach

- IUDR metabolism applied to MMR- cancers



■ *Treatment failure risk-state-transfer approach*

- TEL-AML1 patients as guides for BCR-ABL patients



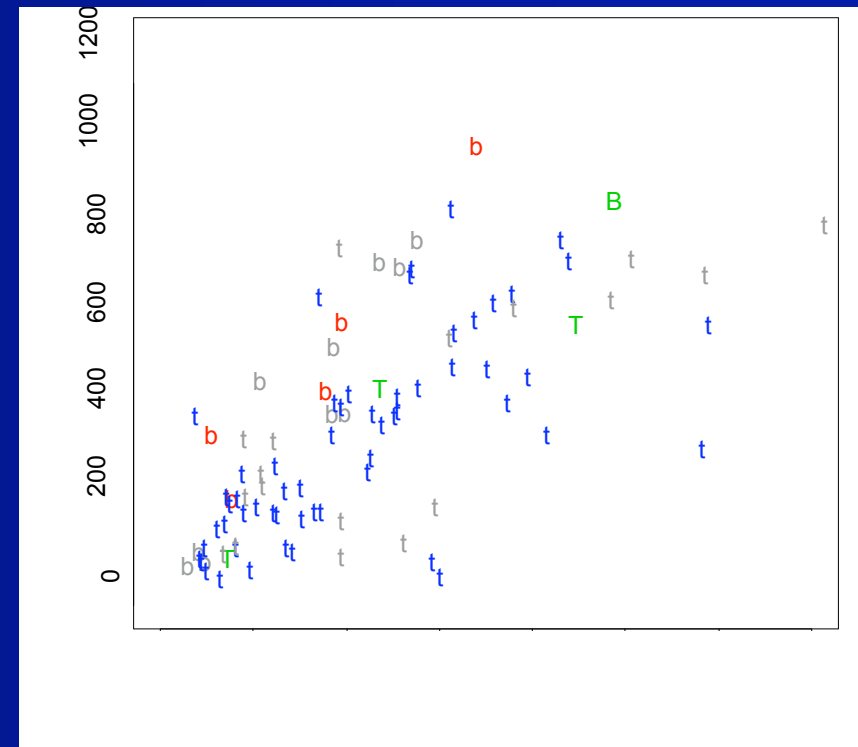
“Cause” could be replaced by secondary events essential to survival-limiting malignant cell populations, but closer to rds is better since => less chance of a subpopulation growing back

Model contents

Risk State Transfer

- **T**: TEL-AML1 with HR
- **t**: TEL-AML1 with CCR
- **t**: other outcome

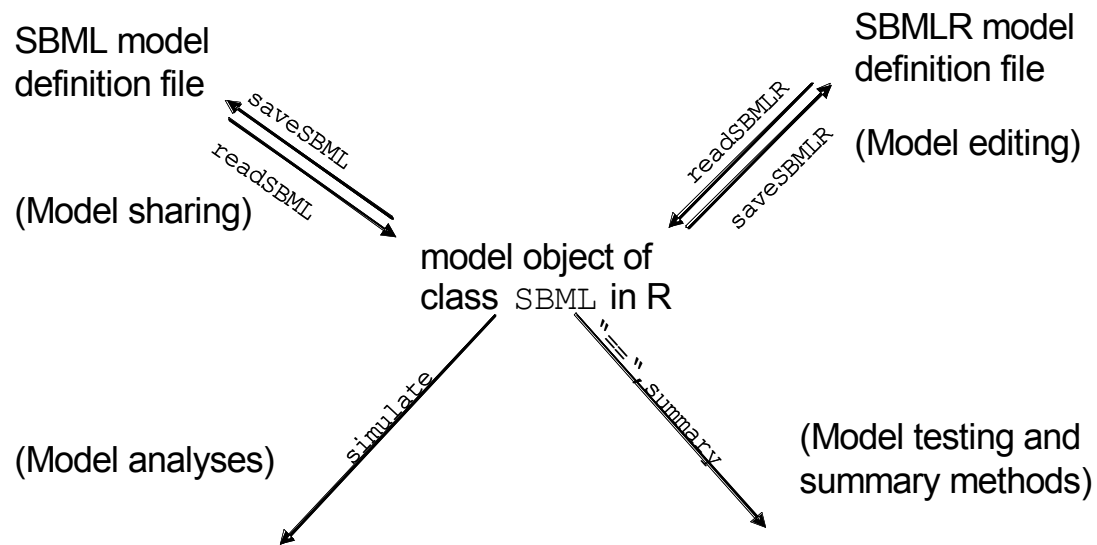
- **B**: BCR-ABL with CCR
- **b**: BCR-ABL with HR
- **b**: censored, missing, or other outcome



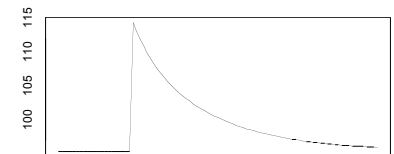
SBMLR: Model Sharing and Use

- **Systems Biology Markup Language (SBML)**
 - A standard for representing biochemical systems
- **R**
 - Free statistics-oriented computational environment
- **Bioconductor**
 - R packages primarily for DNA microarray data analyses
- **SBMLR**
 - An SBML-R interface and model analysis tool

SBMLR



```
library(SBMLR); library(odesolve)
curto=readSBML(file.path(.path.package("SBMLR"),
"models/curto.xml"))
out1=simulate(curto, seq(-20,0,1))
curto$species$PRPP$ic=50
out2=simulate(curto, 0:70)
outs=data.frame(rbind(out1,out2)); attach(outs)
par(mfrow=c(2,1), cex.lab=1.5)
plot(time, IMP, type="l", xlab="minutes", ylab="IMP (uM) ")
```



Research article

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Folate system correlations in DNA microarray data

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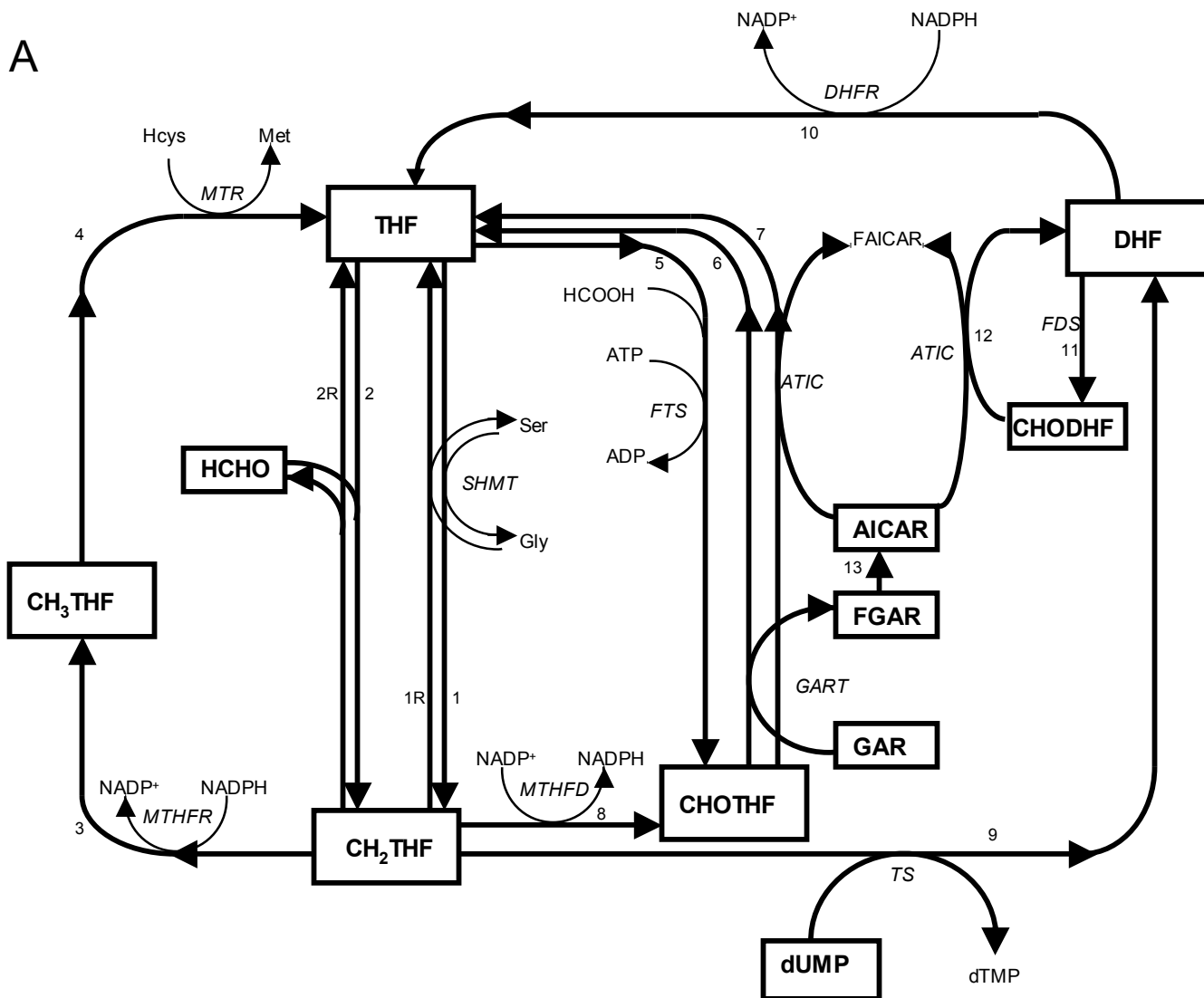
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Accepted: 04 August 2005

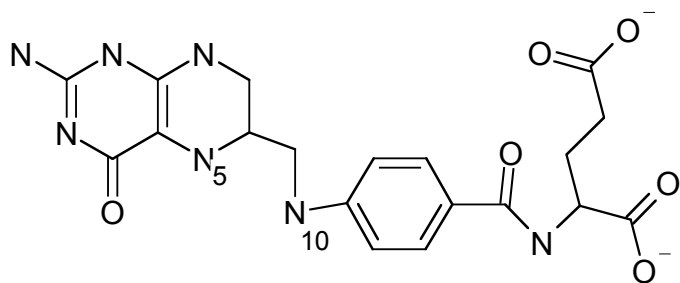
This article is available from: <http://www.biomedcentral.com/1471-2407/5/95>

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B



$$\frac{dDHF^T}{dt} = \sum_{9,12} r_i - \sum_{10,11} r_i$$

$$\frac{d(CH_3THF)}{dt} = r_3 - r_4$$

$$\frac{dHCHO}{dt} = r_{2R} - r_2$$

$$\frac{dTHF}{dt} = \sum_{1R,2R,4,6,7,10} r_i - \sum_{1,2,5} r_i$$

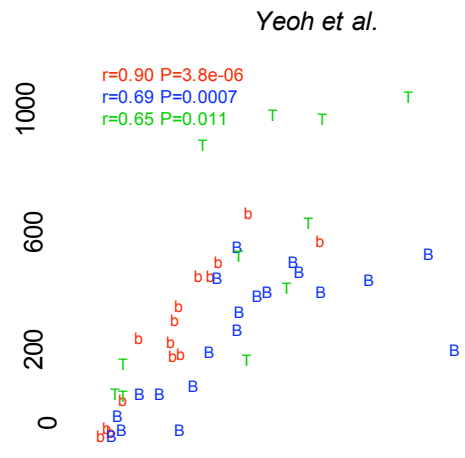
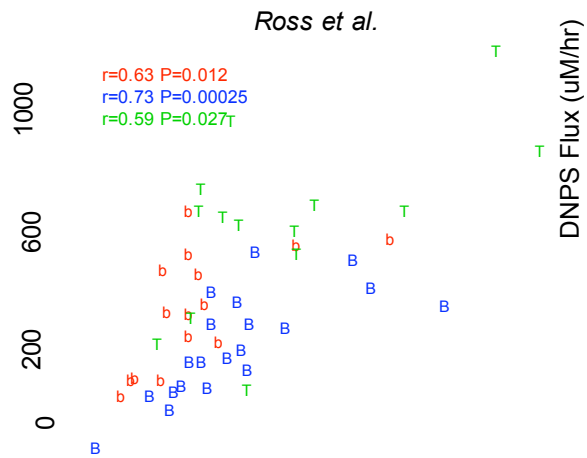
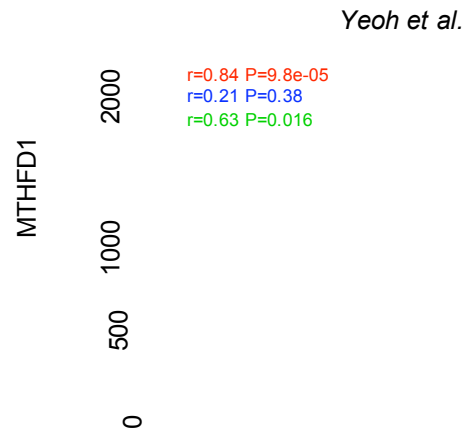
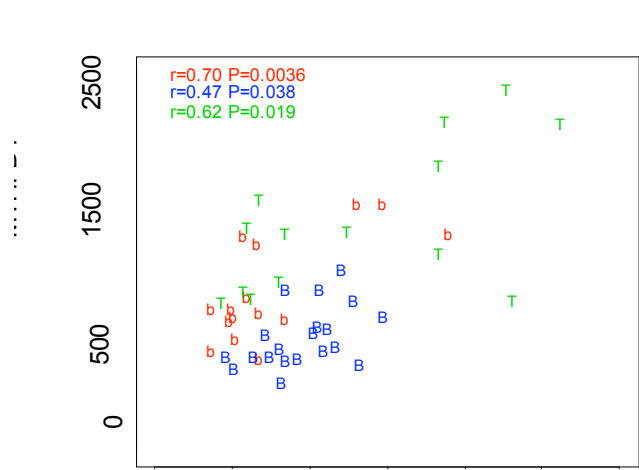
$$\frac{dCHOTHF}{dt} = \sum_{5,8} r_i - \sum_{6,7} r_i$$

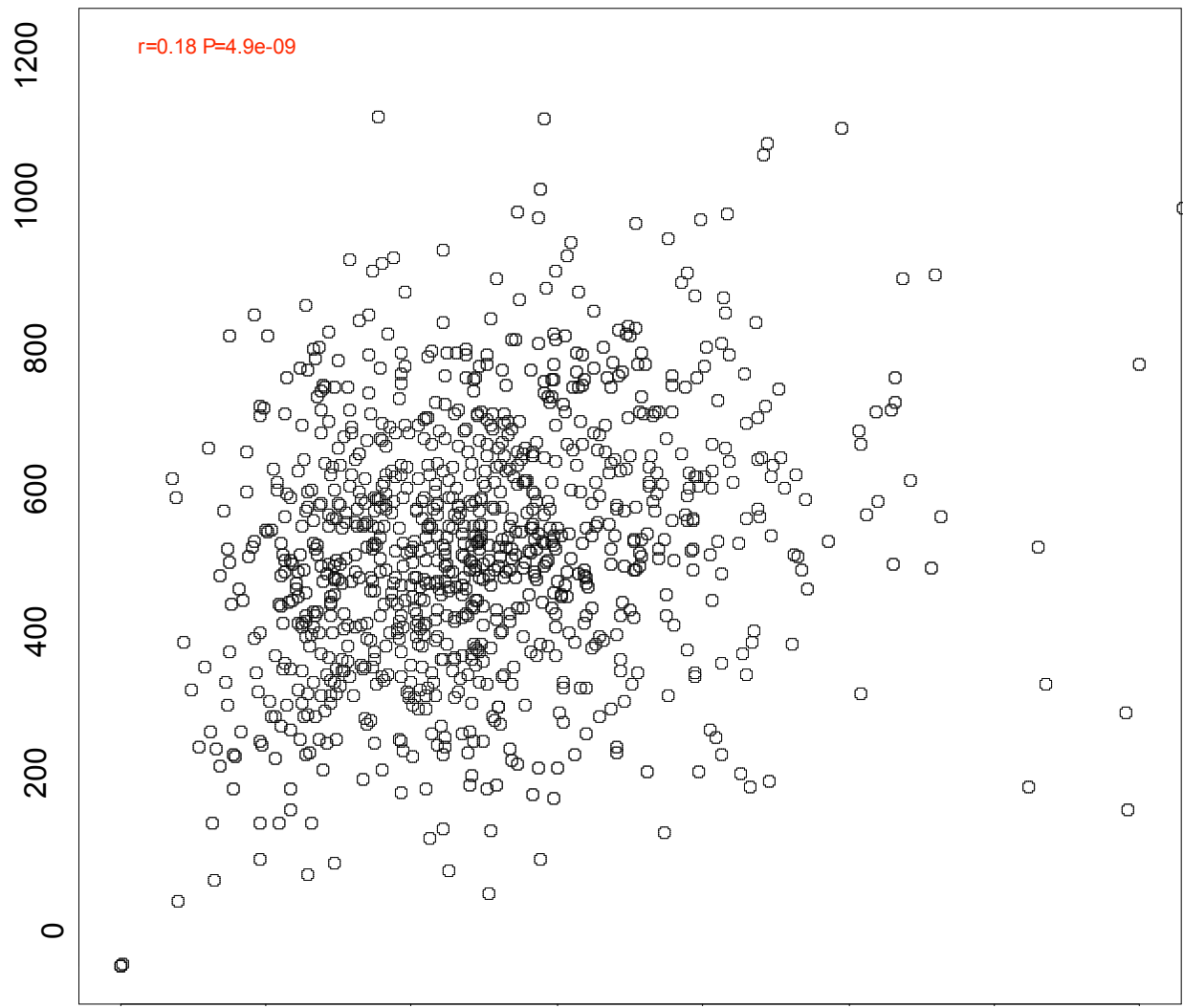
$$\frac{dFGAR}{dt} = r_6 - r_{13}$$

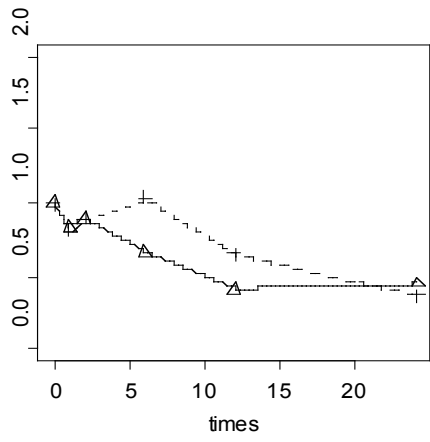
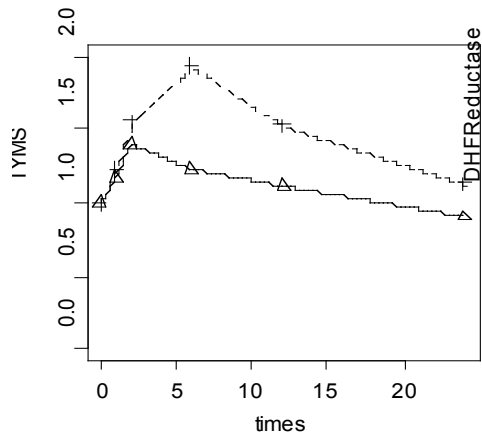
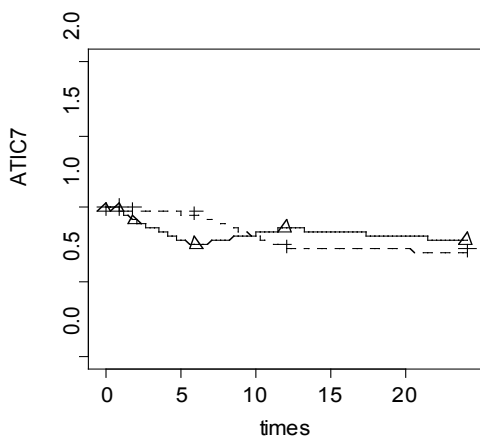
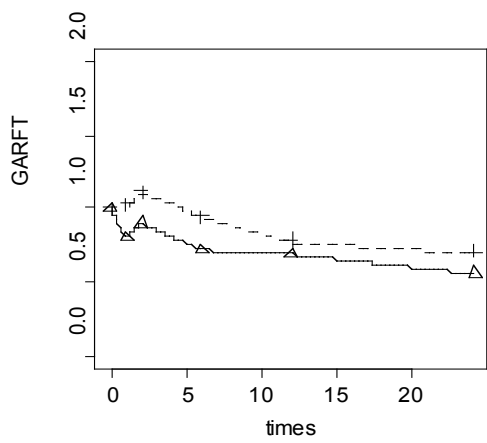
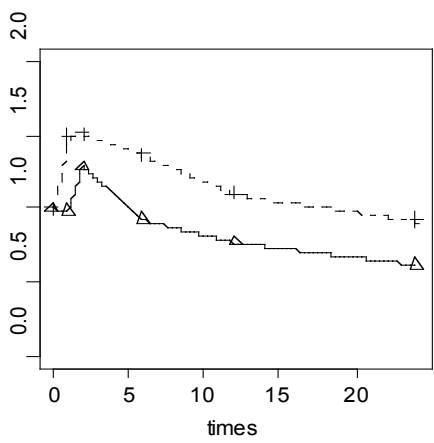
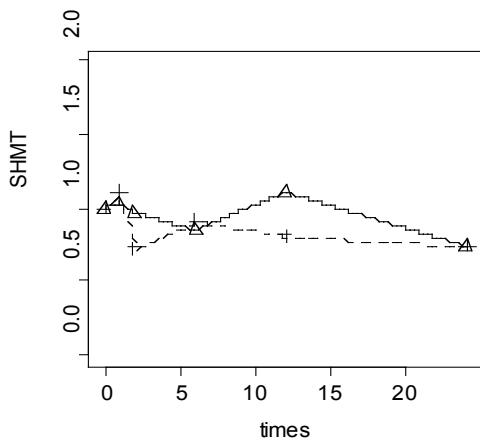
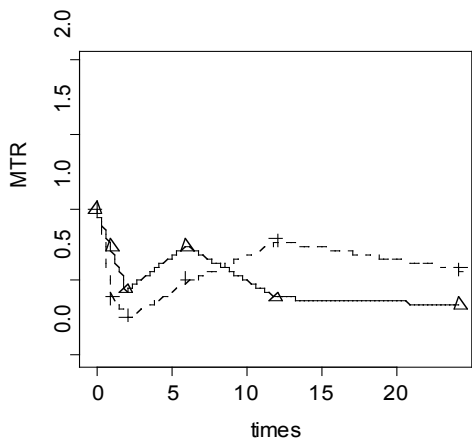
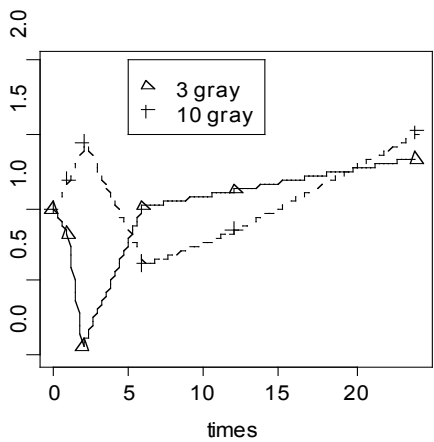
$$\frac{d(CH_2THF)}{dt} = \sum_{1,2} r_i - \sum_{1R,2R,3,8,9} r_i$$

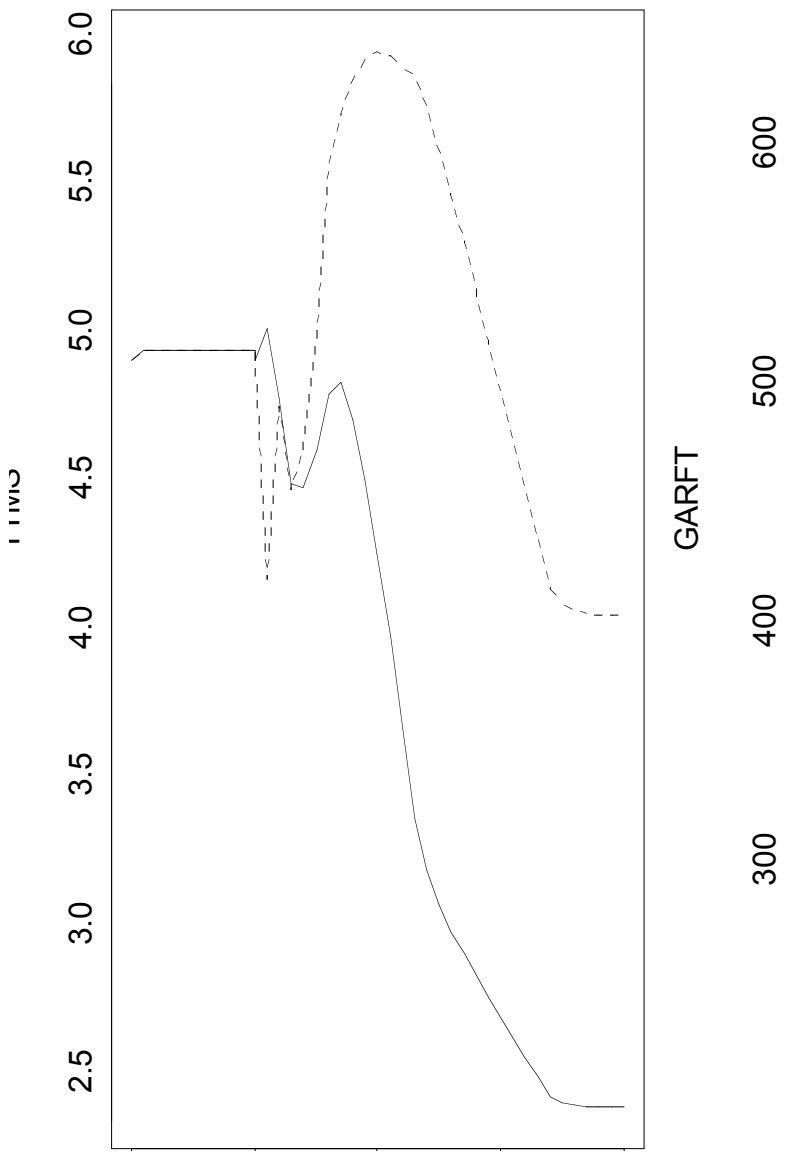
$$\frac{dCHODHF}{dt} = r_{11} - r_{12}$$

$$\frac{dAICAR}{dt} = r_{13} - r_7 - r_{12}$$









Conclusions

- Post IR mRNA replacement likely precedes DNA repair => need direct data analyses.
- Pathway analyses reduce dimensions and multiple testing of correlations.
- Conceptual models are essential

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- Thank you